Original Article

Clinical Profile and Outcome of Pediatric Inflammatory Multisystem Syndrome Temporally Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Series in Eastern India

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Abstract

Objective: The objective of this study is to delineate the characteristics and outcome of Pediatric Inflammatory Multisystem Syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARSCoV2) infection (PIMS-TS) in Eastern Indian settings. **Materials and Methods:** We conducted a prospective observational multicentric study from May 2020 to August 2020, collecting data on clinical profile, investigation findings, and outcome of the children aged 1 month–12 years admitted with the features of coronavirus disease 2019 (COVID-19) related hyperinflammation satisfying criteria for PIMS-TS from three tertiary care hospitals of Kolkata. **Results:** A total of 38 patients fulfilling the criteria of PIMS-TS were recruited. The median age of the study population was 5 years (1.9–8 years). Gastrointestinal symptoms were present in 33 (86.6%) of patients. Nasopharyngeal swab for COVID-19 reverse transcriptase-polymerase chain reaction was positive in 19 (50%) of patients, and immunoglobulin G antibody against COVID-19 was found in 12 (66.6%) of patients, whereas 19 (50%) of patients had a positive contact history of SARS-Co-V2 exposure. The features of Kawasaki, like illness with coronary changes, were seen in 12 (32%) cases, whereas myocarditis with ejection fraction <55% was reported in 17 (45%) of patients. Intensive care admissions were needed in 27 (71%) patients, and inotropes were given in 18 (47%), whereas four patients required mechanical ventilator support. Immunotherapy was used in 32 (84%) of patients. The outcome was good, with one death. **Conclusions:** PIMS TS has varied clinical presentation ranging from milder cases to severe cardiac dysfunction with shock. However, timely intervention and prompt initiation of immunomodulators can improve the prognosis.

Keywords: *COVID-19, immunotherapy, myocarditis, pediatric inflammatory multisystem syndrome temporally associated*

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Introduction

Coronavirus disease 2019 (COVID-19) infection caused by SARS-CoV2 was initially thought to cause milder disease in children. Most of them were asymptomatic and rarely needed intensive care unit admission.[1,2] However, from April 2020, several reports from Europe and North America have described clusters of children <18 years of age having severe illness and requiring admission to intensive care unit with a multisystem inflammatory condition having features of multiorgan failure and shock.[3-5] This new entity was

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first described as Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV2 infection (PIMS-TS) by the Royal College of Pediatrics and Child Health.[6] Subsequently, the World Health Organization and US Centers of Disease Control named it Multisystem Inflammatory Syndrome in Children and adolescents (MIS-C).[7,8] Although PIMS shares some features similar to atypical Kawasaki disease (KD)/KD shock syndrome/Toxic shock syndrome but prominent clinical signs are essentially different.[9] The exact pathogenesis is not known, but an immune-mediated injury has been implicated. Rapid recovery has been reported with intravenous immunoglobulin (IVIG) and steroids. The diagnosis of PIMS will depend on the fulfillment of some defined criteria based on age, clinical and laboratory findings, exclusion of other potential causes, and positive serology or contact history.

Materials and Methods

This prospective multicentric study was performed in three tertiary care institutes of Kolkata from May 2020 to August 2020. Children between the ages of 1 month to 12 years, with clinical and laboratory features, suggest PIMS-TS attending with positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) or serology or contact history to COVID-19-positive patients. Those who did not give consent and had incomplete data were excluded. Being a descriptive study, we did not go for a formal sample size calculation. Sampling was purposive. Necessary ethical permission has been sought through the Institutional Ethics Committee.

Data regarding clinical features, duration of symptoms, organ involvements such as the mucocutaneous, respiratory, cardiovascular, gastrointestinal, and nervous system, signs of shock, saturation in room air, and vital parameters were noted. Bedside echocardiography was done with a special focus on coronary artery changes and ejection fraction (EF) measurement. Chest X-ray findings and laboratory parameters include routine investigations such as complete hemogram, serum electrolytes, liver function, renal function; blood culture, urine culture, dengue IgM, and scrub typhus IgM to rule out other potential microbial pathogens causes were done. Inflammatory markers such as C-reactive protein (CRP), serum ferritin, procalcitonin; cardiac biomarkers such as pro-Brain natriuretic peptide (BNP), and markers for coagulopathy such as fibrinogen, d-dimer values were recorded. COVID status of the patients was also searched for either doing RTPCR from the nasopharyngeal swab or by serology testing. RT-PCR tested the samples in an Indian Council of Medical Research approved medical laboratory designated by the Government of India, and the reporting was done through the RT-PCR app by the caregiver following the generation of appropriate Identification Number. Contact history of SARSCoV2 exposure was also enquired. Data on pediatric intensive care unit (PICU) admission rate, median length of PICU stay, respiratory support, inotropic requirement, different immunomodulator therapy such as IVIG, methylprednisolone, oral prednisolone, biologics, and outcome were taken.

