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COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based cohort study from Kerala, India

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Title page

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based cohort study from Kerala, India

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Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based cohort study from Kerala, India

Abstract:

Objective: To study the epidemiological factors, clinical profile, and outcomes of COVID-19 related multisystem inflammatory syndrome in children (MIS-C), to compare the clinical profile across age groups, to study medium-term outcomes, and to identify parameters associated with disease severity.

Design: Hospital-based prospective cohort study.

Setting: Two tertiary care centers in India.

Participants: Diagnosed cases of MIS-C using the case definition of Centres for Disease Control and Prevention.

Results:

We report 41 cases (males- 23) with MIS-C, the mean age at onset was 6.16 ± 4.0 years and 33(80%) were previously healthy. Mucocutaneous symptoms were present in all the 19(100%) cases in the 5-12 years age group compared to 13(72%) cases in the less than 5 years age group (p= 0.019). Echocardiogram was abnormal in 23(56%) cases, and coronary abnormalities were noted in 15(37%) cases. Immunomodulatory therapy was administered to 39(95%) cases, steroids and IVIg both were used in 35 (85%) and only steroids were used in 3(7%) cases. Intensive care was required in 36(88%) cases, mechanical ventilation in 8(20%), inotropic support in 21(51%) and 2(5%) cases died. Mechanical ventilation requirement in MIS-C was associated with presence of shock requiring inotropic agents, hyperferritinemia, high D-dimer, high aspartate aminotransferases (AST), and low erythrocyte sedimentation rates (ESR) ($p < 0.05$). Thirty-seven patients completed 3 months follow-up by April 2021, only 6 (16%) patients had some residual sequelae in the form of echocardiographic changes which were showing an improving trend.

Conclusions: MIS-C cases in our cohort had varied clinical manifestations ranging from fever with mild gastrointestinal and mucocutaneous involvement to fatal multiorgan dysfunction. Immediate and medium-term outcomes remain largely excellent except for the echocardiographic sequalae in a few patients which are also showing a resolving trend. Initial presentation with shock, hyperferritinemia, high D-dimer, high AST, and low ESR were associated with requirement of mechanical ventilation.

Original research

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based cohort study from Kerala, India

Introduction :

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS -CoV-2) is rapidly evolving. As of June 01 2021, there have been 170,426,245 confirmed cases of coronavirus disease 2019 (Covid-19) globally, including 3,548,628 deaths.[1] Earlier studies reported that COVID-19 infection in children was either asymptomatic or mild with only small proportion requiring hospitalisation and lesser mortality in them as compared to adults.[2]

In May 2020 several European countries reported clusters of hyperinflammatory processes in children with clinical manifestations of atypical Kawasaki disease and shock and the possibility of its link with SARS-CoV-2 was considered.[3–6] Later, Centers for Disease Control and prevention (CDC) and World Health Organization (WHO) released health advisories and defined these cases as multisystem inflammatory syndrome in children (MIS-C) associated with Covid-19.[7,8] MIS-C is a rare but severe and potentially fatal condition.[9,10]

The pathogenesis of MIS-C is not well understood. It is known that SARS-CoV-2 enters cells by binding to angiotensin-converting enzyme 2, which is highly expressed in cardiac myocytes, alveolar cells, vascular endothelium, and a small subset of immune cells[11]. Evidences suggest that dysregulated innate immune response leading to cytokine storm and endothelial damage might be responsible for multiorgan failure in severe Covid-19 and MIS-C.[12–14]

MIS-C is reported to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease (KD) like phenotype, and Macrophage activation syndrome (MAS). It is a syndromic presentation with overlapping clinical features of KD, sepsis, toxic shock syndrome, and meningitis.[9,14] Moreover, there is no diagnostic test and the risk factors for the development of MIS-C remain unknown. Therefore, it is crucial to identify epidemiology, clinical features, course of illness, prognosis, and outcomes of MIS-C to reduce morbidity and mortality. There is a paucity of data from the Indian subcontinent regarding the clinical course, medium-term outcomes, and risk factors for severe MIS-C .

In this study, we have described clinical profile, medium-term outcomes, varied clinical features in different age groups, and factors associated with severe illness in 41 patients diagnosed with MIS-C from southern Indian state of Kerala.

Methods:

Study design :

This was a hospital-based prospective cohort study conducted at two tertiary care centers from Kerala state of India, from March 2020 to April 2021. The primary objective of this study was to report the baseline characteristics, clinical features, laboratory parameters, echocardiographic findings, treatment, and immediate outcomes of cases admitted with MIS-C. The secondary objectives were (i) to compare clinical presentation and response to therapy across age groups less than 5 years, 5 to 12 years, and more than 12 to 20 years, (ii) to report the medium-term outcomes of MIS-C, and (iii) to report the predictors of severity in MIS-C.

Patient and public involvement :

The study was approved by the institutional ethics committee (IRB-AIMS-2020-335) which involved public representatives as well. A written informed consent was obtained from parents of study participants. Patients were not involved in the designing of the study.

Study definitions:

We used the CDC case definition to define a case of MIS-C.[7] Body mass index (BMI)-based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups comprising of patients more than 5 years of age.[15] For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 standard deviations above WHO child growth standards median; and obesity was defined as weight-for-height greater than 3 standard deviations above the WHO child growth standards median.[16]

Systolic dysfunction was defined by reduced left ventricular ejection fraction (LVEF) in this study. Systolic dysfunction was categorized as mild to moderate when LVEF was 30%-55% and as severe if LVEF was less than 30 %.[17,18]

Echocardiography Z-scores were calculated using Mc Crindle et al. formula using body surface area.[19] Coronary artery abnormalities (CAA) were classified according to the Z-scores on echocardiography.[20] Apart from the size of coronaries, echocardiographic appearance of hyperechogenicity and non-tapering morphology were also noted as abnormalities, wherever present.[21]

For this study, “Incomplete KD” was defined as the presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings.[22] Children who along with the usual clinical features of KD also had few unusual clinical manifestations like pulmonary involvement and renal impairment were labeled “atypical KD”.[22]

Categorization of children with MIS-C

On the basis of age at onset of the disease 3 categories were designed, less than 5 years, 5-12 years, and 12-20 years. All the diagnosed cases of MIS-C were further categorised on the based on requirement of mechanical ventilation. All children with MIS-C who had any residual clinical, laboratory, or echocardiographic changes at the time of discharge were labeled as “recovered with sequelae ”. The discharged patients were followed up at 6 weeks and 12 weeks to report the medium-term outcomes.

Statistical analysis :

SPSS Version 20.0 for Windows (IBM Corporation ARMONK, NY, USA) was used for statistical analysis. All continuous variables were summarized using mean (SD) or median (IQR) depending on their distribution. Categorical variables were expressed in counts and percentages. We used the Pearson Chi-Square test or Fisher's exact test to compare the categorical variables. We used the independent sample t-test or Mann-Whitney test to compare the continuous variables by age group and severity. A p-value of <0.05 was considered statistically significant.

Results:

Baseline Characteristics:

A total of 41 cases (males- 23) who were diagnosed with MIS-C and treated at two tertiary care centers in the southern Indian state of Kerala from March 2020 to April 2021 were enrolled in the study. The peak of COVID-19 cases was followed by a surge in the reporting of MIS-C in November- December 2020, when the active COVID-19 cases were on a decline. (**figure 1)**

A temporal link with COVID-19 infection was identified in all patients in our study either in the form of serological testing or close contact with active COVID-19 case within preceding one month. Sixteen (39%) patients had a history of close contact with an active COVID-19 case. Two patients (5%) were having active COVID-19 infection when they developed MIS-C features, and 2(5%) patients had previously confirmed acute COVID-19 infections and had recovered within the last 6 weeks. The first four cases (10%) did not undergo antibody assay due to regulatory restrictions on clinical use of antibody testing at that time. In the study, 28(76%) patients were positive for COVID-19 IgG and 7(19%) were positive for COVID-19 IgM antibody**.(Supplementary figure 1)**

The mean age of onset was 6.16 ± 4.0 years. Thirty-three (80%) cases were previously healthy whereas 8 (20%) had co-existing comorbidities. Three (8%) cases were obese ang one was overweight. Three (7%) patients who had co-existing neurological disorders- two were on antiepileptic therapy for seizure disorder, while one had congenital hydrocephalus for which surgical intervention was done. One of the patients had a surgically corrected congenital heart disease and one patient had bronchial asthma controlled on inhaled long-acting beta-agonists. **(Supplementary table 1)**

Clinical Characteristics : (Table 1, figure 2A and figure 2B)

Fever was present in all patients at presentation. Among other constitutional symptoms fatigue was noted in 27(66%) cases and loss of appetite in 24(59%) cases. The most common organ system involved was the gastrointestinal (GI) system in 37 (90%) cases. Abdominal pain and diarrhea were the most common symptoms of GI involvement seen in 32(78%) cases each followed by nausea or vomiting in 23(56%) cases, pancreatitis was noted in 2(5%) cases, and one patient (2%) had presented with appendicitis. One case had presented as intussusception during surgical reduction of same mesenteric lymph node was biopsied and an ill formed granuloma and neutrophilic infiltrate were detected on histopathology

The median duration of fever at the time of hospitalization was 4 days (Interquartile range IQR 3-5 days) and the mean duration of GI symptoms at the time of hospitalization was 3 ± 1.3 days.

The second most common manifestation was mucocutaneous which was present in 36(88%) cases. The most common mucocutaneous involvement was conjunctivitis in 29 (71%), which was bilateral nonexudative, and non-purulent. Rash was noted in 25 (61%) cases, was predominantly maculopapular rash over the trunk, extremities, and periorbital region. Oropharyngeal changes of red lips/ red tongue or cheilitis were present in 20 (49%) cases, and the acro-ischemic lesion was noted in one case. [23]

Thirty-two (78%) patients had both GI and mucocutaneous involvement. Muscle aches or myalgias were reported in 27 (66%) cases.

The cardiovascular system was involved in 22(54%) cases clinically, it was manifested by the presence of shock requiring inotropic agents.

Neurological symptoms were present in 21(51%) cases. Headache was reported in 10 (24%) cases, meningismus was noted in 6 (15%) cases, 19(46%) cases had either irritability, somnolence, or altered mental status, and one patient had ataxia.

Fifteen(37%) cases had lymphadenopathy either cervical or mesenteric. Cervical lymphadenopathy was noted on clinical examination and mesenteric lymphadenopathy was detected on radiological imaging.

Lower respiratory symptoms were there in 13(31%) cases, shortness of breath was in 12(29%) and cough was in 4(10%) cases. Upper respiratory symptoms were noted in 5(12%) cases, sore throat was reported by 3(7%) cases, and nasal congestion or rhinorrhoea was reported in 2(5%) cases. Peripheral extremity changes of edema of hands and feet were noted in 11(27%) cases.

All the clinical features were assessed for their association with age categories. Mucocutaneous symptoms were present in all 19(100%) cases in the 5-12 years age group compared to 13(72%) cases in the less than 5 years age group (p=0.019).

Table 1: Clinical characteristics of MIS-C cases across the age categories:

	Total (n=41) no. (%)*	< 5 years (n=18) no. (%)*	5-12 years (n= 19) no. (%)*	>12-20 years (n=4) no. (%)*
Males	23 (56)	9 (50)	11 (58)	3 (75)
Any constitutional symptoms	41 (100)	18 (100)	19 (100)	4 (100)
-Fever	41 (100)	18 (100)	19 (100)	4 (100)
-Fatigue	27 (66)	10 (56)	14 (73)	3 (75)
-Loss of Appetite	24 (59)	9 (50)	12 (63)	3 (75)
Any Gastrointestinal (GI) symptoms	37 (90)	16 (89)	17 (90)	4 (100)
- Abdominal Pain	32 (78)	12 (67)	16 (84)	4 (100)
- Diarrhoea	32 (78)	12 (67)	16 (84)	4 (100)
- Nausea or vomiting	23 (56)	11 (61)	8 (42)	4 (100)
- Pancreatitis ¶	2 (5)	0 (0)	1 (5)	1 (25)
- Appendicitis †	1 (2)	0 (0)	1 (5)	0 (0)
- Intussusception§	1 (2)	0 (0)	1 (5)	0 (0)
Duration of fever at the time of admission/ diagnosis (days) - median (IQR)	4.0 (3.0-5.0)	3.5 (2.8-5.0)	5.0 (3.0-7.0)	4.5 (3.3-5.0)
Duration of GI symptoms at the time of admission/diagnosis (days) mean ± SD	3.0 ± 1.3	2.6 ± 1.1	3.3 ± 1.5	3.0 ± 1.8
Any changes in peripheral extremities:				
-Swollen hands or feet/ Edema of extremities	11 (27)	5 (28)	5 (26)	1 (25)
Any mucocutaneous changes:	36 (88)	13 (72)	19 (100)	4 (100)
-Rash	25 (61)	9 (50)	13 (68)	3 (75)
- Oropharyngeal changes (Red lips/ tongue/cheilitis)	20 (49)	6 (33)	10 (53)	4 (100)
- Conjunctivitis	29 (71)	9 (50)	16 (84)	4 (100)
- Acro ischemic lesions	1 (2)	1 (6)	0 (0)	0 (0)
Any gastrointestinal **and** any mucocutaneous changes/symptoms	32 (78)	11 (61)	17 (90)	4 (100)
Lymphadenopathy (Cervical /mesenteric)	15 (37)	5 (28)	7 (37)	3 (75)
Cardiovascular symptoms -Shock	22 (54)	7 (39)	12 (63)	3 (75)
Any neurological symptoms	21 (51)	8 (44)	10 (53)	3 (75)

-Headache	10 (24)	2 (11)	5 (26)	3 (75)
-Irritability/ somnolence/ altered mental status/ gait disturbance ††	19 (46)	7 (38)	9 (47)	3 (75)
- Meningismus	6 (15)	1 (6)	4 (21)	1 (25)
Musculoskeletal symptoms				
- Muscle Aches/ myalgia	27 (66)	10 (56)	14 (73)	3 (75)
Any upper respiratory symptoms	5 (12)	0 (0)	5 (26)	0 (0)
-Sore throat	3 (7)	0 (0)	3 (16)	0 (0)
-Nasal congestion/ rhinorrhoea	2 (5)	0 (0)	2 (11)	0 (0)
Any lower respiratory symptoms	13 (31)	5 (28)	5 (26)	3 (75)
-Shortness of breath /dyspnoea	12 (29)	5 (28)	4 (21)	3 (75)
-Cough	4 (10)	0 (0)	2 (11)	2 (50)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

¶ The two patients who had pancreatitis, had severe abdominal pain and vomiting, one out of them was having severe multi-organ involvement including anuric acute kidney injury and succumbed on the day of admission itself.

† One patient had presented with abdominal pain, vomiting, and an appendicular lump on clinical and radiological assessment.

§ One patient had a clinical presentation of intussusception, she was subjected to surgical reduction of intussusception and the biopsy of which showed ill-formed granuloma and neutrophilic infiltrate.

††One patient had presented with fever, irritability, and ataxia; she was noted to have bilateral conjunctivitis and maculopapular skin rashes. COVID-19 associated cytotoxic lesion of the corpus callosum was found on subsequent neurological assessment.[24]

Laboratory investigations and echocardiogram:

(Table 2, cut off values of parameters used are listed in parentheses and footnotes of table 2)

At the time of hospitalization anemia was noted in 20(49%) cases, leukopenia in 2(5%), lymphopenia in 26(63%), thrombocytopenia in 13(31%), and pancytopenia in 2(5%) cases.

Among the inflammatory markers, C-reactive protein (CRP) was elevated in all cases; there was a marked elevation of CRP (>100mg/L) in 23 (56%) cases. Procalcitonin was done in 16(39%) cases and it was elevated in all of these cases. D-dimer was high in 40(98%) cases, serum ferritin was high in 22(54%) cases and hypoalbuminemia was noted in 31(76%).

Transaminitis was noted in 19(46%) cases, acute kidney injury was identified in 4(10%) cases and hyponatremia in 9(22%) cases and during their hospital stay.

N-terminal pro B type natriuretic peptide (NT-proBNP) was done in 19(46%) cases, it was elevated in 18(95%) cases and troponin was done in 30(73%) cases, it was elevated in 10(33%) cases. Fibrinogen was done in 11(27%) cases and hypofibrinogenemia was noted only in one case. Erythrocyte sedimentation rate (ESR) was done in 14 (34%) cases and it was high in 10(71%) cases.

Cardiac assessment with an electrocardiogram (ECG) and echocardiography was done in all patients. **Figure 2B** shows a graphical representation of salient features of cardiac assessment. An abnormal ECG was noted in 8(20%) cases; bradycardia was present in 5(12%) cases, ST-T changes and complete heart block were noted in one patient each. Echocardiography was abnormal in 23(56%) cases. Coronary artery abnormalities were noted in 15(37%), only hyperechoic or non-tapering coronaries in 3(7%), dilated coronaries in 4(10%), and small coronary aneurysms in 8 (20%) cases.

Left ventricular dysfunction was found in 10(24%) cases- mild to moderate in 9(22%) cases, and severe dysfunction was noted in one case (2%). There was pericardial effusion in 10(24%) cases, mitral valve regurgitation in 6(15%) cases, and global or septal hypokinesia in 4(10%) cases.

Table 2: Laboratory investigations and echocardiogram *¶

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12-20 years (n=4)
Hemogram at the time of presentation :				
Hemoglobin (Hb) g/L (Mean ± SD)	107.7 ± 16.2	103 ± 17.3	110.9 ± 12.3	106 ± 27.4
Total leukocyte count (TLC) 10^9/L (Mean ± SD)	11.21 ± 4.8	12.87 ± 5.4	10.52 ± 3.5	7.05 ± 4.6
Platelets (PLT) 10^9/L (Mean ± SD)	248 ± 167	303 ± 159	220 ± 176	131 ± 26
Anemia (Hb <110 g/L) - no. (%)	20 (49)	10 (56)	7 (37)	3 (75)
Leukopenia (TLC < 4.0 x 10^9 cells/L) - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Thrombocytopenia (PLT < 150 x 10^9 cells/L) - no. (%)	13 (31)	3 (17)	7 (37)	3 (75)
Pancytopenia† - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Lymphopenia†† - no. (%)	26 (63)	7 (39)	15 (19)	4 (100)
Peak values :				
CRP mg/L - Mean ± SD or Median (IQR)	119 ± 79	86 ± 63	145 ± 84	146 (64-234)
Positive CRP (>1 mg/L)	41 (100)	18 (100)	19 (100)	4 (100)
CRP (1-50) mg/L- no. (%) CRP (51-100) mg/L- no. (%) CRP (>100) mg/L- no. (%)	10 (24) 8 (20) 23 (56)	7 (39) 5 (28) 6 (33)	2 (11) 3 (16) 14 (73)	1 (25) 0 (0) 3 (75)
Procalcitonin µg/L - Median (IQR) no./total no. (%)	 8.9 (1.6-51) 16/41 (39)	 11.4 (1.5-54.2) 8/18 (44)	 3.7 (1.5-13.8) 5/19 (26)	 48 (7.2-53.0) 3/4 (75)
High Procalcitonin (>0.5 µg/L) - no./total no. (%)	16/16 (100)	8/8 (100)	5/5 (100)	3/3 (100)
Ferritin µg/L Median (IQR)	350 (170-733)	189 (98-429)	570 (266-961)	777 (180-1332)
High ferritin (>300 µg/L) - no./total no. (%)	22 (54)	7 (39)	13 (68)	2 (50)
D-dimer mg/L Median (IQR)	2.5 (1.1-4.3)	1.5 (0.9-3.3)	3.8 (1.5-5.2)	2.6 (1.6-4.2)
High D-dimer (> 0.5 mg/L) - no.(%)	40 (98)	18 (100)	18 (94)	4 (100)
Sodium mmol/L Mean ± SD	135 ± 5	135 ± 6	135 ± 5	137 ± 4

Hyponatremia (Sodium <135 mmol/L)- no.(%)	9 (22)	3 (17)	5 (26)	1 (25)
Albumin g/L (Mean ± SD)	28.6 ± 7.11	29.49 ± 6.88	28.32 ± 7.86	26.54 ± 4.71
Hypoalbuminemia (Albumin < 35g/L) -no.(%)	31 (76)	14 (78)	13 (68)	4 (100)
AST IU/L Median (IQR)	35.0 (27.0-76.5)	28.0 (22.5-47.5)	34.0(23.0-60.0)	110.0 (37.0-351.0)
ALT IU/L Median (IQR)	29.5 (22.3-51.0)	40.0 (27.5-63.5)	29.0 (20.0-45.0)	89.0 (35.5-442)
Transaminitis ‡ -no.(%)	19 (46)	9 (50)	7 (37)	3 (75)
Acute Kidney Injury (AKI) ‡‡	4 (10)	1 (6)	1 (5)	2 (50)
Sterile pyuria— no./total no. (%)	10/20 (50)	4/10 (40)	4/7 (57)	2/3 (67)
Proteinuria— no./total no. (%)	6/20 (30)	1/10 (10)	3/7 (43)	2/3 (67)
Troponin ng/L Median (IQR) -no./ total no. (%)	 16 (6.7-30) 30/41 (73)	 19 (6.0-41.2) 12/18 (67)	 10.2 (4.0-35.6) 14/19 (74)	 19.3 (14.5-27.4) 4/4 (100)
Elevated Troponin (>20 ng/L) -no./ total no. (%)	10/30 (33)	6/12 (50)	3/14 (21)	1/4 (25)
NT-ProBNP (pg/mL) Median (IQR) -no./ total no. (%)	1845 (403-6840) 19/41 (46)	4342 (815-7803) 8/18 (44)	529 (248-4647) 9/19 (47)	3530 (2679-4382) 2/4 (50)
Elevated NT-proBNP (>125 pg/mL) -no./ total no. (%)	18/19 (95)	8/8 (100)	8/9 (89)	2/2 (100)
Fibrinogen g/L Mean ± SD - no./total no. (%)	 3.9 ± 1.78 11/41 (27)	 3.5 ± 0.8 3/18 (17)	 4.2 ± 2.2 7/19 (37)	 3.37 1/4 (25)
Hypofibrinogenemia (Fibrinogen <2.0 g/L) -no./ total no. (%)	 1/11 (9)	 0/3 (0)	 1/7 (14)	 0/1 (0)
ESR mm/h Mean ± SD - no./total no. (%)	 33.4 ± 20.7 14/41 (34)	 35.3 ± 15.9 7/18 (39)	 41.2 ±24.4 5/19 (26)	 7.5 ± 0.7 2/4 (50)
High ESR (>20) - no./total no. (%)	10/14 (71)	6/7 (86)	4/5 (80)	0/2 (0)
Cardiac assessment: Abnormal ECG Bradycardia Complete Heart Block § ST T changes	 8 (20) 5 (12) 1 (2) 1 (2)	 3 (17) 1 (6) 1 (6) 0 (0)	 4 (21) 3 (16) 0 (0) 1 (5)	 1 (25) 1 (25) 0 (0) 0 (0)
Abnormal Echocardiography	23 (56)	11 (61)	9 (47)	3 (75)
Normal coronaries	26 (63)	9 (50)	14 (73)	3 (75)

Abnormal coronaries (Hyperechoic/ non tapering/ dilatated/ aneurysm)	15 (37)	9 (50)	5 (26)	1 (25)
Only hyperechoic / non tapering coronaries	3 (7)	3 (17)	0 (0)	0 (0)
Dilated coronaries	4 (10)	3 (17)	1 (5)	0 (0)
Small Aneurysm in coronaries	8 (20)	3 (17)	4 (21)	1 (25)
Systolic Dysfunction Mild to moderate (LVEF 30-55%) Severe (LVEF <30%)	10 (24) 9 (22) 1 (2)	3 (17) 2 (11) 1 (6)	6 (32) 6 (32) 0 (0)	1 (25) 1 (25) 0 (0)
Pericardial effusion	10 (24)	6 (33)	2 (11)	2 (50)
Global/septal hypokinesia	4 (10)	3 (17)	1 (5)	0 (0)
Mitral Valve regurgitation	6 (15)	3 (17)	2 (11)	1 (25)
Pulmonary Artery Hypertension	3 (7)	0 (0)	2 (11)	1 (25)

* Percentages may not total 100 because of rounding.

