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ORIGINAL ARTICLE

Multisystem inflammatory syndrome in children: clinical presentation, management, and short- and long-term outcomes

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Abstract

Objective In this study, it was aimed to evaluate the demographic, clinical and laboratory characteristics of MIS-C patients in our hospital, to share our treatment approach, and to assess the outcomes of short- and long-term follow-up.

Methods MIS-C patients who were admitted and treated in our hospital between July 2020 and July 2021 were evaluated. Demographic, clinical, laboratory, and follow-up data were collected from patient records retrospectively.

Results A total of 123 patients with MIS-C (median age, 9.6 years) were included the study. Nineteen (15.4%) were mild, 56 (45.6%) were moderate, and 48 (39%) were severe MIS-C. High CRP, ferritin, pro-BNP, troponin, IL-6, and D-dimer values were found in proportion to the severity of the disease ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.005$, $p<0.001$), respectively. Two (1.6%) patients died. The mean follow-up period was 7.8 months. Valve failure, left ventricular dysfunction/hypertrophy, coronary involvement, and pericardial effusion were the most common cardiac pathologies in the short- and long-term follow-up of the patients. In the long-term follow-up, the most common reasons for admission to the hospital were recurrent abdominal pain (14.2%), cardiac findings (14.2%), pulmonary symptoms (8%), fever (7.1%), neuropsychiatric findings (6.2%) and hypertension (3.5%). Neuropsychiatric abnormalities were observed significantly more common in severe MIS-C patients at follow-up ($p=0.016$). In the follow-up, 6.2% of the patients required recurrent hospitalization.

Conclusion MIS-C is a serious and life-threatening disease, according to short-term outcomes. In addition to the cardiac findings of patients with MIS-C, long-term outcomes such as neuropsychiatric findings, persistent gastrointestinal symptoms, fever and pulmonary symptoms should be monitored.

Key Points
- *In MIS-C patients, attention should be paid not only to cardiac findings, but also to symptoms related to other systems.*
- *Patients should be followed up in terms of neuropsychiatric findings, persistent gastrointestinal symptoms, fever and pulmonary symptoms that may occur during follow-up.*

Keywords COVID-19 · Hyperinflammation · MIS-C · Pediatric

Abbreviations

BNP	Brain natriuretic peptide
CRP	C-reactive protein
COVID-19	Coronavirus disease 2019
IL	Interleukin
ICU	Intensive care unit
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
LVEF	Left ventricular ejection fraction
MIS-C	Multisystem inflammatory syndrome in children
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

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Introduction

Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory disorder which is affecting multiple organs caused by severe acute respiratory syndrome

coronavirus-2 (SARS-CoV-2) [1]. MIS-C usually occurs 4–6 weeks after infection, suggesting that the disease is caused by post-infectious immune dysregulation [2]. Diagnostic criteria are fever, high inflammatory markers, involvement of at least two systems (cardiac, renal, respiratory, dermatological, hematological, gastrointestinal, and neurological) and exposure to SARS-CoV-2 or evidence of COVID-19 infection (RT-PCR, antigen testing, or serology positive). Laboratory findings include elevated markers of inflammation, hypercoagulability, and myocardial damage [2]. Cardiac findings (left ventricular dysfunction, myocarditis, pericarditis, valve insufficiency, coronary artery ectasia, or aneurysm) or shock symptoms and signs (hypotension, hypoxemia, altered consciousness) are the most important findings in determining morbidity and mortality [3].

In treatment, intravenous immunoglobulin (IVIG), corticosteroids and, if necessary, biological agents (anakinra, tocilizumab, infliximab) are used. Aspirin and/or anticoagulants are commonly administered in children with MIS-C [4]. It is clear that, if appropriate treatment is provided on time, the prognosis will generally be good [5].

Given the worldwide fluctuations in COVID-19 and virus mutations, it is important to predict MIS-C and its possible complications. Although the short-term outcome of MIS-C appears to be favorable with supportive care and immunomodulatory treatment, long-term follow-up data are limited and studies on long-term outcomes continue. Long-term management of MIS-C is based on experience with other inflammatory conditions such as Kawasaki disease (KD) [6, 7]. In the long-term follow-up, the most common findings are cardiac such as coronary artery aneurysm, myocardial dysfunction, valve regurgitation, and also myocardial edema and fibrosis in cardiac magnetic resonance imaging [8–13]. Moreover, there are few data on non-cardiac complications after discharge, such as gastrointestinal and minor neurological abnormalities [11, 13].

