

OPEN

Association of Nonrecovery of Kidney Function After Pediatric Acute Kidney Injury With 5-Year Kidney and Nonkidney Outcomes

IMPORTANCE: Acute kidney injury is common in critically ill children, but the long-term outcomes are not well defined.

OBJECTIVES: Evaluated whether nonrecovery of kidney function, following acute kidney injury, was associated with postdischarge mortality, healthcare utilization, and chronic kidney disease.

DESIGN: Retrospective, two-center, observational study.

SETTING: Two ICUs at tertiary children's hospitals in Montreal, QC.

PARTICIPANTS: Pediatric patients (age ≤ 18 yr) with index admission to intensive care between January 1, 2003, and March 31, 2005. Children were excluded if they 1) died during admission, 2) did not have serum creatinine or urine output measured, 3) did not develop acute kidney injury, 4) could not be linked to administrative health data, and 5) (for chronic kidney disease outcome) had pre-existing renal disease by chart review, baseline estimated glomerular filtration rate measurement, or administrative health data codes.

MAIN OUTCOMES AND MEASURES: Three-hundred seventy-eight patients' data were included for long-term mortality and healthcare utilization outcomes; 316 patients for long-term chronic kidney disease outcome. Outcomes were defined using provincial administrative healthcare data diagnosis, procedure, and billing codes.

MAIN RESULTS: Nonrecovery of kidney function, defined as serum creatinine greater than or equal to $1.5\times$ baseline at ICU discharge, occurred in 51 patients (13%). Nonrecovery of kidney function was not associated with long-term mortality (at 5–7 yr following hospital discharge), increased hospitalizations or emergency department visits (at 30-days, 1-year, and 5-yr follow-up), or increased physician visits (at 1- and 5-yr follow-up). Nonrecovery was associated with increased 30-day physician visits (adjusted relative risk, 1.40; 95% CI, 1.13–1.73) and chronic kidney disease diagnosis within 5 years of discharge (adjusted hazard ratio, 4.92, 95% CI, 1.77–13.70).

CONCLUSIONS AND RELEVANCE: Nonrecovery of kidney function following an episode of acute kidney injury in critically ill children is associated with nearly five-fold increased risk for long-term chronic kidney disease. Acute kidney injury nonrecovery may be a useful marker to identify patients that are particularly important to follow-up post discharge for chronic kidney disease detection.

KEY WORDS: acute kidney injury; chronic renal insufficiency; critical care outcomes; mortality; pediatrics; recovery of function

Acute kidney injury (AKI) occurs in at least 15% of children in the ICU (1–3). AKI in this population is associated with ICU and hospital mortality and with length of stay and mechanical ventilation (4, 5). In hospitalized adults, AKI is known to be strongly associated with long-term incidence

Emma H. Ulrich, MD, FRPC¹

Erin Hessey, MSc¹

Sylvie Perreault, BPharm, PhD^{2,3}

Marc Dorais, MSc⁴

Philippe Jovet, MD, PhD, MBA^{2,3}

Veronique Phan, MD, MSc^{2,3}

Michael Zappitelli, MD, MSc⁵

Copyright © 2022 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.0000000000000614

and progression to chronic kidney disease (CKD), end stage renal disease, and increased risk for cardiovascular events and death (6–14). As a result, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends routine follow-up after hospitalization with AKI (15).

Research on the association of pediatric AKI with long-term kidney outcomes is limited, largely due to the lack of non-AKI comparison groups in previous studies. However, observational studies have demonstrated a high prevalence of hypertension and CKD in children with a history of hospitalization-associated AKI, relative to the general pediatric population (16–18). For children undergoing cardiac surgery, the association between postoperative AKI and long-term CKD or hypertension is controversial (19, 20). We previously showed that in children admitted to the ICU, AKI is associated with increased risk for 5-year mortality (21), increased healthcare utilization (22), hypertension (17), and CKD (18) using administrative data. However, identifying which patients should be followed after an episode of AKI remains elusive in the current context, where follow-up of children with AKI after hospital discharge is not the standard of care (19, 23). Previous adult studies have shown that lack of kidney function recovery after AKI was associated with higher risk for mortality, CKD, and other morbidities (24–27). Several studies have defined nonrecovery as the presence of any AKI by KDIGO criteria, including serum creatinine (SCr) greater than 1.5 times baseline by discharge from hospital or other clinically relevant time points (28–31). One study performed in children undergoing ventricular assist device implantation reported that patients with persistent postimplant AKI at discharge (i.e., nonrecovery from AKI based on SCr > 1.5× baseline at 3 mo) had significantly higher rates of CKD at 1-year post heart transplant (30). Nonrecovery of AKI before hospital discharge may therefore be a clinically useful marker, which is easily applicable across different types of patients, for risk-stratifying patients for systematic follow-up after discharge.

We hypothesized that in critically ill children with AKI during ICU admission, nonrecovery of kidney function before hospital discharge is associated with long-term kidney and nonkidney outcomes. In children admitted to two PICUs, we evaluated the extent to which nonrecovery (defined as SCr \geq 1.5× baseline at hospital discharge) was associated with postdischarge

1) mortality, 2) healthcare utilization, and 3) CKD, as defined using administrative healthcare data.

