Clinical profile and outcomes of multisystem inflammatory syndrome in children associated with COVID-19 virus after surgery for congenital heart defects

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ABSTRACT

Introduction : To study the clinical presentation, laboratory profile, echocardiographic details, management, and outcomes of children who were diagnosed to have multisystem inflammatory syndrome in children (MIS-C) in the immediate postoperative period after surgery for congenital heart defects (CHDs).

Materials and Methods : This is a prospective case–control study that included children diagnosed to have MIS-C in the postoperative period based on clinical signs, rise in inflammatory markers, and echocardiographic features of ventricular dysfunction or coronary involvement. Management included intravenous immunoglobulin (IVIG), steroids, and antiplatelet medications in addition to routine postoperative care. Out of the 461 children who underwent surgery for CHD between April 1st, 2021, and November 30th, 2021, 18 children were diagnosed with MIS-C. After the initial routine postoperative course, all 18 children had sudden worsening in clinical and laboratory parameters. Other causes such as bacterial infection were ruled out. All of these children had features of MIS-C with ventricular dilatation and dysfunction, coronary artery involvement, and reactive COVID-19 immunoglobulin G antibody. There was a significant improvement in coronary artery dimensions after IVIG administration ($P = 0.001$). The involvement of the left main coronary artery was associated with significantly increased length of intensive care unit (ICU) and hospital stay ($P = 0.019$). Mean ICU and hospital stay was prolonged in the MIS-C group. There were two deaths in this group due to severe left ventricular dysfunction.

Conclusions : During the pandemic, a proportion of patients undergoing elective cardiac surgery may develop unexpected worsening in clinical status due to MIS-C. A high index of suspicion and prompt treatment with IVIG and steroids may be helpful in improving outcomes.

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INTRODUCTION

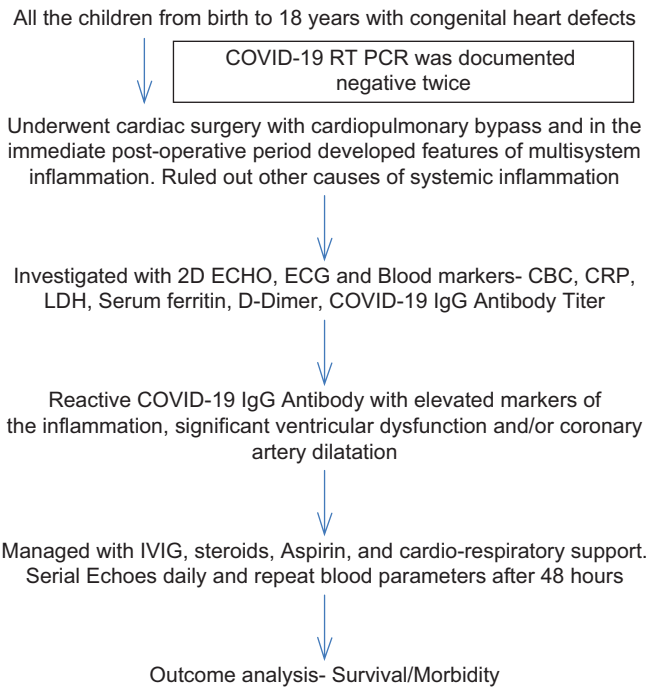
The COVID-19 pandemic, caused by SARS-CoV-2 has a lesser incidence in children compared to adults. In a study by Stokes *et al.*, children <20 years of age accounted for 5.2% of the total infections.[1] The clinical manifestations of COVID-19 virus infection in children involve isolated respiratory or gastrointestinal systems or can have multisystem involvement with significantly elevated inflammatory markers and the clinical spectrum can mimic Kawasaki disease.[2,3] Profound inflammatory response is known as pediatric inflammatory multisystem syndrome – or multisystem inflammatory syndrome in children (MIS-C) and shown to have a temporal association with COVID-19.[4-7] The WHO defined MIS-C as fever of >3 days with signs and symptoms of inflammation with multisystemic involvement without obvious infectious cause for inflammation in a child with the evidence of COVID-19, i.e., reverse transcription–polymerase chain reaction (RT-PCR) or antigen test or antibody positive or exposure to COVID-19 patient.[5] Assessment by two-dimensional echocardiography is advised for the assessment of ventricular function and dilatation of coronary arteries. We sought to assess the clinical profile and outcomes of MIS-C postcardiac surgery in children at our institute.

