Acute Kidney Injury in Pediatric Inflammatory Multisystem Syndrome Temporally Associated With Severe Acute Respiratory Syndrome Coronavirus-2 Pandemic: Experience From PICUs Across United Kingdom

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Objectives: To study the prevalence, evolution, and clinical factors associated with acute kidney injury in children admitted to PICUs with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2.

Design: Multicenter observational study.

Setting: Fifteen PICUs across the United Kingdom.

Patients: Patients admitted to United Kingdom PICUs with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 between March 14, 2020, and May 20, 2020.

Interventions: None.

Measurements and Main Results: Deidentified data collected as part of routine clinical care were analyzed. All children were diagnosed and staged for acute kidney injury based on the level of serum creatinine above the upper limit of reference interval values according

to published guidance. Severe acute kidney injury was defined as stage 2/3 acute kidney injury. Uni- and multivariable analyses were performed to study the association between demographic data, clinical features, markers of inflammation and cardiac injury, and severe acute kidney injury. Over the study period, 116 patients with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 were admitted to 15 United Kingdom PICUs. Any-stage acute kidney injury occurred in 48 of 116 patients (41.4%) and severe acute kidney injury in 32 of 116 (27.6%) patients, which was mostly evident at admission (24/32, 75%). In univariable analysis, body mass index, hyperferritinemia, high C-reactive protein, Pediatric Index of Mortality 3 score, vasoactive medication, and invasive mechanical ventilation were associated with severe acute kidney injury. In multivariable logistic regression, hyperferritinemia was associated with severe acute kidney injury (compared with nonsevere acute kidney injury; adjusted odds ratio 1.04; 95% CI, 1.01–1.08; $p = 0.04$). Severe acute kidney injury was associated with longer PICU stay (median 5 days [interquartile range, 4–7 d] vs 3 days [interquartile range, 1.5–5 d]; $p < 0.001$) and increased duration of invasive mechanical ventilation (median 4 days [interquartile range, 2–6 d] vs 2 days [interquartile range, 1–3 d]; $p = 0.04$).

Conclusions: Severe acute kidney injury occurred in just over a quarter of children admitted to United Kingdom PICUs with pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2. Hyperferritinemia was significantly associated with severe acute kidney injury. Severe acute kidney injury was associated with increased duration of stay and ventilation. Although short-term outcomes for acute kidney injury in pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 appear good, long-term outcomes are unknown. (*Crit Care Med* 2020; XX:00–00)

Key Words: acute kidney injury; children; coronavirus disease 2019; coronavirus; intensive care, children; multisystem inflammatory syndrome in children; pandemic; pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2

Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was declared a global pandemic by World Health Organization (WHO) in March 2020, and by June 20, 2020, nearly 9 million people got affected and resulted in nearly half a million deaths (1). Initial reports from China, confirmed subsequently from Europe and North America, indicated that children appear to be affected less frequently and less severely by COVID-19 (2). However, from March onward, clinicians in the United Kingdom (UK), Europe, and the United States (US) started reporting children with an unexplained inflammatory condition possibly associated with COVID-19. Case definitions for this condition, called pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) pandemic in the UK and multisystem inflammatory syndrome in children (MIS-C), in the US, have now been published by the UK Royal College of Pediatrics and Child Health (RCPCH), the US Centers for Disease Control and Prevention, and the WHO (3–5). Diagnostic criteria common to all case definitions include presence of fever, inflammation, and multiple organ involvement, predominantly cardiac dysfunction and shock. Published reports of this inflammatory condition (referred hereafter as PIMS-TS) indicate that it shares features of, but is distinct from, other inflammatory conditions such as Kawasaki disease (KD), toxic shock syndrome, and KD shock syndrome (6–12).

Approximately 10% of all patients admitted to the PICUs develop acute kidney injury (AKI), the frequency of which increases with increasing severity of patient illness (13, 14). Worsening severity of AKI has been associated with a stepwise increase in 28-day mortality (15). In the largest case series of PIMS-TS published so far ($n = 58$, 29 of whom required PICU admission), elevation of serum creatinine above upper limit for age was seen in 22% of cases, although further details regarding factors associated with AKI in this condition, or details of progression of AKI and its relationship with patient outcomes, were not reported (8). The etiology and pathogenesis of AKI may be multifactorial: it could develop in PIMS-TS as a part of multisystem involvement secondary to hypovolemia, low cardiac output state, vasculitis, or immune-mediated inflammation. AKI is also a known complication in KD and is reported in about one-third of these patients (16). In adults with typical features of acute COVID-19 infection, AKI has been reported in approximately 30% of patients (17–19). Since PIMS-TS is a postinfectious inflammatory response condition, complications may be substantially different to those seen in active SARS-CoV-2 infection. Factors associated with AKI in PIMS-TS, its course, and relationship with patient outcomes are currently unknown. In this report, we aim to describe the prevalence, evolution, and clinical factors associated with AKI in a cohort of children admitted to UK PICUs with PIMS-TS over a 9-week period from March 2020 to May 2020.

