RESEARCH ARTICLE

Long-term Mortality After Acute Kidney Injury in the Pediatric ICU

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ABSTRACT

OBJECTIVES: (1) To evaluate the association between acute kidney injury (AKI) in the PICU and long-term mortality and (2) to determine the extent to which adding the urine output (UO)–defined AKI alters the association.

METHODS: A 2-center retrospective cohort study of children (≤18 years old) admitted to the PICU between 2003 and 2005 for noncardiac surgery, with follow-up until 2010. Patients with end stage renal disease, no provincial health insurance number, who died during hospitalization, or could not be linked to administrative data were excluded. One hospitalization per patient was included. AKI was defined by using serum creatinine criteria and/or UO criteria. Mortality was ascertained by using administrative data. Cox regression analysis was performed to evaluate the association between AKI and long-term mortality.

RESULTS: The study population included 2041 patients (55.7% male, mean admission age 6.5 ± 5.8 years). Of 2041 hospital survivors, 9 (0.4%) died within 30 days, 51 (2.5%) died within 1 year, and 118 (5.8%) died within 5 to 7 years postdischarge. AKI was independently associated with 5- to 7-year mortality (adjusted hazard ratio [95% confidence interval]: 3.10 [1.46–6.57] and 3.38 [1.63–7.02], respectively). Including UO did not strengthen the association.

CONCLUSIONS: AKI is associated with 5- to 7-year mortality. Because this is an observational study we cannot determine if AKI is causative of mortality or of the pathophysiology. However, patients with AKI represent a high-risk group. It is reasonable that these patients be considered for targeted follow-up until future researchers better elucidate these relationships,

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Acute kidney injury (AKI) is common in the PICU and is associated with poor hospital outcomes.[1–9] Several studies in adults reveal that AKI is a risk factor for posthospital discharge mortality.[10–15] Some studies have revealed that hospitalized children with AKI appear to have higher long-term mortality rates than the general pediatric population; however, these studies lacked non-AKI comparison groups, precluding the ability to evaluate the association of AKI with mortality.[16,17] It thus remains unclear if pediatric AKI is associated with postdischarge mortality, and if so, what the magnitude of association is. This is important to elucidate to understand the health impact of AKI, inform prevention strategies (eg, increased monitoring of serum creatinine [SCr], avoid fluid overload, avoid nephrotoxins and contrast agents), identify patients at highest risk for postdischarge mortality, and appropriately target these patients for follow-up.

Most authors of pediatric AKI research have defined AKI using acute SCr change.[1,5,7,18–21] However, the contemporary AKI definition also stages AKI by using the criteria of decreased urine output (UO). A large multinational study revealed that children with stage 3 urine output–defined acute kidney injury (UO-AKI) had nearly twice the rate of 28-day mortality compared with those with SCr-defined AKI.[2] The association between UO-AKI and long-term mortality is unknown.

We hypothesized that pediatric AKI is associated with postdischarge mortality and that including UO to define AKI will strengthen this association. Our objectives were (1) to evaluate the association between noncardiac surgery acute kidney injury in the PICU (PICU-AKI) and 30-day, 1-year, and 5- to 7-year mortality and (2) determine the extent to which including UO in the AKI definition alters the association.

METHODS

Design, Setting, and Patient Selection

We conducted a retrospective cohort study of children admitted to 2 tertiary PICUs in Montreal, Canada. Children ≤18 years old admitted to the PICU between January 1, 2003, and March 31, 2005, were included ($N \approx 3400$). Patients with preexisting chronic dialysis or a renal transplant (based on diagnostic codes from hospital medical archivists and cross-referencing institutional dialysis and transplantation records) or no provincial health insurance number were excluded a priori ($n = 901$). For this analysis, we only included the first hospitalization per patient (excluded $n = 14$) and excluded postcardiac surgery patients ($n = 355$), hospital nonsurvivors ($n = 79$), and patients who could not be linked to administrative mortality data ($n = 10$). Approvals were obtained from institutional ethics boards and the Commission d'accès à l'information du Québec, provincial data monitoring board, before study initiation. Requirement for patient consent was waived. A unique encrypted identification number was assigned to patients, and the merged medical chart and administrative data were only accessible to an independent biostatistician.

