A new disease with unknown sequelae: Six-month multidisciplinary follow-up and outcomes of Paediatric Inflammatory Multisystem Syndrome (PIMS-TS) patients at a UK tertiary paediatric centre

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Declaration of Interest: The named authors have no declarations of interest to declare. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Manuscript word count: 3474

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Abstract

Background
Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), is a new, rare post-infectious complication of SARS-CoV-2. We aim to describe the 6-month outcomes of PIMS-TS.

Methods
A cohort of children (<18 years old) meeting diagnostic criteria for PIMS-TS admitted to Great Ormond Street Hospital (London, UK), between April 4th and September 1st 2020 were followed by a multidisciplinary team of specialists at regular intervals over 6 months after their acute admission.

Findings
46 children were identified. Median age at presentation was 10·2 years (IQR 8·8-13·3), 65% were male and 80% from ethnic minority groups.

At 6-months, systemic inflammation resolved and 38/42 (90%) who had positive SARS-CoV-2 IgG within 6-weeks of admission remained seropositive at 6-months. Echocardiograms were normal in 44/46 (96%), and gastrointestinal symptoms which were reported in 45/46 (98%) at onset were present in 6/46 (13%). Objective renal, haematology, and otolaryngology findings largely resolved by 6-months. Whilst minor abnormalities on neurological examination were identified in 24/46 (52%) and 18/46 (39%) at 6-weeks and 6-months respectively, we found minimal functional impairment (6-months Expanded Disability Status Scale median score 0, IQR 0-1).

Median manual muscle test-8 scores improved from 53/80 (IQR 43-64) during hospitalisation to 80/80 (IQR 68-80) but 45% demonstrated six-minute walk test results <3rd centile for age/sex at 6-months.

PedsQL parental (19%) and self-report (22%) revealed severe emotional difficulties at 6-months. 31% of parents reported anxiety about possible PIMS-TS relapse in their child with 20% taking additional isolation precautions and 22% were concerned about ongoing medical vulnerability. 98% patients were back in full-time education by 6-months.

Interpretation
Despite initial severe illness, by 6-months few organ-specific sequelae were observed. Ongoing concerns requiring physical re-conditioning and mental health support remained and physiotherapy assessments revealed persisting poor exercise tolerance. Longer-term follow-up will help define the extended natural history of PIMS-TS.

Funding source: None

Abstract word count: 300

Introduction

In April 2020, a novel post-infectious hyper-inflammatory syndrome now termed paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was identified.[1] PIMS-TS is a distinct post-infectious entity unlike the primary respiratory manifestations and outcomes seen in both adult and paediatric COVID-19.[2,3] In excess of 250 cases were identified in the UK and Ireland from March-June 2020, presenting with a constellation of clinical features which included: fever, rash, conjunctival injection, and gastrointestinal symptoms, sometimes progressing to multi-organ failure requiring paediatric intensive care (PICU).[4,5]

Although the acute phase of PIMS-TS has been characterised, the short, medium, and long-term sequelae remain unclear.[1,3] Similarly, little is known about rehabilitation requirements post hospital discharge. In this study we present the six-month multidisciplinary clinical team (MDT) outcomes of the first 46 paediatric patients treated at a large tertiary paediatric hospital in the UK.

Methods

All patients <18 years old admitted to Great Ormond Street Hospital (GOSH), between April 4th and September 1st 2020, fulfilling the Royal College of Paediatrics and Child Health (RCPCH) diagnostic criteria for PIMS-TS were included.[6] As the data analysis was retrospective and no additional data were collected beyond those required for standard medical care, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was not required. A clinical audit was registered with GOSH NHS Foundation Trust Audit Committee (#2857).

Patients were prospectively reviewed by multiple specialties in a recently set up PIMS-TS MDT clinic. A new ward-based day case service was established in order to accommodate sequential reviews and investigations by multiple specialties. Patients were seen by the MDT at a minimum of two further time points post-hospital discharge; six weeks and six months. Electronic clinical records were reviewed by two investigators (JP, OA), who collected baseline and follow-up data.

