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Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study

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Summary

Background In April, 2020, clinicians in the UK observed a cluster of children with unexplained inflammation requiring admission to paediatric intensive care units (PICUs). We aimed to describe the clinical characteristics, course, management, and outcomes of patients admitted to PICUs with this condition, which is now known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).

Methods We did a multicentre observational study of children (aged <18 years), admitted to PICUs in the UK between April 1 and May 10, 2020, fulfilling the case definition of PIMS-TS published by the Royal College of Paediatrics and Child Health. We analysed routinely collected, de-identified data, including demographic details, presenting clinical features, underlying comorbidities, laboratory markers, echocardiographic findings, interventions, treatments, and outcomes; serology information was collected if available. PICU admission rates of PIMS-TS were compared with historical trends of PICU admissions for four similar inflammatory conditions (Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome).

Findings 78 cases of PIMS-TS were reported by 21 of 23 PICUs in the UK. Historical data for similar inflammatory conditions showed a mean of one (95% CI 0·85–1·22) admission per week, compared to an average of 14 admissions per week for PIMS-TS and a peak of 32 admissions per week during the study period. The median age of patients was 11 years (IQR 8–14). Male patients (52 [67%] of 78) and those from ethnic minority backgrounds (61 [78%] of 78) were over-represented. Fever (78 [100%] patients), shock (68 [87%]), abdominal pain (48 [62%]), vomiting (49 [63%]), and diarrhoea (50 [64%]) were common presenting features. Longitudinal data over the first 4 days of admission showed a serial reduction in C-reactive protein (from a median of 264 mg/L on day 1 to 96 mg/L on day 4), D-dimer (4030 µg/L to 1659 µg/L), and ferritin (1042 µg/L to 757 µg/L), whereas the lymphocyte count increased to more than $1·0 \times 10^9$ cells per L by day 3 and troponin increased over the 4 days (from a median of 157 ng/mL to 358 ng/mL). 36 (46%) of 78 patients were invasively ventilated and 65 (83%) needed vasoactive infusions; 57 (73%) received steroids, 59 (76%) received intravenous immunoglobulin, and 17 (22%) received biologic therapies. 28 (36%) had evidence of coronary artery abnormalities (18 aneurysms and ten echogenicity). Three children needed extracorporeal membrane oxygenation, and two children died.

Interpretation During the study period, the rate of PICU admissions for PIMS-TS was at least 11-fold higher than historical trends for similar inflammatory conditions. Clinical presentations and treatments varied. Coronary artery aneurysms appear to be an important complication. Although immediate survival is high, the long-term outcomes of children with PIMS-TS are unknown.

Funding None.

Introduction

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with nearly 10·5 million infections and more than 500 000 deaths worldwide as of June 30, 2020.[1] Although approximately 3–5% of adults with SARS-CoV-2 infection require admission to critical care,[2,3] children appear to be relatively spared in terms of both frequency and severity of illness.[4–7] Data published so far indicate that the main reason for admission to intensive care units in children with COVID-19, similar to adults, has been respiratory disease, particularly in children with comorbidities.[8]

From mid-April to early May, 2020, a cluster of children presenting to paediatric intensive care units (PICUs) in the UK with an unexplained multisystem inflammatory

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Research in context

Evidence before this study

Recent reports of a novel inflammatory syndrome resembling Kawasaki disease and toxic shock syndrome in children from many parts of the world represent an important and poorly understood aspect of the evolving COVID-19 pandemic. An initial case definition has been published for this syndrome, called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), in the UK. We searched PubMed up to June 18, 2020, without any date limits or language restrictions, using different combinations of the search terms "paediatric inflammatory multi-system syndrome", "multisystem inflammatory syndrome in children", "atypical Kawasaki", "inflammatory syndrome", "intensive care units, "critical care" OR "critical illness" OR "intensive care", "ICU" OR "PICU". Published reports of PIMS-TS cases so far represent single-centre case series and convenience samples, precluding a detailed analysis of clinical presentations and outcomes, especially in the subset of children requiring critical care.

Added value of this study

This multicentre observational study is the largest cohort of critically ill children with PIMS-TS reported so far, the first nationwide report, and, to the best of our knowledge, the first to describe longitudinal data. Coronary artery abnormalities were seen in a third of cases. Comparisons with historical data indicate at least an 11-fold increase in intensive care admissions for children with an inflammatory syndrome during a 6-week period in April–May, 2020.

