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SARS-COV-2 INFECTION IN CHILDREN OF LVIV REGION

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Introduction: During different epidemic periods of COVID-19, from 3.5% to 28% of pediatric patients required hospitalization [1–3], and the mortality rate was about 0.1% [4–5]. The clinical spectrum of pediatric COVID-19 is wide - from asymptomatic to critically severe disease complicated by acute respiratory distress syndrome, requiring mechanical ventilation [6].

Aim: To analyze the clinical and laboratory features of COVID-19 in children of different ages.

Patients and methods: A prospective study was conducted with the participation of 110 patients aged one to 18 years who were treated with a diagnosis of COVID-19 at the «Okhmatdyt» Hospital in Lviv in 2021-2022. The diagnosis was verified by a positive PCR test for SARS-CoV-2 from a nasocytogram. Three age groups were formed: the first included 28 children aged 1 to 5 years, the second - 33 patients aged 5 to 10 years, the third - 49 patients aged 10 to 18 years. Clinical, laboratory and instrumental signs of the disease were determined in hospitalized patients.

Results: Moderate COVID-19 was diagnosed in 80 patients (72.73%), severe - in 30 (27.27%), ($p < 0.05$). The mean/median values of inflammatory markers in patients with moderate and severe SARS-CoV-2: procalcitonin 0.05±0.03 ng/ml and 2.48±5.27 ng/ml; CRP 12.14±20.90 mg/l and 62.93±79.33 mg/l; IL-6 1.20 pg/ml and 7.50 pg/ml; IL-10 1.87±6.37 pg/ml and 22.64±60.97 pg/ml, in accordance ($p < 0.05$). Elevated D-dimer levels correlated with the severity of COVID-19, increasing in dynamics. The median values of the D-dimer level at the time of hospitalization and in dynamics in children with severe course were: 791.00 ng FEV/ml, 1206.00 ng FEV/ml; in moderate– 368.00 ng FEV/ml, 425.00 ng FEV/ml, ($p < 0.05$). Among all patients with COVID-19, pneumonia was diagnosed in 46 children (41.82%) and in 19 children (63.33%) – with a severe course of the disease.

Discussion: Scientific studies show that severe course of SARS-CoV-2 is more often observed in adolescents, the severity of the disease in different age groups also depends on its strain [3; 7–8]. The implementation of the prediction of severe infectious processes in children is possible when studying the levels of cytokines, procalcitonin, CRP, fibrinogen and troponin [9]. An increase in D-dimer was detected in severe COVID-19 [10–11].

Conclusions: The majority of hospitalized children developed a moderate course of COVID-19. Severe course – in children aged 10–18 years. The values of inflammatory markers were higher in children with severe COVID-19. Pneumonia developed in 41.82% of patients. Elevated D-dimer levels correlated with the severity of COVID-19.

Keywords: COVID-19, SARS-CoV-2, children, cough, pneumonia, diarrhea, D-dimer, thrombocytopenia, interleukins.

Introduction

The clinical spectrum of pediatric COVID-19 is broad – from asymptomatic to critically severe disease. Among the examined children with SARS-CoV-2 infection, asymptomatic, mild, moderate, severe and critical cases were found, which were 29.5%, 56.4%, 12.9%, 1.2% and 0%, respectively [12– 15]. COVID-19 in children can be complicated by pneumonia, acute respiratory distress syndrome, and respiratory failure with the need to use a ventilator [16–18].

During different COVID-19 epidemic periods, from 3.5% to 7% (during 2020-2022) and up to 17%-28% of pediatric patients (during 2023-2024) required hospitalization.Thus, among pediatric patients, an average of 2.5% of patients diagnosed with SARS-CoV-2 required hospitalization, and 0.8% of children needed hospitalization in the intensive care unit (ICU). Among children and adolescents, the highest percentage of hospitalizations (4.6%) was among patients aged 0–4. The main complications of SARS-CoV-2 that cause mortality in children are respiratory distress syndrome, multiple organ failure, and multisystem inflammatory syndrome [4-5, 18].

According to the data of the Lviv Regional Laboratory Center of the Ministry of Health in Lviv Region, during various epidemic periods of COVID-19, about 5–6% of all infected people were children. The incidence of children under 18 ranged from 3.1% to 5.9% of the total number of infected and 3.5 to 7%, and up to 17% of pediatric patients required hospitalization [19], while the mortality rate was about 0.1%.

Aim: To analyze the clinical and laboratory features of COVID-19 in children of different ages: symptoms, frequency of pneumonia, need for oxygen therapy, changes in hemogram, levels of inflammatory markers and coagulation factors.

Patients and methods

A prospective study was conducted with the participation of 110 children aged 1 to 18 who were treated for COVID-19 at Lviv OKHMATDYT Hospital in 2021–2022. The PCR method verified the diagnosis by detecting SARS-CoV-2 RNA from nasopharyngeal swabs. A complex of clinical, laboratory and instrumental signs of the disease course was determined in hospitalized children. Three age groups were formed: the first group included 28 children aged 1 to 5, the second group included 33 patients aged 5 to 10, and the third group included 49 people 10 to 18 years old. All patients and their parents signed an informed consent to participate in the study. The Commission on the Ethics of Scientific Research at the Danylo Halytsky Lviv National Medical University approved the study regarding scientific research and experimental developments with human participation (protocol No. 8 of November 23, 2020). Statistical processing of the obtained results was carried out using the methods of variational statistics with a determination of the median and quartiles (Me (25%; 75% percentiles)), minimum (min) and maximum (max) values of the obtained indicators. Qualitative characteristics are presented as absolute and relative numbers (%). Intergroup comparison was performed using the Pearson test (for relative values) and the Mann-Whitney test (for median values). The minimum level of significance when checking statistical data is $p < 0.05$.

