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Outcomes of Renal Transplantation in Older High Risk Recipients: Is There an Age Effect?

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Background. **The purpose of this study was to evaluate long-term outcomes in high risk renal transplant recipients over 60 years of age compared with those younger than 60 years of age.**

Materials and Methods. **We analyzed outcomes in 131 consecutive renal transplant recipients at our institution between November 2001 and December 2007. Primary outcomes included incidence of delayed graft function (DGF), acute rejection, graft survival, patient survival, and incidence of infections and neoplasms.**

Results. **Older recipients (Over 60 group, $n = 45$) received more organs from extended criteria donors (ECD) or donation after cardiac death donors (DCD) compared with younger recipients (Under 60 group, $n = 86$), 42% *versus* 17% respectively, $P = 0.001$. Multivariate analyses revealed that African American ethnicity and DCD donation had the greatest impact on the incidence of DGF in both groups; $P < 0.05$. Patient survival and graft survival beyond 1 y were similar between the two groups.**

Conclusion. **Our data suggest that long-term transplant outcomes in older, high risk renal transplant recipients are similar to those of younger, high risk recipients. Older recipients' age and high-risk characteristics, such as African American ethnicity and increased sensitization, should not be a contraindication to renal transplantation in the elderly.**

Key Words: **kidney transplantation; elderly; high risk; deceased donors; age.**

INTRODUCTION

The incidence and prevalence of end-stage renal disease (ESRD) in the United States has increased steadily over the past decade. According to the 2008 U.S. Renal Data System report (USRDS), a total of 110,854 patients were newly diagnosed in 2006 with ESRD with a prevalence of 506,255 [1]. Patients aged 60 y and older comprise the fastest growing population with ESRD in the United States. In 2006, this cohort nearly equaled the absolute prevalence counts of patients younger than 60 y with ESRD. In fact, the 2008 USRDS data report the number of individuals under the age of 60 with ESRD totaled 268,962 compared with 237,293 individuals over the age of 60 [1].

Despite these findings, the majority of elderly patients are still not being referred as candidates for transplantation. In 2002, less than 5% of patients older than 60 y receiving dialysis treatment were on the transplant wait list. In subsequent years, little progress has been made in listing the elderly. In 2006, 196,521 patients older than 60 years with ESRD were treated with dialysis, yet only 10% of them were on the wait list for a kidney transplant [1]. Differences in listing practices in the over and under 60 age group most likely arise from concerns regarding the benefits of kidney transplantation in elderly patients with increased rates of comorbid diseases and decreased life expectancies [1, 2].

Furthermore, it is not clear how other high risk characteristics, such as African American ethnicity, sensitization (defined as panel reactive antibodies >20%), and previous transplantation impact elderly transplant recipients compared with their younger counterparts. Therefore, the purpose of this study was to compare long-term outcomes in high risk renal transplant

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recipients over 60 years of age compared with those under 60 years of age who are also high risk. We used age over 60 as our breakpoint for this study for several reasons: (1) they are the fastest growing group with ESRD based on USRDS data, (2) it is considered the accepted older age in other referred publications, and (3) it is the cutoff age that defines an extended criteria donor.

MATERIALS AND METHODS

We performed a retrospective review of all consecutive renal transplant recipients at our institution between November 2001 and December 2007. Recipients were classified into two groups according to their age at the time of transplantation: Under 60 group ($n = 86$) and Over 60 group ($n = 45$). All the patients were followed for at least 1 y. Primary outcomes included the incidence of delayed graft function (DGF, defined as the need for dialysis within the first week post-transplant), biopsy-proven acute rejection, graft survival, patient survival, and the incidence of infections and neoplasms.

All recipients received induction therapy consisting of either basiliximab (20 mg i.v. on the day of operation and a second dose on post-operative d 4) or thymoglobulin (1.5 mg/kg/d × 4 doses). Maintenance immunosuppression consisted of tacrolimus (titrated to trough concentrations of 8–12 ng/mL during the first 6 months post-transplant, then 5–10 ng/mL thereafter), mycophenolate mofetil (1 gm po bid), and chronic corticosteroid therapy (weaned to 2.5–5 mg daily by mo 6).

