RESEARCH PAPER

Differentiating Multisystem Inflammatory Syndrome in Children (MIS-C) and Its Mimics – A Single-Center Experience From a Tropical Setting

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Received: June 20, 2022;
Initial review: July 10, 2022;
Accepted: February 16, 2023.

Objective: Identifying clinical and laboratory indicators that differentiate multisystem inflammatory syndrome in children (MIS-C) apart from other febrile diseases in a tropical hospital setting. **Methods**: Review of hospital records done in a tertiary care exclusive children's hospital for children admitted from April, 2020 till June, 2021. Laboratory values, severe acute respiratory syndrome coronavirus (SARS-CoV-2) serological status, and clinical signs and symptoms of patients with MIS-C, and those with similar presentations were analyzed. **Results**: 114 children fulfilled the inclusion criteria (age group of 1 mo-18 y) for whom a diagnosis of MIS-C was considered in the emergency room based on the clinical features. Among them, 64 children had the final diagnosis of MIS-C, and the remaining 50 children had confirmatory evidence of infections mimicking MIS-C such as enteric fever, scrub typhus, dengue and appendicitis. **Conclusion**: Older age group, presence of mucocutaneous symptoms, very high C-reactive protein, neutrophilic leukocytosis, abdominal pain and absence of hepatosplenomegaly favor a diagnosis of MIS-C.

Keywords: *Dengue, Enteric fever, Scrub typhus, SARS-CoV-2.*

Published online: March 10, 2023; **PII**:S097475591600506

Recognition of unique features of multisystem inflammatory syndrome in children (MIS-C) is critical for early recognition and treatment, and this remains a challenge for clinicians, as case definition of MIS-C often overlaps with other common conditions [1-3]. Tropical infections like enteric fever, dengue and rickettsial infection may present with clinical characteristics mimicking MIS-C in low- and middle-income settings [4,5], and may be treated incorrectly as MIS-C, resulting in unnecessary hospitalization and therapy.

We report findings from our retrospective analysis of cases of MIS-C and infections mimicking MIS-C in a pediatric hospital setting.

METHODS

This study was a review of hospital records of all children (aged 1 month to 18 years) admitted between April, 2020 to June, 2021 at our tertiary children hospital, for whom the diagnosis of MIS-C was considered upon arrival in the emergency room. The study was approved by the institutional review board. We compared the clinical and laboratory characteristics of MIS-C group and non-MIS-C groups. Cases identified as having acute coronavirus disease 2019 (COVID-19) were not included.

An initial diagnosis of MIS-C was considered in children with clinical features consistent with World Health Organization criteria for MIS-C [2]. Children who fulfilled the criteria for MIS-C (clinical and laboratory evidence of raised inflammatory markers) was grouped together, while children who had alternative diagnoses, confirmed by laboratory data for other infections including scrub typhus, dengue, enteric fever and appendicitis, were grouped as MIS-C mimics. Complete blood count was done by automated five-part hematology analyzer with Horiba Pentra E60 kit and C-reactive protein was measured with Biosystem CRP reagent by immunoturbidimetry method. Echocardiogram was done for all children who were included in the study as a part of initial evaluation. Dengue fever was confirmed by non-structural antigen/ IgM (Enzyme linked immunosorbent assay) with Bio-Merieux Mini VIDAS kit, and rickettsial infection was confirmed if scrub typhus IgM was positive (Inbios Scrub typhus Detect IgM ELISA). Enteric fever was diagnosed by blood cultures. Appendicitis was diagnosed on the basis of clinical presentation supported by ultrasonographic findings with per-operative confirmation. Confirmed COVID-19 was defined as either positive SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) performed by Indian Council of Medical

Research (ICMR) approved laboratories, and SARS-CoV-2 IgM and IgG antibody test was performed by ELFA method using ICMR-approved YHLO SARS-CoV-2 IgG and IgM antibody titer assay kits (BioMerieux Mini VIDAS). We also gathered data on exposure to SARS-CoV-2, course in the hospital, and outcomes including coronary artery dilatation (*z* score 2 to 2.5) or aneurysms (*z* score >2.5) and left ventricular dysfunction (ejection fraction <55%).

A final diagnosis of MIS-C was made only after two expert pediatric clinicians concurred with the diagnosis based on clinical features and after exclusion of infections based on laboratory data.

Statistical analysis: Data analyzed included demographic data, symptoms, clinical examination findings and laboratory values at the time of presentation. Clinical symptoms and gender were expressed as proportions and chi-square test was used for comparisons. Laboratory parameters were expressed as median (IQR) with Mann-Whitney test used for comparisons. A *P* value <0.05 was considered as significant.