The results. The study involved 110 patients with SARS-CoV-2, whose median age was 9.20 (5,13; 14, 00). 46 boys (41.8%) and 64 girls (58.2%) were among the examined patients. The average age of boys is 10.25 (3.58; 14.78), and girls – 9.00 years (5.58; 13.93). A moderate form of COVID-19 developed in 80 (72.72%) patients, whose median age was 8.00 years (4.98; 13.08), and severe – in 30 (27.27%) patients, with a median age of 12.05 years (7.65; 16.00), ($p < 0.05$).

At the time of hospitalization, the most common symptoms in children were elevated body temperature, which ranged from 37.1 to 40.2 ºC in 105 patients (95.5%), general weakness in 101 (91.8%), deteriorated appetite – in 88 (80.0%), dry cough – in 55 (50.0%) patients (Figure 1).

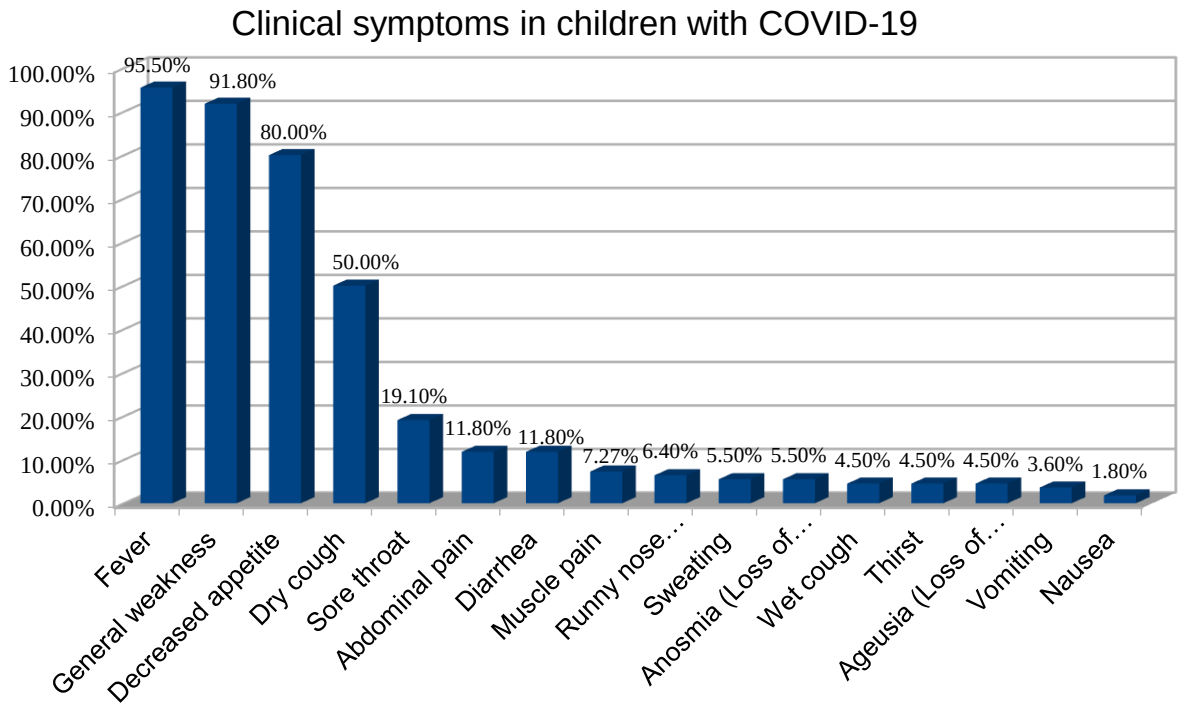

Figure 1. Frequency of clinical symptoms in children with COVID-19 at the time of hospitalization

21 children (42.9%) of the third age group complained of headaches, in contrast to the patients of the second group, where this symptom was found in three children (9.1%) ($p<0.05$). With a severe form of COVID-19, headaches bothered 11 patients (36.7%), unlike children with moderate form – 14 (17.5%). Muscle and joint pain were not so often detected in children of different age groups: two (4.1%) and one (2.0%) patients of the third age group, respectively. One-third of the patients (14 (28.6%)) of the third age group had a sore throat. This clinical sign was observed half as often in children in the second age group. With a severe form of SARS-CoV-2 infection, sore throat was diagnosed in seven patients (23.3%).

On objective examination, hyperemia of the oropharyngeal mucosa was observed in 64 patients (58.2%) with SARS-CoV-2. This symptom was most often detected in patients of the first age group – 19 children (67.9%), slightly less – 20 people (60.6%) of the second age group, and 25 children (51.0%) of the third age group.

A rash was not a characteristic symptom in patients with COVID-19. Only two children (1.8%) had a maculopapular rash, and two (1.8%) had a hemorrhagic rash in patients of the third age group with a severe form of SARS-CoV-2.

Cough bothered 20 children (66.7%) with a severe form of COVID-19 and 40 (50.1%) with a moderate form. Depending on the patient's age, the cough was most often observed in 31 children (63.2%) aged 10 to 18, in 16 children (57.1%) aged 1 to 5, and in 13 patients (34.4%) aged 5 to 10.

Dyspnea bothered all patients with a severe form of COVID-19: combined dyspnea – 21 (70.0%), expiratory – 9 (30.0%). In contrast, in patients with a moderate form, expiratory dyspnea was detected in only one patient (1.3%) ($p<0.05$). Combined dyspnea was diagnosed in a quarter (12 (24.5%)) of patients of the third age group, four children (12.1%) of the second group, and five (17.9%) patients of the first age group.

During auscultation of the lungs, most children (102 (92.7%)) were found to have harsh breathing; it was weakened in different parts of the lungs in 16 children (14%). In patients of the third age group, weak breathing was diagnosed in nine children (18.3%) and dry rales (14.3%) in seven patients. Changes detected during lung auscultation in children of different age groups are presented in Table 1.

Table 1. Lung auscultation data in patients with COVID-19 depending on age.

