www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(2):e120210
doi: 10.7363/120210
Received: 2023 May 30; revised: 2023 Jul 06; accepted: 2023 Jul 08; published online: 2023 Sept 07

Original article

Multisystemic inflammatory syndrome in children post-COVID-19: clinical-biological characteristics of patients in the first year of the pandemic

Luminita Goicea (Spatariu)[1,2], Eugenia Buzoianu[1,2], Ana Maria Davitoiu[1,2], Sorina Chindris[1,2], Andrei Zamfirescu[1,2], Mirela Iancu[1,2], Ioana Ghiorghiu[1,2], Iulia Tincu[1,2], Anca Draganescu[1,3], Ana Dorobantu[2], Gabriela Vlad[1,2], Luiza Bordei[1,2], Vlad Plesca[1,3], Doina Anca Plesca[1,2]

[1]Department of Pediatrics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2]Dr. Victor Gomoiu Children's Clinical Hospital, Bucharest, Romania
[3]Matei Bals National Institute of Infectious Diseases, Bucharest, Romania

Abstract

Introduction: Initially considered the "hidden victims" of the pandemic, children have come into the spotlight regarding the impact of COVID-19 since spring 2020. Against this background, a new entity of multisystemic hyperinflammatory syndrome in the pediatric population with manifestations that overlap with Kawasaki disease has become an increasing focus of attention.

Objectives: The current study was intended to identify some indicators of the severity of pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2/multisystemic inflammatory syndrome in children post-COVID-19 (PIMS-C/MIS-C) and factors predictive of its prognosis, paying attention to both already established factors (cardiac injury markers) and less used parameters (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR]) that could provide valuable information for predicting severe disease development.

Materials and methods: This study was based on a descriptive observational analysis of a group of pediatric patients (0-18 years) in whom the following were identified: persistent fever, the presence of single/multiple-organ dysfunction, a significant biological inflammatory syndrome, a temporal association with SARS-CoV-2 infection (infection/exposure 2-6 weeks previously), and an absence of other conditions that could explain this pattern.

Results: The patients who met the criteria for inclusion in the study during the analyzed period were children aged between 4 months and 17

years and 10 months, with a median age of 5 years (IQR, 3-8.75). All enrolled patients presented fever (with a maximum duration of 9 days) at admission, which was associated at varying rates with digestive, neurological, and skin-mucosal changes, and cardiac manifestations. Three main phenotypes of the condition were outlined (Kawasaki-like, shock-like, and a non-specific form). In the evaluated patients classified into the Kawasaki-like phenotype, higher median values of NLR but lower values of PLR were observed compared with those in the other forms of PIMS-C/MIS-C.

Conclusions: The current study outlines the spectrum of PIMS-C/MIS-C while also emphasizing the importance of establishing certain correlations between biological markers and the evolution of the disease. The use of certain parameters easily obtained from the blood count (NLR, PLR) as well as determining their correlation with disease severity could offer new directions to treat this condition.

Keywords

COVID-19/SARS-CoV-2, multisystemic inflammatory syndrome, child, skin-mucosal damage, cardiac damage, PIMS-C/MIS-C spectrum.

Corresponding author

Luminita Goicea (Spatariu), Department of Pediatrics, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, and Dr. Victor Gomoiu Children's Clinical Hospital, Bucharest, Romania; email: spatariuelenaluminita@gmail.com.

How to cite

Goicea (Spatariu) L, Buzoianu E, Davitoiu AM, Chindris S, Zamfirescu A, Iancu M, Ghiorghiu I, Tincu I, Draganescu A, Dorobantu A, Vlad G, Bordei L, Plesca V, Plesca DA. Multisystemic inflammatory syndrome in children post-COVID-19: clinical-biological characteristics of patients in the first year of the pandemic. J Pediatr Neonat Individual Med. 2023;12(2):e120210. doi: 10.7363/120210.

Introduction

Although the threat posed by the COVID-19 pandemic, which began in 2019, appears to be receding, many unanswered questions remain about SARS-CoV-2 infection and in particular about its impact on the pediatric population.

On 11th March, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak to be a pandemic. Subsequently, COVID-19 continued to surprise the medical and scientific communities, especially in terms of the scale that it reached in a very short time [1-22]. From the very beginning of the COVID-19 era, adults were noted to be particularly affected by SARS-CoV-2 infection while the pediatric population initially seemed to be protected. There was a low incidence of infection in children, while those infected showed only mild or moderate forms of the disease [2, 3]. It is reported in the literature that, in the first months of 2020, the incidence of infection with the new coronavirus was about 3% in the pediatric population. Subsequently, there was an upward trend in this infection rate, but it was much lower than the incidence in adults (6.4%, with a total of 65,000 infected children, April 2021) [4, 6].

At the time of writing, the Centers for Disease Control and Prevention (CDC) has reported an incidence of COVID-19 among children of 17.9%. Despite reports of their lower infection rates, children were subsequently identified as the "hidden victims" of the pandemic [5]. The real risks of exposure of the pediatric population to SARS-CoV-2 began to become known only in April 2020. Specifically, more than a month after the declaration of a pandemic, the National Health Service in the UK sounded the alarm about manifestations similar to Kawasaki disease in a significant number of children as a possible complication of SARS-CoV-2 [7-9]. Subsequently, across the medical sector globally, there was increasing concern about the appearance of a growing number of pediatric cases with manifestations overlapping with those of multisystemic hyperinflammatory syndrome.

Among the cases presented in the literature, there are commonalities in terms of the age of the patients (children over 5 years of age), the presence of fever, the multisystemic damage (digestive, cardiac, neurological, renal, skin), as well as the paraclinical changes, characterized by a notable inflammatory biological syndrome. In addition, attention was drawn to a possible correlation of this condition with exposure to SARS-CoV-2 (most often asymptomatic and/or demonstrated only serologically) [10-12, 22], as well as potential progression of this condition to a severe form.

Having initially been considered a rare post-COVID-19 complication, pediatric inflammatory multisystem syndrome, temporally associated with

SARS-CoV-2 (PIMS-C), as originally described in the UK, has become increasingly identified and reported in more and more institutions around the world. The US CDC and the WHO named the new entity multisystem inflammatory syndrome in children post-COVID-19 (MIS-C) and developed diagnostic criteria for it [11, 12].