RESULTS

A total of 114 children were initially included for analysis based on clinical criteria for MIS-C. Among them, 64 children had a final diagnosis of MIS-C, and the remaining 50 children had confirmed infections mimicking MIS-C [enteric fever (*n*=20), dengue (*n*=6), scrub typhus (*n*=15), and appendicitis (*n*=9)]. Among those initially included, there were no cases of complete Kawasaki disease (KD) phenotype or toxic shock syndrome (TSS) [6].

Among MIS-C mimics, we encountered five children with a co-infection. These children had culture positive enteric fever (*n*=20), appendicitis (*n*=9), and dengue (*n*=6), in whom reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2 was also positive. However, we considered COVID as a bystander in these cases.

Duration of fever prior to presentation was nearly similar in both the groups, with a median of 4.5 days in MIS-C and 6.5 days in MIS-C mimics (**Table I**). MIS-C was more common among older children (median (IQR) age of 9.65 (5.22-17) years. Mucocutaneous symptoms (including rash, oral mucosal changes, conjunctivital congestion) and abdominal pain were more commonly observed in MIS-C (*P*=0.005) (**Table I**). Presence of rash in children was observed more amongst MIS-C cases (*P*<0.001). Organomegaly (hepatomegaly/hepatosplenomegaly) was more commonly observed in children with conditions mimicking MIS-C (**Table I**).

Table I Baseline Characteristics of Children With MIS-C and MIS-C Mimics

	MIS-C (n=64)	*MIS-C mimics (n=50)*	*P value*
Duration of fever (d)[a,b]	4.5 (3-6)	6.5 (4-9)	0.74
Age (y)[a]	10 (5-17)	4 (3-8)	<0.001
Male gender	40 (62)	26 (52)	0.339
Rash	35 (54.6)	7 (14)	0.001
Oral mucosal changes	12 (18.7)	3 (6)	0.050
Conjunctival congestion	29 (45.3)	5 (10)	0.050
Abdominal pain	29 (45)	10 (20)	0.005
Vomiting	18 (28)	20 (40)	0.230
Diarrhea	15 (23)	15 (30)	0.521
Organomegaly	11 (17)	31 (62)	<0.001
Hypotension[c]	9 (14)	5 (7)	0.57

All values in no. (%) or [a]median (IQR). MIS-C: multisystem inflammatory syndrome in children. [b]at presentation. [c]during hospital stay or at admission.

Children with MIS-C had significantly higher CRP (median CRP 132 mg/L) and higher neutrophil-lymphocyte ratio. Among 64 cases of MIS-C, only 9 (14%) children presented with or had hypotension during the course of hospital stay. LV dysfunction was seen in 7 (11%) children with MIS-C, but only two children had LV dysfunction in MISC mimics (one with dengue and one with scrub typhus). There was no evidence of coronary artery involvement in either of the groups (**Table II**).

Table II Laboratory Parameters in Children With MIS-C and MIS-C Mimics

Laboratory values	*MIS-C (n=64)*	*MIS-C mimics (n=50)*	*P value*
Hemoglobin (mg/dL)	10.4 (7.6, 14.5)	9.8 (5.6,13)	0.217
Leukocyte count (x10^9/L)	10.31 (6.77, 13.0)	8.28 (2.3, 9.34)	0.134
Neutrophil-lymphocyte ratio	5.43 (3.11,8.78)	3.76 (2.1,6.17)	0.006
Platelets (x 10^9/L)	246 (141,356)	186 (79,326)	0.225
C-reactive protein (mg/L)	132 (56,242)	53 (31,74)	0.05
Albumin (g/dL)	3.1 (2.7,4)	3.4 (3.2, 4.8)	0.12
Ventricular dysfunction[a,b]	7 (11)	2 (4)	1.00

All values in median (IQR) or [a]no. (%). MIS-C: multisystem inflammatory syndrome in children. [b]by echocardiography.

WHAT THIS STUDY ADDS?

- Older age group, presence of mucocutaneous symptoms, very high C-reactive protein, neutrophilic leukocytosis, abdominal pain, and absence of hepatosplenomegaly favor a diagnosis of MIS-C.