MATERIALS AND METHODS

Design, Setting, and Patient Selection

We performed a secondary analysis using a database that has been extensively described previously (21, 22). The original study was a retrospective cohort study of children (age \leq 18 yr) admitted to two ICUs in Montreal, QC, Canada (Montreal Children's Hospital; Centre Hospital Universitaire Sainte-Justine) between January 1, 2003, and March 31, 2005, to evaluate the association of AKI during ICU admission with 5-year postdischarge outcomes. Only the first hospitalization (index admission) per patient during the study period was included. For the current analysis, exclusion criteria were as follows: 1) death during index admission, 2) lack of either SCr or urine output (UO) data available during ICU admission, 3) did not develop AKI (defined below) during index ICU admission, 4) lack of SCr measured between ICU and hospital discharge (to define AKI nonrecovery), or 5) unable to link medical chart data to provincial administrative health data. Only for analyses pertaining to the CKD outcome, additional exclusion criteria were as follows: 1) pre-existing (pre-ICU) kidney disease (including kidney/urinary tract abnormalities determined by chart review and adjudicated by authors E.H., M.Z.); 2) baseline estimated glomerular filtration rate (eGFR) below normal for age (32–34); or 3) presence of CKD diagnosis code or CKD medication prescription, as per administrative health data codes, within 12 months before index admission. Approvals from the research ethics board of the McGill University Health Centre (study code/approval number 12-015-PED) and the Commission d'accès à l'information du Québec (provincial ethics body) were obtained. Requirement for patient consent was waived.

Data Collection and Sources

Data sources included retrospectively collected medical chart data and provincial administrative health data. Full description of data collection methods has been described previously (21, 22). Briefly, baseline and index ICU variables were collected by retrospective chart review (using data collection forms

pretested for inter- and intrarater reliability) (21, 22), including age, pre-existing kidney abnormalities, primary ICU diagnosis (i.e., cancer, kidney disease, diabetes), variables required to calculate the Pediatric Risk of Mortality (PRISM) II (converted into a death risk rate) (35), treatments (i.e., vasopressor use, need for invasive mechanical ventilation, nephrotoxin exposure), length of stay, and daily ICU SCr and UO data. Nephrotoxins included nonsteroidal anti-inflammatory drugs (NSAIDs) and antimicrobials, including aminoglycosides, vancomycin, acyclovir, and amphotericin. Postdischarge outcome data were obtained from provincial administrative health databases (Quebec Vital Statistics Registry, Régie de l'assurance maladie du Québec (RAMQ), and Med-Echo), from which health data on all subjects were available up until March 31, 2010 (5 yr after the last hospital admission during the study period or ~7 yr after the first hospitalization during the study period). These databases contain mortality data and all inpatient and outpatient billing codes and *International Classification of Disease*, 9th revision and 10th revision diagnosis and procedure codes. Diagnosis codes from the index admission were used to calculate the Pediatric Medical Complexity Algorithm (PMCA), which classifies children with chronic disease according to level of medical complexity (36).

Exposure: Nonrecovery Following AKI

AKI during ICU admission was defined using the KDIGO SCr and UO-based criteria and staged by severity (no AKI or stage 1–3 AKI) (1, 15). The worst of the SCr criteria or UO criteria staging was used to classify AKI severity. Baseline SCr was defined as the lowest SCr 3 months before index admission. If unavailable, we back-calculated baseline SCr using previously described validated methods, assuming normal pre-ICU baseline kidney function for age (21, 22, 33). AKI nonrecovery was defined using the last SCr measured “after” ICU discharge but “before” hospital discharge. Nonrecovery was defined as last SCr greater than or equal to 1.5 times baseline SCr (28, 37).

Outcomes: Mortality, Healthcare Utilization, and CKD

For all outcomes, day 0 of follow-up was the hospital discharge date. The primary outcome was mortality

(determined using RAMQ databases and Québec Vital Statistics Registry). A secondary outcome was healthcare utilization. As previously published, we separately evaluated any hospitalizations, emergency department (ED) visits, and outpatient physician visits (including primary care and specialist visits), expressed as events (visits) per unit time of observation, occurring within 30 days, 1 year, and 5 years after index hospital discharge (defined using RAMQ and Med-Echo databases, as described previously) (22). Another secondary outcome was diagnosis of CKD within 5 years of hospital discharge, using diagnosis, procedure, and medication codes available from RAMQ and Med-Echo databases (**Supplementary Fig. 1**, <http://links.lww.com/CCX/A897>) (full algorithm definition described previously [18, 22]).

Analysis

All analyses were planned a priori and conducted using SAS statistical software, release 9.2 (SAS Institute, Cary, NC) and Stata Version 12 (College Station, TX). Reporting was prepared in accordance with guidelines (38). Associations between patient and ICU characteristics with the exposure and the outcomes (mortality, healthcare utilization, or CKD) were evaluated using univariable analyses appropriate for variable distribution. Variables associated at a p value of less than 0.05 level with both the exposure and outcomes were selected for inclusion in multivariable models. Cox proportional hazards analysis was performed to evaluate the associations between AKI nonrecovery with mortality and between AKI nonrecovery with 5-year postdischarge CKD diagnosis. Modified Poisson regression was performed to evaluate the associations between AKI nonrecovery with 30-day, 1-year, and 5-year healthcare utilization outcomes (expressed as events per unit time). A sensitivity analysis was performed, which was planned a priori, to perform univariable associations between AKI nonrecovery with each outcome, excluding patients who did not have a measured baseline SCr (i.e., patients for whom baseline SCr was estimated).

RESULTS

Patient Characteristics

Of 2,499 eligible ICU patients during the study period, 535 (21%) developed AKI. After exclusions (**Fig. 1**), 378 patients were included in the analysis for

