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Clinical characteristics of children with COVID-19 pneumonia

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Abstract *— For this purpose, 75 children under the age of 18 were included in the study. The test for SARS-CoV-2 virus RNA was positive in the pathological material from the nasopharynx in all examined patients. The control group consisted of 15 healthy children. The patients included in the study were divided into 2 groups according to severity of disease: 49 (65.3%) patients with moderate COVID-19 were included in group I, 26 (34.7%) patients with severe COVID-19 - in group 2. Examination methods included anamnestic, clinical, instrumental and laboratory studies. The most common symptoms among children examined were fever (66 (88.0%)) and cough (74 (98.7%)). Rarely, muscle pains, loss of sense of smell and taste, headaches have been observed in older children. Intergroup comparison revealed higher levels of ferritin, D-dimer and fibrinogen in group II compared with group I. According to the results obtained, the course of the disease in children, in contrast to adults, is more favorable.*

Keywords *— **COVID-19, children, clinical characteristics***

I. İNTRODUCTION

For the first time, at the end of 2019, a new SARS-CoV-2 infection was announced in Wuhan, China [1]. It turned out that the new virus infection - COVID-19 can cause clinical manifestations from a mild form of acute respiratory infection to severe acute respiratory syndrome, accompanied by damage to other organs and systems. The decision of the WHO has declared a pandemic since March 2020 [2]. The fact that COVID-19 is a global threat to health and society in the world has created the basis for its comprehensive study.

Scientific studies show that children of all ages, like adults, are at risk of being infected with the coronavirus, and even play an important role in the transmission of the virus [3]. According to many researchers, coronavirus infection in children is mild, even asymptomatic. However, a severe course of the disease is not excluded. According to researchers, children are a potential source for the spread of COVID-19 infection, and the fact that the disease is asymptomatic and mild in them leads to the assessment of the epidemiological importance of the child population in the spread of the new coronavirus infection [4]. However, in children there is still little information about the biological features of this infection, and there is a need for more research.

The purpose of the study: The study was to investigate clinical characteristics in children with COVID-19 pneumonia.

II. MATERIALS AND METHODS

The contingent of the study was made up of examination results of 75 children under 18 years of age who were diagnosed with COVID-19 pneumonia and received inpatient treatment at Children's

Infectious Diseases Hospital No. 7 in 2021. The control group consisted of 15 healthy children. In the main group, there were 37(49.3%) boys, 38(50.7%) girls, and in the control group 5(33.3%) boys, and 10 (66.7%) girls. Patients included in the study were divided into 2 groups according to the degree of severity: Group I included 49 (65.3%) patients with moderately severe COVID-19 pneumonia, II the group included 26 (34.7%) severely evaluated patients with COVID-19 pneumonia. Typical multisystem inflammatory syndrome (MIS-C) and death were not recorded in the patients included in this study. Examination methods of patients include anamnestic and epidemiological data (learned from the history of the disease and parents). At the same time, clinical, instrumental and laboratory examinations were carried out (general and biochemical blood analysis, cytokines, inflammatory markers - ferritin, fibrinogen, D-dimer). Examinations were carried out during the acute period of the disease. A typical diagnosis of COVID-19 was established by polymerase chain reaction (PCR) of a nasopharyngeal swab according to protocol. The SARS-CoV-2 virus RNA test was positive in the pathological material taken from the nasopharynx of all investigated patients, and unilateral or bilateral pneumonia was determined in the X-ray examination of their lungs.

Exclusion criteria: Congenital heart defects, bronchial asthma, autoimmune disorders, oncological diseases, primary or acquired immune deficiency, chronic diseases are excluded. In order to assess the levels of circulating cytokines (Il-1β, IL-6, IL-18) in blood serum, reagent kits from the company "Vektor Best" (Russian Federation) were used by the enzyme-linked immunosorbent assay (IFA) method. Measurements were carried out on the "Stat Fax 303+" device.

Statistical processing: Statistical data processing was carried out using the methods of variation (U-Mann-Whitney), discriminant (Pearson's Chi-square), correlation (Rho-Spearman), dispersion (ANOVA test, F-Fisher and F-S-Fisher-Snedekor tests) tests, and also using ROC analysis. All statistical calculations were carried out in MS EXCEL-2019 and IBM Statistics SPSS-26 programs. The null hypothesis was rejected at $p < 0.050$.

