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Clinical and Laboratory Findings of SARS-CoV-2 Infection in Children Younger than 6 Months Old: Neutropenia is More Common Not Lymphopenia

Gizem Guner Ozenen , MD[1], Zumrut Sahbudak Bal, MD[1], Nimet Melis Bilen, MD[1], Sema Yildirim Arslan, MD[1], Gunes Ak, MD[2], Gonca Koc, MD[3], Candan Cicek, MD[4], Zafer Kurugol, MD[1] *and* Ferda Ozkinay, MD[1]

[1]Division of Infectious Disease, Department of Pediatrics, Medical School of Ege University, Izmir 35100, Turkey
[2]Department of Clinical Biochemistry, Medical School of Ege University, Izmir 35100, Turkey
[3]Department of Radiology, Medical School of Ege University, Izmir 35100, Turkey
[4]Department of Microbiology and Infectious Diseases, Medical School of Ege University, Izmir 35100, Turkey
Correspondence: Zumrut Sahbudak Bal, Division of Infectious Disease, Department of Pediatrics, Medical School of Ege University, Bornova/Izmir 35100, Turkey. Tel: +905054423192. Fax: +902323889900. E-mail <zumrut.sahbudak.bal@ege.edu.tr>.

ABSTRACT

Background: Studies on age-related differences in clinical and laboratory features of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are limited. We aimed to evaluate the demographic, clinical, laboratory findings of SARS-CoV-2 infection in children younger than 6 months old and compare them with older children.
Methods: A single-center retrospective study, including 209 confirmed SARS-CoV-2 infection cases, was conducted between 11 March 2020 and 1 September 2021. The case group consisted of 47 patients younger than 6 months old, whereas the control group consisted of 162 patients older than 6 months old.
Results: The mean age of the case group was 2.77 ± 1.52 months, and the control group was 101.89 ± 65.77 months. Cough was statistically higher in the control group, and poor feeding was higher in the case group ($p = 0.043$, 0.010). The underlying disease rate was statistically higher in the control group; however, the hospitalization rate was higher in the case group ($p = 0.036$, 0.001). The case group had significantly lower median values of the absolute neutrophil count, hemoglobin and higher median values of white blood cell, absolute lymphocyte count and platelet than the control group ($p < 0.05$). C-reactive protein, fibrinogen values were significantly lower, and procalcitonin, D-dimer, troponin T, N-terminal pro-B-type natriuretic peptide significantly higher in the case group ($p < 0.05$). Lymphopenia was more common in the control group, whereas neutropenia was more common in the case group ($p = 0.001$, 0.011).

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Conclusions: We showed that most children younger than 6 months old had mild and asymptomatic SARS-CoV-2 infection; however, the hospitalization rate was higher, and neutropenia was more common in older children.

LAY SUMMARY

Studies on age-related differences in clinical and laboratory features on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in pediatric patients are limited. We aimed to evaluate the demographic, clinical and laboratory findings of SARS-CoV-2 infection in children younger than 6 months old and compare them with older children. A single-center retrospective study was conducted, including 209 SARS-CoV-2 infection cases. The case group consisted of 47 patients younger than 6 months old, and the control group consisted of 162 patients older than 6 months old. Most children younger than 6 months old had mild and asymptomatic SARS-CoV-2 infection; however, the hospitalization rate was higher than older children. Neutropenia was more common in patients younger than 6 months than older children with SARS-CoV-2 infection, even if underlying diseases were excluded.

