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The Need for New Donor Stratification to Predict Graft Survival in Deceased Donor Kidney Transplantation

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Purpose: The aim of this study was to determine whether stratification of deceased donors by the United Network for Organ Sharing (UNOS) criteria negatively impacts graft survival.
Materials and Methods: We retrospectively reviewed deceased donor and recipient pretransplant variables of kidney transplantations that occurred between February 1995 and December 2009. We compared clinical outcomes between standard criteria donors (SCDs) and expanded criteria donors (ECDs).
Results: The deceased donors consisted of 369 patients. A total of 494 transplant recipients were enrolled in this study. Mean age was 41.7±11.4 year (range 18–69) and 273 patients (55.4%) were male. Mean duration of follow-up was 8.8±4.9 years. The recipients from ECD kidneys were 63 patients (12.8%). The overall mean cold ischemia time was 5.7±3.2 hours. Estimated glomerular filtration rate at 1, 2, and 3 years after transplantation were significantly lower in ECD transplants (1 year, 62.2±17.6 vs. 51.0±16.4, $p<0.001$; 2 year, 62.2±17.6 vs. 51.0±16.4, $p=0.001$; 3 year, 60.9±23.5 vs. 54.1±18.7, $p=0.047$). In multivariate analysis, donor age (≥40 years) was an independent risk factor for graft failure. In Kaplan-Meier analyses, there was no significant difference in death-censored graft survival (Log rank test, $p>0.05$), although patient survival was lower in ECDs than SCDs (Log rank test, $p=0.011$).
Conclusion: Our data demonstrate that stratification by the UNOS criteria does not predict graft survival. In order to expand the donor pool, new criteria for standard/expanded donors need to be modified by regional differences.

Key Words: Kidney transplantation, deceased donor, standard criteria donor, expanded criteria donor, allocation

INTRODUCTION

A rapid growing incidence in chronic kidney disease has led to an increasing number of patients awaiting kidney transplantation, despite a limited supply of organs available for donation.[1-3] The concept of expanded criteria donors (ECDs) for kidney transplantation was proposed as an alternative strategy to increase the donor pool. On the basis of a study by Port, et al.,[4] the United Network for Organ Sharing (UNOS) introduced policy to address allocation issues and to promote use of kidney from ECDs.[5] However, despite increases in available kidneys from ECDs for transplantation, organ shortages remain a major issue. Meanwhile, with increasing numbers of elderly donors with comorbidities, recent studies suggest that clinical outcomes of kidney transplantation using ECDs, compared with standard criteria donors (SCDs), have been improved.[6,7] Accordingly, the definition of ECD needs to be re-evaluated.

The objective of this study was to evaluate whether stratifications of ECD have had a negative impact on graft survival in deceased donor kidney transplantations.

MATERIALS AND METHODS

We conducted a retrospective analysis of all patients who un-

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derwent deceased donor kidney transplantation at Samsung Medical Center and Seoul National University Hospital between February 1995 and December 2009. Exclusion criteria included pediatric recipients (younger than age 18 years), multi-organ transplants, and re-transplantations.

The clinical outcomes of recipients from ECDs were compared with recipients from SCDs. We defined ECD as any donor aged ≥60 years or any donor aged 50–59 years matching two of the following three criteria: cerebrovascular accident (CVA) death, terminal creatinine >1.5 mg/dL, or history of hypertension.[4] SCD was defined as any deceased donor not meeting the above criteria. To evaluate the relationship between donor serum creatinine (sCr) levels and graft survival, we reviewed medical records for initial values at the start of management as potential organ donor in the intensive care unit, peak values, and terminal values.

Graft failure was defined as return to permanent dialysis and transplant nephrectomy after kidney transplantation. Transplant recipient death with functioning was not considered as graft failure. Delayed graft function was defined as the need for at least one hemodialysis within the first week posttransplant. Estimated glomerular filtration rate (eGFR) was calculated using the four variable modification of diet in renal disease (MDRD) equations.

