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## Original Article

# The “After Wave”: Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 in a series of children from Eastern India



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## ABSTRACT

**Background:** The objective of the study is to describe the presentation, treatment and outcomes of children with multisystem inflammatory syndrome with COVID-19 (MIS-C) in a tertiary care centre in Eastern India.

**Methods:** Retrospective data of children diagnosed with MIS-C during the SARS CoV-2 pandemic were obtained from hospital records. Clinical details, laboratory profile, treatment protocol and outcomes of children with MIS-C between 01 Nov 2020 and 30 June 2021 were analysed.

**Results:** Ten children (7 males) with a mean age of 6.8 years (median age 5.5 years, interquartile range 3.75–9.5) were analysed. COVID-19 RT-PCR was negative in all patients, whereas the IgG COVID antibody was positive in all children (100%). Seven children (7/10) had a history of contact with SARS CoV-2–positive adults. Five (5/10) children presented with cardiogenic shock. All children had evidence of a hyperinflammatory syndrome. Nine children (9/10) had predominant gastrointestinal and cardiovascular involvement. None had echocardiographic evidence of coronary dilatation or aneurysms either on admission or on follow-up. The elevated neutrophil lymphocyte ratio and D-dimer were found in all patients. All children responded to immunomodulatory treatment. None had residual deficit on discharge or at 4-week follow-up. There was no mortality.

**Conclusion:** Children with MIS-C have good prognosis if early immunomodulatory treatment is instituted. Further prospective studies for long-term outcomes in children with MIS-C are required it being a novel entity recently described.

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## Introduction

The risk of severe pulmonary disease and death caused by severe acute respiratory syndrome due to the corona virus-2 (SARS CoV-2) virus has been the highest in adults since the origin of the ongoing pandemic. It was largely believed that the children are usually spared; however, few of them may rarely experience either a mild acute or an asymptomatic infection not requiring medical intervention.<sup>1</sup> Despite this, a few weeks later, a handful of children go on to develop a severe secondary inflammatory condition known as Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS), also known as Multisystem Inflammatory Syndrome in Children (MIS-C).<sup>2,3</sup>

It was during April–May 2020 about 4–8 weeks after the peak incidence of SARS CoV-2 in several countries, when paediatric intensive care specialists across the world first started reporting a multisystem inflammatory syndrome in children (MIS-C) related to SARS-CoV-2 with leading journals publishing several reports of this rare entity and its complications.<sup>3,4</sup> Predominantly children had fever and indications of a multi-system inflammation with some of them being extremely sick with shock and multiorgan failure while others had a clinical presentation of a Kawasaki disease (KD), toxic shock syndrome (TSS) or overlap of KD and TSS.<sup>5,6</sup> Although the clinical spectrum of MIS-C has been characterised since then, much remains to be known about its pathophysiology, optimal treatment, and long-term effects. Therefore, Centre for Disease Control (CDC) has initiated the “Overcoming Covid 19 study” for ongoing surveillance of severe Covid and its effects in the paediatric population.<sup>7</sup> We herein describe the clinical features and the management of children with MIS-C from a tertiary care hospital in Eastern India wherein a large inflow of adult patients with SARSCoV2 infection was witnessed.

## Material and methods

Ten children with MIS-C were treated in our hospital between Nov 2020 and June 2021. Our unit protocol consisted of diagnosing suspected MIS-C cases as per the World Health Organisation (WHO) criteria.<sup>8</sup> Confirmatory cases of children with MIS-C were managed as per American College of Rheumatology (ACR) guidelines.<sup>9</sup> Other common infections were ruled out. Ethical clearance was taken from the institutional ethics committee for data extraction from hospital records, and the details were entered in a Microsoft Excel spreadsheet. Shock was defined as systolic blood pressure (BP) <5th percentile for age requiring either fluid resuscitation and or inotropic support with signs of poor perfusion in the form of tachycardia, restlessness, and sweating. Other system involvement was suggested by the clinical, as well as specific lab parameters. Complete blood count, liver function tests, renal function tests, acute phase reactants, including ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin-dimer and lactate dehydrogenase (LDH) were measured in all patients. Myocardial injury markers, including pro B natriuretic peptide (pro-BNP), troponin-I, creatine phosphokinase myocardial band (CPK-MB), were also measured in

all cases. Echocardiography was performed in all cases to assess the myocardial dysfunction causing reduced ejection fraction, regurgitant valvular lesions and coronary artery abnormalities. Myocardial dysfunction was defined as left ventricular ejection fraction (LVEF)  $\leq 50\%$  with or without evidence of regurgitant lesions and deranged myocardial injury markers. Computed tomography (CT) chest was performed only if clinically indicated.

