Challenging frontiers in renal transplantation
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CHAPTER 10

SUMMARY AND PERSPECTIVES


**CHAPTER 1** provided an introduction to the thesis, and recent developments in kidney transplantation and its future challenges were discussed. Stage 5 chronic kidney disease, also known as end-stage-renal-disease (ESRD), is the most severe stage of chronic kidney disease. In 2016, more than 17,000 patients in the Netherlands required renal replacement therapy. This is an increasing public health issue: the ageing population accompanied by an increase of the incidence of ESRD. It affects the demand for kidney transplantation which is regarded as the optimal treatment for ESRD. Living donor kidney transplants show the best transplant outcomes; however, a portion of ESRD patients are placed on the waiting list for a deceased donor kidney. While waiting for a kidney transplant, most patients must choose one of the other two options for renal replacement therapy: hemodialysis or peritoneal dialysis. Waiting time, increased frailty, and comorbidities can restrict access to transplantation, especially for the elderly patients. Consequently, kidney transplantation is not an option available for every waiting transplant candidate. In response to the shortage of organs and to select the right organ for each patient, this thesis discussed several ways to help clinicians and their patients reach an informed decision on a personalized and optimal course of treatment.

One of the strategies is to improve the match between the life expectancies of donor organs and recipients. An increasing number of elderly patients (≥65 years) receive a donor kidney not only from elderly DBD, but also after controlled DCD. These organs are allocated within the Eurotransplant Senior Program, implemented in 1999. The key components are allocation without prospective matching for human leukocyte antigen in favor of local allocation, in order to reduce cold ischemia time and thus the risk of injury. In **CHAPTER 2**, we evaluated the outcomes following renal transplantation in elderly patients receiving deceased-donor grafts from either young (<65 years) or elderly (≥ 65 years) donors. In elderly patients, engraftment from elderly DCD donors resulted in an increased mortality risk compared with kidneys from young DBD donors. Elderly recipients of kidneys from elderly donors do not experience a survival benefit compared to remaining waitlisted on dialysis. Renal function, which can be taken as a surrogate marker for quality of life, was lower in elderly recipients receiving a graft from an elderly donor than a young donor, and particularly for elderly DCD donors. Also, the incidence of acute rejection in elderly recipients of elderly DBD kidneys was similar to that for young DBD kidneys, but higher in elderly recipients of elderly DCD kidneys. The ESP allocation system aims to achieve short ischemia times. DBD kidneys allocated via ESP had the shortest CIT, however, this was not achieved for DCD grafts. In the elderly DCD grafts, the CIT was not shorter than for kidneys allocated via the regular Eurotransplant allocation program (ETKAS). It could be that reluctance by transplant centers to accept DCD kidneys from elderly donors may have played a role in delaying their allocation. This is discussed in more detail in the next chapter Perspectives. Prolonged CIT, and a greater number of HLA mismatches, may contribute to the relatively high primary non-function rate in elderly recipients receiving elderly DCD grafts, and also to the poorer graft and patient survival rate.
with higher risk for DGF and/or acute rejection. On a positive note, the waiting time for a deceased donor kidney was significantly lower in the ESP group. Not only the ESP group, but also the elderly recipients of younger grafts had reduced waiting times because of the competitive listing for ESP and the regular allocation program of ETKAS. The study results indicate that there is no apparent survival benefit for transplantation when engrafting kidneys from increasingly elderly donors to elderly recipients. Considering this result, patients should be counseled about their survival prospects when accepting standard or expanded donation criteria grafts and given the opportunity to participate in decision making. These findings must be seen in the context of the study period, which involved transplants from 2002 to 2012. A decade later, progress continues to be made in the renal transplant field and the ESP program, which is discussed in the next chapter, Perspectives.

