

Evaluation of Hematological Parameters of Children Diagnosed with COVID-19: Single-Center Experience

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What is known about this study?

- Clinical and laboratory characteristics for COVID-19 in adult patients have been described. Studies on the effects of COVID-19 on pediatric hematologic parameters are limited. Our work; the COVID-19 pandemic is important to show the hematologic literature among pediatric symptomatic patients.

What is already known on this topic?

- As a necessity of crowded family life in our region, the number of patients we detected in the first months of the pandemic as an effect of domestic transmission is substantially high.
- In our study, when we compared the patients, according to the severity of the disease at the time of diagnosis, we did not find any significant difference other than the LDH level.
- Children can have normal laboratory results at the time of diagnosis. Laboratory testing should be repeated based on clinical outcomes.

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ABSTRACT

Objective: Although many pediatric studies on children infected with coronavirus disease 2019 (COVID-19) have been published, the diagnosis, clinical symptoms, laboratory findings, and treatment of COVID-19 in children are still unclear.

Materials and Methods: This study was conducted with an aim to examine the hematological findings of symptomatic pediatric patients diagnosed with COVID-19 in May 2020 at the Pandemic Hospital in Dicle University. Patient records were evaluated retrospectively. This study involved 59 symptomatic pediatric patients with a definite diagnosis of COVID-19 who had positive SARS-CoV-2 RT-PCR test results on nasopharyngeal swab between March 15, 2020 and May 31, 2020.

Results: The records of a total of 10 (16.9%) patients under the age of 1; 21 (35.6%) patients aged 1-10 years, and, 28 (47.5%) patients aged 10-18 years, who had been diagnosed with COVID-19 were evaluated. Based on severity, 35 (59.3%) patients were in the mild group (group 1) and 24 (40.7%) patients were in the moderate-severe group (group 2). The blood parameters of WBC, neutrophil, lymphocyte, monocyte, and thrombocyte counts, the hemoglobin (Hgb) level, and NLR, PLR, MPV, fibrinogen, ferritin, and D-dimer levels were compared between groups, the difference was not statistically significant ($P > .05$). LDH was higher in group 2 ($P = .014$).

Conclusion: Since children infected with COVID-19 show mild clinical symptoms or are asymptomatic, fewer pediatric patients may be detected than adults. Therefore, it should be known that the laboratory findings typical for adults may not accompany the disease in pediatric cases. More studies are needed to determine the most appropriate COVID-19 treatment approach for children, as hospitalization history and testing rates are less reported among children.

Keywords: COVID-19, children, hematology

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which was first identified in Wuhan, China in late December 2019, spread rapidly all over the world and was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020.¹ COVID-19 is a highly infectious viral infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).²

Although COVID-19 is primarily reported as a respiratory tract infection, the resulting data show that it is a multisystemic disease that includes the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems.³ The earliest reported cases were of adult and older patients. The data on children are inadequate as the number of children diagnosed and reported in studies are lower than that of adults. Due to the

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widespread use of diagnostic tests, pediatric cases have also been reported.⁴ The first pediatric case occurred in China, as of January 20, 2020. The family of the 10-year-old had traveled to Wuhan.⁵ Although it was rarely reported in children in the early stages of the pandemic, as the information about COVID-19 increased, it was determined that children could be infected with SARS-CoV-2 as much as adults.^{6,7} Underlying health problems, including chronic respiratory failure, obesity, and neurodevelopmental conditions, are common among hospitalized children who have acute COVID-19.⁸ As of June 28, 2020, there were 198 284 cases of COVID-19 in Turkey, of which 14 388 were children aged 15 or under (7.3%).⁹ The SARS-CoV-2, with the shiny protuberances on its surface, binds to the cells via the angiotensin-converting enzyme II (ACE-2) receptors, which are expressed in the lungs, gastrointestinal tract, kidneys, and heart. Thus, COVID-19 is a multisystem disease.¹⁰

For the clinical management of COVID-19 disease, which can cause multiple systemic implications, laboratory indicators are important for the diagnosis and monitoring of treatment. Although hematologic changes in adults have become obvious, laboratory results in children are still unclear, as the number of studies on children is low. The number of children diagnosed with Covid-19 is gradually increasing due to the high population of children in our region, and the necessity of living in a crowded family environment. Our work is significant, as the first month of the pandemic is related to the symptomatic children diagnosed. In this study, we aimed to evaluate the hematological parameters of symptomatic pediatric patients diagnosed with COVID-19 in our hospital.