Statistical analyses were performed using medians (interquartile range), χ^2 test, univariate and multivariate Cox proportional hazard ratios, odds ratio, and Fisher's exact test. Patient survival and graft survival were calculated by Kaplan-Meier analysis and tested for differences with the Mantel-Cox log-rank test. A P value < 0.05 was considered significant. This study was approved by the Temple University Institutional Review Board.

RESULTS

There were 86 (65.6%) patients in the Under 60 group and 45 (34.4%) in the Over 60 group. Mean time of follow up was 4.8 ± 1.6 y in the Under 60 group and 4.5 ± 1.8 years in the Over 60 group. Patient demographics and transplant related data for the two groups are depicted in Table 1. Median age in the older recipients was 65 y (range 62–69 y) compared to 49 y (range 38–55 years) in younger recipients. Donor age was similar between the two groups. Not surprisingly, a smaller proportion of older recipients received transplants from living donors compared with younger recipients, $P < 0.001$. This high risk population consisted of a majority of African American recipients, 70% in the Under 60 group and 62% in the Over 60 group (Table 1). Median peak panel reactive antibody (PRA) was 12% in the Under 60 group and 9% in the Over 60 group (Table 1). However, at the time of transplant, all patients had a negative crossmatch. Ten percent of the recipients in the Under 60 group had a previous transplant compared with 8% in the Over 60 group, $P = 0.24$. Etiology of ESRD was similar between the groups except for a higher incidence of diabetes mellitus in the Over 60 group, $P = 0.016$.

Older recipients received more organs from extended criteria donors (ECD) and donation after cardiac death donors (DCD) compared with younger recipients, 42% *versus* 17 % respectively, $P = 0.001$ (Table 1). Moreover, older recipients had a 3.4 times increased risk of experiencing DGF compared with younger recipients; OR 3.4; 95% CI (1.378–8.550). However, when all factors were accounted for, including all donor types such as standard criteria donors, living related donors, DCD, and ECD donors, there was no significant increase in the incidence of DGF between older and younger recipients. Multivariate analysis findings revealed that African-American recipients had a 5.2 times increased risk of experiencing DGF than non-African-American recipients in both age groups; $P = 0.03$; 95% CI(1.174–23.431), and recipients of DCD organs had a 10 times increased risk of experiencing DGF than those receiving standard criteria organs (including living donors) or ECD organs; $P < 0.0001$, 95% CI (3.179–31.360).

The overall incidence of acute rejection at 1 y was 8% in the Under 60 group and 11% in the Over 60 group, $P = 0.2$ (Table 2). The incidence of infections, specifically cytomegalovirus, pneumonia, and BK virus was not different between the two groups (Table 2). There was one case of renal cell carcinoma in the Over 60 group and three neoplasms (one case of Kaposi sarcoma, one case of squamous cell carcinoma, and one case of gastric adenocarcinoma) in the Under 60 group, $P = 0.10$.

Patient survival beyond 1 y post-transplant was similar between the two groups, $P = 0.54$ (Fig. 1). Actuarial graft survival at 1, 3, and 5 years in the Under 60 group was compared to 1, 3, and 5 y actuarial graft survival in the Over 60 group , $P = 0.55$ (Fig. 2A). When graft survival was censored for death with a functioning graft, likewise, there was no difference between the two groups; $P = 0.51$ (Fig. 2B). In the Under 60 group, there were six deaths all with functioning grafts. Similarly, in the Over 60 group there were eight deaths; seven of these were deaths with functioning grafts.

Approximately 50% of the graft losses beyond 1 y in the Under 60 group were due to documented immunosuppressive mediation noncompliance. None of the cases in the Over 60 group was lost due to noncompliance.

DISCUSSION

Among individuals with end stage renal disease, those aged 60 y and older comprise the fastest growing population, currently representing almost 47% of the total number of patients with end stage renal disease in the United States [1]. Despite these figures, older patients continue to be underrepresented in the group considered as kidney transplant candidates [1]. Previous data demonstrate that kidney transplantation