Implications of all the available evidence

A small but important number of children in the UK are requiring critical care admission for an unexplained multisystem inflammatory syndrome that might be associated with the COVID-19 pandemic. Uncertainties about the underlying basis of this syndrome and lack of evidence about optimal treatments and follow-up have led to considerable variation in clinical management. Urgent efforts to recruit patients to robust clinical trials of potential treatments to reduce longer-term morbidity (eg, coronary artery aneurysm formation and evolution) are needed to inform clinical practice.

syndrome triggered an alert by NHS England and the UK Paediatric Intensive Care Society.[9] Children with this multisystem illness appeared to have overlapping features of Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome.[10] Since then, similar cases have been reported in the USA[11] and Europe,[12] and received media coverage in the UK.[13] On May 1, 2020, the Royal College of Paediatrics and Child Health (RCPCH) published a case definition and guidance related to this multisystem illness,[10] defining it as a persistent fever, inflammation, and evidence of single or multi-organ dysfunction in a child, with exclusion of any other microbial cause, with or without PCR evidence of SARS-CoV-2. In the UK this condition has become known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), and in the USA it has been defined as multisystem inflammatory syndrome in children (MIS-C), with a more restrictive case definition than that of PIMS-TS.[11] Details about some PIMS-TS cases from the UK and Italy have been published; however, these reports were from single centres or convenience samples, and did not provide detailed longitudinal data to assist in a better understanding of the trajectory and outcome of this condition.[14–16] The majority of children in these studies had a negative PCR test for the SARS-CoV-2 antigen, but had evidence of antibodies, indicating past infection.[14–16] Some of the patients reported in these cohorts were admitted to intensive care units and are therefore included in this Article.

The fact that PIMS-TS has overlapping features with Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome has triggered debate as to whether this is a new condition or an unusual, more severe variant of these previously well known conditions requiring management in the PICU.[17] Comparisons with previous critical care admission rates of patients with inflammatory syndromes are important to ensure that this condition does not reflect an inadvertent re-analysis of the background rate of an already known pathology. Improved knowledge of the clinical course in the subset of children with PIMS-TS needing PICU admission is important to raise awareness about this condition and to identify the main areas of variation in clinical management. We aimed to describe the clinical characteristics, treatments, and outcomes of a cohort of children admitted to PICUs with PIMS-TS in the UK over a 40-day period in April–May, 2020, and to provide the first national report of these patients.

Methods

Study design and participants

We did a multicentre observational study of children aged 18 years or younger who were admitted to PICUs in the UK over a 40-day period (April 1 to May 10, 2020), and who fulfilled the case definition of PIMS-TS.[10] This project was classified as a service evaluation by the Nottingham Research and Innovation team (Nottingham Clinical Effectiveness Team reference 20–235C), and ethics approval was not required. The study team analysed routinely collected de-identified data submitted by

clinicians from the individual PICUs as a local service evaluation. Clinicians obtained written informed consent from parents if required locally. Data were submitted for central analysis by use of a secure, web-based survey tool (SurveyMonkey, San Mateo, CA, USA) and included demographic details, presenting clinical features, underlying comorbidities, laboratory markers, echocardiographic findings, interventions, treatments, and outcomes (survival following discharge from PICU and duration of PICU stay). Serology information was collected if available.

Procedures

We classified comorbidities as minor if primary care management would ordinarily be sufficient (eg, mild asthma), and major if hospital-based management would ordinarily be required (eg, sickle cell disease). Ethnicity was described with UK Government standard groups and compared with reported population rates.[18] We calculated the ratio of observed weight to expected weight (based on the 50th percentile weight for age and sex). Characterisation of shock into vasodilated or vasoconstricted shock was based on the treating clinician's judgment. There were no interventions as part of this study. Investigations and patient management were at the discretion of the relevant responsible medical teams. All patients had SARS-CoV-2 antigen tests done by reverse transcriptase PCR. Serology testing for SARS-CoV-2 was done where available.

The Paediatric Intensive Care Audit Network (PICANet) dataset contains prospectively collected diagnoses for patients admitted to PICUs in the UK. Anonymised summary data were provided for a 5-year period (Jan 1, 2015, to Dec 31, 2019) for all patients admitted to all 23 UK PICUs with a primary diagnosis of four similar inflammatory conditions (Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome). The database was searched for Read(CTV3) codes Y70QV, XUauZ, G7510, A3Ay1, X70Il, X20E8, XUwry, X20E7, and XUgRm. PICANet reports all incidences lower than five per week as "<5".

Statistical analysis

Results are presented as numbers and proportions for categorical data and as medians and IQRs for continuous data. Data analyses were done in Microsoft Excel 2010.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Data on 78 patients admitted to PICUs between April 1 and May 10, 2020, and meeting the case definition for PIMS-TS were submitted. Initial presenting features of 29 of these patients have been reported in a recent study[16] focusing on the definition of this novel condition (eight of these 29 patients had previously been described in a correspondence article[14]). Cardiac features in six patients and renal features in 23 patients have also been presented in single-centre reports.[19,20] Details of presentation, intensive care course, evolution in treatment over time, and longitudinal laboratory data in a national cohort have not been published previously. Of the 23 National Health Service (NHS) hospital trusts with PICUs in the UK, 15 submitted PIMS-TS data (median three per unit, range 1–24), four reported zero patients, and two were not admitting any children during the study period (having been converted to adult ICUs during the COVID-19 surge). The two closed units were cardiac units, and their paediatric patients were admitted to neighbouring PICUs. Two PICUs did not share data. The total number of PICU admissions of PIMS-TS cases by week (and the cumulative number of admissions) are shown in figure 1. The cumulative expected number of admissions derived from historical UK PICANet data for similar inflammatory conditions requiring PICU admission is also shown, showing an increase in cases above the expected number from the week beginning April 20.