In this study, it was aimed to evaluate the demographic, clinical and laboratory characteristics of MIS-C patients in our hospital, to share our treatment approach, and to assess the outcomes of short- and long-term follow-up.

Material and methods

Patients

The present retrospective study comprised children who met the WHO criteria for MIS-C and were admitted between July 2020 and July 2021 to our hospital [1]. The WHO criteria included fever, rash, shock, heart failure, coagulopathy, gastrointestinal manifestations in the presence of elevated acute phase reactants, evidence of recent COVID-19 infection, and exclusion of other possible causes.

Ethics

Ethics committee approval was received from the Scientific and Ethics Committee of our hospital (Approval number: E2-21–580).

Inclusion and exclusion criteria

Patients with other disease explaining their symptoms were excluded. Except for two patients who died during hospitalization, patients with a follow-up period of less than one month were also excluded from the study.

Data collection

Data were collected from patient files retrospectively. Age at diagnosis, sex, clinical findings, duration of symptoms, during the hospital stay, follow-up, all initial laboratory parameters including white blood cell count (WBC), lymphocyte count, hemoglobin (Hb), platelet counts (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver and kidney function tests, ferritin, D-dimer, markers of myocardial inflammation (troponin/Pro-BNP), interleukin (IL)-6, and fibrinogen levels, abdominal ultrasonography findings, and treatment were recorded. Complete blood count, CRP, ESR, liver and kidney function tests, and ferritin values were recorded in the first week and first months of follow-up. Echocardiographic findings on admission and during follow-up (first week, first month, and third month) were also collected.

Patients were clinically classified as mild, moderate, and severe MIS-C according to their vasoactive requirement (based on vasoactive inotropic score), the need for respiratory support, and organ damage [14]. Left ventricular ejection fraction (LVEF) was based on modified Simpson's method and categorized as either normal ($\geq 55\%$), or mild (45–54%), moderate (30–44%) or severe impairment ($< 30\%$) [15]. According to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, acute kidney injury was defined as an increase in serum creatinine of 0.3 mg/dL within 48 h or an increase in serum creatinine that was 1.5 times the baseline within 7 days [16]. The serum creatinine level recorded in the 6–12 months prior to hospitalization was used as a reference to define the increase in serum creatinine. These criteria defined patients with high creatinine as having acute kidney injury.

Definition of short-term and long-term outcomes

The findings that develop during hospitalization and within the first month after discharge are included under the heading of "short-term outcomes"; and the findings developing

1 month after discharge were evaluated under the title of "long-term outcomes." For patients who were hospitalized for MIS-C, follow-up visits were arranged in accordance with general standard practice of our hospital, in the first week and first month after discharge from the hospital. The visits included medication reconciliation, follow-up of the clinical course after the hospitalization, and clinical, laboratory and cardiac evaluations. Also, cardiac and clinical evaluations were performed at the third month follow-up.

Statistical analyses

The statistical analyses were performed using the SPSS software version 25. The normal distribution of the variables was investigated using visual (histograms, probability plots) and analytical (Kolmogorov–Smirnov/Shapiro–Wilk tests) methods. Descriptive statics are presented using medians and interquartile ranges (IQR) for the non-normally distributed and ordinal variables and frequencies for the categorical variables. In the comparisons between groups, Mann–Whitney *U* test was used for the non-normally distributed variables and ordinal variables, and Chi-squared or Fisher's tests were used for the categorical variables. A *p*-value smaller than 0.05 was considered to show a statistical significance.

Results

Demographic characteristics

One hundred twenty-three patients with MIS-C, of which 78 (63.4%) were male (male-to-female ratio = 1.73:1), were included in the study. The median age of the patients was 9.6 years (min–max: 1.4–17.4 years) at the onset of the disease. The median duration was 4 weeks (2–12) between possible SARS-CoV-2 exposure and occurring of MIS-C symptoms in 64 patients with a history of contact with COVID-19. The median follow-up time was 7.8 months (IQR: 4.7–10.7).

