

Patient and Graft Outcomes from Deceased Kidney Donors Age 70 Years and Older: An Analysis of the Organ Procurement Transplant Network/United Network of Organ Sharing Database

Disaya Chavalitdhamrong,¹ Jagbir Gill,¹ Steve Takemoto,² Bhaskara R. Madhira,¹ Yong W. Cho,² Tariq Shah,² and Suphamai Bunnapradist^{1,3}

Background. The organ shortage has resulted in more use of older deceased donor kidneys. Data are limited on the impact of donor aged 70 years and older on transplant outcomes. We examined patient and graft outcomes of renal transplant from expanded criteria donors (ECDs) aged 70 years and older, using the Organ Procurement Transplant Network/United Network of Organ Sharing database.

Methods. We identified 601 deceased donor transplants from donors older than 70 years from 2000 to 2005. The follow-up time was until May 2007. Allograft and patient survival were compared between recipients of transplants from older ECDs (age ≥ 70) and younger ECDs (age 50–69). The relative risk of graft loss and patient death were determined using multivariate models.

Results. The adjusted relative risks of overall graft loss (hazards ratio [HR] 1.37; 95% confidence interval [CI] 1.19–1.58), death-censored graft loss (HR 1.32; 95% CI 1.09–1.61), and patient death (HR 1.37; 95% CI 1.15–1.64) were greater among recipients of transplants from older ECD kidneys. The relative risk of patient death was lower when older ECD kidneys were transplanted into recipients older than 60 compared with recipients aged 41 to 60. In contrast, the relative risk of death-censored graft loss was not increased when older ECD kidneys were transplanted into recipients older than 60.

Conclusions. Transplants from older ECD kidneys are associated with a higher risk of graft loss and patient death. The risk was highest when older ECD kidneys were transplanted into recipients younger than 60 years.

Keywords: Kidney transplantation, Donors, Marginal, Graft survival, Allocation.

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The organ shortage continues to be a major issue in kidney transplantation. The disparity between organ supply and demand has led to the implementation of various strategies to more efficiently use the current potential donor pool. One such strategy includes the use of expanded criteria donor (ECD) kidneys (1) including the use of organs from extremely old deceased donors (≥ 70 years old). Until recently these organs from older donors would likely have been discarded based on the donor's advanced age (2). Donor age has long been identified as a dominant predictor of allograft survival in kidney transplantation (3, 4). By definition, ECD transplantation is associated with inferior outcomes com-

pared with standard criteria donor transplants (4–8). Although it is known that outcomes vary among ECD transplants, the impact of using extremely old donors on transplant outcomes remains largely unknown.

The objective of this study was to evaluate transplant outcomes among recipients of ECD transplants from older donors (donor age ≥ 70) compared with all other ECD transplant recipients using data from the United Network of Organ Sharing (UNOS)/Organ Procurement Transplant Network (OPTN).

MATERIALS AND METHODS

Study Design

A cohort study of ECD transplants was conducted using the OPTN/UNOS database as of May 2007. We identified 9580 ECD kidney-only transplants between 2000 and 2005. Of these, 601 (6.3%) were from older ECD donors (≥ 70 years of age) and 8979 were from younger ECD donors (50–69 years of age). Multiple organ transplants and dual kidney transplants were excluded.

We first compared donor, recipient, and transplant characteristics of older ECD transplants compared with all other ECD transplants. Next, we identified recipient factors associated with receipt of an ECD transplant from a donor aged 70 years and older. We then compared post-transplantation outcomes, including the rate of delayed graft function (DGF) and acute rejection (AR) at 1 year and the mean serum creatinine level 1-year posttransplant, between each ECD study group. Next, we compared graft

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¹ Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.

² National Institute of Transplantation, Los Angeles, CA.

³ Author correspondence to: Suphamai Bunnapradist, M.D., Department of Medicine, David Geffen School of Medicine at UCLA, 924 Westwood boulevard, Suite 860, Los Angeles, CA 90095.

