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Echocardiographic Findings in Children with Multisystem Inflammatory Syndrome from Initial Presentation to the First Years after Discharge

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What is already known on this topic?

- *Multisystem inflammatory syndrome (MIS-C) is characterized by high fever, gastrointestinal symptoms, and especially cardiac dysfunction, and these findings occur within 2-6 weeks following severe acute respiratory syndrome coronavirus-2 infection.*
- *It has been reported that cardiovascular involvement (CVI) occurs in 56%-100% of pediatric cases with MIS-C and includes myocardial dysfunction, pericardial effusion, valvular dysfunction, arrhythmia, and coronary abnormalities.*
- *The effects of the disease on the cardiovascular system in the middle- and late-term follow-up are not yet known.*

What this study adds to this topic?

- *In this study, we evaluated the cardiovascular abnormalities in children diagnosed with MIS-C in admission, middle- and late-term follow-up periods.*
- *The patients older than 10 years of age and male gender were more frequent in the group with CVI.*
- *Mid-term follow-up showed that symptoms and myocardial dysfunction had resolved by 3-6 months in most of the patients who regularly followed up. No new coronary abnormalities were noted during the follow-up.*

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ABSTRACT

Objective: We aimed to evaluate clinical and echocardiographic features of the children diagnosed with multisystem inflammatory syndrome related to severe acute respiratory syndrome coronavirus-2 infection and determine early and mid-term cardiovascular outcomes.

Materials and Methods: We retrospectively evaluated 38 children who were diagnosed with multisystem inflammatory syndrome in our hospital between November 2020 and November 2021. Cardiovascular evaluations were performed during hospitalization, at the first, the second, and the third months after discharge, and then cardiac evaluation was repeated at 3-month intervals until a median of 24 weeks (range: 9-56 weeks).

Results: The mean age of patients was 9.6 years and 25 patients had cardiovascular involvement. Echocardiography showed that there was left ventricular dysfunction in 11 cases and any coronary abnormalities in 11 cases on admission. Cardiovascular involvement was most frequently seen in patients older than 10 years and of male sex. Severe clinical courses occurred in half of them. The mortality rate was 2.6% during hospitalization. At discharge, complete recovery was achieved in 30 cases and partial recovery was seen in 6 cases; there were 1 case with ventricular dysfunction and 5 cases with coronary abnormalities. At the last polyclinic visit, there was no case with symptoms or myocardial dysfunction, there was only 1 case with persisting coronary aneurysms.

Conclusion: Cardiovascular abnormalities in patients with multisystem inflammatory syndrome show rapid resolution within the first month. We recommend long-term follow-up evaluation for coronary arteries.

Keywords: Cardiovascular involvement, COVID-19, outcomes, pediatric multi-inflammatory syndrome

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Multisystem inflammatory syndrome (MIS-C) is thought to develop due to the hyperinflammatory response triggered by SARS-CoV-2 infection. Multisystem inflammatory syndrome is characterized by high fever, gastrointestinal symptoms, and especially cardiac dysfunction, and these findings occur within 2-6 weeks following SARS-CoV- 2 infection. Patients with MIS-C may also present findings similar to Kawasaki disease (KD) or shock.[1]

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It has been reported that cardiovascular involvement (CVI) occurs in 56%-100% of pediatric cases with MIS-C and includes myocardial dysfunction, pericardial effusion, valvular dysfunction, arrhythmia, and coronary abnormalities.[1-3] If untreated, MIS-C can lead to severe organ dysfunction and death.[3,4]

It has been reported that most cases with MIS-C need hospitalization in the acute phase, the short-term prognosis is favorable and mortality is rare.[1,3] However, the effects of the disease on the cardiovascular system in the middle- and late-term follow-up are not yet known. Most studies performed echocardiography shortly after discharge and focused on myocardial function. It is also not known whether the coronary artery abnormalities in patients diagnosed with MIS-C are related to transient coronary vasodilation during the acute inflammatory phase or the real destruction of the coronary artery wall as in KD. Here, we conducted a single-center retrospective study and evaluated the cardiovascular abnormalities in children diagnosed with MIS-C during admission and the follow-up period.

MATERIALS AND METHODS

Our study, as mentioned above, was a single-center, retrospective observational study in children younger than the age of 18. The children hospitalized for diagnosis of MIS-C between November 2020 and May 2021 were included. Ethics committee approval was obtained from the Ethics Committee of Akdeniz University Medical School dated 23/02/2021, reference number was 2021/70904504/134.

