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ORIGINAL ARTICLE

Recipient age and risk of chronic allograft nephropathy in primary deceased donor kidney transplant

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Summary

Single center and registry data studies have had conflicting results regarding the impact of recipient age on chronic allograft nephropathy (CAN). We tested the hypothesis that advanced recipient age is a risk factor for graft failure due to CAN. All patients who underwent primary deceased donor kidney transplant between January 1, 1995 and December 31, 2000 recorded in the United Network of Organ Sharing (UNOS) database were analyzed for the occurrence of death censored graft loss and by two different definitions of graft loss due to CAN. Kaplan–Meier analysis based on the recipient age, and Cox proportional hazard regression was used to estimate the independent effect of recipient age on the three endpoints of interest. For all endpoints, after age of 9 years, the risk of graft loss declined with each successive decade increase in age. This pattern of risk was similar for both Caucasian and African-American recipients, although for any given age the risk of graft loss was always higher in African-American recipients. Analysis of UNOS data does not support the hypothesis that advanced recipient age is a risk factor for CAN.

Introduction

Chronic allograft nephropathy (CAN) and death with a functioning graft are the most common causes of late graft failure in registry data. Previous analysis of the United States Renal Data System transplant database indicated that advanced recipient age was a risk factor for chronic graft loss excluding patients with graft loss due to death, recurrent disease, graft thrombosis, infection, acute rejection or surgical complications [1]. This study also showed that death censored graft loss was higher for advanced age recipients of deceased donor transplants. This finding is surprising given that advanced recipient age is a major risk factor for death with a functioning graft, which is the most common cause of graft failure in elderly recipients, and that the difference in graft survival between older and younger age recipients is small [2,3].

At least four single center studies have shown that graft loss due to CAN is more common in younger recipients [4–7]. Younger recipients particularly in the teens and 20s are probably at higher risk for immunosuppression noncompliance, have higher rates of early acute rejection and may have more active immune systems that would make them more prone to alloantigen mediated CAN [8–13]. The question of alloantigen-dependent versus independent factors predominating in the etiology of CAN is important in determining target therapies to reduce this common form of graft loss. If advanced recipient age increases the risk of CAN, then alloantigen-independent factors may be more important. On the other hand, if younger recipients are more prone to this complication, it would suggest the former. The purpose of this study was to confirm the hypothesis that older recipients were more prone to graft loss due to CAN than younger recipients using the UNOS database.

Materials and methods

This study used data collected by Organ Procurement and Transplant Network database obtained from the

Standard Transplant Analysis and Research File. All patients transplanted for the first time with a deceased donor between January 1, 1995 and December 31, 2000 were included in the study. The data set end date was January 14, 2005, which allows for at least 4.0 years follow-up on all patients. Because the rate of re-transplantation is higher in younger recipients, only primary transplants were included to limit the effect of this confounding variable.

Three endpoints of interest were used to define chronic allograft loss (CAL), death censored graft loss (DCGL), CAL defined as chronic graft loss coded as chronic rejection or unknown (excluding all known causes of graft failure other than chronic rejection) and CAN defined as graft loss coded as chronic rejection.

As chronic graft loss was the emphasis of this analysis, only patients whose grafts survived the first 6 months were included in the analysis. A total of 37 708 deceased donor recipients with graft survival of at least 6 months were identified. As recipient race has been identified as a strong independent risk factor for chronic graft loss, a subanalysis of the population was carried out based on race (Caucasian, African-American and other).

Kaplan–Meier analysis was used to compare graft survivals for the three different endpoints based on the recipient age group. Log-rank testing was used to determine the statistical significance of the differences in the survival curves. Cox proportional hazard regression was used to estimate the independent effect of recipient age on the three endpoints of interest controlling for relevant risk factors.

The following independent variables were included in the model including donor age, race, and sex, recipient race and sex, acute rejection treatment in the first 6 months, cytomegalovirus (CMV) status of recipient and donor, delayed graft function, cold ischemia time, cause of end-stage renal disease (ESRD), most recent panel reactive antibodies (PRA), year of transplantation, human leukocyte antigen (HLA) mismatch, duration of dialysis prior to transplant and serum creatinine level at 6 months. All covariates were either categorical, or in the case of donor and recipient age, cold ischemia time, duration of dialysis, most recent PRA and creatinine levels at 6 months were stratified into categories. Delayed graft function was defined as the need for dialysis treatment in the first week post-transplantation.