E-mail: bunnapradist@mednet.ucla.edu

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and patient survival between the ECD subgroups and we assessed the risk of graft failure (overall and death censored) and patient death for recipients of ECD transplants from donors aged 70 years and older compared with recipients of ECD transplants from donors 50 to 69 years, using multivariate regression models.

We further stratified the reference group of ECD transplants by donor age (ECD transplants from donors age 50 to 59 years and 60 to 69 years) and repeated the outcomes analyses. Finally, we examined the differential effect of older ECD donors on overall graft survival, death-censored graft survival, and patient survival among different recipient age groups.

Definitions

Expanded criteria donor was defined as per the UNOS definition (9). For the purpose of this study, older ECD transplants were defined as ECD transplants from donors aged 70 years and older and included donors with or without additional comorbidities. Delayed graft function was defined as the need for dialysis within the first week posttransplant. Overall graft survival was determined from the date of transplantation until death, return to dialysis, or the end of the study period. Death-censored graft survival was censored for death with a functioning graft.

Statistical Analysis

Donor, recipient, and transplant characteristics were described using the means \pm standard deviations or frequencies, and group differences were compared with the *t* test or chi-square test as appropriate. Logistic regression analysis was performed to identify factors associated with receipt of an ECD kidney from an older ECD. The time to graft loss was determined using the Kaplan-Meier product limit method and comparisons between groups were made using the log-rank test. Three Cox proportional hazards multivariate regression models were fitted to estimate the relative risks of overall graft loss, patient death, and death-censored graft loss. Donor, recipient, and transplant factors significantly ($P < 0.05$) associated with overall graft loss, patient death, or death-censored graft loss were included as covariates in the respective multivariate model.

A secondary analysis was performed to examine the differential effect of older ECD donors on overall graft survival, death-censored graft survival, and patient survival among different recipient age groups: recipient age 41 to 60 and older than 60 years.

All statistical tests were two-tailed. All statistical analyses were performed using Stata V.9.1.

RESULTS

Baseline Characteristics

A total of 9580 ECD kidney transplants were included. The characteristics of donors, recipients, and transplant are shown in Table 1.

Recipient Characteristics

Recipients of older ECD transplants were of older age (mean age 62.8 ± 11.0 years compared with 56.4 ± 11.7 in recipients of all other ECD transplants), and had less pretrans-

plant dialysis exposure compared with recipients of younger ECD transplants.

Donor Characteristics

Older ECDs comprised fewer donors who were black (4.7% vs. 10.8%), had a history of hypertension (46.3% vs. 70.6%), or who had an elevated terminal serum creatinine more than 1.5 mg/dL (8.0% vs. 15.4%) compared with younger ECDs. When ECDs younger than 70 were further stratified into those age 50 to 59 and 60 to 69 years, we found that ECDs age 60 to 69 and ECDs more than or equal to 70 were similar (data not shown).

Factors Associated With Receipt of Transplant from Deceased Donor 70 Years or Older

Recipients older than 60 years, of black race (compared with non-black), with a body mass index less than 28 kg/m², and with dialysis exposure time less than or equal to 3 years were more likely to receive a kidney transplant from an ECD aged 70 years and older (Table 2).

Transplant Outcomes—Delayed Graft Function, Acute Rejection, Serum Creatinine 1-Year Posttransplant

Posttransplant outcomes for both ECD groups are outlined in Table 3. Delayed graft function occurred in the majority of patients. There were no statistically significant differences in the incidence of DGF (60.4% vs. 63.9%) and AR at 1 year (18.1% vs. 16.8%) between ECD transplants from younger versus older ECDs. A subgroup analysis looking at the incidence of AR at 1 year by recipient age among recipients of ECD transplants revealed an increase in AR with increasing recipient age.

