The Role of Pretransplantation Renal Replacement Therapy Modality in Kidney Allograft and Recipient Survival

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• ***Background:*** **The effect of pretransplantation renal replacement therapy (RRT) modality on allograft and recipient survival outcome is not well understood.** ***Methods:*** **We studied allograft and recipient survival by using US Renal Data System records from January 1, 1990, to December 31, 1999, with a follow-up period through December 31, 2000 (n = 92,844; 60% males; 70% white; 23% black). Pretransplantation and predominant RRT modality during the end-stage renal disease (ESRD) period and number and specific combinations of RRT modalities were evaluated.** ***Results:*** **Compared with hemodialysis (HD), a Cox model showed that peritoneal dialysis (PD) immediately before transplantation predicts a 3% lower risk for graft failure ($P < 0.05$) and 6% lower risk for recipient death ($P < 0.001$). When predominant RRT modality was analyzed (modality used for > 50% of the ESRD time), PD (hazard ratio [HR], 0.97; $P < 0.05$) had a protective effect for graft survival compared with HD. Better recipient survival also was associated with PD (HR, 0.96; $P < 0.05$). Increased number of RRT modalities during the ESRD course was associated with increased risk for graft failure (HR, 1.04 per additional modality used; $P < 0.005$) and recipient death (HR, 1.11 per additional modality used; $P < 0.001$). Any combination or any single modality (except for PD + HD for graft survival and PD + HD and PD + HD + transplantation for recipient survival) had protective effects on graft and recipient survival compared with HD.** ***Conclusion:*** **Our results suggest that compared with PD, HD as an RRT modality immediately before transplantation or as a predominant RRT modality during the ESRD course, used alone or in combination with other RRT modalities, is associated with increased risks for graft failure and recipient death. Increased number of RRT modalities used during the ESRD course is associated with worsening of graft and recipient survival.** ***Am J Kidney Dis*** **46:537-549.**

INDEX WORDS: Kidney transplant; outcome; hemodialysis (HD); peritoneal dialysis (PD); graft failure; prediction.

ALTHOUGH KIDNEY transplantation improves survival in transplant recipients compared with patients with end-stage renal disease (ESRD) remaining on the waiting list,[1] loss of the allograft terminates the patient survival benefit.[2] Recent improvement in immunosuppression has reduced the incidence of acute rejection, but the effect on chronic allograft nephropathy and late graft loss has not been well shown in the literature.[3]

Predictive factors of graft survival have been studied extensively in adults[4,5] and children[6,7] based on data from the United Network for Organ Sharing and North American Pediatric Renal Transplant Cooperative Study.

Donor and recipient age,[8] preexisting donor hypertension and diabetes,[9] non–heart-beating donor,[10] prolonged cold storage time,[11] retransplantation,[12] multiple blood transfusions,[13] and body mass index of donor and recipient,[14] along with other factors, have important roles in graft outcome. However, the ESRD course itself (eg, the modality of renal replacement therapy [RRT], alone or in combination) as a predictor of graft and patient outcomes has not been well studied. Several studies suggested that pretransplantation dialysis modality had an impact on patient outcome.[15-18] However, some reports did not show that long-term graft survival was affected by the modality of dialysis treatment.[19,20] What is established is that increased time on dialysis therapy is associated with decreased survival of transplant recipients.[20]

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The goal of the present project is to perform a retrospective analysis of US Renal Data System (USRDS) records to evaluate the role of renal replacement modalities, number of modalities used, and their combinations in allograft and recipient survival.

METHODS

Data Set

Using the USRDS database, we collected data for all kidney allograft recipients (both pediatric and adults) who underwent kidney or kidney-pancreas transplantation from January 1, 1990, through December 31, 1999. Follow-up data were collected through December 31, 2000.

For recipients of multiple transplants, the most recent one was considered the target transplantation (transplant of interest). Patient records with missing information regarding graft or patient survival were excluded from the study. A total of 92,844 patients with a kidney transplant were identified. Records of patients with prior kidney transplants (n = 11,714) also were identified and analyzed separately.

Outcome

There are 2 outcomes in this study. The first outcome is time between the most recent kidney transplantation and failure of the graft. The second outcome is time between the most recent kidney transplantation and patient death. Both outcomes were modeled by using continuous survival time variables.

The graft failure definition did not include patient death with a functioning graft, the latter determined in the USRDS as a single binary variable. In case the value of this variable was missing and the patient's death date was equal to the graft failure date, we assumed the patient died with a functioning graft unless the cause of death was coded as one of the following: 3200 (graft failure: primary failure), 3201 (graft failure: rejection), 3202 (graft failure: technical), 3299 (graft failure: other), or 3903 (miscellaneous: renal failure).

Allograft outcome was censored at the earliest of the following events: loss to follow-up, patient death, or study completion date (December 31, 2000) and analyzed as days to graft failure or censor. Patient follow-up was censored at the earliest of loss to follow-up or study completion date and analyzed as day to recipient death or censor.

