Patient-relevant outcomes after kidney transplantation

Wang, Y.

Chapter 1

General introduction, aim and outline of this dissertation

Kidney failure and its treatment options

Kidney failure is the final stage of chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) lower than 15 ml/min/1.73m^2[1]. Due to the severely impaired kidney function regarding excreting wastes from the body, balancing electrolytes, and secreting hormones, patients with kidney failure usually experience a number of symptoms (e.g. reduced urine, swollen legs, and fatigue) and complications (e.g. hypertension, hyperkalemia, and anemia)[2]. Over the past decades, kidney failure has become a challenge to the global healthcare system. With the aging population and the increasing incidence rate of diabetes mellitus, obesity, and hypertension, the number of patients with kidney failure is expected to increase[3]. Worldwide, the median number of patients treated for kidney failure was already 144 per million population according to a cross-sectional survey in 2018 covering 79 countries, and the cost to treat these patients could reach up to 2-4% of the overall healthcare budget in some countries[4, 5]. Treatment options for patients with kidney failure include conservative care and kidney replacement therapy (KRT). The latter can be further divided into dialysis (i.e. hemodialysis and peritoneal dialysis) and kidney transplantation[6].

Kidney transplantation: benefits and challenges

Depending on the donor type, kidney transplantation is primarily classified into: living donor kidney transplantation, deceased donor kidney transplantation with donation after cardiac death, and deceased donor kidney transplantation with donation after brain death[7]. Kidney transplantation is the preferred treatment for most patients with kidney failure to restore renal function, improve survival, and gain better health-related quality of life (HRQOL) compared to maintenance dialysis[8]. Additionally, kidney transplantation has been proven to be more cost-effective than maintenance dialysis[9-11]. The annual costs after successful kidney transplantation could even be reduced to less than 20% of the annual dialysis costs[10]. Previous studies also reported a shrinking break-even point to recoup the transplant costs compared with dialysis costs in the past two decades, namely from 43 months to less than 20 months after kidney transplantation[9, 11].

Despite the known benefits of kidney transplantation, there are also challenges, including the donor organ shortage – a long-existing challenge to the kidney transplant community. To alleviate the donor organ crisis, a consensus meeting composed of multiple stakeholders from the American transplant community proposed to expand the donor pool by including the 'expanded criteria donors' in 2002[12]. An 'expanded criteria donor for kidney transplantation' refers to any deceased donor older than 60 years old, or between 50 and 59

years old with at least two of the following clinical characteristics: serum creatinine >1.5 mg/dl, cerebrovascular cause of death, or history of hypertension[13]. Even though an expended criteria donor was found associated with an overall 70% increased risk of graft failure after kidney transplantation compared to a standard criteria donor, previous research also showed survival benefits after transplantation with an expanded criteria donor in certain subgroups (e.g. dialysis patients older than 40 years who have been on the waiting list for a long time)[13, 14]. The past two decades have indeed seen an increase in the use of deceased donors or expended criteria donors[15, 16]. However, the donor organ shortage is far from being solved. According to data derived from the Eurotransplant Registration and Allocation System, around 3.500 patients received single organ kidney transplantation in Europe in 2020, while the number of patients on the waiting list for a kidney transplant exceeded 10.000 in the same year[17]. Given the foreseeable increase in patients with kidney failure and the limited donors, it is important to maximize the value of kidney transplantation for both individual patients and the healthcare system by improving post-transplant outcomes that are considered relevant to patients.

Patient-relevant outcomes after kidney transplantation

According to Porter's value-based healthcare theory, the value of healthcare is defined as outcomes relative to costs and should be around patients[18]. This patient-centeredness is also echoed by patient-centered medical care, which focuses on patients' needs and expectations regarding their healthcare delivery and decision-making process[19]. To facilitate the incorporation of such needs and expectations, healthcare professionals should be able to adequately inform patients about potential relevant outcomes as a result of different treatment options[20]. Following these healthcare models, the kidney disease community has selected a group of essential outcomes to assess the value and improve the quality of healthcare, including, but not limited to, graft and patient survival. In 2017, the Standardized Outcomes in Nephrology – Kidney Transplantation (SONG-Tx) working group proposed the following six core outcomes to evaluate interventions for kidney transplant recipients (KTRs) in clinical trials: graft health, mortality, cardiovascular disease, malignancy, infection, and life participation[21]. In 2018, the International Consortium for Health Outcomes Measurement (ICHOM) CKD working group also published a set of value-based outcomes for patients with CKD, including KTRs, to monitor, compare and improve the quality of clinical practice (**Table 1**)[22]. According to the ICHOM CKD working group, the essential outcomes for KTRs can be divided into three categories: treatment-specific outcomes (i.e. graft function, graft survival, and malignancy), burden of disease (i.e. survival, hospitalization, and cardiovascular disease [CVE]), and patient-reported outcomes (PROs; i.e. general HRQOL, pain, fatigue, physical function, daily activity, and depression)[22]. Due to the absence of an

established definition for patient-relevant outcomes in kidney transplantation, we considered the combined core outcomes selected by these two international initiatives as patient-relevant outcomes in this dissertation. Below, the current status of these patient-relevant outcomes among KTRs will be described.

