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Original Article

Coronavirus disease 2019 in healthy children: What is the effect of household contact?

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Abstract ***Background*:** Coronavirus disease 2019 (COVID-19) in children is milder than in adults. Household virus exposure may affect clinical severity. We aimed to determine the household contact history of patients and its influence on the clinical stage.

***Methods*:** One hundred and seventy-three pediatric patients with COVID-19 as diagnosed with positive real-time polymerase chain reaction for severe acute respiratory syndrome coronavirus-2 aged 1 month to 18 years were included. Demographic data, laboratory and clinical findings, and the history of household contact of the patients were obtained. They were classified according to their clinical stage as mild or moderate-severe.

***Results*:** Sixty patients (34.7%) were asymptomatic, and 113 were symptomatic (65.3%). Of the 173 patients, 138 (79.8%) had at least one family member in the household who was diagnosed as having COVID-19. Hemoglobin, absolute neutrophil count, and absolute neutrophil count /absolute lymphocyte count ratio decreased significantly in patients with household contact. The presence of a household contact did not have a significant effect on the presence of symptoms, clinical course, age, and the sex of the patients. The need for hospitalization was less in the group that had household contact. Being 0–12 months, being female, and being a patient without household contact were independent factors associated with higher hospitalization ratios in logistic regression analysis.

***Conclusions*:** In this study, we found that household contact history did not significantly affect presenting symptoms and clinical course. We detected the rate of hospitalization to be less in the group with only household contact.

Key words child, COVID-19, household, SARS-CoV-2, transmission.

A new coronavirus was identified in late December 2019 in China and declared a pandemic by the World Health Organization on March 11th, 2020.[1,2] Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has infected approximately 180 million people, and over three and a half million patients with COVID-19 have died.[3] Virus transmission dynamics differ by country and community.[3] Fortunately, children are likely to have a milder disease than adults. It also seems that they acquire the virus via household contact and do not play a significant role as carriers to adults, unlike with the influenza virus.[4,5] Schools were closed after the Turkish Ministry of Health announced the first patient with COVID-19 in Turkey. Restrictions have been implemented for the most vulnerable population first; children and those aged over 65 years. These populations were considered more sheltered at the beginning of the pandemic; however, they began to become infected by other household members outside of their places of residence. This appeared to be the way in which children mostly acquired SARS-CoV-2.

There are still ongoing studies regarding the viral pathogenicity and host factors that are searching the question of why some people have an asymptomatic infection whereas others die of COVID-19.[6–8] Some studies suggested that the COVID-19 disease severity might be associated with host genetic background and a high amount of infected family members.[9,10] By contrast, we thought that the duration of viral exposure might worsen clinical outcomes. In our research, we aimed to determine the proportion of patients who had household contact with COVID-19 through family members and whether the presence of household contact might lead to various clinical stage and laboratory findings in the pediatric COVID-19 population.

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Methods

Study design and participants

Our retrospective study was conducted at Health Science University Izmir Tepecik Training and Research Hospital in Izmir. In Turkey, we had pandemic clinics for both pediatric inpatients and outpatients since March 2020. Patients were chosen from these clinics. The inclusion criteria were determined as children having at least one real-time polymerase chain reaction (RT-PCR) positive nasopharyngeal swap sample. Neonates and children with absent laboratory analyses were excluded. Children with underlying facilitating factors that might worsen the disease's course and hinder estimating the effect of household contact on clinical severity were also excluded. At the beginning of the study, 198 pediatric patients infected by SARS-CoV-2 as confirmed in RT-PCR between March 2020 and September 2020 were included; 25 patients were excluded according to the exclusion criteria. One hundred seventy-three patients were included in the final analysis.

Timeline of key events

On March 11, 2020, the Turkish Ministry of Health announced the first patient with COVID-19 in Turkey. On March 16, 2020, on Monday, all face-to-face education was suspended, including day care, nursery, primary, intermediate, high schools, and universities. On April 10, 2020, a weekend curfew was introduced for 30 provinces in Turkey and extended to all 81 provinces in subsequent days.