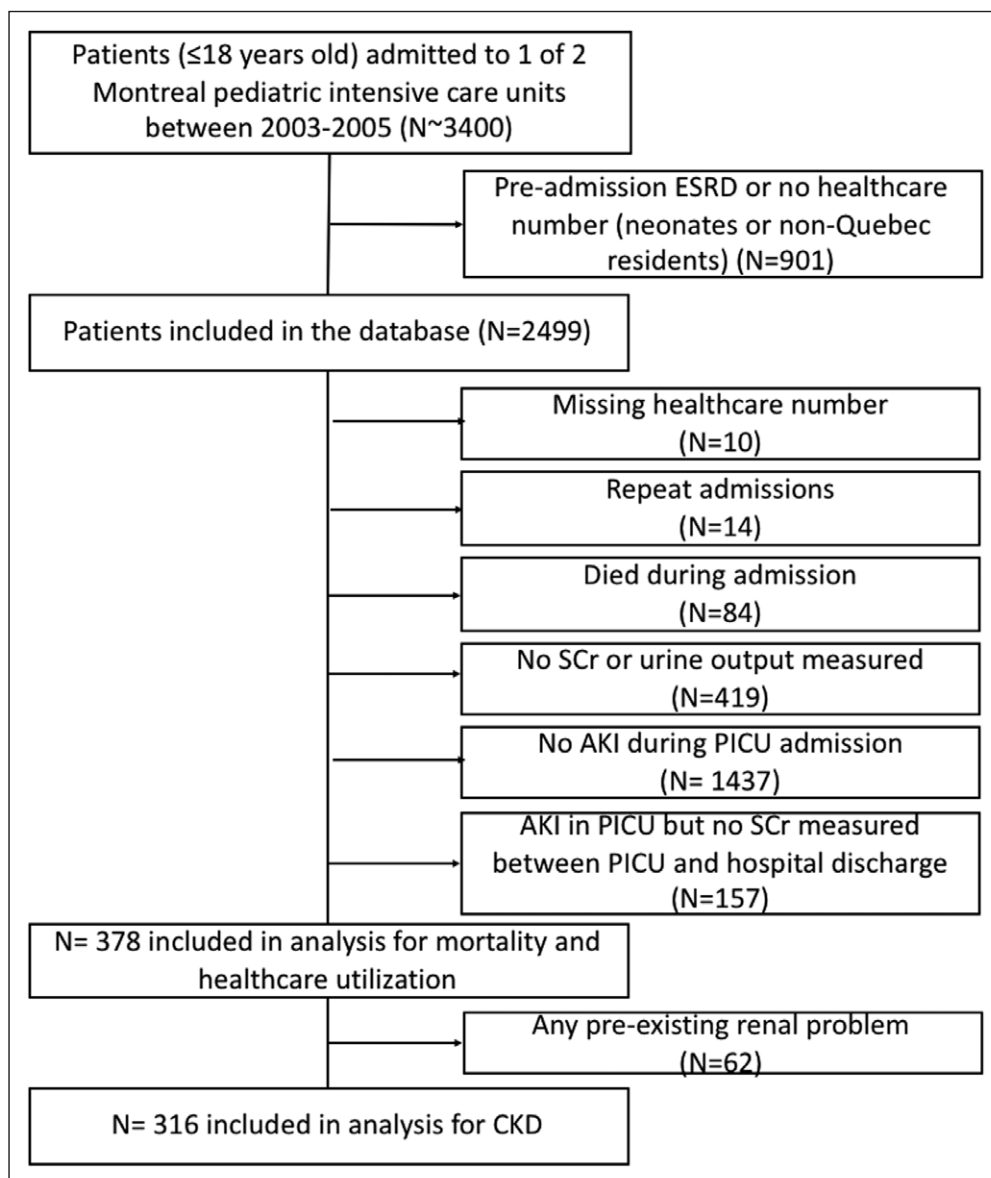


Figure 1. Participant flow diagram. AKI = acute kidney injury, CKD = chronic kidney disease, ESRD = end stage renal disease; SCr = serum creatinine.

long-term mortality and healthcare utilization outcomes (205/378 [54%] male; mean age at admission 5.9 ± 6.0 yr; mean follow-up duration 5.7 ± 1.4 yr). Of these, 316 patients were included in the analysis for long-term CKD outcome (excluding patients with pre-existing kidney disease, reduced baseline eGFR, or CKD diagnostic codes or medications within 12 mo of index admission) (Fig. 1).

Nonrecovery of kidney function occurred in 51 of 378 patients (13%). **Table 1** shows that patients with nonrecovery (vs recovery) were significantly older at ICU admission and had a higher proportion of females. Patients with nonrecovery also had higher proportion of oncologic, kidney and postoperative (noncardiac)

diagnoses, nephrology consultations, and treatment with renal support therapy; they had lower proportions of postcardiac surgery procedures, vasopressor use, NSAIDs use, and mechanical ventilation and had lower PRISM death rate and ICU length of stay.

Association of Nonrecovery With Mortality

Mortality within 5–7 years following hospital discharge occurred in five of 51 children (10%) with AKI nonrecovery and in 28 of 327 patients (9%) with AKI recovery ($p = 0.77$). As shown in **Figure 2A**, in the multivariable model (adjusted for age and PRISM death rate), nonrecovery after AKI was not associated with long-term mortality (adjusted hazard ratio [HR], 1.26; 95% CI, 0.48–3.30).

Association of Nonrecovery With Healthcare Utilization

Figure 2B shows that in multivariable analyses (adjusted for age, admission diagnoses [cancer; renal; diabetes], vasopressor use, need for invasive mechanical ventilation, PMCA score, and pre-existing renal abnormalities), nonrecovery after AKI was not associated with increased relative risk of hospitalization at 30 days, 1 year, or 5 years post hospital discharge. Similarly, **Figure 2B** shows that in multivariable analyses, nonrecovery was not associated with ED visits at 30 days, 1 year, or 5 years.

