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Exponentially increased risk of infectious death in older renal transplant recipients

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Background. The benefit of renal transplantation for patients with end-stage renal disease (ESRD) has been well documented. This benefit is seen throughout all age ranges of patients. However, it has been documented that older renal transplant recipients are at increased risk for death because of infectious causes when compared with younger recipients. The present study addresses whether this increased risk merely parallels an age-related increase in infectious mortality or is reflective of a particular vulnerability in older renal transplant recipients.

Methods. Patients wait-listed and transplanted between 1988 and 1997 were analyzed utilizing the United States Renal Data System (USRDS) database. The primary study end point was patient death secondary to infection. Secondary end points included death secondary to cardiovascular cause and malignancy. Cox-proportional hazard models were utilized with all pertinent variables.

Results. Death related to infectious cause increased exponentially in transplanted patients with increasing age (slope = $2.9^{0.34x}$), while it increased linearly (slope = $1.9x + 8.6$) with increasing age for those patients on the waiting list. Overall mortality increases with age were equal between the wait-listed and transplanted groups.

Conclusions. The overall survival benefit of transplantation is maintained in the older age groups. However, renal transplantation is associated with an increased risk for infectious death beyond the expected age-related increased risk in patients on the renal transplant waiting list. This may have an impact on future immunosuppressive regimens in this population.

The benefit of renal transplantation for patients with end-stage renal disease (ESRD) has been well documented [1–4]. One recent study demonstrated a mortality benefit for patients receiving a renal transplant versus patients who remained on the waiting list [5]. This benefit was seen at all ages of patients; however, it was noted that in older renal transplant patients, the relative benefit appeared to be decreased when compared with younger patients. Other studies have confirmed the survival benefit of renal transplantation in the older ESRD patients [6, 7].

However, a recent multivariate analysis has indicated that older renal transplant recipients were at a considerably increased risk for death by infectious cause compared with younger patients [8]. This study did not look at wait-listed patients, and thus, the authors were unable to determine whether this was due to a normal age-related risk or was exacerbated by the addition of immunosuppression. In support of the concept that older renal transplant patients may be at increased risk of immunosuppression, a single center study noted an increase in serious infections in older patients who received a more intensive immunosuppressive regimen as compared with older patients who received a less intensive regimen [9].

The data mentioned previously in this article indicate that older renal transplant recipients have an increased risk of death secondary to infection as compared with younger renal transplant recipients. However, these previous studies do not address whether this increase in death by infection is merely reflective of an age-related trend in all patients with ESRD or a specific deleterious effect of post-transplant immunosuppression.

METHODS

To compare the risk for infection-related mortality in patients on the waiting list and after primary solitary renal transplantation across age groups, we analyzed patients registered as either transplanted or wait-listed in the U.S. Renal Data System (USRDS) database between 1988 and 1997. The data for the analysis were provided by the U.S. Renal Transplant Scientific Registry and were supplemented with ESRD data from the USRDS. Patients were followed from transplant date until death or the study end date of June 30, 1998. The wait-listed cohort of patients included only patients that had been wait-listed but had not undergone transplantation at the latest

Key words: mortality, infection, age, survival, transplantation, end-stage renal disease, chronic renal disease, kidney failure, immunosuppression.

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Table 1. Demographic characteristics

	Transplanted	Wait listed (never transplanted)
Age *years*	43.6 ± 12.7	48.3 ± 12.5
Gender *male/female*	60%/40%	57.2%/42.8%
Race *Caucasian/AA/other*	70.7%/22.7%/6.5%	54.5%/37.1%/8.3%
Cause of ESRD		
Glomerulonephritis	22.9%	18.7%
Hypertension	17.3%	22.7%
Diabetes	26.4%	35.1%
Polycystic	5.4%	2.3%

Abbreviations are: AA, African American; ESRD, end-stage renal disease; Polycystic; polycystic kidney disease.

