

# The elderly as recipients of living donor kidneys, how old is too old?

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**Current Opinion in Organ Transplantation** 2011, 16:250–255

## Purpose of review

Transplantation of the elderly often invokes strong and sometimes passionate arguments both in support and in opposition. Age alone has not been an absolute contraindication to a life-sustaining organ transplant for several decades.

A comprehensive evaluation of the risks associated with surgery and suppression of the immune system in this often comorbid population becomes the focus. Risk for the recipient, however, must continually be evaluated and frequently updated in the context of that for the donor.

## Recent findings

Following careful and critical evaluation, elderly patients appreciate the increase in life expectancy and improvements in quality of life as demonstrated in their younger counterparts. The outcome of recipients receiving kidneys from living donors has demonstrated superior graft and patient survival compared to deceased donors. Careful monitoring of medication levels for prevention of rejection while avoiding over immunosuppression and infection is critical to ensure such benefit.

## Summary

Transplantation of the elderly via living donation is not only justified but in the appropriately chosen patient, with informed consent of both donor and recipient, is ethically sound. The expectations of both parties must be clearly stated and donor safety must remain the top priority. Living donors must be fully cognizant of the potential risk both in patient and graft survival prior to making such a life-changing decision to donate.

## Keywords

elderly, kidney, living donor, transplant

Curr Opin Organ Transplant 16:250–255  
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1087-2418

## Introduction

The need for a kidney transplant among the population 65 years of age and older is growing. The percentage of individuals 65 years of age and older on the kidney transplant waiting list has increased from 9.6% in 1999 to 16.7% in 2008. The number of new registrants 65 years of age and older has likewise increased from 9.2% of total new registrants in 1999 to 15.3% in 2008 [1]. Added to that, the median age of end-stage renal disease (ESRD) stands at 64.2 years of age as of 2008 [2]. As a result, a more specific strategy is needed for ESRD care for those 65 years and older.

As exemplified by the increased age of the ESRD population, the overall population is aging. According to the US Census Bureau, from 2000 to 2050 the number of individuals aged 65–84 years will increase by 35 million (114%), and the number of individuals 85 years of age and older will increase by 16.6 million (389%) [3]. As recent

peer-reviewed publications have recommended that transplant candidacy be based on biologic age rather than chronologic age, investigators have remained optimistic in regards to transplant opportunities for a group that was once viewed as ‘high risk’ merely based upon year of birth [4,5].

Mortality rates for individuals on dialysis 65 years of age and older are nearly seven times higher than those in the general population [2]. Yet again, transplant improves the cumulative survival of these patients over dialysis as shown by Wolfe *et al.* [6] who conducted a longitudinal study of mortality in 228 552 individuals who were receiving long-term dialysis for ESRD. Individuals 60–74 years of age who received a transplant saw improvement in their cumulative survival rate 1 year post transplant compared to those listed for transplantation alone, with a 4-year projected increase in life span and 61% decrease in the long-term risk of death. Mortality rates of 23.2 deaths per 100 patient-years if left on dialysis decreased to

7.4 deaths per 100 patient-years following transplantation [6]. As organ transplantation is and should continue to be viewed as a gift, efforts to optimize modifiable risk factors including body mass index reduction, smoking cessation and an exercise program are essential for the elderly awaiting transplantation in an effort to ensure that outcomes are optimized [7,8].

Beyond increases in life expectancy, renal transplantation recipients report improved quality of life, including physical and social functioning, mental stability and well being, and global perspective on their future [9–11]. In a study by Cornella and colleagues [12], 81 elderly recipients (>60 years and older) of renal transplants reported improvements in physical functioning (objective physical activity) and mental health (emotional status) on nationally standardized SF-36 questionnaires. These results were found to be equivalent to national age and sex-appropriate norms. It should be appreciated that these results were reported despite a significantly reported incidence of surgical and posttransplant medical complications [12].

