ANNOTATION

of dissertation work by Jaxybayeva Indira Salikhovna on the topic **«Clinical and immunological features of multisystem inflammatory syndrome associated with COVID-19 in children»**, submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10103 – «Medicine»

Relevance of the research topic

Children and adolescents infected with SARS-CoV-2 often experience asymptomatic or milder cases compared to adults. However, there are risks of developing a rare but severe post-infection complication called Multisystem Inflammatory Syndrome (MIS-C) associated with SARS-CoV-2. MIS-C shares characteristics with severe COVID-19, toxic shock syndrome, and Kawasaki disease. This syndrome arises as a delayed immune response to the infection, with most cases peaking 3-6 weeks after the peak of SARS-CoV-2 infection rates [Zhang Q. et al., 2020].

The disease manifests with fever and systemic inflammation, leading to the involvement of multiple organ systems, including the cardiovascular, gastrointestinal (GI), respiratory, renal, neurological, mucocutaneous, and hematological systems [Feldstein L. R. et al., 2020]. Key laboratory criteria for diagnosing MIS-C associated with SARS-CoV-2 include elevated inflammatory markers such as CRP, ferritin, procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and D-dimer [Miller A.D. et al., 2021].

The admission of patients to the Intensive Care Unit (ICU) is one of the most important indicators of the severity of MIS-C associated with SARS-CoV-2. Systematic reviews have shown that due to multi-organ involvement, the rate of ICU admission ranges from 50-80%, with a mortality rate of 2-5% [Patel J.M., 2022]. The high risk of ICU admission in most patients with MIS-C associated with SARS-CoV-2 is associated with cardiac dysfunction (Kıymet E. et al., 2021). Results of cardiovascular system (CVS) instrumental studies often reveal various abnormalities. Electrocardiogram (ECG) deviations may include sinus tachycardia, heart block, and non-specific ST anomalies. Echocardiography (Echo) may demonstrate reduced left ventricular (LV) systolic function with an ejection fraction of less than 55%, valvular regurgitation, and coronary artery anomalies such as aneurysm and dilation, although they are less common than in classic Kawasaki disease (Das N. et al., 2023). Given the wide spectrum of clinical manifestations of the disease, identifying factors associated with a more severe outcome is crucial for prognosis and selecting necessary therapy.

According to foreign authors, the development of MIS-C is associated with high immune activation and increased cytokine production [Mazer M.B. et al. 2022]. The initial immunological studies dedicated to this condition described NK cell cytopenia [Carter M.J. et al. 2020]. Another distinctive feature is lymphopenia ranging from mild to moderate severity with a decrease in total T lymphocytes, CD4 and CD8 T cells, and B lymphocytes [Lee P.Y. et al. 2020].

One of the promising directions in modern immunology is the search, evaluation, and subsequent determination of the role of the most significant surface antigens

expressed on immune cells in the implementation of normal immune responses and in pathology. While the exact pathophysiological mechanism and risk of autoimmune reactions have not yet been established, the results of studies utilizing multidimensional immunological methods help refine the pathogenetic mechanisms and indicate specific diagnostic and prognostic approaches. Taking the above into account, in our study, we determined the expression of activation markers (HLA-DR, CD25), immune regulation (CD279), and apoptosis (CD95) in patients with MIS-C associated with SARS-CoV-2, which had not been previously assessed in other studies of these patients.

Therefore, MIS-C associated with SARS-CoV-2 is a severe pathological condition that requires comprehensive study, both in terms of diagnosis and treatment methods. The therapy for this disease aims to suppress hyperactive immune responses and cytokine storms. The preferred medications are immunomodulators in the form of mono- or combination therapies, including systemic glucocorticoids, intravenous immunoglobulins, as well as biological agents [Irfan O. et al. 2021].

Considering the high percentage of cardiovascular system involvement and the relatively recent emergence of the disease, it is also relevant to follow up with these patients in the long term to identify potential complications, as existing data on long-term consequences are limited.

