Transplantation

The Impact of Residual Renal Function on Graft and Patient Survival Rates in Recipients of Preemptive Renal Transplants

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**Background:** Transplantation before the initiation of dialysis is associated with prolonged allograft survival. It is unclear if this benefit is attributable to greater residual renal function or to avoidance of dialysis exposure. The authors performed an analysis to determine whether higher renal function at transplant was associated with increased patient and graft survival rates. **Methods:** The authors identified individuals who between 1994 and June 2000 were ≥ 18 years and had undergone a living donor renal transplant (Tx) as initial form of renal replacement therapy. Pre-Tx and 6-month estimated glomerular filtration rates (eGFR) were calculated using the 4-variable Modification of Diet in Renal Disease formula. Survival was compared in those with a pre-Tx eGFR ≥15 mL/min to those with an eGFR less than 15 mL/min, after adjusting for demographic variables, co-morbidities, and transplant characteristics. Survival rate then was adjusted for calculated propensity scores. **Results:** A total of 4,046 patients were included. Mean pre-Tx eGFR was 9.9 mL/min (0.9 to 57.1 mL/min). There was no difference in graft survival rates by strata of eGFR in any of the tested models, even after correcting for propensity score (hazard ratio, 0.95; 95% confidence interval, 0.69 to 1.30). There was no correlation between pre-Tx eGFR and 6-month post-Tx eGFR ($r^2 = -0.005$). **Conclusion:** Recipients of preemptive transplants fair equally, regardless of the eGFR at which they receive their transplant. There was no relationship between pre-Tx eGFR and 6-month eGFR, suggesting that post-Tx renal function is independent of the level of pre-Tx renal function. These data suggest that preemptive kidney transplantation should be delayed as long as possible, provided the patient does not have uremic symptoms, and dialysis can be safely avoided. Am J Kidney Dis 42:1275-1282.

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**INDEX WORDS:** Preemptive; kidney; transplant; survival; lead-time bias.

With the increasing incidence of end-stage renal disease (ESRD), the number of individuals seeking a transplant also has increased. Over the past 10 years, there has been a doubling in the number of individuals on the cadaveric transplant waiting list.1 With this increased duration of wait, many individuals are pursuing living donor kidney transplants. An issue of great clinical importance is the timing of living donor transplantation. Studies have found that transplantation before the initiation of dialysis (preemptive) is associated with a reduced incidence of acute rejection and longer allograft and patient survival.2-7 A limitation of these studies is that the analyses may have been biased by greater residual renal function in those who received a preemptive transplant compared with those who received their transplant after initiation of dialysis. Greater residual renal function has been associated with improved survival rates in both peritoneal and hemodialysis patients.8-10 It remains unclear if the benefits of preemptive transplantation are attributable to the lack of exposure to dialysis or to the higher residual renal function at the time of transplantation. In addition, all of these studies have been observational in nature, leading to the possibility that the results reported are significantly confounded by lead time bias, in that those who initiate renal replacement therapy at a higher glomerular filtration rate (GFR) will have a prolonged graft survival compared with those undergoing a delayed transplant (lower GFR or after initiating dialysis) simply because time keeping for graft survival starts earlier.11 For example, an individual with an estimated GFR (eGFR) of 15 mL/min before transplantation would have a 2-year-greater allograft survival rate compared with an individual with an eGFR of 5 mL/min.
assuming a loss of 5 mL/min/y, and the transplanted renal function is additive to the native renal function.

Using a national cohort, we conducted a retrospective analysis to determine the impact of residual renal function on both allograft and patient survival rates in those undergoing a primary preemptive living donor kidney transplant.

**MATERIALS AND METHODS**

The study was approved by the institutional review board of the University of Minnesota. All demographic information and follow-up data were supplied by the US Renal Data System (USRDS) and collected by the United Network for Organ Sharing (UNOS).

