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Should We Perform Laboratory and Radiographic Evaluations for All Children with COVID-19?: A Single-Center Experience

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Abstract

Background The diagnostic and treatment strategies for children are limited because of the small number of children with COVID-19. A large proportion of infected children are asymptomatic or have mild symptoms. We report our experience regarding clinical characteristics, laboratory, radiologic findings, and outcomes of children with COVID-19.

Materials and Methods This retrospective single-center study was conducted on children with COVID-19. The data on epidemiologic characteristics, clinical features, laboratory, and radiologic findings of patients were extracted from the hospital information management system records, and patients' forms filled upon admission.

Results The median age of children was 121 months, 46.8% of the patients were females and 53.2% were males. Of the 581 children assessed, a total of 222 (38.2%) had positive test results; 69 of them (31.1%) were asymptomatic. The median absolute lymphocyte and eosinophil counts were statistically significantly lower in symptomatic children ($p = 0.001$; $p = 0.02$). Neutrophil lymphocyte ratio was statistically significantly higher in the symptomatic children ($p = 0.001$). Of 72 computed tomography scans, 35 (48.6%) were normal, and only 29 (40%) were consistent with classic/probable/indeterminate COVID-19 predominant pattern.

Conclusion Our results showed a few laboratory abnormalities in asymptomatic polymerase chain reaction positive children; therefore, unnecessary investigation might be avoided and clinicians should consider clinical symptoms.

Keywords
- children
- COVID-2019
- clinical features

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Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), first appeared in December 2019 in Wuhan, China. The World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020.[1] After our first case in Turkey on March 11, a total of 225,173 cases and 5,596 deaths in our country has been confirmed. Most of the infected children are asymptomatic or present with atypical symptoms, such as low-grade fever, vomiting, diarrhea, mild fatigue, and cough without any signs of pneumonia or shortness of breath.[2–7] Several epidemiological, clinical, laboratory, and treatment studies also a few systematic reviews and meta-analyses determined the epidemiological, clinical characteristics, and laboratory findings of pediatric COVID-19 disease.[2,7,8] Unfortunately, there are no clear global diagnosis and treatment guidelines for infection in children due to the small number of pediatric patients with COVID-19. It is uncertain that which children need laboratory and radiographic examinations. The scientific board established by the Turkish Ministry of Health has developed treatment and follow-up guidelines for clinicians in a very short time and has updated guidelines according to the ongoing development of the pandemic. In this study, we aimed to summarize a single-center experience regarding clinical presentation, laboratory, radiological findings, and outcomes of children with COVID-19 according to the polymerized chain reaction (PCR) test results between symptomatic and asymptomatic patients.

Materials and Methods

Study Design

We performed a retrospective evaluation of 581 children aged 0 to 18 years old with suspected COVID-19 admitted to the University of Health Science, Department of Pediatrics, Prof. Ilhan Varank Sancaktepe Training & Research Hospital from March 16, 2020 to April 26, 2020. Informed consent was obtained from all parents before hospitalization and during all procedures. Approval was received from the ethical committee of the institution (B.10.1.TKH.4.34.H. GP.0.0.1/139). A confirmed case of COVID-19 was defined as a child with exposure history, clinical symptoms associated with COVID-19, and together with abnormal chest radiography or computed tomography (CT0 scan and positive polymerase cain reaction (PCR) test. Complete blood count, blood biochemistry, and infection biomarkers were performed. Blood culture and procalcitonin (PCT) were used in the differential diagnosis of secondary bacterial infections. Nasopharyngeal swab RT-PCR assay for detecting SARS-CoV-2 coronavirus was performed according to the WHO's guidelines.

