ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 04 | April - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"A STUDY ON DEMOGRAPHIC PROFILE, CLINICAL PRESENTATION AND OUTCOME IN CHILDREN WITH MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN RELATED TO SARS-COV-2 IN TERTIARY CARE HOSPITAL"

Paediatrics

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ABSTRACT

Background: Severe acute respiratory- syndrome-coronavirus-2 (SARS-CoV-2) is a novel coronavirus which continues to spread and remains a threat to human life across the globe.The pediatric population infected with virus are usually asymptomatic or exhibit mild symptoms. Multisystem inflammatory syndrome in children (MIS-C) is a new dangerous childhood disease that occurs weeks after a mild or asymptomatic SARS-CoV-2 infection. This occurs 3–4 weeks after an asymptomatic infection. Healthy children may manifest some combinations of cardiac dysfunction, gastrointestinal problem, fever, fatigue, or rash. This is postulated to be related to systemic inflammatory response due to coronavirus disease (COVID-19). **Objectives**: To evaluate the clinical profile of children having MIS-C and Therapeutic outcome of multisystem inflammatory syndrome in children associated to Sars-Cov-2. **Material & Methods:** The present study is an prospective eobsevational study conducted in Department of Paediatrics, Niloufer hospital, Hyderabadduring the period of December 1st 2021 to December 31st 2021. **Results**: Among the 80 newborns with thrombocytopenia, 47(59%) are preterm and 32 (41%) are terms, majority of cases are due to sepsis 44 (55%), RDS 12 (15%), MAS 8 (10%), PIH 40 (50%), PROM 24 (30%). Out of 80 newborns survival rate is 82.5% and mortality rate is 17.5% among the mortality cases sepsis is the major cause. **Conclusion:** Multisystem inflammatory syndrome is a serious and life-threatening disease in children, which mandates multispecialty involvement as cardiac and neurologic complications are significantly high. Immunotherapy is the cornerstone in management; however, selection of the exact drug may need further studies.

KEYWORDS

Multisystem inflammatory syndrome in children (MIS-C),Severe acute respiratory- syndrome-coronavirus-2 (SARS-CoV-2),

INTRODUCTION:

- Severe acute respiratory- syndrome-coronavirus-2 (SARS-CoV-2) is a novel corona virus which continues to spread and remains a threat to human life across the globe.
- The pediatric population infected with virus are usually asymptomatic or exhibit mild symptoms. Multisystem inflammatory syndrome in children (MIS-C) is a new dangerous childhood disease that occurs weeks after a mild or asymptomatic SARS-CoV-2 infection.
- This occurs 3–4 weeks after an asymptomatic infection. Healthy children may manifest some combinations of cardiac dysfunction, gastrointestinal problem, fever, fatigue, or rash.
- This is postulated to be related to systemic inflammatory response due to coronavirus disease (COVID-19). This rare syndrome shares common features with other pediatric inflammatory conditions including Kawasaki disease (KD), staphylococcal and streptococcal toxic shock syndromes (TSSs), bacterial sepsis, and macrophage activation syndrome.
- Many such case are being observed in our state and reported from different health-care facilities, hence, we related these unexplained serious manifestations in some of the children to MIS-C.
- Hence, we planned to conduct a prospective study on these observations. In this study, we analyzed the data to have a clearer image of disease spectrum for early recognition and management.

AIM

To evaluate the clinical profile & immediate outcome of multisystem inflammatory syndrome in children associated to COVID

OBJECTIVES:

- To evaluate the clinical profile of children having MIS-C
- Therapeuticoutcome of multisystem inflammatory syndrome in children associated to Sars-Cov-2.

