KIDNEY TRANSPLANTATION IN THE ELDERLY

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LIST OF PAPERS


ABBREVIATIONS

AZA  azathioprine
CCI  Charlson comorbidity index
CKD  chronic kidney disease
CsA  cyclosporine A
CVD  cardiovascular disease
DM  diabetes mellitus
ECD  expanded criteria donor
ESP  Eurotransplant Senior Program
ESRD  end stage renal disease
HLA  human leukocyte antigen
HR  hazard ratio
HD  hemodialysis
IL-2R  interleukin 2 receptor
KDRI  Kidney Donor Risk Index
LYFT  Life Years From Transplant
MMF  mycophenolate mofetil
NHANES  National Health and Nutrition Examination Survey
RCT  randomized clinical trial
PD  peritoneal dialysis
RRT  renal replacement therapy
1. INTRODUCTION

1.1 Kidney transplantation

Since the first unsuccessful attempt in 1933 (1;2), kidney transplantation has progressed from being an experimental investigation to a safe and more or less routine clinical procedure. The first kidney transplantation to achieve a successful, long-term outcome was undertaken in Boston in 1954 by a team led by Dr. Joseph E Murray (3;4). A kidney was transplanted between two identical twins. Kidney function was restored and the recipient survived with good kidney function until suffering cardiac death eight years later. The donor suffered no serious side effects. Clearly, this success was of limited practical value since identical twins are rare. For his pioneer work with transplantation, Murray was awarded the Nobel Prize for medicine in 1990.

The success of the transplantation in 1954 inspired pioneering groups in Boston and Paris to perform unrelated transplantations using total body irradiation and corticosteroids as immunosuppression (5;6). This non-specific mode of immunosuppression was, however, both cumbersome and associated with serious side effects and unacceptable mortality rates from infections. In 1961, azathioprine (AZA) was introduced as an immunosuppressant for use in human organ transplantation (7;8). The immunosuppressive effect of AZA was reversible and could be achieved with a relatively low incidence of side effects. It now became possible to perform transplantations between individuals who were not genetically identical. Consequently, kidney transplantation became a viable treatment for selected patients with end stage renal disease (ESRD). At that time, graft survival at one year using AZA and steroids was approximately 50% (9).
Increased knowledge of the immunological mechanisms responsible for the development of rejection, and eventually the introduction of cyclosporine A (CsA) in 1982, resulted in further improvements in graft survival following kidney transplantation (10). Since then, new and more potent immunosuppressive drugs such as mycophenolate mofetil (MMF) and the interleukin 2 receptor (IL-2R) antagonists have been developed. The use of these drugs has led to even further reductions in acute rejection rates (11). These advances have made it possible to start large scale transplantation programmes and today kidney transplantation is the preferred treatment option in patients with ESRD eligible for the surgical procedure (12).

In Scandinavia, the first kidney transplantation was attempted at Rikshospitalet in Oslo, Norway in 1956. The first transplantation in Scandinavia to achieve a successful long-term outcome, however, was performed at Ullevål hospital in 1963. The recipient survived for 22 years before dying from a ruptured aortic aneurysm (13). Since 1983, as part of a national policy, all solid organ transplantations in Norway have been performed at Rikshospitalet. The number of kidney transplantations conducted at Rikshospitalet has steadily increased and now totals between 250 and 300 procedures per year.

1.2 Ageing population

The average age of the Norwegian population has increased markedly over the last three decades. The number of Norwegians aged 70 years or older has increased from 320,000 (8% of the total population) in 1970 to more than 500,000 (11% of the total population) in 2008. Based on a conservative estimate, this figure is likely to rise to approximately 840,000 (14% of the total population) by 2030 (14).
Similar demographic changes are taking place across most of the western world. In the European Union, it is estimated that the proportion of people older than 65 will increase from 16.7% in 2005 to 28.4% by 2050 (15). Similarly, in the United States, the proportion of people older than 65 is expected to increase from 12.4% in 2005 to 21.6% by 2050 (16). The increase in the elderly population has consequently led to a rise in morbidity rates.

1.3 Epidemiology and treatment options for elderly ESRD patients

Common risk factors for chronic kidney disease (CKD) include hypertension, cardiovascular disease (CVD), diabetes mellitus (DM), family history of CKD, and older age. The National Health and Nutrition Examination Survey (NHANES) is a series of health examination surveys, begun in 1960, designed to monitor the health and nutritional status of
the non-institutionalized, general population in the United States. The most recent survey was conducted between 1999 and 2004 and included 14,632 people aged ≥20 years (17). Data from this NHANES showed that the risk of CKD in people aged over 60 was much higher (odds ratio 5.89), compared with those aged between 20 and 39 (18). Data from the Norwegian Renal Registry in 2008 showed that vascular/hypertensive disease was the number one underlying cause of CKD and accounted for 27% of all new patients starting renal replacement therapy (RRT) (19). In patients older than 70 starting RRT, this figure rises to 46% (personal information – Torbjørn Leivestad October 2009).

CKD is staged according to severity from stage 1 to stage 5. RRT is usually not started before the patient has reached stage 5. Many elderly patients with stage 4 CKD have slowly declining kidney function and die before reaching stage 5 (20). Despite this, elderly patients have been the fastest growing ‘population’ requiring RRT both in Europe and in the United States (21-25). In 1980, the median age of patients starting RRT in Norway was 53 years. This had increased to 65 years in 2008 (19).

Figure 2. Age of new patients at start of RRT in Norway 1990 - 2008. Data retrieved from the Norwegian Renal Registry. Reprinted with permission from Torbjorn Leivestad.
As shown in Figure 2, the median age of patients starting RRT has stabilised during the last decade. Similar trends are observed in other countries (18;26). It is possible that the efforts made to prevent the development of ESRD, especially among patients with hypertension, have led to this stabilization. On the other hand, the absolute number of elderly patients in need of RRT will still increase substantially owing to the ageing populations described in section 1.2.

