RESEARCH PAPER

Epidemiological and Clinical Profile of Pediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARS-CoV-2 (PIMS-TS) in Indian Children

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Background: We describe the demographic, clinical and laboratory findings along with the treatment and outcomes among children meeting the case definition of Pediatric Inflammatory Multisystem Syndrome - Temporally associated with SARS-CoV-2 (PIMS-TS).

Methods: We analyzed the clinical and laboratory findings of children who presented with PIMS-TS during an 8-week period from May 4, 2020 to July 8, 2020.

Results: We report 19 children with a median age of 6 year (IQR: 13 months-16 years), who met the case definition of PIMS-TS. All of them presented with fever. Multi organ involvement (79%), mucocutaneous involvement (74%), cardiovascular symptoms (63%) and gastrointestinal symptoms (42%) were the other features. Elevated levels of C-reactive protein was found in all of them and the majority of them had evidence of coagulopathy; intensive care admissions were needed in 12 (63%) and vasoactive medications were given to 6 (31.5%) children. There were no deaths.

Conclusion: Children with PIMS-TS present with a wide range of signs and symptoms. Fewer children in this series had coronary artery abnormalities, and there was a low incidence of RT-PCR positivity with high presence of SARS-CoV-2 antibodies.

Keywords: *COVID-19, Hyper-inflammatory syndrome, Kawasaki disease, MIS-C, Toxic shock syndrome*.

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The impact of the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been widespread. Initial reports worldwide showed that most children are asymptomatic or have mild or moderate disease [1-3]. However, there are now several reports of the pediatric multisystem inflammatory synd-rome associated with COVID-19 (PIMS-TS) in children globally [4-11].

In early May, the first published report of PIMS-TS or multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C) was reported from India from our center. [11]. We hereby describe the demographic, clinical and laboratory findings of a series of cases of PIMS-TS seen since then in our center, so as to provide Indian data related to this syndrome.

METHODS

This study was conducted at a tertiary care children's hospital in Chennai, India. We analyzed children presenting to our hospital from May 4, 2020 to July 8, 2020 (8 week period), who satisfied the case definition of PIMS-TS as defined by Royal College of Paediatrics and Child Health (RCPCH) [12]. Retrospectively, four children admitted during the month of April, 2020 were also included, as they met the criteria specified by RCPCH PIMS-TS definition. Data on the following parameters were collected: demographics, clinical findings, radiological findings, underlying comorbidities, echocardiographic findings, laboratory investigations, treatment received including intensive care interventions and outcome. This data is a part of a larger COVID-19 study in children presently undergoing at our institution, and was approved by the ethics committee. All children were included in the study after written informed consent of the caretaker.

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 or positive antibody test performed with ICMR-approved YHLO SARS-CoV-2 IgG and IgM antibody titer assay kits (Shenzhen YHLO Biotech Co. Ltd.) as per manufacturer's instructions.

Designated doctors and the study nurse collected all details in standardized and approved case report forms, which were then entered into to the Microsoft Excel spreadsheet. Vital signs (tachycardia, tachypnea and hypotension) were classified according to normal values for the age [13]. Data on various laboratory markers were collected and elevated levels were defined in relation to the normal levels for the age [14,15]. Cardiovascular involvement was described as children needing any of the following: fluid bolus (>20 mL/kg) with or without vasoactive medications, an echocardiogram showing decreased left ventricular function (EF <55%), coronary artery abnormality, pericarditis or pericardial effusion, electrocardiogram (ECG) evidence of arrhythmias with or without elevated levels of troponin or pro BNP.

Statistical analyses: Data are presented as median (IQR), numbers and proportions. Statistical analyses were performed using SPSS version 24.0.

RESULTS

A total of 19 children with a median (IQR) age of 6 years (13 months-16 years) who met the criteria of PIMS-TS were included in this series. Between May 1 and July 8, 2020, 15 children were identified and four children were identified in April, 2020.

