ORIGINAL ARTICLE

Profile of Multisystem Inflammatory Syndrome in Children Related to COVID-19: A Multicentric Study from South India

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Abstract

Multisystem inflammatory syndrome in children (MIS-C) is a severe complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection associated with significant morbidity and can be fatal if left unrecognized.

A retrospective multicentric study was carried out at five tertiary care centers in South India, to evaluate the clinical profile of children admitted with MIS-C associated with SARS-CoV-2 infection. Cases of MIS-C diagnosed during October 2020 to December 2021 were included. Diagnosis of MIS-C was based on World Health Organization (WHO) criteria. All children underwent echocardiography at admission, discharge, and 4–6 weeks of follow-up. Children with MIS-C were treated with intravenous immunoglobulin (IVIG) and/or steroids. We compared younger children (<5 years of age) with older ones to determine if age at presentation could predict severity in children with MIS-C. A total of 81 children were diagnosed to have MIS-C during the study period. The mean age of presentation was 6.8 years. Around 29.6% of the children had a shock at admission and 54.3% had myocardial dysfunction. The average duration of a pediatric intensive care unit (PICU) stay was 6.6 days. Anti-SARS-CoV-2 antibodies were found to be positive in 75.3% of patients. Children with high N-terminal prohormone of brain natriuretic peptide (NT-proBNP) had more severe presentations. All children responded promptly to IVIG and steroids and the mortality was 0%. No difference was noted in terms of outcome between younger (<5 years) and older children. A significant proportion of children with MIS-C present with shock and myocardial dysfunction. Anti-SARS-CoV-2 antibodies were positive in 75% of children whose primary infection went unnoticed. We hereby report one of the largest cohorts of MIS-C patients from the Indian subcontinent.

Keywords: Anti-severe complication of severe acute respiratory syndrome coronavirus 2 antibodies; Coronavirus disease 2019; Intravenous immunoglobulin; Multisystem inflammatory syndrome in children; Myocardial dysfunction; Kawasaki disease.

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Introduction

The SARS-CoV-2 virus from its time of inception in December 2019 till date has had a myriad clinical spectrum of illnesses. MIS-C is now one of the well-recognized complications of this infection seen mostly in the pediatric age-group.[1–3] The studies done so far have found MIS-C to have clinical features similar to those found in Kawasaki disease, macrophage activating syndrome, and toxic shock syndrome.[4] MIS-C has a predilection to primarily affect the cardiovascular system and gastrointestinal (GI) system.[5] IVIG and corticosteroids have been the main therapeutic options.[6] This retrospective observational study describes the clinical profile of patients with MIS-C, response to IVIG and steroids, and short-term outcome on follow-up.

Aims and Objectives

- To study the clinical profile and laboratory profile of children admitted with MIS-C associated with SARS-CoV-2 infection.
- To evaluate the difference in clinical presentation, treatment response and prognosis in younger (<5 years) and older (>5 years) children with MIS-C.
- To analyze the treatment response and short-term outcomes in children with MIS-C.

Materials and Methods

A multicentric retrospective study was conducted between August 2020 and December 2021 in five centers in South India (Aster CMI; Aster RV; Aster Women and Children Hospital, Bengaluru, Karnataka; Aster Medcity, Kochi and Aster MIMS, Calicut, Kerala, India). Children who fulfilled the WHO criteria of MIS-C were included in the study.[7] Children in the study group had positive coronavirus disease 2019 (COVID-19) polymerase chain reaction (PCR) test, or positive serology and/or contact with a person who had COVID-19 infection.

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Data was collected on predesigned proforma and the following details were noted—demographic data, duration of illness, clinical features at presentation, contact history suggestive of exposure to COVID-19 infection in the previous 1–2 months, laboratory parameters including inflammatory markers, two-dimensional echocardiography (2D ECHO), the clinical outcome at discharge and follow-up. COVID-19 reverse transcription (RT)—PCR test and COVID-19 antibody test using enzyme-linked fluorescent assay were performed on all patients. Cardiac dysfunction was considered in all patients requiring 20 mL/kg fluid bolus, inotropes, 2D ECHO abnormalities (ejection fraction <50%, coronary artery diameter Z-score of >2, elevated markers of cardiac injury [troponin I (trop I), creatine phosphokinase-MB, NT-ProBNP].[8]

The temperature was recorded periodically after starting IVIG/IV-methylprednisolone therapy to assess the response to the medication. The choice of immunomodulator was individualized based on the treating physician's assessment.

