Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Kidney and blood pressure abnormalities 6 years after acute kidney injury in critically ill children: a prospective cohort study

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BACKGROUND: Acute kidney injury (AKI) in pediatric intensive care unit (PICU) children may be associated with long-term chronic kidney disease or hypertension. Objectives: To estimate (1) prevalence of kidney abnormalities (low estimated glomerular filtration rate (eGFR) or albuminuria) and blood pressure (BP) consistent with pre-hypertension or hypertension, 6 years after PICU admission; (2) if AKI is associated with these outcomes.

METHODS: Longitudinal study of children admitted to two Canadian PICUs (January 2005–December 2011). Exposures (retrospective): AKI or stage 2/3 AKI (KDIGO creatinine-based definition) during PICU. Primary outcome (single visit 6 years after admission): presence of (a) low eGFR (<90 ml/min/1.73 m^2) or albuminuria (albumin to creatinine ratio >30 mg/g) (termed "CKD signs") or (b) BP consistent with ≥pre-hypertension (≥90th percentile) or hypertension (≥95th percentile).

RESULTS: Of 277 children, 25% had AKI. AKI and stage 2/3 AKI were associated with 2.2- and 6.6-fold higher adjusted odds, respectively, for the 6-year outcomes. Applying new hypertension guidelines attenuated associations; stage 2/3 AKI was associated with 4.5-fold higher adjusted odds for 6-year CKD signs or ≥elevated BP.

CONCLUSIONS: Kidney and BP abnormalities are common 6 years after PICU admission and associated with AKI. Other risk factors must be elucidated to develop follow-up recommendations and reduce cardiovascular risk.

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INTRODUCTION

Over 15% of children in the pediatric intensive care unit (PICU) develop acute kidney injury (AKI).[1,2] AKI is independently associated with mortality, length of stay and mechanical ventilation duration.[1–4] Animal studies and adult epidemiological studies demonstrate that AKI may progress to chronic kidney disease (CKD) or hypertension (HTN).[5–7] The pathophysiology of acute to chronic kidney disease includes ongoing inflammation, peritubular capillary loss with chronic hypoxia, interstitial fibrosis and chronic damage to remaining healthy nephrons.[5,7] CKD and HTN are treatable cardiovascular risk factors which, if present in childhood, may lead to long-term increased morbidity.[8,9]

Studies of children with AKI have shown a high prevalence of CKD and HTN at variable follow-up times after hospital discharge;[10–12] however, few studies included non-AKI controls.[10] One study performed in neonates undergoing extracorporeal membrane oxygenation, who were followed up for a median of 8 years, showed that of all factors evaluated, only AKI (vs. no AKI) was associated with the presence of CKD during follow-up.[13] However, recent studies of children undergoing cardiac surgery showed that CKD and HTN 5 years after discharge were common, but not consistently associated with post-operative AKI.[14,15] Thus, the association of AKI with long-term CKD and HTN in children remains unclear. This uncertainty precludes the confident development of evidence-based guidelines for pediatric AKI follow-up and may contribute to the current lack of AKI follow-up in pediatric care.[16] Understanding the association between pediatric AKI and long-term CKD and HTN development will guide follow-up recommendations, enable more consistent follow-up by primary care providers and nephrologists, and may allow early intervention for kidney and cardiovascular disease reduction.

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We hypothesized that CKD and HTN are common in children previously admitted to the PICU and that AKI increases long-term risk for CKD or HTN development. During a single study visit performed 6 years after admission to the PICU, we estimated the prevalence of low-estimated glomerular filtration rate (eGFR) or albuminuria (as a surrogate measure for signs of CKD) and of blood pressure consistent with pre-HTN and HTN. We also examined the association between AKI and these outcomes.

MATERIALS AND METHODS

Design, setting and subject selection

This was a cross-sectional cohort study performed at 6 years ± 6 months after admission to the Montreal Children's Hospital (Montreal, Canada) or Stollery Children's Hospital (Edmonton, Canada) PICUs. Inclusion criteria were: PICU admission of ≥2 calendar days, between January 2005 and December 2011; <18 years old at PICU admission. Exclusion criteria were: pre-existing kidney transplant or dialysis; baseline (pre-illness) eGFR <30% normal for age[17] or known chronic kidney conditions (e.g., tubulopathy, glomerular diseases); unwillingness to return to the study center for assessments or lived too far (>3.5-h drive) from the study center for home visits. Children admitted to the PICU for cardiac surgery were excluded from the analysis due to their unique AKI risk factors and already similar published research.[14] Institutional Research Ethics Boards approved the study. Parents/legal guardians provided written informed consent (assent from children >7 years old) to participate.

Study population sources

Participants were recruited from two cohorts of patients:

1. Montreal Children's Hospital PICU cohort (Montreal only): This was a previously studied and previously described Montreal PICU cohort. These patients originally participated in a prospective PICU study to validate AKI biomarkers.[18] Subjects from this cohort, who consented to being contacted for future studies, were reviewed for eligibility and contacted by phone at about 5–6 years after the original PICU study participation.
2. The "Mailing" cohort (Edmonton and Montreal): All patients at both sites who were previously admitted to PICU were identified via hospital databases, reviewed for eligibility and mailed invitations to contact us for study information. Responders were contacted, re-reviewed for eligibility and invited to participate.