Patients with advanced CKD have different options for active treatment:

1. Dialysis, either as haemodialysis (HD) or peritoneal dialysis (PD).
2. Preemptive kidney transplantation.
3. Kidney transplantation after the start of dialysis.

Traditionally, elderly patients with advanced CKD have been selected for dialysis treatment, with only a small minority being considered for kidney transplantation. Elderly patients with severe comorbidity may be found unfit for active treatment although this may not lead to any shortening of their life expectancy (27). In some cases it is extremely difficult to decide whether a patient will tolerate, and thereby benefit from, dialysis treatment. Most elderly patients with advanced CKD develop symptoms that may either be suggestive of uraemia, or simply be a consequence of advanced age and/or comorbidity. In such cases it is sometimes necessary to start acute dialysis treatment in order to save the patient’s life, and then decide subsequently if the treatment should be permanent or not. An important factor in this process is how long the patient is expected to survive, with or without active treatment. A recent report describing the outcome of 8,977 chronic dialysis patients showed that the mortality rate in patients with ESRD had not changed over the last 12 years, despite a significant increase in the age of the dialysis population (28). The authors’ hypothesis is that selected patients benefit from the improvements in dialysis technology, uraemia
management, and treatment of dialysis-related complications. Interestingly, in patients aged over 74, the mortality rate significantly decreased during the 12 year observation period. Several strategies have been developed to predict early and long-term prognoses in CKD (29-31), and these may be used to help select patients eligible for RRT.

Kidney transplantation is generally regarded as the best treatment option for patients with ESRD (12;32-35). Previous studies indicate that selected elderly patients, despite having a limited life expectancy, often benefit from kidney transplantation (36-39). Consequently, the proportion of elderly patients on transplant waiting lists has increased during the last years. In 2008 in the United States, more than 15% of patients on transplant waiting lists were aged over 65 (40), compared with only 7% in 1997 (25). Similarly, in Europe, the proportion of kidney transplant recipients over the age of 65 has increased from 3.6% in 1991 to 19.7% in 2007 (41). The majority of previous reports concerning transplantation in ‘elderly patients’ have generally involved patients aged between 60 and 70 (36;42-46). There are few reports describing kidney transplantation outcomes in patients above 70 years old, and the most important of these publications are based on registry data from multiple centres reflecting various transplant protocols (24;38). Compared with age-matched dialysis patients, previous studies have indicated that survival and quality of life is favorable after transplantation even in recipients aged 65 - 70 (36;38;47-49).

1.4 Selection of elderly patients for kidney transplantation

The increasing number of elderly patients with ESRD presents great challenges for physicians. One such challenge is how to select which elderly patients with ESRD whom are most likely to benefit from kidney transplantation. Traditionally, a standard comorbidity
screening and treatment algorithm has been employed, independent of patient age. Patients with less comorbidity tend to be accepted for transplantation, while those with greater comorbidity receive life-long dialysis treatment.

In general, the degree of comorbidity, in particular diabetic nephropathy and cardiovascular disease, at the time of transplantation, has a deleterious effect both on recipient and allograft survival (50;51). There is, however, limited information available relating to the effects of comorbidity in kidney transplant recipients at an advanced age. Several scoring systems have been proposed to assess the burden of comorbidity at the time of kidney transplantation. The Charlson comorbidity index (CCI) has been validated as the best predictive tool for measuring comorbidity in this setting (52). The CCI score ranges from 0 (no comorbidity) to 24 (maximum comorbidity). The lowest possible CCI score at the time of kidney transplantation is 2 (the presence of pre-transplant kidney failure). The CCI score has been validated in patients older than 60 years (53), but it has not previously been evaluated as a prognostic index for mortality or graft loss in recipients older than 70 years.

1.5 Donor organ pool and allocation strategies

A major concern in kidney transplantation is the lack of organs. In general, there are far more patients on waiting lists than there are available organs. By March 31st 2008, 6,784 patients were waitlisted for a kidney transplant in the UK, whereas only 1,437 deceased donor and 829 living donor transplantations were performed the previous year (54). This inevitably means increased waiting times, and patients dying while on waiting lists. By the end of 2008, 10,687 patients were registered on the Eurotransplant kidney waiting list (55). Among these, 52% had been on the waiting list for more than two years, and 75% had been
on dialysis for more than two years. It would be difficult, even unethical, to expand the number of patients eligible for kidney transplantation, without simultaneously expanding the number of organs available. Strategies for expanding the overall donor pool include increased use of living donors (56-60), donation after cardiac death programs (61-65), altruistic living donation (66), introduction of standardized donor management protocols (67) and increased use of expanded criteria donors (ECD) (68-70). ECDs are defined as all deceased donors older than 60 years, and those aged 50 to 59 with at least two of three medical criteria: hypertension, cerebrovascular cause of death or serum creatinine level above 132.6 μmol/L (1.5 mg/dL) (56;71-73). An important issue in the allocation process is to match the suspected life of the transplant to the suspected life of the recipient. By avoiding giving young kidneys to elderly recipients it is possible to increase the overall graft life and thereby utilize the graft source as optimal as possible (74). Recently, a kidney donor risk index (KDRI) has been developed for estimating the risk of graft failure after transplantation (75). The Eurotransplant Senior Program (ESP) was launched in 1999 as an alternative old-for-old organ allocation system (76), and in the United States, a new allocation system named Life Years From Transplant (LYFT) is being considered (77).