MATERIALS AND METHODS

Study Design

This is a multicenter observational study of children less than 18 years old, admitted to PICUs in the UK over a 7-week period (from March 14, 2020, to May 20, 2020), who fulfilled the case definition of PIMS-TS as described by the UK RCPCH. We excluded children with known renal disease and those who were on chronic dialysis.

Ethics and Data Security

The project was classified as a service evaluation project by the King's College Hospital Research and Innovation team (CH-058-20), and ethics approval was not required. Study PICUs extracted data collected as part of routine clinical care from local clinical systems, deidentified the data, and submitted it to the central study team using password-protected datasheets via a secure National Health Service server. Individual sites registered the study as a local service evaluation.

Clinical and Biochemical Data

Data collected included demographic details, presenting clinical features (fever, rash, conjunctivitis, respiratory distress, gastrointestinal symptoms, and neurologic symptoms), underlying comorbidities, reason for PICU admission, and laboratory tests including markers of inflammation (C-reactive protein [CRP], ferritin, lactate dehydrogenase [LDH], creatine kinase [CK], and D-dimers). Values at admission and the highest value during the course of PICU stay were collected. Echocardiographic findings, admission, and highest values of markers of cardiac dysfunction (troponin, CK, and N-terminal pro B-type natriuretic peptide [NT-pro-BNP]) were recorded. Patients who presented in shock were classified as hypovolemic, vasodilatory, or vasoconstrictive shock based on the treating clinician's judgment. Amount of fluid resuscitation, use of inotropes and vasopressors, use of mechanical ventilation (invasive and noninvasive), continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) were recorded. We calculated the Pediatric Index of Mortality (PIM3) score as a marker of severity of illness at admission (20). All patients had SARS-CoV-2 antigen tests performed by reverse transcriptase polymerase chain reaction (PCR). Serology for SARS-CoV-2 was performed where available. Clinical management of all patients was at the discretion of the local PICU and multidisciplinary team.

Renal Parameters

Serial values of serum creatinine and urine output as well as use of nephrotoxic drugs (listed in **Supplementary Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F913), fluid balance, and the use of diuretics were collected on a daily basis for the first 7 days of PICU admission. As most of our patients were previously healthy and presented acutely, a baseline creatinine measurement was often unavailable, precluding us from using the Kidney Disease for Improving Global Outcomes (KDIGO) criteria (21). We therefore referenced serum creatinine values for our cohort against age-specific upper limit of reference interval (ULRI) values according to the published guidance from the British Association of Pediatric Nephrology. These ranges were proposed at the Pediatric Laboratory Medicine Network meeting in 2014 (22). All children were diagnosed and staged for AKI daily until PICU discharge or the first 7 days in PICU, whichever was longer, based on the rise of serum creatinine above the ULRI (AKI stage 1: 1.5–2× ULRI; AKI stage 2: 2–3× ULRI; stage 3: > 3× ULRI). Patients with creatinine above the ULRI for height and sex that was not high enough to reach stage 1 AKI were classified as having renal dysfunction. Patients were divided into two groups: no AKI/stage 1 AKI and stage 2/3 AKI (severe AKI). We used the Schwartz formula to calculate estimated glomerular filtration rate (eGFR) for all patients on a daily basis for the first 7 days of PICU or until PICU discharge. The daily progression of AKI was observed up to 7 days from admission to PICU.

Statistical Analysis

Our main outcome measure was the presence of severe AKI at/during PICU admission. We studied the association between the demographic factors, clinical and biochemical parameters (at PICU admission and the highest values during PICU stay), and severe AKI. In addition, we evaluated the association of severe AKI with the length of PICU stay, duration of mechanical ventilation, and PICU mortality. Univariable logistic regression analysis was used to investigate the relation between the explanatory variables and severe AKI (outcome), ensuring that only variables with less than 20% missing data and a plausible link to severe AKI were used, recognizing that there was little previous experience of PIMS-TS, and therefore, selection of explanatory variables was difficult. All statistically significant variables ($p < 0.05$) in univariate analyses as well as those clinically deemed to be relevant were entered into multivariable logistic regression models to explore their association with severe AKI. As per previously published guidance (23) in order to avoid overfitting, the most parsimonious model with the best model fit, as assessed by area under curve, was reported. A two-sided p value of less than or equal to 0.05 was considered statistically significant.