Eleven children (8.9%) had comorbidities [operated congenital heart disease ($n=2$), Fanconi anemia ($n=1$), juvenile idiopathic arthritis ($n=1$), osteosarcoma ($n=1$), vitiligo ($n=2$), asthma ($n=3$), inflammatory bowel disease ($n=1$)].

Clinical, laboratory and imaging findings at admission

MIS-C was mild in 19 (15.4%), moderate in 56 (45.6%), and severe in 48 (39%) patients. Fever was the first and common sign. Median duration of fever was 4 days (min–max: 1–10). The most common presenting symptom after fever is gastrointestinal findings (80.5%). KD-like presentation was found 50 (40.7%) patients. Severe MIS-C patients had significantly older age, longer symptom duration, also prolonged length of hospital stay and intensive care hospitalization than mild-to-moderate MIS-C patients ($p=0.034$, $p=0.005$, $p<0.001$, $p<0.001$, respectively). The clinical and laboratory characteristics of the patients are shown in Table 1. High CRP, ferritin, pro-BNP, troponin, IL-6, and D-dimer values were found related to the severity of the disease ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.005$, $p<0.001$, respectively). Elevated liver enzymes were found in 41 (33.3%) of the patients, and acute kidney injury in 28 (22.8%) patients at admission.

Cardiac abnormalities were present in 80 (65%) patients at admission. The median LVEF was 65% (58–70). Left ventricular dysfunction, valve insufficiency, pericardial effusion, and myocarditis were significantly more common in severe MIS-C patients compared to mild/moderate MIS-C patients ($p<0.001$, $p<0.001$, $p=0.003$, $p=0.003$, respectively). Echocardiography and abdominal ultrasonography findings are shown in Table 2. The abdominal ultrasonography findings of 6 (4.9%) patients were consistent with acute appendicitis, so, appendectomy was performed.

Short-term outcomes in hospitalization

Sixty-seven patients (54.5%) had hypotension, 47 (38.2%) of whom required vasoactive drugs. Seven (5.7%) children required mechanical ventilation. Thrombus developed in 4 (3.3%) patients and fungal sepsis occurred in 2 (1.6%) patients.

Intravenous immunoglobulin (IVIG) was administered to all patients except two patients. IVIG dose was adjusted according to the hemodynamic status, LVEF, and Kawasaki-like symptoms of the patients. IVIG therapy was applied 1 g/kg/day (max 70 gr) as a divided dose in 2 days in 59 (48%) patients, and 61 (51.2%) patients had IVIG 2 g/kg/day as single dose in 1 day. Corticosteroid was given to 84.6% patients and anakinra to 34.4%. Tocilizumab was administered to 2 patients who did not respond to anakinra. Plasmapheresis was performed to 19.5% of patients. The duration of corticosteroid use was longer in severe MIS-C patients ($p<0.001$). The treatments administered to the patients are given in Table 3.

One hundred twenty-one patients were discharged with a median hospital stay of 12 days (8–16.5). Two patients (1.6%) died as a result of heart failure and arrhythmia.

At the 1st week after discharge, the most common complaints of the patients were gastrointestinal system complaints 10 (8.3%), rash 6 (5%), arthralgia 6 (5%), fatigue 5 (4.1%), myopathy 3 (2.5%), and fever 3 (2.5%) also; liver enzymes were elevated in 57 (49.1%) patients, and acute kidney injury in 2 (1.8%) patients.

