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Course of Multisystem Inflammatory Syndrome in Children in the Republic of Belarus Depending on the Age

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Abstract

Introduction. In the spring of 2020, public health agencies around the world promptly issued warnings about a rare hyperinfectious disease in children, presumably a post-infectious immune response to COVID-19, using slightly different diagnostic criteria and nomenclature. The CDC Infection Control Center (USA) and WHO have named the disease multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. MIS-C is a new phenomenon reported worldwide and is temporarily associated with COVID-19.
Purpose. To research the clinical and laboratory features of multisystem inflammatory syndrome in children depending on the age.
Materials and methods. 78 children with a diagnosis of multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 were observed in the City Children's Infectious Clinical Hospital of Minsk, Republic of Belarus from May 2020 to March 2023. The diagnosis was established according to the 2020, 2023 criteria of CDC/WHO. This research was approved by the Ethics Committee. Parents of the children had signed an informed consent to participate.
Results. During the periods of circulation of SARS-CoV-2 variants age distribution of sick children had some peculiarities. During the Wuhan MIS-C circulation, 67% of the sick children were aged 14 years and older, however during the Omicron circulation, 44% were under 3 years old. The MIS-C phenotype, similar to complete and incomplete Kawasaki

disease (KD), was diagnosed in 62 (79%) patients. Upon admission to the hospital, 67 (86%) children had a febrile temperature. Usually, the rash developed on 2–4 days of illness and was observed in 64 (82%) children, while it was more often registered in children older than 3 years – 50 (64%). Mucosal lesions occurred in the form of scleritis in the 3–7 years group – 86% of patients, and cheilitis in the 1–3 years group – 85% of children. 49 (63%) children had gastrointestinal dysfunction, regardless of age. Only 22 (28%) patients had neurological disorders. Although, 43% of neurological symptoms were registered at the age group of 1–3 years. Lymphadenopathy developed in 37% of children, manifested by enlarged mesenteric and cervical lymph nodes. It was more common in two age groups: 3–7 years and 7–14 years in 45 and 41%, respectively. According to radiography / computer tomography of the chest organs, interstitial changes or pneumonia were registered in lungs of 33 (42%) children. Cardiovascular damage was manifested in the decrease of the heart index in 20 (26%) children. It was significantly more frequent in children of the oldest age group (0–3 – is not revealed, 3–7 years 3 (14%), 7–14 years – 10 (27%) and 14–18 years – 7 (58%), (p – value 0.03). Myocarditis was not age–specific. It was found in 29 (37%) children. Pericarditis (with a minimum amount of fluid) – in 20 (26%) children. In the results of the general blood test, neutrophilia was most often found. It was determined in 51 (65%) patients. In 0–3 years age group neutrophilia was found in 6 children (86%). Lymphocytopenia was detected in 52 (67%) patients, being more often observed in the 7–14 years age group – 29 (78%), (p-value 0.01). Anemia was more frequent in the 3–7 years age group – 17 (77%) children, (p-value 0.06). Thrombocytopenia was found in 22 (28%) children and was not age–specific. Increase in the erythrocyte sedimentation rate (ERS) was more common in the 14–18 years age group – 10 (83%) children. Acute-phase markers of inflammation such as C-reactive protein (CRP) and procalcitonin (PCT) were elevated in 99% of children. In older groups, CRP was higher compared to the younger ones (p-value 0.01). PCT was higher in the 0–3 years group – 8.4 [95% CI 2.1; 16.6] ng/ml.
Conclusion. All 78 observed children with MIS-C had a moderate and severe course of the disease. 77 children were successfully cured. One of the patients died. He was admitted to the hospital with signs of shock, severe hypotension, cardiovascular and respiratory insufficiency and had concomitant endocrine pathology. According to the pathomorphological conclusion, he also had signs of congenital cardiovascular pathology.
Keywords: coronavirus disease 2019, children, multisystem inflammatory syndrome, epidemiology of COVID-19, SARS-CoV-2, Wuhan, Delta, Alpha, Omicron

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Течение мультисистемного воспалительного синдрома у детей в Республике Беларусь в зависимости от возраста

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Резюме

Введение. Весной 2020 г. учреждения здравоохранения многих стран мира в срочном порядке объявили о редком гиперинфекционном заболевании у детей, предположительно являющимся постинфекционным иммунным ответом на COVID-19. Центры по контролю и профилактике заболеваний (CDC) (США) и ВОЗ назвали заболевание мультисистемным воспалительным синдромом (MIS-C) у детей, связанным с COVID-19.
Цель. Изучение клинико-лабораторных особенностей мультисистемного воспалительного синдрома у детей в зависимости от возраста.
Материалы и методы. С мая 2020 г. по март 2023 г. в Городской детской инфекционной клинической больнице г. Минска (Республика Беларусь) пролечено 78 детей с диагнозом «мультисистемный воспалительный синдром» (MIS-C), ассоциированный с COVID-19. Диагноз устанавливался согласно критериям CDC/WHO 2020 и 2023 гг. Это исследование было одобрено комитетом по этике, и родители детей подписали информированное согласие на участие.
Результаты. Распределение по возрасту заболевших детей имело некоторые особенности в периоды циркуляции вариантов SARS-CoV-2. Во время циркуляции «Ухань» MIS-C 67% заболевших детей были в возрасте 14 лет и старше, а в период циркуляции «Омикрон» 44% имели возраст до 3 лет. Фенотип MIS-C, подобный полной и неполной форме болезни Кавасаки (БК), диагностирован у 62 (79%) пациентов. При поступлении в стационар 67 (86%) детей имели фебрильную температуру. Как правило, сыпь развивалась на 2–4-й день от начала заболевания и наблюдалась

