Challenging frontiers in renal transplantation
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CHAPTER 1

INTRODUCTION AND OUTLINE OF THE THESIS
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The practice of renal transplantation is currently facing numerous challenges. The incidence of end-stage-renal-disease (ESRD) is increasing. Donor and recipient age are also increasing, and transplant candidates often struggle with multimorbidity. Renal transplantation still remains the optimal treatment for ESRD. This success increases the demand for transplantation, but the donor pool is not increasing at the same rate. Consequently, access to transplantation is limited and ESRD patients must endure long waiting times for a deceased donor kidney. To address the organ shortage, an upward trend is observed in extending the donor criteria such as age limits and the number of accepted comorbidities resulting in an increasing number of suboptimal donor kidneys being transplanted.

To meet this growing need for donor organs and select the right organ for each patient, several strategies can be employed. First utility of the donor organs might be improved by smarter allocation with better matched longevity of the donor organ and the recipient. To accomplish this, an essential tool will be finding predictors for graft failure to optimize transplant outcomes. Furthermore, better tissue matching between donor and recipient is important as is personalized medicine for the patient with treatments being tailored to the individual patient based on their predicted risk of disease instead of a ‘one-size-fits-all’ approach. Finally, donor logistics may need to be improved to increase donor quality and lower cold ischemic time.

Nephrologists must inform patients about their renal impairment, about the risks of progression to ESRD and, once renal failure occurs, about the different forms of renal replacement therapy. Therefore, nephrologists need structured information about the outcomes of the available treatment options, which are conservative treatment, dialysis, and kidney transplantation with a deceased or living donor kidney. Although transplantation is regarded as the most optimal treatment, it is also not suited or available for all patients. In addition, nephrologists must translate epidemiological data to the individual patients, discuss the different possibilities and come to an agreement with the patient about which treatment suits him or her best considering his or her physical and mental states.

This thesis is the product of a fruitful collaboration between nephrologists, transplant surgeons, pathologists, transplant coordinators, biologists, nurses, and policy makers. The chapters in this thesis provide tools to help the clinician and his or her patient to reach an informed decision for a personalized and optimal course of treatment.

The importance of functioning kidneys
Kidneys regulate crucial life-supporting processes in our body. The kidneys determine fluid status, filter blood and remove waste products, and regulate blood acidity and bone health by activating vitamin D. Furthermore, the kidneys make several hormones that regulate blood pressure and oxygen transport. Diabetes, obesity, and hypertension are omnipresent in our
A progressive decrease of the kidneys’ filtration capacity is called chronic kidney disease (CKD). A large Dutch epidemiological study from the Groningen region estimated that 1.7 million Dutch inhabitants (>10%) suffer from chronic kidney damage, leading to an increased risk of cardiovascular disease and mortality.

CKD is defined as abnormalities of kidney structure present for >3 months. The severity of CKD is classified in five stages, reflecting a reduction of the glomerular filtration rate (GFR). CKD stages 4 and 5 correspond to a GFR below 30 and 15 mL/min, respectively. Loss of kidney function to CKD stage 4 is often irreversible, and in the long-term leads to ESRD. This corresponds to CKD stage 5, also called kidney failure, the most severe stage of CKD. In 2016, more than 17,000 patients in the Netherlands required renal replacement therapy.

Renal replacement therapies for ESRD patients
If the kidneys fail to function, a decision must be made between conservative, maximal supportive therapy and renal replacement therapy (RRT). RRT consists of either kidney transplantation or dialysis. Dialysis is the process of clearing the blood of waste products using either an artificial kidney (hemodialysis) or the body’s peritoneal membrane as a filter (peritoneal dialysis). The benefits of dialysis for elderly patients who often suffer from multiple (renal) comorbidities, have been questioned. In recent years, the concept of conservative supportive therapy with withholding dialysis has gained attention for such elderly patients.

Kidney transplantation is the organ transplant of a kidney, donated by either a living or a deceased donor. Studies on kidney transplantation have generally shown favorable results with improved survival compared to waitlisted patients remaining on dialysis. Also, compared to dialysis, renal transplantation has a favorable risk profile for cardiovascular outcomes and quality of life. Given the success of kidney transplantation, the demands for kidney organs increased dramatically over recent decades (Figure 1). However, Dutch dialysis patients who are eligible for transplantation wait for more than three years for a deceased donor kidney and, in 2016, more than 10% of patients died while on the waiting list. Some ESRD patients are deemed not transplantable due to their clinical condition, and another 25% who are actively waiting will never be transplanted. While waiting for a kidney, their clinical condition deteriorates, or they die on the waiting list. Furthermore, higher risk patients are being accepted for transplantation.

