

# Acute kidney injury in paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) is not associated with progression to chronic kidney disease

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## ABSTRACT

**Background** Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) is a rare complication of SARS-CoV-2 associated with single or multiorgan dysfunction.

**Objective** We aimed to evaluate the incidence of acute kidney injury (AKI) and risk factors for kidney dysfunction in PIMS-TS, with reporting of 6-month renal follow-up data. We also evaluated renal involvement between first and second waves of the SARS-CoV-2 pandemic in the UK, the latter attributed to the Alpha variant.

**Design** A single-centre observational study was conducted through patient chart analysis.

**Setting** Data were collected from patients admitted to Great Ormond Street Hospital, London, UK, between April 2020 and March 2021.

**Patients** 110 patients <18 years of age.

**Main outcome measure** AKI during hospitalisation. AKI classification was based on upper limit of reference interval (ULRI) serum creatinine (sCr) values.

**Results** AKI occurred in 33 (30%) patients. Hypotension/hypoperfusion was associated with almost all cases. In univariate analysis, the AKI cohort had higher peak levels of triglycerides (OR, 1.27 (95% CI, 1.05 to 1.6) per 1 mmol/L increase) and C reactive protein (OR, 1.06 (95% CI, 1.02 to 1.12) per 10 mg/L increase), with higher requirement for mechanical ventilation (OR, 3.8 (95% CI, 1.46 to 10.4)) and inotropic support (OR, 15.4 (95% CI, 3.02 to 2.81)). In multivariate analysis, triglycerides were independently associated with AKI stages 2–3 (adjusted OR, 1.26 (95% CI, 1.04 to 1.6)). At follow-up, none had macroalbuminuria and all had sCr values <ULRI. No discrepancy in renal involvement between pandemic waves was found.

**Conclusion** Despite a high incidence of AKI in PIMS-TS, renal recovery occurs rapidly with current therapies, and no patients developed chronic kidney disease.

## INTRODUCTION

A novel syndrome affecting children and young people (CYP) which has clinical overlap with Kawasaki disease, toxic shock syndrome and macrophage activation syndrome was first reported by the South Thames Retrieval Service in London, UK, in April 2020 in the context of the evolving SARS-CoV-2 pandemic.<sup>1</sup> In the UK, this condition was named paediatric inflammatory multisystem syndrome

## What is already known on this topic?

- Kidney dysfunction occurs in both acute SARS-CoV-2 infection as well as in paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).
- Acute kidney injury (AKI) in PIMS-TS is attributable to a combination of pre-renal injury and immune system dysregulation.
- Due to the novel nature of PIMS-TS, there are limited follow-up data on renal outcomes for those who have experienced AKI secondary to this condition.

## What this study adds?

- AKI occurred in 30% of children and young people admitted with PIMS-TS, who had higher peak levels of triglycerides and C reactive protein, and a higher requirement for mechanical ventilation.
- Renal follow-up data up to 6 months following discharge have so far found that kidney function had fully normalised without progression to chronic kidney disease.
- There was no difference in AKI incidence and renal outcomes between the UK's first and second waves of the SARS-CoV-2 pandemic, the latter associated with the dominance of the Alpha variant.

temporally associated with SARS-CoV-2 (PIMS-TS) and the Royal College of Paediatrics and Child Health (RCPCH) was the first to publish a case definition.<sup>2</sup> The Centers for Disease Control and Prevention and the WHO subsequently released their own definitions for this condition, naming it multisystem inflammatory syndrome in children (MIS-C).<sup>3,4</sup>

In June 2020, we reported on the incidence of acute kidney injury (AKI) in hospitalised CYP with SARS-CoV-2 infection at Great Ormond Street Hospital (London, UK).<sup>5</sup> We observed that AKI was more common in CYP with SARS-CoV-2 who met diagnostic criteria for PIMS-TS, with 73% of AKI cases occurring in this cohort. These findings

**Table 1** Baseline characteristics of all 110 patients admitted with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)

