







COVID-19 Infection in Well-Appearing 30- to 90-Day-Old Infants with Fever without a Source

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ABSTRACT

Fever without a source (FWS) is common clinical status in the young infants. The aim of this study was to evaluate the clinical and laboratory findings of coronavirus disease (COVID-19) infection in well-appearing infants with FWS. Well-appearing febrile infants between 30 and 90 days who were evaluated as FWS in the pediatric emergency department and tested for COVID-19 were divided into two groups: COVID-19 (+) and (–). The clinical and laboratory findings of the patients were compared. The study included 95 febrile infants with FWS, and the mean age was 59.62 ± 16.82 days. The nasopharyngeal COVID-19 polymerase chain reaction test results of 29/95 (30.5%) patients were positive, while 66/95 (69.5%) were negative. The complaints of irritability and nasal congestion were found to be significantly more common in COVID-19-positive patients ($p = 0.04$ and $p = 0.041$, respectively). The hospitalization rate ($p = 0.009$), length of hospital stay ($p = 0.026$), initiation of antibiotic treatment ($p < 0.001$) and duration of antibiotic treatment ($p = 0.036$) were significantly lower in the COVID-19 (+) patients. The C-reactive protein (CRP, $p < 0.001$), absolute neutrophil count (ANC, $p < 0.001$), absolute lymphocyte count (ALC, $p = 0.015$), white blood cell (WBC, $p < 0.001$) and systemic immune-inflammation index (SII, $p < 0.001$) were found to be significantly lower in the COVID-19 (+) patient group. There was no significant difference between the groups in terms of neutropenia, lymphopenia or leukopenia. COVID-19 infection may present as an FWS. During the pandemic period, testing for COVID-19 among infants who were evaluated as FWS may reduce unnecessary hospitalizations and antibiotic treatments, and shorten hospital stays and duration of antibiotics.

KEYWORDS: COVID-19, fever without a source, infant

INTRODUCTION

Fever is one of the most common reasons for visiting the pediatric emergency department (PED) with infants younger than three months [1, 2]. As a result of clinical evaluation, signs and symptoms specific to the source of infection cannot be detected, are defined as fever without a source (FWS), and are common in the infant age group. It may be due to a simple viral infection or serious bacterial infections (SBI), such as bacteremia, bacterial meningitis or urinary tract infections [1–4]. The new coronavirus disease (COVID-19), which emerged at the end of 2019, has caused a pandemic affecting the whole world. COVID-19 infection in children generally causes a mild clinical status; fever, cough, sore throat, runny nose, diarrhea and vomiting are the most common complaints in children [5–7]. During the pandemic period, studies reported that some infants with FWS were diagnosed with COVID-19; therefore, it was recommended that infants with FWS be evaluated for COVID-19 [8, 9].

The aim of this study was to evaluate the well-appearing 30- to 90-day-old infants with FWS, who tested for nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR) to identify SARS-CoV-2, and to compare COVID-19 positive and negative patients according to clinical and laboratory findings.

MATERIALS AND METHODS

Study design and clinical protocol

Our hospital is a tertiary pediatric hospital located in Ankara (the capital of Turkey), and approximately 120 000 patients applied to our emergency department annually during the pandemic period. Patients who were between 30- and 90-day-old and tested nasopharyngeal RT-PCR to identify SARS-CoV-2 in the PED between 11 March 2020, the date of the first case in our country, and 30 September 2021 were retrospectively identified through the file registry system. We tested patients for SARS-CoV-2 according to our national COVID-19 guidelines and the clinician's decision [10].

The inclusion criteria for this study were being between 30 and 90 days old, applying to the PED with a complaint of fever and evaluated as FWS, appearing well, and having been tested nasopharyngeal RT-PCR

to identify SARS-CoV-2 on admission. FWS was defined as no evident source of infection and a temperature $\geq 38.0^{\circ}\text{C}$ [2, 4]. Patients with nonspecific complaints (e.g. cough, nasal congestion and diarrhea) who did not detect a fever source were included in the study. The clinical appearance of the patients was evaluated by a pediatric emergency specialist, and well-appearing infants were included in the study. Patients who were started on antibiotic therapy 48 h before their admission to the pediatric emergency department, patients with a septic or ill appearance, were vaccinated within 48 h, had a fever longer than five days, were known to have immunosuppression or chronic disease, or had a fever source were excluded from the study (Fig. 1).

