Original Article

Mortality Indicators with Clinical Profile of Multisystem Inflammatory Syndrome in Children during SARS-CoV-2 Second Wave in India: A Tertiary Referral Center Experience

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Abstract

Background: Post-COVID-19 cases are being reported with features of hyperinflammatory state causing multiple system dysfunctions in previously healthy children. **Objectives:** To describe clinical characteristics, laboratory, and radiological profile of children affected with COVID-19-related multisystem inflammatory syndrome postsecond wave in India and compare them with respect to adverse outcome. **Materials and Methods:** This prospective, observational study was conducted in the department of pediatrics of a tertiary care center in Eastern India over a period of 3 months. Demographic data, clinical details, biochemical parameters, and treatment with clinical outcome were recorded. Children who survived the clinical course were compared with those died during hospital stay. **Results:** Thirty-five children with a median age of 4.8 (3.9) years were included who were admitted between June 16 and September 15, 2021. Only 17.14% had reverse transcription-polymerase chain reaction positivity previously with 77.14% had positive COVID-19 serology. Most common features were fever (100%), edema (68.6%), gastrointestinal (71.4%), mucocuteneous (65.7%), cardiovascular (57.1%), and neurological symptoms (45.7%). Twenty (57.1%) children had shock at presentation. Decreased ejection fraction (<55%) was the most common echocardiographic feature (37.14%) followed by coronary dilatation (20%). Majority (77.14%) of the patients required intensive care with inotrope requirement in 62.86% cases. Forty percent patients were intubated with mean duration of 9.94 (±10.5) days. All patients received methylprednisolone and 76% were given intravenous immunoglobulin. Tocilizumab was used in three patients. Nine patients died (25.7%) with overall median pediatric intensive care unit stay of 13 (14) days. **Conclusion:** Of the parameters described, we have found shock, heart failure, neurological involvement at presentation, infancy, and laboratory parameters such as C-reactive protein, CPK, D-Dimer, and lactate dehydrogenase were the predictors of mortality.

Key words: COVID-19, hyperinflammation, Kawasaki, multisystem inflammatory syndrome in children, shock

Introduction

COVID-19 disease, caused by SARS-CoV2 virus, has affected around 385 million people worldwide since its inception on November 2019 to January 2022. Active COVID-19 disease has been showing rapid, severe and aggressive clinical course with hyperinflammatory state and severe lung damage typically during seconding week of illness coinciding with reduction in viral load.[1] Although children are less affected and have a milder disease course, 0.4% of global COVID-19 deaths have occurred in pediatric and adolescent age group. Till January 2022, 11.77% of total COVID cases in India were recorded in population below 20 years.

Lately, post-COVID-19 cases were reported with the features of hyperinflammatory state causing multiple system dysfunctions in previously healthy children.[2,3] This post-COVID phenomena was initially termed as paediatric multisystem inflammatory syndrome temporarily associated with SARS-CoV2 (PIMS-TS) by Royal College of Physician of Child Health.[4,5] Thereafter, numerous pediatric cases with severe disease course have been reported worldwide

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with fever, shock, Kawasaki-like syndrome (or toxic shock syndrome, ultimately leading to damage of cardiovascular, nervous system, gastrointestinal systems unlike predominant respiratory system involvement in active COVID infection.[6-8] The World Health Organization (WHO) and Center of Disease Control had termed this novel illness as multisystem inflammatory syndrome in children (MIS-C) with specific defining criteria.[9,10]

Clinical presentation of this novel entity overlaps with other common diseases, especially in tropical countries such as India where the prevalence of various infectious diseases is high. Therefore, it has become demand of the hour to study and understand the disease spectrum, presentation, progression, and finally outcome of MIS-C to develop early clinical suspicion and prompt detection of this disease. A few risk factors have been proposed in various western literatures that may predict severity of disease in children. However, there is a paucity of adequate data regarding clinicobiochemical and radiological features of MIS-C, especially in the Indian sub-continent. With rapid rise of MIS-C cases during worldwide third COVID-19 wave, we planned to analyze the clinico-demographic features, laboratory parameters, and compare them in accordance with severe disease course of MIS-C during the second wave.