у 64 (82%) детей, при этом чаще регистрировалась у детей старше 3 лет – 50 (64%). Поражения слизистых встречались в виде склерита в группе детей 3–7 лет – 86% пациентов, а хейлит в группе детей 1–3 лет – 85%. Дисфункцию желудочно-кишечного тракта имели 49 (63%) детей независимо от возраста. Только 22 (28%) пациента имели неврологические нарушения, которые в 43% случаев регистрировались в возрасте 1–3 года. Лимфаденопатия развилась у 37% детей, проявлялась увеличенными мезентериальными и шейными лимфатическими узлами, чаще встречалась в двух возрастных группах – 3–7 лет и 7–14 лет у 45 и 41% соответственно. По данным рентгенографии / компьютерной томографии органов грудной клетки у 33 (42%) детей регистрировались интерстициальные изменения в легких или пневмония. Поражение сердечно-сосудистой системы проявлялось снижением сердечного индекса у 20 (26%) пациентов и статистически значимо чаще встречалось у детей старшей возрастной группы (0–3 года – 0; 3–7 лет – 3 (14%); 7–14 лет – 10 (27%) и 14–18 лет – 7 (58%) (p-value 0,03)). Миокардит выявлен у 29 (37%) детей, одинаково часто в исследуемых группах, перикардит (с минимальным количеством жидкости) – у 20 (26%) детей. По результатам общего анализа крови наиболее часто определяли нейтрофилез – у 51 (65%) пациента, из них в группе детей 0–3 года – у 6 (86%). Лимфоцитопения была выявлена у 52 (67%) пациентов, чаще наблюдалась в возрастной группе 7–14 лет – 29 (78%) (p-value 0,01), анемия чаще встречалась в группе детей 3–7 лет – у 17 (77%) (p-value 0,06). Тромбоцитопения выявлена у 22 (28%) детей и не зависела от возраста. Повышение показателя скорости оседания эритроцитов (СОЭ) чаще встречалось в возрастной группе детей 14–18 лет – у 10 (83%). Острофазовые маркеры воспаления, такие как С-реактивный белок (СРБ) и прокальцитонин (ПКТ), были повышены у 99% детей. В старших группах СРБ был выше по сравнению с младшими (p-value 0,01). ПКТ был выше в группе детей 0–3 лет – 8,4 (95% ДИ 2,1; 16,6) нг/мл.

Заключение. Все 78 наблюдаемых детей с MIS-C имели среднетяжелое и тяжелое течение заболевания. Один пациент, поступивший в стационар с признаками шока, выраженной гипотензией, сердечно-сосудистой и дыхательной недостаточностью и сопутствующей эндокринной патологией, умер, остальные выписаны с выздоровлением. По данным патоморфологического заключения он имел также признаки врожденной патологии со стороны сердечно-сосудистой системы.

Ключевые слова: коронавирусная инфекция 2019, мультисистемный воспалительный синдром, эпидемиология COVID-19, SARS-CoV-2, Ухань, Дельта, Альфа, Омикрон

■ INTRODUCTION

In the spring of 2020, public health agencies around the world promptly issued warnings about a rare hyperinfectious disease in children, presumably a post-infectious immune response to COVID-19, using slightly different diagnostic criteria and nomenclature. The CDC Infection Control Center (USA) and WHO have named the disease multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. MIS-C is a new phenomenon reported worldwide and is temporarily associated with COVID-19. The frequency of MIS-C in children is estimated to be less than 1% in patients with confirmed COVID-19 infection. However, the epidemiology of MIS-C may change due to the ongoing wave-like spread of Omicron variants [1]. Some data suggest that MIS-C has

become less common and less serious in the Omicron variant compared to earlier variants [2–7]. According to researchers MIS-C cases in young people infected with SARS-CoV-2 were 0.4–5.5/100 000 [8]. The reported cases of the disease in children of Asian origin are similar or slightly more common than in Caucasians. This contrasts with a particularly high incidence of Kawasaki disease (KD) in children of Asian origin [9]. Current evidence suggests that vaccination against COVID-19 is rarely associated with the development of MIS-C and can protect children from it. It is still difficult to explain why some children develop MIS-C after infection with SARS-CoV-2, while others do not. It is possible that individual host factors are responsible for the abnormal inflammatory response in MIS-C. MIS-C is a violation of the regulation of autoimmune-mediated disease in genetically susceptible patients who underwent COVID-19 with an interval of 2–6 weeks [8].

At the end of the pandemic, in January 2023, the CDC published new MIS-C criteria for determining the case – fever of any duration is sufficient to meet this criterion, while previously fever lasting ≥24 hours was taken into account [10]. The criterion of systemic inflammation now corresponds only the level of CRP ≥3 mg /dl, however other markers of the acute phase are not. MIS-C is now found in ≥ 2 out of 5 organ systems, instead of ≥2 out of 7, since the categories of kidneys, respiratory organs and neurology are excluded, and the category of the heart is now divided into two criteria: (1) shock and (2) heart damage, which is determined by a low ventricular ejection fraction (≤55%), coronary artery abnormalities or elevated troponin levels. The dermatological category currently includes mucosal lesions, including rashes, inflammation of the oral mucosa, injections into the conjunctiva, or limb injuries. These criteria strongly resemble the classic symptoms of KD, but without unilateral lymphadenopathy. The defeat of the gastrointestinal tract is now manifested by abdominal pain, vomiting or diarrhea. Finally, the hematological examination was simplified, since the presence of thrombocytopenia (<150,000 cells/ml) or a low absolute number of lymphocytes (<1000 cells/ml) remains. Age <21 years, a serious illness requiring hospitalization, and the absence of a more likely alternative diagnosis remain criteria for the incorrect determination of the case (Table 1).

Table 1
World Health Organization case definition (All 6 criteria must be meat)

1	Age 0 to 19 years
2	Fever for >3 days
3	Clinical signs of multisystem involvement (at least 2 of the following): – Rash, bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs (oral, hands, or feet). – Hypotension or shock. – Cardiac dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin/BNP). – Evidence of coagulopathy (prolonged PT or PTT; elevated D-dimer). – Acute gastrointestinal symptoms (diarrhea, vomiting, or abdominal pain)
4	Elevated markers of inflammation (eg, ESR, CRP, or procalcitonin)
5	No other obvious microbial cause of inflammation, including bacterial sepsis and staphylococcal/ streptococcal toxic shock syndromes
6	Evidence of SARS-CoV-2 infection Any of the following: – Positive SARS-CoV-2 RT-PCR. – Positive serology. – Positive antigen test. – Contact with an individual with COVID-19

Laboratory criteria for confirmed cases of MIS-C require positive tests: by reverse transcription PCR (RT-PCR) for the presence of SARS-CoV-2 RNA or the determination of a specific antigen or the determination of IgG antibodies against SARS-CoV-2 within 60 days after the disease. The definition of a probable case of MIS-C corresponds to an epidemiological relationship, interpreted as close contact with a probable or confirmed case of COVID-19 within 60 days after the disease in addition to the required clinical criteria [8].

■ PURPOSE OF THE STUDY

To study the clinical and laboratory features of multisystem inflammatory syndrome in children, depending on the age, who were on inpatient treatment.

■ MATERIALS AND METHODS

78 children with diagnosis "multisystem inflammatory syndrome in children" (MIS-C) associated with COVID-19 were observed in the City Children's Infectious Clinical Hospital of Minsk, Republic of Belarus from May 2020 to March 2023.

This research has been approved by the Hospital Ethics Committee. All parents signed an informed consent to the inclusion of patients in the research. In the course of this research, the principles set out in the Helsinki Declaration (ethical considerations) were observed.

Inclusion and exclusion criteria: participants who met the CDC case definition parameters for MIS-C and had multisystem and hyperinflammatory conditions were considered for inclusion in the research. These participants had signs, symptoms and high laboratory indicators.

