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Mortality after kidney transplant failure: The impact of non-immunologic factors

JOHN S. GILL, REKHA ABICHANDANI, ANNAMARIA T. KAUSZ, and BRIAN J.G. PEREIRA

Department of Nephrology, Tufts-New England Medical Center, Boston, Massachusetts, USA

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Background. One third of cadaveric kidney transplant recipients suffer graft loss within five years of transplantation. Non-immunologic factors that predict mortality among non-transplant patients also may be potentially modifiable risk factors for mortality among patients with transplant failure.

Methods. Applying multivariate survival analysis to data from the United States Renal Data System, we determined the effect of immunologic or transplant related factors and non-immunologic factors on mortality in patients who initiated dialysis after kidney transplant failure in the United States between April 1995 and September 1998.

Results. A total of 4741 patients were followed for a median ± standard deviation of 15 ± 11 months after initiation of dialysis after transplant failure. The majority of the 1016 (21%) deaths were due to cardiac (36%) or infectious (17%) causes. Patients in the following groups had an increased risk for all-cause mortality: older patients [hazard ratio (HR) = 1.04 per year, 95% confidence interval (95% CI) 1.03–1.04], women (HR = 1.31, 95% CI 1.10–1.56), patients of white race (HR = 1.94, 95% CI 1.32–2.84), patients with diabetes (HR = 1.76, 95% CI 1.43–2.16), peripheral vascular disease (HR = 1.94, 95% CI 1.54–2.43), congestive heart failure (HR = 1.26, 95% CI 1.05–1.53), drug use (HR = 2.23; 95% CI 1.08–4.60), smokers (HR = 1.35, 95% CI 1.01–1.81), first transplant recipients (HR = 1.32, 95% CI 1.02–1.69), and patients with a higher glomerular filtration rate (GFR) at dialysis initiation (HR = 1.04 per mL/min higher, 95% CI 1.02–1.06). Those with private insurance (HR = 0.67, 95% CI 0.49–0.93) and higher serum albumin (HR = 0.73 per g/dL higher, 95% CI 0.64–0.83) had a decreased risk for all-cause mortality. Acute rejection, antibody induction, donor source, duration of graft survival and the maximum attained GFR during transplantation did not predict all-cause mortality.

Conclusions. Non-immunologic factors predicted mortality among patients with transplant failure but immunologic and transplant related factors did not. Prevention, early diagnosis and treatment of co-morbid conditions and the complications of chronic kidney disease may improve the survival of patients with transplant failure.

Key words: renal transplantation, chronic kidney disease, co-morbid conditions, graft failure, patient survival, end-stage renal disease.

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Kidney transplantation is the preferred method of renal replacement therapy for patients with end-stage renal disease (ESRD). Compared to patients on dialysis, transplant recipients have greater survival [1], better quality of life [2], and consume fewer health care resources [3]. Despite improvements in immunosuppression, overall patient care and the increasing use of live donors, a return to dialysis after transplant failure remains a common outcome. Over one third of cadaveric kidney transplant recipients suffer graft loss within five years of transplantation [3]. Patients who initiate dialysis after transplant failure have high mortality and derive a survival advantage from repeat transplantation, but only 15% of such patients will receive another transplant [4].

Traditionally, research on outcomes in kidney transplant recipients has focused on immunologic factors and therapies. Less attention has been paid to non-immunologic factors, such as the complications of chronic kidney disease (CKD) and co-morbid disease, which could affect morbidity and mortality among these patients. Through the course of allograft loss and return to dialysis, patients who experience allograft failure are re-exposed to the complications of CKD. Moreover, the success of kidney transplantation has allowed nephrologists to transplant a greater number of older patients and those with a higher burden of co-morbid disease [3]. Consequently, the complications of CKD such as malnutrition, anemia and cardiovascular disease, which predict clinical outcomes among "first-time" dialysis patients [5], need to be examined among those who return to dialysis after transplant failure. Indeed, we have recently shown that kidney transplant recipients who initiate dialysis after transplant failure in the United States had mean hematocrit (27.5%) and serum albumin (3.3 g/dL) values that were low, and not significantly different from "first-time" dialysis patients [6]. Therefore, we determined the effect of both immunologic or transplant related variables and non-immunologic factors on mortality among kidney transplant recipients who initiated dialysis after transplant failure in the United States.

METHODS

Study population

All adult patients (≥18 years of age) were studied who initiated dialysis after kidney transplant failure for whom a new Health Care Financing Administration (HCFA) 2728 form was completed and included in the 1999 update of the Medical Evidence Standard Analysis File (Medevid file) of the United States Renal Data System (USRDS).