Serum creatinine at 1 year posttransplant was significantly higher among transplants from older ECDs (2.1 mg/dL) compared with transplants from younger ECDs (1.9 mg/dL). Of note, there was no significant difference in DGF, AR, and serum creatinine level at 1-year posttransplant between ECD transplants from donors aged 50 to 59 and 60 to 69 years.

Transplant Outcomes—Allograft Survival and Patient Survival

Figure 1 displays Kaplan-Meier curves for overall allograft survival, patient survival, and death-censored allograft survival among recipients of ECD transplants from donors aged 70 years and older compared with donors aged 50 to 69. Both overall graft survival and patient survival were inferior among recipients of ECD transplants from older ECDs, compared with younger ECDs. Three and five years overall graft survival rates of ECD transplant from donors 50 to 69 years were 69.3% and 54.9% (compared with 62.0% and 44.0% from donors ≥ 70 , log-rank $P < 0.001$). Three- and five-years patient survival rates for ECD transplants from donors 50 to 69 years were 81.8% and 70.7% (compared with 75.1% and 58.2% from donors ≥ 70 , log-rank $P < 0.001$). However, after censoring for death with a functioning graft, graft survival was not significantly different between recipients of ECD transplants from younger and older donors. Table 4 shows the results of Cox multivariate regression analyses for overall graft

TABLE 1. Donor, recipient, and transplant characteristics by ECD age group

Characteristics	Donor age 50–69 yr (N=8,979)	Donor age ≥70 yr (N=601)	P
Donor characteristics			
Male (%)	48.1	47.6	0.80
Race (%)			
White	75.7	85.2	<0.001
Black	10.8	4.7	
Hispanic	9.8	7.7	
Other race	3.7	2.5	
Trauma as a cause of death (%)	9.0	14.1	<0.001
History of hypertension (%)	70.6	46.3	<0.001
History of diabetes mellitus (%)	11.7	9.0	0.050
Terminal serum creatinine >1.5 mg/dL (%)	15.4	8.0	<0.001
BMI (kg/m ²) (%)			
<28	21.4	24.1	0.008
28–32	27.0	30.8	
>32	51.6	45.1	
Recipient characteristics			
Mean age (years)	56.4±11.7	62.8±11.0	<0.001
Age (%)			
<40 yr	10.3	5.5	<0.001
41–60 yr	48.8	24.1	
>60 yr	40.9	70.4	
Male (%)	62.4	60.9	0.472
Race (%)			
White	49.7	51.3	0.332
Black	30.5	30.3	
Hispanic	11.2	9.0	
Others	8.5	9.5	
Re-graft (%)	7.0	6.0	0.348
Body mass index (kg/m ²) (%)			
<28	58.8	64.1	0.001
28–32	22.4	23.3	
>32	18.8	12.7	
Peak panel reactive antibody (%)			
0–10	77.7	80.6	0.113
11–50	13.4	12.9	
>50	8.9	6.5	
Duration of dialysis			
No dialysis	11.9	13.3	0.007
<3 yr	38.6	44.1	
3–5 yr	28.8	26.5	
>5 yr	20.7	16.1	
Hypertension (%)	84.6	85.4	0.605
Cardiovascular disease (%)	13.8	15.4	0.297
Diabetes mellitus (%)	26.61	30.5	0.057
Cerebrovascular disease (%)	3.0	3.4	0.624
Peripheral vascular disease (%)	4.5	5.3	0.359
Transplant characteristics			
Cold ischemic time (%)			
0–24 hr	75.51	78.5	0.292
25–36 hr	20.44	18.3	
>36 hr	4.05	3.2	
HLA-DR mismatch (%)			
0 DR	9.6	10.5	0.001
1 DR	40.3	43.1	
2 DR	41.8	42.6	

loss, patient death, and death-censored graft loss among recipients of ECD transplants from donors aged 70 years and older compared with all other ECD transplants. The following covariates were included in all three models: do-

nor history of diabetes mellitus, recipient ethnicity, recipient diabetes mellitus and dialysis exposure time. In addition, donor ethnicity, donor history of hypertension, donor terminal serum creatinine, primary versus re-raft,

