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Benefit of kidney transplantation beyond 70 years of age

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Abstract

Background. Kidney transplantation generally improves long-term survival in patients with end-stage renal disease. However, in patients older than 70 years of age, only limited data are available that directly compare the potential survival benefit of transplantation versus dialysis.

Methods. All patients aged above 70 years who started dialysis between 1990 and 2005 and were waitlisted for kidney transplantation were included in the study. They

were categorized according to time periods of inclusion (1990–99 vs 2000–05). Survival rates of altogether 286 dialysis patients were analyzed with a Kaplan–Meier model, as well as with a time-dependent Cox model. Comparisons were made between those who received a transplant and those who did not, and further between the two time periods.
Results. Median age at inclusion was 73.6 years (interquartile range 72.3–75.6). Two hundred and thirty-three patients (81%) received a kidney transplant during follow-up. Transplant recipients experienced an increased mortality in the first year after transplantation when compared to waitlisted patients. Patients starting dialysis between 1990 and 1999 had no significant long-term benefit of transplantation; HR for death 1.01 (0.58–1.75). In contrast, there was a substantial long-term benefit of transplantation among those starting dialysis after 2000; HR for death 0.40 (0.19–0.83), $P = 0.014$.
Conclusions. Survival after kidney transplantation in patients over 70 years has improved during the last decade and offers a survival advantage over dialysis treatment. Our experience supports the use of kidney transplantation in this age group if an increased early post-operative risk is accepted. This transplant policy may be challenged for priority reasons.

Keywords: dialysis; elderly patients; epidemiology; kidney transplantation; patient survival

Introduction

Elderly patients are by far the fastest growing population requiring renal replacement therapy (RRT) both in Europe and in the USA [1–4]. Patients above 65 years of age constitute >15% of the waitlisted patients in the USA in 2009 [5] compared to 7% in 1997 [3]. Kidney transplantation is in general regarded as the treatment of choice both with respect to survival, quality of life and costs [6–12]. If successful, the advantages of kidney transplantation appear to be the same for elderly as for young recipients [13–19], but data are limited for kidney transplant recipients above 70 years of age.

Most reports comparing survival of kidney transplant recipients and patients on dialysis are based on registry data from multiple centers and have major limitations. The selection and work-up procedure of transplant recipients vary between centers and the same goes for choice of immunosuppressive protocols and follow-up procedures. Dialysis treatment also differs significantly between centers. Such variations may have substantial impact on patient survival. Obviously, it is unethical to perform a prospective, randomized controlled trial comparing dialysis and transplantation in eligible potential transplant recipients. Rikshospitalet is the only transplant center in Norway, serving ~4.8 million inhabitants. All candidates for transplantation have to fulfill the same criteria for acceptance, and the recipients receive a uniform treatment and follow-up after transplantation. During the last 20 years, a relatively large number of patients above the age of 70 have been transplanted at our center [13]. The primary objective of the present study was to assess the effect of kidney transplantation versus continued dialysis on mortality in recipients that started dialysis treatment at the age of 70 years or more and fulfilled the requirements to receive a kidney allograft. A secondary objective was to compare the post-transplant outcome related to different time periods, reflecting different immunosuppressive protocols that were used during the study period.

Materials and methods

Study design

Data of all patients aged 70 years and older, not previously transplanted, who had started dialysis from 1990 throughout 2005 and were accepted at the transplantation waitlist, were retrieved from the Norwegian Renal Registry. Survival analyses were performed comparing those patients remaining on the waiting list with those who were transplanted. For patients being transplanted, additional data concerning comorbidity at the time of transplantation, immunosuppressive treatment and other data related to the transplant procedure were retrieved from the hospital records and the Norwegian Renal Registry. Start of study was set at the time of waitlisting for deceased donor transplantation, at the time of acceptance for living donor transplantation or at start of dialysis (latest of those). All patients were followed until death or end of study (1 May 2008).

