Patterns of kidney injury in pediatric nonkidney solid organ transplant recipients

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The incidence of acute kidney injury (AKI) and its impact on chronic kidney disease (CKD) following pediatric nonkidney solid organ transplantation is unknown. We aimed to determine the incidence of AKI and CKD and examine their relationship among children who received a heart, lung, liver, or multiorgan transplant at the Hospital for Sick Children between 2002 and 2011. AKI was assessed in the first year posttransplant. Among 303 children, perioperative AKI (within the first week) occurred in 67% of children, and AKI after the first week occurred in 36%, with the highest incidence among lung and multiorgan recipients. Twenty-three children (8%) developed CKD after a median follow-up of 3.4 years. Less than 5 children developed end-stage renal disease, all within 65 days posttransplant. Those with 1 AKI episode by 3 months posttransplant had significantly greater risk for developing CKD after adjusting for age, sex, and estimated glomerular filtration rate at transplant (hazard ratio: 2.77, 95% confidence interval, 1.13-6.80, P trend = .008). AKI is common in the first year posttransplant and associated with significantly greater risk of developing CKD. Close monitoring for kidney disease may allow for earlier implementation of kidney-sparing strategies to decrease risk for progression to CKD.

KEYWORDS
heart transplantation, kidney disease, kidney failure/injury, liver transplantation/hepatology, lung transplantation

1 | INTRODUCTION

Solid-organ transplantation is a lifesaving procedure for children with end-organ disease and has resulted in dramatically improved survival. Prolonged survival, however, has uncovered significant morbidity among childhood recipients.[1] Chronic kidney disease (CKD) is a common comorbidity among the nonrenal solid organ transplant population that often progresses to kidney failure, leading to increased mortality.[2] In children, the reported incidence of CKD in heart, lung, and liver recipients ranges from 29% to 38%, depending on the organ transplanted,[3-7] but these studies used inconsistent definitions with variable follow-up. Reported risk factors for CKD include use of cyclosporine as primary immunosuppression, older age at transplant, pretransplant diabetes, and impaired kidney function prior to transplant.[3,5,7,8]

Acute kidney injury (AKI) is common among adult nonkidney solid organ transplant recipients. Rates of AKI range from 52% to 76% after heart, liver, and lung transplants using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [9-11] or Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) AKI criteria.[12] In the pediatric population, the incidence of AKI after nonkidney solid organ transplant is relatively unknown. The definitions used currently for children are the pediatric RIFLE criteria based on percentage decrease in estimated glomerular filtration rate (eGFR), and the Acute Kidney Injury Network and KDIGO criteria both based on percentage increase in serum creatinine from a baseline creatinine value.[13,14] Understanding the burden of AKI in the pediatric nonkidney solid organ transplant population will enable physicians to better inform families of risk for kidney injury after transplant and associated morbidity and mortality.

Peritransplant kidney function has also been shown to be an important risk factor for chronic kidney dysfunction in the adult nonkidney solid organ transplant population.[9,15-17] A recent study of adult liver transplant recipients, however, found that the decline in kidney function over the first year posttransplant was more strongly associated with posttransplant mortality than GFR at the time of transplant.[18] Understanding when AKI occurs and how it may impact future kidney function is of paramount importance in the solid organ transplant population as it can aid in identifying those at risk for chronic kidney dysfunction and allow for earlier implementation of kidney-sparing strategies to halt or slow progression to kidney failure. The relationship between posttransplant AKI with CKD and mortality has not been investigated in children. This study determined the incidence rate of acute and chronic kidney injury and examines their relationship among childhood recipients of nonkidney solid organ (heart, lung, liver, and multiorgan) transplants.

2 | METHODS AND MATERIALS

2.1 | Study design and population

All first-time recipients <18 years old who received a nonkidney solid organ transplant, including heart, lung, liver, and multiorgan transplant

(any combination of bowel, liver, stomach, and pancreas) at the Hospital for Sick Children between January 1, 2002 and December 31, 2011 were eligible for this study. Children followed for fewer than 90 days posttransplant (12 transferred care to other hospitals and 22 died) or who had hemodialysis or renal failure prior to transplant (n = 7) were excluded, resulting in a cohort of 303 children. Ethics approval for this study was obtained from the Hospital for Sick Children Research Ethics Board.

