RESEARCH PAPER

Profile of Cardiac Involvement in Children After Exposure to COVID-19

MUNESH TOMAR,[1] MAITRI CHAUDHURI,[2] TANVI GOEL,[1] VIKAS AGARWAL,[1] SHIFA BIDHAN,[3] AMIT JAIN,[4] ANUJ RASTOGI,[5] VINEET SAXENA,[6] HARIRAJ SINGH TOMAR[7]

[1]*Department of Pediatrics, LLRM Medical College, Meerut, Uttar Pradesh.*
[2]*Department of Pediatrics, Manipal Hospital, Bangalore, Karnataka.*
[3]*Department of Pediatrics, Military Hospital, Meerut, Uttar Pradesh.*
[4]*Anand Skin and Child Care Center, Meerut, Uttar Pradesh.*
[5]*Department of Pediatrics, Jaswant Rai Superspeciality Hospital, Meerut, Uttar Pradesh.*
[6]*Department of Pediatrics, Medwin Hospital, Meerut, Uttar Pradesh,*
[7]*Department of Pediatrics, Nutema Hospital Meerut, Uttar Pradesh.*

Correspondence to:
Dr Munesh Tomar, Consultant, Pediatric Cardiologist, LLRM Medical College, Meerut, Uttar Pradesh 250 002.
drmuneshtomar@gmail.com
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Objective: To evaluate the incidence and pattern of cardiac involvement in children post-COVID (coronavirus disease) infection in a tertiary care referral hospital in India. **Methods**: A prospective observational study was conducted including all consecutive children with suspected MIS-C referred to the cardiology services. **Results**: Of the 111 children with mean (SD) age 3.5 (3.6) years, 95.4% had cardiac involvement. Abnormalities detected were coronary vasculopathy, pericardial effusion, valvular regurgitation, ventricular dysfunction, diastolic flow reversal in aorta, pulmonary hypertension, bradycardia and intracardiac thrombus. The survival rate post treatment was 99%. Early and short-term follow-up data was available in 95% and 70%, respectively. Cardiac parameters improved in the majority. **Conclusion**: Cardiac involvement post COVID-19 is often a silent entity and may be missed unless specifically evaluated for. Early echocardiography aids in prompt diagnosis, triaging, and treatment, and may help in favorable outcomes.

Keywords: *Coronary aneurysm, Intracardiac thrombus, MIS-C, Pericardial effusion, Ventricular dysfunction.*

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In the global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV- 2), most children showed minimal symptoms; however, a subset developed hyper-immune multiorgan inflammation [1,2]. The Centers for Disease Control and Prevention (CDC) defined this as multisystem inflammatory syndrome in children (MIS-C) [3], with some similarities with Kawasaki disease. The cardiovascular manifestations of MIS-C included arrhythmias, coronary vasculopathy, ventricular dysfunction, valvular regurgitation, and pericardial effusion. Other complications like intracardiac thrombus, shock and myocarditis were infrequently reported [4-7]. Immunomodulation has been found to have a promising role in the management of MIS-C.

METHODS

A prospective observational study was conducted between June, 2021 and September, 2021, enrolling consecutive children with suspected MIS-C [3], referred to pediatric cardiologists in a tertiary care hospital in northern India, post second wave of coronavirus disease (COVID-19). Children with bacterial sepsis and other alternative diagnosis, were excluded. Demographic, anthropometric and clinical data including clinical presentation, treatment and early and short-term outcomes were recorded. Laboratory data were assessed under three broad categories, organ function tests, and inflammatory and cardiac markers.

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Cardiac evaluation was done by twelve lead electrocardiogram (ECG), and echocardiography as per American Society of Echocardiography guidelines [8] and cross evaluated by another cardiologist blinded to clinical data. As per American Heart Association guidelines [9], the coronary arteries were classified as no involvement (*z* score <2), dilatation only (*z* score ≥2-<2.5), small aneurysm (*z* score ≥2.5-<5), medium aneurysm (*z* score ≥5-<10) and large aneurysm (*z* score ≥10). The first cardiac evaluation was performed within 7 days of onset of symptoms and follow-up between 10-14 days post therapy. Survivors were planned for subsequent cardiac assessments at 1 month, 3 months and at 1 year.

Statistical analysis: Data were analyzed by SPSS v 20.0 trial version. Fisher exact test was used to compare categorical data. Kruskal-Wallis test was used to compare data which was not normally distributed. *P* value <0.05 was considered statistically significant.

RESULTS

A total of 111 children (74 males), with mean (SD) age of 3.5 (3.6) years were studied. Seven (6.3%) were neonates, 26 (23.4%) were infants, and majority 78 (70.2%) were between 1 and 14 years of age. SARS-CoV-2 antibodies were positive in 94.5%, none were RT-PCR positive, and contact tracing was positive in 13.5%.

