Clinical and socioeconomic aspects of kidney transplantation

Mirjam Laging

Clinical and Socioeconomic Aspects of Kidney Transplantation

Klinische en socio-economische aspecten van niertransplantatie

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Introduction

According to the Dutch Kidney Foundation (Nierstichting) 1 in 10 inhabitants of The Netherlands suffer from impaired renal function (1). Chronic kidney disease (CKD) is a life threatening condition that is associated with an increased risk of cardiovascular disease. Patients with stage 5 CKD, end stage renal disease (ESRD), require renal replacement therapy (RRT). In The Netherlands the number of patients undergoing RRT is growing (Figure 1). At the start of 2016 16,727 patients were on RRT, that is 0.1% of the Dutch population (2). The increase of patients on RRT may be caused by an increase in CKD patients, an increase in the number of patients accepted for RRT, and an improvement of survival of patients on RRT.

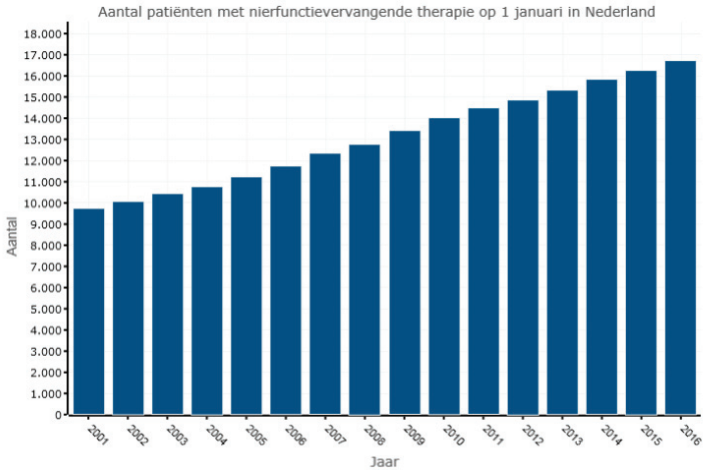

Figure 1. Number of patients on renal replacement therapy on January 1 in the Netherlands per year. Source: Renine 1-1-2016, Nefrovisie (2).

Compared to dialysis and deceased donor kidney transplantation, living donor kidney transplantation (LDKT) is the best treatment for patients with ESRD resulting in higher life expectancy and better quality of life (3-5). However, comparison of mere treatment options for patients with ESRD is complex, because of wide variation in patient characteristics and the lack of randomized controlled studies. Patients accepted for kidney transplantation are a selected

group of end stage renal disease patients. They are selected on physical condition and on an acceptable peri-transplant death risk.
Ideally, all patients with ESRD should be transplanted if their condition allows this. However, some patients choose to start or remain on dialysis, whereas others experience contraindications to transplantation. Acceptance criteria for kidney transplantation have been subject to change over time. While age above 40 years used to be an absolute contraindication in the early years of transplantation, currently even old age is only a relative contraindication. Nowadays, absolute contraindications are metastatic solid tumor, active infections, severe liver disease, and serious heart conditions. Though without absolute contraindications, patients with relative contraindications are less often referred for transplantation than patients without any contraindication (6). These patients with relative contraindications are often elderly, have comorbidities, or have incomplete management of the language. It is questionable whether these patients should be rejected for transplantation. It is not known if they are doing worse after transplantation.
Once patients have been accepted for transplantation, the next challenge is to find them a kidney with the best possible outcome. A living donor kidney transplantation is not attainable for all patients accepted for transplantation, as not all ESRD patients succeed in finding a suitable living donor. Patients without a living donor, will be placed on the deceased donor waiting list for kidney transplantation. However, placement on the waiting list does not guarantee that patients receive a kidney offer. Waiting times vary between patients, dependent on ABO blood types and human leukocyte antigen (HLA) typing, between 0 and 5 years. For patients with high titers of HLA antibodies waiting times may reach up to 10 years.

Factors influencing access to kidney transplantation

Inequality in access to kidney transplantation results from several factors. Medical factors, such as ABO blood type and sensitization, may complicate finding a match (7). For highly sensitized patients and patients that are incompatible with their donor in terms of ABO blood type or a positive crossmatch, the acceptable mismatch program and the Dutch national living donor kidney exchange program were developed (8, 9). Alternatively, ABO

incompatible donor-recipient pairs can participate in ABO-incompatible transplantation programs, in which recipients are pretreated to lower the concentration of isoagglutinins anti-A or anti-B before transplantation (10). Likewise, desensitization of highly sensitized patients and recipients of HLA incompatible transplants increases transplant chances for this patient population (11, 12). Though age is not a factor used in deceased donor kidney allocation programs, recipient age is associated with reduced access to kidney transplantation, because elderly patients are less likely to be referred (6, 13, 14).

The presence of comorbidity may also reduce accessibility to transplantation (6, 15). Important factors reducing access are cardiovascular disease, diabetes, obesity, HIV, and other infections. The cause of ESRD influences access as well, as patients with diabetic ESRD have been demonstrated to have reduced access (14, 16).

Several studies showed that patients living in socially deprived areas had a lower chance to be considered for transplantation. Socioeconomic factors influencing access were ethnicity, education level, income, substance abuse, marital status, and socioeconomic status (6, 14, 15, 17-20).

More specifically, access to LDKT was influenced by recipient age, ethnicity, socioeconomic status, ABO blood type, and panel reactive antibody (21-24). Modifiable factors such as knowledge, communication, and early transplant awareness were found to be associated with the ethnic inequalities in access (22, 25).

Factors influencing patient and graft survival

Various recipient, donor, donor-recipient combination, and transplant factors influence patient and graft survival. Throughout the years survival improved considerably, because of better immunosuppressive medication and improved surgical and diagnostic techniques, while the increasing number of LDKT played a role as well (Figure 2).

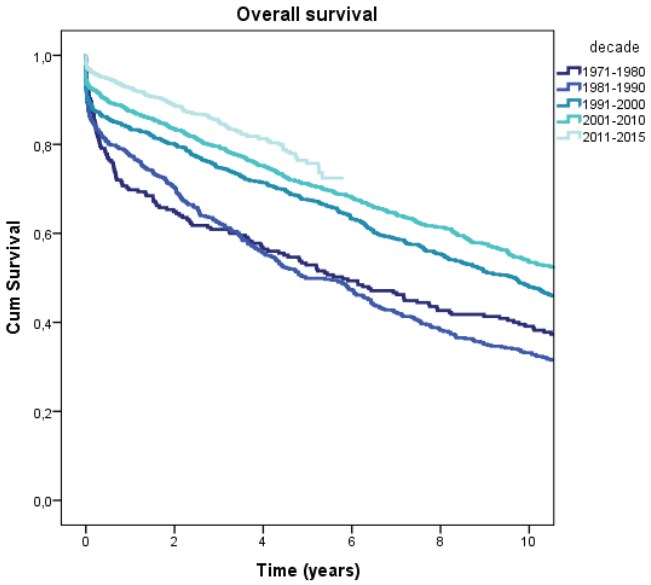

Figure 2. Kaplan-Meier survival curve comparing overall graft survival per decade in the population transplanted in Rotterdam between 1971 and 2015 with a living or deceased donor kidney.

The scope of research in transplantation broadened from mainly immunological and surgical factors in the early years to non-immunological and social factors in recent years. Most studies on the influence of socioeconomic variables on the influence on survival have been performed in the USA, showing that they have an influence on graft and patient survival (20, 26, 27). Would that also hold true for a socially organized country as the Netherlands with an adequate health system with equal chances for everyone?

The influence of HLA mismatches has been studied in various ways and though unmistakably important, it raises questions (11, 28-35). How important is HLA matching compared to other variables influencing graft survival? Should we reject a completely HLA mismatched living donor kidney in order to wait for a better HLA matched deceased donor kidney? The same question holds for donor age. Should we reject an older living donor in order to hope and wait for a younger deceased donor kidney?

The influence of comorbidity on the results of renal transplantation can only be properly studied in a population with a high proportion of comorbidities. As

patients with comorbidity have limited access to transplantation, literature is hampered by relatively low numbers (36, 37). Besides, the effect of comorbidity on survival after kidney transplantation has mostly been studied using a general score from which applicability to the transplant population can be questioned (38). A new study in a population with a high number of patients with comorbidities, using a customized score, is warranted.

Aims and outline of this thesis

The aim of this thesis is twofold: first, to find out which factors influence access to living or deceased donor kidney transplantation. The other aim is to find out which factors influence graft and patient survival once transplantation is performed. All studies were performed using large samples from a single center cohort.

In **chapter 2** we describe what happens to patients that are being placed on the waiting list for kidney transplantation. Outflow patterns for patients on the waiting list are visualized. The influence of age on these patterns is described. In **chapter 3** both clinical and socioeconomic factors influencing access to living donor kidney transplantation are studied. The effect of these factors on graft and patient survival is described in **chapter 4**. In **chapter 5** we study the influence of donor age on graft survival censored for death in a multivariable model. In **chapter 6** the influence of HLA mismatches on graft survival censored for death is studied, corrected for various other factors. In **chapter 7** the influence of comorbidity on graft and patient survival is studied. We describe the development of a new score, the RoCKeT score, to measure the degree of comorbidity in transplant patients. Finally, in **chapter 8** a general discussion of the results obtained in this thesis is provided.

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2

Increasing age decreases the chance to become transplanted: A plea for stimulating living donation for elderly patients

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Abstract

Age criteria for kidney transplantation have been liberalized throughout the years resulting in more waitlisted elderly patients. In this retrospective cohort study we analyzed how age influenced the chance to become transplanted. Between 2000-2013, 2643 patients were placed on our regional waiting list. Waiting time was defined as the period between start dialysis and being delisted. Patients were categorized according to age at inflow. In February 2016, 1907 (72%) patients had been transplanted, 290 (11%) had been delisted without a transplantation, 256 (10%) had died, and 190 (7%) were still waiting. When comparing the age groups, outflow patterns were completely different. Within 6 years 93% of the population <25 years had received a transplant, the vast majority from a living donor. In the population >64 years 55% had been transplanted, slightly more than half of the recipients with a living donor kidney. In the population >54 years without a living donor approximately 50% had died or had been delisted without a transplant and will never become transplanted. In order to improve the survival of patients over 54, living donor kidney transplantation should be promoted in this population.

Introduction

Over the years, acceptance criteria for kidney transplantation have been eased. For instance, strict age criteria for transplantation have been liberalized (1-3), resulting in an increase in the representation of elderly patients on the waiting list. In most studies, elderly was defined as 65 years and older. Although recipient age is known to be an important independent variable determining the all-over outcome of kidney transplantation, patient survival is better in the elderly population that received a kidney transplantation, compared to dialysis (2-4). However, age is still an important factor for non-referral (5, 6).

Patients are preferentially transplanted with a living donor kidney, because the outcomes of living donor transplantation are superior compared with those of deceased donor transplantation (7). Besides, living donor transplantation can be performed without the delay of waiting time. When no living donor is available, patients accepted for transplantation are placed on the waiting list for a deceased donor transplant. In our center a liberal policy regarding acceptance of donation after cardiac death (DCD) and donation after brain death (DBD) kidneys for transplantation is applied. Our center participates in Eurotransplant Senior Program (ESP). In the Netherlands the availability of deceased donor organs has been stable throughout the years. In the Eurotransplant area, waiting time starts when dialysis is started. Unfortunately, waiting times may be up to several years, while both age and waiting time are important risk factors for death on the waiting list (8, 9).

In many countries living donor transplantation is performed on a large scale or even outnumbers deceased donor transplantation. However, patients that do not find a willing or suitable living donor remain dependent on the waiting list for a deceased donor kidney. How are the chances for a kidney transplant of patients on the waiting list and what is the influence of age on these chances?

To answer these questions, we studied whether outflow reasons differed between age groups.

Materials and methods

Study sample

Between January 1, 2000 and December 31, 2013 2663 patients had been placed on the regional waiting list for kidney transplantation. Twenty patients were removed from the waiting list; 6 due to wrong listing and 14 since they had recovered from their disease. Consequently, 2643 patients were included in this retrospective cohort study (see Figure 1). Waiting time was defined as time between first dialysis date and being removed from the waiting list. For enlisted transplant patients whose transplant failed within 90 days, waiting time for the previous transplant was added to current waiting time.

The waiting list was retrieved from Eurotransplant. For patients for whom no start dialysis date was present in the Eurotransplant database, patient files of our hospital system were checked. This resulted in 147 corrections. In 56 cases (2.1%) information on dialysis could not be retrieved from the patient file. In these cases Eurotransplant data were used which means that for these patients waiting time was zero as dialysis was supposed not to have been initiated. Patients were categorized according to age at inflow on the waiting list: group 1: <25 (n=122), group 2: 25-44 (n=603), group 3: 45-54 (n=591), group 4: 55-64 (n=757), and group 5: >64 years (n=570). In the oldest age group 58 patients were above 74 years and 7 patients were 80 years or older. Reasons of outflow from the waiting list were: 1) died or delisted, 2) still on the waiting list, 3) deceased donor kidney transplantation (DDKT), and 4) living donor kidney transplantation (LDKT). Patients transplanted outside Eurotransplant received a living donor kidney and thus were included in LDKT. Observation was until February 9, 2016.

Statistical analyses

Chi-square tests were performed to test the difference in outflow reasons between the age groups and ABO blood types. For transplanted patients, patient survival with functioning graft was studied using Kaplan-Meier survival analysis. Survival curves were generated to test the influence of age. Follow-up was until graft failure, death, or end of observation (February 9, 2016). Cases with missing values were excluded. SPSS version 21 (IBM Corporation, Armonk, NY)

was used to perform all statistical analyses. *P*-values <0.05 were considered significant.

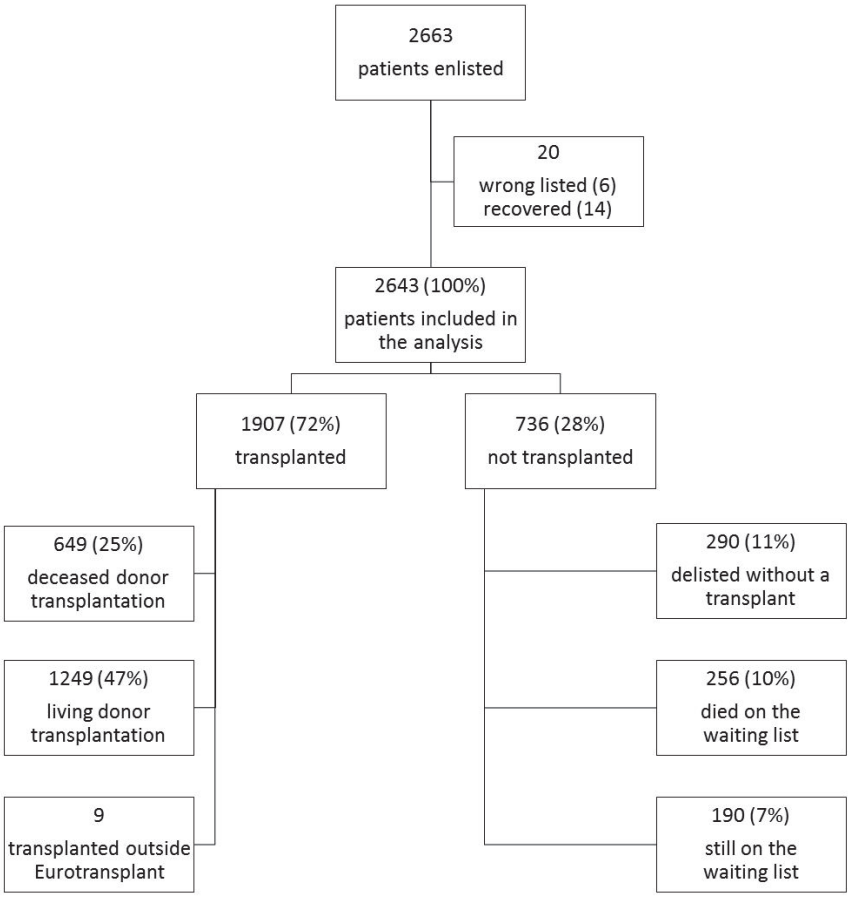


Figure 1. Flowchart of outflow of patients enlisted between January 2000 and December 2013. End of observation was February 9, 2016.

Results

Out of the 2643 waitlisted patients 1907 (72%) had been transplanted before February 2016: 649 patients had received a DDKT, 1249 a LDKT, and 9 had been transplanted outside Eurotransplant (Figure 1). Out of the 736 (28%) patients that had not been transplanted 290 had been delisted without a kidney transplantation and 256 had died while on the waiting list. The remaining 190 (7%) patients were still waiting in February 2016.

In Figure 2 the reasons of outflow per year for the total population and per age group are shown. The X-axis shows waiting time in years after dialysis was started, the Y-axis shows the percentage of patients. White represents the patients still waiting. In none of the age groups 100% was waiting at time point 0 which means that patients were preemptively removed from the list because of transplantation or because of death or illness. Figure 2 shows that preemptive transplantation (time point 0) decreased with age group, while the percentage of patients that had died or had been delisted before start of dialysis increased with age.

After 6 years on the waiting list 93% of patients in the youngest group had been transplanted, the vast majority (75% of total outflow) with a LDKT (Figure 2; light blue). Both the percentage of patients transplanted after 6 years and the proportion of LDKT decreased with increasing age. In group 55-64 years 66% and in group >64 only 55% had been transplanted, the latter slightly more than half (30% of total outflow) with a LDKT. The differences between the age groups occurred within the first few years. In all age groups most LDKTs had been performed within 2 years after start dialysis. However, this accounted for the majority (70%) of younger patients but only for a minority (25%) of older patients. From 2 years onwards, LDKT leveled off, while the proportion of DDKT (middle blue) gradually increased over time. In the first few years the proportion of patients that had died or had been delisted without a transplant (dark blue) increased with age. After 2 years 23% of patients in the oldest age group had died or had been delisted. The percentage leveled off after 4 years. In the oldest two age groups yearly more patients had died or had been delisted compared with those that had received a DDKT.

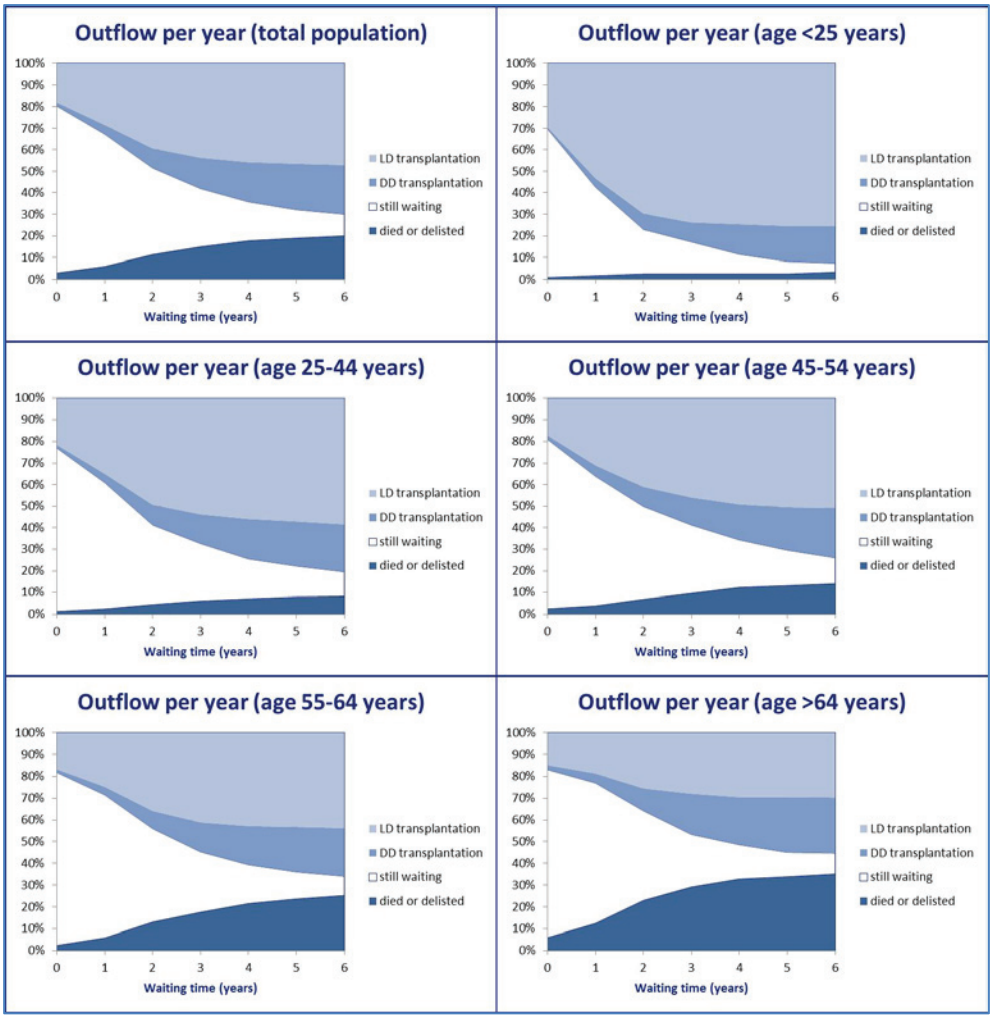


Figure 2. Percentage of patients that died/were delisted (dark blue), still waiting (white), or underwent deceased donor (DD; middle blue) or living donor (LD; light blue) kidney transplantation per year for the total population and for each age category. Patients that were not still waiting on time point 0 had been pre-emptively transplanted, had died or had been delisted before dialysis had started.

