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Increased Immunogenicity and Cause of Graft Loss of Old Donor Kidneys

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Abstract Donor age was identified recently as a major factor that determines long-term outcome after transplantation, but the mechanism that is responsible for increased graft loss of old donor kidneys is unknown The influence of donor age on graft survival was assessed retrospectively in 514 consecutive first cadaveric transplants that were treated with cyclosporine maintenance immunosuppression Donor age ≥50 yr (relative risk [RR] = 1 7, 95% confidence interval [CI], 1 2 to 2 6), acute rejection (RR = 2 0, 95% CI, 1 3 to 3 0), and type of rejection (RR = 3 3, 95% CI, 2 0 to 5 3) had a significant impact on graft survival However, when subsets of patients who entered subsequent intervals after transplantation were analyzed, donor age was not an independent predictive factor of graft loss Donor age (RR = 1 53, 95% CI, 1 19 to 1 98), human leukocyte antigen-DR mismatch (RR = 2 28, 95% CI, 1 78 to 2 92), and recipient age (RR = 1 34, 95% CI, 1 05 to 1 72) were associated significantly with acute rejection episodes Delayed graft function alone was not associated independently with the occurrence of early acute rejection (RR = 1 24, 95% CI, 0 96 to 1 61) The timing of the rejection episodes of old donor kidneys was not different, and the excess rejection prevalence was attributable entirely to interstitial (grade I) types of rejection Interstitial rejection episodes in kidneys from old donors had a significant ($P < 0\ 05$) negative impact on graft survival Beyond the first year, poor renal function and proteinuria were significant risk factors for graft loss, regardless of rejection Our data fit best the hypothesis that increased graft loss of older donor kidneys results from an increased incidence of acute interstitial rejection episodes in the early posttransplantation months It is proposed that kidneys from older donors are more immunogenic than kidneys from young donors and that acute rejection episodes result in functional deterioration Contrary to interstitial rejection in kidneys from younger donors, kidneys from old donors seem to have an impaired ability to restore tissue

The increasing gap between demand and availability of human kidneys for transplantation has resulted in the use of non–heart-beating donors and donors with an abnormal renal structure or function, including donors who are older than 50 yr Between 1988 and 1995, there was a 172% increase in the number of cadaveric donors who were older than 50 yr, which resulted in a doubling of the fraction of older donors from 12 to 25% (1) In Eurotransplant, up to 25% of cadaveric transplants in 1998 came from donors who were older than 55 yr (2)

The use of kidneys from old donors is associated with an increased risk of delayed graft function and an increased rate of graft loss later on An analysis of 43,000 adult cadaveric transplants revealed a higher prevalence of delayed graft function, increased need for postoperative dialysis treatments, and a higher serum creatinine concentration at discharge in recipients of old donor kidneys compared with patients who received a kidney from a young donor (3) At 5-yr, there was a 25% difference in graft survival rate between transplants from young and old donors, and the projected graft half-life decreased from 10 2 yr if the donor was between 16 to 20 yr of age to 5 yr for grafts that came from donors who were 60 yr of age Finally, a number of investigators have reported on the adverse effect of donor age on posttransplantation graft function (4,5), although not all centers found such an effect (6)

In a large multivariate analysis, donor age was identified as the most important factor that determines long-term outcome after kidney transplantation (7) According to that analysis, 30% of variability in long-term outcome could be explained by donor age However, not all variables known to determine late graft loss, such as the acute rejection history, were included in the analysis The reason for the increased rate of graft loss is unknown The present study was undertaken to examine factors that determine the loss of kidney transplants from old donors

Materials and Methods

Patients

For the present study, all 663 consecutive first cadaveric renal transplants that were performed in the Leiden University Medical Center between June 1983 and June 1997 were identified in our

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transplant database Only recipients who were treated with cyclosporine (CsA)-based immunosuppression (n = 514) were included in the present analysis Recipients who also received mycophenolate mofetil were excluded The database contains donor variables (age at time of death, gender, cause of death) and recipient variables (age at time of transplantation, gender, original disease, panel reactive antibodies), transplant factors (human leukocyte antigen-A [HLA-A], -B, and -DR mismatches, cold ischemia time, warm ischemia time), and posttransplantation features including immunosuppressive regimen, cyclosporine trough levels, delayed graft function, rejection history (time to first acute rejection episode, number of rejection episodes, histopathologic type of rejection), dipstick proteinuria, and renal function Kidneys were allocated by Eurotransplant according to a standard algorithm on the basis of matching for HLA We aimed to accept kidneys with no more than two mismatches with a priority for HLA-DR matching By policy, kidneys from donors with known long-standing hypertension or diabetes mellitus were not accepted for transplantation After transplantation, patients were followed until death, return to dialysis, or June 1, 2000 Patient death with a functioning graft was censored as a cause of graft loss Censoring non–renal-related deaths from the assessment of long-term graft survival allows for more accurate association of risk factors and graft survival Eighteen patients (3 5%) received a graft that never functioned because of thrombosis (n = 8), tubular necrosis and severe vascular rejection (n = 5), bleeding (n = 2), undetected antibody-mediated rejection (n = 2), or infection (n = 1) Primary nonfunction was found more often in kidneys from older donors (7 7 *versus* 1 9%, $P < 0.005$) These patients were excluded from the study Delayed graft function was defined as the need for dialysis for at least 7 d posttransplantation The standard immunosuppressive regimen consisted of prednisone and CsA and, in some patients (n = 31), azathioprine None of the patients received prophylactic treatment with poly- or monoclonal antibodies The cumulative incidence of acute rejection episodes in the first 6 mo was 57 5% and was confirmed by biopsy in 91 6% of the cases Graft histology was evaluated retrospectively according to the Banff '97 classification (8) Patients who had one or more rejection episode(s) with arteritis on biopsy were classified as undergoing grade II rejection Acute rejection episodes were treated according to a standard protocol consisting of methylprednisolone 1 g intravenously for three consecutive days, a 10-d course of antithymocyte globulin at a dose of 5 mg/kg guided by absolute lymphocyte counts, or again methylprednisolone for the first, second (or steroid-resistant), or third rejection episodes, respectively BP, number of antihypertensive drugs, dipstick proteinuria, serum creatinine, and endogenous creatinine clearance (sequential 24-h collections) were collected at regular intervals throughout the entire follow-up period