Definitions of this condition have been developed at several leading institutions globally, such as the CDC and the WHO. Although they differ in some regards (duration of fever, age of patients), they still have in common the presence of fever in children not due to other factors, an association with a significant biological inflammatory syndrome, and single/multiple-organ damage, which are potentially correlated with recent infection with or exposure to the SARS-CoV-2 virus. Upon surveying the epidemiological data presented in the literature, it has been considered that PIMS-C/MIS-C appeared after an interval of 2-6 weeks from the peak incidence of SARS-CoV-2 infections in the general population [9, 11, 12].

Starting in April 2020, reports of new cases of PIMS-C/MIS-C among children began to be published from more and more countries, describing the spectrum of PIMS-C/MIS-C as involving three different phenotypes: Kawasaki-like, shock-like, and non-specific [7, 8, 9]. Since the first case reports from the UK, PIMS-C/MIS-C has been viewed as a new entity with substantial overlap with Kawasaki disease [7, 10, 16, 22].

The exact incidence of PIMS-C/MIS-C is difficult to determine. At the time of writing, the CDC has described that 9,480 cases (79 deaths) have been reported in the USA. However, it is a substantial challenge to establish the actual incidence worldwide, given the evolution of the pandemic in waves as well as the introduction of vaccinations for children [1-3]. Having been considered as a postinfectious complication rather than as a direct result of the acute disease, PIMS-C/MIS-C appears to affect a small proportion of the pediatric population, having not only immediate consequences but also long-term effects (especially cardiac damage, long COVID manifestations) that require careful research.

Justification of the study

The current study follows initial research conducted by the authors at Dr. Victor Gomoiu Children's Clinical Hospital, Bucharest, Romania, during the first year of the pandemic. This study aimed to establish clinical patterns of SARS-CoV-2 infection among hospitalized pediatric patients [13]. At the start of the study, it was observed that, during the period corresponding to the beginning of the second pandemic wave in Romania (1st August, 2020, to 31st December, 2020), there was an increase in the number of cases of acute SARS-CoV-2 infection in children over 5 years of age. Under these circumstances and taking into account that, since the first wave of the pandemic, numerous cases of PIMS-C/MIS-C have been described worldwide, it is important to outline the clinical-biological status of this entity and to increase vigilance in its early diagnosis, given its potential to develop into a severe condition. At the same time, increasing emphasis is being placed on detecting the prognostic factors of this post-COVID-19 complication [15, 17, 19].

In the literature, it is stated that, among patients diagnosed with PIMS-C/MIS-C, there is a slight predominance of males, but this is not considered a factor predictive of a poor prognosis [17]. Heart disease is one of the most concerning clinical manifestations in terms of the diagnosis of PIMS-C/MIS-C. In the context of PIMS-C/MIS-C, heart disease has been a focus of increased interest for establishing factors potentially predictive of patients at high risk. In addition to the use of heart injury markers already known from other inflammatory/infectious diseases (troponin, NT-proBNP), increased attention has been paid to other factors that could be associated with the risk of severe PIMS-C/MIS-C. Hematological parameters such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are easily obtained by performing a blood count, are often used in the diagnosis of inflammatory or infectious diseases and subsequently in assessing their prognosis [17, 18]. Given that PIMS-C/MIS-C is considered a hyperinflammatory condition with an infectious trigger, it is considered that these hematological parameters should also be assessed in this entity. Numerous studies in adults diagnosed with respiratory infections (pneumonia of various etiologies including SARS-CoV-2) have shown a link among PLR, disease severity, and prognosis. At present, there is particular interest in assessing the potential correlation between hematological parameters, severity levels, and prognosis of SARS-CoV-2 infection. However, very few studies have assessed the usefulness of these parameters in the diagnosis and monitoring of infectious diseases (especially SARS-CoV-2 infection) in children

[14, 19, 20]. Despite this, it has been shown that PLR can be used as a prognostic factor in pediatric conditions such as Henoch-Schönlein purpura, acute joint rheumatism, measles, appendicitis, or even type 1 diabetes [20]. In adults, NLR has been proven to be useful as a severity marker in COVID-19 [19].

Methods

The objective of this study was to identify the epidemiological characteristics of the patients included in this study, locate them within the spectrum of PIMS-C/MIS-C, and identify potential indicators of disease severity and prognosis. Given that few studies have differentiated cases along the PIMS-C/MIS-C spectrum and shown the correlation of PIMS-C/MIS-C subtypes with the clinical evolution of cases, we aimed to reveal the clinical-biological differences between patients who met the criteria for classification into the Kawasaki-like phenotype and those included in the other phenotypes, to better understand the disease. An attempt was also made to establish correlations between different hematological markers, easily obtained from the blood count (NLR, PLR), and disease progression, in order to establish factors predictive of a severe disease outcome. Although the lack of standardization of the reference ranges of such hematological markers in the pediatric population makes it difficult to demonstrate their usefulness with certainty, we consider that they warrant exploration.

To pursue the above objectives, a descriptive observational study of pediatric patients (aged 0-18 years) was conducted. It included patients with the following features: persistent fever, presence of single/multiple-organ dysfunction, inflammatory biological syndrome, temporal association with SARS-CoV-2 infection (infection/exposure 2-6 weeks previously), and an absence of other conditions with a similar clinical picture. During the clinical trial, 4,146 patients were admitted to the hospital, 103 of whom were diagnosed with acute infection with the SARS-CoV-2 virus. Among these patients, 18 met the diagnostic criteria for PIMS-C/MIS-C.

The criteria for inclusion in the study were based on the international guidelines for the diagnosis of PIMS-C/MIS-C, developed by the WHO/CDC [11, 12], but also on the application of the Pediatric Multisystemic Inflammatory Syndrome Management Protocol Post-COVID-19, 1st Edition, developed and approved at Dr. Victor Gomoiu Children's Clinical Hospital. These criteria are presented in **Tab. 1**. The assessment and classification of the cases considered the three classical phenotypes of PIMS-C/MIS-C, as found in international guidelines and protocols, but also in the local protocol of the above-mentioned hospital.

Table 1. Criteria for inclusion of patients in the study.

