Long-Term Outcomes of Children Undergoing Dialysis-treated AKI: Some Opinions and Prospects

In a recently published article in *JASN*, Robinson *et al.* performed a retrospective study reporting the long-term kidney outcomes after childhood dialysis-treated AKI (DT-AKI). This topic is very important, and there is currently very limited evidence on this issue, especially in studies with a large population and long follow-up. The study found that pediatric survivors of DT-AKI had significantly increased long-term risks of kidney failure, death, major adverse kidney events, CKD, and hypertension, as compared with comparators.

I believe the methods in this article are clear. However, I would like to point out some suggestions that may make the conclusions more convincing.

Firstly, one of the biggest limitations of this article is a lack of a definition of AKI on the basis of laboratory tests, which may lead to miscoding of the study exposure. Although the authors have excluded children with an inborn error of metabolism or poisoning, survivors of DT-AKI may still include some patients without AKI, such as those with high potassium or other emergencies. However, if the researchers defined DT-AKI as a combination of an AKI diagnosis and the requirement of acute dialysis, instead of only using acute dialysis codes, it would greatly reduce their misclassification errors. Secondly, the choice of comparator group for the study appears to be discussed. Only 28 of 6,752 matched children were patients with AKI. Thus, the effect of DT-AKI on outcomes could be overestimated by selecting patients without AKI as the comparator group. The ideal comparator group should be patients with AKI but who are not on acute dialysis. Thirdly, death and kidney failure are in a competitive relationship and there is a significant difference in the incidence of death and kidney failure (approximately 3:1). Therefore, the effect of the composite end point may be largely due to death. As we all know, it is not easy to observe the end point of kidney failure in children during follow-up. I suggest that using the change of serum creatinine or eGFR as a surrogate end point may be more meaningful for kidney progression in children. Finally, I am quite confused about why the final model only included ten variables instead of the 31 variables listed in the baseline table 1. Did the authors have a process to select these variables? I think some variables, such as age, income, rural status, and admission to the intensive care unit, have a great influence on outcomes, which should be included in the final model.

In summary, a larger sample size and more rigorous design studies are needed to further investigate the prognosis of children with DT-AKI.

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REFERENCES


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Pediatric Acute Kidney Injury Survivors Need Risk Stratification and Individualized Follow-Up

We read with great interest “Long-term kidney outcomes following childhood acute kidney injury receiving dialysis: A population-based cohort study” by Robinson et al.1 In this retrospective cohort study, 1699 pediatric survivors of dialysis-treated AKI were followed up for a median of 9.6 years to evaluate long-term kidney outcomes. The study suggested that survivors of AKI were at significantly increased risk of a composite outcome of kidney failure or death versus matched comparators. Interestingly, no such difference was observed in the subgroup analysis of patients who underwent cardiac surgery during their dialysis-treated AKI admission.

Irrespective of children or adults, AKI is a major cause of morbidity and mortality with a complex etiology. Different types of AKI, such as septic AKI and surgery-associated AKI, may have distinct pathologic mechanisms and, hence, require different preventive or therapeutic strategies. Although the early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury trial, mainly focusing on surgery-associated AKI, found early RRT compared with delayed RRT reduced mortality over the first 90 days, the initiation of dialysis early versus delayed in the intensive care unit trial on septic AKI identified no significant difference in 90-day mortality.2 One of our studies revealed that serum neutrophil gelatinase-associated lipocalin could be used as a predictor for successful RRT discontinuation in patients with nonseptic AKI, rather than in those with septic AKI.3 In the study by Robinson et al.,1 it might be similarly speculated that pediatric survivors of cardiac surgery-associated AKI and other types of AKI had different clinical trajectories in later life, thus necessitating risk stratification and adaptive follow-up surveillance.

As the authors discussed, previous studies of pediatric AKI bear conflicting results. This inconsistency might be partly attributed to notable heterogeneity in terms of study design, sample size, follow-up, and end points. One strength of the current research is the application of the major adverse kidney events end point, which is recommended by the National Institute of Diabetes and Digestive and Kidney Diseases workgroup to capture clinically important, patient-centered outcomes.4 This study was also advantaged by the utilization of health administrative databases, thus assembling a large patient cohort with minimal loss to follow-up. It is worth mentioning that the authors used the acute dialysis code rather than the classic Kidney Disease Improving Global Outcomes or RIFLE criteria to define dialysis-treated AKI, which was unfit for earlier stages of AKI. Meanwhile, the cause of AKI was not clearly specified. With a code of cardiac surgery during index hospitalization, a child was suspected to have cardiac surgery-associated AKI, but the diagnosis should be further validated. We believe that large-scale prospective cohort studies using standardized end points, such as major adverse kidney events, are warranted to guide risk stratification and individualized management for pediatric survivors of AKI of different etiologies.