Study procedure, data collection

Procedure. A study visit was performed at the participant's home or at the study center, at 6 years ± 6 months after the index PICU discharge. The main purpose of the study visit was to obtain kidney and blood pressure outcome data. Blood (1.5–5 ml) and urine (random specimen, 5–30 ml, in a collection cup, collection bag or from the diaper using cotton balls, as appropriate) were collected during the visit. Urine samples were collected at the time of the visit and were not first-morning samples. Three height measures (SECA 217 stadiometer, SECA, Hamburg, Germany; measuring tape if limited mobility) and weight measures (UC-321 PL Precision Health scale, A&D Medical, Milpitas, CA; barefoot; bulky clothing removed) were taken; the average was calculated and expressed as percentiles.[19] Three automated blood pressure measures were performed (Omron HEM-711AC, Omron Healthcare, Inc., Bannockburn, Illinois; regularly calibrated) in a quiet setting (efforts to reduce anxiety; before blood work), with the participant seated, using size-appropriate cuffs on the right arm (unless contraindicated, then left arm was used). When automated blood pressure was unsuccessful, auscultatory blood pressure was performed. Average blood pressure was used to calculate blood pressure percentile.[19]

Study visit clinical data. Questionnaires included past medical history/comorbidities (categorized manually as presence/absence of separate organ comorbidities which were then adjudicated) and medications (Supplemental Fig. 1, online, example case report form). Study staff were blind to past AKI status.

Study visit laboratory data. Blood and urine specimens were kept on ice, centrifuged at 2000 RPM for 15 min at 21 °C, separated into aliquots and stored at −80 °C until analysis at the Montreal Children's Hospital laboratory (blinded to clinical data). Blood was measured for serum creatinine (SCr) (enzymatic, isotope-dilution mass spectrometry-traceable). Urine was measured for albumin (nephelometry, Prospec II, Siemens, Erlangen, Germany) and creatinine (modified Jaffe assay).

Retrospectively collected index PICU admission data. After study visits were performed, health records from the index PICU hospitalization were reviewed by research assistants different from the staff who performed study visits. Data collected retrospectively included: pre-PICU history (including kidney disease and HTN), a modified Pediatric Risk of Mortality III (PRISM III) score[20] (excluding creatinine component to avoid correlation with AKI), presence/absence of sepsis (based on 'sepsis' diagnosis in admission, discharge or progress notes) and PICU treatments and outcomes (e.g., diagnoses, vasopressors, diuretics, nephrotoxins (including non-steroidal anti-inflammatory drugs, aminoglycosides, acyclovir, ganciclovir, amphotericin and vancomycin), dialysis, ventilation, admission/discharge dates). Daily PICU SCr values and baseline SCr (lowest SCr in the 3 months before PICU) were also collected.

Main exposure: AKI. The primary exposure was AKI during PICU, ascertained retrospectively, and defined based on the SCr criteria of the Kidney Disease: Improving Global Outcomes (KDIGO) definition (≥1.5 times baseline within 7 days or ≥26.5 µmol/l SCr rise from baseline within 48 h). When baseline SCr was unknown (which is typical for the majority of PICU patients),[1,16,21] it was estimated using the Chronic Kidney Disease in Children (CKiD) SCr-based bedside GFR (eGFR) equation;[22] we assumed baseline eGFR = 120 ml/min/1.73 m^2 in children >2 years old and we assumed age-specific normative GFR values in children <2 years old, as described.[17,21] When height was missing, a validated age-based eGFR equation was used to estimate baseline SCr, as described.[23,24] We previously showed that this method of estimating baseline SCr (using age-based normative values and height-independent equations) led to very low bias in baseline SCr estimation.[21] We also evaluated severe AKI (≥stage 2; SCr ≥2 times baseline) as an exposure, which has been associated with short-term morbidity and mortality.[1] We did not retrospectively collect urine output data, required for applying the KDIGO urine output criteria for AKI definition, due to common occurrence of missing urine output values and the presence of high center/physician variability in catheterization practices. Therefore, only the SCr criteria for AKI definition were used. We a priori decided to keep in the analysis those patients with no SCr measures in PICU to avoid outcome estimates being biased. For primary analyses, patients with no SCr available were classified as non-AKI, as previously performed in adult studies (with a rationale that they were likely less ill and at lower risk for AKI).[25]

Outcomes: 6-year signs of CKD, pre-HTN or worse and HTN, assessed at a single study visit. The presence of signs of CKD (hereafter referred to as CKD_{signs} was based on the accepted definition of Stage 2 CKD: presence of eGFR <90 ml/min/1.73 m^2 or albuminuria (urine albumin/creatinine >30 mg/g).[26]

The presence of blood pressure consistent with pre-HTN and HTN was based on definitions in The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (≥90th percentile or ≥95th percentile, respectively) or using adult guidelines if ≥18 years old.[27]

The primary outcomes were composite outcomes of either (a) presence of CKD_{signs} (i.e., low eGFR or albuminuria) or presence of blood pressure consistent with pre-HTN or worse (≥pre-HTN), and (b) presence of CKD_{signs} or blood pressure consistent with HTN. Of note, according to CKD and HTN definition guidelines, performing more than one visit is ideal for diagnosis; we only performed one study visit and thus only had one measurement period available to determine outcomes. For this reason, rather than referring to Stage 2 CKD as an outcome, we refer to "CKD_{signs}" (low eGFR or albuminuria) to acknowledge the lack of repeat measures. For the purpose of this study, for simplicity, we refer to the presence of abnormal blood pressure during the single study visit as ≥pre-HTN and HTN, acknowledging that ideal diagnosis should be made with blood pressures from more than one visit.