The inclusion criteria included the proof of SARS-CoV-2 infection: positive reverse-transcriptase polymerase chain reaction (RT-PCR), positive immunoglobulin M (IgM), immunoglobulin G (IgG) in a rapid test, positive enzyme-linked immunosorbent assay, antigen assay, or known contact with a confirmed COVID-19 patient. The American Heart Association criteria were used to define KD.[5] The MIS-C criteria described by the Center for Disease Control and Prevention (CDC) were used for the definition of cases with MIS-C.[6] The cases who had inadequete follow-up data were excluded, and we also excluded the case who did not meet the criterion of MIS-C.

We evaluated electrocardiographic and echocardiographic finding records, the need for intensive care, the presence of shock with inotropic support or fluid resuscitation, and the need for invasive/non-invasive mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) and medical treatment.

Echocardiographic Study

Echocardiographic examinations were performed during hospitalization and repeated after discharge from the hospital at the follow-up, it was done once a month for the first 3 months, then it was repeated at 3-month intervals.

Echocardiographic studies were performed using commercially available echocardiography machines (Vivid 7 pro, 3-MHz transducer; GE, Horten, Norway and IE33 Philips, Eindhoven, The Netherlands) and all echocardiographic examinations were recorded in a computed recording system. Two-dimensional, M-mode, Doppler, conventional continuous-wave (CW), pulsed wave (PW), and color Doppler measurements were obtained according to the pediatric guidelines of the American Society of Echocardiography.[6] Left ventricular (LV) dysfunction was defined as a left ventricular ejection fraction (LVEF) of <55%.

The left main coronary, left anterior descending coronary, and right coronary arteries (CAs) were routinely measured, and the *z* score was calculated. Aneurysm and coronary artery dilation were defined by a *z* score ≥2.5 and a *z* score of 2.0-2.49, respectively.[7] The largest diameter of coronary arteries was determined during hospitalization.

Cardiovascular involvement was defined if the patient had at least one of the abnormalities listed below:

- left ventricular dysfunction (LVEF equal to or less than 55%);
- shock, hemodynamic disturbance, and the need for vasopressor treatment;
- coronary abnormality (coronary artery *z* score more than +2.0);
- pericardial effusion;
- valvulitis of more than a mild degree; and
- arrhythmias and conduction abnormalities.

In April 2020, reports from the United Kingdom and Italy documented a severe shock-like illness in children with features of incomplete KD or toxic shock syndrome. In our unit the shock-like presentation was defined if the patient had signs of cardiovascular collapse requiring volume resuscitation and vasopressors or requiring intensive care.

Considering the previous literature data,[8] intravenous immunoglobulin (IVIG) and steroids were used as the first-line treatment of MIS-C patients in our unit.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp.; Armonk, NY, USA). Numeric variables were expressed as mean ± SD, median, range (minimum–maximum), and categorical ones as percentages (%). The normality assumption of the variables was checked by the Shapiro–Wilk test. Independent *t*-test and Mann–Whitney *U* tests were used in the comparison of group averages according to the normal distribution. Friedman's 2-way analysis of variance by ranks, test of within-subject effects, and pairwise comparison tests were used to compare the follow-up measurements of the patients. Statistical significance was assumed at $P < .05$. Chi-square test was used to compare the categorical variables.

RESULTS

During the study period, positive nasopharyngeal SARS-CoV-2 polymerase chain test results were found in 633 children (including hospitalized and outpatient clinics) in our hospital laboratory database. We identified 38 patients who met the CDC criteria for MIS-C and had laboratory evidence of SARS-CoV-2 infection.

Demographic, Clinical, and Laboratory Characteristics of Multisystem Inflammatory Syndrome Patients

The mean age of the patients with MIS-C was 9.6 years (SD: 5.6) (range: 0.8-18 years) and 18 patients (47.3%) were older than 10 years, and 23 patients (60.5%) were of male sex. Comorbid diseases were found in 7 cases (18.4%), chronic renal failure (n = 1), hepatocellular carcinoma (n = 1), paroxysmal dystonia (n = 1), miliary tuberculosis (n = 1), type 2 diabetes mellitus (n = 1), tubulointerstitial nephritis (n = 1), and seasonal allergic rhinitis (n = 1), but none had preexisting heart disease. The latent period was identified in 27 cases (71%), with a median of 4 weeks (range: 1-9 weeks). We identified 19 patients (50%) who met the CDC criteria for mild form MIS-C; however, moderate and severe form disease was observed in 5 (13.1%) and 14 (36.8%) cases, respectively.

