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Post-transplant renal function in the first year predicts long-term kidney transplant survival

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Post-transplant renal function in the first year predicts long-term kidney transplant survival.

Background. Improvements in long-term kidney graft survival have been recently noted. However, the reasons for this were unclear. This study examined post-transplant renal function within the first year as an independent variable influencing long-term survival.

Methods. The influence of demographic characteristics (age, sex, race); transplant variables (cadaver versus living donor, cold ischemia time, HLA mismatching, delayed graft function and transplant year), and post-transplant variables (immunosuppressive agents for the prevention of acute rejection, clinical acute rejection and post-transplant renal function in the first year) on graft survival were analyzed for 105,742 adult renal transplants between 1988 and 1998. Renal function in the first year was expressed as serum creatinine at six months and one year and delta creatinine (change in serum creatinine between 6 months and 1 year). Graft half-life was used to measure long-term survival.

Results. During this 11-year period, the one-year serum creatinine values for cadaver recipients steadily improved, from 1.82 ± 0.82 mg/dL in 1988 to 1.67 ± 0.82 mg/dL in 1998 ($P < 0.001$), as did the graft half-life. There was a progressive decline in graft half-life for each incremental increase of six month, one year and Δ creatinine for living and cadaver donor transplants as well for cadaver transplants with donor age > and ≤50 years. The Relative Hazard (RH) for graft failure was 1.63 (1.61, 1.65; $P < 0.0001$) with each increment of 1.0 mg/dL of serum creatinine at one year post-transplant and it increased to 2.26 (2.2, 2.31; $P < 0.0001$) when the Δ creatinine was 0.5 mg/dL. The RH reduction for graft failure was substantially lower for the years 1993, 1996, 1997 and 1998 when post-transplant renal function was not included in the model ($P < 0.05$). However, the RH reduction per year was not different when post-transplant creatinine was included in the model, 1.01 (0.94 to 1.05; $P = 0.89$).

Conclusion. In conclusion, one-year creatinine and Δ creatinine values predict long-term renal graft survival. Recent improvements in graft half-life are related to conservation of renal function within the first year post-transplantation.

Key words: serum creatinine, graft survival, renal transplant, cadaveric grafts, living donor grafts.

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Renal transplantation remains the treatment of choice for end-stage renal disease (ESRD) in regards to patient survival [1]. A recent analysis of the UNOS/OPTN transplant database, confirmed that long-term renal graft survival measured as graft half-life has improved from 1988 to 1996 [2]. Many risk factors are known to influence long-term graft survival. Among these include: recipient age, race, presence of diabetes, delayed graft function (DGF), HLA mismatching, and acute rejection episodes [2–4]. Improvement in half-life was seen even after an adjustment for these risk factors, indicating that additional, unidentified factors remain.

Renal function within the first year of transplantation also has been reported to an important factor influencing graft survival [4–8]. Previous studies that examined renal function have either been from a single center in the context of acute rejection episode or have utilized discharge creatinine values [4–8]. Therefore, it has not been possible to separate the effects of renal function and other confounding variables such as acute rejection and DGF.

The purpose of this study was to examine renal function in the first year of transplantation as an independent variable in determining long-term renal graft survival. Our hypothesis was that preservation of renal function in the first year might provide additional explanation for improvements in graft half-life that have been noted recently. To accomplish this we reviewed 105,742 adult renal transplants in the United States performed between 1988 and 1998.

METHODS

All adult recipients who underwent primary or repeat renal transplantation with a graft from living and cadaveric donors in the United States between January 1988 and December 1998 were studied. Data were obtained from all 256 kidney transplant programs as reported to the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS).

These data were analyzed according to the methodology defined in this section. Patients who had multiorgan transplants such as kidney/pancreas and pediatric recipients (age <18 years) were excluded. These patients were followed until November 2000.

Post-transplant renal function considered in this study was defined as: serum creatinine at six months and one year and Δ creatinine (the change in creatinine from 6 months to 1 year). Patients were stratified into six groups according to their six month and one year post-transplant serum creatinine values: <1.0, 1–1.5, 1.6–2.0, 2.1–2.5, 2.6–3.0 and >3.0 mg/dL. They were also divided into seven groups, according to their Δ creatinine value: <0.1, 0.1–0.2, 0.3–0.4, 0.5–0.9, 1.0–1.9, 2.0–2.9, and ≥3.0 mg/dL. Patients were further stratified according to organ source: living and cadaver donor transplants, and cadaver donor transplants according to donor age ≤ and >50 years. The Kaplan-Meier method was used to estimate graft survival [9]. A maximum likelihood estimate of the projected half-life (median value) was calculated assuming exponentially distributed graft survival times. Additional analyses were performed after censoring patients who died while their grafts were functioning.

