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Echocardiographic Findings in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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ABSTRACT

Background: Multisystem inflammatory condition in children (MIS-C) has been defined as a condition related with COVID-19 and characterized by hyperinflammation and multiorgan involvement in children. MIS-C's cardiac involvement is a frequent and dangerous issue. One of the most used diagnostic imaging techniques in cardiology is echocardiography, which is frequently used to diagnose, treat, and monitor patients with any suspected or confirmed cardiac condition.

Objective: To assess echocardiographic findings in children suffered from MIS-C during hospitalization

Patients and Methods: A prospective study conducted at our Pediatric Department in Menoufia University Hospital. During the study period, echocardiographic evaluation was carried for 39 children with MIS-C and age-matched 39 healthy controls. Patients were evaluated daily by echocardiography until discharge or death. Two points were set for analysis; first on detection of any cardiac involvement (Echo1) and second on the day before discharge or death (Echo2).

Results: Among patient group, the most affected system was the cardiovascular system (87 %). Left ventricular systolic dysfunction (LVSD) (56%) and valvular involvement (53%) were the most predominant features while the coronary abnormalities (15%) were the least predominant feature. One out of six patients had a coronary artery dilatation and the others had coronary artery aneurysms. LVSD and diastolic dysfunction (DD) were worse in patients with MIS-C than in healthy group. On echo 2, 95.5% of the patients who had systolic dysfunction still had it. No patient with diastolic dysfunction returned to normal even with preserved or improvement of left ventricular ejection fraction (LVEF).

Conclusion: Our findings revealed that the most prevalent echocardiographic abnormalities in MIS-C patients were ventricular dysfunction accompanied with myocarditis-like conditions, which persisted in the echo 2. Coronary anomalies were the least prevalent. However, mid- and long-term follow-up studies are required for MIS-C patients.

Keywords: MIS-C, LVSD, DD, COVID-19, 2D echocardiography.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the source of the COVID-19, which has infected people of all ages in almost every nation on the planet [(1)].

In more recent times, a number of facilities in the US and Europe have documented signs of toxic shock syndrome or comparable sickness to Kawaski disease in children who have tested positive for COVID-19 [(2)].

A hyperinflammatory syndrome with multiorgan dysfunction is the hallmark of the condition, which has been dubbed MIS-C and seems to be a delayed post-infectious response that occurs 2–6 weeks after a largely asymptomatic or mildly symptomatic SARS-CoV-2 infection. Heart involvement, vascular shock, increased inflammatory markers, and a prolonged fever are typical symptoms. Decreased myocardial function, coronary artery dilatation or aneurysms, and pericarditis are examples of cardiac involvement [(3)].

Limited data are available in the literature about cardiac manifestations of MIS-C among the Egyptian children. So, our study was set out to assess the echocardiographic abnormalities in Egyptian children with post COVID MIS-C.

PATIENTS AND METHODS

This was a single-center prospective study conducted at our pediatric department in Menoufia University Hospital during the period from February 2021 to May 2024. During the study period, echocardiographic evaluation was carried on 78 patients, 39 (MIS-C) patients who were tested positive for COVID-19 IgG and presented with multisystem organ affection and age-matched 39 healthy controls who were tested negative for COVID-19 IgG and were healthy.

They came to the outpatient clinics at our hospital to have their chest discomfort or heart murmurs evaluated, but they had no anatomical or functional heart problems. All patients had a post-COVID MIS-C diagnosis were in the hospital, as defined by the US Centers for Disease Control and Prevention [(4)] and the WHO [(5)].

Patients who had underlying cardiac diseases either congenital or acquired, history of any disease that may affect the cardiac function or patients with malignancy who received chemotherapy were excluded.

All children were subjected to detailed history taking and thorough clinical examination with recording of relevant demographic and clinical data.

Laboratory investigations were done for patients including (CRP, ESR, procalcitonin, ferritin, D-dimmer, fibrin degradation products (FDPs), and troponin) and for controls including (CBC, liver and renal function tests, prothrombin time (PT) and international normalised ratio (INR).

