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Acute kidney injury in Pediatric Inflammatory Multi-system Syndrome Temporally associated with SARS-CoV-2 pandemic (PIMS-TS): experience from Pediatric Intensive Care Units across United Kingdom

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ABSTRACT

Objectives: To study the prevalence, evolution and clinical factors associated with acute kidney injury (AKI) in children admitted to pediatric intensive care units (PICUs) with Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS).

Design: Multicentre observational study.

Setting: 15 PICUs across the United Kingdom (UK).

Patients: Patients admitted to UK PICUs with PIMS-TS between 14 March 2020 and 20 May 2020.

Interventions: None.

Measurements and Main Results: De-identified data collected as part of routine clinical care was analysed. All children were diagnosed and staged for AKI based on the level of serum creatinine above the upper limit of reference interval (ULRI) values according to published guidance. Severe AKI was defined as stage 2/3 AKI. Uni- and multi-variable analyses were performed to study the association between demographic data, clinical features, markers of inflammation and cardiac injury, and severe AKI. Over the study period, 116 patients with PIMS-TS were admitted to 15 UK PICUs. Any-stage AKI occurred in 48/116 patients (41.4%), and severe AKI in 32/116 (27.6%) patients, which was mostly evident at admission (24/32, 75%). In univariable analysis, body mass index, hyperferritinemia, high C-reactive protein (CRP), Pediatric Index of Mortality 3 (PIM3) score, vasoactive medication and invasive mechanical ventilation (IMV) were associated with severe AKI. In multivariable logistic regression, hyperferritinemia was associated with severe AKI (compared to non-severe AKI, adjusted odds ratio 1.04, 95% CI 1.01-1.08, p=0.04). Severe AKI was associated with longer PICU stay (median 5 days [IQR 4,7] vs 3 days [IQR 1.5,5], p<0.001) and increased duration of IMV (median 4 days [IQR 2,6] vs 2 days [IQR 1,3], p=0.04).

Conclusions: Severe AKI occurred in just over a quarter of children admitted to UK PICUs with PIMS-TS. Hyperferritinemia was significantly associated with severe AKI. Severe AKI was associated with increased duration of stay and ventilation. Although short-term outcomes for AKI in PIMS-TS appear good, long-term outcomes are unknown.

Keywords: acute kidney injury; children; PIMS-TS; MIS-C; coronavirus; intensive care, children; pandemic; COVID-19

INTRODUCTION

Novel Coronavirus Disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV2) was declared a global pandemic by World Health Organization (WHO) in March 2020, and by 20 June 2020, had affected nearly 9 million people 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 less frequently and less severely affected by COVID-19 [2]. However, from March onwards, 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 Multi-system Syndrome Temporally Associated with SARS-CoV-2 Pandemic (PIMS-TS) in the UK, and Multi-system 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 (CDC) and the WHO [3-5]. Diagnostic criteria common to all case definitions include presence of fever, inflammation and multi-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 (TSS) and Kawasaki disease shock syndrome (KDSS) [6-12].

Approximately 10% of all patients admitted to the pediatric intensive care units (PICU) 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 aetiology and pathogenesis of AKI may be multifactorial: it could develop in PIMS-TS as a part of multi-system 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 post infectious 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 to May 2020.

METHODS

Study design

This is a multi-centre observational study of children less than 18 years of age, admitted to PICUs in the United Kingdom over a 7-week period (14th March 2020 to 20th May 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, de-identified the data, and submitted it to the central study team using password protected datasheets via a secure NHS 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, creatine kinase 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 judgement. Amount of fluid resuscitation, use of inotropes and vasopressors, use of mechanical ventilation (invasive and non-invasive), 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 multi-disciplinary team.

