

Time Dependency of Factors Affecting Renal Allograft Survival

SURAZEE PROMMOOL,* GIAN S. JHANGRI,† SANDRA M. COCKFIELD,* and PHILIP F. HALLORAN*

Departments of *Medicine (Division of Nephrology) and †Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada.

Abstract. The function of renal transplants can deteriorate at any time posttransplant, but the risks and mechanisms may differ at different times posttransplant. Survival of 522 consecutive cadaveric renal transplant recipients followed for at least 6 mo were analyzed, with patient death censored. The overall risk factors in univariate analysis were acute rejection requiring antibody therapy (AR), delayed graft function, elevated serum creatinine at 6 mo, high panel-reactive antibodies, and donor age ≥ 55 yr, with borderline effects of recipient age and female gender. These risks were studied in each of three intervals posttransplantation: ≤ 6 mo, 6 mo to 5 yr, and > 5 yr. Of the 135 graft failures, 53 occurred ≤ 6 mo, 61 between 6 mo and 5 yr, and 21 beyond 5 yr. By multivariate analysis, the

risks for graft failure in interval ≤ 6 mo were AR (hazard ratio (HR) = 4.86, $P < 0.001$); delayed graft function (HR = 1.47, $P = 0.06$); and high panel-reactive antibodies (HR = 2.04, $P = 0.03$). Between 6 mo and 5 yr, the risks for graft loss were AR (HR = 2.87, $P < 0.001$) and serum creatinine at 6 mo ≥ 150 $\mu\text{mol/L}$ (HR = 3.69, $P < 0.001$). Beyond 5 yr the risk factors were donor age ≥ 55 yr (HR = 5.87, $P = 0.002$), with a borderline effect of kidneys from female donors (HR = 2.28, $P = 0.07$). HLA-A, -B, and -DR matching and presensitization had most of their effect through early AR and impaired function. The results indicate that risks for graft loss are time-dependent: early losses correlate with injury and rejection, but late events correlate with donor age and possibly workload.

If patient death with a functioning graft is not considered, the majority of late graft loss is due to chronic allograft nephropathy (CAN), previously called chronic rejection (1–5). CAN is a state of impaired renal allograft function at least 3 mo posttransplant, independent of acute rejection, overt drug toxicity, and specific disease entities, preferably with a compatible biopsy. New immunosuppressive drugs have markedly improved short-term allograft survival, but long-term allograft survival has shown less change (6,7). This observation raises questions about the conventional assumption in transplantation that CAN is immune-mediated and is due to or predicted by early rejection. CAN is a diagnosis of exclusion since the pathology is not specific (<http://tpis.upmc.edu/tpis/schema/KNCode97.html>). Indeed, the pathology overlaps the changes of human aging and age-related diseases in native kidneys: tubular atrophy, interstitial fibrosis, and fibrous intimal thickening of small arteries. Some definitions of CAN include an arbitrary rate of progression, but the rate of progression is irregular (8) and is not *per se* a criterion for defining a renal disease. Thus, CAN should be considered a final common pathway of a variety of stresses to renal tissue. These stresses may operate at different times after transplantation, and the

same pathology may reflect different disease processes, immune or nonimmune. The early stresses are reflected in the power of the immunologic risk factors such as high panel-reactive antibodies (PRA) and HLA mismatching, as well as measures of acute injury: brain death (comparing living *versus* nonliving donors) and mode of brain death (stroke *versus* trauma). The early events in the transplant course—delayed graft function (DGF) and acute rejection requiring antibody therapy (AR)—also reduce graft survival.

We know less about the factors that cause very late loss of transplanted kidneys, *e.g.*, after 5 yr or more. Some early risks may be so high that they preclude survival into the later intervals. The influences of these early events will decline as the kidneys carrying this risk are lost. Thus, the role of early events in late graft loss may be different from their role in early or intermediate graft failure, and assumptions about the causes of graft failure in the early interval may not continue to be valid for the very late era.

The present study aimed to define whether known risks for graft survival operated differentially over time. We retrospectively analyzed all cadaver transplants in our center by dividing the course into three posttransplant intervals: ≤ 6 mo, 6 mo to 5 yr, and > 5 yr. We identified the risk factors for the entire course, and then analyzed the relative impact of these risk factors on the probability of graft loss in each interval. The results indicate that the risk factors operate differentially over time. Graft loss before 5 yr is predominantly associated with early AR and acute renal injury (DGF), whereas graft loss after 5 yr does not reflect these factors, but is affected by donor age.

Received May 10, 1999. Accepted August 12, 1999.

Correspondence to Dr. Philip F. Halloran, Division of Nephrology and Immunology, #303, 8249-114 Street, Edmonton, Alberta, Canada T6G 2R8. Phone: 780-407-8880; Fax: 780-431-0461; E-mail: phil.halloran@ualberta.ca

1046-6673/1103-0565

Journal of the American Society of Nephrology

Copyright © 2000 by the American Society of Nephrology

Table 1. Causes of graft loss^a

Characteristic	Interval 1 ≤6 mo (n = 522, 100%)	Interval 2 6 mo to 5 yr (n = 463, 88.7%)	Interval 3 >5 yr (n = 187, 35.8%)	All Intervals (n = 522, 100%)
Graft lost	53	61	21	135
Death with functioning graft	6	25	20	51
Graft functioning (at the time of analysis)				
available for the next interval	463	187	NA	NA
not reached the end of the interval	0	179	142	321
Lost to follow-up	0	11	4	15
Reason for graft lost				
acute rejection	23	7	1	31
CAN	2	35	16	53
never functioned	12	0	0	12
PTLD	2	1	0	3
recurrent disease	1	11	1	13
technical	9	2	0	11
other	4	4	2	10
unknown	0	1	1	2

^a CAN, chronic allograft nephropathy; PTLD, posttransplant lymphoproliferative disease.

