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Research Article

Clinical and Laboratory Features of COVID-19 in Different Pediatric Age Groups

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Abstract

The purpose of the study was to analyze and compare the clinical and laboratory results of COVID-19 disease in different pediatric age groups. Our research shows that children of all ages are vulnerable to COVID-19. For this purpose, 75 patients aged from 1 month to 17 years were included in the study. Patients were divided into three age groups: up to 1 year, 1-3 years, 4-17 years. The diagnosis of patients with COVID-19 was confirmed by a polymerase chain reaction (PCR) nasopharyngeal swab, and an X-ray examination of their lungs determined unilateral or bilateral pneumonia. Clinical manifestations of the disease in children were characterized by intoxication of varying severity. It is clear from the study that common symptoms across all age groups were fever and cough. Loss of smell and taste, muscle pain, and headache, characteristic of COVID-19, were recorded mainly in the 4-17 years. Lethargy, cyanosis, reduced reaction to the environment, and muscle hypotension were more often observed in children under 1 year of age. Laboratory examination revealed an increased level of anti-inflammatory cytokines (IL-1x, IL-6, IL-18), ferritin, fibrinogen, D-dimer in children. The biological mechanisms that determine age-related differences in the disease are still not fully understood, but the proposed hypotheses can be explained by age-related differences in the activity and maturity of the immune system of infants and adults.

Keywords: COVID-19; Pediatric Age Groups; Clinical Features

İntroduction

The fact that COVID-19 is a global threat to the health and society of the whole world has created the basis for its comprehensive study. SARS-CoV-2, having increased contagiousness, affects many cells, tissues and organs, but the disease is clinically manifested by respiratory symptoms. When studying the clinical manifestations of COVID-19, it was found that, despite the fact that children of all age groups can be affected, children have an asymptomatic or mild course of disease compared to adults [1-3]. However, even with an asymptomatic course of the disease, the spread of the virus can continue for a very long time, and therefore children are the main potential source of the continuation of the pandemic.

Some authors attribute this type of reaction of the child's organism to the COVID-19 infection with age-related characteristics of the immune system, less exposure of the respiratory system to unfavorable and harmful environmental factors, the presence of other viruses in the upper respiratory tract in children, age characteristics of ACE-2 receptors (a cell receptor for coronaviruses), and some authors explain that children receive vaccinations according to the preventive schedule (which regulates acquired immunity) and etc. However, these hypotheses do not have reliable evidence and indicate the importance of further research [4,5].

The purpose of the study was to determine age differences in clinical characteristics and laboratory results in pediatric patients with COVID-19.

Research Materials and Methods

The work was carried out in 2021-2022 at Children's Infectious Diseases Hospital № 7 of the Azerbaijan Republic. 75 children (assessed as moderate and severe) with a positive diagnosis of COVID-19 (PCR) were included in the study. A typical diagnosis of COVID-19 was established and confirmed by polymerase chain reaction (PCR) of a nasopharyngeal smear according to protocol. The diagnosis of pneumonia was confirmed by chest X-ray. Clinical data, epidemiological anamnesis, instrumental and laboratory examinations (general and biochemical analysis of blood, cytokins) were included in the examination methods of children. Patients with a positive COVID-19 (PCR) test but without clinical or radiological signs of the disease were considered asymptomatic. We did not include asymptomatic patients in our study. Typical multisystem inflammatory syndrome (MIS-C) and mortality were not noted in the patients included in this study.

The age limit of children was between 1 month and 17 years old. 35 healthy children were examined for comparison and they formed the control group. The gender distribution revealed that there were 37 (49.3%) boys and 38 (50.7%) girls among patients, 17 (48.6%) boys and 18 (51.4%) girls in healthy group. During the examination, no significant gender differences were noticed between the children.

The characteristics of the pathology of the respiratory system in children are mainly related to the age of the patients. Because the immune system undergoes a complex maturation process from birth to adulthood, age-related differences in the immune and inflammatory response may have important implications in determining the severity of COVID-19. Taking this into account, in order to compare the clinical features of the disease according to the age of the children included in the study, the patients were divided into three age groups: <-1 years old - 22 children (29.3%), 1-3 years old - 10 children (13.3%), 4-17 years old - 43 children (57.3%). The distribution of children depending on the severity of the disease showed that the severe course of COVID-19(PCR) infection was dominated by children under 1 year of age. Thus, the severe course of the disease was observed in 53.8% (n = 14) children under 1 year of age, in 7.7% (n = 2) children 1-3 years of age and in 38.5% (n = 10) children 4-17 years of age. In the group of patients with a moderate course, children under the age of 1 year were 16.3% (n = 8), at the age of 1-3 years-16.3% (n = 8), at the 4-17 years old -67.3% (n = 33). 29 of the examined patients (38.7%) applied to the hospital during the first 3 days of the disease. 41 children (54.7%) were admitted to the hospital on 4-7 days of the disease, and in less cases -5 (6.7%) patients were admitted to the hospital later than the onset of clinical manifestations. Children were examined during the acute period of the disease.

