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Expanded criteria donor kidneys for retransplantation United Network for Organ Sharing update: proceed with caution

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Summary

This study analyzed outcomes of retransplantation from expanded criteria donors (ECD) over the last two decades to determine the benefits and risks of using ECD kidneys for retransplantation. Data from the United Network for Organ Sharing database were collected and analyzed. Graft survival, death-censored graft survival, and patient survival for retransplantation with ECD kidneys (re-ECD) were reported and compared with primary transplantation with ECD kidneys (prim-ECD) and retransplantation with standard criteria donor kidneys (re-SCD). Re-ECD kidneys had higher risk of graft failure compared with prim-ECD (hazard ratio [HR] = 1.19) and to re-SCD (HR = 1.76). Patient survival was better in re-ECD compared with prim-ECD (HR = 0.89) but was worse than re-SCD (HR = 1.82). After censoring the patients who died with a functioning graft, re-ECD had a higher mortality risk compared with prim-ECD (HR = 1.45) and re-SCD (HR = 1.79). Transplantation improves quality of life and reduces healthcare costs, and due to the risk associated with resumption of hemodialysis and the longer waiting list times for SCD kidneys, there is a benefit to accepting ECD kidneys for select patients requiring retransplantation. Although this benefit exists for select patients, retransplantation with ECD kidneys should be undertaken with trepidation, and appropriate informed consent should be obtained.

Introduction

The two treatment options for renal allograft failure are retransplantation and return to dialysis. Roughly fifteen percent of patients who are on the waiting list have experienced failure of at least one allograft [1]. Despite the elevated risk of graft failure, patients who undergo repeated kidney transplantation have superior outcomes when compared to resuming dialysis [2–6].

There has been an inability to meet the demand for transplantable organs. In an attempt to overcome this challenge, the expanded criteria donor (ECD) system was developed. According to the Organ Procurement and Transplantation Network (OPTN) policies, ECD donors are those >60 years old, or those that are age 50–59 with at least two of the following diagnoses: a history of hypertension, serum creatinine >1.5 mg/dl, or stroke as the cause of death. The use of an ECD kidney shortens the amount of time a patient spends on the renal transplant waiting list. However, primary transplantation with ECD kidneys is associated with a 70% greater risk of premature graft failure within the first year of transplantation [7].

The recently introduced kidney donor profile index (KDPI) is a continuous variable system devised to further quantify donors and marginal kidneys. This system ranks kidneys based on the kidney donor risk index, which

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represents the risk of graft failure compared to the average donor [8]. Kidneys are assigned a score from the 1st to the 100th percentile compared to an OPTN cohort. This KDPI system has yet to be validated clinically and is currently under investigation for its utility in predicting outcomes in kidney transplant recipients [9,10].

Some single-center studies have shown that ECD kidneys are associated with decreased short-term allograft survival in retransplantation recipients [11–13]. One study reported equivalent benefit when ECD kidneys were used in retransplantation compared with initial transplantation [14]. However, a larger retrospective study (1994–2004) of patients undergoing repeat renal transplantation, including 292 patients who received ECD kidneys, reported no survival benefit when compared to those patients who remained on the waiting list. This study showed improved retransplant survival only for those who received standard criteria donor (SCD) kidney retransplantation [15]. Aggressive use of ECD kidneys can ultimately increase the number of transplants performed. Using marginal kidneys for primary transplantation has been shown to decrease overall healthcare costs compared with dialysis [16]. However, with the decreased graft survival of ECD kidneys, it is uncertain whether ECD kidney use in retransplantation is equally beneficial for both patients and transplant programs.

In this longitudinal study, we explored the last two decades of the United Network for Organ Sharing (UNOS) database to elucidate graft survival, death-censored graft survival and patient survival for retransplantation with ECD kidneys and compared this to primary transplantation with ECD kidneys. We also evaluated the results in cases of retransplantation with SCD kidneys. This study attempts to reveal the benefits and risks of retransplantation using ECD kidneys and to provide some insight into the types of patients who may benefit the most from using ECD grafts for retransplantation.

Materials and methods

Patient selection

We analyzed retrospective, right-censored, longitudinal data from Unet^{SM}, a database system established and operated by UNOS to maximize the efficient use of deceased donor organs through equitable and timely allocation. Organ Procurement Organization (OPO) staff members submit donor information using Unet^{SM}. Data assembled from donor registrations, transplant recipient registrations, and waiting lists were used to characterize donors, kidney allografts, and recipients.

All primary ECD and repeat kidney transplantations performed from April 1, 1994 through June 30, 2013 were included in the study. Recipients of multi-organ transplants and those who received only primary SCD kidney transplants were excluded from the study. Selected transplant recipients entered the study on the day of transplantation and remained in the study until an adverse event (patient death or graft failure) occurred or until their last follow-up.

