DOI: 10.7860/IJNMR/2022/57302.2354

Original Article

Paediatrics Section

# Clinical Profile and Outcome of Multisystem Inflammatory Syndrome in Children (MIS-C): A Retrospective Study

MILIND M SURYAWANSHI[1], CHANDRAKANT M BOKADE[2], DIPAK M MADAVI[3], SHAMAMA SUBUHI[4], LAKSHMIKANT A ROHADKAR[5], ANWESHA SINGH[6]




## ABSTRACT

**Introduction:** Multisystem Inflammatory Syndrome in Children (MIS-C) is a life-threatening complication of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. It can also present with multisystem involvement including circulatory shock, systemic inflammation, and mucocutaneous and dermatologic involvement. Children infected with Coronavirus Disease-2019 (COVID-19) are mostly asymptomatic but those having co-morbidities are at a greater risk of getting severe infections.

**Aim:** To study the clinical profile and outcome of children with MIS-C.

**Materials and Methods:** This was a single-centre retrospective hospital-based observational study conducted at Indira Gandhi Goverment Medical College, Nagpur, Maharashtra, India. MIS-C protocol was developed at the Institutional level as per the World Health Organisation (WHO) and Indian Academy of Paediatrics (IAP) guidelines. Children admitted with MIS-C upto the age 18 years, were included as per the diagnostic criteria of MIS-C given by the WHO. The data pertaining to the demographics, clinical findings, underlying comorbidities, echocardiographic findings, laboratory investigations, and treatment received including intensive care interventions and outcomes were obtained from patient hospital records from 1st May 2021 to 30th September 2021.These collected data were obtained and statistical analysis was performed in patients treated for MIS-C.

**Results:** The study included 18 children, who were diagnosed with MIS-C, with a median age of six years. Most of them presented with fever 12 (66.67%), followed by gastrointestinal symptoms 11 (61.1%). Elevated levels of C-reactive protein were found in all of them (58.04±34.87 mg/L). The majority of children needed intensive care admissions 17 (94.45) and vasoactive medications were given to 8 (44.45%) children. Steroids were given in all children and Intravenous Immunoglobin (IVIG) in 7 (38.9%), and a combination was used in 10 (55.55%) children. Co-morbidities were seen in 4 (22.22%) children (two sickle cell disease, one diabetes mellitus type 1, and one had global developmental delay. Mortality was noted in 4 (22.22%) children, and none of them had any co-morbidities.

**Conclusion:** The majority of the children with MIS-C in this study presented with acute febrile illness and shock and required intensive care. In children with pre-existing comorbidities, the outcome is surprisingly good.


**Keywords:** C-reactive protein, Co-morbidity, Mortality

## INTRODUCTION

Multisystem inflammatory syndrome following COVID-19 infection from the western world was first reported in January 2020 [1-3]. The World Health Organisation (WHO) circulated a preliminary case definition for multisystem inflammatory disorder temporally associated with COVID in children and adolescents (MIS-C) for reporting surveillance and outlining treatment strategies for this disorder [4].

During the second wave of the COVID pandemic, adults were more affected than children with Severe Acute Respiratory Syndrome-Coronavirus 2 infection, but in the next wave, children and infants were found to have more serious consequences of infection [5]. SARS-CoV-2 infection-related multi-system inflammatory syndromes in children (MIS-C) is a dreaded complication [6]. SARS-CoV-2 infections in most children result in less severe COVID-19 than infections in adults [7-9]. However, a subset of children present with severe multisystem inflammation associated with recent SARS-CoV-2 infection or COVID-19 exposure in the weeks before [10-14]. MIS-C has a strong epidemiological and laboratory association with SARS-CoV-2 infection [15,16].

In India, the case reported by Rauf A et al., describes the classical presentation of MIS-C, which shares features similar to Kawasaki disease [17]. Later it was found in other cities, including Nagpur, which was one of the adversely affected cities in central India during the second wave of COVID-19.

Hence, the aim of the study was to assess the clinical profile, presenting symptoms, laboratory findings, therapy received, and outcomes among infants and children those meet the WHO case definition of MIS-C.

## MATERIALS AND METHODS

This was a single-centre retrospective hospital-based observational study conducted at Indira Gandhi Government Medical College, Nagpur, Maharashtra, India. MIS-C protocol was developed at the Institutional level as per WHO and IAP guidelines [18]. The data was collected and analysed during the period December 2021 to Feb 2022.

