RESEARCH PAPER

Cardiac Outcome of Children With SARS-CoV-2 Related Multisystem Inflammatory Syndrome

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Objective: To study the cardiac outcomes of patients with multisystem inflammatory syndrome in children (MIS-C) after 6-month of diagnosis. **Methods:** This review of hospital records was conducted on MIS-C patients (aged <21 years) who completed a six-month follow-up. The baseline demographic, clinical, laboratory, and treatment characteristics during the acute phase, and echocardiographic findings during follow-up were collected. **Results:** 116 patients (61.2% male, median age 7 years) with MIS-C were included in the study. At the time of admission, cardiac abnormalities were present in 70.7% of MIS-C patients, and the most common cardiac abnormalities were valve failure (50.9%), followed by ventricular dysfunction (39.7%), and pericardial effusion (23.3%). Six month after diagnosis, cardiac abnormalities were found in 10.3% of patients, and patients had lower rates of ventricular dysfunction (P<0.001), valve failure (P<0.001), pericardial effusion (P<0.001), and coronary involvement (P<0.001) as compared to the baseline. Intravenous immunoglobulin (IVIG) and steroid treatment significantly reduced the odds of occurrence of ventricular dysfunction (P=0.002), valve failure (P=0.004), and low ejection fraction (P=0.002) in comparison to IVIG treatment alone. **Conclusion:** While most MIS-C patients had abnormal echocardiographic findings at admission, only 10.3% of patients had cardiac abnormalities during follow up.

Keywords: *Echocardiography, Ejection fraction, Management, Ventricular dysfunction.*

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Multisystem inflammatory syndrome in children (MIS-C) is a severe systemic hyper-inflammatory disease with multi-organ involvement that follows severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1]. Patients with MIS-C present with a variety of clinical characteristics, including cardiac manifestations similar to Kawasaki disease (KD). There have been several studies regarding left ventricular (LV) systolic dysfunction and coronary artery dilation in MIS-C [1-4]. The incidence of coronary artery aneurysms ranges from 14-24%, and 31-58% of patients have been reported to have LV systolic dysfunction [1-3]. Few studies reported the incidence of pericardial effusion and valvar regurgitation in MIS-C; however, one study found that 33% of patients had pericardial effusions, 25% had mitral regurgitation, and 17% had tricuspid regurgitation [3].

There is limited data regarding longitudinal follow-up of MIS-C such as cardiovascular involvement. Therefore, we conducted this study to evaluate the cardiac outcomes of MIS-C patients six months after diagnosis.

METHODS

This multicenter study was conducted on children and adolescents with MIS-C who were younger than 21 years, during April, 2020 to September, 2022. The study included patients who were diagnosed with MISC-C six months before presentation and were referred to hospitals affiliated with the two study centers. Patients with congenital heart disease, previous history of cardiac dysfunction, and previous history of Kawasaki disease were excluded from the study. Subspecialty physicians at each hospital had diagnosed patients with MIS-C using CDC criteria [5].

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Age at diagnosis, gender, clinical manifestations, hospital stay duration, initial laboratory parameters including white blood cell count, hemoglobin, platelet counts, erythrocyte sedimentation rate (ESR), liver function tests, and details of treatments were entered in the study forms. Details of echocardiographic findings on admission and at six-month follow-up were also collected. According to the

vasoactive need (based on vasoactive inotropic score), the need for respiratory ventilation, and organ damage, patients were clinically categorized as having had mild, moderate, or severe MIS-C [6].

Informed consent was obtained at the time of echocardiography from all patients or from their parents/legal guardians. The study protocol was approved by the institutional ethics committee in accordance with the Helsinki Declaration guidelines.

