6-month multidisciplinary follow-up and outcomes of patients with paediatric inflammatory multisystem syndrome (PIMS-TS) at a UK tertiary paediatric hospital: a retrospective cohort study

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Summary

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

Methods This retrospective cohort study comprised children (aged <18 years) who fulfilled the UK Royal College of Paediatrics and Child Health (RCPCH) diagnostic criteria for PIMS-TS and were admitted to Great Ormond Street Hospital (London, UK) between April 4 and Sept 1, 2020. Patients were followed up by a multidisciplinary team of specialists at 6 weeks and 6 months after admission. Biochemical and functional outcomes were analysed.

Findings 46 children were included in this study. The median age at presentation was 10·2 years (IQR 8·8–13·3), 30 (65%) patients were male and 16 (35%) were female, 37 (80%) were from minority ethnic groups, and eight (17%) had pre-existing comorbidities. All patients had elevated markers of systemic inflammation at baseline. None of the patients died. By 6 months, systemic inflammation was resolved in all but one patient. 38 (90%) of 42 patients who had positive SARS-CoV-2 IgG antibodies within 6 weeks of admission remained seropositive at 6 months. Echocardiograms were normal in 44 (96%) of 46 patients by 6 months, and gastrointestinal symptoms that were reported in 45 (98%) of 46 patients at onset were present in six (13%) of 46 patients at 6 months. Renal, haematological, and otolaryngological findings largely resolved by 6 months. Although minor abnormalities were identified on neurological examination in 24 (52%) of 46 patients at 6 weeks and in 18 (39%) of 46 at 6 months, we found minimal functional impairment at 6 months (median Expanded Disability Status Scale score 0 [IQR 0–1]). Median manual muscle test-8 scores improved from 53 (IQR 43–64) during hospital admission to 80 (IQR 68–80) at 6 months, but 18 (45%) of 40 patients showed 6-min walk test results below the third centile for their age or sex at 6 months. PedsQL responses revealed severe emotional difficulties at 6 months (seven [18%] of 38 by parental report and eight [22%] of 38 by self report). 45 (98%) of 46 patients were back in full-time education (virtually or face to face) by 6 months.

Interpretation Despite initial severe illness, few organ-specific sequelae were observed at 6 months. 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.

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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), also known as multisystem inflammatory syndrome in children (MIS-C)—was identified.[1] PIMS-TS is a distinct post-infectious entity unlike the primary respiratory manifestations and outcomes seen in both adult and paediatric patients with COVID-19.[2,3] More than 250 cases of PIMS-TS were identified in the UK and Ireland from March to June, 2020, presenting with a constellation of clinical features that included fever, rash, conjunctival injection, and gastrointestinal symptoms, sometimes progressing to multi-organ failure requiring admission to the paediatric intensive care unit (PICU).[4,5]

Although the acute phase of PIMS-TS has been characterised, the short-term, medium-term, and long-term sequelae remain unclear.[1,3] Similarly, little is known about rehabilitation requirements after discharge from hospital. We aimed to analyse 6-month outcomes in a cohort of paediatric patients with PIMS-TS treated at a large tertiary paediatric hospital in the UK.

Research in context

Evidence before this study

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was first defined in April, 2020, after recognition of a unique post-viral inflammatory condition in children. We searched PubMed for follow-up data about PIMS-TS, published up to March, 2021, using a combination of the following search terms: "PIMS-TS", "MIS-C", "paediatric inflammatory multisystem syndrome", "multisystem inflammatory syndrome in children" AND ("outcomes", "follow-up", "outpatient", "quality of life", OR "function"). We found that the available evidence was predominantly limited to PIMS-TS cohorts in the acute phase of illness. We therefore aimed to define longer-term, multi-disciplinary follow-up outcomes after hospital admission in patients with PIMS-TS.

Added value of this study

In this retrospective cohort study, we describe a range of outcomes in patients with PIMS-TS, including biochemical and functional outcomes measured up to 6 months as part of a multidisciplinary follow-up clinic. We found that whereas cardiac, gastrointestinal, renal, haematology, and otolaryngology outcomes largely resolved at 6 months, muscular fatigue and emotional lability were common. Long-term, serious end-organ damage occurred in some patients but was uncommon in this cohort. This analysis highlights the importance of physical rehabilitation and mental health provision for patients with PIMS-TS following discharge from hospital.

Implications of all the available evidence

Our results can help to guide families and health-care providers about the natural history of PIMS-TS. Because PIMS-TS is a novel condition, long-term, holistic, and multidisciplinary follow-up of patients will be important.

Methods

Study design and population

Patients aged 18 years or younger, fulfilling the UK Royal College of Paediatrics and Child Health (RCPCH) diagnostic criteria for PIMS-TS,[6] and admitted to Great Ormond Street Hospital, London, UK, between April 4 and Sept 1, 2020, were included in this cohort study. 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 the Great Ormond Street Hospital NHS Foundation Trust Audit Committee (number 2857). Because retrospective data were collected from clinical reviews only, consent from patients and parents or guardians was not obtained.

