End-Stage Kidney Disease After Pediatric Nonrenal Solid Organ Transplantation

AUTHORS: Rebecca L. Ruebner, MD, MSCE,^a Peter P. Reese, MD, MSCE,^{b,c} Michelle R. Denburg, MD, MSCE,^a Peter L. Abt, MD,^d and Susan L. Furth, MD, PhD^{a,b}

^aDivision of Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and ^bCenter for Clinical Epidemiology and Biostatistics, ^cRenal Division, Department of Medicine, and ^dDepartment of Surgery, Transplant Institute, University of Pennsylvania, Philadelphia, Pennsylvania

KEY WORDS

nephrology, transplant, end-stage renal failure

ABBREVIATIONS

AKI—acute kidney injury

CF—cystic fibrosis

CI—confidence interval

CKD—chronic kidney disease

CKiD—Chronic Kidney Disease in Children study

eGFR—estimated glomerular filtration rate

ESKD—end-stage kidney disease

GFR—glomerular filtration rate

HR—hazard ratio

IQR—interquartile range

SOT—solid organ transplantation

SRTR—Scientific Registry of Transplant Recipients

USRDS—US Renal Data System

Dr Ruebner conceptualized and designed the study, performed all statistical analyses, and drafted the initial manuscript; Drs Reese and Furth assisted in the conceptualization and design of the study, assisted in the statistical analyses, and reviewed and revised the manuscript; Dr Denburg assisted in the statistical analyses and reviewed and revised the manuscript; Dr Abt assisted in the conceptualization of the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-0904

doi:10.1542/peds.2013-0904

Accepted for publication Aug 5, 2013

Address correspondence to Rebecca Ruebner, MD, MSCE, Children's Hospital of Philadelphia, Division of Nephrology 1 Main, 34th St and Civic Center Blvd, Philadelphia, PA 19104. E-mail: ruebner@email.chop.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: End-stage kidney disease (ESKD) causes significant morbidity and mortality after solid organ transplantation. Adults commonly develop advanced kidney disease, particularly after liver and intestinal transplantation. Previous pediatric studies have not compared the relative incidence of ESKD by organ type.

WHAT THIS STUDY ADDS: This national cohort study shows the highest risk of ESKD among pediatric lung and intestinal transplant recipients, reflecting unique organ-specific causes of kidney injury. Our findings have implications for screening for and treating early kidney disease in transplant recipients.

abstract

OBJECTIVES: Adult solid organ transplant (SOT) recipients commonly develop advanced kidney disease; however, the burden of end-stage kidney disease (ESKD) in children after SOT is not well-described. The objectives of this study were to determine the incidence of ESKD after pediatric SOT and the relative risk by SOT type.

METHODS: Retrospective multicenter cohort study of children, ages ≤18 years, who received SOTs from 1990 through 2010 using Scientific Registry of Transplant Recipients data linked to the US Renal Data System. We performed a competing risks analysis to determine cumulative incidence of ESKD (chronic dialysis or kidney transplant), treating death as a competing risk, and fit a multivariable Cox regression model to assess hazard of ESKD by organ type.

RESULTS: The cohort included 16 604 pediatric SOT recipients (54% liver, 34% heart, 6% lung, 6% intestine, and 1% heart–lung). During a median follow-up of 6.2 years (interquartile range 2.2–12.1), 426 (3%) children developed ESKD. Compared with liver transplant recipients, in whom the incidence of ESKD was 2.1 cases per 1000 person-years, in adjusted analyses the highest risk of ESKD was among intestinal (hazard ratio [HR] 7.37, $P < .001$), followed by lung (HR 5.79, $P < .001$) and heart transplant recipients (HR 1.79, $P < .001$).

CONCLUSIONS: In a 20-year national cohort of pediatric SOT recipients, the risk of ESKD was highest among intestinal and lung transplant recipients. The burden of earlier stages of chronic kidney disease is probably much higher; modifiable risk factors should be targeted to prevent progressive kidney damage in this high-risk population. *Pediatrics* 2013;132:e1319–e1326

Advances in transplantation have led to improved outcomes among pediatric transplant recipients. The types of organs successfully transplanted in children have also become broader, with a particular recent increase in intestinal and multivisceral transplants.^{1–3} As patient survival continues to improve, chronic kidney disease (CKD) will probably affect a greater number of children after non-renal solid organ transplantation (SOT). CKD, and in particular end-stage kidney disease (ESKD), is associated with significant morbidity and increases the risk of death after SOT.^{4–6} Evaluating the incidence of ESKD after pediatric SOT is of critical importance to help guide clinicians in identifying children at highest risk and monitoring those patients for early signs of kidney disease. Early identification of CKD may allow implementation of measures to slow progression to or possibly prevent ESKD.

Risk factors for kidney injury after SOT include long-term exposure to calcineurin inhibitor–based immunosuppression, pretransplant kidney dysfunction, peritransplant acute kidney injury (AKI), hypertension, and diabetes.^{7–16} The risk of ESKD in adult SOT recipients varies by organ transplanted.⁴ This variability may be explained by differences in the burden of baseline comorbidities, variations in intensity of immunosuppressive regimens, and distinct rates of peritransplant AKI. The relative incidence of ESKD in pediatric SOT recipients may differ from that in adults, given unique causes of end-stage organ disease among pediatric transplant recipients and different organ-specific risk factors for kidney injury.