Figure 2B also shows that although nonrecovery after AKI was associated with increased physician visits at 30 days, 1 year, and 5 years after discharge in univariable analyses, nonrecovery was only associated with increased

TABLE 1.
Comparison of Patient Characteristics by Nonrecovery

Variables	AKI and Nonrecovery, N = 51	AKI and Recovery, N = 327
Baseline characteristics		
Age, yr	3.06 (10.46) ^d	6.68 (10.11)
Female sex	30 (59%) ^d	143 (44%)
Center 1 ^a	14 (27%)	92 (28%)
ICU diagnosis		
Cardiac surgery	2 (4%) ^e	148 (45%)
Cardiac (nonsurgical)	4 (8%)	9 (3%)
Diabetes	0 (0%)	12 (4%)
Gastrointestinal	3 (6%)	22 (7%)
Infection (excluding bronchiolitis)	11 (22%)	46 (14%)
Neurologic or neurosurgical	3 (6%)	16 (5%)
Oncologic	8 (16%) ^e	2 (1%)
Kidney disease	10 (20%) ^e	5 (2%)
Respiratory	3 (6%)	10 (3%)
Trauma	1 (2%)	19 (6%)
Other ^b	6 (12%)	38 (12%)
Pre-existing kidney disease ^c	41/327 (12.5%) ^e	21/51 (41.2%)
Postoperative (noncardiac)	17 (33%) ^e	44 (14%)
PRISM II score	7.0 (12.0) ^d	12.0 (9.0)
PRISM death rate	2.0 (8.7) ^e	6.1 (14.1)
ICU treatment characteristics		
Vasopressor use	9 (18%) ^e	173 (53%)
Any nephrotoxic antibiotics	22 (43%)	124 (38%)
Nonsteroidal anti-inflammatory drugs use (yes/no)	4 (8%) ^d	77 (24%)
Mechanically ventilated (yes/no)	20 (40%) ^e	244 (75%)
ICU length of stay (d)	1.9 (6.4) ^e	4.2 (8.7)
Hospital length of stay (d)	16 (20)	18 (23)
Kidney related		
Nephrology consultation during admission	26 (51%) ^e	57 (17%)
Renal support therapy in ICU (yes/no)	8 (16%) ^e	4 (1%)
AKI stage		
Stage 1	18 (35%)	198 (61%)
Stage 2	9 (18%)	75 (23%)
Stage 3	24 (47%)	54 (17%)
Outcomes		
5–7 yr mortality	5 (10%)	28 (9%)
Chronic kidney disease	5 (10%)	14 (4%)

AKI = acute kidney injury, PRISM II = Pediatric Risk of Mortality II.

^aPatients were admitted to one of two ICUs in Montreal, QC, Canada.

^bIncludes hematologic (nononcologic), inborn error of metabolism and metabolic (noninborn error of metabolism), immunologic, intoxication, burn, orthopedic, otolaryngologic, endocrinologic (nondiabetes), and bronchiolitis

^cExcluded from chronic kidney disease analysis.

^d $p < 0.05$.

^e $p < 0.001$.

Continuous variables reported as median (interquartile range) and categorical variables reported as number (percentage).