Data collection of the patients

The patients were divided into two groups according to the nasopharyngeal RT-PCR test results. The patients' age, gender and whether they had contact with COVID-19 patients were recorded. Furthermore, whether or not the patients had any complaints accompanying the fever at the time of their admission was recorded, as well as blood, urine and cerebrospinal fluid results. The blood, urine and CSF culture results of the patients were evaluated. The patients were evaluated for leukopenia, neutropenia and lymphopenia. Leukocyte counts were evaluated separately according to the age of the patients [11]. The white blood cell (WBC) count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), immature granulocyte (IG) percentage and systemic immune-inflammation index (SII) values were noted. The SII was calculated using the following formula: $\text{platelet} \times \text{neutrophil/lymphocyte count}$. The immature granulocyte percentage was calculated using an automated hematology analyzer, Sysmex XN-1000. Whether or not the patients were hospitalized, the length of the hospital stay and antibiotic therapy status were recorded.

Ethical approval

The protocol for this study was approved by Dr. Sami Ulus Maternity and Child Health and Diseases Training and Research Hospital Ethics Committee (E-21/11-230).

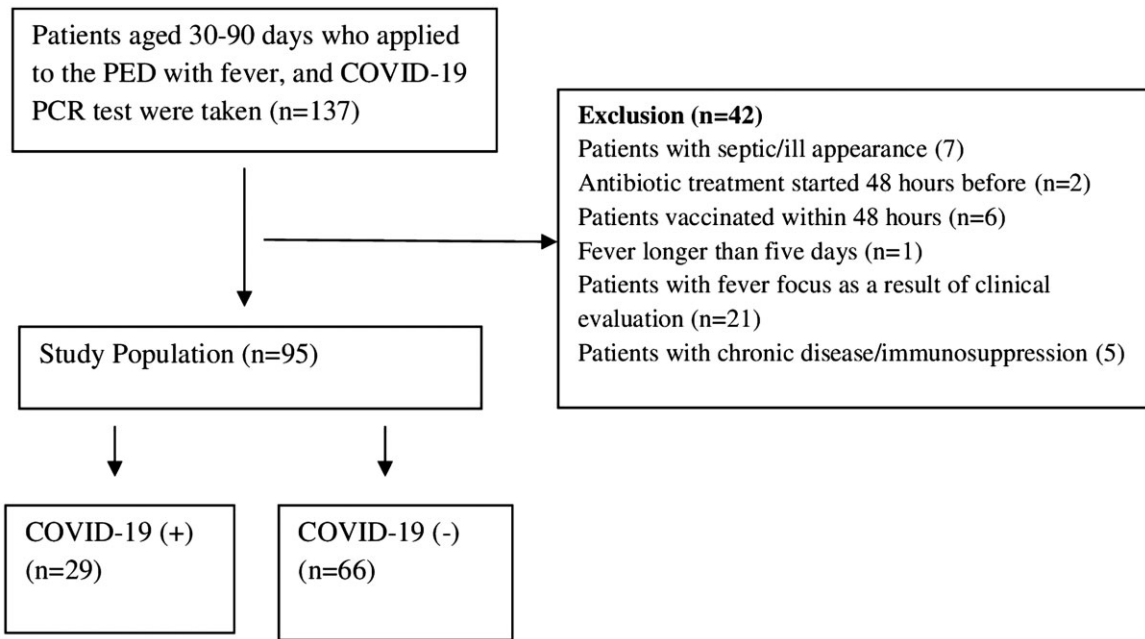


Fig. 1. Flow chart of study and inclusion–exclusion criteria.