### Part 1: inequalities in access to transplantation for older recipients

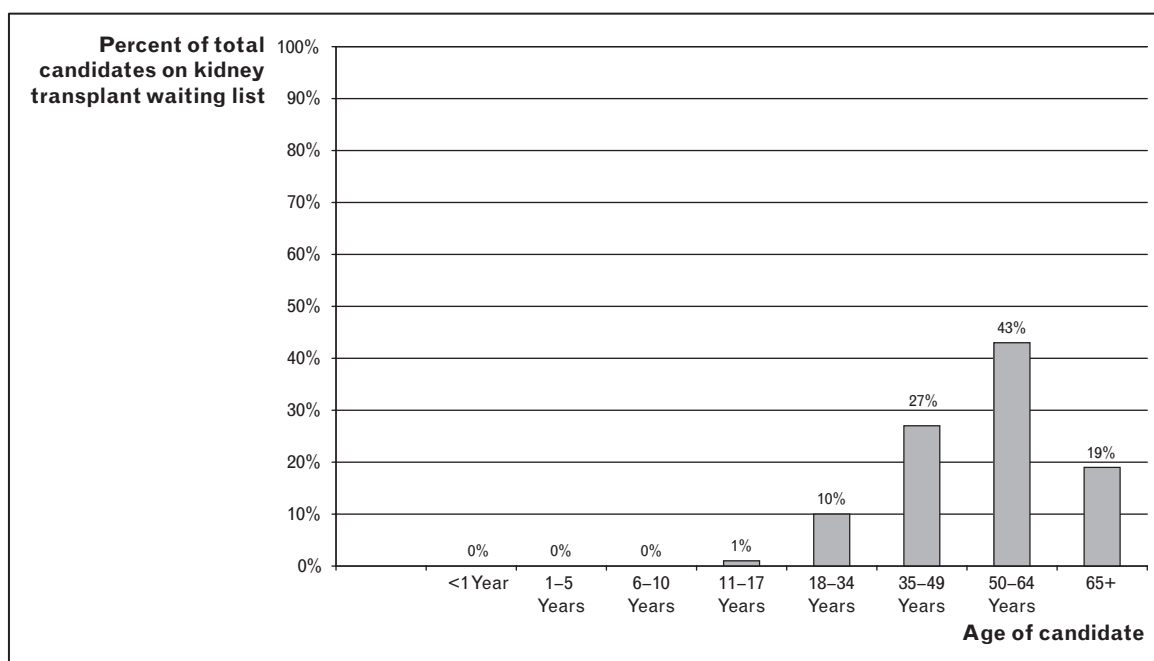
Individuals in the USA who are 65 years of age and older made up 16.7% of the active waiting list for kidney transplant at the end of 2008 (Fig. 1), but only 16.3%