Table 2. Characteristics of cadaveric renal transplant recipients from January 1987 to September 1998 (n = 522) grouped as number suitable for analysis in each interval^a

Variable	Interval 1 ≤6 mo (n = 522, 100%)	Interval 2 6 mo to 5 yr (n = 463, 88.7%)	Interval 3 >5 yr (n = 187, 35.8%)
Donor age (mean ± SD)	34.1 ± 15.6	33.9 ± 15.5	33.5 ± 14.4
% donor age ≥55 yr	9.6	8.5	6.5
% donor female	40.4	40.1	34.8
% donor CMV+	49.7	49.5	52.9
Recipient age (mean ± SD)	42.9 ± 14.1	42.9 ± 14.1	42.1 ± 13.3
% recipient age ≥55 yr	21.6	21.6	19.8
% recipient female	36.4	36.3	39.0
% recipient CMV+	70.6	69.9	69.0
% retransplant	21.3	20.5	18.2
% disease recurrent	7.3	7.6	9.1
% with PRA high ≥50%	15.2	13.6	15.8
% with PRA recent ≥50%	6.5	6.4	6.5
HLA-A,B mismatch (mean ± SD)	2.8 ± 1.0	2.8 ± 1.0	2.8 ± 1.0
HLA-DR mismatch (mean ± SD)	1.2 ± 0.7	1.2 ± 0.7	1.1 ± 0.6
% HLA-A,B mismatch >2	62.8	62.0	62.4
% HLA-DR mismatch >1	33.6	31.7	29.2
% S _{Cr} at 6 mo ≥150 μmol/L	NA	36.6	32.3
% DGF	32.2	29.8	30.5
% rejection AB	19.2	19.4 ^a	18.7 ^b

^a CMV, cytomegalovirus; PRA, panel-reactive antibodies; S_{Cr}, serum creatinine; DGF, delayed graft function.

^b In interval 1, we included only the rejections occurring before 6 mo. Otherwise, we included all rejections requiring antibody therapy. There were no rejections requiring antibody therapy in the third interval.

The results suggest that processes causing CAN and late graft loss are dependent on the time posttransplant, and that management should be potentially tailored to these changing risks.

Materials and Methods

A prospective database was created of 522 consecutive renal transplants performed at the University of Alberta Hospital between Jan-

Table 3. Factor affecting graft survival function: Cox regression univariate analysis^a

Variable	Graft Survival Time							
	Interval 1 ≤6 mo		Interval 2 6 mo to 5 yr		Interval 3 >5 yr		All Intervals	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Donor age ≥55 yr	1.88 (0.88 to 4.00)	0.104	1.20 (0.48 to 3.00)	0.70	5.87 (1.92 to 17.94)	0.002	1.88 (1.13 to 3.14)	0.016
Donor female	1.06 (0.60 to 1.89)	0.83	1.43 (0.86 to 2.39)	0.17	2.31 (0.98 to 5.45)	0.057	1.39 (0.98 to 1.96)	0.07
Recipient age ≥55 yr	0.74 (0.36 to 1.51)	0.41	0.40 (0.17 to 0.93)	0.03	1.13 (0.37 to 3.37)	0.83	0.62 (0.38 to 1.01)	0.055
Recipient female	1.25 (0.72 to 2.16)	0.42	1.01 (0.60 to 1.70)	0.97	0.75 (0.30 to 1.87)	0.54	1.05 (0.74 to 1.49)	0.78
HLA-A,B mismatch >2	1.53 (0.84 to 2.78)	0.16	1.14 (0.67 to 1.93)	0.63	0.89 (0.37 to 2.13)	0.80	1.22 (0.86 to 1.75)	0.27
HLA-DR mismatch >1	1.91 (1.11 to 3.29)	0.019	1.24 (0.72 to 2.12)	0.43	0.44 (0.15 to 1.30)	0.17	1.29 (0.90 to 1.83)	0.16
PRA high ≥50%	2.64 (1.44 to 4.84)	0.002	0.99 (0.47 to 2.08)	0.97	0.99 (0.29 to 3.35)	0.98	1.54 (1.00 to 2.37)	0.048
PRA recent ≥50%	1.30 (0.46 to 3.61)	0.62	1.67 (0.72 to 3.88)	0.24	0.72 (0.10 to 5.37)	0.75	1.36 (0.73 to 2.53)	0.33
S _{Cr} at 6 mo ≥150	NA		4.58 (2.64 to 7.95)	<0.001	2.01 (0.85 to 4.75)	0.11	3.64 (2.31 to 5.73)	<0.001
DGF	2.30 (1.34 to 3.94)	0.002	1.93 (1.16 to 3.19)	0.011	1.22 (0.50 to 2.94)	0.67	1.93 (1.37 to 2.70)	<0.001
Rejection AB ^b	4.75 (2.77 to 8.14)	<0.001	3.81 (2.31 to 6.29)	<0.001	1.11 (0.40 to 3.03)	0.84	3.17 (2.26 to 4.45)	<0.001

^a HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 2.