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Modified OSF score was calculated and recorded for each patient on admission [6].

Transthoracic echocardiography was done using Philips HD 11 device with 3-8 and 1-3 echocardiography was done daily until discharge or death by an experienced pediatric cardiologist and any abnormalities were recorded. For patients with cardiac involvement, two points were set for analysis; first on detection of any cardiac involvement (Echo1) and second on the day before discharge or death (Echo2).

Standard echocardiographic measures were performed in accordance with the American Society of Echocardiography's 2013 recommendations, and the following parameters were recorded: ejection function (EF), fractional shortening (FS), and early (E) and late (A) mitral inflow peak velocities [7].

Echocardiographic examination of the coronary arteries was done in accordance with the 2017 American Heart Association (AHA) guideline for Kawaski disease, with measurements taken from inner edge to inner edge and avoiding branching sites that may have normal focus areas. The Boston Z-score method was used to compute the coronary artery z scores [8].

LVSD is defined as decreased left ventricular pumping function and is identified in M-mode echocardiography by an LVEF less than 55% [9]. Left ventricular DD is described as the ventricle's inability to fill to a normal end-diastolic volume. It is distinguished by an inversion of the mitral early and late diastolic E/A Doppler waves with a ratio <0.8 [10].

Ethical approval:

The study was approved by the Local Ethics Committee of Menoufia University and informed written consent was obtained from the parents of the participants before enrollment [IRB No.:1/2023PEDI19]. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Version 20.0 of the IBM SPSS software program was used to examine the data that were supplied into the computer. Percentage and numbers were used to describe the qualitative data.

The distribution's normality was confirmed using the Shapiro-Wilk test. IQR, median, mean, and SD were used to characterize quantitative data. Student t-test for normally distributed quantitative variables, Mann-Whitney test for abnormally distributed quantitative variables, Fisher's exact test for correction for X^2-test when more than 20% of the cells have expected count less than 5, and chi-square test for categorical variables were the tests used to compare between different groups. Statistical significance was defined as a P value of less than 0.05.

RESULTS

Seventy-eight patients were enrolled in this study, 39 children with MIS-C and age-matched 39 healthy controls. Regarding the gender of the patients and controls, 22 males in patient group (56.4%) and 25 in controls (64.1%).

The mean age of the patients was 5.89 ± 4.47 years while in controls was 6.6 ± 4.99 years. The comparison between the two studied groups according to the anthropometric measurements (weight, length, BMI and body surface area (BSA)) was statistically insignificant. Compared to the healthy group regarding the vital signs, the heart rate, the respiratory rate, the temperature and the systolic and diastolic blood pressure were significantly higher in the patient group. Our patients had lower platelet count and hemoglobin (HB) level than the controls.

They had higher levels of AST and ALT compared to the control group. Creatinine and blood urea nitrogen levels (BUN) of MIS-C patients were reported to be higher than the control group. Also, they experienced a higher INR and prolonged PT comparable to the control group. There was a highly statistically significant difference between both groups as regard to their laboratory data **(Table 1)**

Table (1): Comparison of demographic, clinical and laboratory data between patient and control group