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages (%). Missing data were excluded from statistical analysis. Pearson chi-square test and/or Fisher exact test were used to compare categorical variables between the groups. Student t test and the Kruskal-Wallis test were used to compare continuous variables between the groups, depending on the normality of the distribution. All analyses were performed using the STATA software (Version 14.2, StataCorp, TX) and Excel Version 2016 (Microsoft, Redmond, WA).

RESULTS

Out of 24 UK PICUs, 15 admitted patients with PIMS-TS and submitted data for 116 children admitted with PIMS-TS between March 14, 2020, and May 20, 2020. Initial presenting features of 78 of these patients have been reported previously, although no details regarding AKI in this cohort have been published (24). Cardiac and renal features in six and 23 patients, respectively, have also been presented in single-center reports (8, 12, 25).

As shown in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/F913), the median age was 11 years (IQR, 7–14 yr) and the majority of patients were male (66%); nearly one-half were of Afro-Caribbean ethnicity (45%) and a quarter were Asian (26%). Comorbidities in these patients are summarized in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/F913). None had chronic kidney disease. The main presenting symptoms included fever and gastrointestinal symptoms (68% had abdominal pain and over half had diarrhea and vomiting). Nearly half of the patients (49%) presented with vasodilated shock, requiring vasoactive medications (54%). At admission, inflammatory markers (CRP, lactate, ferritin, LDH, and CK) and markers of cardiac involvement (troponin, CK, and NT-pro-BNP) were significantly raised. A third of patients (35%) required invasive mechanical ventilation (IMV) for a median duration of 3 days (IQR, 1–5 d), whereas another 21% received noninvasive ventilation. Three patients required

ECMO. Nephrotoxic agents were administered in over half of the patients (57%). The median length of PICU stay was 4 days; only 14 patients (12%) were admitted for 7 or more days.

Overall, any-stage AKI occurred in 48 of 116 children (41.4%) at/during the PICU admission. Renal dysfunction that did not meet the AKI criteria was present in an additional 19 of 116 children (16.4%). Severe AKI was present in 32 of 116 children (27.6%).

Renal Characteristics at Admission

Median serum creatinine of all patients at PICU admission was 61 micromol/L [IQR, 37–90 micromol/L], median urine output at 24 hours of admission was 1.1 mL/kg/hr [IQR, 0.7–1.9 mL/kg/hr], and the majority had been administered a fluid bolus (74/116, 63.8%). The majority of children did not have AKI at admission (78/116, 67.2%). Among children with AKI in the study sample, the majority presented with AKI at the time of admission (38/48, 79.2%). Similarly, the majority of children with severe AKI presented with severe AKI at admission to the PICU (24/32, 75%).

Evolution of AKI

Of the 78 children who did not have AKI at admission, nine developed AKI during their PICU stay. By day 2, nearly all of the children who had any-stage AKI had developed it (47/48, 98%), whereas all children who had severe AKI had developed it (32/32, 100%). Overall, renal function appeared to improve over time in PICU both in terms of drop in serum creatinine and rise in eGFR (**Fig. 1**). Serum creatinine decreased in severe AKI from a median of 103 to 43 micromols/L, whereas the eGFR in this group increased from a median of 55 to 126 mL/min/1.73 m^2. Apart from three patients, AKI in all other patients had resolved by the time of discharge from PICU (one had stage-1 and two had stage-2 AKIs). **Figure 2** summarizes the evolution of AKI over the first 7 days of PICU stay.