III. RESULTS

The analysis of the epidemiological anamnesis showed that the vast majority of cases of the disease described in children were related to their contact with family members and/or other sick children with COVID-19. This clearly shows human-to-human transmission. Most of the COVID-19 patients were urban residents. Thus, 63 (84.0%) of the patients were urban residents, and 12 (16.0%) were from the region. This is explained by the fact that cities are the main centers of the spread of COVID-19, accounting for 90% of the recorded cases of the disease. The brunt of this crisis is felt in cities, as most of them have an overburdened healthcare system.

Patients' breathing was counted in the hospital, SpO2 level was determined with the "Pulse Oximeter CMS50C" device. Laboratory examinations: general and biochemical analyzes of blood were performed, coagulogram results were analyzed. During the x-ray examination of the lungs in the patients were observed infiltrative shadows of different sizes. All examined patients had a moderate or severe course of the disease. During our study, the clinical picture of the disease was typical for the studied pathology. Thus, the main leading symptoms in patients confirmed to be positive for COVID-19 (PCR) were fever and cough. Rarely, muscle pains, loss of sense of smell and taste, headaches have been observed in older children. From the total sample, fever in 66 patients (88.0%), cough in 74 patients (98.7%), dyspnoe in 13 patients (17.3%), loss of sense of smell and taste in 5 patients (6.7%), headache in 7 patients (9.3%), muscle pain in 13 patients (17.3%), vomiting in 14 patients (18.7%), diarrhea was observed in 7 patients (9.3%). Sluggishness was observed in 21 patients (80.0%), cyanosis in 8 patients (30.8%), muscle hypotonia in 16 patients (61.5%). Sp02 -97.7±0.2 in group I; Sp02-92.5±0.7 ($p<0.001$) was recorded in group II. In the radiological examination, 33 (67.3%) children in group I had one-sided pneumonia, 16 (32.7%) children had bilateral pneumonia, 16 (61.5%) children in group II had one-sided pneumonia, and 10 (38.5%) children had bilateral pneumonia (P=0.615).

During the study, the clinical manifestations recorded in the patients who tested positive for COVID-19 (PCR test) are described in the table 1.

Table 1 Clinical symptoms of confirmed patients with positive COVID-19 (PCR test).

	I group n=49	II group n=26	Px^2	Pu
	absolute number, %	absolute number, %		
Temperature	45(91,8%)	21(80,8%)	0,160	0,163
Cough	48(98%)	26(100%)	0,463	0,466
Loss of sense of smell and taste	2(4,1%)	3(11,5%)	0,218	0,221
Headache	3(6,1%)	4(15,4%)	0,189	0,192
Muscle pain	6(12,2%)	7(26,9%)	0,110	0,112
Dyspnea	3(6,1%)	10(38,5%)	0,001	0,001
Vomiting	5(10,2%)	9(34,6%)	<0,010	<0,010
Diarrhea	1 (2,0 %)	6(23,1%)	0,003	0,003
Sluggishness	–	21(80,8%)	–	
Cyanosis	–	8(30,8)	–	
Muscle hypotonia	–	16(61,5%)	–	

Note: The statistical significance of the difference between the indicators of the groups:

$P\chi 2$- according to the Chi-square Pearson criterion

P_U – according to the Mann-Whitney criterion

As for the analysis of hematological blood parameters in patients with COVID-19 (PCR), in our previous studies, various variations were observed in the acute period of the disease. Thus, in the analysis of peripheral blood, moderate leukocytosis, lymphocytosis, a tendency to thrombocytopenia, a slight increase in the level of ESF, CRP were observed. Other indicators were within the reference level [5].

The comparison of the average indicators of inflammatory markers - ferritin, D-dimer, fibrinogen and sytokines in the blood serum of patients confirmed positive for COVID-19 (PCR) is shown in table 2.