Seventy-eight children were observed with the diagnosis of "Multisystem inflammatory syndrome in children" (MIS-C) associated with COVID-19. The diagnosis was established according to the 2020, 2023 criteria of CDC/WHO [8]. There was no significant concomitant pathology in the observed cohort.

The cohort of research participants was divided into 4 age groups: 0–3 years – early age; 3–7 years – preschool age; 7–14 years – school age; 14–18 years – puberty age.

Upon admission to the hospital, patients were excluded from full or incomplete KD and toxic shock syndrome (TSS). The following studies were carried out: general blood test with platelet count and white cell formula, erythrocyte sedimentation rate (ESR); a biochemical study with determination of C-reactive protein (CRP), urea, creatinine, liver functional tests (AlAT, AsAT); lactate dehydrogenase (LDH), ferritin, creatinine phosphokinase (CPK and CPK MB), protein, albumin, procalcitonin (PCT); coagulogram (prothrombin time, international normalized ratio, activated partial thromboplastin time); BNP: brain natriuretic peptide; N-terminal pro-BNP (NT-pro-BNP); chest radiography; electrocardiogram (ECG).

Virological examination for coronavirus infection included determination of SARS-CoV-2 RNA by polymerase chain reaction (PCR); determination of specific antibodies of immunoglobulin M (IgM) and class G (IgG) to SARS-CoV-2 qualitatively and quantitatively in enzyme immunoassay (ELISA). PCR and ELISA methods were also used to exclude Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Parvovirus B19, Enterovirus infection and Respiratory viruses. Testing for other pathogenic microorganisms was carried out by generally accepted bacteriological methods. The clinical material for these studies was biological material from the upper respiratory tract, blood, blood serum, feces.

Statistical methods of result processing

At first, the analysis of compliance of the kind of distribution of quantitative indicators was carried out with the law of normal distribution. It was performed using the Shapiro-Wilk criterion. Based on the results of the preliminary analysis, nonparametric methods of descriptive statistics were used in the calculations.

Quantitative indicators of the study are represented by median and quartiles in the form of median [95% CI]. Comparison of quantitative indicators between three groups was carried out according to the Kruskal – Wallis criterion.

Qualitative indicators are represented by frequencies and percentages in the group. The chi-square criterion was used in the study of conjugacy tables. If chi-square criterion assumption was violated, the exact Fisher criterion had been used.

All calculations were carried out in the R Project for Statistical Computing, version 4.1. The results of the analysis were considered statistically significant if $p<0.05$.

■ RESULTS

In the anamnesis of children with MIS-C, 24 (31%) parents noted a case of COVID-19 infection in the family about a month before the development of symptoms. However, other 54 (69%) children had COVID-19 infection in an asymptomatic form. Average time interval from the onset of symptoms to hospitalization in the 0–3 years age group was 3 [95% CI 1; 5] days; in the group of children aged 7–14 years was 4 [95% CI 3; 5] days (p-value 0.298) (Fig. 1).

In our research the onset of symptoms in MIS-C children was 2–6 weeks from the first signs of acute infection to the appearance of typical symptoms of the disease, which is consistent with data from a number of other studies [9, 11]. However, some authors have reported rare cases of MIS-C occurring more than 6 weeks after acute SARS-CoV-2 infection [12]. The average age of children diagnosed with MIS-C in our research was 8.4±4.3 years, which is also consistent, for example, with the results of a research conducted in the USA, where the age of patients was 9 [95% CI 5–13] years [13]. According to world studies, most cases of MIS-C were observed in older children (≥5 years) and adolescents [2, 9, 11, 14].

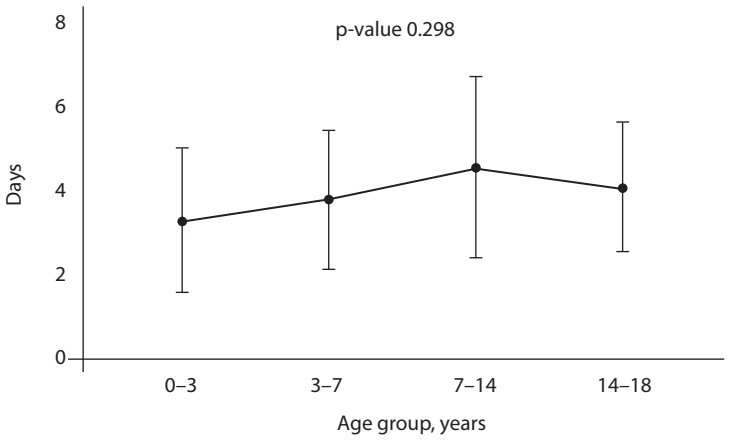

Fig. 1. Duration of the disease from the onset of the disease to hospitalization

In the age groups in our research, cohorts of children aged 3–7 years – 22 (28%) and 7–14 years – 37 (47%) children prevailed.

According to the gender structure, boys predominated in all groups regardless of age – 53 (68%) children (p-value 0.932). In the research of scientists from the USA were differences in gender and age of the patients: the ratio of boys and girls was approximately 1:1 in patients aged 0 to 4 years and gradually increased for subsequent age categories to 2:1 for patients aged 18 to 20 years [13]. In a retrospective review of pediatric patients with MIS-C admitted to Moshan Stanley Children's Hospital in New York, the median age of patients with MIS-C was 9.0±5 years and there were no obvious differences by gender (51.1% male, 48.9% female) [14]. In a research involving 783 patients with MIS-C in the period from March to June 2020, 55% were men (n=435) [14].

The body mass index was calculated by program «WHO Anthro», these standards were developed using data collected in the World Health Organization Multicentre Growth Reference Study. The majority of children in our research 44 (56%) had a normal body mass index (BMI) ≤5 and ≥ 85, recorded equally often in all children regardless of age 4 (57%), 11 (50%), 22 (59%) and 7 (58%), respectively. Body weight deficiency was more often observed in children in the 3 to 7 years age group– 8 (36%). Older groups of children had excess body weight: in 7 to 14 years age group – 8 (22%), in 14 to 18 years – 4 (34%). However, no statistical difference was revealed (Table 2).