KEYWORDS: COVID-19, SARS-CoV-2, children, neutropenia

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (COVID-19) has caused a global pandemic and led to more than 4 800 000 deaths worldwide [1]. The incidence of the disease and the rate of severe cases are lower in children than in adults; for this reason, COVID-19 vaccine candidates are usually tested and administered in adolescents and adults [2–4]. COVID-19 usually presents as an asymptomatic or milder disease in children; however, it may be severe in infants under 1 year of age, obese children and children with chronic diseases [5]. Younger patients can have different laboratory findings than adults, and leukopenia was the most commonly reported finding in children; however, in neonates and infants, the most common abnormality was reported as lymphocytosis [6]. Sun *et al.* [7] evaluated 36 infants under 1 year of age and reported that most infants have lymphocytosis and elevated CD4 and interleukin (IL)-10 levels, different from adults. During the pandemic, the number of younger children diagnosed with COVID-19 increased significantly due to the lack of masks in this age group and the lack of availability of vaccines against COVID-19 in younger children [8]. Therefore, it is essential to know the predisposing factors for severe COVID-19 in younger children. Studies on SARS-CoV-2 infection during infancy are limited [7–10]. Therefore, we aimed to evaluate the demographic, clinical and laboratory findings of SARS-CoV-2 infection in children younger than 6 months old and compare them with older children. The secondary aim is to determine the risk factors and their role in predicting the prognosis.

MATERIAL AND METHODS

Study design and study population

A single-center retrospective study was conducted between 11 March 2020 and 1 September 2021, in Ege University Children's Hospital, a tertiary-level hospital in the west part of Turkey. SARS-CoV-2 infection was diagnosed according to the Turkey Ministry of Health COVID-19 Guideline and confirmed cases defined as the cases in which SARS-CoV-2 was detected by molecular methods from nasopharyngeal and throat swab specimens [11]. The inclusion criteria include patients who tested positive for SARS-CoV-2 infection in both outpatient and inpatient settings and aged between 0 and 18 years old. Patients with a history of prematurity and/or no laboratory analyses and/or no clinical findings in medical records at admission were excluded. The scheme of the study design is shown in Fig. 1. Our criteria for hospitalization of patients with SARS-CoV-2 infection: Tachypnea, respiratory distress, poor feeding, high fever for 3–5 days, SARS-CoV-2 positive but asymptomatic patients who required hospitalization due to underlying disease, moderate to critical SARS-CoV-2 infection.

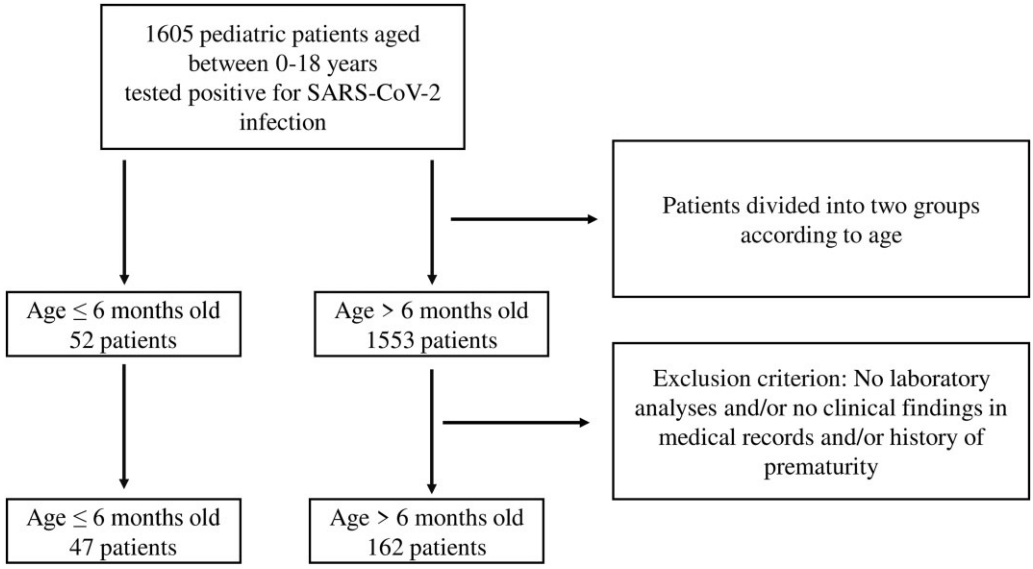

Fig. 1. Scheme of the study design.