Standard immunosuppressive protocol following kidney transplantation at our center was changed during the study period. In the first era (1990–99), all recipients received triple immunosuppression with cyclosporine, azathioprine and steroids. From 2000, azathioprine (AZA) was stopped and intravenous basiliximab (2000) was added. From 2001, all recipients received cyclosporine, steroids and mycophenolate mofetil (MMF). Therefore, we divided the study population into two groups according to the year of dialysis start (1990–99 versus 2000–05). In addition, we performed Kaplan–Meier survival analysis in those patients eventually

Table 1. Baseline characteristics of the study population

	All ($n = 286$)	Transplant ($n = 233$)	Waitlist ($n = 53$)	P value
Months on dialysis before waitlisting; median (range)	7.0 (0–40.6)	6.8 (0–40.2)	8.0 (0.6–40.6)	NS
Age at start of dialysis; median (range)	73.1 (70.0–81.0)	72.9 (70.0–81.0)	73.6 (70.2–80.2)	NS
Age at entering waitlist; median (range)	73.6 (69.5–82.1)	73.4 (69.5–82.0)	74.5 (71.0–82.1)	NS
Haemodialysis/peritoneal dialysis	77%/23%	76%/24%	85%/15%	NS
Female gender	85 (30%)	75 (32%)	10 (19%)	NS
Diabetes nephropathy	12 (4%)	7 (3%)	5 (9%)	0.05
Glomerulonephritis	88 (31%)	69 (30%)	19 (36%)	NS
Pyelonephritis	28 (10%)	25 (11%)	3 (6%)	NS
Familiar/hereditary renal disease	27 (9%)	22 (9%)	5 (9%)	NS
Vascular diseases	109 (38%)	91 (39%)	18 (34%)	NS
Other/unknown	22 (8%)	19 (8%)	3 (6%)	NS

P values indicate comparison of patients eventually transplanted with those remaining on the waitlist never receiving a transplant.

Table 2. Baseline characteristics all patients placed on the transplant waitlist

	1990–99 (n = 173)	2000–05 (n = 113)	P value
Months on dialysis before waitlisting; median (range)	5.9 (0–40.6)	8.9 (0–40.4)	0.001
Age at start of dialysis; median (range)	73.1 (70.0–81.0)	73.0 (70.0–81.0)	NS
Age at entering waitlist; median (range)	73.6 (69.5–81.3)	73.6 (70.1–82.1)	NS
Haemodialysis/peritoneal dialysis	82%/18%	70%/30%	0.02
Female gender	56 (32%)	29 (26%)	NS
Diabetes nephropathy	5 (3%)	7 (6%)	NS
Glomerulonephritis	67 (39%)	21 (19%)	<0.001
Pyelonephritis	20 (12%)	8 (7%)	NS
Familiar/hereditary renal disease	16 (9%)	11 (10%)	NS
Vascular diseases	48 (28%)	61 (54%)	<0.001
Other/unknown	17 (10%)	5 (4%)	NS

receiving a transplant, comparing patients transplanted between 1990 and 1999 with those who were transplanted between 2000 and 2008.

The dialysis patients received either haemodialysis or peritoneal dialysis or a combination of these, simultaneously or in sequence. The vast majority of patients were treated in haemodialysis, and we have analyzed peritoneal dialysis and haemodialysis together as one group in the statistical analysis.

Statistics

Two-sided unpaired *t*-test or Mann–Whitney test was used as appropriate to compare groups. Fisher's exact test was used to analyze binary data. Survival data were assessed with the Kaplan–Meier method. Survival in the waitlist group was counted from start of dialysis or time of waitlisting (latest of those) to death or censoring due to transplantation or end of study (1 May 2008). Survival in the transplant group was counted from the time of transplantation to death or censoring due to end of study (1 May 2008). Furthermore, the data were analyzed in a time-dependent Cox model [20], censoring patients from the waitlist group at time of transplantation. In the time-dependent Cox model, the waitlist group was chosen as indicator versus the transplant group. Logistic regression analysis was used to identify risk factors for acute rejection episodes. The analyses were implemented using SPSS® 15.0.