2.2 | Data collection/measurement

All clinical data (age, sex, diagnosis, organ transplanted, height, weight, blood pressure, medication level, serum creatinine, and prior hemodialysis) were obtained through electronic medical records for both inpatient and outpatient data sources until death, transition to an adult clinic, lost to follow-up, or censor date June 30, 2012.

eGFR was calculated for each serum creatinine measurement available using the closest height measurement within 60 days based on the modified Schwartz equation.[19] If height within 60 days was not available, height z-score from the most recent height measurement was used to calculate the new height, assuming steady growth. World Health Organization growth charts were used for children aged 0 to 2 years, and Centers for Disease Control and Prevention (CDC) growth charts were used for children older than 2 years, as per CDC recommendations. Children completely missing height data (n = 3) were set to the mean height z-scores of their respective organ group cohort. All eGFR measurements >150 mL/min per 1.73 m^2 were winsorized to 150 mL/min per 1.73 m^2 using similar criteria from the CKD Epidemiology Collaboration.[20]

2.3 | Definitions

2.3.1 | Acute kidney injury

Baseline creatinine was defined as the lowest serum creatinine value within 3 months prior to the serum creatinine used to diagnose AKI. AKI was defined as an increase in serum creatinine >26.5 μM (0.3 mg/dL) within 48 hours or an increase in serum creatinine >1.5 times the baseline creatinine value within the previous 7 days based on the KDIGO criteria.[21] AKI events in the first week posttransplant were defined as perioperative AKI events. There was also a minimum 7-day period between AKI events, based on the Acute Kidney Disease Quality Initiative consensus for acute kidney disease.[22] Data to examine urine output criteria were not available. The number of repeated AKI events was determined over the first year posttransplant. A figure illustrating multiple AKIs events is shown in Figure 1B.

2.3.2 | Chronic kidney disease and end-stage renal disease

CKD was defined as an average eGFR <60 mL/min per 1.73 m^2 over any 6-month period starting at day 90 posttransplant and events were then validated through chart review (Figure 1C). The 6-month period

FIGURE 1 Patterns of kidney function. Different patterns of changes in kidney function observed post nonrenal solid organ transplant. The red horizontal line is drawn at 60 mL/min per 1.73 m^2 indicating the threshold below which chronic kidney disease is defined. A, Perioperative kidney dysfunction common in transplant population with recovery over time and no further kidney disease. B, Multiple episodes of acute kidney injury (AKI) denoted by the green vertical lines. C, Chronic kidney disease (CKD) with the onset marked with a vertical red line. D, End-stage renal disease (ESRD) with the onset marked with a vertical blue line. eGFR, estimated glomerular filtration rate
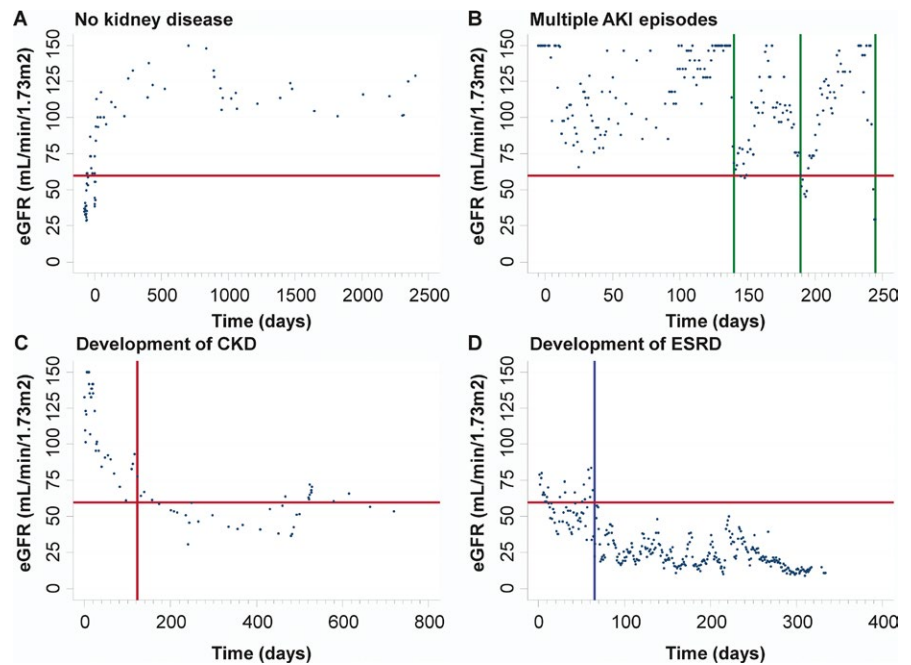
was used instead of the standard 3-month period to be more conservative in defining CKD, as many children had long AKI episodes that would meet criteria for CKD but recovered shortly afterward. End-stage renal disease (ESRD) was defined as initiation of renal replacement therapy (either dialysis or a kidney transplant), or an average eGFR <15 mL/min per 1.73 m^2 for any 3-month period (Figure 1D).

