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Determinants of Discard of Expanded Criteria Donor Kidneys: Impact of Biopsy and Machine Perfusion

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We examined factors associated with expanded criteria donor (ECD) kidney discard. Scientific Registry of Transplant Recipients (SRTR)/Organ Procurement and Transplantation Network (OPTN) data were examined for donor factors using logistic regression to determine the adjusted odds ratio (AOR) of discard of kidneys recovered between October 1999 and June 2005. Logistic and Cox regression models were used to determine associations with delayed graft function (DGF) and graft failure. Of the 12536 recovered ECD kidneys, 5139 (41%) were discarded. Both the performance of a biopsy (AOR = 1.21, p = 0.02) and the degree of glomerulosclerosis (GS) on biopsy were significantly associated with increased odds of discard. GS was not consistently associated with DGF or graft failure. The discard rate of pumped ECD kidneys was 29.7% versus 43.6% for unpumped (AOR = 0.52, p < 0.0001). Among pumped kidneys, those with resistances of 0.26–0.38 and >0.38 mmHg/mL/min were discarded more than those with resistances of 0.18–0.25 mmHg/mL/min (AOR = 2.5 and 7.9, respectively). Among ECD kidneys, pumped kidneys were less likely to have DGF (AOR = 0.59, p < 0.0001) but not graft failure (RR = 0.9, p = 0.27). Biopsy findings and machine perfusion are important correlates of ECD kidney discard; corresponding associations with graft failure require further study.

Key words: Biopsy, delayed graft function, discard rates, expanded criteria donors, glomerulosclerosis, graft failure, machine perfusion

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Introduction

The use of organs from expanded criteria donors (ECDs) has increased significantly over the past several years, and recipients of ECD kidneys have a survival benefit when compared with candidates who remain on the waiting list (1,2). Based on data from the Scientific Registry of Transplant Recipients (SRTR), ECD kidneys have been defined as kidneys from donors aged 60 years or above, or from donors aged 50–59 years with at least two of the following: cerebrovascular accident (CVA) as cause of death, terminal serum creatinine >1.5 mg/dL or a history of hypertension (3). When compared with kidneys from a reference group of normotensive donors aged 10–39 years with a terminal creatinine <1.5 mg/dL and death from other causes, kidneys from donors meeting the ECD definition have a relative risk (RR) of graft loss greater than 1.70. The ECD allocation system was designed to facilitate the allocation of kidneys from these donors (4). Despite the increase in ECD transplants and concerted efforts by the Organ Procurement and Transplantation Network (OPTN) and the organ procurement organization (OPO) community to increase ECD use, discard rates for procured ECD kidneys remain high (5).

ECD kidneys, by definition, have a high rate of graft failure, which contributes significantly to high discard rates. While preimplantation biopsy and machine perfusion are employed in the evaluation and management of kidneys from ECD donors (5), the impact of these practices on utilization and outcomes is uncertain. Therefore, we report on the relationship of biopsy and pumping characteristics to

ECD discard rates, delayed graft function (DGF) rates and transplant outcomes.

Methods

Data sources

The study used the SRTR/OPTN database, which includes data on all organ donors and transplant recipients in the United States, supplemented by the SRTR with mortality information from the Social Security Death Master File. Analyses of kidney discard examined all kidneys procured for transplantation in the United States between October 25, 1999, and June 30, 2005. Analyses of DGF and graft failure examined all kidneys transplanted in the United States between October 25, 1999, and June 30, 2004. The database includes information about pumping of kidneys by the OPO. Information about pumping by the transplant center was not available for this analysis. The predicted RR of graft failure was determined according to the RRs given for combinations of the four donor characteristics used to define ECD kidneys in the study by Port et al. (3). DGF was defined as the need for dialysis within 1 week of transplantation. The rate of ECD kidney recovery by donation service area (DSA) was determined as the percentage of kidneys recovered for transplantation out of the number of ECD kidneys available from deceased donors of at least one organ in the United States between October 25, 1999 and June 30, 2005.

Analytical methods

All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC). Unadjusted rates of discard were calculated as the percentage of kidneys procured for transplantation but not transplanted out of all kidneys procured for transplantation. The Pearson correlation coefficient r was used to determine the correlation between discard and recovery rates of ECD kidneys and between discard rates of ECD kidneys and percentage of ECD transplantations out of total kidney transplantations for each DSA. Logistic regression was used to determine the adjusted odds ratio (AOR) of discard for various donor factors among all kidneys, ECD kidneys and standard criteria donor (SCD) kidneys. Except in analyses testing the effect of adjusting for each individual DSA (i.e. area of each OPO) as a covariate, generalized estimating equations were used to account for clustering at the OPO level, assuming a compound symmetry covariance structure. This method accounts for the fact that kidneys recovered within an OPO may be more similar to each other than to kidneys recovered in other OPOs due to OPO-specific practices. In analyses testing the effects of adjusting for each DSA as a covariate, the contribution of the adjustments for DSA/OPO was tested using the likelihood ratio test.

Additional logistic regression models were used to determine whether factors predictive of discard were predictive of DGF. Generalized estimating equations were used to account for clustering at the OPO level, as described above. Cox regression models were used to determine whether factors predictive of discard were predictive of graft failure. Standard errors were adjusted for OPO clustering. Graft failure was defined by a record of graft failure, retransplantation or return to maintenance dialysis and was censored at the earliest of death, last follow-up or last expected follow-up. Creatinine clearance at 1-year posttransplant was calculated using the Cockroft Gault formula. For those with graft failure before 1 year, a value of 10 mL/min was assumed. The relationship between biopsy results and creatinine clearance at 1 year was analyzed with ordinary least squares linear regression. The adjusted mean creatinine clearance is the mean creatinine clearance for those in each group who also have zero (reference) for all the other parameters in the model, and is therefore different (in this case, greater) than the unadjusted creatinine clearance for each group.

