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Original Article

Comparative Analysis of Clinical and Laboratory Data in Children with Multisystem Inflammatory Syndrome Associated with SARS-CoV-2 in the Republic of Kazakhstan

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Abstract. ***Background and Objectives*: Data with more severe mutations of the SARS-CoV-2 virus, compared with the original wild-type strain of COVID-19 disease, were reported worldwide. The study aims to describe the clinical and laboratory manifestations of a multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 in the Republic of Kazakhstan and to compare the severity of the disease depending on the time of the circulating variant of SARS-CoV-2 virus.**

***Material and methods*: A retrospective, multicentre, nationwide study of 89 children with MIS-C who received inpatient treatment from August 1, 2020, to December 1, 2021. The patients were allocated into two groups: 1(2020) - 45 children and 2 (2021) - 44 children. Study periods were characterized by the circulation of different strains of the SARS-CoV-2 virus.**

***Results*: In children with MIS-C in 2021, acute renal failure, disseminated intravascular coagulation syndrome, and shock were statistically more frequently found, which led to fairly common admittance to the intensive care unit. When comparing laboratory data, the children with MIS-C in 2021 had higher values of inflammation markers: ferritin, procalcitonin, erythrocyte sedimentation rate, leukocytes, and neutrophils. Furthermore, these children had a lower level of lymphocytes than children with MIS-C in 2020.**

***Conclusions*: MIS-C is a severe, life-threatening systemic disease characterized by multiple organ damage and important inflammatory changes in laboratory parameters. A more aggressive clinical course of MIS-C in 2021 may be associated with the emergence of new SARS-CoV-2 strains.**

Keywords: Children; MIS-C; Variants of SARS-CoV-2.

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Introduction. Acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which elicits COVID-19, is mild or asymptomatic in children, with a few reported deaths.[1] However, all viruses, including SARS-CoV-2, accumulate mutations over time, affecting their properties, such as the rate of spread and severity of associated symptoms and the effectiveness of vaccines and treatment medication.[2] In late 2020, a new Delta variant of SARS-CoV-2 B.1.617.2 virus emerged, posing an increased risk to public health and rapidly spreading worldwide.[3] In Scotland, a study was conducted on patients with the Delta variant of SARS-CoV-2, showing that patients were younger and had twice the risk of hospitalization than the Alpha variant.[4] The same excessive causality between B.1.617.2 and severe COVID-19 has been found in England[5] and Canadian[6] studies, but the above studies did not analyze data separately among children. According to the latest report from the US Centers for Disease Control and Prevention, the differences in severity and duration of illness between Delta and previous variants in children are unclear; since the number of cases of children in the U.S. has recently increased, the proportion of hospitalized children requiring intensive care has not changed.[7] A study in England examining children infected with the Delta variant of SARS-CoV-2 showed that these children had more clinical symptoms than children infected with the Alpha variant. However, the duration and severity of the disease did not differ when compared.[8]

In the United States, the Centers for Disease Control and Prevention (CDC)[9] and the World Health Organization (WHO)[10] published MIS-C case definition criteria that included childhood age, fever, multiple organ involvement requiring hospitalization, increased inflammatory biomarkers, absence of alternative diagnosis and positive for SARS-CoV-2 infection by PCR and/or serology. However, in the latest and largest U.S. study from the CDC, researchers say there are some shortcomings in diagnosing children with MIS-C. One of which is that the MIS-C case definition is broad, which may lead to the accidental inclusion of patients with a history of COVID-19 suffering from other acute inflammatory diseases such as severe acute COVID-19, Kawasaki disease, toxic shock syndrome, and other serious illnesses.[11] Given the more severe course of COVID-19 in children during the circulation of the Delta variant in 2021, the objective of our study was to compare the clinical and laboratory features of MIS-C in children depending on the circulation of the SARS-CoV-2 strain in the Republic of Kazakhstan.

Materials and Methods. Taking into account the MIS-C case definition criteria published by the CDC and WHO, a clinical protocol was developed for the diagnosis and treatment of COVID-19 and MIS-C in children in Kazakhstan.[12] Using the resources of the Scientific Center of Pediatrics and Pediatric Surgery, a multidisciplinary working group was formed that included experts in various pediatric specialties. In addition, each MIS-C case was entered into a national registry and discussed by an expert group. As a result, each patient in our study met the diagnostic criteria defined by the WHO and CDC for MIS-C.

