



ORIGINAL CLINICAL SCIENCE

End-stage renal disease after pediatric heart transplantation: A 25-year national cohort study

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risk factors

BACKGROUND: End-stage renal disease (ESRD), defined as the need for chronic dialysis and/or kidney transplantation (KTx), is a known complication after heart transplant (HTx). However, factors associated with ESRD are not well elucidated. The objectives of this study were to determine the prevalence, risk factors, and outcomes associated with ESRD after pediatric HTx.

METHODS: Scientific Registry of Transplant Recipients data were linked, using direct identifiers, to the United States Renal Data System to identify patients (aged ≤ 18 years) who underwent primary HTx between 1989 and 2013. Risk factors for ESRD and death were analyzed using Cox regression analysis.

RESULTS: Combining the above 2 databases identified ~25% additional HTx patients who developed ESRD that were not captured by either database alone. During a median follow-up of 11.8 years, ESRD developed in 276 of 6,901 patients (4%). The actuarial risk of developing ESRD after HTx was 3% at 10 years and 16% at 20 years. Age at HTx > 1 year, African-American race, year of HTx before 2000, hypertension, diabetes mellitus, re-HTx, acute dialysis, graft failure, and hospitalized infection were significant risk factors for ESRD development. Those who remained on chronic dialysis had higher risk of death than those who received KTx (hazard ratio, 31.4; 95% confidence interval, 20.8–48.4; $p < 0.0001$).

CONCLUSIONS: ESRD after pediatric HTx is more prevalent in HTx survivors than documented by a transplant database alone. A number of factors develop at or after HTx that increase the risk for developing ESRD. Use of KTx in post-HTx ESRD is associated with improved survival.

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Over time, the pediatric heart transplant (HTx) recipient's survival has improved with reduced early post-transplant mortality.^{1–3} End-stage renal disease (ESRD), defined as a need for chronic dialysis and/or kidney transplant (KTx), is a well-recognized complication after pediatric HTx, with a previously reported incidence of 3%.^{4,5} Even though ESRD

is a predictor of 2- to 6-fold increased risk of death after HTx,^{4,5} the prevalence, risk factors, and outcomes associated with ESRD are not well elucidated. ESRD necessitating KTx is being increasingly recognized^{4–7} and poses an increased demand on an already scarce donor pool.⁸ Early recognition of potential risk factors is important because this may help discern strategies to slow progression to or prevent this complication in this vulnerable population.⁵

Pediatric HTx recipients are now surviving for decades after HTx surgery.⁹ As they age, the likelihood of ESRD increases considerably over time. Unfortunately, the data

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collection becomes incomplete as patients transition from specialized pediatric care to adult care services.¹⁰ Because of limitations in analyses derived from single-center studies, registries have been used to better understand outcome after solid-organ transplantation.⁴⁻⁷ The Scientific Registry of Transplant Recipients (SRTR) is a mandatory reporting database of all solid-organ transplants performed in the United States since 1987.¹¹ Similarly, the United States Renal Data System (USRDS) is a national ESRD registry that maintains clinical records on ESRD patients with Medicare as their primary insurance since 1988.¹²

Linkage of major databases has lately been adopted to overcome limitations of capture and extended follow-up in single registries, thereby increasing the power to evaluate the long-term outcomes.^{4-7,13} One potential limitation of linkage occurs when direct identifiers are not available, necessitating probabilistic matching using demographic covariates, an imprecise method. We hypothesized that linking the SRTR with USRDS using direct identifiers would identify HTx recipients who had ESRD that were not recorded by SRTR. Our objective was to use these linked databases to determine the prevalence, risk factors, and outcomes associated with ESRD in a national cohort of pediatric HTx recipients who underwent primary HTx during a 25-year period.