¶ CRP denotes C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, ESR Erythrocyte sedimentation rate, ECG Electrocardiogram, LVEF left ventricular ejection fraction, IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

† Pancytopenia defined as hemoglobin <110 g/L, total leukocyte count < 4.0 x 10^9/L and platelets < 150 x 10^9/L.

†† Lymphopenia defined as <3000 lymphocytes/µL (<2 years age) , <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

‡ Transaminitis defined as AST or ALT >40 IU/L.

‡‡ Acute Kidney Injury (AKI) is defined as any of the following: increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours[25].

§One patient had presented with fever and drowsiness, noted to have complete heart block treated with a pacemaker, IVIG, and steroids however patient succumbed on the first day of admission itself.

Clinical course, treatment, and immediate outcomes: (Table 3)

A total of thirty-six (88%) patients required intensive care; the median duration of ICU stay was 3.5 days (IQR 3-5 days). Twenty-one(51%) patients required inotropes and mechanical ventilation was required in 8(20%) cases. Treatment was provided as per the standard treatment guidelines for MIS-C.[6,26,27] Immunomodulatory therapy was administered to 39(95%) cases, steroids and IVIg both were used in 35 (85%) and only steroids were used in 3(7%) cases. Antiplatelets were used in 37 (90%) cases Anticoagulation was used in 3 (7%) patients. Empirical broad-spectrum antibiotics were started for all the patients at the time of hospitalization and were discontinued after the blood and urine cultures were noted to be sterile. **(Supplementary figure 2)**

Two (5%) patients died during the treatment of the acute phase. The first patient was 4 year old girl who was positive for both COVID-19 RTPCR and antibodies with a complete heart block; she continued to deteriorate despite pacemaker, mechanical ventilation, supportive care, and standard treatment for MIS-C and expired on the same day of hospitalization. The second mortality was a 17 year old boy who had severe multi-organ dysfunction, deteriorated rapidly despite prompt immunomodulation, hemodialysis, and mechanical ventilation, and succumbed to it within 24 hours of hospitalization.

The mean length of hospital stay was 8.2 ± 4.7 days, among the patients who recovered from MIS-C. Thirteen patients (32%) recovered with some residual sequelae, primarily echocardiographic abnormalities. Remaining 26 (63%) cases recovered without any residual changes at the time of discharge. **(Supplementary figure 3 and 4)**

Table 3: Clinical course, treatment, and immediate outcomes*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12 years (n=4)
Intensive care unit (ICU) requirement -no.(%)	36 (88)	15 (83)	18 (95)	3 (75)
Median duration of ICU stays among patients who required ICU in days (IQR)	3.5 (3.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-7.0)	4.0 (1.0-9.0)
Mechanical ventilation - no.(%) †	8 (20)	2 (11)	4 (21)	2 (50)
Median duration of mechanical ventilation in days among patients who required it (IQR)	3.0 (1.0-12.5)	8.0 (1.0-15.0)	4.0 (3.0-17.0)	1.0 (1.0-1.0)
Inotropic agent requirement - no.(%)	21 (51)	7 (39)	11 (58)	7 (39)
Median number of days patients were on inotropes among the patients it was used (IQR)	2.0 (2.0-3.0)	3.0 (1.8-6.0)	2.0 (2.0-3.0)	2.0 (0.5-2.0)
Aspirin low dose	37 (90)	16 (89)	18 (96)	3 (75)
IVIG	36 (88)	15 (83)	18 (95)	3 (75)
Repeat IVIG	1 (2)	1 (6)	0 (0)	0 (0)
Steroids	38 (93)	16 (89)	18 (100)	4 (100)
Steroids and IVIG	35 (85)	15 (83)	17 (90)	3 (75)
Anticoagulation	3 (7)	1 (6)	1 (5)	1 (25)
Mean length of hospital stay excluding deaths (days) ± SD	8.2 ± 4.7	8.0 ± 6.1	8.1 ± 3.1	10.3 ± 43.5
Immediate outcome (At the time of discharge) Recovered with sequalae Recovered without sequalae Death	 13 (32) 26 (63) 2 (5)	 5 (28) 12 (67) 1 (6)	 7 (37) 12 (63) 0 (0)	 1 (25) 2 (50) 1 (25)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

† Only non-invasive mechanical ventilation was used in one patient in >12 years age group, all others required invasive mechanical ventilation.

Follow up at 6 weeks after discharge :

All discharged patients (n=39) remained clinically stable during 6 weeks follow up, there was no abnormality on clinical assessment in any case. Echocardiographic changes were also at improving trend in all cases. Eight (21%) cases had persisting coronary alterations on echocardiogram at 6 weeks- hyperechoic or non-tapering thick-walled coronaries in 5 (13%) cases, coronary dilation in 2(5%) and small coronary aneurysm in one case. However, the echocardiographic coronary alterations had improved from their baseline status during the acute illness. Persisting mild left ventricular systolic dysfunction and pulmonary artery hypertension (PAH) were noted in one case each. **(Supplementary table 2)**

Medium-term outcome at 3 months follow-up : (Table 4)

Thirty-seven patients had finished their 3 months follow-up by April 2021. All patients were clinically stable, echocardiographic changes were improving in all of them. At 3 months follow up 4(11%) patients were on Aspirin for residual coronary changes, one patient was on diuretics for left ventricular dysfunction, and one patient was on Phosphodiesterase-5 inhibitors for PAH.

Table 4: Cardiac outcomes at 3 months follow up (n=37) ¶

	Total (n= 37) no. (%)*	< 5 years (n=17) no. (%)*	5-12 years (n= 17) no. (%)*	>12 years (n=3) no. (%)*
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal Coronaries	4(11)	3(18)	1(6)	0(0)
Hyperechoic / non tapering coronaries	2 (5)	2 (12)	0 (0)	0 (0)
Dilatation	1 (3)	1 (6)	0 (0)	0 (0)
Small Aneurysm	1 (3)	0 (0)	1 (6)	0 (0)
LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
PAH	1 (3)	0 (0)	1 (6)	0 (0)
Recovered with sequalae ¶¶	6 (16)	3 (18)	3 (18)	0 (0)
Ongoing treatment in any form at 3 months follow up	6 (16)	3 (18)	3 (24)	0 (0)
Aspirin	4 (11)	2 (12)	3 (18)	0 (0)
Treatment of LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
Treatment of PAH	1(3)	0 (0)	1 (6)	0 (0)

¶ Only 37 patients had finished their 3 months follow-up by April 2021. LV dysfunction denotes- left ventricular dysfunction and PAH is pulmonary arterial hypertension.

* Percentages may not total 100 because of rounding.

¶¶ Sequalae refers to any residual structural or functional cardiac abnormality on echocardiography.

Comparison of MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation: (Table 5)

We categorised MIS-C patients into two groups based on requirement of mechanical ventilation. These two groups were compared statistically for various clinical, laboratory and echocardiographic parameters, salient statistically and clinically significant findings are listed in **table 5**.

Out of 8 patients who required mechanical ventilation, 7(88%) had presented in shock treated with ionotropic agents, whereas out of 33 cases who did not require mechanical ventilation 14 (42%) had presented in shock necessitating use of ionotropic agents; the difference was statistically significant (p=0.045).

Serum D-dimer, serum ferritin, and aspartate aminotransferase (AST) were significantly high and ESR was significantly low in patients of MIS-C requiring ventilatory support as compared to them who did not require it ($p < 0.05$).

Table 5: Bivariate Comparison of various clinical and laboratory parameters in MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation*

Clinical and laboratory parameters of MIS-C cases	Mechanical ventilation required (n = 8)	Mechanical ventilation not required (n = 33)	p-value ‡
Presence of shock requiring inotropic agents – no. (%)	7 (88)	14 (42)	**0.045**
Median D-dimer mg/L (IQR)	4.5 (2.9-16.3)	2.3 (1.0-3.9)	**0.016**
Median serum ferritin µg/L (IQR)	1178.0 (717.0-23840.0)	266.0 (153.0-555.0)	**0.001**
Median ESR mm/h (IQR) - no./total no. (%)	8.0 (7.0-10.0) 3/8 (38)	40 (27-51) 11/33 (33)	**0.016**
Median serum AST IU/L (IQR)	188.0 (37.8-741.2)	33.0 (26.0-60.5)	**0.008**
Median serum procalcitonin µg/L (IQR) - no./total no. (%)	5.4 (2.1-41.5) 4/8 (50)	11.1(1.6- 51.0) 12/33 (36)	0.716
Median serum NT-proBNP pg/mL (IQR) - no./total no. (%)	3533.5 (2141.5-46767.5) 6/8 (75)	1138.0 (349.0-6725.0) 13/33 (39)	0.096
Median serum troponin ng/L (IQR) - no./total no. (%)	55.2 (14.5-945.3) 4/8 (50)	15.0 (4.8-29.2) 26/33 (78)	0.143
Median absolute lymphocyte count (IQR)	825 (521-2218)	1588 (895-3489)	0.061
Lymphopenia at admission -no. (%)§	7 (88)	19 (58)	0.220
Mean CRP mg/L ± SD	101.0 ± 85.3	123 ± 78.9	0.474
Median serum ALT IU/L (IQR)	141.0 (25.0-543.0)	29.0 (21.0-43.5)	0.113
Presence of coronary abnormalities - no. (%)	4 (50)	11 (33)	0.434
Presence of LV dysfunction - no. (%)	3 (38)	7 (21)	0.378

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, CRP C-reactive protein, SD standard deviation, and ALT alanine aminotransferase.

‡ p-value was calculated by applying appropriate statistical tests according to the distribution of the data. Independent sample t-test or Mann-Whitney tests were applied to compare the potential markers of severity. A p-value of <0.05 was considered statistically significant.

§ Lymphopenia defined as <3000 lymphocytes/µL (<2 years age) , <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

Discussion:

In this study, we have described 41 cases of MIS-C associated with COVID-19 from two tertiary care centers from the Kerala state of India from March 2020 to April 2021. These two centers are geographically located on the western coast of India, one at the northern end and the other in the center of Kerala state. **Figure 3** shows a heat map of syndrome clusters in MIS-C cases in our study.

Comparison with other studies:

We compared our study results with those of a systematic review by M. Ahmed et al. which involved 662 cases of MIS-C from 39 studies published from January 2020 to July 2020; similarities were noted on slight male preponderance (56% in our study *v* 52%), constitutional symptoms (100% *v* 100%), intensive care requirement (88% *v* 71%), mechanical ventilation requirement (20% *v* 22%), inotrope requirement (51% *v* 60%), mean length of hospital stay (8.2 days *v* 7.9 days). Laboratory parameters reflecting inflammatory, coagulative, and cardiac involvement were also similar. However, there were striking differences in our cohort which included a large number of previously healthy individuals (80% in our study v 52%), especially we had a smaller proportion of overweight or obese cases (10% *v* 24%), younger age of onset (mean age 6.16 years *v* 9.3years), high frequency of conjunctivitis (71% *v* 51%), more common myalgia (66% *v* 13%), more cases with irritability /somnolence (46% *v* 10%), more number of cases with lymphadenopathy (37% *v* 14%), more frequent coronary dilation and aneurysms (29% *v* 15%), and systolic dysfunction was less frequent (24% *v* 45%).[9] As MIS-C is a new disease with little literature on its clinical presentations across ethnic groups, these disparities could be a reflection of that in Indian patients of MIS-C.

In the comparison of our study with the two largest case series from the USA, we had a smaller number of patients in the age group of more than 12 years (10% in our study *v* 24% *and* 26%).[28,29] These studies are a major part of the aforementioned systematic review.

There are two case series of MIS-C are reported from India. The first one is from Chennai, a city on the eastern coast of South India, it had 19 MIS-C cases on comparison with our study we found that our cohort had more frequent gastrointestinal symptoms (90% in our study *v* 42%), a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 58%), and more common coronary involvement (37% *v* 16%).[30] Another case series is from Mumbai, a city on the same coast as ours, comprising 23 cases of MIS-C; compared to their study also we observed a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 39%), higher frequency of abdominal pain (78% *v* 52%), and conjunctivitis (71% *v* 52%).[31] Other available clinical and laboratory parameters from these two studies were similar to our study, description of body habitus of patients was not available from both of the studies.

As the clinical phenotype of these cases was thought to be similar to KD, we compared our results with existing literature on KD and we noticed that percentage of cases developing coronary artery aneurysms in our MIS-C cases were less than that of untreated KD (20% *v* 25%) but more than of that KD treated with optimum IVIG (20% *v* 5%). IVIG resistance or requirement of a second dose of IVIG or alternative immunotherapy was less frequent in MIS-C in comparison to KD (2% *v* 10%).[32,33] However, none of the patients developed medium-sized or giant coronary aneurysm or thrombosis of coronary contrast to KD where it is reported in 1% of treated cases.[34]

Novelties in the study :

This study is among the first to report on medium-term outcomes following MIS-C. While it is gratifying to note that most cases remained clinically well at 3 months follow-up, the persistence of echocardiographic abnormalities in 6 patients emphasises the need for careful follow-up.

The only other published report on intermediate-term follow-up following MIS-C is a recently published study by *Penner* et al. that reports outcomes at 6 months following MIS-C in a single center cohort from the UK.[35] In comparison with our study, the similarity was noted in context to full subsidence of inflammation (100% in our study *v* 98%). The difference in near-complete resolution of echocardiographic sequelae (84% in our study *v* 96%) could be due to our 3-month follow-up *v* the 6-month follow-up in the aforementioned study. The striking difference was that in our cohort none of the patients had persistent gastrointestinal symptoms, mucocutaneous changes, or minor neurological abnormalities as reported in the above-mentioned study.

MIS-C requires a high index of suspicion for diagnosis and warrants prompt treatment. There is a paucity of literature in MIS-C to define severe and non-severe cases and prediction of severity in a given case. As all of the MIS-C cases required hospitalization, most of these required intensive cares, and mechanical ventilation was required in 20% cases. In our study we found that the presence of shock requiring inotropic agent, high ferritin, high D-dimer, high AST, and low ESR were associated with the requirement of mechanical ventilation in MISC cases ($p<0.05$). The constellations of these parameters could reflect an ongoing process of Macrophage Activation Syndrome (MAS) in MIS-C cases requiring mechanical ventilation. Our findings are comparable with a retrospective surveillance study from USA which enrolled 1090 patients of MIS-C and reported that thrombocytopenia, lymphopenia, high NT-ProBNP, high D-dimer, and high ferritin increases the odds of severe outcomes and the need for intensive care.[36]

Limitation of the study:

1. As the study was conducted at two tertiary care centers it might underestimate the mild MISC cases and could be skewed towards high morbidity and mortality due to referral bias.
2. In our study we have not looked at impact of MIS-C on mental health of children during medium term follow up.

Unanswered questions and future research:

1. What could be the risk factors for the development of MIS-C?
2. Is there any genetic predisposition for MIS-C?
3. MIS-C cases need to be followed for long-term outcomes.

Conclusions:

MIS-C is a new disease in context to COVID-19 pandemic and we are still continuing to learn about this clinical syndrome. There have not been many publications from Indian subcontinent on clinical presentation and subsequent progression of MIS-C.

While the clinical profile of our cohort has been similar to world-wide reports, our study demonstrated that in India we see a younger age at onset, more mucocutaneous changes and a smaller number of patients with co-existent comorbidities.

In our study we observed echocardiographic sequalae in 30% cases at the time of discharge, 27% cases at 6 weeks follow up, and only 16% cases at 3 months. Overall immediate and medium-term outcomes remain largely excellent however, because MIS-C is a new entity, ongoing follow-up for several years to study the disease's natural history is certainly warranted.

Risk factors for the development of severe MIS-C remain unknown, however, we found that requirement of mechanical ventilation was associated with shock requiring inotropic agents, high levels of D-dimer or ferritin or AST, and low ESR.

What is already known on this topic:

1. MIS-C is a rare but critical association of COVID-19 infection in children.
2. MIS-C is known to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease-like phenotype, and macrophage activation syndrome.

What this study adds:

1. This is the largest cohort of first wave of MIS-C from India. Indian patients with MIS-C seem to present at a younger age with more frequent mucocutaneous changes and lesser comorbidities as compared to western studies.
2. The medium-term outcome of MIS-C patients is excellent; however, we need to monitor echocardiogram at subsequent follow up visits in selected patients.
3. We were able to associate few parameters like shock requiring inotropic agents, hyperferritinemia, high D-dimer, high AST, and low ESR with requirement of mechanical ventilation.

References:

1 WHO Coronavirus (COVID-19) Dashboard. Covid19.who.int. 2021. https://covid19.who.int (accessed 2 June 2021).

2 Sanna G, Serrau G, Bassareo PP, *et al.* Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. *European Journal of Pediatrics* 2020 May 30;179 1079-87. doi:10.1007/s00431-020-03699-0

3 Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet* 2020;**395**:1771–8. doi:10.1016/S0140-6736(20)31103-X

4 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;**395**:1607–8. doi:10.1016/S0140-6736(20)31094-1

5 Jones VG, Mills M, Suarez D, *et al.* COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hospital Pediatrics* 2020;**10**. doi:10.1542/hpeds.2020-0123

6 Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians.RCPCH.2021. https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance / (accessed on 2 June, 2021).

7 Centers for Disease Control and Prevention. Multisystem inflammatory syndrome. 2020. https://www.cdc.gov/mis-c/hcp/ (accessed 21 April 2021).

8 Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.Who.int.2021.https://www.who.int/newsroom/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (accessed 2 June 2021).

9 Ahmed M, Advani S, Moreira A, *et al.* Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine* 2020;**26**. doi:10.1016/j.eclinm.2020.100527

10 Rubens JH, Akindele NP, Tschudy MM, *et al.* Acute covid-19 and multisystem inflammatory syndrome in children. *The BMJ* 2021;**372**. doi:10.1136/bmj.n385

11 Hamming I, Timens W, Bulthuis MLC, *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology* 2004;**203**:631–7. doi:10.1002/path.1570

12 Liu J, Li S, Liu J, *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. medRxiv. 2020. doi:10.1101/2020.02.16.20023671

13 Li H, Liu L, Zhang D, *et al.* SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;**395**:1517–20. doi:10.1016/S0140-6736(20)30920-X

14 Jiang L, Tang K, Levin M, *et al.* COVID-19 and multisystem inflammatory syndrome in children and adolescents. *The Lancet Infectious Diseases* 2020;**3099**. doi:10.1016/S1473-3099(20)30651-4

15 Khadilkar V, Yadav S, Agrawal KK, *et al.* Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. *Indian Pediatrics* 2015;**52**. doi:10.1007/s13312-015-0566-5

16 Obesity and overweight. Who.int. 2021.https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 2 June 2021).

17 Lai WW, Geva T, Shirali GS, *et al.* Guidelines and Standards for Performance of a Pediatric Echocardiogram: A Report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *Journal of the American Society of Echocardiography* 2006;**19**. doi:10.1016/j.echo.2006.09.001

18 Lopez L, Colan SD, Frommelt PC, *et al.* Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *Journal of the American Society of Echocardiography* 2010;**23**. doi:10.1016/j.echo.2010.03.019

19 McCrindle BW, Li JS, Minich LL, *et al.* Coronary Artery Involvement in Children With Kawasaki Disease. *Circulation* 2007;**116**. doi:10.1161/CIRCULATIONAHA.107.690875

20 Manlhiot C, Millar K, Golding F, *et al.* Improved Classification of Coronary Artery Abnormalities Based Only on Coronary Artery z-Scores After Kawasaki Disease. *Pediatric Cardiology* 2010;**31**. doi:10.1007/s00246-009-9599-7

21 Khanna G, Sargar K, Baszis KW. Pediatric Vasculitis: Recognizing Multisystemic Manifestations at Body Imaging. *RadioGraphics* 2015;**35**. doi:10.1148/rg.2015140076

22 Shenoy B, Singh S, Zulfikar Ahmed M, *et al*. Recommendations Indian Academy of Pediatrics Position Paper on Kawasaki Disease. *Indian Pediatrics*. 2020 May 28;**57.** doi:10.1007/s13312-020-2033-1

23 Kappanayil M, Balan S, Alawani S, *et al.* Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: a case report. *The Lancet Child & Adolescent Health* 2021;**5**. doi:10.1016/S2352-4642(21)00055-9

24 Lin J, Lawson EC, Verma S, *et al.* Cytotoxic lesion of the corpus callosum in an adolescent with multisystem inflammatory syndrome and SARS-CoV-2 infection. *American Journal of Neuroradiology* 2020;**41**:2017–9. doi:10.3174/ajnr.A6755

25 Kellum JA, Lameire N, Aspelin P, *et al.* Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012;**2**:1–138. doi:10.1038/kisup.2012.1

26 Hennon TR, Penque MD, Abdul-Aziz R, *et al.* COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. Progress in Pediatric Cardiology. 2020;**57**. doi:10.1016/j.ppedcard.2020.101232

27 Henderson LA, Canna SW, Friedman KG, *et al.* American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis and Rheumatology* 2020;**72**:1791–805. doi:10.1002/art.41454

28 Feldstein LR, Rose EB, Horwitz SM, *et al.* Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine* 2020;**383**. doi:10.1056/NEJMoa2021680

29 Riollano-Cruz M, Akkoyun E, Briceno-Brito E, *et al.* Multisystem Inflammatory Syndrome in Children (MIS-C) Related to COVID-19: A New York City Experience. *Journal of Medical Virology* 2020;:0–3. doi:10.1002/jmv.26224

30 Dhanalakshmi K, Venkataraman A, Balasubramanian S, *et al.* Epidemiological and Clinical Profile of Pediatric Inflammatory Multisystem Syndrome-Temporally Associated with SARS-CoV-2 (PIMS-TS) in Indian Children. *Indian Pediatrics*. 2000 Nov 15;**57**(11):1011-14. doi:10.1007/s13312-020-2025-1

31 Jain S, Sen S, Lakshmivenkateshiah S, *et al.* Multisystem Inflammatory Syndrome in Children With COVID-19 in Mumbai, India. *Indian Pediatrics*. 2020 Nov. 15;**57**(11):1015-1019. doi: 10.1007/s13312-020-2026-0

32 McCrindle BW, Rowley AH, Newburger JW, *et al.* Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;**135**. doi:10.1161/CIR.0000000000000484

33 Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2019;**140**. doi:10.1161/CIR.0000000000000703

34 Dajani AS, Taubert KA, Takahashi M, *et al.* Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;**89**. doi:10.1161/01.CIR.89.2.916

35 Penner J, Abdel-Mannan O, Grant K, *et al.* 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *The Lancet Child & Adolescent Health* Published Online First: May 2021. doi:10.1016/S2352-4642(21)00138-3

36 Abrams JY, Oster ME, Godfred-Cato SE, *et al.* Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *The Lancet Child & Adolescent Health* 2021;**5**:323–31. doi:10.1016/s2352-4642(21)00050-x