From 2010 to 2015, the incidence of recipients 75+ transplanted with kidneys from deceased donors was between 10 and 20 transplants annually.\(^1\) In 2016, more than 2,000 patients 75 years and older were on dialysis.\(^{1,4}\) This indicates that access to transplantation in this age group is very low.\(^3\) In CHAPTER 3, we evaluated the impact of an increased age of 75 years or more at time of transplantation, as a rapidly increasing demand is expected in the near future. The findings show that outcomes of recipients aged 75 years and older transplanted with kidneys from mainly elderly deceased donors are comparable to the results of recipients between 65 and 74 years of age. As expected given the higher age, the 75+ group had a significantly higher proportion of death with functioning graft compared to the recipients aged 65-74. We estimated a three-year patient survival rate of 70% (62% with a functioning graft), and a five-year rate of 40% (32% with a functioning graft) for recipients aged 75+. Among the most prevalent causes of death were those related to infection and cardiac failure, and for a high proportion the cause was uncertain. In Chapter 2, we showed that elderly recipients of young (<65y) grafts have a survival benefit compared with transplant candidates remaining on dialysis; however, in the ESP, the survival of kidney transplantation for both groups was shown to be equivalent.\(^6\) We could unfortunately not stratify the waitlist analysis for 75+ candidates due to small numbers in this category. Death-censored graft failure rates were low among 75+ recipients (15.6% at 5 years), and most occurred within the first year after transplantation (9.9% at 1 year). In this age group, it is within this first year that the risk of mortality was the highest among those who lost their graft. The most prevalent causes of graft loss were primary non-function, rejection, and infection. The elderly recipients aged 75+ years and older probably represent a selected group, and the donor and transplant factors were not significantly associated with death-censored graft failure.

In CHAPTER 4, we compared the results of uncontrolled DCD (uDCD) kidneys with controlled DCD (cDCD). Our results show that graft and recipient survival of uDCD kidneys are acceptable and similar to that for cDCD kidneys, while the high primary non-function (PNF) rate is a reason for major concern. Once a uDCD donor kidney starts functioning, renal
transplant function at one year and five years after transplantation is comparable to a cDCD kidney. If censored for primary non-function, five-year graft survival rates were comparable between uDCD and cDCD transplants. The most important difference between the groups was the almost twofold higher rate of primary non-function for uDCD kidneys. In an etiological analysis, we discovered three variables that influence the incidence of primary non-function between the DCD groups: first warm ischemic time, cold ischemic time, and donor age. As a result, a short first warm ischemic time (WIT), a short period of cold ischemic time (CIT), and careful selection of the uDCD for age are required. In our study, the 1st WIT and CIT were longer in uDCD compared with cDCD. The longer 1st WIT is due to the unplanned nature of uDCD, whereas the longer CIT might be explained due to a later initialization of HLA-typing and matching. It may also be possible that some centers were reluctant to accept such a kidney in the allocation process. In the Perspectives chapter, we discuss this in more detail. The mean donor age was already significantly lower in uDCD, which mitigated the PNF incidence in uDCD. Although the incidence of PNF was high, a majority of recipients of uDCD kidneys were relisted and retransplanted. If WIT and CIT injury are improved with uDCD kidneys, these donors can be a valuable expansion of the donor pool. Furthermore, other factors that influence warm ischemic injury—such as time between cardiac arrest and resuscitation, and the hemodynamic profile and oxygen saturation of the donor in the agonal phase—may be improvable targets. It was not possible in this study to gather this information.