TABLE 2. Odds of receiving a transplant from expanded criteria donor age ≥ 70 yr

	OR (95% CI)	P
Recipient age		
>60	3.73 (3.10–4.49)	<0.001
0–60	1.00	
Recipient ethnicity		
Black	1.25 (1.03–1.51)	0.021
Non-black	1.00	
Recipient BMI (kg/m ²)		
<28	1.19 (1.00–1.42)	0.047
≥ 28	1.00	
Dialysis duration		
≤ 3 yr	1.26 (1.06–1.50)	0.009
>3 yr	1.00	

TABLE 3. Transplant outcomes, by ECD age group

	Donor age		P
	50–69 yr	≥ 70 yr	
25% Decline in serum creatinine in 1st 24 hr (%)	42.4	38.1	0.044
Delayed graft function ^a (%)	60.4	63.9	0.093
Acute rejection (%)			
At discharge	7.6	8.0	0.719
Within 6 mo	15.7	13.7	0.218
Within 1 yr	18.1	16.8	0.451
Serum creatinine (mg/dL)			
At discharge	4.2 \pm 3.0	4.0 \pm 2.5	0.114
At 6 mo	1.9 \pm 1.0	2.0 \pm 0.9	0.059
At 1 yr	1.9 \pm 0.9	2.1 \pm 0.9	0.022

^a Delayed graft function was defined as the need for dialysis in the first week posttransplant.

peak panel reactive antibody (PRA), and cold ischemic time were included in the model for overall graft loss and death-censored graft loss. Human leukocyte antigen mismatch was also included in the model for overall graft loss.

According to the multivariate analysis, recipients of transplants from older ECDs had a higher relative risk of graft loss (hazard ratio [HR] 1.37; 95% confidence interval [CI]: 1.19–1.59), patient death (HR 1.37; 95% CI: 1.15–1.64), and death-censored graft loss (HR 1.32; 95% CI 1.09–1.61) compared with recipients of transplants from younger ECDs.

In addition, according to the multivariate analysis, recipients at highest risk for graft loss included black recipients (HR 1.39; 95% CI 1.24–1.56), those with a regrant (HR 1.28; 95% CI 1.10–1.50), those with a peak PRA more than 50% (HR 1.23; 95% CI 1.08–1.41), those with more than 5 years of dialysis exposure (HR 1.64; 95% CI 1.40–1.92), and those with diabetes mellitus (HR 1.19; 95% CI 1.08–1.30).

Expanded Criteria Donor More Than or Equal to 70 Compared With Expanded Criteria Donor 60 to 69 Years

The results of Cox multivariate regression analyses for overall graft loss, patient death, and death-censored graft loss among recipients of ECD transplants from donors aged 70 years and older compared with recipients of ECD transplants from donors aged 60 to 69 are shown in Table 4.

According to this analysis, recipients of transplants from older ECDs had a higher relative risk of overall graft loss (HR 1.24; 95% CI 1.07–1.43) and patient death (HR 1.21; 95% CI 1.01–1.45) and trended toward a higher risk of functional graft loss (HR 1.18; 95% CI 0.97–1.44).

Transplant Outcomes—Allograft Survival and Patient Survival by Recipient Age (Younger Recipients Defined as Age 41 to 60; Older Recipients Defined as Age More Than 60)

Table 5 shows the results of a secondary analysis where transplant recipients were stratified by age: 41 to 60 years and more than 60 years. The relative risks of overall graft loss, patient death, and death-censored graft loss among recipients of transplants from older ECDs were computed for each recipient age group. The following covariates were included in all three models: donor history of diabetes mellitus, recipient ethnicity, recipient diabetes mellitus, and dialysis exposure time. In addition, donor ethnicity, donor history of hypertension, donor terminal serum creatinine, primary versus regrant, peak PRA, and cold ischemic time were included in the model for overall graft loss and death-censored graft loss. Human leukocyte antigen mismatch was also included in the model for overall graft loss. Recipients aged 40 years or younger were very few and were excluded from this analysis.