Table 1 Clinical, demographic, and laboratory characteristics of MIS-C patients

	All patients ($n=123$)	Mild/moderate MIS-C ($n=75$)	Severe MIS-C ($n=48$)	p value
Gender, male[*]	78 (63.4)	49 (65.3)	29 (60.4)	0.58[b]
Age at diagnosis (years)[†]	9.6 ± 4.4	8.9 ± 4.6	10.6 ± 4	0.034[a]
Duration of symptoms (day)[‡]	4 (3–5) [g]	3 (2–4) [f]	4 (3–5) [e]	0.005[c]
Hospitalization time (day)[‡]	12 (8–16.5)	10 (8–13)	15 (12–19)	< 0.001[c]
İntensive care hospitalization *n* (%)	67 (54.5)	22 (29.3)	45 (93.8)	< 0.001[b]
İntensive care duration (day)[‡]	6 (3–8)	3 (2–6)	7 (4–9)	< 0.001[c]
Kawasaki-like MIS-C *n* (%)	50 (40.7)	29 (38.7)	21 (43.8)	0.58[b]
Clinical findings *n* (%)				
Abdominal pain *n* (%)	63 (51.2)	38 (50.7)	25 (52.1)	0.88[b]
Vomiting *n* (%)	63 (51.2)	36 (48)	27 (56.3)	0.37[b]
Diarrhea *n* (%)	40 (32.5)	21 (28)	19 (39.6)	0.18[b]
Conjunctivitis *n* (%)	34 (27.6)	19 (25.3)	15 (31.3)	0.47[b]
Skin rash *n* (%)	32 (26)	19 (25.3)	13 (27.1)	0.83[b]
Headache *n* (%)	18 (14.6)	9 (12)	9 (18.8)	0.30[b]
Pulmonary symptoms *n* (%)	16 (13)	6 (8)	10 (20.8)	0.039[b]
Lymphadenopathy *n* (%)	13 (10.6)	8 (10.7)	5 (10.4)	0.97[b]
Laboratory findings				
WBC (10^9/L)[‡]	9.4 (6.9–13.7)	9.4 (6.88–13.5)	9.4 (7.2–14.6)	0.63[c]
Lymphocyte count (10^9/L)[‡]	0.92 (0.65–1.36)	1.07 (0.68–1.78)	0.8 (0.54–1.03)	0.005[c]
Hemoglobin (g/dL)[†]	12.2 ± 1.7	12.4 ± 1.5	12 ± 1.9	0.17[a]
Platelet (10^9/L)[‡]	210 (140–272)	235 (168–298)	153 (111–235)	< 0.001[c]
ESR (mm/h)[†]	43.7 ± 23.7	42.5 ± 22.7	45.4 ± 25.2	0.52[a]
CRP (mg/dL)[†]	148.6 ± 73.5	127 ± 57.9	182.5 ± 82.7	< 0.001[a]
AST (U/L)[‡]	34 (23–53)	33 (23–44)	36 (23–58)	0.32[c]
ALT (U/L)[‡]	26 (17–42)	23 (16–40)	30 (22–61)	0.012[c]
Creatinine (mg/dL)[‡]	0.5 (0.4–0.66)[e]	0.47 (0.37–0.63)	0.59 (0.45–0.89)	0.006[c]
Ferritin (μg/L)[‡]	252 (147–664)[e]	206 (123–364)	502 (242–1441)	< 0.001[c]
D–dimer (mg/L)[‡]	3.07 (1.54–5.3)[d]	2.04 (1.2–4.3)	4.07 (2.7–6.63)	< 0.001[c]
Troponin (ng/L)[‡]	11 (2.5–86)	2.6 (2.5–26)	91.5 (13–341.8)	< 0.001[c]
Pro-BNP (ng/L)[‡]	1222 (210–4698)[e]	500 (128–1634)	3214 (1630–8072)	< 0.001[c]
IL-6 (pg/mL)[‡]	94.2 (38.6–212)[f]	69.2 (32.2–132.5)	154 (50.6–284)	0.005[c]

[†]Mean ± standard deviation

[‡]Median (ınterquartile range)

[a]Independent-samples *T* test

[b]Chi-square

[c]Mann-Whitney *U*

[d]1 patient not available for assessment

[e]2 patients not available for assessment

[f]3 patients not available for assessment

[g]5 patients not available for assessment

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; WBC, white blood cell

In the 1st month follow-up after discharge, the most common complaints (data of 109 patients) were gastrointestinal system complaints 18 (16.5%), arthralgia 9 (8.2%), fever 8 (7.3%), chest pain 8 (7.3%), fatigue 3 (2.7%). and rash 3 (2.7%) also; 14 (14.9%) patients had elevated liver function tests and 4 (4.7%) patients had acute kidney injury.