We investigated the first warm ischemic insult to the kidneys during the agonal phase in Chapter 5. In 409 cDCD donor kidney transplantations, only 8 cases exceeded 90 minutes of agonal phase which was within the limit of two hours in our national protocol. Longer periods of agonal phase were associated with a significantly increased risk of DGF, and tended toward an increased risk of primary non-function though this failed to reach significance. Agonal phase duration was not associated with death-censored graft failure at three years. When considering increasing the agonal phase upper limit to 3 or 4 hours, it is questionable whether such a change is likely to increase the number of DCD donors to a degree that outweigh the costs. In 2016 in the Netherlands, 159 DCD procedures were started of which 109 DCD donations were effectuated. Of the 50 procedures that were not effectuated, 31 DCD donors did not fulfill the criteria of the 2-hour standby-time. By implementing an upper limit of 4 hours, the donor pool would only be extended by 2 to 3 eligible DCD donors per year. This is because the duration of agonal phase is hard to predict, and can last for more than 72 hours. The costs of increasing the limit are related to the recovery teams who must remain available for a longer period with a low probability of actual effectuation of organ retrieval. We analyzed two parameters used frequently during the agonal phase: minutes of oxygen saturation, SpO2 > 60% or SpO2 < 60%, and minutes of systolic blood pressure, SBP > 80 mmHg or SBP < 80 mmHg. We found that duration of SBP<80mmHg was associated with increased risk of DGF. In DCD donor kidneys aged 60 years and older, duration of agonal phase and functional WIT (starting from
SBP<80mmHg to cold perfusion) appeared to be less important than for younger donors for an outcome of DGF. Surprisingly, the period of SpO2<60% was not associated with an increased risk of DGF; however, the period of SpO2>60% did significantly influence the risk of DGF. Agonal phase parameters as measured in this study were not significantly associated with PNF, renal function at 3 months, or graft failure at 3 years. The interplay of donor-derived (e.g., warm ischemic injury and inflammatory signaling) and recipient-derived (reperfusion injury and innate and adaptive immune responses) factors might be far more complex. In conclusion, the agonal phase and its parameters require further research attention to expand the DCD donor pool safely.

In chapter 6, we investigated the association of CIT and graft failure, and whether this association was different for DBD than for cDCD kidneys. Our results indicate that, regardless of whether kidneys are from DBD or cDCD, CIT is associated with an increased risk of graft failure. Only for recipients of kidneys from cDCD donors was the mortality risk increased with increasing CIT. Furthermore, we found that in recipients of cDCD donor kidneys, the risk of graft failure increased more with each extra hour of CIT as compared to DBD donor kidneys. With a reference CIT at 10 hours, the risk of graft failure was significantly increased after 14 hours for cDCD donor kidneys, and after 17 hours of CIT for DBD donor kidneys. Therefore, our data can help to optimize the scheduling of the surgery. Interestingly, after 22 hours of CIT, this risk was significantly higher in cDCD kidneys as compared to DBD kidneys. This additional risk of accepting cDCD kidneys with increased CIT as compared to DBD kidneys was also observed for the non-composite outcome of death-censored graft failure, but not for mortality. At a CIT of 19 hours, the risk of graft failure was significantly higher in recipients of kidneys from 60-year-old cDCD donors versus 60-year old DBD donors. The same additional risk for graft failure was seen in the Eurotransplant Senior Program for cDCD donor kidney recipients. In contrast, 30-year-old cDCD and DBD kidneys showed no difference in outcomes. Our findings suggest that, given the availability of a cDCD donor kidney with an extent of WIT that is considered acceptable, the additional cold ischemia injury of at least one extra hour does alter the long-term graft failure risk.

In chapter 7, we presented a joint model to predict death-censored graft failure from static baseline clinical data and dynamic longitudinal trajectories of serum creatinine (SCr) and urinary protein-creatinine ratios (PCR). We included 238 renal transplanted patients from our tertiary referral hospital with 13062 SCr measurements and 9616 PCR measurements. The joint model was then used to construct a personalized monitoring strategy and to compare it with the fixed-term one-size-fits-all monitoring protocol in our tertiary referral hospital. We demonstrated that SCr has better discriminative ability for risk of graft failure than PCR. Static baseline clinical data was associated with the evolution of SCr, and, if it was included in the model for death-censored graft failure, donor and transplant characteristics were no longer associated. Nephrologists routinely supervise both the current SCr and PCR levels and their
increase. Indeed, our results suggest that not only the current value of SCr is important, but also how rapid the rate of increase of this SCr value was. Also, we challenged our hospital’s one-size-fits-all fixed screening protocol. The goal was to compare an empirical personalized screening schedule based on the joint model with the currently used fixed schedule, consisting of 20 SCr measurements over the first year after transplantation and every 3 months thereafter, which is mainly based on prior expert opinion. With the joint model, which is inherently patient specific, we found that a personalized screening approach may result in obtaining fewer SCr measurements while the time to intervene and overcome the risk for graft failure was noninferior to the fixed schedule. When we extrapolate our results to show the potential of the personalized screening approach, assuming a fixed screening approach that is similar to the one used at our hospital, an estimate of $500 per screening and the prevalence and incidence of transplanted patients in the Netherlands, the personalized screening could reduce annual costs in the Netherlands by >$14.500.000.