Materials and Methods

This is a prospective observational study carried out in a tertiary care teaching hospital of eastern India during June 16 to September 15, 2021.

Study population

Children of age group 1 month–12 years admitted in the pediatrics department of the institute were enrolled in the study if they met the WHO defined criteria of SARS-CoV-2-induced MIS-C.[9]

Data collection

A structured pro forma was made beforehand for the data collection of demography, clinical presentation, laboratory parameters, and treatment modalities received. Detailed history of previous underlying comorbidities, chronic illness, duration, and nature of fever and other associated clinical entities with description were noted in all the cases along with demographic data. Details of physical examination and system wise findings were noted from the clinical records.

Blood samples were sent for biochemical investigations such as, complete blood count, erythrocyte sedimentation rate (ESR), liver function test, serum electrolytes, renal function test reports along with evidence of hyper inflammation like serum Ferritin, C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), creatine phosphokinase-MB (CPK-MB), and N-terminal pro-B type natriuretic peptide (NT-pro BNP) on admission. Initial values of the blood parameters were recorded in the pro forma. Infective organisms such as malaria, scrub typhus, leptospirosis, and other bacterial infections were ruled out. Bedside point of care echocardiography was performed to look for chamber dilatation, valvular abnormalities, myocardial contractility, and pericardial involvement. Coronary artery dilatation measurement was performed by the cardiologists. Specific examinations such as chest X-ray, electroencephalogram, and magnetic resonance imaging (MRI) brain were performed in patients whenever indicated as per decision of the treating consultants.

All the patients were treated with strict adherence to the standard guideline by Government of India, Ministry of Health and Family Welfare (MOHFW).[11] Details of treatment received in form of respiratory support, inotrope requirement, diuretics, blood component transfusion, anti-thrombotic therapy, and anti-inflammatory medications (steroids, intravenous immunoglobulin [IVIG], immunomodulators) were noted. Total duration and type of respiratory support required, hospital and pediatric intensive care unit (PICU) stay, if needed, were also recorded. Final outcome, mortality, and residual disabilities were taken into account.

For outcome measurement, the patients were categorized depending on their clinical courses into two groups, Group A, survivor group and Group B, adverse outcome group consisting patients who died during hospital stay. A comparative analysis of clinical, biochemical and treatment profile was done between these two groups.

Ethical permission

The proposed study was granted ethical clearance by the Institutional Ethical Committee. Informed consent in written form was taken from respective parents/guardians of participants before inclusion in the study population. The study was conducted as per Declaration of Helsinki. All tests were performed according to relevant guidelines and indications.

Statistical analysis

All the data regarding parameters under study were maintained in Microsoft excel 2007 spreadsheet. Further statistical analysis was done using the Statistical Package for the Social Sciences version 20.0 (IBM SPSS Corp. 2011. Armonk, NY, USA) for Windows.

Normality of data distribution was checked using the Shapiro–Wilk test. Categorical variables were presented in terms of number and percentage (%). The Chi-square test and Fisher's exact test were used to test the association between the outcome and categorical variables under study. Normally distributed continuous variables (Parametric data) were expressed using mean ± standard deviation (SD) and nonnormal continuous variables using median (interquartile range [IQR]). Student's independent test and Mann–Whitney's test were used to compare the means of respective continuous variables. $P < 5\%$ was considered to be statistically significant.

Results

A total of 41 patients were admitted with features and findings consistent with MIS-C during the postsecond wave COVID-19 peak and excluding six patients without

consents, 35 patients were enrolled in the study. This enrolled children had a median (IQR) age of 4.8 (3.9) years with male predominance (60%) and 15 (42.85%) cases had various co-morbidities. Detailed baseline characteristics are provided in Table 1. Only 6 (17.14%) children had a history of active COVID-19 infection confirmed by the reverse transcription-polymerase chain reaction (RT-PCR) test and 27 (77.14%) children had high SARS-CoV-2 immunoglobulin G (IgG) antibody titer in chemiluminent microparticle immunoassay (Reference range: Positive >50 AU/mL).

