Survival prediction of patients starting renal replacement therapy

Aline Hemke
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1

Introduction
INTRODUCTION

END STAGE RENAL DISEASE

Kidneys are important for several processes in the human body. The main functions of kidneys are: the filtering of blood and the removal of (toxic) waste products and excess water through urine, the regulation of blood acidity, and the production of hormones and enzymes that help to regulate production of blood cells, blood pressure, bone metabolism and growth hormone. In case of kidney damage, reflected by a reduction of the glomerular filtration rate (GFR) for three or more months, a patient suffers from chronic kidney disease (CKD)[1]. The severity of CKD is classified in five stages. Some patients unfortunately progress towards stage 5, which is severe illness with poor life expectancy. The GFR in this stage is less than 15 ml/min/1.73 m² as opposed to 90-140 ml/min/1.73 m² in healthy individuals; this is also called end stage renal disease (ESRD). ESRD is a major health problem, affecting more than 16000 patients in the Netherlands (www.nefrovisie.nl). This thesis is aimed at predicting long-term patient survival for end stage renal disease patients at the moment of the start of renal replacement therapy.

RENAL REPLACEMENT THERAPY

Patients with ESRD need renal replacement therapy (RRT) to survive. In the Netherlands every year approximately 2000 new ESRD patients start RRT (www.nefrovisie.nl). There are two types of RRT: dialysis and kidney transplantation, which both have become available since the 60’s of the last century. Both of them are life-sustaining therapies, giving the ESRD patient options to prolong his/her life substantially.

The number of prevalent patients with RRT in the Netherlands shows a steady increase in the last 15 years and currently exceeds 16000, while the number of dialysis patients has stabilized in the last six or seven years (figure 1). The Netherlands has a high transplantation rate compared to most other countries in Europe; approximately 60% of all patients with RRT (in 2014: 967.2 per million population) were patients with a transplanted kidney (www.era-edta.com).

DIALYSIS

Dialysis is the process of clearing the blood from toxins and removing excess water and salt. This can either be done outside the body, filtering the blood with help of an artificial kidney (hemodialysis), or within the body using the peritoneal membrane as a filter (peritoneal dialysis).

Hemodialysis (HD) treatment can be received in a hospital or a dedicated outpatient dialysis centre, but it can also be performed at home. Each dialysis session takes three to eight hours. Usually at least three or four sessions per week are necessary. HD patients can suffer from ‘dialysis hangover’ after each dialysis session: due to changes in blood composition, they feel very tired after a dialysis session. They also have dietary restrictions as well as a very limited liquid intake to prevent an accumulation of water and waste products in between dialysis sessions. Common complications of HD are hypotension and vascular access thrombosis.

Peritoneal dialysis (PD) can be performed at home or in a nursing home. In case of PD the dialysis solution has to be infused into the patient’s abdominal cavity. The two most common forms of PD in the Netherlands are Continuous Ambulatory PD (CAPD) and Continuous Cyclic PD (CCPD). In case of CAPD the patient manually has to empty and fill two to three liters of dialysate every four to six hours during the day. In case of CCPD the changes of dialysate are performed (at night) by machine. The possibility to perform PD depends on the medical condition of the patient, on the social situation, and on the patient’s willingness and capability to be responsible for the dialysis treatment him/herself. Common complications are ultrafiltration failure, and peritonitis (often combined with catheter-exit-site infections).
The advantages of PD over (center) HD are the continuous character of the treatment, that less dietary/fluid intake restrictions are prescribed, that dialysis can be done at home, and that it takes less time. Despite the fact that many studies comparing HD and PD showed conflicting results[2-8], for most patient groups in the first period of RRT PD is preferred over HD[9-11].

KIDNEY TRANSPLANTATION

Kidney transplantation is the placement of a renal graft, which can be donated by either a deceased or a living donor, in the body of the patient. Kidney transplantation is a well-accepted form of RRT since the discovery of effective immunosuppressive medication (azathioprine and prednisone) in the sixties. In the Netherlands the first renal transplant was performed 50 years ago (1966) at the University Hospital of Leiden.

The Dutch Transplant Foundation (NTS), which is responsible for the organization of organ and tissue donation, allocation and transplantation in the Netherlands, was founded in 1997. For deceased organ transplantation the NTS has outsourced donor acceptance and organ allocation to Eurotransplant.

As a consequence of the success of the kidney transplantation program, in the Netherlands the waiting list for deceased donor kidneys has grown and mean waiting time gradually increased from approximately 1 year in the eighties of the last century[12] to 4.5 years in 2006. Since then the mean waiting time has decreased to approximately 3.5 years in more recent years (www.transplantatiestichting.nl). The average waiting time varies with patient characteristics that influence allocation probability, like blood group, HLA classification, immunization, and medical urgency. Due to the improved outcome of transplantation as a result of more effective immunosuppressive drugs, as well as changes in the ESRD population (older, more diabetes and an increased number of co-morbid conditions), higher risk patients are being accepted for transplantation in recent years[13,14].

Not all patients are eligible for transplantation: some patients are not transplantable due to an inferior clinical condition, which is more often the case in elderly patients. In addition, about 25% of all waitlisted patients will unfortunately never be transplanted mainly because their clinical situation deteriorates while waiting and they are delisted or die on dialysis before a suitable kidney graft becomes available[13]. Due to the persistent donor shortage, criteria for the inclusion of organs of deceased donors have been extended, which led to the introduction of the term ‘marginal donors’ or ‘extended criteria’ donors (ECD), as opposed to the standard criteria donors (SCD)[15]. There are many ways to define a marginal donor, but usually these are older donors, with several complications. The use of marginal or ECD-donors in general has resulted in higher numbers of kidneys that do not function at all (primary non function, PNF), or have a delayed graft function (DGF) after transplantation, and a decrease in graft function and survival compared to SCD. For example, kidneys from ECD donors have been associated with more than 1.7 times the risk of graft failure compared to ‘ideal’ deceased donor kidneys[16]. In the last decades the pool has been further expanded with the use of donations after cardiac death (DCD), with also an increased PNF and DGF compared to donations after brain death (DBD)[17].

Besides deceased kidney transplantation there is a very active living donation program in the Netherlands, which has led to an enormous increase of the donor pool. Living donation was at first restricted to genetically related donors, but currently also unrelated, cross-over (exchange of organs between two living donor-recipient couples where direct donation is not possible[12]) and even anonymous living donors are accepted for transplantation (www.transplantatiestichting.nl). For the transplant recipient this is a good development; living donor grafts show superior graft survival[18] and because there is no waiting list ESRD patients can avoid health damage due to prolonged dialysis duration[19,20]. Since 2008 the number of kidney transplantations from living donors has exceeded the number of transplantations from deceased kidney donors (figure 2).
CHOICE OF RENAL REPLACEMENT THERAPY: DIALYSIS VERSUS TRANSPLANTATION

Therapy choice depends on patient condition (urgency and eligibility), therapy possibility (availability), and preference.

For most patients kidney transplantation is the preferred therapy, since patient survival and quality of life are better compared to dialysis[18,20-24]. A transplanted kidney replaces all functions of the native kidney and can restore kidney function within normal ranges, while with dialysis no more than 10% of normal clearance is reached. Dialysis patients generally rate their quality of life (QoL) lower than transplant patients[22,25], which is not surprising considering the health impact as a result of limited clearance and the necessity to adapt their daily life drastically.

Despite the favorable outcomes of kidney transplantation in comparison with dialysis treatment, transplanted patients are exposed to several risks and complications both on the short and long term after transplantation[18,26]. Living with a transplanted kidney implies lifelong immunosuppressive drug intake (in order to prevent rejection of the graft), which increases the chance on (viral) infections, malignancies and cardiovascular disease. Despite the use of immunosuppressive drugs, patients risk chronic graft rejection, which is also related to non-immunological factors (e.g. ischemic damage, nephrotoxicity due to the use of calcineurin inhibitors and donor age). Peri-operative risks and short and long term complications after transplantation also lead to an increased mortality risk for transplanted patients compared to the general population.

When a marginal donor kidney is offered, a physician has to consider the advantages and disadvantages, in terms of survival as well as quality of life, of transplanting this organ with inferior prognosis in his/her patient compared to continuing dialysis and waiting for a better kidney offer. Careful consideration of the advantages and disadvantages of a specific transplantation is necessary and renal transplant candidates should be informed about the risks and benefits of renal transplantation compared to dialysis.

CONSERVATIVE THERAPY AS AN ALTERNATIVE FOR RRT

Despite the fact that kidney failure will eventually lead to death if renal function is not being replaced, there is a trend towards careful consideration, in shared decision making, of withholding from dialysis and prolonging life at acceptable quality with conservative treatment[27-31]. Conservative treatment is comprised of medication as well as dietary restrictions and lifestyle changes that are directed to limiting the burden on kidneys, decreasing kidney disease symptoms and optimizing quality of life. With the appropriate treatment, patients who decline RRT can live a considerable time (months till even years). Conservative treatment therefore recently has been suggested as an important alternative to discuss when counseling (elderly) patients about renal replacement[27,29,30]. Actually, this was most likely the standard of care in the first decade(s) of RRT, when strict acceptance criteria were necessary to allocate scarce resources to those patients most likely to benefit. With the growth of dialysis facilities, the number of older and higher risk patients on RRT has grown exponentially, but it is questionable whether renal replacement treatment is always the right choice for these patients. For the frail elderly ESRD patient, for whom kidney transplantation is not feasible and dialysis is too burdensome conservative therapy might be the preferential treatment.

PREDICTION MODELING AND DECISION SUPPORT

Good ESRD patient guidance could profit from discussing survival prospects and treatment options already at the beginning of the RRT. Generally, kidney transplantation is the preferred treatment for most ESRD patients. However, at the start of renal replacement it is not clear yet which patients will eventually be transplanted. Therefore, a survival prediction model for all ESRD patients starting RRT, regardless of future treatment choices, is desirable. Such a RRT survival prediction model might help patients to understand the survival implications of ESRD, to (re)set survival expectations and it might be helpful in shared patient-physician discussion of future treatment perspectives. However, such a general model was not available yet. Existing prediction models were either focused on survival on the transplant waiting list[18,20,24,32], dialysis survival until transplantation[33], or survival after renal transplantation[34,35], and were therefore not suitable to predict overall survival at the start of RRT. The primary aim of this thesis is to develop and validate a model to predict long-term patient survival chances regardless of future treatment choices.

Although a general RRT survival prediction model is desirable at the start of RRT, it cannot be used to decide which treatment is preferable for a specific patient. Although physician and patient probably might agree that renal transplantation is the best treatment option, the decision whether or not to accept a donor kidney offer is rather complicated when it concerns a marginal donor kidney. Marginal donor kidneys are often associated with inferior graft survival, but waiting for a better kidney offer prolongs dialysis time, which is associated with inferior patient outcomes. It would...
Survival expectations. Furthermore, a survival prediction model could also be used in further RRT research, e.g. to stratify patients according to survival risks in clinical trials. In chapter 2-3 we investigate the possibilities to predict long-term survival for patients starting RRT. From RENINE we selected all patients from 1995-2005 and by split sample analysis we developed and internally validated a prediction model for renal patient survival based on a small set of readily available registry variables (chapter 2). In NECOSAD data, we further explored the possibilities to enhance prediction model performance by using clinical data and laboratory data in addition to (or instead of) the registry variables (chapter 3). In chapter 4 we describe the external validation study of the earlier mentioned registry model, for the same timeframe, in 9 European countries reporting to the ERA-EDTA.

A possible limitation of the presented prediction models is that changes in RRT practice might lead to deterioration of their performance in future cohorts. Chapter 5, which is directed to explain the decline of PD-usage in the Netherlands, shows which changes actually have occurred in RRT in the last 15 years.

The second aim of this thesis is to predict which patients might profit from certain marginal donor kidney transplants in order to support a difficult decision whether to accept a marginal donor kidney offer. In chapter 6 we therefore compare the survival of marginal (Extended Criteria Donor) and regular (Standard Criteria Donor) transplants in general and for specific patient groups.

In chapter 7 we summarize our main findings, discuss how they meet our aims, and identify future research opportunities.

REGISTRY DATA

A large share of the work in this thesis is based on data from the Dutch renal replacement registry (RENINE), which is hosted by Nefrovisie. For renal transplantations there is an exchange of information between RENINE (from Nefrovisie) and the Dutch organ transplant registry (NOTR) from the Dutch Transplant Foundation. RENINE data are also forwarded to the European Renal Association / European Dialysis and Transplant Association (ERA-EDTA). An important strength of RENINE is the fact that it includes all renal replacement therapies in the Netherlands from the start of this program (the first Dutch dialysis patient) in 1964. Patient data and treatment history (therapy and centre changes) are collected from the first treatment until death of the patient. As RENINE was established in 1986, information over the period before 1986 consists of the corrected and supplementary data from the ERA-EDTA and Eurotransplant. Until 2014, the Dutch renal replacement registry collected only a limited number of variables. The advantage is that RENINE ensures high data quantity and quality, with low numbers of missing data. The drawback is that extensive adjustment in multivariable analysis is not possible. We therefore also used data from NECOSAD. In NECOSAD (Netherlands Cooperative Study on Adequacy of Dialysis) an extensive array of additional clinical data has been collected, but only for a study cohort of patients starting dialysis.

AIMS AND OUTLINE OF THE THESIS

The general goal of this thesis is to contribute to the knowledge about ESRD patient survival prediction.

The first aim is to predict RRT patient survival from the start of RRT in order to support initial patient counseling. A general survival prediction is basic information, which might help patients to understand the implications of RRT, and to (re)set their survival expectations. Furthermore, a survival prediction model could also be used in further RRT research, e.g. to stratify patients according to survival risks in clinical trials. In chapter 2-3 we investigate the possibilities to predict long-term survival for patients starting RRT. From RENINE we selected all patients from 1995-2005 and by split sample analysis we developed and internally validated a prediction model for renal patient survival based on a small set of readily available registry variables (chapter 2). In NECOSAD data, we further explored the possibilities to enhance prediction model performance by using clinical data and laboratory data in addition to (or instead of) the registry variables (chapter 3). In chapter 4 we describe the external validation study of the earlier mentioned registry model, for the same timeframe, in 9 European countries reporting to the ERA-EDTA.

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In chapter 7 we summarize our main findings, discuss how they meet our aims, and identify future research opportunities.
INTRODUCTION

Evaluations, Classification and Stratification. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Comparing the incomparable: hemodialysis versus peritoneal dialysis in

REFERENCE LIST


15. UNOS. Expanded Criteria Donor. 2013. Ref Type: Online Source


INTRODUCTION

Survival prognosis after the start of a renal replacement therapy in the Netherlands: a retrospective cohort study


Abstract

Background
There is no single model available to predict the long term survival for patients starting renal replacement therapy (RRT). The available models either predict survival on dialysis until transplantation, survival on the transplant waiting list, or survival after transplantation. The aim of this study was to develop a model that includes dialysis survival and survival after an eventual transplantation.

Methods
From the Dutch renal replacement registry, patients of 16 years of age or older were included if they started RRT between 1995 and 2005, still underwent RRT at baseline (90 days after the start of RRT) and were not registered at a non-renal organ transplant waiting list (N=13868). A prediction model of 10-year patient survival after baseline was developed through multivariate Cox regression analysis, in one half of the research group. Age at start, sex, primary renal disease (PRD) and therapy at baseline were included as possible predictors. A sensitivity analysis has been performed to determine whether listing on the transplant waiting list should be added. The predictive performance of the model was internally validated. Calibration and discrimination were computed in the other half of the research group. Another sensitivity analysis was to assess whether the outcomes differed if the model was developed and tested in two geographical regions, which were less similar than the original development and validation group. No external validation has been performed.

Results
Survival probabilities were influenced by age, sex, PRD and therapy at baseline (p<0.001). The calibration and discrimination both showed very reasonable results for the prediction model (C-index = 0.720 and calibration slope for the prognostic index = 1.025, for the 10 year survival). Adding registration on the waiting list for renal transplantation as a predictor did not improve the discriminative power of the model and was therefore not included in the model.

Conclusions
With the presented prediction model, it is possible to give a reasonably accurate estimation on the survival chances of patients who start with RRT, using a limited set of easily available data.
temporary needed therapy to the intended treatment and to exclude patients who only have to undergo renal replacement therapy for a short period of time. The primary renal disease (PRD) is coded in the registry according to the ERA-EDTA coding system and for our analysis grouped into 6 categories. PRD ‘unknown’ is a specific category, as the nephrologist was not able to define the original kidney disease, so these are probably shrunken kidneys. If the PRD is missing, it could be any disease, and therefore it is different from PRD unknown. The included patients are Dutch residents of 16 years of age or older at the start of RRT, who started RRT in the period of 1995-2005, who still underwent a RRT at baseline, and who were not registered at the waiting list for another organ transplant than kidney (N=14783). Selected patient and treatment characteristics were sex, age at start of RRT, PRD and therapy at 90 days, and the outcome was patient survival.

**The primary kidney disease ‘unknown’ is included as a separate category in the prognosis, as these are probably shrunken kidneys, whereby it was no longer possible to determine the original disease. This is a specific recognisable category of patients, and therefore this is a separate diagnosis in the prognostic formula.**

Exclusion criteria were not registered PRD (N=518), recovered kidney function (N=322), lost to follow-up (N=48), unknown kidney transplant type (N=20), transplant failure before baseline (N=3) or home hemodialysis as baseline therapy (N=4). The final study group consisted of 13868 patients (Table 1). The events from 90 days after the start of RRT till death or end of the study (1/1/2010) were analyzed; the follow-up period was maximized at 10 years. For the development and validation of the prediction model, the study group was randomly divided in a development (N=6934) and a validation group (N=6934).

### Table 1 Demographics of patients, N=13868

<table>
<thead>
<tr>
<th>Patients starting a renal replacement therapy in 1995-2005, ≥16 years of age, with a registered primary renal disease and peritoneal dialysis, hemodialysis or a functioning kidney transplant at 90 days after the start</th>
<th>Development group %</th>
<th>Validation group %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>N=13868</td>
<td>N=6934</td>
<td>N=6934</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60.2</td>
<td>61.1</td>
<td>59.4</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-44 year</td>
<td>17.1</td>
<td>17.6</td>
<td>16.7</td>
</tr>
<tr>
<td>45-64 year</td>
<td>36.9</td>
<td>36.9</td>
<td>36.9</td>
</tr>
<tr>
<td>65-74 year</td>
<td>28.4</td>
<td>28.4</td>
<td>28.4</td>
</tr>
<tr>
<td>75 year or older</td>
<td>17.6</td>
<td>17.2</td>
<td>17.9</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>16.7</td>
<td>16.6</td>
<td>16.8</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>25.3</td>
<td>25.2</td>
<td>25.3</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12.3</td>
<td>12.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>9.0</td>
<td>8.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Other diseases*</td>
<td>21.4</td>
<td>21.8</td>
<td>21.0</td>
</tr>
<tr>
<td>Unknown**</td>
<td>15.2</td>
<td>14.9</td>
<td>15.5</td>
</tr>
<tr>
<td>Start year renal replacement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995 – 2000</td>
<td>50.3</td>
<td>50.9</td>
<td>49.6</td>
</tr>
<tr>
<td>2001 – 2005</td>
<td>49.7</td>
<td>49.1</td>
<td>50.4</td>
</tr>
<tr>
<td>Therapy at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplantation</td>
<td>3.0</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>65.7</td>
<td>65.5</td>
<td>65.9</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>31.3</td>
<td>31.7</td>
<td>31</td>
</tr>
</tbody>
</table>

*The group ‘other diseases’ consists of the subcategories interstitial nephritis (9.4%), other congenital and hereditary kidney diseases (1.5%), other multisystem diseases (5.4%) and other primary renal diseases (5.1%).

**The primary kidney disease ‘unknown’ is included as a separate category in the prognosis, as these are probably shrunken kidneys, whereby it was no longer possible to determine the original disease. This is a specific recognisable category of patients, and therefore this is a separate diagnosis in the prognostic formula.

### STATISTICAL ANALYSIS

The analysis was performed using SPSS 19 and STATA. Survival was analyzed with Kaplan Meier and log rank tests. Linearity of the influence of patient age on survival was assessed with Kaplan Meier stratified by different age groups. The proportionality assumption has been tested by visual inspection of the Schoenfeld residuals plot. For the survival prognosis from 90 days after the start of RRT, multivariate Cox regression analysis was performed in the development group. The formula for the survival probability at time t, S(t), is S(t)=exp(-H(t)). Here H(t) is the cumulative hazard that is calculated from the baseline hazard (H0) as H(t)=H0(t)*exp(prognostic index). The prognostic index (PI) is the sum of the parameter estimates from the Cox regression multiplied by the patient characteristics for a specific patient. To validate the prediction model, the predictive performance was assessed by computing the calibration and the discrimination of the prediction model for the 3, 5 and 10 year survival in the validation group. Calibration refers to the agreement between observed outcomes and predicted survival probabilities. This was measured by a) the calibration in the large, which indicates the extent that predictions are systematically too low or too high, b) a calibration plot for ten deciles according to the predicted survival, which is plotted against the observed survival, which ideally should be on the 45-degree line, and c) the calibration slope, which should be 1. The discrimination is the ability of the model to distinguish subjects with different outcomes. This was measured by the concordance (or C-) index. A C-index of 0.5 indicates the model has no discriminative power, while a model with a C-index of 1.0 has a perfect discriminative power. As a sensitivity analysis we assessed the consequences of our choice not to include information about registration on the waiting list as one of the predictors in the model and the choice for random (instead of geographical) development and validation group stratification.
RESULTS

The overall 10-year survival of patients on RRT at baseline was 34%. From the total cohort (N=13968) 8418 patients died within 10 years (60.7%). The number of censored cases was 5450 (39.3%). The mean follow-up time was 5.6 years, the median was 5 years, the minimum was 0.25 and the maximum was 10 years. A prediction model of 10-year patient survival after baseline (90 days after the start of RRT) was developed through multivariate Cox regression analysis (with age, sex, PRD, and therapy at baseline as possible predictors). Based on the visual inspection of the Schoenfeld residual plots the proportionality assumption has not been rejected. Age had a linear relationship with survival. The model was developed in the development group and validated in the validation group. In the development group the number of patients at risk at 1,3,5 and 10 year were: 6934, 5190, 3879 and 1223. In Table 1 the development and validation group were compared and found to be not different except for a small variation in sex distribution. In Table 2 the Cox regression model is presented with the baseline hazards for the referent patient group (H0) in Table 3.

Table 2 Cox regression model for patient mortality 90 days after start of renal replacement therapy

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Parameter estimate</th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary renal disease</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>-0.280</td>
<td>0.756</td>
<td>0.639-0.894</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>0.331</td>
<td>1.392</td>
<td>1.232-1.573</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.767</td>
<td>2.154</td>
<td>1.899-2.444</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.407</td>
<td>1.502</td>
<td>1.324-1.705</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.296</td>
<td>1.345</td>
<td>1.178-1.535</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Therapy at 90 days</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>-0.131</td>
<td>0.877</td>
<td>0.817-0.943</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>-1.634</td>
<td>0.195</td>
<td>0.117-0.325</td>
<td>&lt;0.001</td>
</tr>
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<td>Male sex</td>
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<td>1.070</td>
<td>1.005-1.139</td>
<td>0.04</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.054</td>
<td>1.055</td>
<td>1.052-1.058</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* The sum of (the product of) parameter estimates gives the value of the prognostic index of a patient

To illustrate how these results can be used to compute a survival probability, consider the following example: a 50 year old male diabetic patient, that was initially treated with peritoneal dialysis has a prognostic index (PI) of ((age*0.054=)50*0.054=)2.7)+((male=)0.067)+((diabetes=)0.767+((peritoneal dialysis=)-0.131)=3.40. Then, the 1-year survival for this patient is: exp(-(0.0030*exp(3.40)))=exp(-0.09)=91%. The 5-year survival for this patient is: exp(-(0.0171*exp(3.40)))=exp(-0.51)=60%. The 10-year survival for this patient is: exp(-(0.0333*exp(3.40)))=exp(-1.0)=37%. The model can be used in a simple Excel sheet to draw an individual survival prediction curve.

To assess the predictive performance of the model, the calibration and discrimination were computed in the validation group. The calibration in the large, or overall calibration, was good with a 50.4% predicted versus 49.5% observed 5-year survival and 32.9% predicted versus 34.4% observed 10-year survival.

