TRENDS IN KIDNEY TRANSPLANT OUTCOMES IN CHILDREN AND YOUNG ADULTS WITH CYSTINOSIS

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Abstract

Temporal changes in kidney transplant outcomes for children and young adults with cystinosis are unknown. We used the Scientific Registry of Transplant Recipients to identify all kidney transplants performed for cystinosis during 1987-2017 in patients < 31 years at transplant. We divided time into three equal eras (1987-1997, 1998-2007, and 2008-2017) to assess temporal changes in outcomes using Cox proportional and linear regression models. We examined 441 transplants in 362 patients. Age at ESRD increased over time (12.1 vs.13.3 vs.13.4; p=0.046). Eras 2 and 3 had lower risk of acute rejection (aHR 2 vs.1: 0.45; p=0.0002) (aHR 3 vs.1: 0.26; p <0.0001) compared with era 1. 5-year mean eGFR was higher for eras 2 (difference 2 vs.1: 9.2 ml/min/1.73m2; p=0.005) and 3 (difference 3 vs.1: 12.9 ml/min/1.73m2; p=0.002). The risk of death was lower for era 2 (adjusted hazard ratio (aHR):0.25; p=0.01). Seventy-three patients were retransplanted. The 5-year patient (94.2% vs. 92.5%; p=0.57) and graft survival (79.1% vs. 74.1%; p=0.52) were similar between primary vs. second transplants. Age at ESRD onset, delayed graft function, acute rejection, 5-year mean eGFR and patient survival have improved over time. Kidney retransplantation is associated with excellent outcomes in children and young adults with cystinosis.

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Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disease with an estimated incidence of 1 in 100,000 to 1 in 200,000 live births [1]. It is caused by a defect in a lysosomal transporter, cystinosin, which transports cystine from the lysosome into the cytoplasm. Without a functioning transporter, cystine accumulates in the lysosomes, forms crystals and leads to a progressive multi-organ disease.[1,2] Cystinosis has three distinct manifestations based on the severity of the mutations in the CTNS gene that encodes the transporter: infantile, juvenile and non-nephropathic ocular cystinosis. Infantile cystinosis, which is the most prevalent form of cystinosis, manifests as the renal Fanconi syndrome and, if left untreated, causes progressive tubulointerstitial and glomerular disease, which results in end-stage renal disease (ESRD) within the first decade of life [1,3,4].

Clinical course of cystinosis was revolutionized in 1994 when the US Food and Drug Administration (FDA) approved cysteamine for the treatment of cystinosis.[5] Cysteamine depletes nearly 90% of intracellular cystine by converting it into a water-soluble metabolite, cysteine, which exits the lysosomes without the defective transporter.[2] Early initiation of cysteamine retards cystine accumulation in various organs and significantly delays the onset of various renal and extra-renal manifestations of cystinosis including ESRD, hypothyroidism, diabetes, pulmonary dysfunction, pancreatic insufficiency, and neuromuscular disease.[6-8]

Although cysteamine has been shown to delay ESRD,[7,8] it does not prevent the need for renal replacement therapy.[9,10] Kidney transplant is the treatment of choice for patients with ESRD,[11] and cystinosis constitutes the underlying cause of ESRD in 1-2% of all pediatric kidney transplant recipients.[12] Previous studies have shown superior kidney transplant outcomes in patients with cystinosis compared with other causes of ESRD.[13,14] However, kidney transplant outcomes have not been examined recently. Whether kidney transplant outcomes have changed for patients, who were born in the era of the widespread availability of cysteamine, is unknown.

We used the Scientific Registry of Transplant Recipients (SRTR) database to examine the long-term outcomes of kidney transplant in patients with cystinosis. The objective of this study was an in-depth evaluation of the temporal changes in kidney transplant outcomes for children and young adults with cystinosis. Considering the favorable effect of cysteamine on the clinical course of cystinosis and the improvement in post-transplant immunosuppression, we hypothesized that patient and graft survival would progressively improve over time. We also examined the incidence and outcomes of kidney re-transplantation in cystinosis patients. To our knowledge, this is the largest and the most comprehensive study of kidney transplant outcomes in children and young adults with cystinosis in the United States.

Method

The institutional review board (IRB) of the University of Minnesota approved this study.

Data Source

We performed a retrospective cohort study using data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. [15]

Study Population

We used the SRTR database to identify all kidney transplant recipients, aged younger than 31 years at the time of their first transplant, who received a kidney transplant in the United States, for end-stage renal disease due to cystinosis, between October 1, 1987 and December 31, 2017. All recipients fulfilling the inclusion criteria were included to eliminate selection bias. We divided the study period into three equal eras (1987-1997, 1998-2007, and 2008-2017) to assess

temporal changes in kidney transplant characteristics and outcomes. Temporal changes were analyzed over 10-year intervals to allow adequate sample size for each era.

Study Variables

We evaluated changes over time in the following characteristics: age at listing, age at dialysis, age at transplant, race, preemptive transplant, dialysis duration, panel reactive antibody (PRA), HLA mismatch, cold ischemia time, recipients' body mass index (BMI), donor type and biological relation, induction and maintenance immunosuppression, and delayed graft function. For patients who lost their graft or died, we examined the causes of graft loss or death. We defined the date at ESRD as the earlier of the dialysis initiation date or the date of transplant. We calculated a kidney donor profile index (KDPI) for each deceased donor to determine the risk of kidney failure for a given donor compared with a reference donor population. We also studied temporal changes in donor age, race and gender.

Study Outcomes

We studied 5-year overall graft survival, death-censored graft survival, patient survival, post-transplant lymphoproliferative disease (PTLD) free survival, acute

rejection free survival and estimated glomerular filtration rate (eGFR) at 5 years (calculated using the modified Schwartz equation).[16] We also evaluated changes in these outcomes over time. For patient survival, we followed the transplant recipients from the date of transplant to the earlier of the date of death or the end of SRTR follow up (December 31, 2018). For graft survival, we followed the recipients from the date of transplant to the earliest of the date of graft loss, date of death, or end of SRTR follow up. For death-censored graft survival, we censored the follow up at death. For 5-year mean eGFR determination, we only included patients with follow time/survival time of greater than or equal to five years.

For acute rejection, we used both the transplant forms and the follow up forms in the SRTR database to identify variables that captured acute rejection. The date the form was filed was designated as the date of acute rejection. We followed patients for acute rejection from the date of transplant to the earliest of the date of rejection, date of graft loss, date of death, or end of SRTR follow up.

We also examined the incidence of re-transplantation after primary graft loss, and evaluated the graft survival, death-censored graft survival, patient survival, and acute rejection after re-transplantation.

Statistical Analysis

We compared continuous and categorical variables among the three study eras using the Wilcoxon rank-sum test, and Chi-square or Fisher's exact test, respectively. We used log rank test to compare patient survival, graft survival, PTLD free survival, and acute rejection free survival between the study eras. We used Kaplan-Meier method to estimate 5-year post-transplant survival.