See Online for appendix

Procedures

Patients were prospectively reviewed by multiple specialties in a PIMS-TS multidisciplinary outpatient clinic that had been set up in May, 2020. A new ward-based day-case service was established to accommodate sequential reviews and investigations by multiple specialties. Patients were seen by the multidisciplinary team at a minimum of two further timepoints after discharge from hospital: at 6 weeks and 6 months. Electronic clinical records were reviewed by two investigators (JP and OA), who collected baseline and follow-up data.

Recent SARS-CoV-2 infection was confirmed by RT-PCR of nasopharyngeal samples, positive serology, a clear epidemiological link to an infected contact, or a combination of the above. Serology testing evaluated IgG antibodies to the SARS-CoV-2 nucleocapsid protein and, from June, 2020, to the spike protein (Epitope Diagnostics; San Diego, CA, USA). After June, 2020, anti-spike protein antibody tests were done on all patients presenting with PIMS-TS. Retrospective analysis of patients with negative nucleocapsid antibody results was done on available stored samples. Follow-up serological assays were done on the anti-spike assay.

Pre-defined treatments and laboratory tests of systemic and organ-specific inflammation outcomes at each timepoint are outlined in the appendix (p 1). All echocardiogram reports were reviewed by senior paediatric cardiologists. Abnormal echocardiogram results at presentation and follow-up were defined as: coronary artery aneurysms or dilatation (Z-score >2), pericardial inflammation, abnormal ventricular function (ejection fraction <0·55 or visualised hypokinesis), significant valvulopathy, or a combination of the above. Abnormal abdominal ultrasound or CT results were defined as: inflammatory liver changes, hepatosplenomegaly, ileocolitis, or significant peritoneal lymphadenopathy, or a combination of the above.

Various outcomes were assessed by physicians and therapists at 6 months; here, we list the outcomes assessed as part of this study. The Expanded Disability Status Scale (range 0–10, with higher levels indicating higher levels of disability) was calculated by a senior paediatric neurologist (YH).[7] The 6-min walk test and the manual muscle test-8 (scored out of 80, with higher scores indicating better strength) were carried out by two senior physiotherapists (SM and another senior physiotherapist supervised by SM). Published normative values from healthy child and adolescent controls were used to group the patient scores into centiles.[8] 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 scores fell between one and two SDs below the population mean, or severe problems if scores were more than two SDs below the population mean.[9] For the Paediatric Index of Emotional Distress, a clinical cutoff score of 20 identified those patients who required further clinical assessment and intervention.[10] Structured interviews were also done, asking parents or guardians the following questions: did they have concerns about a PIMS-TS relapse in their child? Have they taken any additional isolation precautions beyond current UK Government guidance? Did they feel that their child was vulnerable medically due to PIMS-TS? And would they (the parent or guardian only, not the child) be willing to be vaccinated with a COVID-19 vaccine once available?

Statistical analysis

Descriptive statistics were used to summarise 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, duration 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 (sex, ethnicity, SARS-CoV-2 PCR and serology positivity, proportion of patients with proteinuria, hypertension, raised retinol binding protein [RBP]-to-creatinine ratio, abnormal faecal calprotectin, echocardiogram, abdominal imaging, evidence of thrombus on doppler ultrasound, ventilation and inotrope requirement, and treatment with methylprednisolone, intravenous immunoglobulin, or anakinra). Comparisons were made between patients aged 12 years and younger versus those older than 12 years, and patients with and without neurological findings.[11]

Role of the funding source

There was no funding source for this study.

Results

46 patients were included in this study. The number of admissions of PIMS-TS cases by week from April 4 to Sept 1, 2020, is shown in the appendix (p 4).

Median age at presentation was 10·2 years (IQR 8·8–13·3), 30 (65%) patients were male and 16 (35%) were female. 37 (80%) were from minority ethnic groups: 16 (35%) African-Caribbean, 11 (24%) South Asian, and ten (22%) from other backgrounds (table 1). Patients' demographic, clinical, laboratory, and radiographic features are summarised in tables 1 and 2. The median duration of symptoms before initial treatment was 7·0 days (IQR 5·0–8·3). No differences in baseline clinical features were detected between patients aged 12 years and younger and those older than 12 years (appendix p 2). Eight (17%) patients had comorbidities: four with autism, two with sickle-cell disease, one with asthma, one with type 1 diabetes, and one with spina bifida; one patient had both autism and sickle-cell disease.

	All patients (n=46)
Age at presentation	10·2 (8·8–13·3)
Sex	
Female	16 (35%)
Male	30 (65%)
Ethnicity	
White*	9 (20%)
South Asian†	11 (24%)
African-Caribbean	16 (35%)
Other‡	10 (22%)
Body-mass index, kg/m²	18 (17–22)
Comorbidities§	8 (17%)
SARS-CoV-2 PCR-positive at admission	12/45 (27%)
SARS-CoV2 IgG-positive at admission	36/42 (86%)
Mechanical ventilation	16 (35%)
Duration of ventilation, days	0 (0–1)
Inotropic support	22 (48%)
Duration of inotropic support, days	0 (0–2)
Low-molecular-weight heparin	35 (76%)
Total duration of admission, days	11 (8–16)
Immunotherapies	40 (87%)
Intravenous methylprednisolone (%)¶	25 (54%)
Intravenous immunoglobulin (%)	38 (83%)
Anakinra (%)	6 (13%)
No immunomodulation	6 (13%)