Factors Associated With AKI

Comparison of patients with no AKI/stage-1 AKI versus severe AKI is shown in **Table 1**. There were differences in ethnicity, body mass index (BMI), PIM3 score, serum ferritin, CRP, LDH, serum troponin, number of nephrotoxic agents, receipt of vasoactive medication, and IMV. Of note, 31% of patients with severe AKI received two or more nephrotoxic drugs compared with 10% in the no AKI/stage-1 AKI. In univariate analyses, patients who had severe AKI were more likely to have a higher BMI (odds ratio, 1.02 [95% CI, 1.00–1.04] per unit increase), a higher ferritin (odds ratio, 1.04 [95% CI, 1.01–1.8] per 100-unit increase) and higher PIM3 score (odds ratio, 2.32 [95% CI, 1.04–5.19] per 10% increase) (**Table 2**). When these three variables were entered into a multivariate model, hyperferritinemia was the only factor independently associated with

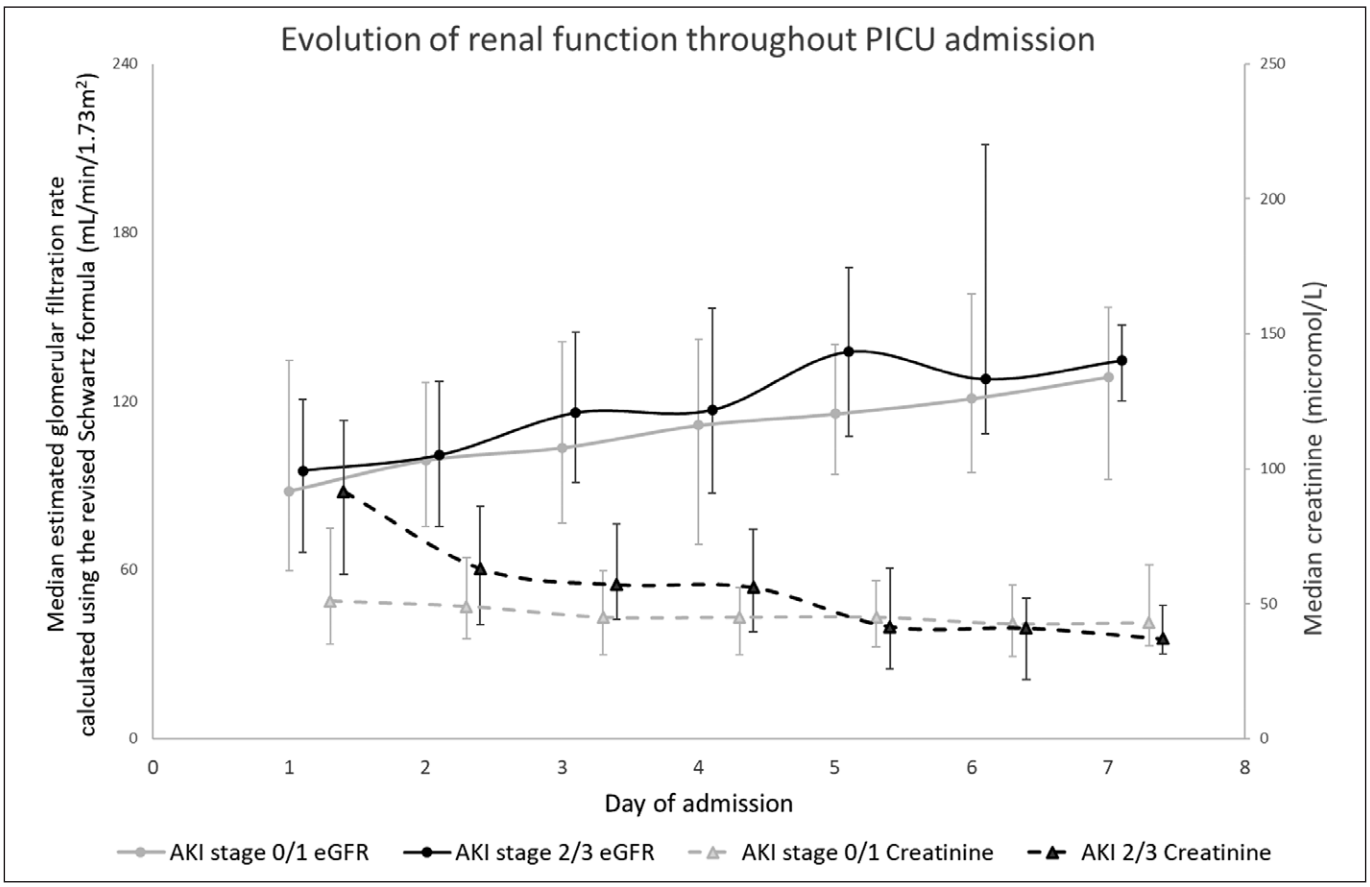

Figure 1. Evolution of renal function (serum creatinine and estimated glomerular filtration rate [eGFR]) during the course of PICU stay. AKI = acute kidney injury.

the presence of severe AKI, as shown in **Table 3** (adjusted odds ratio, 1.04; 95% CI, 1.01–1.08).