After analyses were complete, new HTN guidelines were published.[28] We therefore also defined outcomes by these new guidelines in secondary analyses (whereby "pre-HTN" is referred to as "elevated blood pressure" by the new guidelines, but the designation for HTN is the same). For composite measures (e.g., low eGFR or albuminuria, for presence of CKD_{signs}), when one value was missing, patients were classified as having the outcome if the other outcome was abnormal; when one value was missing but the other outcome was normal, the composite outcome was classified as missing. Secondary outcomes were the separate components of each of the composite outcomes (i.e., eGFR, albuminuria and blood pressure percentiles evaluated separately).

Power

Prior to obtaining funding for and initiating this study, there were almost no data available upon which to estimate required sample size (only a few studies which only included AKI patients had been published). We performed a pilot study to demonstrate feasibility of and evaluate barriers for performing home-based study visits and to estimate event rates. Together with previously published long-term data on CKD and HTN outcomes available only in AKI patients at that time, our target sample size was aimed to (a) allow reasonably precise estimation (95% precision level of atleast ±5%) of prevalence of CKD_{signs} of ~25% and prevalence of HTN at ~17%, and (b) to have >95% power to detect an AKI vs. non-AKI difference in outcome of at least ~20%, assuming that ~40% of our study sample would have had past AKI (as our pilot study suggested sicker patients would be more likely to respond to mailed invitations). The initial target sample size was to include 98 subjects from the previously studied Montreal Children's Hospital PICU cohort (Montreal only, previously studied cohort) and 128 children from the newly formed Mailing Cohort (Montreal and Edmonton; we had assumed only a 10% response rate from mailed letters). The response rate from mailed letter invitations was slightly higher than expected and our AKI exposure rate was lower than expected (see Results). We therefore decided to include all subjects who responded, leading to our final sample size which was higher than our target sample size.

Statistical analysis

Outcome prevalence (%) and eGFR, blood pressure percentile and albumin to creatinine ratio (mean, standard deviation (SD)) were calculated for the whole cohort and by AKI status. Characteristics were compared by AKI status and 6-year outcome status using appropriate univariable tests. Associations between AKI and outcomes were evaluated by univariable logistic regression (reporting unadjusted odds ratio (OR), 95% confidence intervals (CI)) and multiple logistic regression was used to estimate adjusted ORs. Covariates for each multivariable regression model were selected for inclusion in the model if they were associated with the composite outcome (at p-value = 0.2) of CKD_{signs} or ≥pre-HTN (when this was the outcome) or with CKD_{signs} or HTN (when this was the outcome), in univariable analysis. We a priori planned to evaluate effect modification by determining if interaction terms of AKI with other covariates were statistically significant (interaction terms with p-value < 0.1 were kept in the multivariable models).

Two sensitivity analyses were performed; one excluding patients with no AKI status available and the second, using the 2017 blood pressure guidelines. Analyses were performed using Stata statistical software (Version 12.0, StataCorp, College Station, TX).

RESULTS

Study population, AKI and 6-year composite outcome prevalence

The analysis cohort included 277 patients (Fig. 1). Response rate of patients contacted from the previously studied Montreal Children's Hospital PICU cohort and the "Mailing" cohort from both sites, are shown in Fig. 1; consent rate in responders was ~80% in both cohorts (Fig. 1). Responders and non-responders did not significantly differ in gender distribution and PICU length of stay; non-responders were older (Supplemental Table S1 (online)). Comparison of Edmonton vs. Montreal participants is shown in Supplemental Table S2 (online).

Sixty-nine patients (25%) developed AKI in PICU. Patients with AKI had more frequent SCr measures during the study period; patients with AKI had at least one SCr measure on 90% of study days, whereas non-AKI patients had at least one SCr measure on 50% of days ($p < 0.05$). Participants were followed at mean 5.7 (SD 1.1) years after admission. The primary outcomes were present at follow-up in 77/264 (29%) patients with available data (i.e., $n = 264$ with blood, urine or blood pressure collected) for CKD_{signs} or ≥pre-HTN and in 60/262 (23%) for CKD_{signs} or HTN. Three patients in the total cohort (one without AKI and two with AKI) had eGFR < 60 ml/min/1.73 m^2 at follow-up. Table 1 shows PICU admission characteristics between patients with vs. without AKI and Table 2 compares characteristics between patients with vs. without 6-year outcomes (CKD_{signs} or ≥pre-HTN; CKD_{signs} or HTN). Baseline SCr was estimated in 214 (77%) patients (76% of non-AKI vs. 81% of AKI patients, $p = 0.4$). Patients with vs. without baseline SCr had similar characteristics except patients without a baseline SCr were significantly younger (median 1.5 vs. 2.5 years old, Supplemental Table S3 (online)).

Univariable association of AKI with primary composite outcomes and individual outcomes

AKI and severe AKI were more common in participants with vs. without 6-year CKD_{signs} or ≥pre-HTN (Table 2 lower portion, 34% vs. 21% had AKI, respectively, $p = 0.04$; 16% vs. 8% had severe AKI, respectively, $p = 0.045$). A similar but non-statistically significant association was found between AKI and CKD_{signs} or HTN (Table 2).

