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Outcome differences between young children and adolescents undergoing kidney transplantation

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ABSTRACT

Background/Purpose: Although graft loss remains the biggest challenge for all pediatric kidney transplant (KT) recipients, unique challenges exist within different age groups. We aim to evaluate the different characteristics and graft survival outcomes of young children and adolescents undergoing KT.
Methods: Children who underwent isolated KT between 2000 and 2013 at our institution were included in this retrospective analysis. Patient characteristics and outcomes were compared using student's t-test, chi-square test, Kaplan-Meier curve and Cox proportional hazards model.
Results: Of 73 children who underwent KT, 31 were <12 (young children), and 42 were ≥12 years old (adolescents). Overall patient survival was 100%. The younger group had superior 5-year (100% vs. 75.5%) and 10-year (94.4% vs. 43.8%) graft survival ($p = 0.008$). Factors predictive of poor graft survival on multivariate analysis were older age at transplantation (HR 1.2, CI 1–1.4, $p = 0.047$), female gender (HR 9.0, CI 1.9–43, $p = 0.006$), and acute rejection episodes (HR 13, CI 2–90, $p = 0.008$). The most common causes of graft loss were acute and chronic rejection episodes and immunosuppression nonadherence.
Conclusion: Adolescents undergoing KT have inferior graft survival compared to younger children. In adjusted modeling, children with older age, female gender, and acute rejection episodes have inferior graft survival.

Kidney transplantation (KT) is the treatment of choice for children with end-stage renal disease (ESRD), as it improves growth and increases life expectancy compared to dialysis [1,2]. Significant improvements in pediatric KT outcomes have been made over the past four decades across all recipient subgroups, with approximately a 5% decrease in both risk of patient death and graft loss with each more recent year of transplantation [3]. These improvements are probably due to better immunosuppression, alloantibody detection and infectious disease prevention [4]. Despite these advances, there is still a large discrepancy between patient survival and graft survival, which results in many pediatric recipients eventually requiring retransplantation.

Multiple factors may affect patient and graft survival, including recipient and donor age, recipient race and gender, transplant and transfusion history, HLA mismatches, episodes of rejection and post-transplant complications, among others [5,6]. While the age most commonly associated with increased risk is infancy, several studies have identified lower graft survival among patients undergoing KT during adolescence and early adulthood [7–9].

A report from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) showed that graft survival rates improved steadily from 1987 to 1999 but remained relatively stable between 2000 to 2010, with the 5-year living donor (LD) graft survival of 84.3% and the 5-year deceased donor (DD) graft survival of 78% [5]. The factors that contributed to this leveling off have not been well defined. The aim of this study was to evaluate patient and graft survival in children and adolescents who underwent kidney transplantation at our institution from 2000 to 2010 with the goal of identifying causes of graft loss and risk factors for poor graft survival.

1. Methods

1.1. Study population

We performed a retrospective study of all children (≤18 years old) who underwent kidney transplantation between January 2000 and December 2013 at University Hospitals Rainbow Babies and Children's

Abbreviations: KT, kidney transplant; ESRD, end stage renal disease; HLA, human leukocyte antigen; NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies; LD, living donor; DD, deceased donor; HR, hazard ratio; CI, confidence interval; CAKUT, congenital anomalies of the kidney and urinary tract; PD, peritoneal dialysis; HD, hemodialysis; LRRT, living related renal transplant; DDRT, deceased donor renal transplant; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomeruloephritis; SRTR, Scientific Registry of Transplant Recipients.

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Hospital in Cleveland, Ohio. Patients were excluded if they had a prior or concomitant non-renal solid organ transplant. If patients had undergone a previous kidney transplant prior to 2000, data were collected with the focus on the transplant that occurred after 2000. Patients were divided into two groups based on age at kidney transplantation: young children <12 years, and adolescents ≥12 years. Age 12 was chosen to compare adolescents in middle school and high school that undergo various physiological and social changes from elementary school and younger children [10,11]. Patient demographics, operative and perioperative data, short and long-term outcomes, as well as donor demographics, relationship, and donor-recipient HLA matching data were recorded. The Institutional Review Board of University Hospitals approved the study (IRB #11-13-15).

1.2. Study outcomes

The primary outcome of interest was allograft survival, defined as the time between date of transplantation and either date of graft failure (marked by retransplantation or return to dialysis) or last date of follow-up with a functioning graft. Other outcomes of interest were length of stay, delayed graft function, causes of graft loss, disease recurrence and allograft rejection. Delayed graft function was defined as requirement for dialysis within the first week after transplantation.

1.3. Statistical analysis

Descriptive statistics were used to produce frequencies and percentages for dichotomous variables and mean with standard deviations for continuous variables. Categorical variables were compared using the Chi-square test and continuous variables were compared using independent-sample *t* test. To evaluate factors associated with allograft loss, we developed a Cox Proportional Hazards model and performed a univariate and multivariate analysis. Crude and adjusted hazards ratios (HRs) with 95% confidence interval (95 % CI) and *p* values are reported. All variables with a *p* value <0.100 on univariate analysis were included in the multivariate model. Patients who were lost to follow-up were censored at the time of last follow-up. Time to allograft loss between the two age groups was compared using the Kaplan-Meier method and the log-rank test. A *p* value ≤0.05 was considered statistically significant throughout the analysis. Statistical analysis was performed using SPSS version 21.0 (SPSS, Inc., Chicago, IL).