Procedures, data collection and definitions

According to the most recent guidelines related to COVID-19 published by the Turkish Ministry of Health, both oropharyngeal and nasopharyngeal swab samples were obtained from suspected cases, and an RT-PCR test was performed.[11] Demographic data, such as age, sex, nationality; laboratory findings including hemoglobin, white blood cell (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelets, the ratio of ANC/ALC, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), ferritin, D-dimer, albumin, creatinine kinase, and blood urea, as well as the incidence of lymphopenia and, neutropenia, which were determined according to the normality of the age, were obtained.[12,13] Clinical findings relating to the patients, including fever, cough, runny nose, sore throat, myalgia, abdominal pain, diarrhea, and dyspnea were obtained, and household contact history, complete blood count, and biochemistry analysis were recorded.

"Household" was defined as the members of a family who lived together in the same house. During the disease's incubation period, the first person contacted was accepted as the index case. Household contact was defined in cases where the index case was a family member as part of a household. Contact condition was assessed in two groups as "with household contact" and "without household contact" according to the presence of a family member with COVID-19 diagnosed with nasopharyngeal and oropharyngeal RT-PCR testing. Two patients had both family and friend contact and these were counted in the "with household contact" group because they had family contact first.

Nasopharyngeal swabs were obtained from all family members of the index case via Turkey's contact tracing team. All positive tested children's families therefore underwent nasopharyngeal swab sampling. When we categorized patients as "with household contact" and "without household contact," no family member of either group had not been tested.

According to the Contact Tracing, Outbreak Management, and Patients' Home Monitoring section of the COVID-19 guideline published by the Turkish Ministry of Health, the contact situation was divided into two groups: high-risk contact (close contact) and low-risk contact. High-risk contact included the people who were faced with a COVID-19 patient for 15 min or longer and at a 1 m distance or closer; people who look after a COVID-19 patient; people who had direct contact with a COVID-19 patient's secretion such as sputum, saliva, or been exposed to a COVID-19 patient's cough or sneeze; people who attended simultaneously at the same indoor places such as hospitals, school buses, public transportation with a COVID-19 patient; students and teachers sharing the same class; people who had physical contact such as kissing or hugging; people living in the same household; people working in the same office; people sharing the same room in a dormitory or a hotel, with a COVID 19 patient, unless people wore a mask. The conditions listed above were accepted as low-risk contacts if the people wore a mask throughout the contact. High-risk contact also included people traveling in the same intercity bus or train compartment with a COVID-19 patient, and passengers in close proximity (sitting in two fronts or two back or two side seats) of a plane with a COVID-19 patient, with or without wearing a mask.[11] All patients with high-risk contacts underwent a SARS-CoV-2 PCR test, even if they were asymptomatic, whereas asymptomatic patients with low-risk contact were not tested.

Cases were classified into two separate groups as "symptomatic" and "asymptomatic" in our study. The symptomatic cases group was also split into "mild" and "moderate-severe." In accordance with the Treatment of Adult Patients section of the COVID-19 guideline published by the Turkish Ministry of Health, we established our own mild, moderate, and severe clinical disease classification because there was no specific guidance in the Management and Treatment of Children section.[11]

The mild stage was characterized by the possible existence of flu-like signs such as fever, myalgia, cough, sore throat while lacking dyspnea (respiratory rate < 24/min and SpO2 > 93% in room air) and having normal lung radiography and computed tomography (CT) screening. All criteria had to be met in the mild stage conditions.

The moderate stage was characterized by the presence of mild to moderate pneumonia signs in chest screening with a respiratory rate of <30/min and SpO2 > 90% in room air.

The severe stage was characterized by the detection of bilateral diffuse pneumonia signs in chest screening and/or tachypnoea (respiratory rate is >30/min and/or SpO2 < 90% in room air).[11] The presence of at least one criterion in the severe stage conditions was determined sufficient to include the patients in the severe stage group.

Statistical analysis

Statistical analysis was performed using the SPSS v24.0 statistical package (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the subjects' baseline characteristics, depending on the normality of distribution. Values for continuous variables were provided either as means ± standard deviations or as medians (interquartile range). Frequencies of nominal variables are presented as percentages. Comparisons between groups for categorical variables were made using the χ^2 test. For two group comparisons of independent variables, Student's *t*-test was used as a parametric test, whereas the Mann–Whitney *U*-test was the preferred nonparametric test. For regression analysis of the independent variables of the hospitalization ratio, binary logistic regression analysis with the backward Wald elimination method was used. Statistical significance was defined as *P* values less than 0.05.