Figure 2 demonstrates that with increasing AKI severity, there was a non-statistically significant graded rise in 6-year prevalence of CKD_{signs} (19% for non-AKI to 32% for severe AKI, Fig. 2a). This graded AKI-outcome relationship was not evident for the outcomes of ≥pre-HTN or for HTN (Fig. 2a). Figure 2b shows that there was a statistically significant graded rise in prevalence of the composite outcome of CKD_{signs} or ≥pre-HTN across worsening AKI severity categories ($p < 0.05$), with the prevalence of CKD_{signs} or ≥pre-HTN being significantly higher in the Stage 2 or 3 AKI severity category compared to the No or Unknown AKI category (~45 vs. 25%, respectively, $p < 0.05$).

When individual components of the composite outcomes were examined as continuous variables, eGFR at follow-up was significantly lower in the AKI group (117 ± 29 vs. 132 ± 34 ml/min/1.73 m^2, $p = 0.002$). Other individual outcomes (e.g.,

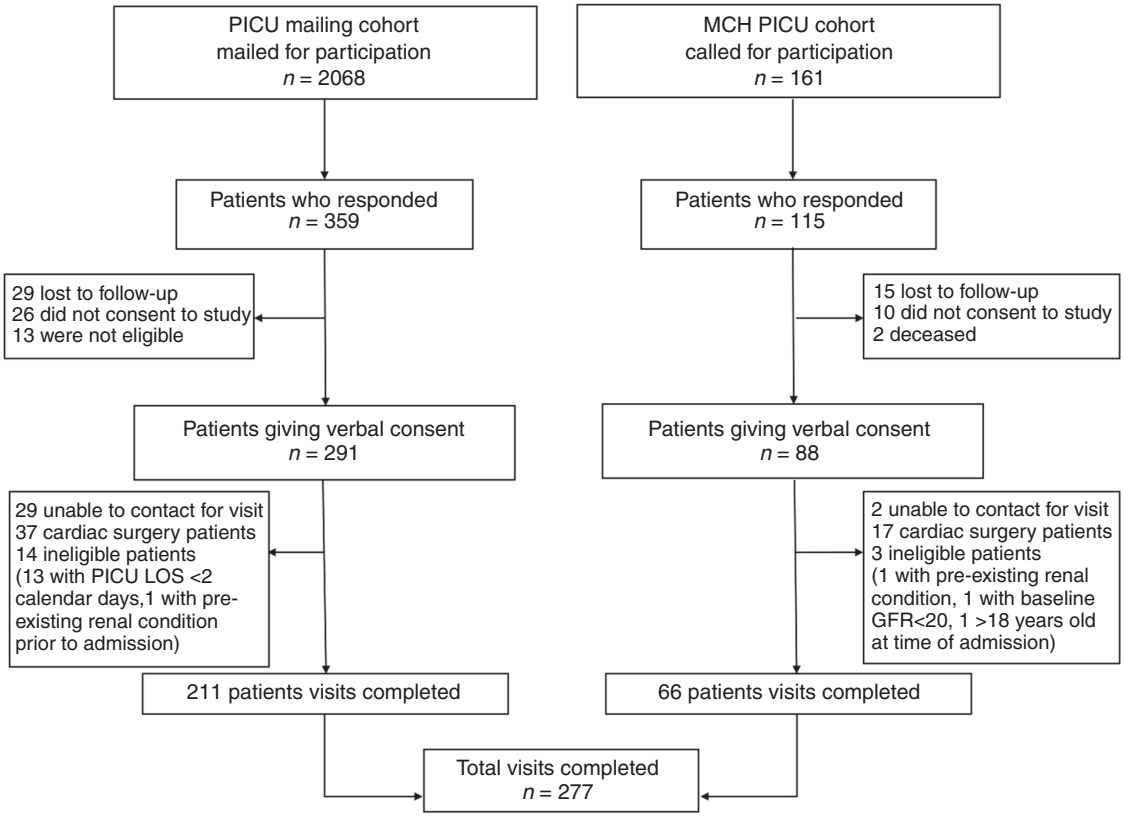

Fig. 1 Study flow. PICU pediatric intensive care unit, MCH Montreal Children's Hospital, LOS length of stay, GFR glomerular filtration rate.

albuminuria, blood pressure percentiles) were not statistically significantly different between AKI vs. non-AKI groups (Supplemental Table S4 (online)).

Multivariable analysis of relationship between AKI and 6-year outcomes

AKI and severe AKI were associated with 2.2 and 6.6 higher adjusted odds of 6-year CKD_{signs} or ≥pre-HTN ($p = 0.02$ and $p = 0.01$, respectively, Table 3). When the 6-year outcome was CKD_{signs} or HTN, neither AKI nor severe AKI were significantly associated (Table 3).

Sensitivity analysis: excluding participants with unknown AKI status

Patients who were known to not have AKI during PICU admission (i.e., SCr was available during PICU admission to ascertain AKI status) had significantly higher proportion of males, higher illness severity markers and longer length of stay vs. the 57 patients with unknown AKI status (i.e., no SCr was available during PICU admission) (Supplemental Table S5 (online)). When excluding patients with unknown AKI status, point estimates of ORs for AKI-outcome associations were almost identical to those in Table 3 (Supplemental Table S6 (online)).

Sensitivity analysis: applying new HTN guidelines

Twenty-one additional patients had HTN by the 2017 guidelines; 27 additional patients had elevated blood pressure (2017 guideline nomenclature for pre-HTN). Overall, 16 additional patients had CKD_{signs} or elevated blood pressure and 11 additional patients had CKD_{signs} or HTN, by the 2017 blood pressure guidelines. Associations between AKI and 6-year outcomes were in similar directions, but attenuated when 2017 blood pressure guidelines were used (Supplemental Table S7 (online)). Only severe AKI remained significantly associated with CKD_{signs} or ≥elevated blood pressure (adjusted OR 4.5, 95% CI 1.1–18.6, $p = 0.04$, Supplemental Table S7 (online)).