Data are n (%), n/N (%), or median (IQR). *White ethnicity breakdown: eastern European (n=4), British (n=2), Ashkenazi (n=2), French (n=1). †South Asian defined as: Indian, Bangladeshi, Pakistani, Nepali, or Sri Lankan. ‡Other ethnicity breakdown: mixed (n=6), Arab (n=2), South American (n=1), Turkish (n=1). §Comorbidities: autism (n=4), sickle-cell disease (n=2), asthma (n=1), type 1 diabetes (n=1); spina bifida (n=1); one child had two comorbidities. ¶Intravenous pulse steroids 10–30 mg/kg (maximum 1 g per day) for 3–5 days followed by a tapering dose starting at 2 mg/kg of prednisolone (maximum 60 mg per day) over 2–3 weeks.

Table 1: **Baseline demographic and clinical features of the whole cohort**

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

15 (33%) of 46 children were found to have significant abnormalities on initial echocardiogram. 22 (48%) of 46 required inotropic support. One patient required

	Baseline	6 weeks	6 months
C-reactive protein (normal range: 0–20 mg/L)	281 (167–319); n=46	0 (0–0); n=46	0 (0–5); n=44
Lactate dehydrogenase (normal range: 360–730 U/L)	973 (728–1169); n=44	542 (477–601); n=45	527 (475–635); n=44
Ferritin (normal range: 15·1–70·0 µg/L)	915 (475–1650); n=46	26 (17–35); n=46	26 (20–37); n=45
Troponin (normal range: 0–34 ng/L)	123 (21–379); n=45	0 (0–0); n=46	20 (10–26); n=4*
NT-proBNP (normal range: 23–157 pg/mL)	5218 (747–21618); n=36	38 (20–63); n=43	20 (20–26); n=8*
Maximal platelets (normal range: 150–450 × 10⁹/L)	500 (373–682); n=46	327 (284–366); n=46	309 (265–364); n=43
Minimal platelets (normal range: 150–450 × 10⁹/L)	148 (110–189); n=46	..	..
Fibrinogen (normal range: 1·7–4·0 g/L)	6·3 (6–7); n=46	3 (2–3); n=46	3 (2–3); n=42
D-dimers (normal range: 0–312 µg/L)	4945 (2562–7827); n=46	138 (86–214); n=46	122 (77–166); n=42
Minimum lymphocyte count (normal range: 1·2–5·2 × 10⁹/L)	0·7 (0·5–1); n=46	3 (2–4); n=46	3 (2–4); n=43
Creatine kinase (normal range: 60–335 U/L)	82 (52–183); n=39	71 (51–91); n=44	108 (80–152); n=42
Alanine transferase (normal range: 10–45 U/L)	76 (48–126); n=46	17 (11–21); n=46	19 (15–24); n=44
Creatinine (µmol/L), age-dependent normal	63 (42–92); n=46	40 (32–47); n=46	45 (39–52); n=44
Minimum albumin (normal range: 37–56 g/L)	26 (22–30); n=46	43 (42–45); n=46	46 (45–48); n=44
Proteinuria (%)	5/46 (11%)	4/43 (9%)	1/44 (2%)
Elevated RBP-to-creatinine ratio (%)	3/46 (7%)	2/40 (5%)	..
Total 25-hydroxyvitamin D concentrations at presentation (normal range >50 nmol/L)	23 (14–44); n=38	66 (36–83); n=11	69 (45–88); n=41
Abnormal echo at baseline (%)	15/46 (33%)	1/46 (2%)	2/6 (33%)
Abnormal ultrasound scan or CT scan of abdomen (%)	9/27 (33%)	4/20 (20%)	1/5 (20%)
Evidence of thrombus on doppler ultrasound	2/46 (4%)	0/2 (0%)	..

Data in parentheses are IQRs, unless otherwise stated. Data not measured are denoted as '..'. NT pro-BNP=N-terminal pro-brain natriuretic peptide. RBP=retinol binding protein. *Once normalised, cardiac markers were not re-checked in extended follow-up unless indicated by the cardiology team.

Table 2: **Laboratory and radiographic results at baseline and at 6 weeks' and 6 months' follow-up**