Statistical Analyses

Characteristics among groups were compared with the use of cross tables with Fisher's exact tests and t tests for categorical and continuous variables, when appropriate Graft survival was estimated with the use of Kaplan-Meier life tables and compared for the different categories with the use of the Wilcoxon-Gehan test The risk for graft loss in the different categories was analyzed with the use of Cox regression Relevant factors for allograft loss in univariate analysis were fitted into a multivariate model All analyses were performed with the use of the SPSS statistical software package (Version 9 0, SPSS, Inc , Chicago, IL)

Results

In the total population (n = 496), overall graft survival was 91 8% at 1 yr and 83 6% at 5 yr after transplantation Table 1 shows that in both the univariate and the multivariate analysis, donor age (relative risk [RR] = 1 72, 95% confidence interval [CI], 1 15 to 2 58), acute rejection history (RR = 1 95, 95% CI, 1 28 to 2 99), and the histologic pattern of rejection (RR = 3 26, 95% CI, 2 01 to 5 28) had a significant impact on graft survival During the study period, the donor age (mean ± SD) increased significantly from 39 0 ± 12 6 yr (1983 to 1986) and 40 3 ± 13 3 yr (1987 to 1992) to 42 7 ± 13 6 yr (1993 to 1997), but the proportion of donors who were 50 yr or older was not significantly different in these periods

The characteristics of the study population grouped according to donor age are summarized in Table 2 In this cohort of patients, there were no significant differences between the two groups with respect to the degree of histocompatibility, grade of sensitization, recipient age or gender, cold ischemia times, and pretransplantation BP (Table 2) The majority of older donors were females, resulting in an increased female-donor-to-male-recipient ratio in the old donor group Initial immunosuppression and average CsA trough levels at the time of rejection and at follow-up (week 6, months 3 and 6, years 1, 2, and 5) were not different in recipients of kidneys from donors who were 50 yr or older or who were younger than 50 yr The cumulative incidence of acute rejection episodes in patients who received a graft from a donor who was 50 yr or older was significantly higher ($P < 0.005$), whereas the timing of the first rejection episode was not different from rejections that occurred in kidneys from younger donors (Figure 1) Histopathologic analysis (Figure 2) showed that the increase in acute rejection episodes in kidneys from older donors was attributable entirely to an increase in grade I or interstitial type of rejection episodes ($P < 0.005$) In the univariate analysis, donor age ≥50 yr (RR = 1 50, 95% CI, 1 17 to 1 94) and delayed function (RR = 1 36, 95% CI, 1 05 to 1 76) both were associated with the occurrence of acute rejection episodes in the first 6 posttransplantation months For further analysis, the recipients were divided into four groups patients with donors aged <50 yr and immediate graft function (group I, 50 1% of patients), those with young donors but delayed graft function (group II, 20 6%), recipients with donors ≥50 yr and immediate function (group III, 18 0%), and those with both older donors and delayed function (group IV, 11 3%) The cumulative incidence of acute rejection episodes grouped according to donor age and presence or absence of delayed graft function is plotted in Figure 3 The risk of acute rejection episodes was significantly higher in kidneys from older donors with immediate function (group III RR = 1 68, 95% CI, 1 21 to 2 35) and those with delayed function (group II RR = 1 40, 95% CI, 1 01 to 1 94, group IV RR = 1 76, 95% CI, 1 20 to 2 56) In the multivariate model (Table 3), delayed graft function *per se* was not a significant risk factor for acute rejection (RR = 1 24, 95% CI, 0 96 to 1 61) In contrast, HLA-DR mismatch ≥1 (RR = 2 28, 95% CI, 1 78 to 2 92), donor age ≥50 yr (RR = 1 53, 95% CI, 1 19 to 1 98), recipient age <50 yr (RR = 1 34, 95% CI, 1 05 to 1 72), and total number of mismatches (RR = 1 27, 95% CI, 1 14 to 1 43) were associated significantly with acute rejection episodes The increase in acute rejection episodes of old donor kidneys was higher both in recipients ≥50 yr ($P <$

