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Biomarker profile in pediatric inflammatory multisystem syndrome temporarily associated with SARS-CoV-2 (PIMS-TS)/multisystem inflammatory syndrome in children (MIS-C)

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Pediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C) is a post COVID-19 multisystem inflammatory syndrome in children and adolescents <21 years of age. It is slowly emerging in India with clinical features overlapping with Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS). Ten PIMS-TS cases admitted in a pediatric hospital between July and Sept 2020 were compared with 19 Kawasaki Disease (KD) patients' data. The median age of PIMS-TS was 6 years (older to KD), 80% were males. PMS-TS cases had high inflammatory markers: CRP, ferritin, interleukin (IL)-6. Other distinct features were lymphopenia, hypoalbuminemia, and hyponatremia. Serial measurements of CRP showed high baseline values with subsequent decrease. NT-Pro BNP level was extremely elevated; suggestive of cardiac injury. All patients recovered. Laboratory features of PIMS-TS present a unique pattern of intense inflammation, and cardiac involvement that is different from features of pre COVID-19 KD. CRP remains a useful, inexpensive marker for PIMS-TS diagnosis and clinical progression.

Keywords: CRP, Ferritin, Interleukin-6, Inflammatory syndrome, Kawasaki disease, MIS-C, NT-ProBNP, PIMS-TS, SARS-CoV-2

The profiling of Coronavirus Disease 2019 (COVID-19) symptoms in the pediatric cohort tells that the manifestation of the disease differs considerably from the adult spectrum[1,2]. While the Centre for Disease Control and Prevention (CDC) in the US reported that children account for only 8.6% of confirmed COVID-19 cases, there are no prevalence data in India[3,4]. Some children require hospitalization and intensive care as a result of multisystem inflammatory conditions (MIC) that develop post COVID-19 several weeks after exposure[5]. This COVID-19 associated multisystem inflammatory syndrome in children (MISC) and adolescents is referred to as Pediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2 (PIMS-TS)[6] and later labeled as MIS-C (a multisystem inflammatory syndrome in children) associated with COVID-19[7,8]. The disorder emerged gradually as observed by pediatricians all around the globe in children with unusual febrile illness, elevated inflammatory markers and multisystem involvement with considerably overlapping features of Kawasaki disease (KD) and Toxic Shock Syndrome (TSS), yet is quite a distinct entity by itself[9-12]. PIMS-TS has also therefore been variably termed as Kawasaki-like disease or incomplete Kawasaki disease.

The association of PIMS-TS with COVID-19 needs to be ascertained with a positive test for SARS-Cov-2 showing the presence of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR), antigen, or antibody (Immunoglobulin G), or exposure to others with COVID-19 within the four weeks before the onset of symptoms. However, the sensitivity and specificity of the tests along with the unavailability of testing of contacts hampers the establishment of an association for all practical cases. Nonetheless, PIMS-TS is being rapidly reported by regions greatly affected by SARS-Cov-2, including India, with similar trends and timelines that point exclusively to the hyperinflammatory host response to SARS-Cov-2 infection[13].

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Abbreviations: CBC, Complete blood count; CDC, Centre for disease control and prevention; COVID-19, Coronavirus Disease 2019; CRP, C-reactive protein; IL, Interleukin; KD, Kawasaki Disease; MIC, Multisystem inflammatory conditions; MIS-C, Multisystem Inflammatory Syndrome in Children; NT-ProBNP, NT-Pro Brain Natriuretic Peptide; PIMS-TS, Pediatric Inflammatory Multisystem Syndrome temporarily associated with SARS-CoV-2; RT-PCR, Reverse transcriptase polymerase chain reaction; TSS, Toxic shock syndrome

Analyses of PIMS-TS cohort from England[14], US[15], France[16], and more recently from Mumbai Metropolitan area[17], paints a clearer picture of the new disorder in children, although much remains unknown about the pathogenesis and long term outcomes. PIMS-TS occurs 2-4 weeks after infection with SARS-CoV-2. It is uncommon compared to the real prevalence of the infection in adolescents below 21 years of age. Antibody detection against the virus is reasonably common, but the virus per se is detected in a much smaller proportion.