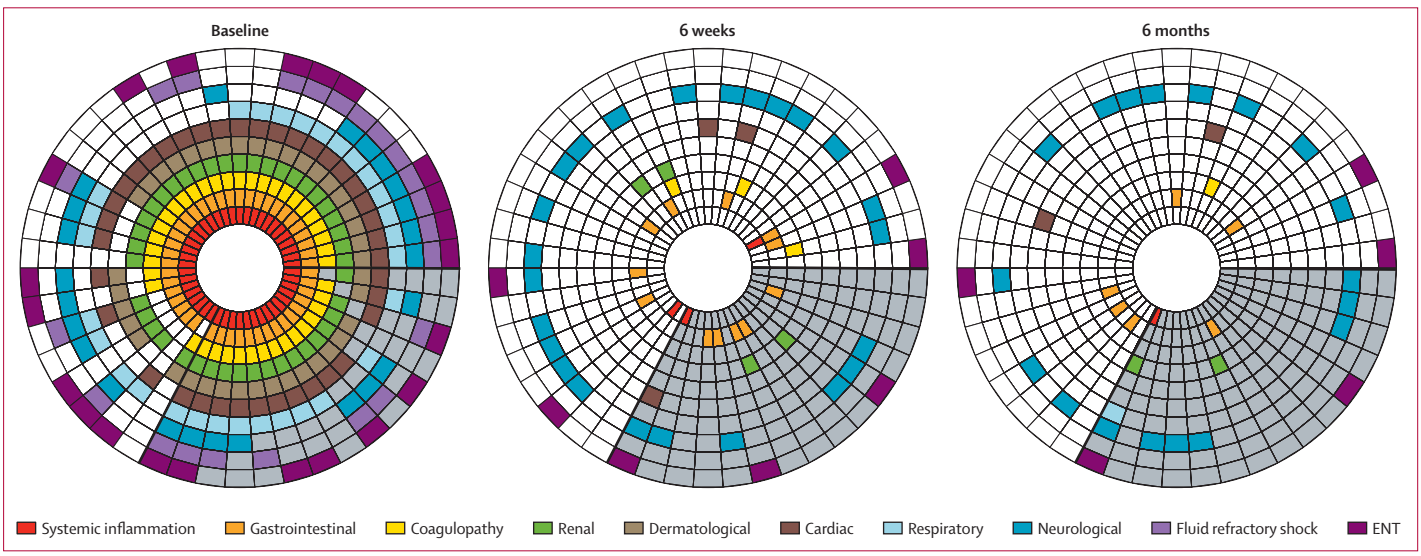


Figure 1: **Systems involvement at baseline (A), 6 weeks (B), and 6 months (C)**
The systems of each patient are shown; each radial segment represents one patient. Patients aged 12 years or younger are shown in the sections with white backgrounds, and those older than 12 years are depicted in the sections with grey backgrounds. Individual patients (segments) are presented in the same location across the three timepoints. Systemic inflammation refers to raised C-reactive protein (>20 mg/L) or ferritin (>300 µg/L). Gastrointestinal involvement refers to abdominal symptoms, raised faecal calprotectin (>50 µg/g), or abnormalities on abdominal imaging, or a combination of the above. Coagulopathy refers to raised fibrinogen (>4 g/L) or evidence of thrombus on doppler ultrasound. Renal involvement refers to raised creatinine for age, low albumin (<35 g/L), or evidence of proteinuria on urinalysis. Dermatological involvement refers to skin rash or any mucous membrane involvement. Cardiac involvement refers to raised troponin (>34 ng/L), N-terminal pro-brain natriuretic peptide (>157 pg/mL), or abnormal echocardiogram. Respiratory involvement refers to any clinically significant respiratory symptoms or the need for mechanical ventilation, or both. Neurological involvement refers to any neurological signs or symptoms, abnormalities on neuroimaging or electroencephalography. Fluid refractory shock refers to inotropic support requirement. Ear, nose, and throat (ENT) involvement refers to dysphagia, anosmia, or dysphonia.

extracorporeal membrane oxygenation. 38 (84%) of 45 patients had raised troponin and 31 (86%) of 36 had raised N-terminal pro-brain natriuretic peptide (NT-proBNP).

24 (52%) of 46 patients had neurological involvement at presentation. Symptoms reported were headaches (n=24), dysarthria or dysphonia (n=6), visual or 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 or delirium (n=14), ataxia (n=4), peripheral neuropathy (n=3), abnormal eye movements or saccades (n=2), and facial asymmetry or weakness (n=1). Encephalopathy and hallucinations were present before intensive care admission and treatment with corticosteroids in all 24 patients.

Seven (44%) of 16 patients who underwent neuroimaging (MRI scans of the brain with or without the 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). 14 (93%) of 15 patients who underwent electroencephalography (EEG) had an excess of slow wave activity (ranging from mild to severe encephalopathy). Mild myopathic and neuropathic changes were seen in four of seven patients who underwent nerve conduction studies and electromyography (EMG). Children with neurological involvement were more likely to be ventilated (p=0·0060), for a longer duration (p=0·010), and require inotropic support (p=0·030), and have higher D-dimers at presentation (p=0·047; appendix p 3).

Renal involvement (raised creatinine, proteinuria, hypoalbuminaemia, or a combination of the above) was present in 42 (91%) of 46 patients during hospital stay. None required renal replacement therapy.

Gastrointestinal involvement (abdominal pain, diarrhoea or vomiting, or abnormal abdominal imaging) was present in 45 (98%) of 46 patients before or during hospital stay. Nine (33%) of 27 patients who had abdominal imaging during admission had clinically significant abnormalities. Four (9%) of 46 patients were overweight (BMI >25 kg/m²) and median BMI was 18·4 kg/m² (IQR 16·7–21·6). Total 25-hydroxyvitamin D concentrations were insufficient (<50 nmol/L) in 33 (87%) of 38 patients, with a median of 21 nmol/L (IQR 14–43).