Continuous variables are described as means±standard deviations and ranges. Differences between groups were compared with the t-test or chi-square test. The time to graft failure and patient death was determined using the Kaplan-Meier method, and log-rank test was used to compare groups. To identify factors associated with graft failure, we used Cox regression analysis. All *p*-values <0.05 were considered statistically significant.

Table 1. Donor Baseline Demographics and Characteristics (n=365)

Variable	n (%)
Male	260 (71.2)
Age (yr), mean±SD (range)	37.4±15.0 (1–82)
0–29	115 (31.5)
30–39	78 (21.4)
40–49	91 (24.9)
50–59	59 (16.2)
≥60	22 (6.0)
Hypertension	73 (19.1)
Diabetes mellitus	18 (3.7)
Cause of brain death	
CVA	170 (46.6)
Trauma	154 (42.2)
Hypoxia	23 (6.3)
Brain tumor	7 (1.9)
Others	11 (3.0)
Acute kidney injury[8]	
Stage 0	313 (85.8)
Stage 1	38 (10.4)
Stage 2	11 (3.0)
Stage 3	3 (0.8)

CVA, cerebrovascular accident.

RESULTS

Baseline characteristics of the deceased donors are shown in Table 1. Mean age of donors was 37.4±15.0 years. Seventy-three (19.1%) patients had a history of hypertension. The primary cause of brain death was CVA (n=170, 46.6%). The overall mean cold ischemia time (CIT) was 5.7±3.2 hours (range 1.7–18.2 hours). During donor management, acute kidney injury defined by clinical practice guidelines[8] occurred in 77 patients (14.5%).

A total of 493 recipients from 365 deceased donors were categorized as SCD (n=430, 90.5%) and ECD (n=63, 11.5%). Mean duration of follow-up was 8.8±4.9 year and 53 patients (45 SCD, 10.5% and 8 ECD, 12.7%) were lost to follow-up. The characteristics of the recipients and posttransplant outcomes are outlined in Table 2. Mean CIT was similar in both groups (SCD 5.7±3.2 hours vs. ECD 5.4±3.1 hours, *p*>0.05). There were significant differences in recipient age (SCD 40.7±11.1 years vs. ECD

Table 2. Recipient Demographics and Outcomes (n=493)

Variable	SCD (n=430)	ECD (n=63)	*p* value
Male, n (%)	230 (53.5)	43 (68.3)	0.028
Age (yr), mean±SD	40.7±11.1	48.7±10.6	<0.001
Cold ischemia time (hr)	5.7±3.2	5.4±3.1	NS
Post-transplant eGFR (mean±SD, L/min/1.73 m^2)			
1 yr	62.2±17.6	51.0±16.4	<0.001
2 yr	62.3±18.2	53.9±13.5	0.001
3 yr	60.9±23.5	54.1±18.7	0.047
4 yr	59.9±20.0	55.4±15.2	NS
5 yr	59.0±23.1	53.4±19.9	NS
Delayed graft function, n (%)	26 (6.0)	6 (9.5)	NS
Biopsy-proven acute rejection within 1 yr, n (%)	42 (12.4)	7 (15.9)	NS

ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; NS, not significant; SCD, standard criteria donor.

48.7±10.6 years, $p<0.001$) and sex distribution (male, SCD 53.5% vs. ECD 68.3%, $p<0.05$). The mean eGFR within 3 years posttransplant was significantly higher among recipients from SCDs, compared with recipients from ECDs (1 year, 62.2±17.6 vs. 51.0±16.4, $p<0.001$; 2 year, 62.3±18.2 vs. 53.9±13.5, $p=0.001$; 3 year, 60.9±23.5 vs. 54.1±18.7, $p=0.047$). However, there were no significant differences in the mean eGFR at 4 years and 5 years posttransplant. The incidences of delayed graft function and acute rejection at 1 year between recipients from SCDs and ECDs were not significantly different.

In univariate analysis, risk factors for graft failure were donor age (≥40 year), CVA, history of hypertension, and CIT (≥7.5 hours). Among these, donor age (≥40 years) was associated with significantly increased risk for graft failure in multivariate analysis (hazard ratio 2.202, $p=0.009$). In analyses of associations between donor sCr (initial, peak, and terminal values) with graft survival, we were unable to determine a cut-off value of negative impact for graft failure (Table 3).

