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Clinical and laboratory predictors of long-COVID in children: a single center retrospective study

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Abstract. – OBJECTIVE: The majority of children experience a mild course of acute Coronavirus Disease 2019 (COVID-19). Only few studies have looked at long-term recovery from COVID-19 infection in children. The purpose of this study was to identify the predictors of long-COVID by performing a thorough analysis of the clinical, laboratory, and demographic characteristics of children with COVID-19.

PATIENTS AND METHODS: Between August and October 2021, data were obtained retrospectively from the medical records of 251 children diagnosed with COVID-19 at a tertiary single-center hospital. The prognostic effects of admission-related factors were compared between patients who experienced long-lasting symptoms and those who did not.

RESULTS: Long-COVID symptoms were noted in 12.4% of patients. Joint pain (7.6%), lumbago (4.8%), and headache (3.2%) were the most common symptoms. The mean onset of long-COVID symptoms was 1.35±0.49 months. The onset of long-COVID symptoms was 4 weeks after initial diagnosis in 64.5% of patients and 4-8 weeks later in 35.5% of the patients. The mean duration of long-COVID symptoms was 5.32±2.51 months. Children with long-COVID had higher leukocytes, neutrophils, monocytes, basophils, platelets, and D-dimer when compared with patients without long-COVID ($p < 0.001$). Leukocytes, neutrophils, monocytes, platelets, and D-dimer had the highest AUC in the ROC analysis (0.694, 0.658, 0.681, 0.667, and 0.612, respectively) and were statistically significant.

CONCLUSIONS: Despite the majority of children with COVID-19 having mild or asymptomatic acute disease, the majority of long-COVID symptoms were associated with functional impairment between 1 and 9 months after the start of the infection. Increased leukocytes, monocytes, neutrophils, platelets, and D-dimer appear to be the most powerful laboratory predictors for long-COVID and monitoring these predictors may assist clinicians to identify and follow-up patients with higher risk for long-COVID.

Key Words:
Long-COVID, Children, Predictors, Laboratory, COVID-19.

Introduction

Children have a milder course of acute Coronavirus Disease 2019 (COVID-19) than adults and the prevalence is lower in the pediatric population[1,2]. As the COVID-19 infection rises, there is growing concern about persistent symptoms after the initial infection, dubbed "long-COVID". Long-COVID refers to signs and symptoms that persist or develop after acute COVID-19 and cannot be explained by another diagnosis. There is currently no consensus on the definition or duration of this syndrome. Long-COVID, according to the NICE guidelines, includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks after acute COVID-19) and post-COVID-19 syndrome (12 weeks or more after acute COVID-19)[3].

Long-COVID is becoming more common in adults[4]. However, only few studies[5-18] have looked at children's long-term recovery from COVID-19. According to these studies, 4-66% of children experienced long-COVID-19 symptoms such as headaches, fatigue, muscle and joint pain, respiratory symptoms, nasal congestion, abdominal pain, constipation, diarrhea, insomnia, difficulty concentrating, and loss of smell and taste[5-18].

Therefore, it is crucial to identify the long-COVID's predictors for understanding the disease's pathophysiology. In the current study, we aimed at identifying the predictors of long-COVID-19 infection by performing a thorough analysis of the clinical, laboratory, and demographic characteristics of children with and without long-COVID-19 infection.

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Patients and Methods

We performed a retrospective study on 250 children aged 0-18 years with confirmed SARS-CoV-2 infection by polymerase chain reaction (RT-PCR) on a nasopharyngeal swab and a control group of 250 healthy children who had not tested positive for SARS-CoV-2 at Ankara Atatürk Sanatorium Training and Research Hospital between August and October 2020. All applications of these patients to the hospital were reviewed retrospectively from the hospital registry system for one year from the date of diagnosis. We recorded long-term symptoms and the duration of "long-COVID" in children who had previously been diagnosed with COVID-19. The diagnostic criteria of the NICE guidelines for long-COVID were used. According to the guidelines, this includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks after acute COVID-19) and post-COVID-19 syndrome (12 weeks or more after acute COVID-19)[3].