Patient age	0-18 years
Hospitalization in Dr. Victor Gomoiu Children's Clinical Hospital, Bucharest	Between 31.03.2020 - 31.12.2020
Fever	Above 38°C, started at least 72 hours before the presentation
Evidence of single/ multiple organ damage (determined for admission reasons and clinical-paraclinical evaluation)	**Gastrointestinal**: • abdominal pain, diarrhea, vomiting, • acute abdomen, • jaundice, • modification of liver function
	Cardiovascular: • hypotension, shock, oliguria, • myocardial dysfunction, • pericardial exudate, • coronary damage
	Respiratory: • cough, odynophagia, • respiratory failure/hypoxemia, • pleurisy, pulmonary infiltrated
	Cutaneous and mucosa: • conjunctivitis, palpebral edema/ erythema, • mucositis, • rash, • hands/feet edema
	Neurological: • headache, confused state, • syncope, • meningism
	Renal: • oliguria, • edema, • nitrogen retention
	Hematologic: • lymphadenopathy, • blood count changes, • coagulopathy
Paraclinical evidence of inflammation	**Inflammatory markers**: • C-reactive protein, • fibrinogen, • erythrocyte sedimentation rate, • ferritin, • procalcitonin
COVID-19 association	Positive SARS-CoV-2 IgG antibodies
Exclusion of other diagnoses	Without other microbiological evidence, including bacterial sepsis, staphylococcal/ streptococcal toxic shock, etc.

To classify the cases into one of the classical phenotypes of the PIMS-C/MIS-C spectrum, we took into account the following criteria:

1. PIMS-C/MIS-C Kawasaki-like: fever, associated characteristics similar to classical Kawasaki disease (rash, conjunctivitis, enanthema, palmoplantar edema or erythema, lymphadenopathy, coronary impairment);
2. PIMS-C/MIS-C shock-like: fever, associated traits similar to septic shock;
3. PIMS-C/MIS-C non-specific form: fever, associated with biological inflammatory syndrome without meeting any of the criteria of shock or Kawasaki disease.

We analyzed parameters obtained from the patients' records, such as demographic data, medical history, epidemiological context (contact with, exposure to, or infection with SARS-CoV-2 within 2-6 weeks before presentation), symptoms at admission, clinical evolution, and the results of paraclinical investigations collected at admission (according to the hospital's investigative protocol). To establish whether the analyzed parameters were predictive of severity we decided to divide the patients into two groups. The first group included patients presenting features that allowed the diagnosis of PIMS-C/MIS-C Kawasaki-like phenotype, while the second group included patients with the other mentioned phenotypes.

Concerning patients with comorbidities, we would like to mention that we excluded from the analyzed group patients with pathological antecedents such as congenital heart malformations, congenital immune deficiencies, autoimmune diseases, or genetic diseases associated with cardiovascular pathology. We established these exclusion criteria under the condition that PIMS-C/MIS-C is a new entity with a hyperinflammatory substrate that is still incompletely elucidated and in which the degree of cardiac damage may vary. Therefore, to reduce possible interferences, we did not include patients who have presented the characteristics mentioned above in the analyzed group. During the analyzed period, the initial group included: a male adolescent diagnosed with agammaglobulinemia and Klinefelter's syndrome, who was undergoing background treatment with Gammanorm®; an adolescent girl diagnosed with systemic juvenile rheumatoid arthritis; and an adolescent with Marfan's syndrome and aortic dilatation.

We should also mention that the present study was not designed to address the therapeutic management of patients diagnosed with PIMS-C/MIS-C.

The obtained data were processed using Microsoft® Excel®. This study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the hospital.

Results and discussion

During the analyzed period (31st March to 31st December, 2020), a total of 4,146 patients were admitted to the hospital, 18 of whom (0.43%) met the necessary criteria for the diagnosis of PIMS-C/MIS-C. The first patient was hospitalized and diagnosed with PIMS-C/MIS-C in September 2020.

Starting in August 2020, Romania was struck by the second wave of the pandemic. This led to a significant increase in the number of cases in the general population, including among children [13]. In this epidemiological context and taking into account the data provided in the literature on the incidence of PIMS-C/MIS-C at the global level, we followed the appearance of the first cases of PIMS-C/MIS-C in the clinic. Upon considering the trend of SARS-CoV-2 infection in the population, during the studied period a correlation of such infection with PIMS-C/MIS-C matching that in the literature was observed [18]. For example, the first case diagnosed in the clinic appeared approximately 1 month after the start of the second wave of the pandemic (**Fig. 1**).

Regarding the epidemiological characteristics, the patients who met the inclusion criteria in this study were children aged between 4 months and 17 years and 10 months, having a median age of 5 years (IQR, 3-8.75). Although data in the literature mention a median age of 9 years (8-11 years) [15, 16, 21], for PIMS-C/MIS-C diagnosis, in the analyzed group we have observed a lower median age. Thus, older age of the patients represent one of the main differences between PIMS-C/MIS-C and Kawasaki disease. Relating this information to the severity of disease detected in the patients included in the group, it is observed that a younger age could represent a favorable prognostic factor, as mentioned elsewhere [17].

Regarding the sex of the patients, it was found that, as also mentioned by the CDC, the majority of patients were male (61%) [2, 9]. Meanwhile, none of the patients included in the study had associated comorbidities. Among the enrolled patients, 10 (56%) lived in an urban area.