Because the determinants of discard for kidneys from donors after cardiac death (DCD donors) were assumed to be different from those of kidneys from donors after brain death, they were excluded from all analyses except as described in Table 1. Some risk factors for ECD kidney discard were compared with those for SCD kidneys, which are defined as kidneys from donors after brain death who do not meet the ECD definition.

Results

Of the 48796 SCD kidneys procured during the study period, 8% (3887) were discarded. In contrast, 41% (5139) of 12536 ECD kidneys were discarded. In a logistic model including all recovered kidneys, ECD kidneys were more than four times (AOR = 4.35, $p < 0.0001$) and DCD kidneys were more than three times (AOR = 3.05, $p < 0.0001$) as likely to be discarded as non-ECD kidneys (Table 1). When compared with the odds of ECD kidney discard, the AOR for DCD kidney discard was 0.70 ($p = 0.0004$).

Table 1: Adjusted odds of discard for all deceased donor kidneys (n = 63 983)

Donor characteristic	% Discarded	% of all organs	Adjusted odds ratio	p-Value
DCD (ref = non-DCD)	20.8 (8.0)	4.1	3.05	<0.0001
ECD (ref = non-ECD)	41.0 (8.0)	19.6	4.35	<0.0001
Pumped (ref = not pumped)	15.2 (14.8)	13.9	0.57	0.0006
Biopsy[1] (ref = no biopsy)	7.9	68.9		
0–5% glomerulosclerosis	18.6	18.4	1.50	<0.0001
6–10% glomerulosclerosis	30.7	4.3	2.40	<0.0001
11–15% glomerulosclerosis	41.0	2.0	3.49	<0.0001
16–20% glomerulosclerosis	57.2	1.4	6.81	<0.0001
20%+ glomerulosclerosis	75.5	3.7	16.92	<0.0001
Diabetes (ref = no diabetes)	39.5 (13.5)	5.6	1.89	<0.0001
Male (ref = female)	13.4 (17.2)	58.7	0.96	0.16
African American (ref = non-AA)	17.8 (14.6)	12.2	1.27	<0.0001

Adjusted for listed factors as well as diabetes status missing, biopsy information missing, percentage glomerulosclerosis missing and pumping information missing.
[1]For biopsy versus no biopsy: OR = 2.08; $p < 0.0001$.

Table 2: Adjusted odds of discard by ECD RR group and biopsy results (n = 12 536)

Donor characteristic	% Discarded	% of ECD organs	Adjusted odds ratio	p-Value
Diabetes (ref = no diabetes)	57.3 (38.4)	13.8	1.96	<0.0001
Biopsy[1] (ref = no biopsy)	38.5	24.8		
0–5% glomerulosclerosis	26.5	35.9	0.57	<0.0001
6–10% glomerulosclerosis	38.7	12.0	0.98	0.84
11–15% glomerulosclerosis	47.2	6.2	1.39	0.0006
16–20% glomerulosclerosis	65.4	4.5	3.04	<0.0001
20%+ glomerulosclerosis	83.1	12.3	7.22	<0.0001
Male (ref = female)	42.4 (39.7)	47.8	1.24	<0.0001
African American (ref = non-AA)	47.0 (40.2)	11.6	1.43	<0.0001
Pumped (ref = not pumped)	29.7 (43.3)	18.8	0.52	<0.0001
ECD RR Group				
1.70–1.99	31.4	44.0	1.00	ref
2.00–2.39	40.8	27.2	1.70	<0.0001
2.40+	55.9	28.8	2.90	<0.0001

Adjusted for listed factors as well as biopsy information missing, percentage glomerulosclerosis missing and pumping information missing.
[1]For biopsy versus no biopsy: OR = 1.21; p = 0.02.

Impact of biopsy on kidney discard

Among all kidneys, those that were biopsied were more likely to be discarded (AOR = 2.08, $p < 0.0001$), as were those from diabetics (AOR = 1.89, $p < 0.0001$) and African American donors (AOR = 1.27, $p < 0.0001$) (Table 1). The odds of discard increased progressively with increasing degrees of glomerulosclerosis (GS), ranging from an AOR of 1.50 for kidneys with 0–5% GS (compared with those not biopsied) to 16.92 for those with greater than 20% GS (Table 1).

ECD kidneys were biopsied in 74.8% of cases, compared with 18.7% of cases for SCD kidneys. Overall, biopsied ECD kidneys had a higher rate of discard than ECD kidneys that were not biopsied (AOR = 1.21, p = 0.02); kidneys from male (AOR = 1.24, $p < 0.0001$ compared with female) and African American (AOR = 1.43, $p < 0.0001$, compared with non-African American) ECD kidney donors also had a higher rate of discard. With increasing GS on biopsy, the odds of ECD kidney discard compared with those not biopsied increased from an AOR of 0.57 ($p < 0.0001$) for ECD kidneys with GS of 0–5% to 7.22 ($p < 0.0001$) for ECD kidneys with GS in excess of 20% (Table 2). In contrast to that of ECD kidneys, the AOR of discard for biopsied SCD kidneys was 4.21 ($p < 0.0001$, Table 3) compared with those not biopsied. Similar to the overall model in Table 1, all levels of GS were associated with higher odds of discard than SCD kidneys that were not biopsied.