METHODS

In this study, patients aged 0-18 years who were hospitalized in the Children's COVID-19 service with positive SARS-CoV-2 RT-PCR test result from the nasopharyngeal swab, between March 15, 2020 and May 31, 2020, at the Pandemic Hospital within the Dicle University Hospital, were evaluated retrospectively. The approval was obtained from the Republic of Turkey Ministry of Health and the Local Ethics Committee of Dicle University Faculty of Medicine (Reference Number 16.07.2020 - 312.).

Symptomatic COVID-19 patients were evaluated. Patients older than 18 years, with incomplete file records, inaccessible laboratory tests, and with hematological or systemic diseases were not included in the study.

All data were obtained retrospectively from hospital records from day 1 of hospitalization.

The age of the patients (in months), length of hospitalization, sex, age group, the severity of the disease, and details of family members with COVID-19 who have improved, were gathered as data.

White blood cell (WBC) count in peripheral blood, neutrophil, monocyte, and lymphocyte counts, Hgb level, platelet value, mean platelet volume (MPV), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), serum ferritin level,

lactate dehydrogenase (LDH) level, and prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio, fibrinogen, and D-dimer levels from coagulation tests were examined in the study.

The severity of the disease was classified as mild, moderate, severe, or critical, according to clinical characteristics, laboratory results, and chest x-ray results (11), as follows:

- Mild: Cases with symptoms of upper respiratory tract infection, such as fever, fatigue, myalgia, cough, sore throat, or nasal discharge, but normal on respiratory system examination.
- Moderate: Pneumonia with fever and cough, but without dyspnea and hypoxemia.
- Severe: Fever and cough developed early with dyspnea, and arterial oxygen saturation <92%.
- Critical: Cases that rapidly develop acute respiratory distress or respiratory failure, and that tend to develop shock, encephalopathy, myocardial impairment, coagulation abnormalities, and acute renal damage.

The patients were divided into 2 groups based on their symptoms, and the study data were compared. The patients in group 1 had mild symptoms; and patients in group 2 had moderate symptoms. Three patients with hematologic or systemic disease were in the clinically critical group, and these patients were not included in the assessment. None of the patients we assessed was critical.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). The descriptive statistics of the numerical parametric variables were calculated as mean $\pm$ standard deviation, and non-parametric variables were calculated as the median (minimum-maximum), and categorical variables were expressed as a percentage (%). While evaluating the study data, the suitability of the parameters of normal distribution was evaluated by the Shapiro-Wilk test, and the Student's *t*-test was used to compare the groups. *P*-values based on two-sided tests were considered statistically significant at less than .05.

RESULTS

A total of 59 symptomatic pediatric patients with a specific diagnosis of COVID-19 with SARS-CoV-2-positive RT-PCR were evaluated retrospectively. A total of 26 (44.1%) of the patients were female and 33 (55.9%) were male. The mean age of the patients was found to be 107.42 ± 68.4 months (2 months-220 months). The mean length of hospital stay of the patients was found to be 4.9 ± 3.32 days. A total of 10 (16.9%) patients under the age of 1; 21 (35.6%) patients aged 1-10 years, and 28 (47.5%) patients aged 10-18 years who had been diagnosed were evaluated. Fifty (86.6%) patients had contact with a family member with COVID-19. When the disease was classified according to severity, 35 (59.3%) patients were in the mild group and 24 (40.7%) patients were in the moderate-severe group. The

Table 1. Demographic and Clinical Characteristics of the Patients

	Min-Max	Mean $\pm$ SD
Age (months)	2-220	107.42 $\pm$ 68.4
Length of hospital stay (days)	1-13	4.9 $\pm$ 3.32
	n	%
Gender		
Female	33	59.3
Male	26	41.7
Age group		
<1 years	10	16.9
1-10 years	21	35.6
>10 years	28	47.5
The severity of illness		
Mild	35	59.3
Moderate	24	40.7
Family members with COVID-19		
Yes	50	86.6
No	9	13.4

F, female; M, male; Min, minimum; Max, maximum; n, total number of patients; SD, standard deviation. Data presented as mean $\pm$ standard deviation or median value (the minimum-maximum) and number/percentage values.

demographic and clinical characteristics of the patients are summarized in Table 1.