#### Key points

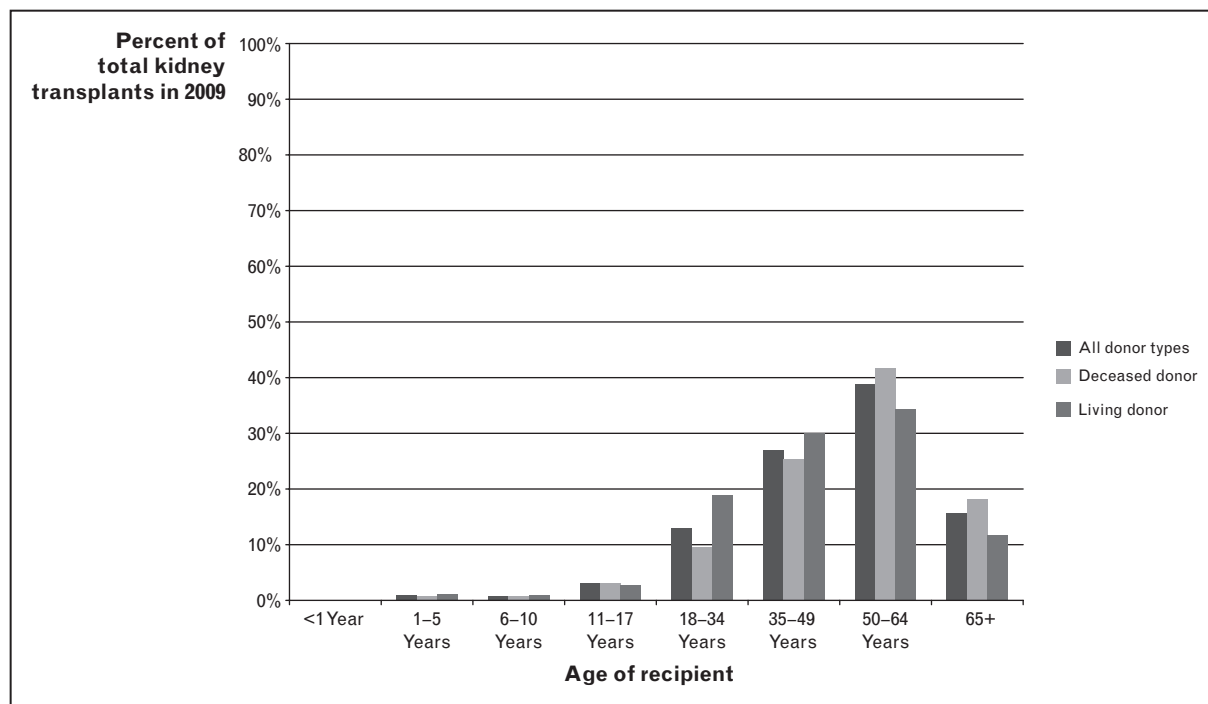
- As the population is aging, increasing numbers of elderly individuals are developing ESRD of whom, many would benefit from kidney transplantation.
- Older recipients demonstrate improved patient and graft survival following transplantation with living donors.
- A careful evaluation of the comorbidities of this group is mandatory to justify the risks of live organ donation.
- Expectations of both the donor and the recipient must be clearly communicated in order to achieve appropriate goals.

of the transplants for 2008. With respect to the source of transplant, individuals 65 years of age and older receive 18% of deceased donor kidneys but only 12% of living donor kidneys for that same year (Fig. 2) [13]. The number of kidney transplants for individuals in the USA who are 65 years of age and older is growing, but to the greatest degree among deceased expanded criteria donor (ECD) kidneys with an increase from 16.4% (203 of 1235 total deceased ECD kidneys) in 1999 to 35.7% (683 of 1912 total deceased ECD kidneys) in 2008. At the same time, the numbers for deceased standard criteria donor (SCD) kidneys increased from 7.7% (525 of 6808 total deceased SCD kidneys) in 1999 to 13.7% (1181 of 8639 total deceased SCD kidneys) in 2008. Interestingly,

**Figure 1** Kidney transplant waiting list



Current OPTN/UNOS data reflecting the percentage of patients listed for kidney transplantation based upon age group. Source: Based on OPTN data as of December 10, 2010.

**Figure 2 Donor sources based upon age group**

Current OPTN/UNOS data reflecting the distribution and source of kidney transplants performed based upon age group. Source: Based on OPTN data as of December 10, 2010.

the numbers for living donor kidneys transplanted in the elderly increased proportionally from 4.7% (222 of 4718 total living donor kidneys) in 1999 to 11.0% (655 of 5966 total living donor kidneys) in 2008. The unadjusted graft survival for this living donor cohort was 95.6 and 73.7% at 1 and 5 years, respectively [1].

This is not uniquely a US phenomenon. In the UK, individuals 60–69 years of age make up 24% of active transplant list patients, but only 13% of transplant recipients. For those 70 years and older, they make up 7% of the waiting list but only 5% of transplant recipients [14].

Misconceptions regarding the criteria for transplantation often impede early referral to a transplant center resulting in a disproportionate time of the elderly on dialysis. Although individuals with chronic kidney disease (CKD) are encouraged to be referred to a transplant center upon reaching stage 4 CKD or prior to the initiation of dialysis, a number of impediments, both real and perceived, prevent many from preemptive transplantation [15,16,17]. Although increases in the numbers of preemptive transplants have been demonstrated across all age groups from 1995 to 2009, the elderly represent both the smallest percentage increase over this time period and the smallest percentage over each calendar year [13].