DISCUSSION

This is the first multicenter, long-term study with primary outcome data collection, performed in a heterogeneous PICU population, evaluating AKI (vs. non-AKI) as a risk factor for long-term development of signs of CKD and HTN. At a single study visit 6 years after PICU admission, 29% of patients had either low eGFR, albuminuria or blood pressure at >pre-HTN thresholds, and 23% had either low eGFR, albuminuria or blood pressure above thresholds for HTN. By contrast, the Canadian child population pre-HTN and HTN prevalence, also evaluated at a single time-point using automated blood pressure devices, are 2.1% and 0.8%, respectively; prevalence of CKD Stages 3–5 (defined by eGFR <60 ml/min/1.73 m^2) estimated in European children was 55–60 per million of age-related population.[29,30] AKI was associated with ~2-fold higher odds for CKD_{signs} or ≥pre-HTN; severe AKI was associated with a 6.6-fold higher adjusted odds for CKD_{signs} or ≥pre-HTN. When the new 2017 pediatric HTN guidelines were applied, the association of AKI with long-term kidney outcomes was attenuated. A crucial finding from our study is that this population is overall at very high risk for late kidney and blood pressure abnormalities. This is concerning; HTN is a leading cause of death worldwide, is treatable and tracks into adulthood.[28] Child onset CKD is associated with premature vascular disease.[9,31] Non-cardiac PICU patients comprise the largest proportion of PICU admissions, are highly heterogeneous and are often discharged to general practitioner care. Understanding late AKI outcomes in this population is needed to plan how post-discharge care should be performed. Specific risk factors, including AKI, must be elucidated to direct appropriate follow-up practice.

Table 1. Demographic, PICU and AKI data comparing patients with vs. without AKI at PICU admission.

Variables	AKI	
Demographic variables	No/unknown AKI $n = 208$	Any AKI $n = 69$
Gender, *n* (%), male	129/208 (62)	38/69 (55)
Age at visit, median (IQR), years	7.3 (8.1)	9.6 (9.2)***
PICU factors		
Age at PICU admission, median (IQR), years	1.4 (6.5)	3.8 (9.0)***
Mechanical ventilation, *n* (%)	110/208 (53)	38/69 (55)
Vasopressor use, *n* (%)	45/208 (22)	26/69 (38)**
Nephrotoxic medication use, *n* (%)[a]	67/208 (32)	35/69 (51)**
Modified PRISM III (excluding creatinine score), median (IQR)	6 (7.5)	10 (11)***
PICU days of stay, median (IQR)	2 (4)	3 (7)
Hospital days of stay, median (IQR)	8 (13)	14 (16)***
Proportion days with creatinine measured, median (IQR)	0.5 (0.8)	0.9 (0.5)***
>1 past medical history item, *n* (%)	94/207 (45)	34/67 (51)
Baseline eGFR (ml/min/1.73 m^2), median (IQR)	91 (67)	120 (29)***
Abnormal baseline eGFR, *n* (%)	18/208 (9)	1/69 (2)*
PICU diagnosis, *n* (%):		**
Neurological	37/208 (18)	11/69 (16)
Respiratory	35/208 (17)	6/69 (9)
Ear, nose, throat	24/208 (12)	2/69 (3)
Diabetes	8/208 (4)	5/69 (7)
Trauma	7/208 (3)	9/69 (13)
Other	97/208 (47)	36/69 (52)
Sepsis diagnosis, *n* (%)	27/208 (13)	13/69 (19)
Need for dialysis, *n* (%)	0/208 (0.0)	1/69 (1)

AKI acute kidney injury, *PICU* pediatric intensive care unit, *IQR* interquartile range, *PRISM* Pediatric Risk of Mortality, *eGFR* estimated glomerular filtration rate
*Indicates $p < 0.05$; ** indicates $p < 0.01$; *** indicates $p < 0.005$
[a]Nephrotoxic medications assessed were non-steroidal anti-inflammatory drugs, aminoglycosides, acyclovir, ganciclovir, amphotericin and vancomycin

A systematic review on studies evaluating long-term kidney outcomes of pediatric AKI, showed that children with AKI are at much higher risk for CKD (defined mainly by abnormal eGFR) and HTN compared to the general pediatric population.[10] However, none of the studies in that review included non-AKI patients, to evaluate whether AKI itself (vs. other factors) is associated with CKD and HTN. In children with variably defined AKI and at variable follow-up times, low eGFR, proteinuria and HTN prevalence have been described to be as high as 50–60%, 10–50% and 3–15%, respectively.[11,12] Since these reports, some non-general PICU patient studies have included non-AKI groups. In children studied after cardiac transplant, only patients without recovery from AKI were at increased risk for later decreased eGFR.[32] Two studies in children undergoing cardiac surgery showed opposite results regarding the association between AKI and 5-year CKD or HTN.[14,15] In critically ill neonates and neonates treated with extracorporeal membrane oxygenation, followed 5–12 years later (including non-AKI patients), AKI was associated with future reduced eGFR, HTN or proteinuria.[13,33] In one of those studies, at a median of 8.2 years after neonatal extracorporeal membrane oxygenation, the prevalence of low eGFR or proteinuria was 17%, prevalence of HTN was 19% and 10% of patients had pre-HTN (defined using the 2004 blood pressure guidelines);[13] these estimates are similar to those of our study, except a higher prevalence of HTN was found. This difference may be attributable to the longer follow-up duration and the higher risk patient population studied. Moreover, that study found a 4-fold higher odds for developing signs of CKD or HTN in neonates with AKI during extracorporeal membrane oxygenation, similar to our measured effect of association.