The aim of the dissertation research: to investigate the clinical and immunological characteristics of multisystem inflammatory syndrome associated with SARS-CoV-2 in children in the Republic of Kazakhstan.

Objectives of the study:

1. Determine the clinical and laboratory features of multisystem inflammatory syndrome associated with SARS-CoV-2 in children.
2. Identify risk factors influencing the severity of the disease and conduct ROC analysis to determine the probability of hospitalization in the ICU of patients with MIS-C associated with SARS-CoV-2.
3. Investigate, in a comparative aspect, the status of the immune response among children with MIS-C associated with SARS-CoV-2 depending on the severity of the disease and patients who have had COVID-19 without developing MIS-C.
4. Conduct a dynamic study of cellular and humoral immunity in children with MIS-C associated with SARS-CoV-2 at 3 time points (acute phase, at 3 and 6 months).
5. Examine the health status of children in follow-up after MIS-C and modify the algorithm for dynamic observation of MIS-C convalescents associated with SARS-CoV-2.

Scientific novelty:

1. The clinical and laboratory characteristics, as well as the course of the new pediatric multisystem inflammatory syndrome associated with SARS-CoV-2, have been studied for the first time in the Republic of Kazakhstan.

2. A comprehensive study of the immune profile (determination of cellular parameters, levels of immunoglobulins, and cytokines) in children with multisystem inflammatory syndrome associated with SARS-CoV-2 has been conducted for the first time.

3.For the first time, the health of children after recovering from multisystem

inflammatory syndrome associated with SARS-CoV-2 has been studied in a follow-up period of 2 years or more.

Practical significance:

1. Comprehensive study of the clinical and immunological characteristics of multisystem inflammatory syndrome associated with SARS-CoV-2 during the COVID-19 pandemic, establishment of a patient registry from the first diagnosis identification, and analysis of interim and final research outcomes have facilitated timely medical assistance to children with this condition.

2. The investigation of changes in cellular and humoral immunity has helped demonstrate the role of immune dysregulation in the pathogenesis of multisystem inflammatory syndrome associated with SARS-CoV-2.

3. Follow-up studies over a period of more than 2 years have allowed us to identify long-term consequences after the disease, providing the basis for optimizing the algorithm for dynamic monitoring of children who have experienced multisystem inflammatory syndrome associated with SARS-CoV-2.

Methods of the investigation:

We conducted a three-stage combined retrospective and prospective study (approved by the Local Ethics Committee of the National Medical University named after S.D. Asfendiyarov, IRB No. 1147). Written informed consent was obtained from the parents of the children for their participation in the study.

The materials of the study were collected from 15 regional pediatric medical organizations in Kazakhstan. From August 1, 2020, to August 1, 2023, under the auspices of the Scientific Center of Pediatrics and Pediatric Surgery, 285 consultations of children with suspected MIS-C were conducted via the ZOOM platform, and the diagnosis was confirmed in 100 patients.

For all patients, an individual registration card was created, including the following parameters: epidemiology, clinical manifestations, laboratory and instrumental studies, and therapy.

Clinical research methods:

1. Testing to detect the infectious agent (PCR and ELISA for SARS-CoV-2).
2. Complete blood count (CBC), biochemical tests (ALT, AST, total protein, albumin, creatinine, urea, amylase, IL-6, alkaline phosphatase, creatine kinase, lactate dehydrogenase).
3. Inflammatory markers (ferritin, procalcitonin, CRP, fibrinogen, D-dimer, ESR).

Peak values (maximum and minimum) of laboratory parameters from medical records were entered into the database for statistical analysis.

Immunological research methods:

The material for immunological research was venous blood obtained from the cubital vein.

Immunological analysis was performed using flow cytometry on a FACSCANTOII flow cytometer (Becton Dickinson, USA). The following panel of antibodies was used in the study: CD3, CD4, CD8, CD16, CD20, HLA-DR, CD25, CD95, CD279.