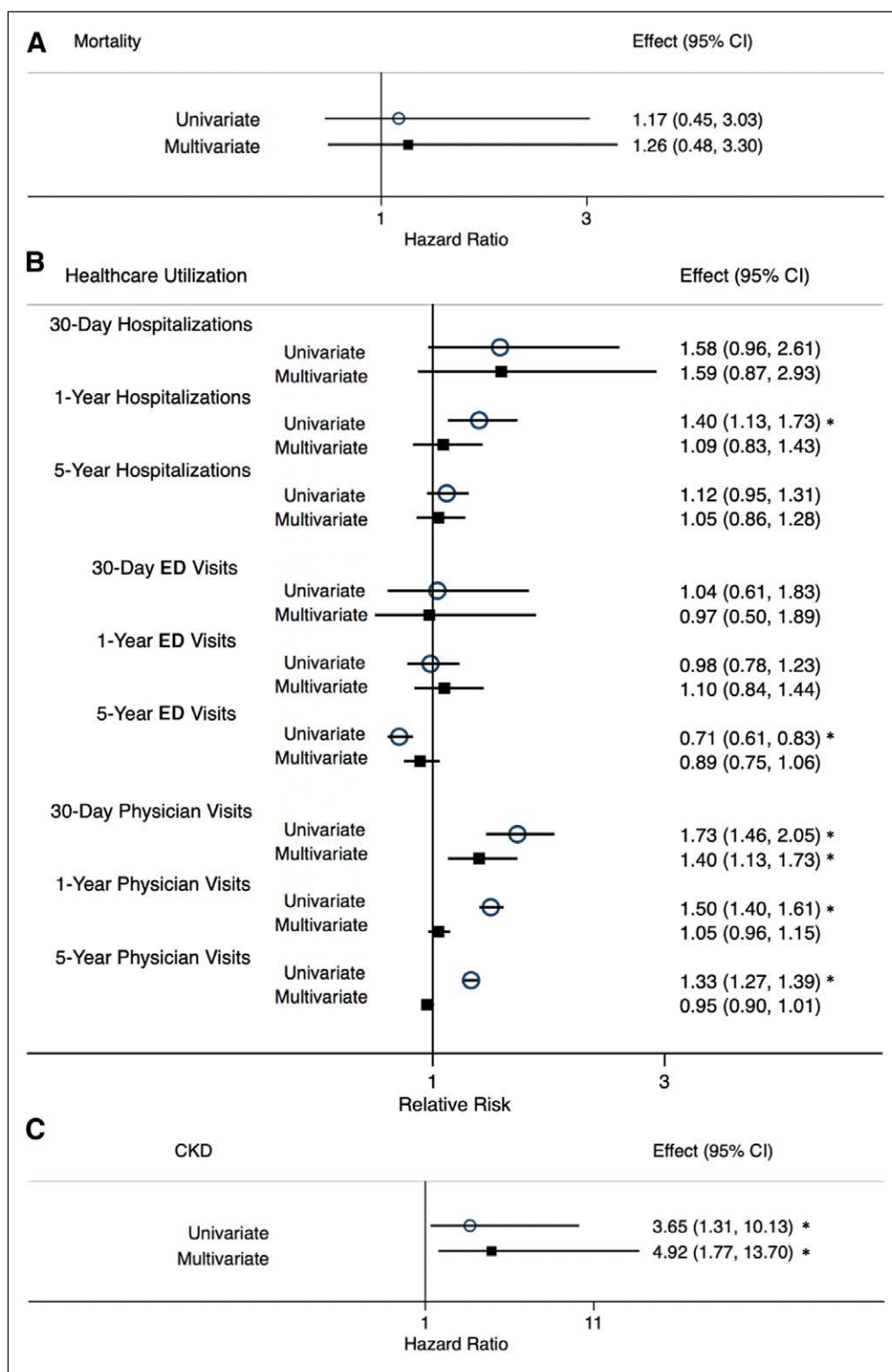


Figure 2. Univariable and multivariable analysis of association of nonrecovery of renal function after acute kidney injury (AKI) with long-term outcomes. **A**, Mortality at 5–7 yr ($n = 5$ AKI and nonrecovery; $n = 28$ AKI and recovery) hazard ratios (95% CI) is evaluated using Cox proportional hazard analysis. **B**, Healthcare utilization ($n = 51$ AKI and nonrecovery; $n = 327$ AKI and recovery) relative risk (95% CI) is evaluated using modified Poisson regression. **C**, Chronic kidney disease at 5 yr ($n = 5$ AKI and nonrecovery; $n = 14$ AKI and recovery) hazard ratio (95% CI) is evaluated using Cox proportional hazard analysis. * $p < 0.05$. CKD = chronic kidney disease, ED = emergency department.

physician visits at 30 days in multivariable analyses (adjusted relative risk, 1.40; 95% CI, 1.13–1.73).

Association of Nonrecovery With CKD

CKD diagnosis at 5 years following hospital discharge occurred in nine of 30 children (30%) with nonrecovery after AKI and in 30 of 286 patients (10%) with recovery after AKI ($p = 0.002$). In the multivariable analysis (adjusted for age, PMCA score, and nephrotoxic antibiotic exposure), nonrecovery was associated with nearly five-fold increased risk for CKD diagnosis within 5 years of discharge (adjusted HR, 4.92; 95% CI, 1.77–13.70, shown in Fig. 2C).

Sensitivity Analysis

When excluding children without measured baseline SCr, the magnitude and directions of associations between nonrecovery and outcomes were very similar (Fig. 3 A–C).

DISCUSSION

We found that nonrecovery of kidney function following AKI in critically ill children is associated with increased risk for diagnosis of CKD, as defined using administrative health data. To our knowledge, this has not been previously reported in the

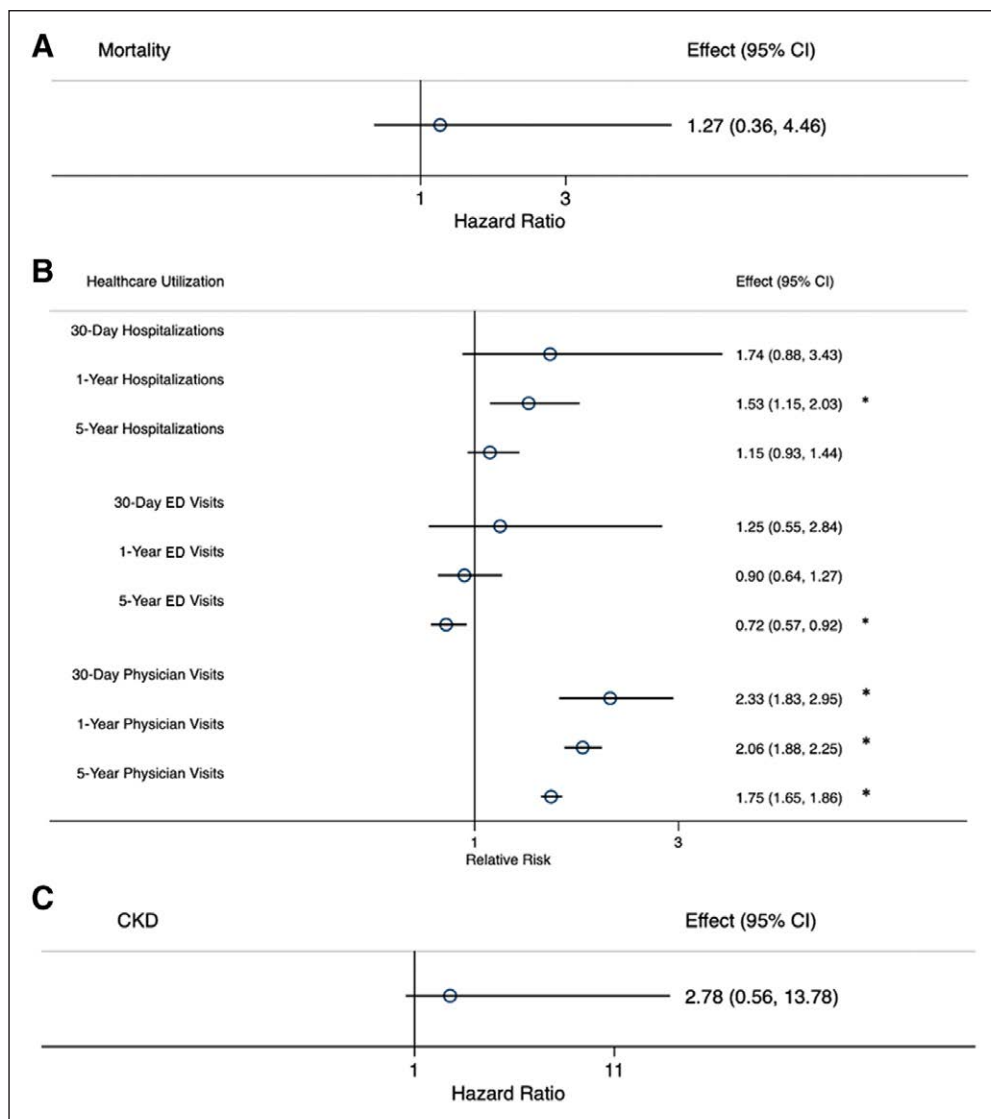


Figure 3. Univariable analysis of association of nonrecovery of kidney function after acute kidney injury with long-term outcomes (excluding patients without a measured baseline serum creatinine). **A**, Mortality at 5–7 yr hazard ratios (95% CI) is evaluated using Cox proportional hazard analysis. **B**, Healthcare utilization relative risk (95% CI) is evaluated using modified Poisson regression. **C**, Chronic kidney disease at 5 yr hazard ratio (95% CI) is evaluated using Cox proportional hazard analysis. * $p < 0.05$. CKD = chronic kidney disease, ED = emergency department.