In a nutshell, children present with high grade fever lasting for 8-9 days with features of skin rash, mucositis and conjunctivitis, vomiting and diarrhea and abdominal pain, many of which are similar to features of KD. This is accompanied by increased inflammatory markers such as C-reactive protein (CRP), ferritin, neutrophil counts, and lactate dehyrogenase (LDH). Anemia, lymphopenia, hypoalbuminemia and hypercoagulation indices are other distinguishing features. Systemic involvement of two or more organs is common. Shock, cardiac injury shown by high concentrations of troponin and brain natriuretic peptides, coronary aneurysms and gastro-intestinal findings such as appendicitis require intensive care support. The majority of patients survive following treatment with immunomodulating agents (intravenous immune globulin, glucocorticoids, interleukin-1 or 6 inhibitors) and incidence of death is rare (2-4%)[2,9-17].

Because PIMS-TS show overlapping clinical features with KD, therefore, laboratory features of both PIMS-TS and preCOVID-19 KD were explored in this study.

Materials and Methods

Patients who were admitted to Institute of Child Health, Kolkata between July 7 and September 30; 2020 were included if they (1) were 18 years or younger; (2) presented with a clinical syndrome characterized by prolonged fever, systemic inflammation, shock, end-organ dysfunction, and were diagnosed with PIMS-TS or KD; and (3) and were tested for Interleukin (IL) -6 and NT Pro Brain Natriuretic Peptide (NT Pro BNP) and other inflammatory markers and assessed for hematologic parameters, renal, liver, and cardiac function. Demographic details and outcome assessments of the cases were recorded. Additionally historical data of patients of KD were accessed from hospital records.

Statistical analysis

The Student's *t*-test, the χ^2 method, and Fisher's exact test were used for continuous and categorical variables. Mann Whitney non-parametric test was used to determine differences between non-normal test variables. D'Agostino and Pearson omnibus normality test was used to determine the distribution of data. P <0·05 was considered to determine significance. Analysis of data was performed on Medcalc version 8.0, Mariakerke, Belgium.

The Institutional Ethics Committee (ICH/IEC/48/ 2020 dated 31.07.2020) approved the study with a waiver of informed consent.

Results

Demography and outcome

Ten patients of PIMS-TS and 3 patients of KD admitted during the study period were included. Retrospective data of 16 patients of KD who were admitted to the hospital earlier in 2019-2020 have also been included for comparison. Baseline characteristics are provided in (Table 1). PIMS-TS patients were older in age (compared to KD). Patients were admitted with common symptoms of high-grade fever, conjunctivitis, mucositis, edema, erythematous rash, vomiting and diarrhoea.

All the PIMS-TS were negative for the PCR tests to detect SARS-CoV-2 virus and all but one patient had a positive IgG antibody against SARS-CoV-2. This patient had contact with his father who had tested positive from the PCR test for SARS-CoV-2.

Of the 10 PIMS-TS cases, 4 needed PICU support. All the PIMS-TS were completely recovered. One of the ten PIMS-TS patients was referred for cardiac management and was tested for IL-6.

There was one patient of diagnosed with Systemic lupus erythematosus (SLE) was admitted with active SARS-CoV-2 infection and is included for comparison of laboratory features with PIMS-TS which is a post-COVID-19 phenomenon. One of the 3 KD patients also had active SARS-CoV-2 infection.

Table 1 — Demographic and outcome in PIMS and KD patients

	PIMS –TS, n=10 Median (IQR)	KD, n=19 Median (IQR)	*P* value
Age, Years	6 (4-10)	1.3 (0.75-2.2)	0.0002
Sex, Males (%)	8 (80%)	10 (~50%)	0.23
Length of Stay, days	7 (6-11)	7 (6-9)	0.89
Outcome			
Discharged	9	19	
Death	0	0	
Referred	1	0	

Laboratory investigations

All PIMS-TS patients had evidence of a marked inflammatory state (Table 2). CRP level was significantly elevated [median, 201 mg/L (IQR, 127-301)] in 9/10 patients. IL-6 [median, 78 pg/mL (IQR, 57-206)], and ferritin [850 ng/mL (IQR, 540-1230)] were also raised, along with neutrophilia, and lymphopenia. NT-proBNP concentrations were elevated in 100% (10/10) patients showing severe myocardial dysfunction. Anemia, transaminitis and increased LDH concentration were as observed in some subjects. Creatinine remained within the normal range for all. Hyponatremia was a marked feature in all 10 patients.