Discard rates also increased in the presence of each of the individual components of the ECD definition. Each year of donor age above age 50 was associated with a 12% increase ($p < 0.0001$), death from CVA with an 18% increase (p = 0.053) and a history of hypertension with a 69% increase ($p < 0.0001$) in the AOR of discard. A serum creatinine at allocation of >1.5 mg/dL was particularly predictive of discard, with an AOR of 3.45 ($p > 0.0001$) (Table 4). These characteristics predictive of allograft failure were combined to generate risk categories for transplant failure. The odds of ECD discard increased with increasing allograft failure category, from an AOR of 1.00 for ECD kidneys with an RR between 1.70 and 1.99 to an AOR of 2.90 for ECD kidneys with an RR of allograft failure of 2.40 or greater (Table 2). Unadjusted discard rates ranged from 19% for

Table 3: Adjusted odds of discard for SCD (n = 48 796)

Donor characteristic	% Discarded	% of SCD organs	Adjusted odds ratio	p-Value
Diabetes (ref = no diabetes)	21.2	3.5	1.46	0.0017
Biopsy[1] (ref = no biopsy)				
0–5% glomerulosclerosis	12.6	13.1	2.68	<0.0001
6–10% glomerulosclerosis	19.7	2.3	4.45	<0.0001
11–15% glomerulosclerosis	28.9	0.9	7.23	<0.0001
16–20% glomerulosclerosis	42.0	0.6	12.39	<0.0001
20%+ glomerulosclerosis	59.6	1.5	25.12	<0.0001
Male (ref = female)	7.2	61.1	0.87	0.0009
African American (ref = non-AA)	10.6	12.5	1.27	0.0002
Pumped (ref = not pumped)	7.8	10.5	0.64	0.102

Adjusted for listed factors as well as biopsy information missing, percentage glomerulosclerosis missing and pumping information missing.
[1]For biopsy versus no biopsy: OR = 4.21; $p < 0.0001$.

Table 4: Adjusted odds of discard by ECD components (n = 12 536)

Donor characteristic	Adjusted odds ratio	p-Value
Serum creatinine >1.5 mg/dL	3.45	<0.0001
CVA as cause of death	1.18	0.053
Hypertension	1.69	<0.0001
Donor age (per year above 50)	1.12	<0.0001

Adjusted for listed factors and those in Table 2 (except ECD RR group) as well as biopsy information missing, percentage glomerulosclerosis missing and pumping information missing.

ECD kidneys with the least GS and the lowest projected RR of graft failure to 90% for ECD kidneys with greater than 20% GS and high RR (Figure 1). In adjusted models, the AOR of ECD kidney discard within each RR category increased with increasing degrees of GS on biopsy (not shown).

Method of kidney preservation and discard

Machine perfusion by the OPO was used in 18.8% of ECD kidneys. Pumped ECD kidneys were discarded in 29.7% of cases, compared with 43.6% for ECD kidneys that were not pumped. In the logistic model of ECD discard, pumped ECD kidneys were 48% less likely to be discarded than those not pumped ($p < 0.0001$) (Table 2). This contrasts with the 36% reduction in the odds of discard for pumped SCD kidneys (AOR = 0.64, $p = 0.102$). Pumped ECD kidneys with high resistance values were associated with higher odds of discard (Figure 2). ECD kidneys with terminal resistances <0.18 and between 0.18–0.25 mmHg/mL/min were discarded only 12.6% and 14.0% of the time, respectively (Figure 2). When compared to ECD kidneys with terminal resistances of 0.18–0.25 mmHg/mL/min, those with resistances of 0.26–0.38 mmHg/mL/min had a 25.7% discard rate (AOR = 2.50, $p < 0.0001$) and those with resistances >0.38 mmHg/mL/min had a 53.1% discard rate (AOR = 7.88, $p < 0.0001$).

Local variation in kidney discard rates

There was substantial variation in unadjusted discard rates for both ECD and non-ECD kidneys among DSAs; the discard rate for ECD kidneys ranged from 14% to 60% (Figure 3). In a logistic model adjusting for various donor factors, there was a nearly 10-fold difference in the AOR of discard between the DSAs with the highest and lowest adjusted discard rates (0.44–3.86). For all classes of kidneys, including pumped ECD kidneys, and in all RR categories, the inclusion of DSA effects significantly improved the fit of the discard model, indicating that DSA practices were significant determinants of discard (Table 5). However, inclusion of DSA effects did not diminish the significance of the other factors in the discard model outlined in Table 2 (not shown), suggesting that they are independent factors.

To determine whether DSAs that are more likely to discard ECD kidneys are also more likely to discard SCD kidneys, DSAs were divided into tertiles based on ECD discard rates. A logistic model of discard indicated that DSAs with high ECD discard rates were also more likely to discard SCD kidneys (Figure 4). It is notable, however, that the differences between the high- and the low-discard tertile DSAs were smaller for SCD (AOR = 1.86 for the high-discard tertile compared with the low-discard tertile, $p < 0.0001$) than for ECD kidneys (AOR = 2.69, $p < 0.0001$). There were no significant interactions between the other discard predictors and tertiles of ECD discard (not shown), further demonstrating that the effects of DSA on discard are not based on these specific donor characteristics.