The records were noted by the trained residents posted in the Covid designated ward and subsequently reviewed by the senior faculties of the department of pediatrics of the institute. All the data were collected in predesigned proforma. Data were compiled in a Microsoft Excel spreadsheet. Statistical analysis was performed using the SPSS, IBM statistics for windows, US IBM Corporation, Version 22, revision 2019, (Armonk, New York, USA). Data have been summarized by routine descriptive statistics, namely mean and standard deviation for numerical variables, when normally distributed, and median and interquartile ranges (IQRs), when skewed, and counts and percentages for categorical variables. The comparison between subgroups was made using appropriate inferential statistics, with $P < 0.05$ as the cutoff for statistical significance in such comparisons.

Results

A total of 38 patients, fulfilling criteria for PIMS TS during our study period were recruited. The median age of our study population was 5 years (IQR–1.9–8), minimum age being 4 months and maximum being 11 years out of them, 26 (68%) were male. The predominant presenting symptom was fever 38 (100%) followed by gastrointestinal symptoms 33 (86.8%). Neurological manifestations were present in 13% of patients. One had congenital heart disease. COVID-19 RT PCR in the nasopharyngeal swab was positive for 19 patients (50%), whereas IgG antibody against SARSCoV2 was found in 66% of patients and only contact history positive was in 7 patients (18%). On examination, 52% patients had SpO_2 <94% in room air, and features of circulatory failure were seen in 47% patients. Screening echocardiography revealed coronary artery dilatation with z score ≥2.5 in 12 (32%) patients, whereas 45% had features of reduced cardiac contractility (EF 20%–50%), six had mild pericardial effusion. Bilateral pleural effusion had bilateral patchy infiltrates in the lung field in 18% of patients. Seventy-one percent of patients needed intensive care admission [Table 1].

Table 1: Demographic, clinical profile, laboratory parameters, and outcome in patients with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (*n*=38)

Parameters	*n* (%)
Age (years), median (IQR)	5 (1.9-8)
Age distribution	
≤5 (years)	22 (57)
Boy: girl	1.8:1
Length of hospital stay (days), median (IQR)	10 (7-12)
Clinical presentation	
Fever	38 (100)
Rash	29 (76)
Conjunctivitis	23 (60.5)
Respiratory distress	20 (52)
Loose stool	15 (39)
Pain abdomen	9 (24)
Vomiting	9 (24)
Neurological symptoms	5 (13)
COVID status	
Contact history of SARSCoV2 exposure	19 (50)
COVID-19 RT-PCR positive	19 (50)
COVID-19 IgG antibody positive (18 were tested for antibody)	12 (66)
Examination findings	
SpO_2 <94% in room air	20 (52)
Tachypnea	20 (52)
Persistent tachycardia	15 (39)
Shock	18 (47)
Laboratory parameters, median (IQR)	
TLC (/mm^3)	13,190 (11975-15202.5)
ALC (/mm^3)	2562 (1264.75-3649.5)
Platelet count (L/mm^3)	1.98 (1.16-3.98)
CRP (mg/L)	142 (101.85-292.5)
Ferritin (ng/mL)	1334 (821.5-1731.5)
Pro BNP (pg/mL)	1385 (1340.5-7471.5)
Procalcitonin (ng/mL)	1.4 (1.2-5.12)
Fibrinogen (mg/dL)	569 (470-749)
D-dimer (mcg/mL)	3.95 (2.505-15)
CXR findings	
Infiltrates	7 (18)
Pleural effusion	7 (18)
Echocardiography findings	
CAA	12 (32)
Reduced ejection fraction	17 (45)
Pericardial effusion	6 (16)
Respiratory support	
No	14 (37)
NRM	11 (29)
HHHFNC	9 (24)
Mechanical ventilation	4 (10.5)
Immunotherapy	
IVIG only	18 (47)
MP only	1 (2.6)
IVIG+MP	13 (34)
Infliximab	2 (5.2)
Outcome	

Contd...