Evidence of a prothrombotic state (raised fibrinogen or thrombi on doppler studies, or both) was present in 40 (87%) of 46 patients during hospital stay. Two (4%) of 46 patients had thrombi (unprovoked vena cava in one and line-associated internal jugular in the other). No pulmonary emboli were reported.

29 (63%) of 46 patients reported upper or lower respiratory symptoms, or both (cough, coryza, pharyngitis, or dyspnoea) before or during hospital stay. 16 (35%) of 46 patients needed mechanical ventilation, although the duration was typically short. 22 (48%) of 46 patients had dysphonia, anosmia, or dysphagia, or a combination of the above symptoms, at presentation before or during hospital stay.

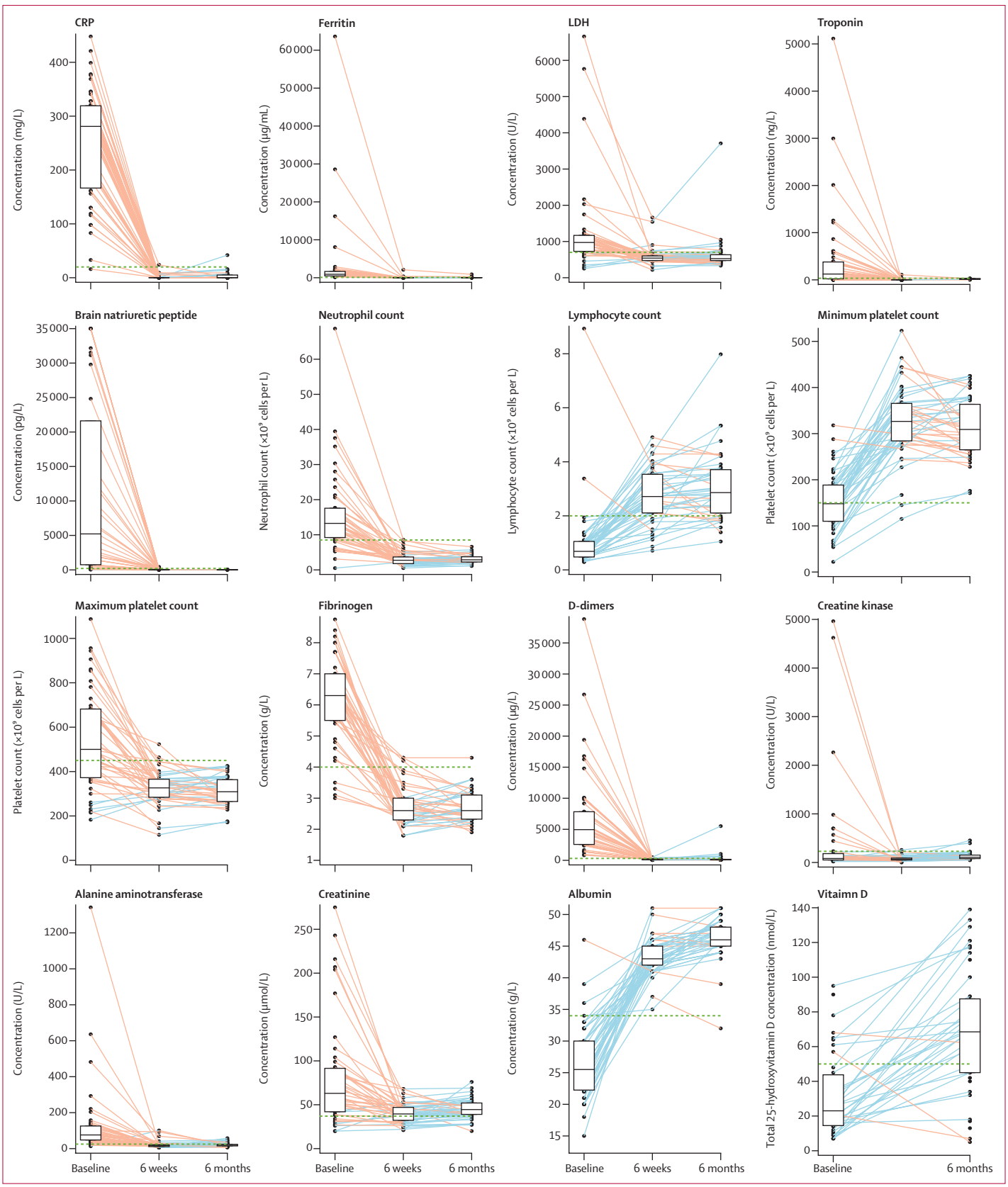
Dermatological or mucous membrane involvement (polymorphous rash, conjunctivital injection, or erythematous mucous membranes) was present in 39 (85%) of 46 patients before or during hospital stay.

Patients showed improvement in both inflammatory markers (figure 2) and systems involvement (figure 1) at 6 weeks and 6 months of follow-up. There were no deaths. Three patients were re-admitted to hospital (four hospital admissions in total): one for PIMS-TS relapse with new-onset encephalopathy treated with steroids and intravenous immunoglobulin, and three for infectious complications (pneumonia, urosepsis, and skin and soft tissue infection).