TABLE 1

Baseline Patient Demographics and Transplant Related Data

	Under 60 group ($n = 86$)	Over 60 group ($n = 45$)
Recipient age in years, median (range)	49 (38–55)	65 (62–69)
Gender (n, male/female ratio)	56/30	26/19
Donor serum creatinine in mg/dL, median (range)	1.4 (1.1–1.8)	1.5 (0.95–1.65)
Donor age in years, median (range)	40 (29-48)	44 (26-53)
Ethnicity, n (%)		
African American	60 (70)	28 (62)
Caucasian	11 (13)	8 (18)
Hispanic	10 (12)	7 (16)
Asian	4 (5)	1 (2)
Other	1	1 (2)
BMI in kg/m^2, median (range)	27 (23–31)	26 (24–30)
ESRD etiology, n (%)		
Diabetes mellitus*	20 (23)	20 (44)
HTN	66 (77)	35 (78)
Glomerulonephritis	4 (5)	6 (13)
Congenital abnormality	1 (1)	0
IGA nephropathy	3 (3)	0
PCKD	6 (7)	3 (7)
FSGS	2 (2)	0
Lupus	2 (2)	0
Pyelonephritis	4 (5)	0
Good pasture syndrome	1 (1)	0
Cadaveric donor (%)	69%	93%
Living donor (%)*	31%	7%
Previous transplant (%)	10%	8%
ECD/ DCD donor source (%)*	17%	42%
Peak PRA %, median (range)	12 (4–28)	9 (0–26)
Induction therapy, n		
Simulect	81	39
Thymoglobulin	5	6

Range = 25th, 75th interquartile range.
*$P < 0.05$.

TABLE 2

Transplant Outcomes

	Under 60 group ($n = 86$)	Over 60 group ($n = 45$)
Length of stay in days, median (range)	5 (4–6)	7 (5–10)
Incidence of DGF, n (%)*	10 (12)	14 (31)
Standard criteria donor	4 (5)	5 (11)
Extended criteria donor	1 (1)	2 (4)
Donation after cardiac death	5 (6)	7 (16)
Acute rejection at 1 year (%)	8%	11%
Infections, n	7	7
Cytomegalovirus disease	2	1
Pneumonia	4	5
BK virus nephropathy	1	1
Neoplasms, n (%)	3 (3%)	1 (2%)

Range = 25th, 75th interquartile range.
*$P < 0.05$.

portends superior outcomes over dialysis as treatment for end stage renal disease regardless of the age or donor type [2–5]. These studies report improved patient survival at 1, 3, and 5 y in patients older than 60 y treated with kidney transplantation compared with those remaining on dialysis [2–5].

Prior studies have shown that patient survival at 1, 5, and 10 y after transplantation is significantly lower in patients older than 60 y compared with those under 60 y [2, 6, 7]. Several authors have proposed that such results stem from the higher presence of comorbidities and subsequent higher mortality rate of elderly patients [2, 6, 7]. In our analysis, we also observed a higher incidence of early mortality in the Over 60 group. However, when we analyzed patient survival beyond 1 y post-transplant, since this is the methodology used to determine the true half life of the allograft, the mortality was similar between the two groups.

Likewise, the actuarial graft survival was not significantly different between the two groups in our study, which is similar to previous analyses [2, 6, 7]. Moreover, our recipients represent a high risk population consisting of a majority of African American patients with elevated panel reactive antibodies.

Death-censored graft survival was also not statistically different between both age groups, similar to that reported in other publications [2, 6–9]. This takes into account the fact that older recipients have a higher proportion of deaths with a functioning graft compared with recipients under the age of 60 [6–9]. In fact, death is the leading cause of graft loss in older renal transplant recipients.

While we found that the incidence of acute rejection at 1 y was higher in the Over 60 group, this was not statistically significant. Other studies have also failed to demonstrate statistically significant differences in the incidence of acute rejection between younger and older recipients both in Europe [10–12] and in the United States [6, 13]. Nonetheless, other authors have reported that elderly patients may have a lower risk of acute rejection compared with younger recipients [14, 15], a phenomenon supported by some data suggesting that metabolism of immunosuppressive medications may be altered with increased age [16]. Further studies must be conducted to clarify if acute rejection rates are truly lower in recipients older than 60 y of age compared with younger recipients before recommendations regarding immunosuppression intensity in this population are modified.