Based on the prognostic index, ten deciles of patients were distinguished and the observed probability for 3, 5 and 10-year survival was plotted against the predicted probability in each risk stratum, constituting the calibration plot (Figure 1). The calibration slope, which ideally is 1.0, was assessed by a Cox regression analysis using the prognostic index as the only variable, and had an outcome of 0.948, 0.990 and 1.025 for the 3, 5 and 10-year survival respectively. The discriminative power of the prediction model was assessed with the concordance index and the resulting outcome of the C-index was 0.707 (95% CI: 0.698-0.717), 0.716 (95% CI: 0.708-0.724) and 0.720 (95% CI: 0.712-0.728) for the 3, 5 and 10-year survival respectively.

To show robustness of our model, we also performed sensitivity analyses.
As a first sensitivity analysis the model has been extended with the registration on the kidney waiting list at 90 days, combined with the therapy at 90 days and presented together in the model as the status at 90 days. This model had a similar validity to our current model with a discrimination of 0.724 and a calibration in the large equal, and a calibration by deciles almost equal, to that of the current model.

As the development group and validation group were very similar, we also assessed the influence of dividing the research cohort into two geographical regions, based on the ZIP-codes of the patients’ addresses. The two resulting comparable sized regions differed from each other in age-distribution, PRD-distribution, starting period, therapy at 90 days and transplantation rate. One of these regions also differed from the development group on all mentioned items; the other only differed in PRD-distribution. Two sensitivity analyses have been performed. The first was the development of a model in one region and validating the outcome in the other region. Parameter estimates of this alternative model did not differ substantially from our original (and final) model. This model had a similar validity to our final model with a discrimination of 0.711 and a calibration almost equal to that of the final model.
The final model was also validated in the two separate regions. The model performed well in both regions, with a similar discrimination (C=0.71) and calibration slopes of the prognostic index of 0.982 and 1.040 respectively (data not shown).

DISCUSSION

A prediction model was developed to estimate survival probabilities at 90 days based on a basic set of patient characteristics (age at start of RRT, sex and PRD) and the RRT therapy at 90 days. The main strength of the current prediction model is that it is based on the complete cohort of Dutch patients in 1995-2005. The predictive performance of the model is adequate, as demonstrated by validity tests on calibration and discrimination of this model, which could thus be used to inform patients about their survival prognosis at baseline.

The model uses treatment information at 90 days after the start of RRT, as the intention to treat. There is a clear difference in survival between patients who are on dialysis or who are being transplanted in an early stage. From previous studies we know that a better survival for kidney transplantation can be related to both advantages of the therapy as well as the better condition of the patient[2,12]. There is also a survival difference between patients starting on hemodialysis and peritoneal dialysis, which is also known from literature on this topic. Research has shown that patients starting on hemodialysis have more co-morbidities than patients starting on peritoneal dialysis[13-15]. In the prognostic formula the therapy modality therefore is included as one of the indicators of patient condition, as no other clinical information is available in the complete Dutch patient cohort. Like the ERA-EDTA, the Dutch renal registry only collects a few parameters on all patients. Further research should establish whether the treatment at 90 days, in combination with age and PRD, is a good alternative for clinical parameters indicating the patient’s condition.

Registration on the kidney transplant waiting list at 90 days was not included as one of the predictors. Other studies have shown the survival benefit of patients registered at the waiting list, compared to dialysis patients not listed for transplantation[12,13,16], suggesting that this predictor is related to patient condition. For that reason we performed a sensitivity analysis to test the possible additional value of this predictor. The additional predictive performance, however, was negligible. Possibly this could indicate that there is an overlapping risk profile between dialysis patients listed and not listed for transplantation as has been showed by an American study[17], where they found that many ESRD patients viable for transplantation were not listed while higher risk patients had been listed rapidly. The comparable performance of the prediction models with and without registration on 90 days suggests that the chance to be in a better general condition and/or to be transplanted is not only reflected in registration on the waiting list, but is also covered by the other predictors (age at start, PRD and therapy at 90 days). Another reason not to include registration on the kidney transplant waiting list as a predictor in our model is the fact that the time point of registration is very arbitrary in the Netherlands. There was a very large variation in registration time in Dutch population, and many patients were registered on the waiting list for kidney transplantation after the period of 90 days, which was our baseline for inclusion. It is not very likely that there is a difference in condition between patients that are registered at 90 days or, for instance, at 91 days after the start of RRT.

Some potential limitations of this study should also be noted.

First, the moderate discriminative power of the prediction model (C-index of 0.720) shows further improvement possibilities. In this study the age, PRD, and therapy at 90 day are considered to be substitutes for more accurate clinical indicators on the condition of patients. Adding clinical patient characteristics, like GFR, proteinuria, and (historical) co-morbidities, would probably improve the individual prediction. An English study showed that the addition of comorbid condition data and laboratory data could indeed lead to improvement of the predictive power of the prognostic model from 0.69 to 0.75[1]. On the other hand the additional effect may be limited, as age and PRD are highly correlated with comorbidity, as has also be shown by a European study[18] and a single centre study in the US[19]. It is therefore desirable to study for the Dutch situation whether clinical data correlate with data already used in this model and whether they can improve the discriminative power of the prediction model.

Another limitation of the study is that the model is only internally validated in the validation group, and the model has not been externally validated in an external cohort. It would be desirable to test the model in another patient group. This could be a patient cohort from another country or another period. The generalizability of the model to another country, however, is doubtful, as countries differ in dialysis and transplantation possibilities. This should be subject for further research. The fact that our model focuses on long term survival, makes external validation in a more recent cohort difficult. Regular evaluation of the model is needed as treatments improve in time and RRT-population, treatment possibilities and choices, both in dialysis and transplantation, change.

Finally, note that the prediction model presented in this study can only be used to inform patients about their survival chances from 90 days after their start of RRT.
The patients for whom the model can be used, should have survived the first 90 days of RRT and the therapy choice for their RRT therapy has been made earlier. This prediction model is not suitable to be used for the choice of the therapy modality at the start of the RRT or for the acceptance or decline of a specific transplant kidney offer. The therapy choice should be based on preferences of the patient and physician, as is also the case for the choice to accept or decline a specific transplant kidney offer. For the choices between therapies and the probability of death on therapies new designs are currently emerging, based on competing risks instead of the Kaplan Meier method[20]).

CONCLUSIONS

In conclusion, with the presented prediction model it is possible to give a reasonably accurate estimation on the survival chances of patients who start with RRT, using a limited set of easily available data. Future research should establish whether it is possible to improve the predictive performance of the prediction model using more clinical parameters.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS’ CONTRIBUTIONS

All authors have contributed to the results of this paper.

ACH, MH and MD have worked on the design, analysis, and interpretation of the data and WW, FD en AJH have worked on the design and interpretation of the data. All authors have worked on drafting/revising the article, providing intellectual content, and final approval of the version to be published.

ACKNOWLEDGEMENTS

We would like to thank all centres participating in the renal replacement registry in the Netherlands and the Dutch organ transplant registration.

REFERENCE LIST


Abstract

Background
Risk prediction models can be used to inform patients undergoing renal replacement therapy about their survival chances. Easily available predictors such as registry data are most convenient, but their predictive value may be limited. We aimed to improve a simple prediction model based on registry data by incrementally adding sets of clinical and laboratory variables.

Methods
Our dataset includes 1835 Dutch patients from NECOSAD. The potential survival predictors were categorized on availability. The first category includes easily available clinical data. The second set includes laboratory values like albumin. The most laborious category contains GFR and Kt/V. Missing values were substituted using multiple imputation. Within 1225 patients we recalibrated the registry model and subsequently added parameter sets using multivariate Cox regression analyses with backward selection. On the other 610 patients, calibration and discrimination (C-index, integrated discrimination improvement (IDI) index and net reclassification improvement (NRI) index) were assessed for all models.

Results
The recalibrated registry model showed adequate calibration and discrimination (C-index = 0.724). Adding easily available parameters resulted in a model with 10 predictors, with similar calibration and improved discrimination (C-index = 0.784). The IDI and NRI indices confirmed this, especially for short term survival. Adding laboratory values resulted in an alternative model with similar discrimination (C-index = 0.788), and only the NRI index showed minor improvement. Adding GFR and Kt/V as candidate predictors did not result in a different model.

Conclusion
A simple model based on registry data was enhanced by adding easily available clinical parameters.

INTRODUCTION
In the Netherlands, approximately 2000 new patients with end stage renal disease (ESRD) start chronic renal replacement therapy (RRT) every year. In order to inform these patients at the start of their treatment on their survival chances it is desirable to take into account information on survival irrespective of the renal replacement therapy. This is challenging as transplantation prolongs life expectancy considerably, but whether and when a given patient will be transplanted is unclear. Pre-existing models or comparative studies could not be used for this purpose. They are focused on one part of the treatment process by looking at dialysis survival until transplantation[1], patient survival from the time of wait listing[2-5], or survival after transplantation[6,7]. A risk prediction model for mortality in all incident RRT patients in which dialysis and transplant mortality are included, would be a helpful tool for clinicians to give a survival prognosis at the start of RRT. Furthermore such a model could be used for stratification for either the comparison of patient populations in different dialysis or transplant centers, or baseline risks in comparative studies[8], or for patient selection within studies[9] on dialysis, wait listing or transplantation.

For a prediction model to be useful in clinical practice it should have good predictive performance and preferably be based on easily available information. Routinely collected registry data, such as demography and primary kidney disease, are convenient candidates but their predictive value may be limited. Investing in collecting extra information may improve performance of the model. A British study showed that the predictive power of a model could be improved by adding clinical patient characteristics, like co-morbidities and laboratory data[1]. Also some studies on renal or cardi-vascular diseases assessed the additive prognostic power of new markers[10-12]. However, collecting additional data is not always worth the effort. This is relevant for both study design and reflections on quality indicators.

Previously, we explored the possibility to predict ten year RRT patient survival using the Dutch renal replacement registry (Renine), which collects a limited number of variables from all Dutch patients with chronic RRT[13]. The resulting model was based on four predictors: age at the start of RRT, primary renal disease (PRD), therapy at 90 days after starting RRT and patient sex. Although its discriminative power was fairly adequate with a C-index of 0.720, there is room for improvement.

Therefore, we aimed to analyze whether the performance of a model for ten year survival of patients starting RRT based on easily available registry data could be improved by incrementally adding sets of medical history, clinical and laboratory variables as potential predictors, using data from a Dutch study cohort in which these variables were prospectively collected.
SUBJECTS AND METHODS

For this study we used data from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD). NECOSAD is a multicenter, prospective cohort study in which 38 Dutch dialysis centers participated and which contains detailed clinical data. Informed consent was obtained from all patients before inclusion, and the medical ethics committees of all participating centres approved the NECOSAD study. In NECOSAD, incident adult dialysis patients were included at the start of dialysis, between 1997 and 2007 and the database includes 2051 patients. Data on comorbidity, age and smoking status were collected at the start of dialysis. The Charlson comorbidity score at the onset of dialysis was based on a score list of 15 different comorbid conditions, completed by the patients’ nephrologists. Body mass index (BMI), blood pressure, functional status (Karnofsky score) and laboratory values were collected at three months. The Karnofsky score is a clinician-assessed 10 level scale of functional status, with scores ranging from 10 (moribund) to 100 (normal functionality, without limitations). The glomerular filtration rate (GFR), at three months was used, which was calculated as the mean of 24-hour creatinine and urea clearance. The adequacy of dialysis treatment at three months was estimated using the dialysis Kt/Vurea per week, calculated as urea dialysis clearance corrected for distribution volume (V) according to Watson. The weekly value is used since both hemodialysis (HD) and peritoneal dialysis (PD) patients are included in the study. The other part of the total Kt/V is urine Kt/V which is on average 0.8 in incident NECOSAD patients[14].

As a point of departure, we considered the previously developed prediction model based on four variables from the Renine data[13] to which we refer as the ‘registry’ model. As we aimed to make a comparison to the ‘registry’ model, patients were excluded from the NECOSAD cohort if one of the four predictors were missing: 208 patients were excluded because of a non-registered PRD and 6 patients were excluded because of a missing therapy at 90 days. Additionally 2 patients were excluded because of erroneous data. Our study sample thus included 1835 patients (table 1). Like the registry model, we chose 90 days as the baseline of the study to ensure enough time to switch from a temporary needed therapy to the intended treatment and to exclude patients who only have to undergo RRT for a short period of time. Therefore, all possible predictors were determined at or before baseline. The events from 90 days after starting RRT till death were analyzed; 60.1% of the patients had an event. Patients were censored if they were lost to follow-up or recovered (N=21), or at the end of the study (1/1/2010) (N=352) (mean follow-up duration 7.1 years (st.dev. 2.4)), or at the maximum follow-up length of 10 years (N=360); transplantation was not censored.

In addition to the four registry variables, 19 candidate predictors collected for NECOSAD were used for model development (table 1). These candidate predictors were selected based on literature and clinical experience, and clustered in three variable groups based on data availability. The 3 additional variables sets were added incrementally, starting with the ‘easy’ parameters, which can all be obtained within the timeframe of 30 minutes (or one consult).

STATISTICAL ANALYSIS

Several methods for model updating and testing their predictive ability exist[10-12,16-18]. Potential new predictors should always be considered in relation to established predictors, instead of evaluating them in isolation[16]. We chose not to force predictors from a previous step into the next model, but allowed for substitution if the additional variables proved to be better predictors. The additional candidate predictors were clustered in three variable sets based on availability for the nephrologists (table 1).

As there were missing values on the additional candidate variables (table 1), we applied multiple imputation[19,20] before developing and validating the new models. Non-normally distributed variables were transformed to variables with a more normal distribution either logarithmically (cholesterol, phosphate, calcium and Kt/V) or by taking the square root (GFR and Karnofsky score) before imputing. Although the Karnofsky score was registered as a categorical variable, it is of an ordinal nature and was therefore imputed continuously[21]. After imputation, the imputed values were retransformed into the original units. We ran 10 imputations, resulting in 10 different datasets. According to Rubin’s rules the average results of the 10 datasets were used for both model development and model validation[22].

The dataset was randomly divided in a group for model development (N=1225) and a group for model validation (N=610). The development and validation group were compared with ANOVA and Chi-square test.

For the development of the prediction models multivariate Cox regression analyses were performed. The proportionality assumption was tested by visual inspection of the log–log plots[23]. As a first step the ‘registry’ model, with age, PRD, therapy at 90 days and sex, was re-estimated in the development group. After that, three additional variable sets were added to the registry variables incrementally. In the first model extension (further referred as the ‘easy’ model) a set of easily available medical history and clinical candidate predictors was added: history of smoking, angina pectoris, cerebrovascular accidents, diabetes mellitus, malignancies, gastro-intestinal disease,
myocardial infarction, peripheral vascular disease, and further BMI, Charlson comorbidity score, ethnicity and Karnofsky score (table 1). In the second model extension (further referred as ‘elaborate’ model), on top of the above mentioned variables we added blood pressure and some laboratory measurements: cholesterol, phosphate, calcium, and albumin (table 1). In the final model extension we added the most laborious variables to the candidate predictor list: GFR and Kt/V. Backward selection, with a conservative p-value of 0.15 to limit the risk of overfitting, was used to determine the variables that best predicted patient survival. We used all variables that were significant in at least 7 (out of 10) imputed datasets.

The predictive performance of each model was assessed for 10, 5 and 3 year survival[13] by determining their calibration and discrimination in the validation group[24,25]. Calibration refers to the agreement between observed and predicted outcomes. This was measured by a) the calibration in the large, indicating the extent that predictions are systematically too low or high, b) a calibration plot for ten deciles according to the predicted survival plotted against their observed survival, (ideally a 45-degree line), and c) the calibration slope, which is the regression coefficient with the prognostic index as the only predictor (ideally equals to 1). The discrimination is the ability of a model to distinguish between subjects with and without the outcome. This was measured by the concordance or C-index. A C-index of 0.5 indicates no discriminative power, while a C-index of 1.0 indicates perfect discriminative power. In recent literature other performance parameters have been suggested to compare models, as very large ‘independent’ associations of the new markers with the outcome are required to result in a meaningfully larger C-index when a model with standard risk factors already has reasonably good discrimination[18]. Two new ways of assessing performance improvement are net reclassification improvement (NRI) and integrated discrimination improvement (IDI)[26]. As the NRI is less useful when no established risk cut-offs exist, we tested the continuous NRI[27]. This is the sum of the percentage of persons with the event with a higher risk score in model B compared to model A and the percentage of persons without the event with a lower risk score in model B compared to model A. The NRI has a value between -2 and 2. The IDI is the difference between a) the predicted survival in the group with an event minus the predicted survival in the new model and b) the same subtraction calculated for the previous model[18].

To assess the robustness of our results additional sensitivity analyses have been performed: limiting the backward selection removal criterion to p=0.10 and relaxing this criterion to p=0.20 and a complete case analysis. Correlations have been tested with Pearson correlation coefficient for continuous variables and Spearman’s rho for ordinal variables. Analyses were performed using SPSS 21® and Microsoft Access®.

RESULTS

The NECOSAD patient cohort is described in table 1. Compared to the complete Dutch ESRD patient cohort (N=13868), which was the basis for development of the previously published ‘registry’ model, there were no differences on age or sex. However, there were differences in therapy at baseline and PRD. As expected, as pre-emptive transplantation was not included, there were less transplanted patients at baseline in the NECOSAD cohort (0.4% instead of 3% in the ESRD cohort), in favor of PD, while the HD% was similar. In NECOSAD there were less patients with diabetes and renal vascular disease (37.4% versus 42%) and there were more patients with glomerulonephritis and cystic kidney disease (24.2% versus 21.5%). Additionally the NECOSAD patients were more often transplanted with a deceased donor kidney (data not shown). The development and validation group of the NECOSAD cohort were not different with regard to all predictors except from the percentage suffering from angina pectoris (table 1).

Table 1: Baseline characteristics of the study population, candidate predictors presented per model

<table>
<thead>
<tr>
<th></th>
<th>Development group N=1225</th>
<th>Validation group N=610</th>
<th>Total cohort N=1835</th>
<th>Missing data total cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, (stdev))</td>
<td>59.4 (15.4)</td>
<td>60.4 (14.4)</td>
<td>59.7 (15.1)</td>
<td>0</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>60.2</td>
<td>63.3</td>
<td>61.3</td>
<td>0</td>
</tr>
<tr>
<td>Primary renal disease (%)</td>
<td>Diabeties</td>
<td>16.3</td>
<td>15.6</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td>Renal vascular disease</td>
<td>20.0</td>
<td>23.3</td>
<td>21.1</td>
</tr>
<tr>
<td></td>
<td>Glomerulonephritis</td>
<td>14.0</td>
<td>12.8</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>Cystic kidney disease</td>
<td>10.5</td>
<td>10.8</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>Other diseases</td>
<td>20.1</td>
<td>21.3</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>19.0</td>
<td>16.2</td>
<td>18.1</td>
</tr>
<tr>
<td>Therapy at baseline (%)</td>
<td>Hemodialysis</td>
<td>64.2</td>
<td>65.1</td>
<td>64.5</td>
</tr>
<tr>
<td></td>
<td>Peritoneal dialysis</td>
<td>35.8</td>
<td>34.9</td>
<td>35.5</td>
</tr>
<tr>
<td>Extra variables Model 'Easy'</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>Never smoked</td>
<td>33.4</td>
<td>30.5</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>Smoking in past, longer than 3 months before RRT start</td>
<td>39.2</td>
<td>42.1</td>
<td>40.2</td>
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<tr>
<td></td>
<td>Smoking in past, shorter than 3 months before RRT start</td>
<td>4.8</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>22.6</td>
<td>22.4</td>
<td>22.5</td>
</tr>
</tbody>
</table>
### Development group Validation group Total cohort Missing data total

#### BMI - kg/m² (%)
- <20: 10.4, 7.7, 9.5, 138
- 20-30: 80.3, 81.9, 80.8
- 30-35: 7.2, 7.2, 7.2
- >35: 2.1, 3.2, 2.5

#### Angina pectoris (pain in rest or light physical activity) (%)
- No malignancy: 91.5, 88.0, 90.3, 20
- Malignancy in past: 6.0, 8.6, 6.9
- Malignancy: 2.5, 3.5, 2.8

#### Cerebrovascular accidents (%)
- 8.7, 8.4, 8.6, 18

#### Diabetes mellitus (%)
- 22.5, 22.9, 22.6, 19

#### Malignancies (%)
- No malignancy: 91.5, 88.0, 90.3, 20
- Malignancy: 6.0, 8.6, 6.9
- Malignancy in past: 2.5, 3.5, 2.8

#### Stomach-intestine events (%)
- 6.4, 4.6, 5.8, 18

#### Myocardial infarction (%)
- 13.3, 12.7, 13.1, 18

#### Peripheral vascular disease (%)
- 15.7, 14.1, 15.2, 17

#### Charlson comorbidity score (%)
- 0-1: 20.2, 17.7, 19.3, 0
- 2: 13.1, 12.3, 12.8
- 3: 13.8, 13.6, 13.7
- 4: 16.0, 16.2, 16.0
- 5: 16.9, 15.9, 14.4
- 6: 11.6, 12.0, 11.7
- 7: 6.5, 6.6, 6.5
- 8-11: 5.2, 5.7, 5.4

#### Karnofsky score (%)
- Normal till some complaints/illnesses (Karnofsky scores 100, 90, 80): 66.6, 64.2, 65.8, 125
- Capable to take care of oneself but not to do work/normal activity till the need of much help and frequent medical care (Karnofsky scores 70, 60, 50): 31.2, 32.7, 31.7
- Not capable to do much by him/herself, needs special help and care (Karnofsky scores 40, 30, 20, 10, 0): 2.2, 3.0, 2.5

### Extra variables Model 'Elaborate'

#### Mean Arterial Pressure (MAP)** - mmHg (mean, (stdev))
- Development group: 102.6 (11.9)
- Validation group: 102.9 (13.2)
- Total cohort: 102.7 (12.3)

#### Cholesterol - mmol/l (mean, (stdev))
- Development group: 5.01 (1.31)
- Validation group: 5.06 (1.34)
- Total cohort: 5.03 (1.32)

#### Phosphate - mmol/l (mean, (stdev))
- Development group: 1.82 (0.56)
- Validation group: 1.81 (0.52)
- Total cohort: 1.82 (0.55)

#### Calcium - mmol/l (mean, (stdev))
- Development group: 2.36 (0.25)
- Validation group: 2.37 (0.26)
- Total cohort: 2.36 (0.26)

#### Albumin - g/l (mean, (stdev))
- Development group: 36.1 (5.1)
- Validation group: 36.2 (5.4)
- Total cohort: 36.1 (5.2)

### Extra variables Model ‘Extended’

#### GFR - ml/min (mean, (stdev))
- Development group: 4.08 (3.10)
- Validation group: 4.15 (3.72)
- Total cohort: 4.10 (3.31)

#### Kt/V dialysis per week - Watson (mean, (stdev))
- Development group: 2.32 (0.95)
- Validation group: 2.35 (0.94)
- Total cohort: 2.33 (0.94)

---

* Different in development and validation group (p<0.05)
** MAP is calculated as: diastolic blood pressure + 1/3 (systolic - diastolic blood pressure)

The results of the recalibrated ‘registry’ model were in line with the original results (table 2). Although the regression coefficients for therapy and sex had no p-value below 0.05, they were similar to those of the original published registry model.

The ‘easy’ model included 10 predictors: age, PRD, history of smoking, angina pectoris, malignancies, myocardial infarction, peripheral vascular disease, and BMI, Charlson comorbidity score, and Karnofsky score (table 3). The ‘elaborate’ model included 14 predictors: age, therapy at 90 days, PRD, history of smoking, angina pectoris, malignancies, myocardial infarction, and peripheral vascular disease, and BMI, Charlson comorbidity score, Karnofsky score, cholesterol, phosphate, and albumin (table 3). In the final extension of the model GFR and Kt/V were excluded from the model by backward selection, making the ‘extensive’ model the same as the ‘elaborate’ model and thus redundant. For the ‘easy’ and ‘elaborate’ model variables, the proportionality assumption was not rejected, based on visual inspection of the log-log plots.
The regression coefficients; the calculation is shown in the online supplementary appendix.

The prognostic index of a patient, which is used for the survival prediction estimates, can be calculated from the regression coefficients; the calculation is shown in the online supplementary appendix.