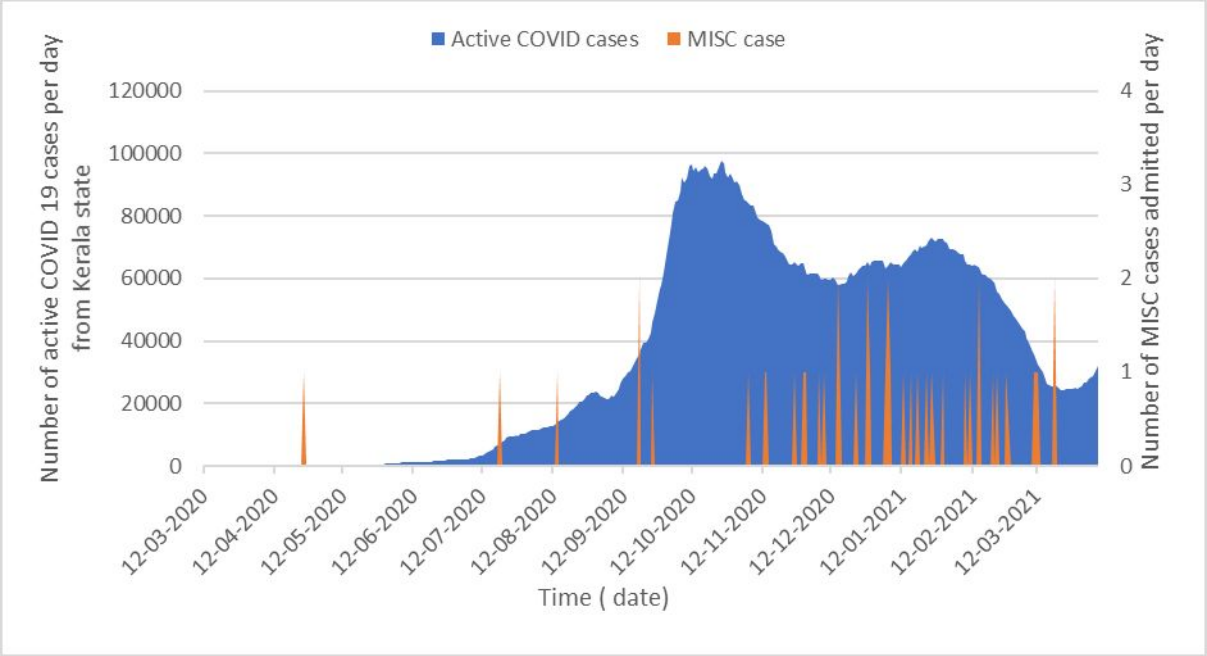


Figure 1: Temporal correlation of Active COVID-19 cases and MIS-C cases in the Southern Indian state Kerala

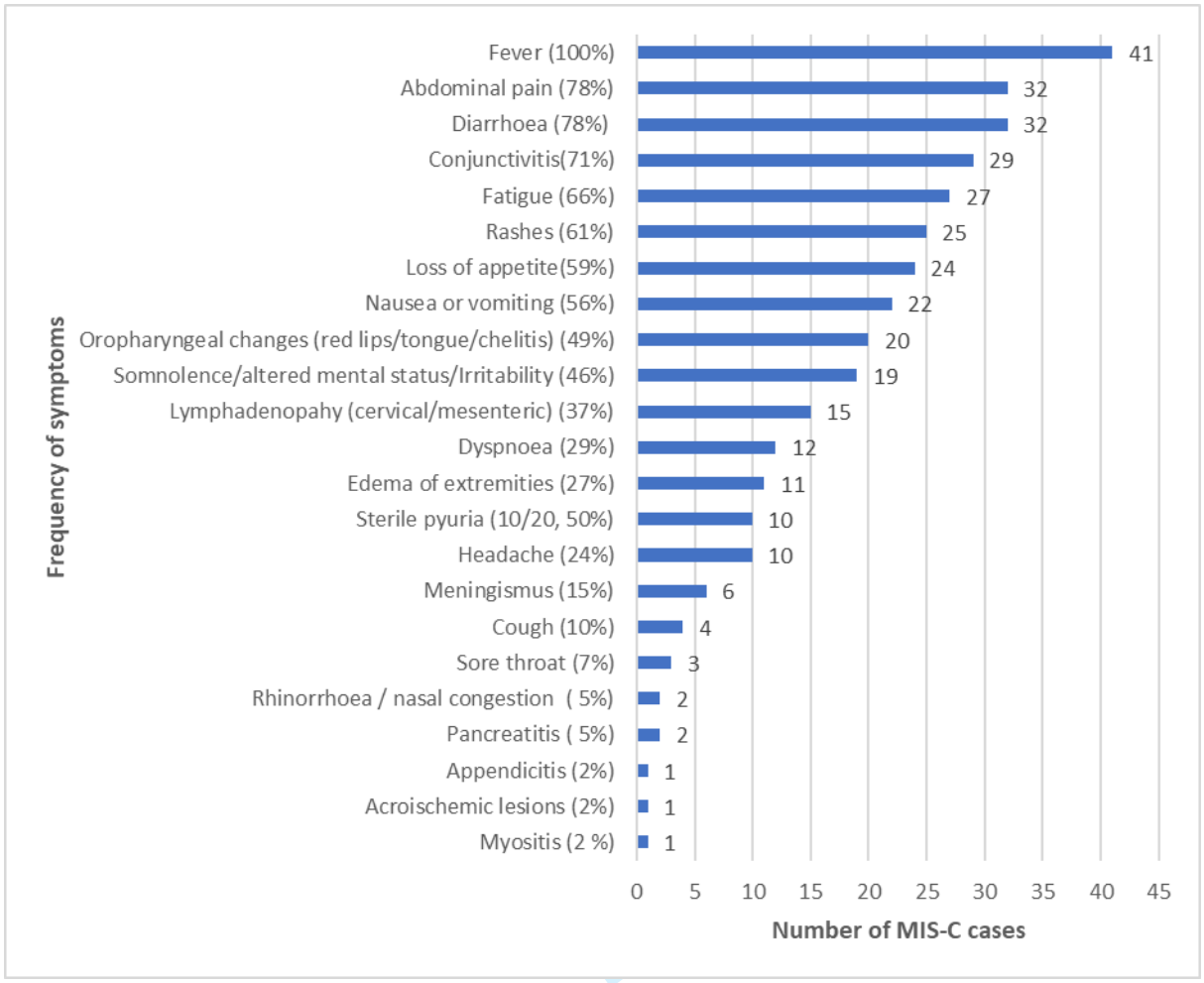


Figure 2A: Frequency of symptoms in MIS-C cases

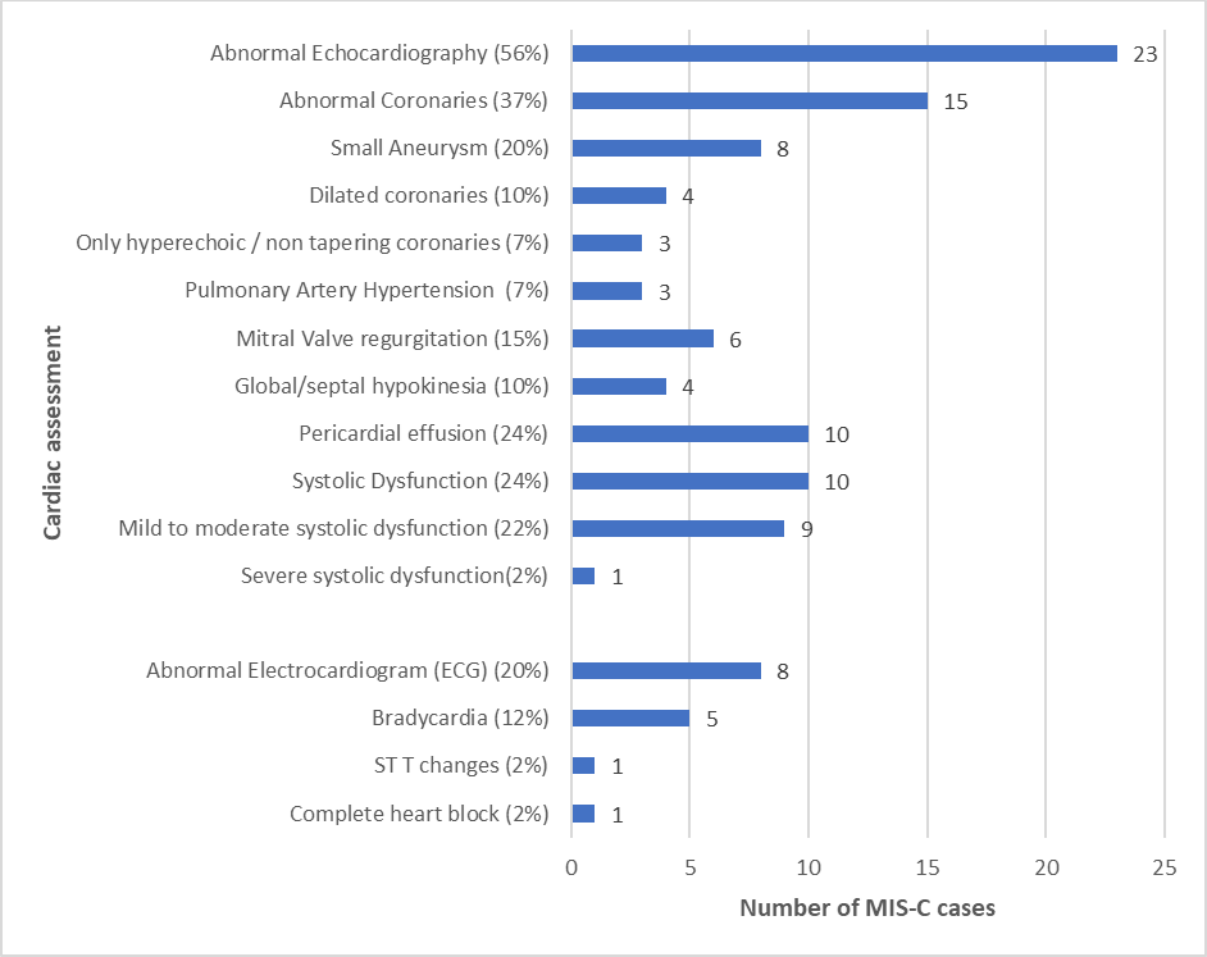


Figure 2B: Cardiac assessment during acute phase of MIS-C

	< 5 years (n=18) -no. (%)	5-12 years (n= 19) -no. (%)	>12 years (n= 4) -no. (%)
Dermatological/ mucocutaneous	13 (72)	19 (100)	4 (100)
Gastrointestinal symptoms	16 (89)	17 (90)	4 (100)
Incomplete/ atypical Kawasaki disease	13 (72)	15 (79)	3 (75)
Shock	7 (39)	12 (63)	3 (75)
Macrophage activation syndrome like features	6 (33)	7 (37)	4 (100)
Neurological symptoms	7 (39)	6 (32)	2 (50)
Respiratory Symptoms	4 (22)	1 (5)	2 (50)

1-5%	6-25%	26-50%	51-75%	76-100%

Figure 3: Heat map of syndrome clusters based on clinical presentations (Percentages may not total 100 because of rounding and overlapping clinical features)

Supplementary Table 1: Demographic and baseline characteristics*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12- 20 years (n=4)
Males – no.(%)	23 (56)	9 (50)	11 (58)	3 (75)
Body habitus – no.(%)**				
- Underweight	3 (7)	1 (6)	2 (11)	0 (0)
- Normal weight	34 (83)	17 (94)	15 (79)	2 (50)
- Overweight	1 (2)	0 (0)	0 (0)	1 (25)
- Obese	3 (7)	0 (0)	2 (11)	1 (25)
Presence of comorbidities- no. (%)				
- Any	8 (20)	2 (11)	3 (16)	1 (25)
- Obesity or overweight	4 (10)	0 (0)	1 (5)¶	1 (25)
- Cardiovascular disorders†	1 (2)	0 (0)	1 (5)	0 (0)
- CNS disorders§	3 (7)	2 (11)	1 (5)	0 (0)
- Chronic lung disease‡	1 (2)	0 (0)	1 (5)	0 (0)

*Percentages may not total 100 because of rounding. BMI = Body Mass Index, CNS = Central Nervous System

** BMI based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups >5 years of age. For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and obesity was defined as weight-for-height greater than 3 standard deviations above the WHO child growth standards median. Underweight was defined in terms of weight for age using the WHO child growth standards for children below 5 years of age and using IAP WHO combined BMI growth charts for older children.

† One patient had large atrial and ventricular septal defects which were closed surgically.

§ Among 3 patients with CNS disorders, two had a seizure disorder, and one had hydrocephalus requiring surgical intervention.

¶ One patient of seizure disorder was obese as well.

‡ One patient had bronchial asthma controlled on inhaled steroids and long-acting beta-agonists.

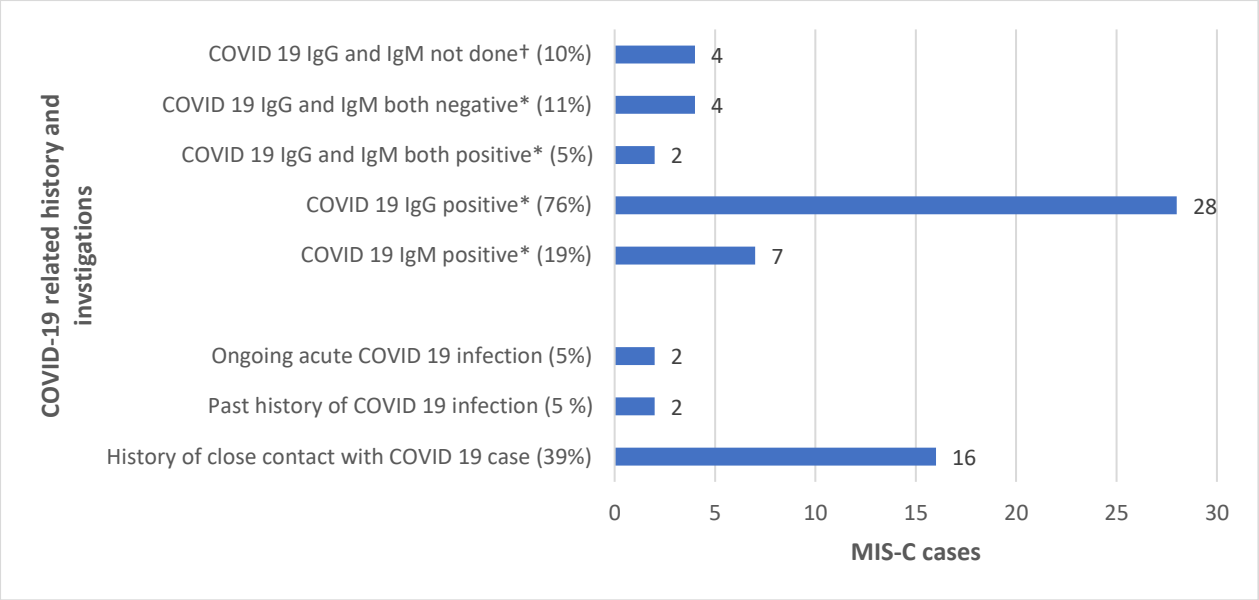
Supplementary table 2: Cardiac outcomes in 6 weeks follow up (n=39) §

	Total (n= 39) no. (%)*	< 5 years (n=17) no. (%)*	5-12 years (n= 19) no. (%)*	>12 years (n=3) no. (%)*
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal coronaries	8(21)	4(24)	4(21)	0 (0)
Hyperechoic/ non-tapering coronaries	5(13)	3(18)	2(11)	0 (0)
Dilatation	2(5)	1(6)	1(5)	0 (0)
Small Aneurysm	1(3)	0 (0)	1(5)	0 (0)
LV dysfunction	1(3)	1(6)	0 (0)	0 (0)
PAH	1(3)	0(0)	1(5)	0 (0)

§ Two patients had expired during the acute phase of MISC.

* Percentages may not total 100 because of rounding.

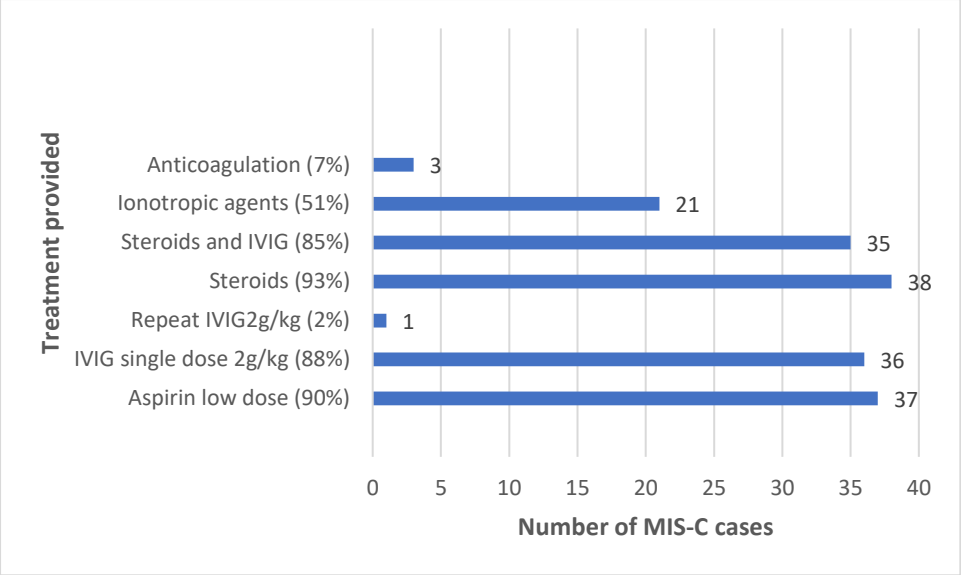
Supplementary figures:



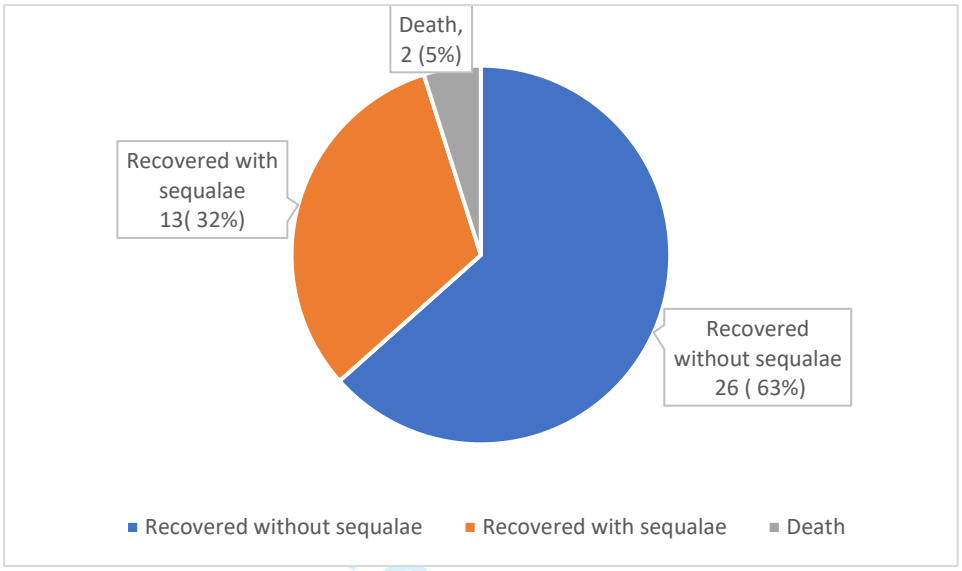
Supplementary figure 1: COVID 19 related history and investigations

† These cases were diagnosed before September 2020 when the COVID antibodies were available at our centers.

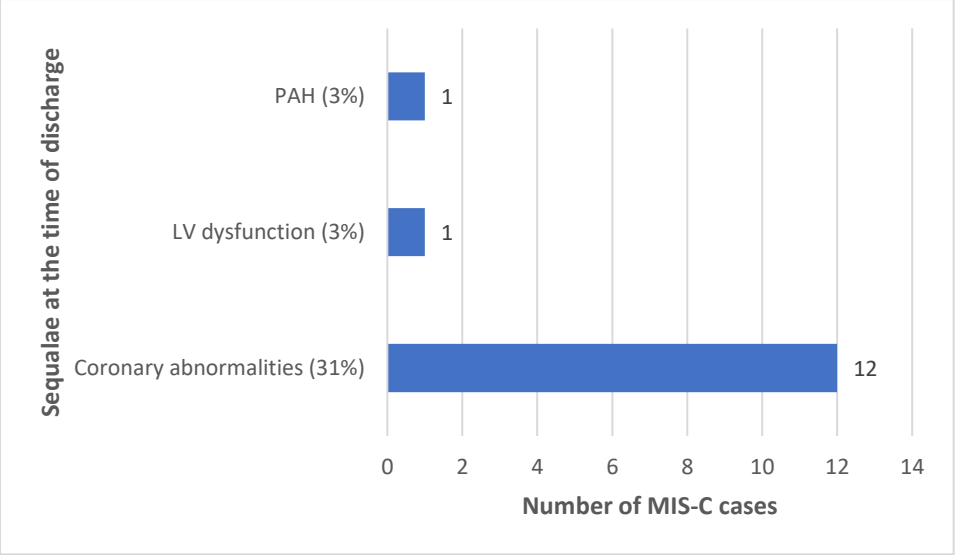
* Investigations are not mutually exclusive.



Supplementary figure 2: Treatment provided to MIS-C cases



Supplementary figure 3: Outcome at the time of discharge (n =41)



Supplementary figure 4: Sequalae at the time of discharge (n =39)

BMJ Paediatrics Open

COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

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Title page

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Ethics statement: This study was approved by the institutional ethics committee- Institutional Review Board of Amrita Institute of Medical Sciences (IRB-AIMS-2020-335) which involved public representatives as well. A written informed consent was obtained from the parents of study participants.

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

Abstract:

Objectives: To study (i) epidemiological factors, clinical profile, and outcomes of COVID-19 related multisystem inflammatory syndrome in children (MIS-C) (ii) clinical profile across age groups, (iii) medium-term outcomes and (iv) parameters associated with disease severity.

Design: Hospital-based prospective cohort study.

Setting: Two tertiary care centers in Kerala, India.

Participants: Diagnosed patients of MIS-C using the case definition of Centres for Disease Control and Prevention.

Statistical analysis: Pearson Chi-Square test or Fisher's exact test was used to compare the categorical variables and independent sample t-test or Mann-Whitney test was used to compare the continuous variables between the subgroups categorised by the requirement of mechanical ventilation. Bonferroni's correction was used for multiple comparisons.

Results: We report 41 patients with MIS-C, mean age was 6.2 (4.0) years, and 33 (80%) were previously healthy. Echocardiogram was abnormal in 23 (56%), and coronary abnormalities were noted in 15 (37%) patients. Immunomodulatory therapy was administered to 39 (95%), steroids and IVIg both were used in 35 (85%) and only steroids in 3 (7%) patients. Intensive care was required in 36 (88%), mechanical ventilation in 8 (20%), inotropic support in 21 (51%), and 2 (5%) patients died. Mechanical ventilation requirement in MIS-C was associated with hyperferritinemia (p=0.001).Thirty-seven patients completed 3 months follow-up by April 2021, of whom 6(16%) patients had some residual echocardiographic changes.

Conclusions: MIS-C patients in our cohort had varied clinical manifestations ranging from fever with mild gastrointestinal and mucocutaneous involvement to fatal multiorgan dysfunction. Immediate and medium-term outcomes remain largely excellent except for the echocardiographic sequelae in a few patients which are also showing a resolving trend. Hyperferritinemia was associated with the requirement of mechanical ventilation.

Original research

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

Introduction:

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS -CoV-2) is rapidly evolving. As of August 13, 2021, there have been 205,338,159 confirmed cases of coronavirus disease 2019 (Covid-19) globally, including 4,333,094 deaths.[1] Earlier studies reported that COVID-19 infection in children was either asymptomatic or mild with only a small proportion requiring hospitalization and lesser mortality as compared to adults.[2]

In May 2020 several European countries reported clusters of hyperinflammatory processes in children with clinical manifestations of atypical Kawasaki disease and shock and the possibility of its link with SARS-CoV-2 was considered.[3–6] Later, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) released health advisories and defined these cases as multisystem inflammatory syndrome in children (MIS-C) associated with Covid-19.[7,8] MIS-C is a rare but severe and potentially fatal condition.[9,10]

The pathogenesis of MIS-C is not well understood. It is known that SARS-CoV-2 enters cells by binding to angiotensin-converting enzyme 2, which is highly expressed in cardiac myocytes, alveolar cells, vascular endothelium, and a small subset of immune cells[11]. Evidences suggest that dysregulated innate immune response leading to cytokine storm and endothelial damage might be responsible for multiorgan failure in severe Covid-19 and MIS-C.[12–14]

MIS-C is reported to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease (KD) like phenotype, and Macrophage activation syndrome (MAS). It is a syndromic presentation with overlapping clinical features of KD, sepsis, toxic shock syndrome, and meningitis.[9,14] Moreover, there is no diagnostic test and the risk factors for the development of MIS-C remain unknown.