SARS-CoV-2 infection was diagnosed by a nasopharyngeal swab real-time reverse transcription-polymerase chain reaction (RT-PCR) and/or rapid antibody test for SARS-CoV-2 (Covid Kavach for Anti SARS CoV IgG antibody kit) as approved by the Indian Council of Medical Research (ICMR). Additionally, a history of contact with a COVID-19 positive patient was also elicited and recorded. The outcome was classified as a residual deficit, coronary abnormalities, or death. Out of the ten children, three were admitted after the first wave was regressing, and seven were admitted after the second wave was regressing.

## Results

The mean age group of the cohort was 6.4 years (Median age 5.5 years, IQR 3.75–9.5), which was higher when compared to the KD cases (non-COVID). All children presented within 5th–7th day of onset of illness. Clinical features of these children on admission are summarised in Table 1. All children were immunised as per the universal immunisation programme, and none had received influenza vaccination. Predominant systems involved were the cardiovascular system, gastrointestinal system, including liver, mucocutaneous and ocular system. Gastrointestinal (GI) involvement was seen in the form of diarrhoea, vomiting and pain abdomen in all cases except Case3. Peak cardiac involvement was seen towards the end of the first week of illness in the form of moderate-severe left ventricular (LV) dysfunction, regurgitant lesions, reduced LV ejection fraction and abnormal myocardial injury markers. Sinus bradycardia without atrioventricular (AV) block and hypertension was recorded in three patients during the second week of illness (D10–11). Only two patients required anti-hypertensive drugs. Central Nervous system (CNS) involvement in the form of abnormal behaviour and altered sensorium mimicking encephalitis with a cytotoxic lesion of the corpus callosum (CLOCC) involving splenium<sup>10</sup> was observed in only one patient (Case3). There was a resolution of symptoms on follow up at four weeks with no residual focal neurological deficit.

All relevant biochemical investigations and echocardiographic findings on admission are depicted in Table 2. We did not find any relationship between the biochemical and the inflammatory markers with the severity of the disease; however, elevated neutrophil–lymphocyte ratio coincided with the severity of illness during the first week. Elevated pancreatic enzymes (amylase and lipase) were recorded in three patients, and hypertriglyceridemia was seen in five patients, which was self-resolving. Thrombocytosis was observed in the second week of illness in eight children (80%) with a mean platelet count of 5.36 lakhs, which resolved on follow up at four weeks post-discharge.

**Table 1 – Demographic and Clinical Parameters in children with MIS-C.**

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case8	Case9	Case10
Sex	F	M	M	F	M	M	F	M	M	M
Age(years)	5	5	7	3	9	13	11	1	6	4
Day of presentation (days)	5	4	5	5	6	7	5	6	6	3
Fever>3 days	+	+	+	+	+	+	+	+	+	+
Mean fever duration (days)	5	6	6	6	7	8	6	7	8	5
GI involvement	+	+	-	+	+	+	+	+	+	+
Rash	+	+	-	+	+	+	+	+	+	+
Bilateral Nonexudative Conjunctivitis	+	-	+	+	+	+	-	-	+	+
Mucocutaneous changes	+	+	-	+	+	+	+	-	+	+
Encephalitis	-	-	+	-	-	-	-	-	-	-
Myocardial dysfunction	+	+	-	+	+	+	+	+	+	+
Hypotension with gallop rhythm	+	-	-	-	+	+	+	-	-	+
Hepatomegaly	+	+	-	+	+	+	+	+	-	+
Pulmonary Basal crepitations	+	-	-	-	+	+	+	-	-	+
History of contact with COVID Positive case	+	+	-	-	+	+	+	-	+	+
RTPCR for COVID	-	-	-	-	-	-	-	-	-	-
Antibody IgG	+	+	+	+	+	+	+	+	+	+
Other Microbial evidence	-	-	-	-	-	-	-	-	-	-
>3 organ system involvement	+	+	-	+	+	+	+	+	+	+

MIS-C -Multisystem inflammatory syndrome in Children, GI-Gastrointestinal, RT -PCR-Reverse Transcriptase polymerase chain reaction.