Statistical analysis used—Pearson Chi-squared test was utilized to analyze the categorical data. A p-value < 0.05 was considered statistically significant.

Results

A total of 81 children between the ages of 1 month to 16 years were included in the group. The mean age of presentation was 6.8 years. Males were predominantly affected (70.3 vs 29.6%) in our study population. Table 1 represents the important demographic and clinical features of the patients in our study. In our study, 4.93% had COVID-19 RT-PCR positive, 75.3% (61/81) had positive COVID-19 serology, and 27% had a positive history of contact with patients with COVID-19 in the last 2 months prior to the appearance of symptoms.

The mean duration of fever at admission was 4.6 days. The most common clinical presentation in our study other than fever was conjunctival congestion (54.3%), rashes (54.3%), and GI symptoms (53%) followed by lymphadenopathy (24.6%). Around 29.6% of the children had shock at admission and 54.3% (44/81) of them had myocardial dysfunction.

Table 1: Demographic data and clinical features in patients with MIS-C

Features	*N = 81*
Age	6.83 years
Male	57/81 (70.37)
Female	24/81 (29.6%)
Fever duration	4.65 days
Conjunctival congestion	44/81 (54.3%)
Rashes	44/81 (54.3%)
GI symptoms	43/81 (53%)
Lymphadenopathy	20/81 (24.6%)
Shock	24/81 (29.6%)
Neurological symptoms	8/81 (9.8%)
Low LV ejection fraction (<50%)	22/81 (27.1%)
Coronary artery abnormalities	8/81 (9.87%)
Treatment with IVIG alone	11/81 (15.3%)
Treatment with steroids alone	9/81 (11.1%)
Treatment with IVIG and steroids	54/81 (66.6%)
Conservative management without steroids and IVIG	5/81 (6.2%)
Average duration of hospital stay	6.6 days

Laboratory parameters were analyzed and important lab investigations have been highlighted in Table 2. Lymphopenia was seen in 24/81 (29.6%). Erythrocyte sedimentation rate (ESR) was elevated in most of the patients with a mean value of 47 mm/hour, D-dimer was also elevated in all our patients with a mean value of 5978 ng/mL. C-reactive protein (CRP) was elevated in all the patients and the mean CRP was 151 mg/mL. Procalcitonin was found to be elevated in all patients where the test was performed (n = 28) and the mean value was 39 ng/mL (normal range < 0.05 ng/mL). Blood cultures were taken from all children in the study population and two children grew coagulase-negative *staphylococcus*, which was a skin commensal. Trop I was elevated in 16 (55%) of the 29 patients in whom the test was done. NT-ProBNP was performed in 33 children and was found to be elevated in 87% (29/33) of which 37.9% of them had cardiac abnormalities in 2D ECHO. In our study, 7/29 (24%) of children with high NT-proBNP had hypotension at admission. Hypotension was more common at presentation in older children (>5 years) as compared to younger children (<5 years), however, it was not found to be statistically significant (p < 0.09).

The 2D ECHO was done in 79 patients on admission or during their hospital stay, out of which 27.8% (22/79) had an abnormal 2D ECHO, the predominant finding is left ventricular (LV) dysfunction, whereas 9.8% of patients had coronary artery abnormalities. ECHO detected early myocardial dysfunction in 15 patients who did not have signs or symptoms of shock at presentation.

Most children (66.6%) with MIS-C were treated with a combination of IVIG and steroids. In our cohort, 9/81 (11.1%) children were treated with steroids alone and 11/81 (15.3%) received only IVIG. Five children were treated conservatively and did not receive any immunomodulation. One child required treatment with tocilizumab (1/81) and anakinra was used to treat 2/81 patients, and they responded to the treatment. One child had macrophage activation syndrome (ferritin—18708 ng/mL) and needed mechanical ventilation along with inotropes. He recovered with IVIG, steroids, and anakinra. Three patients with MIS-C had severe illnesses and needed mechanical ventilation during their hospital stay. All patients with significant cardiac dysfunction received low molecular weight heparin and were discharged on aspirin. No difference was noted in terms of outcome between younger (<5 years) and older children.