Table 2 Statistical analysis of ferritin, D-dimer, fibrinogen, cytokines in COVID-19 (PCR) positive patients (M±m)

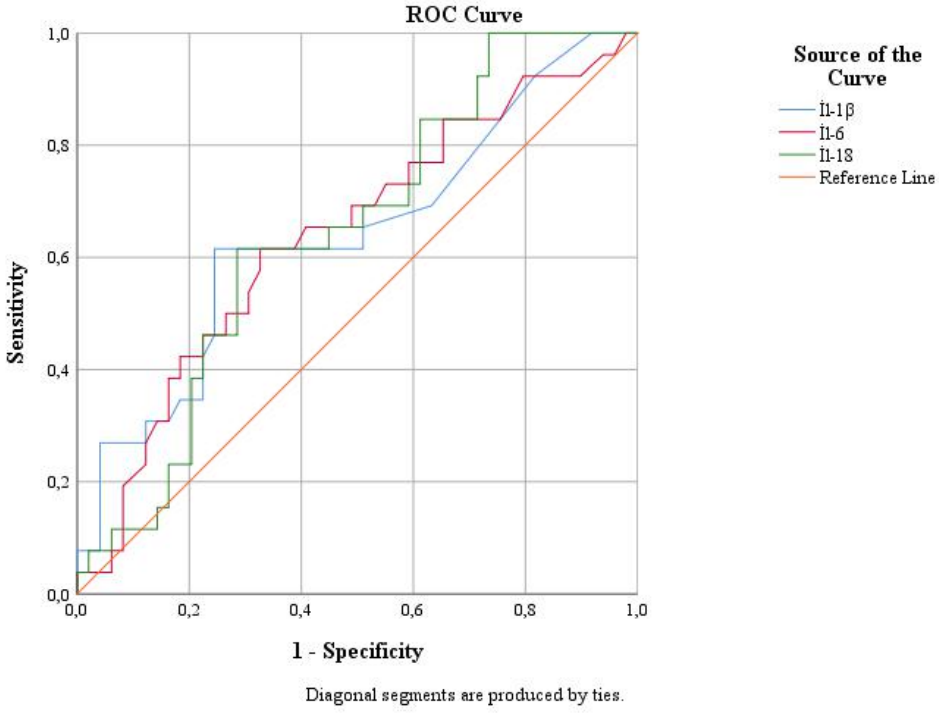
	I group n=49	II group n=26	Pu
Ferritin, ng/mL	196,6 ± 16,8 (52,4 – 510)	268,6±42,6 (66,7-1013)	0,319
Fibrinogen, q/l	327,3± 12,0 (179 - 489)	368,8±22,9 (164 - 582)	0,148
D-dimer, µg/ml	1037,6±378,4 (50-10000)	1504,7±553,8 (50-10000)	0,562
IL-1β, pg /ml	1,24± 0,3 (0,02 – 12,6)	2,97±0,86 (0,04-16,8)	0,044
IL-6, pg/ml	3,54± 0,43 (0,2 - 12,5)	4,79±0,62 (0,3-13,7)	0,048
IL-18, pg/ml	396,1±25,2 (146,5-891)	469,2±34,2 (258-973)	0,041

An increase in ferritin, D-dimer, and fibrinogen was observed in both groups of patients. Ferritin was 196.6 ± 16.8 ng/ml in group I, 268.6 ± 42.6 ng/ml in group II (p=0.319), fibrinogen was 327.3 ± 12.0 g/l in group I, and 368.8 ± 22.9 g/l in group II (p= 0.148). D-dimer concentration (in 57 (76.0%) patients) fluctuated in the upper limits of reference norms in both groups. Thus, in the acute period of the disease, this indicator was 1504.7±553.8 µg/mL in group II, and D-dimer concentration in group I was 1037.6±378.4 µg/mL (p=0.562).

In our study, when we measured the level of pro-inflammatory cytokines IL-1β, IL-6, and IL-18, it was clear from the results that their level increased in children with COVID-19 pneumonia. The level of IL-1β in blood serum in group II was 2.97±0.86 pg/ml (average 0.04-16.8 pg/ml), and in group I was 1.24±0.37 pg/ml (average was 0.02-12.6 pg/ml) (p=0.044). The concentration of IL-6 in blood serum was 4.79 ± 0.62 pg/ml in group II (average 0.3-13.7 pg/ml), in group I 3.54 ± 0.43 pg/ml (0,2-12.5 pg/ml) (p=0.048). The level of IL-18 in blood serum was 396.1±25.2 pg/ml (146.5-891 pg/ml) in group I, 469.2±34.2 pg/ml in group II (average 258-973 pg/ml) (p=0.041).

In the next stage of the study, we performed ROC (receiver operating characteristic) analysis of these indicators to evaluate the diagnostic significance of these indicators during the COVID-19. Specificity and sensitivity of each indicator were evaluated and ROC-curve was constructed.

Fig. 1 shows the informativeness of cytokines in the diagnosis of severity in COVID-19 patients.



