Renal Transplant Survival From Older Donors

A Single Center Experience

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Hypothesis: Despite the observation that kidney transplantations from older donors have an increased risk of failure, the percentage of kidney donors 55 years and older has increased. We explored the risk of allograft failure in a single transplantation center with older (55-79 years) vs younger (18-54 years) donors.

Design: Retrospective cohort review with a mean follow-up of 32 months.

Setting: Academic transplant center.

Patients: Consecutive recipients (n=324) of renal transplants from adult donors.

Interventions: Patients were divided into 4 groups based on donor status (living or deceased) and donor age (≤54 or ≥55 years).

Main Outcome Measures: Allograft survival and function, incidence of acute rejection.

Results: Recipients of older donor kidneys were significantly older (53.6 vs 43.6 years, \( P < .001 \)). Seven allografts (12.7%) failed from 55 transplants from donors 55 years and older, compared with 41 allografts (15.2%) from 269 younger donors (\( P = .63 \)). Renal function was superior following renal transplantation using younger donors (\( P = .004 \)). However, renal function was acceptable in all groups, with a mean±SD serum creatinine level of 1.7±0.4 mg/dL (150±35 µmol/L) among recipients of older donor kidneys. Allograft survival at 1, 2, and 3 years, censored for death with allograft function, did not differ when comparing older vs younger donors.

Conclusions: Most patients receiving allografts from older donors do well. Older donor kidneys provide suitable renal function for many patients on dialysis awaiting transplantation.

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In the United States, the percentage of deceased kidney donors 55 years and older has increased steadily during the past decade.\(^1\) This is the result of 2 simultaneous trends, namely, the decreased mortality from all causes (particularly trauma) in people aged 18 to 35 years and an increased acceptance of older deceased donors for renal transplantation. Despite the requisite use of older donors, kidney transplantations from older donors have an increased risk of failure.\(^2-7\)

Mortality in end-stage renal disease is high, averaging 23% annually for patients on dialysis. The risk of dying on dialysis is proportional to age. Renal transplantation, even with a "marginal" allograft, improves the quality of life of patients with end-stage renal disease and may increase their survival.\(^8\) Although allograft survival is diminished when kidneys are used from older donors, allocating such kidneys to older recipients, particularly those facing prolonged waiting times on dialysis, may be preferable to continued waiting time on dialysis.\(^3\) Such is the philosophy of the expanded criteria donor (ECD) program administered by the United Network of Organ Sharing (UNOS). Expanded criteria donor kidneys are offered to a carefully selected group of recipients who have been advised that such a kidney would provide satisfactory results for them based on their age or degree of medical illness.

We explored the risk of allograft failure in a single transplantation center with older (55-79 years) vs younger (18-54 years) donors. Most older donors met the UNOS criteria for ECD kidneys (age, >60 years; or >50 years, with 2 of the following: death from stroke syndrome, terminal creatinine level >1.5 mg/dL [>133 µmol/L], and history of hypertension). In addition, we compared the results with deceased and living donors within these age groups. Herein, we demonstrate that recipients of kidneys...
METHODS

We conducted a retrospective cohort review of all kidney transplant recipients at Rhode Island Hospital who received a kidney from an adult (age, >18 years) donor. The patients were divided into 4 groups based on donor status: living vs deceased donor and younger vs older donor. Renal function was estimated from serum creatinine levels. The incidence of acute rejection was obtained from hospital records, and all episodes of rejection were confirmed by kidney allograft biopsy. Infections requiring hospital admission or intravenous antibiotics were recorded from hospital records. Simple urinary tract infections treated as an outpatient were not included. Cytomegalovirus infections were documented by blood culture, histologic examination, the presence of new IgM antibody, or polymerase chain reaction. Delayed allograft function was defined as the need for dialysis within 7 days of transplantation. Chronic allograft nephropathy was defined as long-term renal transplant dysfunction associated with proteinuria or biopsy findings of interstitial fibrosis, tubular atrophy, and arteriolar sclerosis. No attempt was made to match allografts by donor and recipient human leukocyte antigens (HLAs), with the exception of awarding HLA matching points for allografts matched at both HLA-B and HLA-DR alleles. This accounted for only 2% of all cadaver renal transplantations.