The Medevid file contains all data from the HCFA 2728 form. This form is completed by the dialysis or transplant center for all patients beginning end-stage renal disease (ESRD) treatment (dialysis or transplantation). For patients with transplant failure, a new 2728 form is required only for those patients who must reapply for ESRD Medicare coverage. During the study period, most transplant recipients were eligible for ESRD Medicare coverage for three years after the time of transplantation. Therefore, the majority of the patients identified for inclusion in the study were patients who had graft survival of greater than three years, exhausted ESRD Medicare coverage, and were required to reapply for ESRD Medicare coverage.

The 2728 form contains information on many of the non-immunologic factors of interest for our current study, including patient demographics, insurance status, employment status, co-morbid conditions, cause of ESRD, pre-ESRD erythropoietin use, dialysis modality and laboratory information. The laboratory information is obtained within 45 days of dialysis initiation and includes serum creatinine, blood urea nitrogen, hemoglobin, hematocrit, serum albumin and the dates that these tests were obtained. Laboratory values that were not obtained within 45 days of dialysis initiation as well as missing and out of range values were excluded. Acceptable ranges for serum albumin, hematocrit and serum creatinine were defined as 0.5 to 6 g/dL, 10 to 50% and >2.0 mg/dL, respectively.

Information regarding immunologic and transplant related factors was obtained from the 1999 update of the Transplant standard analysis files of the USRDS. We studied factors that predict mortality in patients with transplant function including donor source, immunosuppressive medications, and acute rejection [7, 8]. In addition, we included the highest glomerular filtration rate (GFR) attained during the time of transplant function as an index of overall transplant function. Patient death dates and the cause of patient death were obtained from the 1999 update of the Patients' standard analysis file of the USRDS, which contained data collected in the ESRD Death Notification Form (HCFA-2746).

Patients were excluded who initiated dialysis prior to the implementation of the new version of the HCFA 2728 form in April 1995. Patients with more than one 2728 form, patients with invalid USRDS identification numbers and patients with missing or invalid transplant or dialysis return dates also were excluded. In addition, patients with a Medevid record but without a matching record in the Patients' standard analysis file were excluded.

Analytical methods and statistical analysis

Immunologic or transplant related factors and non-immunologic factors were described as the mean and standard deviation for continuous variables and frequency for categorical variables unless otherwise indicated. The chi-square test and *t* test were used to compare these factors between survivors and non-survivors. Glomerular filtration rate (GFR) during the time of transplant function and at dialysis initiation was estimated with an equation derived from the Modification of Diet in Renal Disease Study, which is based on age, gender, race and serum creatinine level (abstract; Levey et al, *J Am Soc Nephrol* 11:155, 2000). GFR was estimated yearly during graft survival and the highest value was defined as the maximum attained GFR. Body mass index (BMI) at the time of dialysis initiation after transplant failure was calculated as body weight in kilograms/(height in meters)^2 (kg/m^2). The duration of ESRD prior to transplantation was calculated as the difference between the first ESRD service date and the date of transplantation. Patient deaths were classified as cardiac, infectious, malignant, cerebrovascular, miscellaneous (including other) and missing.

Mortality from all causes, cardiac mortality and infectious mortality were estimated from the time of dialysis initiation after transplant failure with the Kaplan-Meier product limit method, and group differences were tested with the log rank test. Cox proportional hazards regression was used to determine risk factors for all cause mortality. Separate Cox regression analyses for cardiac death and infectious death were performed. The effects of immunologic or transplant related factors and non-immunologic factors on mortality were reported as hazard ratios and 95% confidence intervals (95% CI), and were calculated from the maximum likelihood parameter estimates of the corresponding variables in the Cox model. The proportional hazards assumption was assessed graphically for each categorical variable considered in the Cox regression with log-log curves. Patients were censored at time of repeat transplantation or the end of study follow-up (Sept. 30, 1998), whichever occurred first. In the Cox models for cardiac and infectious death, patients were censored at the date of death if they died from other causes and were therefore considered at risk of dying of the cause of interest until that time.

All variables significant ($P < 0.10$) in the univariate analyses (Kaplan-Meier or *t* test) were included in the Cox model for all cause mortality. Age, gender, race and cause of ESRD were chosen a priori to be included in

all Cox models. In addition, the duration of ESRD prior to transplantation and the duration of graft survival were included in the Cox model for all cause and cardiac mortality despite the lack of an association with mortality in the univariate analysis. All other variables included in the cardiac and infectious mortality models were chosen using the best subset selection method in SAS software version 8.1 (SAS Institute, Inc., Cary, NC, USA), which orders models by the likelihood score for the specified number of variables. In the Cox regression for all cause mortality, separate hazard ratios were determined before and after one year of graft failure for the following immunologic and transplant related factors; the use of antibody induction therapy, number of acute rejection episodes and the maximum attained GFR during transplantation. A separate Cox model for all cause mortality that excluded patients who died within 30 days of graft failure was performed.

