

Original Article

Clinico-epidemiological Profile of MIS-C Temporally Associated with COVID-19 — A Hospital Based Retrospective, Cross Sectional, Observational Study. What is new ?

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Background : Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) related Multisystem Inflammatory Syndrome in Children (MIS-C) is an acute illness accompanied by hyper-inflammatory syndrome and may require ICU admission and can lead to multi organ failure and shock. The objective of this study was to study the Clinico-epidemiological profile and outcome of children with MIS-C treated with methylprednisolone alone or combined methylprednisolone and Intravenous Immunoglobulin (IVIG)

Materials and Methods : This retrospective, observational, cross-sectional study was conducted in children who were admitted from May, 2021 to April, 2022 satisfying WHO MIS-C criteria. Clinico-epidemiological data were obtained and treatment outcomes were compared between children who received methylprednisolone alone and those who received combined methylprednisolone and IVIG.

Results : Study included 53 children with MIS-C with majority patients ie, 22(41.5%) were infants. Respiratory symptoms were present in 12(22.6%) patients. Gastrointestinal symptoms were present in 19(35.8%) patients. Cardiovascular symptoms were present in 13(24.5%) patients. Neurological symptoms were present in 18(34%) patients. Mucocutaneous symptoms were present in 28(52.8%). Methylprednisolone and IVIG were used as immunomodulator therapy. 31(96.9%) patients who received methylprednisolone alone and 21(100%) patients who received combined methylprednisolone and IVIG got discharged. ICU stay for more than 14 days and invasive ventilation requirement were significantly less in methylprednisolone group (p value 0.011438; p value 0.011993).

Conclusion : Both treatment with methylprednisolone alone and methylprednisolone and IVIG combined showed favourable and comparable outcomes in both the groups.

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Key words : MIS-C, Methylprednisolone, IVIG, COVID-19, SARS-CoV-2.

The COVID-19 pandemic is far from over and it will not be over anywhere until it's over everywhere¹. Multisystem inflammatory Syndrome in Children (MIS-C) is an acute illness accompanied by hyper-inflammatory syndrome and may require ICU admission and can lead to multi organ failure and shock²⁻⁵. There are certain findings that distinguish MIS-C from severe COVID-19⁶. Occurrence of MIS-C also has some racial differences⁷. There is therefore an urgent need for collection of standardised data describing clinical presentations, severity, outcomes and epidemiology^{2,8}. Early diagnosis is important for favourable outcomes⁹. So, it is important to know the clinical profile of MIS-C temporally associated with COVID-19 of the children in this geographical area.

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Editor's Comment :

- Favourable and comparable outcomes were seen with both treatment with methylprednisolone alone and combined methylprednisolone and IVIG.
- Use of methylprednisolone alone without IVIG for treatment of MIS-C patients in resource constraint setups needs to be determined through larger multicentric studies.

There is a continuous evolution of our understanding of SARS-CoV-2 related syndromes in children^{4,10}. Robust information about long-term outcomes needs further study along with immunologic data to improve diagnostic and therapeutic strategies¹¹. Various guidelines have already come up which are progressively being upgraded. Further studies are needed urgently to define the real impact of MIS-C on child health and to elucidate the best clinical and therapeutic approach and true prognosis^{12,13}.

MATERIALS AND METHODS

This retrospective, observational, cross sectional study was conducted in a peripheral resource constraint Tertiary Care Medical College & Hospital in

India. Ethics Committee clearance for biomedical research involving human participation was obtained before the start of the study from the institutional ethics committee. It was conducted for the period from May, 2021 to April, 2022.

Diagnosis of MIS-C was made on the basis of WHO criteria². Children admitted with MIS-C upto 12 years of age were included. Exclusion criteria were infection with dengue, scrub typhus and bacterial sepsis.

SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) was done and SARS-CoV-2 antibody test were done using Electrochemiluminescence Immuno-assay Analyser (ECLIA). Contact with SARS-CoV-2 patient in past was also documented in all patients. Treatment guideline included methylprednisolone alone and methylprednisolone and IVIG combined as immunomodulator. Availability of IVIG was an issue. In its absence, necessary modification was made. Study population had no choice of the treatment they received. Echocardiography was done during admission and was followed up after 4-6 weeks or frequently in some cases as per guidelines. Shock was identified in presence of clinical features as per standard guidelines.