Age groups (years) / **Auscultation data**	**≥1<5 abs. (%)**	**≥5<10 abs. (%)**	**≥10<18 abs. (%)**
Harsh breathing	27(96.4)	30(90.9)	45(91.8)
Weakened breathing in the lower middle parts on the left	0(0.0)	1(3.0)	3(6.1)
Weakened breathing in the lower middle parts on the right	1(3.6)	1(3.0)	3(6.1)
Weakened breathing in the lower middle parts of both lungs	2(7.1)	2(6.1)	3(6.1)
Scattered dry rales over both lungs	1(3.6)	2(6.1)	7(14.3)
Moist rales in the lower-middle parts of both lungs	2(7.1)	0(0.0)	1(2.0)
Crepitation	1(3.6)	2(6.1)	1(2.0)

The blood oxygen saturation of all patients with COVID-19 indicated that the average value of SpO2 when breathing room air was 94.90 ± 4.93% (min – 69, max – 99). In 29 patients who required oxygen therapy, the mean value of SpO2 was 88.79 ± 1.20% (min – 69 and max – 93). During oxygen therapy, the average value of SpO2 increased to 96.83 ±2.44%. Oxygen therapy through a face mask was used in 23 patients.

Additionally, six children required mechanical ventilation. However, ECMO was successfully used in two children with critical hypoxemia that could not be controlled with conventional respiratory support.

In the studied group of patients with COVID-19, 91 persons (82.73%) underwent an X-ray examination of the lungs. A third of patients (33.0%) (95%CI: 23.9-43.1%) showed an increased pulmonary pattern. Among all patients, pneumonia was diagnosed in 46 people (41.82%).

Right-sided focal pneumonia was detected in 17 patients – 18.7% (95%CI: 11.6–27.6%). Damage to the right lung made up the largest share of all examined patients. Left-sided focal pneumonia was diagnosed in six people – 6.6% (95%CI: 2.7–13.0%). Lower lobe left-sided pneumonia was found in four patients – 4.4% (95%CI: 1.4–10.1%). Bilateral pneumonia: focal and polysegmental pneumonia was diagnosed in three – 3.3% (95%CI: 0.8–8.5%) and in five – 5.5% (95%CI: 2.0–11.6%) of patients, respectively. Thymomegaly was diagnosed in six patients – 6.6% (95% CI: 92.7–13.0%) with a moderate form of COVID-19.

In children with a moderate form of COVID-19, the following X-ray examination prevailed: increased pulmonary pattern in 24 – 38.1% (95%CI: 26.7–50.5%); right-sided focal pneumonia in 12–19.0% (95%CI: 10.7–30.0%). At the same time, left-sided pneumonia was diagnosed infrequently: in six patients – three focal and three lower lobes.

Nineteen patients with a severe form of SARS-CoV-2 had radiologically confirmed pneumonia: right-sided focal and bilateral polysegmental pneumonia was diagnosed in an equal number of patients – five people – 17.9% (95%CI: 6.7–34.9%). Bilateral focal, left-sided focal and left-sided lower lobe pneumonia was diagnosed in three patients – 10.7% (95%CI: 2.7–26.0%), in three – 10.7% (95%CI: 2.7–26, 0%) and one person – 3.6% (95% CI: 0.1–15.6%), respectively. Pleurisy was detected in two boys – 2.2% (95%CI: 0.3–6.8%) and pneumothorax in two patients of different sexes. X-ray examination of the lungs revealed changes in patients with a severe form of SARS-CoV-2 (Figure 2).