The determination of the total population of all classes of immunoglobulins was performed using the immunoturbidimetric method. Reagent kits from Abbott Laboratories, USA, were used, and the analysis was conducted on a certified ARCHITECT analyzer (USA).

The levels of cytokines (IL-1b, IL-2, IL-6, IL-10, TNF) were determined using enzyme-linked immunosorbent assay (ELISA) kits from Vector-BEST according to the manufacturer's instructions. The analysis was conducted on a certified Stat Fax-2100 analyzer (USA).

For the detection of IgM and IgG antibodies to SARS-CoV-2 in serum, an enzyme-linked immunosorbent assay (ELISA) method was used with Vector-BEST reagent kits according to the manufacturer's instructions. The analysis was performed on a certified Stat Fax-2100 analyzer (USA).

In the main group, the determination of immunoglobulins and interleukins was performed during the acute phase of the disease in 35 children and six months after discharge in 31 children. In the control group, this investigation was performed once.

Follow-up observation included a retrospective analysis of outpatient records of 94 patients in the electronic system Damumed. Echocardiography data were studied in 58 children, and electrocardiography data in 59 children. A comparative analysis of the dynamics of echocardiography and electrocardiography during the acute phase of the disease and in the outpatient observation period was conducted.

Statistical analysis:

The study involved statistical analysis using the StatTech v. 2.4.5 program. Quantitative data were analyzed for normal distribution, described by means, standard deviations, medians, and quartiles. Categorical data were presented in absolute values and percentages. For group comparisons, Student's t-test, Mann-Whitney U-test, Pearson's chi-square test, and Fisher's exact test were used, as well as Spearman's correlation coefficient and ROC curves. For multiple comparisons, analysis of variance (ANOVA), Tukey's, Games-Howell, Kruskal-Wallis, and Dunn's tests were applied. McNemar's and Wilcoxon's tests were used for paired samples. Graphical representation was performed using Microsoft Excel and Prism 8. The level of significance was set at $p<0.05$.

Research object:

The retrospective study included 100 patients with MIS-C.

Characteristics of the prospective study groups:

The study included 50 patients.

Main group:

- **Group 1**: Children with MIS-C hospitalized in the ICU (MIS-C ICU "+") - 20 children.
- **Group 2:** Children with MIS-C not hospitalized in the ICU (MIS-C ICU "-") - 15 children.
- **Control group:** Conditionally healthy children who had COVID-19 according to IFA data - 15 children (COVID-19 MIS-C "-").

Inclusion criteria:

- Consent to participate in the study (written informed consent from the parents);

– Children diagnosed with MIS-C by the Republican Interdisciplinary Expert Group;

– Conditionally healthy children who had COVID-19 according to IFA data;

– Age under 18 years.

Exclusion criteria:

– Refusal to participate in the study (lack of written informed consent from the parents of the patient);

– Children who were not diagnosed with MIS-C after consultation with the expert group;

– Children with negative IFA for SARS-CoV-2 IgM, IgG;

– Age over 18 years.

The main provisions of the defense:

1. Pediatric MIS-C resulting from SARS-CoV-2 is a severe post-infectious disease characterized by delayed immune dysregulation and a wide range of clinical features, including persistent fever (99%) and involvement of vital organs and systems in 70% of cases.

2. Respiratory and cardiac complications, organomegaly, and changes in laboratory parameters such as anemia, thrombocytopenia, elevated CRP, LDH, transaminases, and hypoalbuminemia were significant predictors of MIS-C severity and increased need for intensive therapy, contributing to critical illness in 50% of patients.

3. Examination of the immune profile in MIS-C patients revealed alterations including decreased CD3, CD4 T-lymphocytes, NK-cells, CD95 apoptosis marker expression, and increased CD19+ B-lymphocytes, HLA-DR+ on B-lymphocytes, and CD25 activation marker expression, substantiating immune dysregulation in pediatric MIS-C.