Table 1 Risk of graft loss in first cadaveric renal transplants on cyclosporine maintenance immunosuppression (Cox regression analysis)[a]

Risk Factor	Univariate		Multivariate	
	RR	95% CI	RR	95% CI
Pretransplantation factors				
HLA mismatch				
A-B-DR	1 12	0 94–1 33	1 05	0 88–1 26
A-B	1 13	0 93–1 38	1 12	0 92–1 38
DR	1 13	0 80–1 62	0 87	0 59–1 28
panel reactive antibodies (≥50%)	1 10	0 66–1 84	1 07	0 65–1 79
gender				
recipient (female)	0 90	0 61–1 32	1 71	0 88–1 96
donor (female)	0 84	0 57–1 25	0 94	0 63–1 41
mismatch female to male	1 15	0 75–1 77	0 94	0 61–1 47
cold ischemic time (per h)	1 00	0 97–1 02	1 00	0 97–1 03
age				
recipient (≥50 yr)	1 09	0 74–1 62	1 16	0 78–1 73
donor (≥50 yr)	1 83[c]	1 23–2 73	1 72[b]	1 15–2 58
Posttransplantation factors				
initial immunosuppression (dual)	0 97	0 47–2 00	0 84	0 40–1 75
delayed graft function	1 27	0 84–1 93	1 16	0 76–1 76
acute rejection episode(s)	2 09[c]	1 37–3 18	1 95[c]	1 28–2 99
type of acute rejection				
no rejection	1 00		1 00	
grade 1	1 48	0 91–2 41	1 38	0 84–2 24
grade 2	3 45[d]	2 14–5 58	3 26[d]	2 01–5 28

[a] RR, relative risk, CI, confidence interval, HLA, human leukocyte antigen
[b] $P < 0\ 05$
[c] $P < 0\ 005$
[d] $P < 0\ 0001$

0 05) and in younger patients ($P < 0\ 01$, Figure 4) The requirement for antithymocyte globulin to treat acute rejection episodes was not significantly ($P = 0\ 21$) different in recipients of kidneys from older donors compared with patients with younger donors

The number of recipients available for evaluation at 1, 5, and 10 yr after transplantation was 418, 291, and 115, respectively The percentage of these patients that received a kidney from a donor who was 50 yr or older was 27%, 25 4%, and 19 1%, respectively Survival according to acute rejection history in relation to donor age is shown in Figure 5 In patients without an acute rejection episode, there was no effect of donor age on graft survival, but a significantly increased ($P < 0\ 02$) rate of graft loss occurred in patients with old donor kidneys and a history of acute rejection To estimate short- and long-term effects of donor age, the posttransplantation time was partitioned into consecutive intervals, and subsets of patients who entered each interval were analyzed The univariate analysis (Table 4) for graft loss in the first year after transplantation identified donor age (RR = 1 94, 95% CI, 1 03 to 3 65), recipient age (RR = 2 04, 95% CI, 1 07 to 3 89), recipient gender, and acute rejection episode(s) (RR = 7 38, 95% CI, 2 62 to 20 76) as significant risk factors Table 5 shows the independent risk factors for graft loss in the multivariate analysis In the multivariate model, donor age was not associated independently with graft loss in the first posttransplantation year (RR = 1 69, 95% CI, 0 89 to 3 19) Survival according to donor age in relation to histologic type of acute rejection is plotted in Figure 6 These data indicated that acute interstitial (grade I) rejection episodes in recipients of kidneys from donors who were older than 50 yr have a powerful negative impact on graft survival

Beyond 1 yr, three factors were associated with graft loss in the univariate analysis (Table 4) a suboptimal graft function at 1 yr, defined as creatinine clearance of 30 to 50 ml/min (RR = 2 51, 95% CI, 1 40 to 4 51) or less than 30 ml/min (RR = 7 25, 95% CI, 3 59 to 14 6), proteinuria (RR = 4 16, 95% CI, 2 36 to 7 33), and donor age (RR = 1 77, 95% CI, 1 06 to 2 96) In the multivariate analysis (Table 6), donor age was not associated significantly with graft loss beyond the first year (RR = 1 50, 95% CI, 0 88 to 2 58) or beyond 5 yr (RR = 1 38, 95% CI, 0 61 to 3 14) Poor renal function was a significant risk regardless of rejection at 1 and 5 yr, as was proteinuria

Discussion

In the present study, we analyzed the interaction between age and acute rejection The principal finding is that kidneys from older donors are more likely to undergo acute rejection

Table 2. Characteristics of study population grouped according to donor age[a]