The patient group consisted of 209 children with a positive SARS-CoV-2 real-time reverse transcriptional polymerase chain reaction (RT-PCR). The patient group was divided into two age groups: younger than 6 months old as a case group and older than 6 months old as a control group. The control group was selected by using SPSS statistical package (version 25 for Windows). A clinical scoring system was used to identify clinical classifications of illness severity in confirmed SARS-CoV-2 infection patients [12, 13]. All Chest X-ray findings were evaluated by the same Pediatric Radiology Specialist (G.K.).

Data collection and analysis

A standardized form was used to collect epidemiological data, laboratory findings and patients' clinical symptoms. Laboratory analysis on admission, including white blood cell (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), hemoglobin (Hb), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, fibrinogen, cardiac troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values was also recorded. Thrombocytopenia was defined as a blood PLT $<150 \times 10^9$/l, neutropenia was defined as ANC $<1.5 \times 10^9$/l and lymphopenia was defined as ALC $<1.5 \times 10^9$/l.

Complete blood counts were performed using Sysmex XN-2000™ automated hematology analyzer (Sysmex Corporation, Kobe, Japan). Plasma levels of fibrinogen (Multifibren* U; Siemens Healthcare Diagnostics) and D-Dimer (INNOVANCE® D-Dimer; Siemens Healthcare Diagnostics) were measured on Siemens BCS® XP Systems automated coagulation analyzer (Siemens Healthcare GmbH) by the modification of the Clauss method and particle-enhanced immunoturbidimetric assay, respectively. Serum CRP (CRP4, Tina-quant CRP IV) levels were measured by particle-enhanced immunoturbidimetric assay on cobas c 702 systems (Roche Diagnostics GmbH). Serum PCT (Elecsys BRAHMS PCT), cardiac Troponin T (Elecsys Troponin T hs) and NT-proBNP (Elecsys proBNP II) levels were measured by electrochemiluminescence immunoassay on cobas e 602 immunoassay analyzers (Roche Diagnostics GmbH).

Nasopharyngeal and oropharyngeal swab samples were collected from all suspected patients on admission. Diagnosis of SARS-CoV-2 infection is made by determining the ribonucleic acid (RNA) of the SARS-CoV-2 virus in the RT-PCR method in respiratory samples. Coyote, Biosciences used to detect RNA of the virus in our Molecular Virology laboratories, adopts the RT-PCR method combined

with fluorescence probes to detect the conserved region of ORFIab and N gene SARS-CoV-2.

Statistical analysis

Statistical analysis was performed with SPSS statistical package (version 25 for Windows). Data were expressed as means ± SD or medians (interquartile range [IQR]) for continuous variables or percentages for categorical variables. Group comparisons were made using the Student's *t*-test for normally distributed data and the χ^2 test for categorical data. The Mann–Whitney *U*-test was used to compare differences in nonparametric data between the groups. Differences and correlations were considered significant at $p < 0.05$.

Ethics

Necessitated permission was obtained from the Ethical Board of Ege University (ethical decision No: 21-11.1T/40, date 18 November 2021).

RESULTS

The case group consisted of 47 patients younger than 6 months old, and the control group consisted of 162 patients older than 6 months old. In patients, younger than 6 months old, the mean age was 2.77 ± 1.52 months, and 63.8% were male. Eleven patients (23.4%) had an underlying disease. The most common symptom was fever (59.6%), followed by cough (14.9%), diarrhea (10.6%) and dyspnea (10.6%). When patients are classified according to the clinical severity of the disease, 12 (25.5%) patients were asymptomatic, 28 (59.6%) mild, 2 (4.3%) moderate, 3 (6.4%) severe and 2 (4.3%) critically ill in the group including patients younger than 6 months old. Chest X-ray was performed in 27 (57.4%) patients and was abnormal in 40.8% of them (lobar consolidation in three patients, paracardiac infiltration in one patient, air trapping in four patients, infiltration plus air tapping in two patients and atelectasis in one patient). Twenty-seven (57.4%) patients were hospitalized, three (6.4%) patients were transferred to the pediatric intensive care unit (PICU), and there was no death in this group.