In Figure 3 the reasons of outflow at the end of observation are shown per age group. Reasons of outflow significantly differed between the age groups (P<0.001). In the youngest age group at the end of observation the majority had received a LDKT (light blue) and 96% had been transplanted with either a

LDKT or DDKT. In the population from 55 years and older a minority had received a LDKT; for patients >64 years even less than a third.
Figure 3 also shows the outflow percentages after exclusion of LDKT. In the population <25 years without a living donor by far most patients (83%) had received a DDKT. Conversely, in the oldest two age groups a minority had received a DDKT whereas almost half of these patients had died or had been delisted without a kidney transplantation.
In the population above 54 years without a living donor, ABO blood type did not have a significant influence on outflow (P=0.436). The percentages that had died or had been delisted at the end of observation were: Blood type A: 49%, AB: 44%, B: 48%, and blood type O: 48% (data not shown).
Kaplan-Meier analysis was used to study survival of transplanted patients. Out of 1907 patients 67 (3.5%) cases had missing values. Consequently, 1840 cases were included in the analysis (614 DDKT and 1226 LDKT). There were 562 events; 322 graft failures (140 DDKT and 182 LDKT) and 240 deaths (105 DDKT and 135 LDKT). Recipient age had a significant influence on patient survival with functioning graft (P<0.001; Figure 4). In the oldest age group after 10 years 37% of patients were still alive with functioning graft. After 2 and 6 years survival was 81% and 61% respectively.

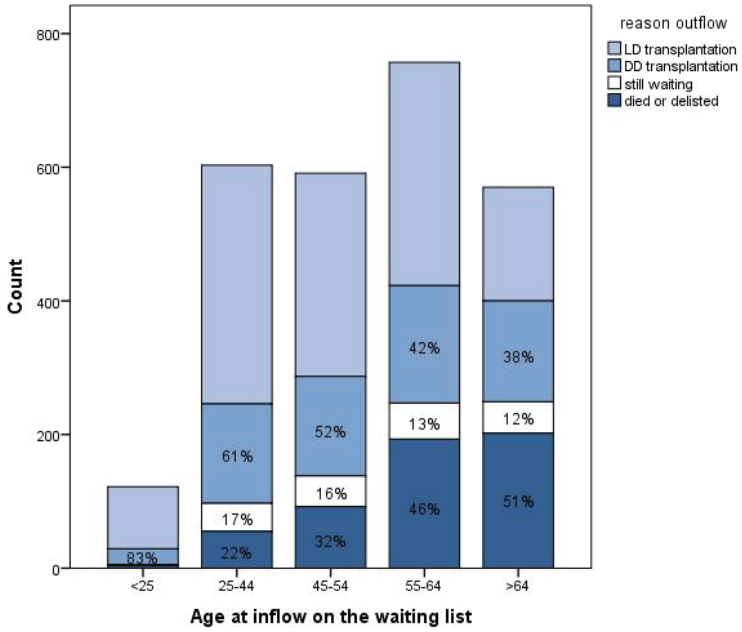
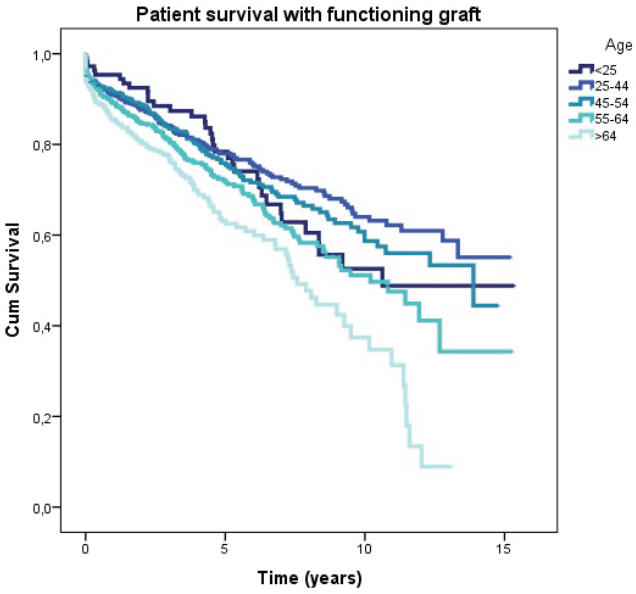


Figure 3. Number of patients that had died/had been delisted (dark blue), were still waiting (white), or had received a deceased donor (DD; middle blue) or a living donor (LD; light blue) kidney transplantation at the end of observation (February 9, 2016) per age category. Percentages given are after exclusion of living donor kidney transplantation.



Number at risk				
Age group				
<25	108	55	16	2
25-44	479	242	81	2
45-54	432	189	57	0
55-64	503	182	41	1
>64	318	97	14	0

Figure 4. Kaplan-Meier survival curve comparing patient survival with functioning graft (P<0.001) for the various age groups. After Bonferroni correction for multiple comparisons (α=0.005) the differences between <25 and >64 years (P=0.002), between 25-44 and 55-64 years (P=0.002), between 25-44 and >64 years (P<0.001), and between 45-54 and >64 years (P<0.001) were significant.

Discussion

For patients that are being placed on the waiting list for DDKT the most relevant question is how long they will have to wait for a kidney offer. To answer that question, the median waiting time can be given. However, that does not take into account other reasons for delisting; LDKT, death, or a worsened condition. Thus, an additional question that should be answered is whether or not they will survive the waiting time and stay in adequate condition until transplantation. To date, only a few papers were published in which all reasons of outflow from the waiting list were taken into account (10-12). In 2009 Schold and colleagues found that nearly half of elderly (above 60 years) waitlisted patients were estimated to die before DDKT (10). However, results were not compared with those of younger patients as they were not included in the study. Moreover, the Kaplan-Meier analysis that was used is known to overestimate outcomes. In this study competing events were not accounted for. Kaplan-Meier analysis provides "conditional" probabilities only, for instance the probability of receiving a DDKT after 5 years if nothing else happens (i.e. death, delisting, LDKT). To overcome the problem of overestimation, the competing risk method can be used to analyze outcomes of patients on the waiting list (11-13). Sapir-Pichhadze et al. recently described the difference in risk estimation by conventional and competing risk analysis (13). The competing risk method predicts individual chances to become transplanted based on specific characteristics/patient profiles. Variables that were found to significantly influence the chance of becoming transplanted were age, ABO blood type, PRA, and HLA frequency (11, 12). However, such individual predictions should be communicated with caution as these chances are no guarantee for an individual. The purpose of the present study was to show what happened to patients of various age groups that had been placed on our waiting list. It is not a risk estimation, but a straightforward method that clearly visualizes outflow patterns for groups of patients. Overestimation is prevented as all outflow reasons were present in the same analysis, excluding competition between events.

In the current study large differences in outflow from the waiting list between the age groups were found. In the highest age categories respectively 25% and 35% of patients on the waiting list were not transplanted because they had died or their condition had worsened. For patients that presented without a living

donor, percentages were even worse. At least half of patients aged >54 years without a living donor will never be transplanted compared with a quarter of patients aged 54 years or younger (Figure 3). As was shown, the number of elderly patients that had died or had been delisted increased profoundly in the first years after start dialysis. As the mean waiting time for DDKT is 3 to 4 years, they cannot afford waiting for a deceased donor kidney. The chance of receiving a DDKT is also influenced by ABO blood type and PRA. In a previous study we found that patients with ABO blood type O and patients with a PRA >85 have a significantly longer waiting time (14). In the present population above 54 years without a living donor and thus dependent on the waiting list for a kidney transplantation, ABO blood type did not have a significant influence on final outflow. Therefore, for all elderly potential recipients on the waiting list, it is important to find a living donor, independent of ABO blood type. However, in the elderly population LDKT lags behind. Their network of contemporaries is small while recipients' adult children are less likely to donate (15). This means that for transplantation elderly are more dependent on deceased donors through the waiting list. It is known that there is a high burden of comorbidity in the population with renal disease that negatively influences survival. When waiting time for a deceased donor kidney transplantation exceeds survival of these elderly patients they wait in vain and will never be transplanted.

A reduction of racial disparity in access to LDKT has been attained by including patients' social networks in education on renal replacement therapies using house call interventions (16, 17). Such interventions may be useful in the elderly population as well. They could try to find peers, relatives, or other persons from their social network to donate to them.

As expected, patient survival was found to be worse for elderly transplant patients. However, their survival was good considering that some had already spent several years on dialysis. It should be kept in mind that transplanted patients are a selection of the population and that only the influence of age on survival was studied. The analyses were uncorrected for donor type, waiting time, comorbidity etc. In previous studies age was shown to be an independent factor influencing both graft and patient survival (18, 19). As uncensored patient survival was studied, Kaplan-Meier analysis was not influenced by competing events.

The strength of this study is that it includes a relatively large patient sample with a low number of missing values. Besides, our study is a plain and comprehensible method to compare outflow patterns in various groups of patients. It surpasses the limitations of Kaplan-Meier analysis, that studies only a single outflow reason at a time, and the complexity of competing risk analysis, that only shows individual effects and no group effects.
In the Eurotransplant area waiting time is calculated from start dialysis onwards. With this uniform definition waiting time depends on patient disease status and not on subjective factors. Patients can be put on the waiting list before dialysis was initiated but their chances are low as long as they are not on dialysis. The definition of waiting time may be different in other allocation systems, where waiting time starts at placement on the waiting list and is independent of start dialysis. This could distort outflow patterns.
A possible limitation of single center studies in general may be generalizability. In our center there is a relatively large population of LDKT recipients. In the population that received a LDKT, younger patients and patients without comorbidity are overrepresented (19). However, still a large percentage of the elderly received a LDKT. Although patient selection on medical reasons cannot be completely ruled out, DDKT allocation is independent of the presence of a LDKT program. After exclusion of the LDKT population it is obvious that the elderly population that is dependent on DDKT lags behind and half of them are removed from the waiting list without a transplant. In centers without a LDKT program, percentages of elderly patients delisted without a transplant may even be worse.
In Eurotransplant deceased donor allocation, apart from ESP and pediatric status, age is not a selection criterion for matching. Allocation policy of Eurotransplant is comparable to policies in for instance the USA, UK, Scandinavia, and Australia and New Zealand (20-24). Generally, the most important matching criteria in all allocation systems are ABO blood type, HLA-matching, waiting time, and distance from donor hospital.
Another limitation is that no information on transplantable urgency was available. The proportion of (temporarily) not transplantable elderly patients could be higher than the proportion of (temporarily) not transplantable younger patients. This may have led to longer waiting times, less transplants, and more

delisting/deaths in the older age groups. In the future transplantable urgency should be registered so that in follow-up studies this information can be taken into account to verify the outflow patterns. Ideally, all periods of being temporarily not transplantable should be taken into account, as it may reflect the less fit patients.

In conclusion, the chances for kidney transplantation of patients aged >64 years on the waiting list are low. This holds true for patients aged 55-64 years as well. Thus, the disadvantages of aging start at 55 years in the population with renal disease. For elderly patients without a living donor the chance of receiving a DDKT is relatively small as well. They cannot afford waiting for a DDKT. In order to improve their survival LDKT should be promoted in elderly renal disease patients.

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3

Accumulation of unfavorable clinical and socioeconomic factors precludes living donor kidney transplantation

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Abstract

Background. In the past 30 years, the number of living donor kidney transplantations has increased considerably and nowadays outnumbers the deceased donor transplantations in our center. We investigated which socioeconomic and clinical factors influence who undergoes living or deceased donor kidney transplantation.

Methods. This retrospective study included all 1338 patients who received a kidney transplant between 2000 and 2011 in the Erasmus MC Rotterdam. Clinical and socioeconomic variables were combined in our study. Clinical variables were recipient age, gender, ethnicity, primary renal disease, retransplants, ABO blood type, panel-reactive antibody, pretreatment, and transplantation year. Each recipient's postcode was linked to a postcode area information data base, to extract demographic information on urbanization level, percentage non-Europeans in the area, income, and housing value. Chi-square, analysis of variance, and univariable and multivariable logistic regression analyses were performed.

Results. There were significant differences between the recipients of a living versus deceased donor kidney transplantation. In multivariable logistic regression analyses, 10 variables had a significant influence on the chance of receiving living donor kidney transplantation. Clinical and socioeconomic factors had an independent influence on this chance. Patients with ABO blood type O and B have smaller chances. Highly sensitized and elderly patients have smaller chances especially when combined with a collection of other unfavorable factors. Accumulation of unfavorable factors in non-Europeans prevents their participation in living donation programs.

Conclusion. Both clinical and socioeconomic factors are associated with participation in living or deceased donor kidney transplantation. This study highlights the populations that would benefit from educational intervention regarding living donor transplantation.

Introduction

In our center, the number of living donor kidney transplantations (LDKT) has increased considerably during the past 30 years, but LDKT does not seem to be equally accessible for all populations.

A number of clinical factors are known to influence the chance of living donor transplantation, for example, ABO blood type and panel-reactive antibody (PRA). In a previous study, we found that, although 44% of patients on our waiting list have a non-European background, only 15% of actual living donors have a non-European background (1). There are far less living kidney donors in all non-European populations in comparison with the European population, and there are differences in characteristics between European and non-European living kidney donors. However, differences between various non-European populations were not significant. The non-European populations studied immigrated to The Netherlands after the Second World War. Indonesians arrived in the 1950s; Moroccans and Turkish in the 1960s; and Surinamese, Antilleans, and Africans in the 1970s. For many, socioeconomic factors were the driving force behind their immigration. The non-European population that has resided the longest in The Netherlands is the most integrated in Dutch society and has the highest level of LDKT (1). This suggests that although ethnicity is likely to contribute, socioeconomic factors may also play a role in willingness to donate a kidney. These findings led to the following questions: What is the influence of clinical and socioeconomic factors on participation in living versus deceased donor transplantation programs? Is there interaction between these factors and ethnicity in their influence on the chance of living donor transplantation?

Materials and methods

This retrospective study includes all adult renal transplant recipients with a transplantation performed in the Erasmus MC Rotterdam between January 1, 2000, and December 31, 2010. Every potential kidney recipient visits our pretransplant outpatient department once a year. When a patient is suitable for transplantation, LDKT is discussed. Most non-Europeans with incomplete knowledge of the Dutch language bring family members or friends to translate. If not, an independent interpreter can be arranged for their visit. All patients are provided with a booklet and DVD on LDKT available in seven languages. Transplantation-related information is also available on our website in seven languages.

The Central Bureau for Statistics in the Netherlands collects data per postcode area regarding population composition and various demographic variables. A postcode consists of two numbers that represent the region, another two numbers represent the neighborhood, and the last two letters represent the street. The postcode in combination with the number of the house is unique and suffices for delivery of the post. This unique code is also used for other applications. For our study, the numerical part of each recipient's postcode was linked to the Central Bureau for Statistics 2004 postcode area information database to extract demographic information.

Variables studied

The first category is the reference category for that particular variable (between brackets). When no reference category is mentioned, the variable is entered as a continuous variable.

Clinical variables

Age, gender (male), ethnicity (European), primary renal disease in seven categories (glomerulonephritis vs. congenital/hereditary disease, diabetes mellitus, hypertension/renovascular disease, tubulointerstitial disease/obstruction, systemic diseases, and other), year of renal transplantation, ABO blood type (A), previous transplantations (0), previous renal replacement therapy (continuous ambulatory peritoneal dialysis), and maximum PRA.

Postcode-related variables

Urbanization level (high: more than 1500 addresses per km^2 vs. low), percentage non-Europeans in the area (low: less than 10% vs. high), income, and housing value.

Statistics

Statistical analysis was conducted using Statistical Package for the Social Sciences, version 16.0. The chi-square test was used to test the associations between two categorical nominal or ordinal variables. Patient characteristics were compared with a one-way analysis of variance when they were continuous variables. A *P* value less than 0.05 was considered significant. To predict transplantation with a living donor in comparison with deceased donor kidney, univariable and multivariable binary logistic regression analyses were performed.

Results

In the period studied, 513 patients (38%) received deceased donor transplantation and 825 (62%) received living donor transplantation. Four percent of patients had one or more missing values.

When clinical and socioeconomic variables were compared between recipients of a deceased versus LDKT, there were vast differences (Table 1). When clinical and socioeconomic variables were compared between European and non-European recipients, there were also significant differences between these populations (Table 2).

Table 1. Patient characteristics, comparison of renal transplant recipient populations that received a deceased (N=513) versus living (N=825) donor transplant

	Deceased donor	**Living donor**	***P***
Recipient age in years, mean (SD)	52 (14)	48 (15)	<0.001[a]
Gender (male), %	61	64	ns[b]
Ethnicity (non-European), %	41	18	<0.001[b]
primary renal disease, %			
Diabetes mellitus	16	10	0.001[b]
All other			ns[b]
Transplant year, median	2005	2007	<0.001[c]
ABO blood type, %			
A	35	45	<0.001[b]
AB	7	4	0.003[b]
B	17	12	0.007[b]
O	41	39	ns[b]
Retransplants, %	25	15	<0.001[b]
Pretreatment, %			
CAPD	30	31	ns[b]
Hemodialysis	67	38	<0.001[b]
None	3	31	<0.001[b]
Maximum PRA, mean (SD), %	25 (33)	9 (19)	<0.001[a]
Postcode-related variables			
Urbanization (high), %	72	63	0.001[b]
Housing value x €1000, mean (SD)	100 (49)	129 (78)	<0.001[a]
% Non-Europeans (high), %	61	43	<0.001[b]
Income in € per month, mean (SD)	1770 (514)	2001 (647)	<0.001[a]

[a] ANOVA to test significance between recipients of deceased and living donor kidneys.
[b] χ^2 test to test significance between recipients of deceased and living donor kidneys.
[c] Mann-Whitney *U* to test significance between recipients of deceased and living donor kidneys.
ANOVA, analysis of variance; CAPD, continuous ambulatory peritoneal dialysis; ns, not significant; PRA, panel reactive antibodies; SD, standard deviation.

Table 2. Patient characteristics, comparison of European (N=977) and non-European (N=361) renal transplant recipient populations

	European	**Non-European**	***P***
Donor type (living donor), %	68	39	<0.001[b]
Recipient age in years, mean (SD)	50 (15)	48 (14)	0.021[a]
Gender (male), %	64	57	0.014[b]
primary renal disease, %			
Congenital hereditary	20	6	<0.001[b]
Diabetes mellitus	8	24	<0.001[b]
Transplant year	2006	2006	ns[c]
ABO blood type, %			
A	45	33	<0.001[b]
AB	4	9	<0.001[b]
B	10	24	<0.001[b]
O	41	34	0.007[b]
Retransplants, %	19	18	ns[b]
Pretreatment, %			
CAPD	34	25	0.002[b]
Hemodialysis	43	67	<0.001[b]
None	23	8	<0.001[b]
Maximum PRA, mean (SD), %	15 (26)	20 (28)	0.003[a]
Postcode-related variables			
Urbanization (high), %	55	90	<0.001[b]
Housing value x €1000, mean (SD)	128 (74)	80 (33)	<0.001[a]
% Non-Europeans (high), %	36	85	<0.001[b]
Income in € per month, mean (SD)	2044 (638)	1609 (403)	<0.001[a]

[a] ANOVA to test significance between European and non-European patients.
[b] χ^2 test to test significance between European and non-European patients.
[c] Mann-Whitney *U* to test significance between European and non-European patients.
ANOVA, analysis of variance; CAPD, continuous ambulatory peritoneal dialysis; ns, not significant; PRA, panel reactive antibodies; SD, standard deviation.

In univariable analysis, all variables studied exerted a significant influence on the chance of receiving LDKT (data not shown).

In multivariable analysis, 10 of 13 variables contributed significantly to the chance of receiving LDKT (Table 3). Recipients who were transplanted more recently were more likely to have received a living donor transplant. Europeans were more likely to receive living donor transplantation than non-Europeans. ABO blood type A had the best chances. Patients on hemodialysis had a smaller chance in comparison with patients on continuous ambulatory peritoneal dialysis. The chance of living donor transplantation is related to recipient age: the younger, the higher the chances (Figure 1). After correction for all variables

included in the regression analysis, the chance of living donor transplantation in the eldest population turned out to be only 10% of the chances of the youngest population (Figure 1). However, in reality, 87%, of recipients between ages 17 and 20 years (n=45) received a living donor transplantation, and in the population transplanted above 70 years of age (n=82), 42% received a living donor transplantation (Figure 2). So, in reality, elderly patients received LDKT more often than expected based on the results of the regression analysis. A higher maximum PRA was also associated with a lower chance. In multivariable logistic regression analysis, highly sensitized patients are shown to have only 10% the chance of unsensitized patients of receiving living donor transplantation. In reality, 78% of unsensitized patients (PRA 0%) received living donor transplantation, and 11% of highly sensitized patients (PRA above 85%) received living donor transplantation. With regard to postcode-related variables, higher housing value, and living in an urbanized area was associated with a better chance. Living in an area with a high percentage of non-Europeans decreased the chance. The influence of ethnicity was independent of the influence of the postcode-related variables and of pretreatment as there was no interaction between these variables.

Table 3. Results of the multivariable binary logistic regression analysis on the chance of receiving a LDKT

Variable (reference category)	Exp(B)	95% CI	*P*
Recipient age (per year)	0.962	0.952 – 0.972	<0.001
Gender (male)	1.398	1.044 – 1.873	0.025
Transplant year (per year)	1.146	1.095 – 1.199	<0.001
ABO blood type (A)			<0.001
AB	0.275	0.144 – 0.525	<0.001
B	0.515	0.337 – 0.787	0.002
O	0.616	0.455 – 0.833	0.002
Maximum PRA	0.975	0.969 – 0.980	<0.001
Pretreatment (CAPD)			<0.001
None	7.105	3.991–12.650	<0.001
Hemodialysis	0.682	0.507 – 0.916	0.011
Ethnicity (European)	0.494	0.350 – 0.695	<0.001
Postcode-related variables			
% Non-Europeans (low)	0.592	0.426 – 0.824	0.002
Urbanization (high)	0.672	0.483 – 0.935	0.018
Housing value	1.004	1.002 – 1.007	0.002

LDKT, living donor kidney transplantations; CAPD, continuous ambulatory peritoneal dialysis.