Characteristic	Donor Age		
	<50 yr (n = 352)	≥50 yr (n = 144)	P Value
Pretransplantation factors			
HLA-AB mismatch	1.60 ± 1.01	1.53 ± 0.97	0.49
HLA-DR mismatch	0.36 ± 0.54	0.37 ± 0.51	0.94
panel reactive antibodies (≥50%)	79.7	81.5	0.79
recipient age (yr)	47.2 ± 12.5	48.0 ± 12.9	0.53
gender			
recipient male (%)	60.5	66.0	0.26
donor female (%)	39.5	51.4	<0.02
mismatch: female to male	21.9	34.0	<0.01
cold ischemia time (h)	29.0 ± 6.8	28.5 ± 6.5	0.52
BP pretransplantation (MAP; mmHg)	111 ± 15	110 ± 15	0.30
Posttransplantation factors			
initial immunosuppression			
CsA/P (%)	92.6	96.5	
CsA/P/Aza (%)	7.4	3.5	0.15
delayed graft function (%)	29.3	38.7	<0.05
acute rejection (%)	53.0	68.8	<0.005
biopsy confirmed (%)	50.7	66.9	<0.005
delayed graft function	57.9	73.1	<0.05
no delayed function	47.6	62.7	<0.05
BP (MAP; mmHg) at 1 yr	107 ± 11	107 ± 11	0.79
creatinine clearance (ml/min) at 1 yr	69 ± 25	55 ± 21	<0.0005
proteinuria >1+ (%) at 1 yr	42.7	57.9	<0.005

[a] MAP, mean arterial pressure; CsA, cyclosporine; P, prednisone; Aza, azathioprine.

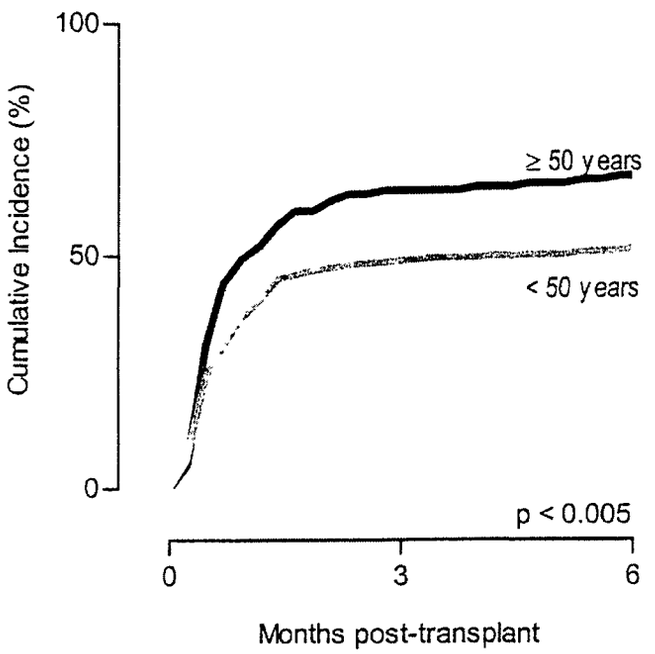

Figure 1. Cumulative incidence of first acute rejection episodes according to donor age in first cadaveric renal transplants.

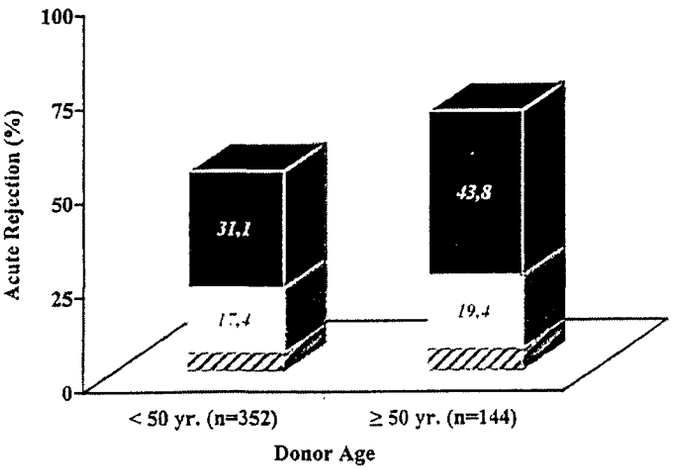

Figure 2. Histopathologic type of acute rejection episodes according to donor age. ▨, clinical; □, grade II; ■, grade I.

episodes in the early posttransplantation period compared with kidneys from younger donors. An increased frequency of acute rejection episodes in kidneys from older donors was noted previously (9). In our patients, the increased incidence of acute rejection was not related to factors such as recipient age or delayed graft function, and the timing of the first rejection episodes was not different from the rejections that occurred in kidneys from younger donors. Analysis of the histopathologic rejection pattern revealed that the increased acute rejection rate was attributable entirely to an increased prevalence in the interstitial types of rejection episodes and not the vascular rejection type. Finally, when we analyzed the impact of ad-