According to the ROC analysis, depending on the degree of severity, all indicators have statistically significant diagnostic value. The area of the ROC curve for the IL-1β indicator is 0.641±0.070; 95% CI: 0.505-0.778: statistically significant with p=0.045. The area of the ROC curve for the IL-6 indicator is 0.639±0.068; 95% CI: 0.506 - 0.773: p=0.041 can be considered diagnostically significant. The area of the ROC curve of the IL-18 indicator is 0.644±0.065; 95% CI: 0.518 - 0.771: p=0.041 can be considered statistically significant.

In the next stage of the research, the goal was to evaluate the points farthest from the reference line (cut-off point) in the coordinates of the ROC-curves, where the total value of specificity and sensitivity is the largest. The calculation was performed on statistically reliable indicators in ROC-analysis. The informativeness of the indicators studied at the cut-off point during COVID-19 is shown in table 4.

Table 3. Results of ROC-analysis in the diagnosis of severity in patients with COVID-19.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
IL-1β	0,641	0,070	0,045	0,505	0,778
IL-6	0,639	0,068	0,048	0,506	0,773
IL-18	0,644	0,065	0,041	0,518	0,771

Table 4 Informativeness of the indicators studied at the cut-off point in COVID-19

Statistical parameters	IL-1	IL-6	IL-18
Cut off point	≥ 1	≥ 3,9	≥ 457
Sensitivity Sn%	61,5±9,5	61,5±9,5	61,5±9,5
Specificity Sp%	75,5±6,1	67,3±6,7	71,4±6,5
GDV %	53±5,3	49±5,5	51±5,4
pPV%	57,1±9,4	50,0±8,8	53,3±9,1
nPV%	78,7±6,0	76,7±6,4	77,8±6,2

Note. Sn- sensitivity; Sp – specificity; GDV- general overall diagnostic value; pPV (nPV) – positive (neqativ) predictive values

The cut off point of IL-1 concentration in blood is 1 pg/ml. At this point, the sensitivity (Se) is 61.5±9.5%, the specificity (Sp) is 75.5±6.1%, and the predictive effect due to positive and negative values is 57.1±9.4, 78.7±6.0, respectively is rated as sufficient. Cut off point for IL-6 ≥ 3.9 pg/ml, Sn=61.5±9.5%, Sp=67.3±6.7%; positive and negative values 50.0±8.8; 76.7±6.4. Cut off point for IL-18 ≥ 457pg/ml, Sn=61.5±9.5%, Sp=71.4±6.5%; positive and negative values 53.3±9.1; 77.8±6,2. As can be seen from the table, IL-1β, IL-18 are sufficiently evaluated for the accuracy of the positive result from the indicators. During the general diagnostic evaluation, the GDV of IL-1β was 53%, IL-6 was 49%, and IL-18 was 51%, which indicates the high diagnostic value of these examined indicators.

In the next stage of the research, the Efficiency influence of factor (EIF) was evaluated with the help of ANOVA dispersion (FS-Fisher Snedekor) analysis

Table 5. The strength of the influence of some studied factors in the diagnosis of the severity of COVID-19 positive patients

İndicators	Cut-off point	EIF (95% CI)	P
IL-1β pg/ml	>1	13,3 (8,6-18,0)	0,001
IL-6 pg/ml	>3,9	7,7 (2,7-12,7)	0,016
IL-18 pg/ml	>457	10,3 (5,4-15,1)	0,005

As can be seen from Table 5, IL-1β has a higher rate of impact on the course of the disease; EIF = 13.3; 95% Cİ-8.6-18.7; p=0.001. The indicators of influence of other factors were as follows: IL-6 - EIF =

7.7; 95% CI- 2.7-12.7; p=0.016; IL-18 - EIF = 10.3; 95% CI- 5.4-15.1; p=0.005. A change in the concentration of cytokines indicates the manifestation of the inflammatory process, the possibility of aggravation of the damage in the lungs.

Table 6. Correlation relations between the clinical and laboratory indicators were studied.