^b In interval 1, we included only the rejections occurring before 6 mo. Otherwise, we included all rejections requiring antibody therapy.

uary 1, 1987 and April 30, 1998, and followed for a minimum of 6 mo. The database includes donor characteristics (age and gender), recipient variables (age at transplant, gender, both recent and peak PRA levels, type of end-stage renal disease), and transplant variables (HLA-A, B mismatches, HLA-DR mismatches, ABO compatibility, cytomegalovirus status). The date of transplant failure was defined as the earliest time of return to chronic dialysis, transplant nephrectomy, or retransplantation. Approximately 25% of patients received prophylactic antilymphocyte antibodies (Minnesota antilymphocyte globulin, rabbit anti-thymocyte globulin [SangStat, Fremont, CA], Upjohn AT-GAM, or anti-CD3 [OKT3]) either for DGF or at the discretion of the attending physician for perceived high immunologic risk. Rejection is diagnosed on the basis of an elevation of serum creatinine, but not all rejections were biopsied. Thus, for purposes of this analysis, only rejections severe enough to warrant treatment with antibody therapy (anti-lymphocyte globulin or OKT3) were analyzed. The term AR as used here refers to rejection requiring antibody therapy. Most episodes thus defined (84%) occurred before 6 mo. The decision for antibody therapy for AR was made on the basis of clinical or histologic severity or resistance to steroid. Pathologic criteria for rejection on biopsy were those that subsequently became the Banff criteria (9). DGF or acute tubular necrosis is defined as requiring dialysis during the first 2 wk posttransplantation and/or urine output <1000 cc in the first 24 h, excluding other causes.

The study was performed by dividing the time posttransplant into three intervals: 1: ≤6 mo; 2: 6 mo to 5 yr; and 3: >5 yr. We included 522 consecutive cadaver donor (CD) transplants, of which 522, 463, and 187 transplants were available for analysis in intervals 1, 2, and 3, respectively. There were 53 graft failures in interval 1, 61 in interval 2, and 21 in interval 3. Comparisons of all the risk factors were performed. The analyses included first transplants and retransplants, but not living donor transplants. Graft survival was censored for patients who died or still had functioning grafts in each interval or who were lost to follow-up. Note that although the risks were all either pretransplant or early post transplant, the risks were analyzed for their impact on graft loss in the early, intermediate, and late intervals. For the analysis of graft survival in the initial 6 mo, only those rejection episodes in the first 6 mo were included; for overall survival analysis and for survival in intervals beyond 6 mo, all rejections occurring before or after 6 mo were included.

Statistical Analyses

Baseline characteristics among groups were compared using χ^2 test and ANOVA for categorical and continuous variables. Survival analysis was performed using the Kaplan–Meier and Cox regression. Variables were screened using Kaplan–Meier survival curves and Cox regression, with the variable of interest as a single main effect. Multivariate models were built in a stepwise hierarchical manner, testing the significance of added terms using the likelihood ratio method.

Results

The causes of graft loss are shown in Table 1. All 522 transplants were available for analysis in the first interval (graft failure ≤6 mo). Of these, 59 were lost in the first interval, 53 due to graft loss and six due to death with function. Thus, 463 grafts (88.7%) were functioning at the beginning of the second interval. During the second interval, 61 failed due to graft loss and 25 due to death with function, while 179 had not reached the end of the interval but were still functioning at the time of

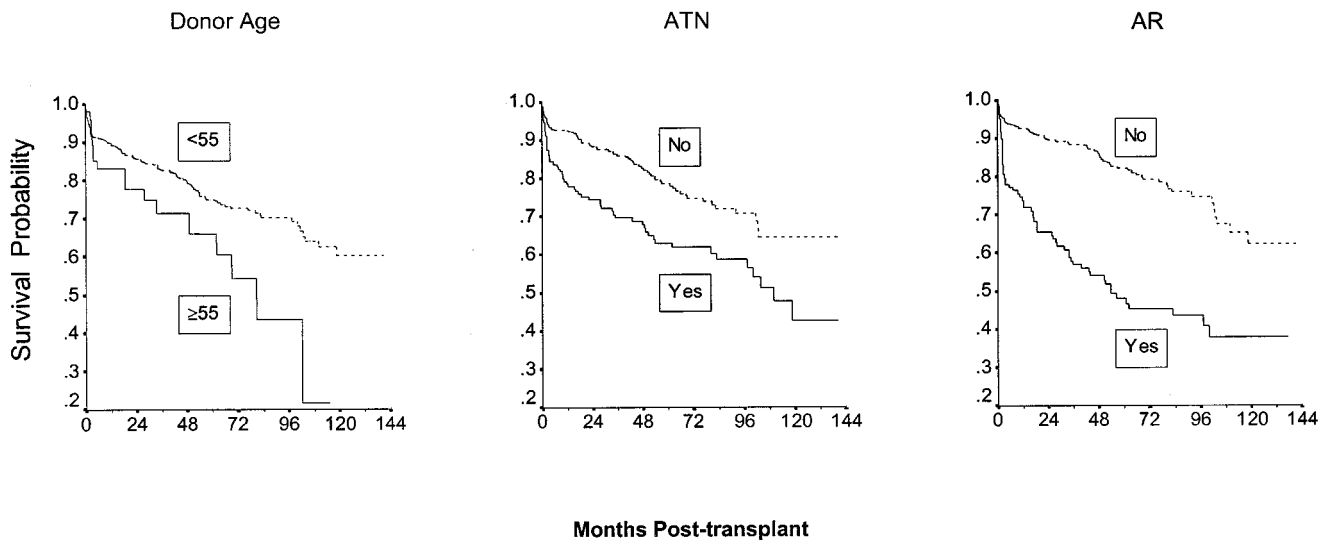


Figure 1. Kaplan-Meier graft survival during the entire period. ATN, acute tubular necrosis; AR, acute rejection.