Exclusion criteria

Congenital heart diseases, bronchial asthma, autoimmune disorders, primary or acquired immune deficiency, chronic diseases.

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.

Determination of the concentration of ferritin in the blood serum of examined children was carried out by the immunoenzyme (IFA) method «Stat Fax 4700» (Germany) and the reagent kit of the company «Alkor Bio» was used. The concentration of D-dimer was performed by the immunoenzyme (IFA) method on the Wondfo device, using the reagent kit of the company «Wondfo Bio-Tech», and the concentration of fibrinogen was carried out on the «Steelex» device using the reagent kit of the «Steelext» company. The determination of the concentration of 25(OH)D3 was carried out in the «Stat Fax 4700» (Germany) enzyme immunoassay (IFA) analyzer using the Pishgaman (Germany) reagent kit.

During the assessment of the role of vitamin D in blood serum, the concentration of the 25(OH)D form was considered an adequate indicator. The level of vitamin 25-(OH)D in the blood was evaluated based on the following criteria: 25(OH)D was considered normal when it was in the range of 30-100 ng/ml, between 20-29 ng/ml (52.5 and 72.5 nmol/l) - insufficiency, between 10-20 ng/ml (<50 nmol/l) - deficiency, less than 10 ng/ml indicated severe vitamin D deficiency.

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. All statistical calculations were carried out in MS EXCEL-2019 and IBM Statistics SPSS-26 programs. The null hypothesis was rejected at $p < 0.050$.

Research Results and their Discussion

The acute period of the disease is characterized by relevant disorders. Symptoms of respiratory tract damage are observed in all age groups. Thus, during the clinical examination, when applying to the hospital, general symptoms were observed in the patients: catarrhal symptoms, cough, fever, signs of intoxication. Fever and cough were the main leading symptoms. Totally, fever was observed in 66 (88.0%) cases, cough in 74 (98.7%) cases.

The increase of temperature was observed in 18 (38.0 ± 0.2) infant under 1 year old, in 8 children (37.4 ± 0.2) of 1-3 age group, and in 40 children (37.6 ± 0.1) of groups 4-17 years old. Disturbances of the gastrointestinal tract manifested in the form of vomiting, diarrhea, nausea.

During our study, muscle pains (30.2%), loss of sense of smell and taste (11.6%), headaches (16.3%), hyperemia of throat (48.8%) were observed mainly in older children.

$Sp0_2$ was 94.5 ± 0.7 in infant under 1 year old, 97.1 ± 0.8 in 1-3 years old, and 96.2 ± 0.5 ($p = 0.017$) in the patients over 4 year. X-ray examination of the lungs is considered one of the main examination methods of respiratory tract diseases. In the x-ray examination of the lungs, infiltrative focuses were observed in all the examined children (Table 1).

	Age group							
	<1 years		1-3 years		4-17 years		Px2	PH
	N	%	Count	%	Count	%		
Sluggishness	14	63,6%	2	20,0%	5	11,6%	0.001*	0,001*
Cyanosis	5	22,7%	1	10,0%	2	4,7%	0,082	0,085
Muscle hypotonia	9	40,9%	2	20,0%	5	11,6%	0,024*	0,025*
Cough	22	100,0%	10	100,0%	42	97,7%	0,686	0,689
Dyspnea	6	27,3%	0	0,0%	7	16,3%	0,161	0,165
loss of appetite	22	100,0%	10	100,0%	40	93,0%	0,313	0,317
Muscle pain	0	0,0%	0	0,0%	13	30,2%	0,003*	0,003*
Vomiting	6	27,3%	1	10,0%	7	16,3%	0,421	0,426
Diarrhea	5	22,7%	0	0,0%	2	4,7%	0,033*	0,035*
Temperature	18	81,8%	8	80,0%	40	93,0%	0,129	0,232
Loss of sense of smell and taste	0	0,0%	0	0,0%	5	11,6%	0,136	0,140
Headache	0	0,0%	0	0,0%	7	16,3%	0,057	0,059
Hyperemia of throat	1	4,5%	3	30,0%	21	48,8%	0,002*	0,002*

Table 1: Clinical indicators of COVID-19(PCR) pozitive children in different pediatric age groups.