Results

From 1990 throughout 2005, a total of 1979 patients aged 70 or more started RRT in Norway. Three hundred and twenty-two patients (16%) were accepted at the transplantation waitlist. Thirty-six patients (11%) received a transplant pre-emptively. The remaining 286 patients were accepted for transplantation and placed on the waiting list. Median age at start of dialysis was 73.1 years (interquartile range 71.4–74.7). Median age at inclusion was 73.6 years (72.3–75.6). Two hundred and thirty-three patients (81%) received a transplant during the observation period. Thirty-seven patients (16%) received a kidney from a living do-

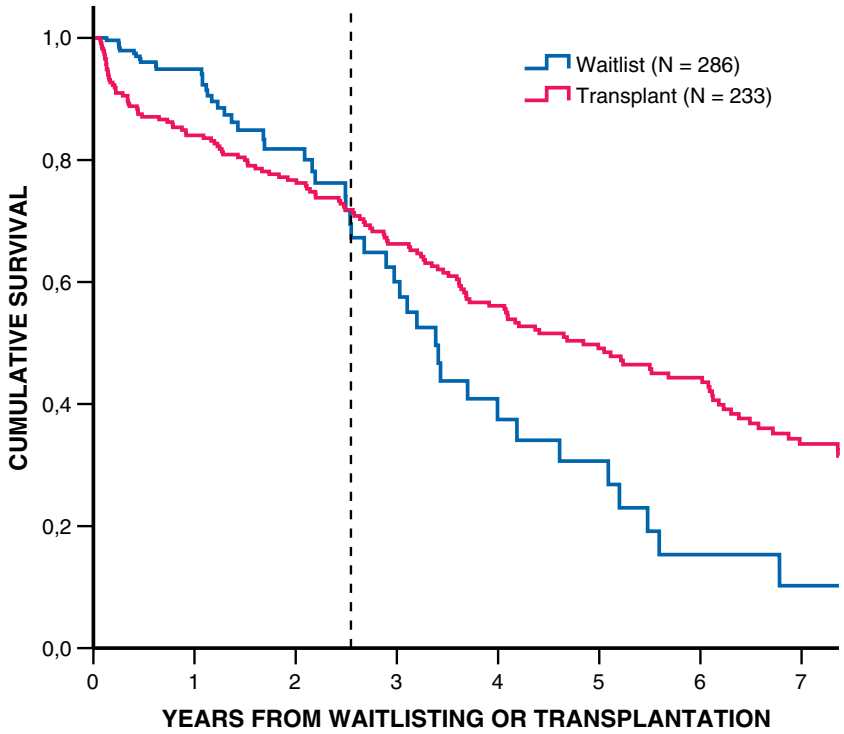

Fig. 1. Kaplan–Meier survival plot: survival of waitlisted patients and patients receiving a kidney transplant. Start of dialysis: 1990–2005. Patients were censored from the waitlist group at the time of transplantation.

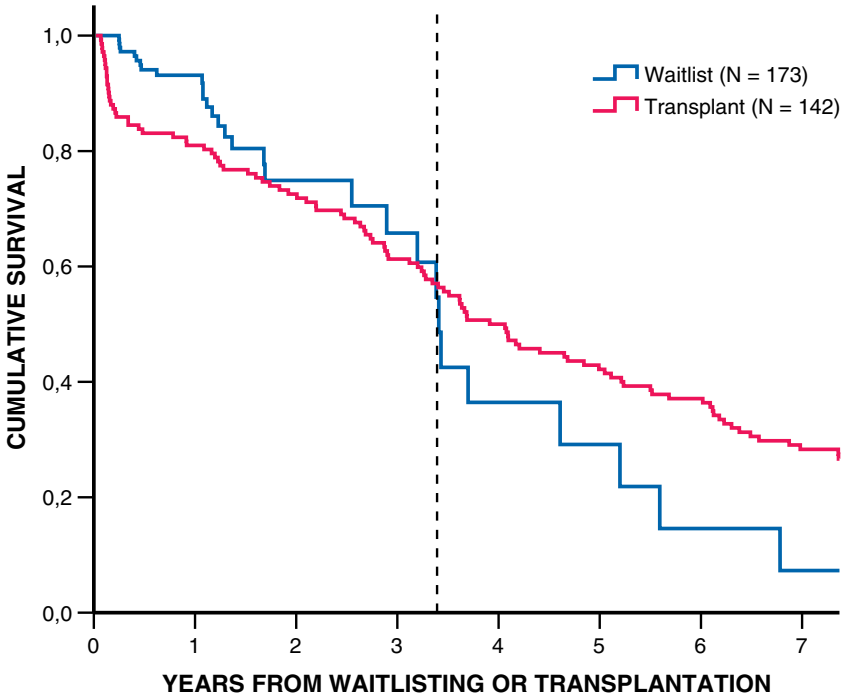

Fig. 2. Kaplan–Meier survival plot: survival of waitlisted patients and patients receiving a kidney transplant. Start of dialysis: 1990–99. Patients were censored from the waitlist group at the time of transplantation.

nor. Median age at time of transplantation was 74.3 years (interquartile range 73.1–76.4). Baseline data comparing those patients receiving a transplant with those who did not are presented in Table 1. Baseline data comparing the two time eras are shown in Table 2. No patient was lost to follow-up.