Table 2: Re-calibrated ‘registry’ model estimated in Necosad cohort compared to published ‘registry’ model

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Published ‘registry’ model</th>
<th>Recalibrated ‘registry’ model - Necosad</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient*</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.054</td>
<td>1.056</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>-0.280</td>
<td>0.756</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>0.331</td>
<td>1.392</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.767</td>
<td>2.154</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.407</td>
<td>1.502</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.296</td>
<td>1.345</td>
</tr>
<tr>
<td>Therapy at 90 days</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>-0.131</td>
<td>0.677</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>-1.634</td>
<td>0.195</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.067</td>
<td>1.070</td>
</tr>
<tr>
<td>Baseline hazards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
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<td>3 year</td>
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<td>5 year</td>
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<td></td>
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<tr>
<td>7 year</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>10 year</td>
<td>0.033</td>
<td></td>
</tr>
</tbody>
</table>

* the prognostic index of a patient, which is used for the survival prediction estimates, can be calculated from the regression coefficients; the calculation is shown in the online supplementary appendix.

The evaluation of the three different models (‘registry’, ‘easy’, and ‘elaborate’) on calibration in the large, calibration slopes and discrimination (C-index), IDI and NRI in the validation group are shown in figure 1 (a-e); the tables with all results are presented in the online supplementary appendix (see www.karger.com/doi/10.1159/000439181).

In all models the calibration plots were close to the 45 degree line (data not shown).

Although the calibration in the large was almost the same in all models, the calibration slopes (ideally 1) and discrimination results of the ‘easy’ and ‘elaborate’ model showed some improvement compared to the ‘registry’ model, with the largest improvement for five and three year survival prediction. The discrimination was tested with the C-index. A C-index of 0.7 is considered reasonable and 0.8 is considered good. Using a C-index of 0.5 as zero, the difference in C-index between the recalibrated ‘registry’ model (0.724) and the ‘easy’ model (0.784) for the ten year survival was plus 27%.

Next, some sensitivity analyses have been performed to check stability of the results. Limiting our backward selection inclusion criterion till \( p=0.10 \) led to the same predictor selection for the ‘easy’ model; only 1 of the 14 predictors (angina pectoris) was eliminated from the selection of the ‘elaborate’ model. Relaxing our criterion till \( p=0.20 \) led to the same predictor selection for both the ‘easy’ and ‘elaborate’ model. Complete case analysis resulted in somewhat smaller models, but predominantly the same final predictor lists. Finally, as GFR and Kt/V were unexpectedly excluded from the final prediction model, we performed an additional analysis to assess their relationship with other model predictors. GFR was a significant predictor both univariately (HR=0.953, \( p=0.001 \)) and in addition to the variables from the ‘registry’ model, but lost its independent predictive value in addition to the ‘easy’ model variables. GFR correlates with Karnofsky score (Pearson Correlation= 0.20; \( p<0.001 \)) and BMI (Spearman Rho= 0.15; \( p<0.001 \)). Kt/V was univariately related to survival (HR=1.304, \( p=0.001 \)).

Next, to illustrate that the models presented in the paper (table 2 and 3) can be used to compute individual patient survival probabilities, we considered two patients. The first is a 59 year old male patient starting hemodialysis with renal vascular disease, BMI=25, smoking longer than 3 months before RRT, no history of angina pectoris, peripheral vascular accident, malignancy and myocardial infarction, Charlson comorbidity score 2, Karnofsky score 80, cholesterol level 5 mmol/l, phosphate 1.8 mmol/l and albumin 36 g/l.
The ‘registry’ model predicts 49% and 26% chances for five and ten year survival respectively. According to the ‘easy’ model the patient’s survival chances are 48% and 22%, so reclassification to a higher risk. Compared to the ‘easy’ model the ‘elaborate’ model predicts slightly higher survival chances (51% and 24% respectively), so here a reclassification to a lower risk. The same patient with glomerulonephritis as PRD has five and ten year survival predictions of 73% and 54% according to the ‘registry’ model. The ‘easy’ and ‘elaborate’ model both reclassify the patient to a lower risk and predict 81%–83% five year and 65%–67% ten year survival chance. In the online supplementary appendix (see www.karger.com/doi/10.1159/000439181) the computational details of the first example are shown as well as the IDI and NRI calculations.

**Table 3: Model ‘Easy’ and Model ‘Elaborate’**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Model ‘easy’</th>
<th>Model ‘elaborate’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.029 1.029</td>
<td>0.031 1.032 &lt;0.001</td>
</tr>
<tr>
<td>Therapy at 90 days PD instead of HD</td>
<td>0.182 1.200</td>
<td>0.073</td>
</tr>
<tr>
<td>GLR</td>
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<td>Reference</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>0.057 1.058</td>
<td>0.121 1.129 0.538</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>0.445 1.560</td>
<td>0.485 1.624 0.002</td>
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<tr>
<td>Diabetes</td>
<td>0.302 1.353</td>
<td>0.321 1.379 0.086</td>
</tr>
<tr>
<td>Other diseases</td>
<td>0.366 1.441</td>
<td>0.384 1.468 0.021</td>
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<tr>
<td>Unknown</td>
<td>0.357 1.429</td>
<td>0.386 1.471 0.016</td>
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<tr>
<td>Smoking</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Never smoked</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Smoking in past, &gt;3 months before starting RRT</td>
<td>0.013 1.013</td>
<td>0.029 1.029 0.757</td>
</tr>
<tr>
<td>Smoking in past, &lt;3 months before starting RRT</td>
<td>0.205 1.227</td>
<td>0.210 1.234 0.267</td>
</tr>
<tr>
<td>Smoking</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;30</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;35</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*The prognostic index of a patient, which is used for the survival prediction estimates, can be calculated from the regression coefficients; the calculation is shown in the online supplementary appendix.*
IMPROVED MORTALITY PREDICTION IN DIALYSIS PATIENTS USING SPECIFIC CLINICAL AND LABORATORY DATA

Figure 1a: Calibration in the large

Figure 1b: Calibration slope

Figure 1c: Discrimination, C-index

Figure 1d: IDI= difference in predicted survival in patients with and without the event
DISCUSSION

While the recalibrated registry prediction model performed well in the NECOSAD cohort, the ‘easy’ model including readily available medical history and clinical predictors showed superior performance. Adding laboratory measurements did however lead to models with only slightly improved predictive power.

The new models showed improved discrimination, whereas the calibration showed similar performance in all presented prediction models. This indicates that for the purpose of comparing patient groups in different countries, or different periods of time, the ‘registry’ model is adequate and preferable because it only uses very common variables. For the purpose of informing patients, the reclassifications and improved discrimination indicate that the ‘easy’ or ‘elaborate’ model are better capable to estimate individual survival chances.

When comparing the ‘easy’ model with the ‘registry’ model the improvements that were found (calibration slopes, discrimination, IDI, and NRI) were most striking for the five and three year survival intervals. An explanation for this could be that where age is the most determining predictor for the long term survival, the effect of other indicators for patient condition is stronger in the shorter term survival predictions.

The ‘elaborate’ model includes three additional laboratory values, which are less easy to obtain than the variables from the ‘easy’ model. The resulting model with 14 instead of 10 variables, is only performing slightly better than the ‘easy’ model. The fact that the laboratory values in the model did not have more impact on the model performance is probably due to the fact that the variation of the laboratory values in this dialysis population is small. The sensitivity analyses that we performed showed that GFR and Kt/V are not included as predictors in a last model, due to the correlation with other model variables. The relationship of GFR and Karnofsky score has also been found in other studies[28,29].

The improvement in discriminative power of our model from a C-index of 0.724 to 0.788 for the ‘elaborate’ model is comparable with the improvement reported by Wagner et al[1]. They elaborated a model with basic patient characteristics (with a C-index of 0.69) with comorbid condition data and laboratory measurements (C-index: 0.75). However, in this study most improvements were made in the last step where laboratory values were added, while in our study most improvements were seen in the second step (‘easy’ model), and the additional laboratory values only led to a marginal further improvement. Probably this is due to the fact that the variables in the ‘easy’ model were very diverse and also includes the functional status (Karnofsky score).

The improvement in discriminating power of our model from a C-index of 0.724 to 0.788 for the ‘elaborate’ model is comparable with the improvement reported by Wagner et al[1]. They elaborated a model with basic patient characteristics (with a C-index of 0.69) with comorbid condition data and laboratory measurements (C-index: 0.75). However, in this study most improvements were made in the last step where laboratory values were added, while in our study most improvements were seen in the second step (‘easy’ model), and the additional laboratory values only led to a marginal further improvement. Probably this is due to the fact that the variables in the ‘easy’ model were very diverse and also includes the functional status (Karnofsky score[28,29]).
the extra effort that is needed to obtain the extra markers. The advantage of the ‘easy’ model is that it uses easily obtainable predictors. For comparison of large populations the ‘registry’ model can suffice, but for smaller populations or individual patient information we would advise the use of the ‘easy’ model. As all prediction models are presented in this paper, physicians could choose either one of the prediction models, based on preference, outcome and the availability of the necessary data.

ACKNOWLEDGEMENTS

We would like to thank all centers participating in the Dutch renal replacement registry and the NECOSAD study.

Our study also has a number of limitations. First, the NECOSAD patients cannot be considered to be a random sample of patients with end stage renal disease who were starting RRT. There is a possible center effect, because not all dialysis facilities in the Netherlands cooperated in this study. Also patient selection bias might influence the results, as patients had a choice whether they wanted to be included in this study. Finally there are some differences in patient characteristics. These differences might explain the fact that in the NECOSAD-cohort therapy at 90 days did not remain significant in all models. We do expect that the therapy at 90 days is still of importance in the total Dutch patient cohort, as patients transplanted preemptively or in an early stage have better survival results. However, despite the differences in patient characteristics, the registry model had an adequate performance in the NECOSAD group. A second limitation of the study is the fact that the models are only internally validated in the validation group of the NECOSAD-cohort. External validation should also be performed in a different patient cohort, for instance from another country or another period of time. Finally, note that the prediction models presented in this study can only be used to inform patients about their prognosis from 90 days after their start of RRT, given their medical history and/or measurement data. The predictors are the input for the survival prediction and the models do not provide evidence that intervening on those predictors prior to the start of RRT will change the predicted outcome, so the models cannot be used for treatment decisions. Prediction models only focus on the combination of variables that best predicts the outcome of interest without proving a causal relationship. Etiological studies of the effect of risk factors on outcome should be used for that goal. Further studies in this area would be desirable to be able to identify patients which would profit most from certain therapies, like kidney transplantation.

In conclusion, the recalibrated simple prediction model, based on only four predictors collected in the Dutch renal replacement registry, was able to give a reasonably accurate estimation of the ten year survival chances of patients starting RRT. Our study showed that it was possible to improve the model with the addition of some easily available medical history and clinical predictors. Additional improvement possibilities, with elaboration of the model with a set of laboratory measurements, were limited. Whether the established model improvements are satisfactory, depends on

score). The improvements of a model for the prediction of the progression of chronic kidney disease to kidney failure (C-index varying from 0.89 to 0.92)[10-12] and the prediction of cardiovascular events in rheumatoid arthritis patients (Framingham risk score C-index: 0.73, elaborated with separate additional biomarkers: C-index varying from 0.73 to 0.81)[11] were roughly comparable to our results.
REFERENCE LIST


Performance of an easy to use prediction model for renal patient survival: an external validation study using data from the ERA-EDTA Registry

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Submitted for publication
Abstract

Background
An easy to use prediction model for long term renal patient survival, based on only four predictors (age, primary renal disease, sex, and therapy at 90 days after the start of renal replacement therapy (RRT)), has been developed in the Netherlands. To assess the usability of this model for use in Europe, we externally validated the model in a wide spectrum of European countries.

Methods
Data from the ERA-EDTA (European Renal Association - European Dialysis and Transplant Association) Registry were used. Nine countries that reported individual patient data to the registry on patients starting RRT in the period of 1995-2005 were included. Patients under 16 years of age and/or with missing predictor variable data were excluded. The external validation of the prediction model was evaluated for the 10-year (primary endpoint of interest) and 5- and 3-year survival predictions by assessing the calibration and discrimination outcomes.

Results
We used a dataset of 109,022 patients from 9 countries. The calibration in the large and calibration plots for 10 deciles of predicted survival probabilities showed differences of on average 2.2%, 4.1% and 4.1% in observed versus predicted 10-, 5-, and 3-year survival, with some small variation on country-level. The C-index, indicating the discriminatory power of the model, was 0.71 in the complete ERA-EDTA Registry cohort and varied according to country level between 0.70 and 0.75.

Conclusions
A prediction model for long-term renal patient survival developed in a single country, based on only four easily available variables, has a comparably adequate performance in a wide range of other European countries.

INTRODUCTION

End stage renal disease (ESRD) is a major health problem with high mortality rates, affecting approximately 1000 patients per million population (pmp) in European countries[1]. The overall yearly unadjusted incidence of new ESRD patients starting renal replacement therapy (RRT) is over 100 patients pmp.

For nephrologists it could be helpful to be able to predict long term survival chances for all patients starting with RRT to inform the patient of his/her survival chances. As it is unclear at therapy initiation whether a patient will stay on dialysis or subsequently receive a kidney transplant, it is desirable to use a model for overall survival prediction after the start of RRT, irrespective of whether patients will change treatment modality in a later stage or not. Most existing models are focused on dialysis survival until transplantation[2], survival on the kidney transplant waiting list[3,4] or patient survival after renal transplantation[5,6], or are designed for a specific patient group[7], and therefore cannot be used for overall RRT survival prediction. To this end, in 2013 a straightforward model to predict renal patient survival from the start of a RRT was developed, based on a cohort of incident RRT patients from 1995-2005 in the Netherlands[8]. It predicts 10-year survival based on four commonly available predictors: age at the start of RRT, sex, primary renal disease (PRD) and mode of renal replacement therapy at 90 days (hemodialysis (HD), peritoneal dialysis (PD), or transplantation). Unlike the existing models, this model predicts overall survival from the start of RRT, irrespective of whether patients will change treatment modality in a later stage or not. For individual patient survival predictions it is preferable to take additional clinical parameters into account, as concluded in a later study[9]. However, we think the original straightforward registry model is very valuable for group comparisons and risk stratification in studies.

In order to understand whether this prediction model developed in a patient group from one country is also suitable for use in other countries, it is essential to explore its generalizability in an external validation study[10]. The predictive performance of the model in the Netherlands appeared to be adequate, as demonstrated by internal validation outcomes (good calibration results as well as discrimination (C-index: 0.720)[8]). However, internal validation merely relates to the ‘reproducibility’ of results, while the usability of the prediction model in another country is a question of ‘transportability’ of the model[11]. As countries differ in dialysis and transplantation possibilities (e.g. access to (home) dialysis, and possibility for renal transplantation (with a living or deceased donor)) as well as in patient population characteristics, this could influence survival prediction. In this external validation study, we therefore assessed the performance of the model as a European renal patient survival prediction model, using data from the European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Registry.
SUBJECTS AND METHODS

We used ERA-EDTA Registry data from nine European countries with national or regional registries providing individual level patient data on patients who started RRT between 1995 and 2005 and who still were on RRT on day 90. We included last available follow-up information in the ERA-EDTA Registry until 1/1/2014. We excluded the country where the model was developed (the Netherlands) or with less than 1000 incident patients in our period of interest. The remaining countries that were included in the validation study are: Austria, Belgium (data from the Dutch-speaking and French-speaking Belgian Registry), Denmark, Spain (data from the regional registries of Andalusia, Aragon, Asturias, Basque country, Catalonia, Cantabria, Castile and León, Castile-La Mancha, Extremadura, Valencia), Finland, France, Greece, Norway, and Sweden. Most countries had 100% completeness in the whole study period, with the exception of Spain (coverage increasing from 53% in 1995 to 68% in 2005), and France (coverage increasing from 17% in 2002 to 55% in 2005). We included the patients that were at least 16 years old at the start of RRT. We excluded patients that temporarily stopped renal replacement therapy within 3 months after the start of RRT (N=69, 0.06%), including patient death and patients with missing values on one or more of the remaining prediction variables (63 patients with missing PRD, 0.06%). The events from 90 days after the start of RRT till death or end of the study were analyzed (1/1/2014); the follow-up period was maximized at 10 years. This resulted in a dataset of 109,022 patients.

The original model[8] was developed to predict 10-year patient survival from 90 days after the start of RRT. It was based on age at the start of RRT, primary renal disease (PRD), sex, and therapy at 90 days. The formula for the survival probability at time t, S(t), is S(t)=exp(-H(t)). Here H(t) is the cumulative hazard that is calculated from the baseline hazard (H0) as H(t)=H0(t)*exp(prognostic index). The prognostic index can be calculated, using the values of the four predictors for a specific patient (see table 1) together with their parameter estimates. The primary endpoint of interest was 10-year survival; additionally we evaluated the performance of the model for 5- and 3-year survival.

We analyzed the performance of the model both in the total ERA-EDTA Registry cohort, as well as in the separate countries (anonymously). In order to be transparent and enhance the usability of the model, we followed the recently published TRIPOD checklist[12,13]. In table 1 we therefore provide the renal patient survival prediction model which was also published in BMC Nephrology 2013[8]. The performance of the prediction model was evaluated by assessing both calibration and discrimination. Calibration is the agreement between the probability of developing the outcome of interest within a certain time period (in our case 10-, 5- and 3-year survival) as estimated by the model and the observed outcome frequencies[14]. Measures to represent calibration in our study are the calibration in the large, calibration plots and calibration slopes. ‘Calibration in the large’ is the observed versus predicted survival for the complete patient cohort. The calibration plot is a graphical method to express calibration, by plotting the observed outcome frequencies against the mean predicted outcome probabilities, within subgroups of participants that are ranked by increasing estimated survival probability[14]. Ideally the plots follow a 45 degree line, with an

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**Table 1: Validated RRT survival prediction model as published in BMC Nephrology[8]**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Parameter estimate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>0.054</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Reference</td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>-0.280</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>0.331</td>
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<td>Diabetes</td>
<td>0.767</td>
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<td>Other diseases</td>
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<td>0.296</td>
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<td>0.024</td>
</tr>
<tr>
<td>10 year</td>
<td>0.033</td>
</tr>
</tbody>
</table>

* prognostic index of a patient: the sum of (the product of) parameter estimates

The survival probability at a certain time point, S(t) can be calculated from the prognostic index and the baseline hazard, using the following equation: S(t)=exp(-H0(t)*exp(prognostic index)).

E.g. a male 55 year old patient with Diabetes, that started on HD has a prognostic index of (55 year *0.054+2.97)+0.767 (PRD diabetes) +0.067 (male)=3.804; The 10-year survival prognosis is: exp(-0.033*exp(3.804))≈ 23%
intercept of 0 and a slope of 1[15]. This is also reflected in the calibration slope, which represents the outcome of a Cox regression analysis with the prognostic (risk) index as the only predictor[15] and is thus ideally equal to 1. Discrimination is the ability of a model to distinguish individuals who experience the outcome from those who remain event free[14]. The concordance index (C-index) is the most widely used measure to evaluate discrimination. For a Cox model it represents the chance that, given two individuals, the model assigns a higher risk score to the one that develops the event of interest in the shortest period of time. A C-index of 0.5 indicates no discriminative power and a C-index of 1 indicates perfect discriminative power[16].

RESULTS

The distribution of the prediction model variables (age at the start of RRT, sex, primary renal disease (PRD) and the therapy at 90 days) over the 9 European countries that are used in our external validation study are shown in table 2. Most variation between countries as well as between validation and development cohort is seen in the distribution of PRD and therapy at 90 days.

Table 2: Distribution of prediction variables in ERA-EDTA Registry validation cohort; countries (random order) and total external validation cohort, compared to the development cohort[8]

<table>
<thead>
<tr>
<th>Country</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>Total validation cohort</th>
<th>Total development cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group %</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>16-45</td>
<td>14.5</td>
<td>10.9</td>
<td>17.2</td>
<td>15.2</td>
<td>19.2</td>
<td>11.3</td>
<td>12.5</td>
<td>19.3</td>
<td>14.5</td>
<td>19.3</td>
<td>14.1</td>
<td>17.6</td>
</tr>
<tr>
<td>45-65</td>
<td>39.1</td>
<td>30.1</td>
<td>38.2</td>
<td>33.2</td>
<td>41.3</td>
<td>28.1</td>
<td>31.1</td>
<td>33.8</td>
<td>33.3</td>
<td>34.5</td>
<td>33.2</td>
<td>36.9</td>
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<tr>
<td>65-75</td>
<td>27.9</td>
<td>30.5</td>
<td>27.1</td>
<td>31.1</td>
<td>26.7</td>
<td>28.6</td>
<td>34.6</td>
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<td>26.8</td>
<td>26.9</td>
<td>29.8</td>
<td>28.4</td>
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<td>75+</td>
<td>18.6</td>
<td>28.5</td>
<td>17.6</td>
<td>20.5</td>
<td>12.8</td>
<td>32.8</td>
<td>21.8</td>
<td>21.9</td>
<td>25.5</td>
<td>19.6</td>
<td>22.9</td>
<td>17.2</td>
</tr>
<tr>
<td>PRD %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Glomerulonephritis</td>
<td>14.4</td>
<td>11.9</td>
<td>12.3</td>
<td>14.6</td>
<td>14.5</td>
<td>14.1</td>
<td>15.1</td>
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<td>16.2</td>
<td>13.7</td>
<td>14.5</td>
<td>12.5</td>
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<td>Cystic kidney disease</td>
<td>4.5</td>
<td>5.4</td>
<td>6.5</td>
<td>7.3</td>
<td>9.3</td>
<td>7.1</td>
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<td>6.3</td>
<td>7.2</td>
<td>6.4</td>
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<tr>
<td>Renal vascular disease</td>
<td>16.2</td>
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Figure 1: calibration plots for 10-, 5- and 3-year survival per decile of predicted survival for the complete ERA-EDTA Registry cohort
The calibration in the large for the prediction model in the ERA-EDTA Registry cohort show adequate results, with a difference of 2.2%, 4.1% and 4.1% in observed versus predicted 10-, 5- and 3-year overall RRT survival respectively. The calibration plots for 10 deciles of predicted survival for 10-, 5- and 3-year survival are shown in Figure 1.

The calibration results of the prediction model at the country level show varying results; in 4 countries (countries 1-4) the observed and predicted survival probabilities are similar with an overall difference of < 1% (Figure 2), so the performance of the original model is good. In the other 5 countries the predicted survival probabilities are either slightly higher (country 7) or slightly lower (countries 5, 6, 8, and 9). The average absolute difference between observed and predicted survival over the countries is 3% (0-6%) for 10-year survival, and 4% (0-9%) for 5- and 3-year survival. The calibration slope, with the prognostic index as the only predictor, is 1.012 for the complete ERA-EDTA Registry cohort. For the separate countries the slopes differ from 0.922 till 1.088, which is close to the ideal 1.

The discrimination for 10-year survival, expressed as the C-index, shows adequate performance of the model, with values between 0.70 and 0.75 (Figure 3) for the 10 different countries and 0.71 for the complete ERA-EDTA Registry cohort.
DISCUSSION

With this study we examined the external validity of a previously published renal patient survival prediction model based on four commonly available variables. The model performance in 9 European countries reporting to the ERA-EDTA Registry is adequate, with an overall C-index of 0.71 and an average 10-year calibration difference of 2.2%. The model performance for the long term survival prediction is slightly better than the short term survival prediction, as could be expected as the model has been developed for 10-year survival. The fact that these external validation outcomes are similar to the internal validation results in the country where the model was developed indicates robustness of the model.

These external validation outcomes are remarkable, taking into account the many differences between European countries in ESRD patient characteristics and treatment[1,17-21], as well as mortality rates on dialysis[22]. The performance of the model outside the Netherlands could be hampered, if the differences relate to better treatment prospects, for example: more (living donor) transplants, higher quality of donated kidneys or patients starting RRT at earlier stages of disease. On the other hand, if differences are a consequence of population differences that are either directly or indirectly covered by the model, this should not impact model performance.

The model corrects for differences in patient age, sex, PRD and therapy at 90 days after the start of RRT, as these are part of the prediction model. Indirectly the model probably also partly corrects for differences in patient condition, as some of the model variables (like PRD, therapy and age) are related to patient condition (e.g. hypertension, BMI, cardiovascular disease). Next to clinical variation, there are other differences that might affect ESRD patient care and survival such as, human and environmental factors (dietary habits[23], smoking, physical activity[24], socioeconomic status[25] and birth weight[26], healthcare policies[27] and genetic differences[28]) and access to the waiting list and renal transplantation. Stel et al.[29] conclude from a study in four European countries, that variation in transplantation rates may be due to a combination of factors, including legislation, donor availability, transplantation system organization and infrastructure, wealth and investment in health care, as well as underlying public attitudes/awareness to donation and transplantation. The fact that reimbursement strategies play a role has been confirmed by a study among 5 European countries, the United States and Canada[30]. Finally, Kramer et al. have shown that macroeconomic factors as well as the intrinsic mortality of the dialysis population are associated with differences in the mortality on dialysis between countries[22]. Nevertheless, despite the fact that there probably are factors that influence renal patient care and the mortality on RRT, which are not covered by the model, we have shown that the renal patient survival prediction model is applicable in a wide range of countries. The many differences of the ERA-EDTA Registry cohort compared to the Dutch model development cohort actually makes it a very suitable data set for external validation, which in itself is a major strength of this study.