Table 1. A standard set of value-based outcomes for CKD patients (including KTRs) by the ICHOM CKD working group and the SONG-Tx.

ICHOM			SONG-Tx
Treatment-specific outcomes	**Burden of disease**	**PROs**	**Core outcomes**
Kidney function	Survival	General HRQOL	Graft health
Vascular access survival	Hospital admission	Pain	Mortality
PD modality survival	CVE	Fatigue	CVE
Kidney allograft function		Physical function	Malignancy
Kidney allograft survival		Daily activity	Infection
Malignancy		Depression	Life participation

The table is adapted from Verberne and colleagues, 2018, and Tong and colleagues, 2017[21, 22]. Abbreviation: CKD, chronic kidney disease; CVE, cardiovascular events; HRQOL, health-related quality of life; ICHOM, the International Consortium for Health Outcomes Measurement; PD, peritoneal dialysis; PROs, patient-reported outcomes; SONG-Tx, the Standardized Outcomes in Nephrology – Kidney Transplantation.

Graft survival and patient survival

Existing evidence shows that kidney function can be restored immediately after transplantation in more than half of the KTRs[23, 24]. In the past 30 years, both short-term and long-term graft and patient survival have improved over time regardless of the donor type, despite the aging population with kidney failure[25]. According to estimates from the latest annual report of the European Renal Association (ERA), the 1-year and 5-year graft survival probabilities were higher than 90% and 80% in KTRs regardless of the donor type and the corresponding patient survival probabilities remained above 90%[17]. Transplant registries in the United States, Canada, Australia, and New Zealand also reported similar graft and patient survival patterns over time[26, 27]. However, improving long-term graft and patient survival remains a major goal for the transplant community. In a previous study in KTRs with deceased donors transplanted between 2005 and 2008, the 10-year graft survival probability was only 57% in Europe and ranged from 34% to 48% across different races in the United States[27]. The reported 10-year patient survival probability for KTRs with deceased donors also further decreased to 65% in the Netherlands, 67% in the United States, and 86% in Spain[28, 29].

Hospital admission

Hospital admission is an indicator of disease burden in KTRs[22]. Previous studies showed that up to 21%-32% of the KTRs had one hospital readmission within the first 30 days after their initial hospital discharge after transplantation[30-33]. Hogan and colleagues also reported at least one hospital readmission in 63% of the KTRs during the first year after transplantation and more than one hospital readmission in 39% of the KTRs[33]. When compared to the general population, KTRs had a 6.4 times higher risk of being readmitted to the hospital; after stratification for post-transplant time, the risk of hospital readmission in KTRs was 40 times higher within the first 2 months after kidney transplantation and stabilized at 6 times higher after 3 years[34]. It should be noted that hospital admission not only exerts a negative impact on patients' HRQOL but also significantly increases the medical resource utilization and cost[35, 36].

Infection, CVE, and malignancy

CVE after kidney transplantation is the leading cause of mortality in KTRs with a functioning graft, followed by infection and malignancy[37-40]. A previous study reported 5%, 8%, and 12% of KTRs with CVE in 1 year, 5 years, and 10 years after transplantation[41]. Due to the immunosuppressive treatment, infection is also common in KTRs[37, 40]. A previous study showed that, in the first 6 months after kidney transplantation, up to 18% of KTRs had an infection requiring hospital admission[42]. Other studies also found at least one infection in 31% and 70% of KTRs in the first 2 and 3 years after kidney transplantation[43, 44]. Finally, KTRs are at a two to four times higher risk of malignancies than age- and gender-matched controls from the general population due to their immunosuppressive treatment, altered T cell immunity, and oncogenic viral infection[39]. Existing evidence shows that the prevalence of solid organ malignancy after kidney transplantation can reach 5% after 5 years, 10% after 10 years, and more than 25% after 20 years[39, 45-47].

PROs in kidney transplantation

With the shift towards patient-centered, value-based healthcare, PROs have drawn increased attention as valuable outcomes next to commonly used traditional professional-reported (clinical) outcomes, such as graft function and patient survival. PROs are outcomes reported by patients pertaining to their perceived health (e.g. HRQOL and functional status) and are measured by patient-reported outcome measures (PROMs), usually in the form of a questionnaire[48].