Taking all these developments together, we need to evaluate the outcomes of our transplant programs on a regular basis, taking us in the right direction to be prepared for the future. This is where the field of epidemiology steps in. Epidemiology is defined as the study of determinants of health-related states or events in specified populations, and the application of this study to the control of health problems. Most chapters in this thesis are based on healthcare data from the Dutch Organ Transplant Registry (NOTR) maintained by the Dutch Transplant Foundation, incorporating also data from the Dutch Renal Replacement Registry (RENINE).
hosted by Nefrovisie. With these data, we aim to guide decision making in a variety of often difficult topics in renal transplantation.

**Longevity matching in kidney transplantation**

Given the shortage of organs, policies of allocation have shifted to a more utilitarian approach by transplanting kidneys expected to last the longest in patients expected to live the longest. Although other patient-related outcomes such as quality of life are crucial, prolongation of patient and graft survival may arguably be the most relevant clinical goal. Eurotransplant, a non-profit organization responsible for allocating and distributing organs in several European countries, has instituted the European Senior Program (ESP) to improve utility by giving priority to certain recipient–donor Combinations; for example, by directing older donor grafts to recipients with the shortest expected life spans. This is done by matching chronological age; for example, allocating donors aged ≥65 years to recipients aged ≥65 years. The ESP has been shown to increase the availability of elderly donors, thus reducing time on the waiting list. However, transplanting older grafts may also affect long-term graft and patient survival in older aged recipients. In **CHAPTER 2**, we evaluate the transplant outcomes of the ESP program, comparing them to the outcomes of elderly recipients of younger grafts outside the ESP. We also discuss the dynamic properties of the waiting list, and the alternative of patients staying longer on dialysis.

An increased age at the time of transplantation has an effect on graft survival and death-with-a-functioning-graft is a more common event. Since 2002, the influx of elderly (≥65y) waitlisted patients increased four-fold in the Netherlands (from 88 to 372). Although the proportion of patients older than 75 years of age of deceased donor kidney is relatively small, a rapidly increasing demand in the future is expected. In **CHAPTER 3**, we analyze the outcomes of transplanted patients aged 75 years and older.
Types of kidney donors

There has also been an increase of the living donation program in the Netherlands, which led to reduced waiting time for the deceased donor program (depicted in Figure 2). Donations in the deceased donor program consist of two types: 1) brain-death donation (DBD), and 2) circulatory-death donation (DCD). In contrast to DBD, DCD kidneys suffer from additional warm ischemic injury caused by the lack of blood perfusion of the organs during the agonal phase and after circulatory arrest. Once explanted, donor kidneys are preserved for transport either by static cold storage on ice or by machine perfusion. In the Netherlands, a relatively high proportion of deceased donor kidney transplants come from DCD donors (~50%)\(^\text{(23)}\), and DCD programs are emerging in many other countries\(^\text{(24)}\). DCD kidneys offer a valuable extension of the donor pool, but at the expense of increasing the risk of delayed graft function (DGF) compared with DBD kidneys.\(^\text{(25-27)}\)

Within DCD, another five types can be distinguished, according to the Maastricht classification, and are summarized in Table 1.\(^\text{(28,29)}\) Most DCD kidneys in the Netherlands are classified as controlled (cDCD).\(^\text{(23)}\) cDCD donors are patients in intensive care units for whom further treatment is futile. Within the hospitalized setting of the controlled donor preparations can be made to retrieve the organs immediately after death, keeping the warm ischemic time as short as possible. Uncontrolled DCD (uDCD) donors are patients for whom resuscitation failed. This difference in context implies major logistical effort, both inside and outside the hospital. Critical information, such as the period between circulatory arrest and organ preservation and the efficacy of cardiopulmonary resuscitation (CPR), is sometimes difficult to obtain. Furthermore, uDCD kidneys are potentially subjected to greater injury caused

