Clinical profile and treatment of Multisystem Inflammatory Syndrome in Children (MIS-C) linked to COVID-19 at Tertiary care centre in Western India.

ABSTRACT

Aims: To assess the clinical presentation and therapeutic interventions administered to patients suffering from MIS-C in a tertiary centre in Western India

Study design: This is a cross sectional observational study

Place and Duration of Study: Department of Pediatrics at Rajiv Gandhi Medical College, Chhatrapati Shivaji Maharaj Hospital, Thane, Maharashtra. It was conducted from September 2021-September 2022.

Methodology: Patients were clinically diagnosed as MIS-C based on the the Centers for Disease Control and Prevention (CDC)guidelines and retrospective analysis was carried out by reviewing medical records and complementary exams.

Results: There were 36 children in total, 21 female (58.3%) and 15 males (41.7%) with ages ranging from less than 1 year to 18 years with mean age of 7.2 years. The symptoms were classified based on the organ system involved. Fever was present in most of the patients and Gastrointestinal symptoms in 18 (50%) were the most common followed by respiratory and Central Nervous System symptoms. Investigations revealed that White Blood Cell (WBC) count was predominantly normal in 77.8 %, with lymphocytopenia in 77.8% and reduced Hemoglobin (80.6 %). Inflammatory markers such as D-dimer, Erythrocyte sedimentation rate and serum Ferritin were raised in 94%, 88.9%, 86.1% respectively. Most of the patients 34 (94%), were treated with Intravenous steroids. IV immunoglobulin was given in 29 (80.6%). Out of the total 36 patients, there were 2 deaths.

Conclusion: Although SARS-CoV-2 infection is less severe in children than in adults, some pediatric patients may present with severe symptoms requiring intensive care. This case series of patients with MIS-C post COVID-19 identified patterns of clinical presentation and organ system involvement. Most were treated and responded to steroids and immunoglobulins.

Keywords: Multisystemic Inflammatory Syndrome in Children9(MIS-C), Kawasaki disease, COVID-19, SARS-CoV-2

1. INTRODUCTION

Covid-19 pandemic has been the biggest highlight of 2020-21 and early 2022 and still continues with relatively less number of patients. Multisystem inflammatory syndrome (MIS) is a rare but serious condition associated with COVID-19, in which different organs become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal tract. MIS can affect children (MIS-C) and adults (MIS-A) [1].MIS-C is considered as a syndrome (a group of signs and

symptoms, not a disease) because much remains unknown about it, including its cause and risk factors. Identifying and studying more children who have MIS-C will help eventually to find a cause [2]. Initially, it was observed that children were spared from disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, a month into the pandemic, a novel multisystem inflammatory syndrome in children (MIS-C) emerged [3], The clinical picture includes fever, severe illness, and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2 infection. Some features of MIS-C resemble Kawasaki Disease, toxic shock syndrome, and secondary hemophagocytic lympho-histiocytosis/macrophage activation syndrome. The relationship of MIS-C to SARS-CoV-2 infection suggests that the pathogenesis involves post-infectious immune dysregulation [4].

When to suspect MIS-C [1].

1. Child/adolescent with fever> 3 days
2. Acute GI symptoms (vomiting, diarrhea, abdominal pain)
3. History of COVID-19 or contact with COVID patient in last 3 months
4. Tachypnoea, tachycardia, oliguria out of proportion to the fever
5. Marked prostration or irritability
6. Urticaria, bilateral non purulent conjunctivitis, red lips, inflammation in hands / feet, BCG scar reactivation
7. And no other obvious cause of inflammation including bacterial sepsis, staph. or strep. shock syndrome)

MIS-C may occur a few weeks to few months after acute COVID illness (which could have been mild or asymptomatic) and it has also been seen in neonates (MIS-N) born to COVID positive mothers in the third trimester or during delivery [5]. MIS-C was hypothesized to be mostly post-infectious and distinct from COVID-19 because many patients respiratory specimens were SARS-CoV-2 negative and MIS-C peaked after COVID-19 cases started waning [6,7]. Data on hospitalized children and adolescents with severe acute COVID-19 and MIS-C is limited [8,9].