Ethical approval

Research ethics board approval was obtained for the study from Izmir Tepecik Training and Research Hospital ethics committee, and all investigational procedures complied with the Declaration of Helsinki guiding principles. Written informed consent was provided before participation from the legal caregivers of all participants.

Results

The median age of the patients diagnosed with COVID-19 was 133 (interquartile range (IQR): 48.5–177.5) months. The age distribution of the patients is shown in Figure 1. Ninety patients (52%) were male, and 83 (48%) were female. Sixty (34.7%) patients were asymptomatic and, 98 (56.6%) had mild, 11 (6.4%) had moderate, and four (2.3%) patients had a severe course; symptomatic patients comprised the majority (n = 113, 65.3%). Fever was the most frequent (71.7%) symptom, followed by cough with a ratio of 40.7%. Sore throat, diarrhea, myalgia, dyspnea, abdominal pain, and runny nose were also observed (Fig. 2). Of 173 patients, 138 (79.8%) had at least one family member in the household with COVID-19, and 17 (9.8%) were not infected by household members but had a history of contact with a relative, friend, or neighbor with COVID-19. The contact history was unknown in 18 (10.4%) patients.

It was observed that the presence of a family member with COVID-19 in the household did not have a statistically significant effect on the presence of symptoms, or the age and sex of the patients (P = 0.651, P = 0.463, and P = 0.151 respectively). When evaluating the relationship between the presence of a family member with COVID-19 in the household and the need for hospitalization in children infected with SARS-CoV-2, it was seen that hospitalization was required less in the group who had household contact (P < 0.01). There was no significant relationship between the clinical stage and the presence of household contact (P = 0.219; Table 1). We performed a binary logistic regression analysis using the backward elimination method to define the independent predictors of the hospitalization ratio and the symptom presence. Symptom presence was classified as "asymptomatic" and "symptomatic." Age, sex, and household contact groups were included in the analysis. None of the independent factors, including age, sex, and household contact status, was associated with symptom presence. Patients without household contact had a 7.612-fold increased risk of hospitalization and female patients had a 2.791-fold increased risk compared with male patients and patients with household contact. The 0–12 months old age group had the highest risk of hospitalization. (Table 2).

Considering the relationship between the presence of a family member with COVID-19 in the household and the central distribution measurements of the laboratory parameters in children infected with SARS-CoV-2, ANC, and ANC/ALC ratio and hemoglobin were statistically significant decreased in patients with household contact compared with patients without household contact (P < 0.01, P = 0.013, and P = 0.042 respectively; Table 3). The overall ratios of lymphopenia and neutropenia were found to be 30.2% and 9.5%, respectively. There was no significant relationship between the household contact history groups in terms of lymphopenia and neutropenia (Table 4).

Discussion

To the best of our knowledge, this article is the first in the literature to focus on the effects of household contact in terms of clinical and serum analyses in children. While evaluating the patients' demographic statistics, it was observed that the patients' median age was 11 years (133 months). Some other studies have found lower median ages than in our study.[14–16] COVID-19 severity differs in age groups in children. In Zhang et al.'s study, moderate cases' count was higher than mild cases' count in patients younger than 72 months.[14] Dong *et al.* showed that severe and critical cases were highest in the infant age group.[15] In Wu *et al.*'s study, the median age of children with moderate disease was significantly younger than that of children with mild disease.[16] In Italy, in a study that evaluated patients through the surveillance system, the median age was 11 years, similar to our research. However, the vast majority of the patients were asymptomatic and mainly in the adolescent age group, in contrast with our study.[17] Alongside our high symptomatic cases ratio, among the symptomatic patients, most (98/113, 86.7%) were uncomplicated with pneumonia. Fever and cough were the most frequent symptoms (71.7% and