Our validation study shows a comparably sufficient but moderate discriminative power (C-index: 0.71) of the prediction model in other European countries as was also the case in the Dutch cohort[8]. This indicates that there is room for improvement. In 2013 we showed, based on data from the Netherlands Cooperative Study on Adequacy of Dialysis treatment (NECOSAD) how the original survival prediction model could be improved by adding more clinical data[9]. Especially the reclassifications at patient level implied that individual survival probability is influenced substantially by the clinical condition of the patient, so an extended model is preferably used for individual survival prediction. However, as many countries do not register the required additional data on a regular basis yet, it is not possible to externally validate an extended prediction model in a wide spectrum of European countries. This may be different in the future. Although the validated model is less suitable to be used to predict individual patient survival, the validated renal patient survival model can be used by European countries to predict survival chances for groups of patients, to compare risk groups in different studies, or for risk stratification/selection. For example, the model can be used to select patients with a predicted 10-year mortality risk over 60% to participate in a study, or the model can be used to demonstrate time trends in the incident patient populations in a country by differentiation on risk group (defined by specified ranges of mortality rates). As has been pointed out in the two manuscripts describing the previous models, it is important to note that the model is not recommended for basing clinical treatment decisions[8,9].

The strength of this study is the validation of the renal patient survival model in 9 different European countries, with good or acceptable results in all of these countries. Since we observed some variation at country-level, this study also stresses the importance of external model validation in more than just one country. External validation limited to one single country could lead to over- or underestimated model performance, when the mortality rate in this population is different from the reference population[10,31]. Based on our aim to externally validate the original prediction model, we have evaluated this model without any adjustments. Our validation results show good discrimination, and only slightly inferior calibration outcomes in some countries. Therefore in our opinion, model adjustment was not necessary. However, when the presented prediction model is used in another population with differing mortality rates resulting in inadequate calibration results, it would be recommended...
to recalibrate the model by adjusting the baseline hazard, using actual population data, as described by Toll et al. [32]. In fact, a purpose of future research could be to update the European model to optimize performance, in which case external validation is needed again.

Despite the fact that the prediction model has shown to be valuable in this external validation cohort, there are still some study weaknesses to be noted. The most important limitation of the study is that the model has only been validated in other countries, but not in another period of time. In our study this was not possible, since a more recent cohort does not have 10 years of follow-up yet. However, knowing that RRT population and treatment possibilities as well as treatment quality and survival [21] change over time, regular evaluation, and possible recalibration (as suggested earlier for other populations), of the model is recommended. A second limitation of this study is that for some countries we validated our results on patients from only a limited number of years or from a limited number of regions. Although that might introduce differences at country level, we don’t think that this changes the conclusions of the validation study. In fact model performance might be slightly underestimated in these countries, and for the complete ERA-EDTA Registry cohort, as model performance is more likely to deteriorate in other periods of time, as pointed out in the previous limitation. Finally we should mention that the model uses mainly very straightforward variables, except for the PRD. There might be difficulties to adequately (and uniformly) describe the patient’s disease. However, the PRDs with most (either negative or positive) impact on the survival chances (Diabetes and Cystic Kidney Disease) are relatively easy to detect.

In conclusion, our external validation study shows that a straightforward prediction model for long term patient survival on RRT developed in a single country, based on only four easily available variables, has a comparably adequate performance in a wide range of European countries participating in the ERA-EDTA Registry.

ACKNOWLEDGEMENTS

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REFERENCE LIST

1. ERA-EDTA Registry. ERA-EDTA Registry Annual Report 2013. Academic Medical Centre, Department of Medical Informatics, Amsterdam, The Netherlands. 2015. Ref Type: Report


Causes for the decreased use of peritoneal dialysis as a kidney replacement therapy in the Netherlands
CAUSES FOR THE DECREASED USE OF PERITONEAL DIALYSIS AS A KIDNEY REPLACEMENT THERAPY IN THE NETHERLANDS

Abstract

Objective
Study on the extent and causes of the declining use of Peritoneal Dialysis (PD) as kidney replacement therapy in patients with end stage renal disease in the Netherlands.

Design
Retrospective cohort study.

Method
The prevalence and incidence of the different kidney replacement therapies in the Netherlands from 1995 to 2010 were described. Also 5-year outflow of patients on PD or hemodialysis (HD) in the period 1995-2006 was analyzed with cumulative endpoint and Cox regression analysis.

Results
The absolute number of patients starting with PD between 1995 and 2008 has been relatively stable with about 400 per year. There is a relative decline in the use of PD in the prevalent dialysis population from 15% to 8%. This relates to a relative increase in HD inflow (67% before 2001, 74% in 2009), and kidney transplantations before dialysis (3% before 2002, 9% in 2009), as well as a decreased HD-outflow. The increased inflow on HD is associated with a 67% growth of the incident patient group of 65 years or older, of which the major part (80-85%) undertakes HD. Within the younger patient group (0-65 year) there is an increase in the share of HD, next to the increasing number of preemptive transplantations.

Conclusion
The decline in the prevalence of PD is partly explained by the relative increase of HD inflow, associated with an ageing patient population, the declining HD outflow, and the increase of kidney transplantations before dialysis. The increasing HD-prevalence is made possible by the grown hemodialysis capacity.

INTRODUCTION

In July of 1979, peritoneal dialysis (PD) was introduced in the Netherlands as an alternative to hemodialysis (HD)[1]. The percentage of renal replacement therapy involving PD subsequently rose to a peak level of 15% among the patient population with end-stage kidney disease (including those who had received a transplant). Starting in 2002, the prevalence of PD has decreased again to 8%.

Is this decrease in PD percentage due to the increase in HD capacity since the abolition of the planning system for dialysis centres in 2002, which made it possible to open new dialysis centres without a permit? This question cannot be answered, given that the cause and effect of the increase in HD capacity and the use of HD cannot be viewed separately. However, we can look at the impact of other potential causes.

In a nation-wide study, we specifically studied the ageing of the patient population with end-stage kidney failure (source: www.nefrovisie.nl) and the increase in the number of preemptive kidney transplants (i.e. kidney transplants without prior dialysis) due to the increasing number of living donors in the Netherlands. Given that the prevalence of therapies is determined by the inflow and outflow of patients being treated, we also studied the inflow (incidence) for all kidney replacement therapies (PD, HD and kidney transplantation) and the dialysis outflow.

PATIENTS AND METHODS

Patient selection

For the retrospective study of the incidence, we selected all initial renal replacement treatments (including kidney transplantation) that took place in the Netherlands between 1 January 1995 and 1 January 2010. The data was obtained from the Dutch Renal Replacement Registry (Renine). The incidence in the study period involved a total of 24,068 patients with end-stage kidney failure, a condition which was considered to be present if the patient had received more than four consecutive weeks of renal replacement therapy. Table 1 shows the group of new patients (incidence) for all kidney replacement therapies (PD, HD and kidney transplantation) and the dialysis outflow.
Table 1 Characteristics of 24,068 incident ESRD patients starting a RRT in the Netherlands between 1 January 1995 and 31 December 2009; all numbers are percentages

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**METHODS**

The goal of the analyses was to explain changes in prevalence. We compared the absolute number and the relative percentage of PD compared to HD and transplantation with respect to prevalence and incidence. With respect to prevalence, a comparison was also made regarding the ratio of PD to HD at large centres (> 100 patients) and small centres (< 70 patients). We regarded the incidence as a measure for the popularity of the treatment. The incidence of all renal replacement therapies was analysed, as well as the outflow of patients (within five years) who had been started on PD or HD between 1995 and 2006.

This study’s aim was not to assess patient survival rates, and as such the results cannot be used as a basis for choosing between the types of therapies.

**STATISTICAL ANALYSIS**

The outflow of PD and HD (as the initial therapy provided) was analysed using the SPSS18 software program. With the help of a cumulative-incidence-competitive-risk method[2], the chances of different mutually exclusive study outcomes (death, transplantation and switching to a different type of dialysis) within five years were analysed. The outcomes were censored for recovery, data lost to follow-up and the end date
of the study (1 April 2011). Outflow due to death, transplantation and switching to a different type of dialysis is shown in graphs for three successive cohorts. The hazard ratio per year for these outcomes was calculated by means of a Cox regression analysis, with ‘calendar year’ and ‘old versus young patients’ as variables. In this context, a hazard ratio > 1 signifies a greater relative risk of a certain event, while a hazard ratio < 1 signifies a lower relative risk. In the Cox regression analysis, the ‘calendar year x age category’ interaction term was added to correct for the possible relation between calendar year and the ageing of the population over time.

RESULTS

Prevalence

The total patient population (HD, PD and patients with a functioning donor kidney) increased in the 1995-2010 period by 97%, from 7,512 to 14,782 (Figure 1a). The increase in the absolute number of HD patients, from 2,744 to 5,231 (a 91% increase), was similar to this general increase. The number of patients living with a functioning donor kidney rose by approximately 130%, from 3,640 to 8,400. The absolute number of PD patients (n = 1,151) on 1 January 2010 was nearly identical to the number (n = 1,128) on 1 January 1995. However, the relative percentage of PD in the total patient population fell from approximately 15% in 1995 to 8% on 1 January 2010 (see Figure 1a). This decrease in prevalence occurred at both large and small dialysis centres.

Despite the increase in absolute number of HD patients, the relative percentage of HD has remained relatively stable over the past 15 years, at approximately 35%. Meanwhile, the relative percentage of patients with a functioning donor kidney increased from 50% in 1995-2000 to 57% on 1 January 2010. Since 2001, the number of patients living with a functioning kidney transplant has been larger than the number of patients on dialysis.

Inflow (incidence)

Over the past 15 years, the number of new (incident) patients that started with PD fluctuated around 400 (see Figure 1b). Percentage-wise, there was a decrease from 30% in PD as initial therapy in the 1995-2000 period to 17% in 2009. The inflow for HD and the number of preemptive transplantations increased in both absolute and relative terms.

In the group of patients younger than 65, the absolute and relative PD inflow decreased (Figure 2). At the same time, this group exhibited an absolute and relative increase in the number of preemptive transplantations and the number of patients starting with HD (approximately 12% and 8%, respectively). In the 65+ age group, the number of new patients increased considerably, particularly among those 75 and older. The 65+ group started with PD less frequently than the young patients. On average, 19% of the 65-74 year-olds and 12% of the 75+ age group started with PD. These percentages did not change during the 1995-2009 period.
CAUSES FOR THE DECREASED USE OF PERITONEAL DIALYSIS AS A KIDNEY REPLACEMENT THERAPY IN THE NETHERLANDS

Figure 2a Number of new patients (inflow) <65 years old undergoing hemodialysis (HD), kidney transplantation (TXP) and peritoneal dialysis (PD) in the Netherlands from 1995-2010

Figure 2b Number of new patients (inflow) ≥ 65 years old undergoing hemodialysis (HD), kidney transplantation (TXP) and peritoneal dialysis (PD) in the Netherlands from 1995-2010

Figure 2c Distribution in percentage of the type of therapy (hemodialysis (HD), kidney transplantation (TXP) and peritoneal dialysis (PD)) - patient aged < 65 years old

Figure 2d Distribution in percentage of the type of therapy (hemodialysis (HD), kidney transplantation (TXP) and peritoneal dialysis (PD)) - patient aged ≥ 65 years old
CAUSES FOR THE DECREASED USE OF PERITONEAL DIALYSIS AS A KIDNEY REPLACEMENT THERAPY IN THE NETHERLANDS

The HD outflow for three time periods (1995-1998, 1999-2002 and 2003-2006) is shown in Figure 3a. Univariate Cox regression analysis determined that the relative risk (hazard ratio) per calendar year of death, transplantation and therapy switching to PD was 0.985 (95% Confidence Interval (CI): 0.979-0.992), 1.001 (95%-CI: 0.988-1.013) and 0.967 (95%-CI: 0.953-0.980), respectively. Corrected for age, there was a significantly elevated hazard ratio for transplantation and a significantly reduced hazard ratio for death and therapy switching to PD per calendar year (Table 2). This effect of calendar year and age group was not a result of interaction between both variables (see Table 2).

Table 2  Hazard ratio for death, transplantation or therapy change to another dialysis therapy within 5 years, for patients that have started with hemodialysis (HD) or peritoneal dialysis (PD), calculated with multivariate Cox regression analysis without and with interaction term, over the years 1995-2006*

The PD outflow for the same three time periods is shown in Figure 3b. Univariate Cox regression analysis determined that the hazard ratio per calendar year of death, transplantation and therapy switching to HD was 0.985 (95%-CI: 0.968-1.003), 0.987 (95%-CI: 0.971-1.002) and 0.998 (95%-CI: 0.984-1.013), respectively. Corrected for age, there was a significantly reduced chance of death per calendar year (see Table 2), but this effect of calendar year differed per age group and was stronger in the older age group, as can be concluded from the interaction term between both variables (see Table 2).

Figure 3a Outflow of patients in the five years after starting with hemodialysis (HD) to the end point of death, kidney transplantation (TXP) or peritoneal dialysis: cumulative incidence analysis subdivided into three periods: 1995-1998 (P1); 1999-2002 (P2); 2003-2006 (P3)

Figure 3b Outflow of patients in the five years after starting with peritoneal dialysis (PD) to the end point of death, kidney transplantation (TXP) or hemodialysis: cumulative incidence analysis subdivided into three periods: 1995-1998 (P1); 1999-2002 (P2); 2003-2006 (P3)

Therapy switching/outflow

The HD outflow for three time periods (1995-1998, 1999-2002 and 2003-2006) is shown in Figure 3a. Univariate Cox regression analysis determined that the relative risk (hazard ratio) per calendar year of death, transplantation and therapy switching to PD was 0.985 (95% Confidence Interval (CI): 0.979-0.992), 1.001 (95%-CI: 0.988-1.013) and 0.967 (95%-CI: 0.953-0.980), respectively. Corrected for age, there was a significantly elevated hazard ratio for transplantation and a significantly reduced hazard ratio for death and therapy switching to PD per calendar year (Table 2). This effect of calendar year and age group was not a result of interaction between both variables (see Table 2).
DISCUSSION

Analysis of the identified reduction in the relative percentage of peritoneal dialysis

The absolute number of ‘prevalent’ patients with peritoneal dialysis and the number of new (‘incident’) patients remained nearly identical in the study period, while the number of patients undergoing alternative types of therapies rose significantly. As a result, the relative percentage of PD to both HD and transplantation declined. This drop could not be attributed to a specific category of centres in terms of size. The growth of the HD inflow (incidence) was, among other things, related to an increase of the 65+ age group of patients who are relatively less likely to start with PD. There was also a slight shift of younger patients to HD. The increase in the preemptive kidney transplantations was accompanied by a decrease of the PD incidence and prevalence in younger patients. In addition to the primary inflow in PD, the secondary inflow (after an initial start with HD) also declined.

The majority of patients in the 65+ age group used HD. This percentage hardly changed over the 15 year period. The strong growth of this group was accompanied by a reduction of the percentage of PD across the entire patient population. Others also described that patients aged 65 and older are on average less likely to start with PD than younger patients[3-6]. In principle, PD is an appropriate form of dialysis for elderly patients in light of the lower cardiovascular burden[7]. Explanations for a low incidence in elderly patients are a higher chance of contra-indications due to an increase of comorbidity at an older age[8,9], which makes home dialysis more difficult, the sometimes limited availability of social support[10], and a greater preference for HD compared to other age groups[9]. A lower rate of survival is also suggested in elderly patients who use PD[11], but this has not been found in all studies.

The fact that this elderly patient group has increased so considerably cannot be explained by the ageing of the population. Figures from Renine and Central Bureau of Statistics (CBS) Netherlands show that since 1995 the number of new patients per million residents has hardly changed in all age groups up to 75, while it has doubled in the 75+ age group (www.nefrovisie.nl). Possible alternative explanations include a higher incidence of kidney diseases in elderly patients and change to the treatment criteria for elderly patients with ESRD.

In the younger patients (< 65 years old), the relative percentage of those who were treated with PD decreased by approximately 20%. The percentage of preemptive transplantations in this group increased by approximately 12%. PD patients are generally younger and have less comorbidity than HD patients[4,5]. They are thus generally in better condition, which is a requirement for kidney transplantation[12]. It is probable that PD has been substituted by transplantation to a certain extent in the group of young patients.

At the same time, however, there was also an increase of HD incidence in the younger patients. This was not to be expected based on survival analyses and patient satisfaction with respect to PD. The possible role of the promotion of HD, as opposed to PD, that has been suggested by the media is speculative. In the last 25 years, there have been many publications which compare the survival rates for HD and PD[3-5,7,11,13-18]. The results in the USA were more varied than those in Canada and Western Europe. Canadian and Western European studies mostly found a survival advantage of 2-4 years for PD, particularly with respect to non-diabetic patients. This survival advantage is largely due to the better preservation of residual kidney function in PD therapy.

In some patients, however, a switch to HD is ultimately necessary. This can have an impact on the duration of PD treatment, but that does not appear to be the case in the Netherlands, given that there has been no change in the PD outflow due to a switch to HD therapy over the years. PD also appears to prevail over HD in studies on quality of life[19], or at least produce similar results[20]. The reduced outflow of HD due to a switch to PD therapy in recent years, however, is possibly related to the increased possibility of home hemodialysis and night-time dialysis.

International comparison

The decrease in use of PD in the Netherlands over the past decade is not unique. While the global relative percentage of PD varies greatly, many countries have experienced a decrease in the PD portion of incident patients. In the United States, for instance, the relative percentage of PD use between 2000-2004 decreased by over 50%[18]. There has also been a decrease in Canada, Australia and New Zealand. The trends show more variation in Europe. The possible causes for this decrease are both medical in nature (age, comorbidity, fear of poorer results, such as encapsulating peritoneal sclerosis[21] and non-medical in nature[6,10,18]. Examples of non-medical reasons are the preferences of the patient and caregivers[22], information and time for the decision-making process, social support and late referral or an acute start of renal replacement therapy[10]. A Dutch study found that more than half of the patients have no contra-indications for either PD or HD[9]. The possible contra-indications usually pertain to PD and are associated with an older age, higher comorbidity and the social situation (living alone).

The strong increase of HD incidence coincides with the abolition of the planning system for dialysis centres in 2002 and the increase in the number of dialysis centres and their branches (> 2005). It is clear that both developments are related to each other, but based on the available data it is not possible to distinguish between possible cause and effect. The new centres/branches have absorbed the large inflow of elderly patients, though it is striking that they still start with the same ratio of HD to PD as in the past. The question is also whether the increasing popularity of HD in younger patients is related to more (or, as it may be, fewer) options due to this increased capacity. For this, more insight into the selection process of the physician and patient in the pre-dialysis phase is desired.
Limitations of this study
A limitation of this study is that the Renine database does not contain any medically substantive patient data. No figures are available on the exact expansion of dialysis capacity in the Netherlands, the distribution between regular dialysis and night-time dialysis or any changes in treatment criteria and non-medical considerations for choosing a particular type of therapy.

CONCLUSION
The decrease in the relative percentage of peritoneal dialysis in the prevalent patient population in the final stage of kidney failure is multifactorial and is partly explained by the relatively increased inflow for HD and the reduced outflow from HD due to a switch to PD therapy. The increased HD prevalence is possibly a result of the expansion of the HD capacity and, among other things, is connected to the ageing of the incident patient population with ESRD. There has also been an increase in preemptive kidney transplantations in the younger patients.

REFERENCE LIST


Abstract

Survival of Expanded Criteria Donor (ECD) kidneys and their recipients has not been thoroughly evaluated in Europe. Therefore, we compared the outcome of ECD and non-ECD kidney transplantations in a Dutch cohort, stratifying by age and diabetes.

In all first Dutch kidney transplants in recipients ≥ 18 years between 1995 and 2005, both relative risks (hazard ratios, HR) and adjusted absolute risk differences (RD) for ECD kidney transplantation were analysed.

In 3062 transplantations (recipient age 49.0 (12.8) years; 20% ECD), ECD kidney transplantation was associated with graft failure including death (HR 1.62 [1.44 – 1.82]). The adjusted HR was lower in recipients ≥ 60 years of age (1.32 [1.07 – 1.63]) than in recipients 40-59 years (1.71 [1.44 – 2.02] P = 0.12 for comparison with ≥ 60 years) and recipients 18-39 years (1.92 [1.42 – 2.62] P = 0.03 for comparison with ≥ 60 years). RDs showed a similar pattern. In diabetics, the risks for graft failure and death were higher than in the non-diabetics.

ECD kidney grafts have a poorer prognosis than non-ECD grafts, especially in younger recipients (< 60 years), and diabetic recipients. Further studies and ethical discussions should reveal whether ECD kidneys should preferentially be allocated to specific subgroups, such as elderly and non-diabetic individuals.

INTRODUCTION

In patients with end-stage renal disease, kidney transplantation is the optimal renal replacement therapy (RRT) with regard to survival[1], quality of life[2], and costs[3]. As a consequence, the demand for donor kidneys exceeds the more or less constant supply of organs donated after death[4]. To reduce the number of patients waiting for a kidney transplant, many transplant centres over the world started to accept suboptimal organ donors, referred to as expanded criteria donors (ECD) or marginal donors[5]. Results of these ECD kidney transplantations differ across studies in different regions: some studies reveal no differences in outcome between ECD and non-ECD kidney transplantations[6-10], whereas other studies, including a systematic review and a meta-analysis, tend to show higher rates of graft failure and mortality in ECD kidney transplantations, especially in recipients with diabetes or recipients younger than 40 years of age[11-13]. In the Eurotransplant (ET) kidney exchange program, facilitating cross-border organ exchange from both ECD and non-ECD donors in eight European countries including the Netherlands, graft and patient survival according to ECD status have not been investigated.

Analysing outcome of ECD kidney transplantation in several regions is relevant as kidney transplant procedures across the world differ, among other things, in allocation strategies, cold ischemia times, human leucocyte antigen (HLA) matching, and (initial) immunosuppressive regimens. In addition, a recent meta-analysis shows differences in outcome of ECD kidney transplantation between Europe and North America[13]. If results of a certain region appear to be better, it possibly provides clues for improving ECD kidney transplantation in other areas. If, however, outcome of ET ECD kidneys is similar as in other areas, ET could consider to adapt its allocation policy and allocate ECD kidneys to recipients in whom the influence of ECD status on outcome is minimal. The last decades, other adaptations of the ET-allocation strategy have proven to be successful. First, the acceptable mismatch program, giving priority to highly immunized kidney recipients over the standard allocation procedure based on ABO matching, optimal HLA matching, and short cold ischaemia times, has considerably reduced waiting times in these patients[14]. Second, more recently, the ET Senior Program (ESP; ‘Old for old’) was implemented and its results are successful as well[15,16].

Therefore, the aim of this study was to evaluate outcome of ECD kidney donations in the Netherlands, part of the ET region, in subgroups of patients. In the Netherlands, data on kidney transplantations have been prospectively and retrospectively registered in the Dutch Organ Transplant Registry (NOTR) database. Besides patient and donor characteristics at the moment of kidney transplantation, this registry contains yearly follow-up data. The question of this study is whether graft and patient survival after deceased ECD kidney donations in the Netherlands, between 1995 and 2005, in
adult recipients receiving their first kidney transplantation differ from deceased non-ECD kidney donations in general, and in specific subgroups of kidney recipients, stratified by age and diabetes.

METHODS

This study was performed on NOTR data containing baseline and follow-up data on kidney transplants in the Netherlands. All Dutch kidney transplant centres have committed themselves to provide the required data to this registry. Additional data of kidney transplants and kidney recipients from the ET and the Renine (Dutch Renal Replacement Registry) registries are routinely incorporated in the NOTR registry. As ET allocates all kidney grafts of deceased donors in its region, all deceased donor kidney transplants are registered in the NOTR database; because of the link with Renine, information on renal replacement therapy (RRT) in the recipient before transplantation and death on RRT after graft failure is available in the NOTR.

