Patient selection and immunosuppression

The challenges for elderly transplant start at the very first step. Patient selection is a very important aspect of transplant in elderly, as many factors have to be taken into consideration. Graft loss in the elderly is related commonly to patient death, and therefore the expected patient survival is crucial so as not to lose graft years, especially from a living donor. The two main causes of morbidity and mortality following transplantation are cardiovascular disease and infection. Cardiovascular disease is predominant in the elderly, with the median age at diagnosis of ESRD in the United Kingdom being 64.9 years [1]. In the USA, the number of waitlisted patients aged over 65 years increased from 7% in 1997 [3] to >15% in 2009 [5]. With increasing numbers of elderly patients with ESRD, it has become increasingly important that we are well aware of the available treatment options and the relative risk to benefit profile of each. Dialysis (Peritoneal dialysis or Hemodialysis) and renal transplant are the principal renal replacement therapy modalities available for the elderly ESRD [3]. Renal transplantation is ideally the modality of choice in ESRD patients. It scores over dialysis with respect to patient survival, cost effectiveness and the quality of life [6–12]. However, option of transplantation is offered infrequently elderly patients. It has been reported that < 5% of patients aged 65 years or more, who are on dialysis will receive a renal transplant (1, 2). It has been shown that, the benefits of renal transplant are similar in elderly as compared to the younger recipients [13–19]. Renal transplantation is still controversial in elderly, and the rates of transplantation in elderly are still modest [7]. This could be because of the various ethical issues involving the allocation of the scarce organs, and the controversies regarding the cost-effectiveness of doing a transplant as well as its efficacy in this cohort, and the hesitancy of the physicians to refer them for transplant [8, 9]. Many physicians consider dialysis as a more stable option with acceptable rates of survival and low short term risks. In contrast, renal transplant though may lead to a longer life expectancy with improvement in quality of life, it is considered to have significant short term risks morbidity and mortality. In a Canadian study, it was found that among patients aged over 65 years, 26.5% were not referred for transplantation in the elderly. It scores over dialysis with respect to patient survival, cost effectiveness and the quality of life [6–12]. However, option of transplantation is offered infrequently elderly patients. It has been reported that < 5% of patients aged 65 years or more, who are on dialysis will receive a renal transplant (1, 2). It has been shown that, the benefits of renal transplant are similar in elderly as compared to the younger recipients [13–19]. Renal transplantation is still controversial in elderly, and the rates of transplantation in elderly are still modest [7]. This could be because of the various ethical issues involving the allocation of the scarce organs, and the controversies regarding the cost-effectiveness of doing a transplant as well as its efficacy in this cohort, and the hesitancy of the physicians to refer them for transplant [8, 9]. Many physicians consider dialysis as a more stable option with acceptable rates of survival and low short term risks. In contrast, renal transplant though may lead to a longer life expectancy with improvement in quality of life, it is considered to have significant short term risks morbidity and mortality. In a Canadian study, it was found that among patients aged over 65 years, 26.5% were not referred for assessment for renal transplant, despite having no contraindications [10]. In this short review, we will discuss about some common skepticisms holding us back from transplantation in the elderly.

Donor Selection

Selection of appropriate donors for renal transplant in elderly has been a major hurdle, due to various organ transplant policies, ethical issues etc hampering live transplants. The transplant policies of most organ sharing networks give preference to younger recipients, and the elderly being reserved for expanded criteria donors and discarded kidneys. Hence, Deceased Donor Renal Transplant (DDRT) is the more widely adopted practice, commonly from an expanded criteria donor.

Living donor transplantation helps to alleviate the shortage of deceased donor kidneys in all patients, including the elderly. However, finding a suitable living donor is difficult, which may be even more problematic in case of elderly transplants. The results of live donor transplant are encouraging, with a 5-year survival rate of 76%, as compared to 68% for a non-expanded criteria deceased donor. Deceased donor transplant also do not fare much worse, with a 10 year survival rate of 35% in patients aged >60 years, as compared to 46% in recipients aged 18-30 years. If the availability of donors is sparse, expanded criteria donors can be considered with dual kidney transplant. The kidneys from expanded criteria donors, considered for discardation can be transplanted, maintaining the neprhon dose. The results have been promising, with 82% patient survival at 3-years and a graft survival of 70%.