Data Collection and Sources

PICU hospitalization data were collected by retrospective chart review. Data forms were designed by investigators iteratively and evaluated for interrater and intrarater reliability before data collection began. Also, independent raters from each center rereviewed 50 randomly selected charts to further evaluate reliability (92% of continuous variables had interrater correlation ≥0.90; 96% of categorical variables had ≥90% agreement). Variables included demographics, baseline comorbidities, primary and/or secondary PICU admission diagnoses, documented infection (sepsis, meningitis, pneumonia, or other), invasive mechanical ventilation, pediatric risk of mortality (PRISM) score (converted to predicted death rate by using the published equation),[22] daily medication (vasopressors, steroids, selected nephrotoxins), peak daily SCr values throughout PICU stay (up to 21 PICU days), and daily UO in 8-hour intervals (up to 21 PICU days).

Primary Exposure: AKI

PICU-AKI was defined by using the Kidney Disease: Improving Global Outcomes SCr and/or UO criteria.[23,24] AKI was classified as stage 1 (SCr rises ≥1.5–1.9 times baseline in 7 days or rises ≥26.5 μmol/L within 48 hours or UO is <0.5 mL/kg per hour for 8 hours), stage 2 (SCr rises ≥2.0–2.9 times baseline or UO is <0.5 mL/kg per hour for 16 hours), or stage 3 (SCr rises ≥3.0 times baseline, SCr is ≥353.6 μmol/L, dialysis treatment of AKI, estimated glomerular filtration rate [eGFR] is <35 mL/minute per 1.73 m^2 [if >3 months old], UO is <0.3 mL/kg per hour for 24 hours, or anuric for 12 hours). The maximum AKI stage defined by SCr or UO criteria was used to classify the stage (eg, if classified as stage 2 by UO criteria but classified as stage 3 by SCr criteria, then the classification was stage 3 AKI). Baseline SCr was the lowest SCr 3 months before admission. If this was unavailable, we estimated baseline SCr by back-calculation using the chronic kidney disease in children (bedside equation) eGFR formula[25] (requires height) and assumed age-based normative glomerular filtration rate values (Supplemental Table 5).[26] If height was missing, we estimated baseline SCr using a height-independent eGFR equation (previously validated).[26–28]

Outcome: Mortality

Postdischarge mortality was ascertained by using administrative data from the Régie de l'assurance maladie du Québec (manages all public health insurance programs in Quebec and insures all Québec residents) and the Québec Vital Statistics Registry. Mortality data from January 1, 2003, until March 31, 2010, (5 years after the last hospitalization during our study period) were available. Mortality at 30 days, 1 year, and 5 to 7 years posthospital discharge were defined, in which time 0 was the hospital discharge date, and mortality rates were cumulative. Because of the range of discharge dates, maximal follow-up ranged from 5 to 7 years.

Analysis

Analyses were conducted by using Stata version 12 (StataCorp, College Station, TX). Characteristics of patients with AKI versus without AKI and of survivors versus nonsurvivors were compared by using appropriate univariable analyses as per distribution. Continuous variables were expressed as means, SDs, and medians and categorical variables as numbers and percentages. Analyses were planned a priori, and reporting was prepared in accordance with guidelines.[29]

Kaplan-Meier curves were used to compare mortality in patients with no AKI versus stages 1 to 3 AKI. We performed univariable and multivariable Cox proportional hazards analyses to evaluate the association of AKI with 5- to 7-year mortality (sample size was too small for 30-day and 1-year mortality for multivariable analysis). Variable selection for inclusion in multivariable analysis was based on (1) a priori–selected known AKI risk factors and the decision to include age and sex and (2) evaluating variables associated with 5- to 7-year mortality ($P < .05$) in univariable analyses. Because of our limited number of outcomes, we had to be selective for our multivariable analysis; when selecting PICU diagnostic categories to include, we chose oncology because of its association with mortality in univariable analysis, and infection because it is a known AKI risk factor and has been included in previously published multivariable models.[1] Collinearity of variables was evaluated by examining variance inflation factors. A sensitivity analysis excluding patients receiving dialysis in the PICU was performed to determine if the AKI association with mortality was mainly driven by these patients.

