

EFFECT OF THE USE OR NONUSE OF LONG-TERM DIALYSIS ON THE SUBSEQUENT SURVIVAL OF RENAL TRANSPLANTS FROM LIVING DONORS

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ABSTRACT

Background The effect on allograft survival of the transplantation of kidneys from living donors without the previous initiation of long-term dialysis is controversial.

Methods Using data from the U.S. Renal Data System, we performed a retrospective cohort study of 8481 patients who were or who were not treated by long-term dialysis before receiving a kidney transplant from a living donor. The relative rate of allograft failure for patients who received a transplant without previously undergoing long-term dialysis, as compared with patients who underwent long-term dialysis before transplantation, was assessed by proportional-hazards analysis, with adjustment for potential confounding variables, including the transplantation center and median household income. The association between the receipt of a kidney transplant from a living donor without previous dialysis ("preemptive" transplantation) and the risk of biopsy-confirmed acute rejection within six months after transplantation was evaluated by conditional logistic-regression analysis, with adjustment for the transplantation center.

Results Transplantation of a kidney from a living donor without previous long-term dialysis was associated with a 52 percent reduction in the risk of allograft failure during the first year after transplantation (rate ratio, 0.48; $P=0.002$), an 82 percent reduction during the second year (rate ratio, 0.18; $P=0.001$), and an 86 percent reduction during subsequent years (rate ratio, 0.14; $P=0.001$), as compared with transplantation after dialysis. The reduction in the rate of allograft failure during the first year was attenuated when adjustment was made for the timing of acute rejection within the first year (rate ratio, 0.69; 95 percent confidence interval, 0.44 to 1.10; $P=0.10$). Increasing duration of dialysis was associated with increasing odds of rejection within six months after transplantation ($P=0.001$).

Conclusions Preemptive transplantation of kidneys from living donors without the previous initiation of dialysis is associated with longer allograft survival than transplantation performed after the initiation of dialysis. (N Engl J Med 2001;344:726-31.)

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CADAVERIC kidney transplantation in eligible patients with end-stage renal disease is associated with longer survival than long-term dialysis.¹ Despite efforts to increase the frequency of renal transplantation in the United States, the inadequate pool of donor organs has limited the role of cadaveric transplantation in extending the lives of patients with end-stage renal disease.

In contrast,⁶ living donors are the fastest-growing source of renal allografts in the United States.² Factors that influence the survival of cadaveric allografts, such as delayed allograft function,³⁻⁵ occur infrequently in the case of kidney transplants from living donors, but few other issues that relate to the survival of allografts from living donors have been investigated.

The results of studies of the timing of transplantation relative to the initiation of dialysis, predominantly for cadaveric kidney transplantation, have been conflicting.^{6,7} In the largest study of the timing of transplantation of kidneys from living donors, the rate of allograft survival was approximately 10 percent higher for recipients who underwent transplantation without previously undergoing long-term dialysis than for those who underwent transplantation after long-term dialysis, but the result was not adjusted for potential confounding factors.⁸ Among adult recipients in the United States, approximately 25 percent of transplantations of kidneys from living donors are performed before the initiation of long-term dialysis.⁹ At present, the relation between prior long-term dialysis and allograft survival remains unclear. We conducted a retrospective cohort study using national data to examine the relation between prior dialysis and the survival of kidney allografts from living donors. In a secondary analysis, we investigated the effect of prior dialysis on the probability of biopsy-confirmed rejection within six months after transplantation.

METHODS

Patients

Eligible patients were 18 years of age or older, had received a first kidney transplant from a living donor in the United States between January 1994 and June 1997, and had a known date of first treatment for end-stage renal disease. Patients were followed through June 1998.