The male to female ratio was 1:1.4 and 9 children (47%) were younger than 6 year. Of the 19 children, 15 (79%) were tested for COVID 19 by RT-PCR and serological assays and 11 (58%) were identified as confirmed cases of COVID-19. SARS-CoV-2 was confirmed by RT-PCR alone in three children (16%), one child (6%) had evidence from both RT-PCR and serological assay, 7 children (47%) had positive serological assay alone whereas RT-PCR and serological assay was negative in 4 (27%) children (***Table* I**).

RT-PCR and/or serological assay negative or COVID-19 status unknown children were included as they met the criteria as specified by RCPCH PIMS-TS definition. All children (100%) presented with fever of more than 3 days and six (31%) presented with lymphadenopathy. Multi-organ involvement was seen in majority of the children (15/19, 79%). Cardiovascular symptoms were reported in 12 (63%) children, of which three had coronary artery abnormality at presentation (***Table* I**).

Elevated CRP (median (IQR): 118 (73-298) mg/L) was noted in all 19 children (100%). Coagulation parameters (PT, APTT and INR) were abnormal in 11/15 children (73%) and D-dimer (median (IQR): 4,250 (339 - 7328) ng/mL FEU) was elevated in 13/14 (92.8%) children (***Table* II**).

Chest radiography was performed in 15 children, of which 5 showed evidence of lobar consolidation (unilateral). Ultrasound scan of abdomen was performed in 5 children of whom one was suggestive of as possible appendicitis. CT chest and abdomen was performed in the same child, which showed evidence of right lower lobe consolidation. Coronary artery abnormality (dilatation without aneurysm, *Z* score <2.5) was seen in three children with one of them having evidence of minimal pericardial effusion.

Of the 19 children, 5 (26%) received intravenous immunoglobulins (IVIG) alone, whereas three children (16%) were treated with steroids alone; 8 children (42%) received both IVIG and steroids, and one child received IVIG and tocilizumab. Aspirin was given in 16 (84.2%) children and two children were not given any immunomodulatory agents. All 19 children received broad-spectrum antibiotics at presentation, which were discontinued after negative culture results. No organisms were isolated from blood cultures.

Only one child had underlying co-morbidity (global developmental delay) and one child presented with features mimicking appendicitis along with positive SARS-CoV-2 antibodies. Median length of hospitalization was 6 days (IQR 3-13 days) and 12 (63%) children required PICU support. There was no mortality in our series.

DISCUSSION

This study is the first series from India describing children presenting with PIMS-TS. Consistent with published data from Europe and US, children in this study also presented with signs and symptoms mimicking complete or incomplete Kawasaki disease (KD), toxic shock syndrome (TSS), hemophagocytic lymphohistiocytosis (HLH) and/or macrophage activation syndrome (MAS) [4,5,10]. Although, cardiac dysfunction is the most commonly reported organ dysfunction [5,7,12], a notable finding in our series was that a fewer number of children were identified to have echocardiographic evidence of coronary artery changes (3/19, 16%), though a significant number of children (57%) developed hypotension requiring admission to the PICU for vasoactive medications. Likewise, when compared to the available data, fewer children (42%) in our series presented with gastrointestinal symptoms as against up to 80% in literature [4-6,16], and more than two-third (74%) presented with mucocutaneous manifestations.

Clinical presentation, epidemiology and pathogenesis of PIMS-TS are still unclear and evolving, but cases of PIMS-TS seem to appear few weeks after the COVID-19 peak in the population [5,17,18]. The COVID-19 peak in

Table I Demographic and Clinical Characteristics of Children With PIMS-TS (*N*=19)

