Comparison of Expanded Criteria Kidneys With 2-Tier Standard Criteria Kidneys: Role of Delayed Graft Function in Short-Term Graft Outcome

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Abstract

Objectives: To compare transplant outcomes between expanded criteria donor kidneys and standard criteria donor kidneys.

Materials and Methods: All adult renal transplants from deceased donors performed in Saudi Arabia over a 24-month period were included. Donor and recipient factors were recorded, and their effects on outcomes with expanded criteria donor and standard criteria donor kidneys were compared. Standard criteria donor kidneys were further subgrouped into optimal and suboptimal groups, and outcomes were compared.

Results: A total of 280 deceased-donor kidney transplants were performed during the study period. Of these, 61 (21.8%) involved expanded criteria donor kidneys. Cold ischemia time and prevalence of delayed graft function were similar between expanded criteria and standard criteria kidneys (P = .7 and P = .8). Graft survival rates at 2 years were also similar (93.3% vs 94.6%; P = .8). Delayed graft function exerted a negative effect on 2-year graft survival in both the expanded group (hazard ratio, 4.9; 95% CI 3.2-7.5; P = .001) and the standard group (hazard ratio, 4.6; 95% CI 3.24-7.5; P = .001). No difference was found between the 2 standard criteria subgroups with respect to serum creatinine value at the end of follow-up (P = .8), delayed graft function prevalence (P = .5), or 2-year graft survival (P = .8). The only independent factor affecting graft survival was delayed graft function (P = .001). No independent effect was seen for expanded criteria donor versus standard criteria donor, donor serum creatinine level, or recipient age.

Conclusions: Similar short-term outcomes were found for expanded criteria and standard criteria kidney recipients. Delayed graft function was associated with significant risk of graft loss in both groups, with decreases in 2-year graft survival of 33.3% and 18.3%. No difference was seen between the 2 subtypes of standard criteria donor kidneys.

Key words: Cyclosporin, Tacrolimus, mTOR, Renal transplant, Adverse effects

Introduction

A deceased-donor kidney is classified as an expanded criteria donor (ECD) kidney if the donor is ≥ 60 years of age or is 50 to 59 years of age with at least 2 of the following 3 medical criteria: serum creatinine (SCR) level > 132.6 μmol/L (> 1.5 mg/mL), history of hypertension, or cardiovascular accident as the cause of death.1 All kidneys that do not meet these criteria are considered standard criteria donor (SCD) kidneys. With the use of Cox regression analysis, ECD criteria were developed to specifically identify deceased-donor kidneys with a relative risk of graft loss of 1.7 compared to SCD kidneys.2

One factor in the recent increase and wide acceptance and use of ECD kidneys has been the severe shortage of SCD kidneys combined with the relatively large proportion of ECD kidneys to the...
deceased-donor kidney pool. According to the United Network for Organ Sharing (UNOS), the annual increase in transplant rate is 4%, whereas the increase in the dialysis population is 20%.3 Expanded criteria donor kidneys have been reported to account for 17% to 31% of all deceased-donor kidneys available for transplant.3, 4, 5 In 2010 in Saudi Arabia, 33% of brain death cases resulted from cardiovascular accident, and 18.1% of deceased donors were older than 51 years of age.6 This compares to a cumulative prevalence of 23.2% and 11.2% for the period 1986 to 2010.6 Similar trends of increasing age and comorbidity among deceased donors have been observed in the United States.7 In France, 26.8% of the donors in 2005 were older than 60 years of age.8 The median waiting time for a kidney exceeds 3 years.3, 9 Another factor is the high annual mortality rate in patients awaiting transplant (7%).10 The life expectancy for an ECD recipient is increased by an average of 5 years (range, 3 to 10 years) compared to wait-listed patients. The adjusted annual death rate is 6.3% for wait-listed patients, 4.7% for ECD recipients, and 3.3% for SCD recipients.11 These factors led to a 50% increase in the number of ECD kidneys used during the period 1997 to 2006, compared to an increase of 22.3% in the number of SCD kidneys.12

In this study, we compared outcomes for ECD and SCD kidneys and investigated factors influencing these outcomes. We further subgrouped SCD kidneys into “suboptimal” and “optimal” SCD kidneys. Suboptimal SCD kidneys were defined as those from donors 50 to 59 years of age (with no comorbidities) or donors younger than 59 years of age with isolated hypertension, diabetes mellitus, or cardiovascular accident not causing death.

