Biochemical Evaluation For Diagnosis Of Multisystem Inflammatory Syndrome In Children (MIS-C) In Tertiary Care Hospital Of Central India

Dr. Rizwan Ahmed[1*], Dr. Gouri Rajput[2]

Abstract

Aim of Study: To evaluate biochemical parameters for diagnosis of Multisystem inflammatory syndrome in children (MIS-C)

Background :MIS-C, also known as Pediatric Inflammatory Multisystem Syndrome Temporally related with SARS-CoV-2 (PIMS-TS), is a hyperinflammatory syndrome in children.

- The syndrome has a close temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- Cases in India were reported in May 2020, and the prevalence has increased with the rise in COVID-19 cases across the nation.
- Clinical Presentation:
- Children with MIS-C may develop inflammatory conditions post-infection rather than during the acute infective stage of COVID-19.
- While clinical symptoms in children are generally milder than in adults, a proportion of children require hospitalization and pediatric intensive care.

Method: The Paediatrics Department of the NKPSIMS Medical College in Nagpur has undertaken the observational research. From March 2021 to October 2023 , all kids diagnosed with MIS-C who were hospitalised to our hospital between the ages of 1 month and 18 years were included in the research. All blood tests and inflammatory indicators were examined in all MIS-C patients, and the severity of the condition was treated in accordance with the findings.

Results: Twenty kids were diagnosed with MIS-C following a COVID infection. All kids who met the MIS-C requirements had biochemical evaluations including all blood tests and indicators of inflammation. Increased levels of inflammatory markers were closely associated with severe MIS-C patients. Most instances were mild to severe cases, and they were all treated in accordance with their sickness categorization. One death fell into category 4.

Conclusion: The severity of MIS-C in children was correlated with inflammatory indicators in this study, which will offer insights into current therapeutic management and implications for immediate future research initiatives.

Key words: Inflammatory markers, MIS-C, pandemic , covid-19 , severity.

DOI Number: 10.48047/nq.2024.22.1.NQ24031 **NeuroQuantology 2024; 22(1):307-312**

Introduction :

- MIS-C, also known as Pediatric Inflammatory Multisystem Syndrome Temporally related with SARS-CoV-2 (PIMS-TS), is a hyperinflammatory syndrome in children.
- The syndrome has a close temporal association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

***Corresponding Author :**Dr. Rizwan Ahmed
Address:[1]*Associate Professor NKPSIMS Nagpur
[2]Assistant Professor, Department of Pediatrics, NKPSIMS, Nagpur

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

- Cases in India were reported in May 2020, and the prevalence has increased with the rise in COVID-19 cases across the nation.
- Clinical Presentation:
- Children with MIS-C may develop inflammatory conditions post-infection rather than during the acute infective stage of COVID-19.
- While clinical symptoms in children are generally milder than in adults, a proportion of children require hospitalization and pediatric intensive care.
- Inflammatory Markers in MIS-C:
- Inflammatory markers such as leukocyte count, procalcitonin (PCT), C-reactive protein (CRP), interleukin-6 (IL-6), and interleukin-10 (IL-10) are significantly raised in patients with severe disease or in the intensive care unit.
- Some studies have suggested an association between high PCT levels and severe COVID-19 infection.
- The goal is to conduct a meta-analysis of existing literature to compare levels of inflammatory markers between severe and non-severe COVID-19 patients in children.
- The aim is to provide a clearer understanding of the association between inflammatory markers and severe COVID-19, potentially aiding in diagnosis and predicting disease progression.
- Significance for Clinicians:
- Findings from the study may assist clinicians in monitoring and evaluating the severity and prognosis of COVID-19-associated MIS-C in children

Definition of MIS-C (WHO) CLINICAL CRITERIA[1]:

0–19 years old child with fever >3 days AND—
Two of the following:

- Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).
- Hypotension or shock
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-pro BNP)
- Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)
- Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain)
- Elevated ESR, C-reactive protein, or procalcitonin
- No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
- AND Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

Inclusion criteria:

- Children diagnosed with MIS -C as per WHO criteria, from 1 month – 18 years of age group admitted in our hospital

Exclusion criteria:

- Those who are not willing to participate in study.
- Children not fulfilling WHO MISC criteria.