Methods

Patients

The study population included patients (aged ≤ 18 years) registered in the SRTR who underwent primary (first) and solitary HTx between January 1, 1989, and December 31, 2013. We chose December 2013 as the end date for inclusion of patients to allow for lags in center reporting to SRTR and claims data for ESRD. We monitored these patients through December 2, 2015, the last follow-up date available in the SRTR. Patients with multiple-organ transplants and those who received previous KTx or developed ESRD before primary HTx were excluded. (Definitions including ESRD¹⁴ are provided in [Supplementary Appendix Table S1](#), online at www.jhltonline.org).

Data

In this study, we merged the SRTR database with the USRDS claims data. The SRTR collects data on all donor, wait-listed candidates, and transplant recipients in the United States (U.S.), submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration of the U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Outcomes of death in the SRTR are determined through linkage to the Social Security Death Master File, OPTN death date, and death date in follow-up forms.¹¹ The USRDS maintains records of any changes in vital status or methods of renal replacement therapy, including KTx. To determine the ESRD outcomes, we used the Centers for Medicare and Medicaid Services (CMS) Medical Evidence Report (Form CMS-2728) for chronic dialysis submitted to the USRDS.^{5,15-17} We also reviewed the standard analysis files for the heart and kidney transplant data set to determine the ESRD outcomes

reported by the SRTR. The Institutional Review Board of the Washington University in St. Louis School of Medicine, the SRTR, and USRDS approved the study.

Linkage

The SRTR team constructed an analysis file that contained protected health information (PHI) on all consecutive patients (aged ≤ 18 years) who underwent primary HTx between January 1, 1989, and December 31, 2013. All patients within the analysis file were assigned a unique patient code. This analysis file containing PHI was securely linked to the ESRD database by the USRDS team. The USRDS team then assigned the same unique patient code to all the individual patients who developed ESRD after HTx, in a pre-arranged secure fashion. Final data that we received from the SRTR and USRDS did not contain any PHI. However, the unique patient code assigned by both teams allowed cross-referencing between the 2 data sets.

Statistical analysis

The primary end point was onset of ESRD, as determined by the need for initiation of chronic dialysis and/or KTx or wait-listed for KTx. The term "chronic dialysis" was used for primary HTx recipients who were listed on the USRDS and were receiving any modality of hemodialysis or peritoneal dialysis. Within the SRTR data set, we defined ESRD as the need for chronic dialysis or receipt of a KTx or wait-listed for KTx reported within the KTx section of the SRTR. No patients were exclusively identified in the latter category.

Data were censored at death, lost to follow-up, or December 2, 2015, whichever occurred first. Risk factors for ESRD and death were analyzed using Cox proportional hazard regression analysis as fixed and time-dependent covariates. To examine the effect of ESRD on mortality, we treated ESRD as a time-varying covariate in the Cox regression analysis. Standard Kaplan-Meier analyses were used to examine risk of death among patients who remained on chronic dialysis until death or the end of follow-up compared with those who received KTx. To assess the importance of missing data, a sensitivity analysis was performed. (Details regarding fixed and time-dependent risk-factors analysis and sensitivity analysis are provided in the [Supplementary Appendix](#), online). Estimated glomerular filtration rate (eGFR) was calculated according to the newer bedside Chronic Kidney Disease in Children study formula ($0.413 \times \text{height in cm} / \text{serum creatinine in mg/dL}$) across all ages.¹⁸ Baseline eGFR was calculated at the time of heart transplant. Statistical analysis was performed using SAS 9.4 software (SAS Institute Inc., Cary, NC).

Results

Linkage

The final study cohort included 6,901 primary HTx recipients. As reported in the SRTR, ESRD developed in 217 HTx recipients (3.1%) during the study period, and the USRDS reported ESRD developed in 221 HTx recipients (3.2%). Of those, 162 ESRD patients were identified by both data sets ([Supplementary Fig S1](#), online). However, 55 ESRD patients identified in the SRTR database were missing from the USRDS; likewise, 59 ESRD patients identified in the USRDS were missing from the SRTR. After

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