The data including demographics, clinical symptoms of COVID-19 (fever, cough, shortness of breath, vomiting, diarrhea, smell/taste loss), the severity of the disease, comorbid disease, transfer to the pediatric intensive care unit (PICU), and newborn intensive care unit (NICU); laboratory and radiologically findings (chest radiography, CT) of the patients were obtained retrospectively from our electronic HIS records and patients form filled upon admission. We performed the first examinations on admission (complete blood count, biochemical parameters, acute phase reactants, D-dimer, troponin, prothrombin time [PT], partial thromboplastin time [aPTT], chest radiography, and thorax computed tomography). Fever was defined as an axillary temperature of $\geq$37.8°C. An absolute lymphocyte count (ALC) of less than 1,500 cells/mm^3 was defined as lymphocytopenia. Tachypnea was defined as RR $\geq$70 breaths/min (bpm) in infants and $\geq$50 bpm in older children, and adolescent's tachypnea was defined as $\geq$25 bpm. The severity of COVID-19 was classified as mild (upper respiratory tracts infection symptoms such as sore throat, fever, cough, vomiting, diarrhea, and normal radiographic images), moderate (pneumonia, fever, cough, without hypoxemia and shortness of breath, or asymptomatic chest X-ray/CT lung lesions), severe (respiratory distress, hypoxemia, severe dehydration, and signs of rhabdomyolysis) and critical (respiratory failure requiring mechanical ventilation, organ failure, myocardial injury, and shock). According to the Turkish Thoracic Society (TTS) guideline, the severity of pneumonia was assessed, which classifies children as having mild or severe pneumonia and provides clinical classification criteria for pneumonia, severe and very severe pneumonia.[9] Chest radiography and CT were performed based on history and physical examination. Two experienced radiologists evaluated chest CT findings in accordance with the Thoracic Imaging for COVID-19 Infection Guideline (version 2) of the British Society of Thoracic Imaging (BSTI).[10] CT-scans classification of covid-19 was interpreted as classic/probable/indeterminate accordingly in this study.[10] According to the national guideline, patients with moderate, severe, critical diseases were hospitalized, treated, and followed-up. We closely followed the patients in terms of potential interactions and side effects of all drugs used in the treatment.

Statistical Analysis

SPSS version 21 (SPSS Inc.; Chicago, Illinois, United States) was used for statistical analysis. Kolmogorov–Smirnov or Shapiro–Wilk tests were used for assessing normality, where appropriate. Results were presented as median (interquartile range) for non-normally distributed variables. Categorical variables were presented with frequency and percentage. Comparisons of the groups for continuous variables were determined with Mann–Whitney U test. Chi-square test or Fisher's exact test was used to analyze categorical variables, where appropriate. All tests are two-sided, and the significance level was accepted as $p < 0.05$.

Results

The median age of patients was 121 months (range: 0–219 months), 46.8% ($n = 272$) of them were females, and 53.2% ($n = 309$) were males. Of the 581 children assessed, a total of 222 (38.2%) were PCR positive, 54 (9.3%) had no contact history and had definite clinical signs and symptoms of