MATERIALS AND METHODS

The study was done from April 1st, 2021, to November 30th, 2021, in one of the tertiary pediatric cardiac centers in India. RT-PCR assay for COVID-19 virus was done on admission and after 5 days of quarantine period in the hospital and confirmed to be negative in all patients before surgery. In the immediate postoperative period, children with unexplained clinical deterioration with features of inflammation proven by clinical- and laboratory-based evidence (complete blood count, serum ferritin, D-dimer, and serum lactate dehydrogenase) were further investigated. We used the WHO criteria to define MIS-C as outlined earlier.[5] The additional criteria included clinical, laboratory, or electrocardiogram criteria.[8] Those with infectious etiology for the deterioration, for example., bacterial sepsis were excluded. The temporal correlation with COVID-19 was done with a history of exposure to COVID-19 and reactive COVID-19 immunoglobulin G (IgG) antibody. Exposure to COVID-19 was in the form of any of the relatives or staff involved in taking care of the child who later was found to have manifestations of the COVID-19 infection. Two-dimensional echocardiography was repeated in patients suspected of having MIS-C to assess ventricular function and the status of coronary arteries. Coronary artery involvement was defined as features of perivascular cuffing or luminal irregularity or Z-score of more than +2.[9]

The management of MIS-C included intravenous immunoglobulin (IVIG), injectable, and oral steroids, and antiplatelets in addition to cardiorespiratory support if required.[10] IVIG was given at a dose of 2 g/kg as continuous intravenous (IV) infusion over 48 h and injection methylprednisolone was given as a single daily dose of 30 mg/kg over 1 h for 3 days. Repeat blood investigations and echocardiography were performed serially till the symptoms and signs of inflammation subsided. In case of persistent clinical features of MIS-C after 36 h, IVIG dose was repeated [Flowchart 1]. The Z-scores for coronary artery dimensions were calculated at discharge and during follow-up, a month postdischarge.

IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp., parametric data are expressed as mean + standard deviation and nonparametric data as



Flowchart 1: Hospital protocol for investigations and management of the children with suspected MIS-C. RT-PCR: Reverse transcription–polymerase chain reaction, 2D: Two-dimensional, ECG: Electrocardiogram, CBC: Complete blood count, CRP: C-reactive protein, LDH: Lactate dehydrogenase, IgG: Immunoglobulin G, IVIG: Intravenous immunoglobulin

median with range. Statistical tests included Student's paired-*t* test and Pearson's correlation coefficient, and a $P < 0.05$ was considered statistically significant.

RESULTS

During the study period, 18 out of 461 children (3.9%, 95% confidence interval 2.1%–5.7%) operated for congenital heart defect (CHD) had clinical and laboratory features suggestive of MIS-C. The group of MIS-C included 11 boys and 7 girls, and the median age was 1.6 years (range: 1 month to 7 years). The details of the children with features of MISC are summarized in Table 1.

There was no correlation with the cardiac anatomy and both the groups of patients, i.e., shunt lesions with increased pulmonary blood flow and those with decreased pulmonary blood flow (tetralogy of Fallot physiology) were affected with MIS-C. Unexplained fever and tachycardia were the most common signs. All except one patient had a routine postoperative course in the initial period followed later by sudden worsening after 72 h. The time duration of the presentation after surgery varied from 1 to 10 days. The details of the inflammatory markers at the baseline and after treatment are given in Table 2.