2. MATERIAL AND METHODS

The study was conducted after the approval from the Institutional Review Board and Institutional Clinical Ethics Committee of the tertiary care hospital and medical college in western India. The study is record based and all those patients who were diagnosed as post COVID multisystem Inflammatory Syndrome in children (MIS-C) according to the CDC guidelines published on its website were included in the study. The study group was from newborns to 18 years of age. Data was collected from September 2021 to September 2022. It is comprised of demographic data, presenting clinical symptoms along with the laboratory parameters. The treatment modalities were recorded.

Inclusion Criteria: All the patients from the age group 0-18 years, satisfying the CDC criteria of MIS-C

Exclusion Criteria: The patients who did not fulfil the criteria of MIS-C and had other diagnosis were excluded from the study.

SPSS version 22.0 statistical software package for Microsoft Windows (SPSS Inc., Chicago, IL) and MS-Excel were used for data analysis

3. RESULTS AND DISCUSSION

1. DEMOGRAPHIC PROFILE

Out of the 36 children satisfying the CDC criteria of MIS-C, 21 were female (58.3%) and 15 were male (41.7%). χ^2 (chi-square) test, which was performed to assess the pattern of distribution, returned a non-significant *p*-value (p=0.478). Hence, the seemingly unequal distribution of males and females is not statistically significant. The age distribution ranged from less than 1 year up to 18 years of age with mean age of children being 7.2 years. Table 1 shows the demographic picture of the study population.

Table 1: Demographic picture of study population

GENDER	NUMBER	PERCENTAGE
MALE	15	41.7
FEMALE	21	58.3

AGE	NUMBER	PERCENTAGE
0 year – 5 years	10	27.8
6 years – 10 years	18	50.0
>10 years	8	22.2

2. CLINICAL PRESENTATION

The symptoms were classified based on the organ system involved. Fever was the most common presentation in patients (91.67%) out of which majority (77%) reported having high grade fever of > 103 **°C.** 50% patients reported GI symptoms such diarrhoea, vomiting, abdominal pain and refusal to feed. . 33.3% children with MIS-C had respiratory symptoms like cough and breathlessness. CNS symptoms like febrile seizures, altered sensorium and headache were noted in 30.5% of the children and CVS symptoms were reported in 8.33% of the study population.

Table 2: Clinical symptoms of children with MIS-C

Symptoms	
FEVER	33 (91.67%)
HIGH GRADE FEVER	28 (77.78%)
RECURRENT FEVER	5 (13.89%)
GASTRO INTESTINAL SYMPTOMS	
Diarrhoea	7 (19.44%)
Vomiting	13 (36.11%)
Abdominal pain	5 (13.89%)
Jaundice	1 (2.78%)
Refusal to feed	1 (2.78%)
CNS SYMPTOMS	
Febrile seizures	7 (19.44%)
Altered sensorium	4 (11.11%)

Headache	1 (2.78%)
CVS SYMPTOMS	
Shock	2 (5.56%)
Chest pain	1 (2.78%)
RS SYMPTOMS	
Cough	8 (22.22%)
Breathlessness	12 (33,33%)

3. LABORATORY FINDINGS

3.1 HEMATOLOGICAL FINDINGS

With regards to haematological findings WBC count was predominantly normal (77.8 %) in the study sample. However, lymphocytopenia (77.8%) with reduced Haemoglobin (80.6 %) (as per the normal range for that age group) was noted in a vast majority of the children with MIS-C.