follow-up. The primary study endpoint was patient death secondary to infectious cause. Secondary study endpoints were patient death, death secondary to cardiovascular cause, and death secondary to malignancy. We used Cox proportional hazard models to estimate the impact of age on the risk for patient death in patients on the waiting list as compared with transplanted patients. The Cox proportional hazard models were adjusted for age, race, gender, and cause of ESRD. Age was used as a categorized variable as follows: 18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 64, and more than 64 years. We calculated annual adjusted mortality rates per 1000 patients by age group for patients on the transplant waiting list and transplanted patients. To get a cross-sectional representation of the data, we plotted the adjusted mortality rates by age group as an X-Y scatter. We determined the best fitting curve of the resulting scatter for transplanted and wait-listed patients to obtain an estimate of the rate of increased mortality across age groups via the shape and slope of the best fitting curve. The curve fit was estimated by R^2. Multiple curve estimation procedures (quadratic, cubic, exponential, power, inverse, s, log), were used to determine the best fit between age and adjusted mortality rates.

A probability of type 1 error $P = 0.05$ was considered to be the threshold of statistical significance. For multiple comparisons, the threshold of statistical significance was corrected by the Bonferroni adjustment. All statistical analyses were performed using SPSS software (version 7.0 for Windows 95; SPSS, Inc., Chicago, IL, USA).

RESULTS

The demographic characteristics of the patients on the waiting list at time of wait listing and for and the transplanted patients at the time of transplant are displayed in Table 1.

Figure 1 displays the annual adjusted mortality rates per 1000 patients by age group in wait-listed patients as compared with transplanted patients. The best curve fit of the risk of death across age groups for wait-listed patients as compared with transplanted patients ($R^2 = 0.99$ and 0.95, respectively) was described by a linear relationship. In addition, the slope of the increase was almost identical among the two study groups, 18.4 and 17.6 for wait-listed and transplanted patients, respectively.

Figure 2 displays the cross-sectional increase of the risk for cardiovascular death by age group. As displayed in the figure, the best curve fit was obtained by a linear equation ($R^2 = 0.99$ and 0.96 for wait-listed and transplanted patients, respectively). The slope for transplanted patients was almost half (6.1) as compared with the slope for wait-listed patients (11.5).

Figure 3 shows that the best fit for the adjusted infectious death rates by age group was exponential in the transplanted patients ($R^2 = 0.99$) as opposed to linear ($R^2 = 0.96$) in the wait-listed patients.

Figure 4 displays the annual adjusted malignancy-related mortality rates per 1000 patients by age group in wait-listed patients as compared with transplanted patients. The best curve fit of the risk of death across age groups for wait-listed patients as compared with transplanted patients ($R^2 = 0.96$ and 0.95, respectively) was described by a linear relationship. In addition, the slope of the increase was higher for transplanted patients as opposed to wait-listed patients (1.5 vs. 1.1, respectively).

DISCUSSION

Our study demonstrates that the risk of dying of an infectious cause is increased exponentially in older renal transplant recipients as compared with younger recipients. In contrast, in patients on the waiting list, the risk of dying of an infection increases only linearly with advancing patient age. Thus, with age, the risk of dying of an infection increases in older transplant recipients to a much greater degree than in patients on the waiting list.

The most obvious reason for this would be an increased susceptibility to the immunosuppressive effects of antirejection medication. A large literature regarding humans documents changes in immune function with age and increased susceptibility to infections [10–19]. Thus, it seems plausible that immunosuppression, which is well-tolerated in younger patients, may have more negative effects in older patients. Our data indicate that the increased risk of dying of an infection in older renal transplant patients is not only a function of the general trend toward more infectious vulnerability in older patients, but likely is also secondary to a specifically transplant-related problem, that is, vulnerability of older patients to immunosuppression.

Cardiovascular disease is the most frequent cause of death in older patients. The fact that the overall mortality advantages of renal transplantation are maintained in older recipients makes it likely that the cardiovascular benefit is also maintained. Our analysis supports that