We used the Cox proportional hazard models to estimate the risk of overall graft loss (all-cause graft loss), death-censored graft loss, death, acute rejection and PTLD. We selected variables for multivariable analysis using stepwise regression. The following variables were considered for the multivariable models: age at transplant, race, gender, donor type, preemptive transplant/dialysis duration, HLA mismatch, cold-ischemia time, recipient's BMI. Immunosuppression was not included in the multivariable models because of its high correlation with the eras. We did not consider panel reactive antibody for multivariate analysis due to a large amount of missing data for the earlier eras (85.8% missing for era 1 and 43.2% missing for era 2). We used linear regression to evaluate the effect of era on eGFR at 5 years adjusting for age at transplant, gender, race, donor type, and preemptive transplant. We used logistic regression to assess the effect of era on delayed graft function adjusting for age at transplant, donor type, race, gender, and preemptive transplant. All missing values were omitted from the analyses. We performed our analyses in SAS

version 9.3 (SAS Institute, Cary NC), and considered a two-sided p value of < 0.05 as statistically significant.

Results

Between 1987 and 2017, 441 kidney transplants were performed in 362 children and young adults with cystinosis in the United States. Of the 441 transplanted kidneys, 362 were used for transplant number one, 73 for transplant number two, and 6 for transplant number three. The number of primary transplants performed in era 1, 2, and 3 were 113, 118, and 131, respectively. The number of second transplants performed in era 1, 2, and 3 were 7, 22, and 44, respectively.

The mean follow up time was 6.4 years (SD 5.0) for primary transplants, and 5.2 years (SD 4.4) for second transplants

Baseline characteristics

For primary transplant recipients, the median age at transplant was 14.1 years (range: 2.4-30.9). Fifty one percent were males and 85.1% were whites. Preemptive transplants were performed in 48.3% of recipients. For patients who received pre-transplant dialysis, the median time on dialysis was 11.4 months

(range: 0.03-247.1), and the median waitlist time was 5.6 months (range: 0.0-83.1).

For re-transplants, the median age at transplant was 23.0 years (range: 7.6-43.1). Fifty two percent were males and 84.9% were white. Preemptive transplants were performed in only 21.9% of the second transplant recipients. For those who returned to dialysis before their second transplant, the median time on dialysis was 28.1 months (range: 0.03-166.3), and the median waitlist time was 12.1 months (range: 0.06-90.7).

Primary transplants

Table 1 demonstrates temporal changes in transplant characteristics for primary transplants. We observed no difference in the age at transplant (14.3 vs. 13.6 vs. 14.3 for eras 1, 2 and 3, respectively; $p = 0.43$) and age at listing (13.5 vs. 12.0 vs. 13.0; $p = 0.14$) between eras. However, the median age at dialysis initiation (12.1 vs. 13.3 vs. 13.4 for eras 1, 2 and 3, respectively; $p = 0.04$) and median age at the onset of ESRD (12.1 vs. 13.3 vs. 13.4 for eras 1, 2 and 3, respectively; $p = 0.046$) significantly increased over time. We noticed a significant increase in the number of transplants for Hispanics in the third era (3.5% vs. 3.4% vs. 15.3% for eras 1, 2 and 3, respectively; $p<0.0001$).

We observed an increase in preemptive transplants between era 1 and 2 but noticed a significant decline in preemptive transplants ($p = 0.02$) and living donations ($p = 0.008$) in the third era. We also noticed a significant decline in the number of biologically related donors (46.0% vs. 56.8% vs. 35.9%; $p = 0.004$). Correspondingly, the median number of HLA mismatches significantly increased in the third era (3.0 vs. 3.0 vs. 4.0; $p < 0.0001$).

Table 1 also illustrates the changes in induction and maintenance immunosuppression over time. Compared with no induction, the use of induction immunosuppression (polyclonal and monoclonal induction) significantly increased over time ($p < 0.0001$). Similarly, the use of tacrolimus and mycophenolate increased compared with cyclosporine ($p < 0.0001$) and azathioprine ($p < 0.0001$), respectively.

We observed a significant reduction in the incidence of delayed graft function for primary transplants over the study period (10.7% vs. 0.85% vs. 3.8%; $p = 0.002$).

Transplant outcomes

Univariate analysis

We observed a significant temporal improvement in the mean eGFR at 5 years (47.3 vs. 57.3 vs. 62.2 ml/min/1.73m2 for eras 1, 2 and 3, respectively; $p < 0.0003$) (Figure 1).

We found no difference in 5-year overall graft survival (75.6% vs. 82.2% vs. 78.6% for eras 1, 2, and 3, respectively; $p = 0.43$), and 5-year death-censored graft survival (77.5% vs. 83.9% vs. 81.0% for eras 1, 2, and 3, respectively; $p = 0.37$) between the eras (figure 2a and b). Median overall graft survival for era 1 and 2 was 9.0 years and 13.0 years, respectively. We could not determine the median graft survival for era 3 due to inadequate follow up time.

The 5-year patient survival significantly improved over time (89.1% vs. 98.0% vs. 96.0%; $p = 0.03$) (figure 2c). For patients transplanted in era 1, 10- and 20-year patient survival were 78.3% and 59.5%, respectively. For era 2, 10- and 18-year patient survival were 94.9% and 83.9%, respectively.

Figure 3 illustrates 5-year PTLD free and acute rejection free survival. We found no difference in the PTLD free survival between the eras. However, 5-year acute rejection free survival significantly improved over the study period (35.7% vs. 65.0% vs. 78.6%; $p < 0.0001$). For patients transplanted in era 1 and 2, 10-year acute rejection free survival was 35.7% and 65.0%, respectively. The 9-year acute rejection free survival for patients transplanted in era 3 was 76.3%.

Multivariable analysis

After the multivariate adjustment, odds for delayed graft function were significantly higher for era 1 compared with era 2 (Adjusted OR (aOR) - era 2 vs. era 1: 0.09; 95% CI: 0.012-0.77; p = 0.03), and era 3 (aOR - era 3 vs. era 1: 0.37; 95% CI: 0.11-1.18; p = 0.09). Donor type also emerged as a significant predictor of delayed graft function in cystinosis patients (aOR for deceased vs. living: 6.3; 95% CI: 1.4-29.3; p = 0.02).

After adjusting for age at transplant, gender, race, donor type, and preemptive transplant, 5-year mean eGFR was significantly higher for era 2 (mean difference: 9.2 ml/min/1.73 m2; p = 0.005), and era 3 (mean difference: 12.6 ml/min/1.73 m2; p = 0.000) compared with era 1.