In this analysis, competing endpoints could possibly bias the data if CAN hastens a patient's death prior to graft loss more commonly in the elderly cohorts. In order to examine this potential bias, the terminal creatinine in the database within a year of death with a functioning graft was determined. The database had creatinine measures at 6 months, 1 year and yearly thereafter post-transplant. The terminal creatinine was defined as the last creatinine recorded in the year of death with a functioning graft, graft loss or last follow-up post-transplant. Approximately 87% of patient's in the database had a terminal creatinine recorded. By comparing the terminal creatinine and estimated glomerular filtration rates (eGFR) in patients who died with a functioning graft among different age cohorts, patterns of graft function prior to death can be compared. If elderly recipients have more graft dysfunction prior to death than other age groups, it would suggest that death is preempting graft loss and biasing the results toward a protective effect of advanced age on the incidence of graft loss due to CAN. On the other hand, if the terminal graft functions are similar among the age groups, then it is unlikely a bias of this kind is contributing to the effect of age on graft loss due to CAN. The eGFR was calculated using the abbreviated modification of diet in renal disease (MDRD) formula, which included the following variables: age, sex, creatinine, and race [14]. As this formula is only validated in adults, the eGFR was calculated for the age cohorts over 19 years old.

A probability of type 1 error $\alpha = 0.05$ was considered to be the threshold of statistical significance. All statistical analysis was performed using SPSS software (version 11.0 for Windows; SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows the characteristics of the study cohort based on recipient age decade. The recipient characteristics that varied with age included African-American race, which was lower at either extreme of age, and percent of patient with diabetic nephropathy as a cause of ESRD, which was very rare for patients under age 20. Mean donor age increased as recipient age increased. HLA matching was better among older recipients than younger recipients. High-risk CMV mismatching (D^+/R^-) was much more common in younger recipients probably reflecting the lower rate of CMV recipient exposure seen in pediatric population, and the rate of delayed graft function was significantly lower in recipients under the age of 20. The rate of acute rejection in the first 6 months was highest for patients under the age of 20, and slowly declined thereafter with increasing recipient age. Cold ischemia time was slightly longer in older recipients than younger recipients. The mean creatinine at 6 months post-transplant was lowest in pediatric recipients and was similar in all adult groups thereafter.

Figures 1 and 2 show the Kaplan–Meier time-to-event plots for overall graft loss and the three endpoints of interest. The best long-term graft survival was seen in the youngest cohort of patients aged 0–9 years old. Recipients aged 10–19 years and over the age of 59 had the poorest long-term graft survivals. Among adults, the best graft

Table 1. Characteristics of recipient age decades.

	Recipient age group (years)						
	0–9 ($n = 400$)	10–19 ($n = 1173$)	20–29 ($n = 3348$)	30–39 ($n = 7422$)	40–49 ($n = 10\,004$)	50–59 ($n = 9043$)	60 or older ($n = 6318$)
Mean recipient age in years	5.4 ± 2.6	15.2 ± 2.7	25.6 ± 2.7	34.9 ± 2.8	44.7 ± 2.9	54.3 ± 2.9	64.9 ± 4.1
Percent recipient (sex: male) (%)	63.0	55.9	56.2	59.6	61.7	61.2	63.7
Percent recipient (race: Black) (%)	22.3	30.9	33.3	26.5	26.3	26.8	20.8
Percent with diabetes mellitus as a cause of ESRD (%)	0.3	1.1	20.9	38.7	33.7	31.9	28.6
Mean peak PRA	2.1 ± 9.3	2.8 ± 11.7	3.8 ± 13.3	4.2 ± 14.0	4.2 ± 14.3	4.3 ± 14.4	4.2 ± 14.3
Mean donor age in years	24.3 ± 14.4	27.9 ± 15.1	30.5 ± 15.6	31.3 ± 15.6	33.7 ± 16.4	36 ± 17.2	39.3 ± 18.2
Percent donor (sex: male) (%)	63.8	61.9	60.3	62.2	60.4	58.8	58.1
Percent donor (race: Black) (%)	10.8	12.7	12.6	11.8	11.3	10.9	9.1
Mean HLA mismatch	4.0 ± 1.4	3.9 ± 1.5	3.5 ± 1.7	3.5 ± 1.7	3.4 ± 1.7	3.3 ± 1.8	3.2 ± 1.8
Percentage of recipients CMV D^+/R^- (%)	34.3	30.3	25.8	27.3	22.1	18.1	15.8
Percent delayed graft function (%)	9.5	11.9	17.4	17.1	18.9	21.1	22.2
Percent acute rejection in first 6 months (%)	21.8	26.0	24.5	23.7	21.6	18.6	17.1
Mean cold ischemia time (h)	17.6 ± 7.4	18.4 ± 7.7	19.0 ± 8.6	18.8 ± 8.3	19.7 ± 8.6	20.3 ± 8.4	20.6 ± 8.2
Mean creatinine at 6 months (mg/dl)	0.78 ± 0.60	1.40 ± 0.84	1.68 ± 0.83	1.65 ± 0.78	1.63 ± 0.92	1.61 ± 0.84	1.59 ± 0.72