Renal parameters

Serial values of serum creatinine and urine output as well as use of nephrotoxic drugs (listed in supplementary Table 1), 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 criteria (KDIGO) criteria [21]. We therefore referenced serum creatinine values for our cohort against age-specific upper limit of reference interval (ULRI) values according to published guidance from the British Association of Pediatric Nephrology (BAPN). These ranges were proposed at the Pediatric Laboratory Medicine Network (PaLMnet) 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 rise of serum creatinine above the ULRI (AKI Stage 1: 1.5-2x ULRI; AKI Stage 2: 2-3x ULRI, Stage 3: >3x 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 2 groups: no AKI /stage 1 AKI and stage 2/3 AKI (severe AKI). We used the Schwartz formula to calculate estimated GFR (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 demographic factors, clinical and biochemical parameters (at PICU admission and 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 explanatory variables and severe AKI (outcome), ensuring that only variables with <20% missing data and a plausible link to severe AKI were used, recognising 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 over-fitting, the most parsimonious model with best model fit, as assessed by area-under-curve (AUC) was reported. A 2-sided p value ≤ 0.05 was considered statistically significant.

Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are expressed as numbers and percentages (%)..Where data was missing, individual data points were excluded from descriptive statistics, but handled as missing data in logistic models. Pearson's Chi-squared test and/or Fisher's exact test were used to compare categorical variables between groups. Student's *t*-test and the Kruskal-Wallis test were used to compare continuous variables between groups depending on the normality of the distribution. All analyses were performed using STATA software (version 14.2, StataCorp, Texas, United States) and Excel version 2016 (Microsoft, Redmond, United States).

RESULTS

Out of 24 UK PICUs, 15 admitted patients with PIMS-TS and submitted data for 116 children admitted with PIMS-TS between 14th March 2020 and 20th May 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 6 and 23 patients respectively have also been presented in single centre reports [8, 12, 25].

As shown in Supplementary Table 1, the median age was 11 years (IQR 7-14) and the majority of patients were male (66%); nearly one-half were of Afro-Caribbean ethnicity (45%) and a quarter were Asian (26%). None had chronic kidney disease. The main presenting symptoms included fever and gastrointestinal symptoms (68% had abdominal pain; over half had diarrhoea 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, creatine kinase 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) whilst another 21% received non-invasive 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 (12%) patients were admitted for 7 or more days.

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

Renal Characteristics *at admission*

Median serum creatinine of all patients at PICU admission was 61[IQR 37-90] micromol/L, median urine output at 24 hours of admission was 1.1 ml/kg/hour [IQR 0.7-1.9 ml/kg/hour], 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 at admission to the PICU (24/32, 75%).

Evolution of AKI

Of the 78 children who did not have AKI at admission, 9 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%), while 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 of eGFR (Figure 1). Serum creatinine decreased in severe AKI from a median of 103 micromols/litre to 43 micromols/litre, while the eGFR in this group increased from a median of 55 ml/min/1.73 m2 to 126 ml/min/1.73 m2. Apart from 3 patients, AKI in all other patients had resolved by the time of discharge from PICU (one had stage 1 and two had stage 2 AKI). Figure 2 summarises the evolution of AKI over the first 7 days of PICU stay. Supplementary figure-1 shows the weekly distribution of patients with PIMS-TS superimposed by the number of patients with severe AKI.

Factors associated with AKI

Comparison of patients with no AKI/stage 1 AKI versus severe AKI is shown in Table 1. There were ~~obvious~~ differences in ethnicity, 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 2 or more nephrotoxic drugs compared to 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). When these three variables were entered into a multivariate model, hyperferritinemia was the only factor independently associated with 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) which was discontinued at discharge. Three patients received ECMO of which 1 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

days) in patients with severe AKI compared to 3 days (IQR 1.5-5 days) 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 days) compared to 2 days (IQR 1-3 days) in no AKI/stage 1 AKI patients ($p=0.04$).