Methods:

Study design:

This was a hospital-based prospective cohort study conducted at two tertiary care centers from the Kerala state of India, from March 2020 to April 2021. The primary objective of this study was to report the baseline characteristics, clinical features, laboratory parameters, echocardiographic findings, treatment, and immediate outcomes of cases admitted with MIS-C. The secondary objectives were (i) to study the clinical presentation and response to therapy across age groups, (ii) to report the medium-term outcomes of MIS-C, and (iii) to report the predictors of severity in MIS-C.

Patient and public involvement:

The study was approved by the institutional ethics committee- Institutional Review Board of Amrita Institute of Medical Sciences (IRB-AIMS-2020-335) which involved public representatives as well. A written informed consent was obtained from the parents of study participants. Patients were not involved in the designing of the study.

Study definitions:

We used the CDC case definition to define a case of MIS-C.[7] Body mass index (BMI)-based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups comprising of patients more than 5 years of age.[15] For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 SD above WHO child growth standards median; and obesity was defined as weight-for-height greater than 3 SD above the WHO child growth standards median.[16]

Systolic dysfunction was defined by reduced left ventricular ejection fraction (LVEF) . Systolic dysfunction was categorized as mild to moderate when LVEF was 30%-55% and as severe if LVEF was less than 30 %.[17,18]

Echocardiography Z-scores were calculated using Mc Crindle et al. formula using body surface area.[19] Coronary artery abnormalities (CAA) were classified according to the Z-scores on echocardiography.[20] Echocardiographic appearance of hyperechogenicity and non-tapering morphology were also noted as abnormalities.[21]

For this study, “Incomplete KD” was defined as the presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings.[22] Children who along with the usual clinical features of KD also had few unusual clinical manifestations like pulmonary involvement and renal impairment were labeled “atypical KD”.[22]

Categorization of children with MIS-C

Patients were categorised into three groups based on age (<5, 5-12 and 12-20 years) for subgroup comparisons. All patients were further categorised based on the requirement for mechanical ventilation. All children with MIS-C who had any residual clinical, laboratory, or echocardiographic changes at the time of discharge were labeled as “recovered with sequelae ”. The discharged patients were followed up at 6 weeks and 12 weeks to report the medium-term outcomes.

Statistical analysis:

We used SPSS Version 20.0 (IBM Corporation ARMONK, NY, USA) for statistical analysis. All continuous variables were summarized using mean (SD) or median (IQR). Categorical variables were expressed in counts (%). We did a subgroup analysis by categorising the study sample based on the requirement for mechanical ventilation. We used Pearson Chi-Square test or Fisher's exact test for categorical variables and independent sample t-test or Mann-Whitney test for continuous variables. We used Bonferroni's correction for presenting p-values related to multiple comparisons.

Results:

Baseline Characteristics:

A total of 41 cases (males- 23) who were diagnosed with MIS-C and treated at the two tertiary care centers from March 2020 to April 2021 were enrolled in the study.

The mean age of onset was 6.2 (4.0) years. Thirty-three (80%) cases were previously healthy whereas 8 (20%) had co-existing comorbidities. Three (8%) cases were obese, and one was overweight. Three (7%) patients who had co-existing neurological disorders- two were on antiepileptic therapy for seizure disorder, while one had congenital hydrocephalus for which surgical intervention was done. One patient had a surgically corrected congenital heart disease and one had bronchial asthma controlled on inhaled long-acting beta-agonists. **(Supplementary table 1)**

A temporal link with COVID-19 infection was identified in all patients either in the form of serological testing or close contact with active COVID-19 case within preceding one month. Sixteen (39%) patients had a history of close contact with an active COVID-19 case. Two patients (5%) were having active COVID-19 infection when they developed MIS-C features, and 2 (5%) patients had previously confirmed acute COVID-19 infections and had recovered within the last 6 weeks. The first four cases (10%) did not undergo antibody assay due to regulatory restrictions on clinical use of antibody testing at that time. In the study, 28 (76%) patients were positive for COVID-19 IgG and 7 (19%) were positive for COVID-19 IgM antibody**. (Supplementary figure 1)**

The peak of COVID-19 cases was followed by a surge in the reporting of MIS-C in November- December 2020, when the active COVID-19 cases were on a decline. (**Figure 1A and figure 1B)**

Clinical Characteristics: (Table 1, figure 2A and figure 2B)

Fever was present in all patients, fatigue was in 27 (66%) and loss of appetite in 24 (59%). The most common organ system involved was the gastrointestinal (GI) system in 37 (90%) cases. Abdominal pain and diarrhea were the most common symptoms of GI involvement seen in 32 (78%) cases each followed by nausea or vomiting in 23 (56%) cases. Pancreatitis was noted in 2 (5%) cases, and one patient (2%) had presented with appendicitis. One patient presented as intussusception. During surgical reduction, the mesenteric lymph node was biopsied, and an ill formed granuloma and neutrophilic infiltrate were detected on histopathology.

The median duration of fever at the time of hospitalization was 4 days (IQR 3-5) and the mean duration of GI symptoms at the time of hospitalization was 3 (1.3) days.

The second most common manifestation was mucocutaneous involvement which was present in 36 (88%) cases. The most common mucocutaneous involvement was conjunctivitis in 29 (71%), which was bilateral nonexudative, and non-purulent. Rash was noted in 25 (61%) cases, was predominantly maculopapular rash over the trunk, extremities, and periorbital region. Oropharyngeal changes including red lips/ red tongue or cheilitis were present in 20 (49%) cases, and acro-ischemic lesion was noted in one case. [23]

Thirty-two (78%) patients had both GI and mucocutaneous involvement. Muscle aches or myalgias were reported in 27 (66%) cases.

Cardiovascular system was involved in 22 (54%) cases clinically and this manifested as the presence of shock requiring inotropic agents.

Neurological symptoms were present in 21 (51%) patients. Headache was reported in 10 (24%) and, meningismus in 6 (15%). Nineteen (46%) patients had either irritability, somnolence, or altered mental status, and one had ataxia.

Fifteen (37%) cases had lymphadenopathy either cervical or mesenteric. Cervical lymphadenopathy was noted on clinical examination and mesenteric lymphadenopathy was detected on radiological imaging.

Lower respiratory symptoms were present in 13 (31%) patients, shortness of breath in 12 (29%) and cough in 4 (10%). Upper respiratory symptoms were noted in 5 (12%) patients, sore throat in 3 (7%), and nasal congestion or rhinorrhoea was reported by 2 (5%). Peripheral extremity changes of edema of hands and feet were noted in 11 (27%) patients.

Table 1: Clinical characteristics of MIS-C cases across the age categories*

	Total (n=41) no. (%)	< 5 years (n=18) no. (%)	5-12 years (n= 19) no. (%)	>12-20 years (n=4) no. (%)
Males	23 (56)	9 (50)	11 (58)	3 (75)
Any constitutional symptoms	41 (100)	18 (100)	19 (100)	4 (100)
-Fever	41 (100)	18 (100)	19 (100)	4 (100)
-Fatigue	27 (66)	10 (56)	14 (73)	3 (75)
-Loss of Appetite	24 (59)	9 (50)	12 (63)	3 (75)
Any Gastrointestinal (GI) symptoms	37 (90)	16 (89)	17 (90)	4 (100)
- Abdominal Pain	32 (78)	12 (67)	16 (84)	4 (100)
- Diarrhoea	32 (78)	12 (67)	16 (84)	4 (100)
- Nausea or vomiting	23 (56)	11 (61)	8 (42)	4 (100)
- Pancreatitis ¶	2 (5)	0 (0)	1 (5)	1 (25)
- Appendicitis †	1 (2)	0 (0)	1 (5)	0 (0)
- Intussusception§	1 (2)	0 (0)	1 (5)	0 (0)
Duration of fever at the time of admission/ diagnosis (days) - median (IQR)	4.0 (3.0-5.0)	3.5 (2.8-5.0)	5.0 (3.0-7.0)	4.5 (3.3-5.0)
Duration of GI symptoms at the time of admission/diagnosis (days) mean ± SD	3.0 ± 1.3	2.6 ± 1.1	3.3 ± 1.5	3.0 ± 1.8
Any changes in peripheral extremities: -Swollen hands or feet/ Edema of extremities	11 (27)	5 (28)	5 (26)	1 (25)
Any mucocutaneous changes:	36 (88)	13 (72)	19 (100)	4 (100)

-Rash - Oropharyngeal changes (Red lips/ tongue/cheilitis) - Conjunctivitis - Acro ischemic lesions	25 (61) 20 (49) 29 (71) 1 (2)	9 (50) 6 (33) 9 (50) 1 (6)	13 (68) 10 (53) 16 (84) 0 (0)	3 (75) 4 (100) 4 (100) 0 (0)
Any gastrointestinal **and** any mucocutaneous changes/symptoms	32 (78)	11 (61)	17 (90)	4 (100)
Lymphadenopathy (Cervical /mesenteric)	15 (37)	5 (28)	7 (37)	3 (75)
Cardiovascular symptoms -Shock	 22 (54)	 7 (39)	 12 (63)	 3 (75)
Any neurological symptoms -Headache -Irritability/ somnolence/ altered mental status/ gait disturbance †† - Meningismus	21 (51) 10 (24) 19 (46) 6 (15)	8 (44) 2 (11) 7 (38) 1 (6)	10 (53) 5 (26) 9 (47) 4 (21)	3 (75) 3 (75) 3 (75) 1 (25)
Musculoskeletal symptoms - Muscle Aches/ myalgia	 27 (66)	 10 (56)	 14 (73)	 3 (75)
Any upper respiratory symptoms -Sore throat -Nasal congestion/ rhinorrhoea	5 (12) 3 (7) 2 (5)	0 (0) 0 (0) 0 (0)	5 (26) 3 (16) 2 (11)	0 (0) 0 (0) 0 (0)
Any lower respiratory symptoms -Shortness of breath /dyspnoea -Cough	13 (31) 12 (29) 4 (10)	5 (28) 5 (28) 0 (0)	5 (26) 4 (21) 2 (11)	3 (75) 3 (75) 2 (50)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

¶ The two patients who had pancreatitis, had severe abdominal pain and vomiting, one out of them was having severe multi-organ involvement including anuric acute kidney injury and succumbed on the day of admission itself.

† One patient had presented with abdominal pain, vomiting, and an appendicular lump on clinical and radiological assessment.

§ One patient had a clinical presentation of intussusception; she was subjected to surgical reduction of intussusception and the biopsy of which showed ill-formed granuloma and neutrophilic infiltrate.

††One patient had presented with fever, irritability, and ataxia; she was noted to have bilateral conjunctivitis and maculopapular skin rashes. COVID-19 associated cytotoxic lesion of the corpus callosum was found on subsequent neurological assessment.[24]

Laboratory investigations and cardiac assessment:

(Table 2 and table 3 cut off values of parameters used are listed in parentheses and footnotes of tables)

At the time of hospitalization anemia was noted in 20 (49%) patients, leukopenia in 2 (5%), lymphopenia in 26 (63%), thrombocytopenia in 13 (31%), and pancytopenia in 2 (5%) patients.

Among the inflammatory markers, C-reactive protein (CRP) was elevated in all cases; there was a marked elevation of CRP (>100mg/L) in 23 (56%) patients. Procalcitonin was done in 16 (39%) patients, and it was elevated in all. D-dimer was high in 40 (98%) patients, serum ferritin was high in 22 (54%) and hypoalbuminemia was noted in 31 (76%).

Transaminitis was noted in 19 (46%) patients, acute kidney injury was identified in 4 (10%) and hyponatremia in 9 (22%) during their hospital stay.

N-terminal pro B type natriuretic peptide (NT-proBNP) was done in 19 (46%). This was elevated in 18 (95%) patients. Troponin was done in 30 (73%) patients, it was elevated in 10 (33%). Fibrinogen was done in 11 (27%) and hypofibrinogenemia was noted in one patient. Erythrocyte sedimentation rate (ESR) was done in 14 (34%) and it was high in 10 (71%) patients.

Cardiac assessment with an electrocardiogram (ECG) and echocardiography was done in all patients. **Figure 2B** shows a graphical representation cardiac assessment finding. Abnormal ECG was noted in 8 (20%); bradycardia in 5 (12%), ST-T changes and complete heart block were noted in one patient each. Echocardiography was abnormal in 23 (56%) patients. Coronary artery abnormalities were noted in 15 (37%), only hyperechoic or non-tapering coronaries in 3 (7%), dilated coronaries in 4 (10%), and small coronary aneurysms in 8 (20%) patients.

Left ventricular dysfunction was found in 10 (24%) patients- mild to moderate in 9 (22%), and severe dysfunction was noted in one (2%). There was pericardial effusion in 10 (24%), mitral valve regurgitation in 6 (15%), and global or septal hypokinesia in 4 (10%) patients.

Table 2: Laboratory investigations of MIS-C cases across the age categories*¶

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12-20 years (n=4)
Hemogram at the time of presentation:				
Hemoglobin (Hb) g/L (Mean ± SD)	107.7 ± 16.2	103.0 ± 17.3	110.9 ± 12.3	106.0 ± 27.4
Total leukocyte count (TLC) 10^9/L (Mean ± SD)	11.2 ± 4.8	12.9 ± 5.4	10.5 ± 3.5	7.1 ± 4.6
Platelets (PLT) 10^9/L (Mean ± SD)	248 ± 167	303 ± 159	220 ± 176	131 ± 26
Anemia (Hb <110 g/L) - no. (%)	20 (49)	10 (56)	7 (37)	3 (75)
Leukopenia (TLC < 4.0 x 10^9 cells/L) - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Thrombocytopenia (PLT < 150 x 10^9 cells/L) - no. (%)	13 (31)	3 (17)	7 (37)	3 (75)
Pancytopenia† - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Lymphopenia†† - no. (%)	26 (63)	7 (39)	15 (19)	4 (100)
Peak values:				
CRP mg/L - Mean ± SD or Median (IQR)	119 ± 79	86 ± 63	145 ± 84	146 (64-234)
Positive CRP (>1 mg/L)	41 (100)	18 (100)	19 (100)	4 (100)
CRP (1-50) mg/L- no. (%) CRP (51-100) mg/L- no. (%) CRP (>100) mg/L- no. (%)	10 (24) 8 (20) 23 (56)	7 (39) 5 (28) 6 (33)	2 (11) 3 (16) 14 (73)	1 (25) 0 (0) 3 (75)
Procalcitonin µg/L - Median (IQR) no./total no. (%)	 8.9 (1.6-51.0) 16/41 (39)	 11.4 (1.5-54.2) 8/18 (44)	 3.7 (1.5-13.8) 5/19 (26)	 48 (7.2-53.0) 3/4 (75)
High Procalcitonin (>0.5 µg/L) - no./total no. (%)	16/16 (100)	8/8 (100)	5/5 (100)	3/3 (100)
Ferritin µg/L Median (IQR)	350 (170-733)	189 (98-429)	570 (266-961)	777 (180-1332)
High ferritin (>300 µg/L) - no./total no. (%)	22 (54)	7 (39)	13 (68)	2 (50)
D-dimer mg/L Median (IQR)	2.5 (1.1-4.3)	1.5 (0.9-3.3)	3.8 (1.5-5.2)	2.6 (1.6-4.2)
High D-dimer (> 0.5 mg/L) - no.(%)	40 (98)	18 (100)	18 (94)	4 (100)
Sodium mmol/L Mean ± SD	 135 ± 5	 135 ± 6	 135 ± 5	 137 ± 4
Hyponatremia (Sodium <135 mmol/L)- no.(%)	9 (22)	3 (17)	5 (26)	1 (25)

Albumin g/L (Mean ± SD)	28.6 ± 7.1	29.5 ± 6.9	28.3 ± 7.9	26.5 ± 4.7
Hypoalbuminemia (Albumin < 35g/L) -no.(%)	31 (76)	14 (78)	13 (68)	4 (100)
AST IU/L Median (IQR)	35.0 (27.0-76.5)	28.0 (22.5-47.5)	34.0(23.0-60.0)	110.0 (37.0-351.0)
ALT IU/L Median (IQR)	29.5 (22.3-51.0)	40.0 (27.5-63.5)	29.0 (20.0-45.0)	89.0 (35.5-442)
Transaminitis ‡ -no.(%)	19 (46)	9 (50)	7 (37)	3 (75)
Acute Kidney Injury (AKI) ‡‡	4 (10)	1 (6)	1 (5)	2 (50)
Sterile pyuria— no./total no. (%)	10/20 (50)	4/10 (40)	4/7 (57)	2/3 (67)
Proteinuria— no./total no. (%)	6/20 (30)	1/10 (10)	3/7 (43)	2/3 (67)
Troponin ng/L Median (IQR) -no./ total no. (%)	 16 (6.7-30.0) 30/41 (73)	 19 (6.0-41.2) 12/18 (67)	 10.2 (4.0-35.6) 14/19 (74)	 19.3 (14.5-27.4) 4/4 (100)
Elevated Troponin (>20 ng/L) -no./ total no. (%)	10/30 (33)	6/12 (50)	3/14 (21)	1/4 (25)
NT-ProBNP (pg/mL) Median (IQR) -no./ total no. (%)	 1845 (403-6840) 19/41 (46)	 4342 (815-7803) 8/18 (44)	 529 (248-4647) 9/19 (47)	 3530 (2679-4382) 2/4 (50)
Elevated NT-proBNP (>125 pg/mL) -no./ total no. (%)	18/19 (95)	8/8 (100)	8/9 (89)	2/2 (100)
Fibrinogen g/L Mean ± SD - no./total no. (%)	 3.9 ± 1.8 11/41 (27)	 3.5 ± 0.8 3/18 (17)	 4.2 ± 2.2 7/19 (37)	 3.37 1/4 (25)
Hypofibrinogenemia (Fibrinogen <2.0 g/L) -no./ total no. (%)	 1/11 (9)	 0/3 (0)	 1/7 (14)	 0/1 (0)
ESR mm/h Mean ± SD - no./total no. (%)	 33.4 ± 20.7 14/41 (34)	 35.3 ± 15.9 7/18 (39)	 41.2 ±24.4 5/19 (26)	 7.5 ± 0.7 2/4 (50)
High ESR (>20) - no./total no. (%)	10/14 (71)	6/7 (86)	4/5 (80)	0/2 (0)

* Percentages may not total 100 because of rounding.

¶ CRP denotes C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, ESR Erythrocyte sedimentation rate, IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

† Pancytopenia defined as hemoglobin <110 g/L, total leukocyte count < 4.0 x 10^9/L and platelets < 150 x 10^9/L.

†† Lymphopenia defined as <3000 lymphocytes/µL (<2 years age), <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

‡ Transaminitis defined as AST or ALT >40 IU/L.

‡‡ Acute Kidney Injury (AKI) is defined as any of the following: increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours[25].

Table 3: Cardiac assessment of MIS-C cases across the age categories*¶

	Total (n=41) no. (%)	< 5 years (n=18) no. (%)	5-12 years (n= 19) no. (%)	>12-20 years (n=4) no. (%)
Abnormal ECG	8 (20)	3 (17)	4 (21)	1 (25)
Bradycardia	5 (12)	1 (6)	3 (16)	1 (25)
Complete Heart Block §	1 (2)	1 (6)	0 (0)	0 (0)
ST T changes	1 (2)	0 (0)	1 (5)	0 (0)
Abnormal Echocardiography	23 (56)	11 (61)	9 (47)	3 (75)
Normal coronaries	26 (63)	9 (50)	14 (73)	3 (75)
Abnormal coronaries (Hyperechoic/ non tapering/ dilatated/ aneurysm)	15 (37)	9 (50)	5 (26)	1 (25)
Only hyperechoic / non tapering coronaries	3 (7)	3 (17)	0 (0)	0 (0)
Dilated coronaries	4 (10)	3 (17)	1 (5)	0 (0)
Small Aneurysm in coronaries	8 (20)	3 (17)	4 (21)	1 (25)
Systolic Dysfunction	10 (24)	3 (17)	6 (32)	1 (25)
Mild to moderate (LVEF 30-55%)	9 (22)	2 (11)	6 (32)	1 (25)
Severe (LVEF <30%)	1 (2)	1 (6)	0 (0)	0 (0)
Pericardial effusion	10 (24)	6 (33)	2 (11)	2 (50)
Global/septal hypokinesia	4 (10)	3 (17)	1 (5)	0 (0)
Mitral Valve regurgitation	6 (15)	3 (17)	2 (11)	1 (25)
Pulmonary Artery Hypertension	3 (7)	0 (0)	2 (11)	1 (25)

* Percentages may not total 100 because of rounding.

¶ ECG denotes Electrocardiogram and LVEF is left ventricular ejection fraction.

§One patient had presented with fever and drowsiness, noted to have complete heart block treated with a pacemaker, IVIG, and steroids however patient succumbed on the first day of admission itself.

Clinical course, treatment, and immediate outcomes: (Table 4)

A total of thirty-six (88%) patients required intensive care; the median duration of ICU stay was 3.5 days (IQR 3-5 days). Twenty-one (51%) patients required inotropes and mechanical ventilation was required in 8 (20%) cases. Treatment was provided as per the standard treatment guidelines for MIS-C.[6,26,27] Immunomodulatory therapy was administered to 39 (95%), steroids and IVIg both were used in 35 (85%) and only steroids were used in 3 (7%) patients. Antiplatelets were used in 37 (90%) and anticoagulation was used in 3 (7%) patients. Empirical broad-spectrum antibiotics were started for all the patients at the time of hospitalization and were discontinued after the blood and urine cultures were noted to be sterile. **(Supplementary figure 2)**

Two (5%) patients died during the treatment of the acute phase. The first patient was a 4 year old girl who was positive for both COVID-19 RTPCR and antibodies with a complete heart block.She continued to deteriorate despite use of pacemaker, mechanical ventilation, supportive care, and standard treatment for MIS-C. She expired on the same day of hospitalization. The second mortality was a 17 year old boy who had severe multi-organ dysfunction. He deteriorated rapidly despite prompt immunomodulation, hemodialysis, and mechanical ventilation. He died within 24 hours of hospitalization.

The mean duration of hospital stay was 8.2 (4.7) days, among the patients who recovered from MIS-C. Thirteen patients (32%) recovered with some residual sequelae, primarily echocardiographic abnormalities. Remaining 26 (63%) patients recovered without any residual changes at the time of discharge. **(Supplementary figure 3)**

Table 4: Clinical course, treatment, and immediate outcomes*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12 years (n=4)
Intensive care unit (ICU) requirement -no.(%)	36 (88)	15 (83)	18 (95)	3 (75)
Median duration of ICU stays among patients who required ICU in days (IQR)	3.5 (3.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-7.0)	4.0 (1.0-9.0)
Mechanical ventilation - no.(%) †	8 (20)	2 (11)	4 (21)	2 (50)
Median duration of mechanical ventilation in days among patients who required it (IQR)	3.0 (1.0-12.5)	8.0 (1.0-15.0)	4.0 (3.0-17.0)	1.0 (1.0-1.0)
Inotropic agent requirement - no.(%)	21 (51)	7 (39)	11 (58)	7 (39)
Median number of days patients were on inotropes among the patients it was used (IQR)	2.0 (2.0-3.0)	3.0 (1.8-6.0)	2.0 (2.0-3.0)	2.0 (0.5-2.0)
Aspirin low dose	37 (90)	16 (89)	18 (96)	3 (75)
IVIG	36 (88)	15 (83)	18 (95)	3 (75)
Repeat IVIG	1 (2)	1 (6)	0 (0)	0 (0)
Steroids	38 (93)	16 (89)	18 (100)	4 (100)
Steroids and IVIG	35 (85)	15 (83)	17 (90)	3 (75)
Anticoagulation	3 (7)	1 (6)	1 (5)	1 (25)
Mean length of hospital stay excluding deaths (days) ± SD	8.2 ± 4.7	8.0 ± 6.1	8.1 ± 3.1	10.3 ± 43.5
Immediate outcome (At the time of discharge)				
Recovered with sequalae	13 (32)	5 (28)	7 (37)	1 (25)
Recovered without sequalae	26 (63)	12 (67)	12 (63)	2 (50)
Death	2 (5)	1 (6)	0 (0)	1 (25)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

† Only non-invasive mechanical ventilation was used in one patient in >12 years age group, all others required invasive mechanical ventilation.