4. Comparative analysis demonstrated more significant immune profile alterations in children with critical MIS-C (ICU+), indicating a link between ICU hospitalization risk and signs of profound immune dysfunction in these patients compared to the MIS-C ICU- group.

5. Combined immunosuppressive therapy with IVIG and glucocorticoids was effective in 94% of children with MIS associated with SARS-CoV-2, leading to the restoration of cellular and humoral immunity parameters in most patients.

Children after MIS associated with SARS-CoV-2 experienced recurrence, various somatic illnesses, and cardiovascular dysfunction in 2% of cases, highlighting the need for health monitoring and dynamic observation for up to 2 years.

Study Results:

Multisystem inflammatory syndrome associated with SARS-CoV-2 occurred in children of all ages, with a predominance in the group under 5 years old. The average age at the time of hospitalization was 6 years (Min-10 days; Max-17 years; IQR 3-10 years). By gender, boys accounted for 69 (69%), which was more than girls, 31 (31%).

In our study, patients with MIS-C showed involvement of many organs. The most common manifestations of MIS-C based on objective examination and changes in laboratory parameters were fever (99%), gastrointestinal tract involvement (77%),

rash (74%), oral mucosal changes (66%), painful and (70%) edematous (60%) syndromes, conjunctivitis (60%), cardiac involvement (65%), respiratory organ involvement (59%), and liver involvement (57%). Less common were: neurological symptoms (46%), lymphadenopathy (25%), acute kidney injury (21%), and thromboses (4%).

Most children showed changes in complete blood count indicating an inflammatory process: leukocytosis (85%), neutrophilia (95%), lymphopenia (91%), accelerated ESR (93%), as well as anemia (70%) and thrombocytopenia (53%). Elevated primary inflammation markers were identified: C-reactive protein (98%), ferritin (88.9%), procalcitonin (88.6%), IL-6 (73.3%), and D-dimer (82.4%). Other changes in the biochemical blood analysis included hypoproteinemia (79%), hypoalbuminemia (77.4%), elevation of ALT levels (59%), AST (65%), total bilirubin (18%), as well as elevation of creatinine (21%) and urea (25%).

Out of 100 patients with MIS-C 50 children required intensive care unit (ICU) treatment due to the severity of their condition. In order to identify risk factors affecting the severity of the disease course, we calculated the odds ratios (OR) taking into account the available clinical and laboratory manifestations. In the ICU, girls were significantly more often hospitalized (p=0.046; OR 2.4; 95% CI: 1.1 – 6), children with pneumonia (p=0.022; OR 2.6; 95% CI: 1.1 – 6), pleurisy (p<0.001; OR 7; 95% CI: 2.8 – 17.2), myocarditis (p=0.013; OR 3.3; 95% CI: 1.3 – 8.4), pericarditis (p=0.003; OR 2.7; 95% CI: 1.6 – 6.7), acute kidney injury (p<0.001; OR 6; 95% CI: 1.9 – 19.4), anemia (p=0.029; OR 2.7; 95% CI: 1.1 – 6.6), thrombocytopenia (p=0.002; OR 3.6; 95% CI: 1.6 – 8.4), elevated procalcitonin levels (p=0.022; OR 6.1; 95% CI: 1.2 – 30.2), LDH (p=0.024; OR 3.9; 95% CI: 1.2 – 13.2), ALT (p<0.001; OR 5; 95% CI: 2.1 – 11.1), and AST (p<0.001; OR 6; 95% CI: 3.5 – 19.4), as well as hypoproteinemia (p=0.008; OR 4.2; 95% CI: 1.4 – 12.8).

Using ROC analysis, all available laboratory parameters were evaluated. Below are only the prognostic models with statistically significant values.

– Leukocytes: threshold value 17×10^9/л, sensitivity - 59%, specificity - 58%, AUC - 0.640 (95% CI: 0.531 – 0.748), p = 0.017. Hospitalization in the ICU was predicted with leukocyte values above or equal to this threshold.