Outcomes measured

Primary outcomes of interest were patient survival, graft survival, and death-censored graft survival (DCGS) in transplant recipients with a primary ECD kidney transplant (prim-ECD), and retransplantation with a SCD kidney (re-SCD) or an ECD kidney (re-ECD). Patient and graft survival were calculated from the date of transplantation to the date of death, graft failure, or the date of the last follow-up. DCGS was calculated from the date of transplantation to the date of irreversible graft failure or the date of last follow-up during the period when the allograft was still functioning. In the case of death with a functioning graft, the follow-up period was censored at the date of death. Multivariate analysis was completed adjusting for age, gender, race, body mass index (BMI), panel reactive antibodies (PRA), cold ischemia time (CIT), waiting time, HLA mismatch, calendar year, and region of transplantation. Secondary outcomes of interest that were also measured in this study included length of hospital stay, incidence of graft rejection episodes, incidence of delayed graft function, and return to maintenance dialysis.

Statistical analyses

Demographic and clinical information of donors and recipients were compared using the chi-square and Student's t-test for categorical and numerical variables, respectively. Time-to-event analysis was performed using the Kaplan–Meier product limit method and compared using the Cox–Mantel log-rank statistic. Crude mortality rates were computed as number of deaths per 1000 patient-years of follow-up. Cox proportional hazards regression models were fitted to compute hazard ratios. Two-sided probability type 1 error was set at 0.05 for statistical significance. Statistical analysis was performed using SPSS version 21.0 software for Mac (SPSS Inc., Chicago IL USA).

Results

Recipient and donor characteristics

During the two decades, 42.4% (re-ECD = 1658 and re-SCD = 17130) of the total transplant recipients included (N = 44 296) were retransplants. Those in the re-SCD were on average younger than those in the re-ECD group (mean age 42 ± 14 vs. 49 ± 13; $P < 0.001$). Recipients in the prim-ECD group were on average older than those in the

re-ECD group (mean age 58 ± 12 vs. 49 ± 13; $P < 0.001$). Gender distribution across all the groups was similar with males making up a greater proportion than females. Among the retransplant patients, the majority had only one previous graft failure. The median waiting time was longer in re-SCD (620 days) recipients than that of re-ECD (605 days) recipients ($P = 0.018$). The waiting time between prim-ECD and re-ECD was not significantly different ($P = 0.051$). See Table 1 for a detailed listing of the recipient characteristics.

Distributions of age, gender, and BMI of the donors were similar in primary and re-ECD cases. Donors in the re-ECD group were less likely to be obese (21.5% vs. 30%; $P < 0.001$) and less likely to be diabetic (11.5% vs. 13.4%; $P < 0.001$) than those in the prim-ECD group. The re-ECD kidneys were more likely to have come from national share (27%). Table 2 shows the characteristics of the donor populations.

Graft survival

The Kaplan–Meier curve showing overall graft survival in the three groups is shown in Figure 1. These data demonstrate that overall graft survival for the re-SCD group was significantly better than that of the re-ECD and prim-ECD groups ($P < 0.001$). In addition, overall graft survival for the prim-ECD group was significantly better than that of the re-ECD group ($P < 0.001$). As shown in Table 3, those in the re-ECD group had a higher risk of graft failure compared with the prim-ECD group (HR = 1.19, 95% CI = 1.11–1.27, $P < 0.001$). The re-ECD patients also had a significantly higher risk of graft failure compared with re-SCD patients (HR = 1.76, 95% CI = 1.64–1.88, $P < 0.001$). Because these hazard ratios may have been confounded by certain variables related to the recipient and donor characteristics, hazard ratios adjusted for age, gender, race, BMI, most recent PRA, CMV serostatus, time on the waiting list, CIT, transplant region, and year of transplantation were calculated for each comparison. After adjusting for these potential confounding variables, the adjusted hazard ratios changed little from the crude hazard ratios (Table 3).

The Kaplan–Meier curve showing DCGS is shown in Figure 2. After censoring the patients who died with a functioning kidney allograft, overall DCGS was again significantly better in the re-SCD group compared with the other two groups ($P < 0.001$). The DCGS for the re-ECD group was significantly worse than that for the prim-ECD group ($P < 0.001$). As shown in Table 3, re-ECD kidneys had a higher risk of death-censored graft failure compared with prim-ECD (HR = 1.45, 95% CI = 1.34–1.57, $P < 0.001$). This was also true when re-ECD kidneys were compared with re-SCD kidneys (HR = 1.79, 95% CI = 1.65–1.94, $P < 0.001$). The adjusted hazard ratios similarly showed an increased risk of death-censored graft failure in the re-ECD group (Table 3).