Cardiovascular involvement occurred in 25 cases (65.7%). Other system involvements were gastrointestinal (n = 23), cutaneous (n = 9), neurological (n = 10), respiratory (n = 9), renal (n = 3), and endocrine system (n = 2) at the acute stage. Kawasaki-like findings were found in 10 patients (26.3%). All the patients had been hospitalized, and 15 of them (39.4%) needed to be treated in the intensive care unit (median 6 days, range: 3-14 days).

When hospitalized, all the patients had high-grade fever and laboratory evidence of hyperinflammation. Among 38 patients, 34 cases (89.4%) had high c-reactive protein, 20 patients (52.6%) had high erythrocyte sedimentation rate, and 28 patients (73.6%) had high procalcitonin levels. At admission, hemogram controls revealed anemia in 15 patients (39.4%), leukocytosis in 14 patients (36.8%), lymphopenia in 19 patients (50%), and thrombocytopenia in 8 patients (21%). Increased d-dimer levels were detected in 32 patients (84.2%). The evidence of SARS-CoV-2 infection was a positive serology in 28 patients and/or a positive viral nucleic acid test in 10 patients. Blood cultures and nasopharyngeal multiple nucleic acid amplification tests for multiple respiratory pathogens were negative in all patients.

Cardiac Markers

About 28 cases (73.6%) had a high Pro-BNP, and 25 cases (65.7%) had high troponin T levels.

Comparison of Demographic and Clinical Features in Patients with Cardiovascular Involvement

Twenty-five patients had CVI; among them 18 patients (72%) were of male sex, and 17 patients (68%) were older than 10 years old. Kawasaki-like syndrome was seen in 2 (8%) of them and shock findings were seen in 5 patients (20%). The mean age of the patients with CVI was higher than the patients without CVI ($P < .001$). The patients older than 10 years of age and male sex was more frequent in the group with CVI ($P < .001$ and $P = .045$, respectively). Severe form clinical courses occurred more frequently in patients with CVI than the patients without ($P = .008$). Interestingly, Kawasaki-like disease was less frequent in patients with CVI than those in patients without ($P = .001$).

Hospitalization rates in pediatric intensive care units (ICUs) were higher in patients with CVI than in patients without (34.2% vs. 5.2%, respectively, $P = .028$). However, the length of stay in the ICU was similar between patients with or without CVI ($P = .067$) (Table 1).

Cardiovascular abnormalities in our patients are listed below and shown Figure 1.

1. The left ventricular systolic dysfunction occurred in 11 cases (28.9%), among these patients, 5 cases (13.1%) had fulfilled the criteria of shock at presentation. Mild (LVEF 50%-55%), moderate (LVEF 35%-49%), and severe degree systolic dysfunction (LVEF <35%) were seen in 7 (18.4%), 3 (7.8%) and 1 case (2.6%), respectively (Table 2). Among 25 cases with high troponin T levels, 11 cases (28.9%) had left ventricular systolic dysfunction
2. Coronary arterial abnormalities were seen in 11 cases (28.9%) during hospitalization. Among them, 3 cases (7.8%)

Table 1. Demographic and Clinical Features of all Study Group and the Patients With or Without Cardiovascular Involvement

	All Patients	Cardiovascular Involvement		*P*
		No	Yes	
Number of case n (%)	38 (100)	13 (34.2)	25 (65.8)	
Ages (years)				
Mean (SD)	9.6 (5.6)	5.1 (4.2)	11.9 (4.8)	<.001†
Range	0.8-18	0.83-15.5	4.33-18	
0-5 years	11 (28.9)	8 (21.0)	3 (7.9)	<.001*
5-10 years	9 (23.6)	4 (10.5)	5 (13.1)	
10-18 years	18 (47.3)	1 (2.6)	17 (44.7)	
Male sex	23 (60.5)	5 (13.1)	18 (47.3)	.045*
Overweight patient	5 (13.1)	1 (2.6)	4 (10.5)	.498*
Comorbid disease	7 (18.4)	2 (5.2)	5 (13.1)	1.000*
Severe form clinical course	14 (36.8)	1 (2.6)	13 (34.2)	.008*
Shock findings	6 (15.7)	0 (0)	6 (15.7)	.076*
Kawasaki-like disease	10 (26.3)	8 (21.1)	2 (5.2)	.001*
Hospitalization in ICU	15 (39.4)	2 (5.2)	13 (34.2)	.028*
Length of stay in ICU median (range) (days)	6 (3-14)	7 (7)	6 (3-14)	.067**