In this study, all deceased donor kidney transplantations performed in recipients of 18 years and older receiving their first kidney transplant between 1 January 1995 and 31 December 2004 in the Netherlands were included. The inclusion period was chosen to affirm a long follow-up period (up to 2013, at least 8 years). Combined kidney and pancreas transplantations were excluded. Both baseline data and annual follow-up data till February 2013 were used for this study. Most variables used in the analyses were without additional calculations available in the NOTR database, such as dates for graft failure and death. The primary endpoints of this study were time to graft failure and time to death. For graft failure, first both failure of the graft (need of renal replacement therapy) and death were considered as graft failure, and second, failure of the graft alone (with censoring for death). Delayed graft function was not considered as graft failure. The determinant of our analyses was ECD (yes/no). Donor kidneys were retrospectively classified as ECD kidneys if donor characteristics met one of the following criteria: (i) donor age ≥ 60 years at the moment of donation; (ii) donor age 50 – 59 years at the moment of donation and two out of (a) history of hypertension, (b) donor creatinine value >132 µmol/l / 1.5 mg/dl (if more than one donor creatinine value was available, the lowest value was taken for this criterion), and (c) donor death caused by a cerebro-vascular accident (CVA)[5,17]. A donor history of hypertension was considered to be present if hypertension was mentioned in the donor’s medical record or in case of antihypertensive treatment before admission in the hospital. CVA was considered to be the cause of death if the European Dialysis and Transplant Association (EDTA) death cause in the NOTR database was recorded as ‘CVA: Cerebro Vascular Accident Not Otherwise Specified’, ‘CVA: Intra Cerebral Bleeding’ or ‘CVA: Cerebral Ischemia’. Diabetes in the recipients was defined as diabetic renal disease as primary kidney disease or presence of diabetes before transplantation registered in the database. Diabetes was classified as type 1 if the primary renal disease in the database was ‘Diabetes type 1’. If the primary renal disease was registered as ‘diabetes type 2’ or the dichotomous field ‘Diabetes before transplantation’ was ‘Yes’, diabetes was classified as type 2.

Statistical analyses

Descriptive statistics are presented as numbers, percentages and means (standard deviation; SD). Relative risks were analysed using Cox proportional hazards models and given as hazard ratios with 95% CI. In these models, ECD kidney was analysed as a dichotomous determinant of the two outcome variables. Initially, crude models with ECD kidney as determinant were constructed. Thereafter, we adjusted for baseline confounders in two steps. Model 1 was adjusted for characteristics of the recipient (recipient age, previous dialysis duration, panel reactive antibodies (PRA), recipient blood group, diabetes); model 2 for all characteristics of model 1 and characteristics of the transplant procedure and matching (cold ischemia time, HLA sharing, donor blood group, donation after cardiac death (DCD) versus donation after brain death (DBD), year of transplantation). In the Netherlands, the date of registration on the waiting list is the same as the date of initiation of dialysis. Therefore, the time on the waiting list was not added as a separate confounder. Recipient age, sharing HLA, cold ischemia time (hours), and dialysis duration (years) were entered as continuous variables; panel-reactive anti-body (PRA) category (0-5%, 6-84%, >85% PRA activity), transplant year, DCD (yes/no), gender (male/female), donor and recipient blood group and diabetes (yes/no) as categorical variables. As in these analyses few data were missing, complete case analyses were executed. Adjusted absolute risk differences (RD) at three time points (1, 5 and 10 years of follow-up) between the ECD kidney donation and the non-ECD kidney donation were calculated from the obtained Cox models using the corrected group prognosis method as described by Austin[18]. Pointwise confidence intervals of the obtained risk differences were computed via bootstrap resampling (2000 cycles).

Subgroup analyses were performed with respect to recipient age and diabetes. Age was defined as age at the moment of kidney transplantation and divided into three subgroups: 18-39, 40-59 and ≥ 60 years. Statistical testing of HRs among subgroups was performed by adding an interaction term between ECD kidney and age category or diabetes to the Cox models using the appropriate group as reference. Statistical testing of RDs among the groups was performed with independent t-tests using the standard errors obtained with bootstrap resampling. We considered comparing kidney pairs allocated to an old and a younger recipient. However, in the ET-region kidneys of the same donor are often allocated to recipients in different countries.
Therefore, these data are not available in the NOTR (Dutch) database. As a consequence, paired kidney analysis was impossible.

Survival graphs were constructed as raw Kaplan Meier curves without adjustments.

**Sensitivity analyses**

To assess robustness of our results, a number of sensitivity analyses were performed. First, transplant year was replaced by confounders that possibly were more etiologically associated with improvements over time. To this end, we used dichotomous indicators of administration of initial immunosuppressive drugs, such as antibodies (antithymocyte globulin, basiliximab etc.), calcineurin inhibitors (ciclosporin, tacrolimus). Other factors, such as indicators of surgical techniques, the use of certain kidney preservation fluids may have contributed to improvements of the results, but are not available in the database. Second, donor kidney side was added to the confounders in the analyses of graft failure as right kidneys may have worse outcome[19]. As a third sensitivity analysis, absolute risk differences were analysed in prevalent patients in 4 periods after transplantation: 0-3 months, 3-12 months, 1-5 years and 5-10 years, to study whether absolute risk differences between the groups were present during the entire follow-up period. In these analyses, only patients without an event in the preceding period were analysed. Fourth, as graft failure and death are competing risks, which might influence the analysis of death-censored graft failure, graft failure was analysed with a competing risk analysis[20] using graft failure a primary outcome and death as competing outcome. Fifth, we analysed the effect of ECD kidney in strata of previous dialysis duration (< 2 years, 2-4 years, and > 4 years). Sixth, in order to avoid selection bias in type 1 diabetic patients due to the policy to preferentially execute a combined kidney and pancreas transplantation in these patients, analyses in diabetic patients were performed after exclusion of type 1 diabetic patients.

Seventh, to evaluate the robustness of the determinant, we constructed a categorical determinant indicating the four possible combinations of ECD and DBD/DCD. Cox regression analyses were repeated with this categorical determinant using the non-ECD-DBD category as reference.

Eight, possible confounders with a high proportion of missing values, such as BMI and smoking, were analysed in a complete case analysis and after multiple imputation using chained equations (MICE)[21,22]. In the latter, weight, length and smoking were predicted with recipient age, recipient gender, previous dialysis duration, kidney disease, PRA activity, year of transplantation, donor hypertension, donor death cause CVA, DCD or DBD donor type, the dichotomous outcome indicator and the result of the cumulative hazard function[23]. In the Cox proportional hazard models, body mass index (weight/length^2) and smoking were added as confounders to model 2.

All analyses were performed using Stata® 13 and 14 statistical software (Stata Inc, College Station, TX, USA).

**RESULTS**

From a total of 3901 kidney transplantations of deceased donors, we identified 3062 first procedures in recipients ≥ 18 years performed between 1 January 1995 and 31 December 2004 (Figure 1, Table 1).

---

**Table 1**

<table>
<thead>
<tr>
<th>Data model 1 complete</th>
<th>Data model 2 complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>3038</td>
<td>2978</td>
</tr>
</tbody>
</table>

**Figure 1**

Selection of patients and available cases in the analyses.
Table 1: Recipient, donor, transplant procedure characteristics and events

<table>
<thead>
<tr>
<th></th>
<th>All kidney transplants</th>
<th>ECD</th>
<th>Non-ECD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney recipients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3062</td>
<td>619 (20% of total)</td>
<td>2443 (80% of total)</td>
</tr>
<tr>
<td>Male</td>
<td>1814 (59%)</td>
<td>387 (62.5%)</td>
<td>1427 (58.4%)</td>
</tr>
<tr>
<td>Female</td>
<td>1248 (41%)</td>
<td>232 (37.5%)</td>
<td>1016 (41.6%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-39 years</td>
<td>49.0 (12.8)</td>
<td>53.1 (13.0)</td>
<td>48.0 (12.5)</td>
</tr>
<tr>
<td>40-59 years</td>
<td>746</td>
<td>642</td>
<td>104</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>1598</td>
<td>1312</td>
<td>296</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>24.0 (5.5)</td>
<td>24.4 (5.5)</td>
<td>24.0 (5.5)</td>
</tr>
<tr>
<td>Smoking (%)</td>
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<tr>
<td>Yes</td>
<td>11.7</td>
<td>13.3</td>
<td>11.3</td>
</tr>
<tr>
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<td>49.2</td>
<td>53.7</td>
</tr>
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<td>Dialysis duration (years)</td>
<td>3.29 (2.30)</td>
<td>3.14 (2.12)</td>
<td>3.32 (2.35)</td>
</tr>
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<td>Previous dialysis modality (%)</td>
<td></td>
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<td></td>
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<tr>
<td>HD</td>
<td>55.0</td>
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<td>PD</td>
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<td>2.8</td>
<td>1.9</td>
</tr>
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<td>Diabetes (N)</td>
<td>333 (10.9%)</td>
<td>50 (8.1%)</td>
<td>283 (11.6%)</td>
</tr>
<tr>
<td>Blood group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>1282 (42%)</td>
<td>250 (40%)</td>
<td>1032 (42%)</td>
</tr>
<tr>
<td>A</td>
<td>1260 (41%)</td>
<td>247 (40%)</td>
<td>1013 (42%)</td>
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<tr>
<td>B</td>
<td>382 (12%)</td>
<td>90 (15%)</td>
<td>292 (12%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>138 (5%)</td>
<td>32 (5%)</td>
<td>106 (4%)</td>
</tr>
<tr>
<td>PRA (% N)</td>
<td>2684 (87.6%)</td>
<td>566 (91.4%)</td>
<td>2118 (86.7%)</td>
</tr>
<tr>
<td>0-5 %</td>
<td>348 (11.4%)</td>
<td>49 (7.9%)</td>
<td>299 (12.2%)</td>
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<tr>
<td>&gt;85 %</td>
<td>30 (1.0%)</td>
<td>4 (0.7%)</td>
<td>26 (1.1%)</td>
</tr>
<tr>
<td>Kidney donors</td>
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</tr>
<tr>
<td>N</td>
<td>3062</td>
<td>619</td>
<td>2443</td>
</tr>
<tr>
<td>Male</td>
<td>1612 (53%)</td>
<td>303 (49%)</td>
<td>1309 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>1450 (47%)</td>
<td>316 (51%)</td>
<td>1134 (46%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.1 (16.1)</td>
<td>62.7 (5.6)</td>
<td>38.1 (13.9)</td>
</tr>
<tr>
<td>Kidney side (left / right)</td>
<td>1570 / 1492</td>
<td>306 / 313</td>
<td>1264 / 1179</td>
</tr>
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<td>Lowest donor creatinine (µmol/l)</td>
<td>77.7 (42.0)</td>
<td>82.8 (28.6)</td>
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<tr>
<td>Blood group</td>
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<tr>
<td>O</td>
<td>1388 (45%)</td>
<td>280 (45%)</td>
<td>1108 (45%)</td>
</tr>
<tr>
<td>A</td>
<td>1268 (42%)</td>
<td>246 (40%)</td>
<td>1022 (42%)</td>
</tr>
<tr>
<td>B</td>
<td>317 (10)</td>
<td>75 (12%)</td>
<td>242 (10%)</td>
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<tr>
<td>AB</td>
<td>88 (3%)</td>
<td>17 (3%)</td>
<td>71 (3%)</td>
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<td>1 (0.03%)</td>
<td>1 (0.03%)</td>
<td>0 (0.0%)</td>
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<td>Donor death cause CVA</td>
<td>1385 (45.2%)</td>
<td>417 (67.4%)</td>
<td>968 (39.6%)</td>
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<td>Donation:</td>
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<tr>
<td>After brain death (DBD)</td>
<td>2360 (77.1%)</td>
<td>489 (79.0%)</td>
<td>1871 (76.6%)</td>
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<tr>
<td>After cardiac death (DCD)</td>
<td>702 (22.9%)</td>
<td>130 (21.0%)</td>
<td>572 (23.4%)</td>
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</table>

**Transplant procedure / other**

<table>
<thead>
<tr>
<th></th>
<th>All kidney transplants</th>
<th>ECD</th>
<th>Non-ECD</th>
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</thead>
<tbody>
<tr>
<td>Sharing HLA</td>
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<td>2.2</td>
<td>1.9</td>
<td>3.0</td>
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<td>1 (%)</td>
<td>4.6</td>
<td>4.5</td>
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<tr>
<td>2 (%)</td>
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<tr>
<td>3 (%)</td>
<td>35.8</td>
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<td>4 (%)</td>
<td>25.9</td>
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<tr>
<td>5 (%)</td>
<td>11.6</td>
<td>11.3</td>
<td>11.7</td>
</tr>
<tr>
<td>6 (%)</td>
<td>4.9</td>
<td>4.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Cold ischemia time (h)</td>
<td>22.2 (7.5)</td>
<td>22.7 (7.4)</td>
<td>22.0 (7.5)</td>
</tr>
</tbody>
</table>

**Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Follow-up time (years)</th>
<th>Transplant failure (including death) (N)</th>
<th>Graft failure</th>
<th>Death (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(min - max)</td>
<td>7.8 (4.6)</td>
<td>1607 (52.5%)</td>
<td>818 (26.7%)</td>
<td>1183 (38.6%)</td>
</tr>
<tr>
<td>(0 - 18)</td>
<td>6.5 (4.5)</td>
<td>414 (66.9%)</td>
<td>223 (36.0%)</td>
<td>301 (48.6%)</td>
</tr>
<tr>
<td>(0 - 17.4)</td>
<td>8.2 (4.6)</td>
<td>1193 (48.8%)</td>
<td>595 (24.4%)</td>
<td>882 (36.1)</td>
</tr>
</tbody>
</table>

N: number
BMI: body mass index
HLA: Human Leucocyte Antigen
PRA: panel reactive antibodies
ECD: Expanded Criteria Donor
Data are given as mean (SD)
* about 31% missing data for BMI, 50% for smoking

Data were extracted from the NOTR-database in April 2013. Considering data quality: 6% of the cases was considered to be lost to follow-up by the treating transplant centres and NOTR; 68% of the patients without an event had their last follow-up in 2011 or later; 24% in 2008-2010. Table 1 shows the characteristics of the kidney donors, kidney recipients and the transplantation procedures. Among these, ECD criteria were met in 619 kidney transplants (20%). The number of kidney pairs, that is kidneys from the same donor, could not be derived from the database. Over time, the distribution of criteria classifying a kidney as ECD kidney did not change (data not shown).

In general, missing data at the moment of transplantation were below 5%. However, recipient smoking at the moment of transplantation was unknown in about 50% of the cases, recipient body mass index (BMI) in about 30%, and donor diuresis in about 18%. Therefore, smoking and BMI were analysed as confounders in the sensitivity analyses only.
Table 2: Relative risk of graft failure and mortality in patients receiving kidney transplantations with Expanded Criteria Donor kidneys

<table>
<thead>
<tr>
<th>ECD vs non ECD</th>
<th>N</th>
<th>Recipient age 18-39 years</th>
<th>Recipient age 40-59 years</th>
<th>Recipient age ≥ 60 years</th>
<th>No diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft failure including death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.71 (1.53 – 1.91)</td>
<td>1.69 (1.26 – 2.27)</td>
<td>1.66 (1.41 – 1.95)</td>
<td>1.35 (1.13 – 1.63)</td>
<td>1.64 (1.46 – 1.85)</td>
<td>3.03 (2.16 – 4.24)</td>
</tr>
<tr>
<td>Model 1 (recipient characteristics)*</td>
<td>1.58 (1.41 – 1.78)</td>
<td>1.73 (1.29 – 2.33)</td>
<td>1.69 (1.43 – 2.00)</td>
<td>1.34 (1.10 – 1.62)</td>
<td>1.51 (1.33 – 1.71)</td>
<td>2.33 (1.63 – 3.34)</td>
</tr>
<tr>
<td>Model 2 (model 1 and procedure/matching characteristics)*</td>
<td>1.62 (1.44 – 1.82)</td>
<td>1.92 (1.42 – 2.62)</td>
<td>1.71 (1.44 – 2.02)</td>
<td>1.32 (1.07 – 1.63)</td>
<td>1.53 (1.35 – 1.74)</td>
<td>2.60 (1.75 – 3.89)*</td>
</tr>
<tr>
<td><strong>Graft failure - death censored</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.75 (1.50 – 2.05)</td>
<td>1.75 (1.27 – 2.40)</td>
<td>1.92 (1.54 – 2.39)</td>
<td>1.63 (1.19 – 2.22)</td>
<td>1.67 (1.42 – 1.96)</td>
<td>3.29 (1.95 – 5.54)</td>
</tr>
<tr>
<td>Model 1 (recipient characteristics)*</td>
<td>1.85 (1.58 – 2.17)</td>
<td>1.72 (1.25 – 2.38)</td>
<td>1.95 (1.62 – 2.45)</td>
<td>1.59 (1.16 – 2.20)</td>
<td>1.76 (1.50 – 2.09)</td>
<td>3.06 (1.73 – 5.39)</td>
</tr>
<tr>
<td>Model 2 (model 1 and procedure/matching characteristics)*</td>
<td>1.92 (1.63 – 2.26)</td>
<td>1.95 (1.40 – 2.71)</td>
<td>1.99 (1.58 – 2.51)</td>
<td>1.61 (1.13 – 2.29)*</td>
<td>1.82 (1.53 – 2.15)</td>
<td>3.56 (1.91 – 6.64)*</td>
</tr>
</tbody>
</table>

Data are given as hazard ratios (95% CI) obtained with Cox proportional hazards models. 

- a) Adjusted for recipient age, recipient gender, dialysis duration recipient, panel reactive antibody (PRA) activity, recipient blood group, diabetes (not in analyses stratified for diabetes)
- b) Adjusted for model 1 and HLA sharing, donor blood group, cold ischemia time, DCD (versus DBD), year of transplantation

Table 2 shows the relative risks (hazard ratios) obtained with multivariable Cox models, adjusting for possible confounders. These analyses confirm the finding that ECD kidneys perform worse. These effects are most striking in diabetic patients and the young (18-39 years) and middle age category (40-59 years). The adjusted HR for graft failure including death in recipients ≥ 60 years differed statistically significantly from the HR in recipients of 18-39 years of age (P = 0.03). All HRs between diabetic and non-diabetic patients were statistically significant (P ≤ 0.02).
Table 3: Adjusted absolute risk differences (%) of graft failure and mortality at certain time points of follow-up period in subgroups of patients

<table>
<thead>
<tr>
<th>ECD versus non ECD</th>
<th>N</th>
<th>Graft failure including death</th>
<th>Graft failure, death censored</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3062</td>
<td>746</td>
<td>1598</td>
<td>718</td>
</tr>
<tr>
<td>1 year</td>
<td>7.1 (5.2 – 9.2)</td>
<td>9.7 (4.2 – 17.2)</td>
<td>7.4 (4.7 – 10.4)</td>
<td>5.0 (0.9 – 8.9)</td>
</tr>
<tr>
<td>5 years</td>
<td>12.4 (9.2 – 15.7)</td>
<td>16.1 (7.2 – 26.2)</td>
<td>13.0 (8.5 – 17.8)</td>
<td>8.6 (1.4 – 15.1)</td>
</tr>
<tr>
<td>10 years</td>
<td>16.1 (12.3 – 20.2)</td>
<td>20.3 (9.4 – 31.4)</td>
<td>18.0 (12.0 – 24.0)</td>
<td>9.7 (1.7 – 16.4)</td>
</tr>
</tbody>
</table>

Data are given as risk difference (95% CI) obtained with the corrected group prognosis method using Cox proportional hazard model 2 (Table 2). All risk differences are adjusted for recipient age, gender, dialysis duration, recipient, panel reactive antibody (PRA) activity, recipient blood group, diabetes (not in analyses stratified for diabetes), HLA sharing, donor blood group, cold ischemia time, DCD (versus DBD), year of transplantation.

Table 4: Adjusted relative risks of ECD and DCD combinations

<table>
<thead>
<tr>
<th>ECD - non-ECD and DBD/DCD combinations</th>
<th>N</th>
<th>Graft failure including death</th>
<th>Graft failure, death censored</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3062</td>
<td>746</td>
<td>1598</td>
<td>718</td>
</tr>
<tr>
<td>1 year</td>
<td>1</td>
<td>1.14 (0.99 – 1.34)</td>
<td>1.46 (1.01 – 2.10)</td>
<td>1.10 (0.88 – 1.37)</td>
</tr>
<tr>
<td>5 years</td>
<td>1.57 (1.38 – 1.80)</td>
<td>2.01 (1.41 – 2.86)</td>
<td>1.60 (1.32 – 1.95)</td>
<td>1.28 (1.01 – 1.62)</td>
</tr>
<tr>
<td>10 years</td>
<td>2.05 (1.63 – 2.60)</td>
<td>2.42 (1.29 – 4.56)</td>
<td>2.37 (1.70 – 3.30)</td>
<td>1.39 (0.93 – 2.08)</td>
</tr>
</tbody>
</table>

Data are given as hazard ratios (95% CI) obtained with Cox proportional hazards models. Adjusted for recipient age, gender, dialysis duration, recipient, panel reactive antibody (PRA) activity, recipient and donor blood group, diabetes (not in analyses stratified for diabetes), HLA sharing, cold ischemia time, year of transplantation.

DBD: donation after brain death
DCD: donation after cardiac death
Figure 2: Crude Kaplan-Meier graft survival graphs given as proportion not reaching the endpoint graft failure or death according to ECD kidney donation. P-values indicate the difference between ECD and non-ECD recipients and are derived from model 2 (Table 2).
INCREASED RISK OF GRAFT FAILURE AND MORTALITY IN DUTCH RECIPIENTS RECEIVING AN EXPANDED CRITERIA DONOR KIDNEY TRANSPLANT

Figure 3: Crude Kaplan-Meier patient survival graphs given as proportion not reaching the endpoint death according to ECD kidney donation. P-values indicate the difference between ECD and non-ECD recipients and are derived from model 2 (Table 2).

Sensitivity analyses
In the analyses with the initial immunosuppression as confounder, the confounding effect of ‘transplant year’ was explained in part, but not fully, by immunosuppression. Adding kidney side in the second sensitivity analysis did not change the results of model 2 (data not shown). The third sensitivity analysis (data not shown) looking at absolute risk differences of graft failure and mortality within time periods after transplantation (0-3 months, 3-12 months etc.) showed that absolute risks were higher in the first months after transplantation. In all time periods, absolute risks were higher in the ECD kidney recipient group. The fourth sensitivity analysis, using competing risk analysis for graft failure and death as competing risks, showed similar patterns in the subhazard ratio of ECD kidney for graft failure as the Cox models for death-censored graft failure (data not shown). The fifth sensitivity analysis did not show differences among strata of previous dialysis duration. The sixth sensitivity analysis excluding type 1 diabetic patients showed that absolute risk differences between ECD kidney and non-ECD kidney were similar as in the analysis with all diabetics; the relative risk was slightly lower, but did not change the conclusion that the risk of graft failure and death is higher in diabetic patients than in nondiabetics. The seventh sensitivity analysis is described above (description of Table 4). Finally, both in the complete cases analyses and the imputed data sets, recipient smoking and recipient BMI did not appear to be important confounders of the association between ECD kidney and outcomes and effect estimates did not change substantially (data not shown).
DISCUSSION

This study shows that deceased donor kidney transplantation fulfilling ECD criteria is associated with a higher risk of graft failure and (long-term) death of the recipient (even after transplant failure and a subsequent period of dialysis treatment) in the Netherlands. In particular, recipients with diabetes and recipients in the youngest and middle age groups have higher absolute and relative risks.

In the whole cohort, transplantation with ECD kidney grafts results in higher relative and absolute risks of graft failure including recipient death. After adjusting for confounders, the relative risk for graft failure and death tended to be higher in the youngest and middle age groups when compared to the highest age group (model 2, HR 1.92 and 1.71 versus 1.32, P=0.03 and P=0.12 respectively). Absolute risk differences showed a similar pattern. These results suggest that the adverse outcome of ECD kidneys is at least more pronounced in the youngest age group and possibly in the middle age group than in the oldest group. This is in line with previous studies on the donor and recipient age match[24]. The oldest group has the lowest risk associated with ECD kidney transplantation. These effects are even more striking in the recipients receiving an ECD – DCD kidney. Probably, the oldest group has the highest risk for death and ECD kidney transplantation does not add substantially to this risk.