For inclusion in this study, the presence of fever for at least 72 hours before presentation had

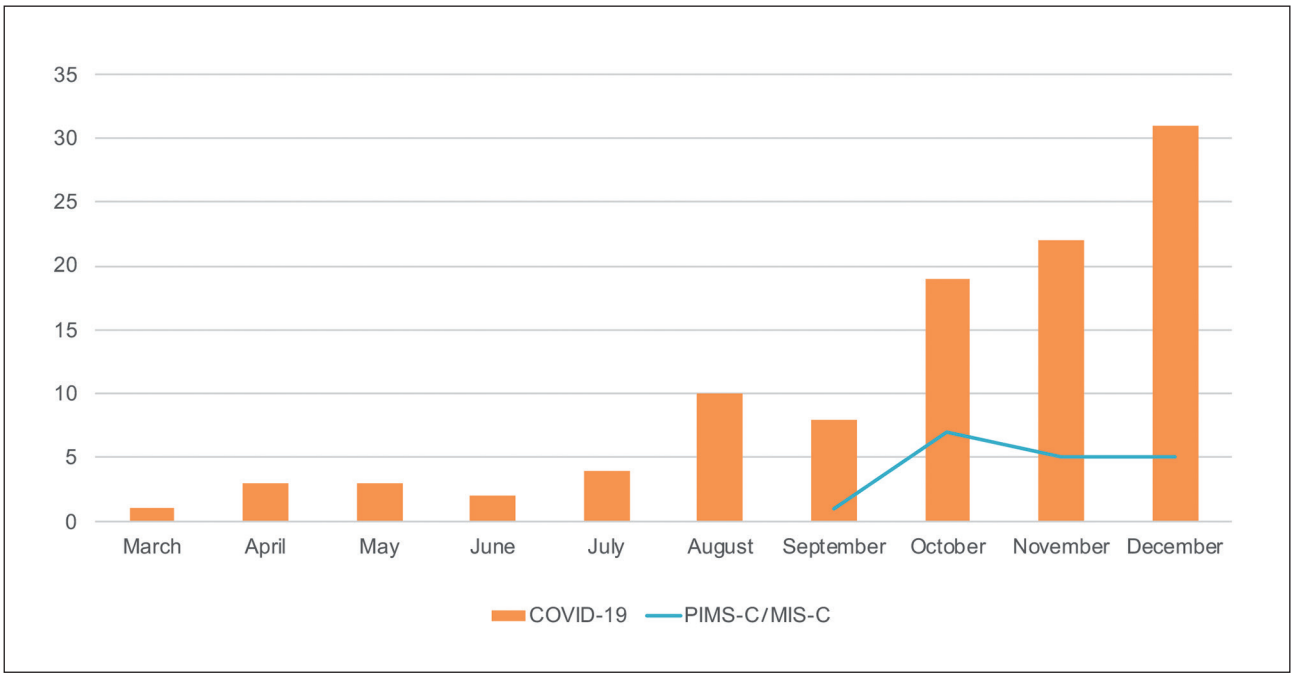

Figure 1. The temporal distribution of PIMS-C/MIS-C cases compared with SARS-CoV-2 infections in the first year of the pandemic.
PIMS-C/MIS-C: pediatric multisystemic inflammatory syndrome temporarily correlated with COVID-19/multisystemic inflammatory syndrome in children post-COVID-19.

originally been set as an essential factor. This was actually found in 17 (94%) patients among those evaluated. One of the patients presented 24 hours after the onset of fever, but given associations with all of the other diagnostic criteria, it was decided that this patient be included in the study.

To rule out other conditions, skin swabbing and cultures of blood sampled from a peripheral venous catheter were performed upon hospitalization, while cerebrospinal fluid was also sampled through a lumbar puncture in cases with neurological manifestations. In addition, serological screening was performed for a wide range of viruses (respiratory syncytial virus, adenovirus, Epstein-Barr virus, cytomegalovirus, influenza A and B viruses, rotavirus, norovirus). With the exception of one patient in whom positive serology for cytomegalovirus was identified (weakly positive IgM antibodies and positive IgG antibodies), no other positive serological tests were detected. It was decided that this one patient be included in the study group, considering that the cytomegalovirus infection most likely occurred subsequent to the onset of PIMS-C/MIS-C.

Upon analyzing the clinical pictures of the patients included in this study, three main phenotypes of the condition were identified, as also mentioned in international guidelines [14-16]. To outline a possible spectrum of PIMS-C/MIS-C for the pediatric patients included in the group, anamnestic data were evaluated (reasons for hospital admission and symptoms present at the time).

The study group was divided into two subgroups as follows: (i) those meeting the diagnostic criteria for the Kawasaki-like phenotype (11 patients) and (ii) the rest of the pediatric patients who were classified into the other mentioned phenotypes (7 patients). The clinical-paraclinical characteristics of the two groups are presented for comparison in **Tab. 2** and **Tab. 3**.

Upon admission, all of the enrolled patients presented with fever (with a maximum duration of 9 days), associated at varying rates with digestive, neurological, or skin-mucosal changes. Upon globally evaluating the 18 patients included in this study, the presence of digestive symptoms (abdominal pain, vomiting, diarrhea) was observed in 56% of the patients. Most of them experienced vomiting (39%) and abdominal pain (33%). This is in accordance with the findings in the literature, which describes the main clinical presentations of patients with PIMS-C/MIS-C as high fever and associated gastrointestinal manifestations [7, 15, 18]. In addition, notable proportions of patients presented with rash (56%), palmoplantar edema/erythema (16%), and conjunctival hyperemia (66%).

Table 2. Clinical and demographic characteristics of the enrolled patients.

Clinical and demographical characteristics		PIMS-C/MIS-C (n = 18)	PIMS-C/MIS-C Kawasaki-like phenotype (subgroup 2) (n = 11)	PIMS-C/MIS-C non Kawasaki-like phenotype [a] (subgroup 2) (n = 7)
Age, median (IQR), years		5 (3-8.75)	5 (3-7.5)	9 (1.5-11.5)
Sex	Male	11 (61)	7 (64)	4 (57)
	Female	7 (39)	4 (36)	3 (43)
Clinical features at admission	Abdominal pains	6 (33)	5 (45)	1 (14)
	Vomiting	7 (39)	4 (36)	3 (43)
	Diarrhea	5 (28)	3 (27)	2 (28)
	Exanthema	10 (56)	9 (82)	1 (14)
	Headache	5 (28)	3 (27)	2 (28)
	Agitation	1 (6)	1 (9)	0 (0)
	Sleepiness	1 (6)	0 (0)	1 (14)
	Myalgia	4 (22)	1 (9)	3 (43)
	Meningism	3 (17)	2 (18)	1 (14)
	Respiratory manifestation	0 (0)	0 (0)	0 (0)
Duration of hospitalization > 7 days		15 (83)	9 (82)	6 (86)
Known exposure to SARS-CoV-2 [b]		7 (39)	4 (36)	3 (43)

Data are presented as n (%), if not otherwise specified.
IQR: interquartile range; PIMS-C/MIS-C: pediatric multisystemic inflammatory syndrome temporarily correlated with COVID-19/ multisystemic inflammatory syndrome in children post-COVID-19.
[a] Non-Kawasaki-like phenotype: patients who did not fulfill the mentioned criteria for the Kawasaki-like form (non-specific form, shock-like form, unclassifiable form) were included; [b] known exposure to SARS-CoV-2 infection: history data related to the presence of contact with a confirmed COVID-19 case or documented COVID-19 infection 2-6 weeks before presentation were taken.