No attempt to impute missing data was made. For patients with missing values for categorical variables, a category of unknown was created and these patients were included in the Cox models. Patients with incomplete information for continuous variables were not included in the Cox models.

RESULTS

Patient characteristics

Among 5170 patients who initiated dialysis after a failed kidney transplant and had a new Medevid record between April 1, 1995 and September 30, 1998, 4741 patients were included in the study. Of the 429 patients excluded from the study, 116 patients had a dialysis return date prior to April 1, 1995, 141 patients were less than 18 years of age, 47 patients had invalid USRDS identification numbers or duplicate Medevid files, 62 patients had invalid transplant dates, 25 patients had invalid dialysis return dates and 38 patients had no record in the Patients' standard analysis file. The excluded patients were significantly younger (33 ± 17 years vs. 43 ± 12 years, $P = 0.01$) and had less diabetes (12 vs. 19%, $P = 0.02$), but were otherwise similar to the study patients (data not shown).

A comparison of non-immunologic factors between survivors ($N = 3725$) and non-survivors ($N = 1016$) is shown in Table 1. Non-survivors were significantly older and more likely to be white, more likely to be first transplant recipients, have ESRD secondary to diabetes, have individual co-morbid diseases, smoke and abuse alcohol. Non-survivors were also less likely to have private insurance and less likely to be employed. The mean duration of ESRD prior to transplantation and the frequency of preemptive transplantation (no dialysis prior to transplant) were similar among survivors and non-survivors. Body mass index (BMI) at the time of return to dialysis was determined for 99% of patients. Non-survivors had a significantly lower body mass index.

Pre-dialysis erythropoietin use could be determined for 99% of the patients. Erythropoietin use was significantly lower among non-survivors (Table 1). The serum albumin at dialysis initiation was available for 67% of all patients and for 68% of the survivors and 67% of the non-survivors. Serum albumin was significantly lower among non-survivors. At dialysis initiation, hematocrit was available for 82% of all patients and for 81% of survivors and 82% of non-survivors. The mean hematocrit at dialysis initiation was significantly higher among non-survivors. GFR at dialysis initiation could be estimated for 88% of all patients and for 88% of survivors and 87% of non-survivors. The mean GFR at dialysis initiation was significantly higher among non-survivors.

A comparison of immunologic and transplant related factors between survivors and non-survivors is shown in Table 2. Non-survivors were more likely to have received a cadaveric donor organ. The duration of graft survival, acute rejection, use of induction immunosuppression, maintenance calcineurin inhibitor use and maximum attained GFR during transplantation were similar among survivors and non-survivors.

Patient survival and cause of death

The median patient follow-up was 15 ± 11 months. Among patients who remained on dialysis, 24% died (987 of 4198), while 5% (29 of 543) of patients who received another transplant died. The estimated one, two and three year patient mortality from all causes was 16%, 25% and 33%, respectively. Cardiac mortality at one, two and three years was 6%, 11% and 13%, while infectious mortality at the same time points was 3%, 5% and 7%, respectively.

Cardiac causes accounted for the majority of deaths (36%) followed by infections (17%), cerebrovascular disorders (6%) and malignancies (2%). Miscellaneous causes accounted for 17% of all deaths with no more than 2% of deaths attributed to any single cause. The cause of death was unknown for 22% of the patients.

Risk factors for all cause, cardiac and infectious mortality

The results of the Cox regression analysis for all cause mortality are shown in Table 3. Non-immunologic factors that predicted all cause mortality included older age, female gender, white race, diabetes as the cause of ESRD, co-morbid conditions (peripheral vascular disease, congestive heart failure), drug use, smoking, lack of previous transplantation and a higher GFR at dialysis initiation. In addition, patients who initiated dialysis with a higher serum albumin and with private only insurance had a lower risk for all cause mortality. None of the immunologic and transplant related factors considered in the

