

Are There Clinical and Laboratory Differences in COVID-19 Infection in Infants and Older Children? Single Center Experience

İnfanlarda ve Daha Büyük Çocuklarda COVID-19 Enfeksiyonunda Klinik ve Laboratuvar Olarak Farklılıklar Var Mıdır? Tek Merkez Deneyimi

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ABSTRACT

Objective: The clinic of coronavirus disease-2019 (COVID-19) infection can vary from asymptomatic to multi-organ failure. COVID-19 infections in infants have a different clinical course than adults and older children. In this study, it was aimed to evaluate the clinical course and laboratory findings of COVID-19 patients. It is also aimed to evaluate whether there is a different clinical or laboratory course of the disease in younger infants.

Material and Methods: In this study, 143 COVID-19 positive 1-216 months aged patients hospitalized and treated between 01.08.2021-30.04.2022 were included. Patients with chronic disease were not included in the study. SPSS version 24 was used for data analysis of the patients in our study. Those with p value of <0.05 were considered significant.

Results: Patients under 1 year of age were defined as Group 1, and those over 1 year of age were defined as Group 2. Of 73 patients in Group 1, 51 (80.8%) were male, 22 (19.2%) were female, of 70 patients in Group 2 45 (56%) were male, 35 (43%) were female (p<0.05). The mean age in Group 1 was 4.3 months (1-10), and in Group 2 it was 130 months (17-215). The most common complaints in Group 1 were fever (44%), cough (34%), and vomiting (13%). In Group 2, the most common complaints were fever (44%), cough (43%), and shortness of breath (27%). The length of stay was 6.1 days (2-15) in Group 1 and 8.3 days (3-24) in Group 2. This difference was statistically significant (p<0.05). Neutropenia was detected in 71.6% of the patients in Group 1 and in 20.5% of the patients in Group 2. The difference between lymphocyte and neutrophil counts between the two groups was statistically significant (p<0.05).

Conclusion: COVID-19 infection in children under one year of age shows differences both clinically and laboratory. In patients under one year of age, COVID-19 infection causes more neutropenia than lymphopenia.

Keywords: COVID-19, infant, lymphopenia, neutropenia

ÖZ

Giriş: Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu kliniği asemptomatikten, çoklu organ yetmezliğine kadar değişkenlik gösterebilmektedir. İnfantlardaki COVID-19 enfeksiyonları erişkin ve büyük çocuklardan farklı bir klinik gidişata sahiptir. Bu çalışmada COVID-19 hastalarının klinik seyri ve laboratuvar bulgularının değerlendirilmesi amaçlanmıştır. Ayrıca daha küçük infantlarda hastalığın farklı bir klinik veya laboratuvar seyri olup olmadığının değerlendirilmesi de hedeflenmiştir.

Gereç ve Yöntemler: Bu çalışmaya 01.08.2021-30.04.2022 tarihleri arasında yatırılarak tedavi edilen 143 COVID-19 pozitif çocuk hastası dahil edildi. 1-216 ay aralığındaki bu hastaların laboratuvar ve klinik verileri retrospektif olarak incelenmiştir. Kronik hastalığı olan hastalar çalışmaya dahil edilmedi. Çalışmamızdaki hastaların verileri analizi için SPSS versiyon 24 kullanıldı. P değeri <0,05 olanlar anlamlı kabul edildi.

Bulgular: Bir yaş altı hastalar Grup 1, 1 yaş üzeri ise Grup 2 olarak tanımlandı. Grup 1'deki 73 hastanın 51'i (%80,8) erkek, 22'ü (%19,2) kız, Grup 2'deki 70 hastanın 45'i (%56) erkek, 35'i (%43) kadındı (p<0,05). Grup 1 ortalama yaşı 4,3 ay (1-10), Grup 2'de 130 ay (17-215). Grup 1'de en sık şikayetler ateş (%44), öksürük (%34), kusma (%13) idi. Grup 2 de ise en sık şikayetlerin ateş (%44), öksürük (%43), nefes darlığı (%27)

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Received: 02.12.2024 **Accepted:** 30.10.2025 **Publication Date:** 14.11.2025