To evaluate effect modification (ie, change in magnitude of AKI mortality association across values of another variable), a preplanned evaluation of all variables included in the multivariable analysis was performed by developing interaction terms with AKI and other variables (eg, AKI × age). Statistical significance of each interaction term was evaluated one by one in a Cox regression that included AKI, the other variable, and the interaction term (eg, AKI, age, and AKI × age). Interaction terms with $P < .1$ in these Cox regressions were included in the final multivariable model. Before analysis, it was decided to perform stratified (subgroup) analyses across variables with significant effect modification of the AKI mortality association.

We performed 2 other sensitivity analyses. First, we determined if including UO in our AKI definition altered the AKI mortality association (versus using SCr only) by repeating analyses using AKI defined by SCr alone. Second, we evaluated the impact of including in-hospital deaths on our results by repeating all analyses including patients who died during admission.

RESULTS

Characteristics

Of 2041 eligible patients (55.7% male, mean age at admission 6.5 ± 5.8 years, mean follow-up 5.9 ± 1.2 years), 1575 (77.2%) patients had SCr measured in PICU, and 1622 (79.5%) had SCr or UO data. AKI occurred in 355 out of 1622 (21.9%) patients. In Table 1, we show the characteristics of patients with AKI versus without AKI during PICU admission.

There was no difference in age or sex distributions between 1-year and 5- to 7-year survivors versus nonsurvivors (Table 2). Nonsurvivors had higher PRISM scores, longer mechanical ventilation, longer PICU and hospital stays, and received more nephrotoxic antibiotics, vasopressors, and steroids (Table 2).

Thirty-Day and 1-Year Mortality

In 30 days posthospital discharge, 9 out of 2041 (0.4%) patients died. AKI versus non-AKI 30-day mortality was 4 out of 355 (1.1%) versus 4 out of 1267 (0.3%), respectively ($P = .08$). In unadjusted Cox regression analysis, AKI was not significantly associated with 30-day mortality (Table 3).

In 1 year postdischarge, 51 out of 2041 (2.5%) patients died. In unadjusted Cox regression analysis, the hazard ratio (HR) of death was not significantly different between the exposed and unexposed groups (Table 3).

Five- to 7-Year Mortality

A total of 118 out of 2041 (5.8%) patients died 5 to 7 years after index hospitalization discharge. The top 3 causes of death identified by the Vital Statistics Registry were neoplasms (27 out of 67 [40%] patients without AKI and 9 out of 30 [30%] patients with AKI), congenital malformations (12 out of 67 [18%] patients without AKI and 7 out of 30 [23%] patients with AKI), and nervous system diseases (8 out of 67 [12%] patients without AKI and 5 out of 30 [17%] patients with AKI). Cause of death was missing for 5 patients without AKI and 4 patients with AKI. In univariable analysis, AKI was associated with 5- to 7-year mortality (Table 2). Kaplan-Meier survival curves by AKI stage revealed that increasing AKI severity was associated with increasing mortality risk over time, most evident after ~1 year postdischarge (Fig 1).

In the adjusted Cox regression analysis, AKI was significantly associated with 5- to 7-year mortality (Table 3). The association of AKI stage 2 or 3 (versus no AKI or stage 1) with mortality was not stronger than the association of any AKI with mortality (Table 3). However, when the association was evaluated by AKI stage, it was evident that patients with stage 2 AKI were at highest risk (stage 1: adjusted HR: 3.27, 95% confidence interval [CI]: 1.50–7.13; stage 2: adjusted HR: 4.29, 95% CI: 1.73–10.66; stage 3: adjusted HR: 2.60, 95% CI: 0.84–7.99). Other risk factors for 5- to 7-year mortality are shown in Supplemental Table 6. When the 12 patients who received dialysis in the PICU for AKI were excluded, the HR was similar and remained statistically significant (data not shown).

Subgroup Analysis on Significant Effect Modifier: Age and Primary PICU Diagnosis

Age at PICU admission was an effect modifier for the association between AKI and 5- to 7-year mortality. To explore this further, we divided our cohort into age quintiles and found that children ≤1 year old had significantly higher rates of AKI compared with children >1 year old (not shown), as previously suggested in the literature.[1,21,30] Therefore, we performed a subgroup analysis on children ≤1 year old versus >1 year old at PICU admission. In Table 4, we show that the association of AKI with 5- to 7-year mortality was of greater magnitude in patients ≤1 year old compared with those >1 year old at PICU admission. Primary PICU diagnosis category (oncologic diagnosis versus infection versus other diagnoses) was also an effect modifier for the AKI mortality association. When diagnosis subgroups were examined separately, AKI was not significantly associated with 5- to 7-year mortality in any of the subgroups (adjusted Cox regression, Table 4).