All 42 patients who underwent RT-PCR testing were negative for SARS-CoV-2 at 6 weeks, as were all eight tested at 6 months. 38 (90%) of 42 patients who had positive serology within 6 weeks remained seropositive at 6 months. One patient who was RT-PCR positive on multiple occasions at baseline never seroconverted, while one patient seroconverted between 6 weeks and 6 months. Four patients were antibody negative at 6 months after previously developing antibodies to SARS-CoV-2 (one was on rituximab treatment). Four patients continued to have low-level serum Epstein-Barr virus PCR titres at 6 months. At 6 months, and a minimum of 4 months off immunosuppression, 17 (39%) of 44 patients had persistently abnormal lymphocyte subsets; most notably, 13 (30%) of 44 had increased γδ cells, two (5%) also had elevated double negative T cells, and four (9%) had persistently low naive T cells.

Systolic function and concentrations of troponin and NT-proBNP were normal in all patients by 6 months. By 6 months, echocardiograms in 44 (96%) of 46 patients had normalised. At 6 weeks, one patient had large coronary artery aneurysms (maximum Z-score 9·18), which remained stable at 6 months but required dual antiplatelet therapy, and one had a residual clinically insignificant pericardial effusion. One patient with underlying sickle-cell disease had marginally enlarged coronaries at 6 months (maximum Z-score 2·9), which were treated with aspirin and less evident at 6 weeks than at 6 months.

At 6 weeks, 24 (52%) of 46 patients had abnormal neurological examinations: proximal myopathy or lower limb weakness (n=18), bilateral or unilateral dysmetria (n=16), abnormal eye movements or 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 6 months, 18 (39%) of 46 patients had abnormal neurological examinations: bilateral or unilateral dysmetria (n=12), hyper-reflexia (n=9), proximal myopathy or lower limb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Ferritin
Concentration (µg/mL)
LDH
Concentration (U/L)
Troponin
Concentration (ng/L)
Brain natriuretic peptide
Concentration (pg/L)
Neutrophil count
Neutrophil count (×10⁹ cells per L)
Lymphocyte count
Lymphocyte count (×10⁹ cells per L)
Minimum platelet count
Platelet count (×10⁹ cells per L)
Maximum platelet count
Platelet count (×10⁹ cells per L)
Fibrinogen
Concentration (g/L)
D-dimers
Concentration (µg/L)
Creatine kinase
Concentration (U/L)
Alanine aminotransferase
Concentration (U/L)
Creatinine
Concentration (µmol/L)
Albumin
Concentration (g/L)
Vitaimn D
Total 25-hydroxyvitamin D concentration (nmol/L)
Baseline
6 weeks
6 months

weakness (n=8), abnormal eye movements or 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), and upper limb weakness (n=1). The median Expanded Disability Status Scale score at 6 months was 0 (IQR 0–1; range 0·0–6·5).

Only three of 15 patients who underwent EEG at 6 weeks had a mild excess of slow activity. At 6 months, no abnormalities were reported in three patients who had further EEGs. Three of four patients who underwent nerve conduction studies or an EMG at 6 weeks had abnormalities: severe axonal motor and sensory neuropathy (affecting peroneal and tibial nerves), mild or borderline axonal neuropathy, and denervation change in thyroarytenoid and cricoarytenoid. One patient had an EMG at 6 months, showing a mild non-length-dependent demyelinating neuropathy affecting the upper limbs.

Creatinine universally normalised during follow-up. Proteinuria on urinalysis was found in four (9%) of 43 children tested at 6 weeks and in one (2%) of 44 at 6 months, with hypoalbuminaemia in another patient. At 6 weeks, two (5%) of 40 patients had a marginally raised urinary RBP-to-creatinine ratio, three (7%) of 42 had raised blood pressure above the 95th centile for their sex, age, and height, and two (5%) of 42 had raised blood pressure above the 99th centile. At 6 months, four (10%) of 42 patients had raised blood pressure above the 95th centile and none had raised blood pressure above the 99th centile. One patient with elevated blood pressure at 6 weeks was maintained on amlodipine.

Persistent gastrointestinal symptoms with or without raised faecal calprotectin were reported in six (13%) of 46 patients at 6 months. Persistent abdominal pain was reported in four (9%) of 46 patients at 6 weeks and in three (7%) of 46 patients at 6 months. One patient had persistent diarrhoea for 6 months. One patient reported new-onset nausea and vomiting and one reported new-onset diarrhoea at 6 months only. Faecal calprotectin was raised in ten (31%) of 32 children at 6 weeks and in one (7%) of 15 at 6 months. Four (20%) of 20 patients undergoing abdominal imaging had abnormalities reported at 6 weeks (one with persistent transverse colitis, one with ileitis, one with inflammatory liver changes, and one with splenomegaly), and splenomegaly persisted in one patient at 6 months. One patient underwent colonoscopy and gastroscopy, which showed patchy chronic inflammatory changes with increased lamina propria eosinophil density throughout the colon and ileum. Liver enzymes typically increased for up to 6 weeks before decreasing. Median BMI increased from 18 kg/m² (IQR 17–22) to 20 kg/m² (19–23) at 6 weeks, and 21 kg/m² (19–23) at 6 months (appendix p 4). After supplementation (400–1000 IU per day, depending on degree of deficiency), total 25-hydroxyvitamin D concentrations increased from 23 nmol/L (IQR 14–44) to 66 nmol/L (36–83) at 6 weeks and to 69 nmol/L (45–88) at 6 months (table 2; figure 2).