Table 1. Non-immunological factors among patients with kidney transplant failure

	All patients[a] $N = 4741$	Non-survivors $N = 1016$	Survivors $N = 3725$	P[b]
Age at graft failure *years*	43 ± 12	50 ± 13	42 ± 12	<0.01
Gender *% male*	59%	59%	59%	0.83
Race				<0.01
White	66%	70%	65%	
Black	27%	25%	27%	
Other	7%	5%	8%	
Number of transplants				<0.01
1	72	81	70	
2 or more	28	19	30	
Cause of end-stage renal disease				<0.01
Diabetes	19%	35%	16%	
Hypertension	18%	16%	18%	
Glomerular disease	32%	23%	34%	
Polycystic kidney disease	5%	5%	4%	
Other	26%	22%	28%	
Co-morbid disease				
Diabetes	22%	38%	18%	<0.01
Congestive heart failure	17%	29%	14%	<0.01
Ischemic heart disease	12%	22%	9%	<0.01
Peripheral vascular disease	8%	17%	5%	<0.01
Stroke	3%	6%	3%	<0.01
Cancer	3%	5%	2%	<0.01
Smoker	7%	9%	6%	0.01
Drug use	1%	1%	<1%	0.83
Alcohol abuse	1%	2%	1%	<0.01
Insurance				<0.01
Private	32%	27%	33%	
Medicare	62%	71%	60%	
Medicaid	30%	29%	30%	
Other	21%	25%	19%	
None	3%	3%	3%	
Employed (full or part time)	23%	13%	25%	<0.01
Dialysis modality				0.90
Hemodialysis	74%	74%	73%	
Peritoneal dialysis	14%	14%	14%	
Pre-emptive transplant	12%	12%	13%	0.30
Duration of ESRD prior to transplant *years*	2.4 ± 3.0	2.4 ± 3.1	2.4 ± 3.0	0.73
Body mass index kg/m^2	25.1 ± 7.3	24.6 ± 6.6	25.2 ± 7.4	<0.01
Erythropoietin use	35%	32%	36%	<0.01
Laboratory parameters				
Serum albumin *g/dL*	3.3 ± 0.6	3.1 ± 0.6	3.4 ± 0.6	<0.01
Hematocrit *%*	27.5 ± 5.9	28.3 ± 6.1	27.3 ± 6.1	<0.01
Glomerular filtration rate $mL/min/1.73\ m^2$	8.4 ± 3.9	9.7 ± 4.8	8.0 ± 3.7	<0.01

[a] The number of patients in whom data was available varied slightly for different characteristics
[b] P calculated from the chi-square test for categorical variables or the t test for continuous variables

Cox regression (donor source, antibody induction, acute rejection, duration of graft survival or maximum GFR attained during graft function < or ≥30 mL/min/1.73 m^2) predicted all cause mortality. A separate model in which the patients who died within 30 days of graft failure were excluded ($N = 32$) yielded similar results (results not shown).

The results of the Cox regression analyses for cardiac and infectious causes of death are shown in Table 4. Risk factors for cardiac death included older age, white race, diabetes as the cause of ESRD, peripheral vascular disease, congestive heart failure, lack of erythropoietin use prior to dialysis initiation and receipt of a cadaveric donor organ. Risk factors for infectious death included older age, female gender, diabetes as the cause of ESRD, peripheral vascular disease and a low serum albumin at dialysis initiation.

Figure 1 shows the Cox-adjusted survival curves for all cause mortality by co-morbid disease status. Compared to patients without diabetes, congestive heart failure or peripheral vascular disease (curve A), patients with congestive heart failure (curve B; $P = 0.01$), patients with diabetes (curve C; $P < 0.01$), and patients with peripheral vascular disease (curve D) ($P < 0.01$) have significantly lower estimated survival. Figure 2 shows the Cox-adjusted survival curves for all cause, cardiac and infectious mortality stratified by serum albumin < or ≥3.5 g/dL. Patients with serum albumin < 3.5 g/dL have significantly higher all cause ($P < 0.01$) and infectious mortality ($P = 0.02$) and non-significantly higher cardiac mortality ($P = 0.10$).

Table 2. Immunological and transplant related factors among patients initiating dialysis after kidney transplant failure

	All patients[a] $N = 4741$	Non-survivors $N = 1016$	Survivors $N = 3725$	P[b]
Year of transplant				<0.01
1965–1979	4%	4%	4%	
1980–1989	39%	45%	38%	
1990–1998	57%	51%	58%	
Donor				<0.01
Cadaveric	75%	84%	73%	
Live	25%	16%	27%	
Duration of graft survival *years*	7.1 ± 4.5	7.2 ± 4.7	7.0 ± 4.6	0.23
Acute rejection				0.56
None	40%	42%	40%	
1	33%	33%	33%	
2 or more	27%	25%	27%	
Antibody induction	21%	17%	22%	0.10
Maintenance calcineurin inhibitor	97%	98%	96%	0.20
Maximum GFR attained during transplant[c] *mL/min/1.73 m²*	51.5 ± 37.0	50.1 ± 24.7	51.8 ± 41.0	0.28