DISCUSSION

Acute kidney injury 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 characterised by fever and an inflammatory state with multi-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. Amongst other factors, mechanical ventilation and obesity were important predisposing factor for severe AKI. 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 post-infectious 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 multi-system 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, Kawasaki disease, Kawasaki shock syndrome, neonates, bone marrow transplant and septic shock) as shown in Supplementary Table-2 [15,16,33, 34, 35, 36, 37, 38, 39]. In the international multicenter AKI study (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 post-infectious antibody mediated severe inflammation. Approximately 60% of our patients presented with vomiting and diarrhoea and all had fever, predisposing them to dehydration. Recently, a single centre study in patients with confirmed SARS-CoV-2 infection reported that 11/24 patients who met PIMS-TS criteria had AKI (45.8%) [24]. In particular, AKI has been reported to occur in approximately 28% of Kawasaki disease 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].

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 hours) 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 optimisation of cardiac function, the impact of early use of 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 to 26% of no AKI/stage 1 AKI patients. 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]. Though ferritin, as an anti-oxidant, can be a marker of renal recovery [47], our finding that hyperferritinaemia 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 2 or more nephrotoxic drugs compared to children with no AKI/stage 1 AKI [48].

Similar to previous studies [15,49-51], we found an adverse effect of AKI on patient outcomes such as mortality, length of stay and duration of ventilation (PICU LOS and LOV were nearly double in patients with severe AKI compared to 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 hours of admission to the PICU). Resolution of AKI occurred in all patients except three. Two of these 3 patients received CRRT and had stage 2 AKI at day 7 whilst the third patient was left with stage 1 AKI at day 7.

Considering the risk of a second surge and further cases of PIMS-TS being reported even in young adults [52,53], the findings of this study are valid for both children and adults and highlight the risk factors for AKI in this condition, and how the impact of AKI could be minimised. This is especially important in those places where PIMS-TS cases have started to be seen adding additional strain to the already stretched resources. There

is an important role of research networks to collaborate internationally to produce guidelines for this novel condition. Incorporating early surveillance to detect AKI would be a positive step for early diagnosis and management in this condition.

Limitations

PIMS-TS is a new condition and novel treatments are being trialled which may influence the prevalence and evolution of AKI. In addition to its retrospective nature, data was collected from 15 different PICUs from across the UK and management of the patients were 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 term [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 non-interventional cohort study, we cannot make statements regarding causal relationships amongst severity of AKI and observed associations. These observations need to be tested in a large cohort of patients.

Conclusion: 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, hyperferritenemia and high PIM3 score at admission. Severe AKI is associated with increased length of stay and length of ventilation. 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.

FIGURE LEGENDS

Figure 1: Evolution of renal function (serum creatinine and eGFR) during the course of PICU stay

Figure 2: Evolution of AKI stratified by the day of PICU admission

Supplementary Figure-1 – Weekly incidence of cases of PIMS-TS and incidence of severe AKI

TABLE LEGENDS

Table 1: Characteristics of study participants cross tabulated by AKI stage during PICU admission

Table 2: Univariable odds of severe AKI during PICU admission as estimated by logistic regression modelling

Table 3: Multivariable odds of severe AKI during PICU admission as estimated by logistic regression modelling

Supplementary Table 1: Baseline characteristics and patient clinical course of the sample population

Supplementary Table 2 : Co-morbidities in the study population

Supplementary Table 3 : Major AKI studies in children comparing incidence of severe AKI and mortality

DECLARATIONS

Conflicts of Interest

All authors declare that the answer to the questions on your competing interest form, www .icmje.org/coi_disclosure.pdf, are all No and therefore have nothing to declare

Financial Disclosure

No funding was received for this project and as such the authors have nothing to declare.

Ethical Statement:

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 analysed routinely collected de-identified data submitted by clinicians from the individual PICUs as a local service evaluation. De-identified data were submitted for central analysis using a secure NHS server with password protected files at either end.

Contribution statement

1 Literature Search

2 Figures

3 Study Design

4 Data Collection

5 Data Analysis

6 Data interpretation

7 Writing

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