ESRD, end-stage renal disease; CMV, cytomegalovirus; HLA, human leukocyte antigen.

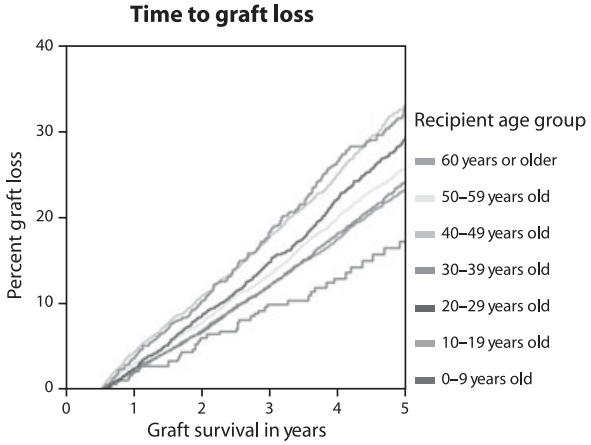

Figure 1 Kaplan–Meier plot of time to graft loss.

survival was seen in the patients between the ages of 30 and 49 years. After censoring for death as a cause of graft loss, the rate of graft loss decreased with increasing recipient age after the age of 9 years old for all graft outcomes. Table 2 shows the rate of graft loss 6 months post-transplant for the three endpoints based on recipient age. Again, there is a strong inverse correlation between recipient age and the rate of graft loss due to three endpoints. When racial subgroups of patients were examined, the relationship between recipient age and the rate of graft loss was the same, although for any given age group African-American recipients had a higher rate of graft loss when compared with Caucasians (Fig. 3). Moreover, the risk of CAN, CGL, and DCGL appeared to level off after the age of 40 years old in Caucasians, while there was a steady decrease for all three endpoints as the recipient age increased in the African-American cohort.

Tables 3 and 4 show the multivariate analysis of risk factors to DCGL and CAN. For both analyses, the risk of CAN and DCGL increased with decreasing recipient age. Recipient age 10–19 years old had the highest hazard ratio of graft loss due to DCGL and CAN.

Table 5 shows the mean and median terminal creatinines and mean eGFRs among the patients who died with graft function based on the age of the recipient. The terminal creatinine was measured a mean of 6.8 months prior to death, and this timing was similar among all the age groups. Very few deaths occurred in the two youngest age cohorts ($n = 19$), and only the recipients age 0–9 years old had a statistically lower mean creatinine than the reference group of 20–29 years old ($P = 0.044$). The mean and median terminal creatinines decreased with increasing recipient age and the mean eGFRs were not significantly different among the age cohorts older than 19 years indicating that graft function prior to death with a functioning graft was similar among the different age cohorts, and that death censoring was not significantly biasing the results toward a protective effect of advance recipient age for CAN.