As inclusive criteria, fever was the most common presentation (100%) with the median (IQR) duration of 7.0 (6.0) days [Supplementary Table 1]. Other frequent clinical presentations [Table 2] were edema (68.6%), followed by rashes (65.7%), vomiting (60%), pain abdomen (54.3%), and altered sensorium (45.7%). Seven children (40%) had features consistent with Kawasaki disease (KD). System wise gastrointestinal abnormalities were in 25 (71.43%) patients followed by mucocuteneous (65.8%) and cardiovascular (57.1%) symptoms. Features of shock were present in 20 patients (57.14%) including two with KD phenotype. Out of them, twelve children had distributive shock and rest eight had cardiogenic shock.

Table 1: Baseline characteristics

Demographic characteristics	Study population ($n=35$), n (%)
Age (years)[$]	4.8±3.9
Gender, males[^]	21 (60.00)
Co-morbidities[^]	15 (42.85)
Obesity[^]	2 (5.71)
SLE/MCTD[^]	2 (5.71)
Acute leukemia[^]	2 (5.71)
Lung pathology[^,€]	3 (8.57)
Congenital heart disease[^]	2 (5.71)
Neurological disease[^,£]	3 (8.57)
Others[^]	3 (8.57)
Evidence of COVID-19 infection	
Positive RT-PCR report[^]	6 (17.14)
Definite contact history[^]	2 (5.72)
Serology positive[^]	27 (77.14)
Recent history of febrile episode[^]	23 (65.71)
Febrile episode without RT-PCR test[^]	17 (54.28)
Interval (days)[$]	20.57±7.7
Nutritional status	
Underweight[^]	14 (40.00)
Normal[^]	18 (51.43)
Overweight[^]	1 (2.86)
Obese[^]	2 (5.71)

[$]Mean±SD, [^]$n$ (%), €Lung pathology included interstitial lung disease, congenital cystic adenomatoid malformation and BPD cases, £Neurological disorders included two cases with seizure disorders and one hydrocephalus. Other comorbidities includes rhabdomyosarcoma, down syndrome and steroid dependent nephrotic syndrome. BPD: Bronchopulmonary dysplasia, SD: Standard deviation, SLE: Systemic lupus erythematosus, MCTD: Mixed connective tissue disease, RT-PCR: Real-time polymerase chain reaction

Detailed laboratory parameters, echocardiographic and radiological findings are summarized in Supplementary Tables 2 and 3. Biochemical abnormalities, most commonly encountered were raised CRP (97.10%) followed by elevated ESR (94.29%), NT-Pro BNP (85.71%), Creatinine phosphokinase (85.71%), D-Dimer (82.86%), Interleukin-6 (75%), LDH (74.29%), hyperferritinemia, hypertriglyceridemia (65.7%), and thrombocytopenia (62.86%). Myocardial dysfunction (ejection fraction <55%) in bedside point of care echocardiography was evident in 13 cases with mean ejection fraction of 54.57 (±8.9%) [Supplementary Table 3]. Coronary artery dilatation (Z score >2.5 SD) was found in 7 (20%) cases. Only 6 children (22.88%) had residual cardiac abnormalities during discharge.

Among 35 patients, 27 (77.14%) required intensive care with median (IQR) duration of PICU stay of 13 (14.0) days [Table 3]. IVIG at a dose of 2 g/kg over 12 h was given to 26 (74.28%) patients, including 20 patients with shock, 7 KD patients and one patient without shock, who didn't respond to low dose methylprednisolone therapy. Intravenous methylprednisolone was received by all the patients of our cohort and among them 22 (62.85%) were given at pulse dose (30 g/kg/day). Biologics (Tocilizumab) was employed in three patients. Twenty-one patients (60.0%) required some form of respiratory support and 14 (40%) children were intubated, five (14.28%) recovered receiving noninvasive ventilation (NIV) and rest two received high flow nasal cannula only. Inotrope infusion was started in 18 (51.43%) children with fluid refractory shock.