1.6 The Norwegian experience with elderly kidney transplant recipients

The Norwegian kidney transplantation waiting list has, up to now, been kept relatively constant at below 50 per million inhabitants. This can be explained by a relative low incidence of ESRD (78) and an active living donor transplant programme (58;79). Patients have been accepted for kidney transplantation using a standard screening algorithm without a formal upper age limit. More than 20 years ago it was reported from our centre that transplantation was feasible even in selected patients beyond 70 years of age (80). Living
donations are also accepted, and in particular spousal donors are becoming increasingly common in this age group. Because we have one large transplant centre serving approximately 4.8 million inhabitants, and a liberal policy with kidney transplantation in elderly patients, we have, to our knowledge, the largest amount of data from a single centre describing kidney transplantation in the elderly.
2. AIMS OF THE STUDIES

The rising number of patients with ESRD placed on transplant waiting lists has led to the re-evaluation of selection criteria for transplantation, including in Norway. A common question is whether high age per se should be a contraindication for transplantation.

Primarily we wanted to evaluate outcomes in kidney transplant recipients older than 70 years and compare them with younger recipients, as well as identify clinical variables associated with good or poor outcome. We also wanted to compare outcomes of transplanted elderly patients with patients of the same age accepted for transplantation who had remained on dialysis while waiting for an appropriate organ. In addition, we also wanted to evaluate the use of older donors for older recipients.

We aimed to answer the following key specific questions:

1. Is kidney transplantation a safe and preferred treatment for elderly ESRD patients without an upper age limit?

2. Are there any pre-transplant or early post-transplant modifiable clinical variables relevant to kidney transplantation outcomes in the elderly?

3. Should kidneys from old deceased donors be discarded owing to their advanced age?

4. Is kidney transplantation superior to dialysis in elderly patients with ESRD?
3. SUBJECTS AND METHODS

3.1 Study design

3.1.1 Papers I - II

Survival data for all patients who received their first single kidney transplant at Rikshospitalet between 1990 and 2005 were retrieved from the Norwegian Renal Registry and analyzed as described in section 3.2.1. The patients were stratified according to their age at transplantation. The ‘elderly’ recipients, defined as those aged 70 years or older were compared with a group of ‘senior’ recipients aged 60 to 69 years old. These two groups were also compared with a control group consisting of ‘average’ adult kidney recipients at our centre (age 45-54 years).

Baseline clinical characteristics of the recipients were retrieved from the registry and from the Rikshospitalet hospital records. Information about traditional risk factors, immunosuppressive treatment, complications and hospitalisations were also retrieved. Comorbidity at transplantation (paper II) was quantified retrospectively using the Charlson Comorbidity Index, as described by Jassal et al (52). The calculation was individually performed for each patient based on review of hospital records.

3.1.2 Paper III

Medical files including survival data of all deceased donors older than 75 years, from whom single kidneys had been transplanted into recipients aged over 50 years, between 1990 and 2007, were retrieved and analysed. Data were retrieved from the same sources as for paper I and paper II. In addition, all graft biopsies obtained at transplantation and during the first
month post-transplantation were retrospectively analysed and scored by a blinded pathologist using both the Banff criteria (81) and the criteria defined by Remuzzi et al. (82).

3.1.3 Paper IV

Survival data for all patients starting dialysis in Norway between 1990 and 2005 were retrieved from the Norwegian Renal Registry. Patients accepted for transplantation and put on the transplantation waiting list were included in the study. Survival analyses using a time-dependant Cox model were performed in order to compare survival rates between transplanted patients and those remaining on the waiting list. In addition, clinical characteristics were retrieved from the registry and hospital records as described for the previous papers.

3.2 Statistics

A two-sided unpaired t-test or Mann-Whitney test was used, as appropriate, to compare groups. In paper I and II, the elderly recipient group was chosen as index for comparative analysis. Owing to the use of two tests to compare the index group versus the two other groups, Bonferroni correction was used and the level of significance for each test was set at 0.025 to achieve an overall level of significance of 0.05. Fisher’s exact test was used to analyse binary data. We performed logistic regression analyses to identify risk factors for acute cellular rejection.
3.2.1 Survival analysis

Survival data were assessed using the Kaplan-Meier method, uni-/multivariate Cox regression analysis, and a time-dependent Cox model (paper IV). The Kaplan-Meier curves were compared by the log rank test. The events defined as end points in the analyses were patient death (all papers), death-censored graft loss (papers I-III) and uncensored graft loss (papers I-III). Patient survival was defined as time from transplantation (all papers) or from waiting list/start of dialysis (waitlist group, paper IV) to patient death or censoring due to loss from follow up (emigration), end of study or transplantation (waitlist group, paper IV). Graft survival was defined as the time from transplantation to patient death, time to loss of graft function with need of dialysis, or to censoring as described for patient death. The graft survival was analyzed in two different models, with or without censoring for death with functioning graft. The analyses were implemented using SPSS® 15.0.

3.2.2 Kaplan-Meier method

The Kaplan-Meier method is commonly used for estimation of survival probability (83;84). Survival is the time to a predefined event, for example death or graft loss used in the present studies. In addition to defining the event, it is also important to define a distinct starting point for survival. In randomised clinical trials (RCT), the survival time is usually measured from the time of randomisation. We chose the time of transplantation as baseline for survival analysis in papers I, II and III. In paper IV, the time of waitlisting or start of dialysis (latest for both) was used as the starting point for the waitlist group, whereas in the transplant group, it was set at the time of transplantation as in the previous papers.
A patient may be censored from the survival analysis if they are, for any reason except for the defined events, lost to follow up or no longer fulfil the inclusion criteria. The most typical example is a patient who has not experienced the event when the study is terminated. These patients will be censored owing to the end of study. In the case of graft survival, death with a functioning graft may be regarded as an event. On the other hand, however, it is not known how long the graft would have survived if the patient had not died. In this case, death with a functioning graft could also be censored, and not counted as an event. Patients who withdraw from the study, for example due to emigration or if a patient chooses to do so, can also be censored from the survival analysis.