The overall graft and patient survivals are shown in Figs. 1 and 2. There was no significant difference in graft survival between recipients from SCDs and ECDs (Log-rank $p>0.05$). However, patient survival was inferior among recipients from ECDs, compared with recipients from SCDs (Log-rank $p=0.011$).

DISCUSSION

To overcome critical organ shortages in kidney transplantation,

Table 3. Risk Factors for Graft Failure

Variable	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Donor age (yr)						
≥40 vs. <40	2.805	1.809–4.350	<0.001	2.202	1.125–3.989	0.009
Cause of donor death						
CVA vs. others	1.616	1.076–2.426	0.021	1.376	0.771–2.455	NS
Categories of donor						
DCD vs. DBD	0.847	0.267–2.680	NS			
Donor sCr (mg/dL)						
Initial level						
>1.5 vs. ≤1.5	0.830	0.533–1.290	NS			
>2.0 vs. ≤2.0	0.610	0.340–1.096	NS			
>2.5 vs. ≤2.5	0.660	0.267–1.628	NS			
>3.0 vs. ≤3.0	0.586	0.185–1.854	NS			
>3.5 vs. ≤3.5	0.507	0.125–2.059	NS			
Peak level						
>1.5 vs. ≤1.5	0.889	0.584–1.352	NS			
>2.0 vs. ≤2.0	0.562	0.323–0.975	NS			
>2.5 vs. ≤2.5	0.640	0.279–1.467	NS			
>3.0 vs. ≤3.0	0.479	0.151–1.515	NS			
>3.5 vs. ≤3.5	0.440	0.108–1.787	NS			
Terminal level						
>1.5 vs. ≤1.5	0.884	0.571–1.369	NS			
>2.0 vs. ≤2.0	0.644	0.365–1.136	NS			
>2.5 vs. ≤2.5	0.738	0.322–1.689	NS			
>3.0 vs. ≤3.0	0.395	0.097–1.607	NS			
>3.5 vs. ≤3.5	0.300	0.042–2.155	NS			
Acute kidney injury[8]						
AKI vs. w/o AKI	0.891	0.480–1.655	NS			
Cold ischemic time (hr)						
≥7.5 vs. <7.5	1.643	1.042–2.590	0.033	1.486	0.911–2.421	NS
Each hour increase	1.047	0.988–1.109	0.122			
Donor comorbidities						
HTN vs. w/o HTN	1.896	1.180–3.046	0.008	1.289	0.725–2.290	NS
DM vs. w/o DM	0.463	0.064–3.335	NS			

AKI, acute kidney injury; CI, confidence interval; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after cardiac death; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; NS, not significant; sCr, serum creatinine; w/o, without.

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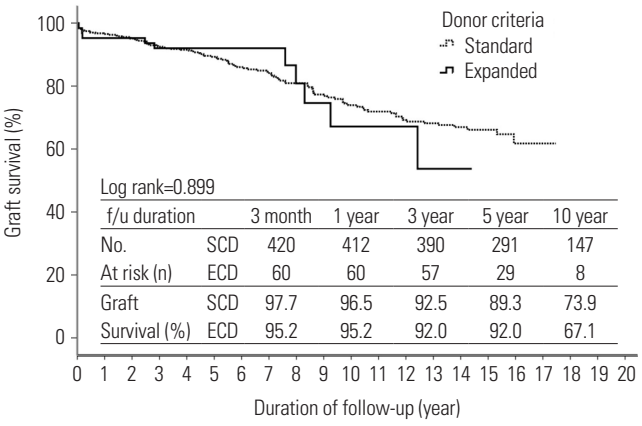

Fig. 1. Death-censored graft survival according to donor type. ECD, expanded criteria donor; SCD, standard criteria donor.