**Inclusion criteria:** Children included in the study were those with MIS-C, less than 18 years of age, admitted between 1st May 2021 to 30th September 2021.

**Exclusion criteria:** Children with alternative diagnoses and incomplete or missing data were excluded. The study was approved by the Institute

Ethics Committee, IGGMC, Nagpur (IGGMC/Pharmacology/IEC/1033-34/2022 dated 20/04/2022).

### Study Procedure

The COVID-19 Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and COVID-19 antibody testing was done in all patients. Information about the demographic features of the children were collected. Clinical details, underlying co-morbidities, echocardiographic findings, and laboratory investigations were extracted from the medical records of each child. Treatment received including intensive care interventions including a mechanical ventilator, Continuous Positive Airway Pressure (CPAP), oxygen by nasal cannula, vasoactive support, intravenous immunoglobin (IVIG), steroids and the treatment outcome was noted, using a case record form. Additionally, a history of contact with a COVID-19 positive patient was also considered. The outcome was classified into discharged or death.

## STATISTICAL ANALYSIS

The data was entered in an Excel sheet and results were expressed in terms of number and percentage.

## RESULTS

During the above study period, 10 children were RT-PCR positive (COVID-19 positive) and admitted to dedicated paediatrics hospital. The study included 18 children, who were diagnosed with MIS-C, with a median age of six years. All the 18 children were antibody positive for COVID-19, 17 were negative for RT-PCR, and only one child was both RT-PCR and antibody positive.

Out of the 18 patients, four had underlying co-morbidities. The most common symptoms were fever, myalgia, and fatigue. Four children (22.22%) were diagnosed to have myocarditis, with features of left ventricular systolic function and elevated cardiac biomarkers along with coronary involvement. Point of care 2D echo could, however, not be done because most of the children were admitted to intensive care units and the facility of 2D echo was not available at bedside [Table/Fig-1].

| Variables | Findings |
|---|---|
| Age, median (in years) | 6 |
| Male | 12 (66.67%) |
| Female | 6 (33.33%) |
| **Co-morbidity** | 4 (22.22%) |
| Sickle cell disease | 2 |
| Type 1 DM | 1 |
| Global developmental delay | 1 |
| **History of contact with COVID positive patient** | |
| Yes | 8 (44.44%) |
| No | 10 (55.56%) |
| **Constitutional symptoms** | |
| Fever, myalgia, and fatigue | 12 (66.67%) |
| **Gastrointestinal (GI) symptoms** | 11 (61.11%) |
| Abdominal pain | 4 |
| Vomiting | 6 |
| Diarrhoea | 1 |
| **Mucocutaneous symptoms** | 4 (22.22%) |
| Rash, conjunctivitis | 3 |
| Oral mucosa involved | 1 |
| **Cardiovascular (CVS) symptoms** | |
| Hypotension | 8 (44.44%) |
| **Respiratory symptoms** | |
| Respiratory distress | 5 (27.78%) |
| **Neurological symptoms** | |
| Headache/irritability/altered mental status | 3 (16.67%) |

**[Table/Fig-1]:** Demographic and clinical characteristics of children with Multisystem inflammatory syndrome (MIS-C).
DM: Diabetes mellitus

C-reactive protein (CRP) was elevated in all children and deranged coagulopathy was also seen in all children. A 17 (94.45%) children required intensive care like Paediatrics Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU) admission. Out of all the admitted patients, 4 (23.52%) children required ventilator support, 8 (47.05%) were dependent on oxygen by nasal cannula and five needed CPAP for respiratory support [Table/Fig-2]. Haemodynamically, 8 (44.45%) children were started on vasopressors. Steroids were administered to all the children (100%), Intravenous Immunoglobulin (IVIG) was started in 7 (38.9%) patients and around 55.55% of the children were treated with both steroids and IVIG, as per treatment protocol. Four children (22.22%) died, and none of them had co-morbidities.