Allografts lost within the first week of transplantation because of technical failure, thrombosis, or primary allograft nonfunction were excluded from analysis. (There was no difference in the percentage of early transplant failures based on donor age: 4.3% of younger donors and 3.6% of older donors.) No allografts were lost in the first week because of acute cellular or humoral rejection. Donors after cardiac death were excluded from the analysis, as our institutional protocol requires that these donors be younger than 35 years, thereby potentially biasing this analysis. Only deceased donor kidneys procured within UNOS region 1 were included, eliminating imported zero-antigen mismatched kidneys from the analysis.

Kidneys from cadaver donors 60 years and older underwent biopsy and frozen section examination before transplantation. Kidneys with less than 10% glomerulosclerosis or less than 20% glomerulosclerosis with minimal interstitial fibrosis and a terminal serum creatinine within the normal range were accepted for transplantation. Allografts with significant long-standing damage or structural loss were used for dual transplantation (2 kidneys for 1 recipient) or discarded. No biopsies were performed before transplantation on kidneys from living donors.

Continuous variables (donor age, recipient age, cold ischemic time, serum creatinine, and length of hospital stay) were expressed as mean±SD. Categorical variables (sex, recipient ethnicity, primary renal disease, donor cause of death, acute rejection, delayed allograft function, and recipient infections) were determined from hospital records and scored as 0 or 1. Where appropriate, univariate relations between variables were determined by simple correlation or linear (least squares) regression analysis. Any differences between continuous variables were analyzed by the $t$ test. Categorical variables were analyzed by $\chi^2$ analysis and Fisher exact test. Survival analysis was accomplished according to the method of Kaplan and Meier.

RESULTS

The mean follow-up was $32±21$ (range, 3-79) months. The follow-up was similar for recipients of older (age, $\geq55$ years) vs younger donors. Renal transplant recipients were divided into the following groups: group 1, live donor 18 to 54 years ($n=168$); group 2, live donor 55 years or older ($n=17$); group 3, deceased donor 18 to 54 years ($n=101$); and group 4, deceased donor 55 years or older ($n=38$). The distribution of donors is given in Figure 1. As expected from the study design, donors from groups 2 and 4 were significantly older (63.3±7.0 vs 38.1±10.0 years, $P<.001$). Recipients of older kidneys were also significantly older (53.6±12.4 vs 43.6±13.1 years, $P<.001$). Deceased donors, excluding donors younger than 18 years and donors after cardiac death, accounted for 42.9% of all transplant organs. Living donors accounted for 57.1% of all donors but only 30.9% of older donors. Therefore, in our population, older donors were more likely to originate from a cadaver source. Cold ischemic time for deceased donor kidneys (all recovered in UNOS region 1) averaged $13.6±6.1$ hours, with no significant difference between groups 3 and 4 ($P=.93$). Six patients received dual renal transplants, 1 from a donor aged 49 years with greater than 20% global glomerulosclerosis and 5 from older (range, 73-79 years) donors.

Figure 1. Distribution of donors by age. Kidney donors 55 years or older were considered older donors for the purposes of this study. Numbers at top of bars indicate number of donors.

from older donors have acceptable renal function and outcomes following renal transplantation.
Seven allografts (12.7%) failed from 55 transplants from donors 55 years and older, compared with 41 allografts (15.2%) from 269 younger donors ($P = .63$). Renal function was worse on average in recipients of older kidneys. The nadir creatinine value within 60 days of transplantation was $1.3 \pm 0.4 \text{ mg/dL}$ (115±35 µmol/L) from younger donors vs $1.46 \pm 0.40 \text{ mg/dL}$ (129±35 µmol/L) from older donors ($P = .02$). This discrepancy in early renal function persisted throughout, and at last follow-up, the mean creatinine value from younger donors was $1.5 \pm 0.6 \text{ mg/dL}$ (133±53 µmol/L) vs $1.7 \pm 0.4 \text{ mg/dL}$ (150±35 µmol/L) from older donors ($P = .01$). No differences were observed in the incidence of acute rejection or delayed allograft function related to donor age. However, the presence of acute rejection significantly decreased allograft survival ($P < .001$). Recipient length of hospital stay was longer in the group receiving a kidney from an older donor ($P = .04$). A striking difference was noted in the likelihood of infection from all causes and cytomegalovirus infection. The disproportionate number of infectious complications in group 4 (older deceased donors) accounted for this difference. Thirty-one recipients (9.6%) in our series now have a serum creatinine level greater than 2.0 mg/dL (177 µmol/L). Within this subgroup, the donors were significantly older ($P < .001$), and there was a higher likelihood of acute rejection (35.5% vs 13.2% in patients with serum creatinine levels <2.0 mg/dL [<177 µmol/L], $P = .001$). When the donor’s renal function was considered inadequate for single allograft transplantation, dual renal transplants were considered. In our series, 6 patients received 2 kidneys (dual transplants), with a mean creatinine of $1.7 \pm 0.8 \text{ mg/dL}$ (150±71 µmol/L). On average, these kidneys were refused by 12 other centers before acceptance as dual allografts. One was lost to patient death from acute myocardial infarction, and the other 5 are functioning well.