Variable	Study sample (n=110)	Missing data
<b>Demographics</b>		
Median age, years (IQR)	10.2 (7.6–12.6)	0
Male (%)	63 (57)	0
Ethnicity		
Black/African/Caribbean/black British (%)	39 (35)	0
Asian/Asian British (%)	33 (30)	
White (%)	19 (17)	
Mixed/multiple ethnic groups (%)	12 (12)	
Other (%)	7 (6)	
Median height, cm (IQR)	143 (125–160)	11
Median BMI centile (IQR)	88 (47–97)	25
Median number of days admitted	8 (6–11)	0
Comorbidities*	6 (5%)	0
<b>SARS-CoV-2 status</b>		
SARS CoV-2 RT-PCR positive (%)	33 (30)	0
Serology positive (%)	105 (95)	0
<b>Symptoms on admission</b>		
Fever (%)	110 (100)	0
Rhinitis (%)	1 (1)	1
Respiratory distress (%)	32 (29)	0
Cough (%)	9 (8)	0
Abdominal pain (%)	80 (72)	0
Diarrhoea (%)	65 (59)	0
Vomiting (%)	66 (60)	0
<b>Admission blood parameters</b>		
Median triglyceride peak, mmol/L (IQR)	2.98 (1.92–3.9)	3
Median ferritin peak, µg/L (IQR)	831 (472–1834)	0
Median CRP peak, mg/L (IQR)	281 (206–328)	0
Median IL-6 peak, pg/L (IQR)	111 (50–324)	53
Median D-dimer peak, ng/mL (IQR)	2736 (1405–5723)	0
Median NT-proBNP peak, pg/mL (IQR)	13 392 (4694–29628)	4
Median troponin, ng/L (IQR)	153 (60–387)	0
Median sodium nadir, mmol/L (IQR)	133 (131–135)	0
Median phosphate nadir, mmol/L (IQR)	0.83 (0.67–0.96)	0
Median lymphocyte nadir, 10 <sup>9</sup> /L (IQR)	0.82 (0.52–1.2)	0
Median albumin nadir, g/L (IQR)	25 (23–27)	1
<b>Renal parameters</b>		
Admission AKI status		
No AKI (%)	77 (70)	0
Stage 1 AKI (%)	13 (12)	
Stage 2 AKI (%)	8 (7)	
Stage 3 AKI (%)	12 (11)	
Urine albumin/creatinine ratio, mg/mmol (IQR)	3.3 (1.8–7)	51
Urine RBP/creatinine ratio, µg/mmol (IQR)	354 (96–3000)	97
Urine NAG/creatinine ratio, U/mmol (IQR)	233 (82–370)	97
Median creatinine peak, µmol/L (IQR)	68 (48–104)	0
Median urea peak, mmol/L (IQR)	6.7 (5.2–11)	0
Median eGFR nadir, mL/min/1.73m <sup>2</sup> (IQR)	79 (51–100)	9
Dipstick proteinuria (%)	8 (7)	33
Dipstick haematuria (%)	21 (19)	24

Continued

**Table 1** Continued

Variable	Study sample (n=110)	Missing data
Kidney ultrasonography		
Not performed (%)	12 (11)	0
Normal (%)	66 (60)	
Abnormal† (%)	32 (29)	
<b>Intensive care</b>		
Requiring PICU admission (%)	98 (89)	0
Median duration of PICU stay, days (IQR)	3 (2–5)	0
Intubation (%)	22 (20)	0
Median duration of mechanical ventilation, days (IQR)	2 (1–3)	0
Inotropic support (IQR)	84 (76)	0
Median duration of inotropic support, days (IQR)	1.7 (1–2)	0
Myocardial dysfunction on echocardiography		
None (%)	63 (57)	0
Mild (%)	30 (27)	
Moderate (%)	14 (13)	
Severe (%)	3 (3)	
<b>Medications</b>		
PIMS-TS therapeutic medications		
Methylprednisolone (%)	91 (82)	0
IVIg (%)	77 (70)	0
Anakinra (%)	8 (7)	0
Tocilizumab (%)	5 (5)	0
Remdesivir (%)	1 (1)	0
Median number of nephrotoxic medications (IQR)	1 (0–1)	0
Nephrotoxic medications		
Vancomycin (%)	4 (4)	0
Gentamicin (%)	6 (5)	0
Amikacin (%)	25 (23)	0
Aciclovir (%)	14 (13)	0
Trimethoprim/co-trimoxazole (%)	2 (2)	0
NSAIDs (%)	27 (25)	0

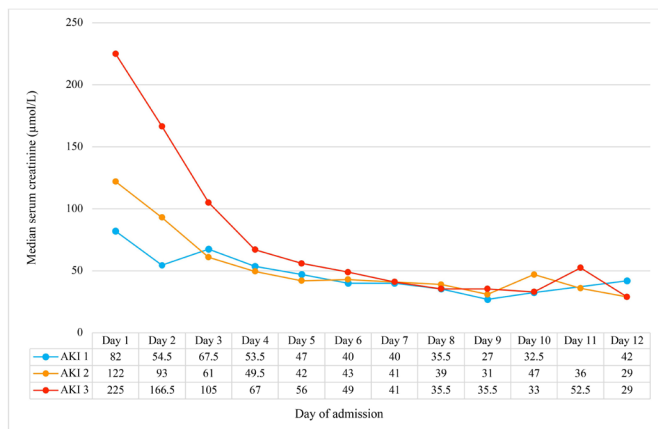
Data are n (%) or median (IQR).