Table 1 Demographics characteristics of 581 children suspected for COVID-19

	RT-PCR			
	All cases	Positive	Negative	*p*-Value
	n = 581	*n* = 222	*n* = 359	
Age (*n* = 581)				
Median (IQR), mo	121 (54–180)	123 (59–177.2)	118 (51–185)	0.84[b]
Gender (*n* = 581)		*n* (%)		
Female	272 (46.8)	106 (47.7)	166 (46.2)	0.72[c]
Male	309 (53.2)	116 (52.3)	193 (53.8)	
No of family members infected (*n* = 581)		*n* (%)		
0 contact[a]	54 (9.3)	11 (5.0)	43 (12.0)	0.001[c]
1 contact	249 (42.9)	103 (46.4)	146 (40.7)	
≥2 contact	257 (44.2)	108 (48.6)	149 (41.5)	
COVID-19 suspected mother NB[a]	21 (3.6)	NA	21 (5.8)	
Clinical symptoms (*n* = 377)		*n* (%)		
Cough[a]	202 (53.6)	98 (64.1)	104 (46.4)	0.00044[c]
Fever	73 (19.4)	21 (13.7)	52 (23.2)	
Smell/taste loss	3 (0.8)	2 (1.3)	1 (0.4)	
Shortness of breath[a]	20 (5.3)	2 (1.3)	18 (8.0)	
Vomiting, diarrhea	79 (21.0)	30 (19.6)	49 (21.9)	
Severity (*n* = 581)		*n* (%)		
Asymptomatic	204 (35.1)	69 (31.1)	135 (37.6)	0.26[d]
Mild	276 (47.5)	118 (53.2)	158 (44.0)	
Moderate	70 (12.0)	25 (11.3)	45 (12.5)	
Severe	25 (4.3)	9 (4.1)	16 (4.5)	
Critical	6 (1.0)	1 (0.5)	5 (1.4)	
Follow-up (*n* = 581)		*n* (%)		
Home	499 (85.9)	197 (88.7)	302 (84.1)	0.12[c]
Hospitalized	82 (14.1)	25 (11.3)	57 (15.9)	

Abbreviations: IQR, interquartile range; NB, newborn; RT-PCR, reverse transcription polymerase chain reaction.
[a]Significantly different groups.
[b]Mann–Whitney U test.
[c]Chi-square test.
[d]Fisher's exact test.

COVID-19; 506 (87.1%) were from families with confirmed infection, and 21 (3.6%) were newborns born to mothers with suspected or confirmed COVID-19. On admission, 53.6% ($n = 202$) of symptomatic children presented with cough, 21% ($n = 79$) with vomiting and diarrhea, 19.4% ($n = 73$) with fever, 5.3% ($n = 20$) with shortness of breath, and 0.8% ($n = 3$) with smell/taste loss. The incidence of cough in the PCR positive group was significantly higher than in PCR negative group. There was no statistically significant difference between PCR positive and negative groups in terms of the incidence of other symptoms (►**Table 1**). Of the 581 children, 377 (64.9%) were symptomatic, and 204 (35.1%) were asymptomatic. Among 377 symptomatic cases, 153 (40.5%) were PCR positive. As shown in ►**Table 2**, the median ALC and the number of children with ALC <1,500 cells/mm^3 were significantly lower in symptomatic than asymptomatic children. The number of children with NLR >3.13 was statistically significantly higher in symptomatic children ($p = 0.049$). The median eosinophil count of asymptomatic children (140) was statistically significantly higher than that of symptomatic children (90) ($p = 0.020$). The proportion of children with an eosinophil count of ≥250 cells/mm^3 was higher in asymptomatic children and an eosinophil count of <50 cells/mm^3 was higher in symptomatic children, but the differences were not statistically significant. No differences were observed in biochemical parameters between groups.

Chest radiography was normal in 181 (63.1%) of 287 children. Abnormality was found in 106 (36.9%) of them. Chest radiography from 107 PCR positive cases was abnormal only in 1 (20%) of asymptomatic and 32 (31.4%) symptomatic children. Of 72 CT scans, 35 (48.6%) were normal and 29 (40.3%) were consistent with classic/probable/

Table 2 Laboratory findings of polymerase chain reaction positive asymptomatic and symptomatic children with COVID-19