Follow up at 6 weeks after discharge:

All discharged patients (n=39) remained clinically stable during 6 weeks follow up. There was no abnormality on clinical assessment in any case. Echocardiographic assessments showed improvement trend in all patients. Eight (21%) patients had persisting coronary alterations on echocardiogram at 6 weeks- hyperechoic or non-tapering thick-walled coronaries in 5 (13%), coronary dilation in 2 (5%) and small coronary aneurysm in one patient. However, the echocardiographic coronary alterations had improved from their baseline status during the acute illness. Persisting mild left ventricular systolic dysfunction and pulmonary artery hypertension (PAH) were noted in one case each. **(Supplementary table 2)**

Medium-term outcome at 3 months follow-up: (Table 5)

Thirty-seven patients finished their 3 months follow-up by April 2021. All patients were clinically stable, echocardiographic changes were improving in all of them. At 3 months follow up 4 (11%) patients were on Aspirin for residual coronary changes, one patient was on diuretics for left ventricular dysfunction, and one patient was on Phosphodiesterase-5 inhibitors for PAH.

Table 5: Cardiac outcomes at 3 months follow up (n=37)*¶

	Total (n= 37) no. (%)	< 5 years (n=17) no. (%)	5-12 years (n= 17) no. (%)	>12 years (n=3) no. (%)
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal Coronaries	4 (11)	3 (18)	1 (6)	0 (0)
Hyperechoic / non tapering coronaries	2 (5)	2 (12)	0 (0)	0 (0)
Dilatation	1 (3)	1 (6)	0 (0)	0 (0)
Small Aneurysm	1 (3)	0 (0)	1 (6)	0 (0)
LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
PAH	1 (3)	0 (0)	1 (6)	0 (0)
Recovered with sequalae ¶¶	6 (16)	3 (18)	3 (18)	0 (0)
Ongoing treatment in any form at 3 months follow up	6 (16)	3 (18)	3 (24)	0 (0)
Aspirin	4 (11)	2 (12)	3 (18)	0 (0)
Treatment of LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
Treatment of PAH	1 (3)	0 (0)	1 (6)	0 (0)

* Percentages may not total 100 because of rounding.

¶ Only 37 patients had finished their 3 months follow-up by April 2021. LV dysfunction denotes- left ventricular dysfunction and PAH is pulmonary arterial hypertension.

¶¶ Sequalae refers to any residual structural or functional cardiac abnormality on echocardiography.

Comparison of MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation: (Table 6)

We categorised MIS-C patients into two groups based on requirement of mechanical ventilation. We did a subgroup analysis using various clinical, laboratory and echocardiographic parameters (**table 6)**. Only hyperferritinemia was significantly associated with requirement of mechanical ventilation (p = 0.001).

Table 6: Bivariate Comparison of various clinical and laboratory parameters in MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation*

Clinical and laboratory parameters of MIS-C cases	Mechanical ventilation required (n = 8)	Mechanical ventilation not required (n = 33)	p-value ‡
Presence of shock requiring inotropic agents – no. (%)	7 (88)	14 (42)	0.045
Median D-dimer mg/L (IQR)	4.5 (2.9-16.3)	2.3 (1.0-3.9)	0.016
Median serum ferritin µg/L (IQR)	1178.0 (717.0-23840.0)	266.0 (153.0-555.0)	**0.001**
Median ESR mm/h (IQR) - no./total no. (%)	8.0 (7.0-10.0) 3/8 (38)	40 (27-51) 11/33 (33)	0.016
Median serum AST IU/L (IQR)	188.0 (37.8-741.2)	33.0 (26.0-60.5)	0.008
Median serum procalcitonin µg/L (IQR) - no./total no. (%)	5.4 (2.1-41.5) 4/8 (50)	11.1(1.6- 51.0) 12/33 (36)	0.716
Median serum NT-proBNP pg/mL (IQR) - no./total no. (%)	3533.5 (2141.5-46767.5) 6/8 (75)	1138.0 (349.0-6725.0) 13/33 (39)	0.096
Median serum troponin ng/L (IQR) - no./total no. (%)	55.2 (14.5-945.3) 4/8 (50)	15.0 (4.8-29.2) 26/33 (78)	0.143
Median absolute lymphocyte count (IQR)	825 (521-2218)	1588 (895-3489)	0.061
Lymphopenia at admission -no. (%)§	7 (88)	19 (58)	0.220
Mean CRP mg/L ± SD	101.0 ± 85.3	123 ± 78.9	0.474
Median serum ALT IU/L (IQR)	141.0 (25.0-543.0)	29.0 (21.0-43.5)	0.113
Presence of coronary abnormalities - no. (%)	4 (50)	11 (33)	0.434
Presence of LV dysfunction - no. (%)	3 (38)	7 (21)	0.378

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, CRP C-reactive protein, SD standard deviation, and ALT alanine aminotransferase.

‡ p-value was calculated by applying appropriate statistical tests according to the distribution of the data. Independent sample t-test or Mann-Whitney tests were applied to compare the potential markers of severity. The Bonferroni's correction was applied for multiple comparisons. A p-value of <0.0035 was considered statistically significant.

§ Lymphopenia defined as <3000 lymphocytes/µL (<2 years age), <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

Discussion:

In this study, we have described 41 cases of MIS-C associated with COVID-19. The patients were treated at two tertiary care centers (Kerala,India) from March 2020 to April 2021. **Figure 3** shows a heat map of syndrome clusters in MIS-C cases in our study.

We compared our study results with those of a systematic review by *Ahmed* et al. which involved 662 cases of MIS-C from 39 studies.[9] Similarities were noted on constitutional symptoms (100% *v* 100%), intensive care requirement (88% *v* 71%), mechanical ventilation requirement (20% *v* 22%), inotrope requirement (51% *v* 60%), and mean length of hospital stay (8.2 days *v* 7.9 days). Laboratory parameters reflecting inflammatory, coagulative, and cardiac involvement were also similar. However, there were striking differences in our cohort which included a large number of previously healthy individuals (80% in our study *v* 52% in *Ahmed* et al.). We had a smaller proportion of overweight or obese cases (10% *v* 24%), younger age of onset (mean age 6.2 years *v* 9.3 years), high frequency of conjunctivitis (71% *v* 51%), more common myalgia (66% *v* 13%), more cases with irritability /somnolence (46% *v* 10%), more number of cases with lymphadenopathy (37% *v* 14%), and more frequent coronary dilation and aneurysms (29% *v* 15%). Systolic dysfunction was less frequent in our cohort (24% *v* 45%).[9]

We had smaller number of patients in the age group of more than 12 years in comparison with the two largest cases series from the USA (10% in our study *v* 24% *and* 26%).[28,29]

There are two case series of MIS-C are reported from India. In comparison with a series of 19 MIS-C patients from Chennai our cohort had more frequent gastrointestinal symptoms (90% in our study *v* 42%), a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 58%), and more common coronary involvement (37% *v* 16%).[30] Comparing with another case series of 23 MIS-C patients from Mumbai, we observed a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 39%), higher frequency of abdominal pain (78% *v* 52%), and conjunctivitis (71% *v* 52%).[31] Other available clinical and laboratory parameters from these two studies were similar to our study.

Because of the similarities in clinical phenotype to KD, we compared our results with existing literature on KD. We noticed that percentage of cases developing coronary artery aneurysms in our MIS-C cases were less than that of untreated KD (20% *v* 25%) but more than of that KD treated with optimum IVIG (20% *v* 5%). IVIG resistance or requirement of a second dose of IVIG or alternative immunotherapy was less frequent in MIS-C in comparison to KD (2% *v* 10%).[32,33] However, none of our current MIS-C cohort patients developed medium-sized or giant coronary aneurysm or thrombosis of coronary in contrast to KD where it is reported in 1% of treated cases.[34]

While it is gratifying to note that most cases remained clinically well at 3 months follow-up, the persistence of echocardiographic abnormalities in 6 patients emphasises the need for careful follow-up.

The only other published report on intermediate-term follow-up following MIS-C is a recently published study by *Penner* et al. that reports outcomes at 6 months following MIS-C in a single center cohort from the UK.[35] There was similarity in context to full subsidence of inflammation (100% in our study *v* 98% in *Penner* et al.). The difference in near-complete resolution of echocardiographic sequelae (84% in our study *v* 96%) could be due to our 3-month follow-up versus the 6-month follow-up in the aforementioned study. The striking difference was that in our cohort none of the patients had persistent gastrointestinal symptoms, mucocutaneous changes, or minor neurological abnormalities as reported in the above-mentioned study.

MIS-C requires a high index of suspicion for diagnosis and warrants prompt treatment. There is a paucity of literature in MIS-C to define severe and non-severe cases and prediction of severity in a given case. As all of the MIS-C cases required hospitalization, most of these required intensive care, and mechanical ventilation was required in 20% patients. We found that hyperferritinemia was associated with the requirement of mechanical ventilation in MISC patients. Our findings are in alignment with a retrospective surveillance study from USA which enrolled 1090 patients of MIS-C. [36] They reported that high ferritin in addition to high NT-ProBNP, and high D-dimer increases the odds of severe outcomes and the need for intensive care.[36]

As the study was conducted at two tertiary care centres it might underestimate the mild cases and could be skewed towards high morbidity and mortality due to referral bias.

Conclusions:

MIS-C is a new disease in context to COVID-19 pandemic and we are still continuing to learn about this clinical syndrome.

While the clinical profile of our cohort has largely been similar to world-wide reports, we observed a few differences in our cohort like younger age at onset, more mucocutaneous changes and a smaller number of patients with co-existent comorbidities. Risk factors for the development of severe MIS-C remain unknown, however, we found that requirement of mechanical ventilation was associated with hyperferritinemia.

We observed echocardiographic sequalae in one third of patients at the time of discharge, which reduced to one in six at three months follow up. Overall immediate and medium-term outcomes remain largely excellent. Ongoing follow-up for several years to study the disease's natural history is certainly warranted.

What is already known on this topic:

1. MIS-C is a rare but critical association of COVID-19 infection in children.
2. MIS-C is known to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease-like phenotype, and macrophage activation syndrome.

What this study adds:

1. In our cohort of MIS-C, patients presented at a younger age with more frequent mucocutaneous changes and lesser comorbidities as compared to western studies.
2. The medium-term outcome of MIS-C patients is excellent; however, we need to monitor echocardiogram at subsequent follow up visits in selected patients.
3. We were able to associate hyperferritinemia with requirement of mechanical ventilation in MIS-C patients.

References:

1 WHO Coronavirus (COVID-19) Dashboard. Covid19.who.int. 2021. https://covid19.who.int (accessed 13 August, 2021).

2 Sanna G, Serrau G, Bassareo PP, *et al.* Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. *European Journal of Pediatrics* 2020 May 30;179 1079-87. doi:10.1007/s00431-020-03699-0

3 Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet* 2020;**395**:1771–8. doi:10.1016/S0140-6736(20)31103-X

4 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;**395**:1607–8. doi:10.1016/S0140-6736(20)31094-1

5 Jones VG, Mills M, Suarez D, *et al.* COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hospital Pediatrics* 2020;**10**. doi:10.1542/hpeds.2020-0123

6 Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians.RCPCH.2021. https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance / (accessed on 2 June, 2021).

7 Centers for Disease Control and Prevention. Multisystem inflammatory syndrome. 2020. https://www.cdc.gov/mis-c/hcp/ (accessed 21 April, 2021).

8 Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.Who.int.2021.https://www.who.int/newsroom/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (accessed on 2 June 2021).

9 Ahmed M, Advani S, Moreira A, *et al.* Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine* 2020;**26**. doi:10.1016/j.eclinm.2020.100527

10 Rubens JH, Akindele NP, Tschudy MM, *et al.* Acute covid-19 and multisystem inflammatory syndrome in children. *The BMJ* 2021;**372**. doi:10.1136/bmj.n385

11 Hamming I, Timens W, Bulthuis MLC, *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology* 2004;**203**:631–7. doi:10.1002/path.1570

12 Liu J, Li S, Liu J, *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. medRxiv. 2020. doi:10.1101/2020.02.16.20023671

13 Li H, Liu L, Zhang D, *et al.* SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;**395**:1517–20. doi:10.1016/S0140-6736(20)30920-X

14 Jiang L, Tang K, Levin M, *et al.* COVID-19 and multisystem inflammatory syndrome in children and adolescents. *The Lancet Infectious Diseases* 2020;**3099**. doi:10.1016/S1473-3099(20)30651-4

15 Khadilkar V, Yadav S, Agrawal KK, *et al.* Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. *Indian Pediatrics* 2015;**52**. doi:10.1007/s13312-015-0566-5

16 Obesity and overweight. Who.int. 2021.https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 2 June 2021).

17 Lai WW, Geva T, Shirali GS, *et al.* Guidelines and Standards for Performance of a Pediatric Echocardiogram: A Report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *Journal of the American Society of Echocardiography* 2006;**19**. doi:10.1016/j.echo.2006.09.001

18 Lopez L, Colan SD, Frommelt PC, *et al.* Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *Journal of the American Society of Echocardiography* 2010;**23**. doi:10.1016/j.echo.2010.03.019

19 McCrindle BW, Li JS, Minich LL, *et al.* Coronary Artery Involvement in Children With Kawasaki Disease. *Circulation* 2007;**116**. doi:10.1161/CIRCULATIONAHA.107.690875

20 Manlhiot C, Millar K, Golding F, *et al.* Improved Classification of Coronary Artery Abnormalities Based Only on Coronary Artery z-Scores After Kawasaki Disease. *Pediatric Cardiology* 2010;**31**. doi:10.1007/s00246-009-9599-7

21 Khanna G, Sargar K, Baszis KW. Pediatric Vasculitis: Recognizing Multisystemic Manifestations at Body Imaging. *RadioGraphics* 2015;**35**. doi:10.1148/rg.2015140076

22 Shenoy B, Singh S, Zulfikar Ahmed M, *et al*. Recommendations Indian Academy of Pediatrics Position Paper on Kawasaki Disease. *Indian Pediatrics*. 2020 May 28;**57.** doi:10.1007/s13312-020-2033-1

23 Kappanayil M, Balan S, Alawani S, *et al.* Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: a case report. *The Lancet Child & Adolescent Health* 2021;**5**. doi:10.1016/S2352-4642(21)00055-9

24 Lin J, Lawson EC, Verma S, *et al.* Cytotoxic lesion of the corpus callosum in an adolescent with multisystem inflammatory syndrome and SARS-CoV-2 infection. *American Journal of Neuroradiology* 2020;**41**:2017–9. doi:10.3174/ajnr.A6755

25 Kellum JA, Lameire N, Aspelin P, *et al.* Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012;**2**:1–138. doi:10.1038/kisup.2012.1

26 Hennon TR, Penque MD, Abdul-Aziz R, *et al.* COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. Progress in Pediatric Cardiology. 2020;**57**. doi:10.1016/j.ppedcard.2020.101232

27 Henderson LA, Canna SW, Friedman KG, *et al.* American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis and Rheumatology* 2020;**72**:1791–805. doi:10.1002/art.41454

28 Feldstein LR, Rose EB, Horwitz SM, *et al.* Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine* 2020;**383**. doi:10.1056/NEJMoa2021680

29 Riollano-Cruz M, Akkoyun E, Briceno-Brito E, *et al.* Multisystem Inflammatory Syndrome in Children (MIS-C) Related to COVID-19: A New York City Experience. *Journal of Medical Virology* 2020;:0–3. doi:10.1002/jmv.26224

30 Dhanalakshmi K, Venkataraman A, Balasubramanian S, *et al.* Epidemiological and Clinical Profile of Pediatric Inflammatory Multisystem Syndrome-Temporally Associated with SARS-CoV-2 (PIMS-TS) in Indian Children. *Indian Pediatrics*. 2000 Nov 15;**57**(11):1011-14. doi:10.1007/s13312-020-2025-1

31 Jain S, Sen S, Lakshmivenkateshiah S, *et al.* Multisystem Inflammatory Syndrome in Children With COVID-19 in Mumbai, India. *Indian Pediatrics*. 2020 Nov. 15;**57**(11):1015-1019. doi: 10.1007/s13312-020-2026-0

32 McCrindle BW, Rowley AH, Newburger JW, *et al.* Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;**135**. doi:10.1161/CIR.0000000000000484

33 Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2019;**140**. doi:10.1161/CIR.0000000000000703

34 Dajani AS, Taubert KA, Takahashi M, *et al.* Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;**89**. doi:10.1161/01.CIR.89.2.916

35 Penner J, Abdel-Mannan O, Grant K, *et al.* 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *The Lancet Child & Adolescent Health* Published Online First: May 2021. doi:10.1016/S2352-4642(21)00138-3

36 Abrams JY, Oster ME, Godfred-Cato SE, *et al.* Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *The Lancet Child & Adolescent Health* 2021;**5**:323–31. doi:10.1016/s2352-4642(21)00050-x

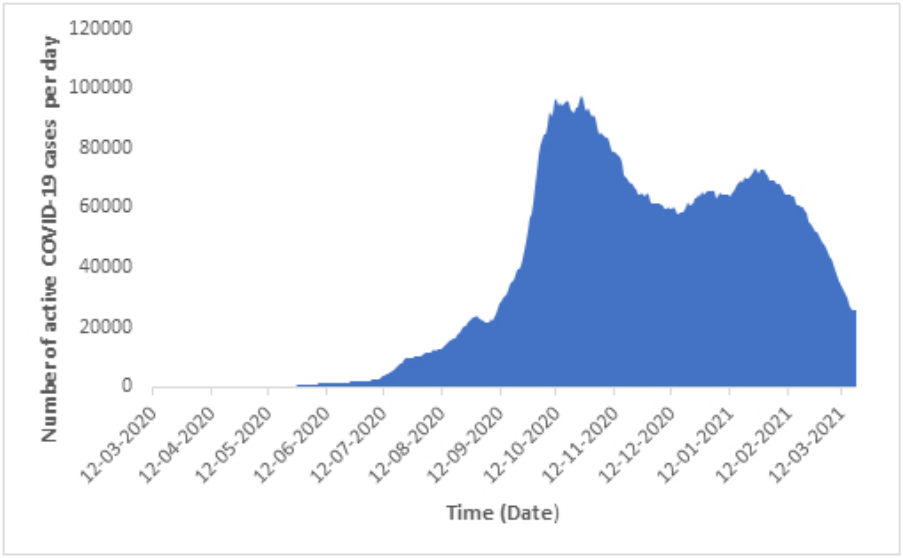
Captions for figures:

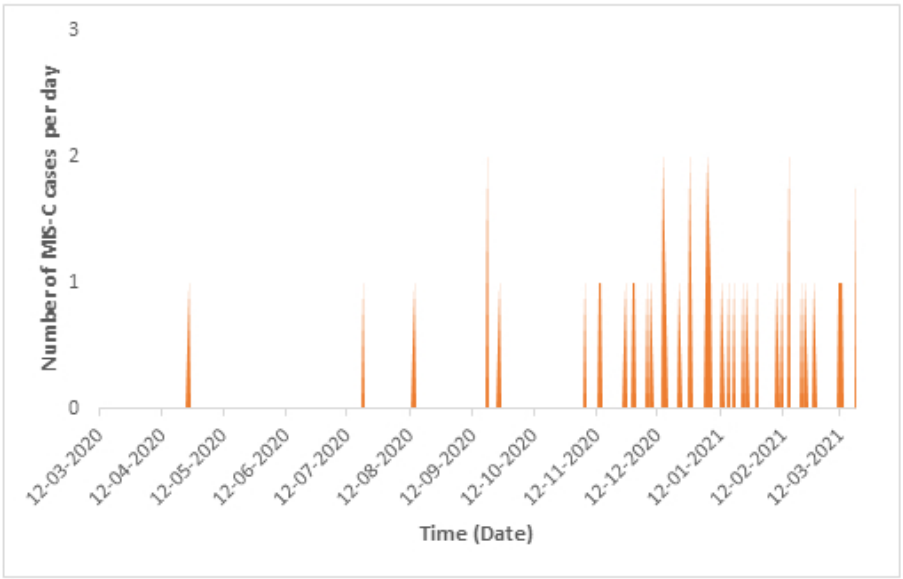
Figure 1: Temporal correlation of active COVID-19 cases (A) and MIS-C cases (B) in the Southern Indian state Kerala

Figure 2: Frequency of symptoms in MIS-C cases (A) and cardiac assessment during acute phase of MIS-C (B)

Figure 3: Heat map of syndrome clusters based on clinical presentations

(Percentages may not total 100 because of rounding and overlapping clinical features)





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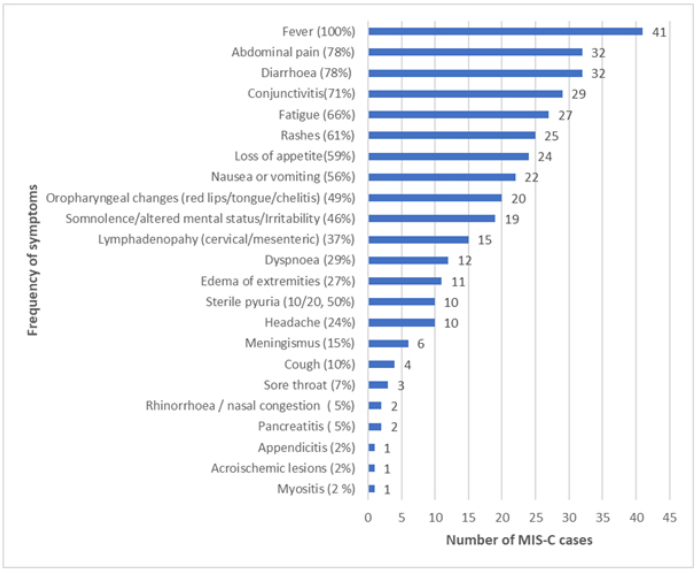

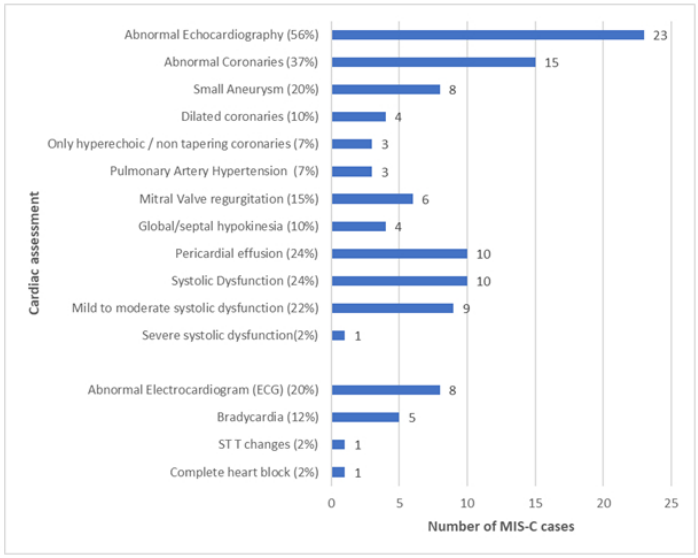

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	< 5 years (n=18) -no. (%)	5-12 years (n= 19) -no. (%)	>12 years (n= 4) -no. (%)
Dermatological/ mucocutaneous	13 (72)	19 (100)	4 (100)
Gastrointestinal symptoms	16 (89)	17 (90)	4 (100)
Incomplete/ atypical Kawasaki disease	13 (72)	15 (79)	3 (75)
Shock	7 (39)	12 (63)	3 (75)
Macrophage activation syndrome like features	6 (33)	7 (37)	4 (100)
Neurological symptoms	7 (39)	6 (32)	2 (50)
Respiratory Symptoms	4 (22)	1 (5)	2 (50)

1-5%	6-25%	26-50%	51-75%	76-100%

378x203mm (38 x 38 DPI)

Supplementary Table 1: Demographic and baseline characteristics*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12- 20 years (n=4)
Males – no.(%)	23 (56)	9 (50)	11 (58)	3 (75)
Body habitus – no.(%)**				
- Underweight	3 (7)	1 (6)	2 (11)	0 (0)
- Normal weight	34 (83)	17 (94)	15 (79)	2 (50)
- Overweight	1 (2)	0 (0)	0 (0)	1 (25)
- Obese	3 (7)	0 (0)	2 (11)	1 (25)
Presence of comorbidities- no. (%)				
- Any	8 (20)	2 (11)	3 (16)	1 (25)
- Obesity or overweight	4 (10)	0 (0)	1 (5)¶	1 (25)
- Cardiovascular disorders†	1 (2)	0 (0)	1 (5)	0 (0)
- CNS disorders§	3 (7)	2 (11)	1 (5)	0 (0)
- Chronic lung disease‡	1 (2)	0 (0)	1 (5)	0 (0)

*Percentages may not total 100 because of rounding. BMI = Body Mass Index, CNS = Central Nervous System

** BMI based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups >5 years of age. For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and obesity was defined as weight-for-height greater than 3 standard deviations above the WHO child growth standards median. Underweight was defined in terms of weight for age using the WHO child growth standards for children below 5 years of age and using IAP WHO combined BMI growth charts for older children.