The long-COVID symptoms of the patients were evaluated based on the complaints of admission to the hospital. The complaints that were applied to the hospital were evaluated by a pediatrician, and the necessary laboratory and radiological imaging tests were performed and evaluated, which provided an objective evaluation. Patients who needed to be evaluated by neurology, cardiology, nephrology, orthopedics, dermatology, and other relevant doctors were evaluated, and these symptoms were not attributed to any other diseases. Children with hematologic or chronic disease were barred from the study.

Data on the following laboratory parameters were collected as follows: complete blood count parameters (CBC), total protein, albumin, fibrinogen, D-dimer, and ferritin. CBC was performed using the ADVIA 2120 Hematology System (Siemens Healthcare Diagnostics, Erlangen, Germany). The biochemical parameters defined above were measured using an Atellica Solution Immunoassay & Clinical Chemistry Analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany). Fibrinogen and D-dimer was analyzed using the Sysmex CS-5100 System (Siemens Healthcare Diagnostics, Erlangen, Germany).

Statistical Analysis

SPSS for Windows, version 22.0, was used to analyze the data (IBM Corp., Armonk, NY, USA). By using the Kolmogorov-Smirnov test, it was possible to determine whether the distribution of continuous variables was normal or not. The Levene's test was employed to assess the homogeneity of variances. For skewed distributions, continuous data were expressed as mean, SD, and median (interquartile range). The number of cases (%) was used to describe categorical data. The Mann-Whitney U test was used to compare statistical differences in non-normally distributed variables between two independent groups. Fisher's exact test or Pearson's Chi-square test were used to compare categorical variables. In all statistical analyses, a p-value < 0.05 was accepted as the significant level. The cut-off value of parameters linked to the risk of long-COVID was established using receiver operating characteristic (ROC) curve analysis.

Results

The mean age for children was 12.75±4.60 years (SARS-CoV-2 positive) and 12.50±4.83 years (control group). In both the COVID-19 and control groups, 49.8% of the children were male and 50.2% were female. There was no statistically significant difference in age or gender between both groups ($p>0.05$) (Table I).

The most common COVID-19 symptoms on admittance were fever (43.4%), sore throat (27.9%), rhinorrhea (24.7%), and cough (20.3%). Asymptomatic patients were 18.7%. The mean duration of the complaints of the COVID-19 patients at the time of admission was 1.26±1.22 days. While the physical examination findings at the onset of the disease were normal in 30.3% of the patients, 69.7% of the patients had upper respiratory tract infections. A chest X-ray was normal in all patients. None of the patients required hospitalization or pediatric intensive care unit admission (Table I).

The leukocytes, lymphocytes, eosinophil, basophil, platelet, red cell distribution width (RDW), and platelet distribution width (PDW) of the COVID-19 group were statistically significantly lower than the control group ($p<0.05$). The monocytes, red blood cell count (RBC), hemoglobin, mean platelet volume (MPV), albumin, D-dimer, fibrinogen, lactate dehydrogenase (LDH), platelet to lymphocyte ratio (PLR) and neutrophil to lymphocyte ratio (NLR) of the COVID-19 group were statistically significantly higher than the control group ($p<0.05$) (Table II).

Table I. Demographic and clinical characteristics of the children with COVID-19 and controls.