According to the ways of admission to our clinic, children transferred from other hospitals prevailed – 37 (47%), less often children were taken by ambulance – 22 (28%), 13 (17%) children independently applied to the emergency department and less often patients were referred by pediatricians of children's polyclinics – 6 (8%) (Table 2). In most

Table 2
Clinical performance in children with MIS-C depending on age

Indicator	Age groups, n (%)					p-value
	Total (n=78)	0–3 years (n=7)	3–7 years (n=22)	7–14 years (n=37)	14–18 years (n=12)	
Sex, n (%)						**0.93**
boys	53 (68)	5 (71)	16 (73)	24 (65)	8 (67)	
girls	25 (32)	2 (29)	6 (27)	13 (35)	4 (33)	
BMI, percentile, n (%):						**0.51**
≤5	17 (22)	1 (14)	8 (36)	7 (19)	1 (8)	
5–85	44 (56)	4 (57)	11 (50)	22 (59)	7 (58)	
≥85	17 (22)	2 (29)	3 (14)	8 (22)	4 (34)	
Income structure, n (%):						**0.23**
transferred from another hospital	37 (47)	2 (29)	11 (50)	17 (46)	7 (58)	
ambulance	22 (28)	3 (42)	3 (14)	13 (35)	3 (25)	
applied to the emergency room on their own	13 (17)	–	6 (27)	5 (14)	2 (17)	
referred from a Child Health Clinic	6 (8)	2 (29)	2 (9)	2 (5)	–	
Hospitalizations, n (%):						**0.91**
intensive care unit	58 (74)	5 (71)	17 (77)	28 (76)	8 (67)	
somatic department	20 (26)	2 (29)	5 (23)	9 (24)	4 (33)	

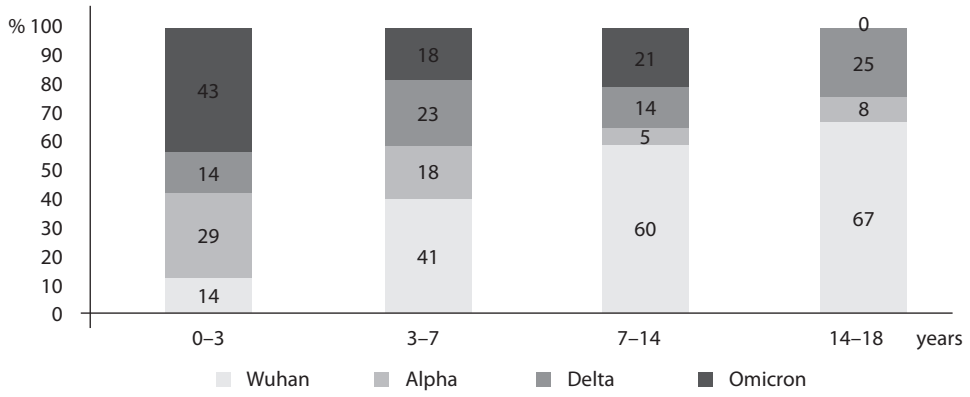

Fig. 2. Frequency of occurrence of MIS-C in various age groups against the background of circulating strains of SARS-CoV-2

cases young children referred for hospitalization by ambulance – 3 (42%), children of the remaining groups transferred from other hospitals – 11 (50%), 17 (46%) and 7 (58%), respectively.

Depending on the circulation of the SARS CoV-2 strain, we noted that MIS-C during the circulation of the Omicron strain became common in the group of children aged 0–3 years – 3 children – (43%) (p-value 0.14), which differs from the circulation period of the Wuhan strain, where MIS-C was mostly observed in the age group of children from 14–18 years – 8 children (67%) (p-value 0.08) (Fig. 2). Although the age of patients during the circulation of the Omicron strain "became younger", no statistical difference was found.

In the majority of 58 children (74%) upon admission, the condition was regarded as "severe" and MIS-C was suspected as the primary diagnosis, which led to hospitalization in the department of Intensive Care. In 20 (26%) children, the condition was assessed as "moderate" and the children were hospitalized in pediatric departments of the hospital, during treatment negative dynamics was observed, which required transfer to the department of Intensive Care. Such cases were mostly registered in children in the age group 14–18 years – 4 (33%) children.

Upon admission to the hospital, all children had hyperthermic syndrome: 67 (86%) children had febrile and only 11 (14%) had subfebrile temperature.

The duration of fever averaged 3 [95% CI 1–4] days. According to a research conducted by American scientists, the average duration of fever was 5 days [95% CI 4; 7] [13]. According to other researchers, fever persists for 3–5 days in most patients, although there are reports of less days. In a research involving 186 patients, 10% had a three-day fever, 12% had a four-day fever, and 78 – 3–5 days or more [15].

Almost all 70 (90%) children had a compensated acid-base state, which averaged 7.41 [95% CI 7.36; 7.43] with glycemic indices averaging 5.95 [95% CI 5.2; 7.1] mmol/l and lactate averaging 1.9 [95% CI 1.4; 2.2] mmol/l. According to the electrolyte composition of the blood, hyponatremia was registered in 21 (27%) children.

In our research, clinically in the majority of children – 62 (79%), the MIS-C phenotype prevailed like complete and incomplete KD, which differs from the data of a research involving 186 patients with MIS-C in 26 states, in which signs similar to KD were

documented in only 74 (40%) [16]. We diagnosed a nonspecific phenotype in the form of signs of shock in 16 (21%) children.

The clinical symptoms of MIS-C, depending on age, are presented in Table 3. The rash was registered in 64 (82%) children, appeared more often on the 2–4 day of the disease. It was large or small-spotted in nature, rarely small-point, hemorrhagic, tend to merge, without typical localization sites.

Rash was more common in children aged 3–7 years – 18 (82%) and 7–14 years – 32 (86%), and at the age of 1–3 years only in 5 (57%), however, we did not find a statistical difference in these groups (p-value 0.7). On the background of therapy, the rash passed on average by 3 [95% CI 1; 5] days.

In other research, on the contrary, a decrease in the number of patients with rash was noted with age. Thus, according to the authors from the USA, the rash was observed in 55.6% of patients. It was most common in the age group from 0 to 4 years (68.1%) with a gradual decrease (from 5 to 9 years – 60.2%, 10–14 years – 49%, 15–17 years – 34% and 18–20 years – 36.4%). Moreover, there was a statistical difference in the frequency of rash occurrence depending on age p<0.0001 [13]. In the Chinese research, skin-mucosal symptoms/signs similar to those observed in KD are more common in children aged 0–5 years than in older patients [8]. The frequency of rash in the cases of MIS-C ranged from 45 to 76% of observations [14, 17, 18].

Mucosal lesions (scleritis, cheilitis) were usually observed in patients on 2–3 days of the disease, and they persisted on average up to 3 [95% CI 1; 6] days. Scleritis was more common in the 3–7 years age group – 19 (86%) children (p-value 0.15), cheilitis (red and swollen lips, strawberry tongue) in the age group 1–3 years – 6 (85%) children (p-value 0.36).

In the research involving 783 patients with MIS-C in the period from March to June 2020, an oral lesion that manifested red or swollen lips was observed in 23 (48.9%) patients, while only 5 (10.6%) had strawberry tongue [17]. It was also found that the lesion of the oral cavity or oropharynx was significantly associated with the presence of systemic rash (p-value 0.04) and conjunctivitis (p-value 0.02) [17]. In our research, sometimes (2% of children) there was a lesion of the genital mucosa, leading to dysuric disorders. In these cases, a urinary catheter was required to relieve urinary retention syndrome.

