

# Preemptive kidney transplantation is associated with survival benefits among pediatric patients with end-stage renal disease



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**Kidney transplantation is the preferred treatment for pediatric end-stage renal disease (ESRD). Preemptive transplantation avoids the increased morbidity and mortality of dialysis. Yet, previous studies have not demonstrated significant graft or patient survival benefits for children undergoing transplantation preemptively versus nonpreemptively. These previous studies were limited by small samples sizes and low rates of adverse events. Here we compared graft failure and mortality rates using Kaplan-Meier methods and Cox regression among a large national cohort of children with ESRD undergoing preemptive versus nonpreemptive kidney transplantation between 2000 and 2012. Among 7527 pediatric kidney transplant recipients in the United States Renal Data System, 1668 underwent preemptive transplantation. Over a median 4.8 years follow-up, 1314 experienced graft failure, and over a median 5.2 years of follow-up, 334 died. Dialysis exposure versus preemptive transplantation conferred a higher risk of graft failure (hazard ratio 1.32; 95% confidence interval: 1.10–1.56) and a higher risk of death (hazard ratio 1.69; 95% confidence interval: 1.22–2.33) in multivariable analysis. Compared with children undergoing preemptive transplantation, children on dialysis for >1 year had a 52% higher risk of graft failure and those on dialysis >18 months had an 89% higher risk of death, regardless of donor source. Thus, preemptive transplantation is associated with substantial benefits in allograft and patient survival among children with ESRD, particularly when compared with children who receive dialysis for >1 year. These findings support policies to promote early access to transplantation and avoidance of dialysis for children with ESRD whenever feasible.**

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Preemptive renal transplantation, which is defined as transplantation before the initiation of dialysis, is well established as the optimal treatment for adults with end-stage renal disease (ESRD),<sup>1</sup> but the benefits of preemptive renal transplantation for children are less clear. For adults, renal transplant recipients have longer survival and improved quality of life compared with dialysis patients.<sup>2</sup> The median waiting time for transplantation for an adult on dialysis in the United States (US) is 4 to 5 years (1416–1813 days),<sup>3</sup> and a longer time on dialysis adversely affects graft and patient survival.<sup>4,5</sup> Preemptive transplantation avoids the morbidity and cost associated with dialysis as well as surgical dialysis access and its complications.<sup>6,7</sup> In contrast, children with ESRD in the US experience much shorter waiting times to transplantation, with a median waiting time of <1 year for a child 1 to 17 years of age, although wide geographic variability in pediatric waiting times has been noted, with a range of 14 to 1313 days across donor services areas.<sup>8</sup>

For children who are dependent on dialysis, there are well-documented adverse effects on cognitive function, growth, anemia, bone mineral regulation, cardiovascular disease, and overall life span compared with transplantation.<sup>9–14</sup> However, the benefits of completely circumventing dialysis for children with ESRD have not been clearly demonstrated. Several studies have demonstrated no differences in patient or graft survival between children undergoing preemptive versus nonpreemptive transplantation,<sup>15–21</sup> and there is some evidence to suggest discrepancies in the graft survival benefits of preemptive transplantations by donor source.<sup>22–24</sup> Importantly, the majority of these studies have been limited by small sample size and few events.<sup>15–24</sup> We hypothesized that, given a large national sample of children with ESRD followed over a decade, we would observe significant patient and graft survival benefits of preemptive versus nonpreemptive kidney transplantation and would be able to discern whether any differences exist across donor source.

## RESULTS

### Baseline characteristics of the overall study cohort

Among the 7527 pediatric transplant recipients included in the study population, 55.2% ( $N = 4157$ ) received a deceased donor (DD) transplant and 44.8% ( $N = 3370$ ) received a

living donor (LD) transplant (Table 1). The majority of DD and LD recipients were white non-Hispanic (49.3%), male (58.9%), and 11 to 17 years of age (59.5%). The most common causes of ESRD were congenital anomalies of the kidney and urologic tract (CAKUT) (45.7%). More than one-half of transplant recipients (54.8%) had public insurance. The mean donor age was 28.7 years, although this was significantly older in the LD recipients. More than one-half (61%) of patients underwent transplantation during the Share 35 Policy era (post September 2005); 28.4% of children with ESRD in this cohort lived in neighborhoods in which >20% of the residents in their ZIP code lived below the poverty level.