Cite this article as: Kandemir Gülmez T, Afat Turgut E, Hitay Telefon A, Erhan MD, Kılıç Çil M, Çelik Ü. Are there clinical and laboratory differences in COVID-19 infection in infants and older children? single center experience. J Eur Med Sci. 2025;6;(2):32-37



olduğu görüldü. Yatış süreleri Grup 1'de 6,1 gün (2-15), Grup 2'de 8,3 gün (3-24) olarak bulundu. Bu farklılık istatistiksel olarak anlamlıydı ($p<0,05$). Grup 1'deki hastaların %71,6'sında, Grup 2'deki hastaların %20,5'inde nötropeni tespit edildi. Her iki grup arası lenfosit ve nötrofil sayıları arası fark istatistiksel olarak anlamlı saptandı ($p<0,05$).

Sonuç: Bir yaş altındaki çocuklarda COVID-19 enfeksiyonu hem klinik hem de laboratuvar olarak farklılıklar göstermektedir. Bir yaş altı hastalarda COVID-19 enfeksiyonu bilinenin aksine lenfopeniden ziyade daha fazla nötropeniye sebep olmaktadır.

Anahtar Kelimeler: COVID-19, infant, lenfopeni, nötropeni

INTRODUCTION

In late 2019, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, which caused pneumonia and respiratory failure cases in Wuhan-China, spread worldwide in a short time (1). While information on the course of coronavirus disease-2019 (COVID-19) in children was insufficient due to the low number of pediatric patients infected with SARS-CoV-2 at the beginning of the pandemic, clearer data on children were revealed later in the pandemic (2). In a review of 16266 research results and 63 publications, it was reported that the mortality risk in children was below 1%. The most common symptoms are fever (58%) and cough (50%). The rate of asymptomatic infection was found to be high (65%) (3).

COVID-19 infection causes complaints in a wide spectrum from mild upper respiratory tract infections to severe respiratory failure in older patients. In a study evaluating COVID-19 infections in newborn infants, it was reported that patients presented with fever, runny nose, vomiting and malnutrition (4). It was observed that pulmonary findings (pneumonia, bronchiolitis, cough...) were more prominent in older children, similar to adult patients. There are publications associating the presence of lymphopenia with critical severe disease in COVID-19 infection (5). When we look at the pathogenesis of the disease, a process that continues with excessive release of inflammatory cytokines is observed (6). These cytokines both cause clinical findings and lead to changes in laboratory findings. In the literature, although lymphopenia is more prominent in patients, neutropenia and thrombocytopenia have also been reported less frequently (7). In COVID-19, mechanisms such as increased lympholysis with viral invasion, increased lympholysis due to cytokine storm caused by the release of various cytokines, and increased lymphocyte destruction with metabolic disorders such as lactic acidosis are held responsible for lymphopenia (8).

Although lymphopenia similar to adults was observed in pediatric patients in the adolescent age group that we followed with COVID-19 infection in our clinic, we observed that neutropenia was more common than lymphopenia, especially in COVID-19 patients under one year of age. Based on this observation, we aimed to evaluate whether children under 1 year of age hospitalized with COVID-19 infection show different clinical and laboratory course.

MATERIALS and METHODS

Demographic, laboratory and clinical findings of 143 pediatric patients aged between 1 month and 18 years who were hospitalized with the diagnosis of COVID-19 between 01.08.2021-30.04.2022 in the Pediatric Infection Clinic of University of Health Sciences Türkiye, Adana City Training and Research Hospital were evaluated retrospectively. The patients were grouped as 73 infants under 1 year of age Group 1 and 70 patients over 1 year of age Group 2. While calculating the laboratory data of the patients, patients whose laboratory findings could be affected due to previous comorbidities (hematologic malignancy, congenital adrenal hyperplasia, sepsis, etc.) were excluded from the study.