2.4 | Statistical analysis

Baseline characteristics were examined by organ group using means and standard deviations for normally distributed data or medians and interquartile ranges (IQRs) for skewed data. Incidence rates of CKD were calculated per 1000 person-years with 95% confidence intervals (CIs). Cumulative incidence of CKD/ESRD was compared across all organ groups using Kaplan-Meier analysis.

The relationship between AKI in the first year and the development of CKD was examined with AKI as a categorical variable (No AKI, 1 AKI, 2 or more AKIs). In order to account for the time to develop the AKI event, AKI status was assessed at fixed time points (landmarks) [23] of 3 months, 6 months, and 1 year posttransplant (Figure S1). This method assessed the number of AKI events that occurred within the first 3 months and the correlation of this number to the development of CKD at any time after those 3 months, for example. Similar methods were used for 6- and 12-month landmarks. The primary outcome of interest was the development of CKD. The risk of CKD as a function of prior AKI episodes by each landmark was estimated using a competing risk regression model (Fine and Gray method) accounting for death and retransplant.[24] Children with AKI events prior to their CKD were manually checked to ensure AKIs were resolved prior to and therefore separate from the CKD event. The eGFR at time of transplant, age, and sex were included as potential confounders, determined a priori, and also confirmed with differences by AKI status. There was considerable

overlap of persons with perioperative AKI and AKI, and thus the 2 were analyzed in separate regression models.

The association of AKI as a binary variable (yes, no) with mortality was examined at the same landmarks accounting for competing risk of retransplant. Similarly, the relationship between CKD/ESRD and patient mortality was also examined. Both mortality analyses were adjusted for age, sex, baseline GFR, and underlying diagnosis.

Slope of eGFR over time was estimated using linear regression. The slopes of eGFR from 3 to 6 months and 3 to 12 months posttransplant were compared for those with no AKI events vs those with 1 or more AKI events within 3 months of transplant using t tests. The risk of developing CKD by AKI severity (Stages 1, 2, and 3) [21] was assessed using a competing risk model. The risk of developing CKD by average tacrolimus level was also assessed using a competing risk model. A Bland-Altman plot was used to assess agreement between estimated and nuclear GFRs measured on the same day for 223 individuals.

Statistical analysis was performed with STATA 14 and a 2-sided $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 303 pediatric nonkidney solid organ transplant recipients were included in the study (Table 1). The majority of the cohort was made up of liver (48%) and heart (41%) recipients. The median age at transplant was 4 years (IQR: 1-12) but lung recipients were notably older at transplant with a median age of 13 years. The main diagnoses for end organ failure were congenital heart disease (42%) and cardiomyopathy (58%) for heart recipients, biliary atresia (35%) and acute liver failure (23%) for liver recipients, and cystic fibrosis (63%) and primary pulmonary hypertension (13%) for lung recipients. The