[a] The number of patients in whom data was available varied for different characteristics
[b] *P* calculated from the chi-square test for categorical variables or the *t* test for continuous variables
[c] GFR (glomerular filtration rate) was estimated yearly during graft survival and the highest value was defined as the maximum attained GFR

Table 3. Predictors of all cause mortality after kidney transplant failure[a] (Cox multivariate regression)

	Hazard ratio	95% CI	P
Age at graft failure *per year higher*	1.04	1.03–1.04	<0.01
Female gender	1.31	1.10–1.56	<0.01
Race *reference other*			
White	1.94	1.32–2.84	<0.01
Black	1.45	0.96–2.17	0.08
Cause of ESRD *reference glomerulonephritis*			
Diabetes	1.76	1.43–2.16	<0.01
Polycystic kidney disease	0.85	0.57–1.26	0.42
Other	1.01	0.82–1.25	0.93
Peripheral vascular disease	1.94	1.54–2.43	<0.01
Congestive heart failure	1.26	1.05–1.53	0.01
Drug use	2.23	1.08–4.60	0.03
Smoking	1.35	1.01–1.81	0.04
Number of transplants *ref ≥2*			
One	1.32	1.02–1.69	0.03
Unknown	0.79	0.55–1.14	0.22
Insurance *reference neither Medicare or private*			
Private only	0.67	0.49–0.93	0.02
Medicare only	1.06	0.83–1.35	0.64
Both Medicare and private	0.99	0.74–1.36	0.43
GFR at dialysis initiation *per mL/min higher*	1.04	1.02–1.06	<0.01
Serum albumin at dialysis initiation *per g/dL higher*	0.73	0.64–0.83	<0.01

[a] Significant variables $P < 0.05$ shown. Other variables included in the Cox model are: duration of ESRD prior to transplant, duration of graft survival, co-morbid conditions at return to dialysis (ischemic heart disease, stroke, cancer), history of alcohol abuse, employment status, obesity at return to dialysis (BMI ≥30 kg/m²), hematocrit at dialysis initiation, pre-dialysis erythropoietin use, donor type, antibody induction, number of acute rejections, and maximum glomerular filtration rate attained during transplant (< or ≥30 mL/min).

DISCUSSION

The estimated two-year mortality rate among patients with transplant failure in our study was 25% and is similar to that reported in other studies [4]. Mortality from all causes was predicted by non-immunologic factors including co-morbid conditions (diabetes, peripheral vascular disease, congestive heart failure) smoking, drug use and low serum albumin levels. In contrast immunologic and transplant related factors (donor source, immunosuppressive medications, acute rejection, duration of graft survival, maximum attained GFR during transplantation) did not predict all-cause mortality. Prevention, early diagnosis and treatment of non-immunologic factors may improve outcomes among these patients.

In comparison to the patients in this study, the estimated two year mortality among similarly aged "first-time" dialysis patients is 20%, while the estimated two year mortality among first cadaveric transplant recipients with graft function is 6% [3]. The aim of our study was to determine the impact of non-immunologic and immunologic or transplant related factors on patient survival and not to compare the survival of patients with trans-

Table 4. Predictors of cardiac and infectious death after kidney transplant failure[a] (Cox multivariate regression)

	Hazard ratio	95% CI	*P*
Cardiac death			
Age at graft failure *per year older*	1.03	1.02–1.05	<0.01
Race *reference other*			
White	2.27	1.19–4.35	0.01
Black	1.43	0.72–2.83	0.30
Cause of ESRD *reference glomerulonephritis*			
Diabetes	1.75	1.27–2.42	<0.01
Polycystic kidney disease	0.81	0.44–1.50	0.50
Other	0.89	0.63–1.26	0.50
Peripheral vascular disease	1.80	1.26–2.59	<0.01
Congestive heart failure	1.40	1.04–1.90	0.03
Erythropoietin use prior to transplant failure	0.74	0.56–0.99	0.04
Donor type *reference live donor*			
Cadaveric	1.60	1.03–2.52	0.04
Unknown donor	1.73	0.93–3.21	0.08
Infectious death			
Age at transplant failure *per year higher*	1.03	1.02–1.05	<0.01
Female gender	1.48	1.01–2.16	0.04
Cause of ESRD *reference glomerulonephritis*			
Diabetes	2.17	1.37–3.42	<0.01
Polycystic disease	1.60	0.76–3.38	0.22
Other	0.90	0.52–1.55	0.14
Peripheral vascular disease	2.01	1.21–3.33	<0.01
Albumin at dialysis initiation *per g/dL higher*	0.64	0.48–0.86	<0.01

[a] Significant variables $P < 0.05$ shown. Other variables in the Cox regression for cardiac death are: gender, co-morbid conditions (ischemic heart disease, stroke), smoking, duration of ESRD prior to transplant, duration of graft survival, type of insurance, number of transplants, glomerular filtration rate, albumin and hematocrit at dialysis initiation. Other variables in the Cox regression for infectious death are race, and glomerular filtration rate at dialysis initiation.