The demographic variables used for covariate-adjusted analyses included age, sex, and race of the recipient and the donor. Other recipient variables included prior transplantation, pre-transplant blood transfusions, titer of serum panel reactive antibody (PRA) in the recipient, whether or not the patient received maintenance dialysis prior to transplant and associated medical conditions such as diabetes as the cause for end-stage renal failure (ESRF). Transplant variables included the source of organ (living or cadaveric donor), duration of cold ischemia time, extent of HLA mismatching, presence or absence of delayed graft function (DGF; defined as post-transplant dialysis within one week after transplant) and year in which transplant was performed. Post-transplant variables included use of antibody induction, discharge maintenance immunosuppression with mycophenolate mofetil or tacrolimus, clinical acute rejection within one year and post-transplant renal function as previously defined. The analyses were performed with and without post-transplant renal function to assess whether transplant year and post-transplant renal function are surrogates for each other.

The multivariate analyses were performed using proportional hazards regression models adjusted for all variables listed above. The relative hazard (RH) for long-term graft failure conditioned on survival to one year and corresponding 95% confidence intervals (CI) were estimated. Reporting bias associated with rapid notification of critical events (graft failure, death) and delayed notification for continued survival was not accounted for in this analysis.

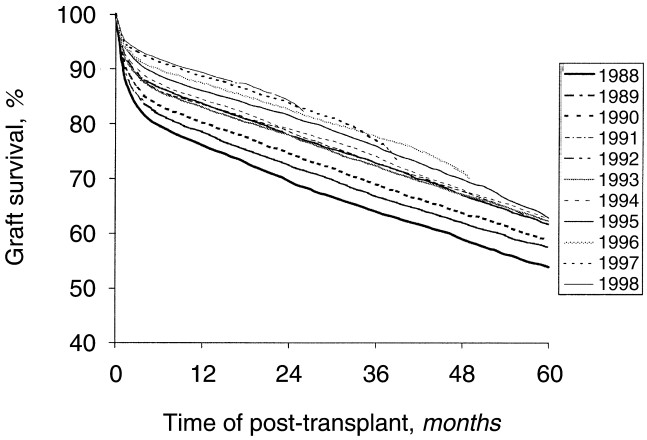

Fig. 1. Kaplan-Meier estimates for graft survival for each year after cadaveric renal transplantation.

RESULTS

A total of 105,742 adult renal transplants (77,582 cadaver and 28,160 living donor transplants) performed in the United States between 1988 and 1998 were included in this study. Of these, 18,589 cadaver transplants were performed using kidneys from donors >50 years. The one-year graft survival rate for living donor transplants in 1988 was 89.7%. This improved to 94.3% in 1998, an increment of 4.6 percentage points. During the same period graft survival rates for cadaver donor transplants improved from 76.0% to 89.3%, an increase of 13.3 percentage points. Figure 1 shows the Kaplan-Meier estimates of survival of renal grafts for cadaver transplant for each year from 1988 to 1998. The cohorts of patients transplanted in recent years have better short and long-term survival rates than patients transplanted in early years.

Figure 2 shows the Kaplan-Meier estimates for cadaver grafts survival according to six month creatinine (Fig. 2A), one year creatinine (Fig. 2B) and Δ creatinine (Fig. 2C) values. Post-transplant creatinine >1.5 mg/dL at six months and one year, and Δ creatinine ≥0.3 mg/dL were associated with a decline in long-term graft survival. Similar survival patterns were noted for living donor grafts as well for cadaver donor grafts from donors ≤ and >50 years of age (not shown). Table 1 shows the graft half-life for various post-transplant renal function groups, with and without censoring for death with a functioning graft. These are stratified according to organ source (living and cadaver donor transplants) as well as cadaver donor age (donor age ≤ and >50 years). A decline in graft half-life was noted with progressive increases in six month and one year creatinine values as well as with increasing Δ creatinine values.

The mean creatinine (±SD) values at six months and one year declined over time. For example, mean creatinine at one year decreased for living donor transplants