– Lymphocytes: threshold value 12%, sensitivity - 64.7%, specificity - 60.4%, AUC - 0.624 (95% CI: 0.514 – 0.735), p = 0.033, the risk of ICU hospitalization was at values below this threshold.

– Hemoglobin: threshold value 94 g/л, sensitivity - 64.7%, specificity - 68.2%, AUC - 0.708 (95% CI: 0.606 – 0.811), p < 0.001, the risk of ICU hospitalization was at values below this threshold.

– Platelets: threshold value 148×10^9/л, sensitivity - 67.6%, specificity - 68.8%, AUC - 0.703 (95% CI: 0.600 – 0.806), p < 0.001, the risk of ICU hospitalization was at values below this threshold.

– CRP: threshold value 91 mg/л, sensitivity - 58.8%, specificity - 66.7%, AUC - 0.625 (95% CI: 0.514 – 0.735), p = 0.033, the risk of ICU hospitalization was at values above this threshold.

– Ferritin: threshold value - 588 g/л, sensitivity - 60.1%, specificity - 64.6%, AUC

- 0.682 (95% CI: 0.569 – 0.796), p = 0.004, the risk of ICU hospitalization was at values above this threshold.

– Procalcitonin: threshold value 5.62 ng/мл, sensitivity - 63.6%, specificity - 64.2%, AUC - 0.690 (95% CI: 0.581 – 0.800), p = 0.002, the risk of ICU hospitalization was at values above this threshold.

In the prospective part of the study, a comparative analysis of the immune profile was conducted among patients with MIS-C, depending on the severity of the disease, and patients who had COVID-19 without developing MIS-C. In both groups of children with MIS-C decrease in the average values of CD3+ T lymphocytes below the reference values was observed (ICU«+» - 52%, ICU«-» - 54%), while in the control group of children with COVID-19 without MIS-C, the indicators were within the normal range (68%). The average values of CD4+ T-lymphocytes were also below the reference values in both MIS-C groups (ICU «+» and ICU «-» 25%), but did not differ statistically from the group of children with COVID-19 without MIS-C (35%).

Relative values of cytotoxic CD8+ T-lymphocytes were within the normal range in children with ICU «+» MIS-C (22%), while in the ICU «-» MIS-C (33%) and COVID-19 MIS-C «-» groups (34%), a significant increase in these cells was noted. In the group of children with MIS-C requiring treatment in the ICU, a decrease in the relative quantity of NK-cells to 4% was observed, while in the comparison groups, these indicators were within the normal range (11% and 12%, respectively).

In the studied groups, the expression of the early activation marker CD25 was determined. When comparing the relative expression value of this marker, it was significantly higher in the group of children with ICU «+» MIS-C compared to children with COVID-19 MIS-C «-» (5%; p=0.001 and 2%; p=0.049, respectively).

In our study, when analyzing the median relative value of the apoptosis marker CD95, weak expression was observed in both MIS-C groups (ICU «+» - 1.5%; ICU «-» - 1.4%), compared to the control group of children (4.6%; p=0.05). When comparing the relative expression value of CD279 in the three groups of our study, no significant differences were found.

The results of the study of the levels of 5 cytokines in the blood serum yielded the following data. The median level of IL-2 was significantly higher in both groups of children with MIS-C compared to the control group of children with COVID-19 without MIS-C. The medians of IL-6, IL-10, and FNO levels were statistically significantly higher in the ICU «+» MIS-C group compared to the COVID-19 MIS-C «-» group. When conducting a correlation analysis between the number of elevated interleukins and the number of affected organs in children with MIS-C a moderate direct correlation was found (p=0.011).