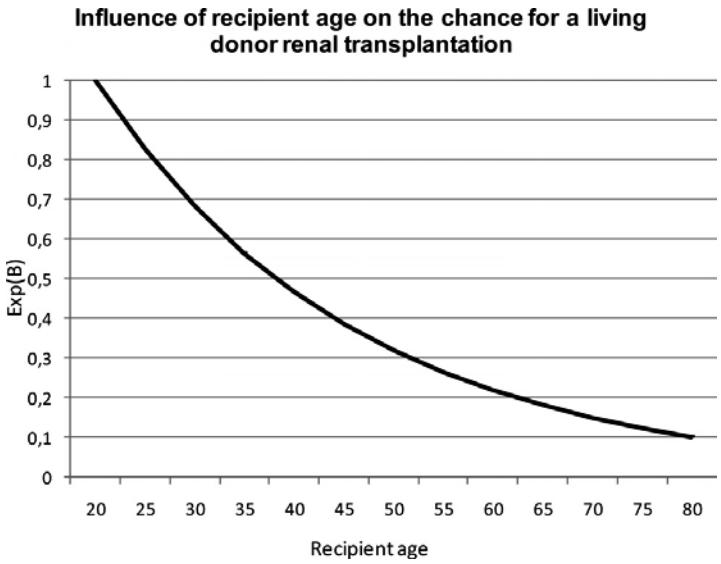

Figure 1. Result of multivariable binary regression analysis. Influence of recipient age on the chance of receiving a living donor kidney transplantation (LDKT) after correction for all other variables present in the analysis. In comparison to patients aged 20 years, patients aged 40 years have 50% chance to get a LDKT.

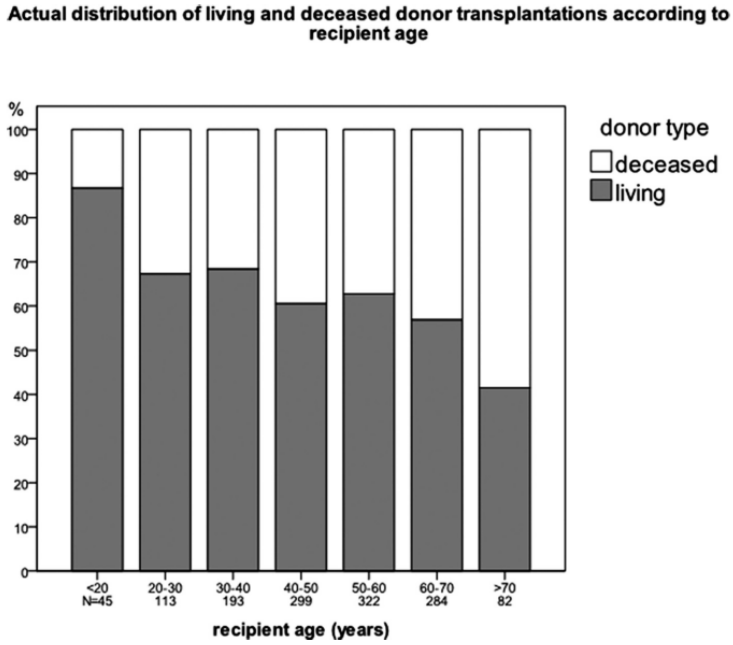

Figure 2. Distribution of living and deceased donor kidney transplantations per age category.

Discussion

This study is a comparison of the populations for whom transplantation became available and shows that the population that made it to LDKT is different from the population that made it to deceased donor kidney transplantation. In this study, only transplanted patients were analyzed. Patients on the waiting list and those delisted from the waiting list were not included.

This study shows that beside clinical factors, socioeconomic factors play an important and independent role in access to LDKT; unfavorable clinical factors are ABO blood type O, high PRA, and high age. These factors have also been shown to be important in other studies (2–5). In direct living donation programs, recipients with blood type O and highly sensitized patients are known to have smaller chances of transplantation (4, 6). With alternative living and deceased donation programs, their chances increase (2, 6). Despite these programs, the chance of receiving a living donor renal transplantation of a patient with a PRA of 27% is only half that of an unsensitized patient, and highly sensitized patients have only 10% chance of living donor transplantation when other variables are the same. The perceived discrepancy with the actual situation in our center where 78% of unsensitized patients and 11% of highly sensitized patients received living donor transplantation means that the highly sensitized patient population that made it to living donor transplantation is a selection of recipients with favorable factors other than PRA. This means that highly sensitized patients with a collection of other unfavorable factors on top of that are even less likely to receive living donor transplantation. Figure 2 shows that the chance for living donor renal transplantation decreases with increasing age. A 40-year-old patient has only half the chance of a 20-year-old patient of receiving living donor transplantation, while for those above 70 years, the chance decreases to only 10%. In this study, the discrepancy with the actual situation where 87% of the population younger than 20 years and 45% of the population between 70 and 80 years received living donor transplantation shows that the elderly population that made it to living donor transplantation is selected on favorable variables other than age. Elderly transplant patients with a collection of unfavorable factors other than age received a transplant through the deceased donor transplantation program.

In The Netherlands, minorities consist of immigrants rather than indigenous people as in some other countries. Minorities are known to have a twofold to threefold higher prevalence of end-stage kidney disease, and they have a smaller chance to be waitlisted and receive kidney transplantation (7–17). The proportion of transplants from living donors is also lower among indigenous than among white transplant recipients in Australia, New Zealand, and the United States (15).

The chance of receiving LDKT is not only related to ethnicity but also to socioeconomic factors (18–22). Socioeconomic deprivation has also been associated with a decreased likelihood of placement on the deceased donor transplant waiting list in the United States and United Kingdom (12, 19, 23–25). Lower socioeconomic status correlates with later referral for dialysis among patients with end-stage kidney disease, later referral for transplant registration, which confounds their ability to get listed for transplantation, and a decreased likelihood of undergoing transplantation either from a living or from a deceased donor (3, 26).

To disentangle the influences of socioeconomic factors and ethnicity, these factors were included in our multivariable analysis. Both socioeconomic factors and ethnicity exerted a significant influence on the chance of receiving a LDKT, and these effects were independent of each other. Non-European patients received living donor transplantation significantly less often than European patients. The socioeconomic factors that significantly and negatively influenced the chance of living donor transplantation were low housing value, low urbanization grade, and high percentage non-Europeans living in the area. In our study, income did not influence the chance for living donor transplantation. It is likely that housing value estimated by postcode is a more accurate reflection of a person's socioeconomic situation than income estimated by postcode.

Unfortunately, unfavorable factors tend to accumulate in the non-European population. An explanation might be that the non-European population studied has been in the Netherlands for a maximum of 60 years. The first generation primarily immigrated for economic reasons and had limited education: there are still 500,000 non-Europeans in The Netherlands who are illiterate. The majority of patients are the first generation living in The Netherlands. This means that

many non-Europeans did not yet achieve the socioeconomic standards that are common in the European population. When European and non-European populations are compared on the variables that influence the chance of living donor renal transplantation (Tables 1 and 2), there are significant differences in PRA, previous treatment, percentage of non-Europeans living in the area, and housing value. The most prevalent European patient has a mean PRA 15%, is not on hemodialysis, and lives in an area with a low percentage of non-Europeans in a house with a mean value of €128,000 (Table 2). In comparison with the reference category, the chance for a living donor renal transplantation of this most prevalent European population is 1 (for European) x 0.69 (for PRA) x 1 (for not on hemodialysis) x 1 (for area) x 1 (for housing value)=0.69 (Table 3). This means 69% chance of receiving a living donor renal transplantation compared with the reference category. However, the most prevalent non-European patient has PRA 20%, is on hemodialysis, lives in a house of €80,000, and lives in an area with a high percentage of non-Europeans. In comparison with the reference category, the chance of a living donor renal transplantation of the most prevalent non-European population is 0.494 (for non-European) x 0.682 (for hemodialysis) x 0.606 (for PRA) x 0.825 (for housing value) x 0.592 (for area)=0.10. The chance dramatically decreases to only 10% in comparison with the reference category, partly caused by unexplained ethnic factors, and partly caused by clinical and socioeconomic factors.

We showed that also in the Netherlands, the chance of LDKT in comparison with deceased donor kidney transplantation is significantly and independently influenced by ethnicity and socioeconomic factors. It is remarkable that socioeconomic factors still exert such an important influence on the chance of receiving living donor transplantation as the medical health system in the Netherlands assures equal health care for all inhabitants, largely excluding economic circumstances as an important factor for decreased access to living donor transplantation. Moreover, all donor costs are paid by the recipient's health company. To explore psychosocial factors that may influence LDKT among patients of diverse ethnic backgrounds, a qualitative study was conducted in our center (27). Focus group discussions and in-depth interviews were conducted among 50, mostly hemodialysis, patients on the deceased donor transplant waiting list. Most patients preferred LDKT (96%), but a living donor

was not available for them. Religion was not perceived as an obstacle to living kidney donation but was felt to promote helping and saving the life of a person. However, individual Faith leader's opinion was felt to be influential and may be negative. The majority of non-Europeans reported they did not comprehend the information given in the hospital, did not actively seek information, and had fears and anxieties and misconceptions regarding the process of organ donation. Our focus group study also showed that our patients had a positive attitude toward home-based education on living do-nor transplantation (28). The effectiveness of this program is currently being tested in a randomized controlled trial. In conclusion, both clinical and socioeconomic factors are independently associated with participation in living or deceased donor kidney transplantation. This study highlights the populations that would benefit from additional educational intervention regarding living donor transplantation.

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4

Understanding the influence of ethnicity and socioeconomic factors on graft and patient survival after kidney transplantation

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Abstract

Background. Studies on the influence of socioeconomic factors and ethnicity on the results of kidney transplantation have led to various outcomes. In this study, we analyzed the influence of a combination of these factors on graft and patient survival in a population of kidney transplant recipients.

Methods. This retrospective study included all 1,338 patients who received a kidney transplant between 2000 and 2011 (825 living, 513 deceased donor transplantations). Both clinical and socioeconomic variables were studied. Clinical variables were recipient age, gender, ethnicity, primary renal disease, maximum and current panel reactive antibodies, ABO blood type, retransplants, pretreatment, time on dialysis, comorbidity, transplant year, total number of HLA mismatches, donor type (living or deceased), age and gender, and calcineurin inhibitor treatment. Each recipient's postal code was linked to a postal code area information database to extract information on housing value, income, percentage non-Europeans in the area, and urbanization level.

Results. In multivariable analysis, graft survival censored for death was significantly influenced by recipient age, maximum panel reactive antibodies, HLA mismatches, donor type, donor age, and calcineurin inhibitor treatment. Patient survival was significantly influenced by recipient age, comorbidity, transplant year, and donor type. Socioeconomic factors and ethnicity did not have a significant influence on graft and patient survival.

Conclusions. Though ethnicity and socioeconomic factors do not influence survival after kidney transplantation, the favorable influence of living donor type is of paramount importance. As non-Europeans and patients with unfavorable socioeconomic variables less often receive a living donor kidney transplant, their survival may be unfavorable after all.

Introduction

The literature on the combined influence of socioeconomic factors and ethnicity on the results of kidney transplantation is inconclusive as a multitude of studies led to various outcomes. Four explanations could cause this inconsistency. The *first* possible explanation is that there is a difference in ethnicity of the population studied, for example, African versus Asian versus European (1-23). Mostly, results of Caucasians are better than results of Africans or African Americans (1-8, 20-23). *Secondly*, the influence of a range of socioeconomic variables has been studied, for example, education, employment status, income, and insurance coverage. Different combinations of parameters have been studied. Results range from a negative effect of socioeconomic factors on graft survival to no effect at all (13-25). A *third* explanation for the inconsistency in the literature could be a difference in access to living donor kidney transplantation for patients with favorable and unfavorable socioeconomic factors and for patients with different ethnicities (26-28). As survival after living donor kidney transplantation is better than after deceased donor kidney transplantation, this could influence the outcome of these studies. *Finally*, the difference in health care systems between countries could be influencing results (22, 23). If access to health care depends on socioeconomic status, patients with unfavorable social factors could be disadvantaged.

Our transplant program does not only serve the indigenous population of the Netherlands but also immigrants from other countries in Europe and other continents, for example, a Dutch black population native to the Caribbean, Northern part of South America and sub-Saharan Africa, and Northern Africa (from where there is large-scale immigration to the Netherlands). All patients who permanently reside in the Netherlands are eligible to receive a kidney transplant. In the Rotterdam area, socioeconomic factors vary considerably between neighborhoods. In a national database, demographic variables are available for each neighborhood in the Netherlands, for example, housing value, income, percentage of non-Europeans living in the area, and urbanization level. Non-European patients and recipients of a deceased donor kidney more often live in socioeconomically deprived areas. Access to living donor kidney transplantation is lower in groups of certain ethnicities and socioeconomic status. As living donor kidney transplantation leads to better graft and patient

survival than deceased donor kidney transplantation, this could have a negative influence on the results of these groups. The National Health system in the Netherlands assures equal care for all inhabitants. We studied the influence of ethnicity and socioeconomic factors on graft and patient survival in our system of equal health care.

Materials and methods

Study Sample

In this retrospective cohort study, all 1,338 kidney transplantations performed in our center from January 1, 2000 until December 31, 2010 were included. Informed consent to use data was obtained from all patients. The immunosuppressive regimen for patients and screening procedure for potential living kidney donors have been described previously (29, 30).

The Central Bureau for Statistics in the Netherlands collects demographic data per postal code area (31). A postal code consists of four numbers and two letters. The first two numbers represent the region, the last two numbers the neighborhood, and the two letters represent the street. For the present study, each recipient's postal code was linked to the Central Bureau for Statistics 2004 postal code area information database to extract demographic information.

Statistical Analysis

We studied both graft failure censored for death and patient death. Follow-up was until February 2013 or until graft failure, death, or lost to follow-up. Differences between European and non-European patients were analyzed using two-tailed independent-samples *t* tests, chi-square tests, and Mann-Whitney *U* tests. Variables that were studied are mentioned in Table 1. In two separate Cox proportional hazards analyses, the influence of these variables was studied: on graft failure censored for death, respectively on patient death. Univariable Cox was used to determine variables to include in the initial multivariable model. Subsequently, variables with non-significant influence were excluded through backward elimination. Initially excluded variables were added to the model to verify whether their influence was significant in multivariable analysis.

Patients were classified into five ethnicities: African (n=112), Arabian (n=48), Asian (n=132), European (n=977), and Turkish (n=69). Socioeconomic factors were housing value, income, percentage non-Europeans in the area (high: more than 10% vs. low), and urbanization level (high: more than 1,500 addresses/km^2 vs. low). Comorbidity was defined as the previous experience with or presence of one or more of the following conditions in addition to the primary kidney disease: cardiac events, cerebrovascular accident, vascular disease, and diabetes mellitus.

The proportional hazards assumption was tested for categorical variables with log-minus-log plots. Statistical Package for the Social Sciences (SPSS) 20.0.0.1 (IBM Corporation, Armonk, NY, USA) was used to perform all analyses. P values less than 0.05 were considered significant. Cases with missing values were excluded from the analyses.

Table 1. Transplantation characteristics for European and non-European patients.

	European N=977	**Non-European N=361**	***P***
Recipient age in years, mean (SD)	50.3 (14.9)	48.3 (13.6)	0.020[a]
Recipient gender (male), %	65	58	0.014[b]
primary renal disease, %			<0.001[b]
Diabetes mellitus	8	24	
Other	92	76	
Maximum PRA, median (%>5%)	4 (29)	4 (39)	<0.001[c]
Current PRA, median (%>5%)	0 (12)	0 (17)	0.436[c]
ABO blood type, %			<0.001[b]
A	44	33	
AB	4	9	
B	10	24	
O	42	34	
Retransplants, %	19	18	0.819[b]
Pretreatment, %	78	91	<0.001[b]
Time on dialysis in days, median (IQR)	475 (7-941)	960 (456.5-1595.5)	<0.001[c]
Comorbidity, %	34	44	0.001[b]
Transplant year, median (IQR)	2006 (2003-2009)	2006 (2003-2008)	0.769[c]
HLA mismatches, mean (SD)	3.1 (1.7)	3.2 (1.5)	0.255[a]
Donor type (living donor), %	69	42	<0.001[b]
Donor age in years, mean (SD)	51.6 (13.3)	48.5 (13.4)	<0.001[a]
Donor gender (male), %	45	48	0.300[b]
CNI as initial immunosuppression, %	95	97	0.133[b]
Housing value x €1000, median (IQR)	115 (86-151)	75 (58-101.75)	<0.001[c]
Income in € per month, median (IQR)	1900 (1600-2300)	1500 (1400-1700)	<0.001[c]
% Non-Europeans (high), %	36	85	<0.001[b]
Urbanization (high), %	57	91	<0.001[b]

[a] Independent-samples *t* test.
[b] Chi-square test.
[c] Mann-Whitney *U* to test significance between European and non-European patients.
CNI, calcineurin inhibitor; IQR, interquartile range; PRA, panel reactive antibodies; SD, standard deviation.

Results

In the study period, 513 patients received a deceased donor kidney and 825 patients received a living donor kidney. Patients were included in this study between January 2000 and December 2010. Observation was until February 2013 so that at least 2 years of follow-up could be obtained. Median follow-up was 4.5 years (54 months). In total, 32 patients were lost to follow-up with median time after transplantation of 25.5 months (range 0-110). Observation of these patients was until they were lost to follow-up. The variables maximum and current panel reactive antibodies (PRA) had five missing values, housing value 22, income 39, and percentage non-Europeans in the area 7.

Table 1 shows transplantation characteristics. Compared to European patients, non-European patients live in neighborhoods with lower housing value, lower income, more non-Europeans, and more urbanization. Significant clinical differences emerged in recipient age and gender, primary renal disease, maximum PRA, ABO blood type, pretreatment, time on dialysis, comorbidity, and donor type and age. There were no significant differences between Europeans and non-Europeans regarding current PRA, retransplants, transplant year, total number of HLA mismatches, donor gender, and calcineurin inhibitor (CNI) treatment.

There were 271 graft failures. In univariable Cox proportional hazards analysis, recipient age, maximum and current PRA, retransplants, pretreatment, time on dialysis, transplant year, donor type, donor age, and CNI treatment had a significant influence on the risk of graft failure censored for death, whereas the influence of ethnicity and socioeconomic factors was not significant (data not shown). Multivariable Cox proportional hazards analysis showed that recipient age, maximum PRA, total number of HLA mismatches, donor type, donor age, and CNI treatment had a significant influence on the risk of graft failure censored for death (Table 2a). The influence of pretreatment and time on dialysis was not significant. Other variables were excluded through backward elimination, including ethnicity and socioeconomic factors.

One hundred seventy-seven patients died. In univariable Cox proportional hazards analysis, recipient age, primary renal disease, time on dialysis, comorbidity, total number of HLA mismatches, and donor type, age, and gender significantly influenced the risk of patient death. Ethnicity and socioeconomic

factors did not significantly influence this risk. In multivariable analysis, recipient age, comorbidity, transplant year, and donor type had a significant influence on the risk of patient death (Table 2b). Ethnicity and socioeconomic factors were excluded through backward elimination.
The proportional hazards assumption was not violated.

Table 2. Results of the multivariable Cox Proportional Hazards Analysis. Failure event is (a) graft failure censored for death, (b) patient death.

Variable (reference category)	**Exp(B)**	**95% CI**	***P***
(a) 271 events[a]			
Recipient age (per year)	0.979	0.970 - 0.987	<0.001
Maximum PRA (per %)	1.006	1.002 - 1.010	0.004
Pretreatment (no)	1.415	0.937 - 2.138	0.099
Time on dialysis (per day)	1.000	1.000 - 1.000	0.065
HLA mismatches (per HLA mismatch)	1.105	1.020 - 1.198	0.015
Donor type (deceased donor)	0.443	0.330 - 0.595	<0.001
Donor age (per year)	1.028	1.018 - 1.039	<0.001
CNI as initial immunosuppression (no)	0.296	0.185 - 0.472	<0.001
(b) 177 events[b]			
Recipient age (per year)	1.061	1.047 - 1.076	<0.001
Comorbidity (no)	1.935	1.408 - 2.657	<0.001
Transplant year (per year)	0.944	0.894 - 0.998	0.041
Donor type (deceased donor)	0.656	0.487 - 0.885	0.006

[a] Event is graft failure censored for death. Final model after backward elimination of the following covariates: recipient gender, ethnicity, primary renal disease, current PRA, ABO blood type, retransplants, comorbidity, transplant year, donor gender, housing value, income, non-Europeans, and urbanization level.
[b] Event is patient death. Final model after backward elimination of the following covariates: recipient gender, ethnicity, primary renal disease, maximum PRA, current PRA, ABO blood type, retransplants, pretreatment, time on dialysis, HLA mismatches, donor age, donor gender, CNI as initial immunosuppression, housing value, income, non-Europeans, and urbanization level.
CNI, calcineurin inhibitor; PRA, panel reactive antibodies

Discussion

The influence of socioeconomic factors and ethnicity on the results of kidney transplantation has been studied in various ways, and these studies led to various outcomes. As different combinations of variables are studied in the literature, it is hard to get a clear overview of those variables that really matter. In some studies, ethnicity was the only variable studied (1-12). In other studies, combinations of various socioeconomic factors were the only variables studied (24, 25). There were also studies that corrected for the influence of ethnicity or socioeconomic factors while the main focus was on the other variable (13-23).

Ethnicity without correction for socioeconomic factors

In most studies on the influence of ethnicity, a negative influence of African ethnicity on graft survival was found (1-8). Eckhoff et al. showed that the effect of ethnicity on the graft failure risk was not constant in the population studied (1). Early graft survival did not display a racial disparity. However, in the constant phase of graft loss, a racial disparity emerged, with African Americans experiencing a higher rate of graft loss over time than non-African Americans. The influence of high immune responder status and CYP3A5 responder status was studied in two different studies (2, 3). The effect of ethnicity on graft survival remained significant in both studies. Finally, in 1999, compared to European ethnicity, a negative influence of African and Arabian ethnicity on the graft failure risk was found in our own population (P=0.023, respectively P=0.019) (4). In a health system providing free post-transplant medication, the negative effect of ethnicity on graft survival disappeared after the introduction of thymoglobulin induction therapy (9).

In one European study, the influence of African ethnicity on graft survival was not significant in univariable analysis (10). In other European studies comparing Asian and Caucasian ethnicity, no difference in graft survival was found between these ethnicities (11, 12).

Socioeconomic factors without correction for ethnicity

In a few studies, socioeconomic factors were tested without correcting for ethnicity (24, 25). They found that less education (24) and income deprivation (25) were predictors of graft loss.