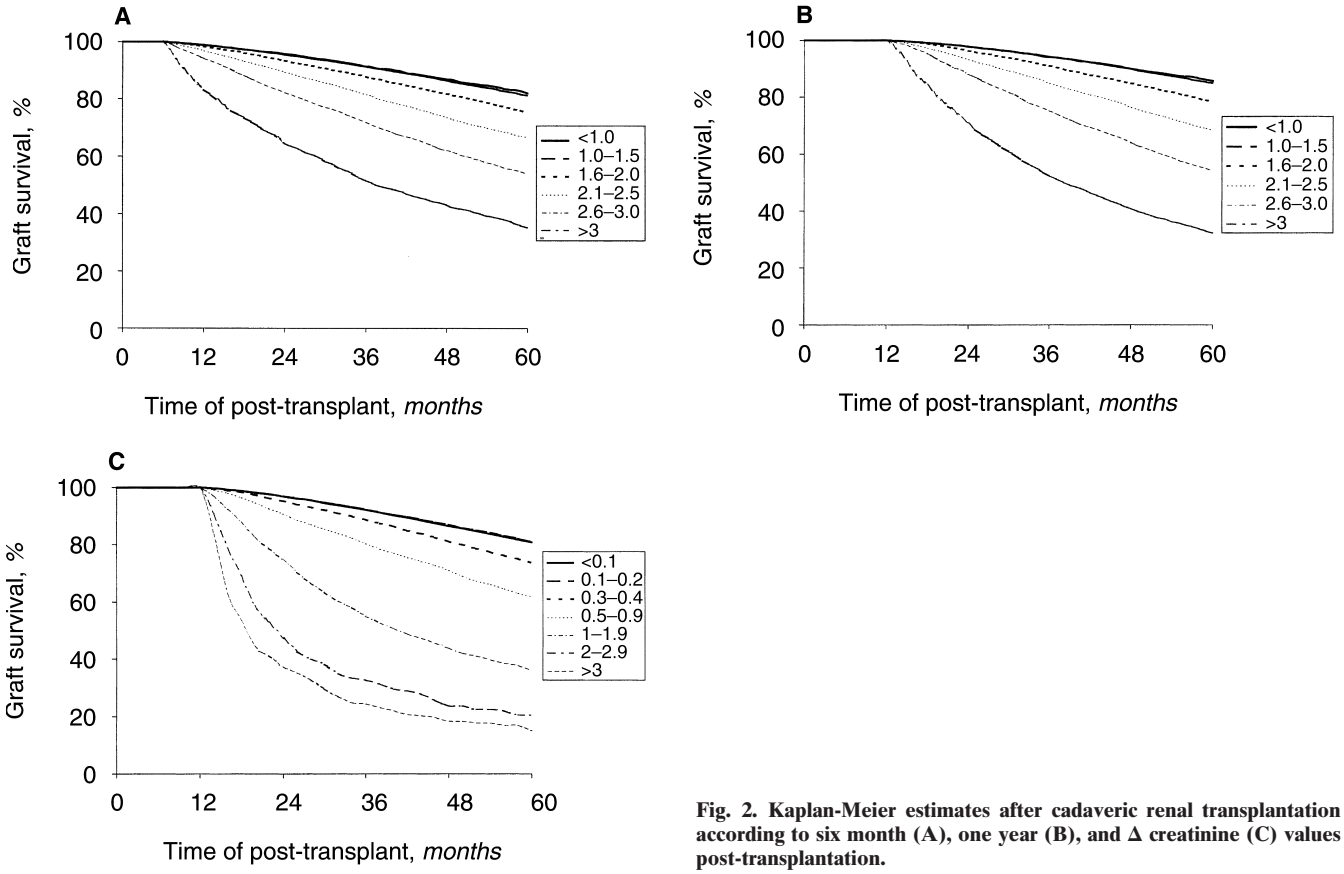

Fig. 2. Kaplan-Meier estimates after cadaveric renal transplantation according to six month (A), one year (B), and Δ creatinine (C) values post-transplantation.

from 1.65 ± 0.89 mg/dL in 1988 to 1.55 ± 0.67 mg/dL in 1998 ($P < 0.001$). During the same period similar changes in renal function were noted for cadaver transplants: 1.82 ± 0.82 to 1.67 ± 0.82 mg/dL ($P < 0.001$), cadaver donor transplants with donor age ≤50 years 1.76 ± 0.79 to 1.58 ± 0.77 mg/dL ($P < 0.001$), and donor age >50 years 2.34 ± 0.93 to 1.99 ± 0.87 mg/dL ($P < 0.001$). Figure 3 shows the cumulative distribution of one-year serum creatinine values for cadaveric recipients for 1988 and 1997. The distribution of serum creatinine was much lower in the cohort of patients transplanted in 1997. Similar trends were observed for serum creatinine at six months post-transplant and in Δ creatinine (data not shown) values.

Figure 4 shows the projected median graft half-life for each year for all cadaver transplants and for cadaver transplants according to one year creatinine values (≤ and >1.5 mg/dL). Overall improvement in half-life was seen for cadaver transplants from 7.9 (7.6, 8.2) in 1988 to 11.2 (10.1, 12.2) years in 1997, an increase of 42%. During the same period, the improvements in half-life in cadaver transplants with creatinine >1.5 mg/dL was 6.2 (5.9, 6.5) to 7.5 (6.7, 8.4) years, an increase of 21%, and for one year creatinine ≤1.5 mg/dL, was from 10.9 (10.2, 11.7) to 19 (15.9, 22.1) years, an increase of 74%.