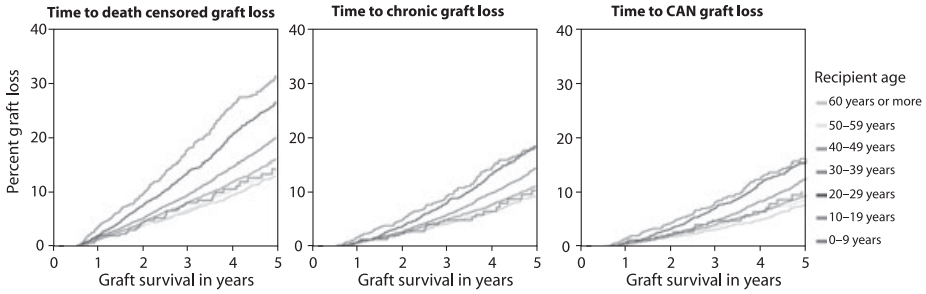

Figure 2 Kaplan–Meier plots of time to death censored graft survival, chronic graft loss and chronic allograft nephropathy graft loss by recipient age decade. Log-rank testing using 60 years or older cohort as comparison. Death censored graft loss: log-rank <0.001 for age groups 10–19, 20–29, 30–39 and 40–49 years. NS for age groups 0–9 and 50–59 years. Chronic graft loss: log-rank <0.001 for age groups 10–19, 20–29, and 30–39 years. Log-rank 0.032 for 40–49 years. NS for 0–9 and 50–59 years. Chronic allograft nephropathy graft loss: log-rank <0.001 for age groups 10–19, 20–29, and 30–39 years. Log-rank 0.001 for 40–49 years and 0.0239 for 50–59 years. NS for 0–9 years.

Table 2. Rate of chronic allograft nephropathy graft loss, chronic allograft loss, and death censored graft loss after the first 6 months post-transplant.

Recipient age group (years)	Rate of death censored graft loss	Rate of chronic graft loss	Rate of chronic allograft nephropathy loss
0–9	3.35	2.28	2.13
10–19	8.62	4.63	3.91
20–29	6.63	4.30	3.71
30–39	4.68	3.14	2.65
40–49	3.84	2.55	2.13
50–59	3.13	2.22	1.84
60 or older	2.93	1.92	1.52

Rates are expressed as events per 100 patient years.

Discussion

The results of this study clearly show that increasing recipient age is associated with a decrease in the incidence of chronic graft failure. The obvious limitation of this study is that the cause of graft failure was based on center reporting and not necessarily confirmed by biopsy of the allograft, and in approximately 10% of cases the cause of graft failure was unknown. As there are no universally accepted diagnostic criteria for CAN short of biopsy, we used multiple definitions for chronic allograft loss, and for all definitions the relationship between recipient age and risk remained the same, we believe strengthening the conclusions of this study. Clearly, the DCGL definition includes patients with other causes of graft loss. The two other endpoints, CAL and CAN probably more closely approximate the true rate of graft loss due to CAN, with the true rate somewhere in between the more and less restrictive definition.

The conclusion of this study is exactly opposite the previous registry study examining this question. The two studies are different in design and contain patients from different eras of immunosuppression. Patients in our study had to have a graft survival of at least 6 months to be included, whereas the former study looked at graft survival from the time of transplant. In the former study,

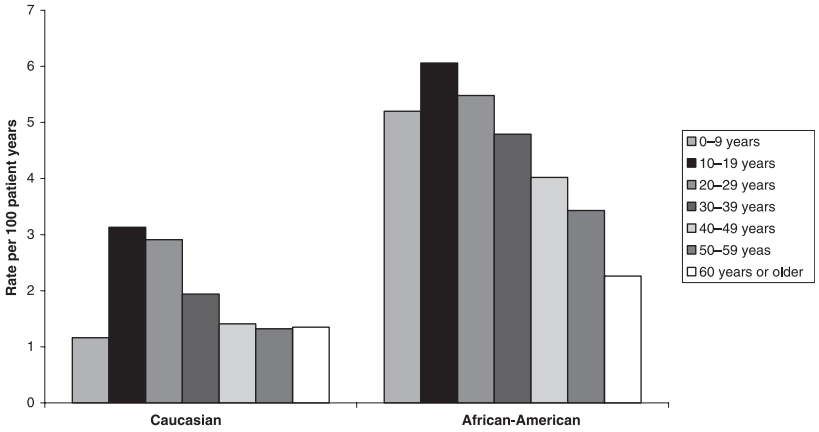

Figure 3 Rate of chronic allograft nephropathy loss based on recipient age decade and race. Rate of graft loss expressed as events per 100 patient years.

Table 3. Cox multivariate analysis of death censored graft survival.