| Investigations | Values |
|---|---|
| **CBC** | |
| TLC (/cmm) (Median-IQR) | 15700 |
| Haemoglobin (gm/dL) (Median-IQR ) | 10 |
| Platelets (lakhs/cmm) (Median IQR ) | 126000 |
| CRP (mg/L) (Mean and SD) | 58.04 and 34.87 |
| Serum creatinine (mg/dL) (Median IQR) | 0.45 |
| Serum ferritin (ng/mL) (Median IQR) | 168 |
| D-dimer (ng/mL) (Median IQR) | 2683 |
| LDH (IU/L) (Median IQR) | 637 |
| **RT-PCR** | |
| Positive | 1 |
| Negative | 17 |
| Serology positive (COVID antibody) | 18 |
| **Echocardiographic features (%)** | |
| Assessment of ventricular dimensions, myocardial dysfunction, and left ventricular ejection fraction | 4 (22.2%) |
| **Treatment Paediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU)** | 17 (94.45%) |
| Mechanical ventilation | 4 (23.52%) |
| Oxygen by nasal cannula | 8 (47.05%) |
| Continuous positive airway pressure (CPAP) | 5 (29.41%) |
| **Vasoactive support** | 8 (44.45%) |
| **Medications** | |
| IVIG | 7 (38.9%) |
| Steroids | 18 (100%) |
| Steroid and IVIG | 10 (55.55%) |
| **Outcome** | |
| Discharged | 14 (77.78%) |
| Death (None of them had any co-morbidities | 4 (22.22%) |

**[Table/Fig-2]:** Biochemical echocardiographic parameters, management, and outcomes in children with Multisystem inflammatory syndrome (MIS-C).
CBC: Complete blood count; CRP: C-reactive protein; IQR: Interquartile range; SD: Standard deviation; LDH: Lactate dehydrogenase; IVIG: Intravenous immunoglobulin

## DISCUSSION

The cohort study reported 18 cases of MIS-C with clinical features, presenting symptoms, and laboratory findings. The results found that

elevated CRP, thrombocytopenia, gastrointestinal (GI) symptoms, mucocutaneous involvement, and shock at presentation are most commonly encountered. Regarding the worldwide distribution of COVID-19, there are relatively fewer cases among children compared to adults. Children tend to have a milder clinical course, as compared to adults. However, especially at the end of the COVID-19 peak after the second wave, paediatricians have started seeing multisystem inflammatory disorders similar to Kawasaki disease or toxic shock syndrome [19].

The present study showed that there was a male predominance of 66.67%, similar to other studies, and the median age was noted as six years, akin to studies done in other parts of the world [6,20-24]. However, a study done by Whittaker E et al., [21] found the median age to be 9.4 years. In the present study, constitutional symptoms like fever, myalgia, and fatigue were seen predominantly. In this cohort, co-morbidities were noted in 22.22% children. In the study done by Ahmed M et al., while 71.0% of children (n=470) were admitted to the intensive care unit, only 11 deaths (1.7%) were reported [20]. In the study conducted by Bagri NK et al., in All India Institute of Medical sciences (AIIMS), New Delhi, four children (12.9%) with multiorgan failure succumbed to illness. All of these were RT- PCR positive and had pre-existing chronic illnesses (one each with chronic kidney disease, seizure disorder, Downs syndrome with Tetralogy of Fallot, rheumatic heart disease) [24].

In the present study, it was found that 94.45% children required intensive care admission. The study by Ahmed M et al., reported that 71% (n=470) of the children had history of admission in ICU [20]. Dhanalakshmi K et al., from Chennai, found that 63% (n=12) required PICU support [23], and there was 88% ICU admissions in a study conducted at two tertiary care centres in Kerala [25].

In the present study, elevated levels of CRP were found in all the 18 children. Similar findings were seen by Dufort EM et al., where all the enrolled children had elevated levels of CRP [11]. Dhanalakshmi K, et al., also showed high levels of CRP in all their study participants [23].

Mechanical ventilation was needed in 23.52% children, in this study. Ahmed M et al., found that 147 children (22.2%) required mechanical ventilation [20]. Bagri NK et al., showed that 22.5% (n=7) required mechanical ventilation, whereas 13 subjects required respiratory support, either through a face mask, nasal cannula or high flow nasal cannula [24]. Tiwari A et al., reported a 20% (n=8) requirement of mechanical ventilation [25].

Sugunan S et al., found only 16% of the cases needed mechanical ventilation [6]. This is probably due to timely institution of methyl prednisolone and IVIg. Notably, this study had zero mortality. Whittaker E et al., reported that 43.10% of the sample were dependent on mechanical ventilation [21]. In the mentioned-study 79% of the children were in shock, while in the present study 44.45% children were on vasopressor support. Jain S et al., showed a dataof39.1% being on a mechanical ventilator in their study [22].