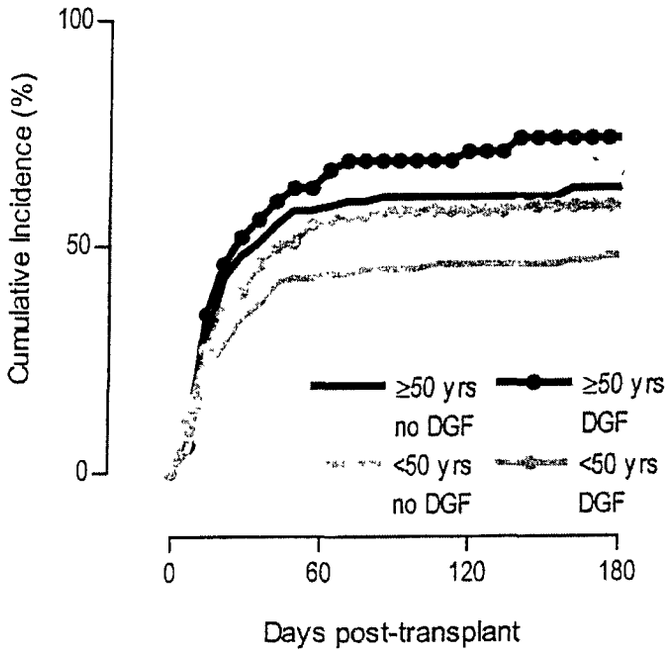

Figure 3. Cumulative incidence of first acute rejection episodes according to donor age and presence or absence of delayed graft function.

vanced donor age on graft survival, a significantly increased rate of graft loss of kidneys from older donors was observed only in the group of patients who had experienced acute rejection episodes. The adverse outcome in this group of patients occurred in the first 5 yr posttransplantation, whereas there was no significant difference beyond 5 yr. Our results suggest that older donor kidneys are more immunogenic than kidneys from young donors and that the prognostic impact of an acute interstitial rejection episode is worse in older kidneys. Thus, the effect may be attributable to an interaction between changes of renal aging and the immune response.

Our results are at variance with the results from other studies. Moreso *et al.* (10) observed increased graft loss of kidneys from old donors when such kidneys experienced acute rejection or delayed graft function without acute rejection. In a time-dependent analysis of risk factors for graft loss, Prommool *et al.* (11) found that delayed graft function and acute rejection were risk factors for graft loss in the first 5 yr but thereafter donor age seemed to be the most important factor. Both studies differed from ours in that prophylactic treatment with antilymphocyte antibodies was administered to a substantial fraction of patients. In addition, in the latter study, delayed graft function was defined as the need for dialysis during the first 2 posttransplantation weeks, and only rejections that required antibody therapy were considered (11). It is conceivable that early and potent immunosuppression attenuates the interaction between renal aging changes, ischemia-reperfusion injury, and the immune response. Acute rejection episodes have an adverse impact on renal allograft outcome (12). In the chain of events that lead to acute rejection and late graft loss, delayed graft function has been proposed to play a role (13,14). In a

Table 3. Risk factors of early acute rejection episodes: multivariate analysis

Risk Factor	RR	95% CI	*P* Value
Cold ischemia time (per h)	0.99	0.97–1.01	0.20
Delayed graft function	1.24	0.96–1.61	0.10
HLA-DR mismatch (≥1)	2.28	1.78–2.92	<0.00005
Donor age (≥50 yr)	1.53	1.19–1.98	<0.005
Recipient age (<50 yr)	1.34	1.05–1.72	<0.05

previous study (15), we showed that delayed graft function is one of several risk factors of acute rejection and suboptimal function at 1 yr, but it was not associated independently with an increased rate of graft loss within the first posttransplantation year. In the present study, we confirmed that delayed graft function alone had no impact on long-term outcome and found that it was not associated independently with an increased incidence of acute rejection episodes in the first posttransplantation months.

Kidneys from older individuals have several structural and functional changes compared with kidneys from younger donors. Longitudinal studies of elderly individuals have shown a diminution in renal reserve, along with functional constraints on the kidney's ability to respond appropriately to challenges of either excesses or deficits (16). Studies of kidneys obtained at autopsies demonstrated a progressive decrease in the number and size of glomeruli with age, resulting in a progressive decrease of the glomerular filtration volume (17,18). In addition to the loss of glomeruli, there is an age-dependent increase in the cortical interstitial volume as a result of progressive interstitial fibrosis (18,19). Most renal biopsies from kidney donors who are older than 40 yr show intimal fibrosis in the smaller arteries, arteriolar hyalinosis, and interstitial fibrosis (20).

One explanation for the increased graft loss is that such

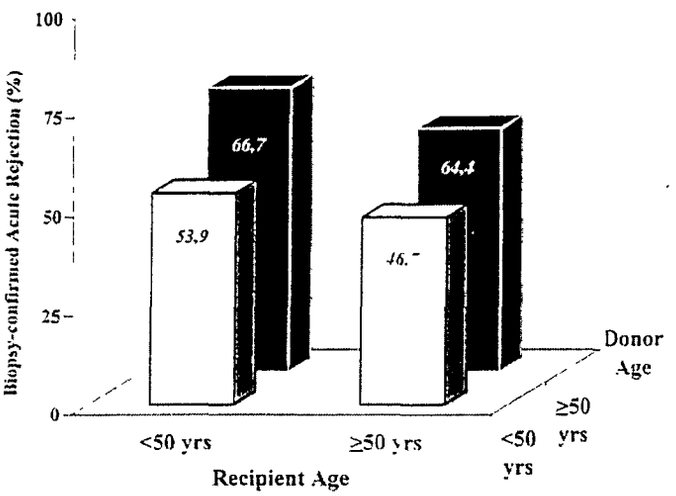

Figure 4. Prevalence of acute rejection episodes according to donor and recipient age.