	COVID-19 group (n = 251) $\bar{x}$ ± SD med (min-max)	Control group (n = 251) $\bar{x}$ ± SD med (min-max)	p
Age (years)	12.75 ± 4.60 14.16 (0.37-17.91)	12.50 ± 4.83 14.02 (0.39-17.92)	0.667
Gender (%)			0.999
Male	125 (49.8%)	125 (49.8%)	
Female	126 (50.2%)	126 (50.2%)	
Onset of symptom to hospital admission (days)	1.26 ± 1.22	–	–
First application symptoms (%)	1 (0-7)		
Asymptomatic	47 (18.7%)		
Fever	109 (43.4%)		
Throat ache	70 (27.9%)		
Rhinorrhea	62 (24.7%)		
Cough	51 (20.3%)		
Headache	33 (13.1%)		
Debility	28 (11.2%)		
Joint pain	25 (10.0%)		
Nausea	20 (8.0%)		
Muscle pain	16 (6.4%)		
Diarrhea	14 (5.6%)		
Lumbago	10 (4.0%)		
Nasal congestion	10 (4.0%)		
Vomiting	7 (2.8%)		
Conjunctivitis	5 (2.0%)		
Loss of taste	4 (1.6%)		
Loss of smell	4 (1.6%)		
Chest pain	2 (0.8%)		
Dyspnea	2 (0.8%)		
First application physical examination (%)			
Normal	76 (30.3%)		
Upper respiratory tract infection	175 (69.7%)		
Long-COVID Symptoms (%)			
Muscle pain	3 (1.2%)		
Headache	8 (3.2%)		
Joint pain	19 (7.6%)		
Lumbago	12 (4.8%)		
Alopecia	3 (1.2%)		
Abdominal pain	5 (2.0%)		
Constipation	3 (1.2%)		

In total, 31 (12.4%) children noted long-COVID symptoms. There was no statistically significant difference in age or gender between patients with and without long-COVID symptoms (p>0.05). Joint pain was reported in 7.6%, lumbago 4.8%, and headache 3.2% of patients, and other long-COVID symptoms were abdominal pain, muscle pain, alopecia, and constipation. Headache and sore throat complaints in the first application were statistically significantly higher in patients with long COVID symptoms than in others (p<0.05). In addition, long-COVID symptoms were found to be statistically significantly higher in patients with upper respiratory tract infection in the first application physical examination (p=0.025). The mean duration of complaints at the time of first admission in patients with long-COVID symptoms (1.97±1.85 days) was statistically significantly higher than in those without long-COVID symptoms (1.16±1.07 days) (p=0.002). The mean onset of long-COVID symptoms after first diagnosis was 1.35±0.49 months. The onset of long-COVID symptoms was one month after initial diagnosis in 64.5% of patients and two months later in 35.5% of the patients. The mean duration of long-COVID symptoms was 5.32±2.51 months (Table III).

Leukocytes, monocytes, neutrophils, basophiles, platelets, and D-dimer were statistically significantly higher in patients with long-COVID symptoms compared to those without long-COVID symptoms (p<0.05) (Table IV). In ROC analysis, the area under the treatment characteristic curve (AUC) for leukocytes, neutrophils,

Table II. Baseline blood parameters of the children with COVID-19 and controls.