Patient survival

After retransplantation, patient crude death rates were 59 and 33 deaths per 1000 patient-years following ECD and SCD retransplants, respectively. The crude death rate for the prim-ECD group was 67 per 1000 patient-years. Figure 3 demonstrates the Kaplan–Meier curves for overall patient survival in the three groups. These overall patient survival data show that the re-SCD group had better overall survival than the re-ECD and prim-ECD groups ($P < 0.001$). However, the re-ECD group had slightly better overall patient survival compared with the prim-ECD group ($P = 0.015$). The hazard ratios for the risk of death in the re-ECD group compared with the other two groups are shown in Table 3. On univariate analysis of re-ECD patients, the risk of death was 82% higher than that of patients with re-SCD (HR = 1.82, 95% CI = 1.64–2.01, $P < 0.001$). Compared to the prim-ECD group, re-ECD had better survival by 11% (HR = 0.89, 95% CI = 0.80–0.98, $P = 0.015$). In the multivariate analysis, the adjusted hazard ratio for mortality risk of re-ECD recipients remained higher than that of re-SCD ($P = 0.002$), but the re-ECD patients had a 25% higher mortality risk than prim-ECD ($P = 0.001$).

Patient survival data were further stratified based on whether the recipient's death was due to graft-failure-related causes. Among the patients who died due to graft-failure-related causes, 1-, 3-, and 5-year patient survival in re-ECD recipients was similar to that in prim-ECD recipients (96.5% vs. 96.7%, 92.0% vs. 93.0%, 87.4% vs. 88.8%, respectively, $P = 0.205$). The 1-, 3-, and 5-year patient survival in the re-SCD group (98.6%, 96.9%, and 95.0%, respectively) was significantly better than that of the re-ECD group ($P < 0.001$). The mortality risk for the re-ECD group was similar to mortality in the prim-ECD group (HR = 1.11, 95% CI = 0.95–1.30, $P = 0.203$), but it was significantly higher than the mortality risk in the re-SCD group (HR = 2.40, 95% CI = 2.03–2.84, $P < 0.001$).

Secondary outcomes of interest

The secondary outcomes evaluated in this study are recorded in Table 4. On average, re-ECD recipients experienced longer hospital stays post-transplant. Postoperatively, a higher proportion of the re-ECD transplant group (37.4%) experienced delayed graft function compared with the prim-ECD (32.6%) and the re-SCD (25.6%) groups. In addition, the re-ECD recipients were more likely to experience primary graft failure and graft thrombosis, and they were more likely to resume maintenance dialysis ($P < 0.001$).

Table 1. Demographic and clinical characteristics of transplant recipients by donor type and transplantation status.

Characteristic	Re-SCD Recipients (*N* = 17 130)	Re-ECD Recipients (*N* = 1658)	Prim-ECD Recipients (*N* = 25 508)	*P* value
Age, mean (SD), median	42 (14), 42	49 (13), 50	58 (12), 60	<0.001
Age group				
[<18]	860 (5.0)	14 (0.8)	60 (0.2)	<0.001
[18–39]	6385 (37.3)	408 (24.6)	1936 (7.6)	<0.001
[40–59]	8016 (46.8)	843 (50.8)	10 718 (42.0)	<0.001
[60–69]	1623 (9.5)	327 (19.7)	9245 (36.2)	<0.001
[≥70]	246 (1.4)	66 (4.0)	3549 (13.9)	<0.001
Male	10 147 (59.2)	1020 (61.5)	16 069 (63.0)	<0.001
Race				
Asian	536 (3.1)	64 (3.9)	1611 (6.3)	<0.001
African American	4354 (25.4)	436 (26.3)	7816 (30.6)	
White Non-Hispanic	10 151 (59.3)	975 (58.8)	12 441 (48.8)	
White Hispanic	1856 (10.8)	158 (9.5)	3077 (12.1)	
Other/mixed/unknown	233 (1.4)	64 (3.9)	563 (2.2)	
Number of Prior TX				
1	15 724 (91.8)	1543 (93.1)	–	<0.001
2	1297 (7.6)	106 (6.4)	–	
>2	109 (0.6)	9 (0.5)	–	
Obese*	3413 (20.6)	345 (21.5)	7508 (30.0)	<0.001
Diabetes				
No	13 007 (80.8)	1134 (73.2)	13 921 (57.5)	<0.001
Yes	2837 (17.6)	379 (23.4)	10 039 (41.5)	
[0–5 Year]	615 (3.8)	67 (4.3)	535 (2.2)	
[6–10 Year]	838 (5.2)	112 (7.2)	4738 (19.6)	
[>10 Year]	34 (0.2)	8 (0.5)	63 (0.3)	
Duration Unknown	1350 (8.4)	192 (12.4)	4703 (19.4)	
Unknown	256 (1.6)	36 (2.3)	269 (1.1)	
Dialysis	15 242 (89.0)	1486 (89.6)	23 075 (90.5)	<0.001
Treated for rejection	783 (4.6)	103 (6.2)	–	<0.001
Waiting time, days†	620 (961)	605 (900)	629 (815)	<0.001
Medical condition at TX				
ICU	50 (0.3)	7 (0.4)	170 (0.7)	<0.001
Hospitalized	325 (1.9)	40 (2.4)	387 (1.5)	
Not hospitalized	16 711 (97.8)	1606 (97.2)	24 900 (97.8)	
CMV positive				
IGG	9508 (55.5)	914 (55.1)	14 133 (55.4)	<0.001
HbsAg	301 (1.8)	31 (1.9)	483 (1.9)	<0.001
HBV core positive	1095 (6.4)	120 (7.2)	2200 (8.6)	<0.001
HCV positive	1121 (6.5)	123 (7.4)	1296 (5.1)	<0.001
Peak PRA> 20	3952 (70.1)	404 (68.5)	2547 (13.7)	<0.001
Most recent PRA>20	2610 (65.6)	271 (65.1)	604 (5.7)	<0.001
Kidney allograft location				
Ectopic	229 (1.3)	36 (2.2)	1482 (5.8)	<0.001
Left	8039 (46.9)	865 (52.2)	12 008 (47.1)	
Right	8862 (51.7)	757 (45.7)	12 018 (47.1)	