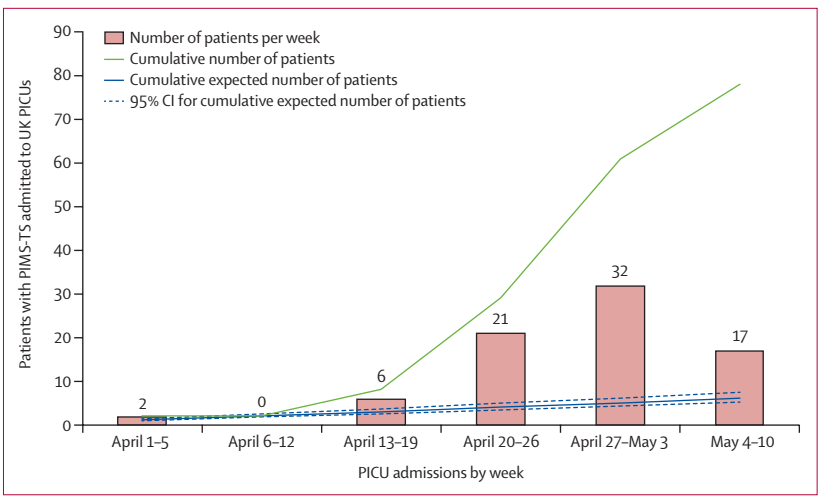

Figure 1: **PIMS-TS admissions per week to UK PICUs, April 1 to May 10, 2020**
The cumulative total, and the expected UK cumulative total of similar conditions (Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome) from the previous 5 years are shown. PICU=paediatric intensive care unit. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

Characteristics of patients are summarised in table 1. The median age was 11 years (IQR 8–14), and two-thirds of patients were male. Only two patients had major comorbidities, and 61 (78%) had none. Patients from Afro-Caribbean and Asian backgrounds were over-represented. In the UK the proportion of children aged 10–14 years from an Asian background is 7% and that of children aged 10–14 years from an Afro-Caribbean background is 8%;[18] by contrast, 28% of patients in this cohort were Asian and 47% were Afro-Caribbean.

For more on the **Paediatric Intensive Care Audit Network** see https://www.picanet.org.uk/

	Patients (n=78)
Sex	
Female	26 (33%)
Male	52 (67%)
Age groups	
<1 year	2 (3%)
1–4 years	5 (6%)
5–10 years	29 (37%)
11–15 years	38 (49%)
16–17 years	4 (5%)
Median age, years	11 (8–14)
Median observed to expected weight ratio	1·22 (1·06–1·41)
Known contact with a COVID-19 case	8 (10%)
Comorbidities	
None	61 (78%)
Usually expected to require primary care	15 (19%)
Usually expected to require hospital care	2 (3%)
Ethnicity*	
Afro-Caribbean	37 (47%; 37–58)
Asian	22 (28%; 19–39)
White	17 (22%; 14–32)
Other	2 (3%; 0–9)
SARS-CoV-2 antigen PCR positive	17 (22%)
SARS-CoV-2 antigen PCR negative	61 (78%)
SARS-CoV-2 IgG serology in PCR positive patients	
Positive	9/10 (90%)
Negative	1/10 (10%)
Not tested	7/17 (41%)
SARS-CoV2 IgG serology in PCR negative patients	
Positive	24/25 (96%)
Negative	1/25 (4%)
Not tested	36/61 (59%)
PCR negative, serology negative, without known COVID-19 contact (ie, met PIMS-TS criteria, did not meet MIS-C criteria)	1/78 (1%)
PCR negative, serology unknown, without known COVID-19 contact (met PIMS-TS criteria, unknown whether would meet MIS-C criteria)	32/78 (41%)
Infections with non-SARS-CoV-2 pathogens	
None	75 (96%)
Bacterial	2 (3%)
Viral	1 (1%)
Outcome	
Discharged from critical care	75 (96%)
Still on critical care	1 (1%)
Died	2 (3%)
Thrombus	3 (4%)
Median length of stay, days (n=71)	5·0 (3·0–6·5)
Clinical presenting features	
Fever	78 (100%)
Shock	68 (87%)
Vasodilated	55 (71%)
Vasoconstricted	13 (17%)
Abdominal pain	48 (62%)
Diarrhoea	50 (64%)
Vomiting	49 (63%)
Any abdominal symptom (pain, diarrhoea, or vomiting)	70 (90%)
Rash	35 (45%)
Conjunctivitis	23 (29%)

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. MIS-C=multisystem inflammatory syndrome in children. *Data are n (%; 95% CI).