TABLE 1 Comparison of Patient Characteristics by AKI (Yes or No)

Variables	No AKI, $n = 1267$	AKI, $n = 355$
Baseline characteristics		
Mean age in years (SD), median	6.45 (5.85), 4.59	7.40 (5.87), 6.25**
Female sex, *n* (%)	574 (45.3)	168 (47.3)
Center 2, *n* (%)	803 (63.4)	255 (71.8)*
PICU diagnosis		
Cardiac (nonsurgical), *n* (%)	71 (5.6)	28 (7.9)
Trauma, *n* (%)	151 (11.9)	37 (10.4)
Renal, *n* (%)	4 (0.3)	15 (4.2)**
Infection (excluding bronchiolitis), *n* (%)	244 (19.3)	86 (24.2)*
Neurologic or neurosurgical, *n* (%)	216 (17.1)	41 (11.6)*
Gastrointestinal[a], *n* (%)	45 (3.6)	27 (7.6)*
Oncologic, *n* (%)	43 (3.4)	12 (3.4)
Respiratory, *n* (%)	125 (9.9)	34 (9.6)
Diabetes, *n* (%)	17 (1.3)	18 (5.1)**
Other[b], *n* (%)	351 (27.7)	57 (16.1)**
Baseline renal abnormality, *n* (%)	22 (1.7)	27 (7.6)**
Postoperative (noncardiac), *n* (%)	481 (38.0)	101 (28.5)*
Mean PRISM score (SD), median	7.26 (5.09), 6	9.63 (6.67), 9**
Mean PRISM death rate % (SD), median	4.33 (7.60), 1.87	8.24 (14.01), 2.77**
ICU treatment characteristics		
Any nephrotoxic antibiotics, *n* (%)	278 (21.9)	126 (35.5)**
Aminoglycosides, *n* (%)	153 (12.1)	87 (24.5)**
Acyclovir or ganciclovir, *n* (%)	42 (3.3)	25 (7.0)*
Amphotericin, *n* (%)	7 (0.6)	9 (2.5)*
Vancomycin, *n* (%)	128 (10.1)	67 (18.9)**
Vasopressors used, *n* (%)	77 (6.1)	82 (23.1)**
Steroids used, *n* (%)	336 (26.5)	130 (36.6)**
NSAIDs used, *n* (%)	144 (9.0)	43 (12.1)
Mechanically ventilated (yes or no), *n* (%)	510 (40.3)	185 (52.1)**
Mean length of mechanical ventilation (SD), median, d	1.74 (3.49), 0	3.51 (5.64), 1**
Bladder catheter (yes or no), *n* (%)	797 (62.9)	279 (78.6)**
Kidney related, *n* (%)		
Nephrology consultation during admission	47 (3.7)	80 (22.5)**
Renal replacement therapy in PICU	0	12 (3.4)**
Outcomes		
Mean PICU length of stay (SD), median, d	3.20 (7.02), 1.29	8.52 (36.66), 2.73**
Mean hospital length of stay (SD), median, d	18.71 (55.91), 9	29.06 (55.35), 13**

AKI was defined by using both SCr and UO. NSAID, nonsteroidal anti-inflammatory drug.

[a] Gastrointestinal includes liver, stomach, pancreas, and intestine.

[b] Includes hematologic (nononcologic), inborn error of metabolism and metabolic (noninborn error of metabolism), immunologic, intoxication, burn, orthopedic, otolaryngologic, endocrinologic (nondiabetes), and bronchiolitis.

* $P < .05$; ** $P < .001$.

Sensitivity Analysis by Using Only SCr to Define AKI

The distribution of AKI stages and a comparison between staging by SCr alone versus SCr or UO is shown in Supplemental Table 7. Percent agreement between AKI by SCr only and AKI by SCr and UO was 96.5% (κ: 0.89; $P < .001$). Fifty-five patients with no AKI by SCr alone were defined as having AKI by UO. One patient without a SCr measurement was defined as having AKI by using UO. When only SCr was used to define AKI, results on the association of AKI with mortality were extremely similar for AKI defined by using SCr and UO criteria, as described above (Table 3).