Independent Variables

The primary variables of interest were those pertinent to RRT from the USRDS database: RRT modality immediately before the current transplantation, predominant RRT modality during the ESRD course (defined as modality used for >50% of the ESRD period; if none of the modalities were used for >50%, the predominant modality was labeled "none"), number of different RRTs used, combination of RRT modalities used (eg, peritoneal dialysis [PD] and hemodialysis [HD] and transplantation), and time course during the pretransplantation period that the patient was treated with a specific RRT modality. We defined the use of a specific dialysis modality by using the "60-day rule," the convention adopted by the USRDS stating that a dialysis modality must continue for at least 60 days to be considered stable and therefore constitute a change in modality.

The final decision about which covariates to include into final models was based primarily on known associations between variables that could cause confounding of the primary variables of interest; therefore, even variables with no significant association with the outcome that were not selected by the stepwise regression, but were deemed to be clinically significant or represent potential confounding, were included in the final model. Results of the stepwise analysis were used only as a supportive tool. Covariates included a recipient comorbidity score that used cardiovascular disease, symptomatic peripheral vascular disease, diabetes mellitus, and hypertension (similar to the Davis comorbidity index,[21] but limited to the comorbid conditions listed that were collected at the time of transplantation); recipient variables (age, sex, race, height, weight, history of hypertension, diabetes, history of prior transplant, total duration of ESRD, total number of transplants, panel reactive antibody levels [mean and peak], education level, primary source of renal care payment, and citizenship); donor variables (heartbeating donor or not, age, sex, race, height, weight, number of matched HLA antigens, and citizenship); and transplantation procedure variables (day of the week for the procedure, season and year of the transplantation, and cold storage time).

Other variables, delayed graft function, episodes of acute rejection, and type of immunosuppressive medications were not included in the models. Delayed graft function and acute rejection may represent intermediate outcome, rather than the confounding factor, and therefore we speculated that adjusting for it might yield false-negative results (type 2 error: failure to reject null hypothesis).

Patients with a prior history of kidney transplantation were analyzed separately and the following variables were added to the analysis: donor type for the transplantation immediately before the current transplantation, age at first transplantation, age at first graft failure, age at transplantation immediately before the current transplantation and at graft failure immediately before the current transplantation, and time between last transplant failure and current transplantation. To reduce lead time bias, the models also were adjusted for total duration of ESRD.

Statistical Analysis

Categorical variables in the subgroups were compared by using cross-tabulation. Continuous variables were summarized by using means and SDs. Kaplan-Meier graphs and Cox regression models were used for survival analysis. To avoid collinearity between the primary variables of interest, we analyzed them in separate Cox models. SAS (SAS Institute, Cary, NC) was used for survival analysis (Kaplan-Meier and Cox proportional hazards models), whereas S-Plus (Insightful, Seattle, WA) was used for descriptive statistics and tree-based modeling for data imputation.

RESULTS

Baseline Characteristics

The data set consisted of 92,844 records of patients receiving kidney or kidney-pancreas transplants starting January 1, 1990, and through December 31, 1999. Study population characteristics are listed in Table 1. Average age was 43.3 years, and 60% were male. The graft failed during the 11 years of the study period in 34.9% of patients. We compared some baseline characteristics in patients on HD and PD therapy as a predominant pretransplantation modality. Average ages were 44.8 ± 13.7 years in HD patients and 41.1 ± 15.1 years in PD patients ($P < 0.001$), comorbidity scores were 0.86 ± 0.81 in HD patients and 0.82 ± 0.78 years in PD patients ($P < 0.001$), pretransplantation durations of ESRD were 2.63 ± 2.86 years in HD patients and 2.11 ± 1.96 years in PD patients ($P < 0.001$), total numbers of transplants before the current one were 1.08 ± 0.31 in HD patients and 1.05 ± 0.25 in PD patients ($P < 0.001$), and peak and mean panel reactive antibody levels were 12.01 ± 21.89 and 5.15 ± 14.83 for HD patients and 9.93 ± 19.47 and 4.15 ± 12.98 for PD patients, respectively ($P < 0.001$ for both). Numbers of matched HLA antibodies between recipient and donor were 1.80 ± 1.52 in HD patients and 1.84 ± 1.54 in PD patients ($P < 0.001$). Finally, donor ages were 34.72 ± 15.64 years in HD patients and 33.81 ± 15.41 years in PD patients ($P < 0.001$).

RRT Modality Immediately Before Transplantation

The Cox model using HD as a reference showed the following results. Having a transplant immediately before the transplantation of interest without dialysis therapy in between was associated with increased risk for graft failure (hazard ratio [HR], 1.65; $P < 0.001$). PD as a modality immediately before transplantation predicts better graft outcome compared with HD (HR, 0.97; $P < 0.05$; Table 2). A similar association was found in the subgroup of patients with a previous history of kidney transplantation: having the transplantation as an RRT modality before the last transplantation without going on dialysis therapy in between poses a greater risk for graft failure (HR, 1.99; $P < 0.001$) in this subgroup of patients (Table 3). The protective effect of PD therapy is not significant in this patient subgroup.

In the analysis of recipient survival in the Cox model using HD as a reference, both prior transplantation (HR, 0.80; $P < 0.005$) and PD (HR, 0.94; $P < 0.001$) had a protective effect on recipient survival compared with HD. This association was confirmed again in the subgroup of patients who had prior transplants, although the difference between PD and reference (HD) patients was not statistically significant (Table 3).