		Condit	T	SpO2	Dyspne	Vomiti	Diarrhe	WBC	RBC	HGB	İl-1β	İl-6	İl-18
Condition	ρ	1,000	0,389	-0,713	0,407	0,298	0,344	0,403	-0,319	-0,238	0,234	0,230	0,238
	p		0,001	0,000	0,000	0,009	0,003	0,000	0,005	0,040	0,043	0,047	0,040
T	ρ	0,389	1,000	-0,319	0,154	0,126	0,287	0,168	-0,140	-0,114	0,206	0,060	0,111
	p	0,001		0,005	0,186	0,281	0,012	0,150	0,230	0,329	0,076	0,609	0,345
SpO2	ρ	-0,713	-0,319	1,000	-0,459	-0,233	-0,357	-0,303	0,426	0,372	-0,097	-0,117	-0,103
	p	0,000	0,005		0,000	0,045	0,002	0,008	0,000	0,001	0,408	0,317	0,377
Dyspnea	ρ	0,407	0,154	-0,459	1,000	-0,039	0,095	0,283	-0,129	-0,029	0,099	-0,048	-0,101
	p	0,000	0,186	0,000		0,743	0,416	0,014	0,269	0,803	0,398	0,682	0,389
Vomiting	ρ	0,298	0,126	-0,233	-0,039	1,000	0,670	0,098	-0,161	-0,074	-0,064	-0,040	0,058
	p	0,009	0,281	0,045	0,743		0,000	0,403	0,167	0,531	0,588	0,731	0,618
Diarrhea	ρ	0,344	0,287	-0,357	0,095	0,670	1,000	0,136	-0,313	-0,249	0,012	-0,048	0,032
	p	0,003	0,012	0,002	0,416	0,000		0,246	0,006	0,031	0,921	0,685	0,787
WBC	ρ	0,403	0,168	-0,303	0,283	0,098	0,136	1,000	-0,142	-0,054	0,205	0,089	-0,036
	p	0,000	0,150	0,008	0,014	0,403	0,246		0,225	0,644	0,078	0,449	0,758
RBC	ρ	-0,319	-0,140	0,426	-0,129	-0,161	-0,313	-0,142	1,000	0,819	0,044	0,079	-0,096
	p	0,005	0,230	0,000	0,269	0,167	0,006	0,225		0,000	0,709	0,503	0,415
HGB	ρ	-0,238	-0,114	0,372	-0,029	-0,074	-0,249	-0,054	0,819	1,000	0,039	0,008	-0,127
	p	0,040	0,329	0,001	0,803	0,531	0,031	0,644	0,000		0,741	0,948	0,276
İl-1β	ρ	0,234	0,206	-0,097	0,099	-0,064	0,012	0,205	0,044	0,039	1,000	0,084	0,297
	p	0,043	0,076	0,408	0,398	0,588	0,921	0,078	0,709	0,741		0,475	0,010
İl-6	ρ	0,230	0,060	-0,117	-0,048	-0,040	-0,048	0,089	0,079	0,008	0,084	1,000	0,341
	p	0,047	0,609	0,317	0,682	0,731	0,685	0,449	0,503	0,948	0,475		0,003
İl-18	ρ	0,238	0,111	-0,103	-0,101	0,058	0,032	-0,036	-0,096	-0,127	0,297	0,341	1,000
	p	0,040	0,345	0,377	0,389	0,618	0,787	0,758	0,415	0,276	0,010	0,003	

Note: ρ – correlation coefficient (ρ-Spearman criterion)

p – statistical significance of the correlation coefficient

The relationships between the patient's clinical condition and cytokines.