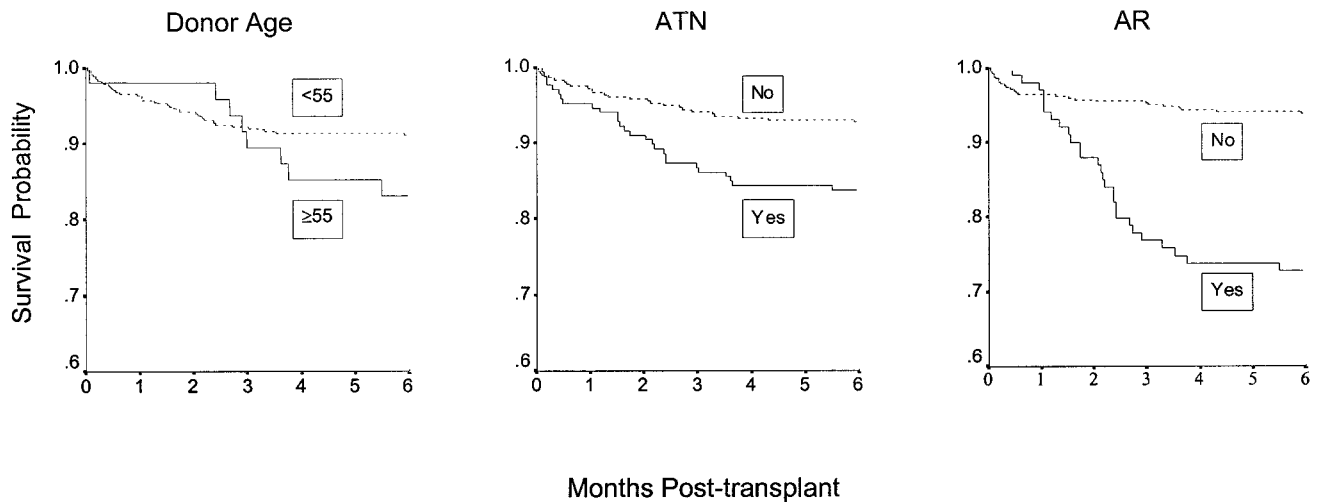


Figure 2. Kaplan-Meier graft survival during the first 6 mo after transplantation.

analysis, and 11 were lost to follow-up. Thus, 187 (35.8%) functioning grafts were available for analysis at the beginning of the third interval (>5 yr). Death with a functioning graft ($n = 51$) was censored as a cause of graft loss. Of the 135 transplants that failed with a surviving patient at the time of graft failure, 53 (39.3%) failed in interval 1, 61 (45.2%) in interval 2, and 21 (15.6%) in interval 3. Most graft loss after the initial 6 mo was due to CAN. We analyzed all 522 grafts for graft loss, with continued function at the time of the analysis censored at the time of the analysis, and loss to follow-up or death with function censored at the time of the event.

Table 2 shows some donor and recipient characteristics for the total grafts that entered each interval. The characteristics of the patients available for analysis in each interval were similar, and no differences were statistically significant. The percent-

age of patients with DGF, with acute rejection as defined, and with elevated serum creatinine at 6 mo is the same in the population available for analysis in all intervals.

We performed univariate analysis of the factors affecting graft survival in the three intervals compared to the overall group (Table 3). In the first 6 mo, the factors significantly associated with graft failure were HLA-DR mismatch >1 (hazard ratio [HR] = 1.91, $P = 0.019$), highest PRA $\geq 50\%$ (HR = 2.64, $P = 0.002$), DGF (HR = 2.30, $P = 0.002$), and AR (HR = 4.75, $P < 0.001$). (Only the AR events before 6 mo are included in the analysis of survival in the first 6 mo, but all AR was included in the analysis of the second and third intervals.) The effect of donor age was borderline at HR = 1.88, $P = 0.104$. In the intermediate interval (6 to 60 mo), the factors associated with graft failure are DGF (HR = 1.93, $P = 0.011$) and AR (HR = 3.81, $P < 0.001$).