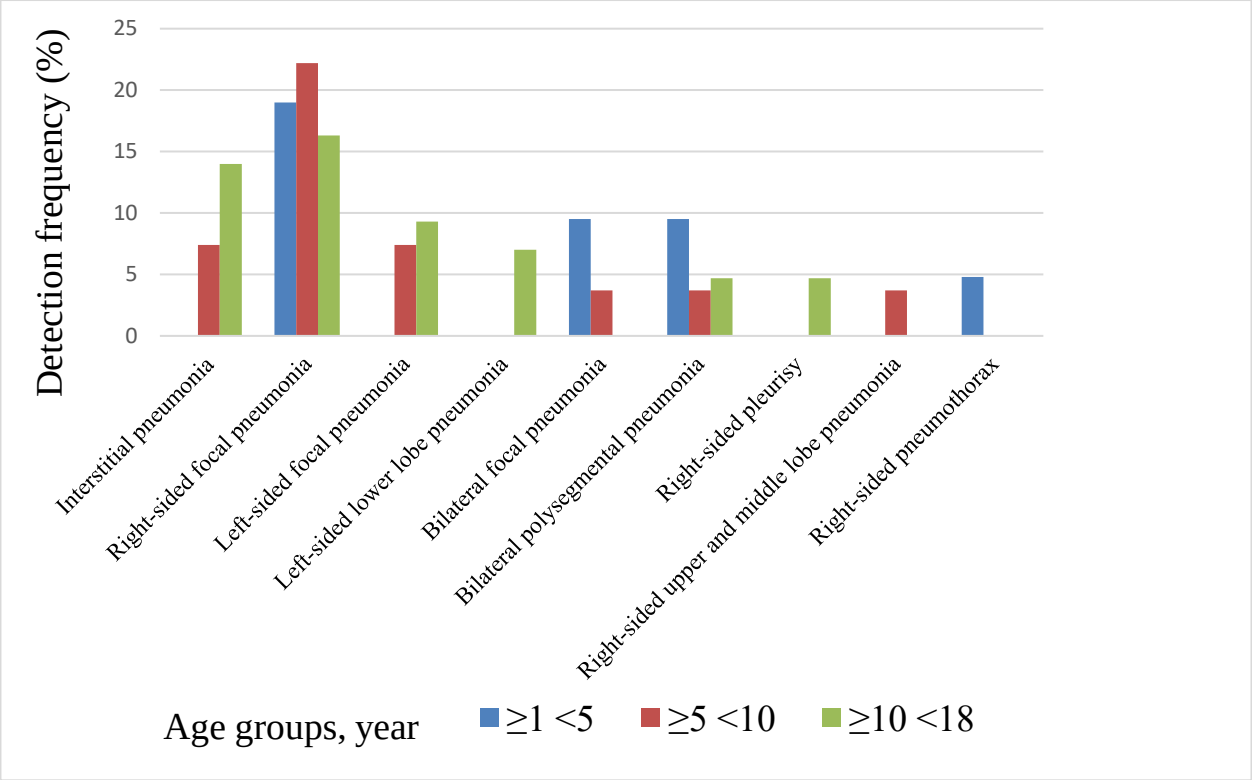

Figure 2. X-ray changes in lung damage in children of different ages

One of the manifestations of COVID-19 in hospitalized children was dyspeptic syndrome, which was manifested by nausea in 2 patients (1.8%), watery diarrhea from 1 to 3 times – in 10 (9.1%) patients, frequent watery diarrhea (more than 3 to 10 times) – in two (1.8%); hemocolitis – in 1 (0.9%), and diffuse abdominal pain in 12 (10.9%) children (Figure 3).

Analyzing gastrointestinal complaints in patients with COVID-19 of the third age group, the presence of watery diarrhea 1–3 times and abdominal pain is statistically significant ($p < 0.05$)

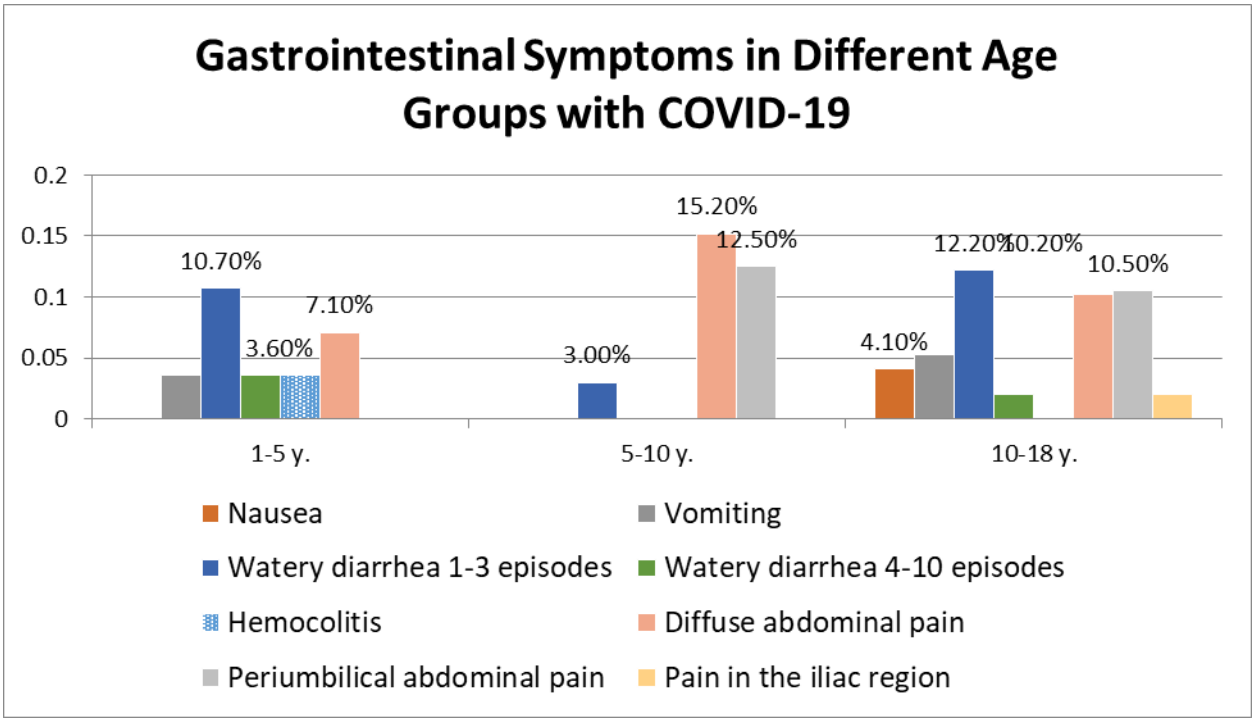

Figure 3. The structure of the gastrointestinal tract clinical symptoms in children with COVID-19

The number of leukocytes, when examining the complete blood count of patients with SARS-CoV-2 at the time of hospitalization, ranged from 2.07×10^9/l to 16.96×10^9/l and 1.84×10^9/l to 18, 95×10^9/l in moderate and severe forms of the disease, respectively. The average value of the indicator of the number of leukocytes was 6.16×10^9/l (4.63; 7.66)

and 5.35×10⁹/l (3.40; 7.90) in moderate and severe forms of COVID-19, respectively ($p > 0.05$). Leukopenia was observed in 14 patients (17.5%) with a moderate form of COVID-19, while leukocytosis was detected in two individuals (2.5%). At the same time, leukopenia was observed in 11 (36.67%) children with a severe form of COVID-19 and leukocytosis in three (10.0%).

The number of leukocytes was monitored on the third day of inpatient treatment. The average value of the number of leukocytes in patients with COVID-19 was 7.04 × 10⁹/l (3.72; 12.30). In patients with a moderate form, the median value of this indicator was 3.74 × 10⁹/l (2.51; 7.93); in the severe form of SARS-CoV-2, it was almost twice as high but within the normal range and was 8.30 × 10⁹/l (5.33; 14.75) ($p < 0.05$). Leukocytosis was observed in 5 (16.67%) children with a severe form of COVID-19, leukopenia in three (3.0%); with a moderate form, leukopenia was found in 5 (6.25%), leukocytosis – in one (1.25%) child.

Analyzing the median values of the number of leukocytes 6.12×10⁹/l (5.44; 8.39), 6.85×10⁹/l (3.92; 7.90) and 5.29×10⁹/l (3.90; 7.00), in patients of the first, second and third age groups, no statistical significance was found ($p>0.05$). The average value of the percentage of neutrophil granulocytes in patients with a moderate form of COVID-19 was 56.50% (46.20; 66.75) and 68.00% (59.03; 74,45) in children with a severe form of SARS-CoV-2. The mean/median values of the indicators of the complete blood count in different age groups are presented in Table 2.