\*Comorbidities were: type 1 diabetes mellitus (n=2), sickle cell disease (n=2) and ventriculoperitoneal shunt for obstructed hydrocephalus (n=2).

†Abnormal kidney ultrasonography consisted of: loss of corticomedullary differentiation and/or increased echogenicity, unilaterally or bilaterally enlarged kidneys (&gt;95th centile), unilaterally small kidney (&lt;5th centile), unilateral ectopic kidney, evidence of scarring, duplex collecting system and pelvicalyceal dilatation. AKI, acute kidney injury; BMI, body mass index; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; NAG, N-acetyl-β-D-glucosaminidase; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro B-type natriuretic peptide; PICU, paediatric intensive care unit; RBP, retinol-binding protein; RT-PCR, reverse transcription PCR.

have since been corroborated in multicentre observational studies.<sup>6,7</sup> A systematic review of MIS-C cases reported an AKI incidence of 16.3% in 662 patients although AKI definition was inconsistent between centres, and patient characteristics were not explored.<sup>8</sup>

Following a second wave of the SARS-CoV-2 pandemic in the UK in January 2021, widely attributed to the rapidly transmissible Alpha (B.1.1.7) variant,<sup>9</sup> our centre experienced a large upsurge in PIMS-TS presentations. We characterise the renal involvement in all 110 PIMS-TS cases admitted to our



**Figure 1** Median serum creatinine values according to AKI staging and day of admission. AKI, acute kidney injury.

centre up to March 2021, and report 6-month renal follow-up data for 39 cases who presented in the first pandemic wave. Furthermore, we report comparisons in renal involvement between both first and second waves, thus exploring whether the Alpha variant is associated with increased pathogenicity.

## METHODS

### Study design and participants

We conducted a single-centre observational study via electronic patient record analysis at Great Ormond Street Hospital. All patients were <18 years at time of hospitalisation and met the RCPCH case definition for PIMS-TS including persistent fever with evidence of systemic inflammation and organ dysfunction.<sup>2</sup> Patients were admitted between 4 April 2020 and 7 March 2021, and were retrieved from a primary site to our centre which acts as a regional tertiary/quaternary referral centre.

### AKI definition

As patients presented acutely, previous serum creatinine (sCr) values were not available to establish baseline kidney function. AKI was defined based on peak sCr values obtained during the patient's admission referenced against age-specific upper limit of reference interval (ULRI) values published by the British Association of Paediatric Nephrology.<sup>10</sup> Reduced kidney function was assumed to be reversible as part of the criteria for defining AKI. AKI stage 1 was defined as  $sCr > 1.5\text{--}2 \times ULRI$ , stage 2 as  $> 2\text{--}3 \times ULRI$  and stage 3 as  $> 3 \times ULRI$ . Estimated glomerular filtration rate (eGFR) was based on the revised Schwartz equation<sup>11</sup>:  $eGFR_{creat} = 36.5 \times (\text{height (cm)} / sCr (\mu\text{mol/L}))$ .

### Procedures

All patients underwent SARS-CoV-2 testing by reverse transcription PCR from nasopharyngeal swabs, and serology testing using IgG antibodies to SARS-CoV-2 nucleocapsid protein or spike protein from June 2020 onwards (Epitope Diagnostics; San Diego, California, USA).

Left ventricular ejection fraction (LVEF) on echocardiography was used to define left ventricular dysfunction: none  $\geq 50\%$ , mild 40%–49%, moderate 30%–39% and severe  $< 30\%$ .

Renal ultrasound findings were reported as not performed, normal or abnormal. Abnormal findings included loss of corticomedullary differentiation and/or increased echogenicity which could be indicative of AKI.

Significant comorbidities constituted those where hospital-based management may be required. Obesity was not included

as a comorbidity as data relating to this were collected by body mass index (BMI) calculation.

After hospital discharge, patients have been followed up at 6–8 weeks and 6 months in a dedicated multiprofessional PIMS-TS clinic.

Presentations before September 2020 are classified as 'first wave', and those thereafter as 'second wave'. Due to the rapid transmissibility of the Alpha variant from October 2020 onwards in the UK, most second wave PIMS-TS cases were postulated to be associated with this. Genotype sequencing was hindered by the limitations of PCR minimum cycle threshold detection as most patients presented some weeks after SARS-CoV-2 exposure.