In the study population, nine children died with mortality of 25.71%. Refractory shock was cause of death in three patients, one patient died with myocarditis developing ventricular fibrillation and rest five patients died due to complications of severe co morbidities. Majority of the nonsurvivors were infants (55.5%). Among the clinical parameters that predicted mortality were prolonged fever, neurological involvement, heart failure, and shock at presentation [Table 4]. Biochemical parameters were compared between two groups, survivors and nonsurvivors. Among them, only CRP ($P = 0.028$), LDH ($P = 0.001$), D-Dimer ($P = 0.02$) and transaminases ($P = 0.002$) levels showed significant differences between two groups [Table 4]. There were noticeable differences in values of serum ferritin, Interleukin-6, but none was statistically significant.

Discussion

MISC is a severe COVID-19 related complication occurring after active COVID-19 infection among paediatric and adolescent age group. It is abnormally enhanced hyper immune response of the body leading to immune-mediated multi organ dysfunction with hyperinflammation and hypercytokinemia.[2,12] Till date, a worldwide consensus regarding diagnostic criteria, treatment protocol, even nomenclature of this novel entity is yet to be developed. Therefore, RCPCH coined terminology

Table 2: Clinical features at the time of presentations

Clinical characteristics	Study population ($n=35$), n (%)
Clinical phenotypes*	
MIS-C with shock	20 (57.14)
MIS-C with predominantly KD like features	7 (20.00)
MIS-C without shock	15 (42.86)
Fever*	35 (100)
Fever duration (days)$	7.0 (6.0)
Edema*	24 (68.6)
Gastrointestinal symptoms*	25 (71.43)
Mucocuteneous symptoms*	23 (65.71)
Cardiovascular symptoms*	20 (57.10)
AKI*	8 (22.9)
Neurological symptoms*	18 (51.43)
Respiratory symptoms*	17 (48.57)
Hematological symptoms*	14 (40.00)
Ophthalmic symptoms*	14 (40.00)
Musculoskeletal symptoms*	5 (14.29)
Multisystem involvement*	
Two systems involved	13 (37.1)
Three systems involved	8 (22.9)
Four or more systems involved	14 (40.0)

*n (%), $Median (IQR). MIS-C: Multisystem inflammatory syndrome in children, KD: Kawasaki disease, IQR: Interquartile range, AKI: Acute kidney injury

Table 3: Treatment, complications, and outcome of the study population

Treatment received and outcomes	Study population ($n=35$), n (%)
MRI abnormalities^	8 (22.88)
IVIg^	26 (74.28)
Methylprednisolone^	
Pulse therapy (30 g/kg/day)^	22 (62.86)
Low dose (2 g/kg/day)	35 (100.00)
Tocilizumab^	3 (8.57)
Rituximab^	2 (5.71)
Plasma therapy^	0
Inotrope requirement^	22 (62.86)
Anti-thrombotic therapy^	20 (57.14)
Respiratory support requirement	
Low flow nasal cannula^	2 (5.71)
High flow nasal cannula^	2 (5.71)
NIV^	5 (14.28)
Duration of NIV (days)$	5.2±4.6
Invasive ventilation^	14 (40.00)
Duration of invasive ventilation (days)$	9.94±10.57
PICU requirement^	27 (77.14)
Duration of PICU stay (days)#	13.00 (14.00)
Outcome, death^	9 (25.71)
Duration of hospital stay (days)#	19.00 (13.50)

$Mean±SD, ^$n$ (%) and #median (IQR). IVIg: Intravenous immunoglobulin, MRI: Magnetic resonance imaging, PICU: Pediatric intensive care unit, NIV: Noninvasive ventilation

Pediatric Inflammatory Multisystem syndrome-temporally related to SARS-CoV2 (PIMS-TS) is interchangeably used with US CDC and WHO proposed MIS-C to refer this dreadful condition.[9,10]