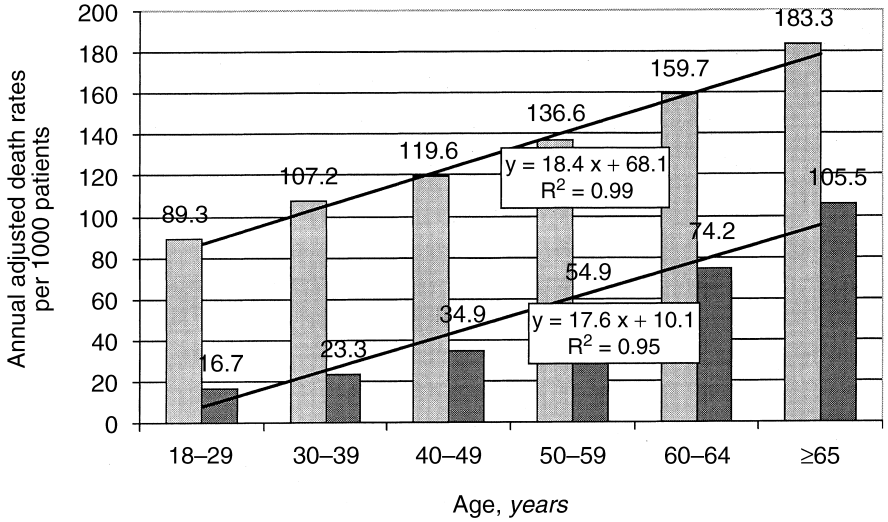

Fig. 1. Mortality in wait-listed (▒) and transplant patients (■). Annual adjusted death rates are per 1000 patients.

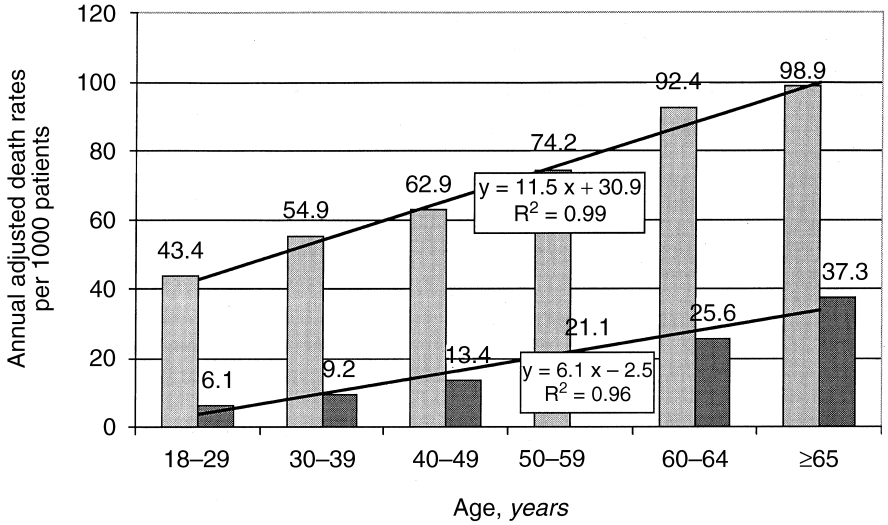

Fig. 2. Mortality secondary to cardiovascular disease in wait-listed (▒) and transplant patients (■). Annual adjusted death rates are per 1000 patients.

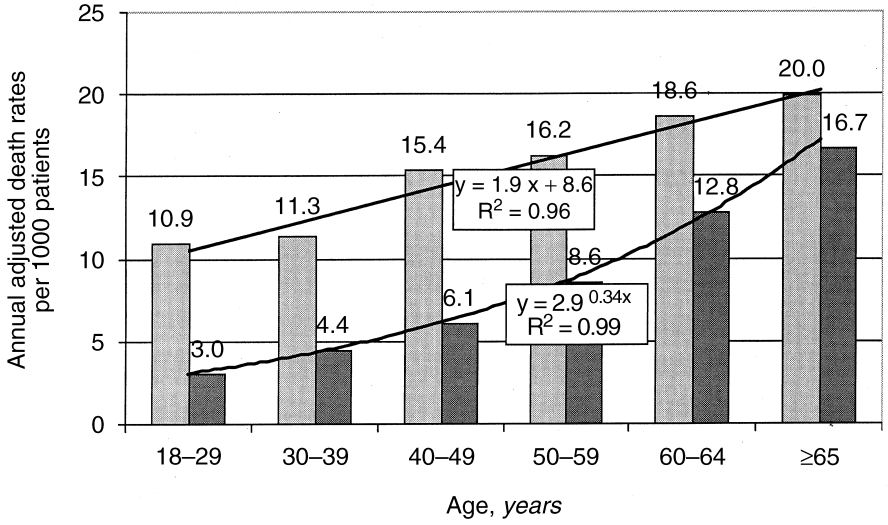

Fig. 3. Mortality secondary to infectious disease in wait-listed (▒) and transplant patients (■). Annual adjusted death rates are per 1000 patients.