AKI, especially ≥Stage 2, was associated with development of signs of CKD or of blood pressure above thresholds for pre-HTN. Risk stratification for follow-up based on AKI stage, as proposed in a recent published description of a novel pediatric AKI survivor clinic, may therefore be appropriate.[34] However, there are clearly other, non-AKI contributing factors, suggested by our results showing a substantial proportion of patients with no AKI or Stage 1 AKI having long-term kidney abnormalities and presence of patients with Stage 2 AKI having no evidence of kidney abnormalities or HTN. In our cohort, participants with signs of CKD or HTN were older at the time of the study visit; reasons for this are unclear, but we propose that at an older age, the overall prevalence of abnormalities, especially blood pressure abnormalities, is more likely to be present. Other factors which may help identify who does, vs. does not, need long-term CKD and HTN screening (e.g., age, lack of AKI recovery, diagnoses), remain unclear. In addition, it remains unclear the extent to which the use of novel kidney tissue injury biomarkers may help predict long-term development of signs of CKD or HTN.

When examining the individual components of our composite outcome (i.e., eGFR, albuminuria, blood pressure percentile), we found less striking differences between AKI groups. We performed and powered this study to examine composite outcomes; therefore, our sample size was limited for examining these individual secondary outcomes. Future studies should thus be powered to ensure the ability to detect differences between these individual kidney and blood pressure outcomes in order to determine which outcomes should be targeted for future interventions and future CKD and HTN post-AKI prevention trials.

The association of AKI with outcomes was attenuated when using the new blood pressure guidelines (known to have lower thresholds for abnormal blood pressure). Perhaps patients classified as elevated blood pressure only by the new guideline have "borderline" blood pressure, thus diluting the AKI-outcome effect. Research should investigate this further together with performing additional measures of HTN evaluation, including 24-h ambulatory blood-pressure monitoring and measures of HTN end organ damage such as echocardiograms.

Our study had limitations. Our sample size was large compared to past studies, but limited for subgroup analyses and statistical adjustments. Consent rate was high, but response to mailed invitations was 17%, thus we cannot confidently exclude bias in our study population; moreover, given that this study was performed in two Canadian centers, generalizability may be limited. When comparing our AKI and patient characteristics to the large multi-center epidemiologic study of PICU patients (the AWARE study) and a previous large retrospective study performed in two Canadian PICUs, our study population had extremely similar AKI rate, sex distribution and severity of illness scores, but a slightly higher proportion of patients who received mechanical ventilation and vasopressor support, suggesting that our population may have been somewhat skewed to more severely ill patients.[1,35] Although our study population only included one patient who received dialysis for AKI, it must be noted that we only studied hospital survivors and dialysis-requiring AKI is known to be associated with a high hospital mortality rate. Twenty percent of participants had unknown AKI status. This limitation is impossible to overcome in retrospective evaluations until consistent monitoring of SCr or other novel and well-accepted kidney injury markers in PICU patients occurs. However, results were almost identical when excluding these participants. As in

Table 2. Demographic, PICU and AKI data comparing patients with vs. without composite outcomes at 6-year follow-up.

Variables	CKD_{signs} or pre-HTN or worse (≥pre-HTN)		CKD_{signs} or HTN	
Demographic variables	No CKD_{signs} or ≥pre-HTN[a] $n = 187$	CKD_{signs} or ≥pre-HTN[a] $n = 77$[b]	No CKD_{signs} or HTN $n = 202$	CKD_{signs} or HTN $n = 60$[b]
Gender, *n* (%), male	112/187 (60)	49/77 (64)	121/202 (60)	38/60 (63)
Age at visit, median (IQR), years	7.1 (5.4)	13.1 (10.6)***	7.4 (8.0)	12.0 (11.1)***
PICU factors				
Age at PICU admission, median (IQR), years	1.2 (5.0)	6.1 (11.1)***	1.5 (6.4)	5.6 (11.5)***
Mechanical ventilation, *n* (%)	101/187 (54)	40/77 (52)	110/202 (55)	31/60 (52)
Vasopressor use, *n* (%)	54/187 (29)	15/77 (20)	56/202 (28)	12/60 (20)
Nephrotoxic medication use, *n* (%)[c]	75/187 (40)	24/77 (31)	79/202 (39)	19/60 (32)
Modified PRISM III (excluding creatinine score), median (IQR)	7 (9)	8 (10)	7 (9)	7 (10)
PICU days of stay, median (IQR)	3 (6)	2 (4)	3 (6)	2 (4)
Hospital days of stay, median (IQR)	9 (13)	9 (15)	9 (13)	9 (15)
Proportion days with creatinine measured, median (IQR)	0.5 (0.6)	0.7 (0.7)	0.5 (0.6)	0.7 (0.7)
>1 past medical history item, *n* (%)	71/184 (39)	47/77 (61)***	80/199 (40)	36/60 (60)**
Baseline eGFR (ml/min/1.73 m^2), median (IQR)	91 (67)	120 (36)**	94 (67)	120 (47)
Abnormal baseline eGFR, *n* (%)	9/187 (5)	7/77 (9)	10/202 (5)	6/60 (10)
PICU diagnosis, *n* (%):				
Neurological	30/187 (16)	16/77 (21)	31/202 (15)	14/60 (23)
Respiratory	27/187 (14)	13/77 (17)	29/202 (14)	11/60 (18)
Ear, nose, throat	16/187 (9)	7/77 (9)	19/202 (9)	4/60 (7)
Diabetes	8/187 (4)	5/77 (7)	10/202 (5)	3/60 (5)
Trauma	8/187 (4)	7/77 (9)	9/202 (5)	6/60 (10)
Other	98/187 (52)	29/77 (38)	104/202 (52)	22/60 (37)
Sepsis diagnosis, *n* (%)	32/187 (17)	6/77 (8)	33/202 (16)	5/60 (8)
Need for dialysis, *n* (%)	1/187 (0.5)	0/77 (0.0)	1/202 (0.5)	0/60 (0.0)
AKI factors				
No AKI (or unknown), *n* (%) vs. Any AKI, *n* (%)	147/187 (79) vs. 40/187 (21)	51/77 (66) vs. 26/77 (34)*	156/202 (77) vs. 46/202 (23)	40/60 (67) vs. 20/60 (33)
No/unknown/Stage 1 AKI, *n* (%) vs. Stage 2 or worse AKI, *n* (%)	173/187 (93) vs. 14/187 (8)	65/77 (84) vs. 12/77 (16)	185/202 (92) vs. 17/202 (8)	51/60 (85) vs. 9/60 (15)