	Patients (n = 39)	Controls (n = 39)	p
Demographic and clinical parameters			
Sex			
Male, n (%)	22 (56.4)	25 (64.1)	0.488
Female, n (%)	17 (43.6)	14 (35.9)	
Age (years)*	5.0 (2.75 – 9.0)	5.0 (2.25 – 9.50)	0.620
Weight (kg)*	19.0 (13.50 – 27.0)	19.0 (13.0 – 32.0)	0.542
Height (m)#	1.08 ± 0.30	1.19 ± 0.35	0.148
BMI (Kg/m^2)#	16.51 ± 2.86	16.45 ± 2.31	0.921
BSA (m^2)*	0.76 (0.59 – 0.99)	0.76 (0.55 – 1.18)	0.576
Heart rate (beat/min)#	124.7 ± 13.32	107.8 ± 18.70	<0.001*
Respiratory rate (RR/min)*	32.0 (28.0 – 48.0)	28.0 (21.0 – 34.0)	0.001*
Temperature (C°)#	38.39 ± 0.54	37.26 ± 0.57	<0.001*
Blood pressure			
Systolic (mmHg)#	101.49 ± 17.85	110.45 ± 8.0	0.006*
Diastolic (mmHg)#	65.41 ± 14.88	72.08 ± 9.19	0.020*
Laboratory parameters			
Hemoglobin (gm/dl)#	8.56 ± 2.13	10.19 ± 1.70	<0.001*
WBCs (10^9/L)*	10.60 (5.80 – 19.10)	6.0 (5.05 – 7.60)	0.005*
Platelet (10^9/L)*	80.0 (60.0 – 247.0)	272.0(233.0 – 340.5)	<0.001*
Serum creatinine (mg/dl)*	0.80 (0.39 – 3.95)	0.40 (0.30 – 0.50)	<0.001*
BUN (mg/dl)*	40.0 (15.50 – 94.0)	15.0 (9.0 – 16.0)	<0.001*
AST (U)*	100.0 (26.0 – 644.5)	27.0 (19.50 – 44.0)	<0.001*
ALT (U)*	80.0 (20.0 – 114.50)	20.0 (9.50 – 25.50)	<0.001*
PT %*	70.0 (47.0 – 85.50)	88.0 (80.0 – 97.0)	<0.001*
INR*	1.36(1.17 – 1.89)	1.25(1.10 – 1.47)	0.028*

Median and IQR: Non-parametric test.
WBCs: white blood cells, BUN: Blood urea nitrogen, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time (PT), INR: International normalized ratio.
Median and IQR: non parametric test.
p: p value for comparing between the two studied groups
*: significant, χ^2: Chi square test was used, *U: Mann Whitney test was used
FE: Fisher Exact test was used

Regarding the clinical data of the patient group, the most affected system was the cardiovascular system, 87 % of the patients had cardiovascular involvement while the least affected system was the gastrointestinal system then the respiratory system. The patients who were admitted in our PICU underwent modified organ system failure scoring (OSF) for prediction of their prognosis. Most of them had a score 8. 15% of them had the worst score 10 and only 10% of them had the best score 3. The median duration of hospitalization for the most patients was 14 days (min-max: 11–20 days). 74.4% of the patients needed PICU admission. The most common therapy used with our patients was systemic corticosteroids (64.1%).The second main line was IVIG (47.7 %). 28% of the patients received IVIG with corticosteroid. There was a high mortality. Out of 39 patients, 23 survived and 16 patients died (59% and 41% respectively). MIS-C patients exhibited an obvious elevation of inflammatory markers, especially with regard to FDPs, ferritin level, D-dimer, CRP, ESR, and procalcitonin showing higher levels **(Table 2).**

Table (2): Clinical and laboratory data of studied patients (Total No= 39 patients)

Clinical variables	No. of patients	%
Systems affected on admission		
Cardiovascular	34	87
Respiratory	5	13
Renal	18	46
Neurological	22	56
Gastrointestinal	6	15
Hepatic	20	51
Hematological	27	69
Modified OSF scoring		
Score 10	6	15
Score 8	11	28
Score 6	9	23
Score 4	9	23
Score 3	4	10
Medication		
IVIG	18	47.4
CRRT	8	20.5
Solumedrol	25	64.1
Plasmapheresis	3	7.7
Inotropes of adrenaline and dobutrex	8	20.5
Supportive (Antibiotics)	39	100
Duration of hospitalization		
Median (min-max) 6 (3-10) days	12	31
Median (min-max) 14 (11-20) days	21	54
Median (min-max) (21-35) days	6	15
Level of Care		
General pediatric unit	10	25.6
PICU	29	74.4
Survival		
Survivors	23	59
Non survivors	16	41
Laboratory parameters		
FDPs (ng/ml) Median (IQR)	500.0 (7.0 – 2000.0)	
Ferritin (ng/ml) Median (IQR)	535.9 (90.0 – 921.0)	
D dimmer (ng/ml) Median (IQR)	5.50(4.0 – 105.0)	
CRP (mg/ml) Median (IQR)	48.0 (24.0 – 91.0)	
ESR (mm) Median (IQR)	95.0(15.50 –100.0)	
Procalcitonin (ng/ml) Median (IQR)	3.0 (1.50-10.0)	
Troponin (ng/l) Median (IQR)	3.0 (0.03 – 107.0)	
	No.	**%**
Negative Troponin	8	20.5
Positive Troponin	31	79.5

Median and IQR: Non-parametric test.