Table 1: **Demographics and clinical features of 78 patients presenting with PIMS-TS to paediatric intensive care units in the UK**

Three patients had co-infections, one viral and two bacterial. None was judged to be clinically causative.

Common presenting features were fever, shock (usually vasodilated), abdominal pain, diarrhoea, and vomiting (table 1). 70 (90%) of 78 patients presented with at least one abdominal symptom. Rash was seen in 35 (45%) patients) and conjunctivitis in 23 (29%). Of 35 patients tested for SARS-CoV-2 IgG serology, 33 were positive, and one of the two negative serology patients was PCR positive. Of the 78 patients in our cohort, 45 (58%) also met all criteria for a MIS-C diagnosis; of the remaining 33 patients, one would definitely not have met MIS-C criteria and 32 did not have a serology test and therefore their MIS-C status could not be determined (appendix).

See Online for appendix

Longitudinal data for the first 4 days of admission are presented in table 2. Data were available for all 78 patients on day 1, and for 36 patients throughout the first 4 days, as we only included data for patients still on intensive care. Patients presented with elevated C-reactive protein, D-dimer, and ferritin, troponin, and lymphopenia. Longitudinal data over the first 4 days of admission showed a reduction in C-reactive protein, D-dimer, and ferritin concentrations towards normal levels. The neutrophil count was stable, although raised, and creatinine and alanine aminotransferase concentrations remained normal. The lymphocyte count increased and the median rose above $1{\cdot}0\times10^9$ cells by day 3. The troponin concentration increased over the first 4 days of admission.

Historical data on the incidence of PICU admissions for the four similar inflammatory conditions (Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome) between 2015 and 2019 showed that the average number of admissions to all UK PICUs combined for the four inflammatory conditions was one admission (95% CI 0·8–1·22) per week, and the annual total number of admissions ranged from 44 to 67. Over the

	Reference ranges	Day 1 (n=78)	Day 2 (n=44)	Day 3 (n=43)	Day 4 (n=36)
Neutrophil count (×10⁹ cells per L)	2·0–7·5	12·3 (10·7–22·9)	13·2 (9·2–17·6)	13·0 (8·9–19·4)	11·9 (7·2–20·0)
Lymphocyte count (×10⁹ cells per L)	1·5–4·0	0·7 (0·4–1·1)	0·9 (0·7–1·6)	1·2 (0·9–1·7)	1·8 (1·0–2·3)
Platelet count (×10⁹ cells per L)	150–400	125 (75–178)	179 (115–272)	187 (109–293)	201 (100–358)
C-reactive protein (mg/L)	<5	264 (192–316)	233 (143–308)	191 (77–283)	96 (39–197)
D-dimer (µg/L)	<500	4030 (2349–7422)	2293 (1319–4638)	3503 (1902–5291)	1659 (646–3792)
Ferritin (µg/L)	12–200	1042 (538–1746)	1152 (473–1529)	842 (495–1422)	757 (484–1198)
Troponin (ng/L)	<10	157 (43–810)	232 (70–829)	355 (66–2252)	358 (30–3015)
Creatinine (µmol/L)	60–120	75 (46–103)	54 (41–77)	48 (34–67)	49 (32–64)
ALT (IU/L)	10–50	50 (30–93)	51 (27–77)	43 (30–68)	51 (35–71)

Data are median (IQR). PICU=paediatric intensive care unit. ALT=alanine aminotransferase.

Table 2: **Laboratory results for the first 4 days of PICU admission**

past 5 years, the highest number of total national admissions was for toxic shock syndrome (n=119) and for haemophagocytic lymphohistiocytosis and macrophage activation syndrome (n=114); Kawasaki disease was less common (30–40 admissions in total; exact numbers were not available due to the small numbers). Full details are provided in the appendix. During the study period, the average number of weekly admissions for PIMS-TS to UK PICUs was 14 (at least 11 times greater than expected for similar conditions), peaking at 32 (at least a 26-fold increase).

Critical care interventions, treatments, and outcomes are shown in table 3. Overall, 36 (46%) of 78 children were invasively ventilated, and three (4%) required extracorporeal membrane oxygenation. A variety of therapies were given, with 59 (76%) of 78 patients receiving intravenous immunoglobulin and 57 (73%) requiring steroids. 17 (22%) of 78 patients received biologic immunomodulation agents (eight received anakinra, seven received infliximab, three received tocilizumab, and one received rituximab; and two patients received two biologics). One child was treated with an antiviral therapy (remdesivir). Treatments were varied and inconsistent; however, over the study period, the proportion of patients being given each therapy increased over time (figure 2). The proportion of patients receiving vasoactive infusions remained constant (five [83%] of six in week 3, 17 [81%] of 21 in week 4, 27 [84%] of 32 in week 5, and 14 [82%] of 17 in week 6), but the proportion of patients on invasive ventilation dropped from five (83%) of six in week 3 to two (12%) of 17 by week 6. Three (4%) patients had significant thrombi, with no pulmonary emboli. Seven (9%) patients received therapeutic anticoagulation (table 3), either due to thrombi or due to concerns about diffuse microthrombi.