A retrospective multicentre study was conducted in children with MIS-C associated with SARS-CoV-2 who received inpatient treatment in multidisciplinary children's medical organizations in 17 regions of Kazakhstan. The study enrolled 89 patients (N=89) diagnosed with MIS-C from August 1, 2020, to December 1, 2021. To compare changes in clinical and laboratory data of the children with MIS-C, they were allocated into two groups: Group 1 included the patients who fell ill and received treatment in 2020 (N=45), and Group 2 consisted of patients who fell ill and received treatment in 2021 (N=44). Among the criteria for diagnosing MIS-C, it was considered the epidemiological data (family history, contact with a patient with COVID-19, a history of COVID-19, etc.), test results for SARS-CoV-2 (PCR swab from the throat or nose, the presence of IgM, IgG antibodies for SARS-CoV-2), general clinical laboratory tests (complete blood count, biochemical studies - alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, creatinine, urea), inflammation markers (ferritin, procalcitonin, C-reactive protein (CRP), fibrinogen, D-dimer). Peak values (maximum and minimum) of laboratory test parameters from medical records were entered into the database for statistical processing. In all patients was assessed the frequency of severity of MIS-C clinical manifestations (fever and its duration, changes in the skin and mucous membranes of the oral cavity, lesions of the central nervous system and gastrointestinal tract, respiratory and cardiovascular systems, the acute renal failure, localization of edema and pain syndrome, conjunctivitis, lymphadenitis, shock and disseminated intravascular coagulation syndrome (DIC).

Ethical Statement. This study was approved locally by the ethics committee of Asfendiyarov Kazakh National Medical University (No. 1147).

Statistical analysis. Statistical analysis was performed via the programme StatTech v. 2.4.5.

Quantitative indicators were assessed for compliance with the normal distribution using the Shapiro-Wilk test (with the number of subjects less than 50) or the

Kolmogorov-Smirnov test (with the number of subjects more than 50). Quantitative indicators with a normal distribution were described using arithmetic means (M) and standard deviations (S.D.), 95% confidence interval limits (95% CI).

If a normal distribution is absent, the quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3).

Categorical data were described with absolute values and percentages.

Two groups in terms of a quantitative indicator with a normal distribution, provided that the variances were equal, were compared using Student's t-test.

Two groups in terms of a quantitative indicator, the distribution of which differed from the normal one, were compared using the Mann-Whitney U-test.

The percentages in the analysis of four-field contingency tables were compared using Pearson's chi-square test (for expected phenomena values greater than 10) and Fisher's exact test (for values less than 10).

Results. In the Republic of Kazakhstan (R.K.), from the beginning of the pandemic until December 1, 2021, 972 292 confirmed cases of COVID-19 were recorded, including 90 283 (9.3%) children. Starting in August 2020, the first cases of MIS-C associated with SARS-CoV-2 began to appear in children. In 2020, 7291 children came down with coronavirus infection COVID-19, and in 2021 - 82 986 children. On average, 86% of children had a mild and asymptomatic course of infection, a moderate course was observed in 13% of children, and less than 1% had an infection in a severe and extremely severe form. However, a comparative analysis of the course of COVID-19 in children by year showed that the number of severe forms doubled in 2021, and extremely severe forms of infection and deaths have been recorded (**Table 1**).

According to the branch of the Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring of the "National Center for Public Health" of the Ministry of Health of the Republic of Kazakhstan, a genetic study was conducted across the country by sequencing in 2020 -56, and in 2021, -582 positive for SARS-CoV-2 laboratory samples, respectively. According to the sequencing results in 2020, all 56 samples belonged to low pathogenic variants of SARS-CoV-2 (B.1.1, B.1, B, A.2, and others). On the other hand, sequencing results in 2021 showed 140 (24%) samples were low pathogenic variants, while 264 (45.5%) samples represented the Delta variant and 178 (30.5%) the Alpha variant of SARS-CoV-2 (**Figure 2**). Thus, in 2021 the circulation of mutated Delta and Alpha variants of the SARS-CoV-2 virus prevailed in the Republic of Kazakhstan, which could be associated with a more severe course of COVID-19 in children.

The first cases of MIS-C started to be reported in children in August 2020 in Kazakhstan (**Figure 1**). In 89 children with MIS-C, the median age was six years (Min-10 days; Max-17 years; Interquartile range (IQR) 4-10 years). There were more boys (72%) than girls (28%). In

Table 1. Comparative characteristics of COVID-19 disease in children by years and severity.

Years	Severity					
	Asymptomatic and mild	**Medium - severe**	**Severe**	**Extremely severe**	**Died**	**Total**
2020	6 250 (85.7%)	1 019 (14%)	22 (0.3%)	0	0	7291
2021	71 813 (86.5%)	10 667 (12.8%)	476 (0.6%)	30 (0.04%)	14 (0.02%)	82 986

Statistics according to the Scientific Center of Pediatrics and Pediatric Surgery and the branch of the Scientific and Practical Center for Sanitary and Epidemiological Expertise and Monitoring of the "National Center for Public Health" of the Ministry of Health of the Republic of Kazakhstan.