Data expressed in mean (SD) or number of cases (%).ICU, intensive care unit.
†Independent *t*-test; *chi-square test; **Mann–Whitney *U* test.

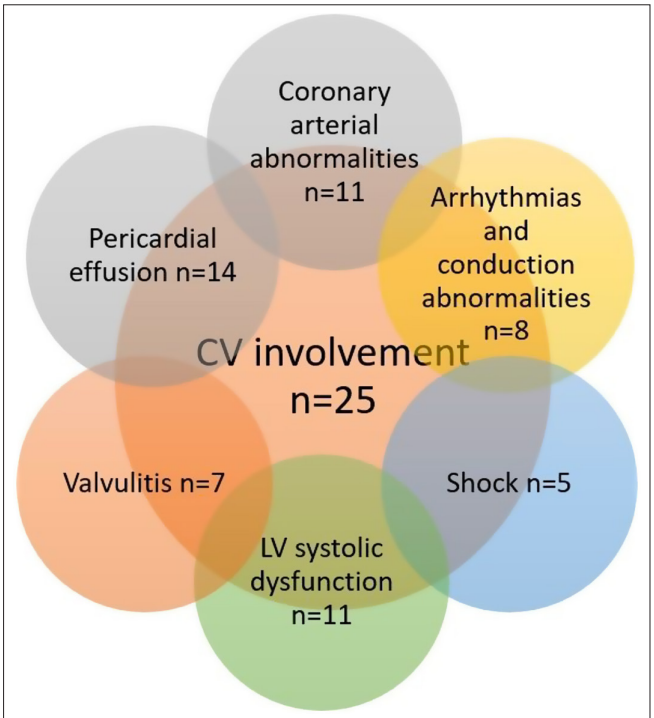

Figure 1. Cardiovascular abnormalities in our patients.

had coronary artery dilatation, and 8cases (21%) had small-sized coronary aneurysms (*z* score ranges: 2.5-3.4).

3. Valvulitis was detected in 7 cases (18.4%), however, none had no more than mild atrioventricular valve and/or semilunar valve regurgitation. Valvulitis was associated with left ventricular systolic dysfunction in 5 cases (13.1%).
4. Pericardial effusion was detected in 14 cases (36.8%), and pericardial effusion was associated with clinical myocarditis or left ventricular systolic dysfunction in 7 cases.
5. Arrhythmias and conduction abnormalities: sinus tachycardia was the most common finding and it occurred in 25 cases (65.7%). Two cases had prolongation of the corrected QT (QTc) intervals and 4 had T-wave alterations. Ventricular ectopic beats (2 cases) and the first-degree atrioventricular (AV) block were detected in 1 case (7.8%). Supraventricular tachycardia (SVT) was observed in 1 case, and 2 cases had experienced ventricular tachycardia.

Treatment During Hospitalization

We used IVIG in 31 patients and intravenous steroids in 25 patients. Anakinra was given in 6 cases due to incomplete clinical and laboratory response to the first-line therapy. Positive inotropic drugs were used in 13 cases, and mechanical ventilation was required in 6patients (15.7%) at the acute stage. Plasmapheresis was used in 8cases (21%). Extracorporeal membrane oxygenation was used in 1 case with fulminant myocarditis.

We initiated enoxaparin in prophylactic doses in 29 patients (76%), especially in cases of severe clinical course, prolonged immobilization, and patients with high D-dimer values. Antiaggregant dose of acetylsalicylic acid was used on all of the patients unless they had thrombocytopenia or bleeding, anti-inflammatory doses were given in 8 patients (21%) mainly in MIS-C patients with Kawasaki-like disease. An antiaggregant dose of aspirin was continued to all patients at follow-up until coronary abnormalities resolved.