Both patients with thrombi completed a course of anticoagulation (one with dalteparin and the other with rivaroxaban) without any concerns. Fibrinogen concentrations typically normalised by 6 weeks and remained normal at 6 months (table 2; figure 2).

Only one patient had 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 or dysgeusia (n=2), and dysphagia (n=1). Ear, nose, and throat (ENT) and speech and language therapy manifestations largely resolved by 6 months, with dysphonia in four children and anosmia or dysgeusia in two children, without clinically significant objective findings (figure 1). One patient required ongoing voice therapy at 6 months following hyaluronic acid injection into the right vocal fold after presumed iatrogenic injury from extracorporeal membrane oxygenation. No abnormalities in the cribriform plate or olfactory tract were found on imaging of patients with anosmia.

Three distinct rashes (hypopigmented [n=1], erythematous maculopapular [n=1], and 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.

The 6-min walk test done at 6 weeks showed that 20 (65%) of 31 patients walked less than the 3rd centile expected distance for their age and sex (table 3). At

	6 weeks (n=31)	6 months (n=40)
<3rd centile	20 (65%)	18 (45%)
3rd–10th centile	6 (19%)	5 (13%)
10th–25th centile	0	4 (10%)
25th–50th centile	3 (10%)	7 (18%)
50th–75th centile	0	6 (15%)
75th–90th centile	1 (3%)	0
>90th centile	1 (3%)	0

Table 3: **6-min walk test scores at 6 weeks' and 6 months' follow-up compared to normative values**

Figure 2: **Trends in serum markers (inflammatory, cardiac, renal, liver, and coagulation) at baseline, and at 6 weeks and 6 months of follow-up, for all 46 patients with PIMS-TS**

Green dotted lines represent the upper end of the normal range for all markers (except for lymphocyte count, minimum platelet count, and total 25-hydroxyvitamin D concentrations, for which the dotted line represents the lower end of normal). At each timepoint, the white box represents the median and IQR for all values of that serum marker. Blue lines represent an increase in values and red lines represent a decrease in values between the different timepoints. CRP=C-reactive protein. LDH=lactate dehydrogenase.

	Physical scale	Emotional scale	Social scale	School scale	Psychosocial scale	Total
Self report (n=38)						
No impairment	30 (79%)	24 (65%)	31 (84%)	32 (87%)	32 (87%)	24 (65%)
Mild impairment	5 (13%)	5 (14%)	4 (11%)	2 (5%)	2 (5%)	10 (27%)
Severe impairment	3 (8%)	8 (22%)	2 (5%)	3 (8%)	3 (8%)	3 (8%)
No data	0	1	1	1	1	1
Parental report (n=38)						
No impairment	25 (68%)	24 (63%)	31 (82%)	30 (79%)	26 (68%)	30 (79%)
Mild impairment	7 (18%)	7 (18%)	5 (13%)	4 (11%)	5 (13%)	1 (3%)
Severe impairment	5 (13%)	7 (18%)	2 (5%)	4 (11%)	7 (18%)	7 (18%)
No data	0	0	0	0	0	0

Table 4: **Frequency of self-reported and parent-reported mild and severe difficulties with the PedsQL 4.0 Generic Core scales at 6 months' follow-up**

6 months, 18 (45%) of 40 patients were below the 3rd centile. The median manual muscle test-8 score was 53 (IQR 43–64) at baseline and rose to 73 (65–78) at 6 weeks and to 80 (68–80) at 6 months. PedsQL responses revealed severe difficulties in physical functioning by parental report in five (13%) of 38 children and by self report in three (8%) children (table 4).

PedsQL responses across emotional, social, school, and psychosocial dimensions are shown in table 4. Emotional lability was reported in 12 (26%) of 46 patients at 6 weeks and in seven (15%) of 46 patients at 6 months. The median Paediatric Index of Emotional Distress score at 6 months was 6 (IQR 5–13), with three (7%) of 46 patients scoring above the clinical cutoff of 20, indicating a risk of clinically significant emotional distress. From the structured interview, 14 (31%) of 45 parents reported anxiety about a possible PIMS-TS relapse in their child, ten (22%) of 45 reported concerns about medical vulnerability of their child as a result of admission to hospital with PIMS-TS, and nine (20%) of 45 reported taking additional isolation precautions beyond UK Government guidance. 33 (73%) of 45 parents expressed sentiments of SARS-CoV-2 vaccine hesitancy. 45 (98%) of 46 patients were back in full-time education by 6 months (virtually or face to face).