Its worldwide incidence in still to be studied, though some studies estimate its occurrence of 2 in 200,000 individuals of paediatric and adolescent age-group.[13] Clustering of cases with this phenomenon have been observed to occur in geographic areas with high burden of COVID-19 infection, usually 2–6 weeks after SARS-CoV-2 peak, justifying temporally association with the disease. Similarly in this study, sudden increase of cases on late June 2021 compared to local COVID-19 peak during second wave around early May, 2021 supports the postviral hypothesis.[7,10,14,15] Our finding of high titre SARS-CoV-2 serology (77.14%) and low RT-PCR positivity (17.14%) further supplements this theory.[12] Moreover, only 7.5% children had any COVID symptoms beforehand, on contrary in our study 54.28% subjects had febrile episodes previously in an interval of 20.57 ± 7.7 days.[16] Nonavailability of RT-PCR test in resource constricted settings is another important barrier in early and prompt diagnosis of MIS-C. In our cohort, 42.85% patients preexisting comorbidities, 3 were paediatric oncology follow-ups. We had two patients with obesity, the most reported co-morbidity in MIS-C in the literature, and strikingly both of them succumbed to death.[17]

Immune-mediated injury of multiple organs in MIS-C is primarily responsible for huge range of clinical presentations ranging from fever to myocardial injury, shock (18) and even MODS. According to systemic review of 953 cases, gastrointestinal symptoms were most frequent (85.6%) similar to our finding (74.29%).[17] Presence of bowel wall edema, ischaemic changes, mesenteric adenitis in MIS-C patients with acute abdomen may be caused by SARS-CoV-2 viral replication in the enterocytes.[2]

Investigators observed children with symptoms consistent to KD, childhood vasculitis, common among Asians, ultimately diagnosed with MIS-C.[7,8] KD predominantly involves coronary arteries resulting in abnormal dilatation or aneurysm formation. Though case definition of MISC is broad enough to met in children with typical KD in presence of high COVID antibody titre,[2] older age group, presence of shock and elevated CRP and NT-Pro BNP can differentiate these two entities.[17] Overall cardiovascular involvement was evident in 79.3%–90% patients[12,17] with subsequent reported complications like shock in 50%–90% patients,[4,15,18] LV dysfunction in 30%–72%, myocarditis in 50%–80%,[12] coronary dilatations in 11.6%–26% and aneurysms in 10%–13%.[17] Interestingly our study showed lesser (57.1%) cardiac involvement but a comparable proportion had shock (57.14%), heart failure (28%) and coronary artery dilatation (20%).

Our study had mucocuteneous (65.7% vs. 57%) involvement concordant to most of previous studies and exanthem was most frequent finding. Neurological manifestations were uncommon (2%–30%) in most Indian studies,[12] though we found strikingly high (51.4%) neurological involvement,

Table 4: Comparison of presenting clinical features and biochemical parameters between two outcome groups