Among the children with MIS-C, two patients died. One of them was operated for a double outlet right ventricle with atrioventricular septal defect repair who was shifted to postoperative ward with normal left ventricular (LV) function and awaiting discharge. He presented with tachycardia and tachypnea on the 7th postoperative day and was noted to have severe LV dysfunction. He was managed with IVIG and steroids along with inotropic support. However, LV dysfunction persisted, and he succumbed due to multi-organ dysfunction. The second patient had ventricular septal defect closure and developed MIS-C on the 6th postoperative day. He required reinitiation of inotropic and ventilator support. He received a second dose of IVIG due to persistently elevated inflammatory markers. Despite aggressive management, the child died on the 10th postoperative day.

There was coronary artery involvement in all the patients either in the form of perivascular cuffing or luminal irregularity or significant dilatation (Z-score> +2), as shown in Table 3 and Figure 1. The coronary

Table 1: The clinical details of patients with features of multisystem inflammatory syndrome in children

Age (years)	Weight (kg)	Diagnosis	Surgery done	CPB (min)	AXC (min)	Day of onset of MISC after surgery	Presentation	ICU stay (days)	Hospital stay (days)	Outcome
0.9	6	Large VSD	VSD closure	83	44	5	Fever, cough, unexplained tachycardia	13	16	Discharged
2.5	9.1	TOF	ICR	179	83	6	Fever, loose stools	7	32	Discharged
0.9	4.1	Large VSD	VSD closure	120	76	5	Fever, cough, unexplained tachycardia	18	19	Discharged
1.6	6.5	Large VSD	VSD closure	46	29	4	Fever, rash, cough, unexplained tachycardia	15	53	Discharged
2.2	6.2	Large VSD	VSD closure	70	38	5	Fever, cough	16	21	Discharged
1.9	6.6	Large VSD	VSD closure	228	141	5	Fever, distress, rash	21	27	Discharged
0.6	4.1	Large VSD	VSD closure	90	46	1	Fever, cough	10	16	Discharged
5	13	SAM + SMM	Resection of SAM and SMM	86	64	4	Cough, wheezing	3	11	Discharged
2.3	9.1	TOF	ICR	111	82	4	Fever, cough	13	18	Discharged
0.42	3.4	DORV AVCD	IVTR	142	82	7	Tachycardia, tachypnea, abdominal distension	13	19	Expired
2.2	8	AP window	AP window repair	77	30	5	Fever, cough	9	31	Discharged
1	5.9	VSD with COA	CoA repair and VSD closure	197	87	4	Fever, unexplained tachycardia	17	28	Discharged
2.1	9	VSD with PDA	VSD closure and PDA ligation	79	48	6	Fever, cough, tachypnea, tachycardia, abdominal distension	3	20	Discharged
7	15	ASD	ASD closure	80	58	4	Fever	2	21	Discharged
0.5	4	Large VSD	VSD closure	173	29	4	Fever, tachycardia	26	27	Expired
2.7	9.4	AVSD	AVSD repair	124	100	10	Fever, cough	2	19	Discharged
0.1	3.7	Cardiac TAPVC	TAPVC repair	127	80	5	Cough, unexplained tachycardia	11	15	Discharged
1.5	8.8	TOF	ICR	128	93	7	Fever, loose stools, unexplained tachycardia	4	17	Discharged

VSD: Ventricular septal defect, TOF: Tetralogy of Fallot, SAM: Subaortic membrane, SMM: Supra-mitral membrane, DORV: Double outlet right ventricle, AP window: Aortopulmonary window, COA: Coarctation of aorta, PDA: Patent ductus arteriosus, ASD: Atrial septal defect, AVSD: Atrio-VSD, TAPVC: Total anomalous pulmonary venous connection, ICR: Intracardiac repair, IVTR: Intraventricular tunnel repair, CPB: Cardiopulmonary bypass, MIS-C: Multisystem inflammatory syndrome in children, AVCD: Atrio-ventricular canal defect, AXC: aortic cross clamp time

dimensions normalized after treatment with IVIG, as shown in Figure 2. Four children (including two children who died) failed to demonstrate improvement in clinical and laboratory parameters and received a repeat dose of IVIG. The remaining 14 children showed improvement within 24 h of IVIG administration. All of these patients with coronary dilatation received aspirin and it was continued for the next 3 months. All children who survived had normal coronary artery dimensions at the first follow-up.