There was a negative correlation between discard rates and recovery rates among DSAs that approached statistical significance ($r = -0.235$, $p = 0.0729$); i.e. those DSAs with higher recovery rates tended to have lower discard rates. Furthermore, in those DSAs with a high percentage of ECD transplants, ECD discard rates were lower than in those DSAs with relatively few ECD transplants ($r = -0.331$, $p = 0.01$).

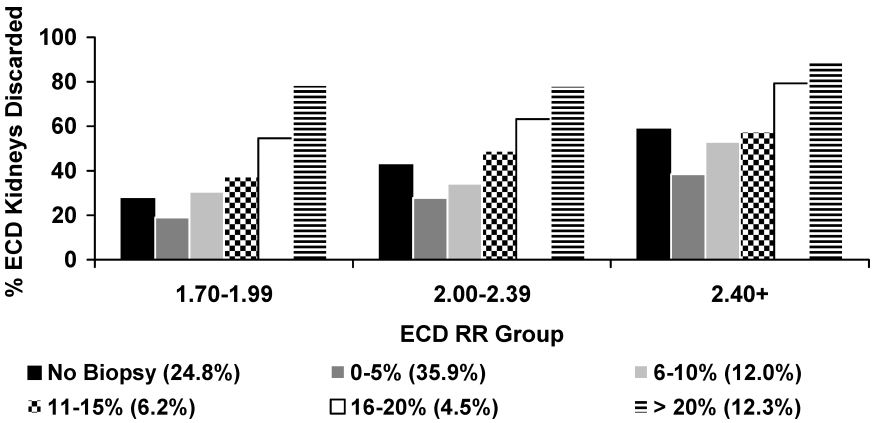


Figure 1: Unadjusted discard rates for ECD kidneys (n = 12 536).

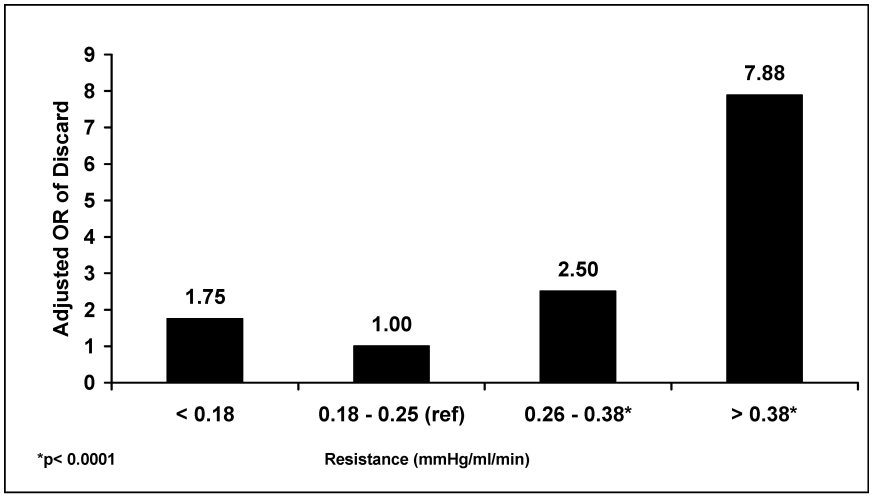


Figure 2: Adjusted odds of ECD discard by resistance level for pumped kidneys (n = 2351).

Adjusted for diabetes, diabetes status missing, percentage glomerulosclerosis, biopsy information missing, percentage glomerulosclerosis missing, sex, African American race, and resistance missing

Kidney biopsy, preservation method and transplant outcome

The AOR of DGF was significantly lower in those ECD kidneys that were pumped (AOR = 0.59, $p < 0.0001$) (Table 6). Compared with a reference group of nonbiopsied ECD kidneys, the AOR of DGF was greater for biopsied ECD kidneys (AOR = 1.16, $p = 0.03$); however, in contrast to the effects on discard, no relationship could be demonstrated between the degree of GS and the odds of DGF. Furthermore, the ECD RR category did not significantly correlate with the odds of DGF.

In a Cox model of ECD graft failure, the RR of graft failure was not significantly different in pumped ECD kidneys (RR = 0.91, $p = 0.27$) (Table 7) compared with those not pumped. The risk of graft failure for biopsied ECD kidneys was also not different from those not biopsied (RR = 0.97, $p = 0.62$). Interestingly, there was no clear relationship

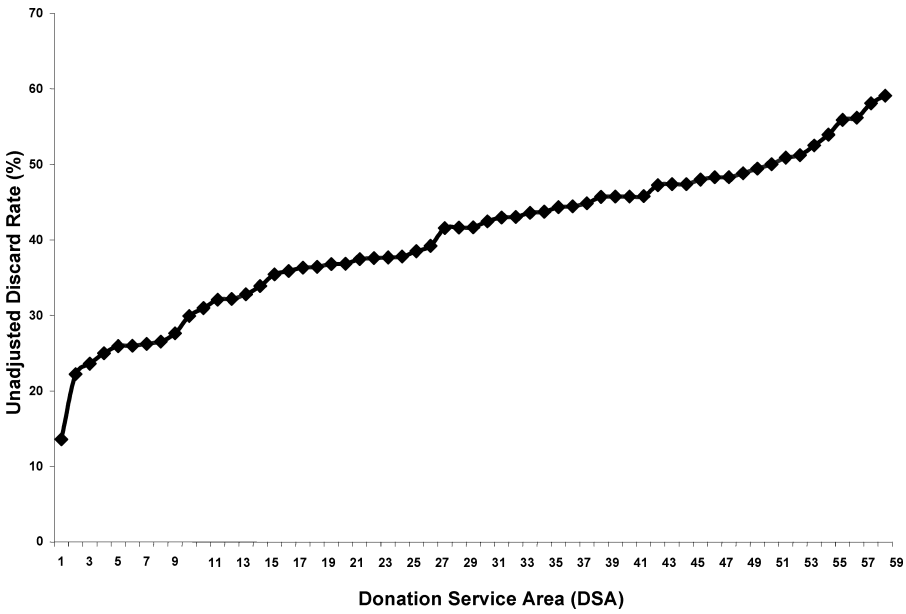


Figure 3: Unadjusted discard rates by DSA for ECD.