AKI literature for children admitted in the general ICU. Nonrecovery of kidney function at hospital discharge after an episode of AKI was not associated with increased mortality or hospitalizations but was associated with increased risk of outpatient physician visits at 30 days.

In this study, patients with nonrecovery of kidney function after AKI had lower illness severity markers compared with those with recovery. This finding was surprising considering the established association between AKI and poorer hospital outcomes (3, 39, 40).

The disproportionate distribution of children undergoing cardiac surgery (4% of the AKI nonrecovery group vs almost half of the AKI recovery group) may at least partially explain why children in the recovery group had higher illness severity in the ICU and more stable kidney function at the time of discharge. Children undergoing cardiac surgery very commonly have small elevations of SCr postoperatively and also significant oliguria, which would classify them as having stage 1 AKI. It is conceivable that children undergoing cardiac surgery with stage 1 AKI might more commonly recover their kidney function compared with noncardiac ICU children. Another possible explanation is that patients with more severe AKI in ICU died prior to hospital discharge and thus did not have the opportunity to be ascertained for nonrecovery prior to hospital discharge.

We previously showed that AKI is independently associated with increased risk of 5–7-year mortality after critical illness in children (23). A large multicenter study, including nearly 17,000 adult patients with stage 2 or 3 AKI, showed significantly increased risk of 1-year mortality in patients without AKI recovery (similarly defined as in our study) at hospital discharge (29). Our study does not support this association in children. Although our study is limited by a small sample size and low event rates, the point estimates (HRs) suggest that even if there is an association of AKI nonrecovery with mortality, it is not a

very strong effect. Future larger studies with a higher proportion of patients with more severe AKI (at least stage 2 AKI or worse) should be performed to better investigate and quantify the increased risk of mortality attributable to nonrecovery from more severe AKI.

Nonrecovery of kidney function was not associated with significantly increased risk of rehospitalization or ED visits. However, nonrecovery was associated with approximately 40% increased risk of outpatient physician visits at 30 days, even when adjusting for medical complexity (i.e., admission diagnoses, illness severity, and PMCA score). Contrary to the adult population where follow-up after AKI is routine, healthcare utilization post-AKI is difficult to study and interpret in the pediatric population, in whom there is currently no pediatric data-driven consensus guideline for optimal follow-up (15). Understanding postdischarge care pathways for children who develop AKI during hospitalization is essential to determining whether increased healthcare utilization is due to increased surveillance and higher illness severity or whether healthcare providers are triggered by elevated SCr at discharge to follow these patients prospectively.

Children with nonrecovery of kidney function had nearly five times significantly increased adjusted risk of CKD diagnosis at 5-year follow-up when adjusting for age, medical complexity (using PMCA score), and nephrotoxin exposure. We recently showed that critically ill children with AKI are at higher risk for CKD development in this cohort using administrative health data; we applied multiple algorithms accounting for stricter definitions of CKD using codes consistent with KDIGO criteria for CKD (including CKD, proteinuria, and dialysis) and broader definitions including outpatient diagnostic codes and CKD-specific medications (18). We also supported this association in a separate prospective study of two Canadian centers using laboratory data (18, 41). There is almost no published literature on the association of predischarge AKI recovery with long-term kidney outcomes and none published in a general PICU population (30). The results of our study suggest that children without renal recovery of AKI before hospital discharge are at risk for long-term kidney dysfunction. Increased AKI severity could be an important driver of this observation considering the higher rate of stage 3 AKI in children with nonrecovery versus recovery at hospital discharge (47% vs 17%). Future studies are needed to determine

other factors that may contribute to this association, including pattern and timing of AKI recovery, ICU/post-ICU care pathways that could be contributing to persistent AKI at discharge (i.e., number and duration of nephrotoxins or severity of fluid overload), and AKI recurrence after discharge. Prospective studies are also needed to confirm the association between nonrecovery and long-term CKD using laboratory markers of kidney dysfunction. Finally, efforts should be made to ensure that when care transfer occurs from ICU to non-ICU wards, communication and documentation about AKI events is performed to maximize the probability that appropriate follow-up ensues.

A recent consensus statement by Chawla et al (42) proposes the term “acute kidney disease” to represent our evolving understanding of the continuum of kidney dysfunction between AKI and CKD. This guideline suggests that patients with persistent AKI or SCr greater than or equal to $1.5\times$ baseline 7 days post-AKI episode are at high risk for morbidity and mortality and recommends closer surveillance of these patients following hospital discharge. However, we and others have shown that follow-up of kidney function after ICU discharge, in children who develop AKI during ICU admission, is quite uncommon (19, 23). It is also noteworthy that in our study, approximately 25% of children who developed AKI in the ICU did not have a repeat SCr measured prior to hospital discharge. Future studies are needed to evaluate specific time points for renal recovery and severity of ongoing kidney dysfunction and their association with long-term outcomes in children. At the very least, our results suggest that an effort should be made to ensure that kidney function be measured after AKI to document recovery from AKI, prior to hospital discharge.