**Study Population**

Individuals 18 years or older who reached ESRD between the years 1994 and June 2000 and who had a first kidney transplant as their initial form of renal replacement therapy (preemptive transplantation) were included. The baseline comorbidities and primary cause of kidney disease were obtained from the Medical Evidence Form 2728. The following causes of kidney disease were identified: diabetes (International Classification of Diseases-9 codes 250.00 or 250.01), glomerulonephritis (codes 582.9, 582.1, 583.1, 583.2, 583.81, 580.4, 583.4, 580.0, 582.0), hypertensive kidney disease (codes 403.9, 440.1, 583.8, 593.81), cystic kidney disease (75313, 75314, 75316, 7595, 7598, 2700, 2718, 2727, 7533, 5839, 7532, 7530, 7567, 7598), and interstitial kidney disease (codes 403.9, 440.1, 583.8, 593.81). The primary outcome measure was allograft failure as defined by the initiation of long-term dialysis, repeat transplantation, or death.

**Glomerular Filtration Rate Prediction**

The values for pretransplant creatinine were obtained from the UNOS kidney recipient registration form. If not supplied, the creatinine reported on the Medical Evidence Form 2728 was utilized. GFR was estimated (eGFR) from the 4-variable Modification of Diet in Renal Disease (MDRD) formula. The MDRD study equation has been validated previously in patients at the onset of ESRD.13

**Statistical Methods**

The level of renal function and its impact on graft survival were analyzed utilizing the National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) strata (GFR < 15 mL/min or ≥ 15 mL/min). In addition, results were analyzed using quartiles of eGFR and creatinine. In addition, we utilized a linear term for both eGFR and creatinine.

Means, standard deviations, and percentages were calculated for all baseline variables. Comparisons of continuous data were through the use of a t test. Categorical values were compared with χ² testing.

Cox regression analysis was performed to determine the effect of pretransplant eGFR strata on allograft survival and to adjust for potential confounders. Four models were constructed. In the first model only K/DOQI strata of eGFR were entered. In model 2, patient characteristics (age, sex, race, primary cause of kidney disease) were added to model 1. In model 3, transplant characteristics (year of transplant, number of human leukocyte antigen [HLA] mismatches, percent of panel reactive antibodies [%PRA]), were added to model 2. In the full model (model 4), baseline comorbidities were added to model 3 (presence or absence of the following: ischemic heart disease, peripheral vascular disease, myocardial infarction, diabetes, cancer history, heart failure). To test the robustness of our results, all analyses also were carried out using death-censored graft survival.

**Propensity Model**

We utilized logistic regression to calculate an estimated propensity score (PS) for each patient. The PS score is the estimated probability that an individual would be assigned to preemptive transplant at a high eGFR over a low eGFR and is utilized to “pseudorandomize” individuals on measured confounders.14 The following variables were included in the final propensity model: age, race, sex, primary cause of ESRD, year of transplant, %PRA, number of HLA mismatches, and comorbidities at baseline (ischemic heart disease, peripheral vascular disease, diabetes, heart failure). In addition, we utilized numerous interaction terms (diabetes and comorbidities, and age and the primary cause of ESRD). Predictive performance of the propensity model was assessed utilizing the c statistic.

Utilizing the predicted PS, an additional proportional hazard model (model 5) was constructed in which tertile of PS was added to our full model (model 4).

We performed a matched analysis in which those with a high eGFR were matched utilizing PS with a variable number (1 to 4) of controls (low eGFR). This was accomplished through a publicly available matching algorithm (optimal match). In the matched cohort, Kaplan-Meier survival curves were constructed to determine time to graft failure. The log-rank statistic was used to test for differences between groups.

In a subgroup of patients with both pretransplant eGFR and 6-month posttransplant eGFR (n = 1,750), we performed linear regression to determine if pretransplant eGFR had any impact on 6-month posttransplant eGFR. Those with missing data on creatinine or demographic factors were excluded. For those with data missing on the cause of ESRD, an indicator variable was utilized.