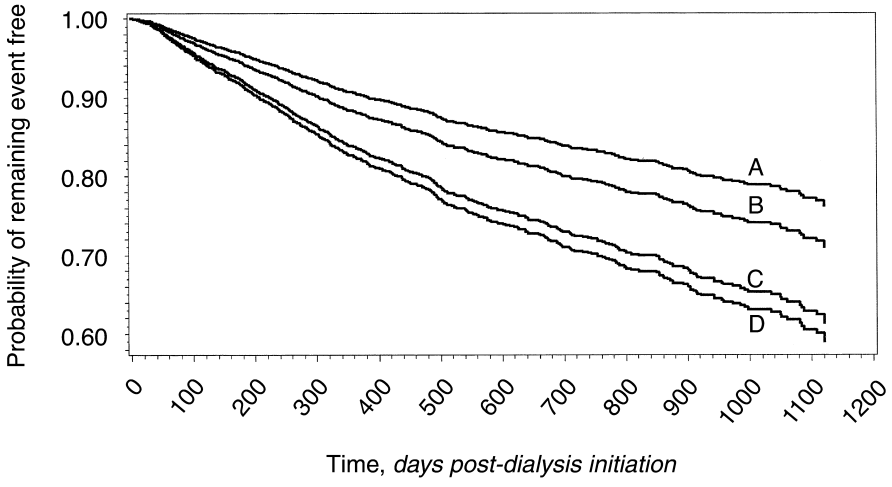

Fig. 1. Adjusted all-cause mortality. (A) Patients without diabetes, congestive heart failure or peripheral vascular disease, (B) patients with congestive heart failure, (C) patients with diabetes, (D) patients with peripheral vascular disease. Compared to patients without co-morbid conditions (A), patients with congestive heart failure ($P = 0.01$), diabetes ($P < 0.01$) and peripheral vascular disease ($P < 0.01$) have lower estimated survival (Cox regression model censored at repeat transplantation).

plant failure to that of other patient groups. Therefore, definitive conclusions regarding the comparative survival of patients with transplant failure cannot be made. Nevertheless, given the relatively young age and low burden of co-morbid disease in this cohort of ESRD patients, we believe that the mortality among patients with transplant failure is unacceptably high.

The finding that cardiac disease accounted for the majority of deaths is consistent with findings from studies in patients with functioning transplants and patients on dialysis [3, 7, 9]. The high prevalence of cardiovascular disease among patients with CKD is in part related to exposure to non-traditional risk factors [10]. In this regard, patients with transplant failure are exposed to both non-traditional CKD related cardiovascular risk factors such as elevated serum creatinine and proteinuria [11] and non-traditional transplant related cardiovascular risk factors such as immunosuppressive medications [9]. The cumulative exposure to these non-traditional cardiovascular risk factors may underlie the cardiac mortality in these patients.

Although the clinical management of co-morbid conditions was not assessed in our study, co-morbid conditions are under-treated among dialysis and transplant