Variable (reference)	H.R.	95% CI for H.R. Lower	Upper	Significance
Donor age in years (20–29 years)				
0–9	1.29	1.10	1.51	0.002
10–19	0.98	0.88	1.09	NS
30–39	1.19	1.06	1.33	0.003
40–49	1.36	1.22	1.52	<0.001
50–59	1.57	1.41	1.76	<0.001
60 or older	2.10	1.85	2.39	<0.001
Donor race (White)				
Black	1.31	1.20	1.43	<0.001
Other	0.95	0.78	1.16	NS
Donor gender (male)				
Female	1.07	1.00	1.14	0.048
Recipient age in years (60 years or older)				
0–9	2.05	1.46	2.88	<0.001
10–19	3.43	2.91	4.03	<0.001
20–29	2.24	1.97	2.53	<0.001
30–39	1.66	1.49	1.86	<0.001
40–49	1.31	1.17	1.47	<0.001
50–59	1.10	0.98	1.23	NS
Recipient race (White)				
Black	1.70	1.58	1.82	<0.001
Other	1.02	0.86	1.18	NS
Recipient gender (male)				
Female	1.11	1.04	1.19	0.002
Cause of ESRD (polycystic kidney disease)				
Diabetic nephropathy	1.86	1.59	2.17	<0.001
Glomerulonephritis	1.48	1.27	1.74	<0.001
Hypertensive nephropathy	1.47	1.26	1.72	<0.001
Other	1.45	1.25	1.69	<0.001
Most recent PRA (0%)				
1–30%	0.99	0.91	1.07	NS
31–100%	1.25	1.08	1.44	0.003
Unknown	1.07	0.87	1.30	NS
CMV status (D^-/R^-)				
D^-/R^+	1.18	1.06	1.32	0.003
D^+/R^+	1.23	1.11	1.37	<0.001
D^+/R^-	1.25	1.13	1.39	<0.001
Missing	1.05	0.89	1.24	NS
Delayed graft function (no)				
Yes	1.26	1.18	1.36	<0.001
Unknown	0.97	0.68	1.37	NS
Acute rejection first 6 months (no)				
Yes	1.46	1.36	1.57	<0.001
Unknown	1.29	1.20	1.40	<0.001
Creatinine at 6 months in mg/dl (<1.0 mg/dl)				
1.0–1.5	1.16	0.97	1.38	NS
1.6–2.4	1.83	1.53	2.19	<0.001
>2.4	2.49	2.08	2.97	<0.001
Unknown	1.58	1.32	1.89	<0.001
Transplant year (1995)				
1996	1.01	0.93	1.10	NS
1997	1.09	1.00	1.20	0.065
1998	1.09	0.98	1.21	NS
1999	1.24	1.09	1.41	0.002
2000	1.38	1.18	1.61	<0.001
HLA mismatch (0)				
1	1.16	0.94	1.43	NS
2	1.33	1.14	1.55	<0.001
3	1.32	1.15	1.51	<0.001
4	1.42	1.24	1.62	<0.001
5	1.55	1.35	1.77	<0.001
6	1.53	1.32	1.78	<0.001
Cold ischemia time in hour (<12 h)				
12–24	1.04	0.95	1.14	NS
24–36	1.07	0.97	1.19	NS
>36	1.19	1.00	1.42	0.055
Unknown	1.03	0.90	1.17	NS

ESRD, end-stage renal disease; CMV, cytomegalovirus; HLA, human leukocyte antigen; NS, not significant.

Donor creatinine and duration of dialysis were also in the model, but they were omitted from the table for brevity's stake. These two variables did not have a significant effect on the outcome of interest.

which included patients from 1988 to 1997, the latest follow-up date was June 30, 1998. Patients transplanted in 1995–1997 would have limited follow-up with the majority having follow-up data <1 year depending on the lag time in reporting outcomes to the database. Also the number of elderly patients receiving deceased donor transplants has been increasing with time. Therefore, the later era (1992–1997) probably contributed the majority of the patients in the elderly cohort studied while this era contributed only a small portion to the subsequent years of survival examined given the limited follow-up time. As CAN is a chronic process, the follow-up time in the study may have been inadequate and caused significant biasing of the results due to era effects (i.e. the majority of the long-term survival occurred in a minority of the elderly cohort). Moreover, it is possible that the pattern of censoring lacked independence and uniformity over the time period, significantly biasing one group when compared with the other. Without access to the database used for the previous analysis, the cause for this discrepancy in results is conjectural at best.