As illustrated in table 2, we found no association between era and overall (p = 0.3) or death-censored graft survival (p = 0.5); however, overall graft survival was significantly associated with age at transplant (p = 0.03), and race (p = 0.01). Patients younger than 10 years at transplant were less likely to lose their graft compared with patients older than 20 years (aHR: 0.43; 95% CI: 0.21-0.87; p = 0.02). Risk of graft loss was also higher in black patients compared with white (aHR: 3.0; 95% CI: 1.5-5.9; p = 0.002).

Era was a significant predictor of patient survival (p = 0.02). The risk of death was similar between era 1 and era 3, however, the risk of death for era 2 was significantly lower than era 1 (adjusted hazard ratio (aHR): 0.25; 95% CI: 0.08-

0.77; p = 0.01). Patients older than 20 years at transplant were more likely to die during the study period compared with those younger than 10 years (p = 0.003) or 10-20 (0.007) years old at transplant. Deceased donors were associated with higher mortality on univariate analysis (HR: 3.0; 95% CI: 1.3-7.0; p = 0.02), however, the association lost significance after multivariate adjustment (p = 0.08).

Compared with era 1, the risk of acute rejection was significantly lower in era 2 (aHR: 0.45; 95% CI: 0.30-0.69; p = 0.0002) and era 3 (aHR: 0.26; 95% CI: 0.16-0.42; p < 0.0001). Acute rejection was also higher in black patients compared with white (aHR: 2.9; 95% CI: 1.6-5.1; p= 0.0004), but there was no difference between Hispanic and white patients (p = 0.58).

We found no association between era and the risk of PTLD; however, the risk of PTLD was significantly higher for deceased donor recipients (aHR: 4.2; 95% CI: 1.04-17.0; p = 0.04).

Causes of graft loss and death

Table 3 outlines the causes of graft loss and death.

Causes of graft loss did not change over time (p = 0.63). Graft losses due to acute rejection decreased from 28.6% to 16.7% from 1987-1997 to 2008-2017; however, the difference was not statistically significant. Of the patients who lost

their graft, median time to graft loss was 5.5 years (range: 0.0-24.7). Fourteen patients (10.3%) lost their graft within the first year. Of these, 6 patients lost their graft to acute rejection, 2 to chronic rejection and 6 to graft thrombosis.

Causes of death did not change significantly over time ($p = 0.64$). No death was attributed to primary graft loss. Of the patients who died, median time to death after transplant was 11.4 years (range: 0.2 to 27.5). The median age at death was 26.9 years (range: 10.5-49.8).

Re-transplantation

Of the 135 patients who lost their first transplant during the study follow up period, 73 patients (54.1%) received a second transplant. Table 4 outlines the characteristics of second transplants.

Median time to retransplantation after graft loss was 13.2 months (range: 0-170.5) (mean 25.2; SD 33).

Eighteen patients (24.8%) lost their second transplant during the median follow up of 5.5 years (range: 0.0-23.3); 4 (30.8%) to acute rejection, 1 (7.7%) to infection, and 8 (61.5%) to chronic rejection. Of these 18 patients, 6 received a third transplant. The median age at third transplant was 26.5 years (range: 13.4-36.8) (mean 27.2 years, SD: 8.3). All 6 patients are currently alive with a functioning graft.

Of the patients who died after the second transplant, 1 (10.0%) succumbed to infection, 2 (20.0%) to cerebrovascular event, 1 (10.0%) to malignancy, and the remaining to miscellaneous or unknown causes. The median age at death after the second transplant was 26.8 years (range: 19.5-44.5).

Primary versus second transplant

There was no difference in gender distribution ($p = 0.88$), race (0.98), and donor type (0.84) between the first and second transplants. However, second transplants were less likely to be preemptive (21.9% vs. 48.3%; $p < 0.0001$) and were associated with a higher recipient BMI (median: 18.7 vs. 22.3; $p < 0.0001$) compared with primary transplants. Second transplants also had a higher median dialysis duration (28.1 vs. 11.5 months; $p < 0.0001$), and a higher median waitlist time (12.1 vs. 5.6 months; $p = 0.001$) compared with primary transplants. The incidence of delayed graft function was also higher for second transplants compared with the primary transplants (12.5% vs. 5.0%; $p = 0.03$).

We found no significant difference in 5-year patient survival between primary versus second transplant recipients (94.17% vs. 92.5%; $p = 0.57$). There was also no difference in 5-year graft survival (79.1% vs. 74.1%; $p = 0.52$) and 5-year death-censored graft survival between primary versus second transplants (81.3% vs. 78.9%; $p = 0.85$). The 5-year acute rejection rates were similar between primary and second transplant recipients (59.8% vs. 64.9%; $p = 0.58$).

Discussion

This is the first study that comprehensively evaluates temporal changes in kidney transplant outcomes for children and young adults with cystinosis in the United States, using the national registry of solid organ transplant recipients. The age at dialysis initiation and age at the onset of ESRD significantly increased over time for patients with cystinosis. The 5-year post-transplant graft function (mean eGFR) ($p < 0.0003$), and 5-year acute rejection rates significantly improved over the study period ($p < 0.0001$). We found no difference in overall or death-censored graft survival over the eras. However, 5-year patient survival progressively improved for children and young adults with cystinosis.

Despite the documented improvement in native renal function with cysteamine availability,[17] we found no temporal change in the age at transplant for patients in our cohort. Using data in the ESPN/ERA-EDTA registry, Van Stralen found a 0.29 years increase in transplant age per calendar year after 1996, among 185 cystinosis patients transplanted between 1979 and 2008.[18] Fewer preemptive transplants and longer waitlist times during the earlier years of our study may possibly explain the lack of change in transplant age for our cohort. Notably, preemptive transplants were performed in only 39% of patients in era 1 compared with 49-57% in eras 2 and 3. Similarly, 14% of recipients in era 1 waited more than 3 years for a kidney compared with 8-9% in later eras. Despite an unchanged median transplant age, we observed a progressive delay in

dialysis initiation and ESRD onset, indicating a progressive improvement in native kidney function for US patients with cystinosis.

HLA mismatch significantly increased for transplant recipients over time. These results reflect sequential changes in allocation algorithms. Priorities for HLA A matching and HLA B matching were eliminated in 1995 and 2003, respectively.[19,20] In 2005, the Share35, deceased donor kidney allocation policy, was implemented in the United States for recipients younger than 18 years, which eliminated HLA matching from the algorithm (except 0 mismatch).[21] Consequently, the prevalence of HLA mismatch increased in the United States during the later years of the study period. For our cohort, the significant decline in biologically related living donation in the recent era also likely contributed to the increasing HLA mismatch.