Younger Recipients of Expanded Criteria Donor Transplants (41–60 Years)

Recipients age 41 to 60 who received ECD transplants from older ECDs had a higher relative risk of overall graft failure (HR 1.42; 95% CI 1.06–1.88), patient death (HR 1.48; 95% CI 1.02–2.15), and death-censored graft failure (HR 1.48; 95% CI 1.06–2.06).

Older Recipients of Expanded Criteria Donor Transplants (Older Than 60 Years)

Recipients older than 60 who received transplants from older ECDs had a higher relative risk of overall graft failure (HR 1.30; 95% CI 1.09–1.55) and patient death (1.26; 95% CI 1.02–1.55). However, the risk of death-censored graft failure was not significantly different between recipients of ECD transplants from donors aged 70 years and older and 50 to 69 years.

Transplant Outcomes—Allograft Survival and Patient Survival by Dialysis Duration Pretransplant and Recipient Diabetic Status

Subset analyses indicate the hazard of graft loss and patient death associated with ECD kidneys from donors older than 70 years was similar regardless of duration of dialysis before transplantation. Nondiabetic recipients of ECD kidneys from donors older than 70 years had a significantly increased hazard of graft loss (HR 1.41, 1.16–1.70) and death (HR 1.55, 1.21–2.00) compared with nondi-

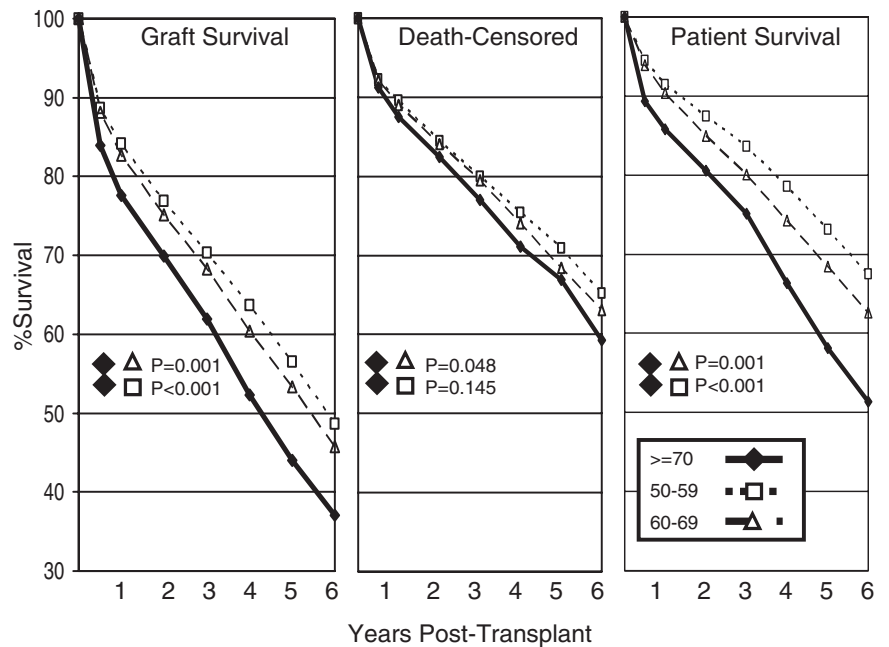


FIGURE 1. Overall graft survival, patient survival, and death-censored graft survival by ECD age group.