Our study has limitations. Our sample size was relatively small for children with nonkidney recovery post-AKI, limiting the inclusion of additional confounding variables in our multivariable analysis. We defined nonrecovery in our study using SCr greater than $1.5\times$ baseline to be consistent with the recently published literature; however, there is not yet a consensus definition of nonrecovery. We defined CKD using administrative health data, which has been shown to have poor sensitivity but very high specificity in a Canadian study (43). Furthermore, in our previous study, we demonstrated that the presence

of AKI during ICU admission, defined in many different ways, was strongly associated with CKD using this definition (18). Although we did not have access to postdischarge laboratory data to confirm diagnosis of CKD, future studies should be performed with available linked laboratory data to confirm the diagnosis and evaluate the severity of CKD. Our data come from ICU admissions occurring about 15 years ago, with long-term follow-up data available until about 10 years ago. However, the incidence of AKI (21%) is consistent with the reported incidence of AKI in a multinational prospective study (3), suggesting that the identification and management of critically ill children with AKI has not changed significantly. To our knowledge, there have been no substantial changes in the long-term follow-up care of children with AKI at either of these two institutions. Furthermore, the use of already available data to determine the extent to which AKI nonrecovery is associated with later outcomes (vs initiating a new resource-intensive data collection process of prospective study) is a strength. Many of our patients did not have a baseline SCr measurement, which is typical for children admitted to the ICU (3, 33). For this reason, we performed a sensitivity analysis excluding patients for whom we estimated baseline SCr. This analysis did lead to a loss of statistical significance for association with CKD diagnosis, likely due to reduced sample size. Although consensus opinion is that estimating baseline SCr is acceptable (by necessity) to do in patients without baseline SCr (42), systematic monitoring of kidney function may become an important component of primary care surveillance of higher risk patients. Another potential limitation which must be addressed is the potential bias associated with evaluating nonrecovery of AKI with later CKD development. It is possible that AKI patients with elevated SCr prior to hospital discharge may have been “appropriately” targeted for postdischarge SCr measurement or physician visits, thereby increasing the probability of CKD detection (compared with those patients without recovery). This potential bias can only be addressed in future prospective studies of children with AKI, irrespective of their recovery status. Our results may not be completely generalizable to other countries, where health system funding and processes and healthcare disparities differ from those in Canada.

CONCLUSIONS

Nonrecovery of kidney function following AKI was associated with increased long-term CKD. There is a need to better understand the pathophysiology of this acute kidney disease state in order to identify potential targets for treatment and to inform prognostic models. As well, there is urgency to develop evidence-based recommendations for follow-up of critically ill children after AKI.

ACKNOWLEDGMENTS

We acknowledge the individuals who performed the data collection and helped with data management at Centre Hospitalier Universitaire Sainte-Justine and the Montreal Children’s Hospital. We thank Mr. Vedran Cockovski for assistance in preparation of this article.

- 1 Division of Pediatric Nephrology, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada.
- 2 Faculty of Pharmacy, University of Montreal, Montreal, QC, Canada.
- 3 Department of Pediatrics, Hospital for Sick Children, Toronto, ON, Canada.
- 4 StatSciences Inc., Notre-Dame de l’Île-Perrot, Montreal, QC, Canada.
- 5 Division of Nephrology, Hospital for Sick Children, Toronto, ON, Canada.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s website (<http://journals.lww.com/ccejjournal>).

Dr. Zappitelli was provided with an operating grant from the Fonds de Recherche du Quebec-Sante to perform this work and with SickKids Research Institute and SickKids Department of Pediatrics Start up Funds to pay for statistical analyses related to this work. The remaining authors have not disclosed any potential conflicts of interest.

This work was performed at Montreal Children’s Hospital, Montreal, QC, Canada; Centre Hospital Universitaire Sainte-Justine, Montreal, QC, Canada.

For information regarding this article, E-mail: Michael.zappitelli@sickkids.ca

REFERENCES

1. Akcan-Arikan A, Zappitelli M, Loftis LL, et al: Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007; 71:1028–1035
2. Blinder JJ, Asaro LA, Wypij D, et al: Acute kidney injury after pediatric cardiac surgery: A secondary analysis of the safe pediatric euglycemia after cardiac surgery trial. *Pediatr Crit Care Med* 2017; 18:638–646