All children having clinical features suggestive of MIS-C in children admitted in pediatric ward and Pediatric Intensive Care unit at NKPSIMS Medical college and Lata Mangeshkar hospital, Nagpur were included in this study. After written and informed consent of the parent the child was enrolled in the study. The participants demographic data, his complaints on admissions, with detailed history and examination was filled in case record sheet. The subject will be investigated and treated as per the hospital protocol. The participants once enrolled were followed till they are discharged from the hospital or death happens.

Inflammatory markers included white blood cell count (WBC) or leukocytes, absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), ferritin, D-dimer, lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR) for comparisons by severity and age. D-dimer was done on -Ichroma 2 machine by sandwich method with normal range of 0-500. Serum ferritin was done on Ichroma 2 machine by sandwich method with normal range of 20-175mg/ml. Serum LDH was done on Dimension EXL 200 machine with normal range of 81-234unit/Ltr. CRP was done on Dimension EXL200 machine with normal range

of 0-5mg/Ltr.CBC was done on Ladvia 5 cell counter(model-2120) by Siemens company.ESR - Westergren method manually done with normal range of 0-10. The patients will be classified according to revised WHO guideline and managed appropriately. Outcome of the disease will be assessed with the levels of the markers.

Inclusion criteria:

- Children diagnosed with MIS -C as per WHO criteria, from 1 month – 18 years of age group admitted in our hospital

Exclusion criteria:

- Those who are not willing to participate in study.
- Children not fulfilling WHO MISC criteria.

Sample size

We have included all the cases of MISC admitted to our wards and ICU who are willing to participate in the study, in the period of 6 months. Total 20 patients were admitted with Diagnosis of MISC which were included in the study.

Observation :

Table 1: Age-wise distribution of children with MIS-C (n=20)

Age-group	Frequency	Percentage
0 – 5	8	40
6 – 10	5	25
>10	7	35
Total	20	100

40 percent of the kids were between the ages of 0 and 5. Children older than 10 years accounted for 35% of the population, while children aged 6 to 10 made up 25%.

Table 2: Gender-wise distribution of children with MIS-C (n=20)

Gender	Frequency	Percentage
Male	11	55
Female	9	45
Total	20	100

According to gender classification, most people with MIS-C were males (55%) and female (45%).

Table 3: Profile of Complete Blood Count in children with MIS-C

Complete Blood Count	Frequency	Percentage
WBC		
Normal	8	40
Raised	8	40
Decreased	4	20
Total	20	100
N/L		
Normal	12	60
Increased	8	40
Total	20	100
HB		
Normal	7	35
Decreased	13	65
Total	20	100
Platelets		
Normal	5	25
Decreased	15	75
Total	20	100

In 40% of patients with a complete blood count, the leukocyte count is normal, and in 60% of instances, the N/L ratio is normal. Leukopenia and a higher N/L ratio were found in 20% and 40% of patients, respectively. In 65% of instances, the hemoglobin level was low, whereas in 35% of cases, it was normal. In 75% of instances, platelets were reduced, while in 25% of cases, they were normal.

Table 4: Liver function test electrolytes and inflammatory markers in children with MIS-C

Liver Function Test	Frequency	Percentage
ALT		
Normal	14	70
Raised	6	30
Total	20	100
AST		
Normal	15	75
Raised	5	25
Total	20	100
Blood Urea		
Normal	16	80
Raised	4	20
Total	20	100
Sr. Creatinine		
Normal	18	90
Raised	2	10
Total	20	100
Sodium		
Normal	14	70
Decreased	6	30
Total	20	100
Potassium		
Normal	18	90
Decreased	2	10
Total	20	100
CRP		
Normal	7	35
Raised	13	65

Total	20	100
ESR		
Normal	5	25
Raised	15	75
Total	20	100
LDH		
Normal	5	25
Raised	15	75
Total	20	100
Ferritin		
Normal	4	20
Raised	16	80
Total	20	100
D-Dimer		
Normal	3	15
Raised	17	85
Total	20	100
Prothrombin Time		
Normal	16	80
Raised	4	20
Total	20	100

Liver enzymes were normal in 70% cases and raised in 30% cases. Kidney function tests were normal in majority cases. Blood urea normal in 80% cases and creatinine normal in 90% cases. Sodium levels were normal in 70% cases and potassium were normal in 90% cases. CRP was raised in 65% cases while ESR was raise in 75% cases, LDH was increased in 75% cases. Ferritin was high in 80% cases
D dimer was raised in 85% cases, Prothrombin levels were normal in 80% cases.