Table 2 Echocardiography and abdominal ultrasonography findings

	All patients ($n=123$)	Mild/moderate MIS-C ($n=75$)	Severe MIS-C ($n=48$)	p value
Echocardiography n (%)				
LV dysfunction	45 (36.6)	13 (17.3)	32 (66.7)	<0.001[a]
Valve failure	58 (47.2)	25 (33.3)	33 (68.8)	<0.001[a]
Pericardial effusion	31 (25.2)	12 (16)	19 (39.6)	0.003[a]
Coronary involvement	14 (11.4)	11 (14.7)	3 (6.3)	0.15[a]
Myocarditis	6 (4.9)	0 (0)	6 (12.5)	0.003[b]
LVEF (%)*	65 (58–70)	68 (64–72)	58.5 (52–65.8)	<0.001 [c]
LVEF n (%)				0.001[a]
30–44	2 (1.6)	0 (0)	2 (4.2)	
45–54	20 (16.3)	6 (8)	14 (29.2)	
>55	101 (82.1)	69 (92)	32 (66.7)	
Abdominal ultrasonography[c] n (%)				
Bowel wall thickening	28 (27.2)	15 (25)	13 (30.2)	0.56[a]
Lymphadenopathy	42 (40.8)	25 (41.7)	17 (39.5)	0.83[a]
Ascites	48 (46.6)	21 (35)	27 (62.8)	0.005[a]
Mesenteric inflammation	16 (15.5)	8 (13.3)	8 (18.6)	0.47[a]
Appendicitis findings	10 (9.7)	8 (13.3)	2 (4.7)	0.19[b]
Hepatosplenomegaly	11 (10.7)	7 (11.7)	4 (9.3)	0.76[b]

*Median (ınterquartile range)

[a]Chi-square

[b]Fisher's exact test

[c]20 patient not available for assessment

LV, left ventricle, LVEF, left ventricular ejection fraction

Eighty-two (68.3%) patients in the 1st week and 65 (59.6%) in the 1st month did not have any complaints in the outpatient clinic control.

Long-term outcomes

Eighty-one (65.9%) patients were followed up in our hospital for more than 6 months. In the long-term follow-up, the most common reasons for admission to the hospital were recurrent abdominal pain (14.2%), cardiac findings (14.2%), pulmonary symptoms (8%), fever (7.1%), neuropsychiatric findings (6.2%), and hypertension (3.5%). Neuropsychiatric abnormalities were observed significantly more common in severe MIS-C patients at follow-up ($p=0.016$). In the follow-up, 6.2% of the patients required recurrent hospitalization.

Patients with severe MIS-C had lower LVEF at the first week, first month, and third month on echocardiography than patients with mild and moderate MIS-C ($p<0.003$, $p<0.047$, $p=0.038$, respectively). Valve failure, left ventricular dysfunction/hypertrophy, coronary involvement, and pericardial effusion were the most common cardiac pathologies in the short- and long-term follow-up of the patients. Echocardiographic findings and the short and long-term prognosis outcomes of mild, moderate and severe MIS-C patients are shown in Table 4.

Discussion

We describe 123 patients younger than 18 years of age who met the criteria for MIS-C associated with SARS-CoV-2 infection. Most children in our study seem to have a favorable short-term prognosis, as reported in other studies revealing short-term findings in MIS-C patients [17–19]. However, long-term follow-up studies in this disease are limited. In our study, it was revealed that patients should be followed up in terms of gastrointestinal, cardiovascular and neurological findings in long-term follow-up.