Table 3. Paraclinical characteristics of the patients.

Paraclinical characteristics	Reference values	PIMS-C/MIS-C (n = 18)	PIMS-C/MIS-C Kawasaki-like phenotype (subgroup 1) (n = 11)	PIMS-C/MIS-C non-Kawasaki-like phenotype [a] (subgroup 2) (n = 7)
Neutrophils (x 10^3/microL)	0-4 years: 1-8.5 5-11 years: 1.5-8 12-18 years: 1.8-8	11.2 (7.78-12.75)	10.5 (8-12.5)	12.4 (8.65-14.7)
Lymphocytes (x 10^3/microL)	0-4 years: 3-9.5 5-11 years: 1.5-7 12-18 years: 1.5-6.5	1.24 (1.02-2.08)	1.28 (1-1.9)	1.17 (1.04-4.09)
Platelets (x 10^3/microL)	150-400	150 (108.5-249.7)	139 (95.5-160)	266 (168-386)
NLR	-	7.06 (4.78-11.32)	8.91 (5.26-11.23)	5.50 (3.38-10.88)
PLR	-	103.6 (78.92-163.7)	96.5 (78.93-139)	115.4 (83.55-184.5)
CRP (mg/L)	< 5	144.4 (53.92-212.7)	134 (41.05-189.05)	162.9 (112.65-246.4)
Ferritin (ng/mL)	14-152	710.4 (491-1,527)	862.1 (520.73-1,625.9)	673 (355.5-968.8)
D-dimer (ng/mL)	> 500 [b]	910 (577.6-1,825)	770.2 (577.62-2,023.7)	941.5 (720.6-1,234.2)
Troponin (pg/mL) [c]	< 14	9 (4.82-20.2)	8 (3-16.3)	16.5 (8.47-191.7)
NT-proBNP (pg/mL) [d]	< 125	1,206 (1,123-1,742)	1,437 (876.5-2,756)	1,156 (1,123-1,286)
Echocardiography changes, n (%)	Pericarditis	5 (28)	4 (36)	1 (14)
	LV dysfunction	4 (22)	2 (18)	2 (28)
	Mitral regurgitation	6 (33)	5 (45)	1 (14)
	Dilation of coronary arteries	2 (11)	2 (18)	0 (0)
	Normal cord	8 (44)	5 (45)	3 (43)

Data are presented as median (IQR), if not otherwise specified.
CRP: C-reactive protein; IQR: interquartile range; LV: left ventricle; NLR: neutrophil-to-lymphocyte ratio; PIMS-C/MIS-C: pediatric multisystemic inflammatory syndrome temporarily correlated with COVID-19/multisystemic inflammatory syndrome in children post-COVID-19.; PLR: platelet-to-lymphocyte ratio.
[a] Non-Kawasaki-like phenotype: patients who did not fulfill the mentioned criteria for the Kawasaki-like form (non-specific form, shock-like form, unclassifiable form) were included; [b] 220-499 ng/ml: procoagulant stage; [c] troponin level could not be determined in 3 patients; [d] measuring the levels of NT-proBNP was not possible in 5 of the patients.

In addition, while suffering from fever, some patients presented various neurological manifestations (drowsiness alternating with psychomotor agitation, headache, meningism). Such manifestations were described as reasons for hospitalization in 10 (56%) of the patients included in this study. Among the 18 evaluated patients, an association with myalgia since the time of admission was described for 4 of them (22%).

SARS-CoV-2 is associated with damage to the respiratory system as the first site of infection. Respiratory manifestations are thus most frequently found in acute infection, but we noted that none of the patients included in the study presented such symptoms at the time of admission.

Evaluating the clinical pictures of the patients included in this study, three main phenotypes of the condition were identified (Kawasaki-like, shock-like, and a non-specific form). However, for 2 patients (11%), the clinical picture did not fit any of these three categories. Considering the recommendations on the internal diagnosis and treatment protocol of PIMS/MIS-C, these 2 cases were considered to involve a particular form of the disease characterized by an association of fever with digestive manifestations. **Fig. 2** shows the sex distribution of PIMS-C/MIS-C, according to phenotype.

The results revealed that 11 (subgroup 1) of the 18 enrolled patients (61%) presented a clinical picture overlapping with the Kawasaki-like form. Meanwhile, 3 of the evaluated patients (17%) presented isolated fever, with which significant paraclinical changes were associated (increased inflammatory markers), which allowed a diagnosis of PIMS-C/MIS-C non-specific form to be established. Notably, all 3 of these patients were female and under 5 years of age (the youngest patient enrolled was 4 months old).

Regarding the spectrum of multisystemic inflammatory syndrome, increasing research has indicated that the presence of skin-mucosal changes in patients with PIMS-C/MIS-C (and, in this case, of the Kawasaki-like phenotype) could represent a less severe prognostic factor, compared with the prognosis of patients classified with other disease phenotypes [14, 17]. Monitoring the two subgroups of patients, we observed that those classified into the group with the Kawasaki-like form had a longer hospitalization period than those classified as having the other phenotypes. This could suggest that this phenotype is associated with a more severe evolution of the disease, which does not correspond to the findings in the literature. However, it should be stated that the hospitalization period is influenced by numerous other factors. There is thus a need for more thorough monitoring of a significant group of patients in order to establish whether there are correlations between disease severity and the form of the illness.