SD, standard deviation; TX, transplant; PRA, panel reactive antibody; ECD, expanded criteria donors; SCD, standard criteria donor.

*Obese = body mass index >30

†Total days on waiting list including inactive time, median (IQR, interquartile range);

Discussion

The aim of this study was to determine whether patients awaiting retransplantation benefit from accepting ECD grafts by comparing outcomes to those that receive SCD grafts for retransplants as well as those that receive ECD grafts for primary transplants. A previous large-scale study from the Scientific Registry of Transplant Research (SRTR:

Table 2. Demographics, clinical, and allograft characteristics of the kidney donors.

Characteristics	Re-SCD	Re- ECD	Prim-ECD	*P* Value
Age mean (SD)	33 (14)	59 (6)	60 (6)	<0.001
Male	10 540 (61.5)	812 (49.0)	12 458 (48.8)	<0.001
Share Type				
Local	11 441 (66.8)	1060 (63.9)	19 101 (74.9)	<0.001
Regional	1275 (7.4)	150 (9.0)	2485 (9.7)	
National	4411 (25.8)	448 (27.0)	3921 (15.4)	
High-Risk donor	930 (5.4)	476 (1.9)	24 (1.4)	<0.001
BMI	26 (6)	28 (6)	28 (6)	0.525
Cause of death				
Anoxia	3186 (18.6)	79 (4.8)	1599 (6.3)	<0.001
CVA/Stroke	4799 (28.1)	1401 (84.6)	21 141 (82.9)	
Head trauma	8583 (50.2)	158 (9.5)	2438 (9.6)	
CNS tumor	137 (0.8)	4 (0.2)	68 (0.3)	
Unknown	399 (2.3)	15 (0.9)	246 (1.0)	
Diabetes duration				
[0–5 Year]	353 (51.9)	98 (55.4)	1645 (50.8)	0.277
[6–10 Year]	114 (16.8)	36 (20.3)	611 (18.9)	
[>10 Year]	116 (17.1)	26 (14.7)	593 (18.3)	
Unknown duration	97 (14.3)	17 (9.6)	387 (12.0)	
Unknown status	680 (4)	177 (10.7)	3236 (12.7)	
HTN	2314 (13.5)	1172 (70.7)	17 737 (69.5)	<0.001
Cigarette use	4787 (27.9)	729 (43.9)	10 717 (42.0)	<0.001
HbsAg positive	641 (3.7)	31 (1.9)	688 (2.7)	<0.001
Glomerulosclerosis [%]				
Right				<0.001
[0–5]	2705 (77.4)	681 (64.9)	10 833 (63.0)	
[6–10]	411 (11.8)	191 (18.2)	3169 (18.4)	
[11–15]	171 (4.9)	83 (7.9)	1437 (8.4)	
[16–20]	54 (1.5)	42 (4.0)	697 (4.1)	
[20+]	104 (3.0)	44 (4.2)	919 (5.3)	
[Indeterminate]	51 (1.5)	9 (0.9)	141 (0.8)	
Left				
[0–5]	2607 (76.2)	687 (65.4)	10 807 (63.6)	
[6–10]	425 (12.4)	184 (17.5)	3102 (18.3)	
[11–15]	165 (4.8)	86 (8.2)	1329 (7.8)	
[16–20]	64 (1.9)	33 (3.1)	670 (3.9)	
[20+]	118 (3.4)	51 (4.9)	954 (5.6)	
[Indeterminate]	44 (1.3)	9 (0.9)	117 (.7)	
CIT Hr. mean (SD)	19 (9.0)	21 (9.0)	20 (9.7)	<0.001
CIT Hrs. *N* (%)	15 738	1522	25 508	<0.001
[0–12]	3626 (23.0)	261 (17.3)	5194 (20.4)	
[12–24]	8553 (54.3)	787 (52.1)	12 293 (48.2)	
[24–36]	3086 (19.6)	374 (24.8)	4916 (19.3)	
[>36]	473 (3.0)	88 (5.8)	3105 (12.2)	

SD, standard deviation; CIT, cold ischemia time; ECD, expanded criteria donors; SCD, standard criteria donor.