There were differences in demographic and post-transplant variables for cadaveric recipients with one year creatinine ≤ and >1.5 mg/dL as shown in Table 2. Those with elevated creatinine at one year (serum creatinine >1.5 mg/dL) were more likely to be male, black and have had a previous transplant. They were less likely to have the diagnosis of diabetes than recipients with creatinine ≤1.5 mg/dL at one year. Donor factors were also different: those with elevated creatinine levels were more likely have been recipients of a kidney from a female donor, black donor, or an older donor. Recipients with creatinine >1.5 mg/dL at one year were also more likely to have cold ischemia time >24 hours, DGF, clinical acute rejection within one year, and less likely to have received a zero-mismatched kidney. Similar differences were noted in patients who had living donor transplant (data not shown). Thus, demographic variables such as donor/recipient age, sex, and race and transplant variables such as cold ischemia time, DGF and acute rejection are key factors contributing to elevated creatinine after transplantation.

Figure 5 shows the graft half-life for cadaver recipients according to the combination of one year creatinine (≤ and >1.5 mg/dL) and Δ creatinine (< and ≥0.3 mg/dL) along with the presence or absence of prior clinical acute

Table 1. Projected median graft half-life in years with 95% CI according to 6 month and 1 year post-transplant creatinine values

			Cadaveric donors	
	Living donors	All cadaveric donors	Donor age ≤50	Donor age >50
6 Month creatinine *mg/dL* (*N*)	(24,512)	(63,106)	(52,045)	(11,061)
<1.0	19.9 (16.8, 23.0)	12.3 (11.3, 13.3)	12.6 (11.5, 13.6)	7.1 (4.5, 9.7)
1.1–1.5	18.0 (17.2, 18.9)	11.5 (11.2, 11.8)	11.7 (11.4, 12.0)	9.5 (8.7, 10.3)
1.6–2.0	13.3 (12.6, 14.1)	8.8 (8.6, 9.1)	9.1 (8.8, 9.4)	7.5 (7.1, 8.0)
2.1–2.5	8.9 (8.1, 9.6)	6.6 (6.4, 6.9)	6.8 (6.5, 7.1)	6.2 (5.8, 6.6)
2.6–3.0	6.1 (5.3, 6.9)	4.8 (4.5, 5.0)	5.0 (4.7, 5.4)	4.3 (3.9, 4.7)
>3.0	3.2 (2.8, 3.7)	3.2 (3.1, 3.4)	3.5 (3.2, 3.7)	2.9 (2.7, 3.2)
6 Month creatinine *mg/dL*				
Death with a functioning graft				
<1.0	36.8 (29.0, 44.6)	26.4 (23.3, 29.6)	26.8 (23.5, 30.0)	18.8 (7.7, 29.9)
1.1–1.5	30.3 (28.4, 32.2)	20.9 (20.2, 21.6)	21.1 (20.3, 21.8)	19.0 (16.7, 21.2)
1.6–2.0	19.1 (17.9, 20.3)	14.1 (13.6, 14.6)	14.3 (13.8, 14.9)	13.1 (12.1, 14.2)