Impact of AKI on Patient Outcomes

Three patients received CRRT with a median duration of 3 days (IQR, 2–4 d), which was discontinued at discharge. Three patients received ECMO of which one patient had stage-3 AKI and received CRRT. Two patients (1.7%) died in PICU, of which one had stage-3 AKI at admission and the other progressed to stage-3 AKI over the course of PICU stay requiring both CRRT and ECMO. The median length of ICU stay was 5 days (IQR, 4–7 d) in patients with severe AKI compared with 3 days (IQR, 1.5–5 d) for no AKI/stage-1 AKI ($p < 0.001$). Duration of mechanical ventilation was longer in severe AKI patients at 4 days (IQR, 2–6 d) compared with 2 days (IQR, 1–3 d) in no AKI/stage-1 AKI patients ($p = 0.04$).

DISCUSSION

AKI is frequently multifactorial, with concomitant ischemic, nephrotoxic, and septic components, and with overlapping pathogenetic mechanisms. Hemodynamic status, inflammation, vascular endothelial, and tubular epithelial cell injury play an important role in the pathogenesis of AKI (26–30). PIMS-TS, as a novel condition characterized by fever and an inflammatory state with multiple organ involvement, might be expected, through several of these mechanisms, to be associated with AKI. We found that AKI affected nearly 40% of PIMS-TS patients within the first 48 hours of PICU stay. Hyperferritinemia was significantly associated with severe AKI, and children with severe AKI had a longer duration of ventilation and PICU stay.

It has been proposed that PIMS-TS may be a postinfectious immune response, since PCR positivity is uncommon (in our cohort, just 16%) and serology frequently demonstrates IgG antibodies (in our cohort, where tested, 48%). Antibodies against spike protein of SARS-CoV-1 have been demonstrated to accentuate inflammation (31, 32); therefore, AKI in the setting of PIMS-TS could be a part of the multisystem inflammatory syndrome precipitated by immune-complex deposition (8).

The relatively high proportion of children with AKI in our cohort (any AKI stage: 41.3%; and severe AKI: 27.6%) is different from the prevalence of AKI in other conditions (general PICU, cardiac, liver failure, KD, Kawasaki shock syndrome, neonates, bone marrow transplant, and septic shock), as shown in **Supplementary Table 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/F914) (15, 16, 33–39). In the international multicenter AKI study (Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology [AWARE]), any-stage AKI developed in 26.9% of patients admitted to PICU and severe AKI developed in 11.6% of all PICU admissions (15). This almost 2.5-fold greater prevalence of AKI in PIMS-TS may be explained by a combination of hypovolemia, cardiac dysfunction, and postinfectious antibody-mediated severe inflammation. Approximately 60% of our patients presented with vomiting and diarrhea and all had fever, predisposing them to dehydration. Recently, a single-center study in patients with confirmed SARS-CoV-2 infection reported that 11 of 24 patients who met PIMS-TS criteria had AKI (45.8%) (24). In particular, AKI has been reported to occur in approximately 28% of KD patients (16). Although the precise mechanism of AKI in KD patients remains unclear, vasculitis of arteries in the kidney, immune-complex-mediated renal injuries, and abnormalities of the T cell immune-function have all been implicated (40, 41).