Predominant RRT Modality

Predominant RRT modality, defined as RRT modality used for more than 50% of the entire ESRD period, was analyzed in a Cox model in relation to graft survival; both PD (HR, 0.97; $P < 0.05$) and transplantation (HR, 0.86; $P < 0.001$) had a protective effect for graft survival compared with HD. Absence of the predominant modality (each modality was used for < 50% of the duration of ESRD or no RRT was used) also was associated with lower risk for graft failure (HR, 0.90; $P < 0.001$; Table 2). These results were illustrated by Kaplan-Meier plots (Fig 1A). In the Cox model, better recipient survival also was associated with both PD (HR, 0.96; $P < 0.05$) and transplantation (HR, 0.82; $P < 0.001$) as predominant pretransplantation RRT modalities. Patients who had no predominant modality during the ESRD course also had better survival compared with HD, although the difference was not statistically significant (HR, 0.921; $P = 0.063$). The worst patient outcome associated with HD is illustrated by Kaplan-Meier plots (Fig 1B). The same trends for graft and recipient survival were found in the subgroup of patients with prior transplants (Table 3).

Number of Different Modalities Used

We calculated the number of different RRT modalities that a patient was exposed to during the ESRD course by using the 60-day rule, in which the change in dialysis technique is considered stable if the patient remained on a new modality for 60 or more days (the 60-day rule does not apply to transplantation). We analyzed the Cox model and showed that number of RRT modalities is a significant predictor of graft failure (HR, 1.04 per additional modality; $P < 0.001$) and recipient death (HR, 1.11 per

Table 1. Baseline Characteristics of Kidney Transplant Recipients at the Time of the Most Recent Transplantation

Recipient characteristics	
Age (y)	43.3 ± 14.2
Sex (% men)	60.3
Race (white/African American/Asian/Native American; %)	70.2/23.0/3.4/0.9
Weight (kg)	72.6 ± 17.2
Height (cm)	169.0 ± 13.7
Primary cause of ESRD (%)	
Diabetes mellitus	25.2
Hypertension	17.2
Glomerulonephritis	25.8
Cystic disease	7.6
Other	24.2
Comorbidity score*	0.8 ± 0.8
History of diabetes (%)	27.2
History of hypertension (%)	52.5
Total duration of ESRD (y)	3.1±3.6
Percent of ESRD time on PD†	22.8 ± 38.0
Percent of ESRD time on HD†	67.3 ± 41.5
Percent of total ESRD duration with transplant†	6.1 ± 20.1
RRT modality immediately before transplantation (%)	
HD	71.3
PD	21.8
Transplantation (dialysis-free retransplantation)	1.1
Unknown	5.8
Predominant RRT modality‡ (%)	
HD	67.3
PD	22.6
Transplantation	6.4
None	3.6
Total no. of transplants (including the current one)	1.2 ± 0.4
Time on the transplant list (y)	1.3 ± 1.1
Peak reactive antibody level (%)	12.1 ± 21.5
Mean reactive antibody level (%)	5.3 ± 14.7
No. of matched HLA antibodies	1.8 ± 1.5
Cold ischemia time (h)	15.5 ± 8.7
Transplant day of the week§	4.0 ± 1.8
History of previous kidney transplant(s) (%)	12.6
Donor characteristics	
Age (y)	34.4 ± 15.5
Sex (% men)	56.2
Race (white/African American/Asian/Native American; %)	82.5/11.5/1.3/0.4
Weight (kg)	72.8 ± 19.0
Height (cm)	164.3 ± 21.9
Terminal serum creatinine level (mg/dL)	0.9 ± 0.3
Terminal blood urea nitrogen level (mg/dL)	12.1 ± 6.1
Living donors (%)	24.8

NOTE. N = 92,844. Continuous variables presented as mean ± SD. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; urea nitrogen in mg/dL to mmol/L, multiply by 0.357.

*The comorbidity score used in our study was calculated based on the following coexisting conditions, each contributing 1 point: cardiovascular disease (defined in the USRDS as symptomatic cardiovascular disease or angina/coronary artery disease), symptomatic peripheral vascular disease, diabetes mellitus, and hypertension.

†Information obtained from USRDS RXHIST file; because of missing/unknown data and the 60-day rule convention adopted by the USRDS (see text), the total is less than 100%.

‡Defined as modality used for greater than 50% of the duration of ESRD.

§Transplant day of the week expressed in numbers starting with Sunday (1 = Sunday, 2 = Monday, etc).

Table 2. Results of Cox Proportional Hazard Model Analyzing Allograft and Patient Survival in the Entire Patient Population

