End-Stage Kidney Disease After Pediatric Nonrenal Solid Organ Transplantation

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 disease, particularly after liver and intestinal transplantation.

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.
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 nonrenal 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, peri-transplant acute kidney injury (AKI), hypertension, and diabetes.7–10 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 2010.8 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 pu-
tative risk factors for ESKD after SOT, which
were included as independent variables
in univariable and multivariable analy-
yses. 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 fil-
tration rate (eGFR), calculated using the
bedside Chronic Kidney Disease in Chil-
dren (CKiD) study formula (0.413 ×
height/serum creatinine) and the serum
creatine 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 trans-
plant recipients had a greater pro-
portion 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 per-
formed sensitivity analyses in which ex-
treme 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
\( \geq 60 \) or eGFR < 60 mL/min per 1.73 m².

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 per-
formed at 174 transplant centers dur-
ing 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 sum-
marized in Table 1. The median age at
SOT was 3.3 years (IQR 0.8–12.4); how-
ever, there was significant variability in
age by organ. Lung transplant recipi-
 ents were the oldest (median 14.1
years; IQR, 9.5–16.9), whereas in-
testinal 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
(8th percentile). There was a nearly
equal distribution of transplants over
the 20-year period except among in-
testinal transplants, which were performed
primarily in the most recent decade.
There were low rates of pretransplant
diabetes except among lung transplant
recipients. Tacrolimus-based immuno-
suppression was used at transplant in
53% of subjects; however, thoracic organ
transplant recipients were more likely
to be treated with cyclosporine-based im-
munosuppression. The majority of chil-
dren 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 m². Estimated GFR was
< 60 ml/min per 1.73 m² in 1783 (11%)
subjects, and 778 (5%) needed acute di-
alysis 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 inci-
dence among liver transplant recipi-
ents (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 trans-
plant recipients (HR 1.79, 95% CI 1.41–
2.27, \( P < .001 \)). There was a stepwise
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 1.38–2.48, 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, in an adjusted model, heart–lung transplant 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 1.98, 95% CI 1.74–2.19, 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

<table>
<thead>
<tr>
<th></th>
<th>All N = 16 604</th>
<th>Liver, N = 8558</th>
<th>Heart, N = 5569</th>
<th>Lung, N = 983</th>
<th>Intestine, N = 957</th>
<th>Heart–Lung, N = 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time (y), med (IQR)</td>
<td>6.2 (2.2–12.1)</td>
<td>7.9 (2.9–13.6)</td>
<td>5.6 (2.0–11.0)</td>
<td>3.1 (1.3–6.5)</td>
<td>3.0 (0.8–6.4)</td>
<td>2.4 (0.4–6.5)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>5353 (32)</td>
<td>2000 (22)</td>
<td>2160 (38)</td>
<td>628 (65)</td>
<td>448 (47)</td>
<td>117 (75)</td>
</tr>
<tr>
<td>Time to death (y), med (IQR)</td>
<td>1.2 (0.1–4.7)</td>
<td>0.5 (0.07–3.8)</td>
<td>1.8 (0.6–6.2)</td>
<td>2.2 (0.7–4.5)</td>
<td>0.7 (0.2–2.1)</td>
<td>1.5 (0.2–3.2)</td>
</tr>
<tr>
<td>1-y mortality, n (%)a</td>
<td>2543 (15)</td>
<td>1137 (13)</td>
<td>900 (16)</td>
<td>191 (20)</td>
<td>267 (28)</td>
<td>48 (31)</td>
</tr>
<tr>
<td>3-y mortality, n (%)b</td>
<td>3535 (24)</td>
<td>1436 (18)</td>
<td>1255 (25)</td>
<td>390 (44)</td>
<td>370 (44)</td>
<td>84 (55)</td>
</tr>
<tr>
<td>5-y mortality, n (%)c</td>
<td>4091 (30)</td>
<td>1585 (22)</td>
<td>1507 (34)</td>
<td>495 (60)</td>
<td>405 (53)</td>
<td>99 (67)</td>
</tr>
<tr>
<td>Mortality rate, per 1000 person-years (95% CI)</td>
<td>43.0 (41.8–44.1)</td>
<td>26.1 (24.9–27.2)</td>
<td>55.9 (53.6–58.3)</td>
<td>140.6 (130.0–152.0)</td>
<td>111.5 (101.6–122.3)</td>
<td>173.1 (144.4–207.5)</td>
</tr>
<tr>
<td>ESKD, n (%)</td>
<td>426 (3)</td>
<td>162 (2)</td>
<td>169 (3)</td>
<td>58 (6)</td>
<td>33 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Preemptive kidney transplant, n</td>
<td>104</td>
<td>49</td>
<td>35</td>
<td>12</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Dialysis with subsequent kidney transplant, n</td>
<td>149</td>
<td>56</td>
<td>57</td>
<td>22</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Chronic dialysis, n</td>
<td>173</td>
<td>57</td>
<td>77</td>
<td>24</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Time to ESKD (y), med (IQR)</td>
<td>8.7 (4.5–12.9)</td>
<td>9.0 (4.5–13.4)</td>
<td>10.2 (6.7–13.9)</td>
<td>7.0 (4.7–9.0)</td>
<td>1.9 (1.0–4.8)</td>
<td>6.8 (5.3–8.0)</td>
</tr>
<tr>
<td>Incidence rate ESKD, per 1000 person-years (95% CI)</td>
<td>3.5 (3.2–3.8)</td>
<td>2.1 (1.8–2.5)</td>
<td>4.4 (3.8–5.2)</td>
<td>13.7 (10.6–17.8)</td>
<td>8.4 (6.0–11.8)</td>
<td>6.3 (2.4–16.7)</td>
</tr>
</tbody>
</table>

med. median.