Reported P values are based on 2-sided tests and were considered significant with α = 0.05. All analyses were performed using the SAS system for Windows, version 8.02 (SAS Institute, Cary, NC).

**RESULTS**

From January 1994 to June 2000, 5,112 individuals over the age of 18 underwent a first preemptive kidney transplantation from a living donor. A total of 1,066 patients were excluded because of missing data. A total of
4,046 individuals subsequently were included in the analysis. Patients excluded from the analysis were significantly different from those retained in the following aspects: they were younger and more likely to be black, to be men, and to have had their transplant in 1994. In addition, they were likely to have their cause of kidney disease missing. Despite these differences, the groups were similar with respect to percentage of graft failures and time to graft failure ($P < 0.0001$; data not shown).

In those included in the final analysis ($n = 4,046$), the mean calculated eGFR at the time of transplant was $9.9 \pm 5.3$ mL/min (range, 0.9 to 57.1 mL/min). When grouped by K/DOQI eGFR strata, those who received a kidney transplant at a higher eGFR were significantly different from those with a low eGFR, based on the following factors: age, sex, and the primary cause of kidney disease (Table 1).

**Table 1. Baseline Characteristics by K/DOQI Strata**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GFR &lt; 15 (n = 3,622)</th>
<th>GFR ≥ 15 (n = 424)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>43.1 (12.3)</td>
<td>41.8 (12.3)</td>
<td>0.001</td>
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<tr>
<td>eGFR (mL/min), mean (SD)</td>
<td>8.6 (2.7)</td>
<td>21.1 (8.4)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Recipient race</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White (%)</td>
<td>84.0</td>
<td>83.7</td>
<td>0.89</td>
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<tr>
<td>Black (%)</td>
<td>11.4</td>
<td>13.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Other</td>
<td>4.6</td>
<td>2.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>46.0</td>
<td>33.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor female (%)</td>
<td>58.8</td>
<td>56.4</td>
<td>0.33</td>
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<tr>
<td>Cause of ESRD</td>
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<tr>
<td>Diabetes (%)</td>
<td>15.6</td>
<td>29.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension (%)</td>
<td>11.5</td>
<td>10.1</td>
<td>0.42</td>
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<td>Glomerulonephritis (%)</td>
<td>24.4</td>
<td>20.1</td>
<td>0.05</td>
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<tr>
<td>Missing (%)</td>
<td>22.2</td>
<td>22.6</td>
<td>0.85</td>
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<tr>
<td>Other (%)</td>
<td>46.0</td>
<td>33.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year of transplant (%)</td>
<td></td>
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<td>1994</td>
<td>9.2</td>
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<tr>
<td>1995</td>
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<td>1996</td>
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<td>20.3</td>
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<td>2000</td>
<td>7.8</td>
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<tr>
<td>Acute rejection episode (%)</td>
<td>2.7</td>
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<td>Comorbidities</td>
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<td>History of ischemic heart disease</td>
<td>2.9</td>
<td>3.8</td>
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<tr>
<td>History of myocardial infarction</td>
<td>1.2</td>
<td>1.7</td>
<td>0.48</td>
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<tr>
<td>History of peripheral vascular disease</td>
<td>1.5</td>
<td>3.5</td>
<td>0.003</td>
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<tr>
<td>History of heart failure</td>
<td>1.2</td>
<td>1.2</td>
<td>0.95</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>49.4</td>
<td>50.5</td>
<td>0.67</td>
</tr>
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</table>

**Unadjusted Outcomes**

The median duration of follow-up was 1,048 days and was significantly longer in those with an eGFR less than 15 mL/min (1,059 versus 935 days; $P = .016$). The majority of this difference is likely because those undergoing earlier preemptive transplant had later transplants compared with those with lower eGFR (median potential follow-up of 1,193 versus 1,130 days [$P = 0.008$]). Overall, there were 443 graft failures (10.9%). Of the graft failures, 111 (25.1%) were owing to death with function and did not differ by pretransplant eGFR strata.