Materials and Methods

All kidney transplants from deceased donors into adult recipients carried out in Saudi Arabia over a 24-month period (January 1, 2009 to December 31, 2010) were included in this study. Donor factors (age, sex, cold ischemia time, cause of death, comorbidities, donor SCr level at the time of kidney retrieval) and recipient factors (age, sex, delayed graft function [DGF], duration of follow-up, SCr level, status of kidney) were recorded. This information was extracted from the Saudi Center for Organ Transplantation registry. Kidneys were classified as ECD or SCD kidneys. A kidney was determined to be an ECD kidney if the donor was ≥ 60 years of age or if the donor was 50 to 59 years of age with at least 2 of the following 3 criteria: SCr > 132.6 μmol/L, history of hypertension, or cardiovascular accident as the cause of death.1

Effects of donor and recipient factors on outcomes in both groups were determined. The SCD group was further subgrouped into SCD-suboptimal (donors 50 to 59 years of age with no comorbidities or < 59 years of age with isolated hypertension, diabetes mellitus, or cardiovascular accident not causing death) and SCD-optimal, and outcomes for these 2 subgroups were compared.

Graft loss was defined as a return to dialysis or death with a functioning graft, and DGF was defined as the need for dialysis during the first week posttransplant. Recipients of ECD kidneys were those best human leukocyte antigen (HLA) matched with the donor among those > 40 years of age with a body mass index (BMI) < 25 and no previous transplant. The immunosuppressive regimen was similar for both groups and consisted of induction with antilymphocyte globulin (ATG) until the graft became functional. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and tapering doses of steroids.

Statistical Analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 19.0, IBM Corporation, Armonk, New York, USA) for descriptive data analysis (means, percentages, and proportions). Group means ± SD were compared by the independent t test and the general linear model multivariate analysis. Categoric data were compared with the Pearson chi-square test. Actuarial survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test. P values < .05 were considered statistically significant

Results

A total of 280 deceased-donor kidneys were transplanted into adult recipients. The median follow-up was 1.4 years, with 76% of cases followed up for at least 12 months. Cause of death was cardiovascular accident for 40% of donors, traffic accidents for 31.9%, brain injury for 16.3%, and other causes for 11.8%. Of all deceased-donor kidneys
used, 21.8% were ECD kidneys and 78.2% were SCD kidneys. Comorbidities among the SCD group were diabetes mellitus (14.1%), hypertension (31.9%), and SCr level > 132.6 μmol/L at the time of organ retrieval (25.9%). Based on this, 46.2% of the SCD kidneys were classified as SCD-optimal and 53.8% as SCD-suboptimal.

Donors and recipients of ECD kidneys were significantly older than donors and recipients of SCD kidneys (ECD: 53.7 ± 3.7 and 34.3 ± 16.8 years; P = .001) (Table 1). The cold ischemia time was similar (13.8 ± 13.0 h and 13.3 ± 7.0 h; P = .7). The prevalence of DGF was also similar (20.0% and 18.6%; P = .8). The actual unadjusted percentage of functioning grafts by the end of the observation period was 93.3% in the ECD group and 94.6% in the SCD group (P = .8). Although the last recipient SCr level was higher in the ECD group, this did not reach a statistical significance (187.5 ± 162.0 and 134.0 ± 159.0 μmol/L; P = .1).

The occurrence of DGF negatively affected 2-year graft survival in the ECD group (66.7% vs 100%; P = .001) as well as in the SCD group (80.0% vs 98.3%; P = .001) (Table 2, Figure 1). No significant difference in 2-year graft survival was seen between ECD kidneys and SCD kidneys regardless of whether the SCr level at the time of kidney retrieval is > or < 132.6 μmol/L (94.0% vs 94.5%; P = .9). In addition, DGF was associated with a significantly higher risk of losing the graft in both the ECD group (RR=4.9, 95% CI 3.2-7.5; P = .001) and the SCD group (HR=4.6, 95% CI 3.2-7.5; P = .001) (Figure 2).

The donor SCr level at the time of kidney retrieval was significantly higher in patients that developed DGF compared to those that did not (161.5 ± 154.0 μmol/L and 107.8 ± 94.0 μmol/L; P = .026) (Table 2). Cold ischemia time was also longer in those that developed DGF (16.8 ± 9.0 h vs 12.4 ± 6.0 h; P = .003). Delayed graft function occurrence was higher with older donors (P = .042) but was not influenced by recipient age (P = .7).

The SCD-suboptimal kidneys accounted for 53.8% of all SCD kidneys, and criteria for this subgroup were diabetes mellitus in the donor.

Table 1. Comparison of demographic data and outcomes of ECD and SCD kidneys.