Pre-emptive transplant has also been attempted in elderly with a better survival benefit. Pre-emptive transplant has also been performed from kidneys discarded of very old donors, with promising results. The death censored 5-year graft survival was 96% as compared to 68% in those receiving transplant after initiation of dialysis. Hence, Elderly patients with end stage renal disease, not on dialysis may benefit from Pre-emptive kidney transplantation.
transplant from elderly deceased donors whose kidneys were to be discarded.

**Patient Survival**

Before offering the option of renal transplant to older patients, it is essential to have a detailed evaluation and ensure that the transplant surgery per se and the immunosuppression do not adversely affect their survival.

The initial experience of renal transplant in elderly, especially deceased donors, was dismal. Simmons et al., in 1971 reported poor survival and graft survival at 1 year among patients >45 years age of 40% and 20% respectively. This is significantly worse compared to the younger recipients. In the initial reports, patient survival of elderly patients after deceased donor transplant was significantly worse compared to patients on dialysis, with a better survival for patients receiving living donor transplants. As a result, in 1977, it was suggested by Najarian et al. that patients more than 45 years of age should not be offered deceased donor transplants.

This view changed with the advent of Cyclosporine A based regimens, and in 1987, Fryd et al. found similar outcomes following deceased donor transplant in patients > 50 years of age as compared to those < 50 years of age. Since these sentinel studies, the upper age limit for offering renal transplantation is being extended farther. 18-31

In a classic article by Wolfe et al. (3), the authors showed that the mortality risk reduction by 68% in patients receiving a renal transplant when compared with the patients who were continuing on the waiting list. Also, they demonstrated a 61% lower mortality among patients aged between 60 and 74 yr and undergoing a renal transplant, compared with the people who remained on the waiting list (3). This mortality risk reduction translated into a projected 4 years increase in lifespan. The survival advantage was also seen in those aged 75 to 79 years, with an increased lifespan of 1 year with renal transplant when compared with the patients on dialysis (3).

However, in this study, elderly patients comprised of only 13% of the all renal recipients (3). In an article by Rao et al., the authors analysed the survival patterns of elderly renal transplant recipients. Of the 5567 patients aged more >70 yr put on the waiting list between 1990 and 2004, 6% had received living donor transplant while 37% had undergone deceased donor renal transplant. The adjusted relative risk of death for all patients receiving a renal transplant was 0.59 (95% CI 1.05-1.65) compared with patients on waiting list (8). The mortality risk varied with time since transplant, with the early post transplant period having the highest risk, higher than dialysis, with a decline decreasing thereafter. The risk of mortality was attenuated by 3 years post renal transplant, with the early post transplant period having the highest risk, higher than dialysis, with a decline decreasing thereafter. The mortality risk equalled that of dialysis at 125 days following renal transplant, and showed a mortality benefit from that time point onwards (8). In view of the high RR for death in the initial period, until 1.5 years after transplant, the transplant patients had a worse survival than the dialysis patients placed on the waiting list (8). The adjusted RR for death was 0.67 (95% CI 0.53-0.86) for patients older than 75 years receiving a renal transplant compared to patients on wait list (8). The survival benefit was significant even for patients with diabetic or hypertension related renal failure, as well as for expanded criteria donor kidneys (8). Another important concern is whether the survival benefit will persist in the elderly recipients who were on the waiting list for a prolonged time. This question was analysed by Gill et al. (9) in their analysis of 63,783 patients undergoing transplant, from the US Renal Data System database. The authors showed an expected survival of 8.2 years following a renal transplant in patients aged >70 years, compared to 4.5 years survival on the waiting list (9). The authors found that the survival benefit with renal transplant decreased with increasing time for patients on waiting list, but there was some persisting benefit even after 3 years on waiting list, with a 2.5 years increased life span after transplant as compared to dialysis. This study showed that the survival benefit, although slightly decreased, persisted to show a significant survival benefit in elderly transplant recipients (8).

The authors also showed a 42% reduction in mortality in renal transplant recipients even in those with long waiting times (compared to patients on dialysis RR 0.59 (95% CI 0.53-0.65) (8). Thus, patients with waiting times of even 3 to 4 years have a significant survival benefit in elderly transplant recipients. However, whether transplant after even longer waiting times would lead to a survival benefit in the elderly patients is still not known.

**Graft Survival**

Transplantation into older individuals with relatively shorter life spans than younger individuals may be associated with the loss of significant allograft years because of death of the older individual before allograft failure. But the positive side is that rejection occurs less commonly in older patients, a finding that may be attributable to age-related “tolerance”.