Two-dimensional standard echocardiography was carried out by skilled cardiac sonographers utilizing the GE Vivid E9 Ultrasound System (GE Healthcare). Abnormal echocardiogram findings were described as pericardial effusion, coronary artery involvement (dilation or aneurysms), significant valvulopathy, ventricular dysfunction (diastolic function using E/A wave ratio and E wave deceleration time, and systolic function through Simpson's biplane method), or any combination of the above. According to the Boston Children Hospital *z* score system, coronary artery dilatation or aneurysm were defined as coronary artery diameter ≥2 to <2.5 *z* score and ≥2.5 *z* score, respectively [7]. Based on a modified Simpson method, the left ventricular ejection fraction (EF) was classified as either normal (≥55%) or low EF (<55%) [8].

Statistical analysis: Categorical variables were described as frequencies (%), and continuous variables were des-cribed as mean (SD) or median (IQR). We compared the demographic, clinical, laboratory, and echocardiographic examination of our patients between mild-to-moderate and severe cases. Besides, we divided patients into two groups based on the two commonly used initial treatments, which were intravenous immunoglobulin (IVIG) plus steroid or IVIG alone, and we compared the cardiac outcomes bet-ween these two types of treatment. In order to compare qualitative data, the chi-square test and, whenever needed, Fisher exact test were used. The Mann-Whitney test was used to compare the quantitative data between the two study groups. To compare the changes in echo-cardiography findings as qualitative data at baseline and the end of follow-up, McNemar test was used. Additional analyses were performed using the multiple logistic regression models to compare the echocardiography findings at the 6-month follow-up between the two treat-ment groups by adjusting the effect of MIS-C disease severity. All statistical analyses were performed using IBM SPSS software version 20.0 (SPSS Inc.), at the significance level of 0.05.

RESULTS

A total of 116 patients (71 males) with MIS-C were enrolled in the study with a median (IQR) age of 7 (5-9) years. MIS-C patients were clinically classified into severe cases (*n*=43, 37.1%), and mild-to-moderate MIS-C patients (*n*=73, 62.9%). Patients with severe MIS-C had significantly longer hospital stay than those with mild-to-moderate MIS-C ($P<0.001$) (**Table I**).

At the time of admission, cardiac abnormalities were found in 82 (70.7%) of MIS-C patients, and the most common cardiac abnormalities were valve failure (50.9%), ventricular dysfunction (39.7%), and pericardial effusion (23.3%). Severe MIS-C patients had considerably higher rates of valve insufficiency ($P<0.001$), ventricular dysfunction (P<0.001), and low EF ($P=0.018$) than mild-to-moderate MIS-C patients.

6-month follow up, cardiac abnormalities were found in 12 (10.3%) of patients (**Table II**). There was a significant decrease in cardiac abnormalities 6 month follow-up viz., ventricular dysfunction ($P<0.001$), valve failure ($P<0.001$), coronary involvement ($P<0.001$), and low EF ($P<0.001$).

On multiple logistic regression, after adjusting for the effect of MIS-C disease severity, cardiac outcomes following 6-month follow-up showed that the odds (95%

Table I Baseline Characteristics of Patients (Aged <21 Years) With Multisystem Inflammatory Syndrome in Children (MIS-C)

Variables	*Mild-to-moderate MIS-C (n=73)*	*Severe MIS-C (n=43)*
Male gender	45 (61.6)	26 (60.5)
Age (y)[a]	7 (5.0-8)	7.5 (5.5-9)
Hospital stays (d)[a,c]	8 (7.0-9)	11 (10-12.5)
Clinical characteristics		
Fever	73 (100)	43 (100)
Abdominal pain	37 (50.7)	23 (53.5)
Nausea/vomiting	28 (38.4)	17 (39.5)
Diarrhea	16 (21.9)	11 (25.6)
Respiratory symptoms	30 (41.1)	20 (46.5)
Skin rash	27 (37.0)	17 (39.5)
Lymphadenopathy	7 (9.6)	4 (9.3)
Neurologic symptoms	12 (16.4)	8 (18.6)
Laboratory findings		
Leukocytes (10^9/L)[a]	8.1 (6.9, 9.8)	7.4 (6.3, 11.45)
Hemoglobin (g/dL)[a]	11.4 (10.3, 12.7)	11.0 (10.4, 12.7)
Platlet (10^9/L)[a,c]	220 (185, 73)	187 (161.5, 213)
ESR (mm/h)[a]	37 (29, 42)	39.0 (29.5, 44)
AST (U/L)[a]	33 (25, 45)	30 (20, 47.5)
ALT (U/L)[a]	34 (21, 44)	30 (20.5, 48.5)
Creatinine (mg/dL)[b]	0.59 (0.15)	0.65 (0.16)
Treatment[c]		
IVIG	50 (68.5)	4 (9.3)
IVIG + steroid	23 (31.5)	39 (90.7)