In the diabetic group, both relative and absolute risks were higher than in the nondiabetic group. The differences in HR and RD were generally statistically significant after correction for confounders in a multivariable model. It indicates that ECD kidneys perform worse in diabetic recipients. Nevertheless, the findings of this study on diabetics should be interpreted carefully, as in our analysis, only 50 diabetic patients received an ECD kidney, and the number of diabetic patients was too low to evaluate interaction between ECD kidney and DCD kidney interaction in this subgroup (12 recipients). In case our results are not a chance finding, this means that the diabetic environment aggravates adverse consequences of ECD kidney transplantation. The mechanisms by which ECD kidney transplantations give rise to worse outcomes cannot be derived from this study. We hypothesize that ECD kidneys will have worse kidney function, even after an uncomplicated transplantation procedure, and that this impaired kidney function determines outcomes of graft and patient survival. In the diabetic patients, it seems plausible that the diabetic environment impairs recovery of tubular and other renal cells from the ischaemia during the transplant procedure, thereby inducing a higher risk of rejection and impaired renal function, which, in turn, induces premature death.

The results of the present study are in line with the general conclusion of a systematic review[12], a recent report on organ quality and recipient age in the United States[25], and an analysis of ECD kidney transplantation in retransplanted patients[26]. However, in the systematic review, the results of the studies analysed were not pooled. Therefore, we cannot compare the sizes of the HRs and RDs of the present study with a pooled counterpart of previous studies. Based on our results, subgroups receiving an ECD kidney that have the lowest relative risk for graft failure and death in comparison with non-ECD kidney recipients, are patients ≥ 60 years and patients without diabetes. Pascual et al. suggested that certain patients with long expected waiting times could be preferential subgroups for receiving an ECD kidney[12]. The hypothesis of Pascual might be supported by a Dutch study on the 5-year results of DCD transplantation that showed that transplantation with DCD grafts appeared to be better than waiting for a DBD kidney while remaining on dialysis[27]. Therefore, we think it is a good idea to select patient groups that would profit most from ECD transplantation with shortened waiting times, compared to the alternative, which is continuing dialysis and waiting for a higher quality kidney graft.

It has been postulated that other classifications than the ECD/non-ECD classification might be more discriminative for organ and recipient prognosis. The present study suggests that a classification using four ECD and DCD/DBD combinations is already better than ECD alone (Table 4). In the USA, the Kidney Donor Risk Index (KDRI) was developed[28] and implemented in 2014 in the UNOS kidney allocation system. In its five categories, almost all ECD donors are within one KDRI category. This means that KDRI’s discriminative capacity may be better in non-ECD kidneys, but not in ECD ones[28]. In practice, KDRI does not predict results of kidney transplantation correctly in all subgroups[29]. In our additional analyses (data not shown), donor age appeared to be the most important factor associated with death and graft failure. Therefore, we agree that ECD kidney is probably not the optimal marker for poor donor quality. Further studies and refinements of classification systems, such as KDRI, are necessary to optimise risk classification before using those systems more extensively in allocation strategies.

Within the ET region, median donor age and, thereby the number of ECD kidney grafts, is steadily increasing in the ET region from 43 years in 1995 to 53 years in 2013[30]. Based on our results, it could be advocated to allocate ECD kidneys, and especially ECD-DCD kidneys, preferentially to recipients of ≥ 60 years and to avoid ECD kidneys in diabetic recipients. The Eurotransplant Senior Program for kidneys from donors of 65 years and older is already an example of matching the age of donor and recipient. This concept of age matching could be extended to younger donors. Avoiding ECD kidneys in diabetic recipients will induce a longer waiting time
for diabetic patients, which might be more harmful than receiving an ECD kidney transplant. Furthermore, this strategy will result in more ECD kidney allocations in the group of nondiabetics, which also raises ethical questions. Another interesting strategy raising ethical questions in a situation of organ scarcity, is allocating a pair of ECD kidneys in younger recipients. In middle aged and older recipients, results of this type of transplantation have proven to be successful[31-33].

From a patient perspective, it is desirable to receive the optimal renal replacement therapy in a certain situation. Possibly, refusing a kidney transplant of poor quality, continuing dialysis and waiting for another kidney transplant might be the optimal solution in some situations. However, in order to evaluate several scenarios at the moment of a kidney transplant offer, complex mathematical simulation models taking into account consequences of a poor kidney transplant, a longer episode on maintenance dialysis and the chance of getting a better transplant offer must be available. At this moment, those models have not been constructed. Two prediction models, the Deceased Donor Score and The Kidney Donor Risk Index predict survival of kidney transplants using donor characteristics[28,34-36]. These models only predict patient and graft outcomes after transplantation but do not take into account recipient characteristics, waiting time on dialysis nor chances of getting a better transplant offer. Therefore, future research should focus on prediction models combining donor, recipient and procedure characteristics. The associations found in our study suggest that recipient characteristics should be evaluated as potential predictors in future prediction models and mathematical simulation models.

Limitations and strengths of this study
The present study has some limitations and strengths. The first limitation is that, although allocation of kidney transplants by ET is executed according to several objective rules, the acceptance of the donor kidney by nephrologists is subjective. The possibility that some nephrologists induce confounding by indication by refusing ECD kidneys if allocated to recipients in a good clinical condition must be considered. As a consequence, adding an estimate of the physical condition of the recipient as a confounder to our analyses could be a reasonable solution, but is impossible since the NOTR database does not contain those data. Other estimates of physical condition such as data on comorbid conditions have a lot of, potentially non-random, missing values in the NOTR registry and, therefore, will not, even after data multiple imputation, alleviate this problem. On the other hand, recipient age is expected to be a strong predictor of physical condition and this variable was taken into account. Second, the number of diabetic patients receiving an ECD kidney is low (50). Especially, results of subgroups in this category (e.g. ECD-DCD subgroup) must be interpreted cautiously. Third, because of many missing values, two potential confounders could not be used in the main analyses: smoking behaviour and body mass index of the recipient. However, in the complete case analyses and the analyses with imputed data, these characteristics did not emerge as important confounders. Fourth, transplant year appeared to be an important confounder. It indicates that kidney transplantation in general has become more successful over time. However, in our analyses the effects of this confounder could not be fully replaced by other confounders, such as induction immunosuppressive therapy with monoclonal antibodies and other initial immunosuppressive therapy. Maybe, other characteristics not included in our analyses, such as the use of kidney preservation fluids, surgical techniques, (early) changes in the immunosuppressive regimen and their dose during follow-up, and effectiveness of anti-rejection therapies, are part of the effect of ‘transplant year’. The transplant period is also associated with changes in kidney allocation. Before 1996 there was only obligatory exchange of full-house HLA matches. After 11 March 1996, allocation of all recipients was regulated with computerized allocation lists (Eurotransplant Kidney Allocation System, ETKAS). In January 1999 the Eurotransplant Senior Program (ESP) was introduced. The ESP allocates kidney from postmortem donors of 65 years and older to recipients of 65 years and older, without the use of a donor HLA typing. The ESP aims at a cold ischemic period that is as short as possible. In the Netherlands, kidneys from ESP donors are allocated to ESP recipients according to the national waiting list. Kidneys from an ESP donor that cannot be allocated nationally are allocated through the regular ETKAS after reporting of the HLA typing. In the Netherlands, ESP donor kidneys are only allocated to never-immunized recipients awaiting a first kidney transplant. Since 1 February 2001, kidneys from both DCD (donation after cardiac death) and DBD (donation after brain death) donors in the Netherlands have been indiscriminately allocated through the standard renal allocation system. Although replacement of transplant year by variables such as immunosuppressive regimens and allocation strategies would gain insight in the mechanism of improvements of outcome over the years, we do not expect this to affect the estimates of ECD donation. Fifth, the effect of kidneys pairs, that is kidneys from the same donor, could not be analysed in our database. Finally, only variables known at the moment of kidney allocation were analysed as confounding variables. As a consequence, factors influencing graft survival, such as the number and type of acute rejections, and the presence of post-transplant anti-HLA donor specific antibodies, even if they were present in the database, were not included in the analyses. Including these covariates may be an interesting question for further research.

However, this study also has several strengths. The first strength is that all recipients of a kidney graft of a deceased donor in the Netherlands within a defined period were included. The inclusion period (1995-2005) affirms a long follow-up period of 8-18 years. 
Second, the main variables in the NOTR database have few missing values. Third, exchange with the Renine registry provides information on long term death, mostly not available in transplant registries. And fourth, we analysed both relative risks and absolute risk differences. Both point into the same direction.

In conclusion, ECD, and especially ECD-DCD kidney transplantation, is associated with a higher risk of graft failure and death. This effect is most striking in young and middle-aged recipients (< 60 years) and in patients with diabetes. In case of persisting scarcity of donor kidneys, further analyses should reveal whether preferential allocation of ECD kidneys to specific subgroups, such as older, nondiabetic patients, is a safe and ethically justified strategy.

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REFERENCES


18. Austin PC: Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. Journal of Clinical Epidemiology 2010, 63: 46-55.


Summary and discussion
SUMMARY AND DISCUSSION

Patients with end stage renal disease (ESRD) chronically need renal replacement therapy (RRT) to survive. As pointed out in the introduction (chapter 1) there are three renal replacement treatment options: kidney transplantation, hemodialysis, and peritoneal dialysis. Generally kidney transplantation is the preferred treatment with the best results, but unfortunately this is not feasible for all patients. However, at the start of RRT it is not clear yet which patients will eventually be waitlisted and transplanted. The first aim of this thesis is therefore to predict survival from the start of renal replacement therapy, irrespective of treatment choices, in order to support initial patient counseling. A general survival prediction is desirable for patients to understand the survival implications of ESRD, and to (re)set their survival expectations. It can further be used for shared patient-physician discussion of future treatment perspectives. Furthermore, a survival prediction model could also be used to stratify patients according to survival risks in clinical trials, which is important to support further research in this ESRD patient group. The second aim of this thesis is to predict which patients might profit from a marginal kidney donor transplant in order to support the difficult decision making process in renal patient care whether or not to accept a marginal kidney donor offer for a specific patient.

For the treating physician it would be helpful to be able to predict long-term survival chances from the start of chronic replacement therapy in order to inform the patient about his/her prognosis. In chapter 2 we present a prediction model for long-term survival of patients starting a renal replacement therapy (RRT) in the Netherlands, using a limited set of easily available registry data from the Dutch Renal replacement Registry (RENINE). The model was developed, and internally validated, on a very large retrospective Dutch patient cohort starting RRT in the period 1995-2005. The complete cohort was randomly divided in a development group and a validation group of equal size. The model was developed for the Dutch patient population aged 16 years or older, starting a chronic renal replacement therapy. With the developed prediction model, using patient age, sex, primary renal disease (PRD), and renal replacement therapy (RRT) at 90 days as variables to calculate mortality risk, it is possible to give an estimation of the 10-year survival (which was the primary interest), as well as 5- and 3-year survival chances for patients starting RRT in the Netherlands. Internal validation was performed by assessing the calibration and discrimination. The calibration showed acceptable outcomes. There were no major deviations between observed and predicted survival probabilities in the calibration plots for all 3 time intervals, and the 10-year calibration slope was 1.025. The discrimination of the model in the validation cohort, measured by the concordance (C-) index, was 0.720 for the 10-year survival prediction, which is reasonable for a prognostic study with such a long time horizon. Two sensitivity analyses have been performed, to indicate how robust the presented model actually is. In a first sensitivity analysis the influence of the inclusion of the waiting list registration status was analyzed. The model improvement using this variable was negligible. Although it is well understood that patients that are (or will be) registered on the waiting list have a better prognosis compared to patients that are never registered, the time point of this waiting list registration is very arbitrary and the situation at baseline is consequently not very differentiating. As a second sensitivity analysis the random division of the patient cohort in a development and validation cohort was changed into a regional division. This did not result in any major differences of the original model or the performance estimates, showing robustness of the original model. The objective of this study was to develop a prediction model that could be used by physicians to inform patients about their survival chances at the start of RRT. The conclusion was that the internal validation results show that the model is suitable for this objective.

In chapter 3 the possibilities to enhance the earlier presented registry model by adding clinical information are presented. Data from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) were used for this purpose. NECOSAD is a prospective study, which contains detailed clinical data on a subset of the Dutch patients starting dialysis; all incident adult patients from 1997-2007 from the NECOSAD database were included. The disadvantage is that the NECOSAD domain is slightly different from the domain for which the original model was developed. Only incident dialysis patients were included and no preemptively transplanted patients, which is a growing group in present time as has been shown in chapter 1 and 5. Since the NECOSAD cohort is different from the complete Dutch cohort, model performance of the registry model in this specific cohort was evaluated first. Further, to have a fair comparison of the original model and the new models, the ‘registry model’ was re-estimated and validated, which was the starting point for evaluation of the predictive performance of the newly developed models. The results of the re-estimated registry model were in line with the original model performance in the Dutch patient population (C-index for 10-year survival: 0.724). From the large set of candidate predictors available in the NECOSAD group, 19 variables were selected based on literature and clinical experience, and subsequently clustered in three variable groups based on data availability. First we added a set of easily available medical history and clinical predictors to the original four registry variables, which resulted in a new model, the ‘easy model’, with 10 predictors: age, PRD, history of smoking, angina pectoris, malignancies, myocardial infarction, peripheral vascular disease, and further BMI, Charlson co-morbidity score, and the Karnofsky (functional) score. The calibration and discrimination outcomes in the validation set showed some improvement in the calibration performance, especially for the 3- and 5-year survival, and a better discrim-
In prediction modeling next to model development, model validation is very important[1-4]. Internal validation, which was performed originally (chapter 2), is essential to indicate stability of the results, but does not guarantee model performance outside the source population[1-3,5]. External validation is needed to indicate generalizability of the results[1-3,5,6].

In chapter 4 the usability of the original registry model (chapter 2) outside the country of development (the Netherlands) is analyzed by external validation in a cohort of nine European countries providing individual patient data to the ERA-EDTA Registry for the same time period as the original model development. This was a suitable external validation cohort, as there are many differences between European countries in ESRD patient characteristics and treatments, as well as in mortality rates on dialysis. Where these differences are undesirable in etiologic studies comparing different therapies, these differences are an advantage in model validation; adequate model performance in an entirely different population is proof of the generalizability of a model. What has been shown is a remarkable similarity in discrimination and calibration outcomes for the complete ERA-EDTA cohort. The performance outcomes for the complete ERA-EDTA cohort were a C-index of 0.71 and a calibration slope of 0.995. For the individual countries the performance was also very acceptable: the C-index varied between 0.70 and 0.75 and calibration slopes ranged from 0.922 till 1.088. These outcomes indicate robustness of the validated registry model. This result implies that the straightforward prediction model for long term patient survival in RRT, the registry model, is also usable for the comparison of risk groups in different studies, countries or periods of time, as well as for risk stratification or selection purposes, in a wide range of European countries.

One of the predictors for the Registry model presented in chapter 2 is the therapy at 90 days, which actually is the intended treatment. Model performance could be hampered when RRT practice changes in time, leading to either different treatment choices for certain patients (and thus different outcomes), or different therapy outcomes due to therapy changes (e.g. medication improvements). In chapter 5 is shown that despite the fact that peritoneal dialysis (PD) is a good alternative for hemodialysis (HD), and sometimes even indicated as preferential, for most patient groups in the first period of RRT[7-14], the relative use of PD has declined in the Netherlands from 15% in 1995 to 8% in 2010. The reasons for the decline in the relative contribution of PD in the past decade in the Netherlands were studied, and we considered whether this could be related to the increasing HD capacity due to the abolition of the planning system for dialysis centres in 2002. This decrease was seen in both large and small centres and was related to a relative increase in the numbers undergoing HD and preemptive kidney transplantation (transplantation before dialysis), as well as to decrease in change of therapy from HD to PD. The increased number of patients starting on HD was associated with the growth of the incident patient group aged 65 years or older, most of whom (80-85%) underwent HD. Within the younger group (0-65 years) there were increasing numbers of patients on HD and preemptively transplanted patients. We concluded from our study that part of the explanation was the fact that in recent years the younger patients, otherwise eligible for PD, have been transplanted preemptively, which is a positive development. Another part of the explanation is that the dialysis population is ageing, resulting in a lower eligibility for PD. However, these developments do not explain all growth of HD. This could also be associated with the increased HD capacity, but is it not clear yet whether this is either a limitation of patient choice (if PD is not being considered as optional alternative) or an extension of freedom of choice (if the larger share of PD in the past was a consequence of limited choice due to a shortage in HD facilities).

As stated in the introduction (chapter 1), due to the shortage of deceased kidney donor grafts, donor criteria have been stretched and marginal donor kidneys (e.g. extended criteria donor (ECD) kidneys[15]) have been accepted for transplantation by many transplant centres all over the world[16]. Although there are also studies that show no difference in outcome of ECD and standard criteria donor (SCD) transplants, generally ECD kidney grafts are thought to have a poorer prognosis than SCD grafts, which is supported by a systematic review and meta-analysis, especially for patients with diabetes or younger than 40 years of age[16,17].
In the Eurotransplant kidney exchange program, facilitating cross-border exchange from both ECD and non-ECD donors in eight European countries including the Netherlands, graft and patient survival according to ECD status had not yet been investigated. Since kidney transplant procedures differ across the world it is essential to analyze the outcomes in different regions. In Chapter 6 the differences in survival of ECD and SCD kidney transplantation in recipients of 18 years of age or older in the period 1995-2005 in the Netherlands are presented. To that end the differences in deceased ECD kidney transplantation and SCD transplantation were analyzed in general, and stratified by recipient age and diabetes. The study was performed on data from the Dutch Organ Transplant Registry (NOTR). The primary endpoints were time until graft failure and time until death. Donor kidneys were retrospectively classified as ECD-kidneys based on the registered donor characteristics. The relative risks of ECD kidney transplantation were analyzed using Cox proportional hazards models both univariate (crude models) and multivariate (models adjusted for confounders) and adjusted absolute risk differences were calculated. Several sensitivity analyses have been performed to show robustness of the results. The presented outcomes confirm the primary thought that in general ECD kidney grafts have a poorer prognosis than SCD grafts. The adjusted differences in graft failure and death (both absolute and relative) were higher for younger recipients and diabetic recipients, which is in line with findings from the literature. Overall, the highest risk of graft failure and death is observed in the group with extended Donation after Circulatory Death (DCD) kidneys, but further refinements of the donor quality classification might be more discriminative for organ and recipient prognosis and therefore more useful in allocation strategies. The study findings raise the question whether ECD kidneys should preferentially be allocated to specific subgroups, such as the elderly and non-diabetic patients, but the question is whether this is safe and ethically desirable.

Having summarized all previous chapters from this thesis, in the following paragraphs we will discuss our main findings, categorized by the aims of this thesis, as well as the future research perspectives.

**SURVIVAL PREDICTION MODELS FOR LONG-TERM ESRD PATIENT SURVIVAL FROM THE START OF RENAL REPLACEMENT THERAPY**

**Comparison of models**

Chapter 2 and 3 present the results of the development and validation of prediction models for long term RRT patient survival: a ‘registry model’ based on only readily available predictors (chapter 2) and two alternative models which include clinical variables: the ‘easy model’ and the ‘elaborate model’ (chapter 3). These models are all aimed at providing individualized survival prediction for patients at the start of renal replacement therapy. For the Netherlands the average population-based 10-year survival is approximately 34%. With the use of our models a more individualized prognosis is possible; the 10 deciles of predicted survival according to our registry model (chapter 2) show a wide variation of survival prediction from 2% in the highest risk decile till 86% in the lowest risk decile. Sharing this information will fulfill the need of patients to be more accurately informed about life expectancy, irrespective of future therapy choices, and thus can facilitate initial patient counseling. For stratification, selection, and group comparison purposes the registry model with only 4 predictors suffices for a wide range of European countries (chapter 4). For information on individual survival probabilities the easy model, based on more clinical variables (chapter 3), is recommended.

Already existing prediction models were focused on either dialysis, waiting list, or transplant survival. Table 1, comparing some of these models with regard to patient domain, baseline and outcome, shows why these models are not applicable to inform all patients starting RRT about their survival prospects.

**Table 1: comparison of some pre-existing prediction models with our ‘registry’ and ‘easy’ model**

<table>
<thead>
<tr>
<th>(Prediction) Model</th>
<th>Domain</th>
<th>Start</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasische et al.: A simple tool to predict outcomes after kidney transplant [22]</td>
<td>Adult patients undergoing deceased kidney transplants (US 2000-2006)</td>
<td>Transplantation (and 7 days and 1-year post-transplant)</td>
<td>5-year graft loss (including death with functioning graft)</td>
</tr>
<tr>
<td>’registry’ prediction model as presented in this thesis</td>
<td>Incident RRT patients &gt;16 years still at RRT after 3 months (Netherlands, 1995-2005)</td>
<td>RRT initiation</td>
<td>10- (and 5- and 3-) year mortality</td>
</tr>
<tr>
<td>’easy’ prediction model as presented in this thesis</td>
<td>Incident dialysis patients &gt; 16 years, still at RRT after 3 months (Netherlands 1997-2007)</td>
<td>Dialysis initiation</td>
<td>10- (and 5- and 3-) year mortality</td>
</tr>
</tbody>
</table>
Wagner et al.[19] predict 3-year mortality in incident dialysis patients in the UK, which actually reflects dialysis survival only, since transplant survival is not taken into account. The dialysis survival is a combination of patient survival for the incident dialysis patients that didn’t undergo transplantation, combined with (100%) dialysis survival until transplantation for the patients that eventually were transplanted; dialysis survival is probably underestimated due to the fact that the ‘best’ patients are being transplanted and their survival is only included until transplantation. Since we are interested in the complete patient survival irrespective of treatment, the model is not suitable for our aim.

In van Walraven’s prediction model[20] 5-year ESRD patient survival is limited to patients eligible for renal transplantation. The motivation to limit the prediction of (integrated) RRT-survival to the waitlisted patients only (an alternative for using propensity scores[23]), is to enable a fair comparison between dialysis and transplant survival by excluding patients that are not transplantable at all. This has also been advocated in other papers in which dialysis and transplant treatments are compared[24,25]. Although this is a sensible restriction for the comparison of dialysis and transplant survival, this makes the model non-applicable to our patient domain. Our domain consists of the complete group of ESRD patients starting RRT, which includes a large group of patients with a non-transplantable status (older and/or frail patients). Another disadvantage for our purpose is that the starting point for the survival prediction in van Walraven’s model is not the start of RRT but the time of registration at the waiting list. This is a different point of time for every patient in the Netherlands where the time on dialysis is used for kidney allocation instead of registration time. Due to these reasons the model from van Walraven is not applicable in the initial counseling of the complete group of RRT patients.

There are many papers focused on predicting patient (or graft) survival after transplantation. One example is the paper by Jassal et al.[21] which presents a visualization of 1-, 3-, and 5-year patient survival probabilities in the form of a table, differentiated by PRD, Charlson comorbidity score and age group. This model cannot be used in initial patient counseling since at the time of start with RRT it is not known yet which patients will eventually be transplanted, except for the preemptively transplanted patients.

The model of Kasiske et al.[22] predicts 5-year graft survival and is the basis for the development of a practical calculator for the risk prediction of graft loss, death censored graft failure and mortality after deceased donor kidney transplantation. Predictions are made from transplantation and at 1 week and 1-year post-transplantation. Therefore this model is primarily helpful for pre- and post-transplant decision making and not to inform patients about their survival probabilities at the start of RRT.

Added value of survival prediction models presented in this thesis

To our knowledge our prediction models are the first models aimed at predicting long term survival chances for the complete group of RRT patients during the initial phase of their therapy, taking into account survival after dialysis combined with survival after a possible transplantation. The models presented in this thesis therefore fill a gap and, unlike the other mentioned models, these are especially useful in the initial counseling of ESRD patients to give a more individualized prediction of long term survival chances. External validation outcomes have also indicated that the use of the registry model is not restricted to the Netherlands, but has comparable performance in a wide range of other European countries.

The performance of the presented models was evaluated by calibration and discrimination measures[1,3-5,26]. Calibration indicates the reliability of the model and measures the agreement between observed and predicted outcome, and was assessed by the calibration in the large (observed versus predicted survival percent- ages), calibration plots for 10 deciles of predicted survival versus observed survival (ideally a 45-degree line), and the calibration slope which is the regression coefficient with the prognostic (risk) index as the only predictor (ideally equal to 1). Discrimination was assessed by a concordance (or C-) index, Harrell’s C-statistic, which can be calculated for Cox regression models and reflects the probability that for a random pair of patients, the one who has the outcome event first has the highest predicted probability of the outcome[27,28]. A value of 0.5 indicates no discrimination and a value of 1.0 indicates perfect discrimination. Independent criteria for the evaluation of adequate (reasonable or good) discrimination are lacking, although there is some consensus that 0.7 is reasonable and 0.8 is good. In line with this, we interpret a C-index of 0.68-0.75 as fair, but modest, discriminatory power. It seems rather low compared to the high C-indices obtained in many diagnostic studies. However because there is not a very close temporal relationship between predictors and outcome in our prognostic setting, one would not expect very high C-indices[28].