	All children	*^RT-PCR / Serology*	
		Positive (n=11)	*Negative/unknown (n=8)*
Age, median (range)	6 y (1y 1m-16y 9m)	8.2 y (2y 10m-16 yr 9 m)	4.2 y (1yr 1 m - 11y 1 m)
Male	8 (42)	4 (36)	4 (50)
Comorbidity	1/19 (5.2)	1/11 (9)	0
RT-PCR positive	4/15	4/11	4 negative, 4 not tested
Serology positive	8/15	8/11	4 negative, 4 not tested
Fever	19 (100)	11 (100)	8 (100)
Lymphadenopathy	6 (31.5)	1 (9)	5 (62.5)
GI symptoms	8 (42)	6 (54.5)	2 (25)
Abdominal pain	8	6	2
Vomiting	6	4	2
Diarrhea	3	3	0
Mucocutaneous	14 (74)	6 (54.5)	8 (100)
Rash	12	4	8
Edema	10	4	6
Congested conjunctiva	9	3	6
Oral mucosa involved	9	2	7
CVS symptoms	12 (63)	9 (81.8)	3 (37.5)
Hypotension	10	9	1
Acute kidney injury	3 (16)	3 (27.2)	0
Respiratory symptoms	8 (42)	5 (45.4)	3 (37.5)
Neurological symptoms	6 (31)	3 (27.2)	3 (37.5)
Meeting KD criteria	7 (36.8)	1 (9)	6 (75)
PICU admission	12 (63)	10 (91)	2 (25)
Mechanical ventilation	0	0	0
HHFNC	1	1	0
Nasal cannula oxygen	4	4	0
Fluid bolus (>20 mL/kg)	10 (52.6)	9 (81.8)	1 (12.5)
Vasoactive support	6 (31.5)	6 (54.5)	0
IVIG used	15 (79)	7 (63.6)	8 (100)
Steroids used	11 (58)	8 (72.7)	3 (37.5)
Tocilizumab (8 mg/kg) used	1 (5.2)	1 (9)	0
Aspirin used	16 (84.2)	8 (72.7)	8 (100)

PIMS-TS: Pediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2; All values in no. (%); GI: gastrointestinal, PICU: Pediatric intensive care unit; HHFNC: High flow nasal cannula oxygen; IVIG: Intravenous immunoglobulin; CVS: Cardiovascular system; RT-PCR: Reverse transcriptase polymerase chain reaction; ^RT-PCR results available in only 15 children – 4/11 were positive in first group, and in second group 4/8 were negative and results were unknown in remaining 4.

the community is possibly yet to occur in several cities in India, and we postulate that we may also see a significant increase of PIMS-TS among children in the coming days.

A positive serologic assay for SARS-CoV-2 or RT-PCR has been a consistent finding in the literature [7,8]; although, there have also been published reports with negative results for SARS-CoV-2 [10]. Most of the children in this study (58%) had laboratory confirmed SARS-CoV2 infection. Serology testing or RT-PCR could not be performed in four children as they presented to us at the beginning of COVID-19 pandemic in Chennai. These four children had no microbiological evidence for other infections. They had multi-organ dysfunction with elevated inflammatory makers (CRP, D-dimer and ESR) in addition to neutrophilia and lympho-penia. However, we plan to perform serological assay in these children during their follow up to establish a link between their symptoms and SARS-CoV-2. PIMS-TS generally tend to occur in older children (reported median age 8 years) [5,6,10], which is

Table II Profile of Laboratory Markers in Children With PIMS-TS (*N*=19)

	All children	*^RT-PCR / Serology*	
		Positive (n=11)	*Negative/unknown (n=8)*
Elevated CRP	19 (100)	11 (100)	8 (100)
Elevated troponin (pg/mL)	1/6 (16.6)	1/5	0/1
Elevated NT pro BNP (pg/mL)	3/4 (75)	3/3 (100)	0/1
&Elevated fibrinogen	7/9 (77.7)	6/7 (85.7)	1/2 (50)
Elevated D-dimer (ng/mL FEU)	13/14 (92.8)	10/11 (91)	2/3 (67)
%Hypoalbuminemia (g/dL)	11/18 (61.1)	7/11 (63.6)	4/7 (57.1)
@Hyponatremia (mmol/L)	11/19 (58)	7/11 (63.6)	5/8 (63)
‡Elevated LDH (U/L)	7/13 (53.8)	4/10 (40)	3/3 (100)
Neutrophilia (per m^3)	13 (68.4)	6 (54.5)	7 (87.5)
Lymphopenia (per m^3)	7 (36.8)	6 (54.5)	1 (12.5)
^High ferritin (ng/mL)	3 (21.4)	3/10 (30)	0/4
Anemia (mg%)	6 (31.5)	5 (45.4)	1 (12.5)
Thrombocytopenia (per mm^3)	3 (15.7)	3 (27.2)	0
#Elevated ESR (mm/h)	9/11 (81.8)	4/5 (80)	5/6 (83.3)
Transaminitis (U/L)	5 (26.3)	4 (36.3)	1 (12.5)
Deranged coagulation	11/15 (73.3)	9/11 (81.8)	2/4 (50)
Abnormal chest *X*-ray	5/15 (33.3)	5/11 (45.4)	0/4
Coronary artery changes*	3	1¥	2
Three systems involved	7 (36.8)	4 (36.3)	3 (37.5)
Four systems involved	6 (31.5)	5 (45.5)	1 (12.5)