Values in no. (%), [a]median (IQR) or [b]mean (SD). P<0.001. ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase; IVIG: intravenous immunoglobulin.

WHAT THIS STUDY ADDS?

- In this retrospective study, only 10.3% patients were found to have cardiac abnormalities on echocardiography, six months after a diagnosis of multisystem inflammatory syndrome in children associated with coronavirus disease (MIS-C).

Table II Echocardiography Findings of MIS-C Patients at Admission and at Six-Month Follow-up

Findings	*Mild-to-moderate MIS-C (n=73)*	*Severe MIS-C (n=43)*
At admission		
Ventricular dysfunction	20 (27.4)	26 (60.5)
Valve failure	27 (37.0)	32 (74.4)
Pericardial effusion	13 (17.8)	14 (32.6)
Coronary involvement	10 (13.7)	6 (14.0)
Low ejection fraction	9 (12.3)	13 (30.2)
At 6-month follow-up		
Ventricular dysfunction	3 (4.1)	4 (9.3)
Valve failure	4 (5.5)	6 (14.0)
Pericardial effusion	0	0
Coronary involvement	1 (1.4)	2 (4.7)
Low ejection fraction	3 (4.1)	4 (9.3)

Values in no. (%). [a]*P<0.001,* [b]*P<0.05.*

CI) of persisting ventricular dysfunction 0.009 (0-0.16), valve failure 0.025 (0.002-0.306), and low EF 0.009 (0 -0.16) in the IVIG plus steroid treatment group were greater than those in the IVIG treatment group, respectively but not for coronary involvement [0.71 (0.03-16.6)].

DISCUSSION

This hospital record review found a 10.3% occurrence of cardiac abnormalities in children who had MIS-C six months back, which were lower in those who were treated with steroids and IVIG both.

According to recommendations, MIS-C patients require long-term follow-up, particularly in the case of cardiac involvement. Due to the similarities between MIS-C and KD, the long-term cardiac sequela has been described in the literature as a coronary artery aneurysm, and it is suggested that it be monitored similarly to KD [4]. Various studies had different rates of cardiac abnormalities on echocardiographic follow-up. One study reported that 16% of MIS-C patients had persisting echocardiographic abnormalities after three months follow-up [11]. Another study found 15.4% of 138 MIS-C patients had residual echocardiographic changes after an average follow-up of 39.9 days [12]. We found that 10.3% of patients had cardiac abnormalities after a 6-month follow-up, which is a longer follow-up than the previous two studies. Bagri, et al. [13] found that following 4-6 weeks of echocardiographic follow-up, one of the 19.4% of MIS-C patients who had a coronary artery abnormality at admission still had coronary artery involvement [13]. Farooqi, et al. [14] reported that 80% of MIS-C patients had mild echocardiographic abnormalities, while 44% of them exhibited moderate-to-severe abnormalities such as coronary involvement. None of the patients had coronary involvement, and 18% still had mild echocardiographic abnormalities following 1-4 weeks of cardiac follow-up [14].