In our study, LVSD (56%) and valvular involvement (53%) were the most predominant features while the coronary abnormalities (15%) were the least predominant feature **(Table 3).** We found that 15% of our patients had coronary abnormalities. 1 out of 6 patient had a coronary artery dilatation with Z score 2.3 and the other had a coronary artery aneurysm with Z score starting from 2.8 up to 9.06 **(Table 4).**

Table (3): Echocardiographic abnormalities recorded in Echo 1 for patient group

Echo Findings	patients (n = 39)	%
Systolic dysfunction	22	56
Diastolic dysfunction	8	20
Pericardial effusion	20	51
Mild	13	33.3
Moderate	6	15.4
Severe	1	2.6
Valvular involvement (mild/moderate /sever mitral regurge)	21	53
Mild	10	25.6
Moderate	10	25.6
Severe	1	2.6
Coronary abnormalities	6	15

Table (4): Description of coronary abnormalities recorded in six of our patients in echo 1:

No. of patient	Coronaries abnormality	Coronaries diameter	Z score
1	Coronary artery dilatation	LMCA: 3.7 mm LAD 2.8 mm CX 2.4 mm RCA 2.5 mm	LMCA: +2.33 LAD: 1.81 Cx: 2.8 RCA : 2.2
2	Coronary artery aneurysm	LMCA: 3 mm	LMCA: +4.2
3	Coronary artery aneurysm	LAD 4.8 mm cx 4.5 mm	LAD : +9.06 Cx: + 7.68
4	Coronary artery aneurysm	LMCA: 3.4 mm	LMCA:+3.7
5	Coronary artery aneurysm	LMCA: 4.5 mm longitudinal with long fusiform dilatation 6 mm CX :2.6 mm - normal RCA diameter	LMCA:+5.3 Cx: +1.99
6	Coronary artery aneurysm	LMCA: 3.9 mm LAD :2.8 mm CX :2.4 mm RCA :2.5 mm	LMCA:+2.8 LAD : +1.81 Cx: 2.8 RCA:2.2

LMCA: left main coronary artery, LAD: left anterior descending artery,Cx: circumflex artery ,RCA: right coronary artery.

On echo 2, we found that 95.5 % of the patients who had systolic dysfunction still had it. 75% of patients who had diastolic dysfunction didn't improve. Only 39% of patients who had valvular involvement (mild/moderate/severe mitral regurgitation) showed improvement. Only 1 patient (17%) of all patients with coronary abnormalities showed improvement with Z score 1.24 **(Table 5).**

Table (5): Comparison between findings in echo 1 and echo 2 (Total no. of patients = 39).

Echo Findings	Echo 1		Echo 2			
			Improvement of findings		Persistence or worsening of findings	
	Total number of patients	%	No	%	No	%
Systolic dysfunction	22	56	1	4.5	21	95.5
Diastolic dysfunction	8	20	2	25	6	75
Pericardial effusion	20	51	13	65	7	35
Valvular involvement (mild/moderate /severe MR)	21	54	8	39	13	61
Coronary Abnormalities	6	15	1	17	5	83
Patient number	**Diameter**	**Z score**	**Improvement of diameter**	**Z score**	**Persistence or worsening of diameter**	**Z score**
1	LMCA: 3.7 mm LAD: 2.8 mm CX: 2.4 mm RCA: 2.5 mm	LMCA: +2.33 LAD: 1.81 Cx: 2.8 RCA: 2.2			LMCA: 3.6	LMCA: +2.1
2	LMCA: 3 mm	LMCA: +4.2	Normal coronaries LMCA: 1.9 mm	LMCA: 1.24		
3	LAD: 4.8 mm cx 4.5 mm	LAD : +9.06 Cx: + 7.68			LAD: 5.2 mm	LAD: +10.2
4	left main coronary artery 3.4 mm	LMCA: +3.7			LMCA: 4 mm	LMCA: +5
5	LMCA: 4.5 mm longitudinal with long fusiform dilatation 6 mm CX :2.6 mm - normal RCA diameter	LMCA: +5.3 Cx: +1.99			LMCA: 4.5 mm-longitudinal with long fusiform dilatation 5.8 mm CX: 2.4 mm - normal RCA	LMCA:+5.3 Cx: +1.51
6	LMCA: 3.9mm LAD :2.8 mm CX: 2.4 mm RCA: 2.5mm	LMCA: +2.8 LAD: +1.81 Cx: 2.8 RCA: 2.2			LMCA: 3.6	LMCA: 2.1