Despite the established superiority of patient and graft survival with living donation,[12,22] we observed the lowest rates of living donation in era 3. This trend is consistent with the overall recent decline in living donation for pediatric recipients. According to the OPTN/SRTR 2016 annual data report, in 2016 only 34.2% of pediatric recipients received a kidney from a living donor compared with 47.2% in 2005.[23] Amaral et al. studied 4766 pediatric patients with ESRD who were transplanted between 2001 and 2009 and found a shift from living to deceased donation with the implementation of Share35 (25 % reduction in living donor transplants for whites, 48% for Hispanics, and 46% for blacks).[24] Like us,

Amaral et al. found a progressive increase in the number of transplants for Hispanic recipients under Share35.

We documented a substantial reduction in delayed graft function for cystinosis patients despite a reduction in living donation. This finding is consistent with a general decrease in delayed graft function in pediatric recipients, likely due to the preferential assignment of higher quality (lower KDPI) kidneys to pediatric candidates. Van Arendonk et al. analyzed 17,446 pediatric kidney transplants performed in the United States between 1987 and 2012 and demonstrated a reduction in the rates of delayed graft function from 19.7% in 1987 to 5.3% in 2011.[25] We observed no difference in the median cold ischemia time across eras; however, Van Arendonk et al. found a significant improvement in cold ischemia time over the years.[25]

The 5-year graft survival for our study cohort ranged between 76-82% over the study period. Cohen et al. retrospectively studied 36 cystinosis patients from five French university centers and found 5-year graft survival to be 92% for patients transplanted between 1980 and 2013.[14] A retrospective study of 36 cystinosis patients from ANZDATA registry found 10-year graft survival to be 80.0% for cystinosis patients transplanted between 1995 and 2008.[3] Van Stralen et al. examined kidney transplant outcomes in 185 cystinosis patients using European registry data and found 5-year graft survival of 86.1% for transplants performed before 1990, 96.9% for transplants performed between 1990-1999, and 100% for

transplants performed thereafter (survival difference was not significant). Although the 5-year graft survival in our study was considerably lower than the European and Australian studies, our results were compatible with 5-year graft survival for all pediatric kidney transplants performed in the United States. Similar to our results, the retrospective analysis by Arendonk et al of 17,446 pediatric kidney transplants showed 5-year graft survival of 77.9% for transplants performed after 2006 in the United States.[25] Since the European and Australian studies were not population based, the difference in results may have been due to selection bias or transplant center effect. Furthermore, our population included races other than white, which may have contributed to our lower 5-year graft survival.

Although we observed no temporal improvements in 5-year graft survival, we found significant temporal improvements in the incidence of acute rejection and graft function (estimated GFR) at 5 years for cystinosis patients. Since acute rejection is associated with a higher incidence of late graft loss,[26] we speculate that improvements in acute rejection would translate into an improvement in graft survival once longer term data become available. Progressive improvements in 5-year mean eGFR also portend better long-term graft survival.

We observed significantly higher risks of acute rejection and graft failure for black recipients compared with white. We found no difference in outcomes between Hispanic and white recipients. Our findings are similar to outcomes of pediatric

transplantation for all causes of ESRD. A retrospective study of 6,216 pediatric kidney transplant recipients, transplanted between 2000 and 2011 in the United States, found that black recipients, but not Hispanic, were at a significantly higher risk for graft loss for both deceased and living-donor transplants. The 5-year graft survival for black patients was only 63% compared with 83% and 81% for Hispanic and white patients, respectively.[27] Chavers et al. examined trends in graft failure among pediatric kidney transplant recipients between 1980 and 2004 and found that 2 and 5-year graft failure rates declined by 53% for white but only 41% for black pediatric kidney transplant recipients over a 25-year period[28].

We found significant improvement in patient survival between era 1 and 2. Van Arendonk et al. also observed temporal improvement in 5-year patient survival in their national study of 17,446 pediatric kidney transplants for all causes of ESRD (90.2% in 1987 vs. 96.9% after 2006).[25] Australian and European cystinosis studies also reported a progressive improvement in survival; however, their findings were not statistically significant.[3,14,18] We found no difference in the causes of death or graft loss between eras. Notably, no patient death was attributed to kidney failure.

We found no change in the incidence of PTLD across eras; however, deceased donor transplant emerged as a risk factor for PTLD for cystinosis patients. Dharnidharka et al. also identified deceased donor transplants as a PTLD risk

factor in their study of 56 PTLD cases between 1987 and 1996 using the North American Pediatric Renal Transplant Cooperative Study database.[29]

We are the first group to report kidney retransplantation outcomes in patients with cystinosis. Half of the patients who lost their first graft were successfully re-transplanted. A 2014 North American Pediatric Renal Transplant Cooperative Study Registry report indicated that 7-year graft survival for primary transplants was 10-15% higher than subsequent transplants.[30] However, we found no difference in 5-year patient or graft survival between primary and second transplant recipients. Our results show that re-transplantation in cystinosis patients is safe and successful despite the progressive extra-renal complications of cystinosis.

Our study had several limitations. Firstly, our data lacked granularity and we were unable to directly evaluate the effect of cysteamine on patient and graft survival. However, our inability to attribute the improvement in kidney transplant outcomes to cysteamine does not compromise the validity of temporal changes in kidney transplant outcomes for children and young adults with cystinosis. Secondly, our study was likely underpowered to detect statistically significant differences in graft survival across eras due to the small numbers of graft loss. Thirdly, although several risk factors for graft loss and mortality were identified, we could not establish causality due to the observational nature of this study. Despite these limitations, this is an important study as it describes long-term

outcomes of kidney transplants for cystinosis in the United States. Since this is a population-based study, there is no selection bias and the results of this study are generalizable to the entire US population.

In conclusion, kidney transplant outcomes for children and young adults with cystinosis have improved over the last three decades. We found progressive improvement in 5-year post-transplant patient survival and kidney function (eGFR). The incidence of acute rejection has also significantly decreased over time. Our results indicate that kidney re-transplantation in cystinosis patients is associated with excellent outcomes and should be considered for patients who lose their first graft.

Disclaimer

Hennepin Healthcare Research Institute (HHRI), as the contractor for the SRTR, has supplied the data reported here. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

Table 1: Baseline characteristics for Primary Transplants.