A third (28 [36%] of 78) of patients were found to have coronary artery abnormalities on echocardiography during PICU admission. 18 had evidence of aneurysms and ten had coronary arteries that were characterised as unusually echogenic. There were no obvious differences in the demographics, presenting features, or level of invasive therapies between patients with any coronary artery abnormality and those with normal coronary arteries, or those who were invasively ventilated and those who were not (table 4).

	Patients (n=78)
Highest level of respiratory support	
No respiratory support	12 (15%)
Oxygen only	12 (15%)
High flow nasal cannula therapy	13 (17%)
Non-invasive ventilation	5 (6%)
Invasive mechanical ventilation	36 (46%)
Extracorporeal membrane oxygenation	3 (4%)
Cardiovascular support	
Fluid bolus	72 (92%)
Inotropic or vasoactive infusion	65 (83%)
Renal replacement therapy	1 (1%)
Drug therapies	
Antibiotics	78 (100%)
Steroids	57 (73%)
Intravenous immunoglobulin	59 (76%)
Immunomodulation with biologic agents*	17 (22%)
Anakinra	8 (10%)
Infliximab	7 (9%)
Tocilizumab	3 (4%)
Rituximab	1 (1%)
Aspirin or other antiplatelet therapy	45 (58%)
Anticoagulation	
Prophylactic	32 (41%)
Therapeutic	7 (9%)
Antiviral therapy (remdesivir)	1 (1%)

PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *Two patients received two biologics: one received anakinra and retuximab; the other received anakinra and infliximab.

Table 3: **Interventions for patients with PIMS-TS admitted to paediatric intensive care units**

Discussion

This report describes the characteristics and outcomes of the largest cohort of patients admitted to the PICU to date with the newly described and unexplained multisystem inflammatory syndrome named PIMS-TS in the UK. This

report is, to the best of our knowledge, the first to describe a national cohort, give full details of the presentation, clinical course on intensive care, and treatments, and also demonstrate longitudinal laboratory results.

We found that the number of UK PICU admissions for PIMS-TS during a 40-day study following the surge of COVID-19 in the UK significantly exceeded the historical numbers of admissions for four inflammatory conditions with overlapping clinical features. These patients were critically unwell with multisystem disease. Although this increase in the number of patients was unexpected, it is still a small proportion of the usual expected 250 unplanned paediatric intensive care admissions in the UK per week, as reported by PICANet. By May 10, around 220 000 people in the UK had tested positive for SARS-CoV-2 infection. Previous data have shown a paediatric symptomatic infection rate of around 2% of the total rate of SARS-CoV-2 infection, which would equate to around 5000 children infected with the virus. This means that the incidence of PIMS-TS requiring intensive care would be 1·5%.

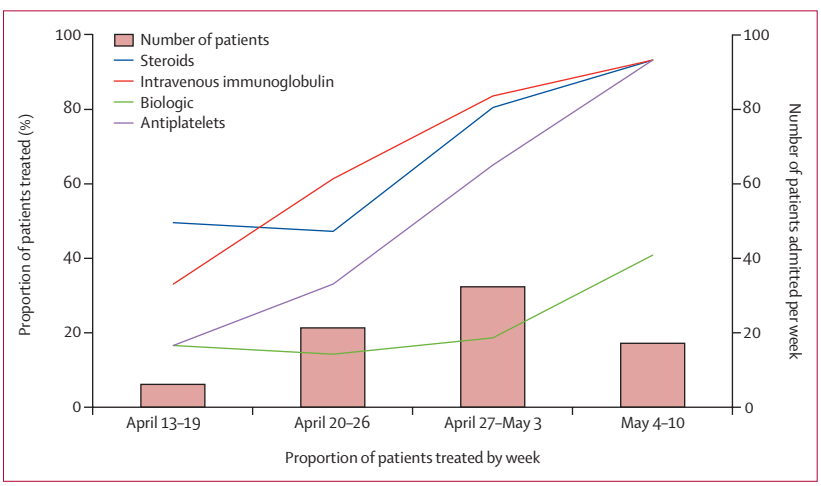

Figure 2: **Number of patients with PIMS-TS admitted to UK paediatric intensive care units, and percentage receiving individual treatments over time**
Weeks with fewer than three patients were excluded. Biologic refers to any of anakinra, infliximab, tocilizumab, or retiximab. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

The emergence of this condition in children might also have a social impact. Until now, the risk of serious illness resulting from COVID-19 in children has been thought to be negligible: even though the risk is still low, there are implications for health-care resources and balancing the need for adult and paediatric intensive care units. Our data also have important implications for any future peaks of PIMS-TS, especially if the rise in cases coincides with a winter surge of other viral infections.