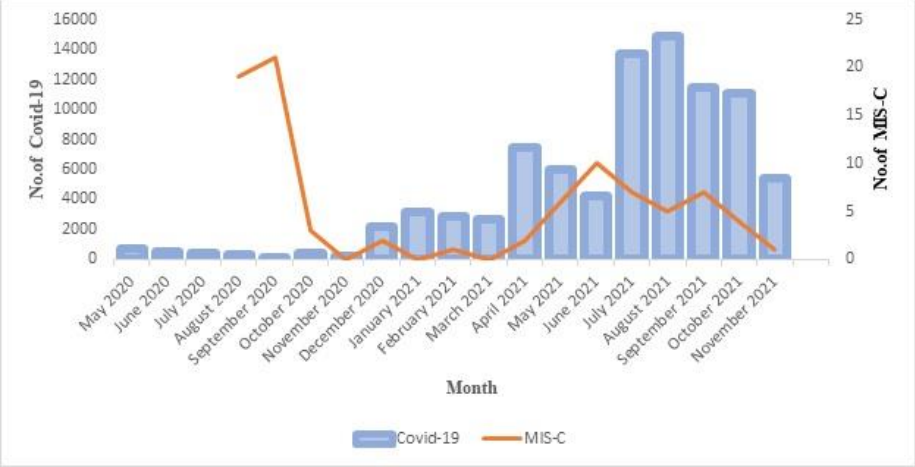

Figure 1. Reported cases of COVID-19 and MIS-C in children in Kazakhstan.

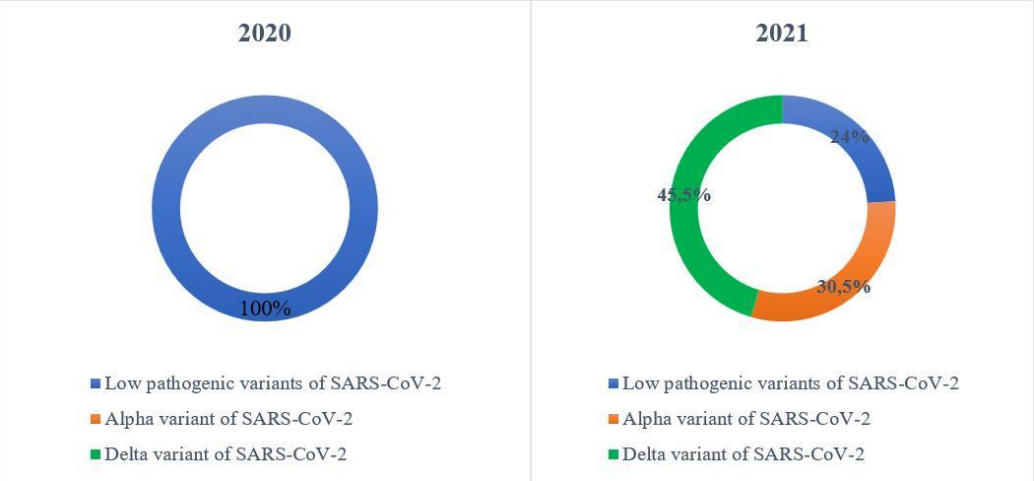

Figure 2. Results of SARS-CoV-2 sequencing by years in the Republic of Kazakhstan

the anamnesis, 36% of children having a history of SARS symptoms had ARVI symptoms (acute respiratory viral infection); in 25% of them, a positive PCR test for SARS-CoV-2 was found. All children had COVID-19 in an asymptomatic, mild, and moderate form. MIS-C developed after Min-2 weeks; Max-12 weeks; Me-6 weeks; IQR 4-6 weeks after a positive PCR test for SARS-CoV-2 or ARVI symptoms. The results of PCR tests for SARS-CoV-2 during hospitalization for MIS-C were positive at 6%; the specific IgG antibodies were in 78%, SARS-CoV-2 IgM antibodies in 14%, total antibodies (IgM and IgG) in 22% of children. 27% of children had an underlying pathology: systemic lupus erythematosus (3.4%), congenital heart defects (10.1%), intrauterine infection (2.2%), obesity (4.5%), cerebral palsy (2.2%), epilepsy (2.2%), protein-energy malnutrition (1.1%), bronchiectasic disease (1.1%).

Children in the first group were more likely to have conjunctivitis (p=0.04, 95% CI: 1.366–20.174) than children in the second group. In the second group, acute renal failure (p=0.037, 95% CI: 1.042–8.828), DIC (p=0.01, 95% CI: 1.366–20.174), shock (p=0.05, 95% CI: 1.02 - 11.721), seizures (p = 0.04) were more common in terms of statistical significance. Furthermore, the children in the second group more often needed treatment in the intensive care unit (ICU) (p = 0.044, 95%, CI: 1.016 - 5.6) than children in the first group, but the length of stay in the ICU and the hospital in both groups did not differ significantly (group 1 - Me five days, IQR 3-7 days; group 2 - Me -7 days, IQR 5-12 days) (**Table 2**).