Recent SARS-CoV-2 infection was confirmed by reverse transcriptase–polymerase chain reaction (RT-PCR) of nasopharyngeal sample, positive serology, and/or a clear epidemiologic link to an infected contact. Serology testing evaluated IgG antibodies to SARS-CoV-2 nucleocapsid protein and from June 2020 to spike protein (Epitope Diagnostics^{TM}). After June 2020 anti-spike protein antibodies

were conducted on all patients presenting with PIMS-TS. Retrospective analysis of those with negative nucleocapsid antibody results was conducted on available stored samples. Follow-up serologic assays were conducted on the anti-spike assay.

Pre-defined treatment and laboratory tests of systemic and/or organ-specific inflammation outcomes at each time point are outlined in supplementary Table 1. All echocardiogram reports were reviewed by senior paediatric cardiologists. Abnormal echocardiogram results at presentation and follow-up were defined as: coronary artery aneurysms/dilatation (Z-score >2), pericardial inflammation, abnormal ventricular function (ejection fraction <0.55 or visualised hypokinesis), and/or significant valvulopathy. Abnormal abdominal ultrasound/CT results were defined as: inflammatory liver changes, hepatosplenomegaly, ileocolitis, and/or significant peritoneal lymphadenopathy.

Physician and therapist assessed outcomes at six months included:

1. Expanded Disability Status Scale (EDSS) calculated by a senior paediatric neurologist (YH).[7]
2. The six-minute walk test (6MWT) and the manual muscle test-8 (MMT8) was carried out by two senior physiotherapists. Published normative values from healthy child and adolescent controls were used to group the patient scores into centiles.[8]
3. Patient-reported outcome measures were assessed via the PedsQL 4.0 Generic Core Scales, which provide measures of physical, emotional, social, and school functioning. Patients were considered to have mild problems if scale scores fell between one and two standard deviations (SD) below population mean, or severe problems if scores were more than two SD.[9]
4. Paediatric Index of Emotional Distress (PI-ED): Clinical cut-off score of 20 identified those that required further clinical assessment and intervention.[10]
5. A structured interview asking parents/guardians: (i) did they have concerns about a PIMS-TS relapse in their child (ii) have they taken any additional isolation precautions beyond current UK government guidance (iii) did they feel that their child was vulnerable medically due to PIMS-TS and (iv) would they be willing to be vaccinated with a COVID-19 vaccine once available.

Descriptive statistics were used to summarise the key clinical, laboratory, and radiological features. Non-parametric statistical tests (Mann–Whitney U and Kruskal Wallis) were used for continuous distributions (age, body mass index [BMI], laboratory investigations, length of mechanical ventilation and inotropic support, and duration of hospital stay), as appropriate given normality, and χ^2 or

Fisher's exact tests were used for nominal data (gender, ethnicity, SARS-CoV-2 PCR and serology positivity, proportion with proteinuria, hypertension, raised retinol binding protein/creatinine ratio [RBP/Cr], abnormal faecal calprotectin, echocardiogram, abdominal imaging, doppler evidence of thrombus, ventilation and inotrope requirement, and treatment with methylprednisolone, intravenous immunoglobulin [IVIg], or anakinra). Comparisons between patients of white ethnicity versus Black, South Asian, and Minority Ethnic groups (BAME), patients 12 years and younger and patients over 12 years, and patients with and without neurological findings were performed.[11]

Univariate logistic regression was used to evaluate age at presentation, sex, co-morbidities, duration of ventilation, and duration of hospital admission as potential predictors of the following outcomes at 6 months: i) 6MWT below 3rd centile, ii) mild or severe difficulties on PedsQL self-report, and iii) mild or severe difficulties on PedsQL parental report. Multivariable analyses were modelled for the same outcomes, including as covariates those variables significant at $p< 0.05$ in the univariate analysis. Results associated with a p value <0.05 were considered significant. Analyses were performed using GraphPad Prism 8 (GraphPad Software).

Role of the funding source

No funder

Results

A total of 46 patients were identified. The number of admissions of PIMS-TS cases by week during that time period are shown in supplementary Figure 1.