Note: *-statistical significance of the difference between the indicators of the age groups:

$P_{\chi 2}$ – according to Chi-square Pearson test

P_H- according to H-Kruskal-Wallis test

* – «0» hypothesis is rejected.

The levels of some laboratory parameters were assessed to determine the functional state of the child's organism. The data of clinical examination of blood in COVID-19 positive patients (PCR test) are shown in Table 2.

	Age group												P_F	P_H
	<1 years				1-3 years				4-17 years					
	M	Me	Q1	Q3	M	Me	Q1	Q3	M	Me	Q1	Q3		
Leukocytes q/l	9,96	9,80	6,6	12,2	7,58	7,10	6,4	9,4	7,09	6,80	4,9	8,4	0,007*	0,009*
Neutrophils %	29,2	25,1	20,8	35,6	42,8	43,5	34,6	55,7	48,5	45,0	40,1	57,5	0,001*	0,001*
Lymphocytes %	56,5	53,5	45,2	72,1	55,6	54,1	40,3	71,2	40,6	40,9	30,1	53,2	0,001*	0,002*
Monocytes %	8,3	5,5	4	12	9,1	8,0	6	10	9,7	9,0	7	12	0,556	0,149
Eozinophils%	2,0	2,0	2	2	2,1	2,0	2	2	2,6	2,0	2	3	0,168	0,144
Erythrocytesq/l	3,90	3,97	3,54	4,32	4,83	4,81	4,64	5	4,53	4,57	4,24	4,85	<0,001*	0,001*
Hemoqlobin Hb q/l	11,0	10,5	9,8	11,3	12,2	11,8	11,3	13,2	12,5	12,5	11,6	13,3	0,002*	0,001*
Trombocytes q/l	298,2	268,0	209	364	285,3	285,5	251	326	276,8	265,0	184	368	0,789	0,915
ESR mm/h	15,1	13,0	8	20	14,9	13,5	10	20	19,5	18,0	9	25	0,290	0,379,
CRP mq/l	7,64	2,50	1,11	6	6,89	2,50	2,5	6	8,23	2,65	2,5	7,25	0,962	0,551

Table 2: Statistical analysis of hemogram in different pediatric age groups of COVID-19 positive (PCR) children.

Note: *- the statistical significance of the differences between indicators of severity of the disease

pF – according to the Fisher F-criterion

P_H- according to H-Kruskal-Wallis test

* – «0» hypothesis is rejected.

As can be seen from the table, during the analysis of laboratory data relatively high blood hematological indicators were recorded in group of patients aged 4-17 years. Although the average indicators of ESR increased in patients compared to their normative indicators, its highest indicator was recorded in patients of older age groups.

So, in age group of 4-17 years, the ESR mean of was 19.5 mm/h , the median was 18,0 mm/h (9-25 in the 1st and 3rd quartiles), in infant up to 1 year old mean of this indicators was 15.1 mm/h , the median was 13,0 mm/h (8-20 in the 1st and 3rd quartiles), in children aged 1-3 years - mean was 14.9 mm/h , the median was 13,5 mm/h (10-20 in the 1st and 3rd), but the differences were not statistically significant.

The amount of CRP (C-reactive protein) in the blood, which is one of the informative markers of the inflammatory process, in patients during the acute period of the disease was higher than the reference level, which indicates the activation of the inflammatory process during SARS-CoV-2 infection. The indicators of other analyzes were almost within the reference level.

Thus, if a relatively significant change is observed in the hematological indicators of blood in the acute period of the disease in COVID-19 (PCR) positive patients, these indicators are not informative in predicting the disease. However, many of these laboratory findings are non-specific.

Given the lack of data on cytokine profiles during COVID-19 in children of different age groups, we investigated the serum levels of

cytokines in children with COVID-19 (PCR) positive pneumonia. In the course of our study, differences in the level of pro-inflammatory cytokines in children with COVID-19 (PCR) positive pneumonia in different age groups were noticed (Table 3).

	Age group												PF	P_H
	<1years				1-3 years				4-17 years					
	M	Me	Q_1	Q_3	M	Me	Q_1	Q_3	M	Me	Q_1	Q_3		
IL-1β	2,59	0,55	0,05	2,2	1,92	0,06	0,05	1,5	1,44	0,40	0,05	1,9	0,442	0,614
IL-6	3,70	3,55	1,5	5,3	5,76	5,75	2,7	7,5	3,70	2,70	1,4	5,6	0,148	0,145
IL-18	469,8	458,6	367,6	540,5	393,2	348,1	308,9	459	403,3	372,5	243,8	510,7	0,317	0,116

Table 3: Levels of cytokines (IL-1β, IL-6, IL-18) in different pediatric age groups of COVID-19 (PCR) positive children.