Study Design

The study design was approved by the institutional review board of the University of Pennsylvania. All demographic information and follow-up data were supplied by the U.S. Renal Data System and collected by the United Network for Organ Sharing. Data on median household incomes in 1989 as linked to residential ZIP Codes were obtained from the 1990 U.S. Census. The potential confounders considered were the age, sex, and race of

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the recipient and the donor (race was classified as white, black, or other); the relationship of the donor to the recipient (parent, child, sibling, spouse, or other); the number of HLA haplotype matches (zero, one, or two); the most recently determined serum levels of panel-reactive antibodies (0 to 100 percent); the cause of kidney disease (diabetes mellitus, hypertension, glomerulonephritis, cystic kidney disease, interstitial disease, unknown or other causes, or data missing); the use or nonuse of antibody-induction therapy; the use or nonuse of hemodialysis or peritoneal dialysis; the duration of dialysis before transplantation (in days); the average number of transplantations of kidneys from living donors performed annually at each transplantation center; and the median household income (in 1989 dollars) for the ZIP Code of the recipient's residence. The covariates considered after transplantation were the presence or absence of delayed allograft function (necessitating dialysis treatment in the first week) and the presence or absence of biopsy-confirmed rejection within 6 and 12 months, as indicated by codes from the *International Classification of Diseases, Ninth Revision* (code 996.80 for transplant rejection or 996.81 for kidney rejection and 55.23 for kidney biopsy). "Preemptive" kidney transplantation was defined as the absence of exposure to dialysis before transplantation, and "nonpreemptive" transplantation was defined as exposure to dialysis of any duration before transplantation. The primary outcome, allograft failure, was defined by the institution of long-term dialysis after transplantation, repeated transplantation, or death.

Statistical Analysis

Proportional-hazards analysis was used to investigate the effect of preemptive transplantation of kidneys from living donors on allograft function.¹⁰ The proportional-hazards assumption was tested by graphical and weighted residual analyses.¹¹ Potential confounding variables were screened in unadjusted models, and if they were associated with allograft survival ($P \leq 0.10$), they were eligible for inclusion in multivariable models used to adjust the relation between preemptive transplantation and allograft survival.¹² Multivariable models were fitted by adding covariates in a forward, stepwise manner and then removing those that did not retain statistical significance according to the Wald statistic ($P \leq 0.05$).¹² To account for potential confounding by the transplantation center, an indicator variable representing the number of preemptive transplantations of kidneys from living donors performed annually at the center was included in separate models. We accounted for the potential underestimation of the standard errors of rate ratios as a result of the nonindependence of observations within a center by using robust estimates of variance.¹³ We replaced the dichotomous variable (preemptive vs. nonpreemptive transplantation) in the models with a series of indicator variables representing the duration of dialysis before transplantation in order to explore the relation between the duration of dialysis and allograft survival.

In a secondary analysis, we explored the association between preemptive transplantation and the risk of biopsy-confirmed acute rejection during the first six months after transplantation, using conditional logistic-regression analysis adjusted for transplantation center. Potential confounding variables were included in the multivariable model according to a stepwise selection procedure in which terms that were significant at the 0.05 level were retained. To characterize further the relation between the duration of prior dialysis and acute rejection, we replaced the dichotomous variable (preemptive vs. nonpreemptive transplantation) in the multivariable model with a series of indicator variables representing the duration of dialysis before transplantation.

All analyses were performed with Stata software (version 6.0, Stata, College Station, Tex.). All reported P values are two-sided.

RESULTS

Patients' Characteristics at the Time of Transplantation

From January 1994 to June 1997, 9130 patients 18 years of age or older received kidney transplants

from living donors in the United States. Six hundred forty-nine patients were excluded because the date of first treatment for end-stage renal disease was unknown or because of prior transplantation. A total of 1819 patients underwent transplantation without prior exposure to dialysis, and 6662 patients underwent transplantation after dialysis was initiated. Five percent of the total number of eligible patients had allograft failure, the primary outcome, by the end of the study (mean [\pm SD] follow-up, 406 ± 290 days) (Table 1). Most allograft failures were defined by the initiation of long-term dialysis.

At the time of transplantation, the characteristics of the patients undergoing preemptive transplantation and those undergoing nonpreemptive transplantation were similar (Table 2). The cause of kidney disease was missing for a larger proportion of the patients who underwent preemptive transplantation than of those who underwent transplantation after receiving dialysis (43.2 percent vs. 3.0 percent), most likely as a result of differences in the administrative process by which these data were collected.