For all models we concluded that performance was sufficient, but limited. Therefore, it could be argued that these models might not perform much better than ‘physician’s gut feeling’. A paper showing the effective use of the ‘surprise question’ (‘Would I be surprised if this patient died in the next year?’)[29] in dialysis patients[30,31], confirms the importance of physician judgement. The additional value of our models is to aid especially the young and inexperienced physicians with objective survival predictions, but even for experienced physicians an objective survival probability estimate might be useful. Generally prediction models can be used for both patient counseling and research purposes[5,26,28,32]. Using these models would provide uniform risk predictions, which can be useful for an objective comparison of risk assessments between studies or countries.
Potential to use the registry prediction model for group comparison, selection and stratification purposes in trials

For group comparisons, restriction and stratification we would recommend the use of the registry model. Patient risk categorization according to this easy to use registry model with only 4 variables is adequate, as has been indicated with the sufficient calibration and discrimination outcomes (chapter 2). Furthermore this model has the advantage of proven applicability (by external validation) for a wide range of European countries (chapter 4). When the model is used on group level consequences of potential misclassification are limited.

Potential to use the easy prediction model for initial patient counseling

At the individual level the use of the easy model (including clinical variables) is recommended, despite the fact that preemptively transplanted patients were not included in model development. We based this conclusion on slightly improved outcomes on calibration and discrimination as compared to the registry model, combined with the two relatively new measures to compare model performance: the Net Reclassification Improvement Index (NRI) and the Integrated Discrimination Improvement Index (IDI)[5,26,33-36]. In chapter 3 we have shown that, compared to the registry model, the easy and elaborate model both correctly reclassify many patients to a higher or lower risk group, which indicates a better survival prediction on individual level. The elaborate model requires more information but is performing only slightly better than the easy model. Therefore we recommend the use of the easy model for this aim.

Potential to use the easy prediction model for the decision to start or refrain from RRT

As has been explained in the introductory section, a recent trend in renal patient care and shared patient-physician decision making is careful consideration of conservative treatment for the frail elderly ESRD patient as an alternative for RRT[18,30,37-39]. A Canadian study on end-of life care preferences and needs has shown that more than 90% of the adult stage 4 and 5 CKD patients presenting at a (pre-)dialysis facility considered it important to be informed on prognosis and 61% of the dialysis patients regretted their decision to start dialysis[18]. Unfortunately dialysis does not always seem to prolong life[40], and only 13% of the elderly patients maintains functional ability after one year of dialysis[41]. Although our prediction models on RRT survival are primarily aimed at predicting long term survival, these models might still be helpful to select patient groups that, according to current care practices, only have a very limited RRT survival prognosis. For these patients conservative treatment might prove an attractive alternative[30,39], due to the fact that hospitalization is avoided and provided that a certain quality of life could be maintained. A timely decision is desired; a review of studies on conservative management of ESRD without dialysis pointed out that unlike withdrawal of dialysis in which imminent death is expected, patients who decline dialysis initiation can live for months to years with appropriate supportive care[42]. Insight in survival probabilities might facilitate the discussion on this with patients and their families/caretakers. Therefore the prediction model should be used in the pre-dialysis facility (only for the intended domain of patients eligible for RRT), since timing is very important and the creation of vascular access should be done after treatment options are carefully considered[43]. In this stage it is not possible to use the elaborate model, which is based on laboratory values at three months after the start of RRT, which might be different in pre-dialysis care. The easy model, however, uses mainly variables at the start of RRT, except for BMI and Karnofsky score, and therefore this model is recommended for the aim of patient counseling in the pre-dialysis phase.

Our registry model is not suitable to be used for choosing a specific RRT modality

Our registry model should not be interpreted as proof for better outcomes of early transplantation instead of dialysis, or PD instead of HD. Our study just shows the possibility to include the therapy at 90 days (the intended treatment) as a predictor for long-term survival. Therapy at 90 days (instead of the start) was chosen as the baseline to ensure enough time to switch from a temporary needed therapy to the intended treatment, and to exclude acute patients who only have to undergo RRT for a short period of time. Predictors are variables that show a correlation with the outcome. Prediction models however are not etiologic (like intervention studies), but descriptive[44]. They do not prove causality, but they give a prognosis based on a set of patient and/or treatment characteristics. Patients were not randomly assigned to the treatment modalities, but were given a certain treatment based on their clinical condition. Waitlisted patients are often considered to be in a better condition and their survival on dialysis would presumably also be better than the survival of patients that have to stay on dialysis because they are not in a transplantable condition[24,25]. This is even more so the case for transplanted patients, which group is probably even in a better medical condition, with less co-morbidities, than the complete group of waitlisted patients[45]. Although physicians might be tempted to use the registry model to ground a treatment decision at start of RRT, the treatment modalities in the model are only a proxy for medical condition. The same holds for subsequent treatment choices. The registry model provides long term survival probabilities from the start of RRT irrespective of the treatment continuation, and assumes that future treatment choices are related to patient characteristics that are included in the model. When individual choices differ from the usual
Choosing beneficial treatments; recent developments

As mentioned earlier, to ground any treatment decisions (either at the start of RRT or later) intervention or etiological studies aimed at comparing the different therapy outcomes on patient prognosis should be used. Despite a relatively high mortality risk in the first months after transplant surgery, in general transplantation is the preferred treatment option for ESRD patients in the long term[24,25,46]. Even the elderly ESRD patients generally profit from transplantation[47-51]. However, there are some recent developments indicating that there still is a desire to develop some support for this (shared) therapy decision process. First illustration of this is the research by Patzer et al.[52] published in 2016 that led to the development of a mobile clinical decision aid. This aid, called iChoose Kidney, compares individualized mortality risk estimates for dialysis versus transplantation. This innovation indicates the desire to have an interactive easy to use technological device to illustrate survival differences based on therapy choices. On the other hand this model does not take the quality of a deceased donor kidney into account, and it is likely to overestimate the transplant survival in the frail elderly patient[53]. All dialysis patients are selected and their dialysis survival is compared to the transplant survival of the patients who were both eligible for transplantation and ‘lucky enough’ to actually receive a donor kidney. Patients not eligible for transplantation often have an inferior clinical condition. Therefore the tool probably overquantifies the average advantage of transplantation over dialysis considering specific patient characteristics, and it doesn’t point out the patients that would profit from waiting for another kidney in case of a marginal kidney offer. Another example of the recent interest in information to facilitate the decision making process is the ‘Nierwijzer’ (www.nierwijzer.nl), which has been launched in the Netherlands in October 2016. This is a website developed by the Dutch kidney patient cooperation together with medical professionals and others, and it contains a series of video fragments to illustrate the consequences of different renal replacement therapies on several topics from the patient’s perspective. These new approaches to visualize or illustrate consequences of treatment choices could facilitate the physician-patient counseling and shared decision-making process for ESRD patients.

LIMITATIONS OF OUR SURVIVAL PREDICTION MODELS

The prediction models are based on past practices

Past and current renal care practices form the basis for the predicted survival probabilities. In our case we predict ten year survival using data from a cohort from 1995-2005. Consequently model performance can be hampered when renal care practices change. In fact renal care practices have changed in time, and might be expected to further change in the future[54]. In chapter 5, for instance, we have seen that especially the younger patients have been transplanted preemptively (with kidneys from living donors) more in recent years, where they were more likely to undergo peritoneal dialysis before. Also transplantation rates and donated kidney quality might vary in time. Including RRT starting year in the model has been considered. However, we decided not to include starting year in the model. In our opinion the prerequisite of a linear improvement in time is doubtful. For the dialysis treatment itself this might be true, due to developments of medication and machines, as well as optimization of dialysate, dialysis frequency and duration[55-58]. Also for the allocation and operation procedure of kidney transplantation as well as the transplantation follow-up treatment this probably holds[59]. On the other hand, the organ quality of transplanted deceased donor kidneys has deteriorated in time (both due to expansion of donor criteria and population changes) and also waiting times/dialysis vintage can fluctuate in time. Changes can either have a positive or negative influence on survival. Other complicating factors are the fact that treatment improvements often are not equally available to all ESRD patients, like illustrated in chapter 5, that patient mix might change (since the success of a treatment can increase its demand), and that special kidney transplant allocation program might be introduced, comparable to the introduction of the old for old, Eurotransplant Senior Program (ESP), in the past decade[60]. All these changes might improve prognosis for only certain patient groups, while prognosis will be the same, or worse, for some other groups. Therefore we would plea for temporal validation[3,6] (e.g. every 5 year) rather than including RRT start year in the model. Despite this, the similar external validation performance outcomes in 9 different European countries with varying renal care practices and patient profiles (chapter 4) are very re-assuring and indicate robustness of the model.

The models are based on past patient profiles

Furthermore, not only the condition of the donor, but also the condition of patients has changed in time, like for example starting condition[61]. Some of these changes will be corrected by the prediction model, when they are included as variables, but other changes will not. The performance of the registry model might be influenced more than the other models by changing patient profiles: the age, sex, PRD, and initial chronic RRT are included, but underlying co-morbidities and conditional factors
with impact on survival probabilities (like for example high BMI and cardio-vascular problems) are not included in the model. Temporal validation[3,6] on more recent cohorts and, if necessary, model updating[4,6,62,63] is also important, especially for the registry model, to deal with changing patient profiles in time.

The models only predict patient survival, not quality of life

Another remark concerning the applicability of the prediction models presented in this thesis in the initial consultation of ESRD patients, is the fact that these models present long-term patient survival outcomes. Another important question that patients starting RRT might have is what the expected impact of RRT is on their quality of life. However, we did not include this outcome in a prediction model. Unlike death, which is a very objective endpoint, the quality of life is a subjective outcome measure which will vary among patients. Also transplanted patients generally experience a better quality of life[64]. For patients it might be helpful to gain insight in the different treatment consequences from a patient’s perspective. Interesting to point out in this context is the earlier mentioned ‘Nierwijzer’ (www.nierwijzer.nl), which is a website developed by the Dutch kidney patient cooperation together with medical professionals and other stakeholders, and contains a series of video fragments to illustrate the different renal replacement therapies from the patient’s perspective.

PREDICTION ON WHICH PATIENTS MIGHT PROFIT FROM MARGINAL KIDNEY TRANSPLANTATION

Due to donor organ shortage the criteria for accepting kidneys for transplantation have been extended to allow the use of organs from ‘marginal donors’. Marginal, often older, donor kidney transplants are often associated with inferior graft outcomes. This leads to re-transplantation and increased risk to get immunized. From a patient’s perspective it is therefore clear that a better quality kidney offer is preferential, but waiting for a better kidney will take more (dialysis) time; not everybody can afford to wait for the next offer. Categorizing marginal kidney donors according to anticipated inferior outcome would help physicians with patient counseling and informed decision-making in case of an organ transplant offer.

What is a marginal donor kidney?

Although the criteria for ‘marginal donors’ are not well defined, there is a definition for Extended (or expanded) Criteria Donor (ECD) and Standard Criteria Donor (SCD) by the United Network for Organ Sharing (UNOS)[65]. ECD Donors are older donors or donors with significant comorbidities, whose relative risk of graft failure was higher compared with a standard donor. The definition of ECD, codified in 2002, is employed to describe kidneys from donors over the age of 60 years without comorbidities or donors over the age of 50 years with two comorbidities among hypertension, death from cerebrovascular accident, or terminal serum creatinine levels >1.5mg/dL (133 µmol/L), and is associated with more than 1.7 times the risk of graft failure compared to SCD donors[15]. The categorization of deceased donor kidneys as either SCD or ECD has the advantage of simplicity, but does not adequately reflect the wide spectrum of donor kidney quality[66]. It is known to misclassify kidneys in both directions: some kidneys labeled as SCD have a reduced graft survival, while some ECD kidneys perform well[67,68]. This has led to the development of more refined approaches to assess the quality of deceased donor kidneys. Nyberg has described the development of a Deceased Donor Score (DDS) categorizing donors in 4 risk categories (grade A-D) using 5 predictors for donor quality[69,70], and Schold et al. have designed a model to calculate the ‘donor risk grade’ I to IV[68]. However, these scores have not been replicated in independent cohorts and neither of these two scores has been widely used in daily practice[67]. The Kidney Donor Risk Index (KDRI) developed by Rao et al.[71] is a ‘clinician-friendly’ refined evaluation of donor quality without requiring donor histology[67] and includes 14 variables, 10 donor factors and HLA B and DR mismatching, cold ischemia time, en bloc transplant, and double kidney transplant[71]. Since these last 4 variables are generally not known at the time that a donor offer is made, and candidate specific, the implemented version is a donor-only KDRI[67]. This US KDRI is based on 10 readily available donor factors and estimates the relative risk of graft survival from a particular deceased donor compared with the median donor, adjusted for recipient characteristics and year of transplant. It is not proposed as the only metric for determining donor suitability, but it should be used as an additional score next to all other factors that have implications for graft outcome. Later a simplified KDRI index (the UKKDRI) based on 5 donor variables has been developed on UK data, with similar performance (a C-index of 0.62)[72]. These KDR indices provide simple clinically useful tools that allow prediction of transplant outcome and thus could aid transplant physicians in patient counseling and the (shared) decision making process.

What is the expected survival after a marginal donor kidney transplant (compared to standard kidney transplantation and dialysis)?

Survival of marginal donor kidney transplants has been compared in several studies with the survival of non-marginal kidney transplants and of dialysis. The results differ across studies: some studies show no difference in outcomes of ECD and SCD transplants[73-76], whereas others show higher graft failure and/or mortality rates, especially in younger and diabetic patients[16,17,77,78]. Although the survival benefits seen in recipients of marginal kidney transplants, at least in some patient groups, seem to be inferior compared with those in recipients of SCD kidneys, their
long-term survival is significantly better than in those remaining on hemodialysis[79,80]. However, the fact that there are excess deaths in ECD recipients during the peri-operative period[78], highlights the need of a careful recipient selection before transplantation[17]. Furthermore, ECD’s also seem less suitable in case of re-transplantations[17].

However, it cannot be ruled out that the reported inferior outcomes of marginal kidney transplantation versus SCD and favorable outcomes of marginal kidney transplantation versus dialysis are confounded by indication. The findings are based on cohort studies instead of clinical trials with random treatment assignment. Transplanted patients usually differ from waitlisted patients, and it is not unlikely that physicians have made some patient selections in their acceptance of ECD kidneys, which might lead to biased comparison results. A problem is that the preferable randomized controlled trial (RCT) is unethical in transplantation versus dialysis comparisons, and this also might be the problem in the comparison of ECD and SCD transplantations.

For which patient should a marginal donor kidney be accepted for transplantation?

The implicit rationale underlying a decision to accept a marginal kidney offer despite eventual inferior graft outcome is that patient prospects for long-term survival for the patient could be enhanced by undergoing such a transplant immediately rather than pursuing dialysis while waiting for a better kidney offer[78]. In fact Schold et al.[81] found that 65 year old patients had longer life expectancy when they accepted an ECD within 2 years of ESRD onset compared with waiting for a SCD or a living donation after 4 years of dialysis. The waiting time for a marginal kidney transplant is often shorter. The advantage of an early transplant is a shorter dialysis vintage, and consequently presumably less health damage before this (first) transplant. For some patients staying on dialysis might even result in deterioration to a non-transplantable condition, or even death, which obviously should be prevented. However, this worst-case scenario will not be the case for every waitlisted patient. Dialysis survival depends on patient characteristics and medical condition; some patients can wait longer for a ‘perfect’ match, due to the fact that they deteriorate less rapidly on dialysis combined with sufficient matchability for a next offer.

Besides these health considerations there also might be (patient) preference for early transplantation because of the positive impact on the quality of life. Deciding whether or not to accept a marginal kidney donor offer asks for a complicated decision support system based on several prediction rules e.g. waiting list/dialysis survival, estimated waiting time for a standard criteria donor kidney, transplant (graft and patient) survival from a marginal compared to a standard criteria donor, and quality of life estimates.

Combining kidney donor risk scores with recipient risk scores

Combining recipient and donor risk scores might help to define which patients will profit most from a marginal kidney donor in comparison to continuing dialysis[66], or who will suffer most from a marginal kidney donor in comparison to a standard criteria donor. It might be suggested to define a minimum KDRI threshold on patient level. If this information is registered on the waiting list and used in the kidney allocation algorithm, this could even help in declining marginal kidney donor discard rates, which are relatively high[15,82]. Currently in the Netherlands only donor age above 65 years of age, donation after cardiac death (DCD) and donation after brain death (DBD) kidneys are explicitly mentioned when an offer is being made. Also, it is possible to register on the waiting list whether a recipient or center accepts DCD donors or not. But due to the arbitrary dichotomy of this characterization many physicians do not use this option and choose to weigh the separate donor characteristics for every offer they get for their patients. The additional subdivision SCD/ECD is better than age alone and may prove easy to use in the future. However, other, more refined, scores like the KDRI might be more discriminatory. A desirable decision support system would be a system that includes both donor and recipient risk scores to assist physicians in the difficult decision making process in case of a marginal donor kidney offer. One step further, and beyond the scope of this thesis, would be the use of KDRI scores in combination with recipient risk scores to improve the allocation efficiency. Suggestions of integrating this utility approach in the allocation scheme have been described by Baskin-Bey et. al[83] combining the DDS with a Recipient Risk Score (RRS). The Eurotransplant Senior Program (ESP) is a currently used example of the allocation of marginal grafts of 65+ donors to 65+ patients with lower expected survival prospects. Others[84], however, indicate risks of the utility approach.

Conclusive remarks

In conclusion, several donor risk scores have been developed (ESP, ECD versus SCD, DDS and KDRI) and some of them have been combined with recipient characteristics or risk scores in order to indicate which patients might profit from a certain marginal kidney offer. Although most study results are promising, these results might partly be biased by confounding by indication: it is likely that patients that have received marginal donor kidneys in the past differ from the patients that received a better quality donor kidney or stayed on dialysis. Randomized clinical trials are the golden standard in the comparison of treatments. In the comparison between dialysis and kidney transplantation RCT’s are unethical since transplantation is the treatment of choice for most patients, which makes it impossible to withhold eligible transplant patients an eventual transplant offer. This might also be the case, but maybe to a lesser extent, for the comparison between different quality donors.
FUTURE PERSPECTIVES

We recommend to do further (etiologic) research to provide the transplant community with a tool that can point out which patient on the waiting list profits most from a given marginal donor kidney offer. This is a very complicated procedure, as discussed earlier, but such a prediction model would be extremely helpful to support the (shared) decision-making process concerning donor kidney offers. The study we presented in chapter 6 was aimed at identifying recipients for whom the adjusted risk differences of an ECD versus a SCD transplantation is relatively low, so for whom it might be beneficial to accept any kidney offer (either SCD or ECD) as soon as possible, avoiding the risk of continuation of the dialysis treatment. Further research is needed to indicate the best marginal donor definition for the Netherlands. This might either be a division like the current subdivision in ECD versus SCD kidneys or ESP kidneys, or the use of a more refined categorization like the KDRI. Further research is needed to discriminate between those waitlisted patients that will benefit from a marginal donor kidney transplantation and those patients that can afford to wait and benefit from a better offer. The resulting prediction model combining the two should at least incorporate variables describing the clinical condition of the patient, donor and organ quality, expected patient survival on dialysis or after transplantation, graft survival, and expected waiting time for a qualitatively better kidney offer.

In general prediction models can be used for comparisons, stratification and patient selection purposes. Our registry model can be used to further support intervention research for ESRD patients in Europe, aimed at improving future survival outcomes. Lenihan et al.[85] also stated that the focus in renal transplantation has shifted towards predicting and the use of these predictions to improve long time survival. Prediction offers the opportunity to alter therapy, to select individual patients for further diagnostic testing, to motivate lifestyle modification, and to manage patient expectations.

The easy model could be used to facilitate patient counseling in clinical practice, when choices in RRT have been made and the patients prognosis is being discussed. Especially for patients in the highest risk groups such predictions can be helpful. Secondly the easy model could possibly be used in pre-dialysis care to facilitate patients in making a choice between RRT and conservative therapy. These patients should be informed about the possibilities of conservative therapy in the light of inferior RRT survival prospects. For this application we would recommend evaluating the ‘clinical’ usefulness of the model.

For all possible applications we would recommend periodic re-evaluation (temporal validation), and eventual model updating[6,62,63,86], since treatment policies and patient characteristics may change over time. External validation in other European countries showed the robustness of the registry model, despite differences in ESRD care and patients, which makes it worthwhile to update the model in the future instead of just making a new one and discarding this knowledge.
SUMMARY AND DISCUSSION

REFERENCE LIST


65. UNOS. Expanded Criteria Donor. 2013. Ref Type: Online Source


SAMENVATTING

Patiënten met eindstadium nierfalen hebben een nierfunctievervangende behandeling nodig om te overleven. Van de drie vormen, hemodialyse, peritoneale dialyse en niertransplantatie, heeft de laatste de voorkeur vanwege de beste overlevingsperspectieven en kwaliteit van leven. Helaas is dit niet voor elke patiënt mogelijk en op het moment dat de behandeling wordt gestart is nog niet helder welke patiënten uiteindelijk op de niertransplantatiewachtlijst geplaatst, en getransplanteerd, zullen worden. Een algemene overlevingsvoorspelling is gewenst voor deze patiënten om de overlevingsverwachtingen vast te stellen en om behandelsondergelijkheden beter te kunnen interpreteren. De eerste doelstelling van dit proefschrift (hoofdstuk 1) is daarom het maken en testen (valideren) van een model om de patiëntoverleven vanaf start nierfunctievervanging te voorspellen. Een dergelijk model kan ook ingezet worden om patiënten te selecteren of onder te verdelen naar overlevingsrisico, bijvoorbeeld bij klinisch onderzoek. Daarnaast is de tweede doelstelling van dit proefschrift om te bepalen welke patiënten het meest gevaarlijk zijn bij transplantatie met een nier van een marginale (oudere en/of conditioneel minder optimale) donor.

In hoofdstuk 2 wordt de ontwikkeling en validatie van een eerste predictiemodel ten aanzien van de 10-jaaroverleven van patiënten die starten met nierfunctievervanging in Nederland beschreven. Bij de ontwikkeling van dit model is gebruik gemaakt van een zeer beperkte set van makkelijke verkrijgbare data van de Registratie Nierfunctievervanging Nederland (RENINE). Het model, welke in de tekst wordt aangeduid als het registry model, is ontwikkeld en intern gevalideerd op een groot retrospectief cohort van Nederlandse patiënten van 16 jaar of ouder die zijn gestart met nierfunctievervanging in Nederland in de periode 1995-2005. Het registry model voorspelt het overlijdensrisico in de eerste tien jaar op basis van leeftijd, geslacht, primaire nierziekte en de therapietijd van 90 dagen na de start. De voorspelkwaliteit van het gepresenteerde model is geëvalueerd met behulp van calibratie- en discriminatiematen [1-5]. De calibratie geeft een inschatting van de betrouwbaarheid van het model en is een maat voor de overeenstemming tussen de geobserveerde en de voorspelde overleving. De discriminatie, ofwel het onderscheidend vermogen, wordt gemeten aan de hand van de ‘concordance’ (of C-index); dit is een weergave van hoe vaak het model juist voorspelt welke van twee patiënten het langst overleeft[6,7]. Aan de hand van deze uitkomsten is geconcludeerd dat het registry model voldoet, maar gezien het bescheiden onderscheidend vermogen van het model werd verder onderzoek naar verbeteringsmogelijkheden aanbevolen.