Current studies of kidney disease after transplantation in children have been limited in assessing the outcome of ESKD given single-center experiences or insufficient follow-up time. In addition, there have been no studies comparing the relative incidence of ESKD between SOT types in pediatric recipients. To address these limitations, we examined

a national cohort of pediatric patients who underwent SOT over a 20-year period to determine the incidence of ESKD and death and determine the variability in risk of ESKD by organ transplanted.

METHODS

Sources of Data

This study used a linked data set from the Scientific Registry of Transplant Recipients (SRTR) and the US Renal Data System (USRDS). The SRTR includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration of the US Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. Outcomes of death in SRTR are determined through center reports and through linkage to the Social Security Death Master File. ESKD outcomes were ascertained through SRTR data on kidney transplantation and Centers for Medicare & Medicaid Services form 2728 for chronic dialysis submitted to USRDS. The institutional review board at the Children's Hospital of Philadelphia deemed this study exempt under provisions of the Code of Federal Regulations 45 CFR 46.101, category 4.

Subjects

The study population included children ≤ 18 years of age who received a first SOT in the United States between January 1, 1990 and March 1, 2010. The SRTR data set was obtained in March 2011. Therefore, March 2010 was chosen as the end date for inclusion of subjects to allow for lags in center reporting to SRTR and claim data for ESKD. SOT was categorized as liver, heart, lung, heart–lung, and intestine (including intestine alone or intestine in addition to liver or pancreas). We excluded a small number

of subjects who had more rare combinations of organs such as liver–heart ($n = 7$), liver–lung ($n = 10$), liver–pancreas ($n = 13$), and pancreas alone ($n = 11$). We also excluded subjects who had ESKD before SOT or subjects who received a combined solid organ–kidney transplant, because these patients may have different risks for ESKD in the allograft compared with a native kidney.

We previously published a subcohort of this population that included the pediatric liver-alone transplant recipients from 1990 to 2010.⁵ The current study includes the liver cohort as the reference group for rate of ESKD.

Analytic Approach

We assessed baseline demographic and clinical characteristics of the study population using medians and interquartile ranges (IQRs) for continuous variables and distributions for categorical variables. The primary end points were death and ESKD, defined as initiation of chronic dialysis or receipt of a kidney transplant. Date of ESKD was considered the first date reported on Centers for Medicare & Medicaid Services form 2728 submitted to USRDS or date of kidney transplant reported in SRTR, whichever occurred first. ESKD was categorized as preemptive kidney transplant if the subject had no dialysis before kidney transplant, dialysis with subsequent kidney transplant, or chronic dialysis if the subject remained on dialysis without receiving a kidney transplant at death or last follow-up. Subjects were followed from the date of SOT until ESKD, death, or March 1, 2011.

Given that mortality was high in this posttransplant population, we treated death as a competing risk in the analysis of cumulative incidence of ESKD. We fit separate multivariable Cox regression models to determine risk factors for ESKD and death. Cox regression for ESKD was censored at death. We inspected graphic displays and statistical tests of

proportionality of hazards to confirm that the proportional hazards assumption was satisfied. On the basis of prior studies about risks for ESKD and clinical experience, we a priori identified putative risk factors for ESKD after SOT, which were included as independent variables in univariable and multivariable analyses. Recipient variables included SOT type, age at transplant, era of transplant, gender, race, type of immunosuppressive therapy at transplant (categorized as cyclosporine-based, tacrolimus-based, or other), and estimated glomerular filtration rate (eGFR), calculated using the bedside Chronic Kidney Disease in Children (CKiD) study formula ($0.413 \times \text{height/serum creatinine}$) and the serum creatinine reported in SRTR at the time of SOT.¹⁷ In addition, to examine the effect of ESKD on mortality, in a separate analysis we treated ESKD as a time-varying covariate in univariable and multivariable Cox regression analyses of death. Key demographic variables and independent variables with $P < .2$ in univariable analyses were tested in multivariable analysis.

Sensitivity Analyses

We examined the degree and distribution of missing data on important baseline covariates. For example, 2051 (12%) subjects lacked creatinine or height to estimate glomerular filtration rate (GFR), and 3590 (22%) lacked diabetes status. Missing data were more likely to be in subjects who underwent transplantation in earlier years. Thoracic organ transplant recipients had a greater proportion of missing eGFR data. In primary analyses, “missing” was created as a separate category for each covariate. To estimate the maximum effect of missing data on outcomes, we performed sensitivity analyses in which extreme values were assigned to subjects with missing data. In the example of eGFR, we categorized subjects for whom eGFR was missing as all having eGFR ≥ 60 or eGFR < 60 mL/min per 1.73 m^2 .

Results were similar to the primary analysis and are not shown.

Analyses were conducted by using Stata 12.0 (Stata Corporation, College Station, TX). All reported P values are 2-sided, and $P < .05$ was the threshold for statistical significance.