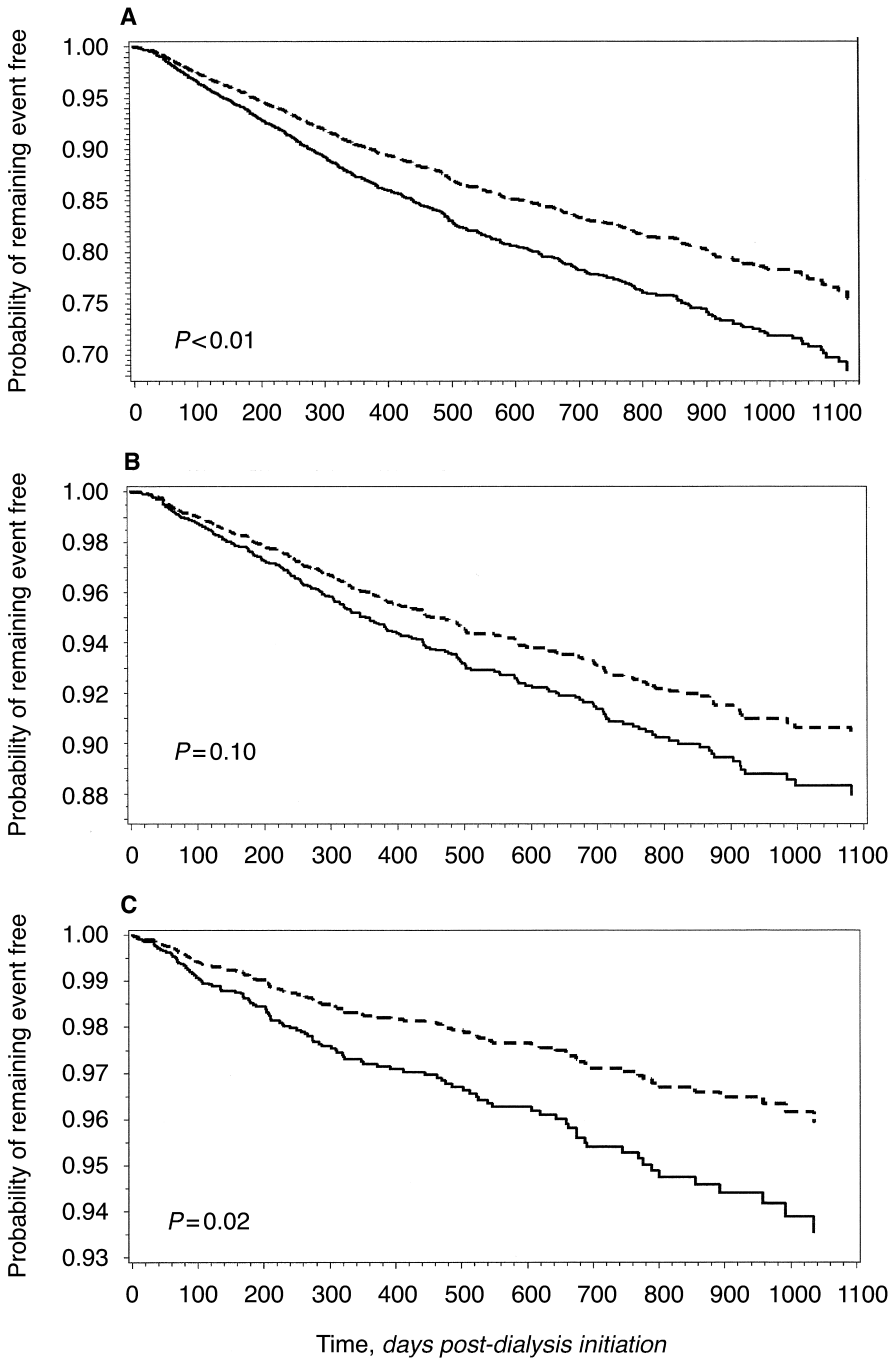

Fig. 2. Adjusted all-cause (*A*), cardiac (*B*) and infectious (*C*) mortality by serum albumin level $<$ or $\geq$3.5 g/dL (Cox regression model censored at repeat transplantation).

patients [12, 13]. A number of factors unique to the transplant population may directly or indirectly impede the clinical management of co-morbid conditions. Prior to dialysis initiation, efforts to preserve allograft function may take precedence over other clinical management issues, resulting in under-diagnosis and under-treatment of co-morbid conditions. Sub-optimal treatment of cardiovascular conditions may result from under utilization of ACE inhibitors, erythropoietin and HMG CoA reductase inhibitors due to concerns of worsened allograft function [14], hypertension [15], and statin-induced myopathy [16], respectively. Fragmentation of patient care and lack of communication between care providers during the transition from transplantation to dialysis may be additional important barriers to the provision of aggressive co-morbid disease management [17]. Finally, the lack of proven efficacy of treatment of co-morbid conditions in this population as well as the perception that transplant recipients are a relatively healthy cohort of ESRD patients may lead to complacency about the treatment of co-morbid conditions.

We determined the effect of complications of CKD

(anemia, hypoalbuminemia) on mortality, and found that patients with low serum albumin at dialysis initiation had a higher risk for all-cause and infectious mortality. Low serum albumin has been previously identified as a risk factor for mortality among patients with graft function [18]. The strong association between serum albumin level and mortality in this study demonstrates that serum albumin is a useful tool to identify high-risk patients. Whether nutritional and non-nutritional interventions can improve serum albumin levels among these patients, and whether an improvement in serum albumin can lead to reduced mortality remains to be seen. In univariate analysis, non-survivors had a significantly higher hematocrit at the time of dialysis initiation compared to survivors. However, the hematocrit level at dialysis initiation was not associated with survival in any of the multivariate analyses. Given the fact that hematocrit levels may fluctuate rapidly, a single hematocrit measurement at the time of dialysis initiation may not accurately reflect the exposure to anemia before and after graft failure. Studies with longitudinal hematocrit measurements during the progression of graft dysfunction and after graft failure are needed to determine the possible association of hematocrit level and mortality.