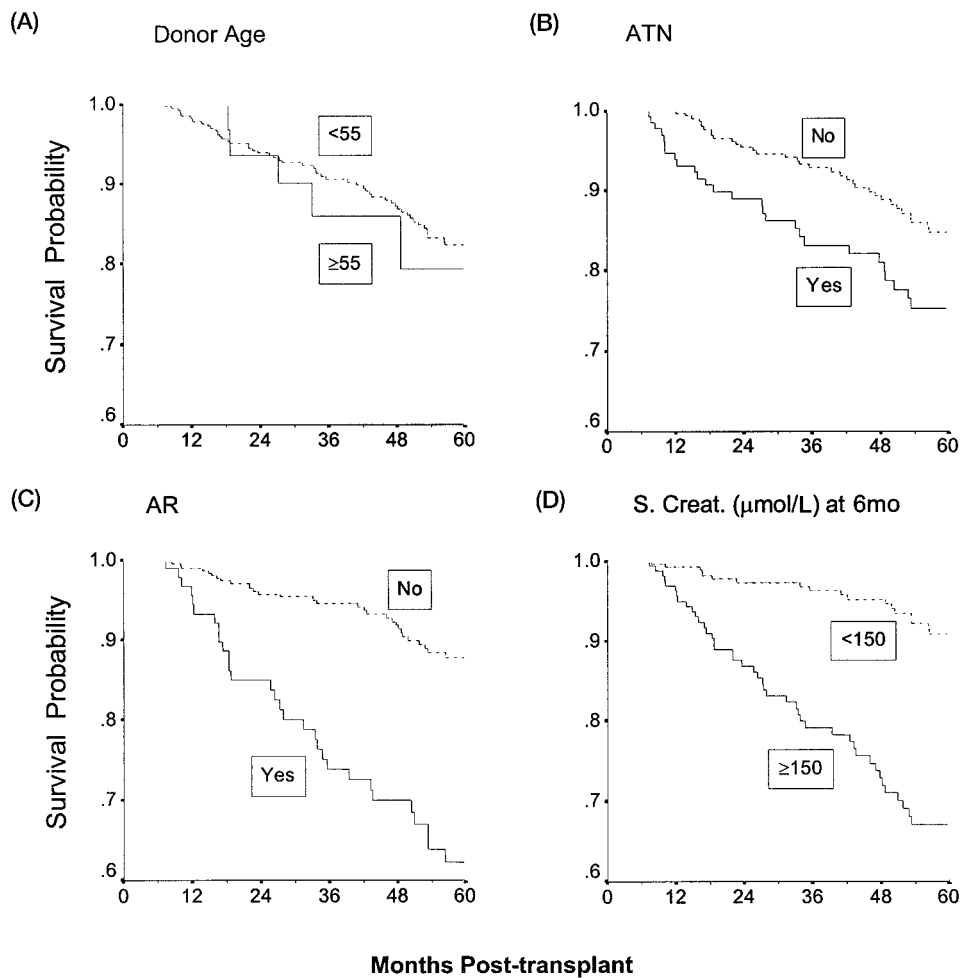


Figure 3. Kaplan–Meier graft survival during the intermediate interval, 6 mo to 5 yr, after transplantation.

Note that all DGF and most AR occurred in the first interval but their influences remained strong in the second interval. Serum creatinine at 6 mo $\geq 150 \mu\text{mol/L}$ strongly correlates with graft loss beyond 6 mo (HR = 4.58, $P < 0.001$). Recipient age ≥ 55 yr was associated with less graft loss. In the first interval this was not significant (HR = 0.74, $P = 0.41$), but it was significant in the second interval (HR = 0.40, $P = 0.03$) and borderline in the overall group (HR = 0.62, $P = 0.055$).

The strongest factor after 5 yr is donor age ≥ 55 yr (HR = 5.87, $P = 0.002$). Kidneys from female donors were associated with increased risk (HR = 2.31, $P = 0.057$). Other factors including AR, DGF, PRA $\geq 50\%$ at peak, and even a high serum creatinine at 6 mo were not significantly associated with graft failure beyond 5 yr.

In the overall group, the significant factors were donor age ≥ 55 yr, AR, high PRA, DGF, and high serum creatinine at 6 mo. The protective effect of older recipient age and the adverse effect of kidneys from female donors just missed significance.

Figure 1 illustrates three factors that significantly affected graft survival in the overall population: AR, DGF, and donor age ≥ 55 . Graft survival (censoring patient death) in each interval is presented in Figures 2 through 4, comparing those grafts with and without the variables DGF, AR, and donor age

≥ 55 yr. Figure 2 shows that graft loss in the first 6 mo reflected the occurrence of AR and DGF but not older donor age. Similarly, the 6 mo to 5 yr graft survival (Figure 3) shows effects of DGF and AR but not older donor age. Figure 3D shows the effect of 6-mo serum creatinine $\geq 150 \mu\text{mol/L}$ on graft survival from 6 mo to 5 yr. However, graft survival beyond 5 yr shows a different pattern: DGF, AR, and 6-mo serum creatinine (not shown) were not significant, but donor age ≥ 55 yr was highly significant.

We used multivariate analysis to examine the independent factors affecting graft survival in each interval (Table 4). In the first 6 mo, the factors significantly associated with graft failure were AR (HR = 4.86, $P < 0.001$), highest PRA $\geq 50\%$ (HR = 2.04, $P = 0.026$), and DGF (HR = 1.74, $P = 0.061$). In the interval 6 to 60 mo, the significant factors for graft failure were AR (HR = 2.87, $P < 0.001$) and serum creatinine at 6 mo $\geq 150 \mu\text{mol/L}$ (HR = 3.69, $P < 0.001$). (Acute rejections occurring in either the first or second intervals were included.) Beyond 5 yr, the major prognostic factor was older donor age (HR = 5.18, $P = 0.004$). The influence of having a kidney from a female donor was borderline ($P = 0.07$) in the interval >5 yr. The analysis represented in Table 4 was not altered significantly when the effect of female donors was included in