	Graft Survival			Recipient Survival		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
RRT modality immediately before current transplantation*						
PD	0.97	0.94-1	<0.05	0.94	0.91-0.97	<0.001
Transplantation	1.65	1.51-1.8	<0.001	0.8	0.68-0.93	<0.005
Unknown	0.92	0.85-1	<0.05	0.87	0.77-0.97	<0.05
Lost to follow-up	1.07	1-1.15	0.069	0.9	0.81-0.99	<0.05
Predominant RRT modality*						
PD	0.97	0.94-1	<0.05	0.96	0.92-0.99	<0.05
Transplantation	0.86	0.81-0.9	<0.001	0.82	0.76-0.89	<0.001
None	0.9	0.84-0.95	<0.001	0.92	0.85-1	0.063
Time spent on HD (y)	1.02	1.01-1.02	<0.001	1.05	1.04-1.05	<0.001
>0-1	1.05	1.01-1.09	<0.05	1.18	1.12-1.24	<0.001
>1-3	1.18	1.13-1.23	<0.001	1.42	1.34-1.5	<0.001
>3-10	1.18	1.12-1.23	<0.001	1.59	1.5-1.7	<0.001
>10-33	1.27	1.16-1.39	<0.001	1.77	1.57-2	<0.001
Time spent on PD (y)	1.02	1.01-1.03	<0.005	1.04	1.03-1.06	<0.001
>0-1	1.04	1.01-1.08	<0.05	1.12	1.07-1.17	<0.001
>1-3	1.08	1.04-1.12	<0.001	1.21	1.16-1.27	<0.001
>3-10	1.13	1.06-1.2	<0.001	1.33	1.23-1.44	<0.001
>10-33	1.28	0.99-1.64	0.057	1.43	1-2.04	0.053
Time spent with prior transplant (y)	0.98	0.97-0.99	<0.001	1	0.99-1.01	0.525
>0-1	0.84	0.78-0.9	<0.001	1.06	0.95-1.19	0.319
>1-3	0.82	0.75-0.9	<0.001	1.08	0.94-1.23	0.291
>3-10	0.72	0.67-0.78	<0.001	1.08	0.95-1.22	0.24
>10-33	0.67	0.6-0.75	<0.001	1.12	0.94-1.33	0.217
No. of different RRT modalities†	1.04	1.02-1.07	<0.005	1.11	1.08-1.15	<0.001
Combinations of RRT modalities*						
PD only	0.93	0.9-0.96	<0.001	0.9	0.86-0.94	<0.001
PD + transplantation	0.87	0.78-0.97	<0.05	0.98	0.83-1.17	0.86
PD + HD	1.09	1.05-1.12	<0.001	1.1	1.06-1.15	<0.001
HD + transplantation	0.74	0.69-0.8	<0.001	0.96	0.86-1.08	0.508
Transplantation only	0.94	0.85-1.05	0.269	0.89	0.75-1.06	0.196
PD + HD + transplantation	0.73	0.67-0.8	<0.001	1.11	0.98-1.27	0.106
None	0.75	0.69-0.81	<0.001	0.81	0.73-0.89	<0.001

NOTE. The Cox model represents multivariate analysis of graft and recipient survival. To avoid colinearity between the primary variables of interest, they were analyzed in separate Cox models. Only primary variables of interest are listed in the table. All models also were adjusted for the following covariates: recipient variables: age, sex, race, height, weight, history of hypertension, diabetes, comorbidity score, history of prior transplant, total duration of ESRD, total number of transplants, panel reactive antibody levels (mean and peak), education level, primary source of renal care payment, and citizenship; donor variables: heart-beating donor or not, age, sex, race, height, weight, number of matched HLA antigens, and citizenship; and transplant procedure variables: day of the week for the procedure, season and year of the transplantation, and cold storage time.

*HD is a reference.

†The 60-day rule is applied.

additional modality; $P < 0.001$; Table 2). In the separate model in the subgroup of patients with prior transplants, number of modalities was not a significant risk for graft failure, whereas it was for recipient death (HR, 1.09; $P < 0.005$; Table 3). These associations are shown by Kaplan-Meier plots: increased number of modalities is associated with worsening of graft survival (Fig 2A), and best graft survival is associated with 0 pretransplantation

Table 3. Results of Cox Proportional Hazard Model Analyzing Allograft and Patient Survival in the Subgroup of Patients With a Prior History of Kidney Transplantation

	Graft Survival			Recipient Survival		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
RRT modality before transplantation*						
PD	0.94	0.86-1.03	0.179	0.97	0.86-1.09	0.603
Transplantation	1.99	1.8-2.21	<0.001	0.74	0.62-0.9	<0.005
Unknown	0.89	0.81-0.98	<0.05	0.79	0.68-0.91	<0.005
Lost to follow-up	0.96	0.75-1.23	0.729	1.05	0.74-1.49	0.772
Predominant RRT modality*						
PD	0.87	0.77-0.97	<0.05	0.92	0.78-1.08	0.285
Transplantation	0.86	0.8-0.92	<0.001	0.8	0.73-0.89	<0.001
None	0.82	0.75-0.9	<0.001	0.84	0.74-0.96	<0.05
Time spent on HD (y)	1.02	1.01-1.03	<0.001	1.04	1.03-1.06	<0.001
>0-1	0.88	0.8-0.98	<0.05	1.18	1-1.39	0.053
>1-3	0.94	0.85-1.04	0.217	1.36	1.15-1.6	<0.001
>3-10	0.96	0.87-1.07	0.479	1.54	1.3-1.82	<0.001
>10-33	1.15	0.98-1.35	0.087	1.83	1.45-2.3	<0.001
Time spent on PD (y)	1.01	0.99-1.03	0.299	1.05	1.02-1.08	<0.005
>0-1	1.02	0.94-1.1	0.716	1.13	1.01-1.27	<0.05
>1-3	0.99	0.91-1.08	0.823	1.24	1.09-1.4	<0.001
>3-10	1.05	0.93-1.18	0.48	1.29	1.09-1.54	<0.005
>10-33	1.13	0.75-1.72	0.555	1.02	0.51-2.06	0.957
Time spent with prior transplant (y)	0.99	0.98-0.99	<0.001	1	0.99-1.01	0.768
>0-1	0.89	0.77-1.02	0.092	0.8	0.66-0.96	<0.05
>1-3	0.9	0.77-1.05	0.176	0.81	0.66-1	<0.05
>3-10	0.8	0.69-0.93	<0.005	0.81	0.67-0.99	<0.05
>10-33	0.74	0.63-0.88	<0.001	0.82	0.64-1.04	0.104
No. of different RRT modalities†	0.99	0.95-1.04	0.688	1.09	1.02-1.16	<0.05
Combinations of RRT modalities*						
PD only	0.6	0.38-0.95	<0.05	0.73	0.42-1.3	0.289
PD + transplantation	0.84	0.7-1.01	0.07	0.73	0.56-0.94	<0.05
PD + HD	1.12	0.84-1.49	0.446	0.94	0.65-1.36	0.724
HD + transplantation	0.79	0.68-0.93	<0.005	0.74	0.6-0.91	<0.005
Transplantation only	0.86	0.71-1.03	0.098	0.62	0.48-0.8	<0.001
PD + HD + transplantation	0.79	0.67-0.93	<0.005	0.86	0.69-1.06	0.16
None	0.92	0.4-2.08	0.838	1.1	0.41-2.99	0.85