AKI acute kidney injury, *CKDsigns* signs of CKD (defined as single-visit low estimated glomerular filtration rate or albuminuria), *Pre-HTN* BP from a single study visit which was above the threshold for pre-hypertension, *HTN* BP from a single study visit which was above the threshold for hypertension, *IQR* interquartile range, *PICU* pediatric intensive care unit, *PRISM* Pediatric Risk of Mortality, *eGFR* estimated glomerular filtration rate

*Indicates $p < 0.05$; **indicates $p < 0.01$; ***indicates $p < 0.005$

[a]Participants were classified as having ≥pre-HTN if blood pressure percentile was ≥90th percentile, thus this group also includes those with HTN (blood pressure ≥95th percentile)

[b]The total number of participants was 277 (208 non-AKI and 69 AKI). Only 264 participants had CKD or ≥pre-HTN data available (187 no CKD or ≥pre-HTN and 77 CKD or ≥pre-HTN); 262 participants were available for the CKD or HTN analysis (202 no CKD or HTN and 60 CKD or HTN), because two patients were missing CKD status, but had blood pressure between the 90th and the 95th percentile (so data were available to classify as pre-HTN, but since blood pressure was not above the 95th percentile, they were classified as missing for the CKD or HTN outcome)

[c]Nephrotoxic medications assessed were non-steroidal anti-inflammatory drugs, aminoglycosides, acyclovir, ganciclovir, amphotericin and vancomycin

previous studies, baseline SCr was unknown in most patients; this problem is impossible to overcome and must be accepted as a fact in pediatric AKI research.[1,21] Fortunately, much recent research in pediatric AKI has attempted to alleviate this problem by using multiple methods to limit unwanted variability caused by missing baseline SCr. Moreover, although we considered several PICU and patient variables for adjustment in multivariable analyses, we were not able to adjust for health and/or AKI events which may have occurred between discharge and the 6-year follow-up visit. Future research should consider determining the extent to which intercurrent health events impact on long-term development of kidney and blood pressure abnormalities. Although we attempted to reduce likelihood of white coat HTN (home visits, calm measures), blood pressure may have been overestimated. However, even if over half participants had white coat HTN, the prevalence of blood pressure abnormalities would still have been very high. For feasibility issues, we measured blood pressure using an oscillometric device which may also contribute to blood pressure overestimation in some children; ideal blood pressure measurement should be performed using auscultatory methods.[28] Though albuminuria prevalence was high, this was consistent with general population-based pediatric estimates and may have been inflated by orthostatic proteinuria.[36,37] Future studies should evaluate this further by performing the more resource-intensive first morning urine collection. Ideally, CKD and HTN should be assessed at ≥2 study visits at least 3 months apart, in order to ensure that strict criteria for outcomes are being evaluated. At the time of study design and initiation, we had almost no data upon which to base our sample size estimates, and resources did not allow for repeated measurements. Thus, our results on proportions of patients with signs of CKD and blood pressure abnormalities must be interpreted with caution. It is likely that our results are an overestimate of actual CKD and abnormal blood pressure, since we did not perform repeat measures. This is important to confirm and/or clarify, so as not to overestimate the burden on disease in this patient population, inadvertently cause distress to families and patients or inappropriately allocate resources to patients who may not require long-term follow-up.