Discussion

In this retrospective cohort study we described the natural history of, and longitudinal physical and psychological outcomes in, 46 patients with PIMS-TS. Demographic characteristics in this cohort were similar to those reported in previous studies, including the over-representation of ethnic minority groups; however, age and sex did not affect the clinical phenotype as previously reported.[1,13] Increased rates of ventilation were secondary to fluid overload from vascular leak and a consequence of sedation requirements, and not generally due to respiratory involvement. No patient died within 6 months, but many had residual new deficits. The majority of patients had severe multisystem involvement during their initial illness including gastrointestinal (98%), neurological (52%), and echo abnormalities (33%), which mostly resolved by 6 months. At the 6-month follow-up, common sequelae included muscular fatigue; neurological sequelae such as proximal myopathy, dysmetria, and abnormal saccades; and anxiety and emotional lability. Biochemical markers or inflammation resolved, and SARS-CoV-2 serology status remained positive in most patients, despite immunosuppression.

The notable reduction in functional exercise capacity in this cohort could be attributed to various factors: the underlying inflammatory nature of PIMS-TS; the high proportion of patients requiring PICU admission, resulting in the possibility of critical illness myopathy; non-compliance with home-based exercise programmes; a pre-illness sedentary lifestyle; and side-effects of high-dose corticosteroid use, which might have contributed to proximal myopathy and increased BMI at the initial 6-week follow-up.[14] These factors are additional to the lack of physical activity opportunities for all young people during the COVID-19 pandemic. Susceptibility to fatigue was still detected at 6 months. A similarly poor performance on the 6-min walk test has been described in adults with COVID-19, with 22–29% showing impairment in walking distance (depending on the severity cutoff).[15] Monitoring of functional abilities of patients with PIMS-TS upon return to school, resumption of sports, and increased physical demands with lessening of social restrictions will be of particular importance as subtle findings might become more prominent.

Neurological findings have also been reported commonly in other PIMS-TS cohorts.[16,17] In our cohort, persistence of subtle findings, which were only noticeable on detailed neurological exams, did not correlate with neurological functional impairment (median Expanded Disability Status Scale score 0 at 6 months). Although 98% of patients had resumed full-time education by 6 months, formal neuropsychology testing was not done and the long-term cognitive effects of PIMS-TS require attention given the high frequency of neurological involvement at presentation.

Although there were initial cardiac concerns, long-term cardiac consequences of PIMS-TS appear to be rare; acute findings are postulated to be a result of cardiac stunning rather than progressive endovascular changes observed in similar conditions, such as Kawasaki disease.[18,19] Nevertheless, two patients in our cohort had persistent changes to coronary arteries, most likely requiring long-term treatment.

Whether other longer-term sequelae will manifest beyond 6 months (eg, inflammatory gastrointestinal pathology or renal disease from acute kidney injury) is yet to be determined, stressing the importance of ongoing multidisciplinary follow-up of patients with PIMS-TS. Iatrogenic effects of steroids and other forms of immunomodulation on infection risk and re-admission to hospital,

and hypertension, as well as kidney, cardiac, and metabolic function require 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 children's lives might explain some of these findings; the PedsQL scores of the general paediatric population during the COVID-19 pandemic are not currently known. Furthermore, parental anxiety was exacerbated by the uncertainties associated with a new disease entity that had no known natural history. Acknowledging families' concerns during follow-up visits and building a trusting relationship between parents and physicians could reduce these anxieties and might 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 multidisciplinary care.[20] Outpatient multidisciplinary follow-up models have been successful in adults and neonates following intensive care admission and in chronic paediatric conditions such as diabetes and epilepsy.[21–23] Nevertheless, there is a scarcity of evidence for structured paediatric multidisciplinary approaches following PICU discharge, and the heterogeneity of multidisciplinary follow-up of adult patients admitted to ICU limits extrapolation of this knowledge to PICU settings.[24] The model of multidisciplinary care in the present study exemplifies the importance of knowledge sharing during the evolving COVID-19 epidemic.[25] This innovative care model for patients with PIMS-TS served to cultivate holistic care of patients while helping to define the natural history of a novel disease.

Limitations of this study include the single-centre design with a possibility of referral bias of the most unwell patients with PIMS-TS (ie, those requiring intensive care). Paediatric controls, both after PICU discharge for other illnesses as well as those unaffected by illness during the COVID-19 pandemic, were not available for comparison and thus the findings must be viewed as hypothesis generating. Similarly, baseline pre-illness testing was not available for analysis to determine functional changes after illness. The study is limited by the retrospective collection of clinically guided investigations, which accounts for variations in follow-up data among participants. Given the rarity of this condition, longer-term prospective multicentre studies would help to validate our findings and further our understanding of PIMS-TS. The strength of this study includes the medium-term holistic nature of the data, with only one patient lost to follow-up before the 6-week follow-up.

Irrespective of treatments received in the acute phase, our patients' outcomes were generally favourable, although severe sequelae did persist in some patients. The health outcomes reported in this study serve to provide guidance to families and health-care providers, and outline general expectations as they relate to the natural history of PIMS-TS.

Contributors

All authors take full responsibility for data collection, data analysis, and data interpretation, the conduct of the research, and submission of the manuscript. JP, OA-M, YH, and KM conceptualised the study. JP and OA reviewed the extracted data from patient records, and reviewed and verified the data contained in the manuscript. All authors were involved in data interpretation and editing of the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication. All authors have seen and approved the final manuscript.

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Declaration of interests

We declare no competing interests.

Data sharing

De-identified patient datasets will be available upon written request to the corresponding author following publication.

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