Note: *- the statistical significance of the differences between indicators of severity of the disease

pF – according to the Fisher F-criterion

P_H- according to H-Kruskal-Wallis test.

In patients aged up to 1 years with COVID-19, mean of IL-1β was 2.59 pg/ml, the median was 0,55 pg/ml (0.05-2,2 in the 1st and 3rd quartiles); in children aged 1-3 years- mean of IL-1β was 1,92 pg/ml, the median was 0,06 pg/ml (0.05-1,5 in the 1st and 3rd quartiles); in 4-17 years group mean was 1,44 pg/ml, the median was 0,40 pg/ml (0.05-1,9 in the 1st and 3rd quartiles).

The mean of IL-6 in children up to 1 years was 3.70 pg/ml, the median was 3,55 pg/ml (1.5-5,3 in the 1st and 3rd quartiles); in patients aged 1-3 years mean was 5,76 pg/ml, the median was 5, 75 pg/ml (2.7-7,5 in the 1st and 3rd quartiles); in 4-17years group the mean was 3,70 pg/ml, the median was 2,70 pg/ml (1.4-5,6 in the 1st and 3rd quartiles).

In children up to 1 year the mean of IL-18 was 469.8 pg/ml, the median was 458,6 pg/ml (367.6-540,5 in the 1st and 3rd quartiles); in 1-3 years group the mean was 393,2 pg/ml, the median was 348,1 pg/ml (308.9-459 in the 1st and 3rd quartiles); and in patients aged 4-17 years mean was 403,3 pg/ml, the median was 372,5 pg/ml (243,8-510,7 in the 1st and 3rd quartiles).

Clinical assessment is invaluable to the clinician, but many biomarkers can provide additional objective information that can have a significant impact on disease progression. Considering this

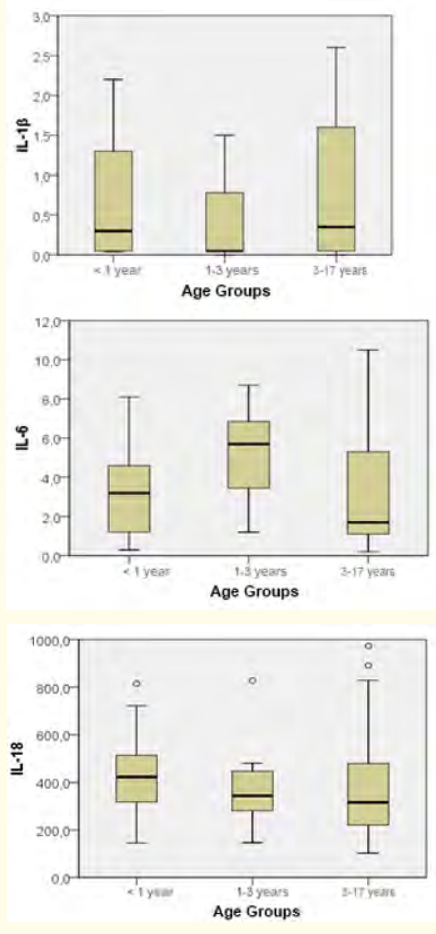


Figure 1: Indicators of the average levels of IL-1β, IL-6, IL-18 in blood serum in different age groups of COVID-19 (PCR) positive children.

point, a statistical analysis of biomarkers (ferritin, fibrinogen, D-dimer (d-dimer in 57 patients) and vitamine D) in children of different ages with COVID-19 was performed (Table 4).

	Age group												P_F	P_H
	<1 years				1-3 years				4-17 years					
-	M	Me	Q1	Q3	M	Me	Q1	Q3	M	Me	Q1	Q3		
Ferritin ng/ml	183,2	139,2	103,6	210,7	206,3	136,4	90,5	356,7	244,7	158,7	123,4	350	0,335	0,294
D-Dimer µg/ml	1358,0	473,0	166,5	1510	288,6	230,0	160	420	1394,5	251,5	137,5	601,5	0,450	0,544
Fibrinogen q/l	361,8	339,5	294	445	291,8	286,0	258	345	343,0	331,0	305	420	0,172	0,148
Vit .D ng/ml	27,8	28,6	24,8	32,5	29,0	29,8	26,8	31,8	22,7	22,1	20,4	25,7	<0,001*	0,001*

Table 4: Indicators of ferritin, fibrinogen, D-dimer and vit. D level in different pediatric age groups of COVID-19 (PCR) positive children.