2.1–2.5	11.8 (10.6, 12.9)	9.3 (8.9, 9.7)	9.3 (8.8, 9.7)	9.3 (8.5, 10.1)
2.6–3.0	7.6 (6.4, 8.7)	6.0 (5.7, 6.4)	6.5 (6.0, 7.0)	5.3 (4.8, 5.8)
>3.0	3.8 (3.2, 4.4)	3.9 (3.7, 4.1)	4.2 (3.8, 4.5)	3.5 (3.2, 3.8)
1 Year creatinine *mg/dL*				
<1.0	21.1 (17.6, 24.5)	14.0 (12.8, 15.1)	14.0 (12.8, 15.2)	11.8 (5.6, 18.0)
1.1–1.5	20.8 (19.7, 21.8)	13.2 (12.8, 13.5)	13.3 (12.9, 13.6)	11.9 (10.8, 13.1)
1.6–2.0	14.6 (13.8, 15.4)	9.4 (9.2, 9.7)	9.7 (9.4, 10.0)	8.3 (7.8, 8.9)
2.1–2.5	8.8 (8.1, 9.6)	6.4 (6.2, 6.7)	6.5 (6.2, 6.7)	6.4 (6.0, 6.9)
2.6–3.0	5.1 (4.5, 5.7)	4.5 (4.3, 4.7)	4.3 (4.1, 4.6)	4.8 (4.4, 5.2)
>3.0	2.3 (2.1, 2.6)	2.4 (2.3, 2.5)	2.3 (2.2, 2.4)	2.7 (2.5, 2.9)
1 Year creatinine *mg/dL*				
Death with a functioning graft (*N*)	(22,712)	(57,971)	(48,054)	(9917)
<1.0	42.7 (32.6, 52.8)	30.7 (26.8, 34.5)	30.9 (27.0, 34.8)	23.6 (6.1, 41.1)
1.1–1.5	38.0 (35.3, 40.7)	25.8 (24.9, 26.8)	25.7 (24.7, 26.8)	27.1 (23.1, 31.0)
1.6–2.0	21.4 (20.0, 22.9)	15.4 (14.9, 16.0)	15.5 (14.9, 16.1)	15.1 (13.7, 16.4)
2.1–2.5	11.4 (10.3, 12.4)	9.0 (8.6, 9.4)	8.8 (8.3, 9.2)	9.8 (8.9, 10.7)
2.6–3.0	6.2 (5.3, 7.0)	5.8 (5.5, 6.1)	5.6 (5.2, 6.0)	6.3 (5.6, 6.9)
>3.0	2.6 (2.3, 2.9)	2.8 (2.6, 2.9)	2.6 (2.4, 2.7)	3.1 (2.9, 3.3)
Δ Creatinine from 6 months to 1 year				
<0.1	17.3 (16.5, 18.1)	10.7 (10.5, 11.0)	11.3 (11.1, 11.6)	8.0 (7.6, 8.4)
0.1–0.2	16.6 (15.4, 17.8)	10.6 (10.2, 11.0)	11.1 (10.7, 11.6)	7.9 (7.1, 8.6)
0.3–0.4	13.1 (12.0, 14.3)	7.7 (7.3, 8.0)	8.1 (7.7, 8.5)	6.2 (5.6, 6.7)
0.5–0.9	7.9 (7.2, 8.7)	5.4 (5.1, 5.6)	5.8 (5.5, 6.1)	4.3 (3.9, 4.6)
1.0–1.9	3.3 (2.8, 3.7)	2.6 (2.4, 2.8)	2.7 (2.5, 2.9)	2.3 (2.0, 2.6)
2.0–2.9	1.7 (1.2, 2.1)	1.4 (1.2, 1.5)	1.3 (1.1, 1.4)	1.7 (1.3, 2.2)
≥3.0	1.1 (0.8, 1.4)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	1.2 (0.8, 1.5)
Δ Creatinine				
Censor for death with a functioning graft				
<0.1	27.7 (26.1, 29.3)	18.2 (17.6, 18.7)	19.3 (18.7, 19.9)	12.9 (12.1, 13.7)
0.1–0.2	25.7 (23.5, 28.0)	18.0 (17.1, 18.9)	19.0 (18.0, 20.0)	13.1 (11.6, 14.6)
0.3–0.4	19.9 (17.7, 22.1)	11.7 (11.1, 12.4)	12.6 (11.8, 13.4)	9.0 (8.0, 10.0)
0.5–0.9	10.4 (9.3, 11.6)	7.4 (7.0, 7.8)	7.9 (7.4, 8.4)	6.0 (5.4, 6.6)
1.0–1.9	3.8 (3.3, 4.4)	3.1 (2.9, 3.3)	3.2 (2.9, 3.5)	2.9 (2.5, 3.2)
2.0–2.9	1.8 (1.3, 2.3)	1.5 (1.3, 1.7)	1.4 (1.2, 1.6)	1.9 (1.4, 2.4)
≥3.0	1.2 (0.8, 1.5)	1.2 (1.0, 1.3)	1.2 (1.0, 1.3)	1.2 (0.8, 1.6)