Kaplan-Meier survival was similar by pretransplant eGFR strata, 89.0% versus 89.3% ($P = 0.87 < 15$ mL/min versus $\geq 15$ mL/min, respectively). When death was censored, there continued to be no effect of eGFR by K/DOQI strata on allograft survival (data not shown).

To determine the impact of early graft failure,
we calculated graft survival in those whose graft survived the first, second, and third years after transplantation. Again, late graft failure was similar regardless of pretransplant K/DOQI strata of eGFR (data not shown).

**Adjusted Graft Survival**

We utilized multiple models to determine the adjusted impact of pretransplant eGFR on graft survival (Table 2). In the first model, only the strata (<15 mL/min versus ≥15 mL/min) of pretransplant eGFR was utilized. Similar to the unadjusted survival, strata of pretransplant eGFR did not significantly affect graft survival. Model 2 consisted of eGFR strata with the addition of patient characteristics, and model 3 comprised model 2 with the addition of transplant characteristics. In neither of these models did pretransplant eGFR affect allograft survival. Finally, the full model (model 4) consisted of model 3 with the addition of baseline comorbidities (Table 2). In all models, the pretransplant strata of eGFR did not significantly affect allograft survival rate.

To determine the impact of pretransplant eGFR on model fit characteristics, we calculated a final model in which all variables were included except pretransplant eGFR. Model fit did not change with the exclusion of pretransplant eGFR from the final model ($\chi^2 = 0.33; P = 0.57$). The effect of eGFR strata was not changed when death was censored as an outcome (data not shown). Finally, in an attempt to assess the robustness of our results, all analyses were performed utilizing alternate measures and strata for renal function at the time of transplant. Figure 1 shows that irrespective of model, pretransplant renal function did not appear to be associated with allograft survival rate.

**Propensity Analysis**

The overall predictive power of our propensity model was fair ($c = 0.65$). Within tertiles of PS,
Baseline characteristics were similar regardless of eGFR strata (Table 3). When individuals were matched by PS, there were 414 individuals with a pretransplant eGFR \(\geq 15\) mL/min, and 1,611 with a pretransplant eGFR less than 15 mL/min. In this matched cohort, baseline characteristics were similar. Kaplan-Meier survival rate was similar irrespective of pretransplant eGFR strata (Fig 2; \(P = 0.75\)).

Our final Cox model was our full model (model 4) from above with the addition of tertiles of PS; the level of pretransplant eGFR (\(\geq 15\) mL/min compared with <15 mL/min) had no impact on graft survival (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.69 to 1.30). An interaction term between strata of eGFR and a time-dependent variable was added to the final model to test for proportionality. This variable
was not significant ($P = 0.44$). Additionally, our results did not change when follow-up time was stratified by years of follow-up.

The Impact of Pretransplant eGFR on Posttransplant eGFR

To determine the contribution of pretransplant GFR to posttransplant GFR, we constructed a linear regression model in those who had both pretransplant and 6-month creatinine recorded ($n = 1,750$). There was no correlation between the log of pretransplant eGFR and 6-month posttransplant eGFR ($6\text{-month eGFR} = 54.288 - 0.2095 \text{ pretransplant log of eGFR}$, adj. $r^2 = -0.005$; Fig 3).

**DISCUSSION**

Our results show that allograft survival is similar regardless of the level of renal function (eGFR) at the time of preemptive transplantation. Individuals who received a preemptive kidney transplant at a higher eGFR were significantly different from those who underwent a delayed transplant. However, even after adjusting for known differences at baseline through the use of proportional hazard models, PSs, and matching, a higher pretransplant eGFR offered no benefit with regard to either patient or graft survival. Our results are fairly robust, in that they are similar regardless of how renal function at the time of transplant was modeled (K/DOQI...
strata, continuous or quartiles of eGFR or creatinine). In addition, our results did not change when death was censored as an outcome. Finally, our results show that there does not appear to be any correlation between pretransplant eGFR and 6-month posttransplant eGFR. This independence of posttransplant eGFR lends further support to the notion that pretransplant eGFR does not affect allograft survival and suggests that the renal function of the graft is not additive to that of the native kidneys.