MATERIALS & METHODS:

This study was conducted in a tertiary care hospital. A written protocol was implemented in in Department of Paediatrics, Niloufer hospital, Hyderabad during the period of December 1st 2021 to December 31st 2021

Type Of Study :
Prospective obsevational study

Duration Of Study : one month

Study Population: Parents of children aged below 18 years

Sample Size : 21

Inclusion Criteria:

- All children who are fulfill the MIS-c criteria
- The criteria for case definition of MIS-C are as follows:
- ever for a minimum of 3 days, and any two of the following,
- Skin rashes or bilateral conjunctival congestion or muco-cutaneous inflammation signs
- Hypotension or shock
- Myocardial dysfunction, pericarditis ,valvulitis,or coronary abnormalities (including echocardiography findings)
- Coagulopathy
- Gastrointestinal problems (diarrhea, vomiting, or abdominal pain). Markers of inflammation such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), or procalcitonin have to be high in the absence of infective causes of inflammation, including bacterial sepsis and staphylococcal or streptococcal shock syndromes.
- There has to be evidence of covid-19 [RT-PCR], antigen test, or serology positivity),or likely contact with patients with covid-19.
- Clinical profile is recorded at admission and patients were followed throughout the course of illness in the hospital and outcome is recorded.
- Immediate resuscitative measures were taken, and specific treatment was started and changed according to patient's course in the hospital. Patients were followed daily till discharge/death to study the outcome.

Exclusion Criteria:
Children whose parents didn't give consent for participation in study.

Statistical Analysis
Data collected was entered in Microsoft Excel 2013 and analysis was done using SPSS version 20.0. Mean with SD was calculated for all continuous variables. Categorical variables were expressed as percentages (proportions)

All categorical variables were compared in the pre and post implementation period using Chi squared test. Student t test were used

to compare continuous variables with the normal and skewed distribution respectively.

Patient's privacy maintained by not publishing the identifying information.

RESULTS:

Primary Outcomes:

- A total of 21 cases of MIS-C from the 1st December 2021 to the 31st December 2021 were seen. Out of them, 15 (71%) were boys, whereas 6 (29%) were girls.
- We found two (9%) cases between 1 and 5 years of age, while 10 (48%) cases were aged between 6 and 10 years, 7 (33%) cases between 11 and 15 years, and 2 (9%) cases were aged above 15-18 years.
- Fever was found in all (100%) cases, while abdominal symptoms were found in 15(71%) cases.
- Loose motion, vomiting, and abdominal pain were the presenting complaints in 7(33%), 10 (48%), and 9 (42%) cases, respectively.
- Respiratory distress at admission was found in 12(57%), while hypotension at admission was found in 8(38%) cases.
- Six cases(28%) children had some form of neurological involvement such as seizures, agitation, or altered sensorium. Seizure was found in three(14%) cases.
- Skin rash was found in six (28%) cases, while conjunctival congestion was found in eight (38%) cases.

Table 1 – Clinical Presentation

Symptomatologyn (%)	
Fever	21 (100)
Abdominal symptoms	15(71%)
Loose motion	7(33%)
Vomiting	10 (48%)
Pain abdomen	9(42%)
Hypotension	8(38%)
Seizures	3(14%)
Respiratory distress	12 (57%)
Congestive heart failure	1 (4%)
CNS involvement	6(28%)
Conjunctival congestion	8 (38%)
Skin rash	6 (28%)

Secondary Outcomes

- Out of 21 patients, 10(40%) received IVIG, while 21 (84%) received steroids, and only steroid was used in 11 children.
- Invasive ventilation was required for 3 (12%) patients, while noninvasive ventilation (NIV) was used for two (8%) children. Inotropic support was required in ten (40%) patients.