2. Results

2.1. Baseline characteristics of recipients and donors

Seventy-five pediatric patients ≤18 years old underwent kidney transplantation between January 2000 and December 2013. Two patients were excluded, as they had a previous or concomitant liver transplant. Of the 73 patients included (38% female, median age of 13 years at transplantation), 31 were <12 years old at KT and 42 were ≥12 years old (Table 1). Five patients had two or more KTs (one in the younger group, four in the older group). Of those, data was captured regarding the first transplant for two patients and regarding the second transplant for three patients, depending on which transplant occurred after the year 2000.

The most common cause of ESRD was congenital anomalies of the kidney and urinary tract (CAKUT), which was more common in the young children group compared to the adolescent group (67.7% vs. 40.5%, p = 0.033). Pretransplant peritoneal dialysis (PD) was more frequently performed in the young children group (72% vs. 40%, p = 0.017). Many children had received both PD and hemodialysis (HD) at different time points and 27.4% of the entire cohort underwent preemptive transplantation.

The majority of children (64%) received a live related renal transplant (LRRT), usually from one of their parents, with a trend for increased LRRT in the young children group and an increased deceased donor renal transplant (DDRT) in the adolescent group. The mean donor age was also lower in the younger group (35 vs. 40 years, p = 0.003). There were no differences in HLA mismatches between the two groups.

Table 1
Baseline characteristics of recipients and donors.

Baseline characteristics	Entire group (n = 73)	Age at KT < 12 (n = 31)	Age at KT ≥ 12 (n = 42)	p-value (<12 vs. ≥ 12)
Age at ESRD	9.7 ± 5.8	4.5 ± 3.8	13.5 ± 3.4	<0.001
Age at KT	11.7 ± 5.3	6.4 ± 3.3	15.5 ± 2	<0.001
Gender (% female)	38.4	30	45	<0.001
Weight (kg)	36.6 ± 20	19.5 ± 6.8	51.2 ± 16	<0.001
Recipient race (%)				
Caucasian	75	74	75	1
African American	16.6	16	17	1
Other	8.3	9.6	7.3	1
Diagnosis (%)				
FSGS	15.1	6.5	21.4	0.103
Other glomerular	15.1	9.7	19	0.335
CAKUT	52.1	67.7	40.5	0.033
Other/missing	17.8	16.1	19	1
Pretransplant dialysis (%)				
Hemodialysis	42.5	35.5	47.6	0.345
Peritoneal dialysis	53.4	71	40.5	0.017
Pre-emptive	27.4	25.8	28.6	1
Extraperitoneal (%)	89	77.4	97.6	0.009
Ureteral stent use (%)	69	58.6	76.2	0.128
Donor (%)				
Live related	64	74.2	57.1	0.148
Live unrelated	10.7	12.9	9.5	0.716
Deceased	24	12.9	33.3	0.057
Mean donor age	37.5 ± 7	34.8 ± 6.8	40.4 ± 6	0.003
HLA mismatches 1–3	64.2	74.1	53.8	0.158
HLA mismatches 4–6	35.8	25.9	46.2	0.158

ESRD: end stage renal disease. KT: kidney transplant. FSGS: focal segmental glomerulosclerosis. CAKUT: congenital anomalies of kidney and urinary tract. HLA: human leukocyte antigen.

2.2. Outcomes and graft survival

The mean follow-up time for the entire cohort was 6 years. The average length of stay was 8 days and did not differ significantly between the two groups. Delayed graft function occurred in 8.2% of patients and occurred more commonly in the adolescent group (Table 2). There was no difference in unplanned return to the operating room within 30 days of transplantation. Five patients (6.8%) had disease recurrence, three with focal segmental glomerulosclerosis (FSGS) within 90 days of transplantation, one with membranoproliferative glomerulonephritis (MPGN) seen on transplant nephrectomy three years post-transplantation and one with mesangial proliferative glomerulonephritis along with primary nonfunction immediately post-transplantation. Recurrent disease was evenly distributed between the two groups (Table 1).

The incidence of acute biopsy-proven rejection was 31.5% for the entire cohort and did not differ significantly between younger children and adolescents. For one third of the patients (33%), their first acute rejection episode occurred within 6 months of transplantation while 37.5% had their first acute rejection episode within 1 year of transplantation. On univariate logistic regression analysis, black race, FSGS diagnosis, male gender, post-transplant CMV infection, and increased donor age predicted acute rejection episodes, while a diagnosis of CAKUT was associated with a lower risk of acute rejection episodes. In a multivariate analysis, black race (OR 14.9, CI 2.7–83, p = 0.002) and FSGS diagnosis (OR 7.7, CI 1.5–39, p = 0.014) remained significant risk factors. On further review of the medical records, we found that 52% of patients' medical providers mentioned suspicion or patient