Socioeconomic factors with correction for ethnicity

After correction for ethnicity, Begaj et al. showed a negative influence of a combination score of socioeconomic factors on overall and patient survival (13), whereas in another study recipients with higher education level, resident aliens (as compared with U.S. citizens), and patients with private insurance were found to have a lower risk of graft and recipient failure (14). On the other hand, Petersen found an effect of pre- and post-transplant employment status on graft and patient survival (15).

Ethnicity with correction for socioeconomic factors

After correction for various socioeconomic factors, some authors did not find an effect of ethnicity on graft survival (16-19). Although a negative influence of African (American) ethnicity on graft survival was shown by Butkus in univariable analysis, ethnicity was not significant in multivariable analysis including recipient age, HLA mismatches, and insurance coverage (16). In this study, type of insurance coverage had a significant influence in both univariable and multivariable analyses. In another study from this author, post-transplant compliance was the only variable related to graft survival in multivariable analysis, whereas African (American) ethnicity was not associated with reduced graft survival (17). These findings had been shown before in a small study that included a low percentage of non-whites (18). In this study, the only significant variables were income and compliance whereas ethnicity did not reach significance.

A significant and negative effect of ethnicity on graft failure risk was found in other studies on the influence of ethnicity that included socioeconomic factors (20-23). College education and employment did not, but ethnicity and insurance coverage did influence the graft failure risk in a population that received their first kidney transplantation (20). After adjustment for poverty, employment status, and clinical covariates, African Americans and Hispanics had higher rates of graft failure compared to whites (21). Though Medicare's lifetime coverage of immunosuppressive medication claims to have offset the income-related disparities in graft survival, income and ethnicity still significantly influenced the graft failure risk in 2008 (22).

After correction for a large number of categories of variables (e.g., socioeconomic variables), Asian and Hispanic or Latino recipients demonstrated consistently superior long-term deceased donor and living donor graft and patient survival compared to white recipients (23). African-American recipients had consistently inferior long-term living donor and deceased donor graft survival relative to the other ethnic groups. These findings suggest that access to care (including immunosuppressive agent coverage) does not seem to completely explain the observed large racial disparities in kidney transplant outcomes.

In the present study, we found that socioeconomic factors and ethnicity do not have a significant influence on death-censored graft survival or patient survival. This holds true for both univariable and multivariable analysis. Though the access to living donor kidney transplantation is influenced by ethnicity and socioeconomic factors, these factors do not influence the prognosis once transplantation has been performed. However, we showed that donor type is an important factor in graft survival, which causes an indirect disadvantage for patients with unfavorable socioeconomic variables.

The strength of our findings is that access to living donor kidney transplantation and graft survival are studied in the same population. Access to living donor kidney transplantation is impaired probably because of a lack of adequately informed living donors in the population with unfavorable socioeconomic factors and non-European ethnicity. On the other hand, the Dutch health system assures equal availability of immunosuppressive medication, securing graft survival. In the United States, health care is dependent on socioeconomic status. This means that immunosuppressive medication is not equally available for all inhabitants, theoretically leading to decreased graft survival for some. An exception to this system is made for veterans and active-duty personnel and their dependents. Although Oliver et al.'s findings are in line with this theory (9), Chakkera et al.'s findings refuted it (20).

Though significance was low, a negative influence of ethnicity on the risk of graft failure was found in our own center without correction for socioeconomic factors in 1999 (4). The negative effect of ethnicity on graft survival that we found in 1999 had disappeared in the present study. The medical health system did not change between then and the present time, undermining the hypothesis that the

availability of the health system is indispensable for graft survival. The only change between these periods was the population of non-Europeans themselves. Most non-Europeans immigrated between the fifties and seventies of the previous century, whereas the numbers of new immigrants decreased considerably after that time. The present non-European population is made up of first-, second-, and third-generation immigrants. They are better integrated and educated than 10 years ago, and their employment status is higher (31).
The influence of ethnicity on graft survival and its relation with various socioeconomic factors has been studied in different settings and populations. When a subject is studied this intensively and outcomes differ considerably, the explanation most probably is that the influence of ethnicity is multifactorial and context dependent. The influence of ethnicity on graft survival probably depends on many factors, for example, HLA matching, poverty, education, employment, degree of integration, a health system with a controlling function, and access to medication. If all these factors are negative, a negative influence of ethnicity on graft survival will be found. However, if these factors are positive, ethnicity may not have any influence on outcome of kidney transplantation at all.
In conclusion, in our study cohort, neither ethnicity nor socioeconomic factors had an important influence on graft and patient survival. Nevertheless, the low prevalence of living donor kidney transplantation in ethnic minorities and socioeconomically deprived patients does influence the ultimate prognosis of this population.
Research shows that fear and a lack of knowledge play a major role in the absence of living donors in this population (32). Active education and information for these patients and potential donors is very important to improve results (33-36).

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5

The relative importance of donor age in deceased and living donor kidney transplantation

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Abstract

In deceased donor kidney transplantation donor age is known to influence graft survival. The influence of living donor age on graft survival is questioned. We compared the influence of living and deceased donor age on the outcome of renal transplantation. All 1821 transplants performed in our center between 1990 and 2009 were included in the analysis. Observation was until April 2012. A total of 941 patients received a deceased donor kidney and 880 a living donor kidney. In multivariable Cox analysis, recipient age, maximum and current panel reactive antibodies, transplant year, HLA mismatches, donor age, donor gender, donor type, delayed graft function, and calcineurin inhibitor (CNI) and prednisone as initial immunosuppression were found to have a significant influence on death-censored graft failure. The influence of both living and deceased donor age followed a J-shaped curve, above 30 years the risk increased with increasing age. Donor type and donor age had an independent influence. The graft failure risk of deceased donor transplantation is almost twice that of living donor transplantation so that a 60-year-old living donor kidney has the same graft failure risk as a 20-year-old deceased donor kidney.

Introduction

To keep pace with the waiting list, more kidney donations are accepted from living extended criteria donors (ECD). Although donor hypertension and obesity play a role, the most prominent characteristic of both living and deceased ECDs is that they are older than standard criteria donors (SCD) (1–5).

In deceased donor kidney transplantation donor age is known to influence graft survival, in living donor kidney transplantation this influence is less clear. The composition of living and deceased donor recipient populations is different in many respects; this probably explains part of the difference in graft survival in these populations.

Until now the influence of donor age has been studied in deceased or living donor kidney transplantation populations separately, ruling out comparison because of heterogeneity of the populations (2, 6–13). Besides, in many studies age was categorized resulting in small elderly populations (3, 9–11, 14). In most living donor populations donor age range is narrow because of donor selection, so the influence of age cannot be studied properly.

Deceased donor kidney transplantations have been performed in our center since 1971 and living donor kidney transplantations since 1981. Only in the very beginning were high recipient and deceased donor age exclusion criteria. The wide distributions in recipient and donor age in our population allowed us to study the influence of age as a continuous variable on the risk of graft failure, both in deceased and living donor kidney transplantation. How important is living donor age and how does it compare to deceased donor age?

Methods

All 1821 transplants performed in our center between January 1990 and December 2009 were included in the analysis. Observation was until April 2012 or until graft failure, death, or lost to follow-up. 27 patients were lost to follow-up with a median time after transplantation of 31 months (0–160). Standard immunosuppression was cyclosporine, prednisone in 1990, but was changed to prednisone, cyclosporine, and mycofenolate mofetil (MMF) in 1996, whereas tacrolimus was introduced in 1998 as substitute for cyclosporine. In patients that started on triple therapy, prednisone was tapered and discontinued at 4 months after transplantation.

Screening of our potential living kidney donors has been described thoroughly (15). Absolute contra-indications for donation are body mass index >35 kg/m2, GFR <80 ml/min, hypertension with end-organ damage, history of invasive malignancies, diabetes mellitus, pregnancy, intravenous drug abuse, major cardio respiratory disease, human immunodeficiency virus positivity, hepatitis B or C infection, psychiatric disorders, and systemic disease. Living donor age itself has never been a contraindication for donation.

In our center deceased donor kidneys are accepted from donation after brain death (DBD) donors and donation after cardiac death (DCD) donors. We primarily accept donors after controlled cardiac death (Maastricht category III). Uncontrolled Maastricht category II donors are accepted under strict conditions only.

We studied graft failure censored for death, uncensored graft failure, and patient death. anova and chi-square tests were performed to test the difference between living and deceased donor populations and between donor age categories. Kaplan–Meier analysis was performed, including donor age and type (living vs. deceased). For Kaplan–Meier analysis, donor age was subdivided into the categories 0–39, 40–59, and 60 years and older. Univariable and multivariable Cox proportional hazard analyses were performed, including all variables mentioned in Table 1 and donor type, which was included as a categorical variable (DBD, DCD, living). Backward elimination was chosen as the method of variable selection. Transplantation year was included to correct for time related changes in diagnostics, treatment options, and experience. Donor and recipient age were included as continuous variables. Initial

immunosuppression was included as six binary variables consisting of any combination of immunosuppressants with or without: (i) CNI (tacrolimus, cyclosporine), (ii) induction therapy (rATG, IL2-blocker, OKT3),(iii) mTOR inhibitor (rapamycin, everolimus), (iv) MMF,(v) prednisone, and (vi) other (azathioprine, trial medication). The proportional hazards assumption was tested for donor type with a log-minus-log plot. The analyses were performed using Statistical Package for the Social Sciences (SPSS) PASW 17.0.2 for Windows (IBM Corporation, Armonk, NY, USA). *P*-values < 0.05 were considered significant.

Table 1. Characteristics for deceased donor (DD) and living donor (LD) kidney recipients.

	All N=1821	**DD N=941**	**LD N=880**	***P***
Recipient age (mean ± SD)	47.8±14.2	49.4±13.5	46.1±14.8	<0.001[a]
Male recipients (%)	62	61	63	ns[b]
Maximum PRA (median; %>5%)	5; 44	9; 58	4; 28	<0.001[a]
Current PRA (median; %>5%)	0; 17	0; 24	0; 10	<0.001[a]
Transplant year (median)	2002	1999	2005	<0.001[a]
Previous transplants (%)				<0.001[b]
0	81	76	86	
1	15	18	11	
2+	5	6	3	
Pretreatment (%)				<0.001[b]
Hemodialysis	55	70	39	
Peritoneal dialysis	29	27	31	
Pre/Trans	16	3	30	
HLA mismatches (mean ± SD)	2.8±1.6	2.6±1.5	3.0±1.7	<0.001[a]
DR mismatches (mean ± SD)	0.8±0.7	0.7±0.7	1.0±0.7	<0.001[a]
Donor age (mean ± SD)	47.6±14.7	45.7±16.1	49.6±12.7	<0.001[a]
Male donors (%)	50	55	44	<0.001[b]
Delayed graft function (%)	24	42	5	<0.001[b]
CNI as initial immunosuppression (%)	95	94	95	ns[b]
Induction therapy (%)	13	14	11	ns[b]
mTOR inhibitor (%)	6	3	10	<0.001[b]
MMF (%)	66	57	75	<0.001[b]
Prednisone (%)	94	93	96	0.005[b]
Other immunosuppression (%)	8	5	10	<0.001[b]

[a] ANOVA to test significance between DD and LD.

[b] Chi-square to test significance between DD and LD.

CNI, calcineurin inhibitor; MMF, mycofenolate mofetil; PRA, panel reactive antibodies; SD, standard deviation.

Results

A total of 941 patients received a deceased donor kidney and 880 a living donor kidney. There were 94 donors after cardiac death (Maastricht category III *n* = 91, Maastricht category II *n* = 3). In Table 1 transplantation characteristics are shown. There were missing values in 15 cases (0.8%). Recipients of a living donor kidney were significantly younger than recipients of a deceased donor kidney, whereas living donors were significantly older than deceased donors. The distribution of donor and recipient age was also different between the living and deceased donor populations (Figure 1a and 1b). Very young donors were present in the deceased donor population but absent in the living donor population. Age in the living donor population was shifted to the right (older donors) in comparison to the deceased donor population. In addition to recipient and donor age there were significant differences between the living and deceased donor populations (Table 1).

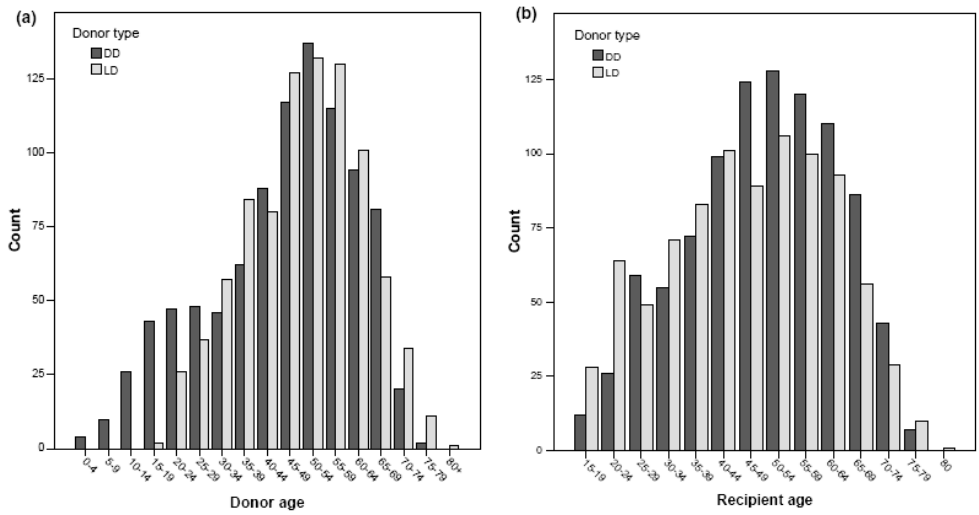

Figure 1. (a) Donor and (b) recipient age distributions in deceased (DD) versus living donor (LD) kidney transplantation.

There were 507 graft failures; 341 in recipients of deceased donor kidneys and 166 in recipients of living donor kidneys. In Table 2 numbers and causes of graft

failure are shown for age categories and donor types. There was no significant difference between the age groups regarding numbers of graft failures (Table 2a). However, in the eldest donor age group never functioning grafts occurred significantly more often and least in the youngest donor age group. When comparing recipients of kidneys from DBD, DCD, and living donors, there was a significant difference in the number of graft failures (Table 2b). Living donor kidneys failed less often than DBD kidneys. The incidences of chronic rejection and recurrence of primary renal disease was also different between the populations.

Table 2. Numbers and causes of graft failure per (a) donor age category and (b) donor type.

	Donor age (years)			
(a)	**≤39**	**40-59**	**≥60**	***P*[a]**
N	492	926	402	
Numbers of failures	134	242	130	0.064
Failure causes (*n*)				
Chronic rejection	68	121	58	0.534
Acute rejection	18	27	14	0.753
Technical problems	17	33	10	0.226
Recurrence primary renal disease	11	15	7	0.624
Never functioning graft	3	23	27	<0.001
Other	17	23	14	0.632
	Donor type			
(b)	**DBD**	**DCD**	**Living**	***P*[a]**
N	847	94	880	
Numbers of failures	317	24	166	<0.001
Failure causes (*n*)				
Chronic rejection	149	5	93	0.003
Acute rejection	41	1	17	0.344
Technical problems	46	3	11	0.039
Recurrence primary renal disease	11	2	20	0.001
Never functioning graft	40	11	3	<0.001
Other	30	2	22	0.409

[a] Chi-square to test significance between all three groups.

DBD, donation after brain death; DCD, donation after cardiac death.

In *Kaplan–Meier analysis*, graft survival censored for death was significantly different in the three donor age categories in the deceased donor population ($P < 0.001$), but not in the living donor population ($P = 0.08$) (Figure 2). Graft

survival censored for death after living donor transplantation was better than after deceased donor transplantation for all donor age categories, $P = 0.008$ for 0–39 years, $P < 0.001$ for 40–59 years, and $P < 0.001$ for 60 years and older, respectively.

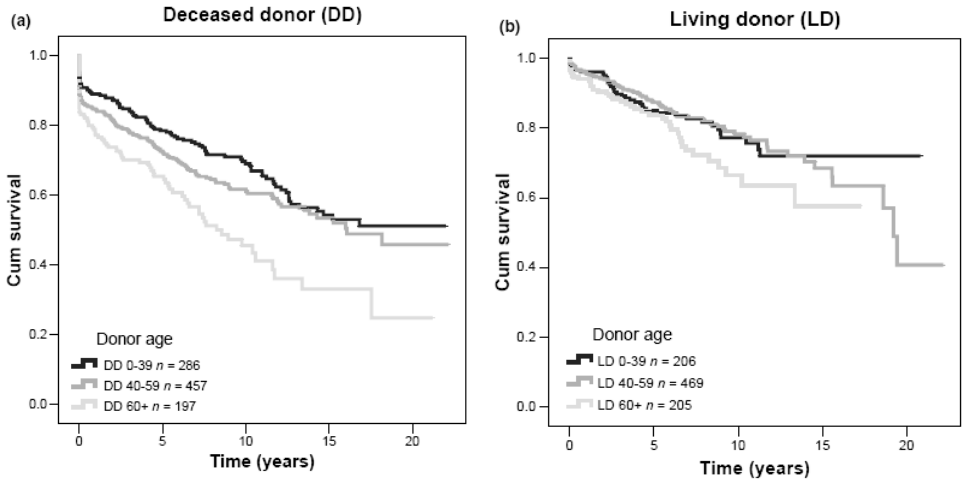

Figure 2. Kaplan-Meier curve comparing death-censored graft survival after (a) deceased donor transplantation ($P < 0.001$) and (b) living donor transplantation (ns) for three donor age categories.

The influence of all variables shown in Table 1 and the influence of donor type on graft failure risk were studied in the *Cox proportional hazards analysis*. In univariable Cox analysis, recipient age, maximum panel reactive antibodies (PRA), current PRA, transplant year, previous transplants, pretreatment, total number of HLA mismatches, donor age, donor type, delayed graft function, and CNI treatment, induction therapy, MMF treatment, and prednisone as initial immunosuppression had a significant influence on the risk of graft failure, censored for death. The influence of donor age was not linear, but exponential (data not shown). The other variables described in Table 1 did not significantly influence this risk. In the final multivariable Cox model, a number of factors were found to have a significant influence on the relative risk (RR or Exp(B)) of graft failure, censored for death (Table 3a). All variables not present in Table 3a

had been excluded via backward elimination in previous runs. The influence of DCD was not significantly different from DBD, whereas the risk of living donation was significantly lower than that of DBD. Donor age had a quadratic influence on the risk of graft failure (Figure 3a). Between the ages of 20 and 40 years graft failure risk hardly changed (relative risk, respectively, 0.60 and 0.63 in comparison to 20-year-old deceased donor). However, between living donor ages of 40 and 60 years the relative risk of graft failure increased from 0.63 to 1.01 in comparison to 20-year-old deceased donor. The interaction terms between donor type and either HLA mismatches, current PRA, maximum PRA, recipient age, and donor age were not significant. There was neither interaction between donor and recipient age nor between donor age and transplant year.
Table 3b shows the results of the multivariable Cox analysis with death and/or graft failure as the event studied (univariable results not shown). As the square of donor age was also significant, the influence of donor age followed a J-shaped curve (Figure 3b).
Table 3c shows the results of the multivariable Cox analysis with patient death as the event studied (univariable results not shown). The proportional hazards assumption was not violated.

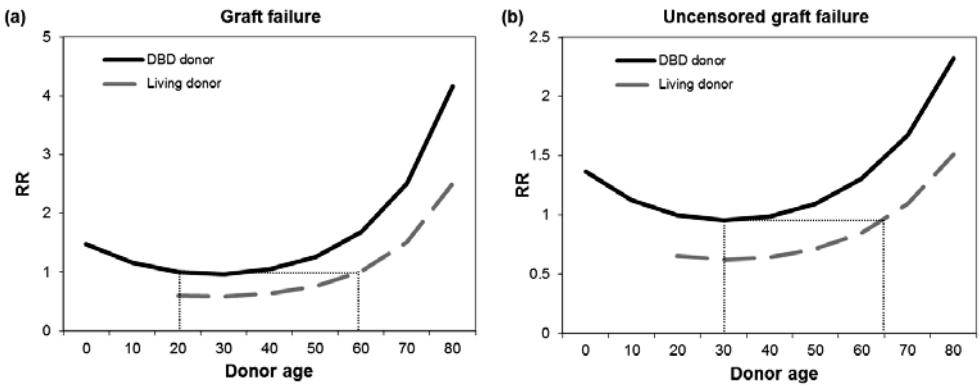

Figure 3. Calculated relative risk (RR) of (a) graft failure censored for death and (b) uncensored graft failure with increasing donor age for donation after brain death (DBD) and living donor transplantation. The reference value is a 20 year old DBD donor. The dotted lines demonstrate the comparison of the risk between recipients of a living donor kidney and a DBD kidney.

Table 3. Results of the multivariable Cox proportional hazards analysis. Failure event is (a) censored for death, (b) uncensored, and (c) censored for graft failure.

Variable (reference category)	Exp(B)	95% CI	*P*
(a) N=1821, 502 events			
Recipient age (per year)	0.984	0.977-0.990	<0.001
Maximum PRA (per %)	0.995	0.990-1.000	0.045
Current PRA (per %)	1.015	1.008-1.021	<0.001
Transplant year (per year)	0.974	0.954-0.993	0.008
HLA mismatches (per HLA mismatch)	1.107	1.040-1.178	0.001
Donor age (per year)	0.970	0.943-0.998	0.033
Donor age^2 (per year^2)	1.001	1.000-1.001	0.001
Donor gender (female)	0.835	0.699-0.998	0.047
Donor type (DBD)			<0.001
DCD	1.056	0.669-1.667	0.816
Living	0.603	0.478-0.760	<0.001
Delayed graft function (no)	2.006	1.629-2.471	<0.001
CNI as initial immunosuppression (no)	0.236	0.174-0.321	<0.001
Prednisone as initial immunosuppression (no)	0.710	0.514-0.980	0.037
(b) N=1821, 832 events			
Recipient age (per year)	1.013	1.007-1.019	<0.001
Maximum PRA (per %)	0.996	0.992-1.000	0.028
Current PRA (per %)	1.011	1.006-1.016	<0.001
Transplant year (per year)	0.978	0.958-0.999	0.037
HLA mismatches (per HLA mismatch)	1.057	1.009-1.108	0.021
Donor age (per year)	0.977	0.957-0.998	0.033
Donor age^2 (per year^2)	1.000	1.000-1.001	0.003
Donor type (DBD)			<0.001
DCD	1.200	0.844-1.706	0.309
Living	0.651	0.543-0.781	<0.001
Delayed graft function (no)	1.770	1.499-2.091	<0.001
CNI as initial immunosuppression (no)	0.282	0.214-0.371	<0.001
MMF as initial immunosuppression (no)	0.812	0.662-0.997	0.047
Prednisone as initial immunosuppression (no)	0.630	0.486-0.817	<0.001
(c) N=1821, 330 events			
Recipient age (per year)	1.071	1.060-1.082	<0.001
Transplant year (per year)	0.941	0.918-0.965	<0.001
Donor type (DBD)			0.012
DCD	1.777	1.027-3.075	0.040
Living	0.783	0.591-1.036	0.087
Delayed graft function (no)	1.341	1.022-1.759	0.034
CNI as initial immunosuppression (no)	0.366	0.208-0.645	<0.001
Prednisone as initial immunosuppression (no)	0.609	0.406-0.915	0.017

CNI, calcineurin inhibitor; DBD, donation after brain death; DCD, donation after cardiac death; MMF, mycofenolate mofetil; PRA, panel reactive antibodies.