RESULTS

Baseline Characteristics

There were 16 604 pediatric SOTs performed at 174 transplant centers during the study period. Liver was the most commonly transplanted organ ($n = 8958$, 54%), followed by heart ($n = 5569$, 34%), lung ($n = 963$, 6%), intestine ($n = 957$, 6%), and heart–lung ($n = 157$, 1%). Among intestinal transplant recipients, 254 (27%) received intestine alone; 350 (36%) received intestine and liver; 337 (35%) received intestine, liver, and pancreas; and 16 (2%) received intestine and pancreas.

The baseline demographic and clinical characteristics of the cohort are summarized in Table 1. The median age at SOT was 3.3 years (IQR 0.8–12.4); however, there was significant variability in age by organ. Lung transplant recipients were the oldest (median 14.1 years; IQR, 9.5–16.9), whereas intestinal transplant recipients were the youngest (median 1.6 years; IQR, 0.9–4.1). The overall median height was the 10th percentile. Although the overall median BMI was the 53rd percentile, lung transplant recipients had a much lower median BMI (12th percentile) in addition to having low median height (6th percentile). There was a nearly equal distribution of transplants over the 20-year period except among intestinal transplants, which were performed primarily in the most recent decade. There were low rates of pretransplant diabetes except among lung transplant recipients. Tacrolimus-based immunosuppression was used at transplant in 53% of subjects; however, thoracic organ

transplant recipients were more likely to be treated with cyclosporine-based immunosuppression. The majority of children had kidney function in the normal range at the time of transplant, with a median eGFR of 95.8 (IQR 70.5–129.4) mL/min per 1.73 m^2 . Estimated GFR was < 60 mL/min per 1.73 m^2 in 1783 (11%) subjects, and 778 (5%) needed acute dialysis before transplant.

Incidence of ESKD After SOT

Table 2 shows the incidence of ESKD and death by SOT type. The overall median follow-up time was 6.2 years (IQR 2.2–12.1); median follow-up time was shorter among lung, heart–lung, and intestinal transplant recipients. Overall, 426 (3%) subjects developed ESKD, with an incidence rate of 3.5 cases per 1000 person-years. The median time from SOT to ESKD was 8.7 years (IQR 4.5–12.9). Preemptive kidney transplantation was performed in 104 (24%) subjects with ESKD. Dialysis was initiated in the remaining 322 (76%) subjects with ESKD; 149 of these subjects eventually received a kidney transplant, and 173 subjects remained on dialysis until death or last follow-up. The incidence rate of ESKD varied by organ, with the lowest incidence among liver transplant recipients (2.1 cases per 1000 person-years) and the highest incidence among lung transplant recipients (13.7 cases per 1000 person-years). Figure 1 shows the unadjusted cumulative incidence of ESKD by SOT type, treating death as a competing risk for ESKD.

Table 3 shows the results of unadjusted and adjusted Cox regression models for ESKD after SOT. Compared with liver transplant recipients, in an adjusted model, intestinal transplant recipients had the highest risk of ESKD (HR 7.37, 95% confidence interval [CI] 4.97–10.94, $P < .001$), followed by lung (HR 5.79, 95% CI 4.18–8.02, $P < .001$) and heart transplant recipients (HR 1.79, 95% CI 1.41–2.27, $P < .001$). There was a stepwise