Note: *- the statistical significance of the differences between indicators of severity of the disease

pF – according to the Fisher F-criterion

P_H- according to H-Kruskal-Wallis test

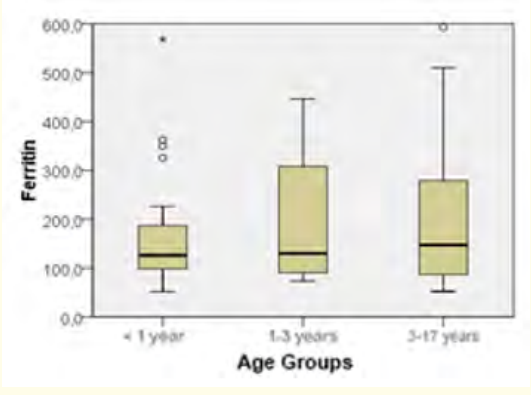
* – «0» hypothesis is rejected.

As can be seen from Table 4, an increase in the level of ferritin, fibrinogen and D-dimer was observed in the patients. Differences in ferritin levels during pneumonia caused by SARS-CoV-2 in different age groups were noted.

The high level of ferritin in blood serum was recorded in patients aged 4-17 years: mean was 244.7 ng/ml, the median was 158,7 ng/ml (123.4-350 in the 1st and 3rd quartiles); ferritin in infant under 1 year mean was 183,2ng/ml, the median was 139,2ng/ml (103.6-210.7 in the 1st and 3rd quartiles); in patients aged 1-3 years- mean of ferritin was 206,3 ng/ml, the median was 136,4 ng/ml (90,5-356,7 in the 1st and 3rd quartiles).

In COVID-19 (PCR) positive patients, among different age groups, the high level of fibrinogen was recorded in the children of up to 1 year - the mean was 361,8 q/l, the median was 339,5 q/l (294-445 in the 1st and 3rd quartiles); for 1-3 years group the mean was 291.8 q/l, the median was 286.0 q/l (258-345 in the 1st and 3rd quartiles); for 4-17 years group the mean was 343,0 q/l, the median was 331,0 q/l (305-420 in the 1st and 3rd quartiles).

Among the patients from different age groups, high D-dimer indicators in the acute period of the disease compared to the reference indicators were mainly observed in patients of 4-17 years group – mean was 1394,5 µg/mL, the median was 251,5 µg/mL (1375-601,5 in the 1st and 3rd quartiles). In the up to 1 year group- mean was 1358,0 µg/mL, the median was 473,0 µg/mL (166,5-1510 in the 1st and 3rd quartiles); in the 1-3 years age group – mean was 288,6 µg/mL, the median was 230,0µg/mL (160-420 in the 1st and 3rd quartiles).



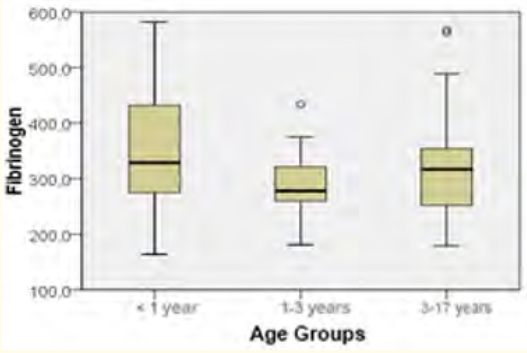


Figure 2: Indicators of average levels of ferritin, fibrinogen, D-dimer in different age groups of children positive for COVID-19 (PCR).

From our research, it became known that an increase in the levels of ferritin, fibrinogen and D-dimer was recorded. The analysis of the levels of ferritin as an inflammatory marker, coagulation factor fibrinogen and D-dimer, can allow determining the progress of the inflammatory process, the clinical course and degree of disease, and studying the state of the hemostasis system.

As can be seen from the table, low levels of vitamin D in blood serum were mainly recorded in the older age group. Thus, vitamin D was 22.7 ng/ml in the children aged 4-17 years (20,4-25,7 in the 1st and 3rd quartiles); 27.8 ng/ml in the infant up to 1 year (24,8-32,5 in the 1st and 3rd quartiles); 29.0 ng/ml (26,8-31.8 in the 1st and 3rd quartiles) in the 1-3 years age group.

The frequency of vitamin D deficiency according to the amount of 25(OH)D in blood serum in different age groups: vitamin D insufficiency in up to 1 year group 40.9%, deficiency - 13.6%; vitamin D insufficiency in 1-3 age group - 50,0%; 76.7% of children aged 4-17 years had vitamin D insufficiency, and 20.9% of patients had a deficiency ($p < 0.001$).