Survival of patients placed on the transplantation waitlist

Among patients remaining on the transplantation waitlist (n = 286), median survival from waitlisting was 3.4 (3.0–3.8) years compared to 4.8 (3.8–5.9) years in the transplant group (n = 233). Five-year survival was 31%

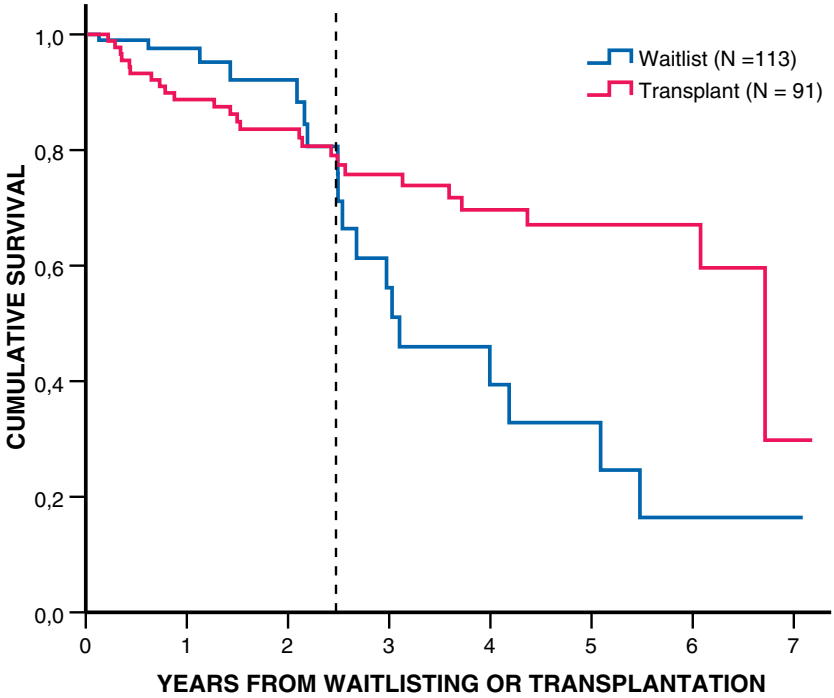

Fig. 3. Kaplan–Meier survival plot: survival of waitlisted patients and patients receiving a kidney transplant. Start of dialysis: 2000–05. Patients were censored from the waitlist group at the time of transplantation.

Table 3. Characteristics of kidney transplant recipients by period of transplantation

	1990–99 (n = 116)	2000–07 (n = 117)	P value
Age; median (range)	74.2 (70.2–81.5)	74.6 (70.2–82.9)	NS
Female recipient	39 (34%)	36 (31%)	NS
Months on dialysis; median (range)	14.0 (1.0–47.0)	12.0 (0.6–71.0)	NS
Haemodialysis/peritoneal dialysis	89%/11%	69%/31%	<0.001
Donor age; median (range)	50.0 (14–78)	57.8 (4–86)	<0.001
Donor age >60 years	30 (26%)	55 (47%)	0.001
Living donor	19 (16%)	18 (15%)	NS
Female donor	50 (43%)	59 (50%)	NS
CMV positive donor	92 (80%)	86 (74%)	NS
Any HLA-A mismatch	86 (74%)	93 (79%)	NS
Any HLA-B mismatch	98 (84%)	102 (87%)	NS
Any HLA-DR mismatch	69 (59%)	56 (48%)	NS
PRA pos recipient	8 (7%)	5 (4%)	NS
Pre-transplant ischaemic heart disease	36 (31%)	40 (34%)	NS
Pre-transplant diabetes mellitus	10 (9%)	16 (14%)	NS
Diabetes nephropathy	3 (3%)	4 (3%)	NS
Charlson Comorbidity Index; median (range)	3 (2–7)	3 (2–10)	NS
Cold ischaemia time (hours); median (range)	14 (1–28)	12 (1–28)	NS
Cyclosporine	116 (100%)	108 (92%)	0.005
AZA	96 (83%)	1 (1%)	<0.001
MMF	4 (3%)	104 (89%)	<0.001
Delayed graft function	19 (17%)	37 (32%)	0.009
Proportion of deaths because of infection	29 (26%)	12 (32%)	NS
Rejection within 90 days	58 (50%)	28 (24%)	<0.001