When analysing laboratory tests, we identified the following statistically significant differences in the complete blood count: the level of leukocytes (p<0.001), neutrophils (p=0.003), and erythrocyte sedimentation rate (ESR) (p=0.04) in children with MIS-C in 2021 were higher than in children in 2020, and lymphocytes were lower (p=0.01) (**Table 2**).

When comparing changes in quantitative indicators of laboratory data, the children with MIS-C cases in 2021 had, on average higher values of ferritin (p=0.02) and procalcitonin (p=0.005) compared to children who came down in 2020. Furthermore, the children with MIS-C in 2021 had higher levels of creatinine (p=0.035) and urea (p=0.011) (**Table 2**).

The following differences were found when analysing the therapy performed in the two groups. The children in the first group were more often prescribed acetylsalicylic acid preparations (p = 0.006, 95% CI: 0.095 - 0.705), compared with children from the second group. In 2021 the children with MIS-C were more likely to need oxygen therapy (p=0.009), transfusion of red blood cells (p=0.014; 95% CI: 1.298–30.805), fresh frozen plasma (p=0.05; 95% CI: 1.02–11.721), dobutamine (p=0.05, 95% CI: 1.02–11.721) and diuretics (p=0.024; 95% CI: 1.112–6.152) (**Table 3**).

At the diagnostic stage, 13 (14.6%) children with MIS-C underwent laparoscopy and appendectomy due to severe pain syndrome; the peritoneal dialysis was determined in 5 (5.6%) children due to the long-term persistence of anuria and an increase in creatinine and urea. In addition, two children (2.5%) underwent a biopsy of the lymph node, and one child (1.2%) underwent resection of a part of the large intestine due to thrombosis of the mesenteric vessels. When comparing these data in the two groups, no statistically significant differences were found (**Table 3**).

Discussion. In this study, we presented the experience of diagnosing and treating children with MIS-C in the Republic of Kazakhstan from August 2020 to December 2021 and compared the severity of MIS-C depending on the time of circulation of different strains of the SARS-CoV-2 virus.

In contrast to the systematic review outcomes conducted by Jun Yasuhara,[13] in which the average age of children with MIS-C was 9.3 years, the average age of children in our study was less. It amounted to 6 years, but higher than in the U.K. cohort (4.6 years).[14] In addition, although previously, the cases of multisystem

Table 2. General characteristics of patients with MIS-C by years.

Parameters	2020	2021	Total	*P- value
Demographics				
Age (Me; IQR)	6 (4-10)	6 (4-10)	6 (4-10)	0.696
Gender (boys/girls)	35/10 (78%/22%)	29/15 (66%/44%)	64/25 (72%/28%)	0.213
Underlying diseases	13 (28.9%)	11 (25%)	24 (27%)	0.879
Incidence of clinical manifestations				
Fever	45 (100%)	43 (97.7%)	88 (98,9%)	0.494
Duration of fever (in days) Me (IQR)	7 (5-9)	7 (5-8)	7 (5-9)	0.431
Rash	36 (80%)	37 (77%)	70 (78.7%)	0.8
Hyperaemia of the palms and feet	16 (35.6%)	8(18.2%)	24 (27%)	0.065
Neurological symptoms	18 (40%)	23 (52.3%)	21 (46.1%)	0.246
Headache	14 (31%)	12 (27.3%)	26 (29.2%)	0.691
Positive meningeal symptoms	3 (6.7%)	1 (2.3%)	4 (4.5%)	0.616
Doubtful meningeal symptoms	4 (8.9%)	7 (15.9%)	11(12.4%)	0.353
Aseptic meningitis	4 (8.9%)	2 (4.5%)	6 (6.7%)	0.5
Hyperesthesia	7 (15.6%)	5 (11.4%)	12 (13.5%)	0.758
Seizures	0 %	5 (11.4%)	5 (5.6%)	**0.026**
Gastrointestinal lesion	33 (73.3%)	36 (83.7%)	69 (68.4%)	0.303
Vomit	20 (44.4%)	25 (56.8%)	45(50.6%)	0.243
Diarrhea	15 (33.3%)	21 (47.7%)	36(40.4%)	0.167
Stomach ache	24 (53.3%)	27 (61.4%)	51(57.3%)	0.444
Heart failure	26 (60.5%)	26 (61.9%)	52 (58.4%)	0.892
Myocarditis	12 (27.3%)	13 (31%)	15 (16.9%)	0.707
Coronary involvement (aneurysm and/or dilatation)	5 (11.4%)	1 (2.3%)	6 (6.7%)	0.202
Pericarditis	17 (38.6%)	12 (27.9%)	29 (32.6%)	0.289
Respiratory disease	25 (55.6%)	28 (63.6%)	53 (59.6%)	0.437
Pneumonia	25 (55.6%)	28 (63.6%)	53 (59.6%)	0.437
Pleurisy	17 (37.8)	21 (48.8%)	38 (42.7%)	0.295
Pain syndrome	30 (66.7%)	34 (77.3%)	64 (71.9%)	0.266
Abdominal pain	24 (53.3%)	27 (61.4%)	51(57.3%)	0.444
Myalgia	17 (37.8%)	11 (25%)	28 (31.5%)	0.194
Arthralgia	9 (20%)	9 (20.5%)	18 (20.2%)	1.0
Chest pain	1 (2.2%)	4 (9.1%)	5 (5.6%)	0.203
Sore throat	6 (13.3%)	2 (4.5%)	8 (9%)	0.206
Edema syndrome	31 (68.9%)	24 (54.5%)	55 (61.8%)	0.164
Edema of face	18 (40%)	14 (31.8)	32 (36%)	0.421
Edema of hands and feet	17 (37.8%)	16 (36.4%)	33 (37%)	1.0
Swelling of scrotum	3 (6.7%)	2 (4.5%)	5 (5.6%)	1.0
Swelling of joints	3 (6.7%)	3 (6.8%)	6(6.7%)	1.0
Conjunctivitis	33 (73.3%)	23 (52.3%)	56 (62.9%)	**0.040**
Oral mucosa lesion	26 (57.8%)	26 (59.1%)	52 (58.4%)	0.900
Hyperaemia of oral mucosa	26 (57.8%)	29 (65.9%)	55 (61.8%)	0.430
Fissures of lips	7 (15.6%)	14 (31.8%)	21 (23.6%)	0.071
Hunter glossitis	3 (6.7%)	4 (9.1%)	7 (7.9%)	0.714
Stomatitis	2 (4.4%)	3 (6.8%)	5 (5.6%)	0.677
Liver damage	23 (51.1%)	25 (56.8%)	48 (53.9%)	0.589