Statistical analyses

Statistical analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine whether they were normally distributed. As the descriptive statistics, categorical variables are expressed as number (n), percentage (%), and continuous variables are expressed as mean (\pm), standard deviation (SD) or median and interquartile range (IQR). Categorical data were examined using the chi-square test. The Mann–Whitney U-test or independent t -tests were employed to compare the values of the two groups [COVID-19 (+) versus COVID-19 (-)]. The value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The study included 95 febrile young infants; 59/95 (62.1%) were male, and the mean age was 59.62 ± 16.82 days. The demographic and clinical characteristics of the patients are shown in Table 1. The nasopharyngeal RT-PCR test of 29/95 (30.5%) infants was positive, while 66/95 (69.5%) were negative. Ten (10.5%) of the patients had a history of

exposure to a COVID-19-positive patient, and seven of these patients had a positive RT-PCR test. Sixty-nine of the patients (72.6%) had different symptoms accompanying fever, 48/95 (50.5%) had a cough, 20/95 (21.1%) had a runny nose and 12/95 (12.6%) had nasal congestion (Table 1). The complaints of irritability and nasal congestion were significantly more common in the COVID-19-positive patients ($p = 0.04$ and $p = 0.041$, respectively). Of all the patients, 64/95 (67.4%) were hospitalized. The rates of hospitalization and length of hospital stay were lower in the COVID-19-positive group ($p = 0.009$ and $p = 0.026$, respectively). Antibiotic treatment was given to 49/95 patients (51.6%). The initiation and duration of the antibiotic treatment were significantly lower in the COVID-19 (+) patients ($p < 0.001$ and $p = 0.036$, respectively) (Table 1). All of the 95 infants had a good clinical course and all recovered.

Blood cultures were taken in 91/95 (95.8%) of the patients, and all were negative. Urine cultures were obtained from 93/95 (97.9%) patients, and nine (9.7%) patients had positive urine cultures [*Escherichia coli* ($n = 6$) and *Klebsiella pneumoniae* ($n = 3$)]. One of the patients with a urinary tract

Table 1. The demographic and clinical characteristics of the patients

	Total (n: 95)	COVID-19 (+) (n: 29)	COVID-19 (-) (n: 66)	p-Value
Age, days	59.62 ± 16.82	56.86 ± 15.74	60.83 ± 17.32	0.292 ^b
Male (%)	59 (62.1%)	18 (62.1%)	41 (62.1%)	0.99 ^c
Hospitalization rate (%)	64 (67.4%)	14 (48.3%)	50 (75.8%)	0.009 ^c
Length of hospital stay, hour	76.92 ± 57.16	47.07 ± 39.36	85.28 ± 58.85	0.026 ^b
Antibiotic treatment (%)	49 (51.6%)	7 (24.1%)	42 (63.6%)	<0.001 ^c
Antibiotic duration time, days	3.86 ± 2.20	2.38 ± 1.68	4.14 ± 2.1	0.036 ^b
Lumbar puncture (%)	22 (23.2%)	5 (17.2%)	17 (25.8%)	0.365 ^c
Urinary tract infection (%)	9 (9.7%)	1 (3.6%)	8 (12.3%)	0.269 ^c
Presence of other symptoms accompanying fever (%)	69 (72.6%)	24 (82.8%)	45 (68.2%)	0.142 ^c
Cough (%)	48 (50.5%)	15 (51.7%)	33 (50%)	0.877 ^c
Rhinorrhea (%)	20 (21.1%)	5 (17.2%)	15 (22.7%)	0.546 ^c
Diarrhea (%)	7 (7.4%)	0	7 (10.6%)	0.097 ^c
Vomiting (%)	5 (5.3%)	2 (6.9%)	3 (4.5%)	0.639 ^c
Irritability (%)	8 (8.4%)	5 (17.2%)	3 (4.5%)	0.04 ^c
Nasal congestion (%)	12 (12.6%)	7 (24.1%)	5 (7.6%)	0.041 ^c

Bold values are statistically significant.

^aValues are expressed as mean with the standard deviation (±) and n (%).

^bIndependent t-test

^cChi-square test.

infection (UTI) was diagnosed with COVID-19 (+). There was no significant difference between the groups in terms of UTI ($p = 0.269$) (Table 1). A lumbar puncture was performed in 22/95 (23.2%) patients, and all cultures were negative.