Table 2 - Demographic Profile

Characteristics	n(%)
Age group (years)	
1-5	2
6-10	10
11-15	7
15-18	2
Sex (male: female)	15:6
Mean age (years)	9
RTPCR positivity	5
Rapid antigen positivity	0
Antibody positivity	20
Both negative	1
Outcome, n (%)	
Discharged	19
Left Against Medical Advise	1
Death	1
Mean duration of stay (days)	12

Laboratory evidence of SARS-CoV-2 was found in 20 patients; 5 were RT-PCR positive, 20 were IgG antibody positive. In one children, RTPCR and antibody were negative, but their parents were RT-PCR positive 5 weeks before

Out of the 21 patients, 22 recovered, while 1 left against medical advice and one died of respiratory complications. None of our patients had coronary abnormality, while one patients had mild cardiac dysfunction at discharge.

Table 3- Therapeutic Option

Therapeutic option	n (%)
IVIG	10(40%)
Steroid	21 (84%)
IVIG + steroid	10(40%)
NIV	2 (8%)
Invasive ventilation	3 (12%)
LMWH	11 (44%)
Inotrope	10 (40%)

- Echocardiography was done in 14 cases: myocardial dysfunction was found in 7(28%), 5 had mild pericardial effusion, while none had coronary dilatation.
- The mean total leukocyte count (TLC) was 12,600/mm^3, neutrophil was 75%, lymphocyte count was 25%, and the mean platelet count was 2 lakh/mm^3.The inflammatory markers such as CRP mean value was 64.4 mg/dL, procalcitonin level was 15.1 ng/mL, while the mean ESR was 80 mm in the 1st hr.
- The mean value of ferritin was 620 ng/mL and that of LDH was 850 U/L, while the mean D-dimer value was 4.2 mg/ml.

DISCUSSIONS:

Among the 21 cases, the mean age in our study population was 9 years, which is comparable to the mean age of 9.5 years in a study done by Sadiq*et al*. in Pakistan.

Three cases were below 5 years of age and 2 cases were above 15 years, while majority (80%) were in between 5 and 15 years' age group, which points toward the vulnerable age group. Though there is a clinical resemblance toward atypical KD, unlike KD, these cases have occurred in older children and adolescents.

Selva*et al*. found marked differences between the antibody responses in children and adults against coronavirus These varying responses were associated with different Fcg receptor-binding properties. Differences in antibody response might contribute to such specific age distribution in our study population.

All children in our study with features of this new inflammatory syndrome fulfilled the WHO criteria for MIS-C for the clinical, laboratory, and echocardiographical features.

Skin rash was found in six (24%) cases, while conjunctival congestion was found in eight cases (32%). Nearly 40% of our children presented with shock and required volume resuscitation and inotropic support. KD-like features of the syndrome seem to be predominant in some case series (Italy).

However, case reports from France and the UK have more acute presentation with shock with features of TSS. However, these data are reported mostly from intensive care unit admissions rather than the general pediatric population. The US data also showed atypical KD-like features in 40% of the patients.However, this variability in clinical manifestations is difficult to distinguish on clinical ground.

Out of 9 patients who had some form of central nervous system involvement, 5 of them had clinical seizures, which adds further to the wide clinical distribution of MIS-C. Magnetic resonance imaging (MRI) of brain was done in three out of six children with seizures.

One child had features of cerebral edema, while two others had normal MRI findings. The child with cerebral edema had normal blood pressure, while the other two children had features of shock. Hence, transient cerebral hypoperfusion as the cause of seizures cannot be ruled out in them.

Chen in his review of six reports on MIS-C found that out of 187 children, 38% had neurological issues. The exact cause of this neurologic complication is not known, but it seems to be different from adult COVID-19 cases where the usual cause is cerebrovascular thromboembolism. Postinfectious immune response might be responsible for neurologic manifestation.

In a study published in *JAMA Neurology*, out of 616 MIS-C cases, 126 (20.4%) children had neurologic involvement. Of the 126 children, 20 had life-threatening neurologic conditions such as severe encephalopathy, stroke, acute demyelinating encephalomyelitis, acute fulminant cerebral edema, or Guillain–Barre syndrome.

Only nine (42.8%) cases had respiratory distress at admission. One child had features of acute respiratory distress syndrome (ARDS) and the rest eight children had features of either shock or pulmonary edema.