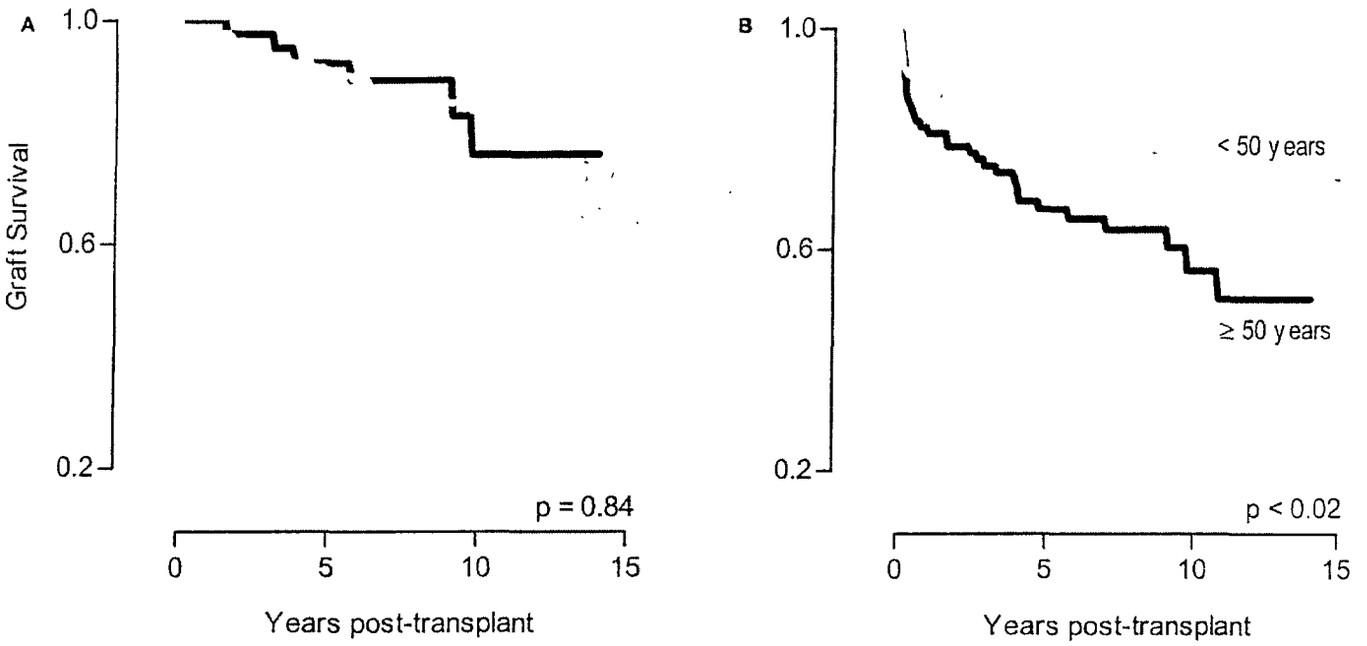

Figure 5. Kidney graft survival according to acute rejection history and donor age in first cadaveric transplants: (A) no rejection; (B) acute rejection.

kidneys have fewer nephrons that function adequately and that the summation of insults and damage results in an early demise of the graft. It also has been proposed that graft parenchymal cells undergo premature senescence or aging as a result of multiple injuries and repair (21). If progressive loss of renal mass or senescence is the mechanism of increased graft loss, then it is expected that grafts from older donors show a progressive decrease of graft survival with time and that the rate of decline of graft function correlates with donor age. Our finding that increased graft loss occurs predominantly in the first 5 posttransplantation years does not support this proposal. Similarly, Kasiske (6) also found no effect of donor age on the rate of decline in graft function between 1 yr and last follow-up.

Our clinical data suggest that the loss of older donor kidneys is related to an increased incidence of acute rejection episodes in the first few posttransplantation months. The correlation between acute rejection episodes and impaired long-tern outcome is well established and often is reported as rejection-related decreases in projected graft half-lives (22). The use of the half-lives concept suggests that an early rejection episode constitutes a continuous risk for graft failure throughout the remaining time of the graft. However, inspection of graft survival curves show that the increased graft loss in the group with acute vascular rejection occurs only in the first few posttransplantation years (23). Modeling of the risk of graft loss over time as a function of the number of rejection episodes demonstrates that the risk of graft loss related to rejection is greatest in the early posttransplantation period (24). In patients with no acute rejection episodes, the risk of graft loss decreased sharply at a few months posttransplantation and at 2 yr reached a low level. Patients with a single rejection episode reached the same low-level graft loss at 3 to 4 yr, whereas for patients with multiple rejection episodes, the risk of graft loss was several times that of the other patients up to 6 yr posttransplantation, at which point it also stabilized at a relatively low level. Thus, our data fit best the hypothesis that increased graft loss of older donor kidneys results from an increased graft loss related to an increased incidence of acute rejection episodes in the early posttransplantation months. We therefore propose that kidneys from older donors are more immunogenic than kidneys from younger donors.