In KTRs, HRQOL, symptom experience, and life participation have been advocated as essential PROs[21, 22]. Life participation will not be discussed further in this dissertation as an official validated PROM for life participation is not yet available[49]. HRQOL is a commonly used PRO in the evaluation of healthcare, and a large body of research has studied HRQOL in KTRs. So far, systematic reviews have summarized studies before 2010, and results indicate a better HRQOL in KTRs compared to dialysis patients, in particular, the domains physical functioning and bodily pain[8, 50]. When compared to the general population or healthy controls, KTRs had lower to comparable HRQOL[51-58]. However, a comprehensive systematic comparison to summarize the most recent evidence is absent. So far, most studies that investigated HRQOL in KTRs have been conducted cross-sectionally or longitudinally but with limited follow-up time. As a result, little is known about the HRQOL trajectory after kidney transplantation, especially in the long term. Symptom experience is another important PRO in KTRs due to the high burden of CKD- and immunosuppressive treatment-related symptoms[22, 59, 60]. Patients' symptom experience consists of two components: the occurrence of a symptom and its burden if present[60]. Two previous studies reported an average of seven symptoms in prevalent Dutch and British KTRs[61, 62]. According to Afshar et al., a lack of energy was the most burdensome symptom in KTRs, followed by sleeping problems[61]. However, more studies in different populations and among incident patients are lacking to provide in-depth knowledge about post-transplant symptom experience in KTRs.

Taken together, the relatively low long-term graft and patient survival; the moderate to high prevalence of hospital (re)admission, CEV, infection, and malignancy; and the suboptimal PROs in KTRs indicate that there is still room for improvements in patient-relevant outcomes after kidney transplantation.

Optimize patient-relevant outcomes after kidney transplantation

Optimizing patient-relevant outcomes after kidney transplantation requires knowledge on interventional targets for suboptimal outcomes and efficient clinical management in KTRs. Traditionally, approaches to improve outcomes after kidney transplantation focus on clinical outcomes. Potential action points for healthcare professionals to improve such outcomes (i.e. graft and patient survival, CVE, infection, and malignancy) have been well studied and summarized[25, 40, 63, 64]. However, when attention is only given to such clinical outcomes, healthcare professionals may neglect what matters to patients and fail to address how patients feel and deliver inadequate healthcare. As mentioned above, outcomes such as hospital admission and PROs are also core outcomes in KTRs[21, 22]. Hospital admissions in KTRs have been studied mainly in the U.S. as a quality indicator for healthcare, with a specific

focus on readmissions within 30 days after kidney transplantation[30, 33]. Due to different hospital admission policies under different healthcare systems and the advocated new role of hospital (re)admission as an indicator for disease burden, studies with geographic variations and different time frames after transplantation are necessary to examine the prevalence of hospital (re)admission and its risks factors in KTRs. As to PROs, existing studies exploring PROs in KTRs mainly focus on HRQOL and have limited follow-up time. Therefore, studies are needed to map HRQOL as well as other PROs (e.g. symptom experience) with sufficient follow-up time after kidney transplantation and to explore their risk factors. This knowledge will increase our understanding of and provide great opportunities to improve the overall value of kidney transplantation.

Achieving optimal outcomes after kidney transplantation also requires active patient engagement in managing their own healthcare and establishing adequate self-management behaviors, such as medication adherence to chronic immunosuppressive treatment, infection prevention, rejection and infection monitoring, and regular exercise[65-67]. Of these behaviors, medication adherence to immunosuppressants has been emphasized explicitly as crucial by the transplant community because medication non-adherence is a known risk factor for suboptimal graft function and graft loss[68, 69]. In recent years, concepts and tools primarily used in research have been increasingly advocated to enhance patient engagement and improve outcomes in clinical practice. One of the most promising concepts related to health behaviors and outcomes in patients with chronic conditions is‘ illness perceptions’. Illness perceptions, which refers to patients’ personal beliefs about their disease, can impact their coping behaviors (e.g. medication adherence) and subsequently health outcomes according to Leventhal’s Common-Sense Model of Self-regulation[70]. Available evidence has shown associations between helpful illness perceptions and favorable self-management behaviors (e.g. adherence to treatment and adequate exercise) and better health outcomes (e.g. HRQOL and decelerated eGFR decline) in patients with other chronic conditions and patients with CKD stage 4-5[71-75]. However, evidence on illness perceptions in KTRs is scarce.