Figure 3. Survival of eight patients counted from date of inclusion in the study to reaching an event (♦) or to censoring due to loss of follow up (patient 3) or end of study (patient 1, 6 and 7). The length of each patient’s line represents their event-free survival in the study.

By using the Kaplan-Meier method, survival in the future can be estimated by analysing data from the past. The probability of survival is calculated for each point of time an event has taken place. For example, if the first event takes place at day 7, the probability of not
having an event during the first 6 days is 1.0. The cumulative probability of survival can be expressed: \(1.0 \cdot \left(1 - \frac{n-y}{n}\right)\), where \(n\) is the total number at risk and \(y\) is the number of events.

If there are 10 patients at the start of the study (day 0), the probability of surviving day 7 is: \(1.0 \cdot \left(1 - \frac{10-1}{10}\right) = 0.9\). If the next event takes place at day 17, the probability of surviving the time period from day 7 throughout day 17 is: \(\left(1 - \frac{9-1}{9}\right) = 0.89\) and the cumulative survival probability from the start of study throughout day 17 is: \(1.0 \cdot 0.9 \cdot 0.89 = 0.8\). If a patient is censored from the study between day 17 and day 33 when the next event takes place, this has to be taken into account when calculating the probability of survival during this interval. We know that 8 patients started this interval, one of them was censored, so only 7 survived until day 33 (n=7). In addition, one patient had an event at day 33 (y = 1) so 6 patients are left after day 33. The probability of survival from day 17 throughout day 33 is: \(\left(1 - \frac{7-1}{7}\right) = 0.86\) and the cumulative probability of surviving day 33 is: \(0.8 \cdot 0.86 = 0.69\). By using these values for cumulative survival, we can construct a Kaplan-Meier plot illustrating how the survival decreases with time.

![Figure 4. Cumulative survival illustrated with a Kaplan-Meier plot.](image-url)
From the plot we can easily interpret the cumulative survival at different times. It is possible to compare the survival between two test groups by using the log rank test (85). The log rank test is principally a chi square test that compares the relationship between observed and expected values. H₀ for the test is that there is no difference between the survival curves of the two groups. The test is convenient to use when the curves do not cross each other and when there are more than 10 subjects in each group. It is important to know that the log rank test is purely a test of significance. It cannot provide either an estimate of the size of the difference between the groups or a confidence interval. The log rank test is further described in statistical textbooks (86;87).

3.2.3 Cox proportional hazard models

A Cox proportional hazard model determines the relationship between hazard rates in different groups of the patient population. It is possible to compare the survival of different patient groups and account for confounding effects (88). In a comparison of two different treatment protocols, the hazard rate for the standard treatment is \( h_0(t) \) and \( h_1(t) \) for the new treatment. If it is assumed that the relationship between the two hazard rates is constant at any point of time during the whole treatment period, the hazard rates are proportional:

\[
\frac{h_1(t)}{h_0(t)} = \alpha \Rightarrow h_1(t) = h_0(t) \cdot \alpha .
\]

The complexity and usefulness of the model can be increased by introducing and adjusting for more variables. To avoid negative values of \( \alpha \), it is convenient to define \( \alpha = \exp(\beta) \).

With several variables included in the model, the equation for \( \beta \) is:

\[
\beta = \beta_1 x_1 + \cdots + \beta_n x_n,
\]

where \( x_1, x_2, \ldots, x_n \) are values of a set of variables and \( \beta_1, \beta_2, \ldots, \beta_n \) are regression coefficients. The variables can be continuous e.g. age, time on dialysis, cold ischaemic time,
or discrete e.g. gender or treatment modality etc. The general proportional hazard model can be expressed as \( h(t) = h_0(t) \exp(\beta_1 x_1 + \ldots + \beta_n x_n) \) where \( h_0(t) \) is denoted as the ‘baseline hazard’. The baseline hazard is a value that describes the hazard before new variables are included in the model. With this model, it is important that the variables are constant during the entire trial. If not, a model with a time dependant variable has to be used.

### 3.2.4 Time-dependant Cox model

In certain settings, as for example when the survival curves of the Kaplan-Meier plot cross each other as a result of changing hazards by time, it is necessary to create a model with a time dependant variable, to evaluate whether survival rates in the groups we are comparing are different from each other. In this case there is a time-varying risk factor (89). In paper IV, we defined two risk factors: 1) being on the waiting list and 2) transplantation. As many patients fall within both the waitlist and the transplant groups, they have two different hazards that need to be compared. In our model, we defined waitlist and transplantation as the two values of the time dependant variables. In addition we introduced several other possible confounders into the model as described in the result section, to ensure that the final result was also adjusted for these variables.
4. RESULTS