	Positive PCR			
	All cases	Asymptomatic	Symptomatic	*p*-Value
Number of cases	***n* = 581**	***n* = 69**	***n* = 153**	
WBC (*n* = 348)				
Median (IQR) cells/mm^3	8,200 (6,400–10,900)	7,600 (5,650–9,400)	6,950 (5,225–8,475)	0.16[a]
Distribution, *n*/total (%)				
>10,000 cells/mm^3	110 (31.6)	4 (16.0)	16 (12.9)	0.75[c]
<4,000 cells/mm^3	13 (3.7)	NA	11 (8.9)	
ALC (*n* = 348)				
Median (IQR) cells/mm^3	2,575 (1,790–3,800)	3,750 (2,515–5,400)	2,015 (1,373–2,893)	0.0001[a]
Distribution, *n*/total(%)				
<1,500 cells/mm^3	63 (18.1)	1 (4.0)	37 (29.8)	0.0069[b]
NLR (*n* = 348)				
Median (IQR) cells/mm^3	1.6 (1.0–2.7)	0.9 (0.4–1.3)	1. 6 (1.0–2.8)	0.0001[a]
Distribution, *n*/total(%)				
≥3.13	73 (21.0)	1 (4.0)	28 (22.6)	0.049[c]
Eosinophil (*n* = 348)				
Median (IQR) cells/mm^3	120 (52.5–250)	140 (100–225)	90 (50–167.5)	0.020[a]
Distribution, *n*/total (%)				
>250 cells/mm^3	86 (24.7)	5 (20.0)	16 (12.9)	0.35[c]
<50 cells/mm^3	70 (20.1)	2 (8.0)	30 (24.2)	0.072[b]
Platelet count (*n* = 348)				
Median (IQR) cells/mm^3	265,500 (226,250–316,000)	273,000 (208,000–295,000)	247,500 (212,250–286,000)	0.49[a]
Distribution, *n*/total (%)				
<150,000 cells/mm^3	6 (1.7)	1 (4.0)	4 (3.2)	
CRP (≥0.05 mg/dL) (*n* = 347), *n*/total (%)	154 (44.4)	11 (44.0)	56 (45.5)	0.89[b]
AST >40 U/liter (*n* = 341), *n*/total (%)	38 (11.1)	3 (12.0)	11 (9.0)	0.71[c]
ALT >40 U/liter (*n* = 340), *n*/total(%)	16 (4.7)	1 (4.0)	5 (4.1)	1.0[c]
LDH >40 U/liter (*n* = 205), *n*/total (%)	205 (100)	17 (100.0)	77 (100.0)	

Abbreviations: ALC, Absolute lymphocyte count; ALT, Alanine aminotransferase; ANC, Absolute neutrophil count; AST, Aspartate aminotransferase; CRP, C-reactive protein; IQR, interquartile range; LDH, Lactate dehydrogenase; NA, not available; NLR, neutrophil lymphocyte ratio; WBC, White-cell count.
[a]Mann–Whitney test.
[b]Pearson Chi-square test.

indeterminate COVID-19 predominant pattern. The CT images from 32 PCR positive cases showed classic/probable COVID-19 predominant pattern, indeterminate for COVID-19 and non-COVID-19 findings in 15 (46.9%), 1 (3.1%), and 2 (6.3%) of children, respectively. The severity of CT findings was determined as mild, moderate, and severe in 17 (58.6%), 7 (24.1%), and 5 (17.3%) of children, respectively (►**Table 3**). Among the comorbidities, asthma was present in six, inflammatory bowel disease in two children, and type1-diabetes mellitus. The median duration of hospitalization was 5 days (range = 1–13). Only three children and three newborns required PICU and NICU admissions, respectively. The symptomatic and supportive treatments were administered to children with symptoms. Drug interactions were closely monitored, and a pediatric cardiologist did ECG monitoring of children treated with azithromycin and chloroquine. No ECG abnormalities were observed in children receiving these treatments.

Discussion

We summarized our experience regarding epidemiological characteristics, clinical presentation, laboratory, imaging findings, and outcomes of COVID-19 in children. The Chinese Center for Disease Control and Prevention published a report of 72 314 COVID-19 infection cases. Among 44,672 (61.8%) positive cases, 416 (0.9%) were aged 0 to 9 years, and 549 (1.2%) were aged 10 to 19 and accounted for 2% of all positive