Blood tests obtained at admission and 48 hours after hospitalization were evaluated. SPSS 24 was used for statistical data. Independent sample t-test was used for parametric calculations and comparisons between groups. Mean values $\pm$ standard deviations were given for laboratory findings. P value 0.05 was considered significant. Ethics committee approval for this study was obtained from University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinical Research Ethics Committee (decision number: 1962, date: 30.05.2022).

Findings

All patients were hospitalized in the ward and followed up. Of the 73 patients in Group 1, 51 (80.8%) were boys and 22 (19.2%) were girls, and of the 70 patients in Group 2, 45 (56%) were boys and 35 (43%) were girls ($p<0.05$). The mean age was 4.3 months (1-10) in Group 1 and 130 months (17-215) in Group 2. Intensive care unit was needed in 5 patients (5.5%) in Group 1 and 11 patients (15.7%) in Group 2 ($p<0.05$). The length of hospitalization was 6.1 days (2-15) in Group 1 and 8.3 days (3-24) in Group 2 ($p<0.05$). There was a statistically significant difference between the groups in terms of the need for intensive care and length of hospitalization ($p<0.05$). When clinical findings were compared between the groups, the most common complaints in Group 1 were fever (44%), cough (34%), and vomiting (13%), while the most common complaints in Group 2 were fever (44%), cough (43%), and dyspnea (27%). In Group 1, diarrhea was more common in Group 1 compared to other findings ($p<0.05$). In Group 2, vomiting, tachypnea and pulmonary findings (pneumonia, bronchiolitis, cough) were more frequent and statistically

significant ($p<0.05$). Demographic and clinical findings of the patients included in the study are given in Table 1.

When the examinations of the patients at the time of admission were analyzed, the total white blood cell count of the patients in Group 1 was $9874/\text{mm}^3$ and the total white blood cell count of the patients in Group 2 was $7186/\text{mm}^3$ ($p>0.05$); the lymphocyte count of the patients in Group 1 was $4877/\text{mm}^3$ and the lymphocyte count in Group 2 was $2009/\text{mm}^3$ ($p<0.05$); neutrophil count was $3493/\text{mm}^3$ in Group 1 patients and $4335/\text{mm}^3$ in Group 2 patients ($p>0.05$); platelet count was $369412.70/\text{mm}^3$ in Group 1 patients and $242603.77/\text{mm}^3$ in Group 2 patients ($p>0.05$). C-reaktif protein was 7.4 mg/L in Group 1 and 35.2 mg/L in Group 2 ($p<0.05$). Procalcitonin was 0.1887 mg/L in Group 1 patients, while procalcitonin was 0.6829 mg/L in Group 2 patients ($p<0.05$).

The total white blood cell count of the patients in Group 1 was $7861/\text{mm}^3$, while the total white blood cell count of the patients in Group 2 was $5815/\text{mm}^3$ ($p>0.05$); the lymphocyte count of the patients in Group 1 was $5107/\text{mm}^3$, while the lymphocyte count of the patients in Group 2 was $2125/\text{mm}^3$ ($p<0.05$); neutrophil count was $1468/\text{mm}^3$ in Group 1 and $2757/\text{mm}^3$ in Group 2 ($p<0.05$); platelet count was $372158/\text{mm}^3$ in Group 1 and $232673/\text{mm}^3$ in Group 2 ($p<0.05$). No significant difference was observed in other laboratory tests of the patients. Detailed data regarding the laboratory findings of the patients are given in Table 2. Table 3 shows the rates of lymphopenia and neutropenia according to age in the patients included in the study. While the frequency of neutropenia was higher in children between the ages of 1-12 months, the frequency of lymphopenia increased in older children.

DISCUSSION

In this study, we evaluated the data of patients diagnosed with COVID-19 in pediatric patients in a 9-month period as the largest and most comprehensive COVID-19 patient treatment and follow-up center in the south and southeast. The patients included in our study had clinical presentation and disease

symptoms that varied between age groups. In the literature, it has been reported that COVID-19 infection usually proceeds with non-specific findings in children. However, there are publications reporting that a small number of patients with symptoms presented with upper respiratory tract infection findings, mostly lower respiratory tract infection (2).