Our results are much more consistent with the published data regarding the risk of death as a cause of graft loss and graft survival rates based on recipient age. The most recent graft survival data shows that the 5-year graft survival for a 18 to 34-year-old recipient of nonexpanded criteria deceased donor kidneys is 67.8% while the graft survival for a recipient age 65 years or older is 61.9% [3]. This is in spite of the fact that, the risk of death with graft function is seven times higher for recipients 65 years

Table 4. Cox multivariate analysis of chronic allograft nephropathy graft survival.

Variable (reference)	H.R.	95% CI for H.R. Lower	Upper	Significance
Donor age in years (20–29 years)				
0–9	1.32	1.06	1.64	0.014
10–19	1.05	0.90	1.22	NS
30–39	1.20	1.03	1.41	0.020
40–49	1.53	1.32	1.77	<0.001
50–59	1.64	1.41	1.92	<0.001
60 or older	2.41	2.03	2.86	<0.001
Donor race (White)				
Black	1.25	1.11	1.41	<0.001
Other	0.83	0.62	1.10	NS
Donor gender (male)				
Female	1.12	1.03	1.23	0.011
Recipient age in years (60 years or older)				
0–9	2.44	1.57	3.81	<0.001
10–19	3.11	2.47	3.93	<0.001
20–29	2.37	2.00	2.81	<0.001
30–39	1.76	1.51	2.06	<0.001
40–49	1.37	1.17	1.59	<0.001
50–59	1.23	1.05	1.43	0.010
Recipient race (White)				
Black	1.76	1.60	1.94	<0.001
Other	1.04	0.85	1.26	NS
Recipient gender (male)				
Female	1.13	1.04	1.24	0.006
Cause of ESRD (PKD)				
Diabetic nephropathy	1.95	1.58	2.41	<0.001
Glomerulonephritis	1.47	1.19	1.82	<0.001
Hypertensive nephropathy	1.50	1.21	1.85	<0.001
Other	1.53	1.25	1.89	<0.001
Most recent PRA (0%)				
1–30%	1.08	0.98	1.20	NS
31–100%	1.38	1.14	1.67	0.001
Unknown	1.13	0.86	1.47	NS
CMV Status (D^-/R^-)				
D^-/R^+	1.08	0.93	1.25	NS
D^+/R^+	1.21	1.05	1.38	0.006
D^+/R^-	1.19	1.03	1.38	0.015
Missing	1.02	1.04	1.24	NS
Delayed graft function (no)				
Yes	1.28	1.17	1.41	<0.001
Unknown	1.05	0.66	1.68	NS
Acute rejection first 6 months (no)				
Yes	1.48	1.34	1.63	<0.001
Unknown	1.22	1.09	1.35	<0.001
Creatinine at 6 months in mg/dl (<1.0 mg/dl)				
1.0–1.5	1.11	0.87	1.41	NS
1.6–2.4	1.83	1.44	2.33	<0.001
>2.4	2.57	2.02	3.28	<0.001
Unknown	1.47	1.15	1.89	0.002
Transplant year (1995)				
1996	0.93	0.83	1.05	NS
1997	1.07	0.94	1.21	NS
1998	1.06	0.91	1.23	NS
1999	1.30	1.09	1.56	0.004
2000	1.21	0.95	1.54	NS
HLA mismatch (0)				
1	1.32	0.98	1.77	NS
2	1.64	1.33	2.03	<0.001
3	1.59	1.31	1.94	<0.001
4	1.79	1.48	2.16	<0.001
5	1.88	1.55	2.28	<0.001
6	1.79	1.44	2.22	<0.001
Cold ischemia time in hours (<12 h)				
12–24	1.08	0.96	1.22	NS
24–36	1.13	0.98	1.29	NS
>36	1.23	0.97	1.55	NS
Unknown	1.08	0.90	1.28	NS

ESRD, end-stage renal disease; CMV, cytomegalovirus; HLA, human leukocyte antigen; NS, not significant.
Donor creatinine and duration of dialysis were also in the model but they were omitted from the table for brevity's stake. These two variables did not have a significant effect on the outcome of interest.

Table 5. Mean and median terminal creatinine in the recipient age groups that died with graft function.