Children with COVID-19 were diagnosed with inflammatory markers disease. The median value CRP level in all patients with COVID-19 at hospitalization was within the normal range and was 6.00 mg/L (4.00; 12.00). At the time of hospitalization of patients, the median value of CRP was 6.00 mg/l (4.00; 6.00) with a moderate form and 12.00 mg/l (6.00; 96.00) – with a severe form ($p < 0.05$). In five (6.25%) patients with a moderate form of COVID-19, an elevated CRP level was detected, and in 16 (53.3%) with a severe form. In the dynamics, on the third day of treatment, this indicator in a moderate form of the disease was 6.00 mg/l (4.00; 24.00) and in severe cases – 18.00 mg/l (6.00; 48.00) ($p>0.05$). The median value of CRP in children of different age groups at the time of hospitalization was: in the first age group – 6.00 mg/l (4.00; 6.00), in the second – 4.00 mg/l (3.00; 12.00); in the third age group – 6.00 mg/l (4.00; 12.00). The maximum CRP level in all age groups was 192 mg/l among 25, 32, and 45 children of the first, second, and third age groups, respectively ($p > 0.05$). After three days, this indicator increased, and in children aged 1 to 10 in the first group was 15.00 mg/l (4.00; 30.00); in the second group, 24.00 mg/l (18.00; 72.00) and normal – 6.00 mg/l [4.00; 24.00] – in patients of the third age group ($p > 0.05$).

One of the important laboratory criteria of inflammation is procalcitonin. Median procalcitonin levels in all patients with COVID-19 upon admission to inpatient treatment was 0.06 ng/ml (0.05; 0.55). The results of the median value turned out to be statistically reliable

procalcitonin at the time of hospitalization depending on the severity of the form of SARS-CoV-2: 0.42 ng/ml (0.05; 1.34) – in patients with a severe form of the disease and 0.05 ng/ml [0.03; 0.06] – in children with a moderate form ($p < 0.05$). In dynamics, this indicator increased, and its median value also differed in patients with different degrees of severity of the disease and amounted to 0.05 ng/ml (0.04; 0.05) in patients with a moderate form of the disease and 0.44 ng/ml (0.11; 7,18) in patients with a severe form.

When studying the dynamics of procalcitonin values, a moderate direct positive correlation was established ($R=+0.636$, $p < 0.05$) on the third day of hospitalization. Differences were also observed among the studied patients in three age groups: the median value of this indicator at the time of hospitalization was the highest in the second age group and constituted 1.64 ng/ml (0.85; 4.32), and was lower – 0.09 ng/ml (0.05; 0.21) – in patients of the first age group. At the same time, in patients of the third age group, the median value of procalcitonin was the lowest and constituted 0.05 ng/ml (0.04; 0.32) ($p > 0.05$). In dynamics on the third day of treatment, the median value of this indicator also increased and was 8.86 ng/ml (0.04; 26.97) in the first age group; 0.76 ng/ml (0.40; 2.22) in the second group and 0.12 ng/ml (0.10; 0.12) in the third age group (Table 3).

Table 2. Dynamics of the complete blood count in patients with COVID-19 in three age groups (taking into account M±SD)

Indicator	Age (years)	Mean/median value**	Min	Max	p
Hemoglobin during hospitalization, (g/l)	≤1>5	118.93±16.79	66	150	p < 0,0001*
	≤5>10	122.44±16.79	93	145	
	≤10>18	131.06±18.17	41	155	
Hemoglobin on the third day of treatment (g/l)	≤1>5	116.60±22.47	90	150	p > 0,05
	≤5>10	123.20±5.81	113	127	
	≤10>18	122.36±23.69	52	149	
The number of leukocytes during hospitalization ($\times10^9$/l)	≤1>5	6.12 (5.44;8.39)	3,32	18,95	p > 0,05
	≤5>10	6.85 (3.92;7.90)	2,07	14	
	≤10>18	5.29 (3.90;7.00)	1,84	16,96	
Neutrophil granulocytes during hospitalization (%)	≤1>5	47.00 (39.50;63.20)	12,3	12,3	p < 0/0001*
	≤5>10	56.00 (47.50;65.00)	34	88	
	≤10>18	65.20 ± 15.52	23	95	
Neutrophil granulocytes on the third day of treatment (%)	≤1>5	70.00 (58.75; 74.00)	31	80	p > 0.05
	≤5>10	65.40 ± 17.77	44	88	
	≤10>18	68.17 ± 14.83	42	91	
Lymphocytes during hospitalization (%)	≤1>5	47.04 ± 19.52	9	82,1	p < 0.002*
	≤5>10	41.00 (30.00; 45.20)	5,29	67,6	
	≤10>18	30.00 (20.00; 40.00)	4	66,4	
Lymphocytes on the third day of treatment (%)	≤1>5	36.00 (14.50; 59.00)	10	68	p > 0.05
	≤5>10	37.00 (20.00; 46.00)	11	56	
	≤10>18	28.50 (14.50; 36.48)	5	55	
The number of platelets during hospitalization ($\times10^9$/l)	≤1>5	248.00 (186.00; 325,00)	16	544	p < 0.005*
	≤5>10	231.34 ± 76.53	48	377	
	≤10>18	179.00 (153.00; 252.00)	52	385	
The number of platelets on the third day of treatment ($\times10^9$/l)	≤1>5	207.50 (120.00; 276.75)	36	306	p > 0.05
	≤5>10	280.00 (197.00; 365.00)	117	415	
	≤10>18	214.00 (177.50; 318.00)	123	549	
The number of leukocytes on the third day of treatment ($\times10^9$/l)	≤1>5	13.40 (9.82;18.60)	6,9	26,2	p > 0,05
	≤5>10	3.92 (3.56;11.20)	3,2	24,7	
	≤10>18	6.21(3.62;8.30)	2,09	16	