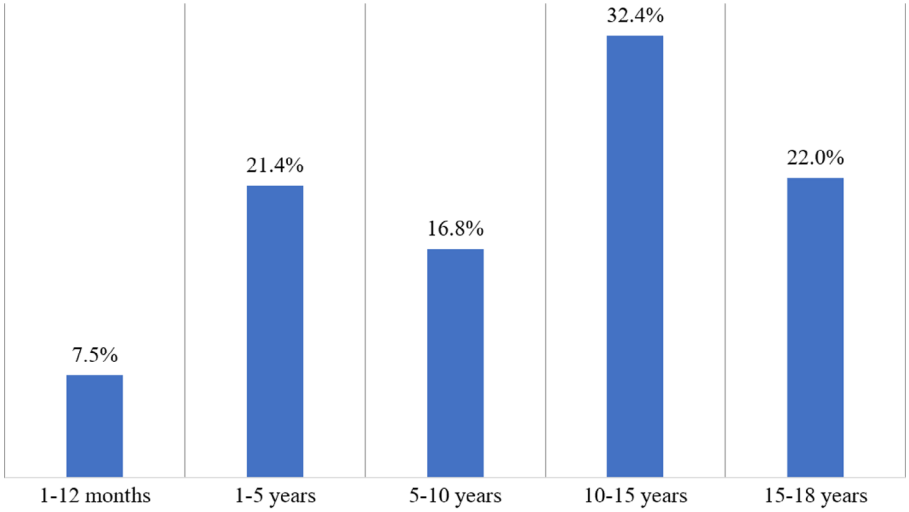

Fig. 1 Age intervals of 173 patients diagnosed with COVID-19.

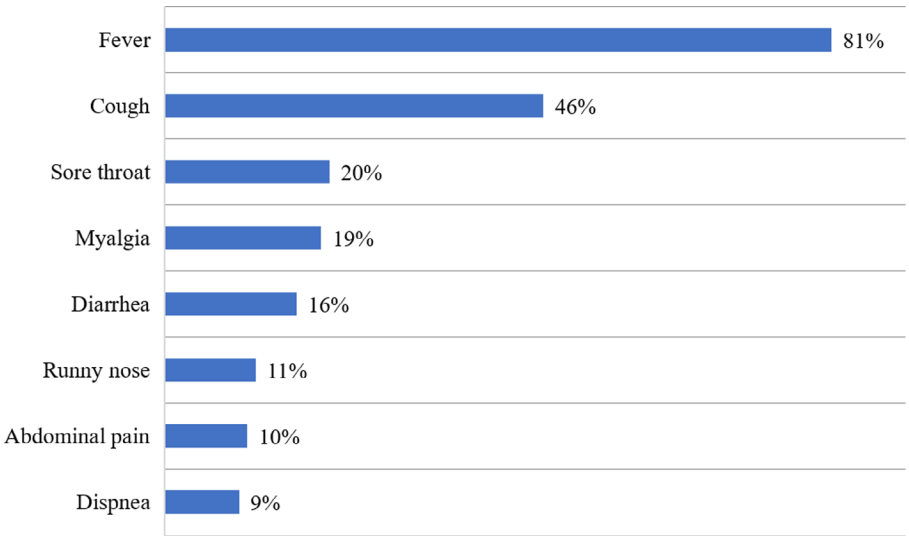

Fig. 2 Clinical findings among 113 symptomatic COVID-19 diagnosed patients. The percentages were calculated among 113 symptomatic patients selected from the total number of 173 patients.

40.7%, respectively), which was consistent with a literature review in both adults and children.[18–21] Moreover, it was observed that diarrhea was present in a significant proportion (14.2%) of children with SARS-CoV-2 infection, similar to other pediatric studies, in contrast with adults.[21,14,22] The differences between adults and children were not limited to clinical findings; one of the most striking findings in previous studies was an indicative and progressive decrease in the lymphocyte count at the onset of the disease in adults, whereas it was mostly normal in children.[23,24] The ALC of approximately two-thirds of patients (69.8%) was normal in our study.

In a literature review, it was shown that many examples of SARS-CoV-2 clusters were linked mostly to indoor settings in general, including households.[25] Since the beginning of the pandemic, children mostly became infected by family members. In Dan *et al*.'s study of 72 pediatric patients, all patients had at least one family member infected with SARS-CoV-2.[26] However, Niccolò *et al*. indicated that 55% of pediatric patients were not infected by SARS-CoV-2 persons within the household, it was attributed to the late lockdown in Italy.[27] In our study, 79.8% of patients had at least one family member in the household who played a role as a carrier for SARS-CoV-2. Even though 9.8% of patients were not infected directly by household members, they had contact with friends, relatives, or neighbors infected with SARS-CoV-2. The latter finding may also count in close contact as in household transmission considering Turkey's daily close relationship with neighbors and relatives, with frequent visits to one another. It may be the best explanation for the occurrence of the family clusters of COVID-19 in Turkey.