Recipient age groups (years)	Mean terminal creatinine in mg/dl with SD	Median terminal creatinine (mg/dl)	Mean terminal eGFR in ml/min/1.73 m^2 with SD
0–9 ($n = 9$)	1.3 ± 0.9	1.1	–*
10–19 ($n = 10$)	2.9 ± 2.5	2.0	–*
20–29 ($n = 58$)	2.3 ± 1.4	2.1	46.1 ± 25.3
30–39 ($n = 225$)	2.1 ± 1.1	1.8	45.3 ± 21.4
40–49 ($n = 491$)	2.1 ± 1.1	1.8	46.0 ± 24.5
50–59 ($n = 690$)	2.0 ± 1.1†	1.7	46.8 ± 25.0
60 or older ($n = 803$)	1.9 ± 0.9‡	1.7	45.4 ± 21.5

*Estimated glomerular filtration rates (eGFR) not calculated for these two age groups because abbreviated MDRD formula not validated in pediatric populations. No significant difference in the mean eGFRs of any of the age cohorts when compared with the reference age group of 20–29 years old. Significance determined by ANOVA testing.
†$P = 0.015$ reference group 20–29 years old.
‡$P < 0.01$ reference group 20–29 years old.

or older when compared with recipients age 18–29 years old [2]. If the rates of CAN were similar or higher in the elderly population, the expected 5-year survival difference between younger and old recipients would be expected to be much larger.

In our opinion, the finding that younger recipients are more prone to CAN favors a greater role of alloantigen-dependent than alloantigen-independent factors

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in the genesis of this common cause of graft loss. Younger recipients have a higher early acute rejection rate, poorer compliance with immunosuppressive medications, and more active immune systems, which may explain the marked differences in the rate of this cause of graft failure [5,6,8–11]. Previous single institution studies have shown that both early and late acute rejection episodes, more severe acute rejections, noncompliance, younger donor age, and inadequate calcineurin dosing are associated with an increase risk of CAN [4–7,11,15–19]. Alloantigen-independent factors associate with CAN have included hypertension, calcineurin nephrotoxicity, advanced donor age, ischemia reperfusion injury, and hyperlipidemia [20–25]. Most of these factors are not recipient age-dependent and the factors that may be recipient age-dependent could actually be worse in older age recipients such as hyperlipidemia and hypertension. Whether these alloantigen-independent factors can be the primary cause of CAN or whether these represent contributing milieu factors that accelerate the damage related to the primary alloantigen-dependent process is not clear. Unfortunately, the pathologic picture we call CAN may represent the culmination of one or more primary pathophysiologic processes making it very difficult in individual patients to determine the appropriate interventions to preserve graft function. Also, among the alloantigen-dependent factors, experimental models and evidence from human CAN indicate a role for all elements of the immune system, including cell-mediated immune responses, humoral immunity, inflammatory cytokines, growth factors, and vasoactive peptides further complicating the selection of target therapies for CAN in individual patients [26–32].

The marked increase in the rate of chronic graft loss in transplants performed in the second decade of life has been attributed in large part to compliance. Unfortunately, graft loss related to compliance is difficult to quantify, and other factors may be contributing to this large difference in outcomes. Patients under the age of 10 years had similar rates of acute rejection in the first 6 months as patient in the 10–19 years of age range suggesting similar cellular immune reactivity to the organ, but a much lower rate of chronic graft loss due to CAN. As most of these patients receive adult organs, it is possible that the relatively high renal transplant mass to body mass ratio in the youngest age group results in a longer graft survival with CAN. Also, the pathopathologic machinery responsible for CAN may improve as children mature into adulthood, and transplantation in young children may be a more privileged time period with regard to CAN.

This relationship between recipient age and chronic graft loss underscores the importance of compliance with immunosuppression. Although overt volitional noncompliance is easy to detect, covert, and nonvolitional noncompliance (i.e. forgetting to take medication or misunderstanding dosing) may be difficult to detect, and it is unclear what level of noncompliance is needed to alter graft outcomes (i.e. occasional missed doses versus prolonged cessation or reduction in dosing). Given the need for informed consent in compliance studies, it is difficult to know the extent of the problem in the general transplant population and how it is affecting the graft outcomes. However, the relationship between recipient age and CAN gives pause for thought that this problem may be greater than we appreciate and efforts to improve compliance may be beneficial in limiting this cause of graft loss.

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