### Statistical analysis

The main outcome measure was the presence of AKI during hospitalisation. Baseline biochemical, clinical and demographic features were assessed to identify associations with AKI. Univariable logistic regression modelling assessed odds of any single variable being associated with AKI stages 1–3. Multivariable modelling, using only three parameters to avoid overfitting, assessed independent association with severe AKI (stages 2–3). ORs are presented with 95% CI range.  $\chi^2$  test compared categorical variables, and Student's t-test compared continuous variables. Results are presented as numbers and percentages (%) for categorical variables, and medians and IQRs for continuous variables. Analyses were performed using Microsoft Excel V.2019 (Microsoft, Redmond, Washington, USA) and R programming language (R Core Team).

## RESULTS

### Baseline characteristics

Data were available for 110 patients with PIMS-TS. Baseline characteristics are summarised in table 1. Median age at presentation was 10.2 years (IQR 7.6–12.6), 63 (57%) were male, 98 (88%) were of non-white ethnicity and median BMI centile was 88 (IQR 47–97). SARS-CoV-2 seropositivity was present in 105 (95%) and PCR positivity in 33 (30%). Fever occurred in all. Diarrhoea and vomiting were present in 65 (59%) and 66 (60%), respectively. Comorbidities were present in 6 (5%). Median duration of hospital stay was 8 days (IQR 6–11) with 98 (89%) being admitted directly to the paediatric intensive care unit (PICU) for a median duration of 3 days (IQR 2–5). Inotropic support was required in 84 (76%) for a median duration of 1.7 days (IQR 1–2). Twenty-two (20%) received mechanical ventilation for a median duration of 2 days (IQR 1–3). Myocardial dysfunction was present in 47 (43%). Four (4%) had underlying kidney abnormalities on ultrasound consistent with congenital abnormalities of the kidney and urinary tract rather than AKI.

### Diagnosis and staging of AKI

Of 110 patients, AKI was diagnosed in 33 (30%): stage 1 in 13 (12%), stage 2 in 8 (7%) and stage 3 in 12 (11%). A further 35 (45%) had peak sCr  $> ULRI$  but not beyond the AKI diagnostic threshold. No CYP were known to have underlying kidney disease prior to admission. None required continuous renal replacement therapy. Of the AKI group, two patients did not experience normalisation of sCr to  $< ULRI$  before discharge although this had occurred at subsequent follow-up. There was rapid normalisation of sCr with the median value for all AKI stages being  $< 100 \mu\text{mol/L}$  by day 4 of admission (figure 1).

**Table 2** Characteristics of patients with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), cross-tabulated with the presence of acute kidney injury (AKI; stages 1–3) during hospital admission

Variable	Non-AKI (n=77)	AKI stages 1–3 (n=33)	P value
<b>Demographics</b>			
Median age, years (IQR)	105 (8.1–13.5)	9 (7.1–10.9)	0.08
Male (%)	46 (60)	17 (51)	0.64
<b>Ethnicity</b>			
Black/African/Caribbean/black British (%)	20 (26)	19 (58)	0.004
Asian/Asian British (%)	27 (35)	6 (18)	
White (%)	16 (21)	3 (9)	
Mixed/multiple ethnic groups (%)	9 (12)	3 (9)	
Other (%)	5 (6)	2 (6)	
Median height, cm (IQR)	144 (124–160)	140 (128–158)	0.55
Median BMI centile (IQR)	80.7 (46–96)	91 (57–99)	0.18
Median number of days admitted	7 (6–10)	9 (8–11)	0.45
Comorbidities*	5 (6)	1 (3)	0.47
<b>SARS-CoV-2 status</b>			
SARS CoV-2 PCR positive (%)	21 (28)	12 (36)	0.34
Serology positive (%)	73 (95)	32 (97)	0.78
<b>Symptoms on admission</b>			
Fever (%)	77 (100)	33 (100)	1
Rhinitis (%)	0 (0)	1 (3)	0.09
Respiratory distress (%)	18 (23)	14 (42)	0.04
Cough (%)	7 (9)	2 (6)	0.72
Abdominal pain (%)	58 (75)	22 (66)	0.35
Diarrhoea (%)	42 (55)	23 (70)	0.14
Vomiting (%)	45 (58)	21 (64)	0.61
<b>Admission blood parameters</b>			
Median triglyceride peak, mmol/L (IQR)	2.9 (1.8–3.7)	3.62 (2.6–4.6)	0.04
Median ferritin peak, µg/L (IQR)	713 (422–1641)	1192 (818–1872)	0.03
Median CRP peak, mg/L (IQR)	262 (182–307)	313 (278–352)	<0.001
Median IL-6 peak, pg/L (IQR)	120 (50–305)	71 (50–439)	0.4
Median D-dimer peak, ng/mL (IQR)	2468 (1351–4581)	5259 (2168–12486)	0.04
Median NT-proBNP peak, pg/mL (IQR)	11 777 (3183–23562)	23 072 (7103–32955)	0.03
Median troponin, ng/L (IQR)	105 (39–266)	301 (116–570)	0.09
Median sodium nadir, mmol/L (IQR)	133 (131–135)	133 (131–135)	0.88
Median phosphate nadir, mmol/L (IQR)	0.83 (0.66–0.96)	0.85 (0.76–0.98)	0.53
Median lymphocyte nadir, 10 <sup>9</sup> /L (IQR)	0.82 (0.52–1.21)	0.8 (0.52–1.15)	0.19
Median albumin nadir, g/L (IQR)	25 (23–29)	24 (22–26)	0.1
<b>Renal parameters</b>			
Median creatinine peak, µmol/L (IQR)	57.5 (42–71)	132 (96–216.7)	–
Median urea peak, mmol/L (IQR)	5.7 (4.8–7.4)	14.2 (9.5–19.7)	–
Median eGFR, mL/min/1.73 m <sup>2</sup> (IQR)	92 (77–118)	41 (24–52)	–
Median urine albumin/creatinine ratio, mg/mmol (IQR)	3 (1.62–4.4)	6.6 (2.7–9.7)	0.04
Median urine RBP/creatinine ratio, µg/mmol (IQR)	267 (77–1451)	3000 (354–3003)	0.17
Median urine NAG/creatinine ratio, U/mmol (IQR)	114 (47–370)	239 (233–264)	0.44
Dipstick proteinuria (%)	4 (5)	4 (12)	0.29
Dipstick haematuria (%)	14 (18)	7 (21)	0.81
<b>Kidney ultrasonography</b>			
Not performed (%)	8 (10)	4 (12)	0.21
Normal (%)	49 (64)	17 (52)	
Abnormal† (%)	20 (26)	12 (36)	
<b>Intensive care</b>			
PICU admission (%)	65 (84)	33 (100)	0.016
Median duration of PICU stay, days (IQR)	3 (2–5)	4 (3–5)	0.18
Intubation (%)	10 (13)	12 (36)	0.005
Median duration of mechanical ventilation, days (IQR)	2.5 (2–5.25)	1.5 (1–3)	0.14
Inotropic support (%)	52 (68)	32 (97)	0.001