Godfred-Cato *et al*. in an USA cohort had reported significant respiratory involvement (63%) in MIS-C. Those patients had higher incidence of RT-PCR positivity and higher mortality rate. In our series, the child who developed ARDS was found to be RT-PCR positive, and she expired despite all supportive care.

Ramcharan*et al*. in their cohort of 15 cases of MIS-C, who were referred for cardiac evaluation, found cardiac dysfunction in 63% of the cases, whereas coronary abnormalities were detected in 93% of the cases. In a recent study from Mumbai, coronary affection was found in 23.8% of cases.

In the present study, the mean TLC was 12,600/mm^3 with a mean neutrophil of 75% and lymphocyte of 25%, which is comparable to the meta-analysis done by Lagunas-Range *et al*. who could find an association between the high white cell count, low lymphocyte count, low platelet count, elevated CRP, and severity.

In three patients, thrombocytopenia (<1.5 Lakh/mm^3) was found, but none had very low platelet count, which could be a point to distinguish this syndrome from severe sepsis or dengue

The inflammatory markers such as CRP, ESR, and procalcitonin were elevated in our enrolled patients with a mean CRP of 64.4 mg/dL. There is increasing evidence in adult studies, that raised levels of CRP are associated with severity and mortality in COVID patients. Majority of our patients have shown positive IgG to SARS-CoV-2, which points toward an association with past COVID infections in these patients

In one cases where both RTPCR and antibodies were negative, the epidemiological connection with past COVID-19 infection could not be ignored, as their parents were RTPCT positive 5 weeks back. The mean D-dimer value was very high (4.2 mg/mL), which is comparable to the elevated D-dimer levels in both pediatric and adult patients with COVID-19.

Evidence from adult studies suggests that elevated D-dimer levels are associated with poor outcome, but therapeutic implications of the high D-dimer are not yet clear. A recent pediatric guideline suggests thromboprophylaxis in children with COVID-19 with risk factors for thrombosis such as presence of central venous catheter, decreased mobility, and past or family history of thromboembolism.

The American College of Rheumatology has recommended the use of therapeutic anticoagulation for cases with ejection fraction <35%, documented thrombosis, and coronary artery zscore of >10. It is still not clear whether MIS-C patients have similar risk of thrombosis like that of acute COVID patients.

However, as these patients have high D-dimer along with multiorgan dysfunction requiring critical care treatment, it is reasonable to start low-molecular-weight heparin (LMWH) for MIS-C. We used LMWH in our patients as per the above guidelines. Myocardial dysfunction was found in 38.1% of patients, while none had coronary dilatation in their first echocardigraphy in our study

Out of 11 children who received only steroid, two children were treated with pulse methyl prednisolone 10 mg/kg/day for 3 days, followed by oral prednisolone at a dose of 1 mg/kg/day for 2 weeks and both of them improved. In other nine patients without significant cardiac involvement, methyl prednisolone was used at a dose of 1 mg/kg/day for few days followed by tapered dose of prednisolone for 2 weeks.

Due to overlap of clinical features, many clinical trials have proposed IVIG as the first choice in the treatment of MIS-C. Whittaker *et al*. reported 100% use for KD-like presentations, 72% for those with shock, and 61% for those with fever and inflammation alone. With such variation in the management of MIS-C patients, there is suboptimal evidence to assess the superiority of various treatments In our study, 40% of the patients required inotropic support despite adequate fluid resuscitation. Early recognition of shock, judicious fluid resuscitation, timely initiation of inotropes, and vasopressors are key factors for favorable outcome

NIV was required in two children for respiratory distress with shock. Similarly, invasive ventilation was required in three children: one for a child with RTPCR positivity with respiratory involvement. One children requiring invasive ventilation expired.