We also determined the association of the level of residual renal function (estimated GFR) at the time of dialysis initiation and pre-dialysis erythropoietin use with mortality because we believe these factors may be surrogates of the quality of delivered CKD care. The finding that patients who initiated dialysis at higher levels of GFR had an increased risk for all-cause mortality is counterintuitive. We believe that this finding reflects the fact that the sickest patients tend to require dialysis initiation at higher levels of residual renal function. The finding that patients who received pre-dialysis erythropoietin were at decreased risk for cardiac mortality is consistent with our hypothesis that this variable may reflect the quality of delivered CKD care. We previously reported that 66% of patients in this cohort who received pre-dialysis erythropoietin had hematocrit levels below 30% [6]. Therefore, the mechanism by which pre-dialysis erythropoietin had a protective effect on cardiac mortality in this cohort is probably not related to anemia management per se, but may reflect other aspects of CKD care not measured in this study.

Previous studies in patients with graft function have found immunologic and transplant factors to be independently associated with mortality [7]. We hypothesized that the effect of immunologic and transplant related factors on patient survival after graft failure may be short lived and, therefore, we determined separate hazard ratios for many of these variables before and after one year of graft failure in the Cox model for all-cause mortality. In addition, to capture the effect of unmeasured factors present during the time of graft function such as hypertension and the chronic exposure to immunosuppressive medications on mortality, the duration of graft survival was included as an independent variable in the Cox regression model for all-cause mortality. This variable also was chosen to account for improvements in transplantation that have occurred over time [19]. These immunologic and transplant related factors were not risk factors for all-cause mortality. We believe that because of the long duration of graft survival among patients in our study, risk factors related to the transplant procedure may no longer be relevant for patient survival after graft failure. The patients in this cohort had a mean duration of graft survival of seven years and therefore these findings may not apply to patients with a shorter duration of graft survival.

The higher relative risk for all-cause mortality among females has not previously been reported. In a study of 19,000 patients with allograft failure, Ojo and colleagues reported a higher risk for mortality among male patients [4]. Compared to that study, our study included patients who had returned to dialysis after a much longer duration of graft survival (median 74 vs. 17 months in the study by Ojo et al). A higher death rate among male patients with graft function [7] may have resulted in a survival bias for those males who returned to dialysis after a long duration of graft survival in our study. In addition, our study included information regarding many co-morbid diseases for which males may be at higher risk (ischemic heart disease, congestive heart failure, stroke, peripheral vascular disease). Indeed, the prevalence of peripheral vascular disease (8.0% for males vs. 6.0% for females, $P = 0.03$) and ischemic heart disease (13% for males vs. 10% for females, $P < 0.01$) was higher among males in this study. In studies that did not include these co-morbid conditions, the higher mortality risk among males may represent male gender acting as a surrogate for these and other unmeasured co-morbid conditions.

Patients with private insurance had a decreased risk for all cause mortality relative to patients who had neither private insurance nor Medicare at the time of dialysis initiation. Private insurance coverage may identify a group of patients who are socioeconomically advantaged and therefore healthier. Alternatively, this finding suggests that there may be differences in patient care after the expiration of ESRD Medicare that continue to have a long-term effect on patient survival after graft failure. After termination of ESRD Medicare, patients faced with the cost of immunosuppressive medications may not be able to afford other medications such as lipid lowering drugs or erythropoietin that may have a beneficial effect on patient outcomes.

A few points merit consideration when interpreting the results of our study. We used a prediction formula that has been recommended to estimate GFR in patients with CKD [20], but has not been validated in transplant

recipients. In addition, despite the large sample size, the well-known limitations of a retrospective analysis of a national database should be considered when interpreting the results of our study.

In summary, our study demonstrates that non-immunologic factors have a significant impact on the survival of patients with kidney transplant failure. Moreover, immunologic and transplant related factors did not predict survival. Prevention, early diagnosis and treatment of comorbid conditions and the complications of CKD both during and after the transplant period may improve the survival of these patients.

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Reprint requests to Brian J.G. Pereira, M.D., Division of Nephrology, New England Medical Center, 750 Washington Street, Box 5224, Boston, Massachusetts 02111, USA.
E-mail: Bpereira@lifespan.org

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