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Authors’ Reply

We thank Zhao et al.,1 and Wei2 for their interest in our manuscript, “Long-term kidney outcomes following childhood acute kidney injury receiving dialysis: A population-based cohort study,”3 and for providing thoughtful feedback. The letter from Zhao et al.1 correctly highlights that outcomes after AKI differ significantly depending on the cause of AKI. AKI caused by isolated, brief insults, where removal of the offending agent is feasible (e.g., hypovolemia or isolated nephrotoxic medication exposure) typically have better outcomes than those with prolonged or recurrent insults (e.g., prolonged ischemia or repeated nephrotoxin exposure in patients with cancer).

On the basis of available data within the Ontario healthcare administrative databases, we cannot precisely identify the etiology of dialysis-treated AKI in our participants. Instead, we included all children with dialysis-treated AKI within Ontario between 1996 and 2017. We performed subgroup analyses evaluating children that underwent cardiac surgery during their hospitalization and those that had prior cardiac surgery or malignancy. Cardiac surgery during hospitalization may be a proxy indicator of cardiac surgery–associated AKI, but we acknowledge that other factors may have caused or contributed to AKI. We found the incidence of kidney failure or death after dialysis-treated AKI was similar between children that did or did not undergo cardiac surgery.4 Whether pediatric cardiac surgery–associated AKI is associated with adverse long-term kidney outcomes remains unclear. Recent prospective studies, including Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI)4 and Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI),5 have not found significant associations between cardiac surgery–associated AKI and CKD or hypertension by 4–5 years. Overall CKD and hypertension incidence in pediatric cardiac surgery populations is high.4,5 We hypothesize that other factors—such as underlying heart disease, residual postoperative defects leading to recurrent surgeries, and other comorbidities—may be stronger mediators of long-term kidney outcomes than postoperative AKI occurrence.

We also evaluated a number of other potential etiologic factors (e.g., sepsis, shock, extracorporeal membrane oxygenation, stem cell transplantation, hemolytic uremic syndrome, and various preexisting comorbidities). Although this provided clues to the potential etiology of each AKI, we cannot fully establish causality using administrative data, which we acknowledge as a study limitation.

Additional large, prospective studies focused on long-term kidney outcomes after pediatric AKI are needed to improve the risk stratification of survivors of AKI. Most current studies have focused on initial AKI hospitalization risk factors. However, a number of postdischarge factors may also significantly contribute to long-term CKD risk and warrant further exploration. Improved risk-stratification tools would help establish criteria for targeted follow-up and CKD prevention strategies (such as dedicated post-AKI follow-up clinics).

As Wei2 highlights, laboratory data were not available in our study, preventing us from further validating the dialysis-treated AKI exposure. However, the administrative codes we used to define acute dialysis have been previously validated with a high positive predictive value (94%).5 In Ontario, accurate billing is required for physician and facility reimbursement, making these codes reliable for identifying acute dialysis. We excluded children with inborn errors of metabolism or poisoning, given that they may have received acute dialysis without an AKI. We believe the vast majority of the included cohort that received acute dialysis in our study had associated AKI.

We did not use a combination of AKI and dialysis codes to define dialysis-treated AKI, given that administrative codes for AKI have a low sensitivity (<15%) in children.7 This would significantly reduce the size of our dialysis-treated AKI cohort. Although understanding differences in long-term kidney outcomes after dialysis-treated versus less severe forms of AKI is important, this was not our focus. For that reason, we used hospitalized patients (without dialysis-treated AKI) as comparators to determine the adverse kidney outcomes attributable to an episode of dialysis-treated AKI. Further, administrative database codes are better at detecting stage 3 AKI than stage 1–2 AKI, which would create selection bias.7

We acknowledge Wei’s2 comment on the greater number of deaths versus kidney failure events contributing to our composite end point. However, the incidence of both kidney failure and death were also separately higher in the dialysis-treated AKI cohort. Due to the absence of laboratory data, change in serum creatinine could not be determined. With regards to adjustment and matching, we matched cases and comparators on the basis of age, sex, and index hospitalization year, and adjusted our Cox models using variables selected a priori. These variables were selected on the basis of their reported associations with long-term kidney outcomes and the reliability of their administrative coding.

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