	COVID-19 group (n = 251) $\bar{x}$ ± SD med (min-max)	Control group (n = 251) $\bar{x}$ ± SD med (min-max)	p
Leucocytes (×10³/μL)	5.90 ± 2.00 5.68 (2.20-11.90)	7.26 ± 1.90 7.10 (2.15-11.35)	**< 0.001**
Lymphocytes (×10³/μL)	1.73 ± 0.93 1.56 (0.46-5.66)	2.98 ± 0.85 2.91 (1.29-5.30)	**< 0.001**
Monocytes (×10³/μL)	0.55 ± 0.24 0.50 (0.17-1.48)	0.50 ± 0.20 0.46 (0.22-1.23)	**0.029**
Neutrophils (10³/μL)	3.51 ± 1.62 3.31 (0.95-8.32)	3.67 ± 1.41 3.61 (0.80-7.00)	0.090
Eosinophil (×10³/μL)	0.10 ± 0.19 0.05 (0-1.92)	0.21 ± 0.18 0.16 (0.01-0.91)	**< 0.001**
Basophil (×10³/μL)	0.02 ± 0.02 0.02 (0-0.20)	0.07 ± 0.14 0.04 (0.01-1.16)	**< 0.001**
Red blood cell (×10⁶/μl)	4.97 ± 0.46 4.90 (3.92-6.73)	4.81 ± 0.40 4.80 (5.90-3.76)	**< 0.001**
Hemoglobin (g/dL)	13.93 ± 1.36 13.90 (10.29-16.63)	13.27 ± 0.92 13.40 (10.91-15.00)	**< 0.001**
Hematocrit (%)	41.56 ± 3.70 41.50 (32.05-50.49)	39.19 ± 3.10 39.20 (30.11-46.51)	**< 0.001**
Mean corpuscular volume (fL)	84.28 ± 6.86 85.17 (55.08-98.23)	83.26 ± 5.52 82.62 (68.19-95.17)	**0.001**
Mean corpuscular hemoglobin (pg)	28.26 ± 2.67 28.66 (16.95-32.05)	28.05 ± 2.15 28.00 (21.13-33.35)	**0.004**
Mean corpuscular hemoglobin concentration (g/dL)	33.58 ± 1.24 33.66 (30.18-37.33)	33.43 ± 1.26 33.60 (29.08-36.72)	0.228
Red cell distribution width (%)	13.36 ± 1.03 13.06 (11.76-16.73)	14.17 ± 1.70 13.72 (11.76-26.00)	**< 0.001**
Platelet (×10³/μL)	238.77 ± 57.15 236.00 (106.82-422.28)	299.78 ± 66.00 290.58 (160.39-512.04)	**< 0.001**
Mean platelet volume (fL)	9.29 ± 1.10 9.18(7.00-12.75)	8.77 ± 1.58 8.77 (5.76-12.30)	**< 0.001**
Platelet distribution width	15.85 ± 0.44 15.81 (14.50-17.03)	16.35 ± 1.01 16.12 (14.68-21.00)	**< 0.001**
Albumin (gr/dL)	4.60 ± 0.25 4.60 (3.80-5.30)	4.54 ± 0.24 4.50 (3.90-5.20)	**0.002**
D-dimer (ng/mL)	522.71 ± 561.01 323.40 (156.80-3700.00)	256.31 ± 76.82 230.00 (170.00-450.00)	**< 0.001**
Fibrinogen (mg/dL)	298.40± 65.39 294.00 (176.40-469.20)	173.92 ± 41.69 160.00 (110.00-280.00)	**< 0.001**
Lactate dehydrogenase (IU/L)	221.16± 59.42 203.49 (119.00-430.44)	138.42 ± 30.95 128.00 (101.00-213.00)	**< 0.001**
CRP (mg/L)	4.88 ± 6.70 2.53 (0.20-42.33)	–	–
Plateletcrit (%)	2.20 ± 0.54 2.14 (1.08-4.28)	– –	
Platelet to lymphocyte ratio	172.87 ± 89.05 155.30 (50.87-461.59)	106.39 ± 30.44 100.91 (52.46-200.56)	< 0.001
Neutrophil to lymphocyte ratio	2.68 ± 1.91 2.25 (0.25-9.22)	1.34± 0.68 1.24 (0.26-3.15)	< 0.001

monocytes, platelets, and D-dimer was calculated as 0.694, 0.658, 0.667, 0.612 and 0.571, respectively, and was found to be statistically significant ($p<0.05$) (Table V). This result shows that leukocytes, neutrophils, monocytes, platelets and D-dimer values can differentiate for long-COVID in COVID-19 patients (Figure 1). In the calculation of the best cut-off point for leukocytes, a cut-off value of 5.345 was calculated with 90.3% sensitivity and 50% specificity. In the calculation of the best cut-off point for neutrophils, a cut-off value of 3.185 was calculated with a sensitivity of 80.6% and a specificity of 51%. In the calculation of the best cut-off point for monocytes, a cut-off

Table III. Demographic and clinical characteristics of the children with and without long-COVID.