On echo 2, the number of patients with systolic and diastolic dysfunction, pericardial effusion and coronary abnormalities were higher among non survivors compared to survivors. However, the difference between both groups was statistically significant regarding diastolic dysfunction only **(Table 6).**

Table (6): Comparison of echo 2 findings between survivors and non survivors

Echo 2 Findings	Survivors (n= 23)		Non survivors (n= 16)		$\square^2$	p
	No.	%	No.	%		
Systolic dysfunction	10	43.5	11	68.8	2.425	0.119
Diastolic dysfunction	0	0.0	6	37.5	10.193*	FEp=0.002*
Pericardial effusion	6	26.1	9	56.3	3.627	0.057
Valvular involvement (mild/moderate/severe MR)	7	30.4	9	56.3	2.599	0.107
Coronary abnormalities	4	17.4	1	6.3	1.048	FEp=0.631

χ^2: Chi square test, FE: Fisher Exact test, p: p value for comparing between the studied groups.

DISCUSSION

Up to 67–80% of children with MIS-C will experience cardiac involvement, which is more prevalent in MIS-C than in Kawasaki disease (KD) [11]. Usually done within 12 hours of hospital admission, an echocardiography may reveal pericardial effusion, coronary artery anomalies, and poor ventricular function linked to myocarditis [12].

In our investigation, there was no statistically significant differences between the patient and control groups according to the anthropometric measurements. This went in the same line with **Biko *et al.*** [13] who showed in their study no statistically significant difference regarding the anthropometric measurements**.**

In our investigation, there was a statistically significant difference in blood pressure, temperature, heart rate, and respiration rate between the two groups. This was comparable to the findings of **Kavurt *et al.*** [14] who studied 50 MIS-C patients and 40 age-matched healthy controls. They found that the MIS-C group had considerably higher heart rates, respiration rates, and temperatures than the controls. This is explained by the fact that MIS-C is characterized by extreme hyperinflammation that results in symptoms such as macrophage-activation syndrome (MAS) and toxic shock syndrome (TSS) [15].

In our study, 87 % of patients with MIS-C exhibited cardiovascular manifestation which was the most affected system. This agrees with the results of **Yousaf *et al.*** [16] who found that 80% of children with MIS-C had cardiac involvement.

The hematological system was the second system to be affected (69%). The least was the respiratory system (13%). It's interesting to note that 46% of the patients in our research had renal dysfunction when they were admitted. According to the study by **Feldstein *et al.*** [11] renal involvement was found in 17% of their MIS-C patients.

The median duration of hospitalization for the most of our patients was 14 days (min-max: 11–20 days). That agreed with a study, which reported that a median hospitalization duration of 12.00 days was recorded and 66% of the patients needed intensive care unit [17]. 74.4% of the patients needed PICU admission and they underwent modified OSF scoring for prediction of their prognosis. Most of them had a score 8. 15% of them had the worst score 10 and only 10% of them had the best score 3. Out of 39 patients, 23 survived (59%) and 16 patients died (41%). That was in the same line with a study carried out by **Acevedo *et al.*** [18] on 71 patients with MIS-C admitted in PICU in Colombia and reported that the mortality rate was significantly greater (9% vs. 1%) than in high-income nations.