<table>
<thead>
<tr>
<th></th>
<th>All (DD) (n=280)</th>
<th>ECD (n=61)</th>
<th>SCD (n=219)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of donor kidney</td>
<td>100.0%</td>
<td>12.6%</td>
<td>87.4%</td>
<td>.001</td>
</tr>
<tr>
<td>Age of donor (y)</td>
<td>36.9 (11.8)</td>
<td>35.7 (3.7)</td>
<td>34.3 (5.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>13.4 (7.2)</td>
<td>13.3 (13.0)</td>
<td>13.3 (7.0)</td>
<td>.7</td>
</tr>
<tr>
<td>SCr at organ retrieval &gt;132.6 μmol/L</td>
<td>25.9%</td>
<td>52.9%</td>
<td>23.1%</td>
<td>.001</td>
</tr>
<tr>
<td>Recipient age (y)</td>
<td>34.6 (16.8)</td>
<td>47.1 (15.7)</td>
<td>33 (16.3)</td>
<td>.000</td>
</tr>
<tr>
<td>Prevalence of DGF</td>
<td>18.7%</td>
<td>20.0%</td>
<td>18.6%</td>
<td>.8</td>
</tr>
<tr>
<td>Patient survival</td>
<td>96.8%</td>
<td>96.7%</td>
<td>96.8%</td>
<td>.95</td>
</tr>
<tr>
<td>Functioning graft</td>
<td>94.4%</td>
<td>93.3%</td>
<td>94.6%</td>
<td>.8</td>
</tr>
<tr>
<td>Recipient SCr at the end of follow-up (μmol/L)</td>
<td>140.4 (160.0)</td>
<td>187.5 (162.0)</td>
<td>134.0 (159.0)</td>
<td>.09</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>521.8 (205.0)</td>
<td>598.1 (157.0)</td>
<td>511.0 (209.0)</td>
<td>.027</td>
</tr>
</tbody>
</table>

Table 2. Factors associated with DGF occurrence and impact on 2-year actuarial graft survival.

<table>
<thead>
<tr>
<th></th>
<th>DGF (mean)</th>
<th>No DGF (mean)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCr at kidney retrieval (μmol/L)</td>
<td>161.5 (154.0)</td>
<td>107.8 (94.0)</td>
<td>.026</td>
</tr>
<tr>
<td>Recipient age (y)</td>
<td>35.7 (16.0)</td>
<td>34.7 (17.0)</td>
<td>.7</td>
</tr>
<tr>
<td>Donor age (y)</td>
<td>40.2 (10.0)</td>
<td>36.3 (12.0)</td>
<td>.042</td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>16.8 (9.0)</td>
<td>12.4 (6.0)</td>
<td>.003</td>
</tr>
<tr>
<td>Recipient SCr at the end of follow-up (μmol/L)</td>
<td>220.0 (266.0)</td>
<td>119.0 (108.0)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Figure 1. Actuarial graft survival curves for ECD versus SCD kidneys. Abbreviations: Cum, cumulative; ECD, expanded criteria donor; SCD, standard criteria donor

Figure 2. Actuarial graft survival curves with and without delayed graft function (DGF). Abbreviations: Cum, cumulative
(12.5%), donor hypertension (28.3%), cardiovascular accident (35.5%), and donors with an SCr level > 132.6 μmol/L at the time of kidney retrieval (23.7%). When comparing SCD-optimal and SCD-suboptimal kidneys, we found no difference in SCr level at the end of the follow-up (131.0 ± 89.0 μmol/L and 137.0 ± 215 μmol/L; P = .8), prevalence of DGF (20.2% and 16.7%; P = .5), or 2-year graft survival (94.1% and 95.0%; P = .8) (Table 3, Figure 3). Results of general linear model analysis showed that the only factor that affected graft and patient survival was the occurrence of DGF (0.001 and 0.018) (Table 4). By multivariate regression analysis, the only independent factor affecting whether the graft was still working or not at the end of the follow-up was the occurrence of DGF (P = .000). No independent effect was seen for ECD versus SCD, donor SCr level at the time of retrieval, recipient age, or transplant center.

**Discussion**

Several studies have reported inferior graft survival and function of ECD kidneys compared to SCD kidneys. After adjusting for confounding factors, graft survival of ECD kidneys at 3 and 5 years was reported to be 84.5% and 68.0% compared to 90.6% and 79.7% for SCD kidneys.\textsuperscript{13} However, some recent reports show improved outcomes with ECD kidneys. This improvement might be attributed to better age matching between donors and recipients, optimized immunosuppression, reduction of HLA-mismatching, and/or reduction of cold ischemia time.\textsuperscript{3, 8, 14, 15}