*PIMS-TS: Paediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2; #median (IQR) ESR: 86 (15-140) mm/h; ^median (IQR) ferritin 238 (220-1230) ng/mL; ‡median (IQR) LDH: 451 (307-751) U/L; @median (IQR) hyponatremia: 132 (130-139) mmol/L; %median (IQR) hypalbumenia: 3 (2.3-3.4)g/dL; &Median (IQR) Fibrinogen: 458 (228-669) mg/dL; PICU: Pediatric intensive care unit; CRP: C-reactive protein (>30 mg/l); Troponin: T (>4pg/mL); NT pro BNP: N Terminal PRO B Type Natriuretic Peptide (>180 pg/mL FEU), Fibrinogen (>400 mg/dL), D-dimer (>500 ng/mL FEU), Hypoalbuminemia (<3.5 g/dL), Hyponatremia (<135mmol/l), LDH (>460 U/l), Neutrophilia (>7700/mm^3), Lymphopenia (<1500/mm^3), Anemia (<9 mg%), Thrombocytopenia (<1.5l/mm^3), Ferritin (>500 ng/mL), ESR-Erythrocyte Sedimentation Rate (>40 mm/hr), Transaminitis- (Alanine amino transferase (ALT)/Aspartate amino transferase (AST) >40IU/l), PT: Prothrombin time; INR: International Normalized Ration >1.2; *Coronary artery changes-dilatation without aneurysms (z score < 2.5); ¥Evidence of minimal pericardial effusion in addition to coronary artery dilatation.*

slightly more than that seen in our patients. Laboratory testing in our group generally showed significant elevation of inflammatory markers, as reported earlier [6,19].

Currently there is no consensus regarding management of children with PIMS-TS; although there has been a recently published review suggesting a treatment flowchart [20]. IVIG (2 g/kg) has been most commonly used as first line therapy with many children receiving additional high-dose steroids [5-7,16]. Nearly half of the children (42%) in this series received both IVIG and steroids, with a few children requiring a second dose of IVIG and one child needing additional immuno-modulatory medication. The role of aspirin in children with hyperinflammation without KD is not yet described, though it has been used by many in PIMS-TS [10,11]. Lack of uniform guideline for management reinforces the fact that further studies are required to establish optimal treatment in PIMS-TS.

The main limitations of the study are relatively smaller number of patients and a shorter duration of study; hence, we are unable to provide data on long-term sequelae of PIMS-TS. Another limitation is absence of serological confirmation of SARS-CoV-2 infection in nearly one-fifth of the children.

Our study is one of the first series from Asia describing PIMS-TS in children. We report fewer coronary artery abnormalities, as compared to the existing data on PIMS-TS. Finally, we also report low incidence of RT-PCR positivity with increased presence SARS-CoV-2 antibodies. This study underscores the occurrence of PIMS-TS in children in India and will increase awareness of the disease among the clinicians, so as to enable early recognition and prompt management.

Ethics approval: CTMRF-KKCTH Ethics committee; No. ECR/676/Inst/TN/2014/RR-17, dated June 2, 2020.
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WHAT THIS STUDY ADDS?

- Lower age and lesser echocardiographic abnormalities were observed among children with PIMS-TS.
- Prompt recognition and treatment with immunomodulatory agents are likely to result in favorable outcome in PIMS-TS.

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