1995–2004) reported significantly worse patient survival outcomes in recipients who received ECD grafts compared with those who received SCD grafts for retransplantation [15]. Our study over the last two decades showed similar results: using ECD kidneys for retransplantation conferred a significantly greater risk of graft failure and death over the use of SCD grafts. Several factors may have contributed to the inferior outcomes in re-ECD recipients. For instance, the re-SCD group was on average younger than the re-ECD group. When the hazard ratios were adjusted for age and other potential confounders the overall survival was still significantly better in the re-SCD group but was reduced by about half. According to an analysis of factors affecting outcomes of kidney transplantation following donation after cardiac death (DCD), retransplantation was associated with poor survival outcomes and increased graft loss [17,18]. Although we did not perform a separate DCD analysis, our ECD group does include DCD kidney allografts, which may

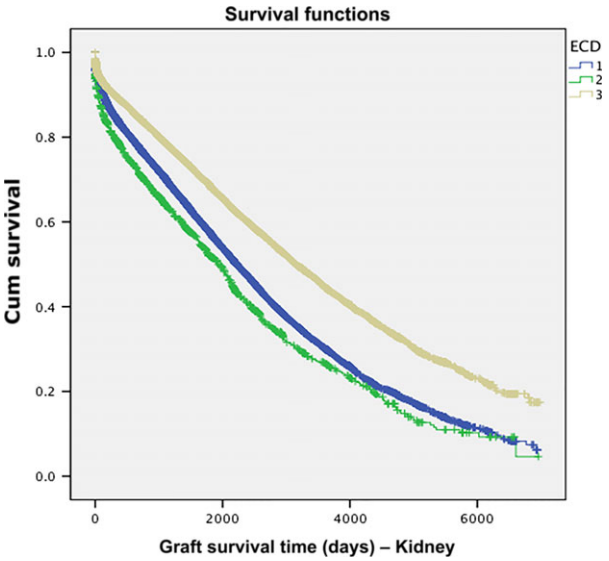

Figure 1 Kaplan–Meier curves for graft survival in primary expanded criteria donors (ECD) transplant recipients (prim-ECD = 1), retransplant ECD recipients (re-ECD = 2), and retransplant standard criteria donor (SCD) recipients (re-SCD = 3). The Log-rank statistic was $P < 0.001$ for prim-ECD vs. re-ECD, prim-ECD vs. re-SCD, and for re-ECD vs. re-SCD.

have contributed to the poorer graft and patient survival in the re-ECD patients. Additionally, the re-ECD group was more likely to experience delayed graft function, to need additional treatment for rejection, to resume dialysis, and to die with a functioning graft. When taking into consideration these characteristics of the patient population receiving the ECD kidneys, it is not surprising that those recipients had poor outcomes compared to the re-SCD recipients.

The clinical dilemma faced by many transplant recipients is whether they should accept an ECD kidney when offered or wait for an SCD graft. Although we did not directly compare the survival of re-ECD patients to those who remained on the waiting list, other similar studies have shown equivalent overall patient survival with these two strategies [15]. Despite the fact that our results confirm a higher risk of graft failure and death when using ECD grafts compared to SCD grafts for retransplantation, it is important to note that recipients of ECD grafts for retransplantation had better overall survival compared with patients who received ECD kidneys as their primary transplant. This suggests that ECD kidneys may provide better utility when allocated to patients with at least one prior failed graft. Other factors such as the reduced incidence of obesity and diabetes in the donors of the re-ECD population may have influenced the overall survival. Also, the prim-ECD group was older than the re-ECD population, and when the hazard ratios were adjusted for age and other factors, the survival benefit was reversed. Additional studies investigating the use of high-risk donor organs in populations stratified by age, medical history, and sensitization may be useful in the future to provide more specific guidance on the allocation of these organs.

There may be other benefits to using ECD kidneys in more select patient populations. For instance, an analysis of transitioning between dialysis and transplantation performed by the US Renal Data System reported higher

Table 3. Hazard ratios of patient mortality and graft failure in Re-ECD transplant recipients compared to re-SCD and Prim-ECD transplant recipients by univariate and multivariate Cox-proportionate regression.