rejection. Recipients with creatinine >1.5 mg/dL with Δ creatinine ≥0.3 mg/dL have a substantially lower projected graft half-life than all other groups regardless of prior acute rejection. Rejection episodes had greatest impact for recipients with serum creatinine ≤1.5 and Δ creatinine ≥0.3 mg/dL.

The results of the proportional hazard analysis are shown in Table 3. The parameter estimate, RH, 95% CI, and *P* value are shown for each recipient, donor, transplant, and post-transplant characteristic included in the final model. Some significant factors that increased the risk of graft failure include recipient variables such as older age, black race, diabetes, and previous transplant. Similarly, older donor age and black donor race increased the risk of long-term failure. Living donor transplant recipients had a decreased risk of graft failure. Transplant variables such as increasing HLA mismatch level and DGF also were associated with increased risk of graft failure.

There was also a significant interaction between the different measures of post-transplant renal function as shown in Figure 6. Serum creatinine increment of 1.0 mg/dL, at one year post-transplant without a change in Δ creatinine, increased RH of graft failure to 1.63 (1.61, 1.65; $P < 0.0001$). However, when this was accompanied with a change in Δ creatinine of 0.5 and 1.0 mg/dL, the RH

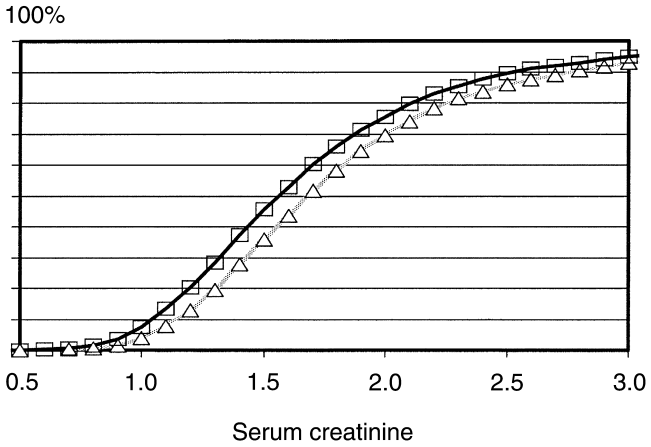

Fig. 3. Cumulative distribution of one-year serum creatinine values for cadaveric recipients transplanted in 1988 (△) and 1997 (□).

of graft failure increased to 2.26 (2.2, 2.31) and 3.13 (2.99, 3.27; $P < 0.0001$), respectively. Thus, increases in both the serum creatinine value at one year and in the Δ creatinine resulted in progressively increasing risks of graft failure. The relatively large values of RH for the combination of these effects indicate the importance of these factors together in predicting long-term graft survival.

When post-transplant renal function was included in the model, the RH reduction per year was 1.01 (0.94 to 1.05; $P = 0.89$). However, if post-transplant renal function was excluded, transplants performed in 1993, 1996, 1997, and 1998 had reduced RH of graft failure compared to transplants performed in other years (1988 to 1992, 1994, and 1995; $P < 0.05$). Because the effect of transplant year was no longer significant when post-transplant renal function was included in the model, it is clear that these variables are surrogates for one another, and improved graft survival rate in recent years is due to improved post-transplant renal function during the same time.

DISCUSSION

The current shortage of organs for transplantation underscores the importance of optimizing long-term graft survival. Since1988, there has been a gradual improvement in one-year graft survival. Thus, in recent years there are more patients with a functioning graft at the end of one year post-transplant. There has also been a steady improvement in graft half-life [2]. This has occurred despite increasing use of older donors. During the period between 1988 and 1997 there also has been a gradual reduction in acute rejection episodes, which is an important predictor for late graft failure [2]. Other variables such as recipient and donor age, elevated PRA, pre-transplant dialysis requirements, presence of diabetes and DGF are known to have a detrimental effect on long-term graft survival [3, 4, 10]. However, improvements in long-term graft survival have been noted even after correcting for these variables [2]. Serum creatinine is not a reliable method for estimating renal function; as it dependent on age, gender, race and body weight. However, these variables were included in the Cox model analysis. From the current study, post-transplant renal function within the first year emerges as an important variable, which influences long-term graft survival. Other key variables for long-term outcome are: donor source (living vs. cadaver), donor age, recipient race and presence of diabetes. When renal function was introduced in the Cox model for late graft failure, the decline in RH between 1988 and 1997 was nullified. This indicated that the improvements in half-life in recent years are in part due to better preservation of renal function within the first year.

In the current analysis, a progressive decline in graft survival rates was noted for all groups, with and without censoring for death with a functioning graft, when the one year creatinine value was >1.5 mg/dL or Δ creatinine was ≥0.3 (Table 1). The improved half-life in recent years was seen predominantly in those patients with a one year creatinine value ≤1.5 (Fig. 4). Since 1988, there has been a gradual decline in mean creatinine values at one year post-transplantation for all groups. The cumulative distribution of one-year serum creatinine has improved in 1997 compared to 1988 (Fig. 3). There also has been a gradual reduction in acute rejection episodes over time [2]. However, when renal function within the first year and clinical acute rejection were included in the regression model for long-term graft failure, it was the one year creatinine and Δ creatinine values that were significant, and not the clinical acute rejection episodes (Table 3). Stratification of cadaveric recipients in this study, according to one year creatinine (≤ or >1.5 mg/dL), Δ creatinine (<0.3 or ≥0.3) values and clinical acute rejection, revealed that renal function is the most important predictor of graft survival (Fig. 5). Thus, in the setting of acute rejection, it is the preservation of renal function that is more important for graft survival.