Lidocaine therapy was given in a case with ventricular tachycardia due to fulminant myocarditis, and amiodarone intravenous infusion treatment was given to the other cases. Antiarrhythmic therapy was terminated after Holter ECG recording was normal at the first-month evaluation.

Outcome

After discharge from the hospital, complete recovery was achieved in 30 cases (79%), and partial recovery was seen in 6 cases (15.7%). A 13-year-old boy with fulminant myocarditis died in the second week of the disease. The mortality rate was 2.6% during hospitalization. All patients had normal cardiac biomarker values, and mild left ventricular systolic function (EF = 53%) was observed in 1 case at discharge.

Thirty-six patients were reevaluated in the fourth week after discharge from the hospital. There were 4 cases with persistent subjective symptoms (fatigue and palpitation). We found a significant difference in the LVEF between the hospitalization period and the fourth-week and follow-up examination ($P < .001$, $P < .001$, respectively) (Table 2). Pericardial effusion and mild left ventricular systolic function (EF = 53%) were observed at the fourth week control visit of a 15-year-old male patient who was diagnosed with hepatocellular carcinoma and received IVIG and steroid treatment with MIS-C diagnosis

The tricuspid valve annular plane excursion rate *z* score mean was found to be 1.32 at the initial examination, 0.86 at the fourth week and it was detected 2.98 at the follow-up echocardiographic examination ($P = 0.026$, $P = .022$, respectively).

We found a significant difference in the right coronary artery (RCA) *z* scores between the hospitalization period and the fourth-week examination, left anterior descending artery (LAD) and left main coronary artery (LMCA) *z* scores between the fourth-week and follow-up examination ($P = .035$, $P = .002$, $P = .03$, respectively). In the fourth week of examination, there were 3 cases (8.3%) with small-sized aneurysms and 2 cases (5.5%) with dilated coronary arteries.

The last examination was performed in 34 cases, with a median of 24 weeks after initial diagnosis (range: 9-56 weeks after initial diagnosis); symptoms had resolved by 3-6 months for most patients who regularly followed-up. Left ventricular systolic function (EF) was normal in 34 cases with MIS-C at the last examinations. The mean of LVEF at the fourth-week control and the last visit was significantly higher than the initial levels ($P < .001$, $P < .001$, respectively). (Table 2) There were significant differences in LMCA and LAD coronary artery *z* scores between the fourth-week examination and the last examination ($P = .03$, $P = .002$, respectively) (Table 2). A 15-year-old girl with a mild aneurysm in the left anterior descending artery and systolic dysfunction during her hospitalization received IVIG and steroid treatment, the left ventricle systolic functions returned to normal at the ninth week of control in this case; however, we observed to have a persistent small-sized coronary aneurysm with a *z* score of 3.5.

Table 2. Echocardiographic Findings During Hospitalization and at the Follow-Up in Patients Diagnosed with Multisystem Inflammatory Syndrome

	During Hospitalization	At the Fourth Week after Diagnosis	At the Follow-Up
	n = 38	n = 36	n = 34
	Number of Case (%)	Number of Case (%)	Number of Case (%)
Left Ventricular Ejection Fraction (%)			
Mean (SD)	61.9 (9.7)	71.4 (5.9)*	71.2 (4.2)**
Left ventricular systolic dysfunction (EF < 55)	11 (28.9)	1 (2.7)	0 (0)
Left ventricular diastolic dysfunction (mitral E/A > 2)	2 (5.2)	2 (5.5)	3 (8.8)
Left ventricular dilatation (LVEDD *z* score >+2)	5 (13.1)	4 (11.1)	2 (5.8)
TAPSE *z* score <-2	4 (10.5)	1 (2.7)	0 (0)
TAPSE *z* score mean (SD)	1.32 (2.14)	0.86 (2.03)[+]	2.98 (2.12)[++]
MAPSE *z* score <-2	8 (21)	2 (5.5)	0 (0)
MAPSE *z* score mean (SD)	0.07 (2.13)	1.14 (1.71)	1.72 (1.98)
Coronary artery abnormality	11 (28.9)	5 (13.8)	1 (2.9)
Any coronary artery *z* score between +2 and +2.5	3 (7.8)	2(5.5)	0 (0)
Any coronary artery *z* score > +2.5	8 (21)	3 (8.3)	1 (2.9)
Right coronary artery *z* score mean (SD)	0.48 (0.93)	0.85 (0.92)[&]	0.38 (0.77)
Left main coronary artery *z* score mean (SD)	0.54 (0.99)	0.75 (1.02)	0.09 (0.89)[@]
Left anterior descending artery *z* score mean (SD)	0.70 (1.15)	1 (1.18)	0.1 (1.02)[‡]