Table 5: Effect of DSA on probability of discard

Study group	Total n	% Discarded	10th percentile DSA	90th percentile DSA
All kidneys	63978	15.0	10.0	21.6
Pumped kidneys	8886	15.2	0	66.7
Non-ECD kidneys	51442	8.6	5.3	12.4
ECD kidneys	12,536	41.0	26.0	52.5
Pumped ECD kidneys	2351	29.7	13.9	72.5
ECD RR 1.70–1.99	5520	31.4	16.7	45.3
ECD RR 2.0–2.4	3411	40.8	18.0	58.3
ECD RR 2.4+	3605	55.9	39.4	73.6
Pumped kidneys (excluding DCD)	7456	14.7	3.1	66.7
SCD	48796	8.0	4.5	11.9
SCD and ECD	61327	14.7	9.9	20.6

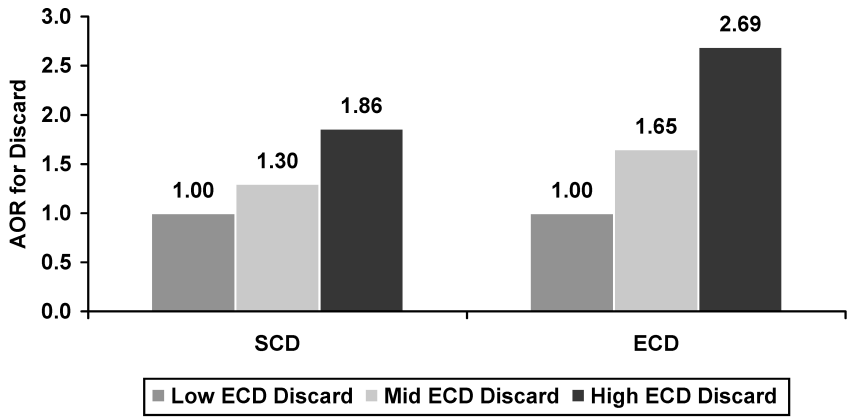
$p < 0.0001$ for test of DSA effect in each of the 11 analyses.

between degree of GS on biopsy and the RR of graft failure ($p = ns$ for all categories compared with no biopsy). In addition, among biopsied kidneys, those transplanted kidneys with GS of 6% or greater did not have higher graft failure rates than those with little or no (0–5%) GS. In a linear regression model for creatinine clearance at 1 year after transplant, most categories of ECD kidneys with GS of 6% or greater had significantly lower adjusted creatinine clearance than those with 0–5% GS or that were not biopsied (Table 8). However, among kidneys with greater than 6% GS, a relationship between categories of GS and graft function was not identified. Failure rates were higher for ECD kidneys from African American (AOR = 1.22, $p = 0.16$) and diabetic (AOR = 1.23, $p = 0.013$) donors and for those in the higher risk of graft failure ECD cohorts.

Discussion

One of the difficulties encountered in attempting to increase the number of kidney transplants has been the identification of marginal kidneys with an acceptable likelihood of graft survival. While the ECD definition has established some uniform criteria for higher-risk kidneys, a great deal of uncertainty and disagreement remains over what constitutes a suitable kidney (6,7).

Efforts to increase the use of ECD kidneys led to the establishment of the ECD allocation system, implemented by the OPTN on October 31, 2002 (4). ECD kidney utilization has increased significantly under the ECD system, from 1230 transplants performed in 2002 to 1609 in 2005 (1). However, despite elements of the system specifically designed to minimize the time to placement and reduce the likelihood of discard due to prolonged cold ischemia, ECD discard rates have not changed under the ECD system, nor have they changed appreciably over the last 5 years (5). Although discard rates for the highest risk (RR > 2.4) ECD kidneys decreased from 68% to 51% under the ECD system between November 2002 and April 2004, this reduction was offset by an increase in the discard rates of the lowest risk (RR 1.7–1.99) ECD kidneys from 24% to 28%. This raises the possibility that, with the institution of a formal ECD definition, kidneys not previously regarded



Adjusted for diabetes, diabetes status missing, race, sex, percentage glomerulosclerosis, percentage glomerulosclerosis missing, biopsy information missing, creatinine clearance, pulsatile perfusion, and pulsatile perfusion information missing

Figure 4: ECD versus SCD discard by DSA tertiles of ECD discard.