Lymphadenopathy	10 (22.2%)	11 (25%)	21 (23.6%)	0.758
Acute renal failure	6 (13.3%)	14 (31.8%)	22 (22.5%)	**0.037**
DIC	3 (6.7%)	12 (27.3%)	15 (16.9%)	**0.011**
Shock	4 (8.9%)	11 (25%)	15 (16.9%)	**0.05**
Thrombosis	1 (2.2%)	3 (6.8%)	4 (4.5%)	0.361
Admittance to the ICU	16 (35.6%)	25 (56.8%)	41 (46%)	**0.044**
Length of stay in the ICU (days; Me;IQR)	5 (3-7)	7 (5-12)	6 (4 – 10)	0.153
Length of hospital stay (days; Me;IQR)	15 (11-20)	13 (10-18)	14 (10 – 20)	0.899
Death	2 (4.4%)	3 (6.8%)	5 (5.6%)	0.677
Quantitative change in laboratory test values				
Parameters	**2020**	**2021**	***P- value**	
Leukocytes (Me; IQR) [× 10 ^{9}/L]	13 (10 – 18)	20 (14 – 24)	**<0.001**	
Lymphocytes % (Me; IQR)	16 (7 – 25)	10 (6 – 14)	**0.012**	
Neutrophils % (Me; IQR)	77 (66 – 85)	84 (78 – 88)	**0.003**	
Hemoglobin (M ± SD) [g/dl]	101 ± 20	99 ± 20	0.663	
Platelets (Me; IQR) [× 10 ^{9}/L]	152 (106 – 238)	134 (83 – 202)	0.264	
ESR (M ± SD) mm/h	31 ± 16	38 ± 18	**0.04**	
CRP (Me; IQR) [mg/L]	107 (42 – 155)	96 (38 – 139)	0.905	
Ferritin (Me; IQR) [ng/ml]	338 (195 – 562)	505 (312 – 850)	**0.022**	
Procalcitonin (Me;IQR) [ng/ml]	2 (1 – 6)	9 (2 – 20)	**0.005**	
Creatinine (Me; IQR) [μmol/l]	43 (33 – 68)	56 (38 – 108)	**0.035**	
Fibrinogen (Me; IQR) [g/L]	4 (2 – 5)	3 (2 – 4)	0.072	
Urea (Me; IQR) [mmol/l]	5 (4 – 6)	6 (5 – 14)	**0.011**	
ALAT (Me; IQR) [U/L]	46 (22 – 80)	52 (25 – 78)	0.51	
AST (Me; IQR) [U/L]	46 (26 – 79)	67 (31 – 114)	0.297	
Total protein (Me; IQR) [g/L]	54 (49 – 60)	54 (49 – 56)	0.665	
Albumin (M ± SD) [g/L]	30 ± 7	29 ± 7	0.541	

* Statistically significant values are highlighted.