Hemogram and CRP tests were taken from 93/95 patients. Leukopenia was detected in nine (9.7%) patients, and neutropenia was detected in eight (8.6%). Of the 13 (14%) patients with lymphopenia, six were in the COVID-19 (+) group, and seven were in the COVID-19 (-) group. There was no significant difference between the groups in terms of neutropenia, lymphopenia or leukopenia. The CRP, ANC, ALC, WBC and SII were found to be significantly lower in the COVID-19 (+) patient group (Table 2).

DISCUSSION

In present study, 95 young infants with FWS were evaluated, and 29/95 (30.5%) of them were COVID-19 positive. The complaints of irritability and nasal congestion were significantly more common in the COVID-19-positive patients ($p = 0.04$

and $p = 0.041$, respectively). The hospitalization rate, length of hospital stay, initiation of antibiotic treatment and duration of antibiotic treatment were significantly lower in the COVID-19 (+) patients. Twenty-two percent of the COVID-19 (+) patients had lymphopenia, and WBC, ANC, ALC, CRP and SII were found to be significantly lower in the COVID-19 (+) patient group.

Fever is one of the most common reasons for visiting the PED with young infants, and cases where the fever source cannot be detected are called FWS [1, 4]. During the pandemic, COVID-19 PCR (+) was detected in some infants younger than 90 days who applied to the PED with a complaint of fever. Therefore, it has been suggested that infants should be tested for COVID-19, especially in periods when there is a history of exposure and the number of cases is high [8, 12–15]. The most common complaints in COVID-19 (+) infants are fever, cough, vomiting, rhinorrhea, irritability and nasal congestion [16–18]. To our knowledge, no study has compared COVID-19-positive and -negative patients in febrile infants evaluated as FWS. In our study, 7 (24.1%) of

Table 2. Comparison of the laboratory findings of the patients

	Total (n: 93)	COVID-19 (+) (n: 27)	COVID-19 (–) (n: 66)	p-Value
CRP, median (IQR), mg/l	3.1 (2.9–11.47)	2.9 (1.5–3.1)	4.5 (2.9–15.1)	<0.001^a
WBC, mean ± SD, × 10 ⁹ /l	9.92 ± 4.61	7.45 ± 2.51	10.93 ± 4.90	<0.001^b
ALC, median (IQR), × 10 ⁹ /l	4.3 (3.02–4.34)	3.63 (2.62–4.88)	5.07 (3.28–6.27)	0.015^a
ANC, mean ± SD, × 10 ⁹ /l	3.67 ± 3.05	2.21 ± 1.08	4.27 ± 3.38	<0.001^b
SII, mean ± SD, × 10 ⁹ /l	350.19 ± 316.7	201.14 ± 98.08	411.16 ± 353.73	<0.001^b
IG %, median (IQR)	0.3 (0.2–0.5)	0.3 (0.3–0.4)	0.3 (0.2–0.5)	0.361 ^a
NLR, median (IQR)	0.59 (0.35–1.26)	0.59 (0.33–0.82)	0.59 (0.35–1.36)	0.203 ^a
Leukopenia (%)	9 (9.7%)	3 (11.3%)	6 (9.1%)	0.716 ^c
Lymphopenia (%)	13 (14%)	6 (22.2%)	7 (10.6%)	0.188 ^c
Neutropenia (%)	8 (8.6%)	2 (7.4%)	6 (9.1%)	0.793 ^c

Bold values are statistically significant.

^aMann–Whitney U-test.

^bIndependent t-test.

^cChi-square test.

CRP, C-reactive protein; IG, immature granulocytes; SII, systemic immune-inflammation index; WBC, white blood cell; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; NLR, neutrophil-lymphocyte ratio; SD, standard deviation; IQR, interquartile range.

29 COVID-19 positive infants had a history of exposure to COVID-19-infected individuals. The most common symptoms accompanying fever were cough (51.7%), nasal congestion (24.1%), irritability (17.2%) and rhinorrhea (17.2%). Nasal congestion and irritability were found to be significantly higher in patients with COVID-19 (+). We recommend that infants younger than 90 days, who are evaluated as FWS in the PED, should be questioned about exposure history for COVID-19, and patients with fever, cough, irritability, runny nose and nasal congestion should be tested for COVID-19.