Continued



Table 2 Continued

Variable	Non-AKI (n=77)	AKI stages 1–3 (n=33)	P value
Median duration of inotropic support, days (IQR)	1 (0–2)	2 (1–3)	0.04
<b>Echocardiography finding</b>			
No myocardial dysfunction (%)	48 (62)	15 (45)	0.1
Myocardial dysfunction (%)	29 (38)	18 (55)	
<b>Medications</b>			
<b>PIMS-TS therapeutic medications</b>			
Methylprednisolone (%)	65 (84)	26 (79)	0.47
IVIg (%)	53 (69)	24 (73)	0.68
Anakinra (%)	5 (6)	3 (9)	0.63
Tocilizumab (%)	3 (4)	2 (6)	0.62
Remdesivir (%)	1 (1)	0 (0)	0.99
Median number of nephrotoxic medications (IQR)	0 (0–1)	1 (0–1)	0.37
<b>Nephrotoxic medications</b>			
Vancomycin (%)	4 (5)	0 (0)	0.31
Gentamicin (%)	4 (5)	2 (6)	0.99
Amikacin (%)	15 (19)	10 (30)	0.22
Aciclovir (%)	7 (9)	7 (21)	0.12
Trimethoprim/co-trimoxazole (%)	2 (3)	0 (0)	0.99
NSAIDs (%)	19 (25)	8 (24)	0.96

Data are n (%) or median (IQR).

\*Comorbidities were: type 1 diabetes mellitus (n=2), sickle cell disease (n=2) and ventriculoperitoneal shunt for obstructed hydrocephalus (n=2).

†Abnormal kidney ultrasonography consisted of: loss of corticomedullary differentiation and/or increased echogenicity, unilaterally or bilaterally enlarged kidneys (>95th centile), unilaterally small kidney (<5th centile), unilateral ectopic kidney, evidence of scarring, duplex collecting system and pelvicalyceal dilatation.

BMI, body mass index; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; IL-6, interleukin 6; IVIG, intravenous immunoglobulin; NAG, N-acetyl-β-D-glucosaminidase; NSAIDs, non-steroidal anti-inflammatory drugs; NT-proBNP, N-terminal pro B-type natriuretic peptide; PICU, paediatric intensive care unit; RBP, retinol-binding protein.