Table 3. Comparative analysis of therapy in children with MIS-C by years.

Therapy	**2020**	**2021**	***P- value**
Intravenous immunoglobulin	35 (77.8%)	37 (84.1%)	0.591
Corticosteroids	40 (88.9%)	40 (93%)	0.714
Biological immunomodulatory drugs	1 (2.2%)	1 (2.3%)	1.0
Anticoagulants	33 (73.3%)	32 (72.7%)	0.949
Acetylsalicylic acid	19 (42.2%)	7 (15.9%)	**0.006**
Antibiotics	44 (97.8%)	44 (100%)	1.0
Dobutamine	4 (8.9%)	11 (25%)	**0.05**
Diuretics	17 (37.8%)	27 (61.4%)	**0.026**
Red cell transfusion	2 (4.4%)	10 (22.7%)	**0.014**
Transfusion of fresh frozen plasma	4 (8.9%)	11 (25%)	**0.05**
Albumen	11 (24.4%)	16 (36.4%)	0.221
Oxygen	5 (11.1%)	15 (34.1%)	**0.009**
Artificial lung ventilation	4 (8.9%)	6 (13.6%)	0.599
Surgical interventions performed	8 (17.8%)	11 (25%)	0.447
Laparoscopy	4 (8.9%)	4 (9.1%)	1.0
Appendectomy	2 (4.4%)	3 (6.8%)	0.677
Peritoneal dialysis determination	1 (2.2%)	4 (9.1%)	0.203

Lymph node dissection	1 (3.3%)	1 (2.3%)	1.0
Resection of large intestine	0%	1 (2.3%)	0.499

* Statistically significant values are highlighted.

inflammatory syndrome associated with SARS-CoV-2 in new-borns were described in some countries,[15] we also observed one case of severe hyperinflammatory syndrome in the new-born (age ten days).

In a US study which enrolled 272 children, specified by Feldstein LR and her team, it was noted that 80% of children needed intensive care. Four patients with MIS-C who died were between 10 and 16 years of age.[16] In contrast to this US study, among our 89 patients two times fewer children were hospitalized in the ICU (which amounted to 47%), and 80% of the children who died were in early childhood (under 2 years old). In another study conducted in Colombia, it was noted that out of 78 patients hospitalized in the ICU, 7 children died, and 71.4% of children who died were under 7 years old.[17] Mortality among infants in our cohort may be related to late diagnosis, as two out of four infants were diagnosed with MIS-C 3–4 weeks after hospital admission. Also, only one child with a fatal outcome received biological immune therapy, but at the time of the appointment of these drugs, he was in an extremely serious condition.

In our study, as in other previously published papers, rash (78.7%), changes in the gastrointestinal tract (68.4%), respiratory lesions (59.6%), and neurological symptoms (46.1%) were common symptoms other than fever.[18,19] In addition, nearly one-fourth of the patients in our cohort (22.5%) had acute renal failure, consistent with a previous systematic review.[20]

When compared with the literature data, heart damage in our cohort's children in the form of myocarditis was observed in 29%, according to other studies - in the range from 20 to 55%; pericarditis in 33% and 22-43%, respectively, coronary involvement in the form of aneurysm and/or dilatation in children with MIS-C was less common and amounted to 6% vs. 8-28% in other studies.[21-22]

More than 90% of children in our study had elevated inflammatory markers such as CRP (97%), ferritin (96%), D-dimer (93%), procalcitonin (91%), as well as leukocytosis (85%), lymphopenia (95%), neutrophilia (91%) and high ESR (91%) in the complete blood count; the similar results were described in other studies.[23-24]

According to the comparative analysis of the MIS-C course in 2020 and 2021 in Kazakhstan, it was found that SARS-CoV-2-associated multisystem inflammatory syndrome became more severe in 2021, confirming a statistically significant difference. So in 2021, life-threatening conditions such as acute renal failure, DIC, shock and seizures, and general hospitalization of children with MIS-C in the ICU were more common. The severity of the MIS-C course in 2021 confirms higher values of inflammation markers: ferritin, procalcitonin, ESR, leukocytes, and neutrophils. One of the important indicators of the complete blood count, which characterizes the severe course of the hyperinflammatory syndrome, is lymphopenia,[25,26] which was also characteristic of children who came down with the disease in 2021. According to the Centres for Disease Control and Prevention, a paper has been published comparing the differences in clinical and laboratory data of children with MIS-C registered after three waves of COVID-19, which specifies that there was an increase in the number of cases of MIS-C with severe hematological and gastrointestinal intestinal lesions ($P<0.001$) after the appearance of the Delta variant of SARS-CoV-2. However, the incidence of some cardiovascular complications such as cardiac dysfunction, myocarditis, shock, and renal failure decreased ($P<0.001$). Likely, hospitalizations to the intensive care unit, including mechanical ventilation ($P<0.001$) and extracorporeal membrane oxygenation (ECMO; $P=0.046$), decreased, as did the length of stay and mortality ($P<0.001$).[12] The authors concede that these data could be related to the introduction of COVID-19 vaccination in children. The discrepancies with our results may be because vaccination for children from 12 years old in the territory of the Republic of Kazakhstan became available only from mid-November 2021.