Discussion

The present study shows that in Kaplan–Meier analysis living donor age appears not to have a significant influence on graft survival censored for death. However, this lack of influence of donor age in Kaplan–Meier analysis could be caused by the fact that this analysis does not take the influence of other variables into account. Moreover, the continuous variable age had to be distributed into arbitrary categories to be suitable for Kaplan–Meier analysis. As shown in Figure 1 age distribution in the deceased and living donor populations is not comparable which means that the results of these separate Kaplan–Meier analyses cannot be compared.

In Cox analysis donor age turns out to have a significant influence on the risk of graft failure censored for death and the risk of uncensored graft failure independent of donor type. This means that donor age influences graft survival in both living and deceased donor transplantation. The risk of graft failure in recipients of a kidney transplantation increases with increasing donor age according to a quadratic equation. However, the risk in deceased donor transplantation is almost twice that of living donor transplantation so that the graft failure risk for a recipient of a 60-year-old living donor kidney is the same as that of a recipient of a 20-year-old deceased donor kidney. As there is no interaction between donor and recipient age regarding graft failure risk it is not necessary to take age difference between donor and recipient into consideration.

In the literature the influence of increasing donor age on the risk of graft failure has been studied in different ways. In some studies the influence of age was studied in Kaplan–Meier analysis where age had to be categorized (16, 17). In other studies age was studied in a Cox analysis, either as a categorical (3, 6, 9–11, 13, 14, 18) or as a continuous covariate (7, 8, 11). Subdivision in categories is arbitrary and not all studies use the same definitions for ‘elderly’ and ‘old’. On top of that, most studies included donor age as a dichotomous variable: old versus young (3, 9–11, 13, 16–18). As aging is a continuous process, its effect most probably follows a continuous line. Categorization probably does not reflect the natural aging process and thus the influence on graft failure risk.

In *deceased donor transplantation*, donor age is known to have a negative effect on overall graft survival (6) and death-censored graft survival (7). In 1999, we described the influence of deceased donor age as a continuous variable on

overall and death-censored graft survival in multivariable Cox analysis as a J-shaped curve (8). The risk of graft failure was highest for recipients of older and extremely young donor kidneys. The risk was lowest for the age categories between 20 and 40 years.

There are few studies that describe the influence of donor age on graft survival in populations that received either *living or deceased donor kidney transplantation*. In all these studies, donor age was included as a categorical variable. In Cox proportional hazards analysis with age as a categorical variable, Matas and colleagues (9) found an unfavorable effect of donor age (≥50) on overall and death-censored graft survival in the population with deceased donor transplantation, but no effect in living donor transplantation population. Kerr and colleagues (10) reported the same results with donors aged 55 years or older. However, both groups performed separate analyses for deceased and living donor transplantation populations. In both studies, the cut-off age for elderly donors was relatively low as was the number of elderly donors included. As we showed, probably as a result of selection, living and deceased donor recipient populations are not comparable (Table 1). This means that the results of separate analyses in two different populations cannot be compared. Although the results of both analyses are different it does not mean that the results of both programs are different.

In UNOS database Gill et al. studied the influence of donor age on graft survival of recipients of living or deceased donor kidneys (14). Age was defined as a categorical variable with four elderly groups above 55 years of age (9.7% of the population) compared with one young population below 55 years (90.3%). An increasing risk of graft failure was found with increasing age independent of donor type. Although the influence of younger donor age categories was not separately analyzed in this study, results for the elderly population showed the same trend we found in our study. In another study, Gill et al. performed a multivariable analysis restricted to elderly recipients aged 60 years or older. They found superior graft survival results with older (>55) living donor kidneys compared to extended criteria deceased donor kidneys, but results were inferior to results from young living donor kidneys (3). Young et al. found no difference for (death-censored) graft loss between older living donor transplantation and deceased SCD in adult recipient transplantation (11).

In *living donor transplantation*, donor age analyzed in multivariable Cox proportional hazards analysis as a continuous variable did not show a significant influence on graft loss (11). However, in this study only 73 (5.8%) elderly donors aged 60 years or older were included. Dols et al. (12) studied donor age as a dichotomous (<60 years vs. ≥60 years) variable. In multivariable analysis they found no difference in death-censored graft survival between recipient populations transplanted with an older living donor kidney and a young living donor kidney. In a population of living donor kidney recipients Toma and colleagues (13) studied the influence of living donor age as a time-dependent variable. They found that living donor age (high ≥60 years vs. low <60 years) was the most important risk factor for long-term overall graft failure. A meta-analysis on the impact of transplantation of kidneys from extended criteria living donors on transplantation outcome revealed that recipients of kidneys from younger living donors had better outcomes than kidney recipients from older living donors (2). Elderly donor age was defined as above 60 years of age.
The meta-analysis also showed that the negative influence of increasing donor age appeared to diminish in time (2). This is in line with our findings during the period 1983–1997 where transplant results improved over time (8). The current study confirms this effect of transplant year on the graft failure risk. A probable explanation is growing experience, improved medical care for concomitant disease, and improvements in diagnostics.
Our study also shows that initial use of CNI and of prednisone is associated with a decreased graft failure and patient death risk, whereas other immunosuppressants have no significant influence.
In the present study we showed that in our population, a kidney from any living donor below age 60 has better graft survival than a 20-year-old deceased donor kidney. Between the ages of 20 and 40 years living donor graft failure risk hardly changes whereas over the age of 40 the relative risk of graft failure increases. This means that awaiting a deceased donor kidney is not an option when a living donor is available. Older living donor kidney transplantation certainly is better than remaining on the waiting list (19).
In conclusion, elderly living donors should not be rejected on the basis of their age only. Although there is an advantage for patients receiving a young living donor kidney (below age 40), even transplantation with an older living donor

kidney provides comparable or better graft survival outcomes than with a deceased donor kidney.

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6

Transplantation results of completely HLA-mismatched living and completely HLA-matched deceased donor kidneys are comparable

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Abstract

Background. Human leukocyte antigen (HLA) mismatches are known to influence graft survival in deceased donor kidney transplantation. We studied the effect of HLA mismatches in a population of recipients of deceased donor or living donor kidney transplantations.

Methods. All 1998 transplantations performed in our center between 1990 and 2011 were included in this retrospective cohort study. Four different multivariable Cox proportional hazard analyses were performed with HLA mismatches as continuous variable, as categorical variable (total number of HLA mismatches), as binary variable (zero vs. nonzero HLA mismatches), and HLA-A, -B, and -DR mismatches included separately.

Results. Nine hundred ninety-one patients received a deceased donor kidney and 1007 received a living donor kidney. In multivariable Cox analysis, HLA mismatches, recipient age, current panel-reactive antibodies, transplant year, donor age, calcineurin inhibitor treatment, and donor type were found to have a significant and independent influence on the risk of graft failure, censored for death. Variables representing the total number of HLA-A, -B, and -DR mismatches had a significant and comparable influence in all analyses.

Conclusions. The influence of HLA mismatches on death-censored graft survival holds true for both deceased and living donor kidney transplantation. However, the relative risk of death-censored graft failure of a 2-2-2 mismatched living donor kidney is comparable with that of a 0-0-0 mismatched deceased donor kidney.

Introduction

Since the very start in 1954, there has been a substantial improvement in both graft and patient survival among those undergoing renal transplantation. In deceased donor kidney transplantation, the importance of human leukocyte antigen (HLA) matching has been controversial. In the 1980s, the influence of HLA matching was found to be very important for graft survival (1, 2). In the 1990s, the importance was put into perspective, as progressive increases in the number of mismatches above zero appeared to have only a relatively small effect on survival compared to the large benefits afforded by the use of kidneys with no mismatches (3). When the effect of HLA-A, -B, and -DR mismatches on the risk of graft failure was studied separately, HLA-DR was the only HLA variable found to be important (4). In the beginning of the 21st century, the positive effect of HLA matching in deceased donor kidney transplantation was confirmed with HLA mismatches as a binary variable: completely HLA-A, -B, and -DR matched versus not completely matched (5). The significance of HLA matching appeared to diminish in time as immunosuppressants improved (6). However, these results were not confirmed in another study (7).

In allocation algorithms for exchange organizations, HLA matching is an important factor. However, the number of studies on the influence of HLA matching in living donor kidney transplantation is low, except for those comparing HLA identical siblings with parents and deceased donors (8). We studied the influence of HLA matching on living donor kidney transplantation results: How does it compare to the influence of HLA on deceased donor kidney transplantation results? What is the influence of different immunosuppressive strategies? What is the influence of other improvements in medical diagnostics and therapies over time?

Materials and methods

Study sample

All 1998 kidney transplantations performed in our center between January 1, 1990 and December 31, 2010 were analyzed. Standard immunosuppressive regimen was cyclosporine combined with prednisone in 1990 but was changed to prednisone, cyclosporine, and mycophenolate mofetil (MMF) in 1996, whereas tacrolimus was introduced in 1998 as a substitute for cyclosporine. Patients were initially treated with triple therapy, but prednisone was tapered and discontinued at 4 months after transplantation.

The screening procedure of potential living kidney donors has been described thoroughly (9). All transplantations were performed after a negative complement-dependent cytotoxicity crossmatch with historical and current sera (10). From 1990 to 2000, HLA-A, -B, and -DR typing was performed serologically on split level at the National Reference Laboratory. In 2000, molecular HLA-A, -B and -DR typing was introduced using sequence-specific oligonucleotides. In recipients and in living donors, HLA typing was performed twice in different blood samples. For 109 transplantations, donor HLA typing was not performed in the reference laboratory. In those cases, local donor and/or recipient HLA typing was used. HLA mismatches were calculated on the serologic split level, both in deceased and living donor kidney transplantation, except for A28, B14, and DR3 (n=218) in accordance with Eurotransplant practice. In 53 other cases, only broad antigens were available. These cases were excluded from the analyses. In living donor transplantation, a high number of HLA mismatches are not an exclusion criterion when the crossmatch is negative. However, in deceased donor transplantation, HLA matching is an allocation criterion in Eurotransplant, aiming at a low number of mismatches.

Statistical analysis

Graft failure censored for death was studied in this retrospective cohort study. Observation was until August 2012 or until graft failure, death, or lost to follow-up. We performed two-tailed independent-samples *t* test, chi-square test, and Mann-Whitney *U* test to analyze the difference between living and deceased donor kidney transplantation populations. Kaplan-Meier analysis was performed with HLA mismatches and donor type (deceased vs. living). Univariable and

multivariable Cox proportional hazard analyses were performed, including all variables mentioned in Table 1 and donor type. In Results, we only describe the results of multivariable analysis in which backward elimination was used to exclude variables with nonsignificant influence. Four models were tested with HLA mismatches included in four different ways: as a continuous covariate, as a categorical covariate with seven categories, as a binary covariate with zero versus nonzero HLA mismatches, and as three categorical covariates; HLA-A, -B, and -DR mismatches. We used the Akaike information criterion to compare the goodness-of-fit between the four models with the four different HLA definitions (11). The proportional hazards assumption was tested for donor type and HLA mismatches with log-minus-log plots. All analyses were performed using Statistical Package for the Social Sciences (SPSS) 20.0.0.1 (IBM, Armonk, NY). $P<0.05$ was considered significant. Cases with missing values were excluded from the analyses.

Table 1. Transplantation characteristics for deceased donor (DD) and living donor (LD) kidney transplantations.

	DD N=991	**LD N=1007**	***P***
Recipient age (years), mean (SD)	49.9 (13.6)	46.6 (14.9)	<0.001[a]
Recipient gender (male), %	62	63	0.579[b]
Maximum PRA, median (%>5%)	8 (56)	4 (27)	<0.001[c]
Current PRA, median (%>5%)	0 (23)	0 (10)	<0.001[c]
Transplant year, median (IQR)	2000 (1995-2005)	2006 (2001-2008)	<0.001[c]
Previous transplants, %			<0.001[b]
0	76	85	
1	18	12	
2+	6	3	
Pretreatment, %			<0.001[b]
Dialysis	97.1	69.1	
No pretreatment	2.5	28.3	
Transplantation	0.4	2.6	
HLA mismatches, mean (SD)	2.7 (1.5)	3.0 (1.7)	<0.001[a]
HLA mismatches, %			<0.001[b]
0	10	10	
1	11	7	
2	22	19	
3	30	28	
4	18	13	
5	7	16	
6	3	8	
HLA zero mismatches, %	10	10	0.942[b]
HLA-A mismatches, %			0.153[b]
0	31	28	
1	49	54	
2	19	19	
HLA-B mismatches, %			0.003[b]
0	22	18	
1	53	51	
2	25	32	
HLA-DR mismatches, %			<0.001[b]
0	38	24	
1	50	53	
2	12	23	
Donor age (years), mean (SD)	46.1 (16.2)	50.0 (12.9)	<0.001[a]
Donor gender (male), %	54	43	<0.001[b]
CNI as initial immunosuppression, %	97	96	0.394[b]
Induction therapy, %	21	23	0.207[b]
mTOR inhibitor, %	3	9	<0.001[b]
MMF, %	60	77	<0.001[b]
Prednisone, %	97	97	0.750[b]
Other immunosuppression, %	5	10	<0.001[b]

[a] Independent-samples *t* test to test significance between DD and LD.
[b] Chi-square test to test significance between DD and LD.
[c] Mann-Whitney *U* test to test significance between DD and LD.
CNI, calcineurin inhibitor; IQR, interquartile range; MMF, mycofenolate mofetil; mTOR, mammalian target of rapamycin inhibitor; PRA, panel reactive antibodies; SD, standard deviation.

Results

Of 1998 transplant recipients, 991 patients received a deceased donor kidney and 1007 received a living donor kidney. Thirteen deceased donor kidney recipients and 14 living donor kidney recipients were lost to follow-up with a median (range) time after transplantation of 24 (0-160) and 33.5 (0-110) months, respectively. Observation of these patients was until they were lost to follow-up. Fifty-three cases were excluded from survival analyses because only broad antigens were available. There were missing values in 4 (0.2%) cases. Cox proportional hazards analyses were therefore performed with 1941 transplantations. In Table 1, transplantation characteristics are shown. Mean HLA mismatches were significantly higher in the living donor transplantation population. A high number of HLA mismatches were more prevalent in living donor-recipient pairs (Figure 1).

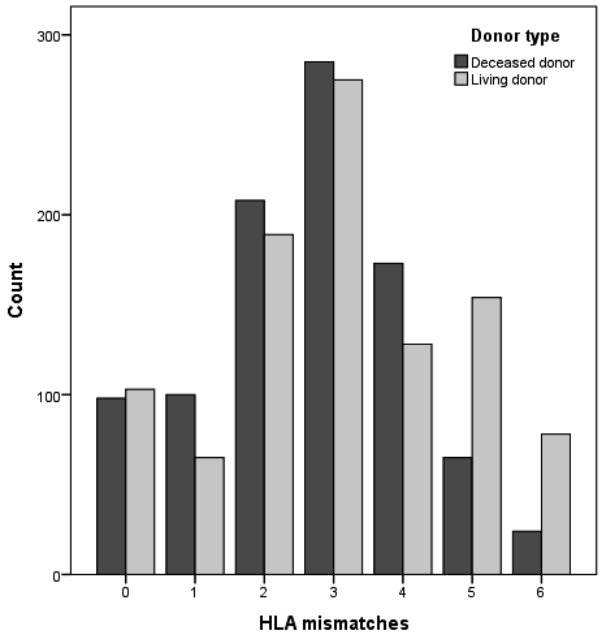
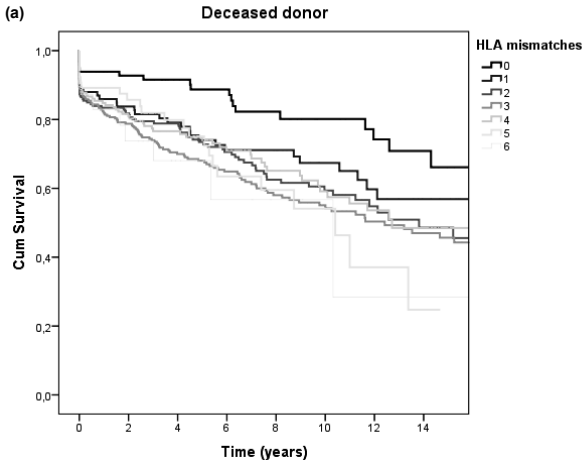


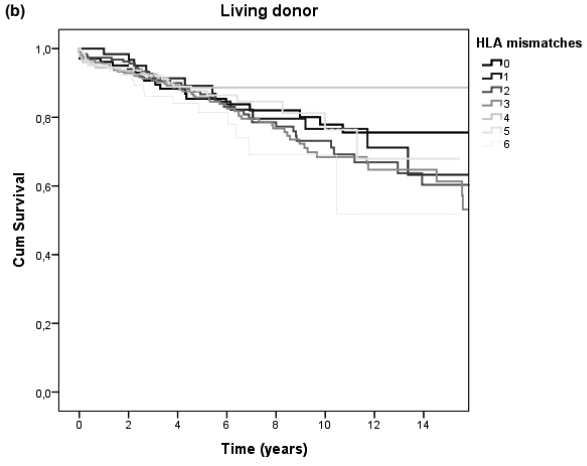
Figure 1. HLA mismatch distribution in deceased and living donor kidney transplantation. The difference in total number of HLA-A, -B, and –DR mismatches between deceased and living donor transplantation was significant (P<0.001).

There was no difference between living and deceased donor transplantation populations in prevalence of zero versus nonzero HLA and HLA-A mismatches. Recipients of living donor kidneys had significantly higher numbers of HLA-B and -DR mismatches compared to recipients of deceased donor kidneys. Besides, there were significant differences between the living and deceased donor transplantation populations concerning recipient age, maximum and current panel-reactive antibodies (PRA), transplant year, previous transplants, pretreatment, donor age, donor gender, mammalian target of rapamycin inhibitor treatment, MMF treatment, and other immunosuppressive treatment (Table 1). There was no significant difference in recipient gender, calcineurin inhibitor (CNI) treatment, induction therapy, and prednisone treatment.
There were 510 graft failures; 335 in recipients of deceased donor kidneys and 175 in recipients of living donor kidneys. In Kaplan-Meier analysis, the difference in graft survival, censored for death between HLA mismatch categories, was significant in deceased donor transplantation but not in living donor transplantation (Figure 2). We tested four multivariable Cox models. In three models, the influence of total number of HLA-A, -B, and -DR mismatches showed the same trend, whether included as a continuous, categorical, or binary variable (all $P<0.001$). In the model with HLA-A, -B, and -DR mismatches included as three categorical covariates, the influence of HLA-A mismatches was significant ($P=0.001$). The influence of HLA-B and -DR was not significant. Because the sum of HLA-A, -B, and -DR mismatches provides a better fit of the model, the total number of HLA mismatches was used in the final multivariable Cox model. According to the Akaike information criterion (11), the goodness-of-fit of the model was best when total number of HLA mismatches was included as categorical variable, followed by total number of HLA mismatches as continuous variable, and eventually total number of HLA mismatches as binary variable. The number of degrees of freedom of HLA mismatches was 6 in the first model and 1 in both other models. Recipient age, current PRA, transplant year, total number of HLA mismatches, donor age, CNI treatment, and donor type were found to have a significant influence on the risk of graft failure, censored for death (Table 2). As shown before, donor age had a quadratic influence on the risk of graft failure (12). The influence of donor gender was not significant. The interaction terms between HLA mismatches and recipient age, transplant year, donor age,

treatment with CNI, and donor type were not significant. There was no interaction between transplant year and donor type. The proportional hazards assumption was neither violated for HLA mismatches nor for donor type. Figure 3 shows the results of two different models: one with total number of HLA mismatches as categorical variable (dots) and the other with total number of HLA mismatches as continuous variable (lines). In both models, the same variables were present in the final model. The combined influence of HLA mismatches and donor type is shown on the calculated relative risk of graft failure censored for death, corrected for the other variables in the final multivariable Cox model. The relative risk increases with increasing total number of HLA mismatches, so that the risk of a zero mismatched deceased donor kidney transplantation is comparable with that of a five or six mismatched living donor kidney transplantation.



Number at risk								
HLA mismatches								
0	98	80	66	56	40	30	24	16
1	100	76	64	48	43	29	21	15
2	208	147	120	95	69	51	30	21
3	285	205	148	120	84	63	50	39
4	173	118	92	65	51	35	25	13
5	65	48	36	20	14	7	4	2
6	24	16	9	5	3	2	1	1



Number at risk								
HLA mismatches								
0	103	88	66	52	45	36	30	20
1	65	59	43	37	29	20	13	6
2	189	172	118	86	62	40	25	18
3	275	229	165	122	76	48	32	21
4	128	99	62	30	17	11	5	1
5	154	122	81	53	29	16	4	1
6	78	65	40	23	7	4	1	1

Figure 2. (a) Kaplan-Meier curve comparing death-censored graft survival after deceased donor kidney transplantation (P=0.017). The difference was significant between 0 and each of the following HLA mismatches: 2, 3, 4, 5, and 6. (b) Kaplan-Meier curve comparing death-censored graft survival after living donor kidney transplantation. The difference between HLA mismatches was not significant (P=0.232).

