

Clinical Spectrum of Children With Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 Infection

JOLLY CHANDRAN,¹ EBOR JACOB JAMES,¹ VALSAN P VERGHESE,² SATHISH KUMAR T,³ KALA RANJINI SUNDARAVALLI E,¹ SIVA VYASAM¹

From¹Pediatric Intensive Care Unit, ²Pediatric Infectious Diseases, and ³Pediatric Rheumatology, Department of Pediatrics, Christian Medical College, Vellore, Tamil Nadu.

Correspondence to:

Dr Ebor Jacob James, Professor,
Pediatric Intensive Care Unit,
Department of Pediatrics,
Christian Medical College and
Hospital, Vellore, Tamil Nadu.
eborjacob@cmcvellore.ac.in
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Objectives: To compare the clinical profile, treatment, and outcomes of PCR-positive and PCR-negative antibody-positive critically ill children with multisystem inflammatory syndrome (MIS-C). **Methods:** This retrospective observational study was done at a tertiary care coronavirus disease 19 (COVID-19) pediatric intensive care unit in India. The baseline characteristics, clinical profile, treatment, and outcomes in seventeen critically ill children diagnosed with MIS-C were analyzed from 1 July to 31 October, 2020. **Results:** Sixteen out of 17 children presented with hypotensive shock and respiratory distress. Mean (SD) age of PCR-negative antibody-positive and PCR-positive children was 11 (4.4) and 5 (3.7) years, respectively ($P=0.007$). The former group had significantly higher mean (SD) D-dimer levels [16,651 (14859) ng/mL vs 3082 (2591) ng/mL; $P=0.02$]. All received intensive care management and steroid therapy; 7 children received intravenous immunoglobulin. 14 children survived and 3 died. **Conclusions:** The outcome of children with MIS-C was good if recognized early and received intensive care.

Keywords: COVID-19, Hypotensive shock, Respiratory distress, Steroids.

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Coronavirus disease (COVID-19) is a contagious pathogen affecting children less commonly than adults with incidence of 1-6.4% and a varied presentation in children [1,2]. In early April, UK clinicians noticed increasing numbers of children presenting with multisystem involvement and symptoms similar to Kawa-saki disease and termed it as hyper inflammatory syndrome from COVID-19 [3]. Most of these children were healthy prior to the presentation.

This study was done to describe the clinical and laboratory features and outcomes in children with multisystem inflammatory syndrome in children (MIS-C) [4], admitted to an intensive care unit, and to compare these features between polymerase chain reaction (PCR)-positive and PCR-negative antibody-positive children.

METHODS

This was a retrospective observational study. The medical records of the patients admitted to the pediatric intensive care unit (PICU) from July to October 2020 were retrieved from the hospitals electronic database and inpatient records after obtaining necessary approval from the institutional review board. The records were analyzed for clinical and laboratory characteristics, treatment modalities and out-

comes in PCR-positive and PCR-negative antibody-positive children.

The diagnosis of MIS-C was based on the WHO case definition, as any child with fever for three or more days and any two of the following, *i*) rash, conjunctivitis and/or mucocutaneous inflammation, *ii*) hypotension (SBP <5th centile), *iii*) features of myocardial dysfunction, *iv*) evidence of coagulopathy, *v*) acute gastrointestinal problems; and elevated markers of inflammation, with no obvious microbial cause on testing (including negative blood cultures, dengue and scrub typhus serology), and a positive COVID-19 test or contact with a COVID-19 patient [4]. The laboratory parameters that were assessed included ferritin, D-dimer, pro-brain natriuretic peptide BNP, troponin-T, procalcitonin, C-reactive protein (CRP), serum albumin and platelets. Diagnosis of SARS-CoV-2 infection was made by real-time reverse transcription-polymerase chain reaction (RT-PCR) assays done from nasopharyngeal swabs of children at admission. The COVID antibody test was done by rapid antibody tests to SARS-CoV-2 by chemiluminescent immunoassay (CLIA) by 2 different kits, Siemens S1-RBD rapid antibody test (total or IgG by Siemens Healthineers) with measuring interval/index value 0.05-10 AU/mL and Roche and Abbott-Nucleocapsid (antibody) with cut off index <1 being non-reactive.