Viral sepsis with SARS-CoV-2 infection has been well described in adults.[21] Such patients meet clinical criteria for shock, are generally SARS-CoV-2 positive on PCR from respiratory secretions, and have predominantly pulmonary, renal, hepatic, and cardiac involvement. Coagulopathy is a feature in adults. In comparison, although D-dimers were high in patients with PIMS-TS, other coagulation tests were usually normal. The notable absence of severe pulmonary and renal symptoms in PIMS-TS is a further differentiating factor between adults presenting with viral sepsis and children presenting with PIMS-TS.

Although Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, and macrophage activation syndrome are four well known inflammatory conditions in children, they cause illnesses that rarely

	Any coronary artery abnormality (n=28)	No coronary artery abnormality (n=50)	Invasively ventilated (n=36)	Not invasively ventilated (n=42)
Median age, years	11 (7–13)	11 (8–14)	10 (8–13)	11 (6–14)
Male sex	16 (57%)	34 (68%)	23 (64%)	29 (69%)
Non-white	23 (82%)	38 (76%)	29 (81%)	32 (76%)
Highest CRP (mg/L)	227 (166–292)	283 (206–328)	294 (225–355)	227 (179–298)
Lowest platelet count (×10^9 cells per L)	143 (95–164)	150 (83–197)	125 (81–168)	151 (96–185)
Lowest lymphocyte count (×10^9 cells per L)	0·70 (0·4–1·2)	0·72 (0·5–1·0)	0·74 (0·5–51·0)	0·70 (0·4–1·1)
Highest ferritin (µg/L)	1205 (536–2468)	1156 (563–1803)	1205 (653–2124)	858 (449–1506)
Highest troponin (ng/L)	187 (49–574)	120 (21–818)	253 (68–892)	147 (45–809)
Highest D-dimers (ng/L)	4990 (2425–7691)	4080 (2538–7537)	4897 (3350–9420)	3660 (2021–6409)
Rash	11 (39%)	22 (44%)	15 (42%)	20 (48%)
Conjunctivitis	9 (32%)	13 (26%)	8 (22%)	15 (36%)
Shock	26 (93%)	42 (84%)	30 (83%)	38 (90%)
Invasively ventilated	10 (36%)	26 (52%)	NA	NA
Inotropic infusion	24 (86%)	41 (82%)	32 (89%)	33 (79%)
Given intravenous immunoglobulin	26 (93%)	33 (66%)	26 (72%)	33 (79%)
Given steroids	25 (89%)	32 (64%)	26 (72%)	31 (74%)

Data are n (%) or median (IQR). CRP=C-reactive protein. NA=not applicable.

Table 4: **Comparison of key demographic characteristics, laboratory tests, therapies, and other presenting features in patients with or without any coronary abnormalities, and those who were invasively ventilated and those who were not**

require PICU admission.[22] The presenting features of these four conditions partially overlap with the presenting features of PIMS-TS; however, none of these conditions was fully consistent with the clinical presentation and natural history seen in our report. Although the case definition for PIMS-TS is broad, there are some definitive blood markers that were largely shared by the cohort. We used the published case definition, which might include some cases that would previously have been diagnosed with Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, or macrophage activation syndrome. Kawasaki disease has been known to have some seasonality,[23] with peaks in presentation up to 2·5 times the background expected rate, including a known association with other coronavirus infections;[24] however, this association is unlikely to account for the fluctuation seen in this study. Kawasaki shock syndrome shares the main features of the clinical presentations detailed in this report, including shock; however, the younger age of patients (<5 years), longer duration of fever, more consistent mucosal involvement, and lack of abdominal symptoms distinguish it from PIMS-TS.[25]

A few days after our study ended, the US Centers for Disease Control and Prevention (CDC) published a more restrictive case definition for MIS-C, which required evidence of COVID-19 exposure within the 4 weeks before the onset of symptoms. Only one patient who met the PIMS-TS definition would definitely not have met the MIS-C criteria. It was unclear whether 32 (41%) of our 78 patients met the stricter MIS-C definition because at the time of presentation many UK hospitals were not offering SARS-CoV-2 serology testing. Both criteria were met in 45 (58%) patients. Emerging evidence of asymptomatic carriers of SARS-CoV-2 also suggests that cases might have unknowingly been in contact with carriers of SARS-CoV-2.[26] It is unclear whether the CDC definition is more sensitive or specific than the RCPCH definition in identifying true cases. A comparison of patients who met the CDC criteria and those in whom the CDC criteria were unclear did not show any clear differences.