The largest *z* score was taken into consideration in all examinations.EF, ejection fraction; TAPSE, tricuspid valve annular plane excursion rate; MAPSE, mitral annular plane systolic excurdion.
*Significant differences in EF between hospitalization period and the fourth-week examination ($P < .001$). Friedman's 2-way analysis of variance by ranks.**Significant differences in EF between hospitalization period and the follow-up examination ($P < .001$). Friedman's 2-way analysis of variance by ranks.
[+]Significant differences in TAPSE between hospitalization period and the fourth-week examination ($P = .026$). Tests of within-subject effects.
[++]Significant differences in TAPSE between the fourth-week and the follow-up examination ($P = .022$). Pairwise comparison tests.
[&]Significant differences in RCA *z* scores between hospitalization period and the fourth-week examination ($P = .035$). Pairwise comparison tests.
[@]Significant differences in LMCA *z* scores between the fourth-week and the follow-up examination ($P = .03$). Pairwise comparison tests.
[‡]Significant differences in LAD *z* scores between the fourth-week and the follow-up examination ($P = .002$). Pairwise comparison tests.

DISCUSSION

In this study, we reported the clinical features of the patients with MIS-C and described the frequency and types of cardiovascular abnormalities and early and mid-term cardiovascular outcomes. The strengths of this study include data on the prognosis of patients with CVI in a cohort followed by one center.

Like previous studies,[4,9-11] reporting the median age of 8-9 years in MIS-C patients, the median age of our patients was 9.6 years, and males were more affected by the disease than females.

It has been noticed that there are similarities between MIS-C and KD, such as persistent fever and oral mucositis, conjunctivitis, and skin rash. However, previous studies showed that gastrointestinal symptoms, cardiac dysfunction, and shock are significantly more common in patients with MIS-C than in patients with KD.[1,12] In our study, Kawasaki-like syndrome was seen in almost one-quarter of our patients, and we also noticed that CVI was seen in only 2 (20%) of them. As suggested Haslak et al,[13] this result may be due to the limitations of the current diagnostic criteria in distinguishing these 2 diseases, as there are increasing numbers of infected individuals and mass vaccination programs.

Cardiac involvement occurs in 66%-100% of patients, according to previous studies, and many studies reported that left ventricular systolic dysfunction and coronary artery dilation or aneurysm are the predominant features.[14] According to previous reports, LV systolic dysfunction occurs in 34-82% of patients with MIS-C,[14,15] and CA abnormalities may be observed in 8%-19% of patients with MIS-C.[9] In addition to these abnormalities, pericardial effusion may be seen in 59% of the cases, and 23%-33% of them may be presented with hypotension and shock.[14] Regarding the frequency of CVI and the clinical and echocardiographic features in our MIS-C patients, our study results were in line with the previous literature.

A systematic review shows that 68%-76% of patients require hospitalization in intensive care units,[14,16] and positive inotropic support, mechanical ventilation, and ECMO were required in 40%, 15%-18%, 2.7% of patients of MIS-C, respectively.[16] The first-line treatment algorithm included mainly immunoglobulin and steroids and successfully modulated the acute inflammatory disease in our cases with MISC with fast management.

Regardless of baseline EF values, 7%-60% of patients with MIS-C may have variable severity of rhythm and electrical conduction abnormalities.[2,17] The most frequently reported electrocardiogram (ECG) anomalies are non-specific and include ST segment changes, QTc prolongation, and premature atrial or ventricular beats. Sinus bradycardia, first- and second-degree atrioventricular blocks and atrial fibrillation were described previously.[2,18] In our study, arrhythmia requiring medication was seen in 3 patients and all had severe myocardial dysfunction. Lidocaine therapy was chosen in a case of ventricular tachycardia due to fulminant myocarditis, and

amiodarone intravenous infusion treatment was given to the other patients during hospitalization.