Data extraction sheet with pre-designed proforma was used to collect data on demographic, clinical symptoms and signs, type of supportive treatment and immunomodulation. Data were entered in statistical analysis software. Chi square test was used for statistical analysis.

RESULTS

This study included total 53 patients. Males were 38(71.7%). 53(100%) patients had positive SARS-CoV-2 IgG antibodies and temporal association with SARS-CoV-2 contact was present in 10(18.9%) patients. Clinical characteristics as shown in Table 1 are maximum number of patients were infants ie, 20(41.5%), 11(20.8%) were of 1-3 years age, 10(18.9%) were of 3-6 years age, 5(9.4%) were of 6-9 years age and 5(9.4%) were of 9-12 years age. The mean age was 2.62 years(SD 3.43). Associated condition such as diabetes was present in 2(3.8%) patients and neurological disease was present in 7(13.2%) patients. Symptom duration before admission was 5 days (IQR 3-7). Respiratory symptoms were present in 12(22.6%) patients which included cough in 10(18.9%), wheezing in 5(9.4%) and respiratory distress in 3(5.7%) patients. Gastrointestinal symptoms were present in 19(35.8%) patients which included diarrhoea in 15(28.3%), vomiting in 10(18.9%) and abdominal pain in 12(22.6%)

Characteristics	No of patients (%) (n=53)
Age	22 (41.5)
0-1 year	11 (20.8)
1-3 years	10 (18.9)
3-6 years	5 (9.4)
6-9 years	5 (9.4)
9-12 years	
Gender	
Male	38 (71.7)
Associated condition	9(17)
Metabolic disease	2 (3.8)
Neurological disease	7 (13.2)
Symptom duration before admission	Median(5),IQR(3-7)
Respiratory symptoms	12 (22.6)
Cough	10 (18.9)
Wheezing	5 (9.4)
Respiratory distress	3 (5.7)
Gastrointestinal symptoms	19 (35.8)
Diarrhoea	15 (28.3)
Vomiting	10 (18.9)
Abdominal pain	12 (22.6)
Cardiovascular symptoms	13 (24.5)
Hypotension	6 (11.3)
Shock	3 (5.7)
Heart failure	4 (7.5)
Neurological symptoms	18 (34)
Convulsion	6 (11.3)
Unconsciousness	10 (18.9)
Acute flaccid paralysis	1 (1.9)
Ophthalmoplegia	1 (1.9)
Mucocutaneous symptoms	28(52.8)
Skin rash (Erythematous, maculopapular, blanchable)	20 (37.7)
Hand/foot (Rash, Edema, desquamation)	5 (9.4)
Erythematous lips/Red tongue/congested oral mucosa/eyes (congestion, discharge)	3 (5.7)
Musculoskeletal symptoms (Myalgia, arthralgia)	5 (9.4)
Haematological symptoms (Mucosal bleeding, petechiae)	2 (3.8)
Metabolic derangements (metabolic acidosis, hyperglycemia)	2 (3.8)
Raised temperature	52 (98.1)
Palpable lymph nodes	5 (9.4)
Chest auscultation - crepitations, wheezing	11 (20.8)
Heart - Murmur	1 (1.9)
Hepatomegaly	5 (9.4)
Splenomegaly	2 (3.8)
Serology positive	53 (100)
History of contact with SARS-CoV-2 patient	10 (18.9)

patients. Cardiovascular symptoms were present in 13(24.5%) patients which included hypotension in 6(11.3%), shock in 3(5.7%) and heart failure in 4(7.5%) patients. Neurological symptoms were present in 18(34%) patients which included convulsion in 6(11.3%), unconsciousness in 10(18.9%), acute flaccid paralysis in 1(1.9%) and Ophthalmoplegia in 1(1.9%) patient. Mucocutaneous symptoms were commonest in our study in 28(52.8%). Skin rash was present in 20(37.7%) patients. Hand/foot involvement was present

in 5(9.4%) patients. Lips, Tongue, Oral mucosa and eye involvement was present in 3(5.7%) patients. Musculoskeletal involvement was present in 5(9.4%) patients. Haematological symptoms and signs were seen in 2(3.8%) patients. Metabolic derangements were present in 2(3.8%) patients. Temperature was raised in 52(98.1%) patients. Hypothermia on examination was present in one patient and this patient had history of fever for four days at the onset. Lymph nodes were palpable in 5(9.4%) patients. Wheezing and crepitations on chest auscultation was present in 11(20.8%) patients. Murmur on auscultation of heart was present in 1(1.9%) patient. Hepatomegaly was present in 5(9.4%) patients. Splenomegaly was present in 2(3.8%) patients.