Table 1: Contd...

Parameters	*n* (%)
Discharged from critical care	36 (95)
LAMA	1 (2.6)
Died	1 (2.6)

IQR: Interquartile range, COVID-19: Coronavirus disease 2019, SARSCoV2: Severe acute respiratory syndrome coronavirus 2, RT-PCR: Reverse transcription polymerase chain reaction, TLC: Total leukocyte count, ALC: Absolute lymphocyte count, CRP: C-reactive protein, ProBNP: Pro-brain natriuretic peptide, CXR: Chest X-ray, CAAs: Coronary artery abnormalities, NRM: Nonrebreathing mask, HHHFNC: Heated humidified high flow nasal cannula, IVIG: Intravenous Immunoglobulin, LAMA: Left against medical advice, MP: Methyl prednisolone

In laboratory parameters, leukocytosis (median 13,190/mm^3) with lymphopenia (median 2562/mm^3) was present in 71% of patients, whereas thrombocytopenia present in 26% of patients. Inflammatory markers were raised in all patients with median CRP-142 mg/L, median ferritin – 1334 ng/ml, median procalcitonin- 1.4 ng/ml. Cardiac enzymes pro BNP (median - 1431 pg/ml) was raised in 63% of patients. Fibrinogen (median – 560 mg/dl) and d-dimer (median - 3.95) were elevated in 68% of patients. Inotropic support was needed in 47% of patients. Oxygen through nonrebreathing mask was required for 11 (29%), heated humidified high flow nasal cannula for 9 (24%), and invasive mechanical ventilation for four patients. IVIG @ 2 g/kg iv infusion over 24 h was given in 31 (81%) patients, 12 of them were given low dose aspirin along with IVIG, and 34% patients were given injection methylprednisolone @10 mg/kg iv for 5 days. Two patients were treated with infliximab. Ninety-five percent patients were successfully discharged and one died of due to extensive bilateral pneumonia with multiorgan failure.

Discussion

Several studies and case reports regarding PIMS TS have been published all over the world, and two series from Western and Southern India till now. Two case reports had been published from Kolkata.[10,11] Our aim in this study was to delineate the clinical characteristics of PIMS TS in eastern India settings. While Chennai[12] reported 19 cases and Mumbai reported 23 cases of PIMS TS,[13] our study had 38 cases of PIMS TS, which is the largest case series in India as far with a slightly lower median age group compared to Western countries. COVID-19 RT-PCR positivity rate and IgG antibody positivity were also higher in our series compared to other series from India. Regarding clinical features, 57% of patients with features of shock requiring inotropes and 16% with coronary artery changes were reported by Dhanalaksmi *et al*.[12] from Chennai. From Mumbai, by Jain *et al*.[13] observed 65% patients of PIMS TS with features of shock and significantly higher incidence of myocarditis with elevated cardiac biomarkers as compared to patients without shock and 26% showed coronary artery abnormalities (CAAs). In our study, we observed the features of shock in 47% and coronary artery dilatations in 32% of cases. In the indexed study, we found that Kawasaki-like features with coronary changes were present in 32%, myocarditis with reduced EF without coronary changes in 45%, and only persistent fever with raised inflammatory markers without coronary or myocardium involvement was present in 23% of cases. This type of categorization was done by Whittaker *et al*.[14] but not done in other series in India. Such categorization helped in recruiting a maximum number of patients; even the milder cases without any coronary involvement and shock were picked up and managed by timely intervention.

One study noted that the 2020 cohort of MIS-C/KD patients had a higher incidence of CAA than those with KD pre-COVID-19 pandemic but yet to establish the interrelationship between these two similar disorders.[15] The use of immunotherapy was also higher (84%) in our series, which significantly affected the outcome. Death observed in our series was much less (2.6%) compared to the other parts of India.

Conclusions

PIMS TS has varied clinical presentation ranging from milder cases to severe cardiac dysfunction with shock. However, timely intervention, prompt initiation of immunomodulators, and supportive care can improve the prognosis.

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Conflicts of interest

There are no conflicts of interest.

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