Our findings have several clinical implications. First, the notable absence of significant respiratory involvement, the low incidence of positive SARS-CoV-2 PCR tests, and the presence of SARS-CoV-2 antibodies in 24 (96%) of 25 patients who were tested following a negative SARS-CoV-2 PCR indicates that PIMS-TS might represent a post-COVID-19 immunological disease that is clinically distinct from acute COVID-19 in children. The low numbers of patients tested for antibody serology was due to the unavailability of the test in those PICUs at that time. Therefore, the value of antiviral drugs in these cases is unclear. Only one patient was treated with remdesivir, who was positive on PCR for SARS-CoV-2. Second, the heterogeneity in clinical presentation seen with PIMS-TS, and variable overlap with previously described entities—such as atypical Kawasaki disease, toxic shock syndrome, haemophagocytic lymphohistiocytosis, or macrophage activation syndrome—meant that there was substantial variation in the range of immunomodulatory treatments given to these children. There is currently no evidence as to which treatments are beneficial, highlighting the need for urgent robust clinical trials; the RECOVERY trial aims to include patients with PIMS-TS. Third, the frequency and extent of multisystem involvement indicates that a multidisciplinary approach (general paediatrics, infectious diseases, cardiology, intensive care, haematology, immunology, pharmacy, and rheumatology) is important for clinical management of these patients. Finally, the lack of long-term follow-up data on these children means that it is difficult to anticipate and plan for their community health-care and surveillance needs following recovery. It is unknown whether these patients might have long-term health problems, particularly those with echocardiographic abnormalities of coronary arteries. We did not identify any differences in clinical presentation or laboratory data to indicate potential prognostic factors for prediction of coronary artery abnormalities.

For more on the **RECOVERY trial** see https://www.recoverytrial.net

The numbers of children from Asian and Afro-Caribbean backgrounds were higher than expected. This finding is consistent with the higher rates of adult patients from ethnic minority backgrounds seen with severe clinical presentations of COVID-19,[27] but higher than expected from previous paediatric intensive care data.[28] A link between ethnicity, incidence, and outcomes is increasingly being recognised in the UK.[27,29] The causes behind this association are not clear, but socioeconomic factors, comorbidities, and differences in the expression of angiotensin converting enzyme 2 have been implicated.[27] We used UK data as our comparison denominator in our study; although the COVID-19 pandemic has affected all regions of the UK, there are regional differences in ethnic group prevalence, and so any regional differences in PIMS-TS incidence might be linked to this regional variation.

In the present study 67% of patients were male; by contrast, in a recent cross-sectional study of children with COVID-19 admitted to 46 PICUs in the USA and Canada, 52% of patients were male.[8] However, the higher proportion of male patients in our study was similar to the experience in adult intensive care in the UK.[29]

The strengths of our study include the multicentre data coverage (data were submitted by the vast majority of PICUs in the UK) and depth of clinical detail captured. Comparison with reliable, historical data from PICANet allowed us to demonstrate a step-change in the need for PICU admission for inflammatory conditions during the COVID-19 pandemic. The main limitation of the study is the retrospective nature of data collection; however, given the relatively short study period, the time interval between PICU admission and data collection was minimal. We are unable to offer any conclusions about the immunological basis behind PIMS-TS, or provide long-term data on these patients, since our study was not designed to do so.

We used PICANet data as the denominator because PICANet has a robust mechanism to obtain national information related to critical care and is audited to ensure consistency. Ensuring 100% case ascertainment was not possible and therefore the numbers might be an underestimate of PICU admissions. The selection of conditions covered by the PICANet search might not have covered all inflammatory conditions, and it is likely that a small number of patients with undiagnosed multisystem inflammatory illnesses were not included in our PICANet search. Moreover, it is likely that a large population of affected patients did not need critical care admission and we might be underestimating the true incidence of PIMS-TS in the hospital population. Recently launched national initiatives (by PICANet and the British Paediatric Surveillance Unit[30]) to study this condition will gather ongoing data. It is unlikely that clinical practice was influenced by the RCPCH alert, as 51 of 78 patients predated the alert. The true incidence of coronary artery aneurysms and other complications will become clearer with longer-term follow-up data. We did not capture the rationale for specific therapies used. Additional therapies that could have been provided after discharge from PICU would not have been captured.

We were also unable to find any clear correlations of presenting features, laboratory tests, and treatments, with the risk of having coronary artery abnormalities or being invasively ventilated. This limitation has implications for those patients who were not unwell enough to be admitted to the intensive care unit. We advise caution and close follow-up for all patients diagnosed with PIMS-TS.

In conclusion, in this large national cohort of children requiring critical care admission for the novel inflammatory condition known as PIMS-TS, we saw significant short-term morbidity in terms of the need for critical care interventions, but mortality was low. Nearly a third of patients had coronary artery abnormalities, although the long-term outcomes for these findings are unclear. An increasing proportion of patients received immunomodulatory therapies during the course of the study period; however, there is as yet no evidence to support any specific treatment, and supportive intensive care remains important. Further evidence from clinical trials and long-term follow-up studies is crucial to inform clinical practice.