Comparison of Laboratory features of PIMS-TS with KD:

Patients with PIMS-TS were generally older than those with KD and higher white blood cell count, neutrophil count, and other inflammatory markers such as CRP and ferritin, as well as more profound lymphopenia, and hyponatremia. The potassium level was also lower (Table 3). They also tended to have lower platelet counts, lower protein, and albumin levels. Alanine aminotransferase activity and hemoglobin were similar between those with PIMS-TS and KD. Comparison values were not available for LDH and IL-6.

Serial measurements of C-Reactive Protein

The CRP level at the time of admission (baseline) was appreciably higher in the PIMS-TS cases compared to either KD or active COVID-19 case (Fig. 1), which decreased gradually with therapy. The patient that was referred to another hospital for cardiac management, had an initial IL-6 of 74.2 pg/mL (day 1) and decreased to 11.6 pg/mL (day 12). Another patient diagnosed with KD having active SARS-CoV-2 infection (Case 11) showed a higher CRP compared to other two KD cases (Cases 12 and 13).

Table 2 — Laboratory features of PIMS-TS children

n=10	Values (baseline, on admission)	Normal Values	Number of PIMS-TS cases with:
Hemoglobin, g/dL	10.2 (9.4-10.7)	> 12	Hemoglobin <9 n= 1 (10%)
White blood cell count ×1000 /mm^3	9.5 (7.3-18.5)	4.5 - 13.5	WBC >13.5 × 1000 /mm^3 n= 4 (40%)
Neutrophil %	80 (68-84)	-	-
Lymphocyte %	14 (11-24)	-	-
Platelet count, /mm^3	1,69,000 (1,18,000-2,57,000)	1,50,000 - 4,00,000	Platelets <1,50,000 n= 5 (50%)
Albumin, g/dL	3.0 (2.7-3.4)	>3.5	Albumin ≤3 n= 6 (60%)
ALT, U/L	27 (17-52)	<35	ALT > 40 n= 3 (30%)
Creatinine, mg/dL	0.46 (0.40-0.56)	0.29 -0.47 (Age specific, for 5 - 7 years child)	Creatinine × 2 ULN n= 0 (none)
Sodium, mmol/L	129.5 (127.0-131.3)	>135	Sodium < 135 n= 10 (100%)
Lactate Dehyrogenase, U/L	283 (238-387)	120 - 300	Lactate Dehyrogenase, >300 n= 1 (10%)
C-Reactive Protein, mg/L	201 (127-301)	<5	C-Reactive Protein >100 n= 9 (90%)
Ferritin, ng/mL	856 (540-1230)	<120	Ferritin >500 n= 8 (80%)
NT-ProBNP, pg/mL	4736 (1110-24451)	<150	NT-ProBNP >400 n= 9 (90%)
Interleukin-6, pg/mL	78 (57-206)	<7	Interleukin-6 > 80 n= 4 (40%)

Data are median (interquartile range), n = number, is the total number of patients with available data. Dashes indicate not applicable.
NT-proBNP, N-terminal pro-B-type natriuretic peptide

Table 3 — Comparison of Laboratory features of PIMS-TS with KD

Median Values (Inter quartile ranges) of:	PIMS-TS (n=10)	KD (n=19)	*P* value
Hemoglobin, g/dL	10.2 (9.4-10.7)	9.6 (8.7-10.3)	0.1434
White blood cell count ×1000 /mm^3	9.5 (7.3-18.5)	19.9 (13.5-24.0)	0.01
Neutrophil %	80 (68-84)	64 (60-69)	0.006
Lymphocyte %	14 (11-24)	30 (25-36)	0.002
Platelet count, /mm^3	1, 69, 000 (1, 18, 000-2, 57, 000)	5, 36, 000 (3, 69, 000-6, 66, 000)	0.0002
Protein Total, g/dL	5.4 (5.1-6.2)	6.1 (5.7-7.1)	0.04
Albumin, g/dL	3.0 (2.7-3.4)	3.5 (3.33.6)	0.04
ALT, U/L	27 (17-52)	27 (17-47)	0.96
AST, U/L	33 (23-55)	38 (28-51)	0.52
Creatinine, mg/dL	0.46 (0.40-0.56)	0.26 (0.20-0.32)	<0.001*
Sodium, mmol/L	129.5 (127.0-131.3)	134 (131.8-135)	0.0006
Potassium, mmol/L	3.50 (3.35-4.00)	4.30 (4.00-4.53)	0.009
C-Reactive Protein, mg/L	201 (127-301)	95 (54-100)	0.001
Ferritin, ng/mL	856 (540-1230)	267 (175-275)	0.005
NT-ProBNP, pg/mL	4736 (1110-24451)	333 (169-557)	0.0005