Table 2. Results of the multivariable Cox proportional hazards analysis with HLA mismatches analyzed as (a) categorical and (b) continuous covariate. Event is graft failure censored for death.

	N=1941, 510 events		
Variable (reference)	**Exp(B)**	**95% CI**	***P***
(a) Categorical covariate			
Recipient age (per year)	0.982	0.975 - 0.989	<0.001
Current PRA (per %)	1.010	1.006 - 1.014	<0.001
Transplant year (per year)	0.974	0.956 - 0.992	0.005
HLA mismatches (0)			<0.001
1	1.506	0.974 - 2.330	0.066
2	1.871	1.288 - 2.719	0.001
3	2.062	1.439 - 2.955	<0.001
4	1.790	1.192 - 2.688	0.005
5	2.117	1.344 - 3.335	0.001
6	3.279	1.936 - 5.555	<0.001
Donor age (per year)	0.982	0.954 - 1.011	0.212
Donor age^2 (per year^2)	1.000	1.000 - 1.001	0.010
Donor gender (male)	1.150	0.964 - 1.372	0.120
CNI as initial immunosuppression (no)	0.298	0.211 - 0.420	<0.001
Donor type (deceased)	0.483	0.394 - 0.593	<0.001
(b) Continuous covariate			
Recipient age (per year)	0.981	0.975 - 0.988	<0.001
Current PRA (per %)	1.010	1.006 - 1.014	<0.001
Transplant year (per year)	0.973	0.955 - 0.991	0.003
HLA mismatches (per HLA mismatch)	1.139	1.071 - 1.211	<0.001
Donor age (per year)	0.981	0.953 - 1.009	0.186
Donor age^2 (per year^2)	1.000	1.000 - 1.001	0.008
Donor gender (male)	1.169	0.981 - 1.394	0.081
CNI as initial immunosuppression (no)	0.302	0.214 - 0.425	<0.001
Donor type (deceased)	0.486	0.397 - 0.594	<0.001

CNI, calcineurin inhibitor; PRA, panel reactive antibodies.

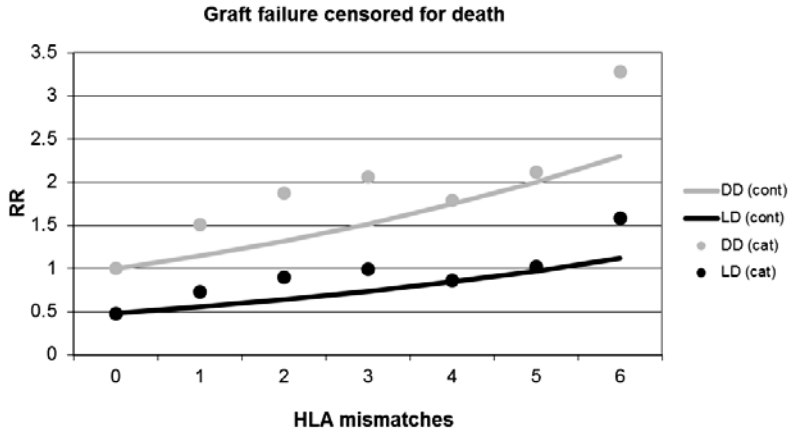


Figure 3. Calculated relative risk (RR) of graft failure censored for death with increasing numbers of HLA mismatches for deceased donor (DD) and living donor (LD) kidney transplantation based on the final multivariable Cox proportional hazards model with total number of HLA mismatches included as continuous variable (cont; lines) and as categorical variable (cat; dots). The reference value is a 0-0-0 mismatched deceased donor transplantation.

Discussion

Over the past decades, kidney transplantation results have improved considerably; however, the contribution of improved HLA matching has not always been clear. In some studies, in deceased donor kidney transplantation, HLA matching was found to be important (1, 2), whereas others primarily showed a benefit for completely HLA-matched donor kidneys (3, 5). The combined effect of HLA mismatches and time was debated as well (6, 7). In our study, we did not find an interaction between HLA mismatches and transplant year. In our study, the influence of HLA mismatches is independent of time.

In all abovementioned studies, HLA mismatches were included as a categorical parameter, but interpretation is hampered, as not all studies agreed on the definition of HLA mismatches. In these studies, HLA mismatches has been defined as total number of HLA-A plus HLA-B (2); total number of HLA-DR plus HLA-B (1); HLA-A, -B, and -DR separately (4); total number of HLA-A, -B, and -DR together (3, 6, 7); and HLA-A, -B, and -DR identical or not (5).

In living donor kidney transplantation, the influence of HLA matching as a categorical variable has been described in a small number of studies. Among other factors, four HLA-A and -B mismatches was shown to be a risk factor for long-term graft failure in living donor renal transplantation, whereas HLA-DR mismatches appeared not to be of influence (13). In a British population, in contrast to the expectations, the degree of HLA-A, -B, and -DR mismatch did not influence graft survival (14). In this study, HLA mismatches on A, B, and DR were included as three separate categorical variables. Two mismatches for A, B, or DR hardly prevailed, which means that a total number of six mismatches was very scarce in this population. Recently, Rizzari et al. described a population of 1632 patients with HLA mismatches defined as 0, 1-2, 3-4, and 5-6. A significant effect of HLA mismatches on the risk of graft failure was found in the highest category mismatches (15).

There is only one small study evaluating the influence of HLA mismatches in both deceased and living donor kidney transplantation (16). Although HLA mismatches 3-6 were associated with a significantly increased risk for antibody-mediated rejection and cell-mediated rejection compared with HLA mismatches 0-2, HLA mismatches did not influence the risk of graft failure censored for

death in this population. In this study, donor type was found not to influence rejection and graft failure.
In the present study, HLA mismatches turned out to be an important factor influencing graft survival independent of donor type. However, the risk of failure in deceased donor kidney transplantation is larger than in living donor transplantation, so that the risk of a completely mismatched living donor kidney is only slightly higher than that of a HLA-A, -B, and -DR identical deceased donor kidney (Figure 3). Although the risk of a high number of HLA mismatches in living donor transplantation is comparable with that of completely HLA-A, -B, and -DR matched deceased donor transplantation, it should be kept in mind that an important disadvantage of a high number of HLA mismatches is that it might lead to sensitization, consequently decreasing chances for a potential subsequent transplant (17). When available, a low number of HLA mismatches should always be preferred, even in living donor kidney transplantation. Nevertheless, when a living donor with a high number of HLA mismatches is available, better-matched deceased donor kidney transplantation in the future should not be awaited, as the effect of HLA mismatches is corrected for by the living donation procedure.
Kaplan-Meier analysis did not show an influence of HLA mismatches on graft survival, censored for death in living donor kidney transplantation. However, Kaplan-Meier analysis only shows what occurred in the population studied. Populations with high and low numbers of HLA mismatches are compared irrespective of the influence of other variables. This means that the effect found could either be the result of HLA mismatches, or of other factors, as recipient condition. Moreover, we showed that our populations of deceased and living donor kidney transplant recipients differ in many respects (Table 1) and therefore cannot be compared with Kaplan-Meier analysis. The Cox proportional hazards analysis, on the contrary, does account and correct for the effect of other variables. A risk analysis can be made for a kidney transplant patient with known variables.
As the definition of HLA mismatches has been variable in the different studies mentioned, we decided to compare the influence of the definition of HLA mismatches in four different models in the same population. The fit of the model was worse with HLA-A, -B, and -DR mismatches included as three separate

variables and best with HLA-A, -B, and -DR mismatches added up to one total number of HLA mismatches in one categorical variable. The fit of the model was intermediate with HLA-A, -B, and -DR mismatches added up to one total number of HLA mismatches in one continuous variable and when included as a binary variable. The strength of this study is that the three different analyses including total number of HLA-A, -B, and -DR mismatches defined in three different ways led to the same outcome. Figure 3 shows that the influence of total number of HLA mismatches whether defined as a continuous or categorical variable is comparable. This shows that the influence of HLA mismatches could be analyzed as continuous covariate in future research.

A limitation of our study is that 11% of splits were not available. This could have caused underestimation of HLA mismatches. Disregarding A28, B14, and DR3 splits is Eurotransplant policy. The policy not to determine these splits not only exists in our center but also holds true for the whole Eurotransplant area.

Our results show that HLA-A, -B, and -DR matching improves outcomes, even in living donor kidney transplantation. However, we also showed that disregarding a living donor kidney with a high number of HLA mismatches to await a deceased donor kidney with a better match does not improve graft survival.

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7

A high comorbidity score should not be a contraindication for kidney transplantation

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Abstract

Background. Currently, potential kidney transplant patients more often suffer from comorbidities. The Charlson Comorbidity Index (CCI) was developed in 1987 and is the most used comorbidity score. We questioned to what extent number and severity of comorbidities interfere with graft and patient survival. Besides, we wondered whether the CCI was best to study the influence of comorbidity in kidney transplant patients.

Methods. In our center, 1728 transplants were performed between 2000 and 2013. There were 0.8% cases with missing values. Nine pretransplant comorbidity covariates were defined: cardiovascular disease, cerebrovascular accident, peripheral vascular disease, diabetes mellitus, liver disease, lung disease, malignancy, other organ transplantation, and human immunodeficiency virus positivity. The CCI used was unadjusted for recipient age. The Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score was developed, and its influence was compared to the CCI. Kaplan-Meier analysis and multivariable Cox proportional hazards analysis, corrected for variables with a known significant influence, were performed.

Results. We noted 325 graft failures and 215 deaths. The only comorbidity covariate that significantly influenced graft failure censored for death was peripheral vascular disease. Patient death was significantly influenced by cardiovascular disease, other organ transplantation, and the total comorbidity scores. Model fit was best with the Rotterdam Comorbidity in Kidney Transplantation score compared to separate comorbidity covariates and the CCI. In the population with the highest comorbidity score, 50% survived more than 10 years.

Conclusions. Despite the negative influence of comorbidity, patient survival after transplantation is remarkably good. This means that even patients with extensive comorbidity should be considered for transplantation.

Introduction

Acceptance criteria for kidney transplantation are continuously eased; for example, currently, even patients in their 80s are considered and accepted for transplantation. A less well-defined criterion that has been eased is the presence of comorbidity. The Charlson Comorbidity Index (CCI) is widely used to express the gradation of comorbidity (1). This score was developed in 1987 in a cohort of patients admitted to a medical service and validated in a population of breast cancer patients. It takes into account both the number and the seriousness of comorbid diseases.

In patients on renal replacement therapy (RRT), the CCI was shown to have a significant influence on mortality (2-6). Survival rates were strongly influenced by age as in these studies the CCI was age adjusted. Other comorbidity indices were also shown to have a significant influence on mortality of RRT patients (7-10).

In most studies on the influence of the CCI on mortality in kidney transplant recipients, a significant effect was found (11-15). In these studies, the most commonly used CCI was unadjusted for age with a high 5-year patient survival, ranging from 90% to 98% in the lowest CCI groups and from 70% to 88% in the highest CCI groups. Graft survival censored for death was not influenced by the CCI (11-13).

Apart from the CCI, a number of other comorbidity measures were found to have a significant influence on graft or patient survival. These were cardiovascular disease, peripheral vascular disease (PVD), history of diabetes, hepatitis C virus infection, human immunodeficiency virus (HIV) positivity, the recipient risk score, and multiple separate comorbidities (16-23).

In all studies, the presence of an increasing burden of comorbidity predicted a lower patient survival. However, the highest comorbidity score was not necessarily the same in all studies as acceptance criteria and definitions of comorbidity were adapted to current knowledge and experience. In potential kidney transplant recipients, not all conditions used in the CCI are present. More serious conditions, for example, metastatic malignancy or untreated acquired immune deficiency syndrome (AIDS) are not present as those conditions preclude transplantation. It can be questioned whether the CCI is applicable to kidney transplant recipients: Are comorbidities of equal influence in kidney

transplant patients, with their predisposition for vascular disease and immunosuppressive treatment, as they are in the general population? Besides, the importance of comorbidities changed since 1987, for example, peptic ulcer disease was no longer considered an important health threat since the introduction of proton pump inhibitors in 1985 (24). For AIDS, highly active antiretroviral therapy is available since 1996, adding HIV-positive patients to the kidney transplant candidate pool (25). In the CCI, cardiovascular interventions are not taken into account though their introduction led to an increase in the number of potential recipients with cardiovascular disease. Extra points are added to the CCI for congestive heart failure, whereas in patients on RRT, this may be the result of cardiovascular disease or overhydration. The subdivision of both diabetes mellitus and liver disease in more or less severe disease unnecessarily complicates the CCI score.

Since the start of our transplantation program in 1971, our center has been very liberal concerning acceptance of patients with comorbidity. Therefore, the comorbidity scores and the number of patients with the highest comorbidity scores in our center are relatively high. Is there a limitation to the number and extent of comorbidities that is acceptable for transplantation? In our population of kidney transplant recipients, we studied to what extent severity and number of comorbidities interfere with graft and patient survival. We tested the individual comorbidity covariates separately, in the CCI, and computed a new comorbidity index with low complexity and high utility, adapted to recent norms and definitions: the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score.

Materials and methods

Patients

In our center, 1728 transplants were performed between January 1, 2000, and December 31, 2012. Most patients were from the Rotterdam region, and also patients from other regions in the Netherlands were referred to our center because of medical complexity and decline by other university hospitals.
A relative cardiovascular contraindication for kidney transplantation was the presence of inducible ischemia on nuclear myocardial perfusion studies or dobutamine stress echocardiography. Unless there were contraindications, a coronary angiography (CAG) was performed. When CAG showed stenoses, treatment was performed before transplantation. When CAG showed abnormalities without treatment options, transplantation was reconsidered. An ejection fraction below 30% was accepted for transplantation when reversibility was expected. Neither the number of myocardial infarctions, coronary stents or bypasses per se, nor the presence of fixed defects were exclusion criteria. Aortoiliac bypasses or stents were not exclusion criteria. Symptomatic PVD was an exclusion criterion for transplantation if there were no options for anastomosis due to severe stenosis (>70%) or circular calcification of all iliac internal and external vessels. Malignancy per se was not an exclusion criterion for kidney transplantation, but depended on type, staging, and time of disease-free follow-up. In general, a remission period of at least 2 years was accepted. For some cancers, such as renal cell and prostate cancer, shorter time intervals were accepted and guided by the histopathological examination of the resected specimen and approval of the treating physician.
All deceased and living donor kidney transplant recipients in the study period were included in this retrospective cohort study. The standard immunosuppressive regimen was triple therapy. Most patients (88%) were initially given prednisone, tacrolimus, and mycophenolate mofetil. Prednisone was tapered and discontinued at 4 months after transplantation. Other immunosuppressants administered were induction therapy, other immunosuppressives, or study medication. The screening procedure of potential living kidney donors has been described previously (26).

Individual comorbidity covariates

Nine pretransplant comorbidity covariates were defined. *Cardiovascular disease* includes myocardial infarction, coronary artery disease, coronary bypass, coronary stent, congestive heart failure, and heart transplantation. *Cerebrovascular accident* (CVA) includes CVA and transient ischemic attack. *Peripheral vascular disease* includes symptomatic PVD, amputation, radiologically proven PVD, stent placement, or bypass. *Diabetes mellitus* includes type 1 and type 2. *Liver disease* includes cirrhosis, fibrosis, decompensated liver, portal hypertension, Child-Pugh A or higher, primary sclerosing cholangitis, liver transplantation, and active or chronic hepatitis B or C. *Lung disease* includes pulmonary hypertension, (asthmatic) bronchitis, bronchiectasis, chronic obstructive pulmonary disease, emphysema, extrinsic allergic alveolitis, and lung transplantation. *Malignancies* in the study population were Grawitz, hematologic, bladder, breast, prostate, testis/seminoma, thyroid gland, cervix, colon, melanoma, larynx, lung, ovary, adrenal gland, chorion, leiomyosarcoma, and ear-nose-throat tumors. Meningioma was also included because of its highly malignant behavior. Skin tumors other than melanoma were not included. *Other organ transplants* were heart, liver, and lung. The *HIV*-positive patients had no detectible HIV load at transplantation.

Comorbidity scores

Two comorbidity scores were computed for each patient. Transplantation of other organs was not included in the comorbidity scores, but was analyzed as a separate variable.

The first comorbidity score was the CCI (1). Limitations of the CCI in the transplant population have been handled according to Jassal et al. (14). For example, no differentiation was made between diabetes and diabetes with end organ damage, and between mild and moderate liver disease. Ulcer disease, dementia, and hemiplegia were not recorded. The influence of connective tissue disease was included in primary renal disease. In contrast to Jassal et al., congestive heart failure with cardiac cause was scored as cardiovascular disease. It was not scored when it was caused by mere fluid overload without an underlying cardiac disease. Because no patients with severe liver disease, metastatic solid tumor, or AIDS were transplanted, 3 or 6 points were not

attached to our patients. Human immunodeficiency virus was not mentioned in the CCI, but we arbitrarily assigned 1 point. In Table 1, the points assigned to the comorbidity covariates composing the CCI are shown. The minimal CCI score of our patients was 2 (as 2 points were added for renal insufficiency). The CCI was unadjusted for age.

The second comorbidity score was the RoCKeT score that was computed for this study. It was developed according to Charlson et al.'s method (1). The score was based on the influence of the comorbidity covariates in multivariable analysis in the presence of all other comorbid diseases. Charlson et al. described 2 methods for point assignment to comorbidities. In the first method, points were assigned when the influence on the risk of patient death was significant. In the second method, points were assigned when the relative risk (RR) was 1.3 or higher. No extra points were added for moderate or severe renal disease because all patients had end-stage renal disease. In the Results section, the composition of the RoCKeT score is described.

Table 1. Points assigned to the comorbidity covariates in the RoCKeT score and the CCI

Comorbidity covariates	**RoCKeT score**	**CCI[a]**
Cardiovascular disease	3	1
CVA	2	1
PVD	2	1
Diabetes mellitus	2	1
Liver disease	2	1
Lung disease	2	1
Malignancy	1	2
HIV	1	1
Renal disease	-	2

[a] CCI as it was applied to the study population. Excluded from the original CCI (similarly to Jassal et al. (14)): dementia, connective tissue disease (included in primary renal disease), ulcer disease, severe liver disease, metastatic solid tumor, and AIDS.
CCI, Charlson comorbidity index; CVA, cerebrovascular accident; PVD, peripheral vascular disease; RoCKeT score, Rotterdam Comorbidity in Kidney Transplantation score.

Statistical analyses

Graft failure censored for death and patient death were studied. Follow-up was until March 2014 or until graft failure, patient death, or loss to follow-up. We analyzed differences between patients with and without comorbidity using 2-tailed independent-samples *t* tests, χ^2 tests, and Mann-Whitney *U* tests. Kaplan-Meier analysis was performed to generate survival curves concerning the influence of the RoCKeT score. Various multivariable Cox proportional hazards analyses were performed to test the independent influence of comorbidity on the risk of graft failure censored for death and on the risk of patient death. In the first model, the influence of the individual comorbidity covariates was studied; in the second model, the CCI; and in the third model, the RoCKeT score. The Akaike information criterion was used to select the model with the best fit (27). In each model, we corrected for the influence of all variables shown in Table 2 and primary renal disease. Primary renal disease was divided into diabetes mellitus and other. Pretreatment was analyzed as a binary variable: yes (hemodialysis, peritoneal dialysis, former transplantation) or no (no RRT). Backward elimination was used to select each final model. To determine the number of covariates in the initial multivariable model, we computed the square root of the number of events (graft failures or deaths). The outcome reflected the maximum total number of degrees of freedom in the model. First, covariates with the lowest *P* values in univariable analysis were included. In the multivariable model, covariates that did not contribute significantly were removed using backward elimination. Subsequently, the covariates with higher *P* values were included followed by backward elimination. This procedure was repeated until all covariates had been included in the model.

All analyses were performed using Statistical Package for the Social Sciences 21.0.0.1 (IBM Corporation, Armonk, NY). *P* values less than 0.05 were considered significant. The proportional hazards assumption was tested using log-minus-log plots. Cases with missing values were excluded from Cox proportional hazards analyses.

Table 2. Transplantation characteristics of patients with and without comorbidity

	No comorbidity N=911	**Comorbidity N=817**	***P***
Recipient age in years, mean (SD)	46.0 (14.2)	56.3 (12.7)	<0.001[a]
Recipient gender (male), %	61	66	0.032[b]
Ethnicity, %			0.035[b]
European	75	69	
African	9	9	
Arabian	3	4	
Asian	9	13	
Turkish	5	5	
Maximum PRA, median (% >5%)	4 (33)	4 (27)	0.361[c]
Current PRA, median (% >5%)	0 (15)	0 (10)	0.061[c]
Retransplants, %	20	16	0.022[b]
Pretreatment, %	77	83	0.004[b]
Time on dialysis in years, median (IQR)	1.2 (0-2.7)	1.7 (0.5-3.2)	<0.001[c]
BMI, median (IQR)	24 (21-27)	25 (22-29)	<0.001[c]
Transplant year, median (IQR)	2007 (2004-2010)	2008 (2005-2011)	0.004[c]
HLA mismatches, mean (SD)	3.0 (1.6)	3.3 (1.7)	0.001[a]
Donor type (living donor), %	68	58	<0.001[b]
Donor age in years, mean (SD)	50.5 (13.4)	51.8 (14.0)	0.053[a]
Donor gender (male), %	46	47	0.665[b]
CNI as initial immunosuppression, %	97	97	0.688[b]

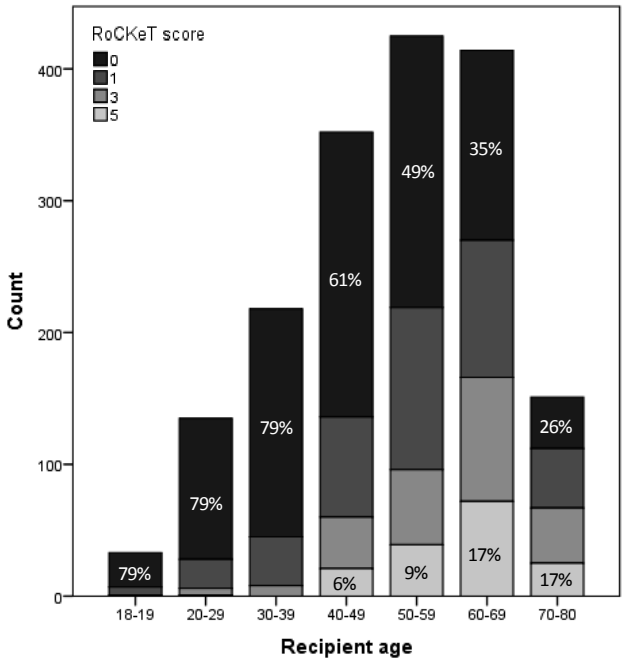
[a] Independent-samples *t* test to test significance between patients with and without comorbidity.
[b] χ^2 test to test significance between patients with and without comorbidity.
[c] Mann-Whitney *U* test to test significance between patients with and without comorbidity.
BMI, body mass index; CNI, calcineurin inhibitor; IQR, interquartile range; PRA, panel reactive antibodies; SD, standard deviation.