Unadjusted Allograft Survival

The proportions of all allografts surviving at one, two, and three years after transplantation were 96.3 percent, 93.4 percent, and 82.9 percent, respectively. These rates of allograft survival are consistent with those published for first renal transplants from living related donors.¹⁴ The unadjusted rates of allograft survival for patients undergoing preemptive and nonpreemptive transplantation are shown in Figure 1 ($P = 0.009$). By three years after transplantation, the patients who underwent preemptive transplantation had a rate of allograft survival of 90 percent, as compared with 81 percent for patients who underwent transplantation after the initiation of long-term dialysis. Both graphical and weighted residual analysis dem-

TABLE 1. OUTCOMES IN THE STUDY GROUPS.*

OUTCOME	PREEMPTIVE TRANSPLANTATION (N=1819)	NONPREEMPTIVE TRANSPLANTATION (N=6662)
	percent	
Delayed allograft function†	2.5	5.1
Biopsy-confirmed acute rejection within 6 mo	5.5	14.6
Allograft failure	3.8	5.8
Death	0.2	0.3
Repeated transplantation	<0.1	0.1
Long-term dialysis	3.5	5.4

*The preemptive-transplantation group had not been treated by dialysis and the nonpreemptive-transplantation group had been treated by dialysis before transplantation.

†Delayed allograft function was defined by the use of dialysis within the first week after transplantation.

TABLE 2. CHARACTERISTICS OF THE STUDY GROUPS AT THE TIME OF TRANSPLANTATION.*

CHARACTERISTIC	PREEMPTIVE TRANSPLANTATION (N=1819)	NONPREEMPTIVE TRANSPLANTATION (N=6662)
Race of recipient (%)		
White	73.8	75.6
Black	20.5	18.3
Other	5.7	6.1
Race of donor (%)		
White	86.3	79.7
Black	9.0	16.1
Other	4.7	4.3
Sex of recipient (% male)	53.4	58.8
Sex of donor (% male)	42.8	42.4
Age of recipient (yr)†	40±12	41±13
Age of donor (yr)†	40±11	8±11
Cause of native-kidney disease (%)		
Diabetes mellitus	15.0	23.5
Hypertension	4.5	15.9
Cystic kidney disease	6.1	5.2
Glomerulonephritis	21.4	35.2
Interstitial disease	6.3	7.9
Other or unknown causes	6.1	9.3
Data missing	40.6	3.0
Duration of dialysis (days)†	0	329±638
Most recently determined serum levels of panel-reactive antibodies (% positive)†	0±10.4	0±13.5
Household income in 1989 (\$)‡	30,503±11,061	31,318±12,014
Relationship of donor to recipient (%)		
Parent	24.8	25.0
Child	11.8	13.1
Sibling	52.5	51.7
Spouse	5.0	4.1
Other	5.9	6.1
No. of HLA matches (%)		
0	13.4	12.7
1	60.2	62.0
2	19.6	18.1
Data missing	6.8	7.2

*The preemptive-transplantation group had not been treated by dialysis and the nonpreemptive-transplantation group had been treated by dialysis before transplantation. Because of rounding, percentages may not total 100.

†Values are medians ±SD.

‡Values are means ±SD.

onstrated a departure from the proportional-hazards assumption.

To accommodate this pattern of change over time in the rate ratios for allograft failure, we fitted separate models for yearly intervals after transplantation. The first model included all patients, and follow-up ended at one year. The second model included patients whose allografts continued to function one year after transplantation, and follow-up ended at two years. The third model included patients whose allografts continued to function at two years after transplantation, and follow-up continued until the end of the study.