In CHAPTER 8 and CHAPTER 9, we externally validated existing prediction algorithms for transplant outcomes. In Chapter 8, we investigated the outcome of DGF, defined as the need for concomitant dialysis within the first weeks after transplantation. The underlying causes for DGF are multiple, and include tubular necrosis, T-cell- and antibody-mediated rejection, and calcineurin inhibitor pharmacodynamics (nephrotoxicity) that result in renal allograft failure within the early transplant period. To identify those cases with an increased risk of developing DGF, various algorithms have been proposed. The objective was to validate the reproducibility of four predictive algorithms by Irish (US), Jeldres (Canada), Chapal (France) and Zaza (Italy) according to a novel framework for external validation. We included 3333 adult renal transplant recipients from all eight Dutch transplant centers between 2002 and 2012 who received a deceased allograft. The four prediction algorithms were reconstructed in our dataset. Their predictive value for DGF was validated by C-statistics, calibration statistics and net benefit analysis. Case-mix relatedness was investigated with a membership model and the mean and standard deviation of the linear predictor. The prevalence of DGF was 37%. Despite a significantly different case-mix, the US algorithm by Irish was best reproducible, with a C-index of 0.761 (range 0.756 - 0.762), and well-calibrated over the complete range of predicted probabilities of having DGF. The U.S. model had a net benefit of 0.242 at a threshold probability of 0.25, compared to 0.089 net benefit for the same threshold in the original study, equivalent to correctly identifying DGF in 24 cases per 100 patients (true positive results) without an increase in the number of false-positive results. In conclusion, the US model by Irish et al. was generalizable and best transportable to Dutch recipients with a deceased donor kidney. The algorithm detects an increased risk of DGF after allocation and enables us to improve individual patient management. Whether a model-guided treatment strategy to prevent DGF will also lead to a decrease in death-censored graft failure is not known, since this depends on the causal effect of DGF on graft failure and the dynamics of alloimmunity, infections and other posttransplant
diseases. In fact, we observed that DGF only has a deleterious effect on death-censored graft survival when elderly patients had received a transplant from an elderly donor.

In Chapter 9, we externally validated the KDRI algorithm, a continuous risk scoring system based on 10 donor factors and 4 transplant factors. To determine external validation, we investigated the following research questions: 1) What is the discriminative ability of the KDRI in the more recent Dutch cohort? 2) How accurately does the KDRI predict graft survival? 3) Are the factors of the KDRI correctly specified for the Dutch situation, and do other donor factors deliver added value? The KDRI shows comparable, but modest discrimination in the Dutch setting, with a C-statistic of 0.63 for KDRI_{full} and 0.62 for KDRI_{donor-only}. The calibration plot shows that the observed and expected survival probabilities of the KDRI_{full} are reasonably consistent. Within the KDRI top-quintiles (KDRI ≥ 1.45), calibration of observed and expected survival show less agreement. A lack of fit was found for three donor factors: age, weight, and cold ischemia time. The coefficients of donor age were lower, except when donor age was <18 years. The coefficient of cold ischemia was higher for Dutch recipients, especially for DCD donor kidneys. When we recalibrated these coefficients, the discriminative ability remained approximately the same. Between 2002 and 2012 we observed a significant gradual increase of the KDRI of 0.02 per year (CI95% 0.013 – 0.022, p<.001). The KDRI seems most suitable to assisting allocation for longevity matching between cohorts of donors and recipients.