In patients older than 6 months, the mean age was 101.89 ± 65.77 months, and 50.6% were male. Sixty-five (40.1%) had an underlying disease. The most common symptom was fever (64.2%), followed by cough (29.6%) and myalgia (15.4%). When patients are classified according to the clinical severity, 30 (18.5%) patients were asymptomatic, 114 (70.4%) mild, 11 (6.8%) moderate, 4 (2.5%) severe and 3 (1.9%) critically ill in the group including patients older than 6 months old. Forty-nine (30.2%) patients were hospitalized, five (3.1%) patients were transferred to the PICU, and there was no death in this group.

When we compared the characteristics of the groups, the rate of male patients was statistically higher in the case group ($p = 0.011$). The underlying disease ratio was statistically higher in the control group ($p = 0.036$). Cough was statistically higher in patients older than 6 months old, and poor feeding was higher in younger patients, p values were 0.043 and 0.010, respectively. The hospitalization rate was statistically higher in the case group ($p = 0.001$). However, there was no difference between the total length of hospital stay, PICU admission, mechanical ventilator support and oxygen support between the groups. When laboratory findings were evaluated, the case group had significantly lower median values of ANC, Hb and higher median values of WBC, ALC and PLT than patients in the control group ($p < 0.05$). Median CRP, fibrinogen values were significantly lower, and PCT, D-dimer, troponin T, NT-proBNP significantly higher in cases younger than 6 months old than older cases ($p < 0.05$). Fifteen (21.9%) patients in the case group had neutropenia, 3 (6.4%) lymphopenia and 3 (6.4%) thrombocytopenia. Lymphopenia was more common in the control group, whereas neutropenia was more commonly observed in the case group, p values were 0.001 and 0.011, respectively. The rate of thrombocytopenia was not statistically different between the groups ($p = 0.618$). Table 1 summarizes the comparison of patient groups' demographic, clinical and laboratory characteristics.

We also compared the patient laboratory characteristics of patient groups when underlying diseases were excluded, and lymphopenia was more common in the control group, whereas neutropenia was more commonly observed in the case group, p values were 0.022 and 0.006, respectively. The rate of thrombocytopenia was not statistically different between the groups ($p = 0.927$). Table 2 summarizes the comparison of laboratory characteristics of patient groups when underlying diseases were excluded.

Table 1. Demographic, clinical, and laboratory characteristics of the patient groups