Characteristics	Survivors (*n*=26), *n* (%)	Nonsurvivors (*n*=9), *n* (%)	Significance
Age <1 year*	5 (19.23)	5 (55.55)	0.038£
BMI >25 kg/m²*	0	2 (22.22)	0.454#
Comorbidites*	10 (38.46)	5 (55.55)	0.372£
Fever duration$	5.0 (3.0)	15.0 (7.0)	0.016
Neurological symptoms*	10 (38.46)	8 (88.89)	0.009£
Heart failure*	4 (15.38)	6 (66.67)	0.003£
Shock*	11 (42.31)	9 (100)	0.003£
Liver failure*	1 (3.85)	2 (22.22)	0.090£
Hemoglobin (g/dL)^	10.15±1.2	9.87±1.5	0.624ı
N: L ratio$	2.54 (5.9)	3.04 (2.3)	0.897¥
Platelet count (×10⁹/L)$	100 (191)	131 (85)	0.540¥
ESR (mm/1st h)$	47.5 (35.0)	38.0 (31.0)	0.222¥
CRP (mg/L)$	43.50 (54.5)	112.0 (133.9)	0.028¥
Triglyceride (mg/dL)$	212.0 (143.2)	323.0 (232.0)	0.424¥
Ferritin (ng/mL)$	849.5 (1558.65)	1769.0 (3054.9)	0.093¥
LDH (IU/L)$	670.0 (601.0)	1792.0 (4022)	0.001¥
PT (s)$	16.0 (4.2)	17.0 (6.1)	0.444¥
APTT (s)$	37.8 (7.25)	38.6 (16.5)	0.956¥
D-dimer (µg/mL)$	3.85 (4.6)	8.4 (9.4)	0.020¥
IL-6 (pg/mL)$	36.1 (47.2)	65.2 (83.5)	0.051¥
NT-pro BNP (pg/mL)$	230.5 (440)	387 (2561.5)	0.224¥
CPK (U/L)$	295.5 (608.7)	2356.0 (4010.5)	0.002¥
SGOT (IU/L)$	54.1 (42.2)	162.0 (736.0)	0.001¥
SGPT (IU/L)$	37.0 (63.5)	141.0 (206)	0.002¥
Albumin (g/dL)^	2.77±0.7	2.58±0.7	0.382ı

**n* (%), $Median (IQR) and ^mean±SD, #Fisher's exact test, £Chi-square test, ıIndependent *t*-test and ¥Mann–Whitney *U*-test. IQR: Interquartile range, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, NT-pro BNP: N-terminal pro-B type natriuretic peptide, CPK: Creatinine kinase, APTT: Activated partial thromboplastin time, PT: Prothrombin time, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase, SD: Standard deviation, IL: Interleukin

with MRI changes in 8 cases. A recent meta-analysis has mentioned neurological manifestations in 27.1% of MIS-C cases,[19] headache (27%) followed by meningism (17.1%) and encephalopathy (7.6%) being the most frequent neurological manifestations in contrast to altered sensorium (45.7%) as per our finding. In previous studies,[17] around 50.3% patients had respiratory system involvement, 29%–35% with radiological infiltrates[17] concordant to our study (34.28%).

Hence, with such a broad range of presentations has made MIS-C very difficult to pick up early. Any child with fever >5 days, multisystem involvement and features consistent to toxic shock syndrome, KD, Kawasaki shock syndrome, Macrophage activation system or haemophagocytic lymphohistiocytosis (HLH)[13] should be thoroughly looked for evidence of elevated inflammatory markers to rule out this entity as the management protocol differs.

There has been lack of consensus in treatment protocol of this emerging phenomenon causing significant differences in treatment strategies in different centres. Early detection, rapid reduction of hypercytokinemia, minimising organ specific injuries, and prevention of long term sequealae are the mainstay of treatment.[20] Majority of studies showed prompt response with IVIG and adjunct steroids.[4,8] Most Indian studies reporting MIS-C during first COVID wave has used IVIG is all patients with or without corticosteroids depending on clinical scenario. Clinical resemblance to KD may be one reason of such intervention. Later MOHFW, Government of India came out with a guideline, which was followed in our study.[11] Around 75% patients in our study received IVIG in immunomodulatory dose. On contrary, in the index study larger number of patients received intravenous Methylprednisolone compared to published Indian reports during 1st COVID wave.[12] Repeat dose of IVIG was given in two patients with refractory MISC who was not responding to methylprednisolone pulse. Among immunomodulators, tocilizumab was used in 8.6% cases compared to 16% in overall studies, that may be due to delay in presentation and early death allowing less options to intervene.[21] One patient received intravenous Rituximab that was reported to be administered in one case only.[15]

Most studies in the literature have shown intensive care requirement in majority of cases of MIS-C in agreement with our study (60%). Inotrope requirement was comparable (51.43%) in our study with 42%–55.3% patients overall.[17,21] There is gross variability in inotrope requirement among different studies, even some reports mentioned inotrope use in as low as 15% cases in contrast to some centres with 90% requirement.[12,22] NIV was required in 13%–31% (vs. 14.28%)

patients and 10%–39% (vs. 40%) needed intubation, both were similar to our findings.[12,17,21]