	Long-COVID symptoms (n = 251)		
	Yes (n = 31 $\bar{x}$ ± SD med (min-max)	No (n = 220) $\bar{x}$ ± SD med (min-max)	p
Age (years)	13.89 ± 4.88 15.95 (1.42-17.56)	12.59 ± 4.55 14.00 (0.37-17.91)	0.050
Gender (%)			0.829
Male	16 (51.6%)	109 (49.5%)	
Female	15 (48.4%)	111 (50.5%)	
Onset of symptom to hospital admission (days)	1.97 ± 1.85 1 (0-7)	1.16 ± 1.07 1 (0-7)	**0.002**
First application symptoms (%)			
Asymptomatic	3 (9.7%)	44 (20.0%)	0.168
Fever	14 (45.2%)	95 (43.2%)	0.835
Throat ache	15 (48.4%)	55 (25.0%)	**0.007**
Rhinorrhea	5 (16.1%)	57 (25.9%)	0.237
Cough	9 (29.0%)	42 (19.1%)	0.198
Headache	9 (29.0%)	24 (10.9%)	**0.010**
Debility	1 (3.2%)	27 (12.3%)	0.219
Joint pain	4 (12.9%)	21 (9.5%)	0.526
Nausea	0 (0.0%)	20 (9.1%)	0.147
Muscle pain	1 (3.2%)	15 (6.8%)	0.701
Diarrhea	0 (0.0%)	14 (6.4%)	0.228
Lumbago	3 (9.7%)	7 (3.2%)	0.112
Nasal congestion	2 (6.5%)	8 (3.6%)	0.356
Vomiting	0 (0.0%)	7 (3.2%)	0.602
Conjunctivitis	0 (0.0%)	5 (2.3%)	0.999
Ageusia	0 (0.0%)	4 (1.8%)	0.999
Anosmia	0 (0.0%)	4 (1.8%)	0.999
Chest pain	0 (0.0%)	2 (0.9%)	0.999
Dyspnea	0 (0.0%)	2 (0.9%)	0.999
First application physical examination (%)			
Normal	4 (12.9%)	72 (32.7%)	**0.025**
Upper respiratory tract infection	27 (87.1%)	148 (67.3%)	**0.025**
Onset of long-COVID symptoms (months)	1.35 ± 0.49		
Onset of long-COVID symptoms (%)	20 (64.5%)		
First month	11 (35.5%)		
Second month	5.32 ± 2.51		
Duration of long-COVID symptoms (months)			
Duration of long-COVID symptoms (%)			
1 month	3 (10.7%)		
3 months	5 (17.9%)		
4 months	1 (3.6%)		
5 months	8 (28.6%)		
7 months	6 (21.4%)		
9 months	5 (17.9%)		
Long-COVID Symptoms (%)			
Muscle pain	3 (9.7%)		
Headache	8 (25.8%)		
Joint pain	19 (61.3%)		
Lumbago	12 (38.7%)		
Alopecia	3 (9.7%)		
Abdominal pain	5 (16.1%)		
Constipation	3 (9.7%)		

value of 0.585 was calculated with a sensitivity of 67.7% and a specificity of 68.9%. In calculating the best cut-off point for platelets, a cut-off value of 439.8 was calculated with a sensitivity of 87.1% and a specificity of 50%. In calculating the best cut-off point for D-dimer, a cut-off value of 439.8 was calculated with 58.1% sensitivity and 68% specificity (Table V).

Table IV. Baseline blood parameters of the children with and without long-COVID.