CONCLUSION:

- Multisystem inflammatory syndrome is a serious and life-threatening disease in children, which mandates multispecialty involvement as cardiac and neurologic complications are significantly high.
- Diagnosis and management of MIS-C is a challenge as the guidelines are evolving and new data are coming up in literature.
- Pediatricians should familiarize themselves with the presentation of this new disease and start aggressive multispecialty management.
- Immunotherapy is the cornerstone in management; however, selection of the exact drug may need further studies.

Limitations:

Thelimitations to the study was small study population and observer variability.

Conflicts Of Interest: None

Funding: No external funding source

Acknowledgements:
We sincerely thank all the participants and the committee for giving permission to our research project.

REFERENCES:

1. WHO. Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19; May 15, 2020. Available from: https://www.who.int/newsroom/commentaries/detail/multisysteminflammatory-syndrome-in-children-andadolescents-with-covid-19. [Last accessed on 2020 Dec 27].
2. Sadiq M, Aziz OA, Kazmi U, Hyder N, Sarwar M, Sultana N, *et al.* Multisystem inflammatory syndrome associated with COVID-19 in children in Pakistan. Lancet Child Adolesc Health 2020;4:e36-7.
3. 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 2020;142:429-36.
4. 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;324:259-69.
5. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MB, *et al.* Multisystem inflammatory syndrome in U.S. Children and adolescents. N Engl J Med 2020;383:334-46.
6. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, *et al.* Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: A multicentre observational study. Lancet Child Adolesc Health 2020;4:669-77.
7. Selva KJ, van de Sandt CE, Lemke MM, Lee CY, Shoffner SK, Chua BY, *et al.* Systems serology detects functionally distinct coronavirus antibody features in children and elderly. Nat Commun. 2021 Apr 1;12 (1):2037.
8. 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;395:1771-8.
9. Chen TH. Neurological involvement associated with COVID-19 infection in children. J NeurolSci 2020;418:117096.
10. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, *et al.* Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 2021;78:536-47.
11. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, *et al.* COVID-19-associated multisystem inflammatory syndrome in children-United States, March-July 2020. Morb Mortal Wkly Rep 2020;69:1074.
12. Ramcharan T, Nolan O, Lai CY, Prabhu N, Krishnamurthy R, Richter AG, *et al.* Paediatric inflammatory multisystem syndrome: Temporally associated with SARS-CoV-2 (PIMS-TS): Cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. PediatrCardiol 2020;41:1391-401.
13. Shobhavat L, Solomon R, Rao S, Bhagat I, Prabhu S, Prabhu S, *et al.* Multisystem inflammatory syndrome in children: Clinical features and management-intensive care experience from a pediatric public hospital in Western India. Indian J Crit Care Med 2020;24:1089-94.
14. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol 2020;92:1733-4.
15. Henry BM, de Oliveira MH, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. ClinChem Lab Med 2020;58:1021-8.
16. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, *et al.* D-dimer levels on admission to predict in-hospital mortality in patients with covid-19. J ThrombHaemost 2020;18:1324-9.
17. Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 2020;7:e438-40.
18. Barnes GD, Burnett A, Allen A, Blumenstein M, Clark NP, Cuker A, *et al.* Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: Interim clinical guidance from the anticoagulation forum. J Thromb Thrombolysis 2020;50:72-81.
19. Loi M, Branchford B, Kim J, Self C, Nuss R. COVID-19 anticoagulation recommendations in children. Pediatr Blood Cancer 2020;67:e28485.
20. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H, *et al.* American College of Rheumatology clinical guidance for pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS C) associated with

SARS CoV 2 and hyperinflammation in COVID 19. Version 1. Arthritis Rheumatol 2020;72 (11):1791-1805
21. Hennon TR, Penque MD, Abdul-Aziz R, Alibrahim OS, McGreevy MB, Prout AJ, *et al.* COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. ProgPediatrCardiol 2020 May 23:101232.
22. Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S, *et al.* Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian Pediatr 2020;57:1015-9.