In the present study, 4 (22.22%) children admitted to the hospital in the intensive care unit died with complaints of acute febrile illness, shock, cardiac involvement, and deranged coagulation profile on ventilatory support. Both IVIG and steroids were used for treatment with vasoactive support. They succumbed to death despite receiving treatment as per protocol. Interestingly, the outcome was good in children (none of them had co-morbidities). Timely intervention resulted into a good outcome. In another study by Ahmed M et al., the mortality was found to be 1.7% (n=11) [20]. Outcome was good in the study by Jain S et al., with 4.34% mortality (n=1) [22]. Two patients died in the study by Tiwari A et al., (n=2) [25]. Studies done by Sugunan S et al., [6] and Dhanalakshmi K et al., [23] found no mortality.

### Limitation(s)

The present study was limited by its small sample size and nature of the study being retrospective.

## CONCLUSION(S)

The majority of the children with MIS-C in this study presented with acute febrile illness and shock and required intensive care. In children with pre-existing co-morbidities, the outcome is surprisingly good. The MIS-C is a new syndrome that developed later in the course of SAR-CoV-2 infection in children. This is a classic example of the cause and effect of SAR-CoV-2 infection, which results in features of MIS-C in children.

### Acknowledgement

Authors would like to acknowledge the paediatricians, paediatric intensivist, and paramedical staff who were involved in the clinical care of the patients admitted in PICU, NICU, and ward of the Paediatrics Department, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.

## REFERENCES

[1] Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S, et al. Detection of Covid-19 in children in early January 2020 in Wuhan, China. N Engl J Med. 2020;382(14):1370-71. Doi: 10.1056/NEJMc2003717. Epub 2020 Mar 12. PMID: 32163697; PMCID: PMC7121643.

[2] Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation. 2022;142(5):429-36. Doi: 10.1161/CIRCULATIONAHA.120.048360. Epub 2020 May 17. PMID: 32418446.

[3] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: An observational cohort study. Lancet. 2020;395(10239):1771-78. Doi: 10.1016/S0140-6736(20)31103-X. Epub 2020 May 13. PMID: 32410760; PMCID: PMC7220177.

[4] World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief (2020). (https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19).

[5] Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open. 2021;4(6):e2116420. Published 2021 Jun 1. Doi:10.1001/jamanetworkopen.2021.16420.

[6] Sugunan S, Bindusha S, Geetha S, Niyas HR, Kumar AS. Clinical profile and short-term outcome of children with SARS-CoV-2 related multisystem inflammatory syndrome (MIS-C) treated with pulse methylprednisolone. Indian Pediatr. 2021;58(8):718-22. Doi: 10.1007/s13312-021-2277-4. Epub 2021 Apr 20. PMID: 33876782; PMCID: PMC8384095.

[7] Dong Y, Mo X, Hu Y, Qi X, Jiang E, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702. Doi: 10.1542/peds.2020-0702.

[8] Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed Coronavirus Disease 2019- COVID-NET, 14 States. MMWR Morb Mortal Wkly Rep. 2020;69(15):458-64. Doi: 10.15585/mmwr.mm6915e3. PMID: 32298251; PMCID: PMC7755063.

[9] CDC COVID-19 Response Team. Coronavirus disease 2019 in children—United States, MMWR Morb Mortal Wkly Rep. 2020;69(14):422-26. Doi: 10.15585/mmwr.mm6914e4.

[10] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. Doi: 10.1016/S0140-6736(20)30566-3. Epub 2020 Mar 11. Erratum in: Lancet. 2020;395(10229):1038. Erratum in: Lancet. 2020;395(10229):1038. PMID: 32171076; PMCID: PMC7270627.