Among the laboratory parameters, mean Total Leucocyte Count was 15935 cells/mm³ (SD 8338), mean platelet count was 209100/mm³ (SD 165194). Mean CRP was 34 mg/L (SD 26). Mean ESR was 48 mm/h (SD 39). Mean Ferritin level was 763 ng/mL (SD 960). Mean D-dimer level was 2746 ng/mL (SD 2506). Mean serum LDH level was 508 U/L (SD 224) (Table 2).

Table 3 shows differences in clinical, treatment measures and outcome in children who received methylprednisolone alone (n=32) or methylprednisolone and IVIG combined (n=21). Coronary artery aneurysm was seen in 1(3.1%) patient in the methylprednisolone group. Multiorgan involvement was seen in 2(6.3%) patients in the methylprednisolone group. Inotrope requirement was seen in 2(6.3%) patients in the methylprednisolone group and 3(14.3%) patients in combined methylprednisolone and IVIG group. ICU stay for more than or equal to 14 days was seen in 9(28.1%) patients in methylprednisolone group and 10(47.6%) patients in combined pulse methylprednisolone and IVIG group. Among respiratory support requirement, 10(31.3%) patients in the

methylprednisolone group and 3(14.3%) patients in combined methylprednisolone and IVIG group required oxygen via nasal prong/face mask. 4(12.5%) patients in the methylprednisolone group and 9(42.9%) patients in combined methylprednisolone and IVIG group required invasive ventilation. 31(96.9%) patients in the methylprednisolone group and 21(100%) patients in combined

methylprednisolone and IVIG group got discharged. Death occurred in one (3.1%) patient in the methylprednisolone group within a short period after admission due to uncorrected shock and metabolic acidosis.

Applying chi square test to requirement of ICU stay for 14 days or more to the two treatment groups, it was significantly less in methylprednisolone group (p value 0.011438). Applying chi square test to requirement of invasive ventilation between the two treatment groups, it was significantly less in methylprednisolone group (p value 0.011993). When chi square test was applied to other parameters mentioned in Table 3, no statistically significant difference was obtained.

DISCUSSION

We report low case fatality from a resource limited peripheral Medical College & Hospital in India. We could not afford to provide IVIG to all patients though we had intention to do so as has been suggested by the WHO protocol. It was not possible largely due to unavailability of IVIG. Total number of cases was 53. Majority patients ie, 22(41.5%) were infants. The mean age was 3.2 years (SD 3.4). In a study done by Manem, *et al*¹⁴ in India, mean age at presentation was 6.7 years (SD3.5). In a study by Sugunan, *et al*¹⁵ median (IQR) age was 7.5 (5-9.5) years. In a study by Dhanalakshmi, *et al*¹⁶ median (IQR) age was 6 years (13 months-16

Table 2 — Laboratory parameters of MIS-C children

Laboratory parameters	Mean (SD)
Total Leucocyte count(cells/mm ³)	15935 (8338)
Platelet count (/mm ³)	209100 (165194)
CRP (mg/L)	34 (26)
ESR (mm/h)	48 (39)
Ferritin (ng/mL)	763 (960)
D-dimer (ng/mL)	2746 (2506)
LDH (U/L)	508 (224)

Table 3 — Difference of clinical, treatment measures and outcome in the treatment groups

Characteristics	Methylprednisolone group (n=32)	Combined methylprednisolone and IVIG group (n=21)	p value
Age	2.62 years (SD 2.97)	4.15 years (SD 3.98)	
Shock	6 patients (18.8%)	3 patients (14.3%)	
CRP (mg/L)	33.8 (SD 26.58)	43.42 (SD 28.78)	
D-dimer (ng/mL)	2682.56 (SD 2339.22)	2571.89 (SD 2119.84)	
Coronary Artery Aneurysm (CAA)	1 patient (3.1%)	0	
Multiorgan involvement	2 patients (6.3%)	0	
Inotropes required	2 patients (6.3%)	3 patients (14.3%)	
ICU stay for 14 days or more	5 patients (15.6%)	10 patients (47.6%)	0.011438
Respiratory support :			
Oxygen via nasal prong/face mask	10 patients (31.3%)	3 patients (14.3%)	
Invasive ventilation	4 patients (12.5%)	9 patients (42.9%)	0.011993
Outcome :			
Discharge	31 patients (96.9%)	21 patients (100%)	
Death	1 patient (3.1%)	0	

years). In a study done at South Africa, median age was 7 years¹⁷. In a study done in US children, median age was 8 (4-13 years)¹⁸. In a study done by Nunez, *et al* median age was 8 years¹⁹.