All children who were SARS-CoV-2 PCR positive or antibody positive fulfilling the MIS-C criteria were managed as per standard WHO treatment guidelines for critical disease including shock and ARDS (based on PaO₂/FiO₂ ratio and chest X-ray) [5], and the American College of Rheumatology (ACR) guidance on treatment of MIS-C [6], which included dexamethasone at 0.15 mg/kg/dose once daily and anticoagulant therapy with low molecular weight heparin (LMWH) at a dose of 0.5 mg/kg/dose twice daily in all children with D-dimer >500 ng/mL. Critically ill children on mechanical ventilation received unfractionated heparin at 5-10 units/kg/hour as an intravenous infusion for 24-48 hours till they were stable, which was then changed to LMWH. Intravenous immune globulin (IVIG) at a dose of 2 g/kg over 2 days was given to children with catecholamine-resistant shock and severe left ventricular dysfunction.

Statistical analysis: Statistical analysis was done using SPSS 23.0 (SPSS Inc.). Percentages and mean (standard deviations) were calculated for categorical and continuous variables, respectively. Independent sample *t*-test was used for comparing the means and two proportions test to compare the proportions between groups.

RESULTS

Over the study period, 415 children were admitted and screened for COVID-19 of whom 215 were admitted to COVID PICU (age range 1 month to 15 years). Thirty-six children (16%) were SARS-CoV-2 PCR positive, of whom 7 (19%) had moderate illness, 5 (14%) had severe and 24 (66%) had critical disease. Of the 24 children with critical disease, 10 (41%) had MIS-C. An additional 7 children with MIS-C were RT-PCR negative but COVID antibody-positive. Three PCR-positive infants aged one month, six months and 11 months had prematurity as a premorbid risk factor, and the 6 month old had also undergone Kasai procedure at 2 months of age for biliary atresia.

Clinical presentations were similar with fever in all and fluid-refractory hypotensive shock in 16 (75% of children being in cold shock) and respiratory distress in 16 children. The comparative clinical features between PCR-positive and PCR-negative antibody positive children are shown in **Table I**. Additional atypical manifestations seen in 2 children included refractory thrombocytopenia in a one-month-old infant and CNS stroke in a 6-year-old who had received steroids prior to admission and did not have respiratory distress or hypotensive shock at admission.

The antibody titre in 7 children who were PCR-negative by Siemens antibody test was >10 AU/mL in all. Roche analyses showed 5 out of 7 being positive with

mean (SD) titres of 72.06 (38.3) while 2 of the children did not have the test done as there was inadequate sample for the second test. The comparative clinical and laboratory features between PCR-positive and PCR-negative antibody positive children are shown in **Table I**.

Blood cultures were sterile, dengue serology was negative, and scrub IgM ELISA was negative in all 17 children, ruling out other microbial causes. Twelve children had moderate-severe LV dysfunction, of whom seven were PCR-positive. Mild pericardial effusion was seen in two of the PCR-negative antibody positive children. Bedside echocardiographic screening showed no evidence of coronary artery ectasia or aneurysm.

Respiratory support was provided through HHFNC in 9 children (including 7 PCR-positive children), non-invasive ventilation in two PCR-positive children and invasive ventilation in five of whom four were PCR-

Table I Characteristics and Laboratory Parameters of Children With Multisystem Inflammatory Syndrome Associated With SARS-CoV-2 Infection

Parameter	SARS-CoV-2 PCR positive (n=10)	SARS-CoV-2 PCR negative (n=7)
Age, y ^a	5 (3.71)	11 (4.4)
Sex ratio (female:male)	1.5:1	0.4:1
Symptomatic prior to ICU admission, d	4.5 (1.9)	4.1 (1.34)
<i>Clinical features, n</i>		
Fever	10	7
Gastrointestinal symptoms	5	6
Respiratory symptoms	5	4
Rash	7	3
Hypotensive shock	10	6
Respiratory distress	10	6
<i>Laboratory parameters^b</i>		
Ferritin (ng/mL)	1118 (838)	2095 (2696)
D-dimer (ng/mL)	3082 (2591)	16651 (14859)
NT ProBNP (pg/mL) ^c	14,139 (18107)	19,158 (22405)
Troponin- T (pcg/mL)	58 (78)	152 (257)
Procalcitonin (ng/mL)	16.5 (15.2)	39.1 (14.8)
C-reactive protein (mg/dL)	105.6 (41.5)	241.0 (159.2)
Albumin (g/dL)	2.75 (0.64)	3.14 (0.49)
Platelets (X10 ⁹ /L)	198 (1.24)	157 (0.76)

^bValues in mean (SD). All PCR negative children were SARS-CoV-2 antibody positive. SARS-COV-2 - severe acute coronavirus 2; PCR-polymerase chain reaction; ICU-intensive care unit; NT ProBNP: N-terminal Pro Brain Natriuretic Peptide. ^aP=0.02; ^cP=0.007. Among children with and without PCR-positivity, ferritin was abnormal in 10 and 6, D-dimer in 9 and 7, NT-ProBNP in 3 and 2, Troponin-T in 5 and 4, Procalcitonin in 3 and 6, and C-reactive protein in 5 each, respectively.