Six months after the illness, most immunological parameters normalized in 31 children with MIS-C. CD3 T-lymphocytes recovered in 87.1% of children but remained low in 12.9%. CD4 T-lymphocytes recovered in 54.8%, remaining low in 45.2%, while CD8 T-lymphocytes remained above normal in 77.4%. NK-cells recovered in 74.2% of children, CD19 B-lymphocytes in 83.9%. The CD3-HLA-DR+ activation marker was normal in 87.1%, HLA-DR on T-cells in 45.2%, CD25 activation marker in 90.3%, while the apoptosis marker remained low in 93.5%.

Of the basic therapy options, systemic corticosteroids were received by 91 (91%) children, IVIG by 82 (82%) children, and only 1 (1%) child received bioengineered immune therapy with tocilizumab. Almost all patients (99%) received antibacterial therapy. Anticoagulant therapy was used in 69% of children, while treatment with acetylsalicylic acid was administered to 28%. The median duration of hospitalization for these children was 18 days, compared to 7 days for children not hospitalized in the ICU. Out of 100 patients, 94 were discharged with improvement, and 6 died.

Taking into account the duration of follow-up observation, all 94 children who had MIS-C were divided into 3 groups:

– Group 1, observed for more than 2 years (since August 2020) - 60 (63.8%) children;

– Group 2, observed for up to 2 years (since August 2021) - 31 (33%) children;

– Group 3, observed for up to 1 year (since August 2022) - 3 (3.2%) children.

After a retrospective analysis of outpatient records, it was found that 25 (26.6%) children after MIS-C had hospitalizations in the clinic for various illnesses. Additionally, another 23 (24.5%) children had entries in their outpatient records with complaints and symptoms related to various organs and systems.

In the first year after experiencing MIS-C children exhibited the highest number of illnesses, including recurrent MIS-C - 2 (2%), anemia - 8 (8.3%), disorders of the autonomic nervous system (ANS) - 10 (10.4%), allergic rashes - 5 (5.2%), weight changes - 3 (3.1%), decreased vision - 7 (7.5%), and reactive arthritis - 2 (2%). In the second year of observation, the following conditions were identified: ANS disorders - 1 (1%), weight changes - 1 (1%), pneumonia - 2 (2%), allergic rashes - 2 (2%). After the second year of observation, pneumonia was observed in 1 (1%) child, and allergic rashes in 1 (1%) child.

In our study, 65% of children with MIS-C experienced cardiovascular system problems during the acute phase of the illness. After recovery, statistically significant decreases in certain echocardiographic changes were observed during outpatient examinations, including reduced left ventricular ejection fraction ($p<0.001$), pericarditis ($p<0.001$), pulmonary arterial hypertension ($p=0.002$), dilation of the right and left heart chambers ($p=0.046$), and valve leaflet thickening ($p=0.046$). However, pulmonary hypertension persisted in one child three weeks after discharge but was not significant (27 mmHg). Coronary artery involvement was observed in 6 (6.5%) children with MIS-C. On repeat outpatient echocardiograms, moderate coronary artery dilation persisted only in 1 child two years after discharge.

Both during inpatient and outpatient evaluations, valvular regurgitations were observed in half of the children with MIS-C. At the outpatient level, there was a decrease in the frequency of mitral regurgitation ($p=0.05$) and a twofold increase in the frequency of pulmonary regurgitation ($p=0.05$) and tricuspid regurgitation ($p=0.002$). All valvular regurgitations were mild or moderate in severity.

Analysis of changes in electrocardiograms at the outpatient level showed a statistically significant decrease in the frequency of ventricular repolarization disturbances ($p=0.013$) and atrioventricular conduction delays ($p=0.05$), but most children still exhibited incomplete right bundle branch block. Additionally, there was

an increase in the frequency of sinus arrhythmias compared to the acute phase of the illness, although the difference was not statistically significant.

Conclusions:

1. MIS-C was characterized by a wide spectrum of clinical symptoms and involvement of four or more organs and systems (70%). Patients exhibited fever in 99% of cases, gastrointestinal tract involvement in 77%, papular rash in 74%, conjunctivitis in 60%, cardiac involvement in 65%, respiratory involvement in 59%, and liver involvement in 57%. In most cases, MIS-C manifested with pronounced pain (70%) and edema (60%) syndromes.