Table 3
Clinical symptoms of MIS-C in children

Symptoms	Age groups, n (%)					p-value
	Total (n=78)	0–3 years (n=7)	3–7 years (n=22)	7–14 years (n=37)	14–18 years (n=12)	
Rash	64 (82)	5 (57)	18 (82)	32 (86)	9 (75)	0.70
Scleritis	55 (70)	5 (71)	19 (86)	25 (68)	6 (50)	0.15
Heilitis	51 (65)	6 (85)	16 (73)	23 (62)	6 (50)	0.36
Gastrointestinal dysfunction	49 (63)	4 (57)	15 (68)	22 (60)	8 (67)	0.89
Neurological disorders	22 (28)	3 (43)	7 (32)	11 (30)	1 (8)	0.41
Lymphadenopathy	29 (37)	0	10 (45)	15 (41)	4 (33)	0.17
Edematous syndrome	35 (45)	4 (57)	9 (41)	19 (51)	3 (25)	0.38

Gastrointestinal tract dysfunction was manifested by pain syndrome, diarrhea, vomiting, refusal to eat and drink and was observed in our research in 49 (63%) children and was equally common in all observed groups (4 (57%), 15 (68%), 22 (60%), 8 (67%), respectively, (p-value 0.89). The duration of the observed symptoms in our research averaged 2 [95% CI 1; 6] days. In one patient aged 11, abdominal pain was imitated by appendicitis, which required a transfer to a surgical hospital for further treatment. One 16-year-old child developed reactive pancreatitis on the background of MIS-C and abdominal pain persisted until 12 days after the start of therapy.

The frequency of gastrointestinal tract lesions according to a number of research was observed from 60 to 100% [14, 17, 18]. In research from the USA, the frequency of abdominal pain was observed in 1153 (66.5%), while it was less common in children aged 0 to 4 years – in 187 (42%), at the age of 5 to 9 years, it was already found in 475 (80.8%), at the age of 10 to 14 years – in 330 (73.2%) and at the age of 18 to 21 – in 37 (67.3%), while there were statistical differences p<001 [13]. In this research, vomiting was observed in 1114 (64.3%) patients, depending on age: at the age of 0 to 4 years – in 233 (52.4%), from 5 to 9 years of increasing frequency – in 426 (72.4%), from 10 to 14 years – in 305 (67.6%), from 15 to 17 years – in 121 (63.4%) and from 18 to 21 years – in 27 (49.1%), which proved a statistical difference of p<0.001[13]. Diarrhea was observed in 931 (53.7%) and did not depend on the patient's age (218 (49%), 331 (56.3%), 246 (54.5%), 105 (55%) and 30 (54.5%), there was no statistical difference p=0.22 [13]. A retrospective review of a prospective observational multicenter international cohort research of hospitalized children with acute COVID-19 or MIS-C from March 2020 to November 2020, 500 (63.3%) of 789 patients had gastrointestinal tract lesions. Patients with gastrointestinal tract lesions were older (average age 8 years), and 18.2% had concomitant pathology of the gastrointestinal tract. Gastrointestinal symptoms and liver disorders were more common in patients with MIS-C [19]. According to research conducted in the USA in the period from January to December 2020, patients with MIS-C predominantly had gastrointestinal symptoms, such as abdominal pain, vomiting and diarrhea, as well as skin rash and conjunctival hyperemia [13].

Neurological disorders such as irritability, confusion, headache, hyperesthesia, hallucination, photophobia were observed in our research in 22 (28%) children and were more often registered at the age of 1–3 years – 3 (43%) children (p-value 0.41). With the age of children, we observed a decrease in the frequency of central nervous system (CNS) lesions (3–7 years – 7 (32 %), 7–14 years – 11 (30%) and 14–18 years – 1 (8%)), which is presented in Table 3.

The results of the research included 1,695 patients (909 (54%) were male, the average age was 9 [95% CI 2.4; 15.3] years, 365 (22%) had documented neurological disorders [21]. Among patients with neurological damage, 322 (88%) had transient symptoms and survived, 43 (12%) developed life-threatening conditions clinically associated with COVID-19, including severe encephalopathy (n=15), stroke (n=12), central nervous system infection/demyelination (n=8), Guillain-Barres syndrome/variants (n=4) and acute lightning-fast cerebral edema (n=4) [21]. Compared with patients without life-threatening conditions (n=322), patients with life-threatening neurological conditions had a higher ratio of neutrophils to lymphocytes (median 12.2 vs. 4.4). Besides, the higher frequency of D-dimer exceeding 3 micrograms/ml in units of fibrinogen equivalent (21 [49%] vs. 72 [22%]). Of the 43 patients who developed a life-threatening neurological lesion

associated with COVID-19, 17 survivors (40%) had a new neurological deficiency upon discharge from the hospital, and 11 patients (26%) died.

Lymphadenopathy developed in 37% of children in the research and was mainly manifested by enlarged mesenteric and cervical lymph nodes. It was more common in the age groups of 3–7 years and 7–14 years – 45% and 41%, respectively (p-value 0.17). According to the literature, lymphadenopathy in patients with MIS-C occurs with a frequency of 6 to 16% [12, 15, 16, 19]. Edematous syndrome in our research occurred in 35 (45%) children. It was more often registered in the 1–3 years age group – 57% of children. Edematous syndrome was manifested by swelling of the face, hands and feet (Table 3).

According to radiography / computer tomography of the chest organs, 33 (42%) children had lung changes in the form of interstitial changes or pneumonia. 22 (28%) children had signs of 2-nd degree respiratory insufficiency and needed oxygen therapy with an average duration of 3 [95% CI 1; 4] days. We did not find statistically significant differences in respiratory system lesions in the age groups. According to ultrasound of pleural cavities, 23 (30%) children had an effusion. 4 (5%) children with MIS-C needed prolonged artificial ventilation.

In the research involving 783 cases with MIS-C between March and June 2020, cough and respiratory failure were reported in 4.5% and 9.6% of cases, respectively. In 41% of cases, changes in the lungs were detected during chest imaging. The severity of the disease was high: 68% of cases required hospitalization in the intensive care unit; 63% needed inotropic support; 244/783 (28%) cases needed some form of respiratory support (138 with artificial lung ventilation), and 31 required extracorporeal membrane oxygenation [17].