4.1 Paper I

In this paper, patient and graft outcomes in 301 ‘elderly’ kidney transplant recipients (≥ 70 years of age) were compared with 513 ‘senior’ recipients (60 – 69 years of age) and a ‘control’ group comprising 512 ‘average’ adult kidney recipients (age 45-54 years). A living donor transplantation was performed in 35% of patients; 17% in elderly recipients, 34% in senior recipients (P < 0.001) and 47% in control recipients (P < 0.001). Preemptive transplantation was performed in 19% of patients; 10% in elderly recipients, 18% in senior recipients (P = 0.003) and 25% in control recipients (P < 0.001). The elderly group had significantly lower rate of acute rejections during the first 12 weeks, compared with both the senior group (P = 0.005) and the control group (P = 0.002). Elderly and senior recipients had a higher incidence of death with a functioning graft during the follow-up: elderly 45%, senior 31% (P < 0.001), control 13% (P < 0.001). Five year patient survival was 56% in the elderly group, 72% in the senior group (P < 0.001) and 91% in the control group (P < 0.001). Cardiovascular disease (34%) and infection (27 %) were the most frequent causes of death. Five year graft survival was 53%, 70% and 84% in the elderly, senior and control groups, respectively. There were however no difference in graft survival when censoring for death with functioning graft. Consequently, the inferior graft survival in the elderly, reflects a natural higher risk of death with functioning graft.
4.2 Paper II

In this paper, potentially relevant clinical parameters for patient survival, graft survival and acute rejection were evaluated in ‘elderly’ (n = 354), ‘senior’ (n = 577) and ‘control’ (n = 563) recipients. Acute rejection during the first 90 days (HR 1.74 [1.34-2.25], P < 0.001), time on dialysis before transplantation (HR 1.02 per month [1.01-1.03], P < 0.001), and donor age ≥ 60 years (HR 1.52 [1.14-2.01], P = 0.004) were all associated with increased mortality in the elderly. Although comorbidity determined by the CCI score was not associated with increased mortality in the elderly group (HR 1.05 [0.98-1.12]), an association was found both in the senior (HR 1.17 per unit increase of the CCI score [1.08-1.27], P < 0.001), and control groups (HR 1.33 [1.19-1.48], P < 0.001). Delayed graft function (HR 3.69 [2.01-6.79], P < 0.001), donor age ≥ 60 years (HR 2.42 [1.30-4.49], P = 0.005) and presence of human leukocyte antigen (HLA) antibodies (HR 3.96 [1.38-11.37], P = 0.011) were independently associated with death-censored graft loss in the elderly. Treatment with AZA rather than MMF, any HLA-A or HLA-DR mismatch, donor age ≥ 60 years, and presence of HLA antibodies were associated with increased risk for early acute rejections (the first 90 days post-transplant) in all age groups.
4.3 Paper III

In this paper we investigated whether using kidneys from deceased donors with advanced age (older than 75 years) may be a way to increase the donor pool available for elderly patients with ESRD. Data from 54 single kidney transplantations using organs from 29 donors older than 75 (median 77.5, range 75.2-86.1) were assessed. Mean recipient age was 70.1 (range 50.6-82.4). 52 grafts (96%) had post-transplant function. Death-censored graft survival rates at 1, 3 and 5 years were 87%, 83% and 83%, respectively. Patient survival was 81%, 75% and 59% at the same time points. At follow up after a mean of 23 months (range 6-144 months), 35 recipients were alive with median serum creatinine level 163 μmol/L (range 103-348). Histological scores of graft biopsies obtained at transplantation and during the first month after transplantation did not predict graft outcome.

Figure 5. Graft outcome measured by serum creatinine after 1 year and at long term. Patients were categorized according to Global Kidney Score (GKS Banff) in graft biopsies obtained at transplantation.
4.4 Paper IV

In this paper we compared the survival of elderly kidney transplant recipients with similar aged patients who were accepted for transplantation but remained on dialysis. All patients older than 70 years who started dialysis between 1990 and 2005 and were waitlisted for kidney transplantation were included in the study. The patients were categorised according to the year dialysis was started (1990-1999 versus 2000-2005). Survival rates of 286 dialysis patients were analysed using a Kaplan-Meier model and a time-dependent Cox model. Comparisons were made between patients receiving a transplant and those who did not. In addition, the two time periods were compared. In the models, patients were censored from the waitlist group at the time of transplantation. The results were adjusted for age, sex, primary kidney disease, type of centre where dialysis was initiated (university vs. non university hospital), time on dialysis before waitlisting and dialysis modality. 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 patients starting dialysis after 2000 (HR for death 0.40 [0.19 – 0.83], P = 0.014). Although transplant recipients had an increased risk of death during the first year after transplantation, they had a long-term cumulative survival benefit compared to those remaining on dialysis. The median survival after transplantation increased from 3.7 (3.0 – 4.4) years in the 1990 – 1999 cohort, to > 6.7 years in 2000 – 2007 cohort. For those who did not receive a kidney transplant, the median survival after time of waitlisting did not change between the two periods; 3.4 (3.3 – 3.7) years versus 3.1 (1.8 – 4.4) years.
5. DISCUSSION

5.1 Importance of results

5.1.1 Paper I

This paper describes the outcomes of elderly kidney transplant recipients at our centre, compared with slightly younger recipients. The survival rates are compared with those described previously in the literature. As expected, the survival of elderly recipients is inferior to that of younger ones. The inferior graft survival reflects a natural higher risk of death with a functioning graft in the elderly. We concluded that the five year patient survival of elderly recipients is acceptable and seems to be better than the survival of age-matched patients on dialysis for whom it is previously described five year patient survival up to 30-35 % (24;90). However, we did not directly compare the survival between transplant recipients and waitlisted patients remaining on dialysis. Since transplant recipients constitute a selected group of patients with less comorbidity than the average age-matched dialysis population, it is not possible to use the results of this study to draw the conclusion that, in elderly patients with ESRD, the prognosis is better after transplantation compared to continuing on dialysis. To investigate this issue further it was necessary to perform a study directly comparing two groups with relatively similar degree of comorbidity. The study was therefore important for launching the subsequent studies, especially the study presented in paper IV.
5.1.2 Paper II