Mortality in our cohort (25%) was higher than most studies with more PICU requirement and longer PICU stay. Most of the children (74%) in our study were referral cases and only 14.29% among them were referred with suspected diagnosis of MISC. Relatively higher proportion of comorbidities, shock at presentation, delay in presentation to health care facilities may be considered as important causes for worse outcome. Moreover, the lack of awareness among general population to get children tested for COVID-19 even in short febrile episode can attribute to delay in diagnosis, especially in resource-restricted settings. We co-administered low dose Methylprednisolone 2 g/kg/day with IVIG[11] instead of initial pulse dose[23] that might have contributed to such results. Lastly, difference in features and severity of this postviral inflammatory phenomenon in different SARS-CoV-2 variants hasn't been studied yet.

Besides prompt diagnosis, severity prediction may be pivotal, especially for initiation of aggressive treatment and ensuring good clinical prognosis. Majority of the studies published reporting MIS-C are descriptive and lacks in-depth analysis, most probably due to very low sample size. However, some reports mentioned obesity as an association to mortality, though significant association was not found in our cohort.[4,16] Gastrointestinal and neurological symptoms,[24] AKI,[25] and myocarditis were associated symptoms with worse clinical outcome, though all had no significant difference between two groups in our study. One study found hepatitis as a risk factor for severity supporting our finding of significant elevation of transaminase enzymes in nonsurvivor group. Lymphopenia, neutrophilia, hyponatremia, CRP, ferritin, NT-pro BNP, and IgG titers were found to be associated with severe disease.[24] However, we found significant differences in CRP, LDH, CPK, and D-Dimer values between outcome groups that signifies contributing role of hyperinflammation, elevated risk of thrombotic events and cardiac involvement in poor outcome.

This is one of the largest cohorts of MIS-C patients affected during the second COVID wave in Eastern India. Moreover, it is a prospective study compared to most of the studies done by retrospective analysis using digital records. Still, we had some limitations like less sample size, single centred study and nonavailability of procalcitonin, troponin level assay in our centre. Long-term follow-up to evaluate further progression coronary artery abnormalities or neurological sequelae would have made the study more relevant.

What is already known?

1. MIS is a post-COVID phenomenon in children that is often occurring after local COVID wave and is associated with dreaded complications
2. High index of suspicion of MIS-C should be kept in mind for the early detection of the condition
3. Early diagnosis and prompt treatment with IVIG and aggressive steroid therapy can help manage dreaded complications related to MIS-C.

What the study adds?

1. Delay in diagnosis and initiation of treatment may cause significant rise in morbidity and mortality among children
2. In resource-poor settings, all children may not get tested with RT-PCR for SARS-CoV-2 during mild febrile episodes. AntiCOVID antibodies should be considered to look for post-COVID complications, if clinically indicated
3. Elevated inflammatory markers, presence of thrombotic events, and cardiac involvement during admission may predict severe course of disease.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Detailed systemic manifestations of multisystem inflammatory syndrome in children among children