The hematological values were evaluated according to age.^{12,13}

When the laboratory parameters of the patients were examined, leukopenia was found in 2 (3.4 %) patients and leukocytosis in 6 (10.2 %) patients; the leukocyte count was within the normal range in 51 (86.4 %) patients. Five patients (8.5%) were diagnosed with neutropenia. Lymphopenia was reported in 1 (1.7%) patient. Lymphocytosis was observed in 12 patients (20.3%) and normal lymphocytes were seen in 46 patients (78%). Four patients (6.8%) in the study had monocytosis, while 55 patients (93.2%) had monocytes in the normal range. Thrombocytopenia

was not observed. Thrombocytosis occurred in 3 patients (5%). The MPV was evaluated as normal.

The Hgb level was found to be low for age in 7 (11.9%) patients. Ferritin was found to be low in 8 patients (13.5%). No patients were diagnosed with hyperferritinemia.

The fibrinogen levels measured were within normal limits. Activated Partial Thromboplastin Time (APTT) elevation was found in 2 patients, and PT was found to be elevated in 5 patients. The D-dimer level was within normal limits for 51 patients (86.4%), and for 8 patients (13.5%), it was > 0.583. Hemorrhage and thrombosis were not detected in the patients. Anticoagulant treatment was not used for these patients. The LDH levels were normal in 37 (62.7%) patients and elevated in 22 (37.3%) patients. The patients' laboratory parameters are given in Table 2.

The mean duration of hospital stay among patients in group 1 (mild clinical condition) was 3.69 $\pm$ 1.91 days, while it was 8.17 $\pm$ 3.48 days for those in group 2 ($P = .012$). When the WBC count, neutrophil, lymphocyte, monocyte, and thrombocyte counts, Hgb level, D-dimer, and NLR, PLR, MPV, fibrinogen, and ferritin were compared between the groups, the difference was not statistically significant ($P > .05$). LDH was higher in group 2 ($P = .014$). The laboratory findings of group 1 and group 2 at admission are shown in Table 3.

DISCUSSION

At the start of the COVID-19 pandemic, it was believed that children were not susceptible to this infection. Children are thought to be less sensitive to SARS-CoV-2, since the function and binding ability of angiotensin-converting enzyme II (ACE2), known as a cell receptor for SARS-CoV, may be lower in children (14).

Over time, this infection started to be reported in children, as family transmission increased. In the study conducted on COVID-19 patients and their contacts, Bi et al. have found the rate of pediatric patients to be 8.1%, and it was reported that the probability of children being infected with SARS-CoV-2 was

Table 2. Laboratory Findings of Patients

Hematological Variables	Min-Max	Mean $\pm$ SD
WBC ($10^3/\mu\text{L}$)	2.4-19.8	7.43 $\pm$ 3.2
Neutrophil count ($10^3/\mu\text{L}$)	0.6-9	3.33 $\pm$ 1.71
Lymphocyte count ($10^3/\mu\text{L}$)	0.4-15	3.14 $\pm$ 2.58
Monocyte count ($10^3/\mu\text{L}$)	0.01-2	0.58 $\pm$ 0.32
Platelet count ($10^3/\mu\text{L}$)	161-638	281.1 $\pm$ 118.2
Hemoglobin (g/dL)	8.8-16.3	12.8 $\pm$ 1.89
MPV (fL)	6.4-16	8.37 $\pm$ 1.74
LDH (U/L)	138-786	253.17 $\pm$ 105.6
Ferritin levels (ng/mL), ref.: (10-291)	3-192	117.8 $\pm$ 56.1
Fibrinogen (mg/dL)	194-468	271.3 $\pm$ 67.4
APTT (sn)	19-41	28.2 $\pm$ 7.9
PT (sn)	10-25	13.2 $\pm$ 2.1
D-dimer (mg/dL), ref.: (0.08-0.583)	0.1-14.8	2.77 $\pm$ 10.19

WBC, white blood cell; MPV, mean platelet volume; LDH, lactate dehydrogenase; PT, prothrombin time; APTT, activated partial thromboplastin time; Ref, references; SD, standard deviation.

