Original Article

Evaluation of Pediatric Patients with COVID-19 in a Turkish University Hospital

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ABSTRACT

Background: Although COVID-19 has a milder course in pediatric patients than in adults, it can have a severe and fatal course in children with an underlying disease (UD). **Aims:** In this study, we aimed to evaluate the demographic, clinical, laboratory, and radiological characteristics, treatment methods, and prognosis of pediatric patients diagnosed with COVID-19. **Patients and Methods:** The files of patients aged 0–18 years diagnosed with COVID-19 were retrospectively evaluated. Clinically and radiologically suspicious cases were accepted as confirmed cases if SARS-CoV-2 PCR positivity was found in nasopharyngeal swab samples. The severity of the disease was defined as asymptomatic, mild, moderate, and severe according to clinical, laboratory, and radiological features. **Results:** A total of 322 pediatric patients, 51.2% male and 48.8% female, were included in the study. The median age of the patients was 12.08 years (1 month–18 years). Of the 322 patients, 81 (25.1%) were asymptomatic. Disease severity was as follows: 218 were (67.7%) mild, 14 were (4.3%) moderate, and 9 (2.7%) were severe. 35.7% of the patients were hospitalized. Six percent were admitted to the intensive care unit, and three (0.93%) patients died. The mortality rate in patients with the UD was 3.3%. **Conclusion:** In our study, we determined that the disease had a more severe course in patients with initial procalcitonin, D-dimer, troponin increase, and thrombocytopenia. Although COVID-19 has a mild course in children, this is unfortunately not true for children with an UD.

KEYWORDS: *Children, COVID-19, SARS-CoV-2, underlying disease*

INTRODUCTION

COVID-19, accepted as a pandemic by the World Health Organization on March 11, 2020, has still not been taken under control and continues to affect the whole world.[1] The incidence of COVID-19 increases with age in children.[2] Children are usually infected by household members, but it is also known that exposure to individuals outside the household is limited as the data are usually from the school closure period. Although it has been reported that the nasopharyngeal viral load of infected pediatric patients is higher than that of adults, the contagiousness of pediatric patients is not clearly known.[3,4] The signs and symptoms of COVID-19 in pediatric patients are similar to adults but generally milder than adults.

The most common symptoms in children are fever and cough. Severe cases in pediatric patients are rare, hospitalization and mortality rates are lower than in adult patients.[5] However, a multisystem inflammatory syndrome caused by COVID-19 in children (MIS-C) can cause a more severe clinical disease and may result in death.[6]

In this study, we aimed to evaluate the demographic, clinical, laboratory, and radiological characteristics,

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treatment methods, and prognosis of pediatric patients diagnosed with COVID- 19.

MATERIALS AND METHOD

The study was conducted retrospectively (April 2020–April 2021) at a tertiary university hospital in Turkey. Republic of Turkey Ministry of Health and Cukurova University Faculty of Medicine Ethics Committee approved the study.

Pediatric patients aged 0–18 years diagnosed with COVID-19 were included. Patients were accepted as confirmed cases if SARS-CoV-2 PCR positivity was found in their nasopharyngeal swab samples. SARS-CoV-2 PCR-negative patients who were clinically and radiologically compatible with COVID-19 and had a history of being in close contact with an index case with PCR-confirmed positivity were also considered as COVID-19. Disease severity was defined according to clinical, laboratory, and radiological features, as described by Dong *et al.*[7] The patient with no clinical and radiological findings but SARS-CoV-2 PCR positivity in the nasopharyngeal swab was considered asymptomatic; the patient with the finding of acute upper respiratory tract infection but without clinical and radiological pneumonia was considered mild, the patient with respiratory tract findings and pneumonia was considered moderate, and the patient with progressive findings such as dyspnea and cyanosis was considered as severe.

Statistical analysis

Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as median and minimum-maximum. The Chi-square test was used to compare categorical measures between groups. Shapiro Wilk test was used for the normality of the distribution. The Kruskal-Wallis test was used for the general comparison of non-normally distributed numerical measures between more than two groups. The Mann-Whitney U test with Bonferroni correction was used for pairwise comparisons of the groups. IBM SPSS Statistics Version 20.0 package program was used for statistical analysis. The statistical significance level was taken as 0.05 in all tests.

RESULTS

Demographic characteristics

We enrolled 322 pediatric patients (51.2% male), and the median age of the patients was 12.08 years (min-max: 1 month–18 years). SARS-CoV-2 PCR was positive in 313 (97.2%) of the patients. The demographic characteristics of the patients are shown in Table 1.