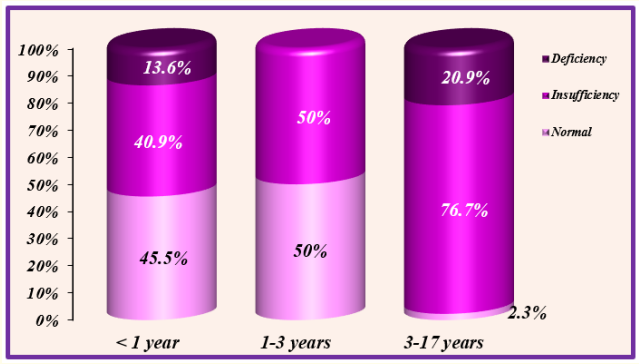


Figure 3: Comparative statistical analysis of vitamin D levels in different pediatric age groups positive for COVID-19 (PCR).

Thus, it is clear from the study that vitamin D deficiency plays a role in the development and exacerbation of the inflammatory process during COVID-19. The study of vitamin D in blood serum can be considered one of the necessary indicators among the factors affecting the development and course of inflammatory processes during COVID-19 in children.

		Age	T	SpO2	Condition	Cough	Dyspnea	loss of appetite	Muscle pain	Vomiting	Diarr Hea	Loss of sense of smell and taste	Head Ache
RBC	ρ	0,395**	-0,140	0,426**	-0,319**	0,027	-0,129	-0,110	0,077	-0,161	-0,313**	0,110	0,041
	p	0,000	0,230	0,000	0,005	0,819	0,269	0,347	0,510	0,167	0,006	0,348	0,725
HGB	ρ	0,498**	-0,114	0,372**	-0,238*	-0,030	-0,029	-0,104	0,133	-0,074	-0,249*	0,168	0,073
	p	0,000	0,329	0,001	0,040	0,801	0,803	0,376	0,254	0,531	0,031	0,150	0,533
HCT	ρ	0,399**	-0,102	0,312**	-0,150	-0,046	0,041	-0,119	0,040	-0,138	-0,270*	0,155	-0,076
	p	0,001	0,396	0,008	0,210	0,703	0,731	0,320	0,739	0,249	0,022	0,193	0,528
IL-1β	ρ	0,077	0,206	-0,097	0,234*	0,103	0,099	0,027	0,110	-0,064	0,012	0,192	-0,026
	p	0,509	0,076	0,408	0,043	0,381	0,398	0,819	0,346	0,588	0,921	0,098	0,828

IL-6	ρ	-0,089	0,060	-0,117	0,230*	0,199	-0,048	-0,049	-0,010	-0,040	-0,048	0,052	0,070
	p	0,447	0,609	0,317	0,047	0,087	0,682	0,678	0,934	0,731	0,685	0,659	0,551
IL-18	ρ	-0,207	0,111	-0,103	0,238*	0,183	-0,101	0,101	0,059	0,058	0,032	0,057	-0,019
	p	0,075	0,345	0,377	0,040	0,117	0,389	0,391	0,618	0,618	0,787	0,628	0,871
Ferr	ρ	0,274*	0,185	-0,205	0,116	0,156	0,251*	-0,099	0,328**	0,106	0,163	0,294*	0,120
	p	0,017	0,111	0,078	0,322	0,182	0,030	0,398	0,004	0,366	0,162	0,011	0,307
ESR	ρ	0,115	-0,004	-0,058	0,069	-0,011	0,032	0,065	0,204	0,013	-0,193	-0,115	0,336**
	p	0,324	0,975	0,624	0,558	0,927	0,787	0,582	0,078	0,914	0,097	0,326	0,003
CRP	ρ	0,169	0,119	-0,020	0,020	0,038	0,265*	-0,031	0,261*	-0,090	-0,202	0,113	0,169
	p	0,169	0,334	0,871	0,872	0,759	0,029	0,799	0,031	0,466	0,098	0,359	0,169
Vit.D	ρ	-0,575**	0,003	0,094	-0,227	0,107	-0,366**	0,146	-0,412**	0,098	0,050	-0,338**	-0,259*
	p	0,000	0,978	0,420	0,051	0,359	0,001	0,211	0,000	0,403	0,672	0,003	0,025
Fibr	ρ	0,114	0,343**	-0,290*	0,168	-0,070	0,297**	-0,075	0,221	0,045	0,050	0,073	0,308**
	p	0,330	0,003	0,012	0,149	0,552	0,010	0,520	0,056	0,701	0,672	0,534	0,007

Table 5: Assessment of correlations between some indicators in children with COVID-19 pneumonia.