### Comparison of non-AKI and AKI groups

The baseline characteristics cross-tabulated with the presence of AKI are summarised in table 2. AKI incidence was higher in those of non-white ethnicity (p=0.004), those with respiratory distress (p=0.04), those admitted to PICU (p=0.016), and in those requiring mechanical ventilation (p=0.005) and inotropic support (p=0.001). Median duration for inotropic support was longer in the AKI cohort (p=0.04). The AKI group experienced higher peak levels of triglycerides (p=0.04), ferritin (p=0.03), C reactive protein (CRP) (<0.001), D-dimers (p=0.04) and N-terminal pro B-type natriuretic peptide (NT-proBNP) (p=0.03). Additional data are summarised in online supplemental appendix 1.

### Univariable and multivariable modelling for AKI

In univariate analysis (table 3), patients with AKI were predisposed to higher peak levels of triglycerides (OR, 1.27 (95% CI, 1.05 to 1.6) per 1 mmol/L increase), CRP (OR, 1.06 (95% CI, 1.02 to 1.12) per 10 mg/L increase), D-dimers (OR, 1.07 (95% CI, 1.03 to 1.14) per 1000 ng/mL increase) and NT-proBNP (OR, 1.03 (95% CI, 1.004 to 1.07) per 1000 pg/mL increase). They were more likely to require mechanical ventilation (OR, 3.8 (95% CI, 1.46 to 10.4)) and inotropic support (OR, 15.4 (95% CI, 3.02 to 281)). A multivariate model (table 4), using non-white ethnicity, triglycerides (per 1 mmol/L increase) and diarrhoea as a presenting symptom, showed only triglycerides to be independently associated with severe AKI (stages 2–3) (adjusted OR, 1.26 (95% CI, 1.04 to 1.6)).

### Comparison of AKI presentations according to time point

Forty-three (39%) patients presented before September 2020, none presented in September and 67 (61%) presented

thereafter (figure 2). AKI incidence did not differ between cohorts presenting before and after September 2020 (33% vs 28.4%, p=0.85).

### Follow-up data

At time of data analysis, 50 patients (46%) had received follow-up at 6–8 weeks, and 39 (36%) at 6 months. Forty-six were included in a recently published PIMS-TS follow-up study by Penner and colleagues but without focus on renal parameters or subanalysis of AKI cases.<sup>12</sup> Of those reviewed at 6–8 weeks (n=50), 15 were from the AKI group (45%). None had macroalbuminuria (urine albumin/creatinine ratio (ACR) >30 mg/mmol) or haematuria on urinalysis. Median urine ACR was 1.1 mg/mmol (IQR 0.7–1.8), retinol-binding protein (RBP)/creatinine ratio was 5.8 µg/mmol (IQR 4.6–7.9) and N-acetyl-β-D-glucosaminidase (NAG)/creatinine ratio was 11 U/mmol (IQR 7.8–14.5). None had sCr values >ULRI. Of those reviewed at 6 months (n=39), 12 were from the AKI group (36%). None had macroalbuminuria or haematuria. Median urine ACR was 4.6 mg/mmol (IQR 2.6–4.5). RBP/creatinine and NAG/creatinine ratios were not reassessed at this stage. All sCr values remained <ULRI. Eleven patients from the AKI cohort (92%) had clinic blood pressure (BP) measurements. One (9%) had a systolic BP between the 90th and 95th centile, and two (18%) had systolic measurements >95th centile.

### DISCUSSION

Our experience with PIMS-TS demonstrates that kidney dysfunction is common. In total, 62% had a peak sCr >ULRI, and 30% developed AKI. AKI incidence in our cohort was greater than that in a multinational trial evaluating PICU admissions of all types.<sup>13</sup> Only 98 (89%) of our patients received PICU-level care so the

**Table 3** Univariable odds of developing acute kidney injury during paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, as estimated by logistic regression modelling

Variable	OR (95% CI)	Wald z statistic	P value
<b>Demographics</b>			
Age (per 1-year increase)	0.99 (0.98 to 1)	-1.64	0.09
Male	0.71 (0.31 to 1.63)	-0.78	0.43
Ethnicity		1.45	0.15
White	1		
Non-white	2.6 (0.79 to 11.9)		
BMI centile (per 5-unit increase)	1.05 (0.98 to 1.13)	1.27	0.2
<b>Symptoms on admission</b>			
Diarrhoea	1.91 (0.82 to 4.72)	1.47	0.14
Vomiting	1.24 (0.54 to 2.9)	0.51	0.61
Respiratory distress	2.41 (1.01 to 5.8)	1.98	0.05
<b>Admission blood parameters</b>			
Triglycerides (per 1 mmol/L increase)	1.27 (1.05 to 1.6)	2.36	0.02
Ferritin (per 100 µg/L increase)	0.99 (0.99 to 1.01)	-0.05	0.96
CRP (per 10 mg/L increase)	1.06 (1.02 to 1.12)	2.68	0.008
D-dimer (per 1000 ng/mL increase)	1.07 (1.03 to 1.14)	2.94	0.003
Troponin (per 10 ng/L increase)	1 (1 to 1.01)	1.94	0.05
NT-proBNP (per 1000 pg/mL increase)	1.03 (1.004 to 1.07)	2.2	0.02
<b>Intensive care</b>			
Mechanical ventilation	3.8 (1.46 to 10.4)	2.71	0.006
Inotropic support	15.4 (3.02 to 28.1)	2.63	0.009
Duration of PICU stay (per 1 day)	1.1 (0.93 to 1.32)	1.17	0.23
Duration of inotropic support (per 1 day)	1.2 (0.97 to 1.54)	1.62	0.1
<b>Medications</b>			
Nephrotoxic medications (per 1-unit increase)	1.26 (0.76 to 2.05)	0.91	0.36