Contributors

PD, CE, EW, HV, BRS, and PR contributed to the literature search. PD and CE contributed to the figures. PD, BRS, and PR contributed to study design. PD, CE, HKK, JL, JB, GW, MJo, BG, PdP, ZM, AD, SP, DS, DI, MJa, OR, NS, MW, RS, and AK contributed to data collection. PD, CE, EW, HV, BRS, and PR contributed to data analysis. PD, CE, HKK, JL, JB, GW, MJo, BG, PdP, ZM, AD, SP, DS, DI, MJa, OR, NS, MW, RS, AK, EW, HV, BRS, and PR contributed to data interpretation. PD, CE, HKK, JL, JB, GW, MJo, BG, PdP, ZM, AD, SP, DS, DI, MJa, OR, NS, MW, RS, AK, EW, HV, BRS, and PR contributed to writing of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Requests for data should be made to the corresponding author.

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References

1 WHO. Coronavirus disease (COVID-19) situation report – 162. June 30, 2020. https://www.who.int/docs/default-source/coronaviruse/20200630-covid-19-sitrep-162.pdf?sfvrsn=e00a5466_2 (accessed July 1, 2020).

2 WHO. Coronavirus disease (COVID-19) situation report – 41. March 1, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200301-sitrep-41-covid-19.pdf (accessed May 16, 2020).

3 CDC. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. March 18, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm (accessed May 16, 2020).

4 Wu Z, McGoogan J. Characteristics and important lessons from the coronavirus disease 2019 outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323:** 1239–42.

5 CDC. Coronavirus disease 2019 in children — United States, February 12–April 2, 2020. April 6, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm (accessed May 16, 2020).

6 Parri N, Lenge M, Buonsenso D, Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in pediatric emergency departments in Italy. *N Engl J Med* 2020; published online May 1. https://doi.org/10.1056/NEJMc2007617.

7 Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr* 2020; published online April 8. https://doi.org/10.1001/jamapediatrics.2020.1346.

8 Shekerdemian L, Mahmood N, Wolfe K, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr* 2020; published online May 11. https://doi.org/10.1001/jamapediatrics.2020.1948.

9 Paediatric Intensive Care Society. PICS Statement: increased number of reported cases of novel presentation of multisystem inflammatory disease. April 27, 2020. https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-27042020.pdf (accessed May 16, 2020).

10 Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. May 1, 2020. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf (accessed May 16, 2020).

11 CDC. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). May 14, 2020. https://emergency.cdc.gov/han/2020/han00432.asp (accessed May 16, 2020).

12 Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and *Novel Case Hosp Pediatr* 2020; **10:** 537–40.

13 BBC. Coronavirus alert: rare syndrome seen in UK children. April 27, 2020. https://www.bbc.co.uk/news/health-52439005 (accessed May 16, 2020).

14 Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395:** 1607–08.

15 Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020; **395:** 1771–78.

16 Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; published online June 8. https://doi.org/10.1001/jama.2020.10369.

17 European Centre for Disease Prevention and Control. Rapid risk assessment: paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children. May 15, 2020. https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment (accessed May 16, 2020).

18 Office for National Statistics. 2011 Census: aggregate data [data collection]. UK Data Service. SN: 7427. 2020. https://doi.org/10.5257/census/aggregate-2011-2 (accessed July 3, 2020).

19 Ramcharan T, Nolan O, Lai CY, et al. Paediatric inflammatory multisystem syndrome: temporally associated with SARS-CoV-2 (PIMS-TS): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. *Pediatr Cardiol* 2020; published online June 12. https://doi.org/10.1007/s00246-020-02391-2.

20 Stewart D, Harley J, Johnson M, et al. Renal dysfunction in hospitalised children with COVID-19. *Lancet Child Adolesc Health* 2020; published online June 15. https://doi.org/10.1016/S2352-4642(20)30178-4.

21 Li H, Lui L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet* 2020; **395:** 1517–20.

22 Hall GC, Tulloh LE, Tulloh RM. Kawasaki disease incidence in children and adolescents: an observational study in primary care. *Br J Gen Pract* 2016; **66:** e271–76.

23 Burns J, Herzog L, Fabri O, et al. Seasonality of Kawasaki disease: a global perspective. *PLoS One* 2013; **8:** e74529.

24 Chang LY, Lu CY, Shao PL, et al. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014; **113:** 148–54.

25 Kanegaye JT, Wilder MS, Molkara D. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009; **123:** 783–89.

26 Arons M, Hatfield K, Reddy S, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med* 2020; **382:** 2081–90.

27 Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of COVID-19? *BMJ* 2020; **369:** m1548.

28 Parslow RC, Tasker RC, Draper ES, et al. Epidemiology of critically ill children in England and Wales: incidence, mortality, deprivation and ethnicity. *Arch Dis Child* 2009; **94:** 210–15.

29 Intensive Care National Audit and Research Centre. ICNARC report on COVID-19 in critical care. https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports (accessed May 16, 2020).

30 Royal College of Paediatrics and Child Health. BPSU study—multisystem inflammatory syndrome, Kawasaki disease and toxic shock syndrome. https://www.rcpch.ac.uk/work-we-do/bpsu/study-multisystem-inflammatory-syndrome-kawasaki-disease-toxic-shock-syndrome (accessed May 16, 2020).