TABLE 1 Demographic and clinical characteristics of 303 children who received nonkidney solid organ transplants between 2002 and 2011

		n (%)/mean±SD/Median [IQR]				
	N	**Heart (n = 125)**	**Lung (n = 22)**	**Liver (n = 144)**	**Multiorgan (n = 12)**	**Total (n = 303)**
Demographics						
Males	303	68 (54.4)	11 (50.0)	81 (56.3)	8 (66.7)	168 (55.5)
Age at transplant (y)	303	3.3 [0.5-12.9]	13.1 [10.8-14.8]	2.8 [0.8-10.2]	1.6 [1.0-3.8]	3.9 [0.7-11.9]
Donor type	303					
Living		0 (0)	0 (0)	59 (41.0)	0 (0)	59 (19.5)
Deceased		125 (100)	22 (100)	85 (59.0)	12 (100)	244 (80.5)
Follow-up time (y)	303	3.6 [1.7-6.1]	2.6 [1.4-3.5]	3.4 [1.4-5.7]	4.6 [1.1-5.9]	3.4 [1.4-5.7]
Clinical characteristics						
Underlying diagnosis	303					
Congenital/genetic		52 (41.6)	16 (72.8)	71 (49.3)	6 (50.0)	145 (47.8)
Acquired		73 (58.4)	3 (13.6)	50 (34.7)	6 (50.0)	132 (43.6)
Other		0 (0)	3 (13.6)	23 (16.0)	0 (0)	26 (8.6)
eGFR at time of transplant (mL/min per 1.73 m^2)	303	88.5 [61.8-106]	114 [94.4-129]	132 [105-143]	124 [86.4-145]	108 [79.9-135]
Mean tacrolimus level (µg/L)[a]	236	11.0 ± 1.2	12.9 ± 2.8	12.0 ± 1.7	14.8 ± 2.8	11.6 ± 1.7

Multiorgan transplants are a combination of any of the following organs: bowel, liver, pancreas, and stomach. Due to small numbers, specific organ combinations are not reported to maintain privacy. eGFR, estimated glomerular filtration rate; IQR, interquartile range.

[a]First 90 days posttransplant.

multiorgan recipients had short bowel syndrome (caused by volvulus, gastroschisis, necrotizing enterocolitis, jejunal atresia), pseudo-obstruction, Hirschsprung disease, and microvillus inclusion disease. Heart transplant recipients had the lowest eGFR at time of transplant with a median of 89 mL/min per 1.73 m^2. Tacrolimus-based immunosuppression was used after transplant in 78% of children and 5% transitioned from cyclosporine to tacrolimus within the first 90 days posttransplant (Table S1). A kidney-sparing protocol of sirolimus with either a low dose of tacrolimus or no calcineurin inhibitor was used in 9% of children.

3.2 | Incidence of AKI, CKD, and ESRD

Children were followed exclusively at the Hospital for Sick Children for a median of 3.4 years (IQR: 1.4-5.6) with an average of 130 creatinine measurements per child. Perioperative AKI (AKI in first week posttransplant) occurred in 67% of children (Table 2). Overall incidence of AKI excluding perioperative AKI was 643 per 1000 person-years with the highest incidence among the multiorgan recipients. Median time to the first AKI event was short (<30 days posttransplant) among all organ groups and the number of AKI events ranged from 0 to 5. Overall, about 8% of children went on to develop CKD, with the highest rates among the lung recipients at 32%. Less than 5 children developed ESRD, all within 65 days posttransplant. The 2-year cumulative incidence of CKD and ESRD for heart, lung, liver, and multiorgan transplants was 8%, 28%, 2%, and 26%, respectively.

Children with AKI had higher eGFR at time of transplant compared to those without (median of 118 [IQR: 80-140] mL/min per m^2 for children with AKI vs 105 [IQR: 79-130] mL/min per m^2 for children with no AKI, P = .05).

3.3 | Relationship between AKI and CKD

Perioperative AKI had a high incidence among our population and was not associated with CKD even after adjusting for age, sex, and eGFR at time of transplant (unadjusted hazard ratio [HR]: 2.06, 95% CI, 0.77-5.52, adjusted HR: 1.84, 95% CI, 0.66-5.1 adjusted; data not shown). Subsequent AKI analysis focused on AKI events that occurred after the first week posttransplant (Table 3). In univariable analyses, having 1 or more AKI episodes in the first 3 months posttransplant was associated with over 2.5 times greater risk of developing CKD (HR: 2.52, 95% CI, 1.03-6.12). After adjusting for age, sex, and eGFR at time of transplant, having 1 AKI episode was associated with 2-fold greater risk of developing CKD at 3 months posttransplant (HR: 2.77, 95% CI, 1.13-6.80). There was also a significant dose-dependent trend for number of AKI events associated with greater risk for development of CKD at 3 months posttransplant (P trend=.008). Similar estimates were obtained for 6- and 12-month landmark analyses but were not significant due to limited power. Competing risk of death and retransplant were accounted for as 17 children died and 11 children were retransplanted before development of CKD.