Hoofdstuk 3 beschrijft hoe het predictiemodel verder verbeterd kan worden door toevoeging van klinische informatie. Voor dit doel is gebruik gemaakt van data van de Nederlandse Cooperatieve Studie naar de Adequaatheid van Dialyse (NECOSAD). Dit is een prospectieve studie waarin gedetailleerde klinische informatie is opgenomen van een subset van de Nederlandse patiënten die zijn gestart met dialyse. Dat betekent wel dat pre-emptieve transplantatiepatiënten (patiënten die zijn transplanteerd zonder voorafgaande dialyse) niet zijn geïncludeerd, terwijl dit toch een groeiende patiëntengroep is in Nederland. Ondanks dit verschil tussen het NECOSAD-cohort en de complete Nederlandse patiëntengroep bleek het registry model ook in deze populatie inzetbaar. Op basis van literatuur en klinische ervaring zijn 19 kandidaat-variabelen geselecteerd uit de NECOSAD-data en ondervoordeeld in drie groepen. Eerst is het registry model uitgebreid met eenvoudig verkrijgbare data over de medische voorgeschiedenis en klinische voorspellers (‘easy model’). Vervolgens werden bloeddruk en een aantal extra laboratoriumwaarden toegevoegd (‘elaborate model’). Het onderscheidend vermogen van het easy model was iets beter dan het (opnieuw geschatte) registry model. De extra voorspellende waarde van het elaborate model ten opzichte van het easy model was zeer beperkt. Het extended model gaf geen verdere verbetering van de voorspelling. We concludeerden dat het originele registry model vooral geschikt is voor groepsvergelijkingen, risicodifferentiatie en patiëntselecties en dat het easy model met meer klinische variabelen de voorkeur heeft voor individuele patiëntvoorspellingen.

Bij voorspelmodellen is validatie in een geheel andere populatie (externe validatie) van groot belang om de generaliseerbaarheid te testen[1,2,4,8,9]. In hoofdstuk 4 is het originele registry model extern gevalideerd in een cohort van negen Europese landen met data van de ERA-EDTA Registratie. Aangezien er veel verschillen bestaan tussen de Europese landen met betrekking tot patiëntkarakteristieken, behandeling en behandeluikomsten van patiënten is dit ERA-EDTA cohort heel geschikt voor externe validatie. De resultaten van het model in de andere Europese landen zijn vergeleken met die in Nederland. Dit impliceert dat het registry model ook bruikbaar is, voor de eerder genoemde doelen, in een groot aantal Europese landen.

Hoofdstuk 5 beschrijft dat ondanks het feit dat peritoneale dialyse een goed alternatief is voor hemodialyse[10-17], het relatieve aandeel van peritoneale dialyse in Nederland is afgenomen van 15% in 1995 tot 8% in 2010. De redenen hiervoor worden in dit hoofdstuk onderzocht. Een deel van de verklaring is dat jongere patiënten, die anders in aanmerking zouden komen voor peritoneale dialyse, in recentere jaren vaker pre-emptief (zonder voorafgaande dialyse) getransplanteerd worden, hetgeen een positieve
ontwikkeling is. Een ander deel van de verklaring is dat er sprake is van vergrijzing van de dialysepopulatie, resulterend in minder geschiktheid voor peritoneale dialyse. Deze ontwikkelingen verklaren echter niet de totale groei van hemodialyse. Een ander deel van de verklaring is dat er sprake is van vergrijzing van de dialysepopulatie, resulterend in minder geschiktheid voor peritoneale dialyse. Deze ontwikkelingen verklaren echter niet de totale groei van hemodialyse. Dit zou ook geassocieerd kunnen zijn met de toegenomen hemodialysecapaciteit sinds 2002, maar het is niet helder of dit heeft geleid tot een beperking van de keuzemogelijkheid voor de patiënt (als peritoneale dialyse minder vaak als optie wordt aangeboden), of juist een toegenomen keuzemogelijkheid (als het grotere aandeel peritoneale dialyse in het verleden een consequentie was van de destijds beperkte hemodialysecapaciteit).

Het tekort aan postmortale orgaandonoren heeft geleid tot het verraad van de donorcriteria met als gevolg dat marginale donornieren wereldwijd door veel transplantatiecentra worden geaccepteerd voor transplantatie[18,19]. In hoofdstuk 6 zijn de resultaten gepresenteerd van niertransplantaties met een specifiek type marginale donor (de zogenaamde ‘extended criteria donor’) in vergelijking met standaard criteria donoren in Nederland. Uit de Nederlandse Ogaantransplantatie Registratie (NOTR) is informatie verkregen over alle niertransplantaties uit de periode 1995-2005 bij volwassen ontvanger en donor. De transplantaties met ‘extended criteria donor’ nieren leidden over het algemeen tot slechtere prognoses dan de reguliere niertransplantaties. De gevonden verschillen in nierfalen en overlijdensrisico waren groter voor de jongere en de diabetische patiënten, overeenkomstig bevindingen uit de internationale literatuur. Het grootste risico werd gevonden in de groep met ‘extended’ nieren van donoren na circulatoire dood. De studiebevindingen roepen de vraag op of ‘extended criteria donor’ nieren bij voorkeur toegewezen zouden moeten worden aan bepaalde patiënten, zoals de oudere en niet-diabetische patiënten, maar het is de vraag of dit ethisch wenselijk is.

Na deze samenvatting van alle voorgaande hoofdstukken in dit proefschrift, worden in de volgende paragrafen de belangrijkste bevindingen bediscussieerd en gerangschikt naar de doelstellingen van dit proefschrift, en worden de toekomstige onderzoeksmogelijkheden gepresenteerd.

**DISCUSSIE**

**Toegevoegde waarde van de overlevingsoorlogsspelingsmodellen gepresenteerd in dit proefschrift**

Voor zover bekend zijn de predictiemodellen in dit proefschrift de eerste modellen bedoeld om de lange-termijn patiëntoverleving te voorspellen voor de hele groep van patiënten met nierfunctievervanging in hun initiële behandelfase, rekening houdend met zowel hun dialyseoeverij overleving als hun mogelijke overleving na niertransplantatie. Eerder ontwikkelde predictiemodellen zijn vooral gefocust op alleen dialyse- of wachtlijstoverleving, of overleving na transplantatie[20-23]. De modellen in dit proefschrift zijn juist gericht op patiëntoverlevingsoorlogsspelings bij aanvang nierfunctievervanging, als nog niet duidelijk is welke therapieën patiënten in de toekomst zullen krijgen.

**Potentieel voor gebruik van de modellen (algemeen of individueel)**

Over het algemeen zijn predictiemodellen geschikt voor patiëntvoorlichting en voor onderzoeksdoeleinden[4,5,7,24]. Ten behoeve van onderzoeksdoeleinden en groepsvergelijkingen bevelen we het gebruik van het registry model aan. De risicodifferentiatie van patiënten volgens dit eenvoudig toepasbare registry model met slechts vier variabelen is voldoende, zoals is aangegeven met behulp van de calibratie- en discriminatie-uitkomsten, zowel in Nederland (hoofdstuk 2), als in een groot aantal Europese landen (hoofdstuk 4). Vergeleken met het registry model, kunnen met het easy en het elaborate model, welke beiden veel klinische gegevens gebruiken, veel patiënten terecht naar hogere of lagere risicogroepen gereclassificeerd worden, hetgeen wijst op een betere voorspelling op individueel niveau. Het elaborate model vereist meer informatie dan het easy model, maar geeft slechts een marginale prestatieverbetering. Op individueel niveau wordt daarom het gebruik van het easy model geadviseerd.

**Potentieel van het gebruik van het easy model voor de beslissing om al dan niet te starten met nierfunctievervangingen behandelingen**

Een recente trend in de nierzorg is dat in geval van zwakkere en/of oudere patiënten, conservatieve behandeling zorgvuldig wordt overwogen als behandelaalternatief[25-29]. Een Canadese studie over de behandelvoorkeuren en -behoefte in de laatste levensfase heeft aangetoond dat meer dan 90% van de volwassen patiënten met ernstig nierfalen het belangrijk vond om over hun prognose geïnformeerd te worden en 61% had achteraf spijt van de beslissing om te starten met dialyse[25]. Onze predictiemodellen zijn vooral gericht op het voorspellen van de overleving op lange termijn na start nierfunctievervanging, en zijn dus mogelijk ook bruikbaar ten behoeve van de selectie van patiëntgroepen die, met de actuele behandelmogelijkheden, slechts een beperkte overlevingsprognose hebben. Voor deze patiënten kan conservatieve therapie een aantrekkelijk alternatief zijn[26,29]. Het easy model heeft voor deze toepassing de voorkeur.
Ons registry model is niet geschikt voor de keuze van een specifieke therapievorm

Ons registry model kan niet gebruikt worden als bewijs voor betere uitkomst van vroege transplantatie ten opzichte van dialyse of peritoneale dialyse in plaats van hemodialyse. Patiënten zijn niet willekeurig verdeeld over de verschillende behandelingen, maar hebben naar aanleiding van hun klinische conditie een bepaalde behandeling ondergaan. Op de wachtlijst geregistreerde patiënten worden vaak gezonder gezien dan de patiënten die aan de dialyse moeten blijven en en de ontransplanteerde patiënten hebben waarschijnlijk een nog betere conditie. Met andere woorden, de behandelmogelijkheden in het model kunnen worden beschouwd als een indicatie van medische conditie. De therapiekeuzes zelf moeten vooral gebaseerd worden op bevindingen uit interventiestudies en niet op predictiestudies.

Het kiezen van de meest gunstige behandeling voor een patiënt; recente ontwikkelingen

Een paar recente ontwikkelingen laten zien dat er wel behoefte is aan een hulpmiddel ter onderbouwing van de keuze tussen transplantatie en dialyse. Zo is in 2016 een publicatie verschenen over een besluitvormingsondersteunende app, genaamd ‘iChoose Kidney’, welke de geïndividualiseerde overlijdensrisico’s van dialyse en niertransplantatie vergelijkt. De app houdt echter geen rekening met de kwaliteit van het donororgaan en het feit dat dialysepatiënten vaak een slechtere klinische conditie hebben en niet transplantabel zijn en zal daarom mogelijk voor sommige patiëntgroepen een te positief beeld van de overlevingsvoordeel van transplantatie geven. Daarom pleiten we voor temporele validatie, gecombineerd met eventuele modelaanpassing (bijvoorbeeld elke 5 jaar). In dit verband is het echter wel bijzonder dat de resultaten van de externe validatie in negen andere Europese landen (hoofdstuk 4) zo goed waren, ondanks verschillen in behandeling en indicatiestelling. Dit impliceert de robuustheid van het huidige registry model.

De predictiemodellen zijn gebaseerd op voormalige behandelmogelijkheden en -keuzes

Eerdere en huidige behandelmogelijkheden voor, en behandelkeuzes van, de patiënten met eindstadium nierfalen vormen de basis voor de berekening van overlevingskansen. In ons geval voorspellen we de 10-jaarsoverleving gebruik makend van een patiëntencohort van 1995-2005. Modelprestaties zouden kunnen tegenmaken als de behandelmogelijkheden en -keuzes veranderen. Dit soort veranderingen komen zeker voor. In hoofdstuk 5 hebben we bijvoorbeeld gezien dat vooral jongere patiënten tegenwoordig pre-emptief getransplanteerd worden met nieren van levende donoren, terwijl ze in het verleden vaker werden behandeld met peritoneale dialyse. Ook veranderen de transplantatiekansen en de nierkwaliteit van de gedoneerde nieren met de tijd. Naast veranderingen op behandelingenniveau zullen ook op patiëntniveau veranderingen optreden, zoals bijvoorbeeld de patiëntconditie bij aanvang van de nierfunctievervangingen behandeling. Een aantal veranderingen zullen automatisch door het model gecorrigeerd worden, aangezien ze als variabelen in het model opgenomen zijn, maar voor andere veranderingen wordt niet gecorrigeerd. Daarom plaatst we voor temporele validatie, gecombineerd met eventuele modelaanpassing (bijvoorbeeld elke 5 jaar). In dit verband is het echter wel bijzonder dat de resultaten van de externe validatie in negen andere Europese landen (hoofdstuk 4) zo goed waren, ondanks verschillen in behandeling en indicatiestelling. Dit impliceert de robuustheid van het huidige registry model.

De modellen voorspellen alleen overleving, niet de kwaliteit van leven

Een andere opmerking betreffende de toepasbaarheid van de voorspelmodellen uit dit proefschrift ten behoeve van de begeleiding van de patiënt is het feit dat deze uitsluitend gericht zijn op de patiëntoverleving en niet op de kwaliteit van leven. Waar overlijden een heel objectieve uitkomstmaat is, is de kwaliteit van leven een subjectieve maat en de perceptie van de kwaliteit van leven zal van patiënt tot patiënt verschillen. Net als bij de overleving is de kwaliteit van leven over het algemeen beter na een niertransplantatie. Voor patiënten kan het echter helpen om geïnformeerd te zijn over de verschillende behandeleffecten. De eerder genoemde ‘Nierwijzer’ kan hierbij helpen doordat hierin de consequenties van de verschillende behandelingen vanuit het patiëntperspectief worden belicht.
Voorspelling welke patiënten baat zouden kunnen hebben bij een marginale niertransplantatie

Vanwege het orgaanekort zijn de donoracceptatiecriteria verruild en worden nu ook nieren van ‘marginale’ (oudere en/of kwalitatief slechtere) donoren voor transplantatie geaccepteerd. Deze worden vaak geassocieerd met slechtere uitkomsten. Een kortere transplantatieoverleven kan leiden tot de behoefte aan een re-transplantatie en een toegenomen risico om geïmmuniseerd te raken.

Wat is een marginale donornier?

Hoewel de criteria voor ‘marginale donoren’ niet heel duidelijk gedefinieerd zijn, is er een definitie voor de uitgebreide (Extended Criteria) donoren van de United Network for Organ Sharing (UNOS); deze beschrijft nieren van donoren ouder dan 60 jaar zonder comorbiditeiten of donoren van 50 jaar of ouder met twee van de volgende comorbiditeiten: hypertensie, overlijden door een CVA of terminale serumcreatinewaarden van >1,5 mg/dL, welke zijn geassocieerd met een 1,7 keer hogere kans op transplantatiefalen in vergelijking met standaard donoren[18]. De indeling in ‘extended’ en standaard donoren is weliswaar eenvoudig, maar niet per se een weergave van het brede spectrum van donorkwaliteiten[37]. Nieren kunnen aan beide kanten gemisclassificeerd worden: sommige standaard nieren hebben een verminderde transplantatieoverleven, terwijl andere ‘extended criteria donor’ nieren juist hele goede uitkomsten hebben[38,39]. Dit heeft geleid tot de ontwikkeling van meer verfijnde benaderingen, zoals de nierdonor-risico-index[38,40,41], die artsen zouden kunnen helpen in hun patiëntbegeleiding en bij (gezamenlijke) besluitvorming; hier zou in Nederland ook verder naar gekeken moeten worden. De onderliggende gedachte bij het besluit om een marginale donornier voor transplantatie te accepteren, ondanks de eventueel slechtere transplantatieoverleven, is dat de lange-termijn patiëntprognose kan worden verbeterd door een dergelijke transplantatie direct te ondergaan in plaats van langer te dialyseren in afwachting van een betere donornier. Het oncologisch risico vergroot niet de overleven, de wacht tijd is namelijk meestal korter. Voor sommige patiënten kan langdurige dialyse leiden tot verslechtering van de gezondheid en uiteindelijk tot een niet-transplantabele conditie, of zelfs overlijden. Naast deze gezondheids-overwegingen, kan er ook een wens (van de patiënt) zijn om snel getransplanteerd te worden, vanwege de positieve uitwerking op de kwaliteit van leven. Een besluit om een marginal nieraanbod te accepteren, vereist een ingewikkeld besluitvormingsondersteunend systeem, dat onder andere rekening houdt met wachtlijst- of dialyseoverleven, de geschatte wacht tijd voor een standaard nier, de transplantatieoverleven met een marginale nier vergeleken met die met een standaard nier, en de kwaliteit van leven.

Voor welke patiënten zou een marginale donornier geaccepteerd moeten worden voor transplantatie?

De onderliggende gedachte bij het besluit om een marginale niertransplantatie te accepteren, ondanks de eventueel slechtere transplantatieoverleven, is dat de lange-termijn patiëntprognose kan worden verbeterd door een dergelijke transplantatie direct te ondergaan in plaats van langer te dialyseren in afwachting van een betere donornier[42,43].

Concluderende opmerkingen met betrekking tot acceptatie marginale donornieren

Verschillende donor-risicoscores zijn ontwikkeld en sommige daarvan zijn gecombineerd met ontvangerkarakteristieken om vast te stellen welke patiënten het meest kunnen profiteren van een bepaald marginaal nieraanbod. Hoewel de meeste studieresultaten veelbelovend zijn, kunnen ze een vertekend beeld geven doordat patiënten die in het verleden een marginaal nieraanbod hebben ontvangen verschillen van de patiënten die een nier van een betere kwaliteit hebben ontvangen of juist aan de dialyse zijn gebleven. Gerandomiseerd onderzoek is de gouden standaard voor de vergelijking van behandelingen, maar dit is hier (net als bij de vergelijking van dialyse en niertransplantatie) onethisch. Toekomstperspectieven

We zouden aanbevelen om, op basis van de resultaten beschreven in hoofdstuk 6, verder onderzoek te doen om te beoordelen welk patiënten op de wachtlijst baat hebben bij acceptatie van een bepaald marginaal donornieraanbod en daardoor een verkorte wacht tijd. Een dergelijk voorspelmomodel zou zeer wenselijk zijn om de (gezamenlijke) besluitvorming betreffende het al dan niet accepteren van een nieraanbod, te ondersteunen. Ook is ten behoeve van bovenstaande verder onderzoek nodig om de beste definitie van marginale donoren, ofwel verschillende donorkwaliteiten, in Nederland te bepalen. Over het algemeen zijn predictiemodellen geschikt voor patiëntvoorziening en voor onderzoekdoeleinden. Ons registry model is voldoende voor de laatstgenoemde toepassing en kan worden gebruikt bij het doen van verder interventieonderzoek gericht op toekomstige overlevingsverbeteringen bij patiënten met eindstadium nierfalen in Europa. Het easy model heeft de voorkeur in de patiëntbegeleiding bij de bespreking van behandelkeuzes en patiëntprognoses. Zeker voor patiënten in de hoogste risicogroepen kunnen dergelijke overlevingsvoorspellingen nuttig zijn. Zo kan het easy model mogelijk ook al in de pre-dialyse zorg worden gebruikt om de keuze tussen het starten van een nierfunctievervangende therapie ofwel een conservatieve behandeling te bespreken met hoge-risico patiënten. Brukbaarheid van het model voor deze toepassing in de ‘klinische’ praktijk zal nog wel onderzocht moeten worden. Voor alle toepassingen is periodieke re-evaluatie en eventuele modelaanpassing aanbevolen[9,44-46].
REFERENCES


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Andries, onze samenwerking startte zo’n 16 jaar geleden. Je stond samen met mij ‘aan de wieg van de NOTR’ en was vanuit het Renine- (en later Nefrovisie-)bestuur jarenlang mijn sparring partner voor de coördinatie van Renine. Dit promotietraject was een bijna logisch vervolg hierop aangezien we nu als gebruiker van deze databases de waarde hiervan konden aantonen. Je hebt in dit al deze functies altijd voor mij betekend en ik bewonder het feit dat jij altijd overal tijd voor wist te maken: of het nou ging om een antwoord op een vraag of het becommentariëren van (de zoveelste versie!) van een stuk, altijd was dit snel! Aangezien dat ook vaak ‘s avonds, in het weekend (‘op een regenachtige zondag’) of in je vakantie was, denk ik dat het ook terecht is om Sterneke te bedanken voor het feit dat zij je daarvoor de ruimte gaf! Ik ben blij dat jij mijn promotor was, en ik één van jouw laatste promovendi, en ik hoop dat we onze fijne samenwerking (nu in een Europees project) nog enige tijd kunnen vervolgen.

Martin, ik weet nog dat jij zelf promoveerde toen je nog maar net in dienst was bij de NTS en nu ben ik jouw eerste promovend! Ik heb onze samenwerking erg gewaardeerd; het was fijn om allerlei nieuwe dingen te leren met betrekking tot het predictie-onderzoek (en om ons beiden te verdiepen in de epidemiologie). Je hebt me verder altijd erg geholpen met jouw geweldige relativeringsvermenigvuldiging en je vaar- digheid om hoofd- en bijzaken te onderscheiden (waardoor jij in staat was vele woorden in mijn artikelen te schrappen, hetgeen zeker niet mijn sterkste punt is). Ik hoop dat wij bij de NTS als onderzoekers nog vele jaren kunnen blijven samenwerken!

Dat brengt me bij mijn tweede copromotor, Dr. Merel van Diepen, en de afdeling epidemiologie van het LUMC, met name Prof. dr. Friedo Dekker, welke heel belangrijk zijn geweest voor dit onderzoek.
Friedo, ik vond het heel fijn dat jij zo enthousiast die samenwerking met ons bent aangegaan en dat je een essentiële inbreng hebt gehad in al mijn artikelen in dit proefschrift. Je hebt gedurende het onderzoek in diverse overleggen altijd kritisch met ons meegedacht en had vaak een hele frisse kijk op de materie. En heel veel dank natuurlijk voor het toevoegen van Merel aan ons team!

Merel, jouw kennis van predictiemodellen was heel belangrijk voor dit onderzoek. Je hebt ons veel geleerd en het was fijn dat we altijd bij je langs konden komen voor advies of praktische hulp. Ook je hulp bij het schrijven van de artikelen was onmisbaar. Heel fijn dat jij, naast Martin, mijn copromotor wilde zijn!

Mijn promotieonderzoek heb ik uitgevoerd bij de NTS en aan deze organisatie ben ik dan ook veel dank verschuldigd voor het mogelijk maken van dit onderzoek. In het bijzonder wil ik Brigitte en Bernadette bedanken voor hun ondersteuning tijdens het promotietraject. Hoewel jullie niet direct inhoudelijk betrokken waren, is jullie voorwaardenscheppende, stimulerende en ondersteunende rol wel degelijk zeer essentieel geweest voor dit onderzoek! Dank aan alle leden van het wetenschappelijk overleg voor hun input bij het oefenen van voordrachten. De NTS is in de tijd dat ik er werk enorm gegroeid, dus het wordt teveel om iedereen bij naam te noemen. Bij deze wil ik daarom alle NTS-collega’s (en ook ex-collega’s) danken voor de belangstelling, de fijne samenwerking, praktische hulp en de gezelligheid o.a. bij de lunch, borrels en congressen. Hetzelfde geldt voor de ET-collega’s (hoewel het directe contact de laatste jaren wat minder intensief is nu bijvoorbeeld onze keukens gescheiden zijn en we elkaar niet meer tegenkomen bij het koffie-apparaat) en mijn ex-collega’s van Nefrovisie.

Verder ben ik veel dank verschuldigd aan de ERA-EDTA voor hun hulp bij mijn externe validatiestudie. In het bijzonder dank aan Anneke Kramer, Maria Pippias en Vianda Stel, voor het leveren van de data, het meedenken en meewerken aan het externe validatie-artikel en de communicatie met de diverse co-auteurs.

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Ik vond, en vind, promoveren doodeng. Wat heerlijk dat ik dan daarin wordt bijgestaan door 2 paranimen: mijn lieve zus Karin en collega Cynthia.

Karin, na enig twijfelen gezien de onbekendheid van de rol van een paranimf, heb je toch besloten deze ‘rol’ te pakken. Daar ben ik echt heel blij mee, aangezien je (al meer dan 45 jaar!) heel belangrijk bent voor mij en ik het dan ook leuk vind dat je hierbij weer mijn ‘getuige’ bent. Frank, ook dank voor jouw steun.

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Lieve Arjan, Marit en Dena; mijn allerlaatste dankwoord gaat uit naar jullie!

Arjan, al weet je dit waarschijnlijk niet meer, jij hebt destijds de doorslag gegeven bij het starten van mijn promotietraject. Discussiërend over de zin van het leven en wat ik nou echt graag zou/had willen doen, kwam jij met de suggestie dat ik door middel van onderzoek ook zou kunnen proberen een (indirecte) bijdrage aan de geneeskunde te leveren. Ik weet niet of je na die tijd nog wel eens getwijfeld hebt aan je advies,
maar je hebt me altijd onvoorwaardelijk gesteund, zowel in praktische als in morele zin, met je heerlijk nuchtere kijk op de dingen als ik weer eens beren op de weg zag. Je bent echt mijn rots in de branding! Lieve Marit en Dena, mijn mooie, lieve dochters. Hoe fijn is het om jullie moeder te zijn! Ik ben zeker wel eens tekort geschoten in mijn aandacht voor jullie, vooral in de laatste fase van mijn onderzoek, maar dat hebben jullie me nooit kwalijk genomen. Ik hoop dat jullie je ook zullen kunnen ontwikkelen in de richting die jullie ambiëren. Maar laten we, voordat het zover is, jullie ontwikkelen, nog heel veel mooie dingen beleven samen als gezin!

**DANKWOORD**

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**CURRICULUM VITAE**