Patient and allograft survivals were excellent in all groups (Figure 2). When the results were censored for death with allograft function, the rate of renal allograft loss was not different when considering younger vs older donors (Figure 3 and Figure 4). Overall, 48 allografts were lost during the entire period. The main cause of allograft loss was death with a functioning allograft (45.8%). Other prominent causes of graft failure included chronic allograft nephropathy (21.6%), acute rejection (12.6%), and recurrent renal disease (8.6%). Multivariate analysis revealed that acute rejection and older recipient age had an adverse effect on allograft survival (Table 2). Conversely, use of a living donor had a beneficial effect ($P = .03$). The same analysis confirmed the lack of correlation between donor age and allograft survival (hazard ratio, 1.01; 95% confidence interval, 0.99-1.03; $P = .29$).
COMMENT

An ideal donor is young and hemodynamically stable, with excellent renal function. However, the number of such donors in the United States has increased by 45% during the past 15 years. Older donors, including those with hypertension and cardiovascular disease, account for most of this increase. In addition, there is a growing disparity between organ availability and need. With 55,355 people awaiting renal transplantation, it is not practical or advisable to wait for an ideal kidney for each recipient. Given this crisis, the transplant community is appropriately motivated to maximize the use of all available organs from deceased donors and to encourage living organ donation, including from older donors, as medically safe. Older donor age is a risk factor for renal allograft failure. Data from the UNOS registry suggest that donor age has less of a negative effect on allograft function when living donors are used; however, even a living donor older than 55 years represents a significant risk for allograft failure. Despite this observation, the carefully selected older living donor may offer substantial advantages compared with continued dialysis. In our series, no kidneys were lost from living donors 55 years or older. Furthermore, the incidence of delayed graft function and recipient complications was similar to that in group 1 patients who received live donor kidneys from younger donors.

A more recent review of the UNOS data confirms that cadaveric kidneys from donors older than 60 years are associated with a 50% survival at 5 years, compared with the graft survival rate of 70% in patients receiving cadaveric donor kidneys from donors aged 19 to 45 years. Older donor kidneys often have lower functional nephron mass and graft arteriosclerosis, making them more susceptible to injury from procurement, rejection, and calcineurin inhibitor exposure. The risk of graft failure must be weighed against the patient's long-term prognosis (expected survival) and the risk of continued dialysis. In the pediatric population, in whom death with a functioning transplant is far less likely to occur, an older donor seems to represent a significant risk for allograft failure and the need for retransplantation. Conversely, older recipients, particularly those for whom prolonged waiting times on dialysis are anticipated, and patients with failing dialysis access may benefit from prompt renal transplantation from an older donor. By implementing this strategy at our center, we demonstrated comparable allograft survival using older donor allografts, but also noted a high incidence of infectious complications and a trend toward higher mortality in older recipients who received kidneys from older deceased donors. Therefore, based on this analysis, a cautionary approach must be advocated, which might include avoiding allografts at high risk for delayed allograft function and reducing immunosuppression to prevent infectious complications.

Some have suggested that kidneys from older donors should have a creatinine clearance greater than 60 mL/min (>1.00 mL/s) and a wedge biopsy performed to document less than 15% glomerulosclerosis. Gaber et al showed that the degree of glomerulosclerosis correlated with renal function, a finding recently confirmed in the United Kingdom. However, others have advised against this strategy, demonstrating that even donor kidneys with glomerulosclerosis greater than 25% can provide suitable renal function. Interestingly, in that same single center analysis, donor age showed the best correlation with short- and long-term renal function. In addition, kidneys with significant interstitial fibrosis and arterial hyalinosis should be avoided. One group has extended the age of kidney donors with normal kidney function without limitation, reporting favorable results for single and dual renal transplants from such donors. In their series of 215 donors older than 60 years, the mean donor age for dual renal trans-
plants was 75±6 (range, 61-89) years and somewhat younger (68±4 years) for single renal transplants.