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Figure 2: Number of yearly transplanted patients according to donor type in the Netherlands. A decline in the number of patients eligible for transplantation on the waiting list is also depicted (grey). (source: Dutch Transplant Foundation, annual stats)
by a more prolonged warm ischemic time, which may result in a higher incidence of primary non-function and DGF. Consequently, uDCD kidneys in the Netherlands have been accepted with some reluctance in the past, and this interest has declined to 1 uDCD donor in 2016 and none in 2017. Nonetheless, a growing interest in the potential of uDCD kidneys is observed in other countries, and there is still potential for uDCD to increase the donor pool, especially with the advent of new preservation techniques. Only recently, the standard preservation technique of transporting the kidney in an ice box, a cheap and reliable method for organ storage, changed towards using machines based on either cold or warm perfusate. One of the currently promising preservation techniques is normothermic regional perfusion (nRP) with ECMO (extracorporeal membranous oxygenation) devices to restore blood flow after the determination of death and before organ recovery. The first nRP results show better short-transplant outcomes, that may improve the uDCD results in the future. In CHAPTER 4, we investigate the transplant outcomes of uDCD kidneys compared to cDCD kidneys. The goal was to check the potential of uDCDs to increase the donor pool. Based on these findings, and the recent developments in preservation techniques, we feel that more effort should be made to make use of this kidney donor potential.

Table 1. Categories of DCD, where Type 1 and Type 2 are further categorized into A and B. And Euthanasia as fifth category is added. (Source: Thuong et al., 2016)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Situation</th>
<th>Defined as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I: Uncontrolled</td>
<td>Found dead</td>
<td>Sudden unexpected circulatory arrest without any attempt of resuscitation by a life-medical team</td>
</tr>
<tr>
<td>IA. Out-of-hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB. In-hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II: Uncontrolled</td>
<td>Witnessed cardiac arrest</td>
<td>Sudden unexpected irreversible circulatory arrest with unsuccessful resuscitation</td>
</tr>
<tr>
<td>IIA. Out-of-hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIB. In-hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category III: Controlled</td>
<td>Withdrawal of life-sustaining therapy</td>
<td>Planned withdrawal of life-sustaining therapy; expected circulatory arrest</td>
</tr>
<tr>
<td>Category IV: Uncontrolled Controlled</td>
<td>Circulatory arrest while life-brain dead</td>
<td>Sudden circulatory arrest after brain death diagnosis during donor life-management but prior to plan organ recovery</td>
</tr>
<tr>
<td>Category V: Controlled</td>
<td>Euthanasia</td>
<td>Medically assisted circulatory arrest with subsequent organ donation</td>
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In CHAPTER 5, we explore ways to optimize the short-term transplant results of cDCD by investigating agonal phase parameters. The agonal phase, i.e., the period between withdrawal of life-sustaining treatment and circulatory arrest, in cDCD potentially exacerbates ischemia/reperfusion injury.
two hours. A single-center study from the UK showed good results for DCD kidneys with a more liberal agonal phase cut-off of 4 hours. Therefore, we wanted to investigate the evidence for the two-hour agonal phase protocol. If the two-hour period could be extended, the next question to solve would be how many DCD kidneys could potentially increase the donor pool. Data about agonal phase is scarce, and only a few studies to date have investigated the agonal phase parameters for DCD donors, possibly because most transplant registries do not routinely record these parameters. If agonal phase parameters cause extra ischemic insult, these parameters may be useful to predict recipient transplant outcomes. Therefore, we analyzed systolic blood pressure and oxygen saturation of the donor during the agonal phase to predict short-term transplant outcomes of cDCD donor kidneys. The help of transplant coordinators, who have recorded these parameters in their own transplant administration books, made it possible to analyze the results for two large transplant centers in the Netherlands.

Investigation of risk factors and support of decision making

Having clear cut-off values for donor and transplant risk factors of transplant failure could aid transplant professionals estimate the quality of a kidney donor organ, and would be highly useful in selecting donors and helping to safely increase the donor pool. The time from cold flushing of the donor organ until the graft is implanted into the recipient, the cold ischemic time (CIT), is well-known to have an impact on kidney graft survival rates. Logistical efforts are made to reduce the time that a kidney is preserved on ice or on in a machine. Prolonged exposure to warm and cold ischemia results in renal tubular cell damage due to the depletion of adenosine triphosphate, build-up of reactive oxygen species, and activation of inflammation and coagulation after reperfusion, which lead to an increased risk of graft failure. In the United Kingdom, longer CIT was shown to be associated with graft failure, with a significant difference between DBD and DCD donor types. Prolonged CIT was associated with reduced kidney graft survival, especially in DCD kidney recipients. In the United States however, this interaction of CIT and deceased donor type was not found. In CHAPTER 6, we investigate whether there are differences in the effects of each extra hour of CIT between DCD and DBD donor kidneys in the Netherlands, and if this difference was influenced by donor age.