Sensitivity Analysis, Including In-Hospital Deaths

Seventy-nine patients died during the index admission (No AKI: 23/1470 [1.6%]; stage 1 AKI: 16/355 [4.5%]; stage 2 AKI: 13/127 [10.2%]; stage 3 AKI: 27/120 [22.5%]). When patients who died during admission were included in the cohort, AKI was associated with 30-day and 1-year mortality (adjusted HR: 3.83, 95% CI: 1.36–10.74; and adjusted HR: 2.66, 95% CI: 1.27–5.58, respectively); AKI remained significantly associated with 5- to 7-year mortality (adjusted HR: 3.13; 95% CI: 1.73–5.65).

DISCUSSION

We found that AKI in PICU survivors was associated with 5- to 7-year posthospital discharge mortality; however, it was not associated with 30-day or 1-year postdischarge mortality.

When hospital mortality was included in our outcome, AKI was associated with 30-day and 1-year mortality. Many studies have revealed the association between PICU-AKI and hospital mortality.[1,5,8] What is unknown is the risk of long-term mortality in PICU survivors with AKI. The increased magnitude of the association between AKI and 30-day or 1-year mortality when hospital mortality was included highlights the importance of how this can bias the association of AKI with long-term mortality. Future authors of studies should distinguish hospital mortality risk from long-term mortality risk.

Including UO in the AKI definition did not substantially change the association of AKI with late mortality. This is important because in research and in clinic, collecting UO data to ascertain AKI is more challenging than evaluating SCr alone (especially if using databases). In the study by Kaddourah et al,[2] patients with stage 3 UO-AKI had nearly 2 times higher rates of 28-day mortality compared with those with

TABLE 2 Comparison of Survivor Versus Nonsurvivor Patient Characteristics at 1 Year and 5 to 7 Years Postdischarge