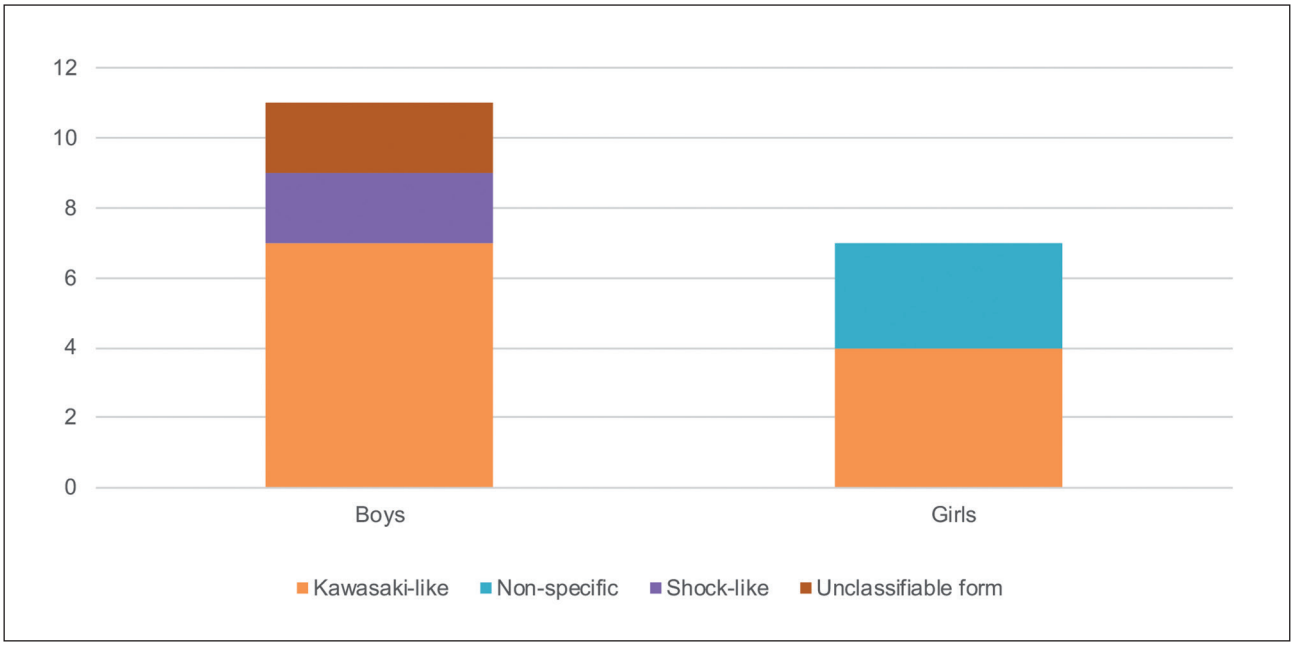

Figure 2. Distribution of the sexes according to the PIMS-C/MIS-C phenotype.
PIMS-C/MIS-C: pediatric multisystemic inflammatory syndrome temporarily correlated with COVID-19/multisystemic inflammatory syndrome in children post-COVID-19.

The temporal association with SARS-CoV-2 infection was analyzed by measuring the levels of SARS-CoV-2 IgG antibodies. All patients had significantly increased titers of these antibodies, confirming that they had contracted the disease. None of the analyzed patients had a positive result in the RT-PCR test for SARS-CoV-2 performed at admission. The possibility of exposure to/contact with COVID-19 in the last 2-6 weeks before the symptomatology occurred, could be established by anamnesis in 39% of patients. We also noted that, as the study was performed in the first year of the pandemic when vaccination against SARS-CoV-2 was not available, none of the enrolled patients benefited from specific immunization.

Among the laboratory investigations, paraclinical investigations were carried out, following a sequence recommended by the diagnostic and treatment protocol of the clinic, in conjunction with the recommendations of international guidelines. The paraclinical characteristics of the patients included in the study group are presented in **Tab. 3**. The biological inflammatory syndrome (an important feature of PIMS-C/MIS-C) was closely monitored. Thus, inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, and ferritin were evaluated. The reference value of CRP for the diagnosis of PIMS-C/MIS-C was considered to be above 50 mg/L. This criterion was met in 13 (72%) of the enrolled patients. Meanwhile, in 4 (22%) of the evaluated patients, CRP values > 30 mg/L were considered positive, allowing the inclusion of these patients in the study, given that other diagnostic criteria were met. One patient presented a CRP value that did not allow classification as suffering from PIMS-C/MIS-C, according to the diagnostic criteria. However, this patient met other criteria so was classified as having incomplete Kawasaki-like form and included in subgroup 1.

Blood count was performed on all of the patients included in the study, providing information on the hematological profile of PIMS-C/MIS-C patients. By analyzing the hematological changes, we attempted to establish new research hypotheses on the mechanisms behind the development of PIMS-C/MIS-C. In terms of the hematological changes detected at admission, lymphopenia was found in 13 patients (72%) and thrombocytopenia in 9 patients (50%).

PLR and NLR were evaluated in an attempt to detect possible correlations of these parameters in patients diagnosed with PIMS-C/MIS-C with the classification into one of the above-mentioned phenotypes. Considering the fact that inclusion in the Kawasaki-like phenotype group could be associated with a milder form of the disease, we followed whether the PLR and NLR differed between the two subgroups.

Rekhtman et al. mentioned that NLR is similar in patients presenting PIMS-C/MIS-C and rash (Kawasaki-like phenotype) [14], compared with the level in those in whom no skin-mucosal changes are described. They also mentioned that there is a significant difference between NLR in patients with PIMS-C/MIS-C and that in those with acute SARS-CoV-2 infection [14].

In the patients included in this study and diagnosed with the Kawasaki-like phenotype, higher median NLR and lower PLR were identified compared with the ratios of individuals with other forms of PIMS-C/MIS-C. The lack of standardization of these values, as well as the small number of patients in the study, prevented the identification of any statistically significant correlations.

The evaluation of cardiac damage was carried out both by measuring the levels of markers of cardiac injury (troponin, NT-proBNP) and by cardiological clinical evaluation and echocardiography. We found that measuring the levels of NT-proBNP was not possible in 5 of the evaluated patients, while troponin level could not be determined in 3 patients. The results on cardiac injury markers identified significantly elevated NT-proBNP values in 12 (92%) of the patients, while troponin had elevated levels in only 6 patients (40%). It was also observed that, in the patients with the highest NT-proBNP values, the echocardiographic evaluation detected significant changes, confirming the more severe cardiac damage, as illustrated in **Fig. 3**. The echocardiographic changes detected in the patients included in the study are presented in **Tab. 3**, following the distribution of these changes in the two subgroups.