In a previously published article, it was reported that children younger than 1 year of age represented 0.27% of all patients of all ages in the USA. In addition, this rate is even lower for newborns and infants (9).

In addition, the clinical presentation of pediatric COVID-19, the disease caused by SARS-CoV-2, differs significantly from that of the elderly. As previously published articles emphasize, infants and children often have mild symptoms and very low mortality rates (10,11).

In our literature review, in a previously published retrospective study, similar to our study, it was reported that COVID-19 infection in children most commonly caused fever and cough symptoms and progressed with mild to moderate clinical findings (12). In another comprehensive article comparing children and adolescents, similar to our study, it was reported that COVID-19 infection caused a milder clinical course in young children (13). In another study by Maltezou et al. (14) it was reported that cough and fever were the most common symptoms during COVID-19 infection in children, while other symptoms included diarrhea, vomiting and dyspnea, although to a lesser extent. The findings of Maltazeu et al. (14) also support this study we have completed.

Patients in Group 1 had milder symptoms such as fever, malnutrition and vomiting and a shorter hospitalization period (6.1 days). On the other hand, patients in Group 2 had a clinically longer need for hospitalization (8.3 days). There was a statistically significant difference between the groups in length of hospitalization ($p<0.005$).

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Table 1. Demographic and clinical findings of the patients included in the study

	Group 1	Group 2	p
	Number of patients (n) and percentage (%)		
Gender			
Female	22 (19.2%)	29 (41.4%)	0.009
Male	51 (80.8%)	41 (58.6%)	
Fever	44 (60.3%)	44 (62.9%)	0.53
Cough	34 (46.6%)	43 (61.4%)	0.086
Diarrhea	12 (16.4%)	7 (10%)	0.023
Vomiting	13 (17.8%)	26 (37.1%)	0.001
Tachypnea	6 (8.2%)	27 (38.6%)	0.001
Lung findings	14 (19.2%)	46 (65.7%)	0.001
Length of stay (days)	6.1	8.3	0.003

Parameters	Group 1	Group 2	p
White blood cell count (mm ³) on admission	9874.60±3676.86	7186.79±4026.54	0.901
White blood cell count (mm ³) after 48 hours	7861.90±2618.01	5815.38±3616.54	0.316
Neutrophil (mm ³) on admission	3493.65±2462.81	4335.85±2270.89	0.805
Neutrophil (mm ³) after 48 hours	1468.27±756.44	2757.69±1679.20	0.001
Lymphocyte (mm ³) on admission	4877.78±2341.31	2009.43±2108.97	0.081
Lymphocyte (mm ³) after 48 hours	5107.94±2384.37	2125.00±2184.78	0.160
Platelet (mm ³) on admission	369412.70±114381.03	242603.77±87941.92	0.265
Platelet (mm ³) after 48 hours	372158.73±129023.15	232673.08±94015.37	0.009
Ddimer (ng/L) at admission	1127.16±1083.22	869.75±652.92	0.305
Ddimer (ng/L) after 48 hours	2087.05±4853.32	1202.56±1191.87	0.007
Fibrinogen (mg/L) at admission	210.18±76.18	300.40±100.71	0.247
Fibrinogen (mg/L) after 48 hours	198.96±75.51	263.60±72.73	0.822
Troponin (ng/L) at admission	28.86±98.23	3.33±2.87	0.722
Troponin (ng/L) after 48 hours	24.44±73.94	2.50±1.04	0.623
Ferritin (µg/L) at admission	210.64±322.58	156.58±234.69	0.973
Ferritin (µg/L) after 48 hours	198.56±286.58	223.98±464.11	0.021
CRP (mg/L)	7.46±12.89	35.20±48.08	0.001
Procalcitonin (mg/L)	0.18±0.17	0.68±0.98	0.001
AST (U/L)	54.07±43.12	42.46±17.74	0.919
ALT (U/L)	33.79±23.67	36.00±30.60	0.036
LDH (U/L)	374.58±127.75	327.67±132.33	0.064

CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Parameters	Group 1 (1 month-12 months) n (%)	Group 2 (12 months-216 months) n (%)	p
Neutropenia according to age at admission	35 (48%)	6 (8.8%)	0.002
Neutropenia after 48 hours according to age	52 (71.6%)	14 (20.5%)	0.000
Lymphopenia at admission according to age	23 (31.3%)	42 (60.2%)	0.001
Lymphopenia after 48 hours according to age	25 (34.3%)	42 (60.2%)	0.002

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In the patients we followed up in our clinic, pneumonia was the most common reason for hospitalization in patients over 1 year of age, while patients under 1 year of age required hospitalization due to clinically resistant fever, malnutrition and bronchiolitis. Severe clinical picture and significant lung involvement were not observed in these patients in Group 1. Yang et al. (5) reported the presence of lymphopenia in critically severe COVID-19 infection in adult patients. Similar to this article, our patients in Group 2 also had lymphopenia in addition to pneumonia. ACE-2 receptors are present on the surface of lymphocytes (15). SARS-CoV-2 can infect

lymphocytes directly through this receptor and may also cause a viral pneumonia since it is also present on the lung surface (16). In our patients over 1 year of age, lymphopenia and pneumonia were observed similar to adult patients, whereas we did not find pneumonia and marked lymphopenia in infants. The fact that there was more lymphopenia and pneumonia in Group 2 supports that ACE-2 receptors are expressed more in older children than in infants.

In addition to the differences in clinical findings, there were also significant differences in laboratory parameters between the patient groups. While neutropenia was more prominent in Group 1, lymphopenia was more prominent in Group 2. While lymphopenia occurred in 20% of Group 1, 60% of patients in Group 2 had lymphopenia. The difference in the predominance of neutropenia or lymphopenia according to age between the groups suggests that this may be the reason for the difference in clinical findings.

There are many opinions on how lymphopenia occurs in COVID-19 (8). Causes such as lympholysis caused by

viral invasion of lymphocytes due to the ACE-2 gene on lymphocytes, disruption of lymphocyte production and destruction balance by cytokine storm causing lymphoid organ atrophy, inhibition of lymphocyte proliferation in the presence of lactic acidosis cause lymphopenia (8). The main cytokines causing cytokine storm are interleukin (IL)-6, IL-2, IL-7. Granulocyte colony-stimulating factor, IFN-8, MCP-1, MIP1- α and TNF- α also cause lymphocyte apoptosis and lymphopenia (8). In patients under 1 year of age, since these immune mechanisms are still immature, lymphopenia does not occur, suggesting that neutropenia occurs with a different immune pathway.

Similar to the predominance of neutropenia found in Group 1, neutropenia but not lymphopenia was reported in a study evaluating infants and newborns under 3 months of age (4). It is known that neutropenia occurs in viral infections including varicella, measles, rubella, hepatitis A and B, influenza, cytomegalovirus, ebstein-barr virus, parvovirus B19, adenovirus and coxsackie in childhood due to decreased production and increased destruction (17). COVID-19 acts similarly to these viral agents, suggesting that it causes neutropenia in children under the age of 1 year.

CONCLUSION

Compared to other age groups, infants had milder clinical course during the course of COVID-19 infection and laboratory findings showed neutropenia, although no significant lymphopenia was observed. In patients under 1 year of age presenting with fever and neutropenia, COVID-19 infection should be considered in the differential diagnosis. The fact that lymphopenia becomes more pronounced as the age of the patient increases suggests that different immune pathways are affected. The affected patient groups and clinical effects also change with variant changes. Although the COVID-19 epidemic period is over, it will continue its seasonal activity in the following years. Therefore, infants should also be evaluated for COVID-19 infection in the presence of neutropenia.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinical Research Ethics Committee (decision number: 1962, date: 30.05.2022).

Informed Consent: This study is a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.K.G., E.A.T., A.H.T., M.D.E., M.K.Ç., Ü.Ç., Concept: Ü.Ç., Design: T.K.G., Ü.Ç., Data Collection or Processing: T.K.G., E.A.T., A.H.T., Analysis or Interpretation: T.K.G., Literature Search: M.D.E., M.K.Ç., Writing: T.K.G., Ü.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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