Our data are very similar to those of Kerr *et al.* (25), who demonstrated that old donor age or the presence of one or more acute rejection episodes are the only factors that are associated with decreased death-censored graft survival. Of interest is the observation that in living donor transplants, only occurrence of an acute rejection episode and not donor age *per se* is associated independently with decreased graft survival (25). Grafts from older donors may already have tissue inflammation at the time of procurement and transplantation, which in turn may increase immune recognition. A variety of types of injury elicit a cascade of inflammatory events that contribute to a general stereotyped response to tissue injury, the injury response (26). In general, antigens that are expressed in normal tissue tend to be ignored, whereas antigens that are expressed in injured tissue are more likely to provoke and activate an immune response (27). The increased immunogenicity may be explained by the presence of proinflammatory cytokines, increased expression of major histocompatibility complex antigens in epithelial and endothelial cells, and the recruitment and activation of antigen-presenting cells (28–30). Injury related to the process of transplantation thus can favor rejection, and

Table 4. Risk factors of graft loss in the first year and beyond year 1 and year 5 according to the univariate analysis

Risk Factor	First Year		Beyond 1 Yr		Beyond 5 Yr	
	RR	95% CI	RR	95% CI	RR	95% CI
Pretransplantation factors						
HLA mismatch						
A-B-DR	1.24	0.94–1.64	1.05	0.86–1.31	1.28	0.90–1.81
A-B	1.31	0.95–1.81	1.03	0.80–1.33	1.22	0.82–1.83
DR	1.07	0.60–1.91	1.17	0.75–1.83	1.48	0.80–2.77
panel reactive antibodies (≥50%)	1.88	0.89–3.95	0.75	0.37–1.53	0.82	0.31–2.18
gender						
donor (female)	1.28	0.68–2.39	1.03	0.62–1.69	1.57	0.75–3.30
recipient (female)	1.86[a]	1.01–3.49	0.88	0.52–1.49	1.13	0.53–2.41
mismatch: female to male	0.96	0.47–1.97	1.29	0.75–2.21	1.75	0.81–3.81
cold ischemia time (h)	1.00	0.95–1.05	1.00	0.96–1.04	0.94	0.88–1.05
age						
recipient (≥50 yr)	2.04[a]	1.07–3.89	0.73	0.43–1.23	1.08	0.50–2.30
donor (≥50 yr)	1.94[a]	1.03–3.65	1.77[a]	1.06–2.96	1.66	0.75–3.68
Posttransplantation factors						
initial immunosuppression (dual)	0.42	0.06–3.06	0.64	0.31–1.53	0.76	0.26–2.24
delayed graft function	1.36	0.70–2.63	0.64	0.72–2.08	1.14	0.52–2.53
acute rejection episode(s)	7.38[c]	2.62–20.8	1.28	0.77–2.11	1.11	0.52–2.35
type of rejection						
no rejection	1.00		1.00		1.00	
grade 1	3.71[a]	1.20–11.5	1.18	0.67–2.06	0.98	0.41–2.35
grade 2	15.4[c]	5.30–44.4	1.50	0.76–2.95	1.38	0.50–3.83
creatinine clearance at 1 yr						
>50 ml/min			1.00		1.00	
30–50 ml/min			2.51[b]	1.40–4.51	2.87[a]	1.25–6.56
<30 ml/min			7.25[c]	3.59–14.6	6.31[b]	1.80–22.2
proteinuria at 1 yr (>1+)			4.16[c]	2.36–7.33	3.01[b]	1.40–6.51

[a] $P < 0.05$.
[b] $P < 0.005$.
[c] $P < 0.0001$.

rejection-related injury in turn may induce inflammation and new immune activation—the injury triangle.

On the basis of the assumption that old patients have attenuated immune responses and a reduced life expectancy, it has been proposed that kidneys from older donors should be allocate to old recipients. Our data indicate that such kidneys are

Table 5. Risk factors of graft loss in various time periods according to the multivariate analysis

Risk Factor	Overall		First Year		Beyond 1 Yr		Beyond 5 Yr	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Pretransplantation factors								
donor age (≥50 yr)	1.72[a]	1.15–2.58	1.69	0.89–3.19	1.75[a]	1.04–2.95	1.77	0.78–3.99
recipient								
age (≥50 yr)	1.16	0.75–1.72	2.27[a]	1.19–4.33	0.76	0.45–1.29	1.15	0.53–2.52
gender (female)	1.31	0.88–1.95	2.22[a]	1.18–4.18	0.91	0.53–1.56	1.11	0.50–2.47
Posttransplantation factors								
acute rejection episode(s)	2.02[b]	1.32–3.10	7.91[c]	2.80–22.4	1.15	0.69–1.92	1.07	0.49–2.32
type of acute rejection								
no rejection	1.00		1.00		1.00		1.00	
grade 1	1.38	0.85–2.24	4.17[a]	1.34–12.9	1.06	0.60–1.87	0.96	0.39–2.32
grade 2	3.26[c]	2.01–5.28	17.40[c]	5.98–50.3	1.36	0.69–2.70	1.32	0.47–3.74

[a] $P < 0.05$.
[b] $P < 0.005$.
[c] $P < 0.0001$.