The echocardiographic evaluation of the study group, which was performed in all patients included in the study, identified pericarditis-type changes in 5 (28%) of the patients, 4 of them presenting a Kawasaki-like phenotype. In addition, mitral regurgitation was found in 6 (33%) of the patients, 5 of them being in subgroup 1. The presence of left ventricular dysfunction was identified in 4 patients (22%). No differences in this regard were found between subgroups 1 and 2. Dilation of the coronary arteries (the main cardiac change

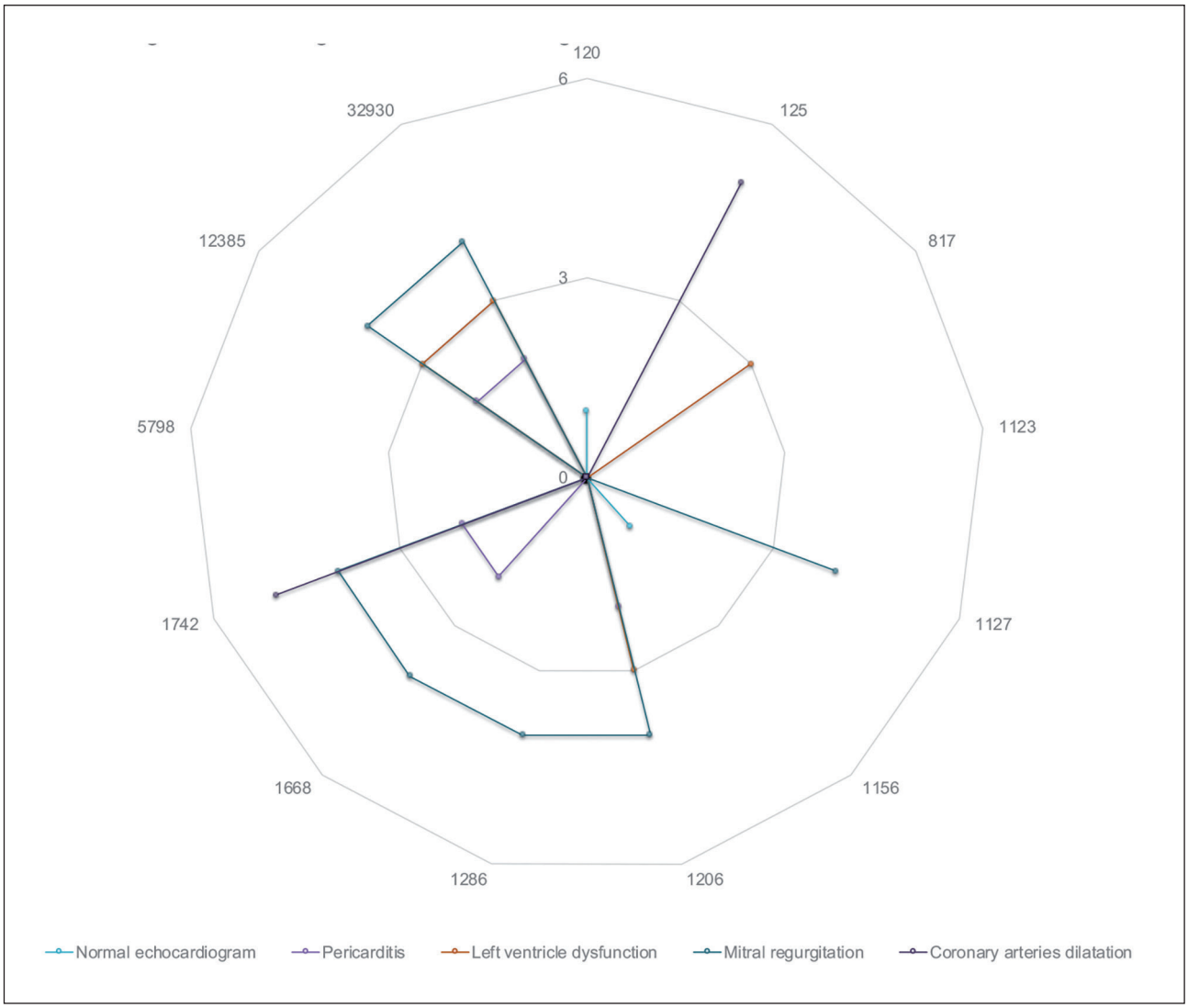

Figure 3. The degree of cardiac damage related to the values of cardiac markers.

described in Kawasaki disease) was observed in only 2 (11%) patients from those analyzed, both presenting a Kawasaki-like phenotype.

Comparing the results obtained in patients from the two subgroups, lower values of certain biological markers (CRP, D-dimers, troponin) were observed in the subgroup with the clinical picture of Kawasaki-like disease than in the subgroup that did not present a rash. This observation is consistent with data from the literature [14]. However, in the analyzed samples, we observed higher ferritin levels in the subset of patients with Kawasaki-like phenotype. These results are divergent from the data in the literature. In this context, we consider it necessary to perform a more extensive analysis of a larger group of patients in order to establish whether there are statistically significant correlations between certain biological markers.

Conclusions

PIMS-C/MIS-C has been a topic of great interest during the COVID-19 pandemic. In the literature, there is an abundance of reports on clinical studies and meta-analyses dedicated to this topic. PIMS-C/MIS-C is considered a serious complication of SARS-CoV-2 infection, found predominantly in the pediatric population. The increase in cases of systemic inflammatory syndrome in children, a syndrome overlapping with Kawasaki disease, in the first year of the COVID-19 pandemic was a concern for the medical profession. The possibility of a correlation between the appearance of a significant number of pediatric cases with manifestations similar to Kawasaki disease on the one hand and SARS-CoV-2 infection on the other hand was raised [7-9]. Currently, the main features that differentiate these two entities are known, but

it is believed that studying PIMS-C/MIS-C could answer many questions about Kawasaki disease that have remained unresolved for half a century. The current study draws attention to the PIMS-C/MIS-C spectrum, but also to the need to establish correlations between biological markers and the clinical evolution of the disease. The use of certain biological parameters easily obtained through a blood count (NLR, PLR) as well as determination of their correlation with disease severity could offer new approaches to treating this condition.