In our analysis, the incidence of delayed graft function (DGF) was higher in the Over 60 group compared with the Under 60 group. It has been suggested that donor factors that may increase the likelihood of DGF are

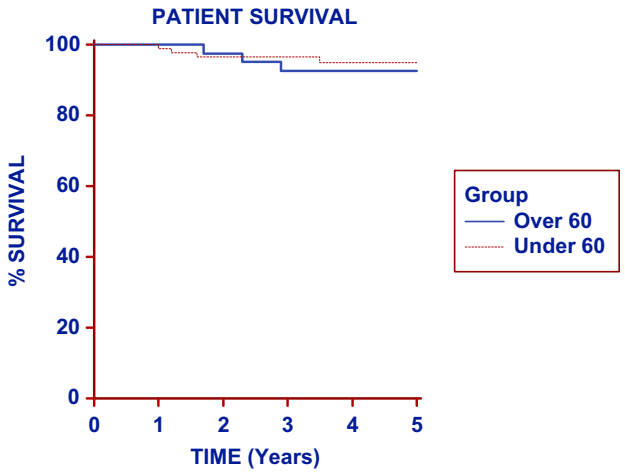

FIG. 1. Kaplan-Meier analysis of patient survival beyond 1 y according to age. Over 60 group (continuous line, $n = 45$) and Under 60 group (dashed line, $n = 86$). Hazard ratio, 1.59; 95% CI (0.33–8); $P = 0.54$. (Color version of figure is available online.)

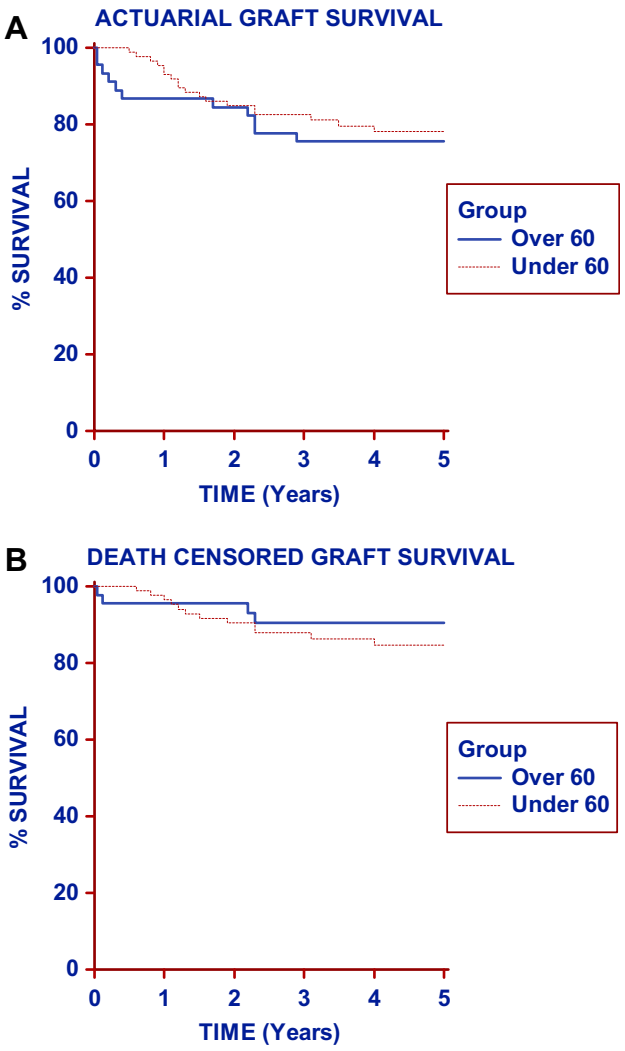

FIG. 2. (A) Kaplan-Meier analysis of actuarial graft survival according to age. Over 60 group (continuous line, $n = 45$) and Under 60 group (dashed line, $n = 86$). Hazard ratio, 1.26; 95% CI (0.58–2.76); $P = 0.55$. (B) Kaplan-Meier analysis of death censored graft survival according to age. Over 60 group (continuous line, $n = 45$) and Under 60 group (dashed line, $n = 86$). Hazard ratio, 0.68; 95% CI (0.25–2.00); $P = 0.51$. (Color version of figure is available online.)