*****Difference attributes to age difference between the groups as because creatinine varies with age. No patient had high creatinine value

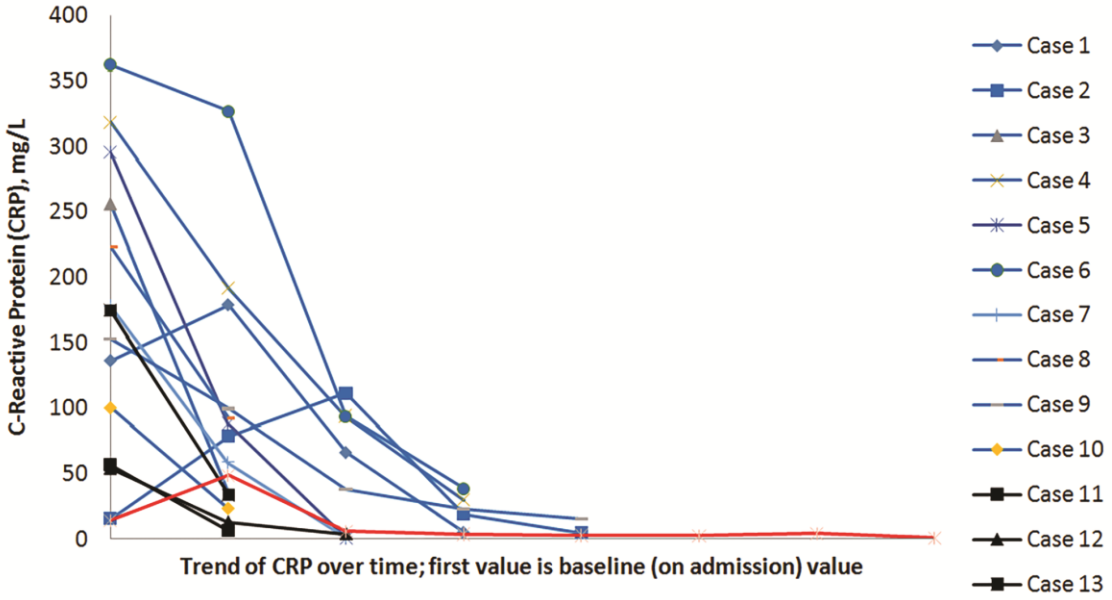

Fig.1 — CRP levels (mg/L) measured serially over time in children presenting with PIMS (Cases 1-10), KD (Cases 11-13) Case 14 line graph (red) are serial values in a SLE patient with active COVID-19 infection and hypercytokinemia

Discussion

There has been an upsurge in the admission of pediatric patients with Kawasaki like features following the COVID-19 pandemic and one of the first alerts came from the Italian pediatric intensivists at Bergamo[18] describing a new unusual inflammatory disorder in children who had no active SARS-CoV-2 infection, but were positive for increased antibodies to the virus. These children tended to be older and sicker compared to classical KD manifestations and needed intensive care support. With RCPCH (The Royal College of Paediatrics and Child Health), WHO and CDC, later, defining this disorder as PIMS-TS or MISC, various early centers of the pandemic in India

too reported treating and managing PIMS-TS at Mumbai[17], Chennai[19]and Kolkata[20]. An article in the Times of India dated September 17, 2020 states that pediatric hospitals of Kolkata have started to receive PIMS-TS cases from the middle of August, 2020 and cases are increasing with time[21]. Laboratory markers have been the hallmark to diagnose, and monitor COVID-19 and now in PIMS-TS cases too, especially in the evaluation of the inflammatory state of the patient[22]. This study has shown that several routinely investigated tests such as CRP have become an effective confirmatory marker to diagnose PIMS-TS. These markers with clinical symptoms have thrown up many differences with KD. CRP level was reported to be extremely high in PIMS-TS[23] and level above 150 mg/L can clearly indicate towards PIMS-TS. While the level in KD was much lower. CRP is inexpensive and can be serially investigated to monitor the efficacy of therapy. While our study did not report ESR, this marker has also been quite effective in monitoring inflammation.