Note.* – the difference is reliable, ** – in the case of a non-Gaussian distribution, the results are given in the form of Me (25%, 75%)

Table 3. Dynamics of the median value of procalcitonin (PCT) at the time of hospitalization (1) and on the third day (2) in children with COVID-19 in three age groups

Age (years) / Value / PCT (ng/ml)	≥1<5 (n 7)	≥5<10 (n 3)	≥10<18 (n 11)	p
Average value 1	2.66± 6.77	2.90± 3.64	0.26± 0.40	p > 0.05
Median value 1	0.09 (0.05;0.21)	1.64(0.85;4.32)	0.05(0.04;0.32)	
Min1	0.01	0.056	0.01	
Max1	18.01	7	1.24	
Average value 2	18.15± 25.86	1.49± 1.93	0.11± 0.02	
Median value 2	8.86 (0.04;26.97)	0.76 (0.40;2.22)	0.12 (0.10;0.12)	
Min 2	0.02	0.043	0.08	
Max 2	54.88	3.68	0.125	

In children with a different course of COVID-19, the median value of ESR at the time of hospitalization was within the normal range and constituted 5.00 mm/h (4.00; 7.75) in patients with a moderate form and 6.00 mm/h (4.00; 20.00) in patients with a severe form, with a minimum value of 1 mm/h and a maximum value of 30 mm/h; with moderate – 2 mm/h and 43 mm/h – with severe form of COVID-19 (p > 0.05). In dynamics, the values of this indicator were 5.00 mm/h (4.00; 8.50) in patients with a moderate form of the disease and 11.50 mm/h (7.75; 19.50) in patients with a severe form of COVID-19 (p > 0.05). In different age groups of the studied patients, the ESR indicator increased during hospitalization in some patients, but its median value did not exceed the age norm. Its maximum value – 43 mm/h was observed in patients of the second age group (among 32 examined), the minimum – 2 mm/h. In the third age group, the maximum value was slightly lower – 40 mm/h with the minimum value – 1 mm/h (in 49 examined). In the first age group, the highest ESR was 25 mm/h, with the minimum value of this indicator – 1 mm/h (among 26 examined patients). While in dynamics, on the third day of treatment in children of the first, second and third age groups, the maximum and minimum values of ESR were 14 mm/h, 2 mm/h; 34 mm/h, 3 mm/h and 45 mm/h, 2 mm/h, in the first, second and third age groups, respectively (Table 4).

Table 4. Dynamics of the ESR value in patients with COVID-19 in different age groups. The data are presented in the form of Me [25%; 75%]

Indicator	Age (years)	Me (25%; 75%)	Min	Max	p
ESR (mm/h) during hospitalization	≥1 <5	5.00 (4.00; 7.50)	1	25	>0.05
	≥5 <10	6.00 (4.00; 8.50)	2	43	
	≥10 <18	6.00 (4.00; 10.00)	1	40	
ESR (mm/h) on the third day of treatment	≥1 <5	9.00 (6.50; 11.50)	4	14	
	≥5 <10	5.50 [3.5; 13.75]	3	34	
	≥10 <18	10.50 (5.00; 19.50)	2	45	

The study of IL-6 was conducted in 53 patients with COVID-19. The average value was 1.20 pg/ml (0.50; 7.00) (with an average value of 12.17 pg/ml). In patients with a moderate form of the disease, the median value of IL-6 was 1.20 pg/ml (0.55; 2.15) (with an average of 10.84 pg/ml); with a severe form – 7.50 pg/ml (0.65; 18.50) in 39 and 14 subjects, respectively ($p < 0.05$). However, the maximum value of 300 pg/ml was found in one patient with a moderate form of SARS-CoV-2. We found that median values of IL-6 depended on the severity of the disease: with a moderate form of the disease, IL-6 was below reference values, while in patients with severe COVID-19, it was 3.95 pg/ml (1.97; 5.92). Median values of IL-6 levels differed significantly in age groups. This indicator was the highest in the second age group and was 1.85 pg/ml (1.35; 15.60), with its maximum value – 300 pg/ml from 17 examined patients. In the first and third age groups, this indicator was 1.80 pg/ml (0.00; 7.00) and 1.15 pg/ml (0.70; 2.90); max – 29 pg/ml and max – 113 pg/ml, respectively.

In the study of IL-10 in blood serum, conducted in 61 patients, its average value was 6.64 ± 30.24 pg/ml. In 47 patients with a moderate form of COVID-19, the average value of IL-10 was 1.87 ± 6.37 pg/ml, and in 14 children with a severe form of the disease, it was 22.64 ± 60.97 pg/ml, ($p < 0.05$). The levels of IL-6 and IL-10 in the blood serum of children of different age groups are presented in Table 5.

Table 5. Median/mean value of the level of IL-6 and IL-10 during hospitalization in patients of three age groups.

Nosology	Age (years)	IL-6 up to 2 pg/ml Me (25%; 75%)	IL-10 up to 5 pg/ml (M±SD)
COVID-19	≥1 <5	1.80 (0.00; 7.00)	5.67 ± 12.08
	≥5 <10	1.85 (1.35; 15,60)	3.53 ± 7.91
	≥10 <18	1.15 (0,70; 2,90)	8.97 ± 42.87

D-dimer is one of the important markers of coagulopathy and has a significant diagnostic value for determining its severity. Thrombotic coagulation disorder is more common in severe cases of SARS-CoV-2. The median value of D-dimer in all patients with COVID-19 at admission was 733.00 ng FEU/ml (231.00; 1246.00) (with its average value of 1462.11 ng FEU/ml). The results of the median value of the D-dimer indicator at the time of hospitalization, depending on the severity of the disease course, turned out to be statistically reliable: 791.00 ng FEU/ml (540.00; 1844.50) in patients with a severe form of the disease and 368.00 ng FEU/ml (149.25; 921.25) – in children with moderate COVID-19 ($p < 0.05$). The value of D-dimer in patients with severe COVID-19 increased in the dynamics of the disease, and its median value on the 3rd day of inpatient treatment was 1206.00 ng FEU/ml (980.00; 2855.00). At the same time, the value of D-dimer in patients with moderate COVID-19 decreased with its median value – 425.00 ng FEU/ml (397.00; 812.50) ($p > 0.05$).