Shannon Doyle et al found 86% one year graft survival in older recipients, which is comparable to younger patients with a 1-year graft survival of 88%. However, they found a significantly reduced 10-year graft survival in the elderly (39% vs 53%). Younger recipients had a significantly better overall graft survival (P < 0.001). The poorer graft survival in the elderly was explained by the increased number of deaths in the older patients. Graft loss due to death was found to be 61% in the elderly, compared to 45% in younger patients. The authors reported that the death censored graft survival in patients more than 60 years of age was equivalent to the younger recipients.

In their study, the leading causes for graft loss included death, rejection (hyperacute and chronic rejection), and hemolytic uremic syndrome. The major causes of mortality being cardiac disease, sepsis, and recurrent disease. The authors also found a significant difference in the interval between transplant and the last treatment received for any malignancy and mortality with a waiting time of 2.2 ± 0.3 years in non-survivors vs 14.0 ± 3.6 years in survivors (P < 0.0001).

Poor graft survival has also been associated with other factors like donor age greater than 50, increased time on waiting list, age group 65–70 years in comparison to those between 60 to 64 years. The presence of delayed graft function, coronary artery disease, or diabetes was not shown to be associated with poor graft outcomes. Use of tobacco was also found to be associated with a poorer graft outcome.

At our centre, the graft survival at 1, 3 and 5 years is 88.9%, 60% and 25% respectively (figure 1) with 21% patients having died with a functioning graft. The major causes for mortality in our centre are sepsis (50%) followed by cardiovascular death (31.3%) (figure 2), with Respiratory infection being the most common cause of sepsis related death (25%). The patient and graft survival at 3 years were better with live donors compared to deceased donors (Table 1).

The immune competence is known to decrease with increasing age and therefore associated with fewer rejections 36-39. Tesi et al. found a significantly better death censored graft survival in patients > 60 years of age. The elderly patients had fewer immunological graft losses, 11% vs 31% (p = 0.0009) with a relative risk for graft loss of 0.36. Also, they found no graft loss secondary to immunological injury after 36 months. At our centre, three patients > 60 years of age had graft loss secondary to chronic rejection between 28 and 70 months post-transplant. A possible explanation for increased graft loss secondary to rejection in some studies may be due to the tendency to use lower levels of immunosuppressants in elderly patients, and also possibly less aggressive management of episodes of acute rejection. The lower rejection rates in elderly patients translate into a decrease in the rate of re-hospitalization, and more elderly patients are readmission-free.

To assess the effect of co-morbid conditions like diabetes and cardiac disease, Schulak et al. conducted a study and divided the patients aged > 60 years into those without both diabetes and cardiac disease (low-risk) (n = 14), and those who had presence of either diabetes or cardiac disease (n = 12).27 He found that patients at low risk had better patient and graft survival rates (p = 0.055). However, Benedetti et al found no such difference.

With improvements in graft survival in the elderly population, there has been more concern about loss of significant allograft
years in the elderly due to death with a functioning graft, which is about 21% at our centre. To overcome this drawback, an approach similar to the Eurotransplant Senior Programme (ESP) policy had been followed. As per this approach, the organs retrieved from donors older than 65 years of age are allocated to patients of similar age. This also leads to better utilisation of expanded criteria donors and also the kidneys considered to be discarded can be transplanted to appropriate recipients. Data from this program revealed that, among 227 patients, one year allograft survival rates were 86 percent which compared favourably with 79 percent survival with the older system.

Quality of Life and Cost effectiveness

Successful renal transplantation improves overall quality of life and relieves the burden and tedium of dialysis among all patients with ESRD. It could be related to amelioration of anaemia, and enhancement of physical, mental and cardiac functions. It has been shown that transplant patients have 18.12% greater quality of life in total aspects of human life (physical, emotional, social, spiritual and financial) compared to patients on hemodialysis.

A 65 year old patient without co-morbidities can gain 1.2 years of life following transplant, and about 1.1 quality-adjusted life years (QALY) at an incremental cost of $67,778 per QALY. The improvement in Life Expectancy (LE) and Quality Adjusted Life Expectancy (QALE) was also observed in those with diabetes and cardiovascular disease, albeit to a smaller extent. Otherwise, patients with no comorbidities continued to have improvement in QALY with transplant even up to the age of 80 yr.