In contrast, a research by **Sai *et al.*** [19] revealed that 77 of the 78 offspring survived, while 1 kid (1.3%) passed away. Similar mortality rates, ranging from 0% to 3%, were also seen in the majority of other Indian and Western investigations [20-22].

We think that these inferior outcomes might be caused by a number of variables, such as shock at entrance, delayed consultation, PICU availability, limited access to healthcare services, and increased cardiac involvement severity.

Most of our patients received systemic corticosteroids (64.1%). The second main line was IVIG (47.7 %). 28% of the patients received IVIG with corticosteroid. 20.5 % of the patients had continuous renal replacement therapy (CRRT) but unfortunately showed minimal efficacy. 20.5% of the patients received inotropes of adrenaline and dobutrex also with very little effect. The least effective therapy was plasmapheresis (7.7%) of the patients and none of them had survived.

Yasuhara *et al.* [23] in their observational studies including 917 MIS-C patients reported that corticosteroids, aspirin, and intravenous immunoglobulin were the most commonly prescribed therapy.

As regard to the inflammatory markers, in our study, MIS-C patients exhibited an obvious elevation of inflammatory markers, especially with regard to FDPs, ferritin level, D-dimer, CRP, ESR, procalcitonin and troponin showing higher levels. A study by **Tang *et al.*** [12] demonstrated that MIS-C patients had high levels of CRP, D-dimer, ferritin, procalcitonin, ESR and troponin.

In this investigation, we reported the echocardiographic findings of the patients with MIS-C daily by echocardiography until discharge or death and any cardiac involvement was recorded. We found that LVSD (56%) and valvular involvement (53%) were the most predominant features, while the coronary abnormalities (15%) were the least predominant feature.

It agreed with **Alsaied *et al.*'s** [24] study, which found that acute myocardial dysfunction was the most prevalent cardiac finding in MIS-C patients. 15% of our patients had coronary anomalies. Only one patient had a coronary artery dilation, whereas the others had a coronary artery aneurysm with a Z score of 9.06. **Feldstein *et al.*** [11] found that the prevalence of coronary artery aneurysms in the setting of MIS-C is around 13%.

By following up the patients by echocardiography daily, we reported their echo findings on the day of their discharge for those who survived and death for those who unfortunately didn't, we found that 95.5 % of the patients who had systolic dysfunction still had it and only 4.5 % showed improvement. That supported the theory of permanent cardiac damage due to hyperimmune effect of MISC and the cytokine storm [25].

75% of patients who had diastolic dysfunction didn't improve while 25% became near normal. **Matsubara *et al.*** [26] observed that the E/A ratio improved and recovered to normal levels, although it remained below normal, indicating persistent LV damage.

In our study, only 1 patient of all patients with coronary abnormalities showed improvement with Z score 1.24. That agreed to research by **Valverde *et al.*** [27] as 69 out of 286 patients with MIS-C exhibited coronary involvement in any of their coronary arteries, and the majority of the coronary abnormalities remained over the short period of follow-up.

On echo 2, diastolic dysfunction was statistically significantly higher among non-survivors compared to the survivors. This was consistent with the findings of **López *et al.*** [28] who discovered a link between mortality and cardiovascular symptoms such as diastolic dysfunction ($p = 0.02$).

LIMITATIONS

The sample size was small and the study was a single center study. We observed patients only during the hospitalization and that short period of follow up didn't evaluate long term cardiac consequences. Also, we used the conventional transthoracic echocardiography, which may not detect the LV deformation or the myocardial strain but it's the most common available bedside machine in most hospitals.

CONCLUSION

We found that cardiovascular system affection was the most prominent system affected. Unlike classic Kawaski disease, coronary arteries could be spared, however systolic dysfunction and pericardial effusion were more commonly affected. Moreover, no patient with diastolic dysfunction survived. Although echocardiography is a key for diagnosis, most patients need more advanced evaluation and longer follow up duration to determine residual long-term cardiac damage.

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