3. Kaddourah A, Basu RK, Bagshaw SM, et al; AWARE Investigators: Epidemiology of acute kidney injury in critically ill children and young adults. *N Engl J Med* 2017; 376:11–20
4. Li S, Krawczeski CD, Zappitelli M, et al; TRIBE-AKI Consortium: Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: A prospective multicenter study. *Crit Care Med* 2011; 39:1493–1499
5. Alkandari O, Eddington KA, Hyder A, et al: Acute kidney injury is an independent risk factor for pediatric intensive care unit mortality, longer length of stay and prolonged mechanical ventilation in critically ill children: A two-center retrospective cohort study. *Crit Care* 2011; 15:R146
6. Amdur RL, Chawla LS, Amodeo S, et al: Outcomes following diagnosis of acute renal failure in U.S. veterans: Focus on acute tubular necrosis. *Kidney Int* 2009; 76:1089–1097
7. Hsu CY, Chertow GM, McCulloch CE, et al: Nonrecovery of kidney function and death after acute on chronic renal failure. *Clin J Am Soc Nephrol* 2009; 4:891–898
8. Ishani A, Xue JL, Himmelfarb J, et al: Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol* 2009; 20:223–228
9. Coca SG, Singanamala S, Parikh CR: Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. *Kidney Int* 2012; 81:442–448
10. Chawla LS, Eggers PW, Star RA, et al: Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; 371:58–66
11. Hsu CY, Hsu RK, Yang J, et al: Elevated BP after AKI. *J Am Soc Nephrol* 2016; 27:914–923
12. Chawla LS, Amdur RL, Shaw AD, et al: Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol* 2014; 9:448–456
13. Wu VC, Wu CH, Huang TM, et al; NSARF Group: Long-term risk of coronary events after AKI. *J Am Soc Nephrol* 2014; 25:595–605
14. Wu VC, Huang TM, Lai CF, et al: Acute-on-chronic kidney injury at hospital discharge is associated with long-term dialysis and mortality. *Kidney Int* 2011; 80:1222–1230
15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2:1–138
16. Sigurjonsdottir VK, Chaturvedi S, Mammen C, et al: Pediatric acute kidney injury and the subsequent risk for chronic kidney disease: Is there cause for alarm? *Pediatr Nephrol* 2018; 33:2047–2055
17. Hessey E, Perreault S, Roy L, et al: Acute kidney injury in critically ill children and 5-year hypertension. *Pediatr Nephrol* 2020; 35:1097–1107
18. Hessey E, Perreault S, Dorais M, et al: Acute kidney injury in critically ill children and subsequent chronic kidney disease. *Can J Kidney Health Dis* 2019; 6:2054358119880188
19. Greenberg JH, Zappitelli M, Devarajan P, et al; TRIBE-AKI Consortium: Kidney outcomes 5 years after pediatric cardiac surgery: The TRIBE-AKI study. *JAMA Pediatr* 2016; 170:1071–1078
20. Madsen NL, Goldstein SL, Frøslev T, et al: Cardiac surgery in patients with congenital heart disease is associated with acute kidney injury and the risk of chronic kidney disease. *Kidney Int* 2017; 92:751–756
21. Hessey E, Morissette G, Lacroix J, et al: Long-term mortality after acute kidney injury in the pediatric ICU. *Hosp Pediatr* 2018; 8:260–268
22. Hessey E, Morissette G, Lacroix J, et al: Healthcare utilization after acute kidney injury in the pediatric intensive care unit. *Clin J Am Soc Nephrol* 2018; 13:685–692
23. Hessey E, Ali R, Dorais M, et al: Renal function follow-up and renal recovery after acute kidney injury in critically ill children. *Pediatr Crit Care Med* 2017; 18:733–740
24. Liaño F, Felipe C, Tenorio MT, et al: Long-term outcome of acute tubular necrosis: A contribution to its natural history. *Kidney Int* 2007; 71:679–686
25. Bucaloiu ID, Kirchner HL, Norfolk ER, et al: Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012; 81:477–485
26. Pannu N, James M, Hemmelgarn B, et al; Alberta Kidney Disease Network: Association between AKI, recovery of renal function, and long-term outcomes after hospital discharge. *Clin J Am Soc Nephrol* 2013; 8:194–202
27. Heung M, Steffick DE, Zivin K, et al; Centers for Disease Control and Prevention CKD Surveillance Team: Acute kidney injury recovery pattern and subsequent risk of CKD: An analysis of Veterans Health Administration Data. *Am J Kidney Dis* 2016; 67:742–752
28. Korenkevych D, Ozrazgat-Baslanti T, Thottakkara P, et al: The pattern of longitudinal change in serum creatinine and 90-day mortality after major surgery. *Ann Surg* 2016; 263:1219–1227
29. Kellum JA, Sileanu FE, Bihorac A, et al: Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017; 195:784–791
30. Hollander SA, Cantor RS, Sutherland SM, et al: Renal injury and recovery in pediatric patients after ventricular assist device implantation and cardiac transplant. *Pediatr Transplant* 2019; 23:e13477
31. Hollander SA, Montez-Rath ME, Axelrod DM, et al: Recovery from acute kidney injury and CKD following heart transplantation in children, adolescents, and young adults: A retrospective cohort study. *Am J Kidney Dis* 2016; 68:212–218
32. Schwartz GJ, Muñoz A, Schneider MF, et al: New equations to estimate GFR in children with CKD. *J Am Soc Nephrol* 2009; 20:629–637
33. Hessey E, Ali R, Dorais M, et al: Evaluation of height-dependent and height-independent methods of estimating baseline serum creatinine in critically ill children. *Pediatr Nephrol* 2017; 32:1953–1962
34. Piepsz A, Tondeur M, Ham H: Revisiting normal (51) Cr-ethylenediaminetetraacetic acid clearance values in children. *Eur J Nucl Med Mol Imaging* 2006; 33:1477–1482
35. Pollack MM, Ruttimann UE, Getson PR: Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988; 16:1110–1116
36. Simon TD, Cawthon ML, Stanford S, et al; Center of Excellence on Quality of Care Measures for Children with Complex Needs (COE4CCN) Medical Complexity Working Group: Pediatric medical complexity algorithm: A new method to stratify children by medical complexity. *Pediatrics* 2014; 133:e1647–e1654
37. Kellum JA, Chawla LS, Keener C, et al; ProCESS and ProGRess-AKI Investigators: The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. *Am J Respir Crit Care Med* 2016; 193:281–287

38. von Elm E, Altman DG, Egger M, et al; STROBE Initiative: The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61:344–349
39. Jetton JG, Boohaker LJ, Sethi SK, et al; Neonatal Kidney Collaborative (NKC): Incidence and outcomes of neonatal acute kidney injury (AWAKEN): A multicentre, multinational, observational cohort study. *Lancet Child Adolesc Health* 2017; 1:184–194
40. Alobaidi R, Morgan C, Goldstein SL, et al: Population-based epidemiology and outcomes of acute kidney injury in critically ill children. *Pediatr Crit Care Med* 2020; 21:82–91
41. Benisty K, Morgan C, Hessey E, et al: Kidney and blood pressure abnormalities 6 years after acute kidney injury in critically ill children: A prospective cohort study. *Pediatr Res* 2020; 88:271–278
42. Chawla LS, Bellomo R, Bihorac A, et al; Acute Disease Quality Initiative Workgroup 16: Acute kidney disease and renal recovery: Consensus report of the acute disease quality initiative (ADQI) 16 workgroup. *Nat Rev Nephrol* 2017; 13:241–257
43. Dart A, Chartier M, Komenda P, et al: Evaluation of administrative case definitions for chronic kidney disease in children. *Pediatr Res* 2020; 87:569–575