The mean (SD) time from onset of symptoms to presentation to cardiologist was 5.4 (2.2) days. Pyrexia was the predominant feature in 92 (82.8%) children, followed by gastrointestinal symptoms in 35 (31.5%) (vomiting 16.2%, loose stools 5.3%, abdominal pain 6.3%), rash in 15 (13.5%), altered sensorium in 4 (3.6%) and generalized swelling in 4 (3.6%). Respiratory distress was universal in neonates while it was observed in 26 (23.4 %) in pediatric group (8.1% had severe and 15% had mild-to-moderate distress). Bradycardia was found in 7 children.

Laboratory investigations revealed anemia in 30 (27%), which was severe (hemoglobin <7g/dL) in 7 (6.3%). Leucolytosis was seen in 15 (13.5%), with increased neutrophil-lymphocyte ratio in 5 (4.5%) and thrombocytopenia in 13 (11.7%). Inflammatory markers were elevated in 105 (94.5%). Mean (SD) C-reactive protein and procalcitonin were 22.3 (30.4) and 8.1 (9.1), respectively. Deranged renal function was noted in 12 children while 15 had elevated transaminases. Abnormal levels of troponin T were seen in 22 (20%) and elevated D-dimer was noted in 40 (36%). D-dimer was >4 times of normal in all children with MIS-C.

ECG evaluation showed all children to be in sinus rhythm, except seven who had bradycardia. Bradycardia was secondary to sinus node dysfunction in six children and Wenckebach phenomena in one child. The findings of echocardiography are shown in **Table I**. A total of 45 (40.5%) children showed ventricular dysfunction with left ventricle affected in 36% and right ventricle in 4.5%. Coronary vasculopathy was detected in 67 children (60.3%) (**Fig. 1**). Left main coronary artery was most commonly affected (56%) followed by left anterior descending (31%). Mean ratio of velocity time integral of reversed and antegrade flows was 0.25. Diastolic flow reversal was associated with low cardiac output in two children and with severe anemia in seven, while in others it may be arteriopathy affecting vascular compliance. Two had moderately severe pulmonary artery hypertension (all neonates). Pulmonary venous hypertension (PVH) was present in one patient with severe left ventricular dysfunction. Two children showed intracardiac thrombus.

Table I Echocardiographic Findings in Patients With MIS-C (*N*=111)

Parameters	*No (%)*
Coronaries	
Normal	44 (39.6)
Dilated	17 (15.3)
Small aneurysm	48 (43.2)
Moderate aneurysm	2 (1.8)
Large aneurysm	0 (0)
Dilated chamber	17 (15.3)
LA/LV	10 (9)
RA/RV	7 (6.3)[a]
LV dysfunction (EF%)	40 (34.2)
Mild (45-<55%)	33 (27.9)
Moderate (30-44%)	6 (5.4)
Severe (<30%)	1 (0.9)
RV dysfunction	5 (4.5)
Pericardial effusion	54 (48.6)
Diastolic flow reversal	19 (17.1)
Structural abnormality	
Ventricular septal defect	2 (1.8)
Left SVC to coronary sinus	2 (1.8)
Coronary artery origin from different sinus	3 (2.7)
Patent foramen ovale	18 (16.2)
Valve regurgitation	87 (78.2)
Tricuspid	
Mild	79 (71.1)
Moderate	8 (7.2)
Severe	1 (0.9)
Mitral[b]	
Mild	51 (45.9)
Moderate	6 (5.4)
Aortic[c]	
Mild	24 (21)

[a]*All neonates.RA: right atrium, RV: right ventricle, LA: left atrium, LV: left ventricle, EF: ejection fraction, SVC: superior vena cava, CS: coro-nary sinus, PFO: patent foramen ovale, DFR: diastolic flow reversal.* [b]*none had severe regurgitation;* [c]*none had moderate or severe regurgitation.*

Table II shows association between increased CRP level and coronary artery involvement. Significantly higher proportion of patients with normal CRP had small aneurysms than the patients with abnormal CRP [OR (95% CI) 3.31 (1.28-8.57); *P*=0.014]. There was no significant association between duration of admission, age in years, BMI, BSA with coronary involvement and ventricular dysfunction.

All patients received immunomodulation. Intravenous immunoglobulin (IVIG) alone was given to 34 (31%), both

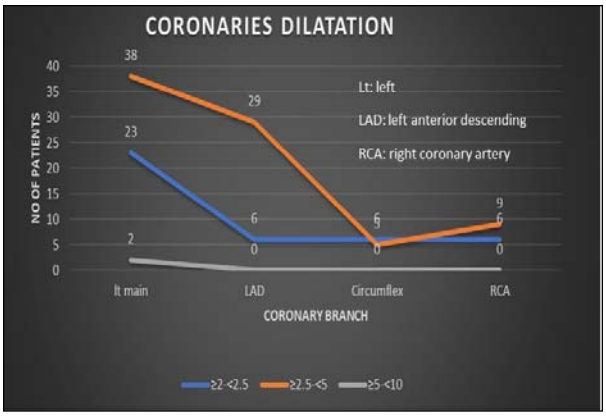

Fig. 1 Coronary artery (left main), left arterior descending (LAD) artery, right coronary artery (RCA) and circumflex artery among children with MIS-C.