NOTE. The Cox model represents multivariate analysis of graft and recipient survival. To avoid colinearity between the primary variables of interest, they were analyzed in separate Cox models. Only primary variables of interest are listed in the table. All models also were adjusted for the following covariates: recipient variables: age, sex, race, height, weight, history of hypertension, diabetes, comorbidity score, total duration of ESRD, total number of transplants, panel reactive antibody levels (mean and peak), education level, primary source of renal care payment, and citizenship; donor variables: heart-beating donor or not, age, sex, race, height, weight, number of matched HLA antigens, and citizenship; transplant procedure variables: day of the week for the procedure, season and year of the transplantation, and cold storage time; parameters of prior transplant(s): donor type for the transplant immediately before the current transplant, age at first transplantation, age at first graft failure, age at transplantation immediately before the current transplantation and at graft failure immediately before the current transplantation, and time between last transplant failure and current transplantation.

*HD is a reference.

†The 60-day rule is applied.

RRT modality. Similarly, 0 modality used before transplantation was associated with the best recipient survival, but increased number of modalities greater than 1 does not affect recipient survival (Fig 2B).

Combination of Different RRT Modalities

We considered 8 different combinations of RRT modalities during the ESRD course independent of the sequence and number of times a patient would return to a particular modality: PD

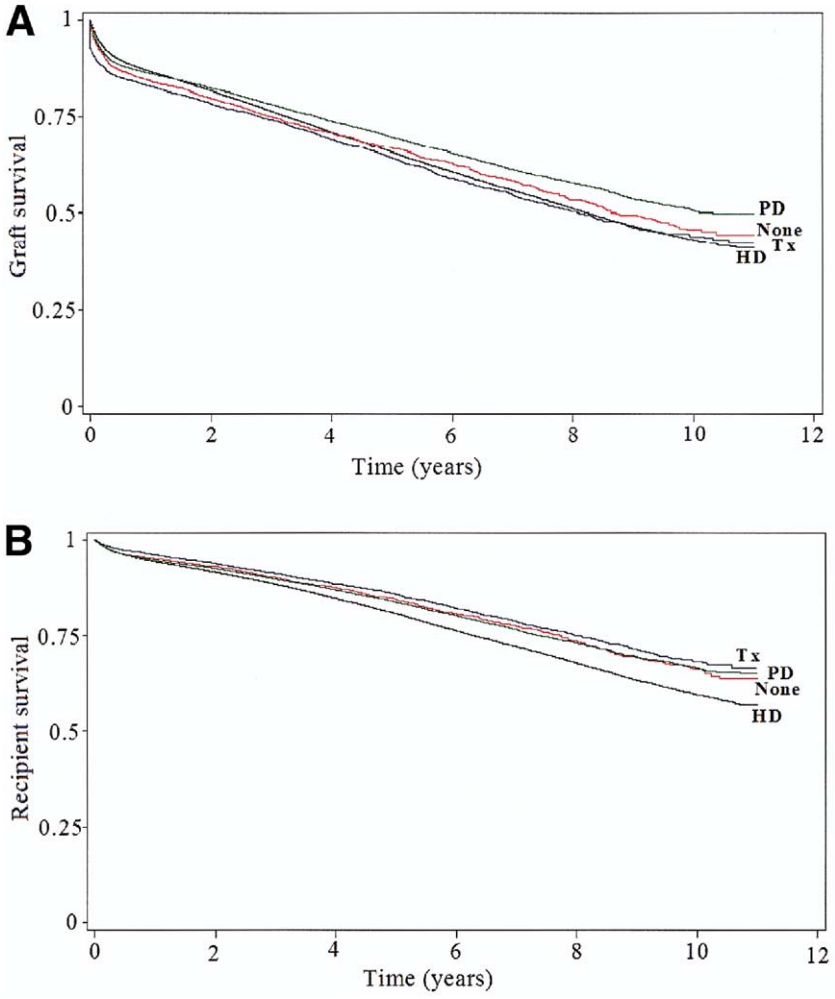

Fig 1. Predominant RRT modality and (A) graft and (B) recipient survival. The worst graft and recipient outcome is associated with HD.