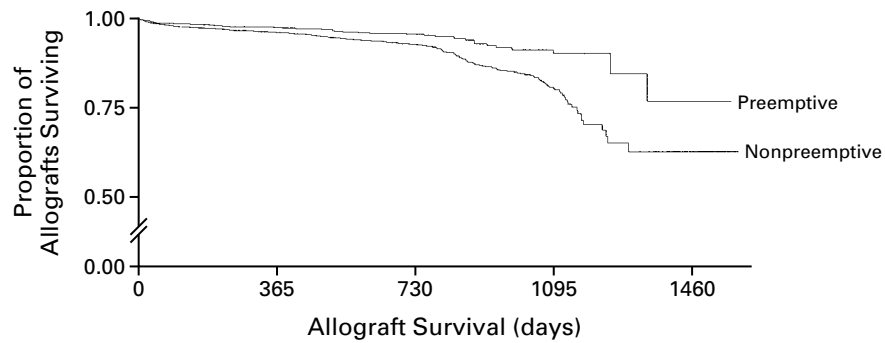
The magnitude of the unadjusted association between preemptive transplantation and the rate of allograft failure is shown in Table 3 for each of the three intervals after transplantation. Preemptive transplantation of kidneys from living donors was associated with a 34 percent reduction in the rate of allograft failure during the first year ($P=0.01$), a 44 percent reduction during the second year ($P=0.07$), and a 62 percent reduction thereafter ($P=0.002$). Other potential predictors that had significant associations with allograft survival in the unadjusted analysis are also shown in Table 3.

Adjusted Allograft Survival

Because of the changing rate of allograft survival in the two groups over time, we fitted three multivariable proportional-hazards models for yearly intervals after transplantation: the first year, the second year, and the third and subsequent years (Table 4). Acute rejection was not initially included in these models, because of the hypothesis that the effect of preemptive transplantation was mediated through acute rejection. The serum level of panel-reactive antibodies was no longer significantly associated with allograft failure after adjustment in any of these models. After adjustment for the cause of the kidney disease, the racial relationship of the donor and the recipient (both nonblack [defined as white or other], both black, or one nonblack and one black), and the presence or absence of delayed allograft function, preemptive transplantation continued to have a strong relation with allograft survival. Preemptive transplantation was associated with a reduction of 52 percent in the rate of allograft failure during the first year after transplantation ($P=0.002$), a reduction of 82 percent during the second year ($P=0.001$), and a reduction of 86 percent during subsequent years ($P=0.001$).

Inclusion of the number of preemptive transplantations of kidneys from living donors that were performed annually at each center and the median household income in each of these models did not substantially change the association between increased allograft survival and preemptive transplantation. When the series of indicator variables representing the duration of dialysis before transplantation replaced the dichotomous variable (preemptive vs. nonpreemptive transplantation), there was no detectable association between allograft survival and increasing duration of dialysis ($P=0.46$ for trend); this lack of association may be related to the inadequate power of the analysis to identify such an association, given the frequency of allograft failure.

To explore whether a decreased incidence of acute rejection is one mechanism by which preemptive transplantation improves allograft survival, we adjusted our multivariable models for the first episode of biopsy-confirmed acute rejection in the first year after transplantation. A reduction in the rate ratio for preemp-



NO. AT RISK					
Preemptive	1819	1778	1336	877	271
Nonpreemptive	6662	6430	4519	2543	786

Figure 1. Kaplan–Meier Estimates of Allograft Survival According to the Use or Nonuse of Long-Term Dialysis before Kidney Transplantation from a Living Donor.

The preemptive-transplantation group had not been treated by dialysis and the nonpreemptive-transplantation group had been treated by dialysis before transplantation. P=0.009 for the comparison between groups.

TABLE 3. UNADJUSTED RATE RATIOS FOR ALLOGRAFT FAILURE, ACCORDING TO SELECTED VARIABLES.

VARIABLE	RATE RATIO (95% CI)*	P VALUE
Preemptive transplantation (yes vs. no)		
1–365 days after transplantation	0.66 (0.48–0.92)	0.01
366–730 days after transplantation	0.56 (0.29–1.06)	0.07
730+ days after transplantation	0.38 (0.21–0.70)	0.002
Duration of dialysis before transplantation (vs. preemptive transplantation)		0.001
First quartile (1–174 days)	1.8 (1.3–2.4)	
Second quartile (175–329 days)	1.4 (1.0–2.0)	
Third quartile (330–623 days)	1.7 (1.2–2.4)	
Fourth quartile (>623 days)	2.2 (1.6–3.0)	
Cause of native-kidney disease (vs. hypertension)		0.001
Diabetes mellitus	0.60 (0.41–0.88)	
Cystic kidney disease	0.60 (0.33–1.10)	
Glomerulonephritis	0.95 (0.69–1.30)	
Interstitial disease	0.83 (0.51–1.30)	
Data missing or other causes	2.3 (1.7–3.1)	
Most recently determined serum levels of panel-reactive antibodies (>0% vs. 0%)	1.8 (1.5–2.2)	0.001
Racial relationship of donor and recipient (vs. both nonblack)		0.002
Black and nonblack†	1.7 (1.3–2.3)	
Both black	1.4 (1.1–1.8)	
Delayed allograft function (yes vs. no)	6.4 (5.1–8.1)	0.001
Acute rejection within the first year (yes vs. no)	3.7 (3.0–4.6)	0.001