Median age at presentation was 10·2 years (IQR 8·8-13·3), 65% (n=30) were male and 80% (n=37) were of BAME groups: 35% (n=16) African-Caribbean, 24% (n=11) South Asian, 22% (n=10) other backgrounds (see Table 1 for specific South Asian and other background ethnicities). Patients' demographic, clinical, laboratory and radiographic features are summarised in Tables 1-2. Median length of symptoms prior to initial treatment was seven days (IQR 5-8·3). No differences in baseline clinical features were detected between patients 12 years and younger and patients over 12 years old (supplementary Table 2). 17% (n=8) had co-morbidities: autism (n=3), sickle cell disease (SCD) (n=2), asthma (n=1), type 1 diabetes mellitus (n=1), and spina bifida (n=1). One patient had both autism and SCD.

Baseline systems involvement

Systems involvement in individual patients is shown in Figure 1. All patients had elevated markers of systemic inflammation at baseline. 27% (12/45) were SARS-CoV-2 PCR positive on admission. 86% (36/42) of patients initially tested for SARS-CoV-2 IgG serology were positive, plus one equivocal result. Two patients were neither PCR positive nor serology positive, however had household contacts with COVID-19 thus meeting RCPCH diagnostic criteria. 25% (9/36) had evidence of Epstein-Barr virus (EBV) co-infection by PCR, either primary or reactivation, one of which progressed to haemophagocytic lymphohistiocytosis after PIMS-TS in a biphasic illness course.

33% (15/46) children were found to have significant abnormalities on initial echocardiogram. 48% (22/46) required inotropic support. One patient required extracorporeal membrane oxygenation (ECMO). 84% (38/45) and 86% (31/36) had raised troponin and N-terminal pro-brain natriuretic peptide (NT-proBNP) respectively.

52% (24/46) had neurological involvement at presentation. Symptoms reported included: headaches (n=24), dysarthria/dysphonia (n=6), visual/auditory hallucinations (n=6), unsteady gait (n=5), and seizures (n=1; secondary to posterior reversible encephalopathy syndrome after steroid administration). Neurological abnormalities were: encephalopathy/delirium (n=14), ataxia (n=4), peripheral neuropathy (n=3), abnormal eye movements/saccades (n=2), and facial asymmetry/weakness (n=1). Encephalopathy and hallucinations were present prior to intensive care admission and treatment with corticosteroids.

44% (7/16) of patients with neuroimaging (CT and/or MRI brain +/- spine) had abnormalities: splenial signal changes (n=4), microhaemorrhages (n=3), subcortical parietal white matter lesions (n=3), leptomeningeal enhancement (n=1), and cerebral oedema (n=1). 93% (14/15) who underwent electroencephalography (EEG), had an excess of slow wave activity (ranging from mild to severe encephalopathy). In 4/7 patients who underwent nerve conduction studies and electromyography (EMG), mild myopathic and neuropathic changes were seen. Children with neurological involvement were more likely to be ventilated ($p=0.006$), for a longer duration ($p=0.01$), require inotropic support ($p=0.03$), and have higher D-dimers at presentation ($p<0.05$) (supplementary Table 3).

Renal involvement (raised creatinine, proteinuria, and/or hypoalbuminaemia) was present in 91% (42/46). None required renal replacement therapy.

Gastrointestinal involvement (abdominal pain, diarrhoea/vomiting, or abnormal abdominal imaging) was present in 98% (45/46). 33% (9/27) who had abdominal imaging during admission had significant abnormalities. 9% (4/46) were overweight (BMI>25), median BMI was 18·4 (IQR 16·7-21·6). Total 25-hydroxyvitamin D levels were insufficient (<50 nmol/L) in 72% (33/46) with a median 21 nmol/L (IQR 14-43).

Evidence of prothrombotic state (raised fibrinogen and/or thrombi on doppler studies) was present in 87% (40/46). 4% (2/46) had significant thrombi (unprovoked vena cava [n=1], line-associated internal jugular [n=1]). No pulmonary emboli were reported.

63% (29/46) children reported upper and/or lower respiratory symptoms (cough, coryza, pharyngitis, dyspnoea). 35% (16/46) needed mechanical ventilation although duration was typically short. 48% (22/46) had dysphonia, anosmia, and/or dysphagia at presentation prior to PICU admission.