only, HD only, transplantation only, PD plus HD, PD plus transplantation, HD plus transplantation, all 3 modalities, and none. We define combinations of RRT modalities by using the 60-day rule described. In the Cox model (HD only was used as a reference group), any combination or single modality (except for transplantation only, PD plus HD, and none) was better than HD only (Table 2). In particular, PD only was associated with an HR of 0.93 ($P < 0.001$). PD plus HD and none were associated with a not statistically significant greater risk. When patient survival was evaluated, modality combinations showing the significant difference with the reference group (HD only) were PD only (HR, 0.90; $P < 0.001$) and none (HR, 0.81; $P < 0.001$) and also PD plus HD (HR, 1.10; $P < 0.001$). When patients with prior transplants were analyzed separately compared with HD alone, PD alone was associated with lower risk for graft failure (HR, 0.60; $P < 0.05$); PD plus HD plus transplantation also was beneficial (HR, 0.79; $P < 0.005$), as well as HD plus transplantation (HR, 0.791; $P < 0.005$; Table 3). When recipient survival was used as an outcome, PD plus transplantation (HR, 0.73; $P < 0.05$), HD plus transplantation (HR, 0.74; $P < 0.005$), and transplantation only (HR, 0.62; $P < 0.0005$) were associated with lower mortality risk.

Number of Years on Specific Dialysis Modality

The Cox model discussed in this section was not adjusted for total duration of ESRD to avoid colinearity with the primary variables of interest. The duration of both dialysis modalities was associated with greater risk for graft failure.

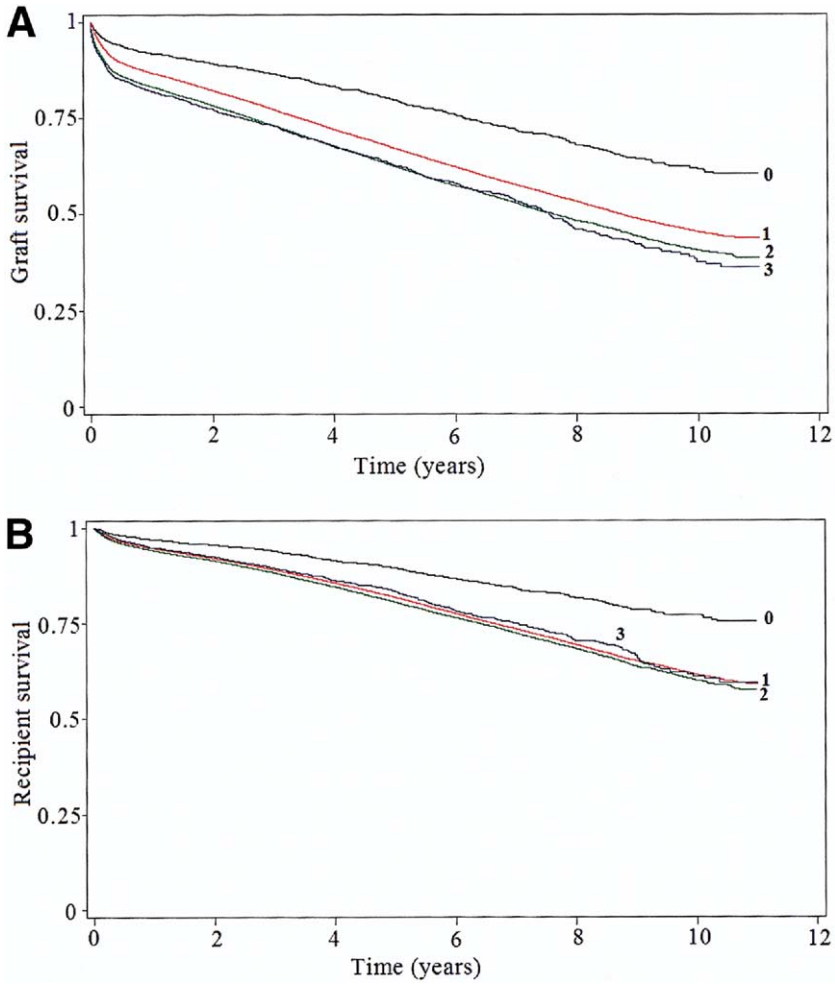

Fig 2. Number of different RRT modalities and (A) graft and (B) recipient survival. Increased number of modalities is associated with worsening of graft survival, and the best graft and recipient survival are associated with 0 RRT modalities (preemptive kidney transplantation).