† One patient had large atrial and ventricular septal defects which were closed surgically.

§ Among 3 patients with CNS disorders, two had a seizure disorder, and one had hydrocephalus requiring surgical intervention.

¶ One patient of seizure disorder was obese as well.

‡ One patient had bronchial asthma controlled on inhaled steroids and long-acting beta-agonists.

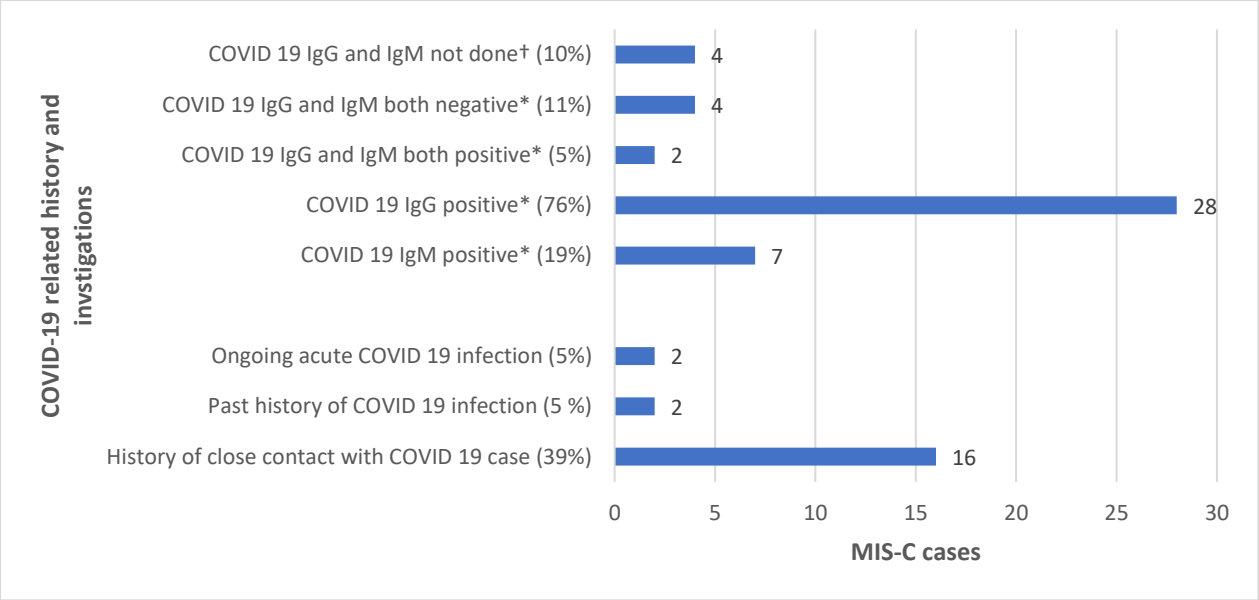
Supplementary table 2: Cardiac outcomes in 6 weeks follow up (n=39) §

	Total (n= 39) no. (%)*	< 5 years (n=17) no. (%)*	5-12 years (n= 19) no. (%)*	>12 years (n=3) no. (%)*
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal coronaries	8(21)	4(24)	4(21)	0 (0)
Hyperechoic/ non-tapering coronaries	5(13)	3(18)	2(11)	0 (0)
Dilatation	2(5)	1(6)	1(5)	0 (0)
Small Aneurysm	1(3)	0 (0)	1(5)	0 (0)
LV dysfunction	1(3)	1(6)	0 (0)	0 (0)
PAH	1(3)	0(0)	1(5)	0 (0)

§ Two patients had expired during the acute phase of MISC.

* Percentages may not total 100 because of rounding.

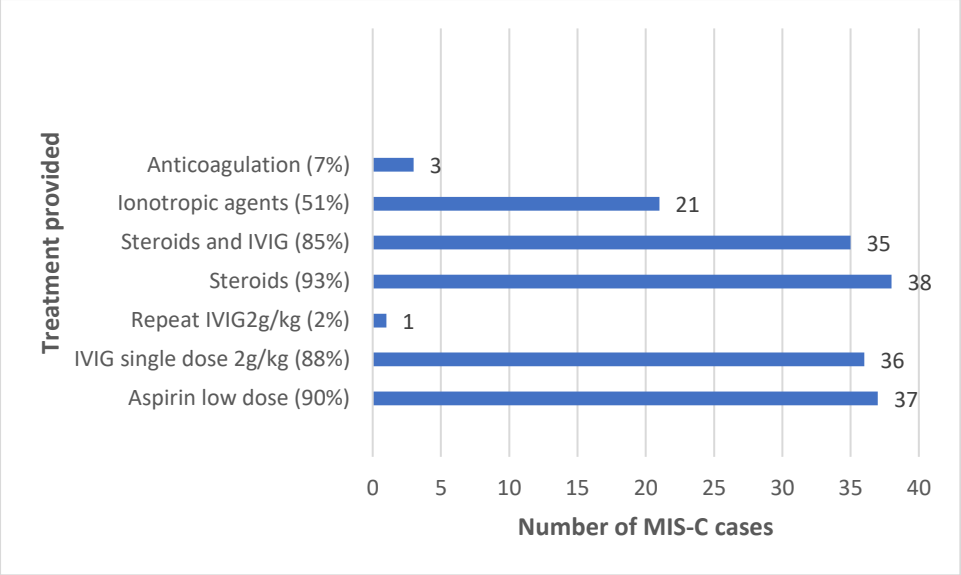
Supplementary figures:



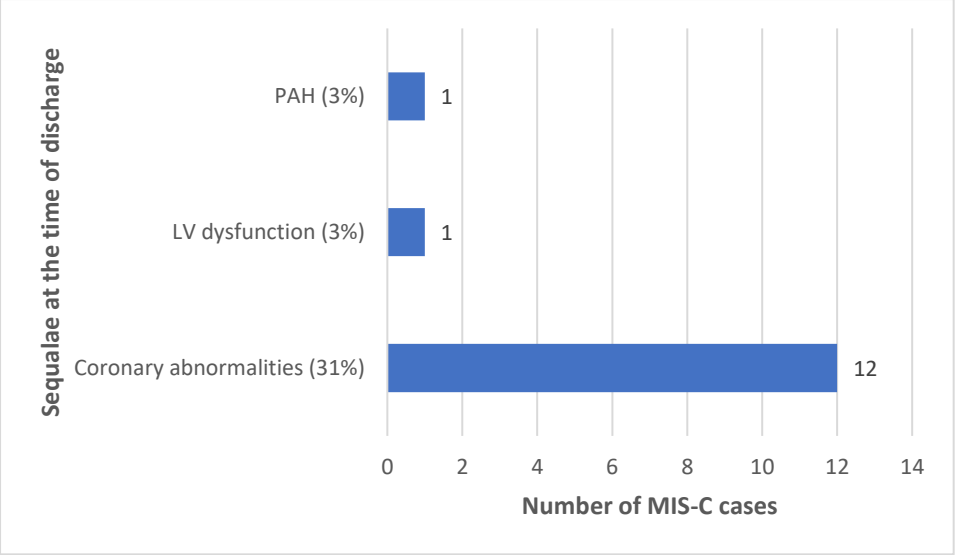
Supplementary figure 1: COVID 19 related history and investigations

† These cases were diagnosed before September 2020 when the COVID antibodies were available at our centers.

* Investigations are not mutually exclusive.



Supplementary figure 2: Treatment provided to MIS-C cases



Supplementary figure 3: Sequalae at the time of discharge (n =39)

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COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

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Title page

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Contributorship Statement: AT took the lead in data curation, formal analysis, software and writing original draft. SB and AR took the lead in conceptualization. SB took the lead in project administration, investigations, resources, and supervision. MR, SB and MK took lead in writing review and editing the manuscript. AR, MK, MR, SK, SS, AV, PC, AV, SJ, SC, RK, and AS provided critical feedback in conceptualization, methodology, drafting and revisions which helped to shape the manuscript.

Ethics statement: This study was approved by the institutional ethics committee- Institutional Review Board of Amrita Institute of Medical Sciences (IRB-AIMS-2020-335) which involved public representatives as well. A written informed consent was obtained from the parents of study participants.

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

Abstract:

Objectives: To study (i) epidemiological factors, clinical profile, and outcomes of COVID-19 related multisystem inflammatory syndrome in children (MIS-C) (ii) clinical profile across age groups, (iii) medium-term outcomes and (iv) parameters associated with disease severity.

Design: Hospital-based prospective cohort study.

Setting: Two tertiary care centers in Kerala, India.

Participants: Diagnosed patients of MIS-C using the case definition of Centres for Disease Control and Prevention.

Statistical analysis: Pearson Chi-Square test or Fisher's exact test was used to compare the categorical variables and independent sample t-test or Mann-Whitney test was used to compare the continuous variables between the subgroups categorised by the requirement of mechanical ventilation. Bonferroni's correction was used for multiple comparisons.

Results: We report 41 patients with MIS-C, mean age was 6.2 (4.0) years, and 33 (80%) were previously healthy. Echocardiogram was abnormal in 23 (56%), and coronary abnormalities were noted in 15 (37%) patients. Immunomodulatory therapy was administered to 39 (95%), steroids and IVIg both were used in 35 (85%) and only steroids in 3 (7%) patients. Intensive care was required in 36 (88%), mechanical ventilation in 8 (20%), inotropic support in 21 (51%), and 2 (5%) patients died. Mechanical ventilation requirement in MIS-C was associated with hyperferritinemia (p=0.001).Thirty-seven patients completed 3 months follow-up by April 2021, of whom 6(16%) patients had some residual echocardiographic changes.

Conclusions: MIS-C patients in our cohort had varied clinical manifestations ranging from fever with mild gastrointestinal and mucocutaneous involvement to fatal multiorgan dysfunction. Immediate and medium-term outcomes remain largely excellent except for the echocardiographic sequelae in a few patients which are also showing a resolving trend. Hyperferritinemia was associated with the requirement of mechanical ventilation.

Original research

Title: COVID-19 related multisystem inflammatory syndrome in children (MIS-C) – A hospital based prospective cohort study from Kerala, India

Introduction:

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS -CoV-2) is rapidly evolving. As of August 13, 2021, there have been 205,338,159 confirmed cases of coronavirus disease 2019 (Covid-19) globally, including 4,333,094 deaths.[1] Earlier studies reported that COVID-19 infection in children was either asymptomatic or mild with only a small proportion requiring hospitalization and lesser mortality as compared to adults.[2]

In May 2020 several European countries reported clusters of hyperinflammatory processes in children with clinical manifestations of atypical Kawasaki disease and shock and the possibility of its link with SARS-CoV-2 was considered.[3–6] Later, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) released health advisories and defined these cases as multisystem inflammatory syndrome in children (MIS-C) associated with Covid-19.[7,8] MIS-C is a rare but severe and potentially fatal condition.[9,10]

The pathogenesis of MIS-C is not well understood. It is known that SARS-CoV-2 enters cells by binding to angiotensin-converting enzyme 2, which is highly expressed in cardiac myocytes, alveolar cells, vascular endothelium, and a small subset of immune cells[11]. Evidences suggest that dysregulated innate immune response leading to cytokine storm and endothelial damage might be responsible for multiorgan failure in severe Covid-19 and MIS -C.[12–14]

MIS-C is reported to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease (KD) like phenotype, and Macrophage activation syndrome (MAS). It is a syndromic presentation with overlapping clinical features of KD, sepsis, toxic shock syndrome, and meningitis.[9,14] Moreover, there is no diagnostic test and the risk factors for the development of MIS-C remain unknown.

There is a paucity of data from the Indian subcontinent regarding the clinical course of MIS-C. In this study, we have described clinical profile, medium-term outcomes, varied clinical features in different age groups, and factors associated with severe illness in 41 patients diagnosed with MIS-C from southern Indian state of Kerala.

Methods:

Study design:

This was a hospital-based prospective cohort study conducted at two tertiary care centers from the Kerala state of India, from March 2020 to April 2021. The primary objective of this study was to report the baseline characteristics, clinical features, laboratory parameters, echocardiographic findings, treatment, and immediate outcomes of cases admitted with MIS-C. The secondary objectives were (i) to study the clinical presentation and response to therapy across age groups, (ii) to report the medium-term outcomes of MIS-C, and (iii) to report the predictors of severity in MIS-C.

Patient and public involvement:

The study was approved by the institutional ethics committee- Institutional Review Board of Amrita Institute of Medical Sciences (IRB-AIMS-2020-335) which involved public representatives as well. A written informed consent was obtained from the parents of study participants. Patients were not involved in the designing of the study.

Study definitions:

We used the CDC case definition to define a case of MIS-C.[7] Body mass index (BMI)-based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups comprising of patients more than 5 years of age.[15] For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 SD above WHO child growth standards median; and obesity was defined as weight-for-height greater than 3 SD above the WHO child growth standards median.[16]

Systolic dysfunction was defined by reduced left ventricular ejection fraction (LVEF) . Systolic dysfunction was categorized as mild to moderate when LVEF was 30%-55% and as severe if LVEF was less than 30 %.[17,18]

Echocardiography Z-scores were calculated using Mc Crindle et al. formula using body surface area.[19] Coronary artery abnormalities (CAA) were classified according to the Z-scores on echocardiography.[20] Echocardiographic appearance of hyperechogenicity and non-tapering morphology were also noted as abnormalities.[21]

For this study, “Incomplete KD” was defined as the presence of fever with less than 4 out of the 5 principal clinical criteria with compatible laboratory or echocardiography findings.[22] Children who along with the usual clinical features of KD also had few unusual clinical manifestations like pulmonary involvement and renal impairment were labeled “atypical KD”.[22]

Categorization of children with MIS-C

Patients were categorised into three groups based on age (<5, 5-12 and 12-20 years) for subgroup comparisons. All patients were further categorised based on the requirement for mechanical ventilation. All children with MIS-C who had any residual clinical, laboratory, or echocardiographic changes at the time of discharge were labeled as “recovered with sequelae ”. The discharged patients were followed up at 6 weeks and 12 weeks to report the medium-term outcomes.

Statistical analysis:

We used SPSS Version 20.0 (IBM Corporation ARMONK, NY, USA) for statistical analysis. All continuous variables were summarized using mean (SD) or median (IQR). Categorical variables were expressed in counts (%). We did a subgroup analysis by categorising the study sample based on the requirement for mechanical ventilation. We used Pearson Chi-Square test or Fisher's exact test for categorical variables and independent sample t-test or Mann-Whitney test for continuous variables. We used Bonferroni's correction for presenting p-values related to multiple comparisons.

Results:

Baseline Characteristics:

A total of 41 cases (males- 23) who were diagnosed with MIS-C and treated at the two tertiary care centers from March 2020 to April 2021 were enrolled in the study.

The mean age of onset was 6.2 (4.0) years. Thirty-three (80%) cases were previously healthy whereas 8 (20%) had co-existing comorbidities. Three (8%) cases were obese, and one was overweight. Three (7%) patients who had co-existing neurological disorders- two were on antiepileptic therapy for seizure disorder, while one had congenital hydrocephalus for which surgical intervention was done. One patient had a surgically corrected congenital heart disease and one had bronchial asthma controlled on inhaled long-acting beta-agonists. **(Supplementary table 1)**

A temporal link with COVID-19 infection was identified in all patients either in the form of serological testing or close contact with active COVID-19 case within preceding one month. Sixteen (39%) patients had a history of close contact with an active COVID-19 case. Two patients (5%) were having active COVID-19 infection when they developed MIS-C features, and 2 (5%) patients had previously confirmed acute COVID-19 infections and had recovered within the last 6 weeks. The first four cases (10%) did not undergo antibody assay due to regulatory restrictions on clinical use of antibody testing at that time. In the study, 28 (76%) patients were positive for COVID-19 IgG and 7 (19%) were positive for COVID-19 IgM antibody**. (Supplementary figure 1)**

The peak of COVID-19 cases was followed by a surge in the reporting of MIS-C in November-December 2020, when the active COVID-19 cases were on a decline. (**Figure 1A and figure 1B)**

Clinical Characteristics: (Table 1, figure 2A and figure 2B)

Fever was present in all patients, fatigue was in 27 (66%) and loss of appetite in 24 (59%). The most common organ system involved was the gastrointestinal (GI) system in 37 (90%) cases. Abdominal pain and diarrhea were the most common symptoms of GI involvement seen in 32 (78%) cases each followed by nausea or vomiting in 23 (56%) cases. Pancreatitis was noted in 2 (5%) cases, and one patient (2%) had presented with appendicitis. One patient presented as intussusception. During surgical reduction, the mesenteric lymph node was biopsied, and an ill formed granuloma and neutrophilic infiltrate were detected on histopathology.

The median duration of fever at the time of hospitalization was 4 days (IQR 3-5) and the mean duration of GI symptoms at the time of hospitalization was 3 (1.3) days.

The second most common manifestation was mucocutaneous involvement which was present in 36 (88%) cases. The most common mucocutaneous involvement was conjunctivitis in 29 (71%), which was bilateral nonexudative, and non-purulent. Rash was noted in 25 (61%) cases, was predominantly maculopapular rash over the trunk, extremities, and periorbital region. Oropharyngeal changes including red lips/ red tongue or cheilitis were present in 20 (49%) cases, and acro-ischemic lesion was noted in one case. [23]

Thirty-two (78%) patients had both GI and mucocutaneous involvement. Muscle aches or myalgias were reported in 27 (66%) cases.

Cardiovascular system was involved in 22 (54%) cases clinically and this manifested as the presence of shock requiring inotropic agents.

Neurological symptoms were present in 21 (51%) patients. Headache was reported in 10 (24%) and, meningismus in 6 (15%). Nineteen (46%) patients had either irritability, somnolence, or altered mental status, and one had ataxia.

Fifteen (37%) cases had lymphadenopathy either cervical or mesenteric. Cervical lymphadenopathy was noted on clinical examination and mesenteric lymphadenopathy was detected on radiological imaging.

Lower respiratory symptoms were present in 13 (31%) patients, shortness of breath in 12 (29%) and cough in 4 (10%). Upper respiratory symptoms were noted in 5 (12%) patients, sore throat in 3 (7%), and nasal congestion or rhinorrhoea was reported by 2 (5%). Peripheral extremity changes of edema of hands and feet were noted in 11 (27%) patients.

Table 1: Clinical characteristics of MIS-C cases across the age categories*

	Total (n=41) no. (%)	< 5 years (n=18) no. (%)	5-12 years (n= 19) no. (%)	>12-20 years (n=4) no. (%)
Males	23 (56)	9 (50)	11 (58)	3 (75)
Any constitutional symptoms	41 (100)	18 (100)	19 (100)	4 (100)
-Fever	41 (100)	18 (100)	19 (100)	4 (100)
-Fatigue	27 (66)	10 (56)	14 (73)	3 (75)
-Loss of Appetite	24 (59)	9 (50)	12 (63)	3 (75)
Any Gastrointestinal (GI) symptoms	37 (90)	16 (89)	17 (90)	4 (100)
- Abdominal Pain	32 (78)	12 (67)	16 (84)	4 (100)
- Diarrhoea	32 (78)	12 (67)	16 (84)	4 (100)
- Nausea or vomiting	23 (56)	11 (61)	8 (42)	4 (100)
- Pancreatitis ¶	2 (5)	0 (0)	1 (5)	1 (25)
- Appendicitis †	1 (2)	0 (0)	1 (5)	0 (0)
- Intussusception§	1 (2)	0 (0)	1 (5)	0 (0)
Duration of fever at the time of admission/ diagnosis (days) - median (IQR)	4.0 (3.0-5.0)	3.5 (2.8-5.0)	5.0 (3.0-7.0)	4.5 (3.3-5.0)
Duration of GI symptoms at the time of admission/diagnosis (days) mean ± SD	3.0 ± 1.3	2.6 ± 1.1	3.3 ± 1.5	3.0 ± 1.8
Any changes in peripheral extremities: -Swollen hands or feet/ Edema of extremities	11 (27)	5 (28)	5 (26)	1 (25)
Any mucocutaneous changes:	36 (88)	13 (72)	19 (100)	4 (100)

-Rash	25 (61)	9 (50)	13 (68)	3 (75)
- Oropharyngeal changes (Red lips/ tongue/cheilitis)	20 (49)	6 (33)	10 (53)	4 (100)
- Conjunctivitis	29 (71)	9 (50)	16 (84)	4 (100)
- Acro ischemic lesions	1 (2)	1 (6)	0 (0)	0 (0)
Any gastrointestinal **and** any mucocutaneous changes/symptoms	32 (78)	11 (61)	17 (90)	4 (100)
Lymphadenopathy (Cervical /mesenteric)	15 (37)	5 (28)	7 (37)	3 (75)
Cardiovascular symptoms -Shock	22 (54)	7 (39)	12 (63)	3 (75)
Any neurological symptoms	21 (51)	8 (44)	10 (53)	3 (75)
-Headache	10 (24)	2 (11)	5 (26)	3 (75)
-Irritability/ somnolence/ altered mental status/ gait disturbance ††	19 (46)	7 (38)	9 (47)	3 (75)
- Meningismus	6 (15)	1 (6)	4 (21)	1 (25)
Musculoskeletal symptoms - Muscle Aches/ myalgia	27 (66)	10 (56)	14 (73)	3 (75)
Any upper respiratory symptoms	5 (12)	0 (0)	5 (26)	0 (0)
-Sore throat	3 (7)	0 (0)	3 (16)	0 (0)
-Nasal congestion/ rhinorrhoea	2 (5)	0 (0)	2 (11)	0 (0)
Any lower respiratory symptoms	13 (31)	5 (28)	5 (26)	3 (75)
-Shortness of breath /dyspnoea	12 (29)	5 (28)	4 (21)	3 (75)
-Cough	4 (10)	0 (0)	2 (11)	2 (50)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

¶ The two patients who had pancreatitis, had severe abdominal pain and vomiting, one out of them was having severe multi-organ involvement including anuric acute kidney injury and succumbed on the day of admission itself.