*CI denotes confidence interval.

†Donor was black and recipient was not, or donor was not black and recipient was black.

TABLE 4. RESULTS OF MULTIVARIABLE PROPORTIONAL-HAZARDS ANALYSIS OF THE ASSOCIATION BETWEEN PREEMPTIVE TRANSPLANTATION AND ALLOGRAFT FAILURE.

MODEL	ADJUSTED RATE RATIO (95% CI)*	P VALUE
First year after transplantation		
Without rejection in model	0.48 (0.30–0.77)	0.002
With rejection in model†	0.69 (0.44–1.10)	0.10
Second year after transplantation		
Without rejection in model	0.18 (0.08–0.42)	0.001
With rejection in model‡	0.19 (0.08–0.44)	0.001
Subsequent years after transplantation		
Without rejection in model	0.14 (0.06–0.30)	0.001
With rejection in model‡	0.16 (0.07–0.35)	0.001

*The rate ratio is for allograft failure in the preemptive-transplantation group as compared with the nonpreemptive-transplantation group. Values have been adjusted for the cause of native kidney disease, the race of the recipient and the donor, the presence or absence of delayed allograft function, the average number of transplantations performed per year at each center, and median household income. CI denotes confidence interval.

†This was a time-dependent term for biopsy-confirmed rejection in the first year.

‡This was an indicator variable for biopsy-confirmed rejection in the first year.

tive transplantation after adjustment for acute rejection would be consistent with this mechanism. During the first year after transplantation, adjustment for acute rejection (as a time-varying covariate) attenuated the effect of preemptive transplantation (P=0.10) (Table 4). When a fixed variable indicating the occurrence of biopsy-confirmed acute rejection in the first year

was included in models for the second and third years, the effect of preemptive transplantation was essentially unchanged.

Finally, we examined the relation between preemptive transplantation and acute rejection, using conditional logistic-regression analysis with adjustment for the transplantation center (Table 5). After other predictors that had significant unadjusted associations with acute rejection were accounted for, there was a significant linear increase in the odds of rejection with an increasing duration of long-term dialysis (adjusted odds ratios, 1.6, 2.3, 3.0, and 4.2 for the first, second, third, and fourth quartiles, respectively, as compared with preemptive transplantation; $P=0.001$ for all comparisons with the preemptive-transplantation group). These observations persisted when this analysis was limited to patients who had Medicare as their primary payer.

DISCUSSION

This study of a national sample of renal-transplant recipients demonstrates that transplantation of a kidney from a living donor performed without the previous initiation of long-term dialysis is associated with a 52 percent reduction in the rate of allograft failure in the first year after transplantation and larger reductions in subsequent years, independently of the transplantation center. This association of greater allograft survival with preemptive transplantation may be mediated, in part, by a reduction in the occurrence of acute rejection.

The results of this study are consistent with previous research. In a single-center study involving 148 children, Schurman and McEnery found that preemptive transplantation of kidneys from living donors, as compared with transplantation performed after the initiation of long-term dialysis, was associated with a greater rate of allograft survival during the first year (85 percent vs. 74 percent) and with a significantly longer allograft half-life (16.9 years vs. 8.0 years).¹⁵ Donnelly et al. evaluated 11,913 patients and reported an increase of approximately 10 percent in the unadjusted rate of allograft survival among patients who received kidneys from living donors without the previous initiation of dialysis.⁸ Neither group of investigators reported multivariable analyses adjusted for potential confounding.