The average time for defervescence after treatment was 2.2 days and the average duration of PICU stay was 6.6 days. The mean

Table 2: Laboratory investigations in children with MIS-C

Parameter	*Observed value (mean)*
Hemoglobin (g/dL)	10.5
Total white blood cell counts (cells/cumm)	14901
Lymphocyte count	1049.8
Platelet count (cells/cumm)	173,865
CRP (mg/L)	151 (<6)
Procalcitonin (ng/mL)	39
Lactate dehydrogenase (U/L)	295
D-dimer (ng/mL)	5978
ESR (mm/hour)	47
NT-ProBNP (pg/L)	6072
Trop I (ng/L)	41
COVID-19 RT-PCR	4/81 (4.93%)
Anti-SARS-CoV-2 antibodies	61/81 (75.3%)

duration of hospital stay was 6 and 8 days in children below and above 5 years, respectively. Patients with hypotension had a mean duration of hospital stay of 7.4 days, whereas those who did not have hypotension had a mean duration of stay of 6.3 days. All children recovered and follow-up ECHO has shown normalization of cardiac function at 6 weeks in those who had myocardial dysfunction at presentation. Follow-up ECHO at 6 months has been normal.

Discussion

Multisystem inflammatory syndrome in children (MIS-C) is an illness that presents typically 4–6 weeks after exposure to SARS-CoV-2 infection. Typical clinical features are high-grade fever for 3 days or more with rashes, conjunctival congestion, GI symptoms, and features of shock resulting from cardiac dysfunction. Other less common presentations are lymphadenopathy and neurological symptoms.[1–3] The most accepted theory of the pathogenesis of this illness is that low titers of nonneutralizing antibodies in affected children lead to incomplete neutralization of the virus resulting in severe disease.[9]

The first few cases of MIS-C were reported from the United Kingdom in the mid of April 2020, when an unusual surge in cases of children presenting with features similar to Kawasaki disease and toxic shock syndrome was noted.[10] Since then, it has been one of the predominant causes of morbidity of COVID-19-related illness in children.

The mean age of presentation in the current study was 6.8 years. This is similar to what has been documented in some of the studies on MIS-C from our subcontinent.[11–13] Fever was noted in all patients and is the hallmark of the disease. GI and mucocutaneous manifestations were noted in 53 and 54.3%, respectively as compared to the meta-analysis reported by Ahmed et al. where 71% of patients had GI symptoms and 56.2% had mucocutaneous involvement.[14] Shock was noted in 29.6%. We tried to compare older (>5 years) and younger children (<5 years) to look for any predictive age-group for severe manifestations. However, 9 (<5 years) and 14 (>5 years) children in both groups had shocked and the difference was not statistically significant. In our study cohort, 41.9% had myocardial dysfunction and 9.8% had coronary abnormalities. In a study done by Matsubara et al. where three cohorts of MIS-C, Kawasaki disease, and control group were compared, only one of the 28 patients in the MIS-C cohort had coronary artery dilatation, while 12/28 (42%) of the patients had low LV ejection fraction.[15]

In our cohort, lymphopenia was a common finding across all the age-groups. CRP was markedly elevated and the mean value was 151 mg/mL. These results are comparable to previously published data.[11–14] Procalcitonin, a calcitonin precursor has been traditionally known to be a biomarker elevated in bacterial sepsis. In patients with septic shock, it has been used to differentiate bacterial from viral infections. However, contrary to conventional thinking, many studies have shown elevated procalcitonin in children with MIS-C. In our study, procalcitonin was done in 28 patients and all of them had high procalcitonin levels (mean value 39 ng/mL). Notably, blood cultures were sterile in all of them, excluding any bacterial infection. A study by Ahmed et al. found high levels of procalcitonin in their patients (mean value = 30 ng/mL) in the absence of bacterial infection.[14] High procalcitonin levels in MIS-C indicate a severe systemic inflammatory response and it cannot be used to distinguish bacterial infection from MIS-C.