The aim of the second paper was to define modifiable clinical parameters relevant to survival after kidney transplantation in elderly recipients. The presence of an acute rejection episode was identified as a variable strongly associated with poor survival. This indicates that it is very important, especially in elderly recipients, to establish an immunosuppressive protocol that prevents rejections. Interestingly, in the senior and control groups acute rejection was only associated with an increased risk of graft loss, not patient death. A possible explanation might be that whereas younger recipients lose their grafts in rejection, the elderly lose their lives because of complications to the rejection treatment. We also defined variables associated with the development of acute rejection episodes and these did not differ between the age groups. In addition, in the elderly group, time on dialysis and advanced donor age were also found to be modifiable variables significantly associated with patient survival. Somewhat surprising, the CCI score did not provide any prognostic information for the elderly, in contrast to the effect of the CCI score observed in the two younger age groups. Our interpretation is that the present screening algorithm used at our centre for selecting patients for transplantation worked sufficiently and in addition, in elderly recipients, age by itself is more important than presence of comorbid conditions. The fact that the median CCI score was only 3 in the elderly group supports the view that patients with serious comorbidity had been effectively disqualified from transplantation. Analyses of comorbidity in European patients requiring RRT indicate that even though comorbidity is an important predictor for mortality, the influence of comorbidity may be less important than expected when adjusted for confounders such as age, gender, primary renal disease, treatment modality and country (91). Reducing time on dialysis before transplantation to a minimum and avoidance of acute rejections should, therefore, be important aims of the treatment in the elderly ESRD population. An old-for-old allocation
strategy may be an effective way to reduce waiting time for aged recipients (76:92-95). However, the risk of using donors of advanced age for transplantation must be weighed against the alternative i.e. permanent dialysis. With increasing waiting lists and a lack of organs, this may be a risk worth taking in order to provide kidney transplants to elderly patients.

5.1.3 Paper III

Even if kidney transplantation is established as the treatment of choice for a relatively large number of selected elderly patients with ESRD, it may not be feasible owing to organ shortages and priority given to younger recipients. With long waiting times, many elderly patients will die or become unsuitable for transplantation before they are offered a transplant (96). Given the present situation with a scarcity of organs worldwide, it is necessary to increase the organ pool if transplantation is to be implemented as a realistic alternative for elderly patients. We suggest that a way of increasing the donor pool is to use organs from elderly deceased donors, that otherwise would not have been made available, to elderly recipients. It has been suggested that pre transplant histology score of the donor kidney might help predict outcome and long term graft function in organs from ECD (97). These “scoring systems” have not been sufficiently evaluated. Thus it is possible that current practice with selection of donor kidneys for transplantation based on donor age and pre-transplant histopathology leads to a reduced number of available kidneys for transplantation. We concluded that donor age and histopathology alone could not supply us with enough information to determine if a kidney should be used for transplantation or not. However, it is important to realize the limitations of the analyses. The study is based on results from a
single centre, it is retrospective and the numbers of ECD transplants are low. Therefore, the results should be interpreted with caution.

5.1.4 Paper IV

In the fourth paper, we directly compared the outcome of kidney transplantation with the outcome of continuing dialysis in patients older than 70 years accepted for transplantation. The most important findings were 1) transplant patient survival over the last decade is superior to dialysis patient survival, and 2) the outcome of transplantation has improved markedly with the intensification of immunosuppressive protocols. There was actually no survival benefit of transplantation in patients included before year 2000. We believe that the most important reason for the improvement of outcome is the change of immunosuppressive protocol that was performed in 2000, as there apart from differences in immunosuppression, virtually were no major baseline differences between the patients of the two time eras. As shown in previous studies (12;38), although transplant recipients have an increased risk of death during the first year after transplantation, there is a significant survival benefit beginning after 2.5 years. In other words, in a selected population of elderly patients with ESRD, kidney transplantation may be the treatment of choice. This supports the statement made by Knoll in a recent review: “Until further evidence emerges, nephrologists should continue to view all of their older patients with ESRD as potential transplant candidates. If functional status is reasonable and no obvious contraindication is present (e.g., recent malignancy), then transplant evaluation should proceed with screening for cardiovascular disease and malignancy as suggested by guidelines” (98).
5.2 Study Design

A prospective randomized clinical trial is generally regarded as the optimal scientific approach for evidence based medicine (99). However, performing RCTs to compare the outcomes of dialysis and transplantation would not be considered ethical owing to the superior quality of life associated with transplantation compared with dialysis. As a consequence, the present studies were given a retrospective, observational design. Using this approach, it is possible to generate and test a hypothesis by identifying significant associations between several factors and outcomes. The potential of an observational study to make causal inferences is however less compared to an RCT (100;101). With a retrospective design, it is important that the groups compared are as equal as possible. In the evaluation of the survival benefit of transplantation versus dialysis (paper IV), the differences in baseline characteristics between the waitlist and the transplant groups were small. Therefore we regard the results as representative and reliable, despite the limitations of the retrospective study design. Obviously, when comparing the outcome in different patient groups, it is also important that the groups are comparable with respect to important outcome parameters. For example, in paper I, it is not surprising that survival in patients aged 60 – 69 years is better than in patients aged greater than 70, knowing that age is one of the most important risk factors for death.

When comparing patients receiving a kidney transplant with those continuing on dialysis, it is extremely important to be aware of the basis used for selecting patients for transplantation. Just comparing the survival of kidney transplant recipients with patients on dialysis would be incorrect, since the patients with least comorbidity are selected for transplantation. In order to make the groups comparable, it was necessary to choose a criterion describing the patients’ eligibility, namely being accepted for the transplant
waitlist. In paper II, it was important that all patients in the analysis were rigorously screened and treated for comorbidities before they were accepted for transplantation. In other words, our finding does not imply that comorbidity is not associated with the outcomes of kidney transplantation in elderly recipients. It only informs us that, in this age group, with the current established medical criteria for waitlisting, evaluation of comorbidity at transplantation does not help us predict patient outcome.