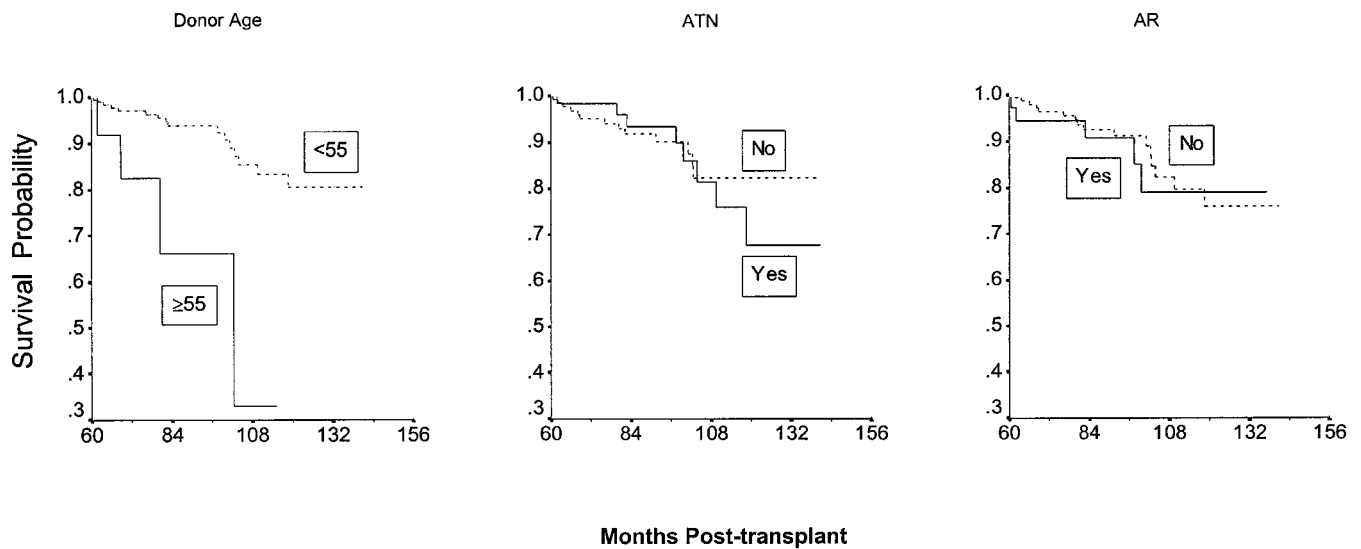


Figure 4. Kaplan–Meier graft survival 5 yr after transplantation.

the model. The addition or deletion of the 6-mo serum creatinine data did not materially change the analysis, except that excluding the 6-mo serum creatinine made the DGF a significant factor in interval 2.

Table 5 analyzes interactions among the variables and is included to explain the mechanisms by which factors such as rejection, mismatch, DGF, and donor age may operate. Older donor age was associated with a twofold increase in the rate of DGF and a fourfold increase in serum creatinine ≥ 150 at 6 mo but not with increased AR. The relationship of donor age to serum creatinine at 6 mo is shown in Figure 5, which illustrates the rise in serum creatinine at ages as young as 35 to 45. Recipients older than 55 showed a tendency to less rejection (NS), and fewer had a high serum creatinine at 6 mo ($P = 0.014$). AB and DR mismatches and high PRA mainly affected the incidence of rejection. High PRA also increased DGF and serum creatinine at 6 mo.

Discussion

This study demonstrates that early and late graft failure (death censored) reflect distinct risk factors. Like most analyses of this subject, the overall population is weighted with early patients and tends to over-represent the early factors: DR mismatches, PRA, AR, DGF, and the serum creatinine at 6 mo. The early interval after transplantation determines the risks of graft loss over the first 5 yr. From the analysis, DGF and AR are the significant prognostic factors for graft failure within 5 yr (both the first and second intervals), consistent with previous reports (10–17). They in turn carry the effect of many pretransplant risks such as HLA mismatches and presensitization. The strong early effects of DGF and AR support the role of acute transplant-related injury and immunologic injury in the early and intermediate intervals after transplant. The effect of donor age increases in relative importance as time passes, while the effect of early injury (DGF) and early, clinically severe immune events lessens. The results support a model in

which early immune and acute injury factors operate early but not late, whereas effects of age and perhaps workload continue to operate late. It is likely that immune injury also contributes to late graft loss, due to processes such as persistent or *de novo* subclinical immune activation (rejection), but we lack measurements of such injury. For example, it is likely that non-compliance contributes to immune events in some cases of late graft loss.

Although analysis of time dependency poses the challenge that the patients were transplanted in different eras, it is reassuring that the population entering the late interval was similar to that entering interval 1. One might have expected that the frequency of the strong risks such as rejection would be lower in the patients who entered interval 3 due to selective loss in previous intervals of those carrying these risk factors, and there was a weak trend in this direction. This tendency may be balanced by the declining frequency of acute rejection in the recent era, and by the tendency of rejection to be in younger patients with lower risks of death. Separation of graft loss due to graft failure from that due to death with a functioning graft should now be the preferred analysis of renal transplant survival. In the past, the censoring of patient death was discouraged because many deaths were due to complications of immunosuppression, but this is no longer the case. Death with function is usually due to comorbidities such as heart disease with no obvious relationship to the status of the transplant. The analysis of graft loss independent of death with function permits a more precise description of the influences on graft survival, which therefore should be a more accurate guide to the interventions required to extend graft function.

The emergence of donor age as a major factor in cadaver graft survival probably reflects the decline of acute rejection and the increasing reliance on older donors to deal with the donor shortage (18,19). The kidney develops characteristic changes termed senescence, which describes the global pathologic and physiologic changes. These include global sclerosis

Table 4. Factors affecting graft survival function: Cox regression multivariate analysis^a

Variable	Graft Survival Time					
	Interval 1 ≥6 mo	Interval 2 6 mo to 5 yr	Interval 3 >5 yr	All Intervals	HR (95% CI)	P Value
Donor age ≥55 yr			5.87 (1.92 to 17.94)			0.002
S _{Cr} at 6 mo ≥150	NA	3.69 (2.10 to 6.48)		3.09 (1.94 to 4.92)		<0.001
Rejection AB	4.86 (2.76 to 8.54)	2.87 (1.72 to 4.81)		2.22 (1.41 to 3.48)		<0.001
DGF	1.74 (0.98 to 3.11)					0.061
PRA high ≥50%	2.04 (1.09 to 3.82)					0.027

^a Abbreviations as in Tables 2 and 3.

of glomeruli, hyalinization and fibrous intimal thickening in small arteries, tubular atrophy, and interstitial inflammation and fibrosis. The GFR and renal plasma flow decline, and the filtration fraction rises (20,21), but it is unknown whether these events are due to the histologic abnormalities or reflect a shift in vasomotion toward vasoconstriction and away from vasodilation. Advanced age is a risk for the development of end-stage renal disease of many types (6), presumably reflecting interactions between the disease mechanisms and aging processes. Nevertheless, some elderly normotensive individuals retain GFR in the normal range (22), and some human populations avoid the arterial changes (23), suggesting that neither the physiologic nor the histologic changes are inevitable.