#### Baseline characteristics of pediatric transplant recipients by donor type and preemptive versus nonpreemptive

A total of 1668 (22.2%) pediatric transplant recipients received a preemptive donor transplant, of which the majority (66.2%) of transplants were LD compared with DD (33.8%) (Table 1). Of patients receiving DD transplants, 13.6% ( $N = 564$ ) underwent preemptive transplantation. Compared with the nonpreemptive DD transplant recipients, the preemptive DD transplant recipients were younger, were more likely to be white non-Hispanic and male, have a diagnosis of CAKUT, have private insurance, and live in wealthier neighborhoods. Among the children receiving LD transplants, 32.8% ( $N = 1104$ ) underwent preemptive transplantation. In the LD recipient group, patients undergoing preemptive transplantation (vs. nonpreemptive transplantation patients) were slightly older but also more likely to be white non-Hispanic and male with a diagnosis of CAKUT, with private insurance, and living in wealthier communities.

#### Characteristics associated with graft failure among preemptive versus nonpreemptive pediatric kidney transplant recipients

A total of 1314 patients (17.5%) experienced graft failure during a median follow-up of 4.8 years (interquartile range, 2.3–7.8) (Table 2). There was a lower proportion of graft failures among patients who received a preemptive versus nonpreemptive transplant (9.5% vs. 19.7%,  $P < 0.0001$ ). Results were consistent across donor type; among patients who received a preemptive DD transplant, 12.9% experienced graft failure, whereas 24% of nonpreemptive DD transplant recipients experienced graft failure ( $P < 0.0001$ ). Among patients who received any LD transplant, there were fewer graft failure events overall compared with those who received a DD transplant (11.2% vs. 22.5%,  $P < 0.0001$ ), but LD recipients who received a preemptive LD transplant still had fewer graft failures compared with those who received pretransplantation dialysis (7.7% vs. 12.9%,  $P < 0.0001$ ). In both DD and LD transplant recipients, patients experiencing graft failure were older, with the majority in the 11- to 17-year age range. Black patients made up a disproportionate percentage of LD and DD transplant recipients experiencing graft failure, representing 33.6% of all graft failures but only 17.3% of the total study

cohort. Similarly, patients with a body mass index >85% made up only 13.5% of transplant recipients but 19.4% of the transplant recipients experiencing graft failure. With regard to etiology of ESRD, graft losses in patients who did not undergo preemptive transplantation occurred more commonly in patients with glomerulonephritides, focal segmental glomerulosclerosis, or lupus. Although these diagnoses were less common among patients undergoing preemptive transplantation, a greater proportion of preemptive transplantation patients with these diagnoses experienced graft loss. Patients who lost their grafts more often had public insurance. Interestingly, number of human leukocyte antigen mismatch had no correlation with graft failure for preemptive transplant recipients, but greater numbers of human leukocyte antigen mismatches were associated with increased graft failure among patients receiving nonpreemptive transplants. Among the preemptive transplant recipients who experienced graft failure, the distribution of those living in poverty reflected the poverty distribution in the overall cohort. In contrast, among the nonpreemptive transplant recipients, graft failure was skewed toward patients living in higher poverty neighborhoods.

#### Time to graft failure

Examination of graft survival rates among DD transplant recipients indicated statistically significant benefits in graft survival for preemptive (vs. nonpreemptive) transplant recipients as early as 2 years post-transplantation (94.9% vs. 91%;  $P < 0.001$ ), a benefit that trended to greater value and significance in a linear fashion, with the most marked difference noted at 5 years (85.4% vs. 76.4%,  $P < 0.0001$ ) (Figure 1a and Table 3). In LD transplant recipients, the graft survival differences between preemptive and nonpreemptive transplantation patients were observed as early as 1 year post-transplantation (99.2% vs. 97.3%;  $P = 0.0002$ ), and, similar to DD transplant recipients, the greatest benefit of preemptive transplantation was evident at 5 years (93.8% vs. 89.2%;  $P < 0.0001$ ) (Figure 1a and Table 3).

Across the entire cohort, any dialysis exposure was associated with a 32% higher rate of graft failure (hazard ratio [HR] 1.32; 95% confidence interval [CI]: 1.10–1.56) on multivariable analysis adjusted for sex, race/ethnicity, age at time of transplantation, etiology of ESRD, panel reactive antibody (PRA), cold ischemia time, insurance status at time of transplantation, neighborhood poverty, and donor type (Table 4). When we categorized the nonpreemptive transplantation group by dialysis duration, significant graft survival benefits were observed in patients undergoing preemptive transplantation and those on dialysis for as little as 6 months. However, when stratified by donor source, the graft survival benefit of preemptive transplantation was statistically significant only compared with children who were on dialysis for >1 year. Compared with children undergoing preemptive transplantation with DD or LD transplants, children on dialysis for >12 months had a 52% higher rate of graft failure (Table 4).

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