Our experience with MIS-C patients suggested that children with MIS-C may present with a spectrum ranging from mild to severe. During initial hospitalization, patients with severe MIS-C may develop life-threatening clinical deterioration and hemodynamic decompensation. These patients may require cardiopulmonary support. In our study, 54.5% of the patients had hypotension, 38.2% required vasoactive drug support and 5.7% needed mechanical ventilation. Sixty-seven (54.5%) patients were followed up in the intensive care unit (ICU). According to studies from Turkey, the rate of intensive care hospitalization was 29.6–46.7%, the need for mechanical ventilation was 11.1–12.4%, and the need for vasoactive drug support was 17.7–35.7% [20–24]. In the review of

Table 3 Treatment approach of moderate and severe MIS-C patients

	All patients ($n=123$)	Mild/moderate MIS-C (n=75)	Severe MIS-C ($n=48$)	p value
Use of corticosteroids[d] n (%)				<0.001[a]
Prednisolone (2 mg/kg)[a]	36 (29.3)	36 (64.3)	0 (0)	
Methylprednisolone (30 mg/kg)[a]	68 (55.3)	20 (26.7)	48 (100)	
Indication for using steroid[e] n (%)				<0.001[a]
Low LVEF/hypotension	68 (68.7)	23 (45.1)	45 (93.7)	
Resistant fever	24 (24.2)	21 (41.2)	3 (6.3)	
Gastrointestinal symptoms	5 (5.1)	5 (9.8)	0 (0)	
Persistent elevation in acute phase reactants	2 (2)	2 (3.9)	0 (0)	
Duration of steroid use[†] (day)	30 (24–36)[f]	27 (22–31.5)	35 (28.3–44.8)	<0.001[b]
Anakinra n (%)	42 (34.4)	6 (8.1)	36 (75)	<0.001[a]
Anakinra dosage (mg/kg/day)[†]	6,6 (5.5–7.7)[g]	5,5 (4.8–6.7)	6.6 (6–7.9)	0.13[b]
Duration of Anakinra use[†] (day)	11 (10–13)[g]	10 (7.3–11)	12 (10–14)	0.060[b]
Plasmapheresis n (%)	24 (19.5)	1 (1.3)	23 (47.9)	<0.001[a]

[†]Median (ınterquartile range)

[a]Chi-square

[b]Mann-Whitney U

[d]104 patients received corticosteroid therapy

[e]5 patients not available for assessment

[f]7 patients not available for assessment

[g]42 patients recieved anakinra

LVEF, left ventricular ejection fraction

Ahmed et al., 71% of the patients were followed in the ICU, and 22.2% of the patients needed mechanical ventilators [25]. Ramcharan et al. reported the need for vasoactive drugs as 67% [15]. In the study of Bagri et al., the need for inotropes was found to be 41.9% and mechanical ventilator support as 22.5% [7]. According to a systematic review (655 patients), intensive care was required in 68% of patients, inotropic support was required in 40%, mechanical ventilation was required in 15% [26]. In our study, the patients' need for intensive care, mechanical ventilators and vasoactive drugs were generally less than in the literature, but the rate of ICU hospitalization was higher than in studies conducted in Turkey.

Abrams et al. reported that troponin, BNP, pro-BNP, ferritin, C-reactive protein, and D-dimer may be helpful in identifying children who may be at increased risk for severe disease outcomes, including admission to the ICU, shock and decreased cardiac function [27]. Two studies from Turkey showed that older age, bradycardia, myocarditis, hypoalbuminemia and hyponatremia were predictive factors for intensive care unit admission [19, 20]. In our study, CRP, ferritin, pro-BNP, troponin, IL-6 and D-dimer levels at admission were higher in patients with serious disease. In addition, low lymphocyte count and thrombocytopenia were also found to be associated with severe disease in our study.

Thrombosis is frequently reported in adults with COVID-19, but is a rare finding in children [7]. Feldstein et al. reported a child with imaging-confirmed symptomatic venous thromboembolism [2]. Similarly, in our study, thrombosis was rarely seen at a rate of 3.3%.

Approximately 80% of patients presented with gastrointestinal symptoms. Abdominal ultrasonography revealed findings consistent with appendicitis in 9.7% of the patients. Appendectomy was performed in 4.9% of these patients. In the literature it has been reported that approximately 10–30% of cases of MIS-C can mimic symptoms of appendicitis [28]. In a case series, 8 (23.5%) of 34 patients underwent appendectomy, and complicated appendicitis was found in three of these patients [29]. It has been reported that MIS-C can mimic appendicitis and the findings will improve with immunomodulatory treatment.