The precision of a study can be threatened by random errors. Random errors leads to increased variation of the data, but do not necessary interfere with the validity. On the other hand, systematic errors may bias the data in a way that threatens the validity of the study. Consequently, systematic errors are far more serious than random errors.

5.2.1 Internal validity

In the retrospective setting it is essential that the data collected are robust and reliable. If not, conclusions are drawn from unreliable sources (‘garbage in – garbage out’). The internal validity of a study is the representativeness of results for the particular population being studied. A study can be biased due to selection of patients to the study (selection bias), due to the measurement of the variables (information bias) or because of missing or incomplete control for confounders.

Selection bias

Selection bias are distortions that result from the procedures used to select subjects and from factors that influence participation (87). By having only one transplant centre serving the whole country and well established routines for reporting data to the registry, the input of data has been very satisfactory. In addition, the data collected in the Norwegian Renal
Registry have been rigorously controlled by the leader of the registry since its establishment, and virtually all patients starting RRT in Norway are included. As a consequence, the data of the Norwegian Renal Registry are probably among the most robust renal registry data world-wide, and the risk of selection bias in the registry data should therefore be almost negligible. However, it is also important that the extraction of data is performed correctly. By a mistake, 53 ‘elderly’, 64 ‘senior’ and 51 ‘control’ recipients transplanted between 1990 and 2005 were missed in the data extraction performed for paper I. The mistake was detected when an updated data set extraction for paper II was performed. However, a new survival analysis on the overall material revealed essentially the same results as originally published.

Information bias

Bias in evaluating an effect can occur from errors in obtaining the information. In addition to registry data, we also used data from hospital records to describe comorbidities, details of immunosuppressive treatment, and complications. Obviously, these data are more prone to individual variation, both by the surgeon/nephrologist responsible for registering data for the individual patient, and by the researcher extracting the data from the records. The variation caused by clinical data registration would mainly cause random errors influencing the precision of the estimates and not the validity. In order to make data extraction as consistent as possible, the process was performed by only one person. It is possible that this procedure may introduce a systematic information bias, for example because of misclassification of conditions giving score in the CCI. However, the finding that CCI score showed prognostic impact on the younger age groups, as expected from former analysis, supports the validity of our calculated indexes. The results could possibly have been even more robust if two researchers had performed the data extraction individually, compared results, and then reached consensus. The review of almost 1500 hospital records would
however be very time consuming, and we therefore decided to restrict this review procedure to one person.

Confounding

Confounding occurs when an investigator tries to determine the effect of an exposure on the outcome, but actually measures the effect of another factor, a confounding variable. A potential confounding variable has the following properties (102):

1. The variable must have an association with the disease i.e. it should be a risk factor for the disease
2. It must be associated with the exposure, which means that it must be unequally distributed between the exposed and the non-exposed groups
3. It must not be an effect of the exposure, nor be a factor in the causal pathway of the disease

![Figure 6. Properties of a confounder (102). Reprinted with permission from the Nature Publishing Group and the author.](image_url)

There are different ways to address confounding during study design including randomisation, restriction or matching. Confounding may also be controlled by adjustments after completion of the study by using stratification or multivariate analysis. In paper IV, the
groups being compared are restricted as they have acceptance for transplantation as a
criterion for inclusion. In addition, the background characteristics reveal only minor
differences between those patients who were transplanted and those who were not. This may
indicate that confounding was no major problem in the analysis. When adjusting for
potential confounders it is essential to know the value of the suspected variable. For
instance, smoking is known to be a risk factor for cardiac death and is therefore a potential
confounder in the survival analyses. Unfortunately, reliable information about smoking was
not available in our data set and by this; we were not available to control our analyses for
smoking habits.

5.2.2 External validity

External validity or generalization describes the relevance of the study to a specified patient
population. Although RRT is conducted at several nephrology units throughout the country,
the transplant activity is centralized at Rikshospitalet. The study, therefore, uses data from a
single transplant centre, which may be regarded as a limitation. It could be claimed that the
study describes the results of a national transplant policy that is not applicable to other
countries. However, the fact that all patients have been treated at the same transplant centre,
following the same acceptance criteria, and the same standard immunosuppressive protocol,
makes these data robust and may also bring additional strength to the study. Furthermore,
the robust and complete national Norwegian registry of RRT patients has made it possible to
perform the study with almost no patients being lost to follow up.
5.3 Methods

5.3.1 Kaplan-Meier method

The Kaplan-Meier method has already been described in detail. Even though the results are estimates of survival and not actual survival figures, the Kaplan-Meier method is generally accepted as the best way to describe survival. If a high percentage of patients included in the analysis reach an event, as was the case in our studies, the result becomes more representative of actual survival. Comparing survival between groups of patients by the log rank test is also well established in the literature (83-85). However, when the survival curves cross each other due to a change of risk in one of the groups, the log rank test is no longer applicable. In this situation it is necessary to introduce a time dependant variable as we did in paper IV.

5.3.2 Cox regression

The Cox proportional hazard regression method is widely accepted as a tool for identifying variables which impact on the outcome in survival studies. It is important to select the variables tested in the model based on best clinical knowledge. By introducing several variables and combining them in a multivariate model, it is possible to adjust the variables for each other and thereby get closer to the real independent impact of each factor. The number of variables included in the model should, as a rule, not exceed 10 % or the square root of the number of events (86). If there are a large number of potential explanatory variables, the variables eventually included in the multivariate model may first be tested in a univariate analysis. Only those variables having significant or near significant influence in the univariate analysis should then be implemented into the multivariate model. In our
analysis of variables associated with patient death in paper II, there were 237 events in the elderly group, and after univariate testing, we eventually implemented 13 variables into the multivariate model. When selecting variables, it is also important to be aware of the effect of, and adjust for, confounding factors. In addition, during the interpretation of the results, it is important to be aware that there may exist unknown or unmeasured confounders not implemented in the model.