† One patient had presented with abdominal pain, vomiting, and an appendicular lump on clinical and radiological assessment.

§ One patient had a clinical presentation of intussusception; she was subjected to surgical reduction of intussusception and the biopsy of which showed ill-formed granuloma and neutrophilic infiltrate.

††One patient had presented with fever, irritability, and ataxia; she was noted to have bilateral conjunctivitis and maculopapular skin rashes. COVID-19 associated cytotoxic lesion of the corpus callosum was found on subsequent neurological assessment.[24]

Laboratory investigations and cardiac assessment:

(Table 2 and table 3 cut off values of parameters used are listed in parentheses and footnotes of tables)

At the time of hospitalization anemia was noted in 20 (49%) patients, leukopenia in 2 (5%), lymphopenia in 26 (63%), thrombocytopenia in 13 (31%), and pancytopenia in 2 (5%) patients.

Among the inflammatory markers, C-reactive protein (CRP) was elevated in all cases; there was a marked elevation of CRP (>100mg/L) in 23 (56%) patients. Procalcitonin was done in 16 (39%) patients, and it was elevated in all. D-dimer was high in 40 (98%) patients, serum ferritin was high in 22 (54%) and hypoalbuminemia was noted in 31 (76%).

Transaminitis was noted in 19 (46%) patients, acute kidney injury was identified in 4 (10%) and hyponatremia in 9 (22%) during their hospital stay.

N-terminal pro B type natriuretic peptide (NT-proBNP) was done in 19 (46%). This was elevated in 18 (95%) patients. Troponin was done in 30 (73%) patients, it was elevated in 10 (33%). Fibrinogen was done in 11 (27%) and hypofibrinogenemia was noted in one patient. Erythrocyte sedimentation rate (ESR) was done in 14 (34%) and it was high in 10 (71%) patients.

Cardiac assessment with an electrocardiogram (ECG) and echocardiography was done in all patients. **Figure 2B** shows a graphical representation cardiac assessment finding. Abnormal ECG was noted in 8 (20%); bradycardia in 5 (12%), ST-T changes and complete heart block were noted in one patient each. Echocardiography was abnormal in 23 (56%) patients. Coronary artery abnormalities were noted in 15 (37%), only hyperechoic or non-tapering coronaries in 3 (7%), dilated coronaries in 4 (10%), and small coronary aneurysms in 8 (20%) patients.

Left ventricular dysfunction was found in 10 (24%) patients- mild to moderate in 9 (22%), and severe dysfunction was noted in one (2%). There was pericardial effusion in 10 (24%), mitral valve regurgitation in 6 (15%), and global or septal hypokinesia in 4 (10%) patients.

Table 2: Laboratory investigations of MIS-C cases across the age categories*¶

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12-20 years (n=4)
Hemogram at the time of presentation:				
Hemoglobin (Hb) g/L (Mean ± SD)	107.7 ± 16.2	103.0 ± 17.3	110.9 ± 12.3	106.0 ± 27.4
Total leukocyte count (TLC) 10_9/L (Mean ± SD)	11.2 ± 4.8	12.9 ± 5.4	10.5 ± 3.5	7.1 ± 4.6
Platelets (PLT) 10_9/L (Mean ± SD)	248 ± 167	303 ± 159	220 ± 176	131 ± 26
Anemia (Hb <110 g/L) - no. (%)	20 (49)	10 (56)	7 (37)	3 (75)
Leukopenia (TLC < 4.0 x 10_9 cells/L) - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Thrombocytopenia (PLT < 150 x 10_9 cells/L) - no. (%)	13 (31)	3 (17)	7 (37)	3 (75)
Pancytopenia† - no. (%)	2 (5)	1 (6)	0 (0)	1 (25)
Lymphopenia†† - no. (%)	26 (63)	7 (39)	15 (19)	4 (100)
Peak values:				
CRP mg/L - Mean ± SD or Median (IQR)	119 ± 79	86±63	145 ± 84	146 (64-234)
Positive CRP (>1 mg/L)	41 (100)	18 (100)	19 (100)	4 (100)
CRP (1-50) mg/L- no. (%) CRP (51-100) mg/L- no. (%) CRP (>100) mg/L- no. (%)	10 (24) 8 (20) 23 (56)	7 (39) 5 (28) 6 (33)	2 (11) 3 (16) 14 (73)	1 (25) 0 (0) 3 (75)
Procalcitonin µg/L - Median (IQR) no./total no. (%)	8.9 (1.6-51.0) 16/41 (39)	11.4 (1.5-54.2) 8/18 (44)	3.7 (1.5-13.8) 5/19 (26)	48 (7.2-53.0) 3/4 (75)
High Procalcitonin (>0.5 µg/L) - no./total no. (%)	16/16 (100)	8/8 (100)	5/5 (100)	3/3 (100)
Ferritin µg/L Median (IQR)	350 (170-733)	189 (98-429)	570 (266-961)	777 (180-1332)
High ferritin (>300 µg/L) - no./total no. (%)	22 (54)	7 (39)	13 (68)	2 (50)
D-dimer mg/L Median (IQR)	2.5 (1.1-4.3)	1.5 (0.9-3.3)	3.8 (1.5-5.2)	2.6 (1.6-4.2)
High D-dimer (> 0.5 mg/L) - no.(%)	40 (98)	18 (100)	18 (94)	4 (100)
Sodium mmol/L Mean ± SD	135±5	135±6	135±5	137±4
Hyponatremia (Sodium <135 mmol/L)- no.(%)	9 (22)	3 (17)	5 (26)	1 (25)

Albumin g/L (Mean ± SD)	28.6 ± 7.1	29.5 ± 6.9	28.3 ± 7.9	26.5 ± 4.7
Hypoalbuminemia (Albumin < 35g/L) -no.(%)	31 (76)	14 (78)	13 (68)	4 (100)
AST IU/L Median (IQR)	35.0 (27.0-76.5)	28.0 (22.5-47.5)	34.0(23.0-60.0)	110.0 (37.0-351.0)
ALT IU/L Median (IQR)	29.5 (22.3-51.0)	40.0 (27.5-63.5)	29.0 (20.0-45.0)	89.0 (35.5-442)
Transaminitis ‡ -no.(%)	19 (46)	9 (50)	7 (37)	3 (75)
Acute Kidney Injury (AKI) ‡‡	4 (10)	1 (6)	1 (5)	2 (50)
Sterile pyuria— no./total no. (%)	10/20 (50)	4/10 (40)	4/7 (57)	2/3 (67)
Proteinuria— no./total no. (%)	6/20 (30)	1/10 (10)	3/7 (43)	2/3 (67)
Troponin ng/L Median (IQR) -no./ total no. (%)	 16 (6.7-30.0) 30/41 (73)	 19 (6.0-41.2) 12/18 (67)	 10.2 (4.0-35.6) 14/19 (74)	 19.3 (14.5-27.4) 4/4 (100)
Elevated Troponin (>20 ng/L) -no./ total no. (%)	10/30 (33)	6/12 (50)	3/14 (21)	1/4 (25)
NT-ProBNP (pg/mL) Median (IQR) -no./ total no. (%)	 1845 (403-6840) 19/41 (46)	 4342 (815-7803) 8/18 (44)	 529 (248-4647) 9/19 (47)	 3530 (2679-4382) 2/4 (50)
Elevated NT-proBNP (>125 pg/mL) -no./ total no. (%)	18/19 (95)	8/8 (100)	8/9 (89)	2/2 (100)
Fibrinogen g/L Mean ± SD - no./total no. (%)	 3.9 ± 1.8 11/41 (27)	 3.5 ± 0.8 3/18 (17)	 4.2 ± 2.2 7/19 (37)	 3.37 1/4 (25)
Hypofibrinogenemia (Fibrinogen <2.0 g/L) -no./ total no. (%)	 1/11 (9)	 0/3 (0)	 1/7 (14)	 0/1 (0)
ESR mm/h Mean ± SD - no./total no. (%)	 33.4 ± 20.7 14/41 (34)	 35.3 ± 15.9 7/18 (39)	 41.2 ±24.4 5/19 (26)	 7.5 ± 0.7 2/4 (50)
High ESR (>20) - no./total no. (%)	10/14 (71)	6/7 (86)	4/5 (80)	0/2 (0)

* Percentages may not total 100 because of rounding.

¶ CRP denotes C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, ESR Erythrocyte sedimentation rate, IQR denotes interquartile range showing 25_{th} and 75_{th} centiles, and SD is the standard deviation.

† Pancytopenia defined as hemoglobin <110 g/L, total leukocyte count < 4.0 x 10_9/L and platelets < 150 x 10_9/L.

†† Lymphopenia defined as <3000 lymphocytes/µL (<2 years age), <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

‡ Transaminitis defined as AST or ALT >40 IU/L.

‡‡ Acute Kidney Injury (AKI) is defined as any of the following: increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours[25].

Table 3: Cardiac assessment of MIS-C cases across the age categories*¶

	Total (n=41) no. (%)	< 5 years (n=18) no. (%)	5-12 years (n= 19) no. (%)	>12-20 years (n=4) no. (%)
Abnormal ECG	8 (20)	3 (17)	4 (21)	1 (25)
Bradycardia	5 (12)	1 (6)	3 (16)	1 (25)
Complete Heart Block§	1 (2)	1 (6)	0 (0)	0 (0)
ST T changes	1 (2)	0 (0)	1 (5)	0 (0)
Abnormal Echocardiography	23 (56)	11 (61)	9 (47)	3 (75)
Normal coronaries	26 (63)	9 (50)	14 (73)	3 (75)
Abnormal coronaries (Hyperechoic/ non tapering/ dilatated/ aneurysm)	15 (37)	9 (50)	5 (26)	1 (25)
Only hyperechoic / non tapering coronaries	3 (7)	3 (17)	0 (0)	0 (0)
Dilated coronaries	4 (10)	3 (17)	1 (5)	0 (0)
Small Aneurysm in coronaries	8 (20)	3 (17)	4 (21)	1 (25)
Systolic Dysfunction	10 (24)	3 (17)	6 (32)	1 (25)
Mild to moderate (LVEF 30-55%)	9 (22)	2 (11)	6 (32)	1 (25)
Severe (LVEF <30%)	1 (2)	1 (6)	0 (0)	0 (0)
Pericardial effusion	10 (24)	6 (33)	2 (11)	2 (50)
Global/septal hypokinesia	4 (10)	3 (17)	1 (5)	0 (0)
Mitral Valve regurgitation	6 (15)	3 (17)	2 (11)	1 (25)
Pulmonary Artery Hypertension	3 (7)	0 (0)	2 (11)	1 (25)

* Percentages may not total 100 because of rounding.

¶ ECG denotes Electrocardiogram and LVEF is left ventricular ejection fraction.

§One patient had presented with fever and drowsiness, noted to have complete heart block treated with a pacemaker, IVIG, and steroids however patient succumbed on the first day of admission itself.

Clinical course, treatment, and immediate outcomes: (Table 4)

A total of thirty-six (88%) patients required intensive care; the median duration of ICU stay was 3.5 days (IQR 3-5 days). Twenty-one (51%) patients required inotropes and mechanical ventilation was required in 8 (20%) cases. Treatment was provided as per the standard treatment guidelines for MIS-C.[6,26,27] Immunomodulatory therapy was administered to 39 (95%), steroids and IVIg both were used in 35 (85%) and only steroids were used in 3 (7%) patients. Antiplatelets were used in 37 (90%) and anticoagulation was used in 3 (7%) patients. Empirical broad-spectrum antibiotics were started for all the patients at the time of hospitalization and were discontinued after the blood and urine cultures were noted to be sterile. **(Supplementary figure 2)**

Two (5%) patients died during the treatment of the acute phase. The first patient was a 4 year old girl who was positive for both COVID-19 RTPCR and antibodies with a complete heart block.She continued to deteriorate despite use of pacemaker, mechanical ventilation, supportive care, and standard treatment for MIS-C. She expired on the same day of hospitalization. The second mortality was a 17 year old boy who had severe multi-organ dysfunction. He deteriorated rapidly despite prompt immunomodulation, hemodialysis, and mechanical ventilation. He died within 24 hours of hospitalization.

The mean duration of hospital stay was 8.2 (4.7) days, among the patients who recovered from MIS-C. Thirteen patients (32%) recovered with some residual sequelae, primarily echocardiographic abnormalities. Remaining 26 (63%) patients recovered without any residual changes at the time of discharge. **(Supplementary figure 3)**

Table 4: Clinical course, treatment, and immediate outcomes*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12 years (n=4)
Intensive care unit (ICU) requirement -no.(%)	36 (88)	15 (83)	18 (95)	3 (75)
Median duration of ICU stays among patients who required ICU in days (IQR)	3.5 (3.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-7.0)	4.0 (1.0-9.0)
Mechanical ventilation - no.(%) †	8 (20)	2 (11)	4 (21)	2 (50)
Median duration of mechanical ventilation in days among patients who required it (IQR)	3.0 (1.0-12.5)	8.0 (1.0-15.0)	4.0 (3.0-17.0)	1.0 (1.0-1.0)
Inotropic agent requirement - no.(%)	21 (51)	7 (39)	11 (58)	7 (39)
Median number of days patients were on inotropes among the patients it was used (IQR)	2.0 (2.0-3.0)	3.0 (1.8-6.0)	2.0 (2.0-3.0)	2.0 (0.5-2.0)
Aspirin low dose	37 (90)	16 (89)	18 (96)	3 (75)
IVIG	36 (88)	15 (83)	18 (95)	3 (75)
Repeat IVIG	1 (2)	1 (6)	0 (0)	0 (0)
Steroids	38 (93)	16 (89)	18 (100)	4 (100)
Steroids and IVIG	35 (85)	15 (83)	17 (90)	3 (75)
Anticoagulation	3 (7)	1 (6)	1 (5)	1 (25)
Mean length of hospital stay excluding deaths (days) ± SD	8.2 ± 4.7	8.0 ± 6.1	8.1 ± 3.1	10.3 ± 43.5
Immediate outcome (At the time of discharge)				
Recovered with sequalae	13 (32)	5 (28)	7 (37)	1 (25)
Recovered without sequalae	26 (63)	12 (67)	12 (63)	2 (50)
Death	2 (5)	1 (6)	0 (0)	1 (25)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, and SD is the standard deviation.

† Only non-invasive mechanical ventilation was used in one patient in >12 years age group, all others required invasive mechanical ventilation.

Follow up at 6 weeks after discharge:

All discharged patients (n=39) remained clinically stable during 6 weeks follow up. There was no abnormality on clinical assessment in any case. Echocardiographic assessments showed improvement trend in all patients. Eight (21%) patients had persisting coronary alterations on echocardiogram at 6 weeks- hyperechoic or non-tapering thick-walled coronaries in 5 (13%), coronary dilation in 2 (5%) and small coronary aneurysm in one patient. However, the echocardiographic coronary alterations had improved from their baseline status during the acute illness. Persisting mild left ventricular systolic dysfunction and pulmonary artery hypertension (PAH) were noted in one case each. **(Supplementary table 2)**

Medium-term outcome at 3 months follow-up: (Table 5)

Thirty-seven patients finished their 3 months follow-up by April 2021. All patients were clinically stable, echocardiographic changes were improving in all of them. At 3 months follow up 4 (11%) patients were on Aspirin for residual coronary changes, one patient was on diuretics for left ventricular dysfunction, and one patient was on Phosphodiesterase-5 inhibitors for PAH.

Table 5: Cardiac outcomes at 3 months follow up (n=37)*¶

	Total (n= 37) no. (%)	< 5 years (n=17) no. (%)	5-12 years (n= 17) no. (%)	>12 years (n=3) no. (%)
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal Coronaries	4 (11)	3 (18)	1 (6)	0 (0)
Hyperechoic / non tapering coronaries	2 (5)	2 (12)	0 (0)	0 (0)
Dilatation	1 (3)	1 (6)	0 (0)	0 (0)
Small Aneurysm	1 (3)	0 (0)	1 (6)	0 (0)
LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
PAH	1 (3)	0 (0)	1 (6)	0 (0)
Recovered with sequalae ¶¶	6 (16)	3 (18)	3 (18)	0 (0)
Ongoing treatment in any form at 3 months follow up	6 (16)	3 (18)	3 (24)	0 (0)
Aspirin	4 (11)	2 (12)	3 (18)	0 (0)
Treatment of LV dysfunction	1 (3)	1 (6)	0 (0)	0 (0)
Treatment of PAH	1 (3)	0 (0)	1 (6)	0 (0)

* Percentages may not total 100 because of rounding.

¶ Only 37 patients had finished their 3 months follow-up by April 2021. LV dysfunction denotes-left ventricular dysfunction and PAH is pulmonary arterial hypertension.

¶¶ Sequalae refers to any residual structural or functional cardiac abnormality on echocardiography.

Comparison of MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation: (Table 6)

We categorised MIS-C patients into two groups based on requirement of mechanical ventilation. We did a subgroup analysis using various clinical, laboratory and echocardiographic parameters (**table 6)**. Only hyperferritinemia was significantly associated with requirement of mechanical ventilation (p = 0.001).

Table 6: Bivariate Comparison of various clinical and laboratory parameters in MIS-C cases who required mechanical ventilation versus those who did not require mechanical ventilation*

Clinical and laboratory parameters of MIS-C cases	Mechanical ventilation required (n = 8)	Mechanical ventilation not required (n = 33)	p-value ‡
Presence of shock requiring inotropic agents – no. (%)	7 (88)	14 (42)	0.045
Median D-dimer mg/L (IQR)	4.5 (2.9-16.3)	2.3 (1.0-3.9)	0.016
Median serum ferritin µg/L (IQR)	1178.0 (717.0-23840.0)	266.0 (153.0-555.0)	**0.001**
Median ESR mm/h (IQR) - no./total no. (%)	8.0 (7.0-10.0) 3/8 (38)	40 (27-51) 11/33 (33)	0.016
Median serum AST IU/L (IQR)	188.0 (37.8-741.2)	33.0 (26.0-60.5)	0.008
Median serum procalcitonin µg/L (IQR) - no./total no. (%)	5.4 (2.1-41.5) 4/8 (50)	11.1(1.6- 51.0) 12/33 (36)	0.716
Median serum NT-proBNP pg/mL (IQR) - no./total no. (%)	3533.5 (2141.5-46767.5) 6/8 (75)	1138.0 (349.0-6725.0) 13/33 (39)	0.096
Median serum troponin ng/L (IQR) - no./total no. (%)	55.2 (14.5-945.3) 4/8 (50)	15.0 (4.8-29.2) 26/33 (78)	0.143
Median absolute lymphocyte count (IQR)	825 (521-2218)	1588 (895-3489)	0.061
Lymphopenia at admission -no. (%)§	7 (88)	19 (58)	0.220
Mean CRP mg/L ± SD	101.0 ± 85.3	123 ± 78.9	0.474
Median serum ALT IU/L (IQR)	141.0 (25.0-543.0)	29.0 (21.0-43.5)	0.113
Presence of coronary abnormalities - no. (%)	4 (50)	11 (33)	0.434
Presence of LV dysfunction - no. (%)	3 (38)	7 (21)	0.378

* Percentages may not total 100 because of rounding. IQR denotes interquartile range showing 25th and 75th centiles, ESR erythrocyte sedimentation rate, AST aspartate aminotransferase, NT-ProBNP N-terminal pro–B-type natriuretic peptide, CRP C-reactive protein, SD standard deviation, and ALT alanine aminotransferase.

‡ p-value was calculated by applying appropriate statistical tests according to the distribution of the data. Independent sample t-test or Mann-Whitney tests were applied to compare the potential markers of severity. The Bonferroni's correction was applied for multiple comparisons. A p-value of <0.0035 was considered statistically significant.

§ Lymphopenia defined as <3000 lymphocytes/µL (<2 years age), <1500 lymphocytes/µL (2-12 years age), and <1000 lymphocytes/µL (>12 years age).

Discussion:

In this study, we have described 41 cases of MIS-C associated with COVID-19. The patients were treated at two tertiary care centers (Kerala,India) from March 2020 to April 2021. **Figure 3** shows a heat map of syndrome clusters in MIS-C cases in our study.

We compared our study results with those of a systematic review by *Ahmed* et al. which involved 662 cases of MIS-C from 39 studies.[9] Similarities were noted on constitutional symptoms (100% *v* 100%), intensive care requirement (88% *v* 71%), mechanical ventilation requirement (20% *v* 22%), inotrope requirement (51% *v* 60%), and mean length of hospital stay (8.2 days *v* 7.9 days). Laboratory parameters reflecting inflammatory, coagulative, and cardiac involvement were also similar. However, there were striking differences in our cohort which included a large number of previously healthy individuals (80% in our study *v* 52% in *Ahmed* et al.). We had a smaller proportion of overweight or obese cases (10% *v* 24%), younger age of onset (mean age 6.2 years *v* 9.3 years), high frequency of conjunctivitis (71% *v* 51%), more common myalgia (66% *v* 13%), more cases with irritability /somnolence (46% *v* 10%), more number of cases with lymphadenopathy (37% *v* 14%), and more frequent coronary dilation and aneurysms (29% *v* 15%). Systolic dysfunction was less frequent in our cohort (24% *v* 45%).[9]

We had smaller number of patients in the age group of more than 12 years in comparison with the two largest cases series from the USA (10% in our study *v* 24% *and* 26%).[28,29]

There are two case series of MIS-C are reported from India. In comparison with a series of 19 MIS-C patients from Chennai our cohort had more frequent gastrointestinal symptoms (90% in our study *v* 42%), a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 58%), and more common coronary involvement (37% *v* 16%).[30] Comparing with another case series of 23 MIS-C patients from Mumbai, we observed a lower proportion of individuals with active COVID-19 during MIS-C (5% *v* 39%), higher frequency of abdominal pain (78% *v* 52%), and conjunctivitis (71% *v* 52%).[31] Other available clinical and laboratory parameters from these two studies were similar to our study.

Because of the similarities in clinical phenotype to KD, we compared our results with existing literature on KD. We noticed that percentage of cases developing coronary artery aneurysms in our MIS-C cases were less than that of untreated KD (20% *v* 25%) but more than of that KD treated with optimum IVIG (20% *v* 5%). IVIG resistance or requirement of a second dose of IVIG or alternative immunotherapy was less frequent in MIS-C in comparison to KD (2% *v* 10%).[32,33] However, none of our current MIS-C cohort patients developed medium-sized or giant coronary aneurysm or thrombosis of coronary in contrast to KD where it is reported in 1% of treated cases.[34]

While it is gratifying to note that most cases remained clinically well at 3 months follow-up, the persistence of echocardiographic abnormalities in 6 patients emphasises the need for careful follow-up.

The only other published report on intermediate-term follow-up following MIS-C is a recently published study by *Penner* et al. that reports outcomes at 6 months following MIS-C in a single center cohort from the UK.[35] There was similarity in context to full subsidence of inflammation (100% in our study *v* 98% in *Penner* et al.). The difference in near-complete resolution of echocardiographic sequelae (84% in our study *v* 96%) could be due to our 3-month follow-up versus the 6-month follow-up in the aforementioned study. The striking difference was that in our cohort none of the patients had persistent gastrointestinal symptoms, mucocutaneous changes, or minor neurological abnormalities as reported in the above-mentioned study.

MIS-C requires a high index of suspicion for diagnosis and warrants prompt treatment. There is a paucity of literature in MIS-C to define severe and non-severe cases and prediction of severity in a given case. As all of the MIS-C cases required hospitalization, most of these required intensive care, and mechanical ventilation was required in 20% patients. We found that hyperferritinemia was associated with the requirement of mechanical ventilation in MISC patients. Our findings are in alignment with a retrospective surveillance study from USA which enrolled 1090 patients of MIS-C. [36] They reported that high ferritin in addition to high NT-ProBNP, and high D-dimer increases the odds of severe outcomes and the need for intensive care.[36]

As the study was conducted at two tertiary care centres it might underestimate the mild cases and could be skewed towards high morbidity and mortality due to referral bias.