Seropositive cases were 53(100%) in our study. History of contact with SARS-CoV-2 patient was present in 10(18.9%) patients. In a study by Dhanalakshmi, *et al* 7 children (47%) had positive serological assay¹⁶. In a study by Manem, *et al* seropositivity was seen in 87(84.3%) cases and history of contact with SARS-CoV-2 patient was present in 16(15.6%) cases¹⁴. In a study in South Africa, 29(30%) children had positive serology¹⁷. Males were 38(71.7%) in our study. In various studies in India, number of males were 55(53%)¹⁴, 21(66%)¹⁵, 8(42%)¹⁶. In a study in South Africa, males were 52.9%¹⁷. In a study in US, 133(53.6%) patients were male¹⁸. Associated conditions and co-morbidities were present in 9(17%) cases in our study. In various studies in India, underlying medical condition was present in 12.5% cases¹⁵ and 5.2% cases¹⁶.

Mucocutaneous symptoms were commonest in our study in 28(52.8%). In various studies in India, it was 90.6%¹⁵ and 74%¹⁶. In a study in South Africa, mucocutaneous involvement was seen in 85% patients¹⁷. In our study, gastrointestinal system involvement was present in 19(35.8%) patients. In other Indian studies, 84% in one study and 42% in another study presented with gastrointestinal symptoms^{15,16}. In a study in South Africa, 85% patients presented with gastrointestinal symptoms¹⁷. Respiratory symptoms were present in 12(22.6%) patients in our study. In other Indian studies, respiratory system involvement was seen in 43.7% in one study and 42% in another study^{15,16}. In a study in South Africa, respiratory symptoms were present in 30% cases¹⁷.

Cardiac involvement was seen in 13(24.5%) cases. It is the most frequently reported organ dysfunction in MIS-C. In other Indian studies, study by Sugunan, *et al* showed cardiac involvement in 90% patients with coronary artery aneurysms being present in 34.4% patients¹⁵. Study by Dhanalakshmi, *et al* showed cardiac involvement in 63% patients with commonest symptom being hypotension in 52.6% cases¹⁶. In a study in South Africa, cardiac involvement was seen in 71% patients which included pericardial effusion (17.6%), mitral regurgitation (36.8%) and coronary artery aneurysms (5.9%)¹⁷. Neurological involvement was seen in 18(24%) patients in our study. In a study by Dhanalakshmi, *et al* neurological involvement was seen in 31% patients¹⁶. In a study in South Africa,

neurological involvement was seen in 29% patients¹⁷.

Treatment with IVIG was a challenge due to unavailability and unaffordability. In our study, children who received methylprednisolone alone had coronary artery aneurysm in 3.1% cases and multiorgan involvement in 6.3% cases. Less number of coronary artery aneurysms in our study might be due to early initiation of therapy with methylprednisolone through its anti-inflammatory activity. Prolonged ICU stay and invasive ventilation requirement were significantly less in patients who received methylprednisolone alone as compared to combined methylprednisolone and IVIG. Favourable outcome was seen in all patients in combined methylprednisolone and IVIG group (100%) and almost all in methylprednisolone group (96.9%) except one (3.1%) patient who presented very late died after a very short period of time after admission due to uncorrected shock and metabolic acidosis in the methylprednisolone group. Early presentation might have improved prognosis.

Small sample sizes, single centred are the main limitations of our study. Though it is a retrospective study, this study can form the basis on which prospective studies can be planned²⁰.

CONCLUSIONS

Majority of our patients (63%) were below the age of 3 years. 100% of our cases were seropositive. Among that, 41.5% were infants. Cardiac involvement was less common in our study reported only in 24.5% cases. Both treatment with methylprednisolone alone and combined methylprednisolone and IVIG showed favourable and comparable outcomes. Only one death occurred in the methylprednisolone group which was not statistically significant. Through multicentric and larger studies, it remains to be determined whether a low cost therapy with methylprednisolone alone without IVIG can be used for treatment of MIS-C patients in resource constraint setups.

Prior publication : Nil

Support : Nil

Conflicts of interest : Nil

Permissions : Ethical Committee approval was taken.

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