It is recommended that infants younger than 90 days with FWS should be evaluated to detect SBI, and infants with a high risk for SBI should be hospitalized and antibiotic therapy should be initiated. It was determined that SBI rates decreased, hospitalization rates and length of stay were shortened in infants older than 29 days with positive respiratory tract viral infection [1, 4, 19]. In a study from Spain, 27 COVID-19 (+) infants with FWS were evaluated; 6/27 (22%) of these patients underwent a lumbar puncture, 24/27 (89%) were hospitalized and 10/27 (37%) were given antibiotic treatment [20]. In this study, the patients were not compared with the COVID-19-negative group. In our study, 29/95 (30.5%) of the patients were COVID-19

positive, and 66/95 (69.5%) were COVID-19 (–). The hospitalization rate, length of hospital stay, initiation of antibiotic treatment and duration of antibiotic treatment were significantly lower in the COVID-19 (+) patients. This may be explained by the clinicians' acceptance of COVID-19 infection as the source of fever after positive RT-PCR test results. Antibiotic treatment of the COVID-19 (+) patients may be discontinued and patients may be discharged earlier than COVID-19 (–) patients after the fever source was detected. In well-appearing FWS infants, RT-PCR to identify SARS-CoV-2 testing can prevent unnecessary hospitalizations and antibiotic treatments, and shorten hospital stays and the duration of antibiotics.

One of the most common laboratory findings in COVID-19-positive infants is lymphopenia. While the rate of lymphopenia was found to be 28.26% in a study evaluating COVID-19-positive infants under one year of age, this rate was 68% in another study [17, 20]. In infants without chronic disease and immunosuppression, COVID-19 infection generally progresses well and there is usually no prominent increase in inflammation markers [8, 14, 15, 17, 18]. In a study in which 46 COVID-19 positive patients under one year old were evaluated, the CRP level was found to be within the normal range in 80.9% of

the patients [17]. In a study of COVID-19 (+) infants younger than 60 days, the median CRP was 0.3 mg/l [18]. Mark, *et al.* [21] evaluated 63 infants younger than 3 months of age, they reported that median CRP was 2.1 mg/l, median ANC $1.20 \times 10^9/l$ and median WBC $7.04 \times 10^9/l$. Iijima, *et al.* [22] evaluated 13 infants ≤ 90 days old with COVID-19; they reported median CRP 0.02 mg/dl, ANC $1.69 \times 10^9/l$ and ALC $5.57 \times 10^9/L$. Similarly, Mithal, *et al.* [14] reported that median CRP was 0.1 mg/dl, ANC was $2.64 \times 10^9/L$, WBC was $8.30 \times 10^9/L$. In our study, 13/95 (14%) patients had lymphopenia, six were in the COVID-19 (+) group and seven were in the COVID-19 (–) group. There was no significant difference between the groups in terms of neutropenia, lymphopenia or leukopenia. The CRP, ALC, WBC and SII were found to be significantly lower in the COVID-19 (+) patient group. Our findings are generally compatible with the literature. If there is no increase in inflammatory markers in young infants with FWS, these patients may be tested for COVID-19 during the pandemic period.

This study had some limitations. It reflects single-center data, was a retrospective study and included a limited number of COVID (+) patients. However, we believe that it will make a positive contribution to the literature due to the limited number of studies that have evaluated infants with FWS about COVID-19 infections.

In conclusion, COVID-19 infection may present as an FWS. The CRP, ANC, ALC, WBC and SII were found to be significantly lower in the COVID-19 (+) patient group. The hospitalization rate, length of hospital stay, initiation of antibiotic treatment and duration of antibiotic treatment were significantly lower in the COVID-19 (+) patients. During the pandemic period, testing for SARS-CoV-2 among infants who are evaluated as FWS may reduce unnecessary hospitalizations and antibiotic treatments, and shorten hospital stays and duration of antibiotics. More studies are needed to evaluate COVID-19 infection in infants with FWS.

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ETHICS APPROVAL

The protocol for this study was approved by the local ethics committee (E-21/11-230).

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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