	Long-COVID symptoms (n = 251)		
	Yes (n = 31 $\bar{x}$ ± SD med (min-max)	No (n = 220) $\bar{x}$ ± SD med (min-max)	p
Leucocytes (×10³/μL)	6.81 ± 1.48 6.53 (4.30-9.59)	5.77 ± 2.03 5.41 (2.20-11.90)	0.001
Lymphocytes (×10³/μL)	1.97 ± 0.88 1.58 (0.91-3.92)	1.69 ± 0.93 1.56 (0.46-5.66)	0.063
Monocytes (×10³/μL)	0.63 ± 0.18 0.64 (0.36-0.85)	0.54 ± 0.25 0.48 (0.17-1.48)	0.003
Neutrophils (10³/μL)	4.10 ± 1.42 4.01 (1.28-6.25)	3.42 ± 1.63 3.18 (0.95-8.32)	0.010
Eosinophil (×10³/μL)	0.09 ± 0.08 0.05 (0.01-0.26)	0.10 ± 0.20 0.05 (0-1.92)	0.624
Basophil (×10³/μL)	0.02 ± 0.01 0.02 (0.01-0.03)	0.02 ± 0.02 0.02 (0-0.20)	0.028
Red blood cell (×10⁶/μl)	5.03 ± 0.49 5.00 (4.21-6.43)	4.97 ± 0.46 4.90 (3.92-6.73)	0.511
Hemoglobin (g/dL)	13.94 ± 1.54 14.41(10.29-16.12)	13.93 ± 1.34 13.90 (10.70-16.63)	0.590
Hematocrit (%)	41.79 ± 3.88 42.53 (32.05-47.12)	41.52 ± 3.69 41.38 (32.10-50.49)	0.279
Mean corpuscular volume (fL)	83.94 ± 7.41 85.70 (61.00-92.31)	84.32 ± 6.80 85.10 (55.08-98.23)	0.817
Mean corpuscular hemoglobin (pg)	28.02 ± 2.93 28.60 (19.70-31.72)	28.30 ± 2.64 28.68 (16.95-32.95)	0.786
Mean corpuscular hemoglobin concentration (g/dL)	33.39 ± 1.16 33.46 (31.16-35.39)	33.61 ± 1.25 33.66 (30.18-37.33)	0.354
Red cell distribution width (%)	13.56 ± 1.18 13.16 (12.15-16.32)	13.33 ± 1.01 13.06 (11.76-16.73)	0.471
Platelet (×10³/μL)	256.16 ± 56.83 269.50 (107.80-330.48)	236.31 ± 56.90 229.25 (106.82-422.28)	0.002
Mean platelet volume (fL)	9.50 ± 1.25 9.20 (7.45-12.75)	9.26 ± 1.08 9.18 (7.00-12.44)	0.463
Platelet distribution width (%)	15.80 ± 0.38 15.80 (14.99-16.63)	15.85 ± 0.45 15.88 (14.50-17.03)	0.544
Albumin (gr/dL)	4.63 ± 0.23 4.69 (4.00-5.00)	4.60 ± 0.25 4.60 (3.80-5.30)	0.248
D-dimer (ng/mL)	641.97 ± 527.59 450.00 (160.00-1,734.00)	504.76 ± 564.91 316.20 (156.80-3,700.00)	0.045
Fibrinogen (mg/dL)	317.65 ± 73.10 321.30 (176.40-469.20)	295.41 ± 63.79 290.00 (176.40-436.56)	0.085
Lactate dehydrogenase (IU/L)	218.07 ± 83.68 188.10 (139.16-430.44)	221.60 ± 55.38 205.52 (119.00-384.00)	0.100
CRP (mg/L)	7.89 ± 11.70 2.90 (0.98-42.33)	4.46 ± 5.57 2.28 (0.20-34.31)	0.051
Plateletcrit (%)	2.41 ± 0.56 2.50 (1.27-3.47)	2.18 ± 0.53 2.10 (1.08-4.28)	0.006
Platelet-to-lymphocyte ratio	152.79 ± 67.88 140.36 (69.55-282.15)	175.61 ± 91.37 157.61 (50.87-461.59)	0.253
Neutrophil-to-lymphocyte ratio	2.54 ± 1.42 2.44 (0.34-6.07)	2.70 ± 1.97 2.18 (0.25-9.22)	0.599