Limitation of the study. Our study has some limitations. Firstly, not all children were probably identified as MIS-C due to diagnostic defects since this pathology is new and doctors are not always wary of this disease. On the other hand, the multisystem inflammatory syndrome can be caused not only by novel coronavirus infection COVID-19 but also by other pathogens, autoimmune diseases, as well as many other identified diseases that may not be detected at the time of hospitalization in children in our cohort, but the presence of antibodies to SARS-CoV-2 expose them to MIS-C. Thirdly, none of the children underwent SARS-CoV-2 genome sequencing, and division into groups was carried out according to the time intervals of the prevalence of circulating virus variants and according to official sources on the identified Alpha and Delta variants in the territory of Kazakhstan.

Conclusions. MIS-C is a severe, life-threatening systemic disease characterized by inflammatory laboratory changes and multiple organ involvement, as evidenced by the high frequency and variety of severe clinical symptoms. During the circulation of Alpha and Delta variants of SARS-CoV-2 in the territory of the Republic of Kazakhstan, a more severe course of MIS-C

was noted, in which more pronounced clinical and laboratory changes were recorded, which required twice as frequently as resuscitation and intensive care due to the development of DIC, shock, and severe kidney damage.

References:

1. Swann O V, Holden K A, Turtle L, Pollock L, Fairfield CJ, Drake TM et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020; 370: m3249. https://doi.org/10.1136/bmj.m3249 PMid:32960186 PMCid:PMC7488201
2. Tian D, Sun Y, Zhou J, Ye Q. The Global Epidemic of the SARS-CoV-2 Delta Variant, Key Spike Mutations and Immune Escape. Front Immunol 2021; 12: 751-778. https://doi.org/10.3389/fimmu.2021.751778 PMid:34917076 PMCid:PMC8669155
3. European Centre for Disease Prevention and Control. Threat Assessment Brief: Emergence of SARS-CoV-2 B.1.617 variants in India and situation in the EU/EEA. Stockholm: ECDC; 2021. Available online: https://www.ecdc.europa.eu/en/publications-data/threat-assessment-emergence-SARS-CoV-2-b1617-variants Accessed on August 19, 2021.
4. Sheikh A, McMenamin J, Taylor B, Robertson C; Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. Lancet 2021; 397(10293): 2461-2462. https://doi.org/10.1016/S0140-6736(21)01358-1
5. Twohig, K.A., Nyberg, T., Zaidi, A., Simon Thelwall,, Mary Sinnathamby, Shirin Aliabadi,et al. Hospital Admission and Emergency Care Attendance Risk for SARS-CoV-2 Delta (B.1.617.2) Compared with Alpha (B.1.1.7) Variants of Concern: A Cohort Study. Lancet Infect. Dis. 2021; 22: 35-42. DOI:https://doi.org/10.1016/S1473-3099(21)00475-8 https://doi.org/10.1016/S1473-3099(21)00475-8
6. Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. CMAJ. 2021; 193(42): E1619-E1625. https://doi.org/10.1503/cmaj.211248 PMid:34610919 PMCid:PMC8562985
7. Siegel DA, Reses HE, Cool AJ, Craig N Shapiro, Joy Hsu, Tegan K Boehmer,et al. Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years - United States, August 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021; 70 (11): 1249-1254. https://doi.org/10.15585/mmwr.mm7036e1 PMid:34499628 PMCid:PMC8437056
8. Molteni, E., Sudre, C. H., Canas, L. S., Bhopal S., Hughes R., Chen L et al. Illness characteristics of COVID-19 in children infected with the SARS-CoV-2 Delta variant. MedRxiv 2021.10.06.21264467. https://doi.org/10.1101/2021.10.06.21264467
9. Centers for Disease Control and Prevention (2020) Emergency preparedness and response: health alert network. https://emergency.cdc.gov/han/2020/han00432.asp Accessed November 10 2020.
10. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19 (2020) www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-COVID-19 Accessed November 10, 2020.