	Age ≤6 months old (*n*: 47)	Age >6 months old (*n*: 162)	*P*-value
Age, months, mean ± SD	2.77 ± 1.52	101.89 ± 65.77	
0–1 months	9 (19.1%)		
1–3 months	19 (40.4%)		
3–6 months	19 (40.4%)		
Gender, male, *n* (%)	30 (63.8)	82 (50.6)	**0.011**
Underlying diseases, *n* (%)	11(23.4)	65 (40.1)	**0.036**
Cardiovascular disease	3 (6.4)	0 (0)	
Neurologic disease	2 (4.3)	15 (23.1)	
Metabolic disease	2 (4.3)	4 (6.2)	
Hematologic-oncologic malignancy	1 (2.1)	13 (20)	
Primary immune deficiency	1 (2.1)	4 (6.2)	
Nephrological disease	1 (2.1)	3 (4.6)	
Pulmonary disease	1 (2.1)	15 (23.1)	
Others	0 (0)	11 (16.8)	
Signs and symptoms, *n* (%)			
Fever	28 (56.6)	104 (64.2)	0.563
Cough	7 (14.9)	48 (29.6)	**0.043**
Diarrhea	5 (10.6)	11 (6.8)	0.382
Dyspnea	5 (10.6)	9 (5.6)	0.220
Poor feeding	4 (8.5)	2 (1.2)	**0.010**
Vomiting	3 (6.9)	8 (4.9)	0.696
Runny nose	2 (4.3)	9 (5.6)	0.725
Clinical classifications of illness severity, *n* (%)			
Asymptomatic	12 (25.5)	30 (18.5)	0.291
Mild	28 (59.6)	114 (70.4)	0.163
Moderate	2 (4.3)	11 (6.8)	0.737
Severe	3 (6.4)	4 (2.5)	0.190
Critical	2 (4.3)	3 (1.9)	N/A
Hospitalization, *n* (%)	27 (57.4)	49 (30.2)	**0.001**
The total length of hospital stay, days, median (IQR)	6 (4–12)	5 (3–7)	0.118
Treatment, *n* (%)	14 (29.8)	32 (19.8)	0.144
Hydroxychloroquine	0 (0)	8 (4.9)	
Antibiotic treatment	8 (17)	19 (11.7)	
Favipiravir	0 (0)	14 (8.6)	
Corticosteroid	1 (2.1)	1 (0.6)	
PICU admission, *n* (%)	3 (6.4)	5 (3.1)	0.300
Mechanical ventilator, *n* (%)	2 (4.3)	3 (1.9)	0.346
HFNC oxygen support *n* (%)	1 (2.1)	2 (1.2)	0.650
Oxygen support, *n* (%)	5 (10.6)	9 (5.6)	0.220

(continued)

Table 1. (Continued)

	Age ≤6 months old (*n*: 47)	Age >6 months old (*n*: 162)	*P*-value
Laboratory findings			
WBC median (IQR)/10^9/l	8.9 (7.1–11.1)	6.2 (4.8–8.9)	**<0.001**
ANC median (IQR)/10^9/l	2.2 (1.3–4.6)	3.0 (2.0–5.3)	**0.037**
ALC median (IQR))/10^9/l	4.2 (2.8–6.6)	2.0 (1.2–2.9)	**<0.001**
Hb median (IQR), g/dl	11.7 (10.6–12.2)	12.4 (11.5–13.3)	**0.002**
PLT median (IQR)/10^9/l	343 (262–449)	235 (197–291)	**<0.001**
CRP median (IQR), mg/l	1 (0.5–5.8)	7.6 (1.3–16.2)	**<0.001**
PCT median (IQR), µg/l	0.19 (0.11–0.21)	0.10 (0.06–0.21)	**0.023**
D-dimer median (IQR), µg/l	1087 (808–1928)	625 (286–1336)	**0.001**
Fibrinogen median (IQR), mg/dl	256 (213–298)	362 (262–387)	**<0.001**
Troponin T median (IQR), ng/l	17 (13–29.5)	13 (13–13)	**<0.001**
NT-proBNP median (IQR), ng/l	1121 (589–1385)	77.1 (22.5–127.2)	**<0.001**
Neutropenia, *n* (%) (<1.5 ×10^9/l)	15 (31.9)	25 (15.4)	**0.011**
Lymphopenia *n* (%) (<1.5 ×10^9/l)	3 (6.4)	51 (31.5)	**0.001**
Thrombocytopenia, *n* (%) (<150 ×10^9/l)	3 (6.4)	14 (8.6)	0.618

Notes: SD, standard deviation; PICU, pediatric intensive care unit; HFNC, high-flow nasal cannula; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; PCT, procalcitonin; NT-proBNP, N-terminal pro B-type natriuretic peptide, N/A: Not applicable. Statistically significant data are written in bold.

Table 2. Comparison of laboratory characteristics of patient groups when underlying diseases excluded

	Age ≤6 months old ($n = 36$)	Age >6 months old ($n = 97$)	*p*-value
Neutropenia, *n* (%) (<1.5 ×10^9/l)	11 (30.6)	13 (13.4)	**0.022**
Lymphopenia *n* (%) (<1.5 ×10^9/l)	3 (8.3)	31 (32)	**0.006**
Thrombocytopenia, *n* (%) (<150 ×10^9/l)	2 (5.6)	5 (5.2)	0.927

Statistically significant data are written in bold.