Discussion

Previous pediatric research revealed that 8-58% of SARS-CoV-2 positive children have "long COVID" symptoms[5-18]. In our study, long-COVID symptoms were seen in 12.4% of children with COVID-19 infection. According to previous research[11,17-20], older school children are more commonly affected than younger school children, and pre-school children, as well as females, are more likely than males to have long-COVID symptoms. Despite the fact that there

Table V. Logistic regression analysis for long-COVID.

	AUC	p	Asymptotic 95% confidence Interval		Cut off	Sensitivity	Specificity
Leucocytes (×10³/μL)	0.694	< 0.001	0.614	0.774	5.345	90.3%	50%
Neutrophils (10³/μL)	0.658	0.005	0.556	0.760	3.185	80.6%	51%
Monocytes (×10³/μL)	0.681	0.001	0.584	0.777	0.585	67.7%	68.9%
Platelet (×10³/μL)	0.667	0.003	0.564	0.770	229.9	87.1%	50.0%
D-dimer (ng/mL)	0.612	0.045	0.500	0.723	439.8	58.1%	68%

was no statistically significant age and gender difference between those with and without long-COVID symptoms in our study, the mean age of both the patient and control groups was found to be compatible with older school children.

Fatigue, loss of smell, and loss of taste, headache, muscle and joint pain were the most reported "long-COVID" symptoms. Other symptoms reported in previous studies[6-8,11,12,14,20-23] were cough, nausea, diarrhea, concentration problems, insomnia, muscle weakness, chest pain, dizziness, and respiratory problems. In line with literature, fatigue, joint pain, lumbago, and headache were the most common symptoms in our study.

It has been reported that long-COVID findings are observed more frequently from the 2nd month, and the majority of children recover in 1 to 5 months[7,11,16]. The onset of long-COVID symptoms was one month after initial diagnosis in 64.5% of our patients, and the mean recovery of long-COVID symptoms was 5.32±2.51 months (min 1 - max 9 months) in our study.

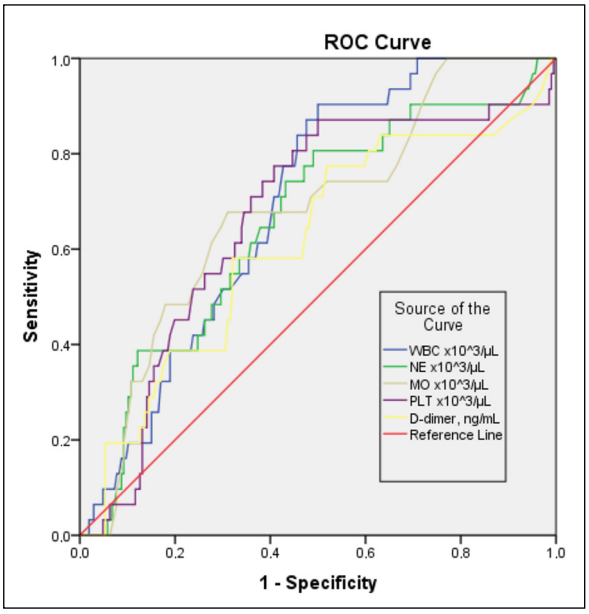

Figure 1. The ROC curves of leucocytes, monocytes, neutrophils, basophiles, platelets, and D-dimer in predicting long-COVID.

Studies[7,19,21,22] have shown that even mild-to-moderate cases are most affected by long-COVID. Children, including those with asymptomatic COVID-19, are also targeted by long-COVID. The majority of studies[7,19,21,22] did not discover any correlation between long-COVID and the severity of the initial illness during acute COVID-19. Similarly, long-COVID symptoms were also detected in our asymptomatic patients. According to Sterky et al[13], there is a link between longer application symptoms and a higher prevalence of persistent symptoms. We also discovered that the duration of complaints at first admission was statistically significantly longer in patients with long-COVID symptoms than in those without long-COVID symptoms.