Thus children admitted with features of viral infections such as KD, TSS or PIMS-TS should undergo basic laboratory investigations including of complete blood count (CBC), CRP, renal function tests, liver function tests, electrolytes estimation, urine routine examination, blood cultures along with COVID-19 RTPCR and serology. Though common findings are anemia, hypoalbuminemia, transaminitis, high WBC counts, neutrophilia, and lymphopenia[14-17], documentation of anemia and transaminitis in this cohort was failed. However, hyponatremia was reasonably asserted. No patient was reported to have acute kidney injury and creatinine level was within a normal level; however, these values may rise with diminishing renal functions[13].

Once diagnosed, the tier 2 investigations such as ferritin, IL-6, procalcitonin, LDH, D-Dimer, fibrinogen, blood gas analysis, blood lactate levels, troponin and NT-Pro-BNP, septic and viral screen, along with other radiological investigations would be helpful to confirm the inflammatory state along with the development of other manifestations in the child such as hypercoagulable state, macrophage activation syndrome (MAS), shock, and myocarditis and to monitor therapy such as the use of IL-6 inhibitor-tocilizumab[13]. High ferritin and IL-6 levels in this study indicated an intense inflammatory state. High ferritin level possibly suggests interplay with MAS. Determination of IL-6 level at the time of admission may be prudent to monitor the use of IL-6 inhibitor therapy[11].

One of the most important biomarkers of PIMS-TS is NT-Pro-BNP, a marker of heart failure. In our study all PIMS-TS patients had significantly elevated NT-Pro-BNP levels, as observed in other study[16]. Further, SARS-CoV-2 IgG is positively correlated with cardiac injury markers such as troponin and CKMB is indicative of clinical worsening and shock. As observed in earlier studies, cases of PIMS-TS children were older than those with KD, and with starkly different laboratory features[23,24]. Children with PIMS-TS tended to have more intense inflammation, namely higher levels of CRP, and ferritin, and had higher levels of markers of myocardial affliction such as NT-ProBNP. These patients have higher neutrophils, lower lymphocytes, lower platelets; and also lower protein, albumin, sodium, and potassium levels. This study however did not record high WBC counts and could be ascribed to some patients having a progressive course of the condition where values may decrease.

Comparison of PIMS-TS with acute COVID-19 shows that these are quite different[13]. In this study, patients with active SARS-CoV-2 infection had lower baseline and peak CRP levels compared to PIMS-TS cases (see Fig 1) during the course of the disease. The hyperinflammatory response of PIMS-TS differs from the cytokine release syndrome of severe acute COVID-19. While there is a commonality with KD, but also differs from this condition with respect to cytokines and biomarkers of endothelial damage [14,25].

The study is limited by the number of patients and marker values may not accurately represent the cohort's features. Nonetheless, marker trends were similar to findings made by other study groups and point to a specific emerging pattern. The current study provides information on the comparison of laboratory features of PIMS and KD; which may be valuable to clinicians to assist in diagnosing and managing PIMS-TS, which is slowly emerging in the country.

Conclusion

PIMS-TS/MIS-C is a new disease entity seen in children and adolescents several weeks after SARS-CoV-2 infection. It has a typical biomarker profile consisting of severely elevated inflammatory markers such as CRP, IL-6, WBC counts, Ferritin, and LDH, along with anemia, hyponatremia and raised NT-ProBNP that can help to differentiate it from KD with

similar clinical presentation. Overall mortality of PIMS-TS/MIS-C is rare and CRP serves as a good prognostic indicator of therapeutic response.

Conflict of interest

All authors declare no conflict of interest.

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