Our results showed excellent short-term outcomes for ECD kidneys, comparable to those of SCD kidneys. This may be the result of the relatively short cold ischemia time for these kidneys (mean, 13.8 ± 13.0 h). Cold ischemia time has been shown to be an important factor for outcome of ECD kidneys. In 1 report, the only factor found to be associated with low estimated glomerular filtration rate in the ECD group was the duration of cold ischemia time.\textsuperscript{16} A reduction of cold ischemia time from 19 hours to 12 hours has been reported to improve 1-year ECD graft survival from 79% to 86%.\textsuperscript{17} We found that the graft SCr level at the end of the follow-up tended to be greater for ECD kidneys, but this difference was not statistically significant (P = .09). Other studies that show similar results to ours. One such study reported that ECD kidneys that had been refused by 2 centers and accepted by a third showed similar graft survival to SCD kidneys (70.4% and 76.7%), with similar patient survival rates.\textsuperscript{8} Stratta and associates reported comparable outcomes for SCD and ECD kidneys (2-year graft survival of 83%).\textsuperscript{14} In addition, UNOS data for 2008 showed 1-year graft survival rates of 92% and 85% for SCD and ECD kidneys.\textsuperscript{3}

The incidence of DGF in our series was similar between ECD and SCD groups. This again may
reflect the relatively short cold ischemia time. However, others have reported a higher rate of DGF with ECD kidneys. Our data clearly showed that DGF was associated with a significant reduction in 2-year graft survival in both the ECD group (reduction of 33.3%; \( P = .001 \)) and SCD groups (reduction of 18.3%; \( P = .001 \)). We also found that DGF was associated with higher SCr level at the end of follow-up (\( P = .0001 \)). Lai and associates also reported that the occurrence of DGF was associated with worse 1-year survival compared to when DGF did not occur (100% vs 85.6%) and also worse 5-year graft survival rates (92.2% and 79.9%) in ECD kidney recipients. Delayed graft function has been reported to have an equally negative effect on 5-year graft survival rates in both ECD and SCD kidneys. However, others have reported that DGF was not associated with a significant difference in 5-year graft survival.

In the present series, a relative risk of 4.6 for graft loss was observed when DGF occurred. Ojo and associates reported that DGF was independently predictive of 5-year graft loss in a group of ECD kidney recipients (RR=1.53; \( P < .001 \)). Delayed graft function in deceased-donor kidneys as a whole has been reported to reduce 1-year graft survival from 91% to 75% (\( P < .0001 \)) and graft half-life from 12.9 to 8.0 years. Differing reports regarding the effect of DGF on outcome may well be related to the multifactorial nature and differing underlying causes of DGF.

The SCD kidneys in the present study were further subgrouped into SCD-suboptimal (donors 50-59 years of age with no comorbidities or donors > 59 years of age with 1 of the following: hypertension, diabetes mellitus, or cardiovascular accident not causing death) and SCD-optimal kidneys (the remaining kidneys). The SCD-suboptimal kidneys accounted for 53.8% of all SCD kidneys, and the criteria this category were diabetes mellitus in the donor (12.5%), hypertension (28.3%), cardiovascular accident (35.5%), and donors with an SCr level > 132.6 μmol/L at the time of kidney retrieval (23.7%). We found no differences in mean SCr level by the end of follow up (\( P = .8 \)), prevalence of DGF (\( P = .5 \)), or 2-year graft survival with (\( P = .8 \)) or without DGF (\( P = .8 \)). Similar excellent short-term results were obtained for donors > 60 years of age with no comorbidities. A study comparing similar groups of kidneys showed a significant long-term difference in these 2 types of kidneys (14% difference in 5-year graft survival; \( P = .001 \)). Nevertheless, that study showed that suboptimal kidneys provided an increased life expectancy of 5 years compared to patients remaining on the waiting list. We recently reported that 26.1% of 517 recipients of deceased-donor kidneys, assessed over a 5-year period, received donor kidneys from donors with an SCr level > 150 μmol/L (1.7 mg/dL) at the time of organ recovery. These kidneys were refused by 2 transplant centers before finally being accepted by a third. We found that the rate of creatinine clearance at organ recovery did not affect graft or patient survival or final graft function but did influence the frequency of DGF. We also found that donor age > 50 years did not affect 1- or 3-year graft survival but was associated with reduced creatinine clearance (63.8 mL/min vs 52.6 mL/min; \( P = .02 \)). In another study, we compared the outcome of 65 patients who received kidneys with an SCr level > 150 μmol/L (1.7 mg/dL) at organ recovery to 188 patients who received kidneys with an SCr level < 97 μmol/L (< 1.1 mg/dL) at organ recovery. In both groups, the SCr level was normal at the time of donor admission to the intensive care unit. We found no difference in 1-, 2-, or 3-year graft or patient survival between the 2 groups, but DGF was again observed more frequently in the former group (47.7% vs 29.8%; \( P = .009 \)).

References