Cardiogenic shock required the addition of vasopressors, non-invasive ventilation and diuretics, as shown in Table 3. The recognition of cardiogenic shock necessitated administering intravenous immunoglobulin (IVIG) (2 gm/kg) along with high dose pulse methylprednisolone (10–30 mg/kg over 3–5 days). The response to treatment was prompt, and children were off vasopressor support within 72 h. All children required intensive care with an average duration of 4 days, while the median time for hospitalisation was 10.5 days. Non-invasive ventilation with humidified high flow nasal cannula was required in four patients with an average duration of 48–72 h. None required invasive ventilation and escalation of immunomodulatory treatment.

None of our patients developed any residual deficit nor had coronary artery dilatation at the time of discharge. Patients were followed up to four weeks following discharge. Myocarditis and other system involvement resolved in all patients at four weeks post-discharge. There was no mortality in our patients.

## Discussion

What remains baffling and perhaps a blessing is that despite the enormous disease burden of SARS CoV2 infection in adults, the prevalence of MIS-C in children remains minuscule (<1%)<sup>11,12</sup> and this was observed in our study too. While the inflow of adult patients with moderate to severe SARS CoV2 infection in intensive care units and Covid wards in our hospital was enormous, it was easing to manage a handful of children with MIS-C. None of the children in our study had a primary SARS CoV2 infection; however, seven (70%) children in our study had a history of contact with a confirmed SARS CoV-2 positive adult in the preceding 4–6 weeks.

It is evident from our case series that the primary system involved in MIS-C appears to be the gastrointestinal system (GI) and the cardiovascular system (CVS) rather than the respiratory system considering the fact that the most frequent symptom reported in other studies, as well as in our study was either abdominal pain, vomiting, diarrhoea and shock.<sup>13</sup> The primary system bearing the burden of the hyperinflammatory state appears to be the CVS considering the echocardiographic evidence of myocardial dysfunction and abnormal myocardial inflammatory cardiac markers. A recent meta-analysis reported GI involvement in 85.4% of children and cardiovascular involvement in 79% with echocardiographic evidence of reduced LV ejection fraction and evidence of shock in 59% of children with MIS-C, which is comparable to that reported in our case series.<sup>14</sup> Severe CVS involvement is particularly glaring in the first week of illness, and therefore, suggesting that all children with suspected or confirmed MIS-C should be aggressively evaluated with urgent echocardiography and cardiac inflammatory biomarkers to assess the cardiac function and to decide further on the need for vasopressor support and anti-thrombotic therapy as was done in our study.

It was proposed by Whittaker et al to classify MIS-C patterns as those with cardiac involvement and shock, those with fever and inflammatory markers without KD and those with features of KD.<sup>3</sup> However, in our study, it was observed that children presented with several overlapping features of fever, elevated inflammatory markers, cardiac involvement with or without shock and yet none had diagnostic features of KD. Similar findings were reported by Jain et al while reporting MIS-C cases during the first wave.<sup>15</sup> While KD has a presence in the younger age group, MIS-C presents in the older age group, as was also seen in our case series where the mean age of presentation was 6.4 years.<sup>14</sup> There were only three children with MIS-C less than five years of age in our series and all of them fulfilled the criteria for MIS-C rather than KD. Our