Note: ρ – correlation coefficient (with Sperman criterion)

p – statistical integrity of the correlation coefficient.

Thus, according to the results of the correlation analysis, a correlation dependence is determined between the patient's condition, cytokine, clinical signs, and some hematological indicators in the COVID-19(PCR) positive patients.

Discussion

Today, there is little information about age differences in clinical and laboratory outcomes of COVID-19 in pediatric patients [5,6]. The analysis of the epidemiological anamnesis of the COVID-19 (PCR) positive patients showed that the vast majority of the disease cases described in children were related to contact with family members or other sick children [2,16].

In our study, moderate form of COVID-19 prevailed among patient. According to the age distribution of patients in our study, patients from up to 1 year of age (29.3%) and from the age group 4-17 years (57.3%) predominated. İn the research of Ding et al., the majority of COVID-19 patients consisted of children aged up to 1 year and older [7,8,9]. However, our research shows that children of all ages are susceptible to COVID-19. Karbuz A. (2021) in his retrospective studies concluded that the difference between both sexes and different age groups cannot be explained by the susceptibility of these groups to pandemic virus infection, because there is not enough data, thus, there is a need to conduct additional studies on this field [10].

According to the results of the epidemiological analysis, the family members were the mainly sources of infection for children. The analysis in the study of Hoang et al. showed that 75.6% of pediatric patients were infected from family members, the similar data were given by Ding -84.4% of children [7,11].

When comparing clinical indicators, significant differences were observed between different age groups. Clinical manifestations of the disease in children were characterized by intoxication of varying severity. Vanetti C. (2023) reported that the immunological profile of SARS-CoV-2 infection in children is age-related [12].

During the study, intoxication was prominent in children aged up to 1 year and older. The degree of its manifestation characterizes the severity and course of the disease. It is known that due to insufficiently formed immunity in children, it can be exposed to a wide range of antigenic effects [13,14]. Some characteristic features of the immune system of children, mainly up to 1 year of age, also

contribute to the simultaneous failure of defense reactions and to the development of an infectious disease. On the other hand, relatively high morbidity indicators in patients under 1 year of age can be explained by the fact that they are the category with high frequency of hospitalizations for epidemiological reasons and increased risk of developing complications [3]. At present, the biological mechanisms that determine the age differences of COVID-19 disease are still not fully understood [15]. However, the hypotheses put forward can be explained by age differences associated with the activity and maturity of the immune systems of infants and adults. In retrospective studies, Dong and some authors reported that children under the age of 1 year are the most vulnerable group [3,8].

During the clinical examination of COVID-19 (PCR) positive patients, nonspecific symptoms: catarrhal signs, cough, fever, signs of intoxication prevailed. Akmayeva M.A, et al. have also come to similar conclusions [2,14], in contrast, Hoang reports that among the common clinical manifestations, fever, rhinorea were very frequently observed symptoms [11]. However, in all patients who were confirmed positive for COVID-19(PCR), regardless of age, the most common symptom was fever, the second was cough [16].

Fever, cough were observed in children under 1 year of age in 81.8%, 100.0%, in children aged 1-3 years in 80.8% and 100.0%, and in 4-17 years in 93.0% and 97.7% of cases, respectively. The analysis showed that lethargy, cyanosis,muscle hypotonia, digestive disorders, etc. it is more often observed in children of the first year of life. Our results are in line with other literary data [15-18].

Specific for COVID-19 signs such as loss of taste and smell (11.6%), muscle pain (30.2%), headache (16.3%) were recorded in 4-17 years age groups. Although loss of smell and taste function and muscle pain are considered the leading symptoms of COVID-19 in children, there is almost a limited amount of information in the literature about this. Some researchers attribute the loss of smell and taste to the function of ACE receptors. ACE is expressed at high levels in various olfactory epithelial cell types in the oral mucosa and tongue, as well as in many tissues, which is a potential mechanism for impaired taste function. On the other hand, loss of sense and taste may be related to direct viral damage to the chemosensory system [19].

Although there is a large amount of data about laboratory indicators in children with COVID-19 (PCR) positive, laboratory differences are not found in pediatric age groups. According to our results, there were no distinctive age-related changes in hematological examination of blood in patients with COVID-19. Only in older children, relatively leukocytosis, ESR and changes in the biochemical analysis of blood, increased levels of CRP were recorded. No significant difference was observed between different ages in other indicators [15,16].