The comparison of symptoms, demographic characteristics and laboratory findings of patients younger than 6 months old according to illness severity did not show statistical differences in the median age and gender between the groups ($p > 0.05$). Severe patients (moderate to critical) had significantly more common underlying disease and dyspnea than non-severe (asymptomatic to mild) patients (p values are 0.001 and 0.000). The median values of CRP, PCT, troponin T and NT-proBNP were statistically higher in severe patients than non-severe patients (p values are 0.045, 0.018, 0.011 and 0.030). There were no statistical differences in the ratio of neutropenia, lymphopenia and thrombocytopenia between the groups ($p > 0.05$). Severe COVID-19 patients required significantly more common hospitalization, PICU admission, mechanical ventilator support and oxygen support than non-severe patients (p values are 0.014, 0.009, 0.001 and 0.000). Table 3 shows the comparison of symptoms, demographic and laboratory characteristics of SARS-CoV-2 infection in patients younger than 6 months old according to clinical classification of illness severity.

DISCUSSION

Children have been reported to have a milder disease than adults with COVID-19 worldwide [5, 10]. However, the clinical and laboratory findings of age groups, even in children, differ due to the general

Table 3. The comparison of symptoms, demographic and laboratory characteristics of SARS-CoV-2 infection in patients younger than 6 months old according to clinical classification of illness severity

Variables	Non-severe[a]	Severe[b]	*p*-Value
Patients, *n* (%)	40 (85.1)	7 (14.9)	
Age, years, (mean ± SD)	2.76 ± 1.43	2.80 ± 2.10	0.965
Gender, male, *n* (%)	27 (67.5)	3 (42.9)	0.211
Underlying diseases, *n* (%)	6 (15)	5 (71.4)	**0.001**
Signs and symptoms, *n* (%)			
Fever	23 (57.5)	5 (71.4)	0.488
Cough	5 (12.5)	2 (28.6)	0.271
Diarrhea	5 (12.5)	0 (0)	0.322
Dyspnea	0 (0)	5 (71.4)	**0.000**
Poor feeding	4 (10)	0 (0)	0.382
Vomiting	3 (7.5)	0 (0)	0.454
Runny nose	2 (5)	0 (0)	0.545
Laboratory findings			
WBC median (IQR)/10^9/l	8.9 (4.9–9.3)	8.5 (5.0–14.3)	0.731
ANC median (IQR)/10^9/l	2.1 (1.8–4.8)	4.9 (1.9–8.5)	0.188
ALC median (IQR)/10^9/l	4.1 (1.5–6.4)	4.5 (12–4.1)	0.872
Hb median (IQR), g/dl	11.7 (11.3–13.0)	10.6 (10.3–13.8)	0.209
PLT median (IQR)/109/l	343 (205–331)	399 (179–363)	0.437
CRP median (IQR), mg/l	1.0 (0.9–7.9)	5.8 (4.6–33.2)	**0.045**
PCT median (IQR), µg/l	0.15 (0.06–0.20)	0.28 (0.05–0.50)	**0.018**
D-dimer median (IQR), µg/l	1103 (293–1325)	1286 (677–2421)	10.00
Fibrinogen median (IQR), mg/dl	248 (245–365)	308 (268–540)	0.642
Troponin T median (IQR), ng/l	17 (13–13)	96 (13–16.5)	**0.011**
NT-proBNP median (IQR), ng/l	658 (34.3–284)	1687 (72.3–1118)	**0.030**
Neutropenia, *n* (%) (<1.5 ×10^9/l)	13 (32.5)	2 (28.6)	0.837
Lymphopenia *n* (%) (<1.5 ×10^9/l)	2 (5)	1 (14.3)	0.354
Thrombocytopenia, *n* (%) (<150 ×10^9/l)	2 (5)	1 (14.3)	0.354
Hospitalization, *n* (%)	20 (50)	7 (100)	**0.014**
The total length of hospital stay, days, median (IQR)	6 (2-28)	12 (4-37)	0.092
PICU admission, *n* (%)	1 (2.5)	2 (28.6)	**0.009**
Mechanical ventilator, *n* (%)	0 (0)	2 (28.6)	**0.001**
Oxygen support, *n* (%)	0 (0)	5 (71.4)	**0.000**