Donor type	Events (%)	Yrs	Event Rate per 1000 Yrs	Crude HR (CI)	AHR (CI)
Graft survival					
Re-SCD	6374 (37)	76367	84	Reference	Reference
Re-ECD	928 (56)	6294	148	1.76 (1.64–1.88)*	1.72 (1.57–1.89)*
Prim-ECD	12308 (48)	99321	124	Reference	Reference
Re-ECD	928 (56)	6294	148	1.19 (1.11–1.27)*	1.23 (1.12–1.36)*
DCGS					
Re-SCD	4474 (26)	76367	59	Reference	Reference
Re-ECD	667 (40)	6294	106	1.79 (1.65–1.94)*	1.84 (1.65–2.06)*
Prim-ECD	7248 (28)	99321	73	Reference	Reference
Re-ECD	667 (40)	6294	106	1.45 (1.34–1.57)*	1.19 (1.06–1.34)*
Patient survival					
Re-SCD	2694 (16)	816527	33	Reference	Reference
Re-ECD	422 (26)	7125	59	1.82 (1.64–2.01)*	1.43 (1.17–1.75)**
Prim-ECD	7155 (28)	106771	67	Reference	Reference
Re-ECD	422 (26)	7125	59	0.89 (0.80–0.98)***	1.25 (1.08–1.44)**

Yrs, total number of patient or graft years; HR, hazard ratio; CI, 95% confidence interval; AHR, adjusted hazard ratio, This multivariate analysis includes adjustments for age, gender, race, BMI, most recent PRA, CMV serostatus, time on waiting list, cold ischemia time, region of transplantation, and year of transplantation; DCGS, death-censored graft survival; ECD, expanded criteria donors; SCD, standard criteria donor.
The *indicates $P < 0.001$, **indicates $P = 0.001$–0.002, ***indicates $P = 0.015$.

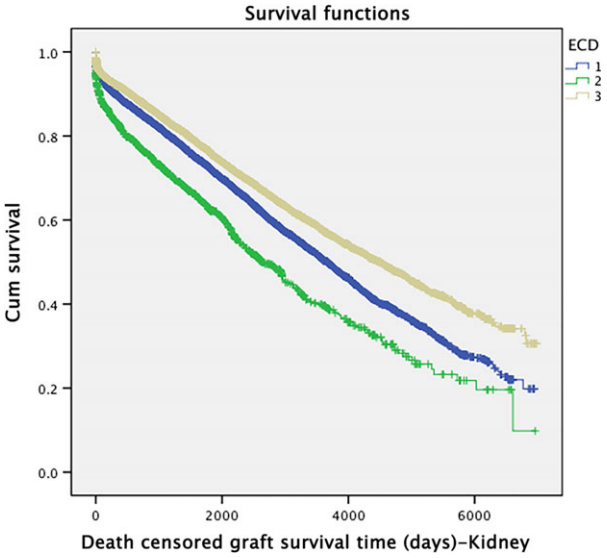

Figure 2 Kaplan–Meier curves for death-censored graft survival in primary expanded criteria donors (ECD) transplant recipients (prim-ECD = 1), retransplant ECD recipients (re-ECD = 2), and retransplant standard criteria donor (SCD) recipients (re-SCD = 3). The Log-rank statistic was $P < 0.001$ for prim-ECD vs. re-ECD, prim-ECD vs. re-SCD, and re-ECD vs. re-SCD.

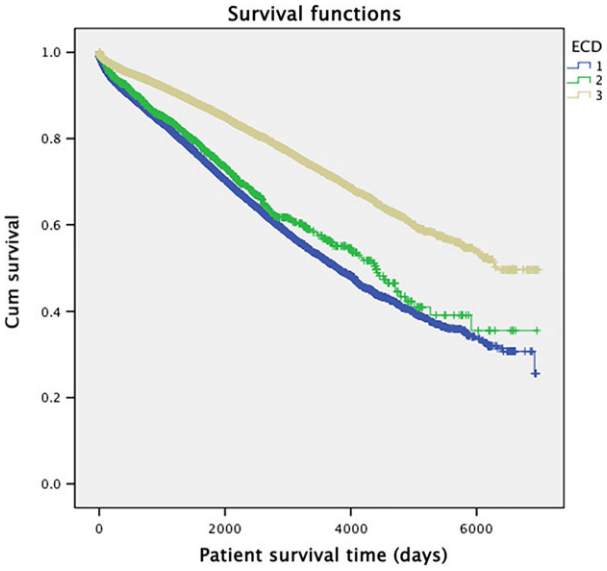

Figure 3 Kaplan–Meier curves for patient survival in primary expanded criteria donors (ECD) transplant recipients (prim-ECD = 1), retransplant ECD recipients (re-ECD = 2), and retransplant standard criteria donor (SCD) recipients (re-SCD = 3). The Log-rank statistic was $P = 0.015$ for prim-ECD vs. re-ECD. The Log-rank statistic was $P < 0.001$ for prim-ECD vs. re-SCD and re-ECD vs. re-SCD.

mortality rates in patients who resume dialysis after failed transplantation than during the peritransplantation period. These mortality rates were both substantially greater than

Table 4. Secondary outcomes of interest by the donor type and re-transplantation status.