Data are odds ratio (95% CI).

BMI, body mass index; CRP, C reactive protein; NT-proBNP, N-terminal pro B-type natriuretic peptide; PICU, paediatric intensive care unit.

comparative incidence of AKI was higher. sCr values peaked at time of admission and rapidly improved during hospital stay. Overall morbidity was worse in those with AKI, reflected by a greater need for PICU admission and longer PICU stay. Invasive respiratory support in the AKI group was more common, suggestive of more extensive multisystem inflammation with higher peak levels of acute phase reactants. A greater requirement for inotropes fits with kidney dysfunction being exacerbated by fluid-refractory shock with a pre-renal 'hit'. Those of black ethnicity made up a larger proportion of the AKI group (58%) compared with the non-AKI group (26%). However, the univariate analysis did not support an association between black ethnicity and AKI. Important considerations are that the definition of AKI in this study depends on ULRI values, rather than comparison against baseline sCr, and that those of black ethnicity are known to have higher baseline sCr compared with peers from other ethnicities.<sup>14</sup> This therefore risks bias towards including more subjects of black ethnicity within the AKI group.

There are known links between AKI and ethnic disparities, although the extent to which genetic, clinical and socioeconomic factors influence this relationship is unclear.<sup>15</sup>

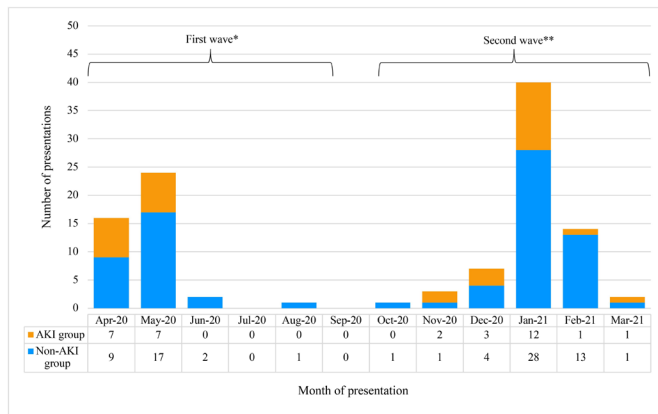
The pathophysiology of PIMS-TS is associated with immune system dysregulation that predominantly occurs after acute infection has subsided, as evidenced by seropositivity in 95% of our cohort versus PCR positivity in only 30%. Why some CYP are predisposed to such an abnormal post-infectious immune response remains unclear. The immunophenotype of the disorder is distinct from that of other similar conditions, such as Kawasaki disease, as manifested by differences in cytokine release which may be secondary to impaired antigen presentation.<sup>16 17</sup> As with acute SARS-CoV-2 infection, the pathogenesis of kidney dysfunction in PIMS-TS is likely multifactorial with an interplay of fluid-refractory hypovolaemic shock, cardiogenic shock and a hyperinflammatory response with release of factors that induce vascular endothelial damage and microvascular thrombosis.<sup>18</sup> None of our AKI cohort was felt to warrant

**Table 4** Multivariable odds of severe acute kidney injury (AKI; stages 2 and 3) during hospital admission for paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, as estimated by logistic regression modelling (AUC=0.74)

Outcome: AKI (stages 2 and 3)	Multivariable analysis (base model)		
	OR (95% CI)	Wald z statistic	P value
Ethnicity (non-white)	2.03 (0.58 to 9.4)	1.04	0.3
Triglyceride level (per 1 mmol/L increase)	1.26 (1.04 to 1.6)	2.21	0.03
Diarrhoea	1.9 (0.77 to 5.04)	1.35	0.17

Data are OR (95% CI).

AUC, area under the curve.