Conclusions:

MIS-C is a new disease in context to COVID-19 pandemic and we are still continuing to learn about this clinical syndrome.

While the clinical profile of our cohort has largely been similar to world-wide reports, we observed a few differences in our cohort like younger age at onset, more mucocutaneous changes and a smaller number of patients with co-existent comorbidities. Risk factors for the development of severe MIS-C remain unknown, however, we found that requirement of mechanical ventilation was associated with hyperferritinemia.

We observed echocardiographic sequalae in one third of patients at the time of discharge, which reduced to one in six at three months follow up. Overall immediate and medium-term outcomes remain largely excellent. Ongoing follow-up for several years to study the disease's natural history is certainly warranted.

What is already known on this topic:

1. MIS-C is a rare but critical association of COVID-19 infection in children.
2. MIS-C is known to present as a hyperinflammatory state with fever, gastrointestinal, mucocutaneous symptoms, atypical Kawasaki disease-like phenotype, and macrophage activation syndrome.

What this study adds:

1. In our cohort of MIS-C, patients presented at a younger age with more frequent mucocutaneous changes and lesser comorbidities as compared to western studies.
2. The medium-term outcome of MIS-C patients is excellent; however, we need to monitor echocardiogram at subsequent follow up visits in selected patients.
3. We were able to associate hyperferritinemia with requirement of mechanical ventilation in MIS-C patients.

References:

1 WHO Coronavirus (COVID-19) Dashboard. Covid19.who.int. 2021. https://covid19.who.int (accessed 13 August, 2021).

2 Sanna G, Serrau G, Bassareo PP, *et al.* Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. *European Journal of Pediatrics* 2020 May 30;179 1079-87. doi:10.1007/s00431-020-03699-0

3 Verdoni L, Mazza A, Gervasoni A, *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *The Lancet* 2020;**395**:1771–8. doi:10.1016/S0140-6736(20)31103-X

4 Riphagen S, Gomez X, Gonzalez-Martinez C, *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;**395**:1607–8. doi:10.1016/S0140-6736(20)31094-1

5 Jones VG, Mills M, Suarez D, *et al.* COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hospital Pediatrics* 2020;**10**. doi:10.1542/hpeds.2020-0123

6 Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS) - guidance for clinicians.RCPCH.2021. https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance / (accessed on 2 June, 2021).

7 Centers for Disease Control and Prevention. Multisystem inflammatory syndrome. 2020. https://www.cdc.gov/mis-c/hcp/ (accessed 21 April, 2021).

8 Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19.Who.int.2021.https://www.who.int/newsroom/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (accessed on 2 June 2021).

9 Ahmed M, Advani S, Moreira A, *et al.* Multisystem inflammatory syndrome in children: A systematic review. *EClinicalMedicine* 2020;**26**. doi:10.1016/j.eclinm.2020.100527

10 Rubens JH, Akindele NP, Tschudy MM, *et al.* Acute covid-19 and multisystem inflammatory syndrome in children. *The BMJ* 2021;**372**. doi:10.1136/bmj.n385

11 Hamming I, Timens W, Bulthuis MLC, *et al.* Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *Journal of Pathology* 2004;**203**:631–7. doi:10.1002/path.1570

12 Liu J, Li S, Liu J, *et al.* Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. medRxiv. 2020. doi:10.1101/2020.02.16.20023671

13 Li H, Liu L, Zhang D, *et al.* SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;**395**:1517–20. doi:10.1016/S0140-6736(20)30920-X

14 Jiang L, Tang K, Levin M, *et al.* COVID-19 and multisystem inflammatory syndrome in children and adolescents. *The Lancet Infectious Diseases* 2020;**3099**. doi:10.1016/S1473-3099(20)30651-4

15 Khadilkar V, Yadav S, Agrawal KK, *et al.* Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. *Indian Pediatrics* 2015;**52**. doi:10.1007/s13312-015-0566-5

16 Obesity and overweight. Who.int. 2021.https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 2 June 2021).

17 Lai WW, Geva T, Shirali GS, *et al.* Guidelines and Standards for Performance of a Pediatric Echocardiogram: A Report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *Journal of the American Society of Echocardiography* 2006;**19**. doi:10.1016/j.echo.2006.09.001

18 Lopez L, Colan SD, Frommelt PC, *et al.* Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. *Journal of the American Society of Echocardiography* 2010;**23**. doi:10.1016/j.echo.2010.03.019

19 McCrindle BW, Li JS, Minich LL, *et al.* Coronary Artery Involvement in Children With Kawasaki Disease. *Circulation* 2007;**116**. doi:10.1161/CIRCULATIONAHA.107.690875

20 Manlhiot C, Millar K, Golding F, *et al.* Improved Classification of Coronary Artery Abnormalities Based Only on Coronary Artery z-Scores After Kawasaki Disease. *Pediatric Cardiology* 2010;**31**. doi:10.1007/s00246-009-9599-7

21 Khanna G, Sargar K, Baszis KW. Pediatric Vasculitis: Recognizing Multisystemic Manifestations at Body Imaging. *RadioGraphics* 2015;**35**. doi:10.1148/rg.2015140076

22 Shenoy B, Singh S, Zulfikar Ahmed M, *et al*. Recommendations Indian Academy of Pediatrics Position Paper on Kawasaki Disease. *Indian Pediatrics*. 2020 May 28;**57.** doi:10.1007/s13312-020-2033-1

23 Kappanayil M, Balan S, Alawani S, *et al.* Multisystem inflammatory syndrome in a neonate, temporally associated with prenatal exposure to SARS-CoV-2: a case report. *The Lancet Child & Adolescent Health* 2021;**5**. doi:10.1016/S2352-4642(21)00055-9

24 Lin J, Lawson EC, Verma S, *et al.* Cytotoxic lesion of the corpus callosum in an adolescent with multisystem inflammatory syndrome and SARS-CoV-2 infection. *American Journal of Neuroradiology* 2020;**41**:2017–9. doi:10.3174/ajnr.A6755

25 Kellum JA, Lameire N, Aspelin P, *et al.* Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney International Supplements. 2012;**2**:1–138. doi:10.1038/kisup.2012.1

26Hennon TR, Penque MD, Abdul-Aziz R, *et al.* COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. Progress in Pediatric Cardiology. 2020;**57**. doi:10.1016/j.ppedcard.2020.101232

27 Henderson LA, Canna SW, Friedman KG, *et al.* American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. *Arthritis and Rheumatology* 2020;**72**:1791–805. doi:10.1002/art.41454

28 Feldstein LR, Rose EB, Horwitz SM, *et al.* Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. *New England Journal of Medicine* 2020;**383**. doi:10.1056/NEJMoa2021680

29 Riollano-Cruz M, Akkoyun E, Briceno-Brito E, *et al.* Multisystem Inflammatory Syndrome in Children (MIS-C) Related to COVID-19: A New York City Experience. *Journal of Medical Virology* 2020;:0–3. doi:10.1002/jmv.26224

30 Dhanalakshmi K, Venkataraman A, Balasubramanian S, *et al.* Epidemiological and Clinical Profile of Pediatric Inflammatory Multisystem Syndrome-Temporally Associated with SARS-CoV-2 (PIMS-TS) in Indian Children. *Indian Pediatrics*. 2000 Nov 15;**57**(11):1011-14. doi:10.1007/s13312-020-2025-1

31 Jain S, Sen S, Lakshmivenkateshiah S, *et al.* Multisystem Inflammatory Syndrome in Children With COVID-19 in Mumbai, India. *Indian Pediatrics*. 2020 Nov. 15;**57**(11):1015-1019. doi: 10.1007/s13312-020-2026-0

32 McCrindle BW, Rowley AH, Newburger JW, *et al.* Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017;**135**. doi:10.1161/CIR.0000000000000484

33 Correction to: Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2019;**140**. doi:10.1161/CIR.0000000000000703

34 Dajani AS, Taubert KA, Takahashi M, *et al.* Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;**89**. doi:10.1161/01.CIR.89.2.916

35 Penner J, Abdel-Mannan O, Grant K, *et al.* 6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study. *The Lancet Child & Adolescent Health* Published Online First: May 2021. doi:10.1016/S2352-4642(21)00138-3

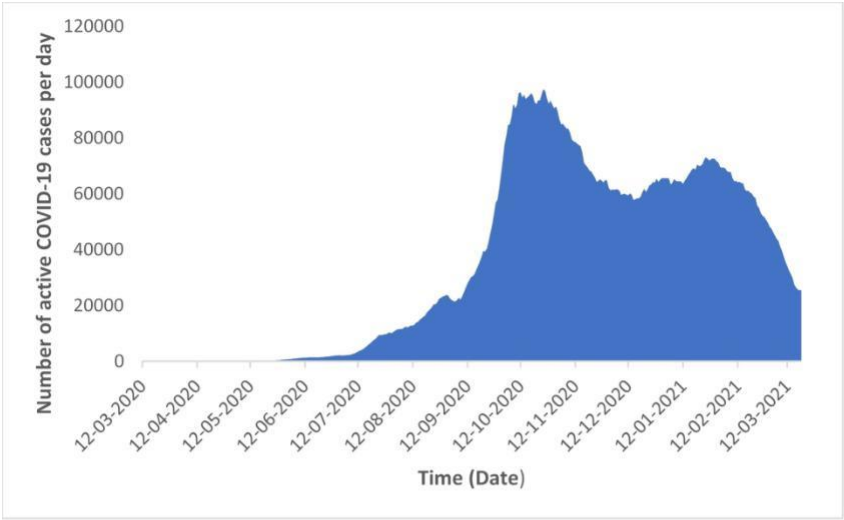
36Abrams JY, Oster ME, Godfred-Cato SE, *et al.* Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *The Lancet Child & Adolescent Health* 2021;**5**:323–31. doi:10.1016/s2352-4642(21)00050-x

Captions for figures:

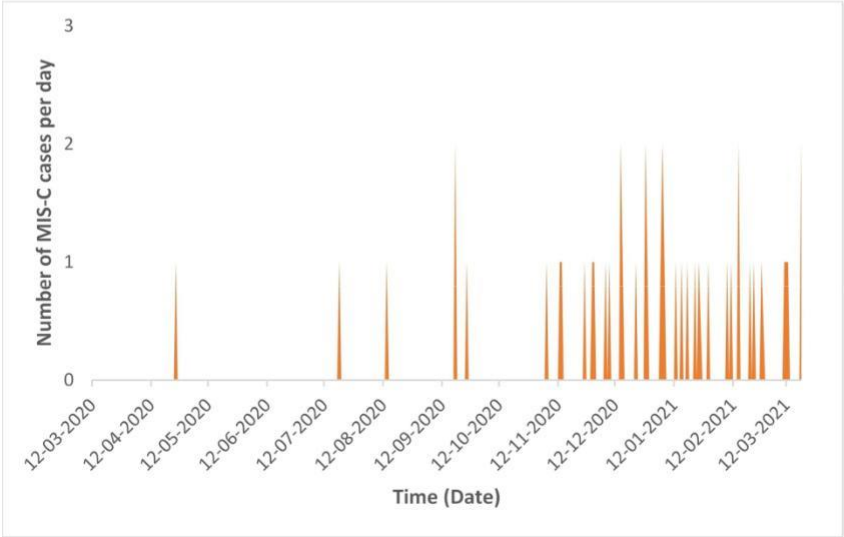
Figure 1: Temporal correlation of active COVID-19 cases (A) and MIS-C cases (B) in the Southern Indian state Kerala

Figure 2: Frequency of symptoms in MIS-C cases (A) and cardiac assessment during acute phase of MIS-C (B)

Figure 3: Heat map of syndrome clusters based on clinical presentations (Percentages may not total 100 because of rounding and overlapping clinical features)



A



B

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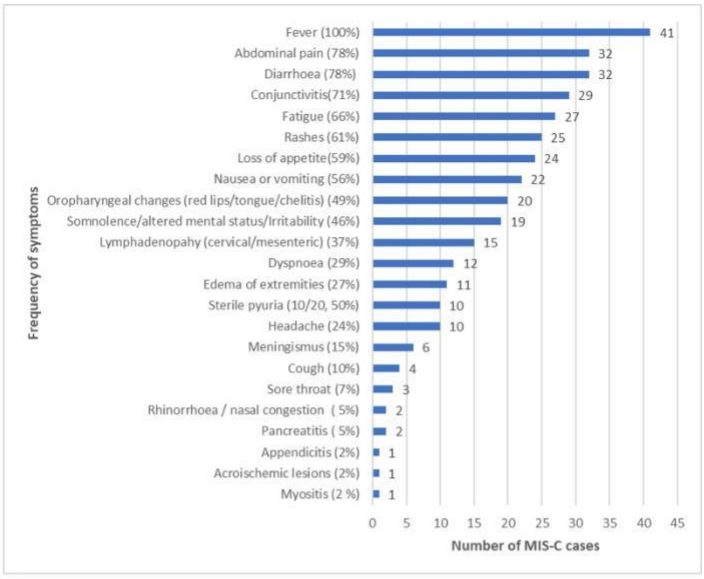
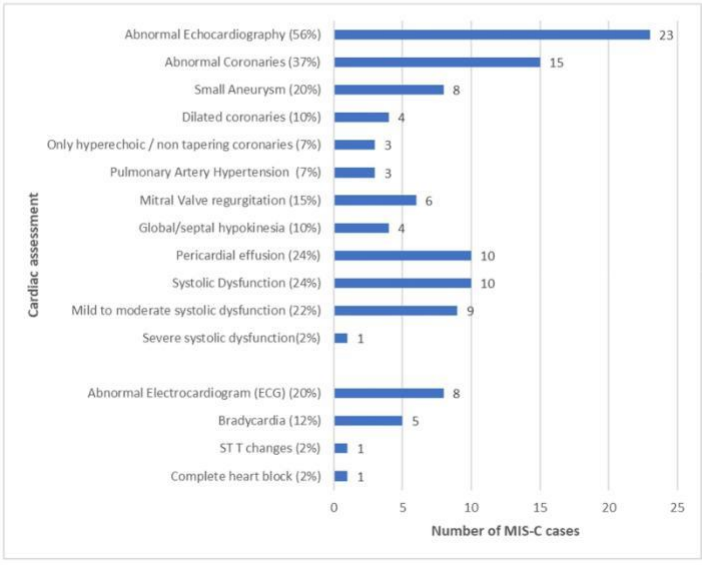


A



B

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	< 5 years (n=18) -no. (%)	5-12 years (n= 19) -no. (%)	>12 years (n= 4) -no. (%)
Dermatological/ mucocutaneous	13 (72)	19 (100)	4 (100)
Gastrointestinal symptoms	16 (89)	17 (90)	4 (100)
Incomplete/ atypical Kawasaki disease	13 (72)	15 (79)	3 (75)
Shock	7 (39)	12 (63)	3 (75)
Macrophage activation syndrome like features	6 (33)	7 (37)	4 (100)
Neurological symptoms	7 (39)	6 (32)	2 (50)
Respiratory Symptoms	4 (22)	1 (5)	2 (50)

1-5%	6-25%	26-50%	51-75%	76-100%

256x127mm (300 x 300 DPI)

Supplementary Table 1: Demographic and baseline characteristics*

	Total (n=41)	< 5 years (n=18)	5-12 years (n= 19)	>12- 20 years (n=4)
Males – no.(%)	23 (56)	9 (50)	11 (58)	3 (75)
Body habitus – no.(%)**				
- Underweight	3 (7)	1 (6)	2 (11)	0 (0)
- Normal weight	34 (83)	17 (94)	15 (79)	2 (50)
- Overweight	1 (2)	0 (0)	0 (0)	1 (25)
- Obese	3 (7)	0 (0)	2 (11)	1 (25)
Presence of comorbidities- no. (%)				
- Any	8 (20)	2 (11)	3 (16)	1 (25)
- Obesity or overweight	4 (10)	0 (0)	1 (5)¶	1 (25)
- Cardiovascular disorders†	1 (2)	0 (0)	1 (5)	0 (0)
- CNS disorders§	3 (7)	2 (11)	1 (5)	0 (0)
- Chronic lung disease‡	1 (2)	0 (0)	1 (5)	0 (0)

*Percentages may not total 100 because of rounding. BMI = Body Mass Index, CNS = Central Nervous System

** BMI based overweight and obesity were defined using Indian standard reference for BMI and it was calculated in age groups >5 years of age. For the cases under 5 years of age, overweight was defined as weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and obesity was defined as weight-for-height greater than 3 standard deviations above the WHO child growth standards median. Underweight was defined in terms of weight for age using the WHO child growth standards for children below 5 years of age and using IAP WHO combined BMI growth charts for older children.

† One patient had large atrial and ventricular septal defects which were closed surgically.

§ Among 3 patients with CNS disorders, two had a seizure disorder, and one had hydrocephalus requiring surgical intervention.

¶ One patient of seizure disorder was obese as well.

‡ One patient had bronchial asthma controlled on inhaled steroids and long -acting beta-agonists.

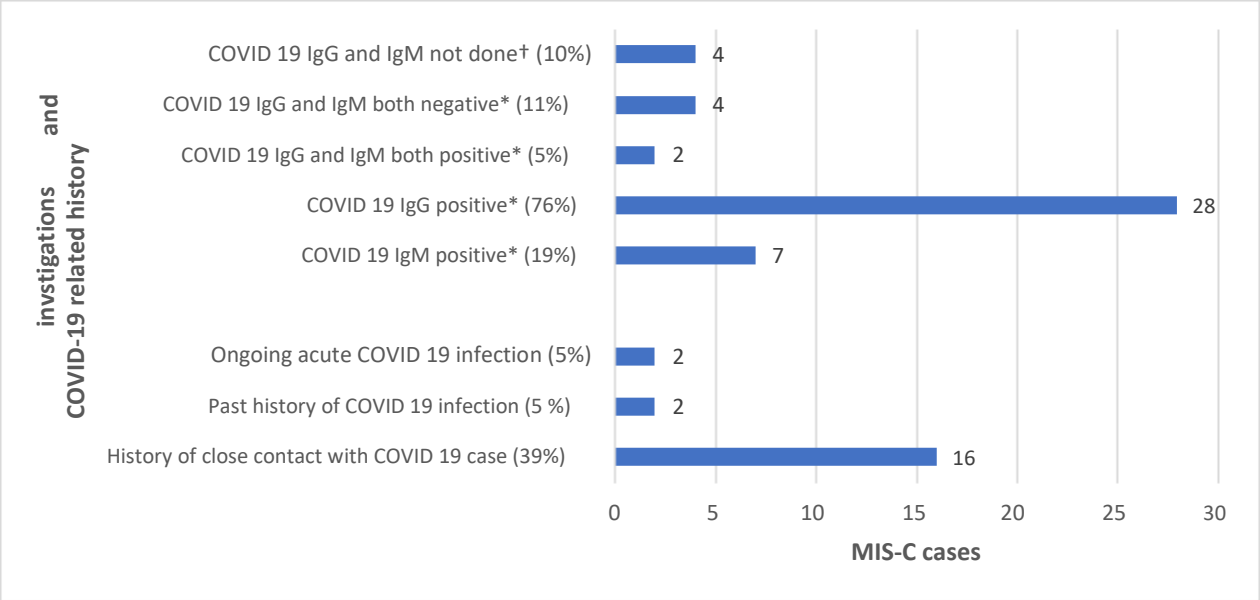
Supplementary table 2: Cardiac outcomes in 6 weeks follow up (n=39) §

	Total (n= 39) no. (%)*	< 5 years (n=17) no. (%)*	5-12 years (n= 19) no. (%)*	>12 years (n=3) no. (%)*
Any abnormality on clinical assessment	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal coronaries	8(21)	4(24)	4(21)	0 (0)
Hyperechoic/ non-tapering coronaries	5(13)	3(18)	2(11)	0 (0)
Dilatation	2(5)	1(6)	1(5)	0 (0)
Small Aneurysm	1(3)	0 (0)	1(5)	0 (0)
LV dysfunction	1(3)	1(6)	0 (0)	0 (0)
PAH	1(3)	0(0)	1(5)	0 (0)

§ Two patients had expired during the acute phase of MISC.

* Percentages may not total 100 because of rounding.

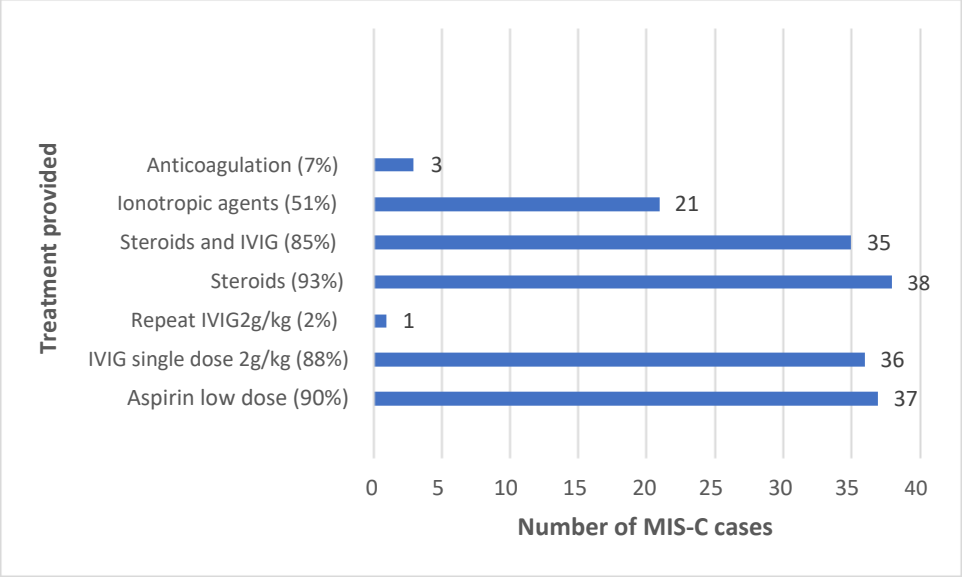
Supplementary figures:



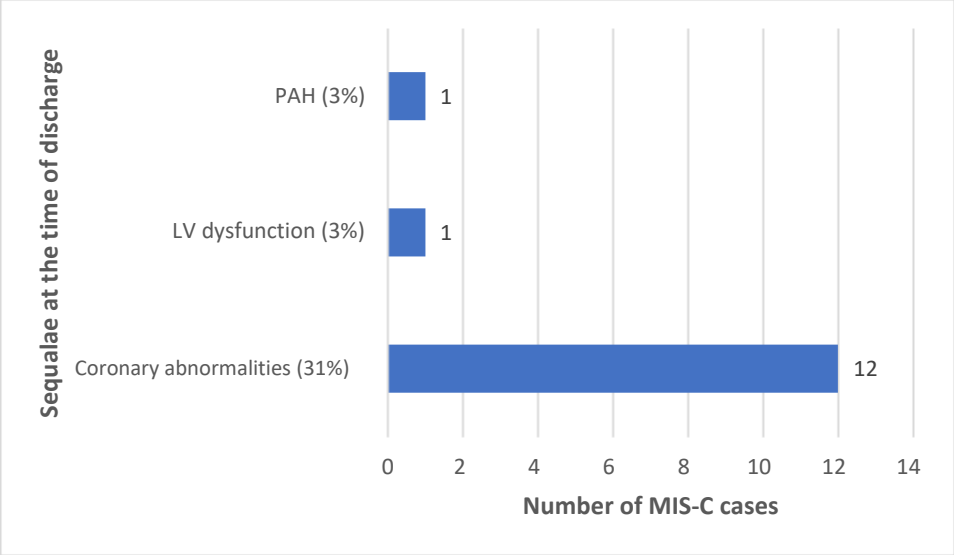
Supplementary figure 1: COVID 19 related history and investigations

† These cases were diagnosed before September 2020 when the COVID antibodies were available at our centers.

* Investigations are not mutually exclusive.



Supplementary figure 2: Treatment provided to MIS-C cases



Supplementary figure 3: Sequalae at the time of discharge (n =39)