Notes: SD, standard deviation; WBC, white blood cell; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hb, hemoglobin; PLT, platelet count; CRP, C-reactive protein; PCT, procalcitonin; NT-proBNP, N-terminal pro B-type natriuretic peptide; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Statistically significant data are written in bold.

[a]Non-severe: asymptomatic to mild.

[b]Severe: moderate to critical

susceptibility to COVID-19 [14]. Studies of clinical and laboratory findings of COVID-19 and severe disease predictors mainly focus on adults, and limited data are available for young children [7, 9]. Our study showed that most children younger than 6 months old had mild and asymptomatic COVID-19; however, the hospitalization rate was higher than for older children. In the laboratory tests, neutropenia was more commonly observed in patients younger than 6 months old, whereas lymphopenia was more commonly observed in older children, as expected.

The most common clinical manifestations reported are fever, cough, fatigue and runny nose in children. Gastrointestinal symptoms such as nausea, vomiting and diarrhea are usually reported in newborns and infants [5, 8]. In our study, the most common symptoms were fever and cough in all ages of children. However, poor feeding was significantly more common in patients younger than 6 months old, and cough was more common in older children. Sun *et al.* [7] evaluated 36 infants under 1 year of age with a mean age of 6.43 months and reported that 61.1% were male and 25% had underlying diseases. The gender distribution and the ratio of underlying disease in our study were similar to Sun *et al.* [7]. The male gender carries a higher risk for COVID-19, particularly in adolescents and adults. This difference may be due to several causes, such as the expression of the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease serine 2, the prevalence of comorbidities, differences in immunological responses and behaviors [15]. However, the various rates of male gender were reported by several studies [5, 7, 8, 12]. Therefore, we cannot conclude that the male gender is a significant risk factor for COVID-19 in children.

Dong *et al.* [12] evaluated 2135 children diagnosed with laboratory-confirmed or suspected COVID-19, and 17.6% of them were younger than 1 year old. Of patients younger than 1 year old, 56.1% were asymptomatic to mild, 33.2% moderate and 10.7% were severe to critical. In our study, among patients younger than 6 months old %85.1 were asymptomatic to mild, 4.2% moderate and 10.7% were severe to critical. The ratio of severe to critical patients diagnosed with COVID-19 was similar to our study group. Raba *et al.* [10] reviewed 160 infants younger than 1 year old and reported that infants and neonates had more severe COVID-19 disease than older children. For the reason of this, they reported the possibility that the immune system in infants is less mature than older children and the inability to develop a cytokine storm, which is responsible for the disease severity that occurred in adults. They reported that 16% of infants were asymptomatic, 11 (7%) of infants were admitted to the ICU, three infants required mechanical ventilation, and the mortality rate was 0.006%. In our study, out of 47 patients younger than 6 months old, only 3 (6.4%) patients were transferred to the PICU 5 (10.6%) and 2 (4.3%) patients required mechanical ventilator support, and mortality was not observed.