The Outcome of Cardiovascular Involvement

Most patients with cardiac involvement show nearly full recovery of left ventricular function and normalization of cardiac inflammatory markers at the short-term follow-up.[11,14,17,19-21] In the acute stage, the mortality rate was reportedly 1.7% in the US and 1.4% in Europe.[16] In our study, the mortality rate was 2.6% during hospitalization.

Only a few studies focus on the resolution of coronary abnormalities and myocardial dysfunction in the longer course of the disease. Ramcharan et al[22] reported no deterioration in cardiac function of their 12 patients with MIS-C at the first-week control echocardiography (ECHO) after discharge. Katharine et al[20] also reported favorable short-term outcomes in 20 patients with MIS-C. They reported that among 13 patients with cardiac involvement, 11 had follow-up ECHO within 30 days after discharge. Of these 11 patients, 9 had normal echocardiograms, 1 had CA dilatation, and 1 had depression of the left ventricular function. In a study by Başar et al[23] it was reported that coronary arteries returned to normal in all their (n = 4 (16.6%)) patients with coronary artery involvement in a short-term follow-up.

Narendra et al[19] followed 31 children with MIS-C at 6-8 months (mean 159 days since onset of illness) after discharge. They reported that the outcome is favorable in children without preexisting comorbidities. Left ventricular systolic dysfunction was detected in 44.8% of their cases at initial evaluation and persisted in 25% of follow-up cases. Coronary artery abnormalities were detected in 6 children (19.4%); all resolved at the last follow-up except one. They concluded that the coronary outcomes at follow-up were reassuring.

Similar to Bagri et al[19], Capone et al[14] reported mildly depressed cardiac functions in 27% of patients at discharge. They performed cardiac magnetic resonance imaging (CMRI) on 11 patients with a myocardial injury during the acute phase of the disease. They did not find myocardial fibrosis, edema, or scarring 2 weeks after the acute phase. All patients resolved systolic myocardial dysfunction and coronary abnormalities until the eighth week. They reevaluated 25 asymptomatic patients in the sixth month and reported that all had normal LV systolic function and normal coronary arteries; however, diastolic dysfunction persisted in 4% of their patients. Kavurt et al reported that LV diastolic dysfunction persisted in the reduced LVEF group during discharge from the hospital.

Wong et al[11] reported that the worst cardiac function occurred in the first week after the onset of fever, and cardiac function normalized in all patients by 6-8 weeks. Coronary dilatation resolved in all; however, like our study, 1 patient who had large aneurysms at presentation had persisting aneurysm after 6 months. They concluded that full cardiac recovery may be expected by 8 weeks and recommended follow-up cardiac evaluation in patients with medium- or large-sized aneurysms.

In our study, 2 cases had persistent cardiac symptoms after discharge from the hospital. The mean of LVEF was found to be significantly higher at discharge than at initial levels. There was 1 case with pericardial effusion. Mild deterioration in left ventricular systolic function continued in 1 of 36 patients in the first-month control; mid-term follow-up showed that symptoms and myocardial dysfunction had resolved by 3-6 months in all the patients. No new coronary abnormalities were noted during the follow-up. However, 1 case had a persistent coronary aneurysm in the ninth week. We used enoxaparin in prophylactic doses in the third quarter of the patients at the acute phase, and an antiaggregant dose of aspirin was continued in all patients until the sixth-eighth weeks after diagnosis.

Our study is limited by its single-center design and small sample size. Due to missing cases, outcomes in the first year after diagnosis could not be defined in all patients. However, the follow-up duration reached at least 6 months in 50% of our cases (19/38 cases). We detected a persistent coronary aneurysm in only 1 child at the follow-up, and this case was no longer followed due to immigration to another country. However, this patient showed that the evaluation of coronary arteries is required at long-term follow-up. We could not perform advanced echocardiographic techniques such as global strain analyses and magnetic resonance imaging because they were not available in our hospital. These techniques might have shown subclinical myocardial injury.

CONCLUSION

This study showed that myocardial dysfunction and coronary abnormalities are the most prominent features in patients with MIS-C. Clinicians should suspect CVI in patients of the male sex, older than 10 years and in severe clinical courses. Echocardiographic abnormalities showed rapid resolution within 6 months. However, coronary aneurysms need regular long-term follow-up.

Ethics Committee Approval: This study was approved by Ethics Committee of Akdeniz University Medical School (date: 23/02/2021, reference number: 2021/70904504/134).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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