Coronary involvement was not associated with an increase in mortality, although left main coronary artery involvement was associated with a prolonged hospital stay. There was no correlation between coronary artery Z-scores and COVID-19 IgG antibody titers. The mean intensive care unit (ICU) and hospital stay was 11.28 ± 6.95 days and 22.77 ± 2.24 days, respectively.

Table 2: Distribution of the laboratory parameters among the children with multisystem inflammatory syndrome in children at baseline and after treatment

	Median (range)	
	Baseline	Posttreatment
CRP (mg/dl)	157.4 (3.6-161)	50.2 (0.3-50.5)
D-dimer (ng/mL)	4977 (823-5800)	4808 (152-4960)
LDH (U/L)	279 (346-625)	717 (72-789)
Platelets (per µl)	491,200 (127,800-619,000)	405,900 (80,100-486,000)
Ferritin (ng/ml)	9856.5 (143.5-10,000)	3952 (38-3990)
TLC (per µl)	17,870 (6120-23,990)	13,670 (3330-37,000)

CRP: C-reactive protein, LDH: Lactate dehydrogenase, TLC: Total leukocyte count

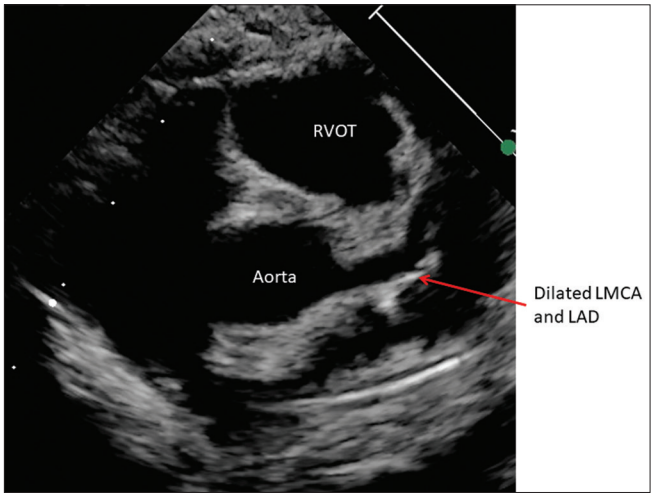


Figure 1: Parasternal short axis view showing dilated left main coronary artery and left anterior descending artery. RVOT: Right ventricular outflow tract, LMCA: Left main coronary artery, LAD: Left anterior descending artery. Red arrow is showing dilated LMCA and LAD

DISCUSSION

In children, COVID-19 infection causes less of respiratory but more of multisystem involvement with a significant inflammatory response, also known as "MIS-C."[11] There are multiple studies in healthy children with structurally normal hearts who developed MIS-C following exposure to the COVID-19 virus.[12]

Similarly, COVID-19 infection is also known in children with CHD who are waiting for cardiac surgery and surgical repair in these children, after an isolation period has not shown any significant difference in outcomes compared to those who did not have COVID-19 infection.[13] Our study was unique in assessing the impact of MIS-C postcardiac surgery in children with CHD.

All children were taken for surgery only if there were two negative RT-PCR reports for COVID-19 done initially on admission and after a 5-day period of in-hospital quarantine. Out of 461 surgeries, 18 children developed features of MIS-C. Although COVID-19 RT-PCR was negative twice in all these children, sudden unexplained worsening prompted us to suspect the same and hence we tested for COVID-19 IgG antibodies. COVID-19 IgG antibodies were positive in all children. We managed these as per prevailing guidelines for children with MIS-C with IVIG, IV steroids, and aspirin at antiplatelet dosage.[14-16] All except two children showed significant improvement in clinical and laboratory parameters, and these 16 children recovered and were discharged from the hospital. The morbidity indicators (mean ICU stay and mean hospital stay) were higher in these children compared to those without MIS-C. In the study done by Borrelli *et al.*, in children with features of MIS-C and no structural heart disease, mortality was very low.[15] However, multicentric study done by Choubey *et al.* showed significantly increased in-hospital mortality (8.1%) and postoperative