[11] Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med. 2020;383(4):347-58. Doi: 10.1056/NEJMoa2021756. Epub 2020 Jun 29. PMID: 32598830; PMCID: PMC7346766.
[12] Feldstein LR, Rose EB, Randolph AG. Multisystem inflammatory syndrome in children in the United States. Reply. N Engl J Med. 2020;383(18):1794-95. Doi: 10.1056/NEJMc2026136. Epub 2020 Oct 21. PMID: 33085854.
[13] Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. and Kawasaki disease: Novel virus and novel case. Hosp Pediatr. 2020;10(6):537-40. Doi: 10.1542/hpeds.2020-0123.
[14] Reese H, Iuliano AD, Patel NN, Garg S, Kim L, Silk BJ, et al. Estimated incidence of Coronavirus Disease 2019 (COVID-19) illness and hospitalization-United States. Clin Infect Dis. 2021;72(12):e1010-e1017.
[15] Ouldali N, Yang DD, Madhi F, Levy M, Gaschignard J, Craiu I, et al. Factor sassociated with severe SARS-CoV-2 infection. Pediatrics. 2021;147(3):e2020023432. Doi: 10.1542/peds.2020-023432.
[16] Abrams JY, Godfred-Cato SE, Oster ME, Chow EJ, Koumans EH, Bryant B, et al. Multisystem inflammatory syndrome in children associated with Severe Acute Respiratory Syndrome Coronavirus 2: A systematic review. J Pediatr. 2020;226:45-54.e1. Doi: 10.1016/j.jpeds.2020.08.003. Epub 2020 Aug 5. PMID: 32768466; PMCID: PMC7403869.
[17] Rauf A, Vijayan A, John ST, Krishnan R, Latheef A. Multisystem inflammatory syndrome with features of atypical Kawasaki disease during COVID-19 pandemic. Indian J Pediatr. 2020;87(9):745-47.
[18] IAP Covid 19 management guidelines for PediatricianV1.1 Apr 27_2021.
[19] Shah SK, Munoz AC. Multisystem inflammatory syndrome in children in COVID-19 pandemic. Indian J Pediatr. 2020;87(9):671-73. Doi: 10.1007/s12098-020-03440-7. Epub 2020 Jul 3. PMID: 32621172; PMCID: PMC7332842.
[20] Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. E Clinical Medicine. 2020;26:100527. Doi: 10.1016/j.eclinm.2020.100527. Epub 2020 Sep 4. PMID: 32923992; PMCID: PMC7473262.
[21] Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;e2010369. [E-pub ahead for print].
[22] Jain S, Sen S, Lakshmiven Kateshiah S, Bob Hate P, Venkatesh S, Udani S, et al. Multisystem inflammatory syndrome in children with COVID-19 in mumbai, India. Indian Pediatr. 2020;57(11):1015-19. Doi: 10.1007/s13312-020-2026-0. Epub 2020 Aug 11. PMID: 32788432; PMCID: PMC7678602.
[23] Dhanalakshmi K, Venkataraman A, Balasubramanian S, Madhusudan M, Amperayani S, Putilibai S, et al. Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome- temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. Indian Pediatr. 2020;S097475591600220. [published online ahead of print].
[24] Bagri NK, Deepak RK, Meena S, Gupta SK, Prakash S, Setlur K, et al. Outcomes of the multisystem inflammatory syndrome in children temporally related to COVID-19: A longitudinal study. Rheumatol Int. 2022;42(3):477-84. Doi: 10.1007/s00296-021-05030-y. Epub 2021 Oct 19. PMID: 34665296; PMCID: PMC8524205.
[25] Tiwari A, Balan S, Rauf A, Kappanayil M, Kesavan S, Raj M, et al. COVID-19 related multisystem inflammatory syndrome in children (MIS-C): A hospital-based prospective cohort study from Kerala, India. BMJ Paediatr Open. 2021;5(1):e001195. Doi: 10.1136/bmjpo-2021-001195. PMID: 34693035; PMCID: PMC8523964.

**PARTICULARS OF CONTRIBUTORS:**
1. Assistant Professor, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
2. Professor and Head, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
3. Associate Professor, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
4. Assistant Professor, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
5. Assistant Professor, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.
6. Junior Resident, Department of Paediatrics, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
Shamama Subuhi,
103C, Aman Pride Apartment, Mahesh Nagar, Katol Road,
Nagpur-440013, Maharashtra, India.
E-mail: shamamasubuhi88@gmail.com

**PLAGIARISM CHECKING METHODS:** [Jain H et al.]
- Plagiarism X-checker: Apr 25, 2022
- Manual Googling: Jun 28, 2022
- iThenticate Software: Aug 20, 2022 (19%)

**ETYMOLOGY:** Author Origin

**AUTHOR DECLARATION:**
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 23, 2022**
Date of Peer Review: **May 27, 2022**
Date of Acceptance: **Jun 28, 2022**
Date of Publishing: **Sep 30, 2022**