With regards to the treatment, IVIG and steroids are the main treatment options for MIS-C patients. Previous studies demonstrated that IVIG plus steroids was linked to better fever course than IVIG alone [15]. Son, et al. [16] reported that patients who received IVIG plus steroids had decreased risks for the left ventricular dysfunction (8% vs 17%). Our findings are in line with this study that IVIG plus steroid treatment significantly reduced the odds of ventricular dysfunction in comparison to IVIG treatment alone. Similarly, Ouldali, et al. [15] demonstrated that treatment with IVIG plus steroids was linked to fewer severe acute consequences, such as acute left ventricular dysfunction and the need for hemodynamic support. Another single-center study [17] concluded that cardiac recovery in those who received IVIG plus steroids was shorter in comparison to those who received IVIG alone. Further studies are required to comprehend the mechanisms underlying the potential effect of steroids in patients with MIS-C.

In conclusion; although, MIS-C is a severe multisystem disorder throughout its acute stage, it has a generally encouraging long-term cardiac outcome. Furthermore, treatment with IVIG plus steroids may reduce the risk of cardiac complications on follow-up.

Ethics clearance: Institutional Ethics Committee, AJA University of Medical Sciences; No. IR.AJAUMS.REC.1401.136 dated Nov 20, 2022.
Contributors: MYZ: conceptualized the study design; analyzed and interpreted the results, and wrote the manuscript; ARG, AM, SS, A Aminian, BD, A Azarfar: recruited patients, collected demographic and clinical data analyzed and interpreted the results; ARG: conceptualized the study design, analyzed and interpreted the results, and commented on and revised the manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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REFERENCES

1. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334-46.
2. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383:347-58.
3. Kelly MS, Valle CW, Fernandes ND, et al. Multisystem inflammatory syndrome in children: cardiac biomarker profiles and echocardiographic findings in the acute and recovery phases. J Am Soc Echocardiogr. 2020;33:1288-90.
4. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259-69.
5. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Accessed on Dec 20, 2023. Available from: *https://www.cdc.gov/mis/mis-c/hcp_cstecdc/index.html*
6. Jonat B, Gorelik M, Boneparth A, et al. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. Pediatr Crit Care Med. 2021;22:e178.
7. Colan SD. Normal echocardiographic values for cardiovascular structures. *In*: Lai WW, Mertens LL, Cohen MS, Geva T, editors. Echocardiography in Pediatric and Congenital Heart Disease. Wiley Online Library, 2016.p.883-901.
8. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J-Cardiovasc Imaging. 2015;16:233-71.
9. Kaushik A, Gupta S, Sood M, et al. A systematic review of multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection. Pediatr Infect Dis J. 2020; 39:e340-6.
10. Sezer M, Çelikel E, Tekin ZE, et al. Multisystem inflammatory syndrome in children: clinical presentation, management, and short-and long-term outcomes. Clin Rheumatol. 2022;41:3807-16 .
11. Tiwari A, Balan S, Rauf A, et al. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): a hospital-based prospective cohort study from Kerala, India. BMJ Paediatr Open. 2021;5.
12. Cattalini M, Della Paolera S, Zunica F, et al. Defining Kawasaki disease and pediatric inflammatory multisystem syndrome-temporally associated to SARS-CoV-2 infection during SARS-CoV-2 epidemic in Italy: results from a national, multicenter survey. Pediatr Rheumatol. 2021;19: 1-11.
13. Bagri NK, Deepak RK, Meena S, et al. Outcomes of multisystem inflammatory syndrome in children temporally related to COVID-19: a longitudinal study. Rheumatol Int. 2022;42:477-84.
14. Farooqi KM, Chan A, Weller RJ, et al. Longitudinal outcomes for multisystem inflammatory syndrome in children. Pediatrics. 2021;148.
15. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA. 2021;325: 855-64.
16. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. N Engl J Med. 2021;385:23-34.
17. Belhadjer Z, Auriau J, Méot M, et al. Addition of corticosteroids to immunoglobulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children. Circulation. 2020;142:2282-4.