Variable	Missing data	1987-1997 N= 113	1998-2007 N= 118	2008-2017 N= 131	P value
Age at transplant (years) Median (range)	-	14.3 (2.4-29.8)	13.6 (6.1-25.9)	14.3 (3.2-30.9)	0.43
Age at listing (years) Median (range)	-	13.5 (2.0-29.0)	12.0 (5.0-25.0)	13.0 (2.0-30.0)	0.14
Age at dialysis (years) Median (range)	-	10.7 (5.4-28.3)	12.0 (6.1-23.6)	12.8 (3.0-29.5)	0.04
Age at ESRD (years) Median (range)	-	12.1 (2.4-29.1)	13.3 (6.1-25.9)	13.4 (3.0-30.6)	0.046
Race	-				<0.0001

White Black Hispanic Other		99 (87.6%) 10 (8.9%) 4 (3.5%) 0 (0%)	109 (92.4%) 5 (4.2%) 4 (3.4%) 0 (0%)	100 (76.3%) 6 (4.9%) 20 (15.3%) 5 (3.8%)	
Donor type Living	-	54 (47.8%)	75 (63.6%)	59(45.0%)	0.008
Preemptive transplant	-	44 (38.9%)	67 (56.8%)	64 (48.9%)	0.02
Dialysis duration (months) Median (range)	-	11.1 (0.65- 247.1)	9.9 (1.1 – 177.1)	13.1 (0.65- 122.3)	0.84
Dialysis duration Pre-emptive transplant ≤ 1 year 1 – 3 years > 3 years	-	 44 (38.9%) 38 (33.6%)	 67 (56.8%) 27 (22.9%)	 64 (48.9%) 33 (25.2%) 24 (18.3%) 10 (7.6%)	0.07

		15 (13.3%) 16 (14.2%)	13 (11.0%) 11 (9.3%)		
cPRA 0 – 20 20-80 >80	162	16 (100%) - -	69 (100%) - -	100 (87.0%) 13 (11.3%) 2 (1.7%)	0.007*
HLA mismatch Median (range)	1	3.0 (0.0-6.0)	3.0 (0.0-6.0)	4.0(0.0-6.0)	<0.0001
Donor relation Biological	-	52 (46.0%)	67 (56.8%)	47 (35.9%)	0.004
Induction immunosuppression No induction Polyclonal** Monoclonal***	10	65 (58.0%) 34 (30.4%)	30 (26.1%) 32 (27.8%)	15 (12.0%) 55 (44.0%) 55 (44.0%)	< 0.0001

		13 (11.6%)	53 (46.1%)		
Maintenance immunosuppression Cyclosporine Tacrolimus	21	 100 (96.2%) 4 (3.9%)	 31 (26.5%) 86 (73.5%)	 1 (0.8%) 119 (99.2%)	<0.0001
Maintenance immunosuppression Azathioprine Mycophenolate Azathioprine and mycophenolate	39	 85 (84.2%) 12 (11.9%) 4 (4.0%)	 4 (3.9%) 96 (94.1%) 2 (2.0%)	 2 (1.7%) 117 (97.5%) 1 (0.8%)	< 0.0001
Cold ischemia time Mean (SD)	62	12.7 (12.1)	8.5 (8.7)	9.2 (8.7)	0.46
Donor KDPI Median (range)	41	 37 (14-90)	 33 (8-82)	 33 (11-100)	0.54

Donor Age Mean (SD)		30.8 (13.3)	34.6 (11.7)	31.8 (12.4)	0.066
Donor Gender Male N (%)	-	59 (52.2%)	54 (45.8%)	80 (61.1%)	0.052
Donor Race White Black Other	-	 103 (91.2%) 10 (8.9%) 0 (0%)	 112 (94.9%) 4 (3.4%) 2 (1.7%)	 116 (88.5%) 12 (9.2%) 3 (2.3%)	0.29
Recipient BMI Median (range)	39	18.2 (7.8- 49.2)	18.7 (12.9- 35.8)	19.1 (13.7- 37.9)	0.27
Delayed Graft Function	-	12 (10.7%)	1 (0.85%)	5 (3.8%)	0.002
Estimated GFR at 5 years Mean (SD)	era 1- 6	47.3 (17.3)	57.3 (17.9)	62.2 (25.2)	<0.0003****

	era 2- 3 era 3- 2				

Abbreviations: ESRD, end-stage renal disease

- * p value by Fisher's Exact Test
- ** Polyclonal: ALG, Atgam, thymoglobulin
- ***Monoclonal: Daclizumab, basiliximab, alemtuzumab, OKT3 (Orthoclone, muromonab)
- ****p value by Wilcoxon-rank sum test

Table 2: Kidney transplant outcomes –Multivariable analysis

Variable	Hazard Ratio (95% Confidence interval)	P value
Patient survival		
Unadjusted		
1987-1997	Ref	
1998-2007	0.21 (0.07-0.64)	0.006

2008-2017	0.36 (0.10-1.3)	0.12
Adjusted[1]		
1987-1997	Ref	
1998-2007	0.25 (0.08-0.77)	0.01
2008-2017	0.35 (0.1-1.2)	0.10
>20 years	Ref	
10-20 years	0.29 (0.12-0.72)	0.007
<10 years	0.10 (0.02-0.46)	0.003
Donor type		
Deceased	2.2 (0.91-5.2)	0.08
Graft survival		
Unadjusted	Ref	
1987-1997	0.76 (0.45-1.18)	0.22
1998-2007	0.67 (0.36-1.2)	0.19

2008-2017		
Adjusted[2]		
	Ref	
1987-1997	0.76 (0.49-1.2)	0.23
1998-2007	0.72 (0.39-1.3)	0.29
2008-2017		
	Ref	
>20 years	0.66 (0.37-1.2)	0.16
10-20 years	0.43 (0.21-0.87)	0.02
<10 years		
	Ref	
White	3.0(1.5-5.9)	0.002
Black	0.63 (0.20-2.0)	0.45
Hispanic		
Death-censored graft survival		
Unadjusted		

1987-1997	Ref	
1998-2007	0.82 (0.51-1.3)	0.39
2008-2017	0.66 (0.34-1.6)	0.22
Adjusted[3]		
1987-1997	Ref	
1998-2007	0.83 (0.52-1.3)	0.43
2008-2017	0.71 (0.37-1.4)	0.31
>20 years	Ref	
10-20 years	0.72 (0.38-1.4)	0.32
<10 years	0.51 (0.24-1.1)	0.08
White	Ref	
Black	3.4 (1.7-6.7)	0.0004
Hispanic	0.72 (0.22-2.3)	0.59
Acute Rejection		

Unadjusted		
1987-1997	Ref	
1998-2007	0.43 (0.29-0.63)	<0.0001
2008-2017	0.27 (0.17-0.41)	<0.0001
Adjusted [4]		
1987-1997	Ref	
1998-2007	0.45 (0.30-0.69)	0.0002
2008-2017	0.26 (0.16-0.42)	<0.0001
White	Ref	
Black	2.9 (1.6-5.1)	0.0004
Hispanic	0.77 (0.31-1.9)	0.58
PTLD		
Unadjusted		
1987-1997	Ref	
1998-2007	2.8 (0.51-15.4)	0.24
2008-2017	3.14 (0.50-19.7)	0.22

Adjusted [5]		
1987-1997	Ref	
1998-2007	4.0 (0.67-23.8)	0.13
2008-2017	3.3 (0.50-21.5)	0.22
Donor type		
Deceased	4.2 (1.04-17.0)	0.04

Abbreviations: PTLD, post-transplant lymphoproliferative disease

[1]Cox model constructed using the stepwise regression to identify confounding factors. Adjusted for age at transplant and donor type. Proportionality hazard assumption not violated

[2]Cox model constructed using the stepwise regression to identify confounding factors. Adjusted for age at transplant and race. Proportionality hazard assumption not violated

[3]Cox model constructed using the stepwise regression to identify confounding factors. Adjusted for age at transplant, and race. Proportionality hazard assumption not violated

[4]Cox model constructed using the stepwise regression to identify confounding factors. Adjusted for race.