TABLE 1 Baseline Characteristics of Pediatric SOT Recipients, 1990–2010

Characteristic	All, <i>N</i> = 16 604	Liver, <i>N</i> = 8958 (54%)	Heart, <i>N</i> = 5569 (34%)	Lung, <i>N</i> = 963 (6%)	Intestine, <i>N</i> = 957 (6%)	Heart–Lung, <i>N</i> = 157 (1%)
Age at transplant (y), med (IQR)	3.3 (0.8–12.4)	2.3 (0.8–10.3)	4.4 (0.5–13.4)	14.1 (9.5–16.9)	1.6 (0.9–4.1)	11.7 (3.8–16.0)
Male gender, <i>n</i> (%)	8459 (51)	4309 (48)	3165 (57)	410 (43)	502 (52)	73 (47)
Race, <i>n</i> (%)						
White	10 041 (60)	5132 (57)	3445 (62)	783 (81)	560 (59)	121 (77)
Black	2935 (18)	1621 (18)	1065 (19)	54 (6)	186 (19)	9 (6)
Asian	616 (4)	369 (4)	200 (4)	20 (2)	21 (2)	6 (4)
Other	3012 (18)	1836 (21)	859 (15)	106 (11)	190 (20)	21 (13)
Year of transplant, <i>n</i> (%)						
1990–1994	3624 (22)	2112 (24)	1244 (22)	156 (16)	55 (6)	57 (36)
1995–1999	3989 (24)	2207 (25)	1300 (23)	278 (29)	161 (17)	43 (27)
2000–2004	4243 (26)	2281 (25)	1364 (24)	248 (26)	316 (33)	34 (22)
2005–2010	4748 (29)	2358 (26)	1661 (30)	281 (29)	425 (44)	23 (15)
Donor type, <i>n</i> (%)						
Deceased	15 293 (92)	7750 (87)	5569 (100)	872 (91)	945 (99)	157 (100)
Living	1311 (8)	1208 (13)	0	91 (9)	12 (1)	0
Diabetes pretransplant, <i>n</i> (%)	200 (1)	67 (0.8)	19 (0.3)	111 (12)	2 (0.2)	1 (0.6)
Hepatitis B, <i>n</i> (%)	307 (2)	151 (2)	121 (2)	20 (2)	13 (1)	2 (1)
Hepatitis C, <i>n</i> (%)	194 (1)	126 (1)	41 (1)	10 (1)	15 (2)	2 (1)
Height percentile, med (IQR)	10.4 (0.4–48.0)	9.5 (0.3–48.8)	17.6 (1.5–56.0)	5.5 (0.6–29.1)	0.4 (0.1–9.3)	12.9 (1.3–44.0)
Wt percentile, med (IQR)	14.9 (1.0–57.9)	21.8 (1.5–65.2)	11.5 (0.9–50.4)	3.6 (0.1–20.6)	13.3 (0.5–52.4)	8.9 (0.4–33.0)
BMI percentile, med (IQR) ^a	52.8 (14.7–85.5)	68.8 (35.2–89.8)	37.4 (7.2–80.2)	11.9 (0.9–43.6)	79.1 (43.6–95.3)	24.8 (2.0–61.8)
Immunosuppressive therapy at time of transplant, <i>n</i> (%)						
Tacrolimus based	8818 (53)	5712 (64)	1787 (32)	394 (41)	875 (91)	50 (32)
Cyclosporine based	6175 (37)	2350 (26)	3218 (58)	515 (53)	11 (1)	81 (52)
Other	546 (3)	209 (2)	269 (5)	29 (3)	30 (3)	9 (6)
Missing	1065 (6)	687 (8)	295 (5)	25 (3)	41 (4)	17 (11)
Pretransplant serum creatinine mg/dL, med (IQR)	0.4 (0.3–0.6)	0.4 (0.2–0.5)	0.5 (0.4–0.8)	0.5 (0.4–0.7)	0.3 (0.3–0.5)	0.6 (0.4–0.7)
Pretransplant eGFR, mL/min per 1.73 m ² , <i>n</i> (%) ^b						
≥90	8069 (49)	5358 (60)	1617 (29)	586 (61)	444 (46)	64 (41)
60–89	3923 (24)	1848 (21)	1600 (29)	158 (16)	283 (30)	34 (22)
30–59	1783 (11)	752 (8)	877 (16)	41 (4)	103 (11)	10 (6)
<30 or acute dialysis	778 (5)	355 (4)	368 (7)	18 (2)	33 (3)	4 (3)
Missing	2051 (12)	645 (7)	1107 (20)	160 (17)	94 (10)	45 (29)

med, median.

^a BMI included only for subjects aged >2 y at time of transplant.^b Using bedside CKiD formula: estimated GFR = 0.413 × height (cm)/serum creatinine.

increase in the risk of ESKD with increasing age at the time of SOT, with the highest risk among subjects ≥15 years at the time of transplant (HR 3.64, 95% CI 2.81–4.71, *P* < .001) compared with age <5 years. Recipients with pretransplant eGFR <60 versus ≥60 mL/min per 1.73 m² had a higher risk of ESKD (HR 1.85, 95% CI 1.41–2.44, *P* < .001), and those who needed acute dialysis had an even greater risk (HR 4.84, 95% CI 2.12–11.07, *P* < .001). Immunosuppressive therapy at the time of transplant was not significantly associated with ESKD in univariable or multivariable analyses.

Incidence of Death After SOT

During the same follow-up time, 5353 subjects (32%) died, with a mortality rate of 43.0 cases per 1000 person-years. Table 2 shows 1-, 3-, and 5-year mortality by organ type. The median time to death after SOT was only 1.2 years (IQR 0.1–4.7). The mortality rate also varied significantly by SOT type, with the lowest rate among liver transplant recipients (26.1 deaths per 1000 person-years) and the highest rate among heart–lung transplant recipients (173.1 deaths per 1000 person-years) (Table 2). Figure 2 shows survival by SOT type.

Table 4 shows the results of unadjusted and adjusted Cox regression models for death after SOT. Compared with liver transplant recipients, in an adjusted model, heart–lung recipients had the highest risk of death (HR 4.51, 95% CI 3.73–5.45, *P* < .001), followed by lung (HR 4.02, 95% CI 3.65–4.43, *P* < .001), intestine (HR 3.57, 95% CI 3.21–3.97, *P* < .001), and heart transplant recipients (HR 1.86, 95% CI 1.74–1.98, *P* < .001). There was a stepwise decline in the risk of death with more recent eras of transplantation. In addition to being independently associated with