Table 5: Antibodies for COVID-19 in children with MIS-C

Antibodies	Frequency	Percentage
Present	18	90
Absent	2	10
Total	20	100

Antibodies were positive in 90% cases and 10% were negative in the study.

Table 6: Radiological Findings in children with MIS-C

Radiological Findings	Frequency	Percentage
X-Ray		
Normal	11	55
Abnormal	7	35
Not done	2	10
Total	20	100
USG		
Normal	7	35
Abnormal	6	30
Not done	7	35
Total	20	100
ECHO		
Normal	8	40
Abnormal	12	60
Not done	0	0
Total	20	100
Dengue		
Positive	3	15
Negative	17	85
Total	20	100
Others		
Present	9	45
Absent	11	55
Total	20	100

Radiologically Chest Xray was abnormal in 0nly 35% and normal in 55% and was not indicated in 10% cases. Ultrasound Abdomen 35% were normal, 35% abnormal, 35% were not done. 2 D ECHO was abnormal in 60% of cases. Other tests like dengue was positive in 15% cases and negative in 85% cases

Table 7: Category of children with MIS-C (n=20)

Categories	Frequency	Percentage
I	3	15
II	3	15
III	4	20
IV	10	50
Total	20	100

According to the severity of illness , four categories of MIS-c , there 15% in each category 1 and category 2 while 20% were in catergory 3 , and 50% were in category 4 admitted in our hospital.

Table 8: Length of Hospital stay children with MIS-C (n=20)

Length of hospital stay	Frequency	Percentage
≤5	4	20
6 – 10	9	45
>10	7	35
Total	20	100

The length of stay in hospital for MIS-C patients were 45% for 6-10 days , while less than 5 days were 20% and those requiring long stay more than 10 days were 35%.

Discussion :

Multisystem Inflammatory Syndrome in Children (MIS-C) is an emerging and rare inflammatory condition associated with SARS-CoV-2 infection in the pediatric population. As the global understanding of this syndrome expands, the need for effective diagnostic strategies becomes imperative, particularly in tertiary care hospitals where the complexity of cases often necessitates a multidisciplinary approach. This discussion will delve into the biochemical evaluation methods employed for the diagnosis of MIS-C in a tertiary care hospital in Central India, emphasizing the significance of specific biomarkers and the

challenges associated with this evolving clinical entity.

1. **Inflammatory Markers:** The inflammatory response is a hallmark of MIS-C, and evaluating specific markers aids in its diagnosis. Studies have shown elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6 (IL-6), and procalcitonin (PCT) in MIS-C patients[12]. The inclusion of these markers in the biochemical profile is crucial for timely identification and differentiation from other febrile illnesses.
2. **Cardiac Markers:** Given the frequent cardiac involvement in MIS-C, assessing cardiac markers such as troponin and brain natriuretic peptide (BNP) is essential[1]. Elevated troponin levels are indicative of myocardial injury, while increased BNP levels suggest cardiac strain. These markers contribute to the comprehensive evaluation of MIS-C, especially in cases where cardiac complications are predominant[3].
3. **Liver and Renal Function Tests:** Comprehensive liver function tests (LFTs) and renal function tests (RFTs) are instrumental in assessing the extent of organ involvement. Abnormalities in alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea, and creatinine levels may provide insights into the systemic impact of MIS-C[3].
4. **Coagulation Profile:** Given the potential for coagulopathy in MIS-C, evaluating markers such as D-dimer is crucial. Elevated D-dimer levels have been associated with increased clotting activity, emphasizing the importance of including coagulation parameters in the diagnostic profile[3].
5. **Challenges and Variability in Marker Levels:** It is important to acknowledge the variability in marker levels among MIS-C patients. Studies have reported inconsistent results regarding the elevation of specific markers, highlighting the need for a nuanced interpretation of the biochemical profile[4]. The challenge lies in distinguishing MIS-C from other inflammatory conditions and viral infections, necessitating a comprehensive clinical assessment.
6. **Diagnostic Algorithm and**
7. **Multidisciplinary Approach:** Developing a diagnostic algorithm that incorporates clinical, laboratory, and imaging findings is essential for a holistic approach to MIS-C diagnosis[3]. A multidisciplinary team, including pediatricians, infectious disease specialists, cardiologists, and intensivists, is pivotal for accurate diagnosis and timely intervention.
8. **Local Considerations and Regional Variation:** Recognizing the regional variations in the prevalence and presentation of MIS-C is crucial. Local epidemiological factors, including the prevalence of specific SARS-CoV-2 variants, may influence the clinical profile and biomarker patterns in MIS-C cases[5].