[5]Cox model constructed using the stepwise regression to identify confounding factors. Adjusted for age.

Table 3: Causes of graft loss and death

Cause of Graft failure* **(number of failed grafts = 90)**	**N (%)**
Acute Rejection	19 (21.1)
Primary Failure	1 (1.1)
Infection	1 (1.1)
Surgical/Urological Complication	1 (1.1)
Graft Thrombosis	6 (6.7)
Recurrent Disease	2 (2.2)
Chronic Rejection	60 (66.7)
Cause of Death** **(number of deaths = 89)**	**N (%)**
Infection	8 (16.3)
Cardiovascular	5 (10.2)
Cerebrovascular	4 (8.7)
Malignancy	4 (8.7)
Trauma	2 (4.1)
Miscellaneous	26 (53.1)

Missing data *45, **40

Table 4: Characteristics of second transplant recipients

Variables	Cystinosis (n = 73)
Age at transplant (years) Median (range) Mean (SD)	 23.0 (7.6-43.1) 23.4 (6.6)
Gender Male	38 (52.1%)
Race White Black Hispanic Other	 64 (84.9%) 4 (5.5%) 6 (8.2%) 1 (1.4%)
Donor type Living	37 (50.7%)
Preemptive transplant	16 (21.9%)
BMI Median (range) Mean (SD) Missing 7	 21.3 (16.4-36.1) 22.3 (4.6)
cPRA	

0 – 20 20-80 >80	33 (52.4%) 13 (20.6%) 17 (27.0%)
Induction immunosuppression No induction Polyclonal Monoclonal	 11 (15.7) 40 (57.1) 19 (27.1)
Maintenance immunosuppression Cyclosporine Tacrolimus	 8 (11.8) 60 (88.2)
Maintenance immunosuppression Azathioprine Mycophenolate	 3 (4.9) 58 (95.1)
Cold ischemia time Mean (SD)	 11.1 (11.5)
KDPI	

Mean (SD) Median	0.47 (0.22) 0.47 (0.11-1.0)
Delayed Graft Function N (%)	9 (12.5)
5-year PTLD free survival	98.0%
5-year acute rejection free survival	64.9%
5-year graft survival	74.1%
5-year death-censored graft survival	78.9%
5-year patient survival	92.5%