We preferentially allocate older donor kidneys to older recipients, especially those with little accumulated waiting time. Such an assignment of these kidneys is possible because of a geographically balanced allocation system that commonly results in multiple offers within a single center and the assignment of ECD kidneys to a waiting list composed of optimal ECD kidney recipients. Although Kasiske and Snyder18 demonstrated that transplanting older kidneys into older recipients does not improve graft survival, such a strategy is reasonable for recipients with a limited life expectancy. Furthermore, reducing the discard rate of cadaver kidneys by using allografts from older donors increases the availability of transplantation. Early transplantation and reduced time on dialysis for patients may be one of the largest benefits to recipients of older donor kidneys.8,19

Not surprisingly, the main reasons for kidney allograft loss in this study were death with a functioning kidney and chronic allograft nephropathy. Such are the leading causes of late graft loss after renal transplantation.20 The contribution of older donor age and inadequate nephron mass to chronic allograft failure is significant, but the exact extent is unclear. Recipient age is also an independent risk factor for chronic allograft failure.3,21 The short-term follow-up afforded by the present study does not allow for an evaluation of the relationship between donor age and chronic allograft nephropathy. However, chronic allograft nephropathy leading to allograft loss was only documented in kidneys from younger donors (groups 1 and 3). Nevertheless, the significant decrement in renal function that we noted for recipients of kidneys from older donors suggests that these allografts may be more prone to chronic allograft failure over time.22 Recipients of older donor kidneys were more prone to bacterial and opportunistic infections after transplantation (Table 3). Most of these infectious complications occurred in older recipients or recipients exposed to an extended course of antilymphocyte antibody induction. Our standard immunosuppressive regimen, antibody induction followed by 3-drug maintenance therapy, was applied to all recipients in our program. Older recipients were likely overimmunosuppressed. Since this study, we have reduced the immunosuppression given to recipients older than 60 years and restrict polyclonal antibody induction to the first week after transplantation.

Older donor kidneys provide good allograft function in most recipients. After proper evaluation, kidneys from older deceased or living donors are appropriate for selected candidates, including older patients awaiting transplantation and those with limited life expectancy based on their severity of illness. Kidneys from older living donors can be used more liberally. Clinicians and patients on the kidney transplantation waiting list must decide whether to accept a particular allograft or to continue waiting while on dialysis. The transplantation of selected kidneys from older donors (based on terminal creatinine, procurement biopsy data, cold ischemic time, and possibly pulsatile perfusion characteristics) may be better than waiting with continued dialysis for some patients. This single center experience supports the recent trend to use kidneys from older donors and expels the notion that marginal donors uniformly provide inferior kidney allografts.

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## References


### Table 3. Outcomes After Renal Transplantation*

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Group 1: LD (n = 168)</th>
<th>Group 2: Older LD (n = 17)</th>
<th>Group 3: CAD (n = 101)</th>
<th>Group 4: Older CAD (n = 38)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed allograft function</td>
<td>4 (2.4)</td>
<td>1 (5.9)</td>
<td>22 (21.8)</td>
<td>6 (15.8)</td>
<td>.47</td>
</tr>
<tr>
<td>Creatinine, 60-day nadir, mg/dL</td>
<td>1.2 ± 0.4</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.5</td>
<td>1.5 ± 0.4</td>
<td>.02</td>
</tr>
<tr>
<td>Creatinine, current, mg/dL</td>
<td>1.4 ± 0.5</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.7</td>
<td>1.8 ± 0.5</td>
<td>.01</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>37 (22.0)</td>
<td>3 (17.6)</td>
<td>21 (20.8)</td>
<td>7 (18.4)</td>
<td>.31</td>
</tr>
<tr>
<td>Infection in first 6 mo</td>
<td>34 (20.2)</td>
<td>3 (17.6)</td>
<td>21 (20.8)</td>
<td>7 (18.4)</td>
<td>.01</td>
</tr>
<tr>
<td>CMV infection</td>
<td>7 (4.2)</td>
<td>8 (7.9)</td>
<td>7 (18.4)</td>
<td>.055</td>
<td></td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>5.8 ± 2.7</td>
<td>5.9 ± 2.2</td>
<td>8.4 ± 3.1</td>
<td>9.8 ± 4.4</td>
<td>.044</td>
</tr>
<tr>
<td>Patient survival, %</td>
<td>93.4</td>
<td>100.0</td>
<td>94.1</td>
<td>96.8</td>
<td>.53</td>
</tr>
<tr>
<td>Allograft survival, %</td>
<td>87.5</td>
<td>100.0</td>
<td>82.1</td>
<td>81.6</td>
<td>.23</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, cadaver (deceased donor); CMV, cytomegalovirus; LD, living donor.
SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

*Data are given as number (percentage) unless otherwise indicated.
†P values are for older (groups 2 and 4) vs younger (groups 1 and 3) donors unless otherwise noted.
‡P value for group 4 vs group 3.
Thomas A. Colacchio, MD, Lebanon, NH: First, I am wondering if you could postulate about the difference in infection rates for your older donors vs younger group. Is there some selection bias embedded in that difference in the racial distribution that you showed in the older vs younger groups?