Outcomes of Interest	Re-SCD *N* = 17130	Re-ECD *N* = 1658	Prim-ECD *N* = 25508	*P* value
LOS days, median (IQR)	6 (3)	7 (5)	6 (5)	<0.001
Biopsied for rejection	485 (2.8)	73 (4.4)	623 (2.4)	<0.001
Treated for rejection				
Within 6 months	2121 (12.4)	257 (15.5)	2897 (11.4)	<0.001
Within 1 year	2179 (12.7)	244 (14.7)	3046 (11.9)	<0.001
Cause of graft failure				
Hyperacute rejection	32 (0.7)	3 (0.5)	25 (0.4)	<0.001
Acute rejection	727 (16.9)	100 (15.6)	921 (13.1)	<0.001
Primary failure	308 (7.2)	80 (12.5)	783 (11.1)	<0.001
Graft thrombosis	221 (5.1)	39 (6.1)	333 (4.7)	<0.001
Infection	94 (2.2)	15 (2.3)	284 (4.0)	<0.001
Surgical Cxn	17 (0.4)	2 (0.3)	21 (0.3)	<0.001
Urological Cxn	17 (0.4)	7 (1.1)	44 (0.6)	<0.001
Recurrent disease	317 (7.4)	20 (3.1)	221 (3.1)	<0.001
Chronic rejection	1652 (38.4)	234 (36.4)	2629 (37.4)	<0.001
BK (Polyoma) virus	63 (1.5)	7 (1.1)	122 (1.7)	<0.001
Unknown	858 (19.9)	134 (20.9)	1645 (23.4)	<0.001
Creatinine DL24Hr	3916 (22.9)	316 (19.1)	4454 (17.5)	<0.001
Delayed graft function	4381 (25.6)	620 (37.4)	8315 (32.6)	<0.001
DWFG	1900 (11.1)	261 (19.8)	5060 (15.7)	<0.001
Maintenance dialysis	3120 (18.2)	490 (29.6)	5007 (19.6)	<0.001

LOS, length of stay; Cxn, complication; DL24 h, delay in spontaneous fall in serum creatinine after transplant; DWFG, death with functioning graft; ECD, expanded criteria donors; SCD, standard criteria donor.

the mortality rate in patients during their initial waiting period [19]. These data show that there is a significant risk in transitioning from hemodialysis to transplantation or vice versa. Based on our data, the use of ECD grafts in re-transplantation potentially prevented 70.4% of patients from needing to resume dialysis. Thus, for select patients who would otherwise resume dialysis between their initial graft failure and waiting for an SCD kidney, the use of ECD grafts may prevent this unnecessary period of increased mortality risk. Although the values of median waiting time were similar, there was a statistically significant reduction in median waiting time for the re-ECD group compared to the re-SCD group. There is a wide variation in waiting times among different transplant regions, making it difficult to define the benefit of this shorter waiting time in the re-ECD group. However, these results suggest that patients in regions with shorter waiting times for SCD organs may not benefit from accepting an ECD organ, while select patients in regions where waiting times are longer may

benefit from an ECD organ for retransplantation. These potential benefits must be weighed with the risks at the time when informed consent is obtained prior to acceptance of the organ for transplantation.

Other socioeconomic factors beyond patient and graft survival outcomes may make the use of ECD kidneys for retransplantation, a more desirable approach than remaining on the waiting list for the possibility of an SCD kidney retransplant. For instance, many studies have assessed the health-related quality of life of patients on dialysis compared to those that get transplanted [20–22]. In general, these studies show that patients who receive a transplant have markedly improved quality of life compared with those remaining on dialysis, and the degree of improvement in quality of life measures varies with the type of dialysis the patient has experienced in the past [22]. While these results have not specifically been evaluated in retransplant patient populations, these studies suggest that the more time a patient can spend without dialysis the better their overall quality of life will be. This may make the option of receiving an ECD retransplant more desirable for some patients especially those who are suffering most from restrictions in their daily life due to dialysis or who are distraught by the idea of what dialysis may do to their quality of life after their first transplant fails. In addition, there are economic benefits for the healthcare system to performing transplantation compared to patients remaining on dialysis. Studies have shown that the cost of maintaining a transplanted patient over a 10-year period is roughly one-third the cost of maintaining a similar patient for 10 years on dialysis [23,24]. These data also suggest that it takes roughly 3 years of graft survival after transplant to save the entire cost of dialysis for those equivalent number of years, and from that point on, transplantation is more financially beneficial [23]. Although there is an increased cost associated with receiving and ECD kidney and especially a retransplant ECD kidney, this cost is only about $20 000 more expensive than using a SCD [25]. Therefore, when considering the use of ECD kidneys for retransplantation, it is also important to note that those patients expected to achieve graft survival for >3 years not only have better quality of life but also benefit financially compared to remaining on dialysis. As these estimates require knowing how long the patient and kidney graft will survive, it is necessary that the selection and matching of these patients with their grafts be optimized to enhance quality of life in an economically responsible manner. Currently, the definitions of ECD and SCD do not adequately project the lifespan of the grafts. However, the new KDPI system is better designed to help in these predictions and help match kidneys and recipients to maximize these clinical, financial, and social benefits of transplantation, utilizing all the organs available.