Table 6: Adjusted odds of DGF for transplanted ECD kidneys (n = 5899)

	Among all ECD n = 5899		Among biopsied n = 4308	
Donor characteristic	Adjusted odds ratio	p-Value	Adjusted odds ratio	p-Value
Pumped (ref = not pumped)	0.59	<0.0001		
Biopsy–% glomerulosclerosis (ref = no biopsy[1])				
0–5%	1.13	0.07	1.00	ref
6–10%	1.29	0.009	1.14	0.13
11–15%	1.10	0.47	0.96	0.74
16–20%	1.50	0.004	1.30	0.04
20%+	1.38	0.07	1.21	0.25
Male (ref = female)	1.20	0.002		
African American (ref = non-AA)	0.98	0.82		
Diabetes (ref = no diabetes)	1.17	0.052		
ECD RR Group				
1.70–1.99	1.00	ref		
2.00–2.39	0.97	0.68		
2.40+	1.11	0.21		

[1]For biopsy versus no biopsy: OR = 1.16; p = 0.03.
Adjusted for factors in table as well as recipient age, sex, race, cause of end-stage renal disease, panel reactive antibody, cold ischemia time and HLA mismatch.

as marginal are now identified as such and that there may be currently unrecognized determinants of discard beyond those covered by the ECD definition, pump characteristics and percentage of GS on biopsy.

The current analyses update those originally developed by the OPTN Organ Availability and Kidney-Pancreas Committees and the SRTR. They demonstrate that, as expected, ECD kidneys are more than four times as likely to be discarded than non-ECD kidneys. The additional finding that DCD kidneys are more than three times as likely to be discarded than non-DCD kidneys is pertinent in light of reports demonstrating comparable graft survival (8). Factors traditionally thought to contribute to graft failure, such as diabetes, are indeed associated with discard of ECD kidneys. In addition, each of the components of the ECD definition is significantly associated with the odds of discard. For these risk factors, there is concordance between acceptance behavior and outcomes.

The use of biopsy is an important practice in the evaluation of ECD kidneys, in contrast to the evaluation of non-ECD kidneys. Three-fourths (74.8%) of ECD kidneys were biopsied in this analysis (compared with 18.7% of non-ECD kidneys), and biopsy findings are the most frequently cited reason for the discard of recovered ECD kidneys (51% in

Table 7: Adjusted RR of graft failure for transplanted ECD kidneys

	Among all ECD n = 5899		Among biopsied n = 4308	
Donor characteristic	RR	p-Value	RR	p-Value
Pumped (ref = not pumped)	0.91	0.27		
Biopsy–% glomerulosclerosis (ref = no biopsy[1])				
0–5%	0.93	0.22	1.00	ref
6–10%	1.05	0.63	1.12	0.26
11–15%	1.16	0.26	1.23	0.13
16–20%	0.99	0.97	1.05	0.76
20%+	1.15	0.35	1.24	0.15
Male (ref = female)	0.96	0.36		
African American (ref = non-AA)	1.22	0.016		
Diabetes (ref = no diabetes)	1.23	0.013		
ECD RR Group				
1.70–1.99	1.00	ref		
2.00–2.39	1.15	0.029		
2.40+	1.36	<0.0001		

[1]For biopsy versus no biopsy: OR = 0.97; p = 0.62.
Adjusted for factors in table as well as recipient age, sex, race, cause of end-stage renal disease, panel reactive antibody, cold ischemia time and HLA mismatch.
Analysis censored for death with graft function.

Table 8: Mean creatinine clearance[1] at 1 year after ECD kidney transplant by biopsy characteristics

Biopsy–% GS	Mean CrCl (unadjusted)	SD (unadjusted)	Mean CrCl (adjusted)	p-Value (adjusted) Among all ECD	p-Value (adjusted) Among biopsied
No biopsy	44.60	23.18	52.61	Reference	
0–5%	45.00	23.54	53.66	0.21	Reference
6–10%	41.52	22.09	50.64	0.09	0.005
11–15%	40.16	23.70	49.03	0.03	0.003
16–20%	42.37	20.03	51.08	0.48	0.230
20%+	38.84	27.15	48.26	0.03	0.005

[1]Creatinine clearance of failed transplants was set at 10 cc/min.
Adjusted for donor age, race, diabetes and pumping status as well as recipient age, sex, race, cause of end-stage renal disease, panel reactive antibody, cold ischemia time and HLA mismatch.

the 18 months following ECD policy implementation) (5). While all biopsied kidneys were more likely to be discarded, this was more striking for SCD than for ECD kidneys. This may reflect the common OPO practice of routinely performing a biopsy on all ECD kidneys, whereas most SCD kidneys are biopsied selectively based on the presence of other donor risk factors. There was a direct relationship between the percentage of GS identified on biopsy and the odds of discard for both ECD and non-ECD kidneys, with a greater than 12-fold difference between ECD kidneys with >20% GS compared with those with less than 5%. Therefore, the perception of the degree of chronic disease as reflected in the biopsy findings was a significant factor in whether a kidney was discarded.

Although biopsy findings were an important determinant of discard, we were unable to demonstrate associations with DGF and graft failure in this registry-based analysis. While we did observe an association between performance of a biopsy and DGF, whether this reflects differences in those kidneys that were selected for biopsy (for those OPOs that do not routinely biopsy ECD kidneys) or a causal relationship could not be established by this study. Among biopsied kidneys, no consistent patterns of DGF or graft failure were identified with respect to GS. This was not likely to be a consequence of unequal follow-up, since follow-up between kidneys with higher and lower degrees of GS were similar (<20% GS –2.80 ± 1.38 years, >20% GS –2.84 ± 1.45, not biopsied/missing –2.98 ± 1.37). While the associations between GS of 6% or greater and graft function, as measured by creatinine clearance at 1 year, were not reproduced in the graft survival analyses, a possible effect over a longer timeframe cannot be excluded.