Variables	1-y Mortality		5–7-y Mortality	
	Nonsurvivors, $n = 51$	Survivors, $n = 1990$	Nonsurvivors, $n = 118$	Survivors, $n = 1923$
Baseline characteristics				
Mean age in y (SD), median	6.3 (5.9), 3.6	6.5 (5.8), 4.5	6.9 (5.7), 5.7	6.4 (5.8), 4.43
Female sex, *n* (%)	21 (41.2)	884 (44.4)	44 (37.3)	861 (44.8)
Center 2, *n* (%)	34 (66.7)	1178 (59.2)	67 (56.8)	1145 (59.5)
PICU diagnosis				
Cardiac (nonsurgical), *n* (%)	5 (9.8)	127 (6.4)	9 (7.6)	123 (6.4)
Trauma, *n* (%)	4 (7.8)	219 (11.0)	4 (3.4)*	219 (11.4)
Renal, *n* (%)	0	19 (1.0)	0	19 (1.0)
Infection (excluding bronchiolitis), *n* (%)	11 (21.6)	387 (19.5)	31 (26.3)	367 (19.1)
Neurologic or neurosurgical, *n* (%)	12 (23.5)	286 (14.4)	29 (24.6)*	269 (14.0)
Gastrointestinal[a], *n* (%)	4 (7.8)	73 (3.7)	9 (7.6)*	68 (3.5)
Oncologic, *n* (%)	5 (9.8)*	53 (2.7)	13 (11.0)**	45 (2.3)
Respiratory, *n* (%)	8 (15.7)	218 (11.0)	16 (13.6)	210 (10.9)
Diabetes, *n* (%)	0	59 (3.0)	1 (0.9)	58 (3.0)
Other[b], *n* (%)	2 (3.9)**	549 (27.6)	6 (5.1)**	545 (28.3)
Baseline renal abnormality, *n* (%)	1 (2.0)	53 (2.7)	2 (1.7)	52 (2.7)
Postoperative (noncardiac), *n* (%)	19 (37.2)	695 (34.9)	43 (36.4)	671 (34.9)
Mean PRISM score (SD), median	10.6 (7.5), 9.0**	7.2 (5.3), 6.0	8.9 (6.3), 8.0*	7.2 (5.3), 6.0
Mean PRISM death rate % (SD), median	10.6 (17.8), 3.2*	4.5 (8.4), 1.9	7.1 (13.9), 2.6*	4.5 (8.3), 1.9
ICU treatment characteristics				
Any nephrotoxic antibiotics, *n* (%)	18 (35.3)*	413 (20.8)	42 (35.5)**	389 (20.3)
Aminoglycosides, *n* (%)	15 (29.4)**	235 (11.8)	37 (31.4)**	213 (11.1)
Acyclovir or ganciclovir, *n* (%)	2 (3.9)	69 (3.5)	8 (6.8)*	63 (3.3)
Amphotericin, *n* (%)	2 (3.9)	14 (0.7)	5 (4.2)**	11 (0.6)
Vancomycin, *n* (%)	10 (19.6)*	200 (10.1)	18 (15.3)	192 (10.0)
Vasopressors used, *n* (%)	11 (21.6)**	150 (7.5)	22 (18.6)**	139 (7.2)
Steroids used, *n* (%)	25 (49.0)**	553 (27.8)	54 (45.8)**	524 (27.3)
NSAIDs, *n* (%)	3 (5.9)	178 (8.9)	7 (5.9)	174 (9.0)
Mechanically ventilated (yes or no), *n* (%)	29 (56.9)*	732 (36.8)	54 (45.8)	707 (36.8)
Mean length of mechanical ventilation in d (SD), median	3.3 (5.4), 1.0*	1.9 (3.7), 0	3.0 (5.5), 0*	1.7 (3.6), 0
Kidney related				
Nephrology consultation during admission, *n* (%)	11 (21.6)**	124 (6.2)	17 (14.4)**	118 (6.1)
Renal replacement therapy in PICU, *n* (%)	0	12 (0.6)	1 (0.9)	11 (0.6)
AKI by SCr only, *n* (%)	12/44 (27.3)	287/1531 (18.8)	30/103 (29.1)*	269/1472 (18.3)
AKI stage 2 or 3 by SCr only, *n* (%)	5/44 (11.4)	124/1531 (8.1)	15/103 (14.6)*	114/1472 (7.7)
AKI by SCr and/or UO, *n* (%)	15/46 (32.6)	340/1576 (21.6)	34/106 (32.1)*	321/1516 (21.2)
AKI stage 2 or 3 by SCr and/or UO, *n* (%)	5/46 (10.9)	137/1576 (8.7)	15/106 (14.2)*	127/1516 (8.4)
Outcomes				
Mean PICU length of stay in d (SD), median	6.3 (13.3), 2.0*	3.6 (16.5), 1.1	11.2 (60.3), 1.9**	3.2 (7.8), 1.1
Mean hospital length of stay in d (SD), median	34.0 (48.6), 16.0**	18.1 (55.9), 8.0	50.3 (109.1), 16.5**	16.6 (50.1), 8.0

NSAID, nonsteroidal anti-inflammatory drug.

[a] Gastrointestinal includes liver, stomach, pancreas, and intestine.

[b] Includes hematologic (nononcologic), inborn error of metabolism and metabolic (noninborn error of metabolism), immunologic, intoxication, burn, orthopedic, otolaryngologic, endocrinologic (nondiabetes), and bronchiolitis.

* $P < .05$; ** $P < .001$.

TABLE 3 HRs and 95% CIs for 30-Day, 1-Year, and 5- to 7-Year Mortality by AKI Ascertainment Method

AKI Definitions	30-d Mortality	1-y Mortality	5–7-y Mortality	
	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
AKI by SCr and/or UO				
AKI, yes or no	3.58 (0.89–14.30)	1.74 (0.94–3.23)	1.74 (1.15–2.61)[b]	3.38 (1.63–7.02)[b]
Stage 2 or 3[c]	—	1.27 (0.50–3.20)	1.76 (1.02–3.04)[b]	1.62 (0.81–3.22)
AKI by SCr only				
AKI, yes or no	2.56 (0.61–10.72)	1.61 (0.83–3.13)	1.81 (1.18–2.76)[b]	3.10 (1.46–6.57)[b]
Stage 2 or 3[c]	—	1.43 (0.56–3.64)	1.97 (1.14–3.41)[b]	1.86 (0.91–3.79)

—, not applicable.

[a] Adjusted for age, sex, primary PICU diagnosis of cancer, primary PICU diagnosis of infection, PRISM score death rate, vasopressors, nephrotoxic antibiotics, and steroids received in the PICU and interaction of AKI × age, AKI × cancer diagnosis, and AKI × infection diagnosis.