The attenuation of the relation between preemptive transplantation and allograft survival, after adjustment for acute rejection, suggests that the association may be mediated at least in part through an immunologic mechanism. The relation between an increased duration of dialysis before transplantation and increased odds of acute rejection by six months further supports the concept of an immunologic effect of dialysis. These findings are consistent with those of Cacciarelli et al.,¹⁶ who examined 325 recipients of cadaveric kidneys; the incidence of acute rejection

TABLE 5. RESULTS OF LOGISTIC-REGRESSION ANALYSIS OF PREDICTORS OF BIOPSY-CONFIRMED ACUTE REJECTION WITHIN SIX MONTHS AFTER PREEMPTIVE OR NONPREEMPTIVE TRANSPLANTATION.

PREDICTOR OF ACUTE REJECTION	ADJUSTED ODDS RATIO (95% CI)*	P VALUE
Duration of dialysis before transplantation (vs. preemptive transplantation)†		0.001
First quartile (1–174 days)	1.6 (1.2–2.2)	
Second quartile (175–329 days)	2.3 (1.7–3.0)	
Third quartile (330–623 days)	3.0 (2.3–3.9)	
Fourth quartile (>623 days)	4.2 (3.3–5.3)	
Race of donor and recipient (vs. both nonblack)		0.001
Black and nonblack‡	0.81 (0.60–1.1)	
Both black	1.5 (1.2–1.8)	
No. of haplotype matches (vs. 0)		0.04
1	0.81 (0.66–0.98)	
2	0.74 (0.58–0.94)	
Delayed allograft function (yes vs. no)	2.6 (2.0–3.4)	0.001

*Values were adjusted for median household income and the average number of transplantations performed per year at each center. CI denotes confidence interval.

† P for trend = 0.001.

‡The donor was black and the recipient was not, or the donor was not black and the recipient was black.

was lowest among the patients who had the shortest duration of long-term dialysis (less than six months).

The biologic plausibility of our findings is further supported by *in vitro* data on immune dysfunction among patients with chronic renal failure.^{17–20} Descamps-Latscha et al.²¹ provided evidence of a greater degree of impairment in the immune system in patients not undergoing dialysis as compared with patients undergoing long-term dialysis. Kaul et al. recently confirmed that the initiation of hemodialysis leads to a significant improvement in T-cell proliferation.²² These findings suggest that exposure to dialysis may diminish the severity of immune dysfunction and thus increase the risk of acute rejection.

There are several potential limitations to this study. First, the patients who underwent preemptive transplantation probably had a higher level of residual function of the native kidney. We were unable to examine directly the contribution of this factor to our findings. However, episodes of delayed allograft function may have been missed in the preemptive-transplantation group because the better-preserved function of the native kidney in these patients may have made dialysis unnecessary even when allograft function was markedly delayed. Nonetheless, the exclusion of delayed allograft function from the multivariable model did not appreciably modify the observed association of preemptive transplantation with improved allograft survival.

Second, the indicators of socioeconomic status were limited to race and the median household income for the ZIP Code of the recipients' residence. Although socioeconomic status may confound analyses of allograft survival, particularly in studies comparing transplantation from cadavers and living donors, our comparison groups most likely had substantial similarities, given their uniform access to a living donor. Third, notwithstanding the inclusion of recipients of kidneys from living donors only and the use of multivariable analyses to minimize confounding, we cannot exclude the possibility that patients who underwent preemptive transplantation were healthier and more compliant with therapy and that these characteristics contributed to the higher rates of allograft survival in these patients.

Finally, our study was not able to answer the policy question of whether preemptive transplantation of kidneys from living donors is a more beneficial strategy than such transplantation after the initiation of dialysis. A trial designed to address this question would randomly assign patients eligible for preemptive transplantation to either preemptive kidney transplantation from living donors or kidney transplantation from living donors after dialysis had been initiated.

In summary, using nationally representative data, we have demonstrated that preemptive transplantation of kidneys from living donors was associated with improved allograft survival. The reduction in the rate of acute allograft rejection suggests that preemptive transplantation may modulate immune mechanisms that shorten allograft survival.

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