SARS-CoV-2-associated MIS-C is a newly defined disease with a generally good prognosis but requires further research. It has been reported that 70–97% of MIS-C patients recovered without sequelae, even if they initially presented with a severe clinical finding [30]. It is recommended that patients be followed in the long-term, especially in terms of cardiac involvement [30, 31]. Due to its similarity to KD, coronary artery aneurysm has been reported in the literature, mostly as a long-term sequela, and it is recommended to be followed up like KD [31, 32]. In the 3rd month echocardiography controls of our patients; 8.7% valve failure, 2.9% coronary involvement, 6.7% left ventricular hypertrophy, 7.7% secundum ASD, and 2.9% left ventricular dysfunction were seen. The rate of cardiac sequelae in long-term follow-up varies between studies. In the study of Bagri et al., the

Table 4 Echocardiographic findings and the long-term prognosis results of mild, moderate and severe MIS-C patients

	All patients ($n=123$)	Mild/moderate MIS-C ($n=75$)	Severe MIS-C ($n=48$)	p value
Echo, first week[e] n (%)				
LV dysfunction	8 (7)	3 (4.3)	5 (11.1)	0.26[d]
Valve failure	33 (28.7)	14 (20)	19 (42.2)	0.010[b]
Pericardial effusion	15 (13)	7 (10)	8 (17.8)	0.23[b]
Coronary involvement	2 (1.7)	1 (1.4)	1 (2.2)	1.00[d]
LV hypertrophy	4 (3.5)	1 (1.4)	3 (6.7)	0.30[d]
Secundum ASD	2 (1.7)	2 (2.9)	0 (0)	0.52[d]
LVEF, first week[†]	68.8 ± 4.2[e]	69.7 ± 4	67.4 ± 4.2	0.003[a]
Echo, first month[f] n (%)				
LV dysfunction	8 (7.5)	4 (6.3)	4 (9.1)	0.71[d]
Valve failure	18 (16.8)	7 (11.1)	11 (25)	0.059[b]
Pericardial effusion	8 (7.5)	4 (6.3)	4 (9.1)	0.71[d]
Coronary involvement	2 (1.9)	0 (0)	2 (4.5)	0.17[d]
LV hypertrophy	3 (2.8)	0 (0)	3 (6.8)	0.067[d]
Secundum ASD	1 (0.9)	1 (1.6)	0 (0)	1.00[d]
LVEF, first month[‡]	68 (66–70)[f]	68 (67–70)	67 (64–70.8)	0.047[c]
Echo, third month[g] n (%)				
LV dysfunction	3 (2.9)	1 (1.6)	2 (4.7)	0.57 [d]
Valve failure	9 (8.7)	4 (6.6)	5 (11.6)	0.48 [d]
Coronary involvement	3 (2.9)	1 (1.6)	2 (4.7)	0.57 [d]
LV hypertrophy	7 (6.7)	4 (6.6)	3 (7)	1.00 [d]
Secundum ASD	8 (7.7)	6 (9.8)	2 (4.7)	0.47 [d]
LVEF, third month[‡]	67 (65–71)[g]	68 (65.5–72)	66 (65–70)	0.038[c]
Clinical findings until the last follow-up period n (%)				
Fever	8 (7.1)[h]	5 (7.4)[i]	3 (6.7)[j]	1.00[d]
Recurrent abdominal pain	16 (14.2)[h]	8 (11.8) [i]	8 (17.8) [j]	0.37[b]
Cardiac involvement	16 (14.2)[h]	8 (11.8) [i]	8 (17.8) [j]	0.37[b]
Neuropsychiatric findings	7 (6.2)[h]	1 (1.5) [i]	6 (13.3) [j]	0.016[d]
Hypertension	4 (3.5)[h]	3 (4.4) [i]	1 (2.2) [j]	1.00[d]
Pulmonary symptoms	9 (8)[h]	2 (2.9) [i]	7 (15.6) [j]	0.028[d]
Pancreatitis	1 (0.9) [h]	0 (0) [i]	1 (2.2) [j]	0.40[d]
Recurrent hospitalization	7 (6.2) [h]	4 (5.9) [i]	3 (6.7) [j]	1.00[d]