Yarali *et al.* [16] evaluated 30 children diagnosed with COVID-19 and showed that most children had a normal leukocyte count despite normal leukocyte count, lymphopenia, neutropenia and neutrophilia were reported in 30%, 23.3% and 13.3% of children, respectively. They reported that neutropenia had not been previously reported in adults diagnosed with COVID-19, and in children, SARS-CoV-2 can be a causative agent of neutropenia. Kosmeri *et al.* [6] reported that most infected children with COVID-19 usually had a normal leukocyte count, and the most common detected WBC abnormality was leukopenia. Lymphopenia was rare in children than in adults due to its immature immune system and expression of ACE2. They also reported lymphopenia was associated with hospitalization in older children. In neonates and infants, the most common abnormality was lymphocytosis [6]. Vakili *et al.* [14] reviewed 54 children diagnosed with COVID-19 and showed that lymphocyte counts varied from lymphopenia to lymphocytosis, and CRP was normal in neonates. In older children, lymphopenia was more common, CRP was normal or elevated, WBC count was conflicting and PCT was elevated. They reported that the difference in laboratory test results of neonates to other age categories was due to the differences in function and maturation of viral receptors for SARS-CoV-2. In our study, the case group had significantly lower median values of ANC, Hb and higher median values of WBC, ALC and PLT than patients in the control group.

Hassan *et al.* [17] compared SARS-CoV-2 positive and negative in infants aged <2 months old who were admitted with sepsis-like syndrome. They showed that the SARS-CoV-2-positive group had significantly lower WBC and ANC with relative lymphocytosis than the negative group. Similar to our report, neutropenia was associated with younger age in children diagnosed with SARS-CoV-infection. In our study, neutropenia was still significantly more common in infants after excluding the patients with an underlying disease due to possible effects on hematological parameters.

Sun *et al.* [7] reported that 36 infants under 1 year of age had increased CRP, PCT and D-dimer in 19.44%, 67.74% and 20.69% of infants, respectively. In our study, PCT, D-dimer and cardiac markers were higher in cases younger than 6 months old than older. However, the normal ranges of cardiac markers have not been precisely defined in neonates. Karlén *et al.* [18] reported that cardiac troponin T levels significantly increased in healthy full-term newborns compared with adult reference values, but no established reference range exists.

Cui *et al.* [19] reviewed 5829 pediatric patients diagnosed with COVID-19, and 17% of them were younger than 1 year old. They reported that 14% of them were critical cases, and the incidence of critical illness and vomiting symptoms was high in children under 1 year old than older children. Among children under 1 year old patients, the proportion of normal imaging was 42%, and the most common lung abnormality was ground-glass opacity (50%) and local and bilateral patchy shadowing (42%). In our study, the ratio of critical patients was lower, and there was no difference in vomiting between younger old and older patients. However, poor feeding was statistically higher in patients younger than 6 months old. In our study, a chest X-ray was performed on 27 patients younger than 6 months old, and 11 (40.8%) patients had an abnormality in the chest X-ray. Computed tomography was performed only on one patient, which was not compatible with COVID-19.

Paret *et al.* [20] evaluated 148 infants <90 days hospitalized for a serious bacterial infection, and 22 (15%) of them diagnose with COVID-19. In their study group, fever was the most common presentation of SARS-CoV-2 (59%), and 2 (9%) were admitted to the ICU. Like this study, the most common symptoms were fever (53.6%), and only 6.4% of the patients were admitted to PICU in our study.

The first limitation of our study is its retrospective nature, and some data may be missed due to retrospective design. Second, it is a single-center study, and a limited number of patients could be evaluated.

In conclusion, studies on age-related differences in clinical and laboratory features of SARS-CoV-2 infection in pediatric patients are limited. Our study showed that patients younger than 6 months old had higher median values of WBC, ALC, PLT, PCT, D-dimer, troponin T and NT-proBNP than patients in the control group. The hospitalization rate was higher, and neutropenia was more commonly observed in patients younger than 6 months old, even if underlying diseases were excluded. The median values of CRP, PCT, troponin T and NT-proBNP were higher in severe patients than non-severe patients. Further studies are needed to understand the laboratory spectrum of SARS-CoV-2 infection in the different age populations in children to help early diagnosis of the disease.

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