## Part 2: outcomes for older individuals with deceased donor transplants

The majority of experience with transplantation of the elderly lies in deceased donation again, in part, demonstrating a selection bias. In a recently published review of OPTN/UNOS data for the 41 090 recipients transplanted between 2004 and 2006, Gore and colleagues [18] demonstrated in a multivariate model, holding all other covariates constant, increasing age was associated with a dramatic increase in the odds of deceased donor transplants (DDTs). Practitioners and patients are often uncertain and/or uncomfortable with the risks of living donation for many over the age of 65. The elderly have an increased risk of cardiovascular events, infections, and malignancy as well as experience significant and more frequent episodes of drug toxicity and medication side effects than younger patients [19,20]. Elderly recipients are more often offered and more likely to accept ECD kidneys [21,22]. Further, policy development in kidney allocation looking to maximize life years gained following transplantation of deceased donors has incorporated 'old for old' strategies. However, the elderly may be at a greater risk of complications and death following transplantation of ECD kidneys due to increased morbidity prior to surgery and poor functional reserve compared with their younger counterparts [9,10,19,20,21,22]. Death with a functioning graft becomes a major cause of graft loss in this cohort.

In a retrospective review of almost 3000 patients enrolled in the Neoral Multinational Observational Study in Transplantation (Neoral-MOST), Salvadori and colleagues [23] examined several highly relevant parameters from univariate analysis on both 1- and 5-year glomerular filtration rate (GFR) and found the most relevant risk factors which were significantly associated with GFR below 65 ml/min were advanced donor age and recipient ages above 60 years. Recipient selection and a careful evaluation and work-up of comorbidities, therefore, are imperative. Wu and colleagues [24] examined the effect of donor and recipient demographics on graft outcomes in elderly recipients. Utilizing the Charlson comorbidity index (CCI) score and establishing a cut-off of age 60, investigators determined baseline comorbidity was a significant predictor of patient survival in all recipients. When looking at deceased donors specifically, increasing numbers of comorbid conditions of elderly recipients was a significant predictor of patient survival not seen in recipients of living donors [24]. Building on this premise, investigators in Toronto using data from the Canadian Organ Replacement Registry developed a series of tables used to predict survival probability based upon the CCI and donor source. Elderly recipients (65 years and older) of DDT demonstrated statistically significant reductions in 1-, 3-, and 5-year graft survival (78.6 vs. 64.7%) compared with those recipients of living donor transplants. Both groups compared demonstrated moderate yet similar comorbidity scores and demographics [25].