Table 3. Laboratory Findings for Mild Patients (Group 1) and Moderate-Severe Patients (Group 2) at Admission

Hematological Variables	Group 1 (n = 35), Mean + SD	Group 2 (n = 24), Mean + SD	P
WBC (10 ³ /μL)	7.33 ± 3.47	7.57 ± 2.82	.552
Neutrophil count (10 ³ /μL)	3.27 ± 1.81	3.42 ± 1.59	.702
Lymphocyte count (10 ³ /μL)	3.12 ± 2.71	3.17 ± 2.44	.953
Monocyte count (10 ³ /μL)	0.56 ± 0.23	0.62 ± 0.37	.240
Hgb (g/dL)	12.9 ± 1.73	12.5 ± 2.12	.251
Platelet count (10 ³ /μL)	254.8 ± 88.18	319.6 ± 145.4	.059
MPV (fL)	8.5 ± 1.79	8.09 ± 1.67	.720
NLR	1.41 ± 0.93	1.58 ± 1.04	.430
PLR	106.7 ± 44.7	118.9 ± 49	.660
Ferritin	107.629 ± 80.72	159.5 ± 47.8	.102
D-dimer	2.68 ± 7.6	2.9 ± 11.1	.913
Fibrinogen	197.8 ± 56.2	228.4 ± 78.6	.290
LDH	235.7 ± 79.8	340 ± 178.7	.014

NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SD, standard deviation. Student's *t*-test, *P* < .05.

as likely as adults.¹⁵ In our study the most common cause of transmission in pediatric patients was contact with a family member diagnosed with COVID-19 (86.9%).

Infants under a year-old are known to be more sensitive and clinically more severely affected than children of other age groups.¹⁶ Considering the age groups in the published pediatric case series, most cases were found to be in children more than 1-year-old. When the gender distribution was examined, although not statistically significant, the rate of males was higher.¹⁷⁻²²

In our study, similar to the literature, the mean age at diagnosis was 107.42 ± 68.4 months (2 months–220 months), and there were 49 patients (83.1%) over the age of 1 year. Ten individuals under 1-year-old in this study had moderate symptoms. Within our series, 33 patients (55.9%) were male. This figure was similar in literature, but was not statistically significant.

In adults, the most common hematological findings of COVID-19 are lymphopenia, neutrophilia, and thrombocytopenia.²³⁻²⁷ In another study comparing COVID-19 patients with other viral disease patients, results of leukopenia, lymphocytopenia, and eosinopenia results were found to be more frequent in COVID-19 patients.²⁸

The clinical and laboratory presentations in the pediatric age group were observed to be different from those in adults.²⁹ The laboratory findings on COVID-19 in children are similar to those in other coronavirus infections. The WBC counts are normal or low with associated neutropenia and/or lymphopenia. Thrombocytopenia can develop. C-reactive protein and procalcitonin values are generally normal. In severe cases, liver enzymes and LDH may be elevated, and abnormal coagulation and high D-dimer levels have been reported in these cases.³⁰

In a study conducted among children with COVID-19, it was stated that while the leukocyte count was normal in 70% of the cases, there was an increase in 20% and a decrease in 10% of the cases.³¹ Lymphocyte counts are generally normal in children and can be said to be associated with relatively mild

immune suppression.^{32,33} Henry et al.³⁴ found lymphopenia in only 3% of the cases in the review of 12 literatures reported from China, including 66 pediatric patients. In 20 children examined by Xia et al.,³¹ WBC was normal in 14 patients (14/20, 70%), decreased in 4 patients (4/20, 20%), and increased in 2 patients (2/20, 10%); and the percentage of lymphocytes decreased in 7 patients (7/20, 35%) and increased in 3 patients (3/20, 15%).

In our study, when the leukocyte counts of children infected with SARS-CoV-2 were examined, the WBC count was found to be normal in 51 (86.4%) patients, increased in 6 (10.2%) patients, and decreased in 2 (3.4%) patients. The lymphocyte counts declined in 1 patient (1.7%) and increased in 12 patients (20.3%), and the lymphocyte counts were normal in 46 patients (78%).