Table 3 Radiological findings of children with COVID-19

	All cases	PCR positive	PCR negative
Chest X-Ray ($n = 287$)			
Normal	181 (63.1)	74 (69.2)	107 (59.4)
Abnormal	106 (36.9)	33 (30.8)	73 (40.6)
Chest CT ($n = 72$)			
Normal	35 (48.6)	14 (43.8)	21 (52.5)
Classic/probable COVID–19	25 (34.7)	15 (46.9)	10 (25)
Indeterminate for COVID-19	4 (5.6)	1 (3.1)	3 (7.5)
Non COVID-19	8 (11.1)	2 (6.3)	6 (15)
Chest CT severity ($n = 29$)			
Mild	17 (58.6)	10 (62.4)	7 (53.9)
Moderate	7 (24.1)	5 (31.3)	2 (15.3)
Severe	5 (17.3)	1 (6.3)	4 (30.8)

Abbreviations: CT, computed tomography; PCR, polymerase chain reaction.

cases. The case fatality rate in children was 0.18%.[11] An article from Spain reported that 41 of the 4,695 confirmed cases (0.8%) in Madrid were children younger than 18. Of the 365 children tested during the first 2 weeks, 41(11.2%) had positive test results.[12] The percentage of positive cases (38.2%) in our study was three times higher than that reported in Spain. The Korean Center for Disease Control and Prevention reported that 201 (4.8%) of 4,212 registered cases were children ≤19 years of age; 32 (15.9%) children aged 0 to 9 years and 169 (84.1%) children aged 1019.[13] Children accounted for 8.3% of all positive patients tested in our hospital. Our pediatric cases' high positive prevalence can be explained by the large number of test performed in asymptomatic children with contact history. Initially, children with contact history or who contacted an infected person and presented at least one symptom were tested. The algorithm was changed rapidly, and the recommendation was to test children with symptoms and signs of COVID-19 regardless of contact history. Reported transmission in children is by close contact with infected adults.[3] The majority of our children (87.1%) had 1 or ≥2 closed contacts with the infected family member. Chinese researchers recently published a study evaluating 2,135 pediatric patients with COVID-19. In accordance with our results in their study, 34.1% of children were laboratory confirmed.[3] Unfortunately, the sensitivity of the PCR test is lower (32–63%). Previous studies showed that the viral RNA RT-PCR swab test's predictivity depends on the site of sampling and on time from exposure to onset of symptoms (stage of disease).[14,15] Therefore, a negative PCR does not rule out the disease, especially if we have a high-clinical suspicion.

Studies revealed that children of all ages are susceptible to COVID-19.[2–9] The median age of our patients was 121 months (range = 9–6 years). Among 2,572 COVID-19 pediatric cases reported from the United States, the median age was 11 years (range = 0–17 years), and the majority of children were aged 15 to 17 years,[5] similar to our study. Contrary to reported slightly male predominance, the gender difference in our study was found to be insignificant.[3] The knowledge about the clinical characteristics of pediatric COVID-19 is limited. Although several mechanisms were discussed, why children with COVID-19 have less severe clinical presentation than adults remains unclear.[16] The most commonly reported symptoms in children are fever, dry cough, and fatigue, while some patients have a sore throat, vomiting, and diarrhea.[1–9] Lu et al[4] evaluated 171 children with confirmed COVID-19 and reported similar to our study that cough was the most frequent symptom (48.5%), followed by pharyngeal erythema (46.2%) and fever (41.5%). Although clinical manifestations in children were generally less severe, young children, particularly infants, were affected more severely than the older. Considering the higher rates of negative test results (70.9%) and diagnosis based only on clinical features among these age groups, the authors suggested that a different respiratory infection than COVID-19 might cause these cases. Recently, unusual manifestations of the disease as a pediatric multisystem inflammatory syndrome (including features of atypical Kawasaki disease or shock) were observed among children and young adults in New York City. Children[17] with underlying diseases such as congenital heart disease, severe malnutrition, and those with immune deficiency or immunocompromised status are at risk for severe disease.[18] A small number of critical cases and mortality in children were reported in some studies.[2–9,12–14] In correlation with these findings, 25 (4.3%) of our cases were severe and 6 (1.0%) were critical, but there was no death in our study.