Figure 1: Mean Estimated Glomerular Filtration Rate per Era

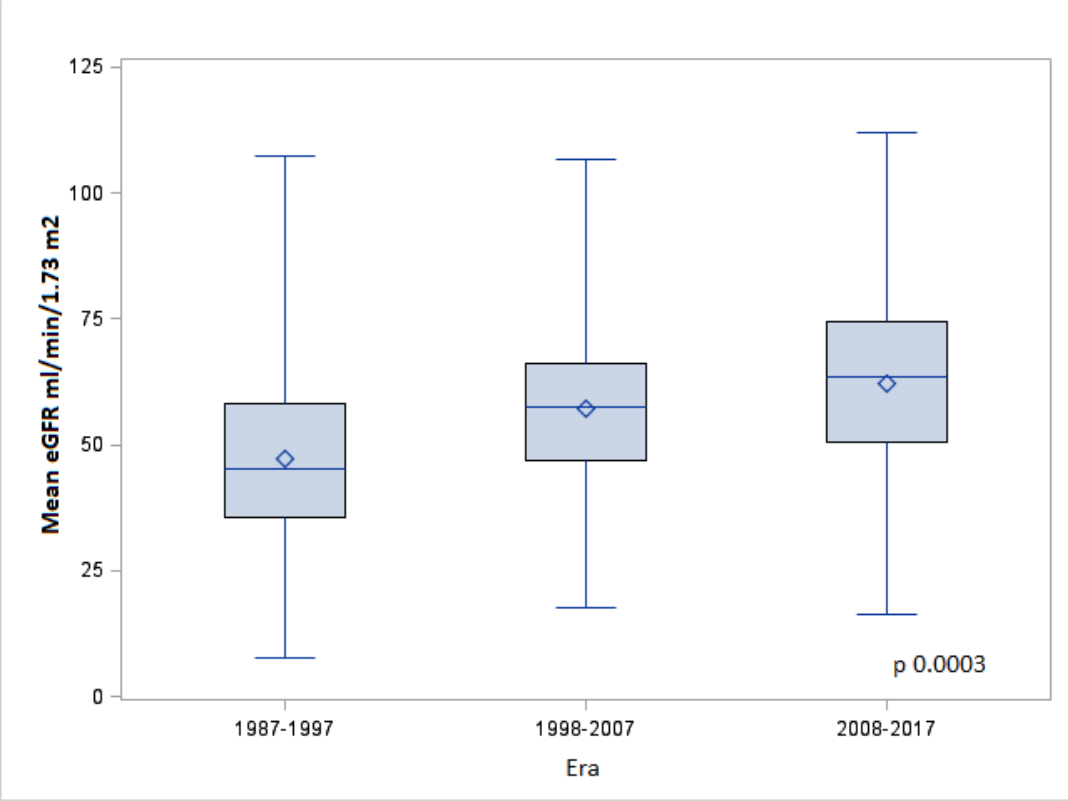


Figure 2a: Five-year Overall Graft Survival

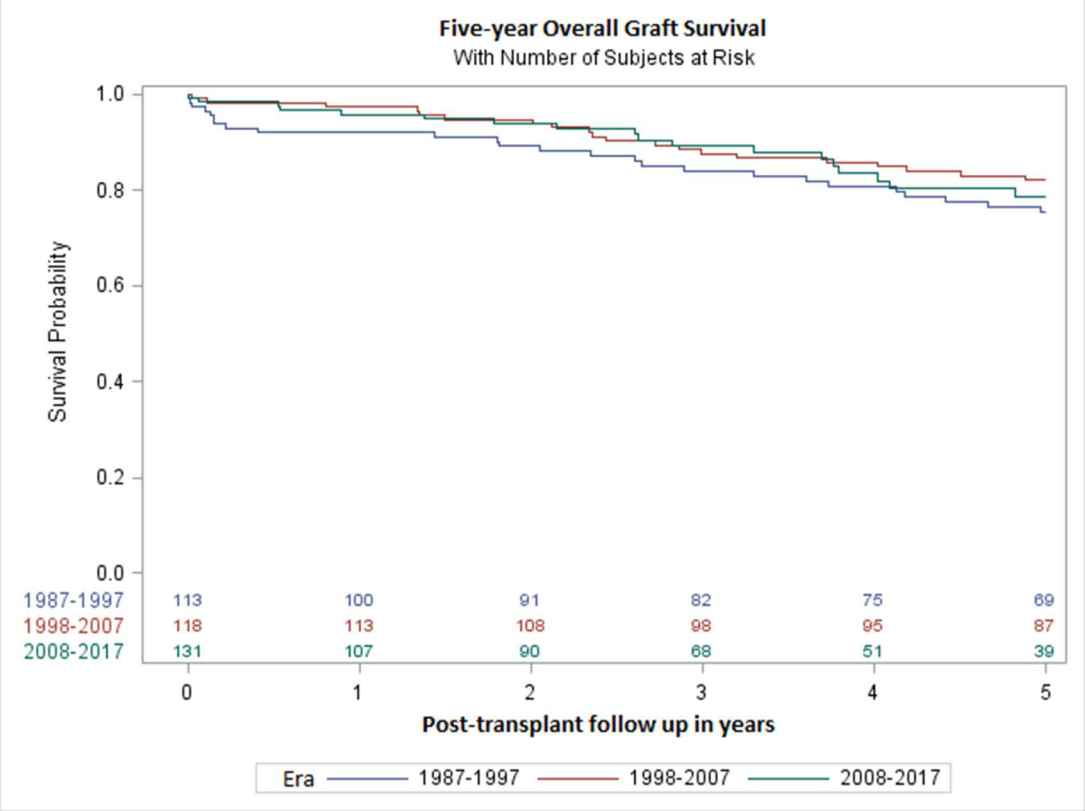


Figure 2b: Five-year Death-censored Graft Survival

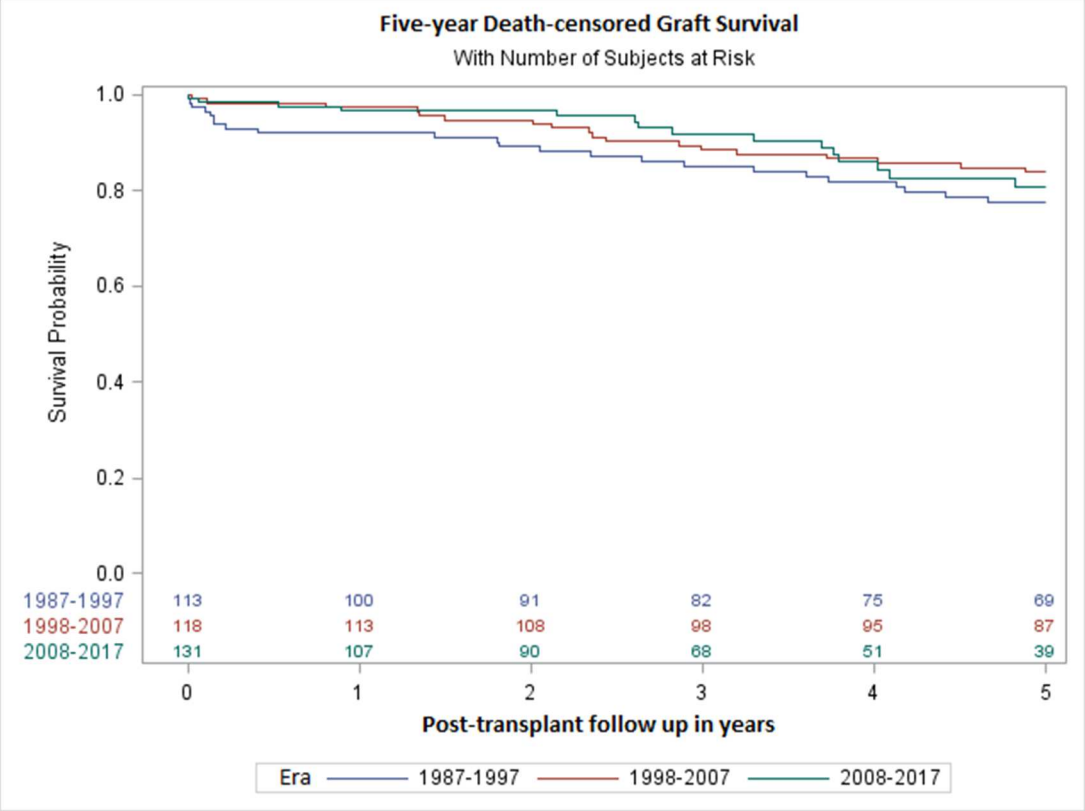