Dr Morrissey: In terms of the infection rate, there was certainly a selection bias on our part to transplant older kidneys into older recipients, and the older recipients were more prone to infection. They received near identical immunosuppression to our other group of patients, and they also received the same prophylaxis, but ultimately were overimmunosuppressed and developed more infections. Recently, we modified our protocol to administer less overall immunosuppression to elderly recipients and have noted fewer infectious complications.

In terms of a selection bias, we have no difference in the percentage of black patients on our waiting list, relative to age. The higher incidence of young blacks receiving young cadaver kidneys may result from an intentional bias on the part of the accepting surgeons and nephrologists, because blacks as a racial group do particularly poorly when transplanted from African American donors and from older donors.

David Hull, MD, Hartford, Conn: Your results are very encouraging, Paul, particularly in New England, since our donor population tends to be a bit older and have fewer traumatic deaths than other parts of the country. We all strive to use these donors, but I would also comment that on the wait list the numbers are increasing dramatically and there is little control of who is on that wait list. In this country, the most common cause of graft failure in recipients older than 55 years of age is patient death, usually from cardiovascular disease, so this is a unique population of patients.

Your results reinforce the findings of others that the use of extended donor kidneys does lead to decreased survival at various time intervals. You must have been somewhat particular about using older donors. People have commented on biopsies and pump preservation. What were your criteria for using older donors and which would you discard rather than use? We are putting older kidneys into less good recipients and somehow that doesn’t seem intuitively appropriate, yet your results are pretty equivalent.

Dr Morrissey: We decide whether to use a kidney based on pulsatile perfusion characteristics and biopsy data. Some of the kidneys that are thought to be inadequate for single cadaver renal transplantation are used for a dual transplant, 2 kidneys for 1 patient, of which we have done 6 at our institution. Currently, using that algorithm in the region, at least 67% of kidneys are usable and about 30% to 33% are discarded. Possibly some of the discarded kidneys in a more aggressive setting could be used as double transplants. At Rhode Island Hospital, we have had good success with that procedure, with 1 allograft lost to death with function and the other currently functioning.

In terms of the survival benefit of, more appropriately, the risk-benefit of using older kidneys in older recipients and possibly compounding the older recipients’ risk, that is something that we have observed at our center. If we use an older kidney, more likely to experience delayed or slow graft function, the older recipient stays in the hospital longer, is more susceptible to complications, and the management is certainly more complicated. The lengths of stay are longer. Tailoring immunosuppression is more difficult than after a typical cadaver transplant.

A. Benedict Cosimi, MD, Boston, Mass: Paul, you are to be applauded for your excellent results in every category, but I was pleased to see your last conclusion that caution still has to be used here. It is evident even in your statistics where the creatinines in your patients from the older donors are in the range of 1.6 to 1.7. As Hanrahan has shown in a nice summary in the New England Journal, the best correlate of long-term graft function is a creatinine of less than 1.5 at 1 year, so those patients presumably will not do as well. What do you tell the recipient when you are offering them the kidney? Say, your next patient up is a 35-year-old doing well on dialysis and there is a 70-year-old kidney. Do you offer them the chance to turn it down or do you tell them, this is a good kidney, we have shown that our survival is excellent with this kidney? How do you handle the consent process?

Dr Morrissey: Let me address that specific situation: a 70-year-old donor for a 35-year-old recipient. Typically, we would not make such an offer to that recipient. We make a medical decision that a marginal kidney is not an appropriate option for that patient. We may discuss the risks and benefits of giving such a kidney to the patient if the patient had been doing poorly on dialysis, had advanced diabetes, or limited life expectancy. Conversely, we may encourage a 55- or 60-year-old recipient when you are offering them the kidney. Say, your next patients presumably will not do as well. What do you tell the recipient when you are offering them the kidney? Say, your next patient up is a 35-year-old doing well on dialysis and there is a 70-year-old kidney. Do you offer them the chance to turn it down or do you tell them, this is a good kidney, we have shown that our survival is excellent with this kidney? How do you handle the consent process?