N-terminal brain natriuretic peptide (NT-ProBNP) is a biomarker that is released in response to ventricular wall stress.[17] It is elevated in both symptomatic and asymptomatic patients with LV dysfunction.[18] Blondiaux et al. studied cardiac MRI findings in patients with MIS-C and reported a positive correlation between high BNP values and myocardial interstitial edema.[19] In our study population, children with elevated NT-ProBNP were found to have significant LV

Table 3: Clinical profile of patients with MIS-C in comparison with previously published case series

Clinical features	*Current study N = 81*	*Shobhavat et al.*[11] *N = 21*	*Dhanalakshmi et al.*[12] *N = 19*	*Ahmed et al.*[14] *N = 622*
Age in years (mean)	6.8 years	7 years	6 years	9.3 years
Fever	100%	100%	100%	100%
Conjunctival congestion	44 (54.3%)	9 (42%)	9 (47%)	343 (51.8)
Skin rash	44 (54.3%)	7 (33%)	12 (63%)	372 (56%)
Lymphadenopathy	20 (24.6%)		6 (31%)	92 (13.8%)
GI symptoms	43 (53%)	16 (76%)	8 (42%)	452 (78%)
Neurological symptoms	8 (9.8%)	–	6 (31%)	129 (19.4%)
Shock	24 (29.6%)	20 (95%)	10 (52%)	397 (60%)
Lymphopenia	24 (29.6%)	13% (absolute lymphocyte count)	(36%)	9.8% (absolute lymphocyte count)
Platelet count	173,865	99,000	150,000	215,000
CRP (mg/dL)	151	98	118	215
NT-ProBNP (pg/mL)	6072	–	–	3604
D-dimer	5978	2664	4250	3500
LV dysfunction	44 (54.3%)	9 (43%)		
Coronary dilatation	8 (9.8%)	5 (24%)	15%	47 (7.1%)
IVIG	65 (80.2%)	11 (52%)	15 (79%)	504 (76%)
Steroids	63 (77.7%)	18 (86%)	11 (58%)	347 (52.3%)
Discharge	81 (100%)	18 (86%)	19 (100%)	651 (98.3%)
Death	0%	3 (14%)	0%	11 (1.7%)

IVIG, intravenous immunoglobulin

dysfunction on echocardiogram (37%), and hypotension was seen in 24% of the children. NT-ProBNP in MIS-C seems to be an independent marker of significant cardiac injury and may be of value at places where echocardiography is not readily available.

The majority of our patients (68.2%) needed combination therapy with IVIG and steroids. A small minority were treated with steroids alone. Recent studies have highlighted shorter hospital stays and better recovery with combination therapy. A study done by Ouldali et al. found that a combination of IVIG and methylprednisolone achieved earlier defervescence, faster recovery of myocardial dysfunction, and shorter duration of ICU stay among children.[6] In a study by McArdle et al., amongst 614 children with suspected MIS-C, 246 received primary treatment with IVIG alone, 208 with IVIG plus glucocorticoids, and 99 with glucocorticoids alone; 22 children received other treatment combinations, including biologic agents, and 39 received no immunomodulatory therapy.[20] This study aimed to compare the outcomes in the three groups in terms of ionotropic support or mechanical ventilation, mortality, and reduction in disease severity. The study so far has not found any statistical significance among the three groups [adjusted odds ratio for the comparison with IVIG alone, 0.77; 95% confidence interval (CI), 0.33–1.82] and in 17 patients who received glucocorticoids alone (adjusted odds ratio, 0.54; 95% CI, 0.22–1.33). The adjusted odds ratios for a reduction in disease severity were similar in the two groups, as compared with IVIG alone (0.90 for IVIG plus glucocorticoids and 0.93 for glucocorticoids alone). It is an ongoing study and results may vary with the addition of more cases. This study has pivotal importance in the management of MIS-C, as IVIG has significant financial implications in resource-limited settings like ours. It would be interesting to see if these children can be treated with steroids alone.

It was heartening to note 0% mortality in our cohort, better than most published studies. Shobhavat et al. from Mumbai reported a very high mortality of 14%.[11] Around 90% of their cohort needed vasoactive support and the high mortality was attributed to delay in the diagnosis. A multicentric study by Ahmed et al. reported a mortality of 1.7%,[14] which is in corroboration with most studies in children with MIS-C. Some important studies on MIS-C have been tabulated (Table 3).

Conclusion

We present the data from five tertiary care centers in South India and discuss the profile of children with MIS-C in detail. While a significant proportion of older children presented with hemodynamic compromise, timely treatment ensured recovery in all cases. Our study reemphasizes the need for early diagnosis and timely treatment in patients with MIS-C.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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