**Table 2 – Biochemical and Echocardiography findings in children with MIS-C.**

Lab parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case8	Case9	Case10
Haemoglobin(g/dl)	8.8	9.5	12.3	13.2	8.8	8.5	7.3	8.2	8.8	7.8
Neutrophilia (%)	81	79	80	79	86	90	81	90	85	88
Lymphopenia (%)	8	7	10	11	5	6	13	9	10	8
NLR Ratio	10.2	11.2	8	11.2	17.2	15	6.2	10	8.5	11
Platelets(lacs)	1.22	1.42	2.22	2.12	1.05	1.52	1.4	1.2	1.1	1.1
Thrombocytosis second week(lacs)	2.39	5.71	2.50	6.06	5.01	7.80	6.09	6.4	5.5	6.2
CRP (mg/L)	382	59	212	45	69.7	161	77	255	120	90
ESR (mm)	62	70	65	49	46	50	60	45	48	64
Procalcitonin(ng/ml)	200	9.2	10	145	10.27	11	3.54	19	32.54	40
Serum ferritin(ng/ml)	7118	723	529	556	1096.77	788.5	1200	1600	478.3	512
LDH(IU)	870	433	678	427	321	306	860	786	324	561
Sodium(millimoles)	128	130	132	129	128	127	130	141	138	139
Albumin(g/dl)	2.5	2.9	3.1	2.0	2.6	2.6	2.3	3.2	3.5	2.5
SGOT/SGPT(U/L)	241/320	280/267	48/40	54/60	114/140	48/44	54/68	244/288	48/58	40/44
Calcium(mg/dl)	7.4	7.8	8.7	7.6	6.3	7.2	7.0	7.2	8.5	8.2
Urea(mg/dl)	67	17	24	22	121	64	42	32	42	46
Creatinine(mg/dl)	1.4	0.3	0.8	0.6	2.9	1.5	1.1	0.9	0.6	1.0
D-Dimer(ng/ml)	5000	3570	2947	4794	4180	2260	2930	6951	3321	7552
Fibrinogen(mg/dl)	575	678	288	712	376	423	520	500	670	428
INR	1.16	1.29	1.1	1.48	1.38	1.4	2.19	1.1	1.17	1.4
FDP	+	+	+	+	+	+	+	+	+	+
Abnormal Pancreatic Function	–	–	–	–	+	+	+	–	–	–
Hypertriglyceridemia(mg/dl)	300	105	350	206	319	325	116	115	110	119
<b>Cardiac Markers</b>										
Trop-I(ng/ml)	0.11	1.0	0.05	0.9	0.12	3.03	0.5	0.12	0.15	1.0
CK-MB (ug/L)	114	97	12	191	1.0	33.7	197	42	1.3	2.7
BNP (pg/ml)	9060	200	20	897	478	3000	433	95	1750	1120
Myoglobin(ng/ml)	388	1.0	1.8	73.4	341	199	86	47.2	177	98
<b>ECHO</b>										
Global hypokinesia	+	+	–	+	–	+	+	–	+	+
LVEF	30%	50%	65%	45%	40%	45%	40%	50%	45%	40%
Regurgitant lesions	–	–	–	+	+	+	+	–	+	–
Coronary dilatation	–	–	–	–	–	–	–	–	–	–
NLR-Neutrophil -Lymphocyte ratio, CRP-C-reactive protein, ESR-Erythrocyte sedimentation rate, LDH-Lactate dehydrogenase, SGOT-Serum glutamic oxaloacetic transaminase.										
SGPT-Serum glutamic pyruvic transaminase-International normalised ratio-Fibrin degradation product, Trop-I-Troponin I, CK-MB-Creatine kinase myocardial band.										
BNP-Brain natriuretic peptide, ECHO-echocardiography, LVEF-Left ventricular ejection fraction.										

patients with MIS-C had higher neutrophil count with lymphopenia and subsequently high NLR rather than lymphocytosis that is predominantly seen in KD.

The primary myocardial injury seems to predominate in children with MIS-C rather than coronary aneurysms, as was seen in our patients. Coronary dilatation and aneurysms are seen in 15–25% of children with KD, whereas none of our patients had evidence of coronary involvement.<sup>16</sup> Among other clinical features, only 2.6–6.5% of children with KD present with shock<sup>17</sup> whereas 50% of children in our case series had a cardiogenic shock on presentation. While other authors have reported KD/KD like illness and coronary aneurysms in their cohorts with MIS-C, we did not uncover such findings in any of our patients.<sup>1,11</sup> Coagulopathy (elevated D-dimer and fibrinogen), and thrombocytopenia are also prominent in MIS-C rather than KD as was seen in our patients. Therefore, it is amply clear that MIS-C and KD are two different entities, and MIS-C should be classified as **MIS-C with shock or without shock** rather than be confused with KD. There being no prototypical representative clinical or laboratory markers suggesting the diagnosis of MIS-C, the key to recognising this syndrome is having a comprehensive knowledge

about its heterogeneous presentation, especially in a child with fever for more than three days duration and multisystem involvement.