Dermatological/mucous membrane involvement (polymorphous rash, conjunctivital injection, erythematous mucous membranes) was present in 85% (39/46).

Systems involvement at follow-up (six weeks and six months)

Patients showed improvement in both inflammatory markers (Figure 2) and systems involvement (Figure 1) at six weeks and six months follow-up. There were no deaths. Re-admission to hospital was reported in three patients (total of four hospital admissions): one for PIMS-TS relapse with new onset encephalopathy treated with steroids and IVIg and three patients for infectious complications (pneumonia, urosepsis, skin/soft tissue infection).

All 42 patients who had RT-PCR testing were negative for SARS-CoV-2 at six weeks as were all eight tested at six months. 91% (38/42) who had positive serology within six weeks remained seropositive at six months. One patient who was RT-PCR positive on multiple occasions at baseline never seroconverted, whilst one patient seroconverted between six weeks and six months. Four patients were antibody negative at six months after previously demonstrating antibodies to SARS-CoV-2 (one associated with rituximab treatment). Four patients continued to have low level serum EBV PCR titres at six months. At six months, and a minimum of four months off immunosuppression, 39% (17/44) had a persistently abnormal lymphocyte subsets, most notably 30% (13/44) had increased

gamma-delta cells, 5% (2/44) of which also had elevated double negative T-cells, and 9% (4/44) persistently low naïve T-cells.

Systolic function and levels of troponin and NT-proBNP were normal in all patients by six months. At six weeks a single patient had large coronary artery aneurysms (maximum Z-score 9.18) which remained stable at six months but required dual anticoagulation and one with a residual small pericardial effusion. A single patient with underlying SCD had marginally enlarged coronaries at six months (maximum Z-score 2.9) treated with aspirin which was less evident at six week follow-up.

At six weeks, 52% (24/46) had abnormal neurological examinations: proximal myopathy/lower limb weakness (n=18), bilateral or unilateral dysmetria (n=16), abnormal eye movements/saccades (n=15), abnormal posturing (n=9), difficulty in tandem walking (n=6), hyper-reflexia (n=5), hyporeflexia (n=4), upgoing plantars (n=2), facial weakness (n=2), sensory abnormalities (n=2), and upper limb weakness (n=1). At six months, 39% (18/46) had abnormal neurological examinations: bilateral or unilateral dysmetria (n=12), hyper-reflexia (n=9), proximal myopathy/lower limb weakness (n=8), abnormal eye movements/saccades (n=7), difficulty in tandem walking (n=4), abnormal posturing (n=3), hyporeflexia (n=2), upgoing plantars (n=2), sensory abnormalities (n=2), facial weakness (n=1), upper limb weakness (n=1). Median EDSS was 0 (IQR 0-1; range 0-6.5).

Only 3/15 patients who underwent EEG at six weeks had a mild excess of slow activity. At six months, no abnormalities were reported in three patients who had further EEGs. 3/4 patients who had nerve conduction studies/EMG at six weeks had abnormalities: severe axonal motor and sensory neuropathy (affecting peroneal and tibial nerves), mild/borderline axonal neuropathy, denervation change in thyroarytenoid and cricoarytenoid. One patient had an EMG at six months, demonstrating a mild non-length dependent demyelinating neuropathy affecting the upper limbs.

6MWT performed at six weeks showed 63% (20/32) walked less than the 3rd centile expected distance for their age and sex (Table 3). At six months, 45% (18/40) were below the 3rd centile. Median MMT8 score at baseline was 53 (IQR 43-64) and this rose to 73 (IQR 65-78) at six weeks and to 80 (IQR 68-80) at six months. PedsQL responses revealed severe diffiuclties in physical functioning by parental and self-report in 14% and 8% of children respectively (Table 4).