The evidence suggests that the donor age effect on survival of cadaver kidney transplants reflects an interaction between age and the stresses of transplantation (24). In the United Network of Organ Sharing (UNOS) registry from 1987–1995, older donor age was the strongest determinant of the transplant course, predicting more day 1 anuria, dialysis, and lower long-term graft survival. In HLA-matched kidneys, the 5-yr survival was 81% at donor age 21 to 30, but fell to 39% at donor age >60. Indeed, the worst results were with older donor kidneys, regardless of matching. The main cause of failure in kidneys of older donors was CAN, indicating that older donor age increases CAN (19). DGF has more impact in kidneys from older donors (25–28). As we have recently reviewed, CAN may reflect accelerated senescence changes due to the abnormal nonimmune and immune stresses of transplantation (29). Thus, stresses inherent in the cadaver renal transplant may interact with the endogenous senescence program to increase the probability of developing CAN. Like senescence changes in native kidneys, CAN may be predominantly a disease of small arteries (30), characterized by fibrous intimal thickening. Thus, the effect of donor age may be a reduced ability to withstand and recover from the stresses of brain death, ischemia, rejection, hyperfiltration, proteinuria, nephrotoxicity, hypertension, and excessive workload. Whether older donor age also increases immune recognition is unclear. For example, the lack of HLA effect in kidneys from old donors argues against an immune effect, but rejection is increased in kidneys from older donors in a recent analysis of the UNOS data (M. Cecka, personal communication).

The tendency of graft survival (recipient death censored) to improve with older recipient age may reflect the attenuation of the recipient immune-inflammatory system with age (31), as reflected by the lower frequency of AR in older recipients (32). In the present study, the incidence of AR was 18.6% in older recipients *versus* 24% in younger recipients, which, although not significant, could still contribute to the lower hazard ratio for graft loss in older recipients (0.62). The possibility of qualitative differences between rejection episodes cannot be excluded and could contribute to the tendency toward better graft survival in older recipients. Lower workload for the renal transplant in older recipients and better compliance may also contribute.

These results suggest a dynamic model for renal transplant survival in which the dominant factors are the quality of the

Table 5. Acute rejection, acute tubular necrosis, and serum creatinine $\geq 150 \mu\text{mol/L}$ ^a

Variable	% AR	P Value	% DGF	P Value	% S _{Cr} ≥ 150	P Value
Donor age in years						
≥ 55 ($n = 49$)	26.5	0.48	51.0	0.004	69.2	<0.001
< 55 ($n = 463$)	22.2		29.8		33.1	
Recipient age in years						
≥ 55 ($n = 113$)	18.6	0.25	32.7	0.91	26.0	0.014
< 55 ($n = 409$)	24.0		32.0		39.5	
HLA-A,B mismatch						
> 2 ($n = 326$)	26.1	0.02	31.3	0.63	35.2	0.55
≤ 2 ($n = 193$)	17.1		33.7		38.3	
HLA-DR mismatch						
> 1 ($n = 170$)	27.6	0.07	30.6	0.55	37.3	0.67
≤ 1 ($n = 336$)	20.2		33.6		35.1	
PRA high $\geq 50\%$						
Yes ($n = 78$)	30.8	0.08	55.1	<0.001	50.0	0.02
No ($n = 434$)	21.2		27.4		34.0	

^a AR, acute rejection. Other abbreviations as in Table 2.

transplanted tissue, rejection, and workload and stresses such as hypertension and nephrotoxins. The well known relationship between measures of renal function and kidney survival (33) is central to this model. The early course of the renal transplant is dominated by donor factors (34), acute injury (DGF), and immune injury. DGF and acute rejection have little long-term impact if the repair mechanisms restore good function. Early rejection episodes have a continuing impact lasting up to 5 yr, by affecting the serum creatinine at 6 mo but also independent of the serum creatinine at 6 mo. In contrast, AR is not an independent predictor of graft loss beyond 5 yr. Older donor age increases DGF and decreases the serum creatinine at 6 mo,



Figure 5. Mean serum creatinine at 6 mo with increasing donor age.

and may increase rejection. But in contrast to AR and DGF, donor age has continuing major long-term effects, which are separable from the effects on early function (*i.e.*, serum creatinine at 6 mo) in multivariate analysis. The fact that donor age is significant even in multivariate analysis including 6-mo serum creatinine suggests that the effect of donor age may not simply be due to reduced nephron number but may also reflect the age of the transplanted tissue *per se*.

Acknowledgments

Dr. Halloran's research is supported by the Medical Research Council of Canada, the Kidney Foundation of Canada, Novartis Pharmaceuticals Canada, Hoffmann-La Roche Canada, the Muttart Foundation Chair in Clinical Molecular Immunology, the Royal Canadian Legion, and the Roche Organ Transplant Research Foundation. We are grateful to the Clinical Trials Program of the University of Alberta Hospital for their ongoing support.