The importance of biopsy as a determinant of utilization and graft outcomes has received increasing attention. While it seems obvious that evidence of chronic injury, especially in the setting of established risk factors such as age and hypertension, should portend poor outcomes, no large studies exist to confirm this. Edwards et al. demonstrated an effect of GS in kidneys with low creatinine clearance on unadjusted, but not adjusted, graft survival (9). Cecka has observed that while biopsy findings are the most frequently cited reasons for discard in the US, performance of biopsy is rarely noted in the Eurotransplant experience, where discard of kidneys from elderly donors is much lower (10). However, Remuzzi found biopsy to be an important instrument in selecting kidneys to be used successfully for dual transplant (11). Among other studies, the impact of biopsy findings on early graft function and graft survival range from no effect to significant effects that correlate with donor age or creatinine clearance to effects that are independent of other donor covariates (12,13).

There are several inherent limitations to the use of registry data in the analyses of biopsy in kidney transplantation. Reliance on frozen section results that are often read in the donor hospital implies variation in the interpretation of individual biopsies. The technique of biopsy employed (wedge vs. core) and the number of glomeruli identified, which are not reported on the deceased donor registration form, may influence biopsy results and interpretations. These limitations are likely to lead to misclassifications that underestimate the effects of different degrees of GS on DGF and graft failure. The OPTN data are also limited to intervals of glomerulosclerosis up to 20%; discrimination within these intervals or among degrees of glomerulosclerosis greater than 20% was not possible. Other relevant biopsy parameters such as interstitial fibrosis and arteriosclerosis, which are not collected and therefore could not be studied, have been identified as potentially greater determinants of graft outcome than GS (12,13).

An additional important limitation to registry analyses of biopsy data is the inherent potential for selection bias. By definition, the transplanted kidneys in this cohort with greater degrees of glomerulosclerosis were more carefully selected, since such kidneys were much less frequently transplanted (only 17% of transplanted ECD kidneys with biopsy showed greater than 10% GS). While the models of DGF and graft failure adjust for a large number of donor, recipient and transplant-related factors, kidneys with higher

degrees of glomerulosclerosis are likely to be more carefully selected for unreported factors, including other biopsy characteristics, which are more likely to be favorable than for kidneys with lesser GS. Such biases would diminish the potential adverse effects of glomerulosclerosis in the outcome models. Clinical trials where biopsies are performed in a standardized fashion and interpreted in a consistent manner, such as the prospective, multi-OPO study currently being performed in New England and Michigan (14), have advantages over registry data in this regard.

While only 19% of ECD kidneys in this study were pumped, there was a significant association between pumping and discard. Although it might seem that those DSAs that pump kidneys may be less likely to discard ECD kidneys based on overall DSA behavior, pumping was associated with lower discard rates even when adjusting for DSA effects. It appears that the effect of pumping ECD kidneys is not merely that kidneys with poor resistance profiles that might have been used are discarded, because this would lead to an increase in the discard rate. Rather, it appears probable that centers are using kidneys that would have been discarded if they were not pumped. While the association with decreased DGF rates is consistent with other single-center and registry studies and at least one meta-analysis of machine perfusion on early graft outcomes (15–18), the literature regarding long-term graft survival is less conclusive.

The mechanisms by which machine perfusion might improve early graft outcomes are controversial and remain to be determined. On the one hand, the information gained during perfusion regarding flow and resistance may permit the selection of kidneys destined to have acceptable outcomes, and the current study clearly demonstrates that terminal resistance is an important consideration in this selection process. Alternatively, the observation that renal flow may increase and resistance may decrease with increasing perfusion time suggests that the hydrostatic effects of machine perfusion may reduce intrarenal vasoconstriction (17). In addition, evidence suggests that additives to pumped preservation solutions may ameliorate ischemia-reperfusion injury (17,19).

It is important to recognize that the association of pumping and discard does not prove a cause-effect relationship. Adjustments may be made to account for the possibility that those DSAs where kidneys are more often pumped may also have practices unrelated to pumping that lead to lower discard rates. However, selection biases may exist within DSAs that may result in the more frequent pumping of kidneys that are less likely to be discarded based on other donor characteristics. Therefore, while it may be tempting to conclude that pumped kidneys are less likely to be discarded, the opposite relationship, that kidneys with a low likelihood of discard are more likely to be pumped, cannot be ruled out. Similar caveats apply to the association between pumping and DGF.

Other limitations to the use of OPTN/SRTR data in analyses of machine perfusion include variability among and within DSAs in perfusion techniques and duration of machine perfusion. In some DSAs, kidneys remain on the pump until transplantation; in others, kidneys are pumped and then placed into cold storage for local transportation. Until recently, the OPTN captured pumping data on the deceased donor registration form only if the kidney was pumped at the recovering DSA. Therefore, data on kidneys that were transported and then pumped at the transplant recipient's center were not captured. This leads to an underestimation of the number of pumped kidneys. The effect of these omissions is to underestimate the effect of pumping on discard, DGF and graft survival, so the differences observed in this study may be larger with more accurate data capture. The revised deceased donor recipient transplant form includes fields for pumping at the transplant recipient center (or DSA), so future analyses should benefit from this modification.