\*First pandemic wave – April 2020 to August 2020

\*\*Second pandemic wave – October 2020 to March 2021

**Figure 2** PIMS-TS cases by month of presentation demonstrating split between AKI and non-AKI presentations, and UK first and second waves of the pandemic. AKI, acute kidney injury; PIMS-TS, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

a kidney biopsy thereby precluding histopathological understanding of kidney involvement, and assessment as to whether renal immune-complex deposition occurs. Early evidence of nephritis in SARS-CoV-2 infection may be a useful predictor for complications such as capillary leak syndrome and the need for respiratory support.<sup>19</sup> With relation to glomerular function, urine ACR values were higher in our AKI cohort. Urine tubular proteins RBP and NAG can act as markers of proximal tubular injury,<sup>20 21</sup> but we observed no difference in tubular proteinuria between groups although this was hindered by lack of assessment in 97 patients (88%).

Certain laboratory parameters were more likely to be elevated in those with AKI although it is difficult to differentiate whether these are prognosticators for kidney dysfunction, or whether they are elevated as a sequela of reduced GFR. D-dimers, for example, are proteins released by fibrinolysis, reflective of a hypercoagulable state. Renal dysfunction predisposes to hypercoagulability and D-dimer elimination occurs partly via the kidney.<sup>22</sup> As such, D-dimers are a non-specific marker of AKI and, furthermore, levels may be affected by confounding factors such as infection and liver dysfunction. It is unexpected that NT-proBNP should be significantly elevated in AKI while there was no echocardiographic discrepancy in the presence of myocardial dysfunction between AKI and non-AKI groups. However, LVEF alone is a crude marker of LV function and additional echocardiographic measurements, including markers of diastolic function, may have yielded a more sensitive assessment of LV dysfunction.<sup>23</sup> Our multivariate model demonstrated an independent association between triglyceride peak and odds of developing severe AKI. Triglycerides were chosen for this model as AKI is not known to be a cause for hypertriglyceridaemia. Severe hypertriglyceridaemia has been shown to exacerbate renal dysfunction, but only in the context of acute pancreatitis.<sup>24</sup> However, pancreatitis is not a distinguishing feature of PIMS-TS, and serum lipase or amylase was not routinely checked due to lack of clinical indication. Hypertriglyceridaemia is also seen in glomerular dysfunction associated with nephrotic syndrome.<sup>25</sup> Although the AKI group had higher urine ACR values, no patients had nephrotic-range proteinuria (>200 mg/mmol) to suggest extensive glomerular involvement. Unfortunately, triglyceride levels

were not reassessed at follow-up to establish whether normalisation occurred. If hypertriglyceridaemia resolves, it is hypothesised that triglycerides may act as an acute phase reactant in PIMS-TS whereby they are intrinsically linked with predisposition to developing AKI. If triglyceride levels do not normalise, then hypertriglyceridaemia may be an underlying risk factor for AKI in PIMS-TS, or for PIMS-TS itself. Of the other multivariate model parameters, non-white ethnicity was chosen due to a higher proportion of non-white individuals being present in the AKI group. Diarrhoea as a presenting symptom was included as this is a potential cause for pre-renal AKI but is not caused by reduced GFR itself.

Most CYP will recover from PIMS-TS although deaths have been reported.<sup>26</sup> The first follow-up study of patients with PIMS-TS at 6 months indicates that cardiac and haematological outcomes are favourable but neurological functional impairment is common.<sup>12</sup> Our renal follow-up data are reassuring so far, with sustained normalisation of sCr and no evidence of persistent nephritis. Three patients had elevated systolic BP (>90th centile) at 6 months but these were automated clinic measurements that may have been impacted by factors including the white coat effect.

By 31 December 2020, the Alpha variant had replaced the wild-type virus in the UK, and was responsible for three-quarters of all new SARS-CoV-2 cases.<sup>27</sup> This variant has since spread globally due to its increased transmissibility.<sup>28</sup> Our data suggest that the second wave experienced in the UK, presumed to be propagated by the Alpha variant, was not associated with increased renal pathogenicity in PIMS-TS cases compared with the first wave.

Our study is limited by its single-centre retrospective design, the higher acuity of patients transferred to our centre due to its tertiary/quaternary nature, small numbers at follow-up and the lack of baseline sCr values to define AKI. There was limited assessment of several parameters including interleukin-6, RBP and NAG, and no follow-up of triglyceride levels.

## CONCLUSIONS

Despite a high incidence of AKI in PIMS-TS, renal recovery occurs rapidly in the context of fluid resuscitation and available therapies. Both short and longer term outcomes for those with AKI are favourable, without evidence of progression to chronic kidney disease. The significance of hypertriglyceridaemia requires further assessment with follow-up to ensure normalisation of levels.

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