TABLE 2 ESKD and Death After Pediatric SOT, 1990–2010

	All <i>N</i> = 16 604	Liver, <i>N</i> = 8958	Heart, <i>N</i> = 5569	Lung, <i>N</i> = 963	Intestine, <i>N</i> = 957	Heart–Lung, <i>N</i> = 157
Follow-up time (y), med (IQR)	6.2 (2.2–12.1)	7.9 (2.9–13.6)	5.6 (2.0–11.0)	3.1 (1.3–6.5)	3.0 (0.8–6.4)	2.4 (0.4–6.5)
Death, <i>n</i> (%)	5353 (32)	2000 (22)	2160 (39)	628 (65)	448 (47)	117 (75)
Time to death (y), med (IQR)	1.2 (0.1–4.7)	0.5 (0.07–3.8)	1.9 (0.1–6.2)	2.2 (0.7–4.5)	0.7 (0.2–2.1)	1.5 (0.2–3.2)
1-y mortality, <i>n</i> (%) ^a	2543 (15)	1137 (13)	900 (16)	191 (20)	267 (28)	48 (31)
3-y mortality, <i>n</i> (%) ^b	3535 (24)	1436 (18)	1255 (25)	390 (44)	370 (44)	84 (55)
5-y mortality, <i>n</i> (%) ^c	4091 (30)	1585 (22)	1507 (34)	495 (60)	405 (55)	99 (67)
Mortality rate, per 1000 person-years (95% CI)	43.0 (41.8–44.1)	26.1 (24.9–27.2)	55.9 (53.6–58.3)	140.6 (130.0–152.0)	111.5 (101.6–122.3)	173.1 (144.4–207.5)
ESKD, <i>n</i> (%)	426 (3)	162 (2)	169 (3)	58 (6)	33 (3)	4 (3)
Preemptive kidney transplant, <i>n</i>	104	49	35	12	7	1
Dialysis with subsequent kidney transplant, <i>n</i>	149	56	57	22	11	3
Chronic dialysis, <i>n</i>	173	57	77	24	15	0
Time to ESKD (y), med (IQR)	8.7 (4.5–12.9)	9.0 (4.5–13.4)	10.2 (6.7–13.9)	7.0 (4.7–9.0)	1.9 (1.0–4.8)	6.8 (5.3–8.0)
Incidence rate ESKD, per 1000 person-years (95% CI)	3.5 (3.2–3.8)	2.1 (1.8–2.5)	4.4 (3.8–5.2)	13.7 (10.6–17.8)	8.4 (6.0–11.8)	6.3 (2.4–16.7)

med, median.

^a 1-y mortality reported for all subjects, as all subjects were eligible for at least 1 y of follow-up time. Percentage reported reflects number of deaths within 1 y divided by total denominator of 16 604 subjects.

^b 3-y mortality reported only for subjects who died within 3 y or had 3 y of follow-up time. Percentage reported reflects number of deaths within 3 y divided by total denominator of 14 949 subjects who either died within 3 y or had 3 y of follow-up time.

^c 5-y mortality reported only for subjects who died within 5 y or had 5 y of follow-up time. Percentage reported reflects number of deaths within 5 y divided by total denominator of 13 481 subjects who either died within 5 y or had 5 y of follow-up time.

FIGURE 1

Cumulative incidence of ESKD among pediatric SOT recipients, treating death as a competing risk for ESKD.

ESKD after SOT, lower eGFR at transplant was also associated with higher risk of mortality (eGFR <60: HR 1.34, 95% CI 1.24–1.44, $P < .001$; acute dialysis: HR 2.81, 95% CI 2.26–3.50, $P < .001$ versus eGFR ≥ 60 mL/min per 1.73 m^2).

Effect of ESKD on Mortality

Among the 5353 subjects who died, 161 had ESKD (3%). Of the 426 subjects with ESKD, 161 (38%) subsequently died after a median of 0.87 years (IQR 0.25, 2.31) after developing ESKD. Treating ESKD as a time-varying covariate, we found that ESKD was associated with a fivefold

higher risk of death in unadjusted analyses (HR 5.04, 95% CI 4.28–5.95, $P < .001$). Adjusting for the other significant risk factors for death described earlier, ESKD remained significantly associated with mortality (HR 3.31, 95% CI 2.80–3.91, $P < .001$). In adjusted analyses, subjects with ESKD who received a kidney transplant (either preemptively or after a period on dialysis), had a 1.52-fold higher risk of death (95% CI 1.17–1.98, $P = .002$) compared with subjects without ESKD. However, among the subjects who remained on dialysis until death or end of follow-up, the HR of

death was 9.92 (95% CI 8.10–12.15, $P < .001$).

DISCUSSION

In this 20-year national cohort of pediatric SOT recipients, we found that ESKD occurred in 3% of children after SOT at a rate of 3.5 cases per 1000 person-years, with the highest risk among recipients of lung and intestinal transplants. This rate is significantly higher than in the general pediatric population, in whom the incidence of ESKD is only 16 cases per million age-related population per year.¹⁸ Mortality rates far exceeded rates of ESKD in all SOT types. Additionally, impaired kidney function at the time of transplant was independently associated with a higher risk of both ESKD and death across organ types. Finally, we found that ESKD significantly increases the risk of mortality after SOT, particularly among those who remain on dialysis. This analysis is the first to identify the risk of advanced kidney disease among pediatric SOT recipients over 2 decades.