All children with MIS-C in our series were managed with immunomodulatory therapy as per the American College of Rheumatology guidelines. Cardiac involvement, especially cardiogenic shock, requires aggressive immunomodulation along with other supportive care. High dose methylprednisolone (10–30 mg/kg) was administered in children with severe presentation (persistent high-grade fever, fluid refractory shock) and was given in five children in our patients along with IVIG at 2 gm/kg. Low dose methylprednisolone at 3–5 mg/kg for 3–5 days was given in moderate cardiac dysfunction without shock in four children. Combination therapy of IVIG and steroids reduces the need for adjunctive second-line therapy, reduces the persistent fever and improves the left ventricular function, as well as the inflammatory markers as was seen in our study.<sup>18–20</sup> Towards the end of the second week of illness, all children were off the intensive monitoring, and inflammatory markers showed a reducing trend. Response to immunomodulatory therapy corroborates the hyperinflammatory nature of MIS-C.



**Table 3 – Treatment regimen used in MIS-C associated with SARSCoV2.**

Treatment	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case8	Case9	Case10
IVIg (2 gm/kg)	+	+	+	+	+	+	+	–	–	+
IV methyl prednisolone (10-30 mg/kg)	+	–	+	–	+	+	+	–	–	+
Low dose methylprednisolone(3 mg/kg)	–	+	–	+	–	–	–	+	+	–
Inotropic support	+	–	–	–	+	+	+	–	–	+
Low Molecular weight heparin	+	+	–	+	+	+	–	–	–	+
Aspirin(3-5 mg/kg)	+	+	–	+	+	+	+	+	+	+
Non-invasive ventilation (HHFNC)	+	–	–	–	+	+	+	–	–	–
Average stay in hospital(days)	14	11	15	14	08	11	10	8	9	10

SARS Cov-2-severe acute respiratory syndrome coronavirus-2, MIS-C-Multisystem Inflammatory syndrome in children, IVIG-Intravenous immunoglobulin, HHFNC- Humidified High-frequency Nasal Cannula.

Children with evidence of moderate to severe myocardial dysfunction, severe elevation of D-dimer, fibrinogen and thrombocytosis are at risk for an LV thrombus, pulmonary embolism, and myocardial infarction and all such children in our series were administered anti-thrombotic therapy with low-molecular-weight heparin and low-dose aspirin (3–5 mg/kg/day max 81 mg). Aspirin should be continued until normal coronary arteries are documented at 4 weeks of illness,<sup>7,9</sup> which was done in our study. Although some studies advocate low molecular weight heparin only in those children with left ventricular ejection fraction <35% or evidence of thrombosis, coronary aneurysm, and Z scores  $\geq 10$ ,<sup>21,22</sup> the detection of these abnormalities may be technically difficult in children. Second-line agents like Anakinra (IL-1receptor antagonist), infliximab (anti-TNF  $\alpha$ ) and tocilizumab (IL-6 antagonist) were required in roughly 19% of patients in a recent systematic review for refractory MIS-C.<sup>14</sup> None of the children in our study required second-line drugs.

Our study had limitations considering the small number of patients evaluated and limited follow up of four weeks post-discharge. We concede to the fact that since awareness of MIS-C is not yet universal mild to moderate cases of MIS-C would have gone unrecognised, and only severe cases were referred to our tertiary care hospital, suggesting referral bias. We acknowledge the fact that due to the small number of cases in our study, no firm conclusions regarding the optimal management strategy and follow up protocol for the echocardiography and coronary abnormalities can be derived. Nevertheless, our limited numbers of MIS-C do add to the scant data available from this part of the country. This is probably the first study from Eastern India highlighting the clinical profile and management options for children with MIS-C. Pooled data from multicentric studies are required to derive protocol-based recognition of this heterogeneous condition and optimal management strategies.

## Conclusion

In the existing circumstances, evaluation of febrile children with multisystem symptomatology, in particular, the gastrointestinal and cardiovascular systems, necessarily requires keeping a differential diagnosis of this treatable hyper-inflammatory syndrome. Management of MIS-C requires prompt intensive immunotherapy. In our case series, we observed a good prognosis among patients with MIS-C

receiving early immune-modulatory therapy. However, it is acknowledged that since MIS-C is a recently recognised entity, long term outcomes of MIS-C, particularly cardiovascular outcomes, will probably emerge in the years to come.

## Disclosure of competing interest

The authors have none to declare.

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