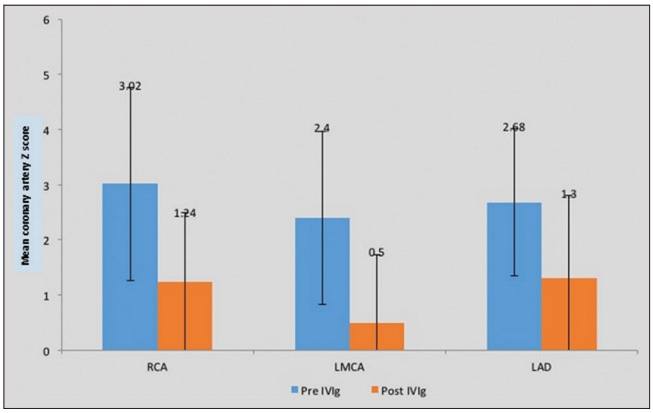


Figure 2: Mean coronary artery dimensions at the baseline and after giving IVIG which shows there was normalization of coronary artery sizes after IVIG administration. IVIG: Intravenous immunoglobulin, LMCA: Left main coronary artery, RCA: Right coronary artery, LAD: Left anterior descending artery

Table 3: Coronary artery dimensions of children with multisystem inflammatory syndrome in children at baseline and before discharge

At diagnosis						Before discharge					
RCA (mm)	*Z* score	LMCA (mm)	*Z* score	LAD (mm)	*Z* score	RCA (mm)	*Z* score	LMCA (mm)	*Z* score	LAD (mm)	*Z* score
1.8	0.8	1.3	−1.5	2	2.63	1.4	−0.04	1.6	−0.71	1.55	0.52
3.4	5.72	3	2.46	2.8	4.94	1.8	0.59	1.9	−1.84	1.9	1.12
3.1	6.51	2.6	2.68	1.6	1.55	2.1	2.87	2	0.85	1.6	1.55
2.6	3.87	3.6	6.26	2	2.67	1.7	0.82	1.8	−0.29	1.5	0.08
3.1	5.48	3.3	3.86	2.2	3.24	1.8	1.12	1.8	−0.32	1.69	0.91
1.76	1	3.2	3.6	2.2	3.25	1.27	−0.64	2.3	1.09	1.27	−1
1.24	−0.05	1.5	−0.5	1.3	0.06	1.24	−0.05	1.5	−0.5	1.3	0.06
3.4	4.5	3	1.58	2.8	3.41	2.5	1.86	2.7	0.83	2.5	2.3
2.34	2.34	2	−0.21	1.7	0.29	1.5	−0.35	1.7	−1.02	1.2	−1.84
2.2	3.6	2.3	2.2	1.4	1.1	1.8	2.1	1.8	0.57	1.2	−0.16
2.4	2.76	2.5	1.32	2.5	4.03	2	1.45	1.8	−0.59	1.98	1.75
1.9	1.72	2.5	1.55	1.9	2.24	2.1	2.4	2.1	0.75	1.2	−1.1
2.5	2.75	3.1	2.66	2.7	4.43	2.5	2.75	2.5	1.07	2.3	2.74
2.7	2.06	3.6	2.72	2.6	2.17	1.8	−0.5	2.8	0.76	2.4	1.47
2.2	3.45	2.3	1.92	1.8	2.7	2	2.74	2.1	1.33	1.88	3.13
2.4	2.3	3.5	3.67	2.4	3.04	1.75	0.31	3.3	3.13	2.3	2.62
1.8	2.11	2.2	1.7	1.7	2.34	1.8	2.11	2.1	1.42	1.7	1.34
2.7	3.52	3.6	4.14	2.6	4.15	2.5	2.9	3	2.52	2.4	3.32