**PERSPECTIVES**

**Eurotransplant Senior Program**

Given the increased risk of mortality in the ESP, often the first question is: should we abandon this program or redefine its criteria? Although the limits of transplanting elderly deceased donor kidneys may have been reached, the waitlisted candidates that remained on dialysis showed no better survival prospects. Nonetheless, the ESP allocation has clear merits. It reduces waiting times for elderly recipients and increases the availability of grafts from younger donors for recipients younger than 65 years of age. The waiting list dynamics are complex. The question is whether a transplant candidate should wait longer for a relatively better quality kidney, meanwhile remaining on dialysis treatment. Elderly recipients of young deceased-donor kidneys only waited for four more months than elderly recipients of an ESP donor kidney. This small difference in waiting time is explained by the competing ESP offer for the majority of elderly patients. If elderly patients would choose to only be listed for regular allocation, their expected waiting time would be similar to their younger counterparts; that is, 12 months longer. Therefore, instead of abandoning the allocation of elderly donors and extending waiting times, efforts should be made to increase safe utilization of grafts from elderly donors. First, it is
important to further decrease the cold ischemia time. The results of the study are based on past practices concerning transplants in the ESP that were procured between 2002 and 2012. Already during this period a decrease in cold ischemic time was observed (see Figure 1), and was further decreased with a median CIT within the ESP of 11.2 hours (IQR 8.8-13.2) in 2016. Possibly, both a growing awareness of the consequences of CIT and a more rapid allocation policy have led to this decrease in CIT. In case of very limited time for allocation, a competitive offer is made to different centers at the same time, and the organ is then sent to the center that accepts the offer first.\textsuperscript{15} We also observed improved graft survival in the elderly recipients of kidneys from deceased donors. For instance, the PNF rate for elderly recipients of elderly DCD grafts was 12.4\% between 2002 and 2012, and fell to 6.1\% between 2012 and 2016. It could be that centers developed relatively more strict criteria for accepting an organ over the years, especially with a high CIT. Better donor management, better surgical engraftment, and better selection of elderly transplant candidates may also have played a role. Since 2016, all deceased donor kidneys were machine perfused. Future studies of machine perfusion cohorts are necessary to identify whether the differential effects of CIT could be related to the storage technique.

![Figure 1](image.png)

\textbf{Figure 1.} Boxplots of cold ischemic time from 2005 to 2016 in the Netherlands, stratified on the Eurotransplant Senior Program.
Eligibility of elderly for kidney transplantation

Generally, kidney transplantation leads to improved quality of life. However, it is yet unclear if quality of life is improved in elderly Dutch transplanted patients compared with dialysis, especially the impact of RRT over time. If the survival benefit of transplantation in elderly patients is equal to that for remaining on dialysis, patient preferences become much more important in decision making. Efforts have been made to document the patient perspective on treatment consequences of RRT in online video fragments (Nierwijzer, www.nierwijzer.nl). Besides quality of life, another component that has attracted considerable attention is frailty. Frailty is a measure of physiologic reserve capacity, defined by Fried et al. (2001) in older adults. Frailty increases early hospital readmission and mortality risk among kidney transplantation recipients, and may therefore be a suitable criterion for risk stratification for kidney transplantation. The rationale behind this, is to know which recipients are at risk, and also to know for which patient a deceased donor kidney should be accepted for transplantation. Geriatric assessments of frailty and studies on quality of life with epidemiology of patient outcomes that can take into account the selection bias for kidney transplantation versus dialysis are needed in the future.

The best study design for creating a decision tool for transplantation in elderly patients would be a randomized clinical trial. However, randomization of treatment with RRT would neither be possible nor ethical. Therefore, the issue lies in correcting for the potential biases in the comparison between patients receiving either a deceased or a living donor kidney transplant and those who remain on dialysis. These compared cohorts are not usually similar in terms of comorbidities, although theoretically the populations have the same probability of obtaining an organ if on the waiting list. The ones not listed for transplantation are thought to have a higher transplant-related risks. The main bias for concern is through confounding by indication or contraindication. For this reason it is important to predict survival from the start of renal replacement therapy, and to support counseling on the prospects from that point. This is also the way to reduce the danger of survival bias. Such bias may occur when transplant studies compare living versus deceased donor types, because the deceased donor transplant recipients have longer waiting times and higher mortality while on the waiting list. Currently, most studies in elderly patients suffer from residual, and mostly unobservable, confounding between cohorts. Although we have tried to minimize the confounding, it is likely that this also affected our study in Chapter 2. To study the comparison of forms of RRT correctly, it is necessary to look-up additional patient-level data to adjust for differences between the transplanted cohort and the waitlisted patients who not get transplanted. Quality of life, frailty, cognitive function, marital status, social network, level of education, income, and type of residence are some factors, amongst others, that need to be taken into account in the comparison, and we were not able to correct for most of these in the studies discussed in Chapters 2 and 3. To develop a full picture of the prospect of elderly patients who approach
ESRD, additional studies will be needed that address the complex decision making between treatment options. Therefore, we chose to consider two regions in the Netherlands to investigate this further, and not on a broader national-level. With the two regions, it is easier to find patient data to adjust for differences between the transplanted cohort and the waitlisted patients who did not get transplanted.