The damage of the cardiovascular system in the research was manifested by a decrease in the cardiac index in 20 (26%) and was statistically significantly more common in children of the older age group (0–3 years – 0, 3 to 7 years – 3 (14%), 7 to 14 years – 10 (27%) and from 14 to 18 years – 7 (58%), p-value 0.03). Dilatation of the left ventricle was registered in 43 (55%) children and was more common in children of the age group 3–7 years – 15 (68%). Dilatation of the right ventricle was present in 5 (6%) children and was more common in the age group 7–14 years – 4 (11%). However, the data is not statistically significant (Table 4). Dilatation of both coronary arteries (CA) was more often registered in comparison to isolated right or left CA. It was found in 16 (20%) children. The right CA – in 11 (14%) children, the left – in 2 (3%) children. Myocarditis was found in 29 (37%) children, pericarditis (with a minimum amount of fluid) – in 20 (26%) children, no statistical differences were found by age groups (p-value 0.73 and 0.67, respectively).

Heart damage is common in MIS-C. In several large studies, approximately 30–40% of children had a decrease in LV function and 8–24% had anomalies of the coronary arteries (CA) [20, 22, 23]. These studies included patients with both severe MIS-C and milder cases. In a number of cases involving only patients with severe diseases, significantly higher rates of LV function decline (approximately 50 to 60%) and CA anomalies (approximately 20 to 50%) were reported [22, 23].

In the research involving 186 patients with MIS-C in 26 states, damage to the cardiovascular system was observed in 149 (80%) and respiratory system in 131 (70%) [16]. The average duration of hospitalization of children in this research was 7 [4; 10] days, 148 patients (80%) received intensive therapy, 37 (20%) – artificial ventilation, 90 (48%) – vasoactive support and 4 (2%) had a fatal outcome [20]. Coronary artery aneurysms

Table 4
Indicators of the cardiovascular system

Indicator	Age groups, n (%)					p-value
	Total (n=78)	0–3 years (n=7)	3–7 years (n=22)	7–14 years (n=37)	14–18 years (n=12)	
Cardiac index l/min/m^2 – reduced – normal – increased	 20 (26) 39 (50) 19 (24)	 0 5 (71) 2 (28)	 3 (14) 8 (36) 11 (50)	 10 (27) 22 (59) 5 (14)	 7 (58) 4 (33) 1 (8)	0.03
Dilatation – right ventricle – left ventricle	 5 (6) 43 (55)	 0 3 (43)	 0 15 (68)	 4 (11) 21 (56)	 1 (8) 4 (33)	 0.23 0.35
Dilatation of CA – left – right – both dilatation	29 (37) 2 (3) 11 (14) 16 (20)	2 (29)	11 (50)	11(30)	5 (41)	0.43
Myocarditis	29 (37)	2 (29)	9 (40)	15 (41)	3 (25)	0.73
Pericarditis	20 (26)	1 (14)	7 (32)	8 (21)	4 (33)	0.67

(z-score ≥2.5) were documented in 15 (8%) patients [22]. In another research involving 1,116 patients (mean age 9.7 years; 45% women), 539 (48%) were diagnosed with MIS-C and 577 (52%) with COVID-19 [19]. Compared with patients with COVID-19, patients with MIS-C were more likely to be aged 6 to 12 years (40.8% vs. 19.4%; absolute difference in risk [RD] – 21.4% [95% CI 16.1; 26.7]; aRR – 1.51 [95% CI 1.33; 1.72] compared to 0–5 years). Compared with patients with COVID-19, patients with MIS-C were more likely to have cardiorespiratory system damage (56.0% vs. 8.8%; RD, 47.2% [95% CI 42.4; 52.0]; aRR, 2.99 [95% CI 2.55; 3.50] compared with respiratory damage), cardiovascular system without respiratory damage (10.6% vs. 2.9%; RD, 7.7% [95% CI 4.7; 10.6]; HR 2.49 [95% CI 2.05; 3.02] in depending on the lesion of the respiratory organs) and skin-mucous membranes without damage to the cardiorespiratory system (7.1% vs. 2.3%; RD 4.8% [95% CI 2.3; 7.3]; HR 2.29 [95% CI 1.84;2.85] depending on the lesion of the respiratory organs) [16]. A total of 398 patients (73.8%) with MIS-C and 253 (43.8%) with COVID-19 were admitted to the intensive care unit, and 10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19 died during hospitalization. Among MIS-C patients with reduced left ventricular systolic function (172/503, 34.2%) and coronary artery aneurysm (57/424, 13.4%), an estimated 91.0% [95% CI 86.0; 94.7] and 79.1% [95% CI 67.1; 89.1], respectively, normalized within 30 days [20]. Cardiac manifestations are frequent, including myocardial and coronary artery damage, and they need to be carefully identified and monitored over time. In a number of studies, heart damage was detected in a high proportion of these patients, including ventricular dysfunction, coronary artery dilation or aneurysm and arrhythmias, which includes cardiological support, immunomodulatory agents and anticoagulants and requires long-term monitoring due to an unclear prognosis and risk of progression of cardiac manifestations [23]. The results of the research, which included 1,080 patients who met the CDC's case definition for MIS-C, included patients between March 11 and October 10, 2020. Hospitalization in the intensive care unit was more likely in patients aged 6–12 years (adjusted odds ratio of 1.9 [95% CI 1.4; 2.6]) and patients aged 13–20 years (2.6 [95% CI 1.8; 3.8]), compared with patients aged 0–5 years and more often in non-Hispanic African-Americans patients compared to non-Hispanic Caucasians

(1.6 [95% CI 1.0–2.4]). Admission to the intensive care unit was more likely for patients with shortness of breath (1.9 [95% CI 1.2–2.9]), abdominal pain (1.7 [95% CI 1.2–2.7]), and patients with elevated concentrations of C-reactive protein, troponin, ferritin, D-dimer, cerebral natriuretic peptide (BNP), N-terminal BNP type pro B or interleukin-6, or a reduced number of platelets or lymphocytes. Similar associations were found with decreased cardiac function, shock and myocarditis. Anomalies of the coronary arteries were more common in male patients (1.5 [95% CI 1.1–2.1]) than in female patients and patients with mucosal lesions (2.2 [95% CI 1.3–3.5]) or injection into the conjunctiva (2.3 [95% CI 1.4–3.7]) [24]. According to American scientific research, most patients with MIS-C developed hypotension or shock, and about 60% were hospitalized in the intensive care unit. Approximately 30% of patients reported myocarditis, cardiac dysfunction, or dilation of the coronary arteries [13].

According to electrocardiography in the research myocardial repolarization disorders occurred in 35 (45%) children, there were no statistically significant differences in the age groups (p-value 0.29). AV blockade of the 1-st degree was recorded in 6 (8%) children, sinus bradycardia in 16 (20%) children.