ASD, atrial septal defect; Echo, echocardiography; LV, left ventricle; LVEF, left ventricular ejection fraction

[†]Mean ± standard deviation

[‡]Median (ınterquartile range)

[a]Independent-samples T test

[b]Chi-square

[c]Mann-Whitney U

[d]Fisher's exact test

[e]8 patients not available for assessment

[f]16 patients not available for assessment

[g]19 patients not available for assessment

[h]$n=113$

[i] $n=68$

[j]$n=45$

patients were followed for 4–6 weeks and coronary artery involvement continued in only one of 19.4% patients with coronary artery abnormality at the last follow-up [7]. Feldstein et al. showed that at the 3–5 months follow-up, in only one case, coronary ectasia was newly detected on echocardiography and cardiac outcomes were not associated with clinical or laboratory features during admission [2]. In the study of Gaitonde et al., 12 MIS-C patients had left ventricular dysfunction in only one patient and residual coronary artery dilatation in two patients at the latest follow-up (mean 45 days after diagnosis) [33]. Tiwari et al. showed that 37 patients completed 3-month follow-up, and 6 (16%) of these had some residual echocardiographic changes [34]. Cattalini et al. reported that after a mean follow-up of 39.9 days, 15.4% of 138 patients showed persistent echocardiographic abnormalities [35]. Farooqi et al. showed that 45 patients had no secondary infection or need for re-hospitalization after 5.8 months of follow-up. However, they reported that tricuspid and mitral valve regurgitation developed in one patient and persistent mild biventricular dysfunction in one patient during this period [10]. In the study of Capone et al., 50 patients who were asymptomatic at the 6th month follow-up had normal echocardiography [9]. In this study, we present the long-term periods of MIS-C patients covering 6 months, and also draw attention to system involvements other than cardiac involvement. The most common symptoms in long-term follow-up were recurrent abdominal pain (14,2%), cardiac findings (14.2%), pulmonary symptoms (8%), fever (7.1%), neuropsychiatric findings (6.2%), and hypertension (3.5%). Penner et al. reported the long-term outcomes of 46 patients with MIS-C. Minor neurological abnormalities developed in 39 patients, gastrointestinal symptoms in 13%, hypertension in 10%, persistent abdominal pain in 7%, mucocutaneous findings in 3, and coronary artery changes in 2 patients. Echocardiography was evaluated as normal in 96% of the patients at 6 months. In the same cohort, at 6-month follow-up, common sequelae were muscle fatigue; neuropsychiatric sequelae such as proximal myopathy, dysmetria, anxiety, and emotional lability [13]. Similarly, neuropsychiatric findings were observed during follow-up in our study. In addition, neuropsychiatric abnormalities were observed significantly more frequently in patients with severe disease at follow-up. The relationship between neuropsychiatric findings and MIS-C has not been clearly stated in previous studies. Afebrile seizure and EEG abnormalities were observed in the follow-up in 3 patients in our study. Although the neuropsychiatric symptoms found in our study may occur by chance, they may also be a long-term complication of MIS-C because they are more common in the general population, the patients were healthy before, there was no family history and they were more prevalent in patients with severe MIS-C. In the follow-up, 6.2% of the patients required recurrent hospitalization (due to recurrent pericarditis, fever, seizure). In this study, the importance of follow-up for persistent gastrointestinal, neurological and pulmonary symptoms along with cardiac findings of MIS-C patients was emphasized.

The retrospective study design is a limitation of our study. Currently, limited data are available to determine whether this disease will have different long-term outcomes from other similar diseases. The multicenter long-term follow-up studies are required to define the acute and chronic devastating effects of MIS-C, transient and permanent cardiac complications, and prognostic factors.

Conclusion

The short-term outcomes of MIS-C indicate that it is a serious and life-threatening disease. Long-term follow-up studies in patients with MIS-C are limited. This 6-month follow-up study of patients with MIS-C showed that attention should be paid not only to cardiac findings, but also to symptoms related to other systems. Patients should be followed up in terms of neuropsychiatric findings, persistent gastrointestinal symptoms, fever and pulmonary symptoms that may occur during follow-up.

Declarations

Disclosures None.

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