Table 3.1 Haematological Findings

HEMATOLOGICAL PARAMETERS		
WBC Count	NORMAL	28 (77.78%)
	REDUCED	8 (22.22%)
Lymphocyte count	NORMAL	8 (22.22%)
	REDUCED	28 (77.78%)
Hb	NORMAL	7(19.44%)
	REDUCED	29 (80.56%)

3.2 INFLAMMATORY MARKERS

Inflammatory markers such as D-dimer, ESR, IL-6, CRP, LDH and Serum Ferritin were evaluated for all the cases and the results have been summarised in figure 3.2. D-dimer, ESR, and Serum Ferritin were raised in maximum patients, 34(94%), 32((88.9%), 31(86.1%) respectively.

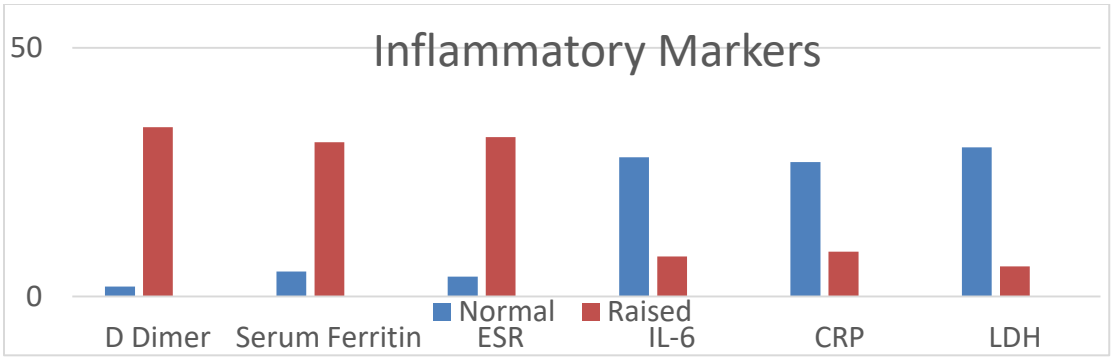

Fig 3.2 Inflammatory markers findings
*X axis represents Inflammatory Markers & Y axis represents no. of patients.

3.3 COAGULATION MARKERS

All Coagulation markers (PT, PTT, INR) were prolonged in patients with MIS-C. Results summarised in table 3.3.

Table 3.3 coagulation marker findings

PARAMETER	RESULT	PERCENTAGE
PT	PROLONGED	18 (50%)
PTT	PROLONGED	10 (27.78%)
INR	RAISED	8 (22.22%)

3.4 OTHER INVESTIGATIONS

1. Other investigations that were done included Chest- x rays and CSF examination. Chest X-ray was done for 20 cases having respiratory complaints but significant radiological finding were seen in only 3 cases. These findings were as follows-

- Left sided lower zone consolidation with mild left sided pleural effusion in one patient
- One patient showed Rt upper zone and bilateral lower zone pneumonia
- One patient showed Right hilar shadow with haziness.

2. CSF examination:

CSF examination was done for the 12 patients who had CNS symptoms. Out of all the samples collected only one had hazy red CSF with lymphocytosis, rest all the samples were found to have normal physical, biochemical and microbiological parameters.

3.5 Treatment Plan

Table 4- Medicines used

MEDICINES USED

INTRAVENOUS STEROIDS	34(94%)
IMMUNOGLOBULINS	29(80.6%)

Most of the patients 34 (94%), were treated with IV steroids like Dexamethasone and Methylprednisolone, I.V. immunoglobulin was given in 29 (80.6%), and antibiotics like Ceftriaxone and Meropenem were given based on antibiotic sensitivity reports. Oxygen was provided by age-appropriate devices for patients experiencing respiratory distress. Only one patient required mechanical ventilation.

Symptomatic management was done for the child as and when required. Supportive measures for symptomatic relief included Phenobarbitone and Midazolam to control seizures. Vitamin K and Low Molecular weight Heparin was given for patients with increased PT and PTT& D-dimer. Paracetamol was prescribed to control the fever. Other drugs which were included in the treatment were Chloroquine, Acyclovir and Artesunate as and when required

Out of the total 36 patients, there were 2 deaths. One was a 9-year-old female with Down's syndrome, who died 3 days post admission of cardiac complications. The second patient was an 8-year-old boy who was on mechanical ventilation since admission for respiratory distress and died after 3 days due to respiratory failure.