Results

In 15% of the 1728 cases, patients had cardiovascular disease before transplantation, 9% CVA, 9% PVD, 20% diabetes mellitus, 4% liver disease, 5% lung disease, 7% malignancy, 2% received another organ transplant, and 0.2%was HIV-positive. The mean CCI was 2.8 ± 1.0, and the median (range) was 2 (2-7). A total of 817 (47%) patients had comorbidity.
Observation was until March 2014 so that at least 14 months of follow-up could be obtained. Median follow-up time was 4 years (range, 0-13 years). In total, 44 patients were lost to follow-up with a median (range) of 25.5 (0-125) months after transplantation. For these patients, follow-up was calculated until the date last seen. There were 13 cases (0.8%) with missing values. Consequently, Cox proportional hazards analyses were performed in 1715 cases.

Development of the RoCKeT score

In multivariable analysis, the following comorbidities (RR) had a significant influence on the risk of patient death and RR of 1.3 or higher: cardiovascular disease (2.5), CVA (1.5), PVD (1.6), diabetes (1.5), liver disease (2.1), and lung disease (1.9). According to Charlson et al., the RRs were rounded up/off to whole points (1). Consequently, cardiovascular disease was given 3 points and the other comorbidities 2 points each. The corrected influence of pretransplant malignancy and HIV on the risk of patient death was not significant. However, the RR of malignancy was 1.4, allowing assignment of 1 point according to Charlson et al. Because there were only 4 patients with HIV, the influence of HIV was not significant, and RR was below 1.3. Because of the clinical relevance of HIV, 1 point was assigned arbitrarily. In Table 1, the points assigned to the comorbidity covariates are shown. All points were added up to create the RoCKeT score. The range of the RoCKeT score was 0 to 9, 53% of patients had a score of 0; no comorbidity. We categorized the RoCKeT score into 0 (N = 911), 1 to 2 (N = 413), 3 to 4 (N = 246), and 5 to 9 (N = 158) points to create larger groups. Of the patients younger than 40 years, 21% had comorbidity compared with 74% of patients aged 70 to 79 years (Figure 1). Comorbidity increased with time. In 2000, 39% of patients transplanted had comorbidity. This percentage gradually increased to 58% in 2012.



N in age group	33	135	218	352	425	414	151
Mean RoCKeT score	0.48	0.47	0.42	1.12	1.51	2.29	2.48
SD	1.00	1.03	0.86	1.67	1.87	2.20	2.10

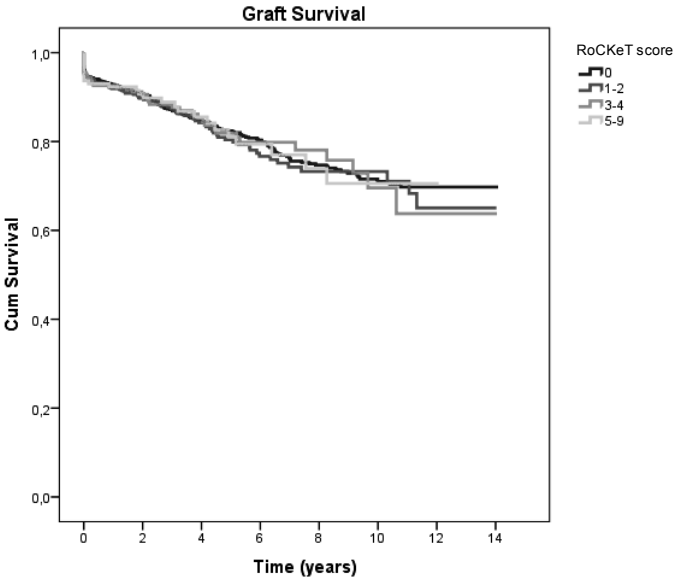
Figure 1. Distribution and means of the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score per age group. The difference between the age groups was significant ($P < 0.001$). Older patients have a higher RoCKeT score.

Pretransplant characteristics

Patients without comorbidity had a score of 0 in the RoCKeT score and a score of 2 in the CCI. There were significant differences in characteristics between patients with and without comorbidity (Table 2). Patients with comorbidity were significantly older than patients without comorbidity and spent more time on dialysis. Moreover, there were significant differences between the populations concerning recipient gender, ethnicity, retransplants, pretreatment, body mass index, transplant year, HLA mismatches, and donor type. Of the patients with comorbidity, 28% had diabetes mellitus as their primary renal disease.

The influence of comorbidity on graft failure

During follow-up, 325 graft failures were noted. *Kaplan-Meier analysis* showed that the difference between the categories of the RoCKeT score was not significant for graft survival censored for death (P = 0.962) (Figure 2). In multivariable *Cox proportional hazards analysis*, the influence of the individual comorbidity covariates was tested in the first model. The number of covariates included in the model was maximum 18 degrees of freedom. The risk of graft failure censored for death was significantly influenced by PVD (P = 0.005) but not by the other comorbidities (Table 3). In the second and third models, the CCI and the RoCKeT score were removed from the model after backward elimination and thus did not have a significant influence on graft failure censored for death.



Number at risk

RoCKeT score								
0	911	719	504	348	240	132	53	3
1-2	413	304	196	108	62	34	13	1
3-4	246	164	102	66	37	16	5	1
5-9	158	103	65	39	22	10	1	0

Figure 2. Kaplan-Meier survival curve of the influence of the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score on graft survival censored for death. There was no significant difference between the comorbidity categories (P = 0.962).

Table 3. Results of the multivariable Cox proportional hazards analysis on the risk of graft failure censored for death

325 events[a]			
Variable (reference category)	**Exp(B)**	**95% CI**	***P***
Recipient age (per year)	0.980	0.972 - 0.988	<0.001
Maximum PRA (per %)	1.007	1.003 - 1.011	<0.001
Peripheral vascular disease (no)	1.642	1.161 - 2.321	0.005
Transplant year (per year)	0.966	0.932 - 1.001	0.054
HLA mismatches (per HLA mismatch)	1.085	1.008 - 1.168	0.030
Donor type (deceased)	0.505	0.396 - 0.643	<0.001
Donor age (per year)	1.029	1.019 - 1.039	<0.001
CNI as initial immunosuppression (no)	0.360	0.228 - 0.570	<0.001

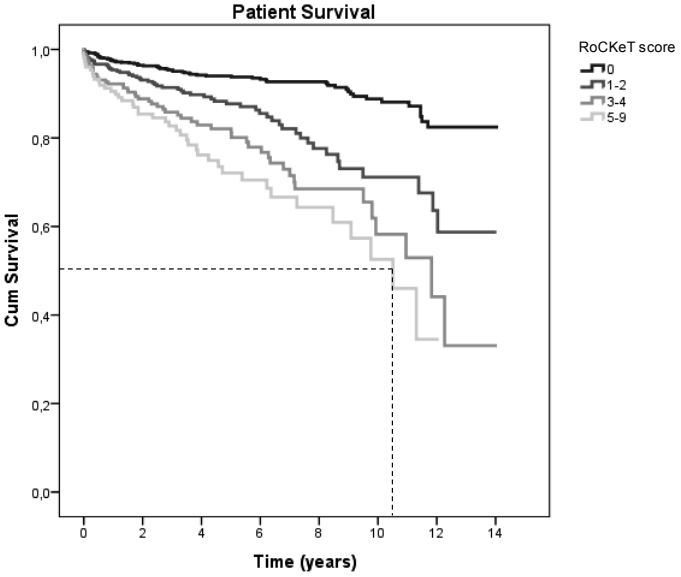
[a] Event is graft failure censored for death. Final model after backward elimination of the following covariates: recipient gender, ethnicity, primary renal disease, current PRA, retransplants, pretreatment, time on dialysis, cardiovascular disease, cerebrovascular accident, diabetes mellitus, liver disease, lung disease, malignancy, transplantation of other organ, HIV, BMI, and donor gender.
BMI, body mass index; CNI, calcineurin inhibitor; PRA, panel reactive antibodies.

The influence of comorbidity on mortality

In the study period, there were 215 deaths. In Kaplan-Meier analysis, we found a significant difference in patient survival between the RoCKeT score categories ($P < 0.001$) (Figure 3). Patient survival of 50% of the patients in the highest comorbidity category was more than 10 years. In the first Cox proportional hazards model with maximum 14 degrees of freedom, mortality was significantly influenced by cardiovascular disease ($P < 0.001$) and transplantation of other organ ($P = 0.001$). Diabetes mellitus as primary renal disease had a significant influence on patient death as well ($P = 0.002$). In the second model, the CCI had a significant influence ($P = 0.005$). In the third model, the RoCKeT score showed a significant influence ($P < 0.001$) (Table 4). The influence of donor type was significant ($P = 0.02$). There was no interaction between recipient age and comorbidity: the influence of comorbidity is independent of age. Figure 4 shows the combined influence of age and comorbidity on patient death. In addition, no significant interaction was found between donor type and comorbidity, time on dialysis and comorbidity, and ethnicity and comorbidity in these analyses. The proportional hazards assumption was not violated.

The Akaike information criterion showed that the model with the RoCKeT score had the best fit, followed by the model with comorbidities included separately.

The fit of the model with the CCI was less good. Both comorbidity indices showed the same trend, though significance levels and RRs varied slightly.



Number at risk								
RoCKeT score								
0	911	719	504	348	240	132	53	3
1-2	413	304	196	108	62	34	13	1
3-4	246	164	102	66	37	16	5	1
5-9	158	103	65	39	22	10	1	0

Figure 3. Kaplan-Meier survival curve of the influence of the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score on patient survival. The overall *P* value was less than 0.001. After Bonferroni correction for multiple comparisons (α = 0.008), the difference between 0 and the other comorbidity categories was significant (*P* < 0.001), as well as the difference between 1-2 and 5-9 (*P* < 0.001). The differences between 1-2 and 3-4 (*P* = 0.010) and between 3-4 and 5-9 (*P* = 0.150) were not considered significant. After 10 years, 50% of the patients in the highest comorbidity category are still alive.

Table 4. Results of the multivariable Cox proportional hazards analysis on the risk of patient death

215 events[a]			
Variable (reference category)	**Exp(B)**	**95% CI**	***P***
Recipient age (per year)	1.061	1.047 - 1.076	<0.001
Ethnicity (European)			0.048
African	0.411	0.201 - 0.840	0.015
Arabian	0.245	0.060 - 1.002	0.050
Asian	0.861	0.553 - 1.338	0.505
Turkish	0.888	0.475 - 1.659	0.710
Time on dialysis (per year)	1.056	0.998 - 1.117	0.058
RoCKeT score (0)			<0.001
1-2	1.685	1.165 - 2.437	0.006
3-4	2.129	1.444 - 3.138	<0.001
5-9	2.700	1.774 - 4.110	<0.001
Transplantation of other organ (no)	2.078	1.102 - 3.921	0.024
Transplant year (per year)	0.935	0.894 - 0.978	0.003
Donor type (deceased)	0.698	0.516 - 0.944	0.020

[a] Event is patient death. Final model after backward elimination of the following covariates: recipient gender, primary renal disease, maximum PRA, current PRA, retransplants, pretreatment, BMI, HLA mismatches, donor age, donor gender, and CNI as initial immunosuppression.
BMI, body mass index; CNI, calcineurin inhibitor; PRA, panel reactive antibodies; RoCKeT score, Rotterdam Comorbidity in Kidney Transplantation score.

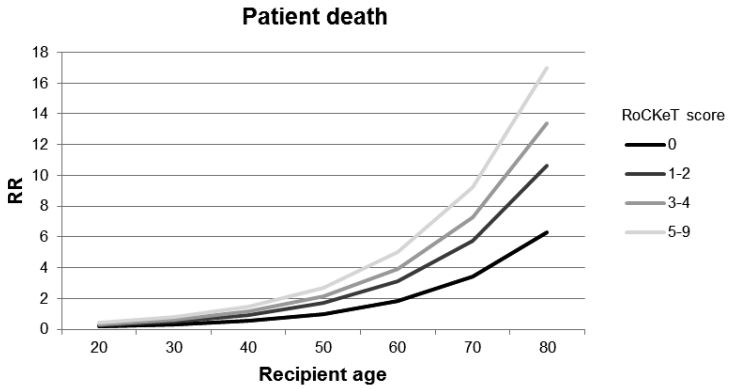


Figure 4. The combined influence of recipient age and the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score on the relative risk (RR) of patient death. The reference value is the risk of a 50-year-old patient without comorbidity (RR = 1). Between ages 50 and 80 years, the RR increases 6 times. The RR of the highest comorbidity score is 2.7 compared with a comorbidity score of 0 (see also Table 4).

Discussion

As treatment options for various medical diseases improve over time, end-stage renal disease patients with comorbidity are more often referred to transplant centers and actually transplanted. There are only a few studies that meticulously describe comorbidity and its influence in their renal transplant population. In 2005, Jassal et al. (14) described comorbidity in their study on 6324 renal transplant patients. Mean age was 42 years, and 29% had comorbidity. In the population of Wu et al. (12), 45% of 715 patients had comorbidity, and mean age was 50 years. In our patient population of 1728 patients, 47% had comorbidity, and mean age was 51 years. However, the definition of comorbidity was not exactly the same in these studies. These studies are on the influence of the presence of multiple comorbidities on patient survival, independent of the heterogeneity within each of the comorbid diseases. Though heterogeneity may exist, it is questionable whether subjective subdivision of comorbidities in multiple categories increases reliability of results. The severity of comorbidities cannot always be measured neither will they be available in retrospective analysis. Moreover, subdivision of comorbidities into multiple categories unnecessarily complicates the score and analysis.

The CCI was previously shown to be a significant predictor of mortality (2-6, 11-15). However, the population the CCI was developed in is totally different from the population of kidney disease patients, questioning its applicability. The recipient risk score was designed to improve deceased donor kidney allocation and was found to have a better fit in this population than the CCI (21, 28). The RoCKeT score had a better fit in kidney transplant recipients than the CCI and turned out to be a significant covariate influencing patient survival which emphasizes its importance in survival and intervention studies.

The scores we tested were unadjusted for age, because in a previous study, we showed that age is an important and independent risk factor for patient death (29). Including age in comorbidity scores would contaminate these scores. The independent influence of age was recognized by others as well (7, 8, 10).

In the current study, the only comorbidity that influenced graft survival censored for death was PVD. This has been described before (17). Difficult anastomoses and/or a decreased flow caused by stenoses might play a role. Patient survival was influenced by the presence of comorbidities. However, even in the

population with comorbidity, patient survival after transplantation is very good. More than 10 years after transplantation, 50% of the patients with a RoCKeT score of 5 to 9 survived, which is far better than the 34% 10-year survival of Dutch RRT patients (hemodialysis, peritoneal dialysis, and transplantation) (30). Published patient survival data in dialysis populations was 30.5% after 8 years and 18.1% after 10 years (31, 32). Despite their good survival after kidney transplantation, patients with serious comorbidity were less likely to be recommended for kidney transplantation by their nephrologists (33, 34). Unless trained or involved in transplantation, nephrologists were less likely to accept patients with comorbidity for kidney transplantation. This suggests that gains could be made in this respect. Apart from survival gains, transplanting patients with comorbidities is more cost-effective than dialysis (35). The survival benefit of transplant patients with comorbidity still holds after a waiting time of up to 3 years (36).

Though survival is far better after transplantation compared with hemodialysis, it should be kept in mind that the population selected for transplantation is a comparatively healthy hemodialysis population. This is an inevitable limitation of our study that causes selection bias. On the other hand, part of this population already survived another few years on hemodialysis before they were transplanted, and survival is calculated from transplantation onward. Though survival of patients with a high comorbidity score is good, this does not imply that all patients with a comorbidity score of 9 should be transplanted. The RoCKeT score was developed to estimate the risks of different and added comorbidities. It is not possible to use the score for the decision to accept or reject a potential transplant patient. For each patient, the individual risks and potential success rate should be evaluated by an experienced physician taking into account all comorbidities and their severity. Our results show that meticulous selection of high-risk patients for kidney transplantation can lead to successful outcomes. In our center, relatively more living compared to deceased donor kidney transplantations are performed. We did not find an interaction between comorbidity and donor type, which means that there is no extra profit for patients with high comorbidity scores when they receive a living instead of deceased donor kidney transplantation compared with any other patient.

Another limitation of this single-center study is the lack of a control group. The ideal control group would be a population accepted for transplantation with comparable baseline characteristics who did not receive a kidney transplant. However, on ethical grounds, a randomized controlled trial for kidney transplantation or not is unacceptable. The population on the waiting list is not comparable to the population transplanted concerning baseline characteristics. The population of patients rejected for kidney transplantation is not appropriate, because in this population, selection bias also plays a major role with the opposite effect. Besides, data are incomplete because rejection may occur in any stage of the process. Some elderly patients or those with comorbidity have not even been referred to a transplant center. The hemodialysis population is a heterogeneous group of patients accepted or rejected for transplantation or unwilling to receive a transplant. Moreover, regional dialysis populations should be included as our transplant population origins from these centers. Unfortunately, these data are not available.

With the intention of generalizing our findings, the RoCKeT score should be validated in other kidney transplant populations. Until now, we did not find another transplant population with information available to test the RoCKeT score. For proper validation, it is important that there is unanimity on the definitions of all different comorbidities.

In conclusion, patient survival is influenced by comorbidity. Compared with the CCI, the RoCKeT score was shown to have a better fit in kidney transplant population. The most important finding of this study is that after transplantation, patient survival is very good for patients with a high burden of comorbidity, compared with published survival data of hemodialysis patients. This means that, despite severe comorbidity, these patients should be considered for kidney transplantation.

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8

Discussion

Over the years, kidney transplantation has become the treatment of preference for end stage renal disease patients. In this thesis, we describe our studies on clinical, demographic and socioeconomic factors that influence access to living or deceased donor kidney transplantation. Furthermore, we studied the relative influence of these factors on graft and patient survival.

Access to kidney transplantation

Because the medical healthcare system in The Netherlands assures equal care for all inhabitants, it might be expected that access to kidney transplantation is equally available for all end stage renal disease patients. However, it is remarkable that there is a preponderance of elderly and non-European patients in the hemodialysis population. One reason might be that this represents the residue of patients deemed unfit for transplantation. This doctor's assessment is subjective and is based on an estimation of both physical or non-physical condition.

Nevertheless, increasing numbers of elderly with or without comorbidity are being referred for transplantation. In chapter 2 we describe the influence of age on outflow once patients have been placed on the waiting list for transplantation. The results showed that the younger the patient the higher the chance that shortly after wait-listing or onset of dialysis the patient will receive a living donor kidney transplantation. In contrast, with increasing age more time is spent waiting for a deceased donor kidney transplantation. A possible explanation for the reduced access of older patients to living donor kidney transplantation may be their difficulties in finding a suitable living donor. Their smaller social network or the reduced health of their peer group compared with that of younger patients may be the cause of this difference. Because of their shorter life expectancy older patients may feel reluctant to accept a kidney from a healthy person, for instance their child. However, the burden of dialysis on top of higher age causes premature aging, loss of condition, and eventually people may become unfit for transplantation or even die without a transplantation. Our study shows that approximately half of the patients above 55 years will never be transplanted when they have to wait for a deceased donor organ. They simply do not survive waiting time for a deceased donor organ in a condition fit enough

to undergo transplantation. Especially this population could benefit from early living donor kidney transplantation.
When observing the transplant recipient population, it is striking that the composition of the population of recipients of living versus deceased donor kidney transplantations is very different. In chapter 3 we studied our transplant population in order to find out what clinical and socioeconomic factors determine the composition of these populations. Compared to recipients of a living donor kidney, recipients of a deceased donor kidney more often are non-European, they more often are diabetics, less often preemptively transplanted and more often on hemodialysis before transplantation and they also more often are highly sensitized. Regarding socioeconomic factors, recipients of a deceased donor kidney more often live in cheaper houses, in an area with a high percentage of non-Europeans, they mostly live in town, and have lower incomes than recipients of a living donor kidney. When comparing European versus non-European recipients of a kidney transplant, non-Europeans less often received a living donor transplantation. All differences mentioned above between recipients of a living versus deceased donor kidney also hold true for European versus non-European recipients. Unfavorable factors prevail in both the recipient population of a deceased donor kidney and in the non-European recipient population. To analyze whether these factors had an independent influence on the chance of receiving a living donor kidney transplantation we performed a multivariable binary logistic regression analysis. In accordance with our findings in chapter 2, we found that increasing age led to a decrease in access to living donor kidney transplantation. A known problem we confirmed is that patients with ABO blood type O have a smaller chance than patients with blood type A. We also found that non-Europeans only have a 50% chance of undergoing living donor kidney transplantation compared with Europeans. Regarding socioeconomic factors potential recipients living in an area with a high percentage of non-Europeans have a smaller chance. This also applies to living in an area with a low housing value. An interesting finding was that the regression analysis revealed that the chance of receiving a living donor kidney was higher for patients living in a highly urbanized area than in rural area, while the percentage recipients living in the most urbanized area was lower for the recipient population of a living donor kidney than for the recipient population of a deceased donor kidney. This means

that the factors that were corrected for accounted for a large part of the influence of urbanization on the access to living donor kidney transplantation. Moreover, the majority of recipients of both populations lived in town.
It is not easy to influence the factors that determine access to transplantation. Clinical factors cannot always be influenced and although socioeconomic factors could change over time, one cannot always control them. Non-Europeans that immigrated a longer time ago are better integrated and have a better social position than non-Europeans that arrived more recently. The next generation climbs on the social ladder and socioeconomic factors usually are more favorable for subsequent generations. Unfavorable factors are rather a matter of time than a factor that can be influenced individually. Newcomers are facing the same problems.
To summarize, access to transplantation was influenced by age. Besides, access to living donor kidney transplantation was influenced by clinical and socioeconomic factors. This was the reason to start home based education for patients without a living donor. Patients and their social network (family and friends) were educated in their own home on the various options of renal replacement therapy. Misconceptions about religious objections against organ donation were relieved. This method turned out to have a positive influence on participation of these patients and their network in living donor kidney transplantation programs. We expect that education will help other patients groups, such as elderly, as well. Recently home based education was added to our standard care for all potential recipients that present without a living donor. However, the problem of non-referral will not be solved by home based patient education. Professionals should learn to be more liberal in referring patients for transplantation as well.