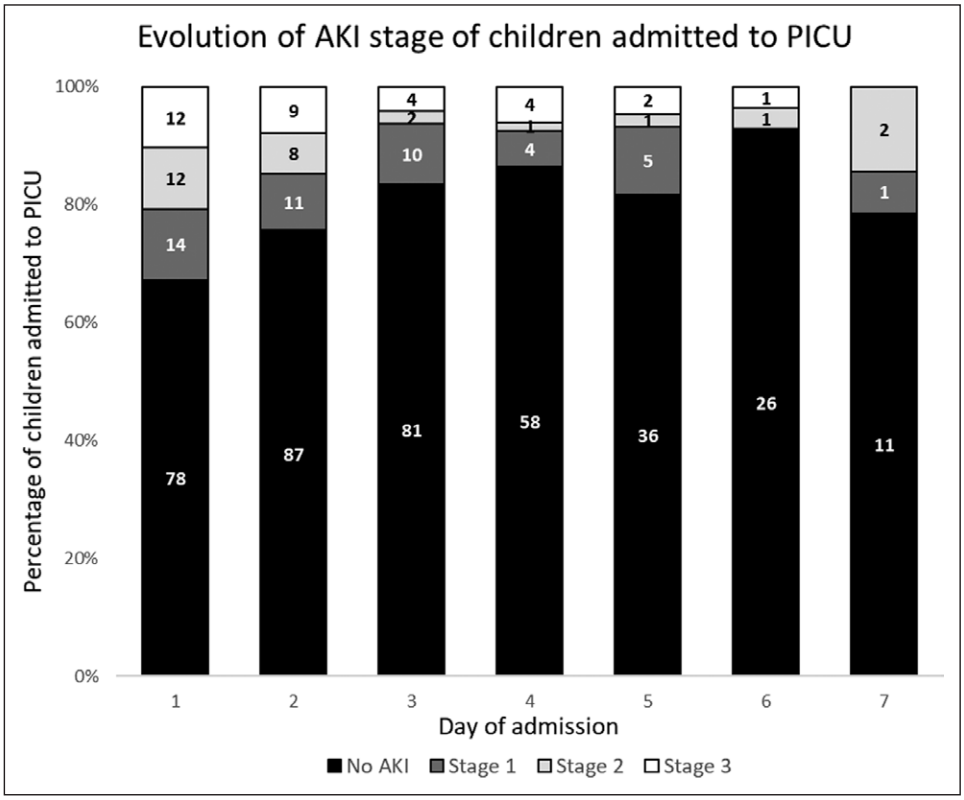

Figure 2. Evolution of acute kidney injury (AKI) stratified by the day of PICU admission. The number of admitted patients on PICU (*y*-axis) decreases progressively from days 1–7 (*x*-axis) as more children get discharged every day; three children remain with persistent AKI at day 7.

Our finding that 75% of the children who developed severe AKI had developed it at PICU admission (and almost all within the first 24–48 hr) reinforces the need for systematic surveillance for AKI in PIMS-TS at the time of PICU admission. Therefore, in addition to fluid resuscitation and use of inotropes/vasopressors for optimization of cardiac function, the impact of early use of

TABLE 1. Characteristics of Study Participants Cross Tabulated by Acute Kidney Injury Stage During PICU Admission

Variables	AKI Stage 0/1 ($n = 84$)	AKI Stage 2/3 ($n = 32$)	p
Demographics			
Median age, yr (IQR)	11 (7–14)	10 (8–14)	0.66
Male (%)	56 (67)	20 (63)	0.67
Ethnicity (%)			
Afro-Caribbean	30 (37)	21 (66)	0.03[a]
Asian	23 (28)	6 (19)	
Caucasian	19 (23)	5 (16)	
Other	9 (11)	0 (0)	
Median body mass index, kg/m^2 (IQR)	19.6 (16.3–24.2)	23.2 (17.5–30.3)	0.02[a]
SARS-CoV-2 status			
SARS CoV-2 polymerase chain reaction (%)	13 (15)	6 (19)	0.67
SARS-CoV-2 immunoglobulin G			
Positive (%)	39 (46)	17 (53)	
Admission parameters			
Median Paediatric Index of Mortality 3 score, % (IQR)	3.9 (1.4–4.8)	6.2 (1.6–10.8)	0.048[a]
Median lactate, mmol/L(IQR)	1.5 (1.2–2.5)	2.1 (1.2–3.3)	0.14
Median ferritin, ug/L (IQR)	426 (209–958)	1,107 (393–2,668)	0.009[a]
Median D-dimers, ng/mL (IQR)	3,745 (2,282–6,288)	5,000 (2,383–7,920)	0.32
Median C-reactive protein, mg/L (IQR)	190 (110–266)	250 (145–332)	0.05[a]
Median lactate dehydrogenase, U/L (IQR)	415 (270–656)	600 (367–1,049)	0.03[a]
Median troponin, ng/L (IQR)	60 (16–473)	436 (143–1,441)	0.001[a]
Median eGFR, mL/min/1.73 m^2	45 (14–79)	55 (46–68)	0.15
Median creatinine, umol/L	49 (32–66)	103 (78–150)	0.001
PICU management			
Admission urine output at 24 hr, mL/kg/hr (IQR)	1.1 (0.7–1.8)	1.1 (0.66–2)	0.8[a]
Admission fluid bolus (%)	51 (61)	23 (72)	0.26
Vasodilated shock (%)	39 (46)	18 (56)	0.34
Vasoconstricted shock (%)	8 (10)	6 (19)	0.17
Number of nephrotoxic agents (%)			
0	61 (73)	19 (60)	0.08[a]
1	14 (17)	3 (9)	
2	8 (9)	6 (19)	
3	1 (1)	4 (12)	
Vasopressor (%)	39 (46)	24 (75)	0.006
Inotropic agent (%)	49 (58)	25 (78)	0.047
Invasive mechanical ventilation (%)	22 (26)	19 (59)	0.001
Median duration of invasive mechanical ventilation, d (IQR)	2 (1–3)	4 (2–6)	0.04[a]
Median duration of PICU stay, d (IQR)	3 (1.5– 5)	5 (4–7)	< 0.001[a]
Day 7 eGFR, mL/min/1.73 m^2	134 (111–149)	126 (89–156)	0.5
Day 7 creatinine, umol/L	43 (36–46)	43 (30–67)	0.6