TABLE 2 AKI and CKD rates for 303 pediatric solid organ transplant recipients

	Heart (n = 125)	Lung (n = 22)	Liver (n = 144)	Multiorgan (n = 12)	Total (n = 303)
AKI					
Number with perioperative AKI event	81	17	96	9	203
Number with at least 1 AKI event after perioperative period	30	10	58	10	108
Median time to first event (IQR), d	23.5 (14-39)	21 (14-28)	22 (13-104)	37 (9-157)	22 (13-74.5)
Median number of AKI events[a] (IQR)	1 (1-2)	1 (1-1)	1 (1-2)	2 (1-3)	1 (1-2)
Median time between AKI events (IQR), d	41 (26-106)	57 (57-57)	44 (21-118)	43 (23-82)	44 (23-106)
CKD					
Number with CKD	11	7	<5	<5	23
Incidence rate per 1000 person-years (95% CI)	23 (13-41)	153 (73-320)	7 (3-19)	25 (3-176)	21 (14-31)
Median time to event, d	212	325	701	226	290

Perioperative AKI defined as AKI event within first 7 days after transplant. AKI events after perioperative period defined as all AKI events within first year posttransplant, excluding those in the first week posttransplant. AKI, acute kidney injury; CKD, chronic kidney disease; IQR, interquartile range.

Due to small numbers, cells <5 are reported to maintain privacy.

[a]For those with at least 1 AKI episode.

TABLE 3 Association of posttransplant AKI episodes with development of CKD accounting for competing risks (death, retransplant) among 303 pediatric transplant recipients

	Unadjusted					Adjusted			
	N	HR	(95% CI)	P	P value for trend	HR	(95% CI)	P	P value for trend
Landmark									
Up to 3 mo after transplant					0.01				.008
0 AKI events	221	ref	—			ref	—		
1 AKI event	64	2.52	(1.03-6.12)	.04		2.77	(1.13-6.80)	.03	
2 or more AKI events	18	3.53	(0.96-13.0)	.06		3.53	(0.94-13.2)	.06	
Up to 6 mo after transplant					0.1				.05
0 AKI events	206	ref	—			ref	—		
1 AKI event	69	1.84	(0.69-4.95)	.2		2.14	(0.79-5.80)	.1	
2 or more AKI events	28	2.24	(0.60-8.27)	.2		2.77	(0.76-10.1)	.1	
Up to 1 y after transplant					0.6				.9
0 AKI events	195	ref	—			ref	—		
1 AKI event	68	1.53	(0.39-6.06)	.5		2.24	(0.54-9.25)	.3	
2 or more AKI events[a]	40	—	—	—		—	—	—	

Model was adjusted for age, sex, and glomerular filtration rate at time of transplant. AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.

[a]At the 1-y landmark, no children with 2 or more events developed CKD.

	Unadjusted			Adjusted		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
AKI						
Up to 3 mo after transplant						
0 AKI events	ref	—		ref	—	
1 or more AKI events	1.59	(0.76-3.31)	.2	1.84	(0.86-3.92)	.1
Up to 6 mo after transplant						
0 AKI events	ref	—		ref	—	
1 or more AKI events	1.73	(0.80-3.75)	.2	2.03	(0.89-4.64)	.1
Up to 1 y after transplant						
0 AKI events	ref	—		ref	—	
1 or more AKI events	1.52	(0.60-3.86)	.4	1.90	(0.70-5.14)	.2
CKD or ESRD						
Up to 3 mo after transplant						
No	ref	—		ref	—	
Yes	5.38	(0.61-47.4)	.1	4.52	(0.41-49.6)	.2
Up to 6 mo after transplant						
No	ref	—		ref	—	
Yes	23.3	(5.09-107)	<.001	30.9	(4.59-208)	<.001
Up to 1 y after transplant						
No	ref	—		ref	—	
Yes	7.85	(2.19-28.1)	.002	10.8	(3.07-38.3)	<.001

Model was adjusted for age, sex, glomerular filtration rate at time of transplant, and underlying diagnosis. AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage kidney disease; HR, hazard ratio.