Table 1: Demographic characteristics of pediatric patients diagnosed with COVID-19

Demographic characteristics	
Age (years)	
Median	12.08
min-max	(1 month-18)
Gender *n*, %	
Male	165 (51.2)
Female	157 (48.8)
Hospitalization *n*, %	115 (35.7)
Intensive care hospitalization *n*, %	7 (2.1)
Hospitalization period (days)	
Median	7
Min-max	(1-37)
Presence of underlying disease *n*, %	
None	233 (72.4)
Leukemia	18 (5.6)
Solid tumor	11 (3.4)
Cardiovascular disease	12 (3.7)
Pulmonary disease	10 (3.1)
Renal disease	9 (2.8)
Metabolic disease	8 (2.5)
Primary immunodeficiency	7 (2.2)
Other diseases	21 (6.5)
Source case *n*, %	
Unknown	207 (64.3)
Household	91 (28.3)
Relatives	17 (5.3)
Friends	3 (0.9)
Teachers	2 (0.9)
Hospital-acquired	2 (0.9)
Presence of additional infection *n*, %	14 (4.3)
Post-exposure SARS-COV-2 PCR positivity time days (*n*=60)	
Median	4
Min-max	0-30

During the study period, none of our patients with COVID-19 developed MIS-C.

Clinical and laboratory characteristics

The most common complaints were fever and cough, 29.5% and 27.6%, respectively. 68.2% of children aged 0–12 months had a fever, and 9.1% had diminished oral intake, which was statistically significant compared to other age groups ($P = 0.04$, $P = 0.02$). 92.8% of patients with taste and smell loss were aged 10 and over, and this rate was statistically significantly higher as the age increased ($P = 0.01$). The symptoms of the patients according to age groups are shown in Table 2. Eighty-one patients (25.1%) were asymptomatic, 218 (67.7%) had a mild course, 14 (4.3%) had a moderate course, and 9

Table 2: Symptoms and findings according to age groups in pediatric patients diagnosed with COVID-19

Clinical Characteristics	0-12 months n=22%	13-60 months n=65%	61-120 months n=57%	121-180 months n=73%	≥181 months n=105%	Total n=322%	P
Symptoms							
Fever	15-68.2	30-46.2	18-31.6	24-32.9	31-29.5	118-29.5	0.04
Cough	4-18.2	12 -18.5	10 -17.5	26 -35.6	37 -35.2	89-27.6	0.18
Respiratory distress	1-4.5	1-1.5	3-5.3	1-1.4	5-4.8	11-3.4	0.53
Loss of taste and smell	0	2-3.1	0	6-8.2	20 -19	28-8.7	0.01
Stomachache	0	4-6.2	4 -7	2-2.7	3-2.9	13-4	0.51
Nausea-vomiting	2-9.1	6-9.2	6-10.5	3 -4.1	6-5.7	23-7.1	0.51
Diarrhea	2-9.1	6-9.2	6-10.5	4 -5.5	8-7.6	26-8.1	0.86
Headache	0	3-4.6	7-12.3	10-13.7	13-12.4	33-10.2	0.16
Sore throat	0	1-1.5	3-5.3	7-9.6	17-16.2	28-8.7	0.06
Musculoskeletal pain (myalgia)	0	1-1.5	6-10.5	8-11	15-14.3	30-9.3	0.03
weakness	0	5-7.7	3-4.1	3-4.1	12 - 11.4	23-7.1	0.27
Rash	1-4.5	2-3.1	0	1-1.4	1 -1	5-1.6	0.42
Oral intake disorder	2 -9.1	1-1.5	0	1-1.4	0	4-1.2	0.02
Runny nose	1-4.5	2-3.1	4-7	3-4.1	2-1.9	12-3.7	0.50
Signs							
Fever	7-31.8	10-15.4	2-3.5	1-1.4	6-5.7	26-8.1	0.01
Tachypnea	3-13.6	5-7.7	0	3-4.1	5-4.8	16-5	0.08
Tachycardia	2-9.5	2-3.1	0	0	0	4-1.2	0.01
Hypoxia	3-13.6	1-1.5	0	0	1-1	5-1.6	0.01
Rash	2-9.1	2-3.1	0	0	1-1	5-1.6	0.03
Ral-Ronkus	3-13.6	5-7.6	2-3,5	0	1-1	11-3.4	0.01

(2.7%) had a severe course. When the age groups were compared, the median age of children with severe disease was found to be younger (19 months) (*P* = 0.01). The rate of patients with underlying disease (UD) being moderate and severe was found to be statistically significantly higher (*P* < 0.01). The comparison of disease severity with demographic, clinical, and laboratory characteristics is shown in Table 3. When the laboratory characteristics were evaluated according to age groups, no significant difference was found.