**Future of uncontrolled DCD donor type**

France and Spain have much more experience with the use of uDCD than the Netherlands.\(^{31-34}\) However, with different DCD practices across different countries and the strict selection of uDCD\(^ {35}\), one should be cautious in generalizing these results. For instance, in the Spanish opt-out donation system, perfusion catheters and NECMO (normothermic extracorporeal membrane oxygenation) can be started before consent is obtained from the family of the deceased donor. In the current opt-in system in the Netherlands, which changes in an opt-out system in 2020, preservation techniques are started after obtaining the consent of the donor in the national donor registry, and always after the obligatory 5-minute no-touch period. Therefore, the 1\(^{st}\) WIT is likely to be longer in the Dutch cohort. After the study of the uDCD was finished, we observed that hardly any uDCD kidneys were accepted for transplantation in 2015 and 2016.\(^ {4}\) In uDCD, the challenge is to decrease the incidence of PNF by mitigating the risk factors. Bringing down 1\(^{st}\) WIT with strict protocols and well-trained professionals, and decreasing CIT by local center allocation might contribute to decreasing the PNF rate. Luckily, CIT has already decreased over the years (see Figure 1). Also, better understanding of DCD donor hemodynamics is needed, because the interplay of donor-derived (e.g. warm ischemic injury and inflammatory signaling) and recipient-derived (reperfusion injury and innate and adaptive immune responses) factors might be far more complex than solely the times of the agonal phase or functional WIT, as we concluded in Chapter 5. An alternative could be a molecular signature of agonal damage that predicts outcome. To reduce the number of discarded donors, an alternative strategy could be dual transplantation. A recent report showed a case series of dual transplanted uDCD kidneys that would have been discarded for single transplantation.\(^ {36}\) With the upcoming of new machine perfusion techniques, like normothermic regional perfusion\(^ {37,38}\), uDCD may still be a valuable source of kidneys. It requires logistical efforts to set-up the uDCD program. uDCD could account for more than 15 transplantations annually, and this should be investigated in the near future.

**Future of the KDRI risk score system in the Netherlands**

For now, the clinical utility of the KDRI remains unclear in the Netherlands. Many consider an advantage of the KDRI to be that it estimates the risk of accepting a donor organ without knowing yet to which recipient the organ will be allocated. However, this is not actually true, because the recipient characteristics do play a role when modeling graft survival, which was
chosen as the outcome for the KDRI. Therefore, the case-mix of the cohort from which the KDRI was derived, the United States,\textsuperscript{14,39} determines the strength of the regression coefficients of the factors of the KDRI itself. To account for different baseline hazards of recipient characteristics (such as higher age and diabetes), stratification of the Cox regression model should be applied. However, stratification also decreases the sample size, so enough transplants should be included to model this. Another important limitation is that the selection of kidneys for transplantation plays a role in the KDRI factors, and therefore the KDRI may be different for different countries (or even regions). It would be interesting to assess an updated KDRI for the Netherlands, including the interactions between KDRI and recipient characteristics (such as age), and to include surrogate (intermediate) outcomes\textsuperscript{40} and their interactions with the KDRI.