PedsQL responses across emotional, social, school, and psychosocial dimensions are shown in Table 4. Emotional lability was reported in 26% (12/46) patients at six weeks and in 15% (7/46) patients at six months. The median PI-ED score at six months was six (IQR 5-13), with 7% (3/46) scoring above

the clinical cut-off of 20, indicating risk of clinically significant emotional distress. From the structured interview, 31% (14/45) parents reported anxiety about possible PIMS-TS relapse in their child, 22% (10/45) reported concerns about medical vulnerability of their child as a result of hospitalisation with PIMS-TS and 20% (9/45) reported taking additional isolation precautions beyond UK government guidance. 73% (33/45) of parents expressed sentiments of SARS-CoV-2 vaccine hesitancy. 98% (45/46) patients were back in full time education by six months (virtually/face-to-face).

Multivariable analysis did not identify any predictors for the following outcomes at 6 months: i) 6MWT below 3rd centile ii) mild or severe difficulties on PedsQL self-report, and iii) mild or severe difficulties on PedsQL parental report.

Creatinine universally normalised during follow-up. Proteinuria on urinalysis was found in 9% (4/43) of children tested at six weeks and 2% (1/44) at six months with hypoalbuminaemia one other. At six weeks, 5% (2/40) had marginally raised urinary RBP/Cr ratio, 7% (3/42) had raised blood pressure (BP) >95th centile for sex/height, and 5% (2/42) raised BP >99th centile. At six month, 10% (4/42) had raised BP >95th centile and none >99th centile. One patient with elevated BP at six weeks was maintained on amlodipine.

Persistent abdominal pain was reported in 9% (4/46) and 7% (3/46) patients at six weeks and six months respectively. One patient had persistent diarrhoea for six months. One patient reported new nausea and vomiting and one new onset diarrhoea at six months only. Faecal calprotectin was raised in 31% (10/32) children at six weeks and 7% (1/15) at six months. 20% (4/20) of those undergoing abdominal imaging had abnormalities reported at six weeks (persistent transverse colitis [n=1], ileitis [n=1], inflammatory liver changes [n=1], splenomegaly [n=1]) with persistent splenomegaly in one. One patient underwent colonoscopy and gastroscopy which demonstrated patchy chronic inflammatory changes with increased lamina propria eosinophil density throughout the colon and ileum. Liver enzymes typically increased up to 6-weeks before decreasing. At 6-weeks and 6-months, median BMI increased to 19·9 (IQR 18·5-22·6), and 20·8 (IQR 18·9-23·4) respectively (supplementary Figure 2). After supplementation, total 25-hydroxyvitamin D levels rose to 66 nmol/L (IQR 36-83) at six weeks and to 69 nmol/L (IQR 45-88) at six months (Figure 2).

Both patients with thrombi completed a course of anticoagulation (dalterparin n= 1; riveroxiban n=1) without concerns. Fibrinogen levels typically normalised by 6-weeks and remained so at 6-months (Figure 2).

Only one patient demonstrated abnormal carbon monoxide gas transfer after correction for alveolar volume. Otherwise, the remaining 18 patients who met the criteria for follow-up testing had spirometry and plethysmography values within normal limits. Full otolaryngology and speech and language results are reported elsewhere.[12] At 6-weeks, self-reported symptoms were: dysphonia (n=6), anosmia/dysgeusia (n=2), dysphagia (n=1). ENT and SALT manifestations largely resolved by 6-months with dysphonia in four children and anosmia/dysgeusia in two children without clinically significant objective findings. One patient required ongoing voice therapy at 6-months following restalyne injection into right vocal fold after presumed iatrogenic injury from ECMO. No abnormalities in the cribiform plate or olfactory tract were found on imaging of those with anosmia.

Three distinct rashes (hypopigmented n=1, erythematous maculopapular n=1; dermographism n=1) were reported during follow-up in three patients, all thought to be unrelated to PIMS-TS. There were no cases of ongoing mucosal changes.

Discussion

In this retrospective study we describe the natural history and longitudinal physical and psychological outcomes in 46 patients with PIMS-TS. Six-month survival was 100% but many patients had residual new deficits. The majority of patients had multisystem severe involvement during their initial illness including 98% gastrointestinal 52% neurological and 33% cardiac, which mostly resolved. At follow up, common sequelae included muscular fatigue, neurologic sequelae such as ataxia and abnormal saccade, anxiety and emotional lability. Biochemical markers or inflammation resolved, and SARS-CoV-2 serology status remained positive in most despite immunosuppression.