5.4 Ethical considerations

In the context of organ shortage, transplantation of elderly patients may become an ethical issue. Even if we have justified that kidney transplantation, when successful, improves both the survival and the quality of life for selected elderly patients with ESRD, an ethical dilemma arises when a kidney is allocated to an elderly person implicating that a young person on the waiting list has to wait longer for an appropriate organ. On the other hand, elderly patients are more likely to die on the waiting list, and it is therefore important to reduce the waiting time as much as possible. It is possible to increase the organ pool by increased use of ECDs as we have described in paper III. An old-for-old 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. This can be implemented without simultaneously increasing the waiting time for younger patients on the list. Giving organs of potential “lower-quality” to elderly recipients, raises further both moral and ethical considerations. The policy of using ECD to older recipients has, however, already been adopted with success in several countries, and elderly transplant candidates are among those who are most likely to receive optimal benefit from ECD kidneys (103).
6. CONCLUSIONS AND IMPLICATIONS

6.1 Paper I

We found no difference in graft survival between elderly, senior and control patients when censored for death with a functioning graft. As expected, the elderly and senior recipients had inferior survival, compared with the control group. Given the poor prognosis of these patients in dialysis we consider a 5-year patient survival rate of 56% in patients over 70 years of age to be acceptable. Elderly patients with ESRD should be considered for transplantation, and a selected group should be offered the option.

6.2 Paper II

Long time on dialysis was associated with reduced survival in kidney transplant recipients over 70 years of age. Low acute rejection rates improved outcomes for elderly kidney recipients. CCI score at transplantation did not provide a benefit in the selection of elderly patients for kidney transplantation, although it is known to be useful in younger patients. To obtain the best results, treatment of elderly recipients should aim at reducing time on dialysis before transplantation and avoid acute rejection episodes.

6.3 Paper III

Kidneys from deceased donors over 75 years perform acceptably as single transplants and should be considered for use in elderly recipients. Two selected histological graft score systems gave no supplementary information on the long-term outcome of the graft.
6.4 Paper IV

Elderly patients (≥ 70 years old) on dialysis treatment, who fulfil the established medical criteria for transplantation, have improved survival following kidney transplantation, compared with patients accepted for transplantation but continuing dialysis. There has been a substantial improvement in long-term survival over the last decade, partly due to a more potent immunosuppressive protocol. Given a sufficient supply of organs, transplantation may be the preferred treatment for selected elderly patients with ESRD.
6.5 Answers to the research questions

Our initial key questions may be answered as follows:

1. Kidney transplantation is safe for selected elderly ESRD patients and should be the preferred treatment without an upper age limit.

2. Time on dialysis prior to transplantation and frequency of acute rejection episodes are modifiable clinical variables relevant to improve kidney transplantation outcomes in the elderly.

3. Kidneys from old deceased donors should not be discarded just because of advanced age.

4. Kidney transplantation is superior to dialysis in elderly patients with ESRD fulfilling the established criteria for acceptance onto a kidney transplant waiting list.
7. FUTURE RESEARCH

7.1 Health economic analyses

Our project was not designed as a health economic study. We have, therefore, not evaluated the economic aspects of transplantation versus continuing dialysis in our elderly study population. Previous studies have revealed that kidney transplantation is the most cost-effective and preferred mode of RRT (33;104). In a paper from Sweden, the annual cost of RRT is estimated to be $70,796 for a patient on haemodialysis, and $46,018 for a patient on peritoneal dialysis. Kidney transplantation is estimated to cost $70,000 during the first year, and $14,159 per year thereafter with a functioning transplant (105). Obviously, the exact costs will vary between countries depending on the organisation and financing of medical care in each country. The costs may also vary according to the age of the patients. A health economic study comparing the costs related to various types of RRT will, therefore, provide important information to help determine future priorities for RRT.

7.2 Prospective evaluation of comorbidity

It may not be possible to perform an RCT comparing the outcomes of kidney transplantation with dialysis. However, it may be possible to investigate the impact of comorbidity in a prospective manner. If comorbidity data (CCI) was reported systematically to the registry at the start of RRT and at the time of transplantation, the effect of comorbidity could be studied prospectively, not only in the elderly, but in all age groups.
7.3 Immunosuppression

In paper II we found an association between acute rejection episodes and poor survival in elderly kidney transplant recipients. In paper IV we found that there were significant improvements in survival after the introduction of newer and more potent immunosuppressive protocols. In the retrospective setting, however, we cannot provide evidence for the causal inference between the level of immunosuppression and the outcome. It has been proposed that MMF is perhaps less safe than AZA in the elderly (106), but our study has shown that survival has improved over the last decade following the introduction of MMF. Furthermore it is debated whether other strategies as for example induction therapy with thymoglobulin/IL-2R antagonist agents or delayed introduction/avoidance of calcineurin inhibitors, may be beneficial in a setting with elderly donors and recipients (107-110). There is definitely a need for further prospective studies evaluating optimal immunosuppression strategies in elderly recipients (111).

7.4. Graft preservation

It is possible, and likely, that grafts from ECDs may benefit from improved methods of graft preservation including artificial extra-corporeal circulation of the graft (112) and new perfusion solutions. In addition, the ideal balance between short ischaemia time and good immunological match has yet to be established.
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