Each year of PD therapy is associated with an HR of 1.02 ($P < 0.005$), and each year of HD therapy is associated with an HR of 1.02 ($P < 0.001$). Conversely, number of years with a functioning graft in the past had a protective effect on current graft survival (HR, 0.98; $P < 0.001$). In the subgroup of patients with a prior transplant, the same trend is true, but the association between duration of PD therapy and graft failure is not statistically significant (Table 2). We performed the same analysis for recipient survival and showed similar associations. The longer the patient was on HD (HR, 1.05; $P < 0.0001$) or PD therapy (HR, 1.04; $P < 0.005$), the greater the risk for dying, whereas number of years with a prior transplant did not make a significant difference. Recipient survival in the subgroup of patients with a prior transplant also was analyzed. Number of years on PD (HR, 1.05; $P < 0.005$) or HD therapy (HR, 1.04; $P < 0.001$) was associated with greater risk for recipient mortality, whereas number of years with a functioning graft was not associated with a significant change (Table 2).

DISCUSSION

Prediction of renal transplant recipient and graft survival presents an important clinical tool, especially in view of the growing shortage of renal transplants. Almost half the transplant recipients die with a functioning graft. In the rest, the allograft fails because of chronic renal allograft dysfunction. Although many risk factors are known (as described), the role of pretransplantation RRT modality in both graft and patient survival was not clear from the literature. In general, prior studies comparing different RRT modalities in relation to transplantation outcome were based on small data sets[16,22];

Table 4. Cross-Tabulation Between RRT Modality Immediately Before the Most Recent Transplantation and Predominant RRT Modality During the ESRD Course

Predominant RRT Modality During the ESRD Course	RRT Modality Before the Most Recent Transplantation				
	HD	PD	Transplantation	Unknown	Total
HD	58,389	1,880	72	2,179	62,520
PD	3,310	16,942	21	711	20,984
Transplantation	2,960	677	952	1,367	5,956
None	1,564	705	20	1,095	3,384
Total	66,223	20,204	1,065	5,352	92,844

NOTE. Predominant RRT modality is defined as a modality used for greater than 50% of the duration of ESRD.

evaluated short-term, rather than long-term, outcome[16,18,23,24]; did not study combination of RRT modalities or were performed 10 to 20 years ago, before significant changes in immunosuppressive regimens[22-26]; and most studies examined graft outcome only, not patient survival. In addition, most investigators evaluated the role of RRT modality immediately before transplantation, rather than predominant modality, as a primary variable of interest. Patients who were on PD therapy for a number of years and were switched to HD therapy immediately before transplantation would be classified as HD in these studies, which introduced a significant degree of misclassification bias. As listed in Table 4, there is significant discrepancy between RRT modality before transplantation and predominant RRT modality in the USRDS data set.

Previous studies of short-term transplantation outcome have yielded somewhat conflicting results. A greater rate of early graft failure was associated with PD therapy, shown by[27]. In the report by Bleyer et al,[18] the investigators evaluated delayed graft function after deceased donor transplantation based on dialysis modality immediately before and found an association between HD therapy and delayed graft function. Similar results were shown by other investigators.[16,17,27–29] Vanholder et al[16] also showed the advantage of PD therapy for short-term outcome: patients on PD therapy had a reduced incidence of acute renal failure. PD therapy is recommended to be chosen as an initial modality in patients who plan kidney transplantation within 2 to 3 years.[30]

Although there was no association between dialysis modality and graft thrombosis in 1 report,[31] several other studies reported an increased incidence of graft thrombosis associated with PD compared with HD.[27,32-35] A greater rate of graft thrombosis in PD patients might occur because hypercoagulable states are not detected as readily in PD patients as in HD patients. A greater rate of acute rejection was associated with PD therapy[16]; however, in other reports, acute rejection rates were not different between patients on PD versus HD therapy before transplantation.[18,26,29,35]

PD was associated with a greater rate of post-transplantation infection compared with patients on HD therapy in some reports,[36] but in others, infection rates between PD and HD patients were similar[16,37] or lower in patients with pretransplantation PD therapy.[38]

When long-term outcome (1 and 5 years) was studied, no difference between dialysis modalities was reported.[26] Similarly, PD and HD showed similar 1-year outcome in a report by Donnelly et al[24] in the mid-1980s. In a small case-control analysis, 1-year transplantation outcome in patients on continuous ambulatory PD therapy was not significantly different from that in HD patients with similar clinical characteristics.[22] Similar long-term graft and patient survival was achieved independent of dialysis modality before transplantation in a retrospective analysis of the first cadaveric graft. Graft and patient survival cases were identical in the HD and continuous ambulatory PD groups (5-year graft survival: continuous ambulatory PD, 67%; HD, 66%; 5-year patient survival: continuous ambulatory PD, 88%; HD, 87%).[25]

No difference in long-term outcome between patients treated with PD compared with HD was shown in other studies.[23,29,39,40] Snyder et al[27] compared long-term transplant outcome between PD and HD patients and showed that, compared

with pretransplantation HD, death-censored long-term graft failure was 15% greater in patients on PD therapy and short-term graft failure was 33% greater. Their analysis was based on 22,776 Medicare beneficiaries with a kidney transplant. Compared with our analysis, the study by Snyder et al[27] used a smaller number of patients and shorter follow-up (3 years), and some baseline characteristics of the study population were different from ours (pediatric patients and those with prior history of transplantation were excluded). Those investigators studied pretransplantation dialysis modality (based on a United Network for Organ Sharing form) adjusted for dialysis modality change as a binary variable, whereas we evaluated the role of both pretransplantation and predominant dialysis modality, as well as number of modalities used and their combinations.