Previous studies have found that those undergoing preemptive kidney transplantation have improved allograft and patient survival rates. A limitation of studies determining the effect of preemptive transplantation on allograft survival is that they may have been influenced by increased residual renal function in those undergoing preemptive transplantation compared with those undergoing transplantation after initiating dialysis. It remains unknown if the benefit of preemptive transplantation is attributable to the lack of exposure to dialysis and dialysis access procedures, insertion of the transplanted organ into a less uremic milieu, or simply the result of lead-time bias.

Our results suggest that the previous benefits attributable to preemptive transplantation are likely the result of a lack of exposure to dialysis. The range of eGFR at which kidney transplants were performed was large, and given that the level of pretransplant eGFR did not materially affect allograft survival, it does not appear that transplantation into a more advanced uremic milieu has any negative affect on allograft survival rate.

A finding of significant surprise was our inability to show lead-time bias in those transplanted with the higher residual renal function. One would have expected that if the transplanted renal function were additive to the existing renal function, those with a higher level of renal function before transplant would have a greater duration until the onset of graft failure. To further clarify this issue, we conducted an analysis on a subgroup of individuals in which creatinine levels were measured both before transplantation and at 6 months posttransplantation. If the effect of the transplanted kidney were to be additive to the native renal function, one would have expected a significant correlation between the pre-transplant eGFR and the 6-month posttransplant eGFR. Our results show that this correlation does not exist. The lack of correlation between the 2 measures suggests that either residual renal function may be entirely lost at the time of transplantation, potentially as a result of calcineurin inhibitor therapy or renal ischemia, leaving the final eGFR entirely dependent on the transplanted kidney, or there exists renal cross talk between the transplanted kidney and those of the recipient. It has been shown previously when a third kidney is transplanted into a rat with functioning native kidneys, the transplanted kidney develops chronic interstitial inflammation and atrophy. Whereas when the native kidneys are removed before the transplant, the transplanted kidney showed compensatory hypertrophy and was capable of normal growth and function. There currently exist no studies that determine the origin of renal function in those undergoing a preemptive transplant.

There are many limitations to our study. First, a number of individuals were excluded from our analysis because of missing data (creatinine and age). These individuals were different from those included on a number of factors. However, their graft survival rate and follow-up time were not different. In addition, there were significant differences in measured factors, in included patients, when individuals were grouped by K/DOQI strata. We have attempted to adjust for these differences in a number of ways, utilizing proportional hazard models, PSs, and matching. Although these methods have minimized the effect of baseline factors, there likely exist unmeasured and unknown differences between groups that remain unadjusted, potentially influencing our results. However, given the robustness of our results, it seems unlikely that a higher eGFR before transplant provides a clinically important increase in either allograft or patient survival rate. At the time of our study our average duration of follow-up was 4 years; we cannot exclude a late benefit of a higher eGFR at the time of transplant. Additionally, our results have utilized reported, nonstandardized creatinine values to calculate eGFR. The measurement of creatinine in different laboratories has variability that may have influenced our findings. Finally, there may exist a small difference in allograft survival rate that our study was not able to show given the
number of events observed. Our study had greater than 99% power to have detected a 50% improvement in allograft survival in those with a pretransplant eGFR ≥15 mL/min. When the magnitude of benefit expected was reduced to 30%, our study only had 63% power to detect a difference.

Our results suggest that given the independence of pretransplant eGFR on both 6-month posttransplant eGFR and allograft survival, an individual should ideally wait until the development of uremic symptoms or volume overload before obtaining a living donor kidney transplantation. A policy of waiting for as long as possible, provided one does not initiate dialysis, will maximize the time to failure of the transplanted kidney. In addition, the benefits to society will be to ultimately maximize the time until a preemptive transplant recipient returns for a subsequent transplant or is in need of dialysis.

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REFERENCES