LMCA: Left main coronary artery, LAD: Left anterior descending artery, RCA: Right coronary artery

mortality (9.3%) ($P < 0.001$ for both) for congenital heart surgeries done during the first wave of the COVID-19 pandemic in India.[17] In our cohort of children with postoperative MIS-C, in-hospital mortality was 11%. Additional studies involving a larger number of patients may help assess the reason for increased mortality in MIS-C postcardiac surgery. A delay in recognition might have also contributed to high mortality.

Chew *et al.* have shown that a rise in inflammatory markers might be secondary to the effects of cardiopulmonary bypass (CPB).[18,19] One of the causes for these inflammatory reactions is the contact of the blood components with the artificial membrane leading to the production or activation of endotoxins inside the body. The ischemia-reperfusion injury and operative trauma are other possible reasons for the inflammatory response. The markers of inflammation may be raised postbypass surgery, but unexplained worsening in clinical status and ventricular function, coronary artery involvement, no signs of infection, positive history of contact with COVID-19 patient, and positive COVID-19 IgG antibodies made us to think for MIS-C. Considering that it takes few weeks to develop postinfection and all children had two negative COVID-19 RT-PCR before surgery, the initial infection would have been several weeks before surgery. Moreover, these inflammatory complications have reduced significantly with the use of techniques such as ultrafiltration and heparin-coated pumps.[11,20] There are studies which show CPB can lead to a reduction in the immune system further leading to the activation of latent infection.[21] The pro-inflammatory condition following CPB could be one of the reasons for the development of MIS-C in children who were asymptomatic and tested negative for SARS-CoV-2 before surgery.

Although it is difficult to prove cause–effect relationship, history of contact, the presence of COVID-19 IgG antibodies with features of generalized inflammation, and raised markers suggest COVID-19 infection as the most likely etiology. There are no guidelines to support routine testing for COVID-19 antibodies before surgery. The contact person may also be having asymptomatic infection and hence we should have a high index of suspicion in any child with unexplained worsening. The mechanism of the action of IVIG has been recently described in two studies. It acts by reducing Interleukin-1 β production by neutrophils, thus reducing the hyperinflammatory response. IVIG inactivates these neutrophils.[22-24] Addition of steroids also helps to reduce the inflammatory response.

The two deaths in our cohort of positive MIS-C cases occurred earlier in the study period and might have been due to a delay in diagnosis. Management with IVIG and steroids reduced mortality to 11.1% but it is still higher compared to surgeries carried out on children without MIS-C. In the multi-centric study done by Sachdeva *et al.*, they also found significantly higher in-hospital mortality rate among COVID-19-positive cases (27.1%) as compared to COVID-negative admissions (9.2%) with $P < 0.001$.[25] Predictors of mortality included the severity of the disease on admission and lower socioeconomic class. Some of the newer imaging modalities such as peak left atrial (LA) strain values might also be useful to identify latent ventricular dysfunction and help in predicting outcomes in these children.[26] The pulmonary manifestations of COVID-19 seem to be more severe and resistant to conventional treatment, independent of COVID-19 RT-PCR status.[27] Hence, early suspicion and prompt use of steroids and IVIG might reduce mortality.

Limitations

Limitations to our study include a smaller sample size and lack of COVID-19 antibody titers before surgery.

CONCLUSIONS

This is a unique study focusing on children who developed MIS-C related to COVID-19 infection in the postoperative period. MIS-C is associated with an increase in morbidity and mortality early in the postoperative settings in our study. It should be suspected in patients after surgery with unusual course with sudden unexplained deterioration especially if associated with worsening of heart function and dilated coronary arteries even if the presurgical RT-PCR for SARS-CoV-2 is negative. IVIG along with IV steroids has been beneficial in these children. Early suspicion and prompt treatment are required to reduce COVID-19 MIS-C-related morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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