In previous studies, discharge creatinine was identified as a strong predictor of transplant survival [4]. The projected median graft half-life for cadaveric transplants with discharge creatinine values of 0.5 to 1.5 mg/dL was 11.5 years. Half-life values for patients with discharge serum creatinine 1.6 to 2.5 and >2.5 mg/dL were 9.6 and 7.2 years, respectively. Discharge creatinine has limited value as many patients are discharged within a few days after transplant, before they reach nadir creatinine levels. This is true especially for recipients of renal transplants from older donors, those with prolonged cold ischemia time and those who experience DGF. One-month creatinine values may be falsely elevated due to higher cyclosporine and tacrolimus levels used to prevent acute rejec-

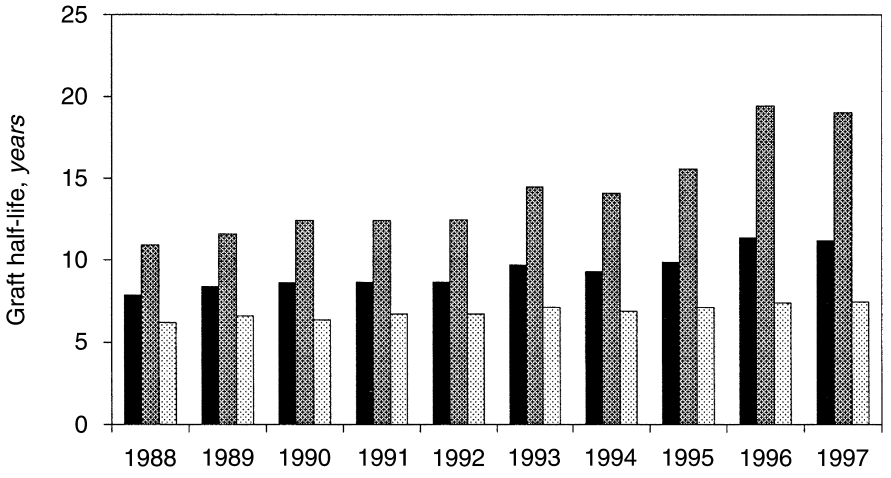

Fig. 4. Projected median kidney half-life for all cadaveric renal grafts for each year (■) and those with one year creatinine values ≤ (▩) and > (▨) 1.5 mg/dL.

Table 2. Summary of recipient, donor and transplant variables (%) for cadaveric transplants associated with elevated 1 year serum creatinine

	1 Year serum creatinine		
	≤1.5 *mg/dL*	>1.5 *mg/dL*	*P* value
Recipient variables			
Male	49.4	71.8	<0.0001
Black	19.3	29.7	<0.0001
Diabetes	22.1	18.4	<0.0001
Previous transplant	13.9	15.8	<0.0001
Donor variables			
Male	67.8	56.6	<0.0001
Black	9.2	10.3	<0.0001
Age >50	9.3	28.3	<0.0001
Transplant variables			
Cold ischemia time >24 hours	34.2	38.3	<0.0001
Delayed graft function	16.2	26.9	<0.0001
Clinical acute rejection	30.2	31.7	<0.0001
Zero mismatch	12.1	9.1	<0.0001

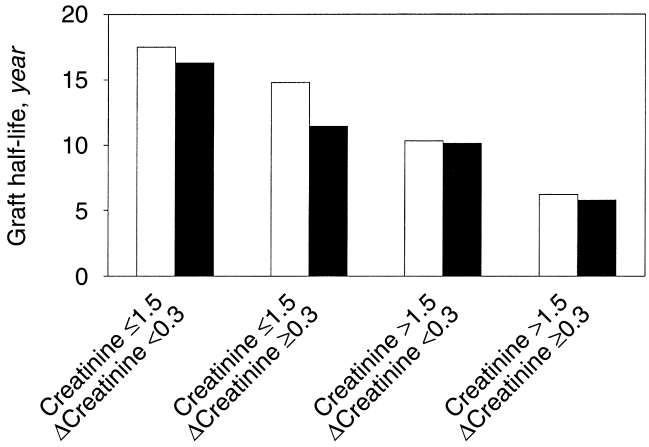

Fig. 5. Projected median graft half-life for cadaveric renal grafts according to one year creatinine (≤ or >1.5 mg/dL), Δ creatinine (≥0.3 or <0.3 mg/dL) and presence (■) or absence (□) of clinical acute rejection within one year post-transplantation.

tion. Hence, this study used six month and one year creatinine values to predict long-term graft survival.

Other investigators using single center studies have noted a strong correlation between serum creatinine at three and six months [5] and at one year with long-term survival [6]. Similarly, a Δ creatinine of >0.5 or >1.0 mg/dL at six weeks or the pattern of creatinine response after acute rejection have been correlated to long-term graft failure [7, 8]. In the current study, all patients transplanted in the US over 11 years were included in the analysis. This provided an opportunity for a more comprehensive analysis to examine the effects of individual variables such as acute rejection episodes, transplant year and post-transplant renal function on long-term graft survival.