Table 1 The effect of household family contact with COVID-19 on demographic and clinical characteristics

	With household contact $n = 138$ (%)	Without household contact $n = 35$ (%)	*P*-value
Presence of symptom			
Asymptomatic	49 (35.5)	11 (31.4)	0.651
Symptomatic	89 (64.5)	24 (68.6)	
Sex			
Male	68 (49.3)	22 (62.9)	0.151
Female	70 (50.7)	13 (37.1)	
Age	Median: 128.5 months (IQR†: 46.75–178)	Median: 161 months (IQR†: 72–176)	0.463
Hospitalization			
Inpatients	9 (6.5)	8 (22.9)	0.004*
Outpatients	129 (93.5)	27 (77.1)	
Clinical stage ($n = 113$)‡			
Mild	79 (88.8)	19 (79.2)	0.219
Moderate-severe	10 (11.2)	5 (20.8)	

†IQR, Interquartile range (Q1–Q3).
‡Asymptomatic patients were excluded.
*Comparisons were made using the Chi-Square (χ^2) test.

The diversity of clinical findings of COVID-19 incited researchers to better understand the underlying factors of severity. There are adult studies showing that older people and those with comorbidities such as diabetes, hypertension, and cardiovascular disease are the most vulnerable group in terms of COVID-19 clinical course.[28,29]

For children, virus exposure may play a role. The effect of exposure intensity on disease severity in children in varicella virus and rubeola virus is a similar topic.[30–33] In 2002 and 2005, Poulsen *et al*. conducted research based on this subject and found that the secondary cases of varicella infection in patients who were infected by family members showed higher fever and pneumonia more frequently.[32,33] In a study by Shi *et al*. in which adult patients with COVID-19 were analyzed, severe cases had a higher incidence of more infected family members; however, in multivariate analysis, older age, male sex, and the presence of hypertension were independently associated with severe disease at admission.[9] On the other hand, in our study, displaying symptoms and clinical stage were not statistically significant between household contact groups, and surprisingly, in contrast to our hypothesis, the need for hospitalization was higher in patients without household contact. Our findings may mainly be attributable to the contact tracing objectives in our country because asymptomatic patients with a low-risk contact are not tested. As a result, some COVID-19 patients "without household contact" were untested, and the actual number of the patients "without household contact" remained unknown.

When we evaluated the laboratory analyses in our study population, ANC, and ANC/ALC ratio, and hemoglobin were statistically significantly decreased in patients with household contact. Decreasing neutrophils might be relevant with immune suppression in the high exposure group. In some studies, there are decreased neutrophil and lymphocyte counts among pediatric patients with COVID-19.[20,21] In a study that evaluated the clinical and immune background of pediatric COVID-19, neutrophil counts were found to be significantly decreased in moderate cases compared with mild cases.[16] However, other researchers indicated that it was mostly normal or even increased due to secondary bacterial infections.[14] When we examined the overall neutropenia and lymphopenia ratio as determined according to age groups in terms of household contact, there was no significant relation. We found no pediatric studies concerning the relationship between ANC/ALC and disease severity. However, most adult studies showed that the ANC/ALC ratio was significantly higher in patients with severe disease,[23,34,35] whereas we found ANC/ALC higher in the group without household contact.

Our study has some limitations. First, we determined the presence of household contact rather than the number of household members infected. Patients were categorized as in the "with household contact" group if there was at least one

Table 2 Logistic regression analysis of the independent variables of the hospitalization ratio

Independent variables	Beta coefficient	SE	Wald statistics	*P*	Exp (β)	95% CI for *exp* (β)	
						Lower	Upper
Age (months)							
0–12	Reference				1†		
13–60	−1.463	0.736	3.948	0.047	0.232	0.055	0.980
61–120	−2.541	0.889	8.169	0.004	0.079	0.014	0.450
121–180	−3.672	0.953	14.852	<0.001	0.025	0.004	0.165
181–215	−1.291	0.709	3.318	0.069	0.275	0.069	1.103
Sex							
Male	Reference				1†		
Female	1.026	0.514	3.990	0.046	2.791	1.019	7.640
Household contact							
With	Reference				1†		
Without	2.030	0.509	15.917	<0.001	7.612	2.808	20.633

†Inpatient: 1, Outpatient: 0.