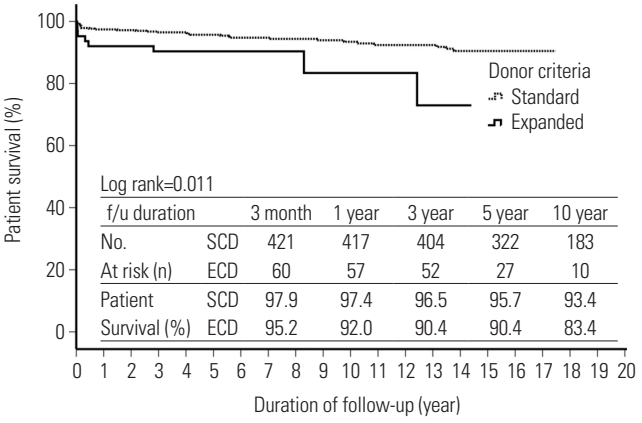

Fig. 2. Patient survival according to donor type. ECD, expanded criteria donor; SCD, standard criteria donor.

it is important to expand the pool of available deceased donor. Studies that have assessed the impact of ECD kidneys on deceased donor transplantations suggest that allocation strategy using the concept of ECD is associated with an expansion in kidney transplantation.[9,10] Despite efforts to effectively reduce discard rates of organs, many patients are still waiting for a suitable organ.[11]

Recently, there have been increases in ECD kidney recipients, especially from elderly or acute kidney injury accompanying with elevation of sCr. However, some authors have reported that clinical outcomes of recipients from ECD kidneys are comparable to those of recipients from SCD kidneys.[12,13] Therefore, we considered that the indices of ECD kidneys need to be revised according to regional differences for expansion of deceased donor pools.

In our analysis, we observed that graft survival was similar in recipients from SCDs and those from ECDs, although the recipients from ECDs showed a poor graft function within 3 years after transplantation. In addition, the incidence of DGF and acute rejection at 1 year posttransplant were not inferior in ECD recipients. These results are in agreement with those of other studies.[14,15]

Four donor factors, including older age (≥40 years), sCr (≥1.5 mg/dL), history of hypertension, and CVA, have been shown to be associated with a significant increase risk for graft failure and identified as indices of ECDs.[4] However, in our study, donor age (40 years or older) was the only independent risk factor of graft failure in Cox regression. While our study focused whether donor sCr levels have an influence on graft survival, no association was found between donor sCr levels at various time points and graft survival. Several studies have documented that the overall results of donors with high terminal sCr, especially accompanying acute kidney injury, are comparable with SCD transplants.[16-19] These findings suggest that sophisticated indices to predict long-term outcomes are required to improve the stratification of ECD kidneys. It is necessary to avoid oversimplification of ECDs because of not represent the reality.[20]

Prolonged CITs and ischemia-reperfusion injury result in inflammation and oxidative damage on endothelial cells and tubular epithelial cells in procured kidney. These changes are potential causes of graft rejection by triggering alloimmune reactivity.[21,22] Previous reports have demonstrated that increased CITs are associated with a significant risk of DGF and graft failure in deceased donor kidney transplantation.[23-25] However, there is a controversy as to how long CIT is associated with graft failure in kidney transplantation. According to a report by Opelz and Döhler[26] increasing ischemia up to 18 hours is associated with graft survival. In a cohort study of 778 kidney transplantation, CIT of >20 hour significantly reduced 5 year graft survival.[27] In addition, analysis of 3839 recipients in a French cohort showed proportional increased risk of graft failure for each additional hour of CIT.[25] In contrast, CIT was not associated with graft survival in our population. We presume that CIT (mean 5.7 hours), compared to other studies, was short because Korea is geographically small.

This study has some limitations. The small number of recipients, especially ECD transplants, could be considered insufficient to detect statistical significance for risk factors of graft failure. In addition, it was possible that posttransplant practices at each tertiary referral center differed, because of the retrospective observational nature of the study. Furthermore, our study was carried out in relatively unrepresentative settings, and we did not analyze national registry data.

In conclusion, ECD kidneys according to UNOS criteria provide unsatisfactory information on graft survival, compared with SCDs. Donors with high creatinine at various time points were not risk factor for graft failure. Modification of criteria considering regional differences for standard/expanded donor is needed to expand donor pools.

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