among waitlisted patients and 49% in transplant recipients (Figure 1). In the time-dependent Cox model, we found no significant difference between the transplant and waitlist groups, even though there was a trend towards an overall reduced risk of death for those who were transplanted; hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.52–1.18, P = 0.25 [adjusted for age, sex, primary kidney disease, type of center where dialysis was initiated (university vs not university hospital), time on dialysis before waitlisting and dialysis modality]. The variables identified as significant/near significant risk factors for acute rejection episodes were immunosuppression with AZA versus MMF; odds ratio (OR) 2.79, 95% CI 1.56–5.38, P = 0.002, any HLA-DR mismatch; OR 2.04, 95% CI 1.11–

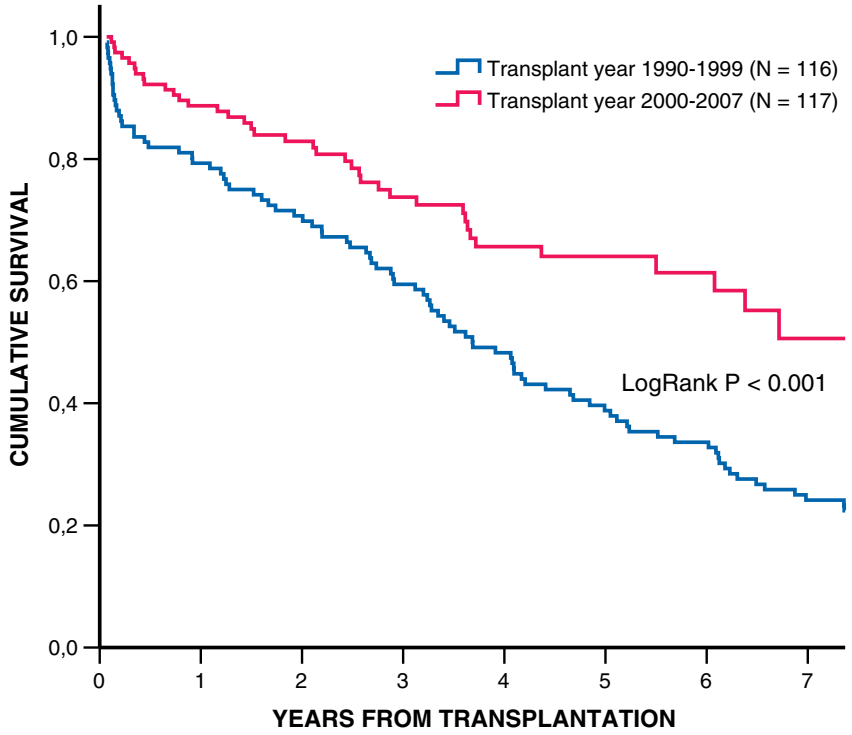

Fig. 4. Survival of kidney transplant recipients according to transplant era.

Table 4. Survival of transplant recipients and dialysis patients on the waitlist

	1990–99				2000 →				
	n	1 year	3 years	5 years	*n*	1 year	3 years	5 years	*P* value
Transplant	116	79%	60%	39%	117	89%	74%	64%	<0.001
Waitlist	173	93%	66%	29%	113	98%	56%	33%	NS

Survival was counted from time of transplantation (transplant) or from start of dialysis (waitlist).

3.78, $P = 0.023$, donor age over 60 years; OR 2.05, 95% CI 1.09–3.86, $P = 0.025$ and cytomegalovirus (CMV) positive donor; OR 2.11, 95% CI 0.98–4.57, $P = 0.058$. The following other variables were also tested in the multivariate logistic regression model without significant impact: recipient age, living versus deceased donor, panel reactive antibody (PRA) positive recipient, any HLA-A mismatch, any HLA-B mismatch and cold ischemia time.