Independent samples t-test was performed to compare equality of means between the initial test results of the death group (2 patients) to the survival group (34 patients). Mean age ($t = 4.134$; $p = 0.003$), TLC ($t = 3.206$; $p = 0.003$) and neutrophil % ($t = 4.073$; $p = 0.000$) were significantly higher in the patients who died compared to the patients who survived. Other evaluated parameters were not significantly different between the two groups; however, larger sample sizes are required to compare the same.

DISCUSSION

The findings in the patients showed multisystem involvement with predominant presenting symptoms being fever and GI symptoms, which was consistent with the presentation in other studies. Fever lasted for five days and was of a high grade. Fever was present before appearance of gastro intestinal symptoms in our patients; this was also observed in another study by Hoste L et al. [3]. Elevated biomarkers like haematological parameters and inflammatory markers elucidated a poor prognosis. [3]

Therapy modalities preferred were steroids and Intravenous Immunoglobulins which helped in management of the defective immunoregulation and cytokine storm. Early therapy increased recovery multi fold. Antibiotics provided a protective cover on the steroid and weak immune system of the child. Development of a standard treatment regime still remains unexplored. However current therapy focuses primarily on subduing the inflammation while providing symptomatic relief and alleviating an emergency situation [6].

In general terms, the clinical manifestations of SARSCoV-2 infection are less severe in Paediatric patients than in adults [11]. The study published by Dong et al. revealed that only 6% of the more than 2,000 paediatric patients included, developed severe clinical symptoms [12], and only a small proportion needed intensive care. The occurrence of severe systemic hyperinflammatory symptoms probably associated with SARS-CoV-2 infection in children has raised concerns among scientific societies [13–16]. This syndrome, whose symptoms mimic those of sepsis, Kawasaki Disease or Toxic Shock Syndrome, has been described in different studies [16–20].

In the current study, 72% of paediatric patients with MIS-C were older than 6 years. This finding contrasts with KD, which is more frequent in children less than 5 years old [21]. These findings are consistent with those observed in the studies published by Whittaker et al. and Verdoni et al. where MIS-C patients are compared with previous cohorts of KD patients showing older age [18, 22].

Fever is the most frequent symptom in patients with MIS-C, with 100% of patients developing a fever in other studies, likewise our study also had 91.67% patients with fever [8, 9,12]. In patients with MIS-C, gastrointestinal symptoms are more frequent than respiratory symptoms, whereas patients with SARS-CoV-2 typically show respiratory symptoms. This finding contradicts the data reported by Shekerdemian et al., who reported a very low incidence of gastrointestinal problems (2%) [23]. In our cases, gastrointestinal symptoms were common in patients with MIS-C. This is in line with the previously described MIS-C case series, in which abdominal symptoms such as abdominal pain, diarrhoea, nausea and vomiting are present in most patients [24, 17–20].

CVS manifestations included hypotension and shock. It was attributed to either acute myocardial dysfunction or systemic hyperinflammation/vasodilatation. In other studies, the cardiac manifestations included coronary artery dilatation or aneurysm. [19]. Cardiac support, immunomodulation, and anticoagulation are the key aspects for the management of the acute phase. Long-term structured follow-up of these patients is required as the prognosis is unclear and there is risk of progression of cardiac complication [10].

The clinical-laboratory manifestations of MIS-C mimic those of KD and TSS, and a high proportion of patients may meet the diagnostic criteria for both diseases [19, 23,25]. Concerning the laboratory parameters, the MIS-C patients presented with severe inflammation, with elevated levels of acute-phase reactants like CRP, exceeding those of SARS-CoV-2. Although absolute leukocyte counts were not very elevated and were similar in the two groups, patients with MIS-C exhibited severe lymphopenia. The clinical interpretation of this finding is challenging. The analytical findings in our series were similar to those previously reported, i.e., lymphopenia without significant leukocytosis and high inflammatory markers. [17–20].