In the fully adjusted model, older age at transplant (per year) was significantly associated with increased risk of CKD development at 6 and 12 months posttransplant (6-month HR: 1.11, 95% CI, 1.01-1.21; 12-month HR: 1.26, 95% CI, 1.08-1.47). Higher eGFR at transplant (per mL/min per 1.73 m^2) was significantly associated with decreased risk of CKD at 3 months posttransplant (HR: 0.99, 95% CI, 0.98-1.00). Female sex was not associated with development of CKD compared to male sex (12-month HR: 2.38, 95% CI, 0.53-10.6).

The slope of eGFR in the first year after transplantation did not significantly differ among those who had an AKI event in the first 3 months vs those who did not (Table S2). Neither severity of first AKI nor average tacrolimus level was associated with increased risk of CKD development (Tables S3 and S4). eGFR and nuclear GFR measurements also had good agreement with a mean difference of −3.89 mL/min per m^2 (95% limits of agreement −59.31, 51.53; Figure S2A). Overall, as GFR increases, the difference between measured and estimated GFR becomes larger, which is expected based on how the eGFR equation was developed (Figure S2B).[19] Appropriately for our study purposes, there is more accuracy evident for measures with lower GFRs (60 mL/min per m^2 and under), which are used to classify CKD and ESRD events.

3.4 | Relationship between kidney injury and mortality

Overall, there were 31 deaths and 13 retransplants in the competing risk analysis. There was no significant difference in risk of mortality for those with 1 or more AKI events compared to those with no events (Table 4). Children who developed CKD or ESRD had high risk of mortality at 6 and 12 months posttransplant, and this association remained significant after adjusting for age, sex, eGFR at transplant, and underlying diagnosis (6 month HR: 30.9, 95% CI, 4.59-208; 12-month HR: 10.8, 95% CI, 3.07-38.3).

4 | DISCUSSION

Kidney disease impacts survival of children after solid organ transplantation. We were able to identify discrete patterns of kidney injury among recipients of pediatric nonkidney solid-organ transplants. Over two thirds of pediatric heart, lung, liver, and multiorgan transplant recipients have at least 1 AKI event in the first week after transplant and about one third have at least 1 AKI event after the first week and up to 1 year after transplantation, with the highest incidence among

multiorgan recipients. The overall incidence of CKD/ESRD is 9%, with lung and multiorgan recipients having the highest rates. Over a median follow-up of 3.4 years, AKI events in the first 3 months (excluding those in the first week) were associated with greater than a 2.5-fold higher risk of CKD, with a significant trend over increasing number of AKI events. Those who developed ESRD in the cohort developed it within a range of 14-65 days after transplantation. Also, developing AKI and subsequent CKD increased the risk of mortality significantly. Due to adverse impact on morbidity and mortality associated with kidney disease, this study provides a rationale to screen early for kidney disease after transplantation and implement strategies to prevent chronic kidney injury.

In our study, lung and multiorgan recipients had the highest rates of AKI and CKD/ESRD. This finding is consistent with prior reports where intestine and lung recipients had the highest incidence of ESRD, followed by heart and liver recipients.[25] In our population, the older age of lung recipients at time of transplant may have contributed to the higher incidence of CKD, as older age has been previously associated with higher risk of CKD/ESRD.[3,8] Additionally, the lung recipients were more likely to receive cyclosporine-based immunosuppression, which may also contribute to the higher incidence among this group. As well, cystic fibrosis is the most common reason for lung transplant in this cohort, which has been linked to limited functional kidney reserve due to chronicity of disease and use of aminoglycosides, and can often complicate assessment of kidney function from lower muscle mass and poorer nutritional state.[26] Multiorgan recipients in this study received mainly intestine transplants with a liver or other visceral organ. Factors contributing to kidney injury in this group include the higher levels of immunosuppression in intestinal transplantation due to the high immunogenicity of the bowel, pretransplant diagnoses of congenital anomalies typically seen in preterm infants that increase risk for kidney dysfunction, as well as hypovolemia in the peritransplant period related to poor fluid absorption.[25] Both lung and multiorgan recipients are at higher risk for CKD and may require minimization of nephrotoxic drugs or other agents such as radiocontrast early after transplant to slow kidney disease progression.