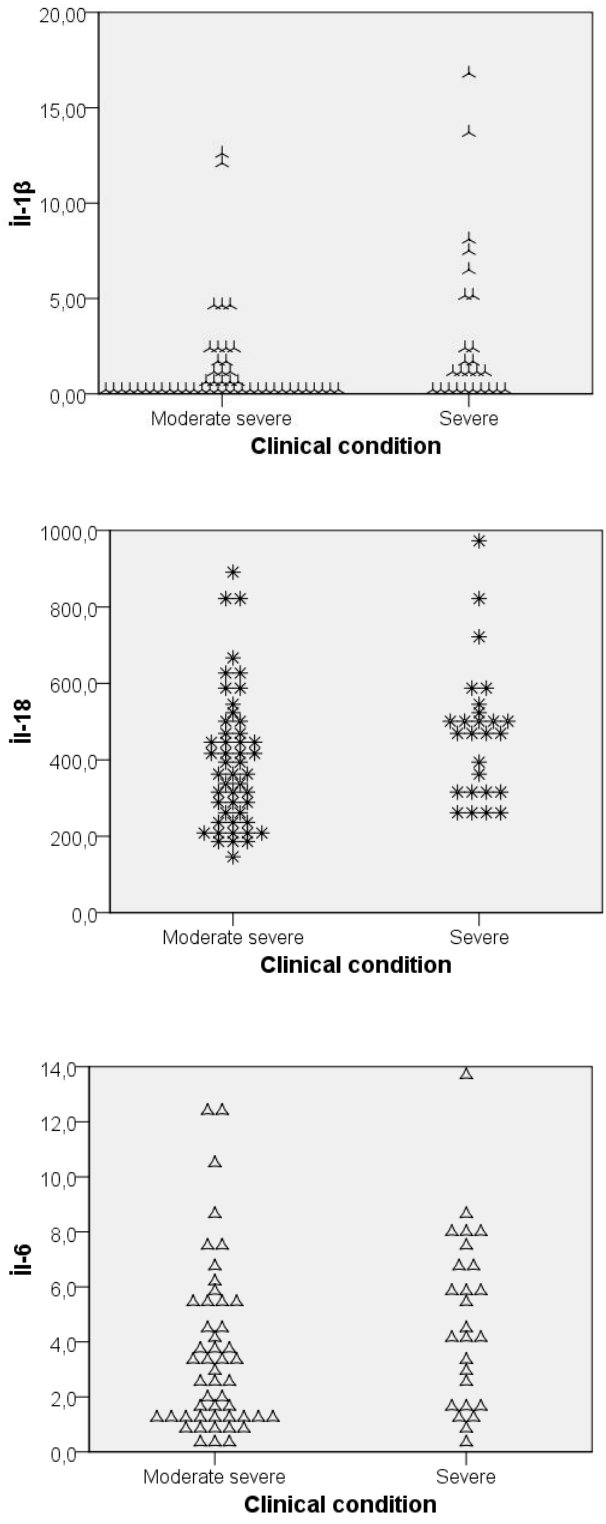


Fig.1. Correlations between cytokines and severity of disease in children with COVID-19.

IV. DISCUSSION

According to the results obtained, the course of the disease in children, in contrast to adults, is more favorable. Ludwigsson (2020) and another researcher came to similar conclusions [6, 7]. The most common symptoms among children examined were fever (66 (88.0%)) and cough (74 (98.7%)). According to the results of a meta-analysis conducted by Yudan D. and et. al (2020) the most common symptoms in children were fever and cough [4]. Dong et al repored that 94% of COVID-19 cases in children have been asymptomatic to moderate [8]. Rarely, muscle pains, loss of sense of smell and taste, headaches have been observed in older children. Sluggishness, cyanosis, muscle hypotonia etc.it was observed mainly in patients with a severe course. Most of the patients in this group were children under the age of 1 and children from the older age group. We think that this can be explained by age differences in the activity and maturity of the immune system in children [9]

Intergroup comparison revealed higher levels of ferritin, D-dimer, fibrinogen and cytokines(IL-1β, IL-6, IL-18) in group II compared with group I. Few studies have examined the laboratory findings in children with COVID-19 is an inflammatory disease.

İn response to the inflammatory process in COVID-19 infection, the level of ferritin, D-dimer, fibrinogen and cytokines significantly increased, which indicates the active level of the inflammatory response in the organism [10, 11, 12]. To date, the interaction of biomarkers in the pathophysiology of the disease in children infected with SARS-CoV-2 has not been fully established.

However, current information is that COVID-19 is an inflammatory disease, and in response to inflammation, biomarkers are induced by many proinflammatory cytokines [13]. Proinflammatory cytokines, which play a role in the pathogenesis of inflammatory diseases and affect their course, play an important role in inflammatory reactions, playing a role in proliferation and differentiation, activation of cells of the immune system. The increased level of proinflammatory cytokines in patients infected with COVID-19 (PCR) can be considered an important factor in the pathogenetic mechanism of exacerbation of the inflammatory process. We believe that these

cytokines are an inadequate or hyperergic reaction of the body to the effects of viral antigen. Determination of ferritin, D-dimer, fibrinogen and cytokines is advisable for early diagnosis and monitoring of the disease in children with a positive reaction to COVID-19 (PCR), depending on the severity of the disease. Many researchers have come to similar conclusions [14, 15, 16, 17]. However, the clinical profiles and pathophysiology of COVID-19 in children remain unclear. There findinqs support the need for future studies to predict the severity of the disease in COVİD-19 infection.

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