Table 3 Comparison of laboratory findings of patients infected with COVID-19 according to the presence of infected family members in the household

	With household contact $n = 138$	Without household contact $n = 35$	*P*-value
Hemoglobin† (g/dL)	12.89 ± 1.62	13.50 ± 1.33	0.042*
WBC‡ (x10^3/μL)	6.1 (4.9–7.6)	6.2 (5.3–10.3)	0.135
Platelets‡ (x10^3/μL)	248 (211–296)	237 (186–297)	0.248
ALC‡ (x10^3/μL)	2.1 (1.4–2.9)	1.7 (1.3–2.4)	0.260
ANC‡ (x10^3/μL)	2.8 (1.9–3.9)	4 (3–4.6)	0.001*
ANC/ALC‡	1.33 (0.92–2.16)	1.82 (1.25–4.66)	0.013*
CRP‡ (mg/L)	2 (0.8–5.3)	3 (0.8–16.9)	0.260
ALT‡ (U/L)	15 (12–21)	14 (11–15)	0.053
AST‡ (U/L)	29 (20–38)	24 (19–33)	0.045*
LDH‡ (U/L)	241 (201–317)	232 (191–306)	0.798
Ferritin‡ (μg/L)	33 (22–53)	39 (27–70)	0.106
D-dimer‡ (μg/L)	340 (230–560)	340 (240–490)	0.376
Albumin‡ (g/dL)	4.5 (4.3–4.6)	4.5 (4.2–4.6)	0.619
CK‡ (U/L)	97 (74–122)	107 (73–141)	0.373
Blood urea† (mg/dL)	22.77 ± 6.81	22.94 ± 6.94	0.900

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CK, creatinine kinase; CRP,C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; SD, standard deviation; WBC, white blood cells.

†The mean and standard deviation were recorded for hemoglobin and blood urea as they were normally distributed.

‡The median and interquartile range values were shown for the parameters that were not normally distributed.

*Student's t-test was used as a parametric test for hemoglobin; Mann–Whitney U-test was performed as a non-parametric test for ANC, ANC/ALC, AST.

Table 4 The relationship between household contact groups and lymphopenia and neutropenia

$n = 169$†	With household contact *n* (%)	Without household contact *n* (%)	*P*-value
Lymphopenia			
Yes ($n = 51$)	39 (29.1)	12 (34.3)	0.552
No ($n = 118$)	95 (70.9)	23 (64.7)	
Neutropenia			
Yes ($n = 16$)	14 (10.4)	2 (5.7)	0.394
No ($n = 153$)	120 (89.6)	33 (94.3)	

†Valid percentages that were calcualted excluding the patients without laboratory analyses were provided in the table.

family member infected with SARS-CoV-2, regardless of the count within families. Second, we were able to determine neither the genetic background of each family nor the numerical expression of the quantity of virus. Third, asymptomatic patients or patients with trivial symptoms with unknown infectious source do not undergo COVID-19 PCR tests. For this reason, a selection bias occurred unavoidably and might affect the disease severity and the rate of hospitalization in both groups.

As a result, pediatric patients with COVID-19 who had at least one family member with COVID-19 did not show a severe course, incompatible with our hypothesis. More studies are needed to gain information about viral exposure and the severity of the disease.

Conclusion

The risk factors for COVID-19 severity in children should be identified, considering its morbidity and mortality worldwide. The findings of the current study suggest that family contact history did not affect clinical course in previously healthy children diagnosed with COVID-19.

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Disclosure

The authors declare no conflict of interest.

Author contributions

G.U. collected the data and wrote the manuscript. A.S., Y.E.K., H.O.H., and N.C.Y. collected the data. M.A.K. reviewed the manuscript. N.O.Y. and F.D.A. provided laboratory support. A.K.A., performed the statistical analyses, and gave technical support and conceptual advice. D.Y.C. contributed the design of the study, critically reviewed and supervised the entire study process. All authors read and approved the final manuscript.

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