IVIG and corticosteroids were administered to 45 (40%), while 32 (29%) received only steroids (due to resource constraints). Low molecular weight heparin was administered to those with documented intra-cardiac thrombi. All were discharged on oral aspirin and continued till normalization of coronaries. Ionotropic support and mechanical ventilation were required for 6 (5.4%) and 11 (10%) children, respectively. The mean (SD) duration of hospital stay was 5.7 (1.9) days. All children, except the infant with giant right atrial thrombus, recovered. Immediate survival rate was 99%.

Early (mean, 12 days) and short-term (mean, 95 days) follow-up data was available in 95% and 70% of children. Early follow-up echocardiography showed improvements in most parameters. Proportion of children with coronary involvement decreased to 56% while 11.3% had increased *z*-scores in first follow up. Cardiomegaly persisted only in five children while significant valvular regurgitation disappeared in all. Ventricular function normalized in 95.5%, pericardial effusion decreased to 1.8% as compared to 48.6% at the onset, while none had pleural effusion. At short-term follow-up, 11 (10%) children showed persistent coronary aneurysm. Ventricular function, pulmonary artery pressure and rhythm normalized in all. The child with Wenckebach phenomenon was lost to follow-up.

DISCUSSION

Our study included mostly young children, in contrast to studies by Dufort, et al. [5] and Rajapakshe, et al. [10]. This may be due to increased awareness among pediatricians who referred all suspected MIS-C to pediatric cardiologists. Our data revealed cardiac involvement in 95.4% of cohort in the form of coronary vasculopathy, ventricular dysfunction, valve regurgitation, and rhythm abnormalities.

As per previous data [11], cardiac involvement was common and reported in 67-80% of MIS-C. Common cardiovascular manifestations were cardiac dysfunction (31-58%), coronary vasculopathy (14-48%), and rhythm abnormalities (6.3-25%).

Our study demonstrated that echocardiography provides significant value to clinical information. Although, none of them are per se diagnostic for MIS-C, rapid exclusion of alternative diagnosis and initiation of therapy provided survival benefit to 99% of the patients. Therapeutically, the recommended protocol of immunoglobulin and steroids could not be initiated in all patients. Data from low- and middle-income nations suggested that steroids can be an acceptable alternative in such situations [12].

MIS-C in neonatal group presented a diagnostic dilemma. Findings observed were cardiomegaly, severe

Table II Association Between C-Reactive Protein and Coronary Artery Parameters

	C-reactive protein, n (%)		*Odds ratio (95% CI)*	*P value*
	Normal	*Abnormal*		
Left anterior descending artery				
Dilated	1 (3.8)	5 (6)	0.938 (0.101-8.718)	0.955
Small aneurysm	12 (46.2)	17 (20.5)	3.312 (1.280-8.574)	0.014
Left main coronary artery				
Dilated	5 (19.2)	16 (19.3)	1.354 (0.392-4.672)	0.631
Small aneurysm	11 (42.3)	27 (32.5)	1.765 (0.644-4.839)	0.269
Moderate aneurysm	1 (3.8)	1 (1.2)	4.333 (0.247-76.046)	0.316
Circumflex artery				
Small aneurysm	3 (11.5)	2 (2.4)	4.891 (0.770-31.082)	0.092
Right coronary artery				
Dilated	1 (3.8)	5 (6)	0.617 (0.069-5.560)	0.667
Small aneurysm	2 (7.7)	7 (8.4)	0.882 (0.171-4.548)	0.881

WHAT THIS STUDY ADDS?

- Ventricular dysfunction and coronary vaculopathy were the most common cardiac abnormalities seen with multisystem inflammatory syndrome in children (MIS-C).
- Most of the echocardiographic parameters improved over a short-term follow-up.

pulmonary hypertension, significant valvular regurgitation, ventricular dysfunction, coronary involvement, thrombus and arrhythmia [13]. Presence of such findings should alert the neonatologists towards presence of MIS-C. However, other respiratory causes and cyanotic congenital heart diseases must be excluded.

The major limitation of our study is that the study was conducted only on children referred by pediatricians to cardiologists; thus, referral bias cannot be ruled out. Advanced cardiac imaging like coronary angiography or MRI was not done due to the emergent situation. Echocardiography was the best rapid diagnostic modality available, and was helpful in early management.

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