The notable reduction in functional exercise capacity in this group may be attributed to a number of factors: the underlying inflammatory nature of PIMS-TS, the high proportion of patients requiring PICU support resulting in the possibility of critical illness myopathy, non-compliance with home exercise programmes, pre-illness sedentary lifestyle, and side-effects of high-dose corticosteroid use, which may have contributed to proximal myopathy and increased BMI at initial follow-up.[16] These factors are additional to the lack of physical activity opportunities experienced by all youth during the COVID-19 pandemic. Fatiguability was also still detected at 6-months. Similar poor performance on the 6MWT is described in adults with COVID-19 with 22-29% having demonstrated impairment in walking distance (depending on severity cut-off).[15] Monitoring of functional abilities

with return to school, sport, and increased physical demand with lessening of social restrictions will be of particular importance as subtle findings may become more prominent.

Neurological findings have also been reported commonly in other PIMS-TS cohorts.[13,14] In our cohort, persistence of subtle findings, only noticeable on detailed neurological exam, did not correlate with neurologic functional impairment (median EDSS score 0 at 6 months). Although 98% were back in full-time education, formal neuropsychology testing was not performed and the long-term cognitive effects of PIMS-TS requires attention given the rate of neurological involvement at presentation.

Though there were initial concerns, long-term cardiac consequences appear rare; acute findings are postulated to be a result of cardiac stunning rather than progressive endovascular changes observed in similar entities such as Kawasaki disease.[17,18] Nevertheless, two patients in our cohort had persistent coronary artery changes requiring lifelong treatment.

It is yet to be determined whether other longer-term sequelae will manifest beyond 6-months, for example inflammatory gastrointestinal pathology or renal disease from acute kidney injury, stressing the importance of ongoing MDT follow-up. Iatrogenic effects of steroids and other immunomodulation on infection risk and re-hospitalisation, hypertension, kidney, cardiac, and metabolic function requires further evaluation.

Beyond physical sequelae, family trauma and anxiety were prominent in our cohort as a direct consequence of the affected child's illness and familial association with a COVID-19 case. Compounded by critical illness, problems arising from the natural disruption of the COVID-19 pandemic on childrens' lives may explain some of these findings; it is not known what the PedQL scores of the general paediatric population currently is. Furthermore, parental anxiety was exacerbated by the uncertainties associated with a new disease entity with no known natural history. Acknowledging families' concerns in follow-up formulating a trusting medical relationship, may reduce these anxieties and can also be helpful in addressing difficult issues such as vaccine hesitancy.

Similar psychological findings have been defined as post-intensive care syndrome which would benefit from MDT care.[19] Outpatient MDT follow-up models have proven successful in adults and neonates post intensive care admission and in chronic paediatric conditions such as diabetes and epilepsy.[20-22] Nevertheless, evidence for structured paediatric MDT approaches following PICU

discharge are lacking and the heterogeneity of adult ICU MDT follow-up limits knowledge extrapolation.[23] This model of MDT care exemplifies the importance of knowledge sharing during this evolving COVID19 epidemic.[24] This innovative model for a novel disease served to cultivate holistic care whilst helping to define the natural history.

Demographic characteristics were similar to previously reported PIMS-TS cohorts, however, we did not observe any phenotypic difference when comparing the ≤ 12 and >12 yr old patients as previously reported.[1,25,26] Increased ventilation rates were secondary to fluid overload from vascular leak and secondary to sedation requirements resulting from neurological involvement. Mirroring ethnic minority preponderance in the largest PIMS-TS cohort in New York, a notable finding was the over-representation of patients of BAME backgrounds (80%) as compared to the UK population.[26] Both environmental and biologic explanations for this overrepresentation are possible.[27,28] In part, this reflects the well-documented increased SARS-CoV-2 infection and severe illness amongst BAME adults and children[27,29]. However, given the key role of the host immune response against SARS-CoV-2 in the pathogenesis of PIMS-TS and the disproportionate impact of other inflammatory conditions on ethnic minority groups, this may also explain the extent of the impact of PIMS-TS on BAME patients.[30,31]