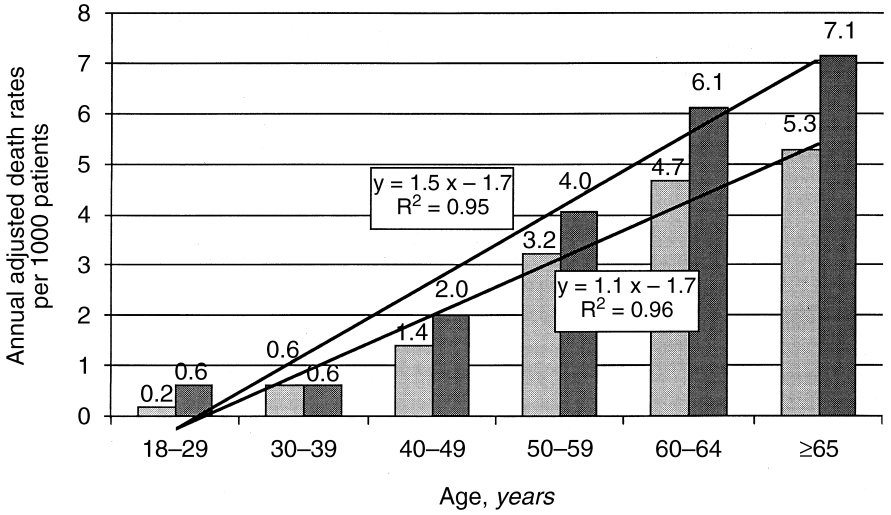

Fig. 4. Mortality secondary to malignancy in wait-listed (□) and transplant patients (■). Annual adjusted death rates are per 1000 patients.

hypothesis. In addition, we found that the slope of the age-related mortality secondary to cardiovascular disease is almost twice as steep in patients on the waiting list compared with transplanted patients. This suggests that with advancing age, patients have an increased benefit in terms of cardiovascular mortality from transplantation. It is possible that this increasing benefit with age in part reflects a selection bias of patients who ultimately receive a transplant as opposed to remaining on the waiting list. However, it is doubtful that this would explain the full effect observed.

It is intuitive that there is no advantage in transplantation for malignancy-related mortality. In fact, our data show a slight overall increase in malignancy-related death rates in patients who underwent transplantation. The slope of the age-related increase in mortality secondary to malignancies is steeper in transplanted patients as compared with patients remaining on the waiting list. This finding suggests that similar to infectious death, the decreased immune function in the older population might make these patients more susceptible to the effects of immunosuppression and the incidence of malignancies.

In terms of overall mortality, our study reinforces previous studies demonstrating that renal transplantation confers a survival advantage over maintenance dialysis for patients with ESRD [5]. Our study demonstrates, as do previous studies, that this survival advantage holds true even in older renal transplant recipients [1, 5–7, 20]. In addition, this study documents that the degree of benefit of transplant versus dialysis for overall mortality is maintained in older renal transplant recipients. By careful slope analysis, the rate of protection remains constant throughout all age groups.

In summary, the risk of death by infectious cause is increased by renal transplantation in older patients. This risk increases exponentially (as opposed to linearly in wait-listed patients) with age, and represents an increased risk secondary to transplantation and more specifically to poorer tolerance to immunosuppression.

On the other hand, the overall mortality benefit of renal transplantation (including the immunosuppressive medications used) versus wait list is maintained in older age groups. Both overall mortality and cardiovascular mortality increase in both wait-listed and transplanted patients with age, but the degree of increase (that is, slope) is not greater in transplant patients.

Our study indicates that the benefits of renal transplantation are maintained in older patients; however, the poorer tolerance of these patients to infectious sequelae of immunosuppression deserves more focused attention.

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