There may be several reasons for the improvement in renal function over time during the first year after transplantation. The improvement has occurred despite increasing reliance on older donors, which are generally associated with poorer graft survival [10, 11]. First of all, there are known factors that influence long-term outcome, such as occurrence of acute rejection, incidence of DGF and HLA mismatching, which have changed favorably over time. In addition, it is likely that acute rejection episodes have been treated effectively since 1988, thereby preserving renal function and increasing kidney half-life. Treatment and prevention of subclinical acute rejection has been noted to preserve renal function over time [12]. It is also possible that cyclosporine/tacrolimus nephrotoxicity has diminished over time. Finally, other factors such as optimizing the use of kidneys from older donors [10, 11], better management of DGF [3, 4, 13], and better control of hypertension and hyperlipidemia may contribute to the preservation of renal function during the first year post-transplantation. The long-term survival improvements in recent years appear to be due to enhanced one-year graft survival (Fig. 1). However, on further care-

Table 3. Cox proportional hazard model results: Risks for long-term graft failure

Variables	Parameter estimate	RH	95% Confidence interval	*P* value
Recipient variables				
Recipient age				
Linear	0.0696			<0.0001
Quadratic	0.0770			<0.0001
53 vs. 43 years		1.07	(1.06, 1.08)	
Recipient female	0.0970	1.10	(1.07, 1.13)	<0.0001
Recipient black	0.3412	1.41	(1.36, 1.46)	<0.0001
Diabetes	0.4653	1.59	(1.54, 1.65)	<0.0001
Hypertensive nephropathy	0.2117	1.24	(1.19, 1.29)	<0.0001
Pre-TX dialysis	0.1950	1.22	(1.16, 1.27)	<0.0001
Pre-TX transfusions	0.0577	1.06	(1.03, 1.09)	0.0001
Previous transplant	0.3193	1.38	(1.32, 1.43)	<0.0001
Most recent PRA 80%+	0.1552	1.17	(1.06, 1.28)	0.0010
Donor variables				
Donor age >50[a]	0.2109	1.23	(1.14, 1.34)	<0.0001
Donor black	0.1398	1.15	(1.10, 1.20)	<0.0001
Transplant variables				
HLA mismatch level[a]	0.0512	1.05	(1.04, 1.06)	<0.0001
Delayed graft function	0.1506	1.16	(1.12, 1.20)	<0.0001
Living donor transplant	−0.2227	0.80	(0.77, 0.83)	<0.0001
Donor age >50 and HLA mismatch[a]	−0.0263	0.97	(0.95, 1.00)	0.0243
Post-transplant variables				
Acute rejection within 1 year	−0.0022	1.00	(0.97, 1.03)	0.8853
Any induction therapy	0.0125	1.01	(0.98, 1.04)	0.4018
Mycophenolate mofetil (MMF)	−0.0041	1.00	(0.94, 1.06)	0.8975
Tacrolimus	0.0282	1.03	(0.95, 1.11)	0.4841
Serum creatinine at 1 year[b]	0.4865	1.63	(1.61, 1.65)	<0.0001
Δ creatinine 1 yr-6 mo[b]	0.7409	2.26	(2.2, 2.31)	<0.0001
1 Year creatinine & Δ creatinine[b]	−0.0874			<0.0001

[a] Due to the interaction, these terms must be considered in combination to determine all values of the relative hazard function
[b] See illustration of the interaction between 1 year creatinine and Δ creatinine in Figure 6

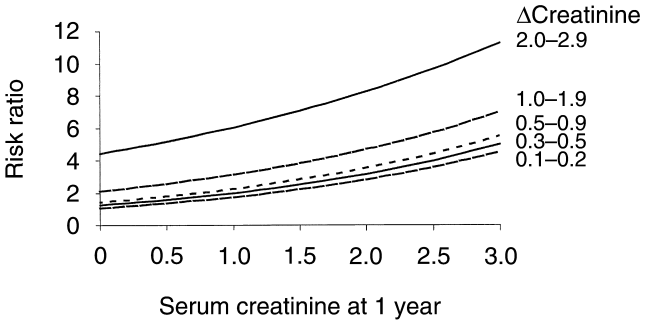

Fig. 6. Relative hazard for graft failure according to one-year creatinine and Δ creatinine values.

ful analysis improvements in graft half-life was noted in cohorts of patients transplanted recently (Fig. 4).

The current study illustrates that events occurring within the first year are of critical importance for long-term graft survival. By using a combination of one year creatinine >1.5 and Δ creatinine ≥0.3 values, subsets of patients with markedly reduced graft half-life can be identified. This provides an opportunity to conduct a secondary intervention trial at an early time point to delay graft failure for this population. Conversely, transplant recipients with a one year creatinine ≤1.5 and Δ creatinine <0.3 have excellent long-term outcomes. Thus, the quality of renal function (creatinine ≤1.5 mg/dL at 1 year) should be implemented as a newer endpoint for primary comparative trials.

In conclusion, one year creatinine and Δ creatinine values are the variables that correlate best with long-term renal graft survival. Recent improvements in graft half-life for the United States can be attributed to better preservation of renal function within the first year after transplantation.

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