Limitations of this study include its single centre nature with a possibility of referral bias of the most unwell PIMS-TS patients (requiring intensive care). Paediatric controls, both post-PICU discharge as well as those unaffected by illness during the COVID-19 pandemic were not available for comparison and thus findings must be viewed as hypothesis generating. Similarly, baseline pre-illness testing was not available for analysis to determine functional change post-illness. The study is limited by retrospective collection of clinically guided investigations which accounts for variations in follow-up data amongst participants.With the rarity of this condition, longer-term prospective multi-centre studies would help to validate our findings and further our understanding of PIMS-TS. The strength of this study includes the long-term holistic nature of the data.

Irrespective of treatments received in the acute phase, our outcomes were generally favourable, although severe sequelae did persist in some. Our health outcomes serve to provide guidance to families and medical providers and outline general expectations as it relates to the natural history of PIMS-TS.

Acknowledgements

In addition to the patients and famillies themselves, we would like to thank Drs Imke Meyer-Parsonson, Sian Pincott, Pascale du Pre, the remainder of the general paediatric, intensive care, infectious diseases, physiotherapy, and psychology teams and all the junior doctors at Great Ormond Street Hospital for the diligent care they provided fot this cohort of patients. In particular we acknowledge Drs Ryan Cheong, Alison Carter, Elena Kurteva, Lieke Hoogenboom, and Tania Ahmad for their assessments in follow-up.

Figure legends

Figure 1: Systems involvement at baseline (A), 6 weeks (B), and 6 months (C). The systems of each patient are shown in a panel; every radial segment represents 1 patient. Each system is coded with a different colour as per the key. Patients ≤12 years old are shown in the section with white background, and those >12 in the section with grey background. Individual patients (segments) are presented in the same location across the three time points. The following definitions were used for systems involvement: Respiratory: any significant respiratory symptoms and/or need for mechanical ventilation; Fluid refractory shock: inotropic support requirement; Dermatological: skin rash or any mucous membrane involvement; Systematic inflammation: raised CRP (>20 mg/L), ferritin (>300 µg/L); Neurological: any neurological signs or symptoms, abnormalities on neuroimaging or EEG; Gastrointestinal: abdominal symptoms, raised faecal calprotectin (>50 µg/g), and/or abnormalities on abdominal imaging; Cardiac: raised troponin (>34 ng/L), NT-pro BNP (>157 pg/ml), or abnormal echocardiogram; ENT: dysphagia, anosmia, or dysphonia; Renal: raised Creatinine for age, low albumin (<35 g/L) or evidence of proteinuria on urinalysis; Coagulopathy: raised fibrinogen (>4 g/L) or evidence of thrombus on doppler.

Figure 2: Trends in serum markers (inflammatory, cardiac, renal, liver and coagulation) at three timepoints, baseline, 6 weeks and 6 months follow-up, for all 46 PIMS-TS patients. The upper end of the normal range for all markers (except lower end of normal for minimum lymphocyte count, minimum platelet count and total 25-hydroxyvitamin D levels) is shown by black dotted lines. At each time point, a white box represents median and interquartile range for all values of that serum marker. Red lines represent an increase in values and green lines represent a decrease in values between the different timepoints.

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Research in Context

Evidence before this study is limited to PIMS-TS cohorts in the acute phase of illness. This is the first study to define longer-term, post-hospitalisation outcomes in PIMS-TS. This cohort analysis highlights the importance of physical rehabilitation and mental health provision post PIMS-TS hospital discharge. Our positive health outcomes serve to provide assurance to families and guidance to medical providers as it relates to the natural history of PIMS-TS.

Author Contribution

The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research. JP, OA, YH, and KM conceptualised the study. JP and OA reviewed extracted information from patient records and reviewed the data contained in the manuscript. All authors have read and revised the manuscript, confirmed their declaration and contributions, and have agreed to conditions noted on the Authorship Agreement Form.

Data Sharing

De-indentified patient datasets available upon written request to corresponding author with publication.