AKI = acute kidney injury, eGFR = estimated glomerular filtration rate, IQR = interquartile range, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

[a]Nonparametric hypothesis test used due to violation of normality assumption.

TABLE 2. Univariable Odds of Severe Acute Kidney Injury During PICU Admission As Estimated by Logistic Regression Modeling

Variables	OR (95% CI)	Wald *z* Statistic	*p*
Demographics			
Age (per 1 yr increase)	1.02 (0.93–0.12)	0.45	0.66
Male	1.2 (0.51–2.80)	0.42	0.67
Ethnicity			
Caucasian	Referent		
Afro-Caribbean	2.66 (0.86–8.25)	1.69	0.09
Asian	0.99 (0.26–3.76)	–0.01	0.99
Body mass index (per 1-unit increase in kg/m^2)	1.02 (1.001–1.035)	20.5	0.04
SARS-CoV-2 status			
SARS CoV-2 PCR	1.26 (0.43–3.66)	0.43	0.67
Admission parameters			
Lactate, mmol/L(per 1-unit increase)	1.20 (0.93–1.59)	1.41	0.16
Ferritin, ug/L (per 100-unit increase)	1.04 (1.01–1.08)	2.75	0.006
D-dimers, ng/ml (per 1,000-unit increase)	–0.01 (–0.07 to 0.44)	–0.42	0.68
C-reactive protein, mg/L (per 100-unit increase)	1.55 (1.05–2.28)	2.22	0.03
Lactate dehydrogenase, U/L (per 100-unit increase)	1.04 (0.98–1.09)	1.35	0.18
Troponin, ng/L (per 100-unit increase)	1.01 (1–1.02)	1.16	0.25
PICU management			
Paediatric Index of Mortality 3 score (per 10 % increase)	2.32 (1.04–5.19)	2.04	0.04
Median urine output at 24 hr, mL/kg/hr (per 1-unit increase)	1.09 (0.77–1.56)	0.49	0.62
Admission fluid bolus	1.65 (0.68–4.01)	1.11	0.27
Vasodilated shock	1.48 (0.65–3.37)	0.94	0.35
Vasoconstricted shock	2.19 (0.70–6.91)	1.34	0.18
Nephrotoxic agents	1.81 (0.77–4.26)	1.37	0.17
Vasopressor	3.46 (1.40–8.58)	2.68	0.007
Inotropic agent	2.55 (0.99–6.55)	1.94	0.05
Invasive mechanical ventilation	4.12 (1.75–9.70)	3.24	0.001
Duration of invasive mechanical ventilation (per one day increase)	1.24 (0.99–1.56)	1.84	0.06
Duration of PICU stay (per one day increase)	1.27 (1.09–1.59)	3.07	0.002

OR = odds ratio, SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2.

anti-inflammatory drugs on severity of AKI in this novel condition needs further exploration.

Development of AKI in PICU patients has been suggested to be reliably predicted by renal angina index, as shown by Basu et al (42). Early nephritis has been identified as a predictor of severe disease in COVID-19 including requirement for mechanical ventilation (43), therefore screening for nephritis at admission may also predict the ICU course in children with PIMS-TS. In our cohort, 59% of patients with severe AKI received IMV compared with 26% of no AKI/stage-1 AKI patients. Development of AKI is an independent risk factor for mortality in patients with acute respiratory distress syndrome. High intrathoracic pressures in ventilated children as a consequence poorly compliant lungs can reduce cardiac output, which results in inadequate renal perfusion; subsequent gas-exchange abnormalities resulting in hypoxemia, hypercarbia, and systemic acidosis could influence renal vascular resistance, altering renal perfusion pressures, resulting in AKI (44, 45) In line with previous work, we identified an association between BMI and AKI in our cohort (46). Although ferritin, as an