Radiological characteristics

Cardiac evaluation and echocardiography were performed on 22 patients during the follow-up. Minimal pericardial effusion was detected in two patients. One hundred ninety-one (59.3%) of the patients had chest X-rays, and 27 (14.1%) of these patients had infiltration. Thorax tomography was performed in 66 (20.4%) patients. Radiologic findings were detected in 26 (39.3%) of the 66 patients; ground glass opacities were present in 11 patients (42.3%), and consolidation in six (23%) patients, both consolidation and ground glass were present in six (23%) patients, pleural effusion was present in two (7.6%) patients. Although the chest X-rays of 13 patients were normal, radiological findings were present in thorax tomography. It was found that

11 (40.7%) of 27 patients with infiltrates on their chest X-ray had a control chest X-ray during hospitalization, and none of the patients evaluated with thorax tomography had a control thorax tomography.

Treatment characteristics and prognosis

71.9% of the patients with a UD and 21.9% of the patients without a UD were hospitalized. The median length of stay of the patients with UD was 8 days (min-max: 1–37), and for those without an UD was 6 days (min-max: 2–13) (*P* < 0.001). 2.1% of all patients and 6% of hospitalized patients needed admission to the intensive care unit. 57.1% of the patients who were followed up in the intensive care unit were patients with a olmayacak. The mean age of the patients requiring intensive care admission was 87.5 months.

Forty-one (12.7%) of the patients were given favipiravir. Remdesivir, Kaletra, and hydroxychloroquine were given to three patients separately. Three (0.93%) patients died due to COVID-19. One patient had an underlying leukemia history with bone marrow transplantation, and the other two had neurometabolic disease. While the overall mortality was 0.9%, in patients with UD, it was found to be 3.37%.

Table 3: Evaluation of demographic, clinical, and laboratory characteristics according to disease severity

Characteristics	Asymptomatic *n*=81	Mild *n*=218	Moderate *n*=14	Severe *n*=9	*P1*
Age (months)					
Median, (min-max)	117 (4-216)	155 (1-219)	82 (15-192)	19 (3-192)	<0.01
Gender					
Male (%)	45 (55.6)	108 (49.8)	8 (57.1)	4 (44.5)	0.69
Female (%)	36 (44.4)	110 (50.2)	6 (42.9)	5 (55.5)	
close contact	9 (11.1)	71 (32.7)	8 (57.1)	3 (30.0)	<0.01
Underlying disease, *n* (%)					
None	58 (71.6)	168 (77.4)	5 (35.7)	2 (20)	<0.01
Leukemia	6 (7.4)	9 (4.1)	1 (7.1)	2 (20)	0.10
Solid tumor	5 (6.2)	5 (2.3)	0	1 (10)	0.16
Cardiovascular disease	2 (2.5)	8 (3.7)	0	2 (20)	0.12
Pulmonary disease	1 (1.2)	8 (3.7)	0	1 (10)	0.29
Renal disease	3 (3.7)	5 (2.3)	0	1 (10)	0.31
Metabolic disease	1 (1.2)	3 (1.4)	2 (14.3)	2 (20)	<0.01
Primary immunodeficiency	1 (1.2)	4 (1.8)	2 (14.3)	0	0.09
Other diseases	4 (19)	12 (57.1)	4 (19)	1 (4.1)	0.02
Symptoms, *n* (%)					
Fever	0	104 (47.9)	10 (71.4)	4 (40)	<0.01
Cough	0	81 (37.3)	5 (35.7)	3 (30)	<0.01
Respiratory distress	0	3 (1.4)	5 (35.7)	3 (30)	<0.01
Stomachache	0	13 (6)	0	0	0.10
Diarrhea	0	23 (10.6)	2 (14.3)	1 (10)	<0.01
Loss of taste and smell	0	27 (12.4)	1 (7.1)	0	0.01
Myalgia	0	27 (12.4)	1 (7.1)	2 (20)	<0.01
Weakness	0	23 (10.6)	0	0	<0.01
Nausea-vomiting	0	21 (9.7)	2 (14.3)	0	<0.01
Headache	0	33 (15.2)	0	0	<0.01
Sore throat	0	28 (12.9)	0	0	<0.01
Laboratory findings, *n* (%)					
Leukocytosis	2 (5.6)	7 (6.8)	1 (7.1)	1 (11.1)	0.79
Neutropenia	4 (11.1)	19 (18.4)	2 (14.3)	1 (11.1)	0.84
Lymphopenia	11 (13.6)	41 (18.9)	4 (28.6)	3 (30)	0.29
Thrombocytopenia	5 (13.9)	11 (10.7)	1 (7.1)	5 (55.6)	<0.01
Increased CRP	10 (34.5)	32 (33.3)	6 (50)	4 (44.6)	0.64
Increased procalcitonin	2 (10)	9 (14.5)	4 (33.3)	5 (55.6)	<0.01
Increased ferritin	6 (46.2)	14 (20.6)	2 (16.7)	3 (50)	0.10
Increased troponin	2 (10)	6 (7.7)	0	5 (71.4)	<0.01
Increased D-Dimer	10 (47.6)	25 (37.9)	7 (63.6)	6 (100)	<0.01
Chest X-ray, *n* %					
Abnormal	50 (61.7)	146 (67.3)	13 (92.9)	9 (90)	0.05
Thorax CT, *n* (%)					
Abnormal	11 (13.6)	38 (17.5)	10 (71.4)	7 (70)	<0.01
Treatment					
Favipiravir	4 (4.9)	24 (30)	8 (61.5)	5 (55.6)	0.04
Steroid	4 (4.8)	3 (1.4)	1 (7.1)	2 (20)	<0.01
Oxygen support	0	2 (0.09)	7 (50)	9 (90)	<0.01
Prognosis, *n* (%)					
Ex	0	0	0	3 (33.3)	<0.01