Survival according to year of transplantation/start of dialysis

When categorizing the study population into two groups according to time for start of dialysis, there was no apparent benefit of transplantation in the first era (1990–99, $n = 173$); HR 1.01 (0.58–1.75). In contrast, there was a marked and significant benefit of transplantation among those starting dialysis between 2000 and 2005 ($n = 113$); HR 0.40 (0.19–0.83), $P = 0.014$. When compared to continued dialysis treatment, the transplant recipients of both eras had increased mortality in the first 12 months after transplantation. The subsequent reduction in mortality leads to a survival benefit starting 3.5 years after transplantation in the first era (Figure 2) and after ~2.5 years in the last era (Figure 3).

The transplant recipients were categorized into subgroups according to time era they were transplanted (1990–99, $n = 116$ vs 2000–07, $n = 117$). Baseline characteristics of the two transplant cohorts are presented in Table 3. There was no difference between the two groups with respect to comorbidity described by Charlson Comorbidity Index [21], proportion receiving a living donor kidney or in HLA-A, -B or -DR mismatch. The median survival after transplantation increased from 3.7 (3.0–4.4) years in 1990–99 to >6.7 years in 2000–07 (Figure 4).

Median survival after time of waitlisting did not change in the waitlist group according to start of dialysis; 3.4 (3.1–3.7) years in 1990–99 ($n = 173$) versus 3.1 (1.8–4.4) years in 2000–05 ($n = 113$). Survival after 1, 3 and 5 years from transplantation in the transplant group and from start of dialysis in the waitlist group are presented in Table 4. Twenty-one recipients (18%) transplanted between 1990 and 1999 died in the first 6 months after the transplantation compared to nine recipients (8%) transplanted between 2000 and 2007 ($P = 0.02$). Among the 21 deaths in the first cohort, 10 were related to infection (five pneumonias, four septicemias and one case of peritonitis), all had received rejection treatment. All nine deaths in the last cohort were caused by infection (four pneumonias, four septicemias and one unspecified infection), four of them received rejection treatment.

Discussion

The results support the notion that, at least during the last 10 years, transplantation appears beneficial and improves patient survival in patients beyond 70 years of age. A prerequisite is a proper transplant work-up of the patients to ensure overall medical fitness for such a procedure. The number of elderly patients requiring RRT increases worldwide. This trend is likely to continue. With current shortage of organs, it may be difficult to find arguments in favor of using a donor kidney in a patient with limited life expectancy, such as the elderly patient. Our data may justify the use of kidney transplantation in patients older than 70 years of age. Apart from a survival advantage, it has generally been accepted that both quality of life and cost are improved by transplantation, but these factors were not the scope of the present study. One may argue that patients at high age should not be offered a kidney transplant due to organ shortage striking many young patients awaiting kidney transplantation. However, in our country, the active policy of transplantation in high age has not lead to an increase in the waitlist.

Elderly kidney transplant recipients had an increased risk of death during the first year after transplantation compared to the age matched dialysis patients remaining on the waiting list. This is in line with what has been described in previous registry analyses [15,16]. There was no survival benefit in the first time era in contrast to a substantial benefit in the last era from 2000. One possible explanation was the change of immunosuppressive protocol in 2000. It is well recognized that acute rejection during the first 3 months after transplantation is a major risk factor for premature death in elderly kidney recipients [22]. When AZA was replaced by basiliximab or MMF, the frequency of acute rejection episodes was reduced by 50%. The mortality risk remained increased in the immediate post-operative period and became comparable with the risk of death on dialysis during the first year, before decreasing considerably to a beneficial long-term effect. A similar finding was reported in the landmark study published by Wolfe *et al.* where they noted 61% lower risk of death at 18 months after transplantation compared with dialysis for patients aged 60–74 years [9].

Organs from old donors are usually allocated to elderly recipients. It has been proposed that elderly recipients, due to a less active immune system, are less prone to develop