WHAT THIS STUDY ADD?

- Multi-system inflammatory syndrome in children (MIS-C) can present as critical illness needing ICU care, and responds well with steroid therapy in the resource-limited setting in the absence of IVIG.

negative antibody positive children. There was evidence of acute respiratory distress syndrome (ARDS) in 8 children, with 4 each of PCR-positive and PCR-negative antibody positive children. Of these 8 children, two improved with non-invasive mechanical ventilation and one improved with heated humidified high flow nasal cannula therapy (HHHFNC), with the total duration of supplemental oxygen ranging from 3 to 5 days. The remaining five required invasive mechanical ventilation. Oxygenation Index ratio in three of these five children was >16, suggestive of severe ARDS. Inotropic support was needed for 14 children, with two inotropes (adrenaline and noradrenaline) needed in five of seven PCR-negative antibody positive children and six of ten PCR-positive children. Two children were treated with peripheral veno-arterial extra-corporeal membrane oxygenation (ECMO) for a period of 7 days for severe cardiac dysfunction with refractory shock. One child received continuous renal replacement therapy (CRRT) for acute kidney injury. All 17 received dexamethasone and 16 had anticoagulant therapy (except the one-month-old with refractory thrombocytopenia), and seven of the seventeen with catecholamine-resistant shock and severe LV dysfunction received intravenous immune globulin. None of the children received tocilizumab or investigational antiviral agents.

The mean duration of ICU stay was 7.3 (range 4 to 19) days. Fourteen (82%) children were discharged. Three children died during the study. One was a 1-month-old infant with refractory thrombocytopenia and multiorgan involvement treated with IVIG and a single dose of methylprednisolone at 30 mg/kg and cyclosporine for probable MAS (macrophage activation syndrome). Two others were adolescents with severe cardiac dysfunction, refractory shock and multiorgan failure, one of whom was on ECMO.

DISCUSSION

This series of seventeen children adds to the growing body of literature from India on manifestations, management and outcomes among critically ill COVID positive children with MIS-C associated with COVID-19 [7,8]. Majority of the children were PCR-positive for SARS-CoV-2 infection while only seven were COVID antibody positive, unlike most reports from Western countries

where PCR-positivity in children with MIS-C is seen in about a-third [9,10]. The majority of children in this study had no major comorbidities comparable to studies from Italy and the US showing that children were mostly well prior to SARS-CoV-2 infection [10-12].

All the children were critically ill needing intensive care admission and inotropic support corresponding to earlier studies [11-13]. Although, they needed respiratory support, less than half of them required mechanical ventilation, similar to other studies that show that children with MIS-C have mild to moderate lung involvement, and that outcomes are good with appropriate respiratory support [11-13].

Within this cohort, children with only COVID-19 antibody positivity were older, and predominantly male. They presented with more gastrointestinal symptoms and had more severe lung involvement needing invasive mechanical ventilation, as well as special supportive therapy including ECMO in two children and CRRT in one child. Levels of inflammatory markers and cardiac enzymes were also higher in this group of children with higher mortality compared to those with PCR-positivity, suggesting that hyperinflammation and cytokine storm are more evident in those presenting later in SARS-CoV-2 infection, probably due to the presence of higher titres of IgG SARS-CoV-2 receptor binding domains that are associated with increased disease severity [14].

The mainstay of treatment in these children remains prompt identification and treatment with anti-inflammatory and immunosuppressive agents. Dexamethasone was given to all children as per the ACR guidance on treatment of MIS-C [6] and the lower mortality in patients on oxygen supplementation or ventilation as demonstrated in the RECOVERY trial [15]. IVIG has been suggested as the primary modality of therapy for MIS-C [6,10,11,13]. However, steroids are a promising option in the resource-limited setting which have shown to be equally effective in children with critical illness with good ICU care [8,11,13]. Larger studies would be beneficial to compare the effect of steroids alone or in combination with IVIG in the treatment of MIS-C.

As COVID-19 antibody testing was not available at our institution during the initial study period, it is possible that some PCR-negative cases of MIS-C may have been

missed. However, as none of the other children with critical illness during that period fulfilled the clinical diagnostic criteria for MIS-C, we feel it was probably minimal. Larger studies would be beneficial to compare the effect of steroids alone or in combination with IVIG in the treatment of MIS-C.

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