A decrease in diuresis to oliguria occurred in 9 (12%) children and more often was registered in children of the older age group 0 (0%), 1 (5%), 4 (11%) and 4 (33%), respectively, revealed a statistical difference (p-value 0.06). According to the literature, acute kidney injury is observed from 8 to 52%, while most cases were characterized by mild damage [16, 20, 23]. Prevention was registered in the research in 50 (65%) children, there were no statistically significant differences in the age group (p-value 0.61). On average, the protein content in urine was 0.28 [95% CI 0.19; 0.37] g/l. According to ultrasound linear dimensions were found in 31 (40%) children. No statistically significant indicator was detected in the adult group (p-value 0.09). According to biochemical blood analysis, elevated urea was observed in 9 (12%) children (by age group: 0 (0%), 2 (9%), 5 (14%), 2 (12%), p-value 0.68). 39 (50%) children had increased creatinine (by age groups 4 (57%), 13 (59%), 18 (47%), 33 (33%), p-value 0.53).

According to the results of a general blood test in 40 (51%) children, leukocytes were within the age norm, in most cases (51 (65%) neutrophilia was detected, which more often occurred in the group of patients "group 0–3 years" – in 6 (86%) (no statistical difference was found p-value 0.82) and lymphocytopenia – in 52 (67%), which was more often observed in the age group 7–14 years – 29 (78%), which is statistically significant (p-value 0.01). Anemia was more common in the group of 3–7 years – 17 (77%) children, which is a statistically significant p-value of 0.06. Thrombocytopenia was detected in 22 (28%) children, no statistically significant differences were found in the groups. Acceleration of erythrocyte sedimentation rate (ESR) was more common in the age group of 14–18 years – in 10 (83%) children (Table 5).

According to coagulogram, activated partial thromboplastin time (APTT), prothrombin index, the international normalized time in most children were within the normal range – 89%, 99% and 88%, respectively. D-dimmer were also elevated in 86% of children and the average indicator was 1397 [95%CI 1139–1655] ng/ml. No statistically significant changes were detected in the groups (p-value 0.79). Fibrinogen A in 86% of children was elevated and averaged 8.5 [95% CI 8; 12] g/l, in the older age groups fibrinogen A was higher compared to the younger groups and amounted to 6.3; 7.8; 9.9; 10.4 g/l, respectively (p-value 0.03) (Fig. 3).

Table 5
Indicators of the general blood analysis at admission

Indicator	Age groups, n (%)					p-value
	Total (n=78)	0–3 years (n=7)	3–7 years (n=22)	7–14 years (n=37)	14–18 years (n=12)	
White blood cells:						
– reduced	7 (9)	0	3 (13)	2 (5)	2 (17)	0.38
– norm	40 (51)	3 (43)	14 (64)	17 (46)	6 (50)	
– increased	31 (40)	4 (57)	5 (23)	18 (49)	4 (33)	
Neutrophils:						
– reduced	2 (3)	0	1 (5)	1 (3)	0	0.82
– norm	25 (32)	1 (14)	7 (32)	14 (38)	3 (25)	
– increased	51 (65)	6 (86)	14 (64)	22 (57)	9 (75)	
Lymphocytes:						
– reduced	52 (67)	3 (43)	15 (68)	29 (78)	5 (42)	0.01
– norm	25 (32)	3 (43)	7 (32)	8 (22)	7 (58)	
– increased	1 (1)	1 (14)	0	0	0	
Hemoglobin:						
– reduced	42 (54)	4 (57)	17 (77)	16 (43)	5 (42)	0.06
– norm	36 (46)	3 (43)	5 (23)	21 (57)	7 (58)	
– increased	0	0	0	0	0	
Platelets:						
– reduced	22 (28)	3 (43)	5 (23)	9 (24)	5 (42)	0.56
– norm	55 (71)	4 (57)	16 (72)	28 (76)	7 (58)	
– increased	1 (1)	0	1 (5)	0	0	
ESR:						
– reduced	0	0	0	0	0	0.21
– norm	20 (26)	4 (57)	6 (27)	8 (22)	2 (17)	
– increased	58 (74)	3 (43)	16 (73)	29 (78)	10 (83)	

According to biochemical blood analysis, there were no changes in liver enzymes, bilirubin. Though, acute-phase markers of inflammation such as CRP and PCT were elevated in 99% of children (Fig. 4). On average, the level of CRP was 156 [95% CI 134; 178] mg/l, in the older groups, CRP was higher compared to the younger ones (p-value

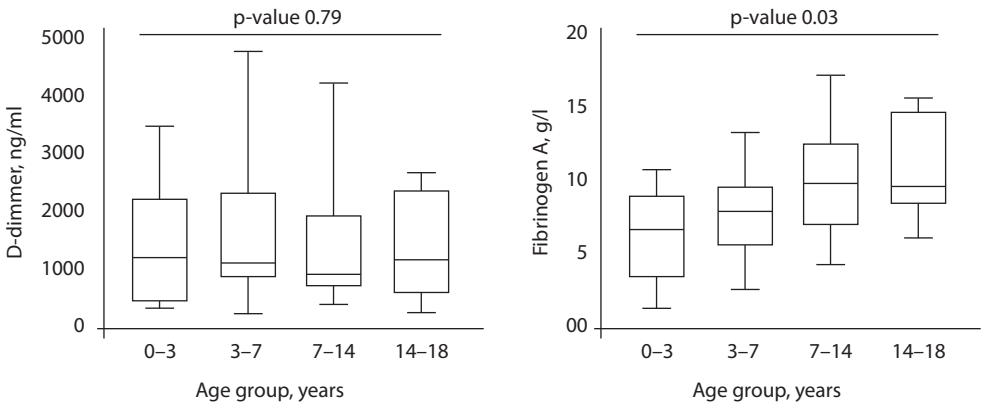

Fig. 3. Changes in the level of D-dimers and fibrinogen in children with MIS-C depending on age

0.01). PCT was higher in the 0–3 year group – 8.4 [95% CI 2.1; 16.6] ng/ml, no statistically significant changes were detected in the groups (p-value 0.96).

According to the literature data, children with MIS-C have the following changes from the general blood count of lymphocytopenia – from 80 to 95%, neutrophilia – from 68 to 90%, mild anemia – 70% and thrombocytopenia – from 31 to 80% [16, 21]. According to research involving 783 patients with MIS-C in the period from March to June 2020, neutrophilia was observed in 345/418 (83%) cases and a high level of CRP in 587/626 (94%) [19]. In research involving 186 patients with MIS-C in 26 states, hematological changes were observed in 142 (76%) patients and the majority of patients (171 [92%]) had an increase in at least four biomarkers indicating inflammation [16]. Patients with MIS-C had a higher neutrophil-to-lymphocyte ratio (median 6.4 vs. 2.7, p<0.001), a higher level of C-reactive protein (median 152 mg/l vs. 33 mg/L; p<0.001) and a lower platelet count (<150×10^3 cells/ml [212/523 (41%) vs. 84/486 (17%), p<0.001]) [20].