We observed an interaction of the KDRI and recipient age: the association between the KDRI and graft failure was higher for younger aged recipients. Other recipient characteristics that interact with the KDRI might be important as well, such as diabetes, history of cardiovascular events, dialysis vintage, and frailty in elderly patients. Given this interaction, a next step could be to define KDRI thresholds for recipients. A way to do this would be to use the same methodological steps as were used for the KDRI, but for a recipient risk index. Such an index is already in use in the United States: the Estimated Post-Transplant Survival Index (EPTS).\textsuperscript{41,42} The EPTS score should be externally validated, and possibly updated with inclusion of other recipient factors appropriate to the Dutch setting. Thereafter, these two risk scores, the KDRI for the donor, and the EPTS for the recipient, could be used in an interaction to model the outcome of graft survival to define thresholds to optimize the utility of the grafts.

A way to optimize longevity matching of donor kidneys and recipients is to use the KDRI; for example, the policy used in the United States of allocating the top 20\% of low-KDRI kidneys to the 20\% of candidates with the best prospect of graft survival.\textsuperscript{43} Similarly, we have the ESP program. Future studies should focus on whether the KDRI is adoptable to be used for allocation for longevity matching between donors and recipients in the Eurotransplant region. However, such a utilitarian approach to allocation could also induce risks (possibly unanticipated ones), and its consequences must be investigated first.\textsuperscript{44,45} Furthermore, to date, our understanding of the causes of graft failure is still inadequate. The discriminative ability of the KDRI and the EPTS is only moderate, with C-statistics between 0.6 and 0.7. It is difficult to reliably derive a highly accurate prognostic algorithm from the demographic and registry-captured data. Although the KDRI and EPTS scores are currently the best tools we have, we should also look for better understanding of the processes involved in graft loss and death. To do so, more etiologic epidemiology is warranted. We also need more knowledge and incorporation of sophisticated variables such as those in genomics, facilitated by advances in complex computational analysis. The transcriptional genomic information may offer new tools to understand, diagnose, and predict events such as acute rejection, acute kidney injury in allografts, chronic allograft injury, and tolerance. One example is a non-invasive method to
predict acute cellular rejection in messenger RNA from the urine cells.\(^46\) We can also incorporate results from machine learning methods to uncover patterns of biopsy histology. Recently, the Dutch kidney foundation (Nierstichting) has approved our grant proposal titled “DEEPGRAFT: A Deep Learning Infrastructure for Biopsy Pattern Discovery and Prognostication in Renal Transplantation.” The ideal biomarker should be able to capture the effect of different pathways affecting graft survival, and should be accurate, reproducible and demonstrate validity.

**Personalized screening and treatment of kidney transplanted patients**

In addition to comparing transplant recipients with waitlisted candidates and the allocation strategies of kidneys, it is also important to improve the patient follow-up after transplantation. More effective methods for translating a patient-focused agenda into research priorities are also needed.\(^47\) To our knowledge, we are the first to tailor screening to the needs of individual patients. The fixed and frequent schedules are often burdensome for the transplant patients. For scheduling, there are two levels of uncertainty: not knowing the failure time and not knowing the serum creatinine measurements.\(^48\) A personalized schedule should be accurate so as to predict the time of intervention as well as avoid the time of failure, depending on the threshold for graft failure. The next step would be to increase sample size to include more risk factors for graft survival, which could facilitate a personalized screening approach. As we included well-known risk factors for graft failure, other biomarkers of interest such as graft histology or longitudinal genomic data could theoretically be introduced. We should also study the joint model in more depth in patients with a primary proteinuric disease that could recur in the graft, especially primary focal and segmental glomerulosclerosis, because urinary PCR should always be incorporated in the outpatient screening approach in this particular group of patients. Finally, our findings need to be externally validated in other observational cohorts, and in a non-inferiority randomized controlled trial, preferably in multiple centers with different fixed screening approaches (current clinical practice).

In conclusion, this thesis demonstrates several ways to optimize the donor potential for kidney transplantation. We discussed utility of the KDRI risk score in the Netherlands, and how it could benefit allocation strategy. In addition, the outcomes of transplantation in the elderly, and the comparison with dialysis, give guidance to transplant professionals and patients in decision making. More research is needed to investigate the benefit of transplantation in the recipients of 75 years and older. Finally, we introduced a new method to tailor screening visits and reduce the burden for transplant patients.
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