2. The main inflammatory markers in MIS-C were: leukocytosis (85%), neutrophilia (95%), lymphopenia (91%), elevated erythrocyte sedimentation rate (93%), increased C-reactive protein (97%), ferritin (88.9%), procalcitonin (88.6%), D-dimer (82.4%), and IL-6 (73.3%). A correlation was found between the level of platelet reduction ($p<0.001$), increase in ferritin ($p<0.001$), and the number of organs involved in the pathological process.

3. In 50% of children with MIS-C, intensive and resuscitation therapy was required. The risk of hospitalization in intensive care units was on average 2.7 times higher in girls and 5 times higher in children with pleurisy, organophosphate poisoning, elevated procalcitonin, LDH, transaminases, and hypoproteinemia. According to ROC analysis, the probability of transfer to intensive care units depended on the threshold values of laboratory parameters: hemoglobin (94 g/L), leukocytes (17x10^9/L), lymphocytes (12%), platelets (148x10^9/L), CRP (91 mg/L), ferritin (588 μg/L), procalcitonin (5.62 ng/mL).

4. The study of the immune response in MIS-C revealed a statistically significant decrease in CD3, CD4 T-lymphocytes, NK-cells, and expression of the CD95 marker, along with an increase in the population of CD19+ B-lymphocytes, HLA-DR+ on B-lymphocytes, and expression of the CD25 activation marker. Elevated levels of IFN-α ($p=0.003$) and IL-6 ($p=0.001$) were identified as prognostically unfavorable factors. Additionally, a correlation was found between the risk of hospitalization in intensive care units and signs of profound immune dysfunction: high relative values of B-lymphocytes ($p=0.002$), high expression of CD3-HLA-DR+ ($p=0.002$) and CD25 ($p=0.049$), and low relative values of NK-cells ($p=0.001$) in these patients.

5. Dynamic assessment of the immune profile in children with MIS-C at three time points revealed the restoration of cellular and humoral immunity indicators in the majority of patients within 6 months from the onset of the disease. An increase in the relative values of T-lymphocytes - CD3+ was observed in 87% of children, CD4+ in 55% of children, and NK cells in 74% of children. A decrease in CD19+ B-cells was noted in 84% of cases, along with a decrease in the expression of CD3-HLA-DR+ in 87% of cases and a decrease in CD25 cells in 90% of cases.

6. The follow-up study did not reveal severe complications following MIS-C. Recurrence of MIS-C was observed in 2% of cases, autonomic nervous system disorders in 11%, respiratory system disorders in 14%, sensory disturbances in 8.6%, and reactive arthritis in 2%. Regarding the cardiovascular system, regurgitations were observed on echocardiography (50% tricuspid, 35% mitral, and 19% pulmonary),

while sinus arrhythmias were noted on electrocardiography in 25% of cases. Persistent involvement of coronary arteries was observed in only 1.7% of patients with positive dynamics in terms of size by the second year of observation.

Practical significance

1. The main reasons for the severe course of MIS-C are cardiac dysfunction (65%) and respiratory organ involvement (59%). This underscores the need for timely and early therapeutic intervention to prevent uncontrolled progression of the systemic inflammatory process and irreversible tissue damage.

2. Early monitoring of the cardiovascular system, regular laboratory monitoring of key inflammatory markers (platelets, CRP, ferritin, procalcitonin, D-dimer, and LDH), and timely administration of immunosuppressive therapy lead to a favorable outcome of the disease in the majority of patients (94%) with MIS-C.

3. The incomplete restoration of cellular and humoral immunity in children with MIS-C underscores the necessity of investigating the immune status dynamically over the subsequent 2 years.