CKD and ESKD are extremely important outcomes after SOT, leading to numerous

TABLE 3 Unadjusted and Adjusted Risk of ESKD After Pediatric SOT^a

	Unadjusted HR of ESKD (95% CI)	P Value	Adjusted HR of ESKD ^b (95% CI)	P Value
SOT type				
Liver	Reference		Reference	
Heart	2.33 (1.88–2.90)	<.001	1.79 (1.41–2.27)	<.001
Heart–lung	3.88 (1.44–10.49)	.007	2.22 (0.81–6.05)	.12
Lung	9.18 (6.76–12.46)	<.001	5.79 (4.18–8.02)	<.001
Intestine	5.81 (3.97–8.50)	<.001	7.37 (4.97–10.94)	<.001
Age at transplant, y				
0 to <5	Reference		Reference	
5 to <10	1.93 (1.43–2.61)	<.001	2.03 (1.49–2.76)	<.001
10 to <15	3.39 (2.64–4.35)	<.001	3.27 (2.53–4.24)	<.001
≥15	3.84 (2.99–4.92)	<.001	3.64 (2.81–4.71)	<.001
Male gender	1.11 (0.92–1.34)	.28	1.04 (0.85–1.26)	.71
Black vs nonblack race	1.15 (0.90–1.48)	.27	1.37 (1.06–1.77)	.016
Year of transplant				
1990–1994	Reference		Reference	
1995–1999	0.83 (0.65–1.05)	.13	0.84 (0.65–1.08)	.18
2000–2004	0.84 (0.62–1.15)	.28	0.80 (0.57–1.12)	.19
2005–2010	0.97 (0.62–1.50)	.88	0.90 (0.57–1.43)	.67
eGFR pretransplant, mL/min per 1.73 m ²				
≥60	Reference		Reference	
<60	1.62 (1.24–2.11)	<.001	1.85 (1.41–2.44)	<.001
Acute dialysis	5.26 (2.33–11.88)	<.001	4.84 (2.12–11.07)	<.001

^a Cox regression for ESKD censored at death.^b Adjusted for other variables in table. **FIGURE 2**

Kaplan–Meier curve of patient survival by SOT type.

comorbidities and premature death. Children with CKD face many complications including hypertension, dyslipidemia, cardiovascular disease, anemia, bone disease, growth retardation, neurocognitive impairment, and poor quality of life.^{4,5,19–25} Our analysis identifies a high-risk population for ESKD; targeting renoprotective interventions to these children in earlier stages of kidney disease may decrease CKD-related morbidity and mortality.

In contrast to previous findings that adult liver transplant recipients have one of the highest risks of chronic kidney failure,⁴ we found that pediatric liver transplant recipients have the lowest risk of ESKD compared with other SOT recipients, probably because the majority had normal eGFR at transplant and few had underlying comorbidities such as hypertension, diabetes, or hepatitis C. Also in contrast to what has been reported in adults, we found that

pediatric lung transplant recipients have one of the highest risks of ESKD. Cystic fibrosis (CF) was the most common indication for lung transplantation in this cohort. These patients are at risk for CKD because of recurrent episodes of AKI from nephrotoxic antimicrobial agents and CF-related diabetes.^{26,27} Furthermore, children with CF are prone to poor growth and low muscle mass, as reflected by the low median height and BMI percentiles in the lung transplant recipients. In these children, serum creatinine may be a poor marker for level of kidney function, so early dysfunction may not be apparent. Newer serum biomarkers such as cystatin C may be more accurate in estimating kidney function in patients with muscle wasting.^{28–32} The CKiD formula incorporating creatinine and cystatin C was developed in a cohort of children with CKD and performs better in estimating GFR in children with impaired kidney function than traditional equations based on creatinine alone.¹⁷

Similar to what has been reported in adults, we found that pediatric intestinal transplant recipients have one of the highest risks of ESKD. The unique factors contributing to kidney injury after intestine and multivisceral transplantation have not been well studied, but contributing factors may include higher levels of immunosuppression due to the high immunogenicity of the gut and hypovolemia in the peritransplant period related to poor fluid absorption.³³ In addition, the most common indications for intestine or multivisceral transplant in children include congenital anomalies such as atresia or volvulus and necrotizing enterocolitis, typically seen in preterm infants, who may have other risk factors for kidney dysfunction.

Although the overall incidence of ESKD in this study was only 3%, ESKD represents only a small proportion of all CKD, and therefore the burden of kidney disease in pediatric SOT recipients is