In our study, contrary to the studies in adults, patients presenting with hyperinflammatory features such as elevated CRP, showed lower prevalence of chest x-ray abnormalities and lesser need of mechanical ventilation. Our study points out differences regarding hyperinflammatory states related to SARS-CoV-2 infection in children as compared to those described in adults. In adults, hyperinflammation is more frequent in the context of COVID-19 bilateral pneumonia whereas in children it is seen in patients with mild or absent respiratory symptoms. In children, increased antibodies against the receptor binding domain of SARS-CoV-2 have been described in patients with MIS-C compared with patients with COVID-19 without hyperinflammatory features [26].

In our population of patients with MIS-C, the use of mechanical ventilation was infrequent (only 1 <3%) as described by Dufort et al. in New York State [7], and lower to the rates described in studies

from other regions as U.S.A., U.K. and France where more than 30% of patients with MIS-C needed mechanical ventilation[23].

As to pharmacological treatments, most patients with MIS-C received antibiotic therapy. The use of immunomodulatory and corticosteroid treatments was also higher in the group of patients with MIS-C. Treatments used in patients with MIS-C are similar to those described in studies from other regions [6, 7, 20]. As to prognosis, the course of MIS-C patients included in our study was favourable; however there was 5.5% mortality. Most patients were discharged from the ward in a few days. It is surprising that despite severe manifestations and multisystem involvement the mortality is low. Other studies describe findings with low mortality in patients with MIS-C (below 3% in all series) [6,7,18, 20].

We are still receiving patients with MIS-C symptoms but we could not include them because of the time constraints for the current study. However, this goes on to prove that the pandemic is not over yet. Despite being recognized as a novel disease world - wide, MIS-C still lacks sensitivity and specificity with respect to the clinical picture and heterogenous multisystem involvement. The development of an algorithm backed by comprehensive studies will aid clinicians in prompt diagnosis and early institution of therapy so that the eventual prognosis is enhanced.

4. CONCLUSION

Although SARS-CoV-2 infection is less severe in children than in adults, some paediatric patients may present with severe symptoms requiring intensive care. this case series of patients with MIS-C due to covid-19, identified patterns of clinical presentation and organ system involvement along with therapy modalities and the response to the therapy. Wide international, multicentre studies are needed to characterize this syndrome more accurately and establish the optimal treatment.

ACKNOWLEDGEMENT

Dean of Rajiv Gandhi Medical College and Chatrapati Shivaji Maharaj Hospital, Kalwa .

Contributors: In this paper we would like to extend our gratitude and acknowledgement to the Pathology and Microbiology department as well as the Biochemistry department.

Funding: None

COMPETING INTEREST

None stated.

AUTHORS' CONTRIBUTIONS

Author 1 designed the study, wrote the protocol, and wrote the first draft of the manuscript.

Author 2 and Author 3 performed the statistical analysis of the study.

Author 3 and author 5 managed the literature searches

All authors read and approved the final manuscript.

CONSENT

Not applicable

ETHICS APPROVAL

Approved by Institutional Review Board and Institutional Clinical Ethics Committee.

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ADDITIONAL ATTACHMENT

Blood Biochemistry

Analyte	Reference Range
WBC Count	**4500-11000/ml**
Lymphocyte count	**3000-4000/ml**
Hb	**11-14.5gms/dl**
PT	**11-13.5 seconds**
PTT	**25-35 seconds**
INR	**0.8-1.1**
D Dimer	**<0.50**
Serum ferritin	**24-336 microgram/L**
ESR	**0-29 mm/hr**
IL-6	**0-43.5 pg/ml**
CRP	**<10 mg/L**
LDH	**105 -333 IU/L**