Leukocytosis was seen in 12 (18.7%) children with MIS-C while leukopenia was seen only in two children (3%). Thrombocytosis was seen in 14 children with MIS-C (21.8%) and thrombocytopenia was seen in 10 children (15.6%). Neutrophil-lymphocyte ratio was found to be higher in MIS-C (P =0.006) compared to MIS-C mimics (5.43 vs 3.46). Extremely high C-reactive protein (CRP) value of more than 100 mg/L was seen in 46 (72%) children with MIS-C, while only 9 (18%) children with enteric fever and scrub typhus had a CRP more than 100 mg/L (P<0.001).

SARS-CoV-2 antibody was positive in majority of the cases of MIS-C (48, 75%) and in MIS-C mimics (37, 74%), while COVID RT-PCR was positive in a few cases of MIS-C (5, 7.8%) and MIS-C mimics (5, 10%). The differences were not statistically significant.

DISCUSSION

The most discriminative predictors of MIS-C were older age group, presence of rash along with significantly raised CRP >100 mg/L and neutrophilic leukocytosis, and absence of hepatosplenomegaly.

Though early reports described MIS-C as a variant of Kawasaki disease, subsequent studies have reported varied presence of KD features and differences in laboratory parameters and demographics between these diseases [7,8]. Among the mucocutaneous symptoms in our study, cheilitis and conjunctival congestion and rash were more commonly observed among the MIS-C cohort. Although, children with MIS-C mimics had various infectious etiologies associated with gastrointestinal system, presence of abdominal pain was more often associated with MIS-C. Presence of hepatomegaly or splenomegaly or both favored a diagnosis of MIS-C mimic. Children with MIS-C may or may not present in overt shock but develop-ment of hemodynamic instability may be an important clinical sign to favor a diagnosis of MIS-C. Among the laboratory parameters, except for CRP >100 mg/L and neutrophilic leukocytosis, lymphopenia and thrombocytopenia have been frequently reported in children with MIS-C [10], but in our series none of these laboratory parameters was statistically significant to differentiate MIS-C and infections. An arbitrary cutoff of >100 mg/L was statistically significant to identify the MIS-C group (P<0.001), unlike the CDC/WHO cutoff of 30 mg/L. Interestingly, leukopenia was observed more often in MIS-C mimics.

Roberts, et al. [9] had reported that children with MIS-C were older; more likely to present with conjunctivitis, oral mucosa changes, abdominal pain and hypotension, and had higher neutrophil-lymphocyte ratios and lower platelet counts. Earlier Indian studies [10,11] have compared the manifestations of MIS-C and dengue and have reported that the presence of mucocutaneous features and highly elevated CRP favored MIS-C while the presence of petechiae, hepatomegaly, and hemoconcentration and high ferritin favored a diagnosis of dengue.

On comparison of both the cohorts, the incidence of seropositive status of COVID antibodies and RT-PCR was nearly equal. Even though the presence of SARS-CoV-2 exposure is considered as one of the diagnostic criteria (PCR/SARS-CoV-2 IgM/IgG positivity), with the reported seropositivity rate of nearly 70% [12] and an expected constantly rising rate, the utility of antibody test positivity in the diagnosis of MIS-C is limited.

Since we included only hospitalized children and our hospital's algorithm suggested considering MIS-C when CRP was ≥30 mg/L, mild cases of MIS-C might have been inadvertently missed. Multivariable logistic regression analysis was not done in our study. Tests for inflammatory makers like ESR, procalcitonin, ferritin, D-dimer were not done for all children. Our study reflects only the local prevalence of alternative diagnoses in a tropical setting. Dengue cases were diagnosed with NS1 ELISA/IgM ELISA and scrub typhus was diagnosed with Scrub IgM ELISA only, and not confirmed with PCR or cultures.

Older age group, presence of mucocutaneous symptoms, very high CRP, neutrophilic leukocytosis, abdominal pain and absence of hepatosplenomegaly favor a diagnosis of MIS-C. Considering seropositivity status alone and overlooking other diagnostic criteria for MIS-C may lead to its over-diagnosis and delay in the initiation of treatment for primary disease. Thorough clinical examination for findings like eschar, organomegaly and appropriate microbiological tests are crucial in the diagnosis of MIS-C mimics.

Ethics clearance: KKCTH IEC Committee; No. IEC 575/2022, dated April 24, 2022.
Contributors: SBS, JS: concept and design; KD, SLR, DN: acquisition, analysis and interpretation of data; SBS, JS, KD, SLR: drafting of the manuscript; SC, DN: statistical analysis; SLR: analysis of laboratory assays; KD, SBS, JS, AVR: critical

revision of the manuscript for important intellectual content; SBS, JS, KD, SLR, DN, AVR, SC: final approval of the version to be published.

Funding: None; *Competing interests*: None stated.

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