TABLE 3. Multivariable Odds of Severe Acute Kidney Injury During PICU Admission As Estimated by Logistic Regression Modeling (Area Under the Curve = 0.74)

Outcome: Severe AKI (AKI Stage 2/3)	Multivariable Analysis (Base Model)		
	OR (95% CI)	Wald *z* Statistic	*p*
Body mass index (per 1-unit increase in kg/m^2)	1.06 (0.98–1.13)	1.49	0.14
Ferritin, ug/L (per 100-unit increase)	1.04 (1.01–1.08)	2.09	0.04
Paediatric Index of Mortality 3 score (per 10% increase)	1.72 (0.58–5.13)	0.97	0.33

AKI = acute kidney injury, OR = odds ratio.

antioxidant, can be a marker of renal recovery (47), our finding that hyperferritinemia at admission was associated with AKI may be related to the intense inflammatory state in PIMS-TS. As shown in a number of studies in critically ill children, including in our cohort, significantly more children with severe AKI had received two or more nephrotoxic drugs compared with children with no AKI/stage-1 AKI (48).

Similar to previous studies (15, 49–50), we found an adverse effect of AKI on patient outcomes such as mortality, length of stay (LOS), and duration of ventilation (PICU LOS and length of ventilation [LOV] were nearly double in patients with severe AKI compared with those with no AKI/stage-1 AKI), with important implications in the setting of a pandemic where ICU resources may be limited. The effect of resource limitation may become even more profound if patients with AKI require CRRT (18). Patients who died in our cohort had stage-3 AKI (one at admission and the other within 24 hr of admission to the PICU). Resolution of AKI occurred in all patients except three. Two of these three patients received CRRT and had stage-2 AKI at day 7, whereas the third patient was left with stage-1 AKI at day 7.

From May 20 (end of our study period) to July 26, 2020, i.e., in over 2 months, 12 of the 15 PICUs reported no new cases, whereas just three units admitted 11 patients with PIMS-TS. Only one of these 11 patents was ventilated. This reduction in PIMS-TS/MIS-C cases can be explained by the reduction in the number of adults (and therefore children) with COVID-19. **Supplementary Figure 1** (Supplemental Digital Content 4, http://links.lww.com/CCM/F916; legend: weekly incidence of cases of PIMS-TS and incidence of severe AKI) shows the weekly distribution of patients superimposed by the number of patients with AKI.

Considering the risk of a second surge and further cases of pediatric PIMS-TS cases, this study highlights the risk factors for AKI in this condition and how the impact of AKI could be minimized. This is especially important in those places where PIMS-TS cases have started to be seen. Since the submission of this manuscript, we are aware of national guidelines being produced for this condition through research networks. Incorporating early surveillance to detect AKI in national guidelines would be a positive step for early diagnosis and management of AKI in this condition.

PIMS-TS is a new condition and novel treatments are being trialed, which may influence the prevalence and evolution of AKI. In addition to its retrospective nature, data were collected from 15 different PICUs from across the UK and management of the patients was determined by individual centers. Complete follow-up of patients was not available. Markers of kidney involvement such as proteinuria and hematuria, which have been shown to be associated with capillary leak and degree of renal damage both in the short and long terms (39), were not performed in all patients. Additionally, we did not have baseline serum creatinine for most patients, as they were previously healthy children. Since this was an observational noninterventional cohort study, we cannot make statements regarding causal relationships among severity of AKI and observed associations. These observations need to be tested in a large cohort of patients.

CONCLUSIONS

Prevalence of AKI in PIMS-TS is high, and most patients who develop AKI do so either at admission or within 48 hours. Factors associated with severe AKI include high BMI, raised CRP, hyperferritinemia, and high PIM3 score at admission. Severe AKI is associated with increased LOS and LOV. Although short-term outcomes of AKI in PIMS-TS appear good, long-term outcomes are less well understood in this cohort, indicating the need for close follow-up by a multidisciplinary team.

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The project was classified as a service evaluation project by the King's College Hospital Research and Innovation Team (CH-058-20), and ethics approval was not required. The study team analyzed routinely collected deidentified data submitted by clinicians from the individual PICUs as a local service evaluation. Deidentified data were submitted for central analysis using a secure National Health Service server with password-protected files at either end.

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