Cardiac damage is an important element in the evaluation of children diagnosed with PIMS-C/MIS-C, which highlights possible correlations between the use of cardiac injury markers and the echocardiographic changes detected in these patients. Thus, long-term monitoring of patients diagnosed with PIMS-C/MIS-C is considered necessary, especially regarding cardiac complications. Given the small size of the two analyzed samples in this study and the low power of the statistical analysis, the purpose of this study was mainly descriptive and this work was intended to generate hypotheses for future research.

Limitations of the study

This study has some limitations, particularly those related to the small size of the studied sample as well as the duration of the analyzed period. Given that the study was initiated at the beginning of the pandemic, before clear criteria for investigating PIMS-C/MIS-C cases were defined, some patients included in the sample did not benefit from full paraclinical investigations. Since there is no definitive diagnostic test for Kawasaki disease, the overlap of symptoms may have led to the erroneous diagnosis of some cases of Kawasaki disease as PIMS-C/MIS-C, or vice versa. In addition, the lack of access to an extensive range of serological analyses prevented the definitive exclusion of other differential diagnoses, which in certain cases have been classified as being associated with SARS-CoV-2 infection.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. WHO. Severe Acute Respiratory Syndrome (SARS). Available at: https://www.who.int/ith/diseases/sars/en, last access: April 2023.
2. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2);145-51.
3. UNICEF. COVID-19 and children. Available at: https://data.unicef.org/topic/covid-19-and-children, last access: February 2023.
4. National Institution of Public Health Romania. Infectia cu noul coronavirus SARS-CoV-2 - situatia la nivel global actualizata zilnic. Available at: http://www.cnscbt.ro/index.php/situatia-la-nivel-global-actualizata-zilnic, last access: December 2022.
5. Spatariu L, Buzoianu E, Chindriș S, Pleșca DA. Clinical and epidemiological characteristics in children confirmed with SARSCoV-2 infection in a non-COVID-19 Pediatric clinical hospital from Romania in the first 6 months of the pandemy. In: Vendemmia S, Vendemmia M. Lo Zibaldone del terzo Millennio. Naples: Cuzzolin Editore, 2020, pp. 235-45.
6. CDC COVID-19 Response Team; Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus Disease 2019 in Children – United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.
7. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.
8. European Centre for Disease Prevention and Control. Rapid risk assessment: paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. Available at: https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment, date of publication: May 2020, last access: April 2023.
9. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). Available at: https://emergency.cdc.gov/han/2020/han00432.asp, date of publication: May 2020, last access: February 2023.
10. Whittaker E, Bamford A, Kenny J, Karaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, Kucera F, Brierley J, McDougall M, Carter M, Tremoulet A, Shimizu C, Herber J, Burns J, Lyall H, Levin M. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324(3):259-69.
11. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance, date of publication: May 2020, last access: February 2023.
12. WHO. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19, date of publication: May 2020, last access: April 2023.

13. Spatariu L, Buzoianu E, Davitoiu A, Chindris S, Zamfirescu A, Iancu M, Ghiorghiu I, Tincu I, Dorobantu A, Plesca V Plesca, DA. Variation of clinical patterns of COVID-19 disease in children in the first year of pandemic. Romanian J Pediatrics. 2021;70(2):114-21.
14. Rekhtman S, Tannenbaum R, Strunk A, Birabaharan M, Wright S, Garg A. Mucocutaneous disease and related clinical characteristics in hospitalized children and adolescents with COVID-19 and multisystem inflammatory syndrome in children. J Am Acad Dermatol. 2021;84(2):408-14.
15. Belay ED, Abrams J, Oster ME, Giovanni J, Pierce T, Meng L, Prezzato E, Balachandran N, Openshaw JJ, Rosen HE, Kim M, Richardson G, Hand J, Tobin-D'Angelo M, Wilson S, Hartley A, Jones C, Kolsin J, Mohamed H, Colles Z, Hammett T, Patel P, Stierman B, Campbell AP, Godfred-Cato S. Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic. JAMA. 2021;175(8):837-45.
16. McCrindle BW, Manlhiot C. SARS-CoV-2-related inflammatory multisystem syndrome in children: different or shared etiology and pathophysiology as Kawasaki disease? JAMA. 2020;324(3): 246-8.
17. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP, Leung JW, Tsang CA, Pierce TJ, Kennedy JL, Hammett TA, Belay ED. 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;5(5):323-31.
18. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, Singh AR, Li S, Tarquinio KM, Jaggi P, Oster ME, Zackai SP, Gillen J, Ratner AJ, Walsh RF, Fitzgerald JC, Keenaghan MA, Alharash H, Doymaz S, Clouser KN, Giuliano JS, Gupta A, Parker RM, Maddux AB, Havalad V, Ramsingh S, Bukulmez H, Bradford TT, Smith LS, Tenforde MW, Carroll CL, Riggs BJ, Gertz SJ, Daube A, Lansell A, Munoz AC, Hobbs CV, Marohn KL, Halasa NB, Patel MM, Randolph AG. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383(4):334-46.
19. Qu R, Ling Y, Zhang Y, Hui Zhi, Wei L, Chen X, Li X, Liu X, Liu H, Guo Z, Ren H, Wang Q. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. J Med Virol. 2020;92(9):1533-41.
20. Chiheri DM, Săsăran MO, Meliţ LE. Rolul determinării volumului trombocitar mediu și a raportului trombocite/limfocite în evaluarea severității infecțiilor respiratorii acute la copii. Romanian J Pediatrics. 2020;69(2):134-9.
21. Dionne A, Son MBF, Randolph AG. An Update on Multisystem Inflammatory Syndrome in Children Related to SARS-CoV-2. Pediatric Infect Dis J. 2022;41(1):e6-e9.
22. Rostad CA, Chahroudi A, Mantus G, Lapp SA, Teherani M, Macoy L, Tarquinio KM, Basu RK, Kao C, Linam WM, Zimmerman MG, Shi PY, Menachery VD, Oster ME, Edupuganti S, Anderson EJ, Suthar MS, Wrammert J, Jaggi P. Quantitative SARS-CoV-2 Serology in Children With Multisystem Inflammatory Syndrome (MIS-C). Pediatrics. 2020;146(6):e2020018242.