DISCUSSION

The median age of our patients was 12.08 years. Twenty-seven percent of the patients were under the age of five, 17.7% were aged 5–10 years, 22.6% were aged 10–15, and 32% were over the age of 15. In the reported studies, the median age of the pediatric patients is widely distributed: The frequency in 0–4 years is 17.4%, in 5–10 years is 18.6%, in 11–13 years is 25.7%, and in

children aged 14–17 years it is 38.3%.[2,7,8] It has been reported that COVID-19 is more frequent and severe in boys.[7-9] COVID-19 was detected more frequently in boys in our study. However, disease severity did not differ according to gender.

The rate of hospitalization due to COVID-19 disease in children has been reported as 5.3%–57.4%.[10-12] In our study, 35.7% of our patients were hospitalized. The presence of a UD is one of the risk factors for the severe course of the disease.[9,10] We found that 71.9% of patients with UD were hospitalized, and 21.9% of patients without UD were hospitalized. In our study, patients with UD had more frequent moderate and severe clinical COVID-19 courses than those without.

It was thought that our high rate of hospitalization was due to the high rate of patients with UD.

Index cases were found in 35.7% of our patients, and 79.1% of these cases were in household contact, such as parents and siblings, while 14.7% were close relatives. These findings support the idea that the index case in children was infected due to household contact, the long-term closure of schools, and the restrictions applied during the working process in Turkey. Similarly, it has been reported in the literature that children are frequently infected in the household.[13] In our study, the median duration of SARS-CoV-2 PCR positivity in children after contact with the index case was four days. In a previous study, the onset of symptoms after the transmission was reported to be 5.8 days on average.[14] In a study conducted in Taiwan, 2500 close contacts of 100 patients diagnosed with COVID-19 were evaluated, and it was determined that the symptoms of secondary cases were developed within six days.[15]

In the meta-analysis evaluating 7780 laboratory-confirmed pediatric cases with COVID-19, 19.3% of the cases were reported as asymptomatic, 42% as mild, 39% as moderate, and 2% as severe.[5] In our study, 218 (67.7%) had a mild course, 14 (4.3%) had a moderate course, and 9 (2.7%) had a severe course. In a meta-analysis evaluating 18 studies, the rate of asymptomatic infection in pediatric patients aged 20 years and younger was reported to be 15-42%.[12,16] 81 (25.1%) of our patients were asymptomatic. Previous studies reported the complaints as fever in 40-71.4%, cough in 37-64.5%, and gastrointestinal in 22% of the patients.[5,8,17,18] In our patients, 29.5% had a fever and 27.6% had a cough, which were the most common complaints, and 19.2% had gastrointestinal complaints.