Assuming a waiting period of 2 year before transplant, renal transplant for 70 year old patients continued to be economically feasible (incremental cost effectiveness [ICE], $79,359 per QALY). But for those more than 75 years of age, and for 70 year old patients with either cardiovascular disease or diabetes, transplant was less economically attractive (ICE $99,553, $126,751 and $161,090 per QALY, respectively). The ICE per QALY increased with age, but remained favourable compared to dialysis even for 80 year old patients (ICE/QALY for transplant $50,000). With increasing time on waiting list, the cost effectiveness ratios increased dramatically (incremental cost/QALY: $15,000, $68,000, and $193,600 for 0, 2, and 4 years on waiting list respectively). The QALE for patients 65 years of age on dialysis equaled that of transplant at 6.7 years. A 65 year old with no comorbidities on being transplanted has incremental benefits of two years life extra, and savings of more than $100,000.

Humar et al. (10) used the SF-36 questionnaire and found that older transplant recipients had a remarkably good quality for life at 1 yr after transplantation. The quality of life scores in the elderly recipients were comparable, and in five of eight domains, they were better than the age matched general population. The three domains where they scored lower were physical functioning, role limitation due to physical health problems, and bodily pain (10). Also, their scores for overall general health perception were similar to younger transplant recipients, and better than the age matched general population (10).

Though transplant is associated with high initial costs, this would be exceeded by the cost of hemodialysis after about 2 years and 10 months. For patients continuing on maintenance hemodialysis, transplantation would lead to a saving of about 3,800 USD per month. And for the elderly patients, it would amount to about 2,400 USD saving per month 16. The cost analysis of patients receiving renal replacement therapy at our centre is as shown in Table 2, with high initial costs of transplant, which reduces over long term and equals that of hemodialysis by about 26 months post transplant. Laupacis et al. (1) have shown that the cost of dialysis in patients older than 60 years was $65,270 per year, while transplant cost $63,708 for the first year and $161,090 in the second year (1). Thus, transplant becomes even more cost effective with longer follow up compared to dialysis, as the dialysis cost remains constant or increases with longer follow up (1). Jassal et al. (11) had performed a decision analysis to examine the cost effectiveness of transplantation in the elderly. They found that the economic results were not favourable in for all subgroups of patients. Patients undergoing a live donor transplant had better economic results regardless of the age at transplant. However, for patients more than 75 years of age, having a wait time of more than 2 years and receiving a deceased donor transplant the transplantation was economically not attractive with the cost per QALY ranging between $99,553 to $231,158 (11). With wait time of more than 4 years, transplant was not economically attractive across all age groups with the cost per QALY ranging from $175,107 to $14,585,442 (11). Their study suggested that live donor transplant would be a better option for the elderly from an economic perspective.

Conclusion

With ageing general population, the ESRD population is also aging. Hence, physicians are expected to have to make increasing number of decisions regarding referral for transplantation and the candidacy in elderly patients. The data suggests that elderly patients on the waiting list experience significant survival benefit with kidney transplantation, even among those who are more than 75 years of age. In addition, older transplant recipients have increased life expectancy and better QALEs and QALYs. From an economic perspective too, transplantation remains a better strategy for the elderly, especially with living donors, or with deceased donors with shorter waiting times. Age alone should not be considered a barrier to kidney transplantation, and until further evidence emerges, treating physicians must consider the option of transplant in all elderly patients with ESRD. The patient must have a detailed evaluation for transplant eligibility and the decision should be made considering the best interests of the patient. The use of rigid age cutoffs for transplant evaluation is not advisable, and should ensure that agism does not have bias or conflict the decision regarding transplantation.

Conflicts of interest: There were no points of conflicts.

Figure 1: Patient and graft survival at 3 years – our experience

![Figure 1: Patient and graft survival at 3 years – our experience](image)

Figure 2: Cause of death in elderly transplant recipients

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| Table 1: Patient and graft survival in live and deceased donors at 3 years post transplant |
|-----------------------------|-----------------------------|
| **Live**                  | **DDRT**                  |
| Patient survival           | 85.7%                      | 50.0%                      |
| Graft survival             | 71.4%                      | 50.0%                      |

| Table 2: Cost analysis of the different renal replacement therapy strategies |
|-------------------------------|-----------------------------|
| **Cost**                      | **Initiation (in Rs.)** | **Monthly (in Rs.)** |
| PD                            | 42,500                      | 25,460                    |
| Early Transplant period       | 45,000                      | 25,600                    |
| Late Transplant period        | -                           | -                         |

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References