Although some abnormalities have been observed, a consistent pattern of characteristic laboratory findings has not yet been identified in children with confirmed COVID-19. Reported laboratory findings are lymphopenia and elevated inflammatory markers.[2,3,6,12] Nonetheless, some authors suggested that we need laboratory and radiographic

examinations.[3] We performed a subgroup analysis of PCR-positive asymptomatic and symptomatic children. Du et al[19] determined that the age of asymptomatic patients was younger than that of symptomatic patients. The median age of our symptomatic children was slightly higher than asymptomatic but not statistically significant. As previously reported, we found a decrease in lymphocyte counts, and an increase in NLR which was significantly higher in symptomatic children.[20] The median eosinophil count was significantly lower in symptomatic children than in asymptomatic. Authors showed that eosinophils are recruited into children's lungs with the respiratory syncytial virus (RSV).[20] However, their role in promoting antiviral host defense remains unclear. Phipps et al.[21] demonstrated that eosinophils promote (in vivo) virus clearance and thus may limit virus-induced lung dysfunction. Slightly increased eosinophil count in our asymptomatic children may play a beneficial role during viral infections as well as COVID-19. The high eosinophil counts in asymptomatic children are considered as a laboratory finding that indicates the presence of mucosal contact with the virus. We speculated that the elevated eosinophil counts in the asymptomatic children demonstrate that the inflammatory response to viral infection has started, and in correlation with this, a decrease in the eosinophil count of symptomatic children may suggest the migration of eosinophils into the damaged tissue. Further studies may elucidate the clinical significance of these findings.

A recently published study reported that radiologic abnormalities were not observed at admission in 2.9% of the patients with severe disease and 17.9% of the patients with mild disease.[22] Studies of radiologic findings in pediatric patients with COVID-19 were limited, and some authors suggested that early chest CT screening "is a feasible clinical protocol in children."[23] Our result shows that nearly 50% of children had normal CT findings. The CT scan images were severe only in 5 of 29 children with classic/probable/indeterminate COVID-19 predominant pattern. Researchers reported a high percentage of lung injury in asymptomatic patients (62.5%), but they did not specify the severity of lung injury.[24] In our study, a CT scan was performed in 40 PCR-negative symptomatic children. Severe CT findings were detected in four of them, which confirmed the importance of clinical symptoms for diagnosis. Given the radiation exposure associated with CT, if children are asymptomatic or symptoms are mild, routine usage of CT might not be recommended. It is unclear which children need antiviral therapy, especially because of the high rate of asymptomatic infected children. We need more information and global guideline for the treatment of pediatric patients. Up to now, no antiviral treatment is officially approved for the prevention or management of COVID-19. Symptomatic and supportive treatment was administered to our patients based on our national treatment guidelines. No ECG abnormality was observed in any of our children who received azithromycin and chloroquine treatment.[25] Our study did not specify the treatments given to each patient individually, as the treatment guidelines frequently change according to new studies in our country and all over the world. Limitation of our study: it is a single-center and data for the beginning of the COVID-19 pandemic. Laboratory results obtained after hospitalization for all patients were not included. In addition, some cases were diagnosed in outpatient settings where records were not well documented, and incomplete or unnecessary laboratory testing was performed. Furthermore, testing for other respiratory viral pathogens was not performed in all patients.

Conclusion

In conclusion, our results showed a few laboratory and radiological abnormalities in asymptomatic positive children. Therefore, unnecessary investigation should be avoided, and clinicians should focus on clinical symptoms. Given the radiation exposure associated with CT, if children are asymptomatic or symptoms are mild/moderate routine use of CT is not recommended. The long-term consequences in children are unknown. We need to share our findings and learn rapidly from each other.

Note

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None.

Conflict of Interest

None declared.

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