Information about the cytokine profile, which plays an important role in the pathogenesis of COVID-19 disease, in children at different ages is almost non-existent. The causal relationship between serum biomarkers and COVID-19 severity or pathogenicity in children is unclear. Given the lack of data on cytokine profiles during COVID-19 in children of different age groups, we studied the serum levels of cytokines in children with COVID-19 (PCR) positive pneumonia. Comparison of cytokines showed that its concentration increased in pediatric age groups. A comparative analysis between age groups also shows that the level of cytokines is relatively increased in children up to 1 year old. Vanetti C. came to similar conclusions [12]. We think that this may be related to the age-related characteristics of cytokine-producing immune system cells and the susceptibility of those to infection in various age periods. Thus, the result obtained shows the role of immune system components in the course of the disease, the release of pro-inflammatory cytokines in the COVID-19 positive patients (PCR). A high increase in the concentration of pro-inflammatory cytokines in the blood of patients with pneumonia caused by the coronavirus is directly related to the activity of the inflammatory process. Presumably, it plays a certain role in the development of a whole complex of clinical symptoms, which determines the aggravation of the disease. This suggests that the immune system, especially immune cells, are quickly activated to resist the invasion and damage of the SARS-CoV-2 virus in children who are still growing and developing, and try to suppress the inflammatory response in the early stages of SARS-CoV-2. Wenjie Lu (2021) and colleagues came to similar conclusions [20]. Qian G. (2021), et al. noted that inflammatory reactions in children with COVID-19(PCR) positive pneumonia are moderate and do not cause cytokine storm [21]. Our study is consistent with data of many other authors. Many researchers, Sun D., Ulhaq Z.S., Curatola A. etc. showed an increase in the cytokine profile of children [22-25]. During the hyperinflammatory reaction, which is the main cause of the severity of the COVID-19 infection, an increase in the

level of inflammatory biomarkers in the blood, including a number of laboratory indicators, is observed. In our study, an increase in the levels of ferritin, fibrinogen and D-dimer was recorded in older age group (4-17 years). Biomarkers play a crucial role in early detection, diagnosis, monitoring and control of treatment. Each of these components, in turn, can be directly decisive for the life of patients. Unfortunately, the precise interaction and proinflammatory properties of biomarkers in the pathophysiology of the disease in COVID-19 positive children have not yet been fully established. However, the available information is that biomarkers in response to inflammation are induced in liver hepatocytes by a variety of cytokines (IL-1β, IL-6, IL-18). We think that the increase in biomarkers in our study was compensatory. According to many researchers, coagulation dysfunction, especially the elevation of fibrinogen, D-dimer, is common in COVID-19 patients, and the degree of elevation is related to the severity of the disease [15,16,26-28]. The analysis of the levels of ferritin, fibrinogen and D-dimer, can determine the progress of the inflammatory process, the clinical course and degree, and the state of the hemostasis system of the patients.

ecently, the interaction between vitamin D and COVID-19 has been the subject of many scientific studies. It is known that vitamin D plays an important role in many chemical and biological processes in the organism. This unique vitamin with anti-inflammatory, antifibrotic and antioxidant effects is a hormone that regulates immune and inflammatory reactions in the organism. As an immunomodulator, vitamin D regulates the organism's innate and adaptive immune response by acting on immune cells, including monocytes, macrophages, dendritic cells, and T- and B-lymphocytes, suppresses the expression of pro-inflammatory cytokines, biologically active substances, prostaglandins. At the same time, vitamin D induces the expression of cathelicidin and β-defensin, two antimicrobial peptides with antibacterial and antiviral effects that destroy the cell membranes of microbes, viruses, bacteria and other pathogenic organisms and play a very important role in innate immunity, increasing their hemotactic activity and toxin neutralization functions, stimulates the activation of interferon signaling pathways [29]. During the study, vitamin D deficiency was mainly observed in the group of 4-17 years. We think this may be due to parental behavior in our society, which may be related to the regular vitamin D supplementation at a young age. Our results are consistent with many researches' data. Studies, conducted by Yılmaz and Shen (2020), Akoğlu (2021) and co-authors also examined the relationship between vitamin D levels and COVID-19 and found that vitamin D deficiency is a risk factor in the development of COVID-19 [30-34]. Based on our research, we can conclude that there is a link between vitamin D deficiency and COVID-19. Research results show that various immunomodulatory properties of vitamin D play a significant role in the risk of developing COVID-19 in children.

Conclusion

Thus, the identification of differences in age groups in pediatric patients can significantly help in understanding the pathogenesis of the disease. Our study has some limitations. There were a small number of children in the age range in our study. Nevertheless, our study supports the need for further studies to understand the different mechanisms of pathogenetic, clinical and laboratory features associated with SARS-CoV-2 in children of different ages.

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