References

1. Ferguson R: Acute rejection episodes: Best predictor of long-term primary cadaveric renal transplant survival. *Clin Transplant* 8: 328–331, 1994
2. Matas AJ, Gillingham KJ, Payne WD: The impact of an acute rejection episode on long-term renal allograft survival (t1/2). *Transplantation* 57: 857–859, 1994
3. Sumrani N, Delaney V, Hong JH: Renal allograft outcome in the cyclosporine era: Comparison between intermediate-term failure and long-term survival. *ASAIO Trans* 37: 623–625, 1991
4. Basadonna GP, Matas AJ, Gillingham KJ: Early versus late acute renal allograft rejection: Impact on chronic rejection. *Transplantation* 55: 993–995, 1993
5. Cole E, Naimark D, Aprile M: An analysis of predictors of long-term cadaveric renal allograft survival. *Clin Transplant* 9: 282–288, 1995
6. USRDS: 1996 Annual Data Report, U.S. Renal Data System, 1996
7. Gjertson DW, Cecka JM, Terasaki PI: The relative effects of

- FK506 and cyclosporine on short- and long-term kidney graft survival. *Transplantation* 60: 1384–1388, 1995
8. Kasiske BL, Heim-Duthoy KL, Tortorice KL: The variable nature of chronic declines in renal allograft function. *Transplantation* 51: 330–334, 1991
 9. Solez K, Axelsen RA, Benediktsson H: International standardization of criteria for the histologic diagnosis of renal allograft rejection: The Banff working classification of kidney transplant pathology. *Kidney Int* 44: 411–422, 1993
 10. Toyotome A, Terasaki PI, Salvatierra O: Early graft function. In: *Clinical Transplants 1987*, 3rd Ed., edited by Terasaki PI, Los Angeles, UCLA Tissue Typing Laboratory, 1987, pp 435–452
 11. Najarian JS, Gillingham KJ, Sutherland DER: The impact of the quality of initial graft function on cadaver kidney transplants. *Transplantation* 57: 812–816, 1994
 12. Troppmann C, Gillingham KJ, Benedetti E: Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. *Transplantation* 59: 962–968, 1995
 13. Yokoyama I, Uchida K, Kobayashi T: Effect of prolonged delayed graft function on long-term graft outcome in cadaveric kidney transplantation. *Clin Transplant* 8: 101–106, 1994
 14. Tesi RJ, Henry ML, Eikhammas EA: Predictors of long-term primary cadaveric renal transplant survival. *Clin Transplant* 7: 345–352, 1993
 15. Cosio FG, Dillon JJ, Falkenhain ME: Racial differences in renal allograft survival: The role of systemic hypertension. *Kidney Int* 47: 1136–1141, 1995
 16. Massy ZA, Guijarro C, Kasiske BL: Clinical predictors of chronic renal allograft rejection. *Kidney Int* 52: S85–S88, 1996
 17. Cosio FG, Pelletier RP, Falkenhain ME: Impact of acute rejection and early allograft function on renal allograft survival. *Transplantation* 63: 1611–1615, 1997
 18. Gjertson DW: A multi-factor analysis of kidney graft outcomes at one and five years posttransplantation: 1996 UNOS update. In: *Clinical Transplants 1996*, 12th Ed., edited by Cecka JM, Terasaki PI, Los Angeles, UCLA Tissue Typing Laboratory, 1997, pp 343–360
 19. Terasaki PI, Gjertson DW, Cecka JM: Significance of the donor age effect on kidney transplants. *Clin Transplant* 11: 366–372, 1997
 20. Fliser D, Franek E, Joest M: Renal function in the elderly: Impact of hypertension and cardiac function. *Kidney Int* 51: 1196–1204, 1997
 21. Epstein M: Aging and the kidney. *J Am Soc Nephrol* 7: 1106–1122, 1996
 22. Lindeman RD, Tobin J, Shock NW: Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc* 33: 278–285, 1985
 23. Tracy RE, Rios-Dalenz JL: Rarity of hypertensive stigmata in aging renocortical arteries of Bolivians. *Virchows Arch* 424: 307–314, 1994
 24. Wyner LM, Novick AC, Hodge EE: Long-term follow-up of kidneys transplanted from elderly cadaveric donors. *World J Urol* 14: 265–267, 1996
 25. Shoskes D, Cecka M: Delayed graft function predicts long-term kidney graft survival independent of early acute rejection or discharge creatinine [Abstract]. Presented at the *17th Annual Meeting of the American Society of Transplant Physicians*, 1998, p 167
 26. Chertow GM, Brenner BM, MacKenzie HS: Non-immunologic predictors of chronic renal allograft failure: Data from the United Network of Organ Sharing. *Kidney Int* 52: S48–S51, 1995
 27. Peeters J, Roels L, Vanrenterghem Y: Chronic renal allograft failure: Clinical overview. The Leuven Collaborative Group for Transplantation [Review]. *Kidney Int* 52: S97–S101, 1995
 28. Cecka JM: The role of HLA in renal transplantation [Review]. *Hum Immunol* 56: 6–16, 1997
 29. Halloran PF, Melk A, Barth C: Rethinking chronic allograft nephropathy: The concept of accelerated senescence [Review]. *J Am Soc Nephrol* 10: 167–181, 1999
 30. Levi M, Rowe JW: Aging and the kidney. In: *Diseases of the Kidney*, 5th Ed., edited by Schrier RW, Gottschalk CW, Boston, Little, Brown, & Co., 1993, pp 2405–2432
 31. Pawelec G, Solana R: Immunosenescence. *Immunol Today* 18: 514–516, 1997
 32. Shoskes DA, Cecka JM: Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 66: 1697–1701, 1998
 33. Opelz G, Sasaki N, Terasaki PI: Prediction of long-term kidney transplant survival rates by monitoring early graft function and clinical grades. *Transplantation* 25: 212–215, 1978
 34. Cosio FG, Qiu W, Henry ML: Factors related to the donor organ are major determinants of renal allograft function and survival. *Transplantation* 62: 1571–1576, 1996