There was significant DSA variation in discard rates that was not attributable to differences in the prevalence of donor risk factors that clearly indicates that different DSAs have different thresholds of use of ECD kidneys. The approach to utilization of ECD kidneys appears to be similar to SCD kidneys, because those DSAs likely to discard ECD kidneys were also more likely to discard SCD kidneys. These different behaviors were not limited to specific donor characteristics but appeared to be broadly applied, because their impact on the odds of discard was not notably changed by consideration of DSA effects. Because discard of ECD kidneys was less likely in DSAs that recovered and transplanted more ECD kidneys, differences among DSAs may reflect different needs for and attitudes toward ECD kidney transplantation. This DSA variation is currently being addressed by several OPTN committees and by the Organ Donation Breakthrough Collaborative, with greater information being communicated to individual OPOs regarding their specific utilization data.

It should not be surprising that approaches to ECD kidneys differ among DSAs, because the estimated benefit of an ECD kidney depends in large part on the likelihood of receiving a non-ECD kidney, which is not equal among DSAs. There are other differences among DSAs not considered in these analyses that may contribute to ECD utilization, including DSA waiting time, attitudes regarding appropriate recipients for ECD kidneys and the composition of the waiting list. However, it is important to recognize that kidneys that are discarded in some DSAs may be readily used in others, and efficient mechanisms to shift ECD kidneys from DSAs and centers with low utilization rates to those with high rates must be developed to maximize overall kidney utilization. To the extent that pumping and perhaps biopsy may facilitate acceptance by centers with high utilization rates under an expedited mechanism, the expansion of these practices may be desirable.

Conclusion

ECD kidneys are frequently discarded due to features that have been previously associated with inferior graft outcomes, such as those criteria that constitute the current ECD definition. Biopsy findings and characteristics of machine perfusion are also important determinants of discard, although their effects on graft outcomes are more difficult to demonstrate. The finding of a lower risk for DGF in ECD kidneys that were transplanted without a biopsy suggests selection and indicates the need for a study with prospective biopsies of all ECD organs. The substantial variation in DSA discard rates is not restricted to specific donor characteristics but is likely to reflect a spectrum of approaches toward ECD transplantation.

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References

1. Scientific Registry of Transplant Recipients. 2005 Annual Report, Table 5.4. Available from: https://www.ustransplant.org, Accessed December 15, 2006.
2. Ojo AO, Hanson JA, Meier-Kriesche H et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. J Am Soc Nephrol 2001; 12: 589–597.
3. Port FK, Bragg JL, Metzger RA et al. Donor characteristics associated with reduced graft survival: An approach to expanding the pool of kidney donors. Transplantation 2002; 74:1281–1286.
4. Rosengard BR, Feng S, Alfrey EJ et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant 2002; 2: 701–711.
5. Sung RS, Guidinger MK, Lake C et al. Impact of the expanded criteria donor (ECD) kidney allocation system on the utilization of ECD kidneys. Transplantation 2005; 79: 1257–1261.
6. Lee CM, Scandling JD, Pavlakis M, Markezich AJ, Dafoe DC, Alfrey EJ. A review of kidneys that nobody wanted: Determinants of optimal outcome. Transplantation 1998; 65: 213–219.
7. Schnitzler MA, Whiting JF, Brennan DC et al. The expanded criteria donor dilemma in cadaveric renal transplantation. Transplantation 2003; 75: 1940–1945.
8. Doshi MD, Hunsicker LG. Short- and long-term outcomes with the use of kidneys and livers donated after cardiac death. Am J Transplant 2007; 7: 121–129.
9. Edwards EB, Posner MP, Maluf DG, Kauffman HM. Reasons for non-use of recovered kidneys: The effect of donor glomerulosclerosis and creatinine clearance on graft survival. Transplantation 2004; 77: 1411–1415.
10. Cecka JM, Cohen B, Rosendale J, Smith M. Could more effective use of kidneys recovered from older deceased donors result in more kidney transplants for older patients? Transplantation 2006; 81: 966–970.
11. Remuzzi G, Cravedi P, Perna A et al. Long-term outcome of renal transplantation from older donors. N Eng J Med 2006; 354: 343–352.
12. Randhawa PS, Minervini MI, Lombardero M et al. Biopsy of marginal donor kidneys: Correlation of histologic findings with graft dysfunction. Transplantation 2000; 69: 1352–1357.
13. Pokorna E, Vitko S, Chadimova M, Schuck O, Ekberg H. Proportion of glomerulosclerosis in procurement wedge renal biopsy cannot alone discriminate for acceptance of marginal donors. Transplantation 2000; 69: 36–43.
14. Lipkowitz GS, Leichtman AB, Christensen LL et al. Procurement, utilization and initial outcome in a prospective ECD study. Am J Transplant 2005; 5S11 (abstract): 350.
15. Sellers MT, Gallichio MH, Hudson SL et al. Improved outcomes in cadaveric renal allografts with pulsatile preservation. Clin Transplant 2000; 14: 543–549.
16. Wight JP, Chilcott JB, Holmes MW, Brewer N. Pulsatile machine perfusion vs. cold storage of kidneys for transplantation: A rapid and systematic review. Clin Transplant 2003; 17: 293–307.
17. Polyak MM, Arrington BO, Stubenbord WT et al. The influence of pulsatile preservation on renal transplantation in the 1990s. Transplantation 2000; 69: 249–258.
18. Matsuoka L, Shah T, Aswad S et al. Pulsatile perfusion reduces the incidence of delayed graft function in expanded criteria donor kidney transplantation. Am J Transplant 2006; 6: 1473–1478.
19. Guarrara JV, Polyak MM, Arrington B et al. Pushing the envelope in renal preservation: Improved results with novel perfusate modifications for pulsatile machine perfusion of cadaver kidneys. Transplant Proc 2004; 36: 1257–1260.