increased age, hypertension (>10 y), creatinine clearance <80 mL/min, vascular sclerosis, increased weight, female gender, and atraumatic death [17]. In our study, while older recipients received a larger proportion of ECD donors (defined as donors older than 60 y of age or aged 50 to 59 y with two of the following three conditions: hypertension, cerebrovascular accident as cause of death, or terminal serum creatinine level >1.5 mg/dL) and DCD organs, the factor that had the most impact on DGF in both groups was African American ethnicity and DCD donation. This study, while small, was an attempt to further clarify data that suggested that DGF rates increased with the age of recipients who received ECD organs, but were similar in recipients who received standard criteria donor organs and organs from a living donor source [6]. Our data suggest that independent of age, factors such as DCD donation and African American ethnicity also had a significant impact on DGF rates. While our data took into account donor age, other donor characteristics, such as warm ischemia time and donor medical histories were not analyzed, and this data set may warrant further investigation.

In our study, most patients in both age groups received induction therapy with basiliximab (a monoclonal antibody directed against the IL-2 receptor on activated T cells) , 81 patients in the Under 60 group (94%) and 39 patients (87%) in the Over 60 group. The remainder received antithymocyte globulin, which is a lymphocyte depleting polyclonal antibody directed against multiple immunologic epitopes. The results of a prospective, randomized, international study comparing induction therapy with either basiliximab or thymoglobulin in renal transplant recipients at high risk for acute rejection or delayed graft function demonstrated similar efficacy with respect to the incidence of graft and patient survival as well as delayed graft function. However, the incidence of acute rejection was higher in the basiliximab group compared with the thymoglobulin group [18]. These data support the use of either agent as an appropriate intervention in high risk renal transplant recipients.

In spite of the potential increased risk for DGF, kidney transplantation with ECD and DCD organs have been shown to result in better outcomes for older recipients than remaining on dialysis and, therefore, represent an important source of organs for transplantation in the elderly [2]. The rise in the use of expanded criteria donor organs and organs retrieved after cardiac death has led to a significant increase in the proportion of

elderly patients with ESRD receiving a kidney transplant in recent times [2]. It is noteworthy that recent studies have shown that benefits of ECD transplantation compared with remaining on dialysis waiting for a standard criteria donor kidney are not present in some subgroups of recipients, for example, patients younger than 40 years [19, 20].

The incidence of hospitalizations and deaths due to infections after transplantation increases with age of the recipient [1, 21, 22]. Cytomegalovirus infection and bacterial pneumonia have been documented as the most common causes of these infectious complications [1, 21, 22]. Similarly, the incidence of neoplasm after transplantation has been shown to be higher in elderly recipients [23]. In our study, no significant difference was found between the two groups regarding infection and neoplasm. However, conclusions cannot be extracted from these results due to the low frequency of both outcomes as well as the relative low number of subjects in our study.

While some studies, including ours, have suggested that recipient age is not an independent factor for worse graft survival, it is a fact that older recipients will die, usually of cardiovascular disease, with a functioning graft [2, 8]. Utilitarianism suggests that allocating a kidney to an older recipient is not the most appropriate use for such a scarce resource. In an attempt to optimize the deceased donor kidney allocation system, the Organ Procurement and Transplantation Network Kidney Committee and the Scientific Registry of Transplant Recipients developed the concept of Life Years from Transplant (LYFT), defined as the difference in the expected median survival for a candidate with a kidney transplant from a specific donor and the expected median survival of the same recipient remaining on dialysis. The committee proposed that prioritizing candidates with higher LYFT scores for each kidney that becomes available could increase the average years of life of a transplant [24]. Nonetheless, this system could discriminate against older recipients since they will always have lower LYFT scores compared with younger candidates. A compromise plan integrating the LYFT score and donor risk index is being developed [25].

Several ethical issues regarding the optimal utilization of the scarce number of organs available are still a matter of debate. However, we conclude that because of the similar graft survival and positive transplant outcomes seen in elderly patients compared with those younger than 60 y, the age of the recipient should not be an independent factor that excludes older patients from being offered the option of kidney transplantation. The presence of comorbidities should be the only clinical criterion for exclusion as kidney transplant candidates in this group of patients.

CONCLUSION

In our experience, long-term transplant outcomes in older, high risk renal transplant recipients are similar to those of younger high risk recipients. Older recipients' age as well as high-risk characteristics, such as African American ethnicity and increased sensitization, should not be a contraindication to renal transplantation.

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