We assessed the level of D-dimer depending on the patient's age. It was found that at the time of admission, the highest median value of D-dimer in patients with COVID-19 of the second age group was 808.50 ng FEU/ml (173.00; 1437.75), while in children of the first, it was 642.50 ng FEU/ml (217.75; 1240.75) and the third – 575.00 ng FEU/ml (336.00; 1230.50) ($p > 0.05$).

Analyzing the results of ferritin-level research in 54 patients with COVID-19 upon admission, it was found that its median value was 63.30 ng/ml (37.15; 207.50). In dynamics (on the third day of treatment), the median value of this indicator was 203.00 ng/ml (74.20; 390.00). In patients with severe COVID-19, the median value of ferritin was 195.00 ng/ml (49.75; 344.00), and in children with a moderate form of the disease – 54.55 ng/ml (35.18; 94.10) ($p > 0.05$). Its median value in children with a severe course of SARS-CoV-2 was higher than on the day of hospitalization and constituted 232.10 ng/ml (73.20; 667.50).

The median value of the ferritin index in the third age group was 63.30 ng/ml (37.15; 128.75), and in the first and second age groups – 84.20 ng/ml (49.75; 412.25) and 51.05 ng/ml (23.93; 267.25) respectively ($p > 0.05$).

When studying D-dimer and ferritin in patients with SARS-CoV-2, no gender dependence was found.

During the analysis of one of the important hemostasis factors – D-dimer – a moderate positive correlation was found between its level and the ferritin index ($r = +0.47$; $p < 0.0004$). A similar positive relationship of average strength ($r = +0.49$; $p < 0.05$) was observed between D-dimer and procalcitonin indicators during hospitalization. A direct,

medium-strength relationship between the D-dimer indicator and the values of inflammatory markers - ESR and CRP were also revealed: ($r = +0.35$; $p < 0.05$) and ($r = +0.33$; $p < 0.05$), respectively.

Discussion.

The clinical spectrum of childhood COVID-19 is vast, from asymptomatic to critically severe disease course [13]. As indicated in scientific studies, in patients of all age groups, the general intoxication syndrome is most often observed as a complex of symptoms associated with the systemic inflammatory process, which is typical for infectious diseases, including COVID-19. It is manifested by increased body temperature, weakness, headache, myalgia, and fatigue observed in our patients. Chinese scientists Guan W.J. et al. (2020) believe that general intoxication syndrome is one of the first manifestations of COVID-19. They indicate that more than 80% of patients with COVID-19 experience weakness, fever, headache, and myalgias [20]. Anosmia and ageusia, although typical symptoms of COVID-19, were rarely seen in children. Among the examined children with SARS-CoV-2, asymptomatic, mild, medium-severe, severe and critically severe forms of the course of COVID-19 are noted, accounting for 29.5%, 56.4%, 12.9%, 1.2% and 0%, respectively [6]. The variable nature of symptoms indicates a wide range of manifestations of COVID-19 in the studied patients, which require monitoring and careful study of various manifestations of SARS-CoV-2 infection in children for effective diagnosis and treatment [7–8, 21].

According to scientists from the USA, the severe form of the disease is more often found in teenagers, although the severity of COVID-19 in different age groups depends on the strain of SARS-CoV-2. Obesity, the most common of all comorbid conditions, is the reason for increasing the risk of a severe form of the disease, mainly in children over 5 years of age [7].

Prediction of a severe infectious process in children is possible by studying the levels of pro-inflammatory and anti-inflammatory cytokines, procalcitonin, CRP and troponin. Scientific studies indicate that ferritin, D-dimer, and coagulogram indicators are markers of severity [10, 11].

Our laboratory results indicated a significant relationship between severity and age, CPP, IL-6, IL-10, and D-dimer levels. Our results are consistent with scientific studies conducted in China [22]. Foreign colleagues found significant increases in CRP, ferritin and procalcitonin levels in severe and critical cases [11].

D. Nizami et al. (2021) note that elevated levels of pro-inflammatory markers such as interleukins correlate with disease severity. These symptoms occur due to the activation of the immune system and the release of cytokines in response to the virus [11].

Coughing is one of the most common respiratory symptoms of COVID-19. Usually, it has a dry, unproductive character. In dynamics, it becomes productive. In severe cases, the cough may worsen due to the development of pneumonia. Huang C. et al. (2020) noted that dry cough was among the most frequent symptoms observed in more than 60% of patients. The authors believe that the cough is associated with damage to the epithelial cells in the respiratory tract caused by the virus [23]. A dry, unproductive cough was also observed in our patients. Shortness of breath is an essential symptom in the severe course of COVID-19, indicating the development of pneumonia or acute respiratory distress syndrome. It can occur due to hypoxia, which develops due to impaired gas exchange in the lungs [18,24]. Zhou F. et al. (2020) showed that dyspnea develops in 55% of patients with a severe course of the disease. It often occurs due to the development of bilateral pneumonia and hypoxia, which can be a precursor to a more serious complication – acute respiratory distress syndrome. The authors emphasized the importance of controlling blood oxygen levels in the early stages of the disease to prevent deterioration [25].