* 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.

+ 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 14 949 subjects who either died within 5 y or had 5 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 m²).

**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

<table>
<thead>
<tr>
<th>SOT type</th>
<th>Unadjusted HR of ESKD (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR of ESKDb (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>2.33 (1.88–2.90)</td>
<td>&lt;.001</td>
<td>1.79 (1.41–2.27)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart–lung</td>
<td>3.88 (1.44–10.69)</td>
<td>.007</td>
<td>2.22 (0.81–6.05)</td>
<td>.12</td>
</tr>
<tr>
<td>Lung</td>
<td>9.18 (6.76–12.46)</td>
<td>&lt;.001</td>
<td>5.79 (4.18–8.02)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intestine</td>
<td>5.81 (3.97–8.50)</td>
<td>&lt;.001</td>
<td>7.37 (4.97–10.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age at transplant, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;5</td>
<td>Reference</td>
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<td>Reference</td>
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<tr>
<td>5 to &lt;10</td>
<td>1.93 (1.43–2.61)</td>
<td>&lt;.001</td>
<td>2.03 (1.49–2.76)</td>
<td>&lt;.001</td>
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<tr>
<td>10 to &lt;15</td>
<td>3.39 (2.64–4.35)</td>
<td>&lt;.001</td>
<td>3.27 (2.53–4.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥15</td>
<td>3.84 (2.99–4.92)</td>
<td>&lt;.001</td>
<td>3.64 (2.81–4.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.11 (0.92–1.34)</td>
<td>.28</td>
<td>1.04 (0.85–1.26)</td>
<td>.71</td>
</tr>
<tr>
<td>Black vs nonblack race</td>
<td>1.15 (0.90–1.48)</td>
<td>.27</td>
<td>1.57 (1.06–1.77)</td>
<td>.016</td>
</tr>
<tr>
<td>Year of transplant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1990–1994</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
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<tr>
<td>1995–1999</td>
<td>0.83 (0.65–1.03)</td>
<td>.13</td>
<td>0.84 (0.65–1.08)</td>
<td>.18</td>
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<td>2000–2004</td>
<td>0.84 (0.62–1.15)</td>
<td>.26</td>
<td>0.80 (0.57–1.12)</td>
<td>.19</td>
</tr>
<tr>
<td>2005–2010</td>
<td>0.97 (0.62–1.50)</td>
<td>.88</td>
<td>0.90 (0.57–1.43)</td>
<td>.67</td>
</tr>
<tr>
<td>eGFR pretransplant, mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per 1.73 m²</td>
<td>≥60 Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.62 (1.24–2.11)</td>
<td>&lt;.001</td>
<td>1.85 (1.41–2.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>5.26 (2.33–11.88)</td>
<td>&lt;.001</td>
<td>4.84 (2.12–11.07)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

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, neuropsychological 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

<table>
<thead>
<tr>
<th>SOT type</th>
<th>Unadjusted HR of Death (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR of Death (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>1.96 (1.85–2.09)</td>
<td>&lt; .001</td>
<td>1.86 (1.74–1.98)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Intestine</td>
<td>3.05 (2.73–3.36)</td>
<td>.001</td>
<td>3.57 (3.21–3.97)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Lung</td>
<td>4.00 (3.65–4.37)</td>
<td>&lt; .001</td>
<td>4.02 (3.65–4.43)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Heart–lung</td>
<td>4.99 (4.14–6.01)</td>
<td>&lt; .001</td>
<td>4.51 (3.73–5.45)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Age at transplant, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;5</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>0.93 (0.85–1.02)</td>
<td>.11</td>
<td>0.90 (0.83–0.99)</td>
<td>.026</td>
</tr>
<tr>
<td>10 to &lt;15</td>
<td>1.21 (1.13–1.31)</td>
<td>&lt; .001</td>
<td>1.05 (0.98–1.14)</td>
<td>.19</td>
</tr>
<tr>
<td>≥15</td>
<td>1.55 (1.42–1.64)</td>
<td>&lt; .001</td>
<td>1.30 (1.21–1.40)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.99 (0.94–1.04)</td>
<td>.73</td>
<td>0.97 (0.91–1.02)</td>
<td>.21</td>
</tr>
<tr>
<td>Black vs nonblack race</td>
<td>1.32 (1.24–1.41)</td>
<td>&lt; .001</td>
<td>1.49 (1.39–1.59)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Year of SOT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1990–1994</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1995–1999</td>
<td>0.87 (0.81–0.93)</td>
<td>&lt; .001</td>
<td>0.83 (0.77–0.90)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>2000–2004</td>
<td>0.73 (0.68–0.79)</td>
<td>&lt; .001</td>
<td>0.68 (0.63–0.74)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>2005–2010</td>
<td>0.50 (0.54–0.64)</td>
<td>&lt; .001</td>
<td>0.53 (0.48–0.58)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>eGFR pretransplant, mL/min per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.45 (1.34–1.56)</td>
<td>&lt; .001</td>
<td>1.34 (1.24–1.44)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>2.39 (1.92–2.97)</td>
<td>&lt; .001</td>
<td>2.81 (2.26–3.50)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

* 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.

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REFERENCES


(Continued from first page)

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Rebecca L. Ruebner, Peter P. Reese, Michelle R. Denburg, Peter L. Abt and Susan L. Furth

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