4. A multidisciplinary approach and the use of systemic corticosteroids and intravenous immunoglobulins constitute an effective treatment strategy for MIS-C. The use of genetically engineered biological drugs in childhood is limited and should only be considered when there is a combination of high levels of IL-6, IL-10, FNO, and inflammatory markers.

5. According to the modified "Algorithm for the dynamic observation of children who have had MIS-C," prolonged monitoring and dynamic cardiovascular system control are not required during the long-term observation period. Unlike Kawasaki disease, the risk of coronary artery aneurysm formation in MIS-C was not as high (1.7%). Therefore, it is recommended to reduce the overall duration of dynamic observation from 5 to 2 years.

Approbation of the results of the dissertation

The results of the conducted research on the dissertation topic were presented and discussed at:

–International Scientific and Practical Conference "COVID-19 Pandemic: Current Issues and Solutions", February 12, 2021, Almaty, Kazakhstan;

–"COVID-19. Clinic. Diagnosis. Treatment. Prevention." Conference, February 24, 2021, Nur-Sultan, Kazakhstan;

–International Scientific and Practical Conference "School of Young Scientists", April 3, 2021, Almaty, Kazakhstan;

–International Scientific and Practical Conference "Life after COVID-19", April 24, 2021, Almaty, Kazakhstan;

–International Scientific and Practical Conference "Current Issues of Biological Safety in Modern Conditions", September 22-23, 2021, Nur-Sultan, Kazakhstan;

–International Scientific and Practical Conference "Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery", April 22, 2022, Almaty, Kazakhstan;

–Scientific-Practical Conference "Comorbid Patient: Multidisciplinary Approach

to the Problem", May 28, 2022, Almaty, Kazakhstan;

–International Scientific and Practical Conference "Science and Youth" April 25, 2023, Almaty, Kazakhstan;

–International Scientific and Practical Conference "Science and Youth" April 25, 2023, Almaty, Kazakhstan;

–1st International Forum "Asfen For Um, New Generation 2023" June 5-6, 2023, Almaty, Kazakhstan;

–VII International Scientific and Practical Conference "Allergology and Immunology: Perspectives and Achievements" (poster presentation) September 21-23, 2023;

–Young Researcher: Challenges and Prospects for the Development of Modern Pediatrics and Pediatric Surgery, October 13, 2023.

Publications. The publications related to the dissertation topic include:

– 3 scientific papers published in journals indexed in the Scopus database with no less than the 25th percentile.

– 3 papers published in journals recommended by the Committee for Quality Assurance in Education and Science of the Republic of Kazakhstan.

– 4 papers presented in the proceedings of international conferences.

– 1 author's certificate obtained.

– Methodological recommendations developed and published: "Diagnosis and Treatment of Multisystem Inflammatory Syndrome Associated with COVID-19 in Children" (issued in 2020) and approved by the Republican Center for Healthcare Development.

Implementations

– Author's certificate for the "Algorithm for Dynamic Observation of Children Who Have Experienced Multisystem Inflammatory Syndrome Associated with SARS-CoV-2" (No. 43302, dated February 27, 2024).

The doctoral candidate's personal contribution includes the selection and justification of the research direction; creation of the research design; organization and implementation of all its stages; collection, processing, and analysis of data; formatting, presentation, and discussion of the dissertation results. The author personally conducted the collection of laboratory material from each patient at all observation stages, and the scope of special research methods was also carried out with the personal participation of the candidate. The candidate participated in organizing interdisciplinary consultations for children suspected of having MIS-C, creating a registry for its analysis, and performing statistical processing. Formulation of conclusions, recommendations, and practical recommendations has been carried out. The author participated in the development of methodological recommendations and also optimized the algorithm for follow-up observation.

The scope and structure of the dissertation. The dissertation spans 129 pages and comprises an introduction, literature review, materials and methods of research, sections presenting the results of the author's own research, conclusion, findings, practical recommendations, and two appendices. The work is accompanied by 26 tables and 22 figures. The bibliography includes 176 sources.