In an effort to stratify patients who are at increased or decreased risk for graft failure, a large number of studies have investigated the value of molecular biomarkers and clinical algorithms for the prediction of long-term graft failure. However, in clinical practice, only a very few of these markers or clinical algorithms are being used on a routine basis. The sole markers that are used routinely in every transplant outpatient clinic are serum creatinine as a readout for the glomerular filtration rate and urinalysis to determine protein leakage as a readout for glomerular and/or tubular dysfunction. This is partly because hardly any study determined the dynamic temporal association between serum creatinine and urinary protein content trajectories with the development of graft failure. The joint model is an interesting statistical model to
simultaneously investigate longitudinal measurement of renal function and urinalysis and time-to-event graft survival data. In CHAPTER 7 we present a joint model that includes static baseline clinical data and dynamic longitudinal trajectories of serum creatinine and urinary protein-creatinine ratios to predict death-censored graft failure. We used this joint model to test whether we could construct a personalized monitoring strategy and compare it to the fixed-term one-size-fits-all monitoring strategy that is currently in use. To the best of our knowledge, we are the first to use such an approach to tailor the screening to the needs of individual patients.

**Validation of existing prediction models**

As mentioned in the previous paragraph, a large number of studies have proposed a prediction algorithm for graft failure, in an attempt to identify patients who are at increased risk; however, hardly any of these models have been generally accepted worldwide.\(^{46-54}\) One of the problems is that prediction models suffer from methodological shortcomings, either in the development process or in the validation process.\(^{55,56}\) Models are rarely externally validated. A model should first be tested in another population with independent data to assure statistical reproducibility and clinical transportability. The two key steps of external validation are calibration (is the model accurate to predict patients with graft failure) and discrimination (ability of the model to discriminate patients who are at risk for graft failure).\(^{57}\) This is the first study in the field of transplantation and nephrology to perform external validation according to the recently proposed external validation framework that emphasizes on the importance of both validation of statistical performance of the model and the investigation of differences in case-mix between cohorts.\(^{58}\) In CHAPTER 8 we report on the largest replication study to date of four available clinical prediction algorithms for delayed graft function, which creates the need for temporary dialysis treatment after transplantation. We also validated the clinical utility of the UNOS/OPTN algorithm for an average Western European country within the Eurotransplant program.

A variety of prediction tools have been proposed to assess the quality of a deceased donor kidney.\(^{46,47,49-54,59}\) Among these, the Kidney Donor Risk Index (KDRI) is the most commonly used prediction tool, and one of the few prediction algorithms adopted in the clinical arena in the United States.\(^{59}\) The KDRI is a continuous risk-scoring system based on ten donor factors and four transplant factors; however, the donor-only KDRI was the version that was implemented in the United States since these factors are generally known at the time of donor organ offer. The KDRI was developed and internally validated in the United States, but not externally validated in the Netherlands. Discrimination of the KDRI in the United States (internally validated) resulted in a C-statistic of 0.62.\(^{59}\) To put this in perspective, the KDRI, with a C of 0.62, ranks only 62% of the grafts correctly to outcome. In CHAPTER 9, we externally validate the KDRI in the Dutch transplant setting. We demonstrate calibration and discrimination of the KDRI, and which donor factors should be updated or additionally included to be used in the Netherlands. One of the goals was to analyze to what purpose the
KDRI could be used: for clinical decision making to accept or refuse a graft, or merely for use in allocation strategies as was originally intended. Finally, we also combined recipient characteristics with the KDRI to evaluate outcomes to investigate allocation strategies for lower-quality deceased donor kidneys. The results aim to provide guidance in the complex decision making involved, for example, in deciding whether to transplant a deceased donor kidney to (an elderly) Dutch patient with ESRD.

REFERENCES