[b] Statistically significant ($P < .05$).

[c] Compared with no AKI or stage 1 AKI. No patients with stage 2 or 3 AKI died 30 d postdischarge.

SCr-defined AKI, suggesting that considering UO might strengthen the mortality association. We excluded patients who died during hospitalization, including over 30% patients with stage 3 UO-AKI (data not shown). Future researchers should assess if UO-AKI is a better predictor of short-term versus long-term mortality and of late renal disease.

In a retrospective study, we could not examine the mechanism of the AKI long-term mortality association. It is conceivable that AKI may have organ effects (eg, cardiac, respiratory) that predispose to increased mortality risk.[31–33] Another hypothesis is that AKI is associated with chronic kidney disease or end stage renal disease; however, this association is unclear in children.[34] Future researchers should elucidate the pathophysiology of this association. With our findings, we suggest that, at least, AKI may be a marker of acute and chronic illness severity, and thus PICU survivors of AKI may require closer follow-up.

In subgroup analyses, AKI was more strongly associated (greater HR) with 5- to 7-year mortality in children ≤1 year old. Watkins et al[21] similarly found that younger age was an independent predictor of AKI and of long-term mortality in children who underwent cardiac surgery. The association of AKI with mortality in older children was less evident. We found that AKI was not associated with late mortality in patients with a primary PICU cancer diagnosis. These children already have poorer prognoses with likely many other factors contributing to long-term mortality, which may supersede the impact of AKI on late outcomes.[35] In patients with other PICU diagnoses, AKI may more significantly impact risk for mortality. This association was no longer significant after adjustments in the other diagnosis subgroup; however, this may be due to decreased power. Authors of future studies should identify AKI patients at highest risk who should be targeted for long-term risk reduction to inform on cost-effective postdischarge follow-up recommendations.

This study is unique from other pediatric AKI studies. Administrative data allowed for a longer follow-up, reliable mortality data, and a relatively large PICU population. Researchers in other studies have evaluated the association between PICU-AKI and long-term mortality; however, most have included hospital mortality, leading to important bias as previously noted, and with shorter follow-up duration.[18–21,36]

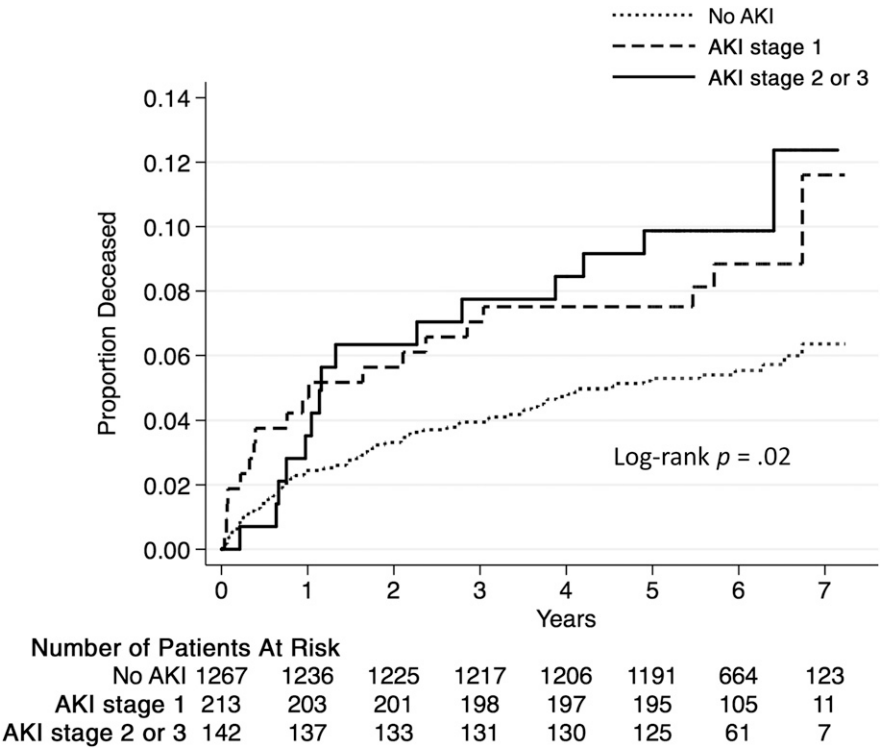

FIGURE 1 Kaplan-Meier curves for 5- to 7-year mortality by AKI strata ($N = 1622$).