In conclusion, the biochemical evaluation for the diagnosis of MIS-C in a tertiary care hospital in Central India necessitates a comprehensive approach. Inflammatory, cardiac, liver, renal, and coagulation markers, along with a multidisciplinary clinical assessment, contribute to the accurate identification of MIS-C cases. The evolving nature of MIS-C demands ongoing research and adaptation of diagnostic strategies to improve patient outcomes.

Conclusion:

Many kids got MIS-C during the second Covid Pandemic wave in 2021. Twenty kids were enrolled in the research, with a predominance of males. Most of these kids had a history of covid infection and tested positive for covid antibodies. All hospitalized patients with MIS-C symptoms underwent biochemical evaluation. Children were divided and treated in accordance with the MIS-C Categories based on the severity of the disease and variations in inflammatory markers. In this study, the severity of MIS-C was clinically correlated with the inflammatory indicators, and there was a statistically significant proportion of close correlation.

Limitation of study:

It was found that the sample size of patients was relatively less so results may vary with more sample size. The second covid wave lasted for short time of 3 months and incidences of MIS-C were also varied in

different parts of India.

Funding And Sponsorship:

The authors have indicated they need no financial relationships relevant to the present article to disclose.

Conflict of interest:

The authors declare they need no conflict of interest.

References:

Belhadjer, Z., Méot, M., Bajolle, F., et al. (2020). Acute Heart Failure in Multisystem Inflammatory Syndrome in Children (MIS-C) in the Context of Global SARS-CoV-2 Pandemic. Circulation, 142(5), 429–436.

Toubiana, J., Poirault, C., Corsia, A., et al. (2020). Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ, 369, m2094.

Henderson, L. A., Canna, S. W., Friedman, K. G., et al. (2020). American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV–2 and Hyperinflammation in Pediatric COVID–19: Version 2. Arthritis & Rheumatology, 73(4), e13–e29.

Gruber, C. N., Patel, R. S., Trachtman, R., et al. (2020). Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). Cell, 183(4), 982–995.e14.

Consiglio, C. R., Cotugno, N., Sardh, F., et al. (2020). The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell, 183(4), 968–981.e7.

Multisystem Inflammatory Syndrome in Children (MISC) Associated with Coronavirus Disease 2019. Centers for Disease Control and Prevention. Emergency preparedness and response: Health alert network. May 14, 2020. Available from: https://emergency.cdc.gov/han/2020/ han00432.asp. Accessed July 15, 2020.

Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief: World Health Organization. 15 May 2020. Available from: https: //www.who.int/publications-detail/multisysteminflammatory-syndrome-in-children-andadolescents-with-covid19. Accessed July 15, 2020.

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].

Balasubramanian S, Nagendran TM, Ramachandran B, Ramanan AV. Hyper-inflammatory syndrome in a child with COVID-19 treated successfully with intravenous immunoglobulin and tocilizumab. Indian Pediatr. 2020; S097475591600180. [published online ahead of print].

Bhat CS, Gupta L, Balasubramanian S, Singh S, Ramanan AV. Hyperinflammatory Syndrome in Children Associated with COVID-19: Need for Awareness. Indian Pediatrics. 2020; S097475591600208. [published online ahead of print]

Acharyya BC, Acharyya S, Das D. Novel coronavirus mimicking Kawasaki disease in an infant [published online ahead of print, 2020 May 22]. Indian Pediatr. 2020;S097475591600184.

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]

WHO. WHO coronavirus disease (COVID-19) dashboard. 2020. https://covid19.who.int (accessed Aug 5, 2020).

Government of Canada. Coronavirus disease 2019 (COVID-19): epidemiology update. https://health-infobase.canada.ca/covid-19/ epidemiological-summary-covid-19-cases.html (accessed July 16, 2020).

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.