TABLE 4. Cox proportional hazard of graft loss, functional graft loss, and patient death for recipients of ECD transplants from donors age ≥ 70

Donor age	Graft survival			Functional graft survival			Patient survival		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
≥ 70 vs. 50–69	1.37	1.19–1.59	<0.001	1.32	1.09–1.61	<0.001	1.37	1.15–1.64	0.005
≥ 70 vs. 60–69	1.24	1.07–1.43	0.005	1.18	0.97–1.44	0.106	1.21	1.01–1.45	0.041

TABLE 5. Unadjusted and adjusted risk of graft loss, patient death, and death-censored graft loss among recipients of transplants from ECD ≥ 70 for the following categories of recipient age: 41–60 and > 60

ECD ≥ 70 versus ECD 50–69	Recipient age 41–60 yr (N=145)		Recipient age > 60 yr (N=423)	
	HR (95% CI)	P	HR (95% CI)	P
Overall graft loss				
Unadjusted	1.35 (1.02–1.79)	0.036	1.21 (1.01–1.44)	0.035
Adjusted	1.42 (1.06–1.88)	0.017	1.30 (1.09–1.55)	0.004
Patient death				
Unadjusted	1.38 (0.96–1.99)	0.085	1.21 (0.98–1.49)	0.069
Adjusted	1.48 (1.02–2.15)	0.040	1.26 (1.02–1.55)	0.030
Death-censored graft loss				
Unadjusted	1.51 (1.08–2.10)	0.015	1.04 (0.80–1.35)	0.782
Adjusted	1.48 (1.06–2.06)	0.020	1.12 (0.86–1.46)	0.404

ECD ≥ 70 , expanded criteria donor transplant from ECD age ≥ 70 yr; ECD 50–69, expanded criteria donor transplant from ECD age 50–69 yr.

abetic recipients of ECD kidneys from donors age 60 to 69 years, whereas diabetic patients did not (HR of graft loss 1.21, 0.92–1.61; HR of death 1.23, 0.89–1.70).

DISCUSSION

There continues to be a growing demand for kidney transplantation, with the number of patients wait-listed having increased from 39,968 to 46,351 from 2000 to 2005. Al-

though ECD kidneys are associated with a greater relative risk of graft failure (RR 1.70) compared with standard criteria donor kidneys (5, 6), ECD kidneys offer a survival advantage compared with wait-listed dialysis patients (10).

Schold et al. (11) reported that outcomes among ECD transplant recipients vary, in part, due to the varying characteristics and quality of organs among ECDs. Among these factors, donor age is most strongly associated with transplant

outcomes. Based on OPTN data as of September 21, 2007, the number of transplants from older ECDs (≥ 65 years) has increased slightly from 7.0% to 8.0% from 2000 to 2005.

We described the characteristics of transplants from older ECDs (donor age ≥ 70) and compared their outcomes with recipients of ECD transplants from younger donors (donor age 50–69). Patients transplanted with kidneys from older ECDs had a higher risk of graft failure and death compared with patients transplanted with kidneys from younger ECDs. The definition of ECD is such that donors age 50–59 years will have more comorbid disease compared with donors older than 60. To better assess the impact of donor age alone, we compared the outcomes of ECD transplants from donors aged 70 years and older to ECD transplants from donors age 60 to 69 and found similar results.

The adverse impact of increasing donor age on post-transplant outcomes is firmly established in the transplantation literature (12) and this observation remains true among recipients of all ages. Meier-Kriesche et al. (13) reported a near doubling of the relative risk of chronic allograft failure among recipients of all ages who received a kidney from a donor age 55 or greater, compared with a donor age 15 to 24 years.

Our findings suggest that this remains true even at extremes of age. Compared with recipients of transplants from donors age 60 to 69, recipients of transplants from donors 70 years and older had a higher relative risk of graft loss and patient death. It is important to note that aside from donor age, donor and recipient characteristics did not substantially differ among the 60 to 69 and 70 years and older groups.