Some common blood parameters are altered by SARS-CoV-2. According to the admission laboratory parameters, the critically ill patients have lower hemoglobin, lymphocyte, and albumin levels, as well as higher leukocytes, neutrophils, NLR, PLR, ferritin, D-dimer, and LDH levels[24-26]. These parameters, which are indicators of severe disease, may also be increased in children who develop long-COVID. We know that an uncontrolled inflammatory response can contribute to long-COVID[27,28]. Increased [18F] FDG uptake, indicative of ongoing inflammation, was found in the bone marrow and blood vessels in COVID-19 survivors who had symptoms that persisted for at least 30 days after discharge[29]. In comparison to their fully recovered counterparts, COVID-19 survivors who experienced persistent symptoms were more likely to have elevated neutrophil, NLR, fibrinogen, D-dimer, ferritin, CRP, and decreased lymphocytes, according to a few studies[30,31], and could potentially be used as long-COVID biomarkers. Unresolved inflam-

mation may only partially account for the pathophysiology of long-COVID and the symptoms of inflammation such as fatigue, myalgia, and joint pain[32,33]. The blood's increased concentration of D-dimer, which is a component of the coagulation cascade and a sign of hypercoagulability. As platelets' mitochondria are responsible for controlling their function, SARS-CoV-2-induced mitochondrial dysfunction in platelets may result in metabolic adversity that can trigger the coagulation cascade and raise D-dimer levels[34]. Activation of coagulation proteins and the formation of D-dimer are both indicators of COVID-19, as is platelet activation. When considered as a whole, the previously stated effect may help to explain why patient's D-dimer levels are elevated[35].

Similar to literature, leukocytes, lymphocytes, platelets, RDW, and PDW of the COVID-19 group were statistically significantly lower, as well as the monocytes, RBC, hemoglobin, MPV, albumin, D-dimer, fibrinogen, LDH, PLR, and NLR of the COVID-19 group were statistically significantly higher than the control group in our study. On the other hand, leukocytes, monocytes, neutrophils, basophil, platelets, and D-dimer levels were statistically significantly higher in patients with long-COVID symptoms compared to those without long-COVID symptoms.

Limitations

The limitation of our study is that, since it is a retrospective study, the long-COVID symptoms of the patients were evaluated based on their complaints of admission to the hospital. Patients may also have had other symptoms that were not bothersome enough to bring them to the hospital. Evaluation of patients with a questionnaire or telephone would have contributed more. On the other hand, in our study, these patients who had complaints that were disturbing enough to apply to the hospital were evaluated by a clinician, and the necessary laboratory and radiological imaging tests were performed and evaluated, which provided an objective evaluation.

Conclusions

In conclusion, the continuum of persistent symptoms in children with long-COVID is described in this study, along with the results of their medical evaluation at a specific pediatric clinic. Despite the majority of patients having a mild acute disease and no prior history of other illnesses, the majority of symptoms were associated with functional impairment between 1 and 9 months after the start of the infection. Our findings indicate that increased leucocytes, monocytes, neutrophils, platelets, and D-dimer levels appear to be the most powerful laboratory predictors for long-COVID. Monitoring the predictors may assist clinicians in identifying and following-up patients with higher risk for long-COVID.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee Approval was obtained from Ankara Atatürk Sanatorium Training and Research Hospital's Ethics Committee (Approval date and number: 09.11.2021/ 2021-2012-KAEK-15/2417).

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Authors' Contribution

Conception and design: Güven D; Acquisition of data: Güven D; Analysis and interpretation of data: Güven D, Buluş AD; Drafting the article: Buluş AD; Supervision: Buluş AD; Validation and final approval: All authors.

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