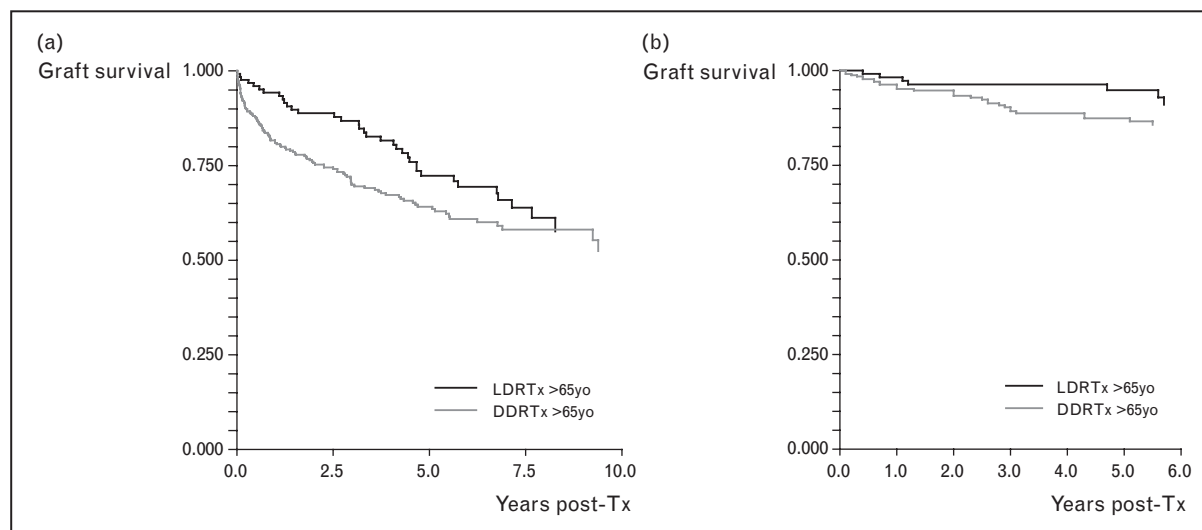
Investigators in Norway recapitulated the above while also highlighting the deleterious effect of time of dialysis or early acute rejection episodes on survival of the elderly following kidney transplantation. Kaplan–Meier analysis showed a significantly lower death-censored 5-year graft survival in the elderly on dialysis more than 12 months vs. those transplanted preemptively or on dialysis less than 12 months (94 vs. 83%;  $P=0.001$ ). Similarly, actuarial 5-year patient survival was significantly higher (60 vs. 44%;  $P=0.021$ ) in elderly recipients with dialysis less than 12 months. Overall, median survival was 5.3 years in the elderly compared with 17.1 years in the control ( $P<0.001$ ). Thirty-one (9%) people in the elderly group died during the first 3 months following transplantation of which almost half (42%) were secondary to infection perhaps secondary to the treatment for early rejection found in this group. Whereas younger recipients lose grafts secondary to rejection, the elderly lose their lives due to complications of the treatment for rejection. In contrast to what has been shown in studies of younger recipients, neither diabetes mellitus nor ischemic heart disease at transplantation had a survival effect on the elderly [26\*].

### Part 3: outcomes for older individuals with living donor renal transplants

In an analysis of the OPTN/UNOS database by Gore and colleagues [18], investigators looked to discern the inequities in the utilization of living donor renal transplants (LDRTs). The review of 41 090 patients in multivariate analysis examined recipient, center, and UNOS region-specific covariates and found older recipients [odds ratio (OR) 0.62, 95% confidence interval (CI) 0.56–0.68] to be the strongest predictor for patients to receive DDT vs. LDRT followed by African-American ethnicity and lower socioeconomic status [18].

Sener and colleagues [27\*] reported their outcomes in 126 LDRT in patients 65 years of age and older over a 15-year period (1992–2007). Compared with recipients under age 65, older recipients of LDRT had older living donors (42 vs. 38 years;  $P<0.01$ ), were more often White, had a higher rate/length of pretransplant dialysis, had similar rates of rejection, and suffered more death with a functioning graft. Kaplan–Meier survival estimates demonstrated differences in overall LDRT graft survival between groups at 1 and 3 years, with the most disparate at 5 years (83.6 vs. 72.3%). Interestingly, the group identified a subset of recipients over the age of 75 ( $n=60$ ). This group, not surprisingly, demonstrated the worst overall survival with 5-year uncensored graft survival of 57.7%. Subgroup analysis of death-censored graft survival in these 60 patients had lower rates of graft survival ( $P=0.01$ ). Comparisons with elderly DDT, however, showed that living donor recipients had superior graft survival both uncensored ( $P=0.04$ ) and death-censored ( $P=0.05$ ). (Fig. 3) Importantly, a multivariate analysis of graft failure for LDRT (including all patients) found recipient age groups of 65–69 years (hazard ratio 1.74) and more than 75 years (hazard ratio 10.3) along with re-transplant (hazard ratio 2.25) to be the most significant variables [27\*].