COVID-19 pneumonia has a viral etiology and is characterized by bilateral lung damage. On computed tomography (CT) of the lungs, so-called “frosted glasses” are often observed, which are a sign of inflammation of the interstitial tissue of the lungs. Pneumonia in COVID-19 can lead to ARDS and require intensive therapy, including mechanical ventilation [26, 27]. Chen N. et al. (2020) examined the radiological data of patients and found that 75% of them developed bilateral pneumonia. This study highlights the relationship between pneumonia severity and the risk of hospitalization in intensive care [28]. Scientists from Italy noted in their observations that the development of severe pneumonia is one of the main reasons for hospitalization in intensive care units, especially in people with concomitant chronic diseases (29). Our research shows that almost half of the patients with COVID-19 were diagnosed with pneumonia (n=46; 41.82%), which in 19 patients (63.33%) was associated with its severe course. In 29 patients who needed oxygen therapy, the average value of SpO2 was 86.84 ± 1.05% (min – 69 and max – 93); 23 children were given oxygen through a face mask; six were on ventilators). ECMO was successfully used in two children with critical hypoxemia that could not be controlled with conventional respiratory support.

According to Palabiyik F. et al., the most frequent localization of pneumonia with COVID-19 is in the lower parts of one lung. Scientists claim that ultrasonographic and radiographic examinations of the chest should be preferred in diagnosis. CT is recommended to be used according to clinical indications in cases of radiological, pathological findings that deserve further evaluation [27, 30-31].

Although COVID-19 is primarily a respiratory illness, some patients may experience gastrointestinal symptoms, including diarrhea. This is thought to be because the ACE2 receptors the virus uses to enter cells are also present in the gastrointestinal tract. In addition to diarrhea, nausea and vomiting may occur. Pan L. et al. (2020) described in their study that approximately 20% of patients with COVID-19 have gastrointestinal symptoms, including diarrhea. These symptoms are explained by the presence of ACE2 receptors in intestinal cells, through which SARS-CoV-2 enters cells [32–33]. Other researchers point to potential gastrointestinal complications due to intestinal mucosal dysfunction [34]. Our own observations also indicate that diarrhea and abdominal pain were statistically significant in the gastrointestinal tract in patients with severe COVID-19 infection ($p < 0.05$).

D-dimer is a protein formed during the breakdown of fibrin, which is the end product of the blood clotting process. An elevated D-dimer level in COVID-19 indicates the activation of the coagulation system. It is a prognostic marker of a severe course of the disease, in particular thromboembolic complications (for example, thrombosis and pulmonary embolism). Elevated D-dimer levels often correlate with increased mortality, and this condition may require anticoagulation [11]. D. Aguilera-Alonso et al. and M. Zaffanello et al. (2021) emphasized in their study that elevated D-dimer levels are associated with a severe course of COVID-19 and a higher risk of death [35-36]. Our studies indicate the reaction of the body, in particular, the blood coagulation system, which is in a hypercoagulable state, and correlation indicators with ferritin and procalcitonin will testify to the tension in the human defense system.

In conclusions:

1. The leading symptoms of COVID-19 in children were fever, weakness, decreased appetite and cough (54.5%), which was most often observed in 31 children (63.2%) aged 10 to 18, in 16 children (57.1%) aged 1 to 5, and in 13 patients (34.4%) aged 5 to 10, and was a manifestation of a severe course (63.2%). Severe COVID-19 developed more often in children aged 10 to 18 (63.2%) ($p < 0.05$).

2. Pneumonia was diagnosed in 41.82% of patients: 48.98% of children aged 10 to 18, 39.39% of children aged 5 to 10, and 32.14% in children aged 1 to 5. Pneumonia was detected in 63.33% of patients with a severe course of COVID-19; oxygen therapy was used in 29 (96.67%), six of whom used mechanical ventilation, and two (6.67%) three- and 15-year-old children received ECMO.

3. On the third day of treatment, the number of leukocytes in children with a severe course of COVID-19 was significantly higher, and the level of platelets was lower than in patients with a moderate-severe course ($p < 0.05$). The average values of the number of leukocytes at admission in patients of the first, second and third age groups did not differ statistically ($p > 0.05$).

4. In patients with a severe course of COVID-19, the levels of inflammatory markers (procalcitonin, CRP, IL-6, IL-10) were significantly higher compared to patients with a moderate-severe course ($p <0.05$). The median of procalcitonin at hospitalization was the highest in children aged 5 to 10 and the lowest in patients aged 10 to 18 ($p > 0.05$). In dynamics, on the third day of treatment, the median value of this indicator increased. The median of CRP at admission in three age groups was within the normal range, rising above the norm in dynamics (on the third day) in children aged 1 to 10 and was normal in patients aged 10 to 18 ($p > 0.05$).

5. Elevated levels of D-dimer were correlated with the severity of COVID-19 and increased dynamically, having positive correlations of moderate strength with ferritin and procalcitonin levels ($p < 0.05$). At the time of hospitalization, the highest median value of D-dimer was found in patients with COVID-19 in the second age group and the lowest in the third.

Practical recommendations.

In patients with SARS-CoV-2, it is necessary to monitor hemogram indicators, inflammatory markers of the disease, and D-dimer on the third day of inpatient treatment. A decrease in the dynamics of the number of platelets and an increase in CRP, procalcitonin, and D-dimer are prognostic signs of the severity of the disease. In COVID-19 patients aged 10 to 18, abdominal pain and the presence of diarrhea should be considered to verify its severe course.

Future Research Directions

The global spread of SARS-CoV-2 indicates a significant mutational variability of the virus, which contributes to various complications after COVID-19, including the development of severe forms of herpesvirus infections (HS1/2, VZV, CMV, EBV, HHV6) and their reactivations, reducing the immune system response, causing multiple organ damage and high mortality. Despite the mild course of the disease in most pediatric patients, the concern of pediatricians about the long-term consequences of SARS-CoV-2 was and is significant. There is evidence that COVID-19 causes acute and long-term effects on the developing central and peripheral nervous systems. Some of the long-term symptoms after COVID-19 may be due to the effects of the infection itself, altered immune function, or other biological factors. Our further research is related to the study of clinical, biochemical, immunological, and genetic data of MIS-C, associated with SARS-CoV-2; acute and reactivated herpesvirus infections in children after SARS-CoV-2 infection, their impact on the nervous, immune, and hematopoietic systems and the possibility of preventing the development of autoimmune processes, generalized forms of the disease, and the lymphoproliferative process.

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