Survival after kidney transplantation

Although the advantage of kidney transplantation over remaining on the waiting list was not explicitly tested in this thesis, the literature shows that survival on dialysis is worse compared to our survival data. However, (graft) survival after transplantation is not equal for all patients or patient groups. We studied the influence of ethnicity and socioeconomic factors on graft and patient survival in chapter 4. Socioeconomic factors that were studied were urbanization level,

housing value, percentage non-Europeans, and income. Although all these factors, apart from income, were found to influence access to living donor kidney transplantation, they neither had an influence on graft survival censored for death nor on patient survival. Apparently the effect of socioeconomic factors is overruled by the success of transplantation. This could be the result of the excellent medical healthcare system in The Netherlands. This assumption is supported by the fact that socioeconomic factors have been found to influence survival in countries with restrictive healthcare systems, i.e. the USA.
Nephrologists and pediatricians are reluctant to accept older living donors as they suppose that renal capacity of an older organ is less. They rather wait for a younger deceased donor kidney. In chapter 5 we studied the effect of donor age on graft and patient survival. We found that the influence of donor age on graft survival followed a J-shaped curve. The best results were found for patients transplanted with a kidney from donors aged 20-40 years. The risk of graft failure was higher for donor ages under 20 years and over 40 years. The shape of the curve is equal for transplants from deceased and living donors, hence independent of donor type. However, the individual risk for each donor is influenced by donor type so that the risk for a 60-year-old deceased donor kidney is much higher than that of a 60-year-old living donor kidney. When taking donor type (deceased versus living), into account, part of the unfavorable effect of high age can be compensated for by a living donor. For instance, the risk of graft failure of a 60-year-old living donor kidney is as low as the risk of a 20-year old deceased donor kidney. This means that it pays to accept a living donor kidney instead of waiting for a young deceased donor kidney. Concerning recipients' graft and patient survival, donor age is not a contraindication for donation in otherwise healthy elderly persons and living donor kidney should be preferred over any deceased donor kidney, independent of donor age.
The same reluctance that is seen for donor age, is also true for HLA matching. Completely mismatched donor-recipient combinations are less easily accepted. As expected, a completely matched kidney leads to the best transplant results (chapter 6). However, an ideally HLA-matched deceased or living donor will not become available for all patients. Participation in alternative donation programs, such as the kidney exchange program, or a long waiting time do not guarantee a better match. Besides, not all patients can afford waiting for a perfect kidney.

The difference in risk of graft failure is highest between 0 and 6 HLA mismatches. In between, there is a gradual increase in risk. The shape of the curves of the failure risk of deceased and living donor kidneys is the same and independent of donor type. However, the risk of the individual kidney depends on donor type so that the risk of graft failure of a totally HLA-mismatched deceased donor kidney is much higher than that of a completely mismatched living donor kidney. In agreement with donor age, part of the unfavorable effect of HLA mismatches can be compensated for by choosing for a living instead of a deceased donor. This puts into perspective the concept of a good match, especially when waiting for a deceased donor kidney, as we showed that the risk of survival of a highly mismatched living donor kidney is lower than that of any deceased donor kidney. This means that any living donor, independent of HLA matching should be preferred over a deceased donor kidney. However, the advantage of a highly mismatched living donor kidney over a 0-mismatched deceased donor kidney counts primarily for the current transplant. In the short term survival is better with a living donor kidney with a high number of HLA mismatches than with a better matched deceased donor kidney. Nevertheless, keeping HLA mismatches as low as possible is favorable for future transplants, as a high number of HLA mismatches may lead to sensitization. The unbalanced donor kidney exchange program may be a solution for compatible donor-recipient pairs with a high number of HLA mismatches. If no match is found once kidney function of the potential recipient becomes critical, it can be decided to perform the directed transplantation after all.

In the past decades, characteristics of potential recipients have changed. Older patients are considered for transplantation, as well as patients with extensive comorbidity. In the seventies, 66% of potential recipients were younger than 41 years. In the last years, only 17% of potential recipients were younger than 41 years, while 59% were between 41 and 65 years old and 24% were above 65 years. Also in the seventies 94% did not have cardiovascular disease whereas only 58% is without overt cardiovascular disease in more recent years. In chapter 7 we describe the influence of comorbidity on graft and patient survival. The conditions supposed to influence survival that we included are cardiovascular disease, cerebrovascular accident, peripheral vascular disease, diabetes mellitus, liver disease, lung disease, malignancy, other organ

transplantation, and human immunodeficiency virus positivity. In addition to including all conditions separately, the gradation of comorbidity can also be expressed by calculated comorbidity scores. Existing comorbidity scores have been developed in the general population in the seventies and have not been validated in the renal transplant population. Besides, they are outdated, using diseases that no longer are a threat for survival like AIDS and stomach ulcers. A new total comorbidity score, the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score was developed based on the presence of all aforementioned conditions. Our score turned out to be the best predictor of patient survival. In order to be generally used, the RoCKeT score should be validated in other kidney transplant populations. Although the risk of death increases with increasing comorbidity, patients experience advantages of transplantation. Survival of transplanted patients with a high comorbidity score is surprisingly good compared to patients that remain hemodialysis dependent. For patients with comorbidity, it is important to be transplanted before dialysis starts in order to prevent their condition to worsen, resulting in even more comorbidity. As patient survival of kidney transplant recipients with extensive comorbidity is better than the reported survival results of hemodialysis patients in the literature, comorbidity should not be a contraindication for transplantation.

Conclusion and comment of recommendation

All studies showed an advantage of living over deceased donor kidney transplantation. We clearly demonstrated the importance of the compensatory effect of donor type in relation to other factors, such as donor age and HLA mismatches. Moreover, by means of living donor kidney transplantation dialysis can be prevented. Pre-emptive transplantation prevents unnecessary deterioration of the physical condition of patients during hemodialysis. Still, access to kidney transplantation is not open for all end stage renal disease patients. There is too much focus on reasons why patients should not be referred for transplantation, while the focus should be on reasons why patients can indeed be transplanted. Our study showed that kidney transplantation is favorable for most patients, even for patients with extensive comorbidity and for elderly patients. Until now, comorbidity and age were reasons for non-referral,

as were inadequate mastering of the language, low intelligence, nonadherence, and poor or precarious social conditions. Also, potential living donors sometimes are rejected because of high age or a high number of HLA mismatches, while our studies showed that these factors should not be contraindications for donation. We believe that a large part of the inequality in access to transplantation can be reduced through increasing awareness about living kidney donation. This does not only apply to patients themselves, but also to their social network and to their nephrologists. Occasionally, patients are referred only several years after hemodialysis has started as they are supposed to have to wait for a kidney offer for a long time. We recommend that nephrologists refer patients to the pre-transplant outpatient clinic at the same time they refer them for hemodialysis preparation. Also patients without a potential living donor should be referred early, as participation in the home based education program may help them find a living donor after all. This prevents them from years of unnecessary waiting for a deceased donor kidney while on dialysis.

9

Summary

Nederlandse samenvatting

Summary

For patients that require renal replacement therapy, kidney transplantation is the best option in terms of outcomes and quality of life. However, not all patients have equal access to transplantation, as for various reasons some are not even referred for transplantation. Though not always obvious, a spectrum of reasons may be responsible for non-referral, e.g. insufficient condition to undergo surgery or inadequate mastering of the language to understand and communicate the transplantation process. Other patients are highly sensitized which complicates finding a match. Once transplanted, graft survival may be hampered by various factors causing a fall back on less favorable options for renal replacement therapy.

The aims of this thesis were to investigate what factors influence access to living or deceased donor kidney transplantation and what factors influence graft and patient survival once transplantation is carried out.

In **chapter 1** a general introduction to the topic of kidney disease and transplantation is given. In **chapter 2** the chances to receive either a living or deceased donor kidney transplant for patients approved for transplantation are described. The most important finding is the difference in outflow patterns between age groups. Whereas the majority of younger patients had received primarily living donor kidney transplants within 2 years, a large proportion of older patients had died or been delisted at that time. Half of patients above 55 years without a living donor, i.e. who are dependent on the waiting list, will not stay in adequate condition to survive waiting time for a deceased donor kidney transplantation.

Chapter 3 contains the description of a retrospective cohort study on the influence of clinical and socioeconomic factors on access to living versus deceased donor kidney transplantation. Apart from known clinical factors, demographic and socio-economic factors also turned out to be determining factors influencing the chance of receiving a living donor kidney transplantation. Non-European ethnicity, percentage non-Europeans living in the area, and low housing value were found to have a negative influence on the chance to receive a living donor kidney. The influence of urbanization level was also significant: living in the countryside decreased chances compared to living in town.

In **chapter 4** we investigated whether the factors found in chapter 3 had an influence on graft and patient survival once transplantation was performed. While various clinical factors were found to influence graft and patient survival, socioeconomic factors did not influence survival.
In **chapter 5** the influence of donor age on graft survival after living donor kidney transplantation compared with deceased donor kidney transplantation was studied. The influence of donor age on the risk of graft failure showed a J-shaped curve. The risk was lowest for donors between ages 20-40 but was higher at younger and older ages. The combined influence of donor age and donor type showed that the risk of graft failure of a recipient of a 60-year-old living donor kidney is comparable to the risk of a recipient of a 20-year-old deceased donor kidney.
In **chapter 6** the relative influence of HLA mismatches on the risk of graft failure was studied in a multivariable model in the presence of important clinical factors. The influence of HLA mismatches was studied using 4 different definitions. Both in living and in deceased donor kidney transplantation graft survival is negatively influenced by higher numbers of HLA mismatches. However, the relative risk of death-censored graft failure of a 2-2-2 HLA mismatched living donor kidney is comparable with that of a 0-0-0 HLA mismatched deceased donor kidney.
Transplantation has become an everyday process that nowadays attracts even people with extensive comorbidities. In **chapter 7** we describe the influence of comorbidities on patient and graft survival. We developed a new comorbidity score, the Rotterdam Comorbidity in Kidney Transplantation (RoCKeT) score, for testing this influence. Though a higher comorbidity score did influence patient survival, patient survival after transplantation was still remarkably good. This means that even patients with extensive comorbidity should be considered for transplantation.
In the general discussion (**chapter 8**) the results of all studies are integrated in order to give a main conclusion. The main conclusion is that survival after living donor kidney transplantation is superior to deceased donor kidney transplantation. Living donor kidney transplantation should be accessible for all patients, also for elderly patients with extensive comorbidity and for patients with unfavorable socioeconomic factors. They should be referred for

transplantation as early as possible to prevent dialysis, even when they present without a potential living donor. As home based education was added to our standard care for these patients, their chance to become transplanted increases.

Nederlandse samenvatting

Met betrekking tot overleving en kwaliteit van leven is niertransplantatie de beste behandeling voor patiënten met eindstadium nierziekte. Niet alle patiënten hebben echter gelijke toegang tot transplantatie. Om verschillende redenen, worden sommige patiënten niet verwezen voor transplantatie. Er is een scala aan mogelijke redenen waarom patiënten niet worden verwezen. Hoge leeftijd, veel comorbiditeit (overige ziekten), onvoldoende conditie om een operatie te ondergaan of onvoldoende beheersing van de taal om het transplantatieproces goed te begrijpen zijn veel genoemde argumenten. Andere patiënten worden wel verwezen maar zijn hoog gesensibiliseerd wat het vinden van een geschikte donor bemoeilijkt. Eenmaal getransplanteerd is de transplantaatoverleving afhankelijk van verschillende al dan niet beïnvloedbare factoren. Na transplantaat falen kan weer worden teruggevallen op minder gunstige opties voor nierfunctie vervangende therapie zoals hemodialyse of buikspoeling.
Het doel van dit proefschrift was om te onderzoeken welke factoren invloed hebben op de toegang tot levende of postmortale (overleden) donor niertransplantatie en welke factoren de transplantaat- en patiëntoverleving na niertransplantatie beïnvloeden.
In **hoofdstuk 1** wordt een algemene inleiding over nierziekte en transplantatie gegeven. De kansen voor het ontvangen van zowel een levende als postmortale donor niertransplantatie voor patiënten die zijn goedgekeurd voor transplantatie worden in **hoofdstuk 2** beschreven. De belangrijkste bevinding is het verschil in uitstroom patronen tussen de leeftijdsgroepen. Hoewel de meerderheid van de jongere patiënten al binnen 2 jaar een, voornamelijk levende, donor nier had ontvangen, was een groot aantal oudere patiënten op dat moment al overleden of van de wachtlijst afgehaald zonder transplantaat. Van de helft van de patiënten boven 55 jaar die zonder een levende donor zijn aangewezen op de postmortale donor wachtlijst, zal de conditie niet goed genoeg blijven om de wachttijd voor een postmortale donor niertransplantatie te overleven. Zij zullen dus nooit worden getransplanteerd.
Hoofdstuk 3 bevat de omschrijving van een retrospectieve cohortstudie naar de invloed van klinische en socio-economische factoren op de toegang tot levende versus postmortale donor niertransplantatie. Naast bekende klinische factoren, bleken ook demografische en socio-economische factoren de kans op het krijgen

van een levende donor niertransplantatie te beïnvloeden. Niet-Europese etniciteit, percentage niet-Europeanen die in de omgeving wonen en een lage woningwaarde bleken een negatieve invloed te hebben op de kans op het ontvangen van een levende donor niertransplantatie. De invloed van stedelijkheid was ook significant: wonen op het platteland geeft lagere kansen op een levende donor nier transplantatie in vergelijking met wonen in de stad. Socio-economische factoren spelen blijkbaar een rol in de mate waarin levende donoren uit het eigen netwerk zich aanbieden.

In **hoofdstuk 4** hebben we onderzocht of de factoren die we hebben gevonden in hoofdstuk 3 ook invloed hadden op de transplantaat- en patiëntoverleving na niertransplantatie. Terwijl verschillende klinische factoren de transplantaat- en patiëntoverleving van de patiënt bleken te beïnvloeden, hadden socio-economische factoren hier geen invloed op. Het Nederlandse gezondheidssysteem garandeert dus goede zorg onafhankelijk van het socio-economische milieu.

In **hoofdstuk 5** werd de invloed van donorleeftijd op de transplantaatoverleving bestudeerd waarbij de resultaten van levende en postmortale donor niertransplantatie werden vergeleken. De invloed van donorleeftijd op het risico op transplantaat falen volgde een J-vormige curve. Het risico was het laagst voor donoren tussen de 20 en 40 jaar, maar was hoger voor jongere en oudere donoren. Uit de gecombineerde invloed van donorleeftijd en donortype is gebleken dat het risico op transplantaat falen van een ontvanger van een 60-jarige levende donor nier vergelijkbaar is met het risico van een ontvanger van een 20-jarige postmortale donor nier. De resultaten van levende donor nier transplantatie zijn dus altijd beter dan die van een postmortale donor nier onafhankelijk van de leeftijd van de levende donor.

In **hoofdstuk 6** werd de relatieve invloed van HLA mismatches op het risico op transplantaat falen bestudeerd. In het multivariabele model werd gecorrigeerd voor de aanwezigheid van belangrijke klinische factoren. De invloed van HLA mismatches werd bestudeerd met 4 verschillende definities van HLA mismatches. Zowel na levende als postmortale donor niertransplantatie wordt de transplantaatoverleving negatief beïnvloed door een toenemend aantal HLA mismatches. Het relatieve risico op transplantaat falen gecensureerd voor overlijden van een levende donor nier met 2-2-2 HLA A-B-DR mismatches is

echter vergelijkbaar met dat van een postmortale donor nier met 0-0-0 HLA A-B-DR mismatches. De resultaten van levende donor nier transplantatie zijn dus altijd beter dan die van een postmortale donor nier onafhankelijk van het aantal HLA mismatches met de levende donor.
Dankzij het succes van niertransplantatie zijn de selectiecriteria voor potentiële ontvangers in de loop der jaren steeds verder versoepeld. Inmiddels worden ook potentiële ontvangers met uitgebreide comorbiditeit voor beoordeling voor niertransplantatie verwezen. In **hoofdstuk 7** wordt de invloed van comorbiditeit op transplantaat- en patiëntoverleving beschreven. Om de invloed van comorbiditeit op de transplantaat- en patiëntoverleving te kunnen beoordelen werd een nieuwe comorbiditeit score ontwikkeld: de Rotterdam Comorbidity in Kidney Transplantation score (RoCKeT score). Hoewel een hogere comorbiditeit score een negatieve invloed heeft op de patiëntoverleving, was de patiëntoverleving na transplantatie nog steeds opmerkelijk goed. Dit betekent dat zelfs patiënten met uitgebreide comorbiditeit groot voordeel kunnen hebben van transplantatie en dus in aanmerking zouden moeten komen voor beoordeling voor geschiktheid voor transplantatie. Van alle comorbiditeiten en comorbiditeit scores was perifeer vaatlijden de enige met een significante en negatieve invloed op de transplantaatoverleving.
In de algemene discussie (**hoofdstuk 8**) zijn de resultaten van alle studies geïntegreerd tot een hoofdconclusie. De belangrijkste conclusie is dat overleving na levende donor niertransplantatie superieur is aan dat na postmortale donor niertransplantatie. Levende donor niertransplantatie zou voor alle patiënten beter toegankelijk moeten worden gemaakt. Ook voor oudere patiënten, voor patiënten met uitgebreide comorbiditeit en voor patiënten met ongunstige socio-economische factoren zou de toegankelijkheid van levende donor nier transplantatie moeten worden vergroot. Om te voorkomen dat patiënten onnodig moeten gaan dialyseren, zouden zij in een vroeg stadium moeten worden verwezen voor beoordeling van de transplantatie mogelijkheid. Een goed moment voor verwijzing naar de pre-transplantatie polikliniek is bijvoorbeeld het moment waarop patiënten van de algemene nefrologie poli naar de pre-dialyse poli worden verwezen. Zelfs wanneer patiënten geen potentiële levende donor lijken te hebben is verwijzing zinvol. Voor deze patiënten werd thuisvoorlichting

toegevoegd aan onze standaard zorg, wat hun kansen om via het levende donor niertransplantatie programma getransplanteerd te worden sterk kan verhogen.

10

Appendices

PhD Portfolio

List of publications

Curriculum vitae

Dankwoord

PhD portfolio

Name:	Mirjam Laging
Erasmus MC Department:	Internal Medicine, Section Nephrology and Transplantation
PhD period:	2010 – 2016
Promotor:	Prof. dr. W. Weimar
Copromotor:	Dr. J.I. Roodnat

1. PhD training

General course

2011	Survival Analysis (NIHES)

Presentations

2010	Annual meeting Dutch Transplant Society (NTV) (Bootcongres), Rotterdam, The Netherlands	oral (2x)
2010	Ethical, Legal and Psychosocial Aspects of organ Transplantation (ELPAT) congress, Rotterdam, The Netherlands	oral
2010	International congress of The Transplantation Society (TTS), Vancouver, BC, Canada	oral
2011	Annual meeting NTV (Bootcongres), Amsterdam, The Netherlands	oral
2011	American Transplant Congress (ATC), Philadelphia, PA, USA	oral
2011	European Society of Organ Transplantation (ESOT) congress, Glasgow, UK	oral
2012	Annual meeting NTV (Bootcongres), Maastricht, The Netherlands	oral (3x)
2012	ATC, Boston, MA, USA	poster (2x)
2012	TTS congress, Berlin, Germany	poster (2x)

2013	ELPAT congress, Rotterdam, The Netherlands	oral
2014	Annual meeting NTV (Bootcongres), Leiden, The Netherlands	oral, poster
2014	World Transplant Congress (WTC), San Francisco, CA, USA	oral (2x), poster
2016	ELPAT congress, Rome, Italy	invited oral, poster

2. Teaching

Lecturing

2012-2016	Lectures for professionals
2014	Minor for students

3. Other activities

2009-present	Member of the NTV
2014	Young Investigator Travel Award for the WTC
2015-present	Reviewer for transplant journals

List of publications

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Curriculum vitae

Mirjam Hol - Laging was born on May 17, 1983 in Zwijndrecht. After finishing secondary education (VWO) at Develsteincollege in Zwijndrecht in 2002, she studied Psychology at the Erasmus University Rotterdam. She wrote her Bachelor's thesis on language comprehension. She completed her internship at the Centre for Man and Aviation (CML) in Soesterberg where she wrote her Master's thesis on cognitive load when selecting pilots. After obtaining her Master's Degree (MSc) in Biological and Cognitive Psychology in 2006, she worked as a tutor and trainer Psychology at the Erasmus University Rotterdam. In July 2009 she started working as a data manager at the department of Internal Medicine, section Nephrology and Transplantation, at the Erasmus Medical Center in Rotterdam. In 2010 Mirjam started her PhD concerning access to and outcomes of kidney transplantation under the supervision of prof. dr. Willem Weimar and dr. Joke Roodnat. She has a special interest in statistical analyses. She used data from the local database in which follow-up information of all patients transplanted in Rotterdam since 1971 and their donors is collected. She collected additional data that were added to the database to enable the present publications. This database research led to this thesis. Mirjam lives in Hendrik-Ido-Ambacht with her husband Jürgen Hol and their daughter Luna (2015).

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