There are a number of limitations that are inherent to this study's design. Our results were obtained from retrospective analysis of the UNOS database; thus, the patients were not randomized to receive either SCD or ECD retransplants. The re-ECD group was in general older and had a higher percentage of patients with diabetes and obesity compared with the re-SCD group, which may have influenced the outcomes of the re-ECD group. A separate regression analysis adjusting for diabetes alone found that the higher percentage of diabetic recipients did decrease the overall survival (data not shown), but the re-SCD group still had better overall survival, and this did not affect the multivariate adjusted hazards ratios as presented in the results. Although this study included a much larger population of patients receiving retransplants than in previous retrospective studies [15], the population size of the re-ECD group was significantly smaller than that of the other two groups in the study, which may have affected the power of the statistical comparisons as well as the distribution of the characteristics among the groups. In addition, there are a wide variety of regimens used for induction therapy, immunosuppression, and treatment of rejection episodes at different transplant centers, variations that were not accounted for in the present study. This study reports results of retransplant patients over a 20-year time period and thus may suffer from some temporal heterogeneity as new concepts and techniques for monitoring recipients for both acute and chronic rejection have emerged. Notably, the year of transplantation was one of the variables included in the multivariate regression analysis to obtain the adjusted hazard ratios. The data regarding cause of graft loss in each of the patients are incomplete in the UNOS database and may also have contributed to significant variations in survival among the groups, which was difficult to adjust for in this study.

One of the key limitations of our study is that the system of dividing donor kidney types into ECD and SCD might not be a sufficient for the optimal utilization of this rare resource. In fact, the most recent OPTN policies for organ sharing in the United States have switched to using the continuous KDPI scale to evaluate donor organs prior to transplant. However, we believe there is utility to our data because the ECD and SCD criteria system was the most widely used and well-known system at the time of this study. In addition, the KDPI system has not been fully implemented outside of the United States. Many transplant centers in Europe still stratify their marginal donors based on criteria that is similar to the ECD criteria and have not yet implemented the KDPI system [26]; thus, our data may help reflect the current practices in these regions where continuous donor risk indices are not used. The future widespread implementation of continuous indices such as KDPI or life years from transplant might improve the utility of

nonideal donor kidneys [27,28]. When applied to the current United States allocation system, an ECD kidney correlates with a high KDPI defined as greater than 70. KDPI, which is a continuous score calculated from 10 different donor characteristics, illuminates the fact that some ECD kidneys have reasonably good estimated quality, and some SCD kidneys have a lower estimated quality than some ECD kidneys [10]. The strengths and weaknesses of the emerging criteria remain largely unknown. A recent study by researchers at John Hopkins University evaluated the survival benefit of transplantation with high KDPI kidneys showing an increased mortality risk in the immediate post-transplantation period followed by a greatly reduced mortality risk for several years following transplantation [9]. These findings suggest that there may be similar patterns in the use of high KDPI grafts in retransplant patients especially for those that may be expected to have more prolonged waiting times for a lower KDPI graft. Future studies will be required to assess the utility of the KDPI system in guiding decisions for the use of high-risk donor organs in the growing population of patients requiring retransplantation.

In conclusion, the survival outcomes in re-ECD recipients were worse than those in re-SCD recipients and similar to prim-ECD recipients. Based on the risk associated with resumption of hemodialysis and the longer waiting list times for SCD kidneys, there is likely a benefit to accepting ECD kidneys for retransplantation in select patient populations. Novel methods to evaluate retransplant recipients as well as methods to evaluate donor organs such as the KPDI system may be useful in implementing more specific guidelines for matching retransplant recipients with an appropriate graft to maximize clinical and economic outcomes.

Authorship

HP: performed research, collected data, and analyzed data. JM and PMS: performed research, analyzed data, and wrote the paper. JP: collected data and analyzed data. JO: designed the study, analyzed data, and wrote the paper.

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