TABLE 4 Unadjusted and Adjusted Subgroup Analysis for Significant Effect Modifiers (Age and Diagnostic Category)

AKI Definitions	5–7-y Mortality, *n* (%)	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Age ≤1 y, *n* = 391[a]			
No AKI, *n* = 347	12 (3.5)	1.00	1.00
AKI, *n* = 60	9 (15.0)[b]	4.62 (1.95–10.96)[b]	5.17 (1.61–16.64)[b]
Age >1 y[a]			
No AKI, *n* = 920	60 (6.5)	1.00	1.00
AKI, *n* = 295	25 (8.5)	1.33 (0.83–2.11)	1.50 (0.84–2.68)
Oncology diagnosis[c]			
No AKI, *n* = 43	11 (25.6)	1.00	1.00
AKI, *n* = 12	2 (16.7)	0.59 (0.13–2.68)	0.24 (0.005–11.54)
Infection diagnosis[c]			
No AKI, *n* = 244	20 (8.2)	1.00	1.00
AKI, *n* = 86	7 (8.1)	1.00 (0.42–2.37)	2.53 (0.65–9.86)
All other diagnoses[c]			
No AKI, *n* = 980	41 (4.2)	1.00	1.00
AKI, *n* = 257	25 (9.7)[b]	2.42 (1.47–3.99)[b]	2.03 (0.91–4.53)

AKI was defined by using both SCr and UO.

[a] Adjusted for sex, primary PICU diagnosis of cancer, primary PICU diagnosis of infection, PRISM score death rate, vasopressors, nephrotoxic antibiotics, and steroids received in the PICU and interaction of AKI × cancer diagnosis and AKI × infection diagnosis.

[b] Statistically significant ($P < .05$).

[c] Adjusted for age, sex, PRISM score death rate, vasopressors, nephrotoxic antibiotics, and steroids received in the PICU and interaction of AKI × age.

This study has limitations. The administrative data did not track whether patients moved out of province. However, during the time frame of this study, on average <0.5% per year of the Quebec population emigrated.[37] Furthermore, there is no reason to believe that the characteristics of the patients with AKI and without AKI who may have moved away differed from those who did not. Although we were able to capture cause of death from the Vital Statistics Registry, the validity of these data is unclear and did not allow us to explore the mechanism of the association between AKI and long-term mortality. We were able to control for many important confounders in our analysis; however, we did not assess rehospitalizations, repeat surgeries, or other treatments that may have occurred after the index admission and may impact long-term survival. We were also not able to control for other underlying comorbidities, chronic illness, or renal function abnormalities that may have been diagnosed outside of the index admission. Because of the retrospective nature of the study, we do not have PICU SCr or UO measurements on >400 patients and therefore could not define AKI in these patients. This is a common limitation in retrospective AKI studies. However, given that AKI may be a marker for long-term mortality risk, it seems reasonable that knowledge translation strategies should be taken to encourage physicians to measure these values in PICU children to ascertain AKI status and identify patients at higher risk of poor outcomes; the impact of such strategies, however, is as of yet unknown. Some patients with UO evaluation did not have a bladder catheter, which may have impacted our ability to truly determine if they attained UO-AKI status or not. However, the effect on the results of this study is likely minimal given that over 85% of patients with UO-AKI had a bladder catheter during admission. Another limitation of all studies in which researchers use SCr to define AKI is the potential for dilution of SCr concentration from severe fluid overload. Future researchers should determine if AKI outcome associations are different when corrections for fluid overload are made.[31,38] Our population is from 2 hospitals in Quebec and includes patients admitted to the PICU from 2003 to 2005 (to have a long follow-up duration), which may limit generalizability. Lastly, as with all observational studies, we could not control for unmeasured variables that may differ between groups and cannot make inferences about the causal relationship between AKI and late mortality.

CONCLUSIONS

Noncardiac surgery PICU survivors with AKI had a higher 5- to 7-year mortality risk. Research on the pathophysiology of AKI's association with late outcomes and current follow-up practices as well as evaluating how to risk-stratify patients will help devise rational follow-up guidelines and justify the testing of implementation strategies of such guidelines.

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