The incidence of leukocytosis (neutrophilia and/or lymphocytosis) in patients infected with COVID-19 is less, and is a precursor of a bacterial infection or superinfection in particular.³⁵ Additionally, current data also show that COVID-19 neutrophil levels may be an indicator of cytokine storm and hyperinflammatory status.³⁶

Neutropenia may be associated with viral infections.³⁷ In our series, neutropenia was detected in 5 (8.5%) patients. A cytokine storm was not observed in any of our patients. The NLR is thought to be a significant marker for demonstrating the severity of COVID-19 disease.³⁸ An elevated NLR value is due to the increased neutrophil count and/or decreased lymphocyte count. The increase in the neutrophil count is due to inflammation, and the decreased lymphocyte count may be due to lymphocyte sequestration in the lung, immune-induced lymphocyte destruction, thymus and bone marrow suppression, or apoptosis.³⁹ Sixty-one patients with COVID-19 were prospectively evaluated, and in the group with advanced age (≥50 years) and a neutrophil/lymphocyte ratio (NLR) ≥3.13, severe illness and intensive care admission were found to be significantly higher, and NLR was evaluated as an independent risk factor for the disease.⁴⁰ In our study, the NLR showed no difference between the groups according to the clinical classification. (*P* = .430). Thrombocytopenia and elevated D-dimer rates are seen as indicators of poor prognosis in patients with

COVID-19.⁴¹ Thrombocytopenia was not found in our study. Three patients (5%) had thrombocytosis, which was considered secondary to vomiting and dehydration. With the replacement of liquid, the platelet count stayed within normal limits.

The mean platelet volume (MPV) is a laboratory marker for platelet function and activity. A higher MPV is more reactive, hemostatic, and produces higher levels of thromboxane. This increased thromboxane causes thrombotic sensitivity, and therefore, causes thrombotic complications.⁴² In our study, the MPV showed no difference between the groups according to the clinical classification.

Patients with COVID-19 were reported to have pathologically increased ferritin levels with reduced Hgb levels.⁴³ However, in our study, Hgb was found to be low in 7 patients (11.9%) by age. Unlike the literature, hyperferritinemia was not detected in any anemic patients. The present anemia was evaluated as iron deficiency anemia, and iron replacement therapy was initiated in these patients after the infection treatment, and the patients were followed-up. There were 8 patients with low ferritin (13.5%). Hyperferritinemia was not detected in any patient.

D-dimer is significantly elevated in patients with severe and fatal COVID-19.²⁵ The data on thrombotic complications in children are limited. It is suggested that such complications with COVID-19 may be rare in children. In our study, the D-dimer level was found to be elevated in 8 (13.5%) patients and normal in 51 (86.4%) patients ($P = 0.583$). No bleeding or thrombosis was detected in any patient. Anticoagulant therapy was not administered in these patients. No thrombotic complications were observed in this study.

COVID-19-associated multisystem inflammatory syndrome, reported among children in Europe and North America, is a rare and serious disorder. The clinical features of the multisystem inflammatory syndrome are similar to those of Kawasaki disease and toxic shock syndrome. The clinical features include fever, hypotension, rash, myocarditis, and gastrointestinal symptoms. There are laboratory results associated with increased inflammatory activity. Symptoms of respiratory tract disease may not be present.⁴⁴ We did not encounter such a case during the period of our study. There have been recent cases of MIS-C in Turkey.⁴⁵

LDH increases in peripheral blood due to ischemia, extreme heat, coldness, dehydration, chemical intoxication, and infectious toxins.^{46,47} When the absolute lymphocyte count and LDH measured in the COVID-19 series of patients in Singapore by Fan et al.¹⁷ were compared between patients in and out of the intensive care unit (ICU), the LDH in COVID-19 patients requiring ICU was, as expected, found to be higher and associated with poor prognosis. In our study, LDH was found to be higher in the moderate-severe group ($P = .014$).

Our work on the COVID-19 pandemic is important to demonstrate hematological documentation in symptomatic pediatric patients. Due to the inevitability of crowded family life in our region, the number of patients we detected in the first months of the pandemic as an effect of domestic transmission was substantially high. It is important to follow domestic contact

and isolation precautions in the case of COVID-19 infection. Although hematological changes in adults have become evident, laboratory results remain unclear because the number of studies in children is low. Our work is important because it concerns the diagnosed and symptomatic children in the first month of the pandemic. The laboratory values of children may be normal at the time of diagnosis. Laboratory tests can be repeated based on clinical outcomes. Our study had limitations such as being single-centered and retrospective, and including symptomatic pediatric patients in the first months of the onset of the pandemic. More research is needed to determine the appropriate procedures for managing COVID-19 in children.

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