We also report that AKI episodes over the first 3 months are associated with the development of CKD. Other studies investigating AKI and long-term kidney dysfunction in adult transplant recipients have reported a similar association. However, these studies defined AKI within the first 3 to 7 days after transplant and were unable to examine the incidence of AKI over a year or analyze repeated AKI events.[9,11] As shown recently, kidney function in the first year after a liver transplant may in fact be a more important indicator for long-term kidney function than in the perioperative period of the transplant.[18] In our cohort, we found that having even 1 AKI episode within the first 3 months places children at greater risk for CKD after adjusting for eGFR at time of transplant, demonstrating the need for regular monitoring of kidney function in this sensitive time period. Recommendations for closer monitoring of kidney function include frequent assessment of serum creatinine and potentially adding cystatin C, monitoring of proteinuria and microalbuminuria, calculation of GFR using modified Schwartz equation, and monitoring of blood pressure with referrals to a nephrologist as appropriate.[27]

In this study, we found that in the first week posttransplant there were many fluctuations in creatinine possibly due to volume status, which is a significant issue in young children.[28,29] Interestingly, AKI events in the first week after transplant were not significantly associated with CKD. Additionally, we found that the CKD criteria put forward by KDIGO captured patients who experienced transient drops in kidney function for up to 3 months rather than those with CKD. Thus, we found that using a 6-month time period of eGFR below 60 mL/min per 1.73 m^2 rather than a 3-month period was more accurate for identifying CKD. With the variation in kidney function among transplant recipients, it was prudent to standardize kidney injury definitions in this population with more stringent criteria and considerations for timing of kidney recovery. However, this may not highlight how many children are at risk due to fluctuating creatinine levels and poor renal reserve, which cannot be estimated with eGFR alone.

This study has a number of strengths. It is the first study to report incidence of AKI among the pediatric nonkidney solid organ transplant population and examines AKI events over time in addition to the perioperative period to better describe the incidence of AKI and its association with CKD. It also has a large sample size for a pediatric transplant cohort, includes multiple organ groups, and comes from a population with universal access to health care and lifelong coverage of medications.

The study also has some limitations. We could not assess whether each episode of AKI was associated with a specific cause for each event such as rejection or infection, which would need to be studied prospectively. The study also used the modified Schwartz formula, which has been known to overestimate low GFR values, is not validated among children under age 2 years, and requires height information, which was not available for all creatinine measurements. Nevertheless, we were able to estimate height using closest height measurement z-scores and correlate the eGFR to nuclear GFR measurements taken on the same day (456 measurements from 223 children) to ensure the eGFR did not significantly deviate from nuclear GFR. In very young children under age 2 years, 96% of eGFR measurements were within the limits of agreement. As well, we could not account for AKI events after the first year because children who were doing well did not come frequently for routine monitoring and had fewer measures of serum creatinine after that time. Finally, as this study took place over time with varying calcineurin inhibitor protocols, it was difficult to examine the risk of AKI and CKD due to cumulative drug exposures, which is an area to explore in the future. We assessed average tacrolimus levels in the first 3 months after transplant as 1 measurement; however, further analysis should take into account time-varying levels. We adjusted for potential confounders; however, due to the limited sample size, residual confounding remains an issue and larger studies are needed to confirm the findings.

AKI and CKD are common in children with nonkidney solid organ transplants, especially among lung and multiorgan recipients. Perioperative AKI is common but not associated with development of

CKD. AKI after the first week and up to 3 months posttransplant is significantly associated with 2.5 times greater risk of developing CKD. After a nonkidney solid organ transplant, children should be monitored closely for changes in kidney function to better identify those at risk for CKD and allow for earlier implementation of kidney-sparing strategies to prevent kidney disease progression.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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