In our study, compared with HD, PD therapy immediately before transplantation has a protective effect on graft and recipient survival. Although the effect size associated with PD therapy is modest, we disprove previous reports claiming a greater long-term risk associated with PD therapy. We evaluated the role of predominant RRT modality during the ESRD course. PD, transplantation, and preemptive or very short-course dialysis therapy had a protective effect for graft and recipient survival. This approach again confirmed an advantage for allograft and recipient survival of PD over HD as a modality immediately before transplantation and as a predominant modality during the ESRD course. Although statistically significant, the effect size of dialysis modality is limited (HRs of 0.97 and 0.94 for graft and recipient survival for PD as an RRT modality immediately before transplantation and HRs of 0.97 and 0.96 for graft and recipient survival for PD as a predominant RRT modality compared with HD, respectively). For comparison, the effect size of other predictors of graft and recipient survival evaluated in our analysis were as follows: recipient age (HR, 1.01; $P < 0.001$; HR, 1.04; $P < 0.001$ per year of life for graft and recipient survival, respectively), recipient history of diabetes (HR, 0.96; $P = 0.48$; HR, 1.11; $P = 0.107$ for graft and recipient survival, respectively), recipient comorbidity score (HR, 1.1; $P < 0.001$; HR, 1.26; $P < 0.001$ per unit increase in score for graft and recipient survival, respectively), living donor compared with deceased donor (HR, 0.68; $P < 0.001$; HR, 0.67; $P < 0.001$ for graft and recipient survival, respectively), donor age (HR, 1.01; $P < 0.001$; HR, 1.01; $P < 0.001$ per year of life for graft and recipient survival, respectively), and number of HLA-matched antigens (HR, 0.94; $P < 0.001$; HR, 0.96; $P < 0.001$ per antigen matched for graft and recipient survival, respectively).

Number of RRT modalities used during the ESRD course is a significant predictor of graft failure and recipient death. Almost any single RRT modality or their combination was associated with better graft and recipient outcome than HD only.

The mechanism of the outcome observed in our analysis is not completely clear. Residual renal function that might be better preserved in patients on PD therapy may contribute to better preservation of kidney function after transplantation.[41] One can hypothesize that the degree of residual renal function is more important for graft and recipient outcome than either PD or HD modality. Unfortunately, we did not have information about residual renal function for the entire study population. Answering this question could be a subject of another research project. Furthermore, body mass index and degree of hypervolemia might be different in PD and HD patients and therefore confound results. The rate of post-transplantation infections associated with HD might be greater compared with PD.[38] In addition, there are some indications that HD membranes and vascular access might cause sensitization in transplant candidates.[42] It has been shown that HD patients have elevated levels of natural killer cells[43] and production of cytokines.[44] Other immunologic differences might exist between HD and PD patients. It was postulated that PD modifies the population of T-helper (T_H) cells, with an increase in percentage of T_H subtype 2 (T_H2) cells and normal percentage of T_H1 cells.[45] T_H2 cells produce interleukin 4 and interleukin 10, which inhibit interferon γ secretion and cell immunity,[46] and increased T_H2 cell fraction may provide additional immunosuppression.

Potential selection bias should be considered when interpreting results of this study. We speculated that the decision regarding dialysis modality was made based on patient age, diabetic status, comorbidity, ability to learn the technique, prior history of abdominal surgeries, dis-

tance to the dialysis center, and status of the vascular access. Adjusting our multivariate models for recipient age, diabetic status, comorbidity index, socioeconomic status (indicated by educational level, primary source of pay for renal care, and citizenship), and duration of ESRD should considerably reduce the selection bias. We recognize that some factors not included in the models (eg, exhausted vascular access) might force selection of the dialysis modality and confound results. Although our models were adjusted carefully for pertinent covariates, the HD and PD populations are different in our study, as well as in other reports. For example, it has been shown that PD patients are more likely to undergo transplantation than HD patients in the group of adults[27] and, to a lesser extent, group of pediatric patients.[47] One can speculate regarding the causes of this discrepancy, eg, demographic characteristics and potentially the more assertive personality of PD patients versus HD patients might make them more aggressive in pursuing transplantation. In our study population, PD was a pretransplantation RRT modality in 21.8% and predominant RRT modality in 22.6% of patients, whereas in the dialysis population, PD patients comprise less than 15%.[48] To explain this phenomenon, Snyder et al[27] proposed that there is a perception among physicians that PD patients may be better candidates for transplantation[16,30] and therefore selection bias, in which potential transplantation candidates are more likely to be placed on PD therapy than HD. Other potential shortcomings should be considered in interpreting results of this retrospective data analysis. Retrospective analysis of a data registry shows the association (but not necessarily causative relationships) between the primary variables of interest and outcome. The sequence of PD and HD for patients receiving both has not been evaluated in this study and might be a subject of future research.

In conclusion, our results suggest that compared with PD, HD as an RRT modality immediately before transplantation or as a predominant RRT modality during the ESRD course, used alone or in combination with other RRT modalities, is associated with increased risk for graft failure and recipient death. Increased number of RRT modalities used during the ESRD course is associated with worsening of graft and recipient survival. PD is a reasonable choice of RRT and should not be avoided in transplantation candidates.

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