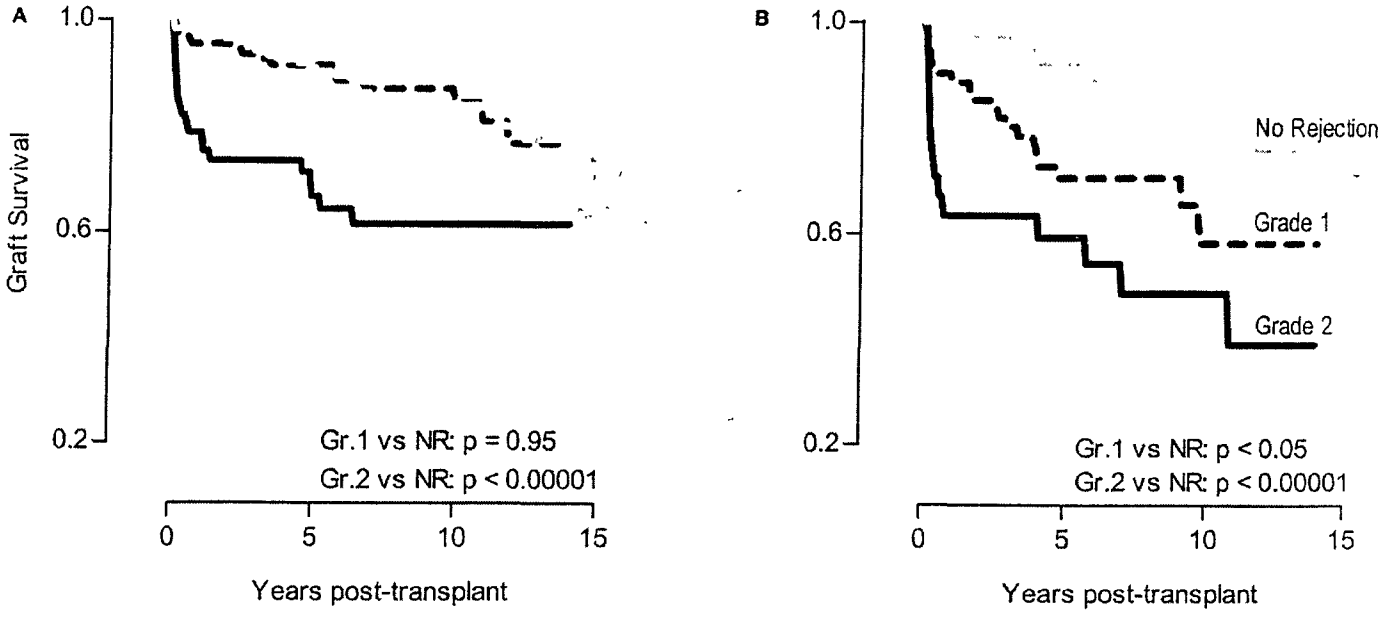

Figure 6. Kidney graft survival according to donor age and histopathologic type of acute rejection in first cadaveric transplants: (A) donor age <50 yr; (B) donor age ≥50 yr.

Table 6. Risk factors of graft loss beyond the first year: multivariate analysis

Risk Factor	Beyond 1 Yr		Beyond 5 Yr	
	RR	95% CI	RR	95% CI
Donor age (≥50 yr)	1.50	0.88–2.58	1.38	0.61–3.14
Creatinine clearance at 1 yr				
>50 ml/min	1.00		1.00	
30–50 ml/min	2.39[b]	1.33–4.31	2.90[a]	1.26–6.65
<30 ml/min	5.22[c]	2.55–10.7	4.78[a]	1.34–17.1
Proteinuria at 1 yr (>1+)	3.58[c]	2.01–6.39	2.83[a]	1.29–6.20

[a] $P < 0.05$.
[b] $P < 0.005$.
[c] $P < 0.0001$.

more immunogenic and therefore may require more intense immunosuppression of the recipient, irrespective of age. Although such an approach may be acceptable for recipients who are younger than 50 yr, it remains to be seen that this is safe for substantially older recipients, *i.e.*, those older than 60 or 65 yr. However, reduction in acute rejection episodes with more immunosuppression does not necessarily result in improved graft survival (31).

The alternative possibility is that the increased incidence of acute rejection episodes is a marker for the biology of the organ. It is conceivable that the old kidneys with acute rejection are different from the old kidneys that do not reject. The finding that approximately one third of the patients who were included in the Baltimore Longitudinal Study of Aging (32) did not show any change in the GFR and the existence of rat strains that do not develop any aging-related renal damage (33) suggest that the renal dysfunction of the elderly may be due to an accumulation of damage induced by minimal, clinically undetected renal disease and is not the consequence of the aging process itself. We suggest that kidneys with more aging-related damage or older kidneys of poorer quality are more immunogenic, which results in an increased incidence of acute interstitial rejection. Contrary to interstitial rejection in kidneys from younger donors, kidneys from old donors seem to have an impaired ability to restore tissue.

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