TABLE 4 Unadjusted and Adjusted Risk of Death After Pediatric SOT

	Unadjusted HR of Death (95% CI)	P Value	Adjusted HR of Death ^a (95% CI)	P Value
SOT type				
Liver	Reference		Reference	
Heart	1.96 (1.85–2.09)	<.001	1.86 (1.74–1.98)	<.001
Intestine	3.03 (2.73–3.36)	<.001	3.57 (3.21–3.97)	<.001
Lung	4.00 (3.65–4.37)	<.001	4.02 (3.65–4.43)	<.001
Heart–lung	4.99 (4.14–6.01)	<.001	4.51 (3.73–5.45)	<.001
Age at transplant, y				
0 to <5	Reference		Reference	
5 to <10	0.93 (0.85–1.02)	.11	0.90 (0.83–0.99)	.026
10 to <15	1.21 (1.13–1.31)	<.001	1.05 (0.98–1.14)	.19
≥15	1.53 (1.42–1.64)	<.001	1.30 (1.21–1.40)	<.001
Male gender	0.99 (0.94–1.04)	.73	0.97 (0.91–1.02)	.21
Black vs nonblack race	1.32 (1.24–1.41)	<.001	1.49 (1.39–1.59)	<.001
Year of SOT				
1990–1994	Reference		Reference	
1995–1999	0.87 (0.81–0.93)	<.001	0.83 (0.77–0.90)	<.001
2000–2004	0.73 (0.68–0.79)	<.001	0.68 (0.63–0.74)	<.001
2005–2010	0.59 (0.54–0.64)	<.001	0.53 (0.48–0.58)	<.001
eGFR pretransplant, mL/min per 1.73 m ²				
≥60	Reference		Reference	
<60	1.45 (1.34–1.56)	<.001	1.34 (1.24–1.44)	<.001
Acute dialysis	2.39 (1.92–2.97)	<.001	2.81 (2.26–3.50)	<.001

^a Adjusted for other variables in table.

certainly much higher. Children with CKD have a steady decline in kidney function over time. In the CKiD multicenter prospective cohort study of children with CKD, GFR declined by median of -4.3 and -1.5 mL/min per 1.73 m² per year in children with glomerular and non-glomerular diagnoses, respectively,³⁴ so with longer follow-up time, it is likely that some subjects in this cohort with earlier stages of CKD would progress to ESKD.

Treating ESKD as a time-varying covariate, we found that ESKD increases the risk of death more than threefold, and more than ninefold among subjects on chronic dialysis. This association with death is similar to the higher risk of mortality from ESKD in the general population.^{21–23} Kidney transplantation has been associated with better survival compared with dialysis.^{35,36} However, the higher risk of mortality among dialysis patients may be partially confounded by selection of healthier subjects for kidney transplantation. It is also important to consider that in this

analysis, ESKD was treated as a time-varying covariate, so subjects were considered unexposed to ESKD until the date of dialysis or kidney transplant. However, this approach does not take into account the effects of CKD on mortality in the time preceding the ESKD event.

This study has a number of limitations. First, as we analyzed registry data, missing data were common for some variables, and misclassification of exposures was possible. For example, 12% of subjects had missing creatinine or height data necessary to estimate pretransplant GFR. There was a disproportionate amount of missing eGFR data among thoracic organ transplant recipients and subjects who underwent transplantation in the earliest eras. However, sensitivity analyses imputing extreme values for eGFR yielded similar results as the primary analysis. Additionally, we had limited information about long-term immunosuppressive regimens and trough concentrations of calcineurin inhibitors. Choice and dosing

of chronic immunosuppression may be an important factor for long-term outcomes in this population, because immunosuppressive regimens vary by organ type and by center practice. The relationship between immunosuppressive therapy and ESKD must be assessed in prospective studies. Finally, although we chose objective, well-captured outcomes of ESKD and death through USRDS and SRTR data, it is possible that some outcomes were missed. However, missing outcomes would probably be non-differential across organ types and would only underestimate the burden of disease in this population.

CONCLUSIONS

In a 20-year national cohort of pediatric SOT recipients, 3% of children developed ESKD. However, the burden of earlier stages of CKD and the lifetime risk of ESKD are probably higher. Screening for early stages of CKD is an important part of routine posttransplant care, particularly among lung and intestinal transplant recipients, who had the highest risk of ESKD. We recommend that all pediatric SOT recipients undergo routine screening, including blood pressure, urinalysis, and estimation of kidney function. Early referral to a pediatric nephrologist is suggested for any patient with hypertension, proteinuria, or abnormal kidney function. Implementation of renoprotective measures in early stages of CKD may slow progressive kidney damage and decrease CKD-related morbidities and death in children needing SOT.

ACKNOWLEDGMENTS

The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US government.