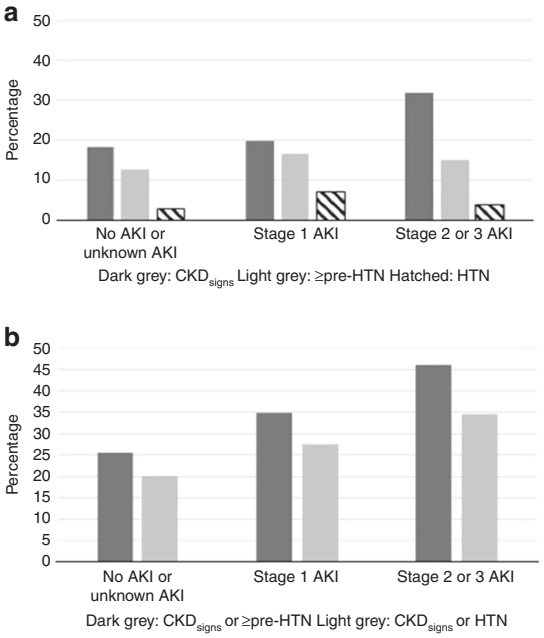

Fig. 2 Prevalence of 6-year kidney outcomes by AKI staging severity. a Prevalence of individual outcomes, CKD signs (low eGFR or albuminuria) (dark), ≥pre-HTN (light) and HTN (hatched), by AKI severity. There was no statistically significant difference in proportions with outcomes across AKI severity groups. **b** Prevalence of composite outcomes, CKD signs or ≥pre-HTN (dark) and of CKD signs or HTN (light) across AKI severity groups. Participants with blood pressure ≥90th percentile were classified as ≥pre-HTN (therefore also includes those with HTN or blood pressure ≥95th percentile). There was a statistically significant increase in proportions with CKD signs or ≥pre-HTN across AKI severity groups ($p = 0.02$). AKI acute kidney injury, CKD_{signs} either low estimated glomerular filtration rate or albuminuria during a single study visit, pre-HTN blood pressure from a single study visit at or above thresholds for pre-hypertension, HTN blood pressure from a single study visit at or above thresholds for hypertension.

In conclusion, 6-year post-discharge prevalence of low eGFR, albuminuria, pre-HTN and HTN during a single study visit is high in patients admitted to PICU; patients with Stage 2 AKI or worse appear to be at highest risk. Future research must strive to identify other clinical and injury biomarker-guided CKD and HTN risk factors, determine the magnitude of CKD and HTN burden at repeat assessments and begin identifying how to best target PICU patients for late kidney outcomes, with a goal of early, cost-effective, accurate and individualized CKD and HTN detection and cardiovascular risk reduction. Studying the outcomes of AKI in hospitalized children has been very challenging, when compared to adult research, as children do not routinely have follow-up blood and urine collected after a PICU admission; thus prospective studies, which take significant time and are associated with high cost, are sorely needed. This study provides evidence that future detailed natural history studies of AKI should be performed in children and provides some information on potential long-term kidney risk to provide to families of children with more severe AKI. Hopefully, a recent large PICU study[1] or others will perform long-term follow-up, providing more granular information on AKI-late kidney outcome associations. Intervention studies of AKI follow-up processes would also be useful in evaluating their effect on outcomes and health care systems costs. This study also supports that clinicians should at least consider follow-up care for CKD and HTN screening in patients with AKI during PICU admission, using an individualized approach, as proposed in recent reviews.[38]

Table 3. Logistic regression analysis of AKI association with primary composite outcomes.

Any AKI	CKD_{signs} or ≥pre-HTN[a] OR (95% CI)	CKD_{signs} or HTN OR (95% CI)
Unadjusted	1.9 (1.0–3.4)*	1.7 (0.9–3.2)
Adjusted	2.2 (1.1–4.4)[b]*	1.7 (0.9–3.4)[c]
AKI Stage 2 or worse		
Unadjusted	2.3 (1.0–5.2)	1.9 (0.8–4.6)
Adjusted	6.6 (1.5–28.3)[d]*	1.9 (0.7–4.7)[c]

AKI acute kidney injury, *CKDsigns* signs of CKD (defined as single-visit low estimated glomerular filtration rate or albuminuria), *Pre-HTN* BP from a single study visit which was above the threshold for pre-hypertension, *HTN* BP from a single study visit which was above the threshold for hypertension, *OR* odds ratio, *CI* confidence interval
*Indicates $p < 0.05$
[a]Participants were classified as having ≥pre-HTN if blood pressure percentile was ≥90th percentile, thus this group also includes those with HTN (blood pressure ≥95th percentile)
[b]Variables adjusted for: age at follow-up, vasopressor use, nephrotoxic medication use, sepsis during admission, >1 past medical history item at admission, and abnormal baseline eGFR
[c]Variables adjusted for: age at follow-up, sepsis during admission, >1 past medical history item at admission, and abnormal baseline eGFR
[d]Variables adjusted for: age at follow-up, vasopressor use, nephrotoxic medication use, sepsis, >1 past medical history item at admission, abnormal baseline eGFR, and nephrotoxic medication use interaction term with AKI

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AUTHOR CONTRIBUTIONS

K.B. formulated the analysis plan, conducted study procedures, managed data, performed most of the statistical analysis and drafted the manuscript. E.H., M.P., S.B. and L.H. helped supervise study progress, formulate the analysis plan, and critically reviewed and revised the manuscript. A.D. and S.L.G. helped conceptualize the study and design, helped formulate the data analysis plan, and critically reviewed the results and manuscript. A.P. helped conceptualize study and design, supervised and coordinated data management and collection, and helped review the results and revise the manuscript. J.A.D. assisted with designing and implementing data collection, and critically reviewed the manuscript. V.C. assisted with statistical analysis, a portion of manuscript writing and critically reviewed the manuscript. A.R.J., R.G.G., D.G. and R.S. helped conceptualize the study, supervised data collection and study progress, interpreted results and critically reviewed the manuscript. C.M. and M. Z. helped conceptualize the study and research question, acquired funding, designed data collection instruments and helped formulate the analysis plan, supervised recruitment and study conduct, performed analysis and revised and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

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