The length of stay in the hospital of children of different age groups did not statistically differ (p-value 0.63 – intensive care unit; p-value 0.69 – hospital) and was 5 [95% CI 4; 7] days in the intensive care unit and 13 [95% CI 11; 17] days in the hospital (Fig. 5).

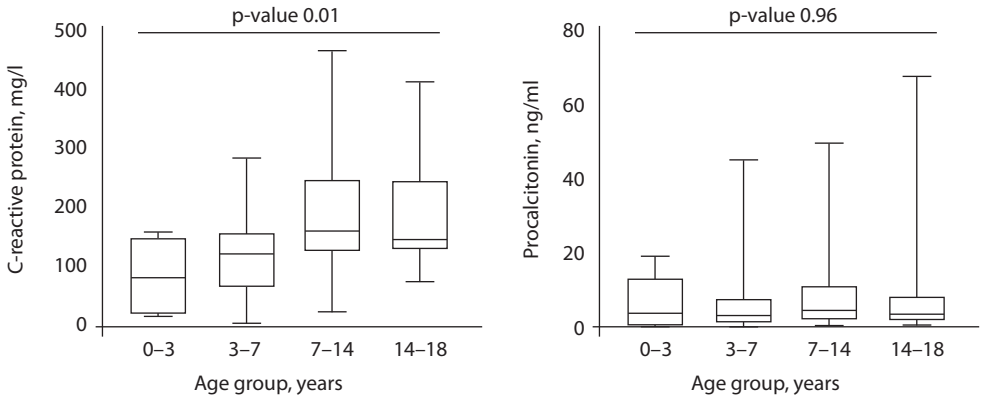

Fig. 4. Changes in acute phase parameters in children with MIS-C depending on age

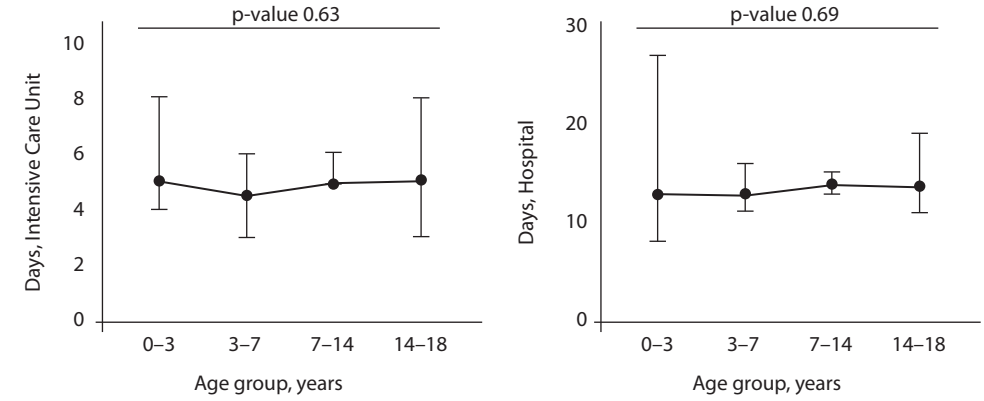

Fig. 5. Duration of hospitalization of children with MIS-C, depending on age

The fatal outcome in our research was observed in 1 (1.2%) adolescent patient during the first wave. He was admitted to the hospital with signs of shock, severe hypotension, cardiovascular and respiratory insufficiency and concomitant endocrine pathology. The autopsy revealed signs of congenital cardiovascular pathology. According to Chinese scientific research, the registered mortality rate varied from 1% to 3%, which is slightly higher than in KD [8]. Despite the fact that concomitant diseases were associated with higher mortality in patients with COVID-19, most patients with fatal cases of MIS-C did not have them. A number of scientific research have shown a clear link between mortality and age [13]. 24 (1.4%) of 1733 patients died in the follow-up, 6 (1.3%) of them aged 0–4 years, 3 (0.5%) from 5 to 9 years, 4 (0.9%) from 10 to 14 years, 5 (2.6%) from 15 to 17 years) children and young adults aged 18 to 21 – 6 (10.9%) people, these differences were statistically significant $p<0.01$ [13].

■ CONCLUSION

The age distribution of sick children had some peculiarities during the periods of circulation of SARS-CoV-2 variants. During the Wuhan MIS-C circulation, 67% of the sick children were aged 14 years and older, and during the Omicron circulation, 44% were under 3 years old. The MIS-C phenotype, similar to complete and incomplete CD, was diagnosed in 62 (79%) patients.

The main clinical and laboratory manifestations of MIS-C was febrile temperature in 62 (86%) children upon admission to the hospital. A rash that developed on 2–4 days of illness and was observed in 64 (82%) children, while it was more often registered in children older than 3 years – 50 (64%). Mucosal lesions occurred in the form of scleritis in the 3–7 years age group – 86% of patients, and cheilitis in the 1–3 years age group – in 85% of children. 49 (63%) children had gastrointestinal dysfunction, regardless of age. Only 22 (28%) patients had neurological disorders. Although, 43% of neurological symptoms were registered at the age group of 1–3 years. Lymphadenopathy developed in 37% of children, manifested by enlarged mesenteric and cervical lymph nodes, it`s more common in the age groups of 3–7 years and 7–14 years – 45% and 41%, respectively. According to radiography/ computer tomography of the chest organs, interstitial changes or pneumonia were registered in the lungs of 33 (42%) children.

The defeat of the cardiovascular system was manifested in the decrease in the cardiac index in 20 (26%) patients. It was significantly more frequent in children of the oldest age group (0–3 – not revealed, 3–7 years (14%), 7–14 years – 10 (27%) and 14–18 years – 7 (58%), p-value 0.03. Myocarditis was not age-related, it occurred in 29 (37%) children, pericarditis (with a minimum amount of fluid) – in 20 (26%) children.

According to the results of a general blood test, neutrophilia was most often detected in 51 (65%) patients. In 0–3 years age group neutrophilia was found in 6 children (86%). Lymphocytopenia was detected in 52 (67%) patients, being more often observed in the 7–14 years age group – 29 (78%) (p-value 0.01). Anemia was more common in the 3–7 years age group – 17 (77%) children, (p-value 0.06). Thrombocytopenia was found in 22 (28%) children and was not age–specific. Increase of the rate of erythrocyte sedimentation (ERS) was more common in the 14–18 years age group – 10 (83%) children. Acute-phase markers of inflammation such as CRP and PCT were elevated in 99% of children. In older groups, CRP was higher compared to the younger ones (p-value 0.01). PCT was higher in the 0–3 year group – 8.4 [95% CI 2.1; 16.6] ng/ml.

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