Impact of Recipient Age on Outcomes from Older Expanded Criteria Donors

Previous findings suggest that ECD kidneys should be avoided in recipients younger than 40 years (1, 10, 14, 15), because they have a higher risk of graft failure. We found that 10% of all ECD kidneys were transplanted into patients younger than 40 years and only 5% of older ECD kidneys were transplanted into patients younger than 40. However, nearly 50% of all ECD transplants and 25% of ECD transplants from donors 70 years and older were among recipients age 41 to 60 years of age. Among recipients of older ECD kidneys, we found that the risk of graft failure and patient death was highest when older ECD kidneys were transplanted into younger recipients (age 41 to 60), suggesting that the recipient age limit should be increased when using older ECD kidneys.

Should Older Expanded Criteria Donors Only Go to Recipients Older Than 60?

For the older transplant recipient, the relative survival benefit of transplantation compared with being wait-listed on dialysis has been repeatedly demonstrated (16–22). Furthermore, as their younger counterparts, older recipients do better when transplanted after a shorter period of dialysis (23). Schold and Meier-Kriesche (14) reported that the higher morbidity and mortality among older recipients justified earlier transplantation using ECD kidneys. Our analysis extends this finding to the use of extremely old ECD kidneys. We found that more than two-thirds of older ECD kidneys were transplanted into patients older than 60 years. Among those older recipients who survived, there was no significantly increased risk of returning to dialysis in

their lifetime. Meanwhile, among younger recipients who survived, those with older ECD organs had a 50% greater risk of returning to dialysis.

This observation is most likely related to recipient characteristics. It is possible that younger recipients who are deemed “acceptable” to receive extremely old ECD kidneys have higher risk characteristics, conferring more risk of graft loss. Although most high risk factors were included in the multivariate model, it is important to note that there may be additional high risk characteristics not captured in the database.

The role of the aging immune system may also play an important role in graft outcomes among older recipients. Using UNOS data, Cecka (15) reported a steady reduction in the incidence of AR with age. Martins et al. (24) reviewed evidence supporting the development of age-related immune dysfunction and outlined experimental and clinical data demonstrating a decrease in the incidence of AR with increasing recipient age. Mechanisms to explain this have included a reduced number of naïve T cells, dysfunctional memory cells, increased sensibility to immunosuppression, reduced T-cell receptors and defective T-cell signaling, increased T-suppressor cells, and altered cytokine profiles.

In our analysis, we also found a higher incidence of AR with increasing age among recipients of ECD transplants. Meier-Kriesche et al. (25) reported a relative risk of rejection of 0.6 among recipients over the age of 60 compared with recipients age 18 to 29 years. Furthermore, the impact of AR on long-term graft survival may be more marked in the elderly than the young (23).

In our analysis, the reference group was recipients of ECD transplants from donors aged 50 to 69 years. To further examine the ideal candidates to benefit from the transplantation of extremely old ECD kidneys, further analysis needs to be conducted and outcomes of recipients from extremely old donors need to be compared with wait-listed dialysis patients. Regardless, based on our analysis we believe that caution should be exercised when older ECD kidneys are considered for transplantation into patients younger than 60 years.

When interpreting the results of this study, it is important to consider limitations of this analysis. Although this is a large retrospective study, the number of ECD transplants from older donors (≥ 70 years old) may not have been sufficient to detect certain significant risk factors on multivariate analysis. In addition, because dual kidney transplants were excluded from this analysis, these results only apply to single kidney ECD transplants. Furthermore, there are limitations inherent to observational studies using retrospective data. For instance, the use of kidneys from extremely old ECDs was more common in the latter time period of the study and this may introduce a selection bias due to changes practice and improvements in immunosuppression over time.

In conclusion, use of older ECD kidneys comprised 6.3% of all ECD transplants during the study period. Older recipients were more likely to receive these organs and 70.4% were transplanted into recipients older than 60 years. Transplants from older ECD kidneys were associated with a higher risk of graft loss and patient death. The risk was highest when older ECD kidneys were transplanted into recipients younger than 60 years.

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