There was no difference in terms of clinical findings when children were classified as under five years old, 5–10 years old, and over 10 years old in a meta-analysis.[12] Another meta-analysis reported that 53% of children under one-year-old had fever and vomiting, and this rate was more common in children younger than one year.[19] Similarly, we found that 68.2% of patients under one had a fever. In line with the previous studies, deprived oral intake was high in our patients under one years. We revealed that the loss of taste and smell was higher in patients 10 years and over. These complaints may not be noticed in young ages, and the families do not mention these complaints in the admission. There is limited data in the literature on complaints according to age groups. When the age groups were compared, the median age of children with severe disease was found to be younger.

In a meta-analysis, 2.1% of pediatric patients had leukocytosis, 5% had leukopenia, 15% had lymphopenia, 9.6% had increased C-reactive protein (CRP), and 8.9% had increased Procalcitonin (PCT).[20] In line with the previous studies, lymphopenia was found in 18.3% of our patients, and leukocytosis was found in 6.8%. In contrast, leukopenia was found in 16% of our patients. The high rate of leukopenia can be explained by the high rate of patients with underlying hematological malignancies. It has been reported that some laboratory parameters (increase in D-dimer, CRP, lactate dehydrogenase, troponin) can indicate the severity of the disease.[21] In our study, there was no relationship between leukocytosis, lymphopenia, neutropenia, and the severity of the disease. Thrombocytopenia and an increase in procalcitonin, troponin, and D-dimer was more common in our severe coursed patients ($P < 0.01$ for all).

Children may have very different radiological findings related to COVID-19: 44% of the patients might have an abnormality in the chest X-ray or thorax tomography.[12] The most frequently reported radiological findings are ground glass opacities (37.2%) and pneumonic infiltration (22.3%). Pleural effusion is generally reported as a rare finding.[5,12] We detected radiological findings on 14.1% of the chest X-rays and 20.4% of thorax tomographies. Since imaging was not performed on all patients, it was thought that imaging findings might have been detected at a lower rate. Similar to the literature, ground glass opacities (42.3%) and consolidation (23%) were the most common findings in thorax tomographies in this study.

In our study, it was found that none of the patients had a control tomography during the hospitalization, and the control Chest Xray were taken in 11 (40.7%) of the 27 patients with consolidation.

There is no treatment recommendation supported by a randomized controlled study yet. In pediatric patients,

case-based treatment is recommended. The decision to use antivirals should be individualized according to the severity of the disease, clinical course, and the presence of UDs that may lead to a severe course of the disease.[22] In our study, antiviral treatment was given to patients with moderate disease, severe disease, and UD in accordance with recommendations. Twelve percent of the patients were given favipiravir, and no adverse events were observed. Data on the use of favipiravir in children are limited in the literature. In a meta-analysis evaluating 7780 patients, the use of remdesivir and other antivirals was reported as 21.8%.[5] In a study from Turkey, it was reported that 2.3% of patients were given favipiravir and hydroxychloroquine together.[23]

In a study in which 25 centers in Europe participated, including 582 children with a median age of five years and diagnosed with PCR-confirmed SARS-COV-2 infection, it was reported that 62% of the patients were hospitalized and 8% were followed in the intensive care unit.[19] In our study, 35.7% of our patients were hospitalized, and 6% of those patients required intensive care. SARS-CoV-2-related death in children and adolescents has been reported rarely. In a previous study, the mortality rate was reported as 0.8%.[5] In another multicenter study, mortality in children aged 0–19 was reported as 0.17 per 100 000 people.[24] It has been reported that the presence of UD is a risk factor for the severe course of the disease and mortality.[9,10] In our study, three (0.9%) of 322 patients were expired, and these three patients had a UD. This finding emphasizes the fact that COVID-19 is more fatal for patients with UD.

CONCLUSION

Although it was defined as a mild disease in pediatric patients at the beginning of the pandemic, it is now known to be severe and fatal, especially in children with UD. Furthermore, an increase in procalcitonin, troponin, D-dimer, and thrombocytopenia in children indicates that the disease will have a severe course. It is known that pediatric patients generally contract the disease from adults with whom they are in close contact, such as family members. Therefore, the vaccination of adults and adolescents for the protection of children is the most effective protection today.

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Conflicts of interest
There are no conflicts of interest.

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