REFERENCES

- Cai J. Intestine and multivisceral transplantation in the United States: a report of 20-year national registry data (1990–2009). *Clin Transpl*. 2009;83–101
- Report OD. Available at: optn.transplant.hrsa.gov/. Accessed October 25, 2012
- Mangus RS, Tector AJ, Kubal CA, Fridell JA, Vianna RM. Multivisceral transplantation: expanding indications and improving outcomes. *J Gastrointest Surg*. 2013;17(1):179–186, discussion 186–187
- Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349(10):931–940
- Ruebner RL, Reese PP, Denburg MR, Rand EB, Abt PL, Furth SL. Risk factors for end-stage kidney disease after pediatric liver transplantation. *Am J Transplant*. 2012;12(12):3398–3405
- Sharma P, Schaubel DE, Guidinger MK, Goodrich NP, Ojo AO, Merion RM. Impact of MELD-based allocation on end-stage renal disease after liver transplantation. *Am J Transplant*. 2011;11(11):2372–2378
- Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. *Clin J Am Soc Nephrol*. 2009;4(2):481–508
- Baran DA, Galin ID, Gass AL. Calcineurin inhibitor-associated early renal insufficiency in cardiac transplant recipients: risk factors and strategies for prevention and treatment. *Am J Cardiovasc Drugs*. 2004;4(1):21–29
- Campbell MS, Kotlyar DS, Brensinger CM, et al. Renal function after orthotopic liver transplantation is predicted by duration of pretransplantation creatinine elevation. *Liver Transpl*. 2005;11(9):1048–1055
- Gonwa TA, McBride MA, Anderson K, Mai ML, Wade H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLT) in the US: where will MELD lead us? *Am J Transplant*. 2006;6(11):2651–2659
- Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology*. 2002;35(5):1179–1185
- Ruebner R, Goldberg D, Abt PL, et al. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. *Am J Transplant*. 2012;12(11):2958–2965
- Pawarode A, Fine DM, Thuluvath PJ. Independent risk factors and natural history of renal dysfunction in liver transplant recipients. *Liver Transpl*. 2003;9(7):741–747
- Lee CK, Christensen LL, Magee JC, Ojo AO, Harmon WE, Bridges ND. Pre-transplant risk factors for chronic renal dysfunction after pediatric heart transplantation: a 10-year national cohort study. *J Heart Lung Transplant*. 2007;26(5):458–465
- Ishani A, Erturk S, Hertz MI, Matas AJ, Savik K, Rosenberg ME. Predictors of renal function following lung or heart–lung transplantation. *Kidney Int*. 2002;61(6):2228–2234
- Canales M, Youssef P, Spong R, et al. Predictors of chronic kidney disease in long-term survivors of lung and heart–lung transplantation. *Am J Transplant*. 2006;6(9):2157–2163
- Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629–637
- United States Renal Data System. 2012 Annual Report. Available at: www.usrds.org/adr.aspx. Accessed June 19, 2013
- Wong CJ, Moxey-Mims M, Jerry-Fluker J, Warady BA, Furth SL. CKID (CKD in Children) prospective cohort study: a review of current findings. *Am J Kidney Dis*. 2012;60(6):1002–1011
- Wong H, Mylrea K, Feber J, Drukker A, Filler G. Prevalence of complications in children with chronic kidney disease according to KDOQI. *Kidney Int*. 2006;70(3):585–590
- Collins AJFR, Foley RN, Herzog C, et al. Excerpts from the US Renal Data System 2009 Annual Data Report. *Am J Kidney Dis*. 2010;55(1 suppl 1):S1–S420, A6–A7
- Chertow GM, Johansen KL, Lew N, Lazarus JM, Lowrie EG. Vintage, nutritional status, and survival in hemodialysis patients. *Kidney Int*. 2000;57(3):1176–1181
- McDonald SP, Craig JC; Australian and New Zealand Paediatric Nephrology Association. Long-term survival of children with end-stage renal disease. *N Engl J Med*. 2004;350(26):2654–2662
- Hendawy A, Pouteil-Noble C, Villar E, Boissonnat P, Sebbag L. Chronic renal failure and end-stage renal disease are associated with a high rate of mortality after heart transplantation. *Transplant Proc*. 2005;37(2):1352–1354
- Villar E, Boissonnat P, Sebbag L, et al. Poor prognosis of heart transplant patients with end-stage renal failure. *Nephrol Dial Transplant*. 2007;22(5):1383–1389
- Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk factors for chronic kidney disease in adults with cystic fibrosis. *Am J Respir Crit Care Med*. 2011;184(10):1147–1152
- Soulsby N, Greville H, Coulthard K, Doecke C. Renal dysfunction in cystic fibrosis: is there cause for concern? *Pediatr Pulmonol*. 2009;44(10):947–953
- Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis*. 2002;40(2):221–226
- Groesbeck D, Köttgen A, Parekh R, et al. Age, gender, and race effects on cystatin C levels in US adolescents. *Clin J Am Soc Nephrol*. 2008;3(6):1777–1785
- Kniepeiss D, Wagner D, Wirsberger G, et al. Serum cystatin C is an easy to obtain biomarker for the onset of renal impairment in heart transplant recipients. *J Thorac Cardiovasc Surg*. 2010;140(3):688–693
- Roos JF, Doust J, Tett SE, Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children: a meta-analysis. *Clin Biochem*. 2007;40(5–6):383–391
- Ylinen EA, Ala-Houhala M, Harmoinen AP, Knip M. Cystatin C as a marker for glomerular filtration rate in pediatric patients. *Pediatr Nephrol*. 1999;13(6):506–509
- Suzuki M, Mujtaba MA, Sharfuddin AA, et al. Risk factors for native kidney dysfunction in patients with abdominal multivisceral/small bowel transplantation. *Clin Transplant*. 2012;26(4):E351–E358
- Furth SL, Abraham AG, Jerry-Fluker J, et al. Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6(9):2132–2140
- Foster BJ, Dahhou M, Zhang X, Platt RW, Hanley JA. Change in mortality risk over time in young kidney transplant recipients. *Am J Transplant*. 2011;11(11):2432–2442
- Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725–1730

(Continued from first page)

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Reese is supported by NIH grant K23 DK078688-01. Dr Furth is supported by NIH grants K24 DK078737 and U01 DK066174. Dr Denburg was funded by a National Kidney Foundation/American KDOQI Research Fellowship, the Nephcure Foundation–American Society of Nephrology Research Grant, and NIH grant K23 DK093556. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.