Additional analysis of UNOS data by Gill *et al.* [28] demonstrated the survival benefit of LDRT in the elderly. Investigators divided recipients into four groups based upon donor source – living donors above 55 years or old living donors (OLD), living donors 55 years or less or young living donors (YLD), SCD, and ECD. Of the 7006 elderly patients that received LDRT, 16.2% received OLD vs. YLD. 12 197 were transplanted with SCD and another 4551 with ECD. Early outcomes were best with YLD, followed by similar outcomes for both OLD and SCD. OLD transplants were found to have inferior 3-year graft survival rates (83.4 vs. 85.7%;  $P=NS$ ) but similar 3-year patient survival rates (87.4 vs. 88.4%;  $P=NS$ ) compared with YLD. OLD had superior graft survival compared with all deceased donor options. ECD was associated with a greater risk of graft loss compared with

**Figure 3 Outcomes of geriatric transplant recipients**

Comparison of graft survival (a, on left) and death-censored graft survival (b, on right) in geriatric patients who received deceased donor renal transplants (DDRTx) and living donor renal transplants (LDRTx). Source: Sener A, Schweitzer E, Munivenkatappa R, *et al.* Deceased donor renal transplantation in the geriatric population demonstrates equal graft survival compared with younger recipients. *Transplantation* 2009; 87:1549–1554.

OLD (hazard ratio 2.36, 95% CI 1.18–4.74) [28]. These data demonstrate a clear survival advantage for the elderly via LDRT despite the age of the donor who has been found to be medically and psychosocially suitable for donation.

As more supportive data for LDRT continues to be published for all age groups, greater numbers of preemptive LDRTs have been recognized. This situation is particularly true in the elderly. As the overall percentage of LDRTs performed in a preemptive fashion has increased from 22.13 to 32.52% from 1995 to 2009, the greatest percentage increase has been seen in the above 65 years age group from 14.29 to 34.79% [13].

Whereas older patients with renal failure may have a higher risk for functional independence following transplantation compared with a younger cohort, the potential for independence in this age group increases with transplantation compared with dialysis. The standard evaluative work-up, however, has remained heavily focused upon cardiovascular risk and malignancy screening [29]. These foci notwithstanding, more clinicians have called for a more thorough and exhaustive evaluation of not only the medical clearance of the elderly prior to listing but also a broader interpretation of the physical function of this cohort prior to the surgical procedure to more comfortably assume the risks of transplantation and live organ donation. Hartman and colleagues [30\*\*] evaluated elderly (over 60 years) renal transplant candidates listed at Wake Forest University Hospital and tested physical performance utilizing two validated tools to assess mobility and disability as an indicator for both early and long-term outcomes

following transplantation. This group was compared with other 'high-risk' groups with heart failure, chronic obstructive pulmonary disease, or high risk for cardiovascular disease. Their results demonstrated that elderly patients with ESRD are comparatively more impaired than what has typically been considered the groups most vulnerable for complications and long-term morbidity following stress such as would be expected following transplantation and immunosuppression. The authors call for more refined tools and testing to better identify those elderly patients seeking transplantation that would justify the risks of LDRT [30\*\*].

Ongoing debate regarding the ethical issues of live organ donation to recipients at the extremes of age ( $\geq 75$  years) reaches no strong conclusion. Opponents state statistical arguments of few life-years gained vs. the small but measurable risk of surgery to a healthy donor, whereas advocates cite the improved lifestyle for both the recipient in this age group and his/her support system (i.e. spouses) for an uncertain yet priceless post-transplant time period. Suffice to say, transplant professionals have an obligation to protect the safety and integrity of organ donation and transplantation. The guiding principles of full disclosure and informed consent are, perhaps, most relevant and hold all involved to a higher standard and understanding.

## Conclusion

Patients aged 60 years and older represent the fastest growing population with ESRD worldwide. This situation is due, in part, to healthier lifestyles, improved

nutrition, and better access to medical care. Data have perpetually shown that all patients regardless of age fair better following kidney transplantation both in terms of survival benefit and overall quality of life measures compared to dialysis. Whereas discussions regarding the utilization of a valuable resource in deceased donor transplantation have shifted to potential life years gained for each donor and each recipient, there still exist both ethical and practical questions regarding living organ donation to the elderly. Certainly, donor safety remains paramount. With potential changes in OPTN/UNOS policy for allocation of deceased donors one would predict that an increasing number of kidney transplants in the elderly would be the result of more interested and viable living donors. To that end, expectations must be clearly defined and data must be clarified to all parties as the need for informed consent both for the potential donor and recipient is absolute.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 267–268).

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