Clinical characteristics	Study population ($n=35$), n (%)
Gastrointestinal symptoms*	
Icterus	5 (14.3)
Vomiting	21 (60.0)
Loss of appetite	4 (11.4)
Diarrhea	12 (34.3)
Pain abdomen	19 (54.3)
Liver dysfunction	3 (8.6)
Mucocuteneous symptoms*	
Purpura	4 (11.4)
Exanthematous rash	23 (65.7)
Cheilitis	7 (22.9)
Desquamation	9 (25.7)
Conjunctivitis	13 (37.1)
Tongue swelling	6 (20.0)
Cardiovascular symptoms*	
Chest pain	3 (8.6)
Heart failure	10 (28.6)
Hypertension	2 (5.7)
Hypotension	17 (48.6)
Arrhythmia	4 (11.4)
Myocarditis	9 (25.7)
Pericarditis	3 (8.6)
AKI*	8 (22.9)
Neurological symptoms*	
Headache	13 (34.3)
Dizziness	3 (8.6)
Altered sensorium	16 (45.71)
Convulsion	12 (34.3)
Syncope	2 (5.7)
Stroke	2 (5.7)
Movement disorder	1 (2.9)
Psychiatric behavior	6 (17.14)
Respiratory symptoms*	
Nasal congestion	5 (14.3)
Rhinorrhea	7 (20.0)
Sore throat	3 (8.6)
Cough	13 (37.1)
Shortness of breath	13 (37.1)
Pneumonia	12 (34.3)
ARDS	7 (20.0)
Pulmonary embolism	4 (11.4)
Hematological symptoms*	
Lymphadenopathy	10 (28.6)
Bleeding manifestations	7 (20.0)
Thrombosis	6 (17.1)
Ophthalmic symptoms*	
Conjunctivitis	13 (37.1)
Blindness	1 (2.9)
Musculoskeletal symptoms*	
Myalgia/fatigue	4 (11.4)
Arthritis	2 (5.7)

*n (%). ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury

Supplementary Table 2: Biochemical abnormalities among the study population ($n=35$)

Characteristics	Reference	Total, n (%)
Anemia	<9 g/dL	12 (34.29)
Leukocytosis	$>12\times10^9$/L	23 (65.71)
Lymphopenia	$<4\times10^9$/L	18 (51.43)
Raised N/L ratio	>3.5	15 (42.86)
Thrombocytopenia	$<150\times10^9$/L	22 (62.86)
Elevated ESR	>25 cm	33 (94.29)
Elevated CRP	>10 mg/dL	34 (97.1)
Hyponatremia	<135 mg/dL	20 (57.14)
Elevated SGPT	>45 IU/L	17 (48.57)
Elevated SGOT	>50 IU/L	22 (62.86)
Hypoalbuminemia	<2.5 g/dL	8 (22.86)
Elevated D-dimer	>0.5 ng/dL	29 (82.86)
Hypertriglyceridemia	>200 mg/dL	23 (65.70)
Elevated LDH	>500 IU/L	26 (74.29)
Hyperferritinemia	>500 ng/dL	23 (65.70)
Hypofibrinogenemia	<150 mg/dL	8 (22.86)
Hypomagnesemia	<2.3 mg/dL	28 (75.0)
Elevated CPK	>130 U/L	30 (85.71)
Elevated IL-6	>25 pg/mL	28 (75.0)
Elevated NT-pro BNP	>125 pg/mL	30 (85.71)

LDH: Lactate dehydrogenase, NT-pro BNP: N-terminal pro-B type natriuretic peptide, CPK: Creatinine kinase, IL: Interleukin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

Supplementary Table 3: Radiological, echocardiographic, and other relevant findings

Characteristics	Study population ($n=35$), n (%)
Chest X-ray abnormalities^	
Pneumonic infiltration	12 (34.28)
Pneumatocele	1 (2.85)
Hyperinflation	3 (8.57)
Pleural effusion	5 (14.29)
ARDS	7 (20.00)
Lung ultrasound^	
B lines	15 (42.86)
Sub-pleural consolidations	10 (28.57)
Irregular pleural lines	5 (14.29)
Echocardiographic abnormalities	
Myocardial dysfunction^,¥	13 (37.14)
Ejection fraction (lowest documented)#	54.57 (8.9)
Chamber dilatation^	4 (11.43)
Coronary artery dilatation (Z score >2.5 SD)^	7 (20.00)
Valvular regurgitation^	2 (5.71)
Residual abnormalities at discharge^	8 (22.88)
EEG abnormalities^	2 (5.71)

¥EF <55%, ^n (%) and #median (IQR). SD: Standard deviation, IQR: Interquartile range, ARDS: Acute respiratory distress syndrome, EEG: Electroencephalogram