Figure 2c: Five-year Patient Survival

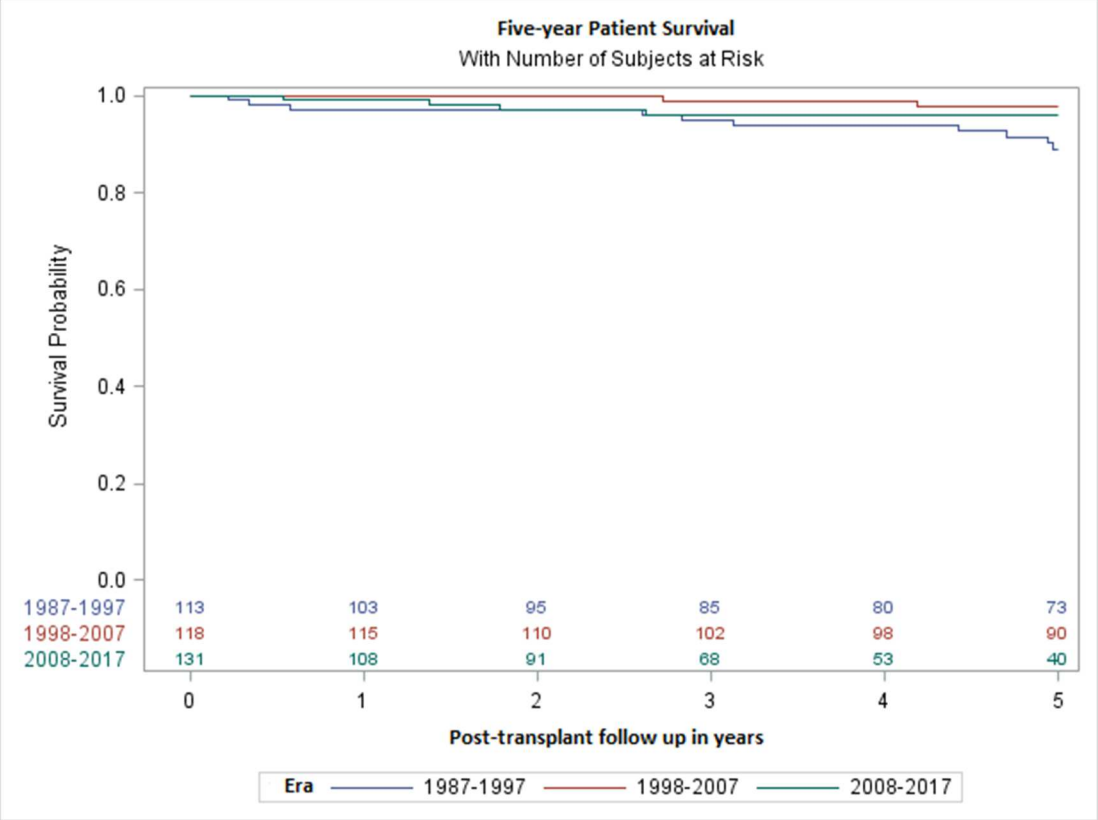


Figure 3a: Five-year PTLD free survival

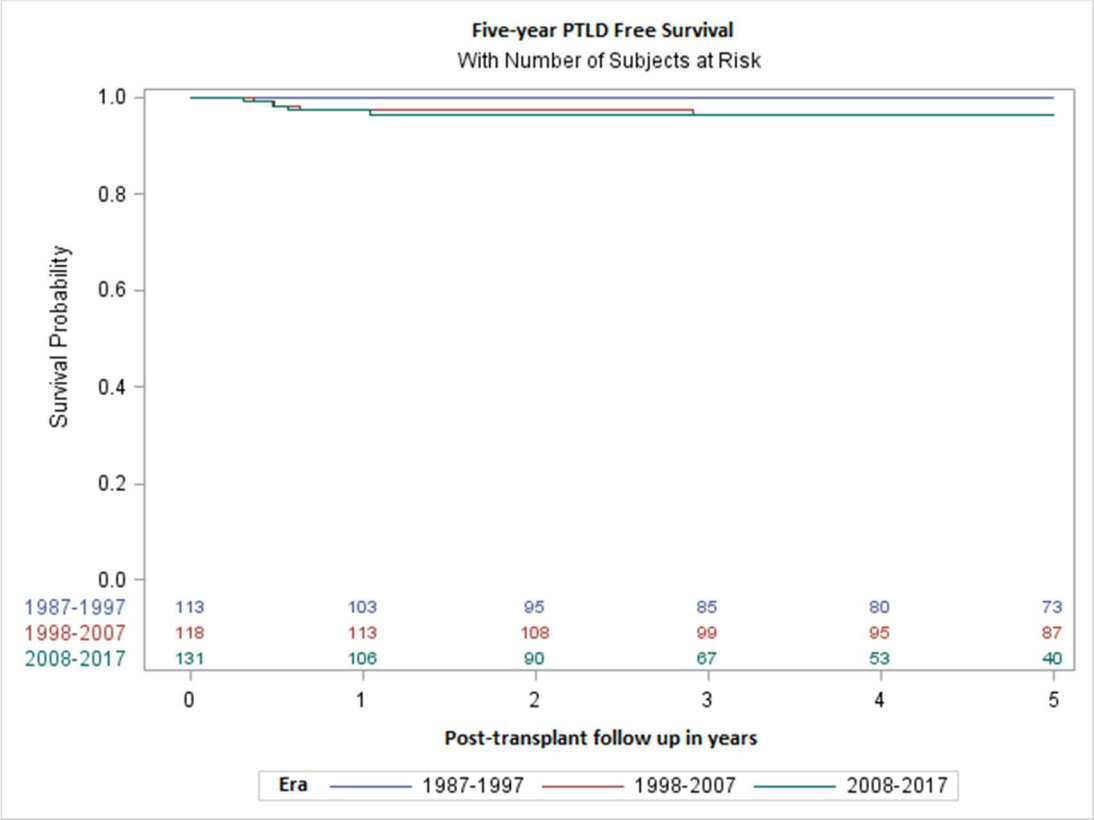
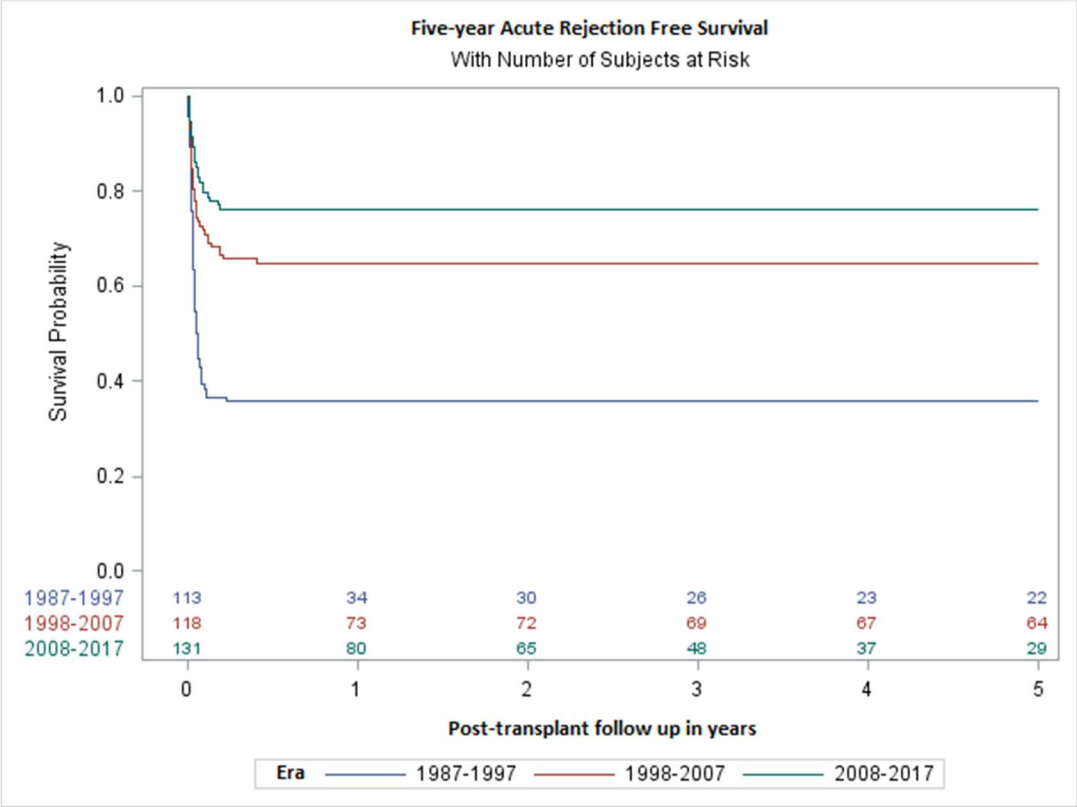


Figure 3b: Five-year Acute Rejection free survival



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