acute cellular rejection compared to younger recipients. However, in a Dutch study published in 2001, the authors claim that older kidneys are more immunogenic and therefore require more intense immunosuppression [23]. In the first protocol of the Eurotransplant Senior Program (ESP), kidneys were allocated locally without HLA matching to obtain short ischaemia time [24,25]. This procedure resulted in a high percentage of acute rejection. In a recent analysis of ESP data, Pratschke *et al.* describe an initially pronounced immune response in elderly recipients receiving grafts from elderly donors [26]. In the new protocol (ESDP), full HLA-DR compatibility is introduced in the allocation protocol to reduce the risk of rejection episodes and thereby reduce the need for rejection therapy and the additional risk of complications due to infection [27]. Our results support the view that immunologic factors are important, especially in elderly transplant recipients. In addition to adequate HLA compatibility, our results also implicate that it is important for elderly recipients to receive adequate immunosuppression early to reduce acute rejection episodes. Too strong immunosuppressive therapy may cause infectious complications. The relative risk of death of transplant recipients compared to dialysis was higher in the first 6 months in the cohort who received the strongest immunosuppressive regimen, and all deaths were caused by infections. However, the absolute number of deaths in the first 6 months was lower among recipients transplanted between 2000 and 2007, and the absolute number of deaths related to infections was almost the same in the periods of 1990–99 and 2000–07.

High donor age and increased time on dialysis before transplantation have been shown to be risk factors for poor outcome, especially in elderly recipients [22]. In the present study, we found no difference regarding time on dialysis, but both the age of the donor and the proportion of donors older than 60 years were significantly higher in 2000–07 (Table 3). The prevalence of delayed graft function was considerably higher in the last era. Despite the negative influence of these variables, the survival was substantially better in the last era, supporting the proposal that adequate immunosuppression to avoid rejection episodes is extremely important in the elderly recipients.

Initially there were stringent acceptance criteria to chronic dialysis therapy and to be listed for a kidney transplant. Gradually these criteria have been loosened, and today we have very few absolute contraindications to RRT. This has led to an overall increase in age and comorbidity of those on the waiting list. Transplantation of elderly patients is a serious ethical issue in the context of organ shortage. The dilemma arises when the allocation of a kidney to the benefit of an elderly person inevitably does 'harm' to a young person, who therefore, does not receive the transplant and continues to wait for an appropriate organ. On the other hand, elderly patients with end-stage renal disease (ESRD) are more likely to die on the waiting list [28], and it is therefore important to reduce the waiting time as much as possible. It may be possible to increase the organ pool by increasing the number of extended criteria donors (ECD). Accepting and transplanting kidneys from even older donors to elderly recipients is one opportunity [24,25,29,30], and in a recent publication from our center, we have demonstrated that kidneys from donors older than 75 could be used with acceptable outcomes in elderly recipients [31]. A policy like this could make it possible to allocate ECD kidneys to elderly recipients on the deceased donor waiting list and thereby reduce their time on dialysis. Giving possibly 'lower-quality' organs to elderly recipients raises further moral and ethical arguments, but an 'old-for-old' policy has already been adopted in several countries and elderly transplant candidates are among those who are most likely to receive optimal benefits from ECD kidneys [32].

Some methodological issues deserve attention. Firstly, all patients in the transplant group have been treated with dialysis for some time prior to transplantation. Therefore, in the Kaplan–Meier analysis, transplant patients have longer total time on RRT than the patients in the waitlist group. This may bias the results of the Kaplan–Meier analysis in favor of those not being transplanted. Secondly, as a result of our study design, all patients, transplanted or not, have met the same selection criteria. There was no difference between the transplant and waitlist groups with respect to age at waitlisting or time from start of dialysis to waitlisting. However, there was a trend towards a higher proportion of female patients and patients on peritoneal dialysis in the transplant group. In addition, there was a significant higher prevalence of diabetes nephropathy among those who were not transplanted. Despite this, we regard the differences between the groups to be minor, especially in the retrospective study setting. In addition, the study is from a single transplant center. This could also be regarded as a limitation to the study. It may be claimed that the study describes the results of a transplant policy not applicable to any other countries or transplant centers. However, the fact that all patients have been treated at the same transplant center, following the same criteria for acceptance and the same standard immunosuppressive protocol, makes the data robust and strengthens the study. Furthermore, the robust and complete national registry of RRT patients has also made it possible to complete the study without any patient lost to follow-up.

Conclusion

In conclusion, elderly patients beyond 70 years of age on dialysis treatment, who fulfill the established medical criteria for waitlisting, will benefit from kidney transplantation compared to continuing dialysis. There is a marked long-term survival benefit which is highly significant after the introduction of newer immunosuppressive protocols. Transplantation should be preferred as the treatment of choice also for elderly patients with ESRD given a sufficient supply of organs.

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Conflict of interest statement. None declared.

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