11. Boranbaeva R.Z., Umesheva K.A., Salieva. S.S., Baesheva D.A., Abdrakhmanova S.T. Coronavirus infection COVID-19 in children. Clinical Protocol for Diagnosis and Treatment - MH RK -2020 - p. 6-23. https://diseases.medelement.com/disease/%D0%BA%D0%BE%D1%80%D0%BE%D0%BD%D0%B0%D0%B2%D0%B8%D1%80%D1%83%D1%81%D0%BD%D0%B0%D1%8F-%D0%B8%D0%BD%D1%84%D0%B5%D0%BA%D1%86%D0%B8%D1%8F-COVID-19-%D1%83-%D0%B4%D0%B5%D1%82%D0%B5%D0%B9-2020/16499
12. Allison D Miller, Laura D Zambrano, Anna R Yousaf, Joseph Y Abrams, Lu Meng, Michael J Wu, et al. Multisystem Inflammatory Syndrome in Children-United States, February 2020-July 2021, Clinical Infectious Diseases, 2021. https://doi.org/10.1093/cid/ciab1007 PMid:34864955 PMCid:PMC8689703
13. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatric Pulmonology. 2021; 56:837- 848. https://doi.org/10.1002/ppul.25245 PMid:33428826 PMCid:PMC8013394
14. Swann OV, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study BMJ 2020;370:m3249. https://doi.org/10.1136/bmj.m3249 PMid:32960186 PMCid:PMC7488201
15. Pawar R., Gavade V, Patil, N, Mali V., Girwalkar A, Tarkasband V, et al. Neonatal Multisystem Inflammatory Syndrome (MIS-N) Associated with Prenatal Maternal SARS-CoV-2: A Case Series. Children 2021 ;8(7): 572. https://doi.org/10.3390/children8070572 PMid:34356552 PMCid:PMC8305422
16. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF., et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med. 2020; 383(4): 334-346. https://doi.org/10.1056/NEJMoa2021680 PMid:32598831 PMCid:PMC7346765
17. Acevedo L, Piñeres-Olave BE, Niño-Serna LF, Vega LM, Gomez IJA, Chacón S, et al mortality and clinical characteristics of multisystem inflammatory syndrome in children (MIS-C) associated with covid-19 in critically ill patients: an observational multicenter study (MISCO study). BMC Pediatr. 2021 Nov 18;21(1):516. https://doi.org/10.1186/s12887-021-02974-9 PMid:34794410 PMCid:PMC8600488
18. Kostik MM, Bregel LV, Avrusin IS, Dondurei EA, Matyunova AE, Efremova OS, et al. Distinguishing Between Multisystem Inflammatory Syndrome, Associated With COVID-19 in Children and the Kawasaki Disease: Development of Preliminary Criteria Based on the Data of the Retrospective Multicenter Cohort Study. Front Pediatr 2021; 9: 787353. https://doi.org/10.3389/fped.2021.787353 PMid:34858909 PMCid:PMC8631532
19. Ozsurekci Y, Gürlevik S, Kesici S, Akca UK, Oygar PD, Aykac K, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic in Turkey: first report from the Eastern Mediterranean. Clin Rheumatol. 2021 Aug;40(8):3227-3237. https://doi.org/10.1007/s10067-021-05631-9 PMid:33576926 PMCid:PMC7879406
20. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T. COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. Pediatr Pulmonol. 2021;56(5): 837-848. https://doi.org/10.1002/ppul.25245 PMid:33428826 PMCid:PMC8013394
21. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021 May;5(5):323-331. doi: 10.1016/S2352-4642(21)00050-X. https://doi.org/10.1016/S2352-4642(21)00050-X
22. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020; 26: 100527. https://doi.org/10.1016/j.eclinm.2020.100527 PMid:32923992 PMCid:PMC7473262
23. Zhao Y, Yin L, Patel J, Tang L, Huang Y. The inflammatory markers of multisystem inflammatory syndrome in children (MIS-C) and adolescents associated with COVID-19: A meta-analysis. J Med Virol. 2021; 93(7): 4358-4369. https://doi.org/10.1016/j.eclinm.2020.100527 PMid:32923992 PMCid:PMC7473262
24. Zhang QY, Xu BW, Du JB. Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment. World J Pediatr. 2021; 17(4): 335-340. https://doi.org/10.1007/s12519-021-00435-y PMid:34013488 PMCid:PMC8134825

25. Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A., et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol. 2020; 2(12): e754-e763 https://doi.org/10.1016/S2665-9913(20)30343-X
26. Borgi A., Khadhraoui H., Louati A., Ayari A., Hajji A., Bouziri A., Menif K., Ben Jaballah N. First Tunisian cluster admissions of critically ill patients with multisystem inflammatory syndrome in children (MIS-C). Mediterr J Hematol Infect Dis 2021, 13(1): e2021023 https://doi.org/10.4084/mjhid.2021.023 PMid:33747404 PMCid:PMC7938928