Finally, PROMs are considered valuable tools to empower patients and increase patient engagement in their healthcare. For patients, PROMs provide an opportunity to express their own opinion regarding their health and healthcare and hence could encourage patients to take up a more active role in their healthcare. For example, the discussion of topics in the consultation room can be prioritized based on health problems reported by patients, outcomes that matter most to them[76]. Furthermore, PROMs can be a potential tool for healthcare professionals to enhance clinical management to achieve better overall health in KTRs. Earlier studies in dialysis and cancer patients have shown improved professionals’

awareness of patients' symptom experience and better symptom management after PROMs implementation[77, 78]. In recent years, efforts have been made to implement PROMs into routine dialysis care in the Netherlands and other countries[79, 80]. However, PROMs are not yet commonly used in routine kidney transplant care.

Aim and outline of this dissertation

This dissertation aims to gain insights into patient-relevant outcomes after kidney transplantation with an emphasis on PROs as well as patients' psychological aspects related to their self-management behaviors (i.e. illness perceptions). The aim of each individual chapter of this dissertation will be introduced below, following the same order as presented in this dissertation.

A functioning graft is the essence of successful kidney transplantation. To achieve optimal graft function after kidney transplantation, adherence to chronic immunosuppressive treatment is of great importance[81]. Previous studies have identified a number of risk factors for medication non-adherence to immunosuppressants. However, the influence of psychological factors such as illness perceptions on medication non-adherence has not been well studied in KTRs. **Chapter 2** presents a cross-sectional study conducted in Leiden University Medical Center (LUMC) to assess the impact of patients' illness perceptions on their self-reported adherence to immunosuppressive medication in prevalent Dutch KTRs with a wide range of time after kidney transplantation. Furthermore, we investigated whether this association differed depending on the time since kidney transplantation to provide further guidance for clinical practice.

Hospital readmission is common in patients after kidney transplantation, which is also advocated as an indicator for disease burden[22, 30]. To our knowledge, hospital readmissions have not yet been well studied in Dutch KTRs. Also, the Netherlands is one of the front runners to increase the use of deceased donors for kidney transplantation due to organ shortage[28]. Therefore, it is of great clinical interest to study the prevalence of hospital readmission in Dutch KTRs and whether donor types influence the risk of hospital readmission. In **Chapter 3**, we investigated the prevalence of 3-month hospital readmission in Dutch KTRs and explored, for the first time in this patient population, whether donor type (i.e. living donor versus deceased donor; donation after cardiac death versus donation after brain death) was a risk factor for 3-month hospital readmission after kidney transplantation using data from the Netherlands Organ Transplant Registry. Although donor type is not always modifiable, tailored care for patients following transplantation with certain donor types is necessary to reduce the risk of short-term hospital readmission in KTRs. To provide further

guidance for clinical practice, we conducted a subgroup analysis to assess whether the influence of donor type on disease burden differed in the young (<65 years) and elderly (≥65 years).

HRQOL is a widely used PRO to evaluate treatment from the patients' viewpoint in scientific research and clinical practice. To understand the merit of kidney transplantation and the potential room for improvement in terms of HRQOL in clinical practice, we conducted a systematic review in **Chapter 4** to map HRQOL in patients after kidney transplantation by summarizing all available literature until now. More specifically, we compared HRQOL of KTRs to that of other relevant populations, including themselves before transplantation, patients on dialysis (i.e. hemodialysis and peritoneal dialysis) with or without being on the waiting list for kidney transplantation, patients with CKD not receiving KRT, the general population, and healthy controls. The results were summarized narratively as a meta-analysis was not feasible due to significant heterogeneity.

The Patient-reported OutcomeS In kidney Transplant recipients: Input of Valuable Endpoints (POSITIVE) study is an ongoing multi-center cohort study to map PROs after kidney transplantation over time in incident Dutch KTRs via implementing PROMs in clinical practice, including HRQOL, symptom experience, and illness perceptions. Using available data from this ongoing study, we explored whether patients' symptom experience (i.e. symptom occurrence and burden) and their illness perceptions about CKD could be a potential interventional target in **Chapter 5**. Specifically, we examined the impact of symptom experience (i.e. symptom occurrence and symptom burden) on HRQOL and investigated whether the influence was mediated by the illness perceptions of their kidney disease.

Despite the increasing attention in patient-centered care, attempts to incorporate patient-reported outcomes in kidney transplant care are limited compared to other disciplines, such as oncology and cardiology. To raise awareness of PROs (e.g. HRQOL and symptom experience) and to promote the use of PROMs in transplantation care, we conducted a narrative literature review in **Chapter 6,** which introduced the concept of PROs and PROMs, summarised the potential benefit of implementing PROMs in kidney transplantation care and commonly-used PROMs for KTRs, and described the ongoing multi-center longitudinal cohort study, the POSITIVE study, to showcase the first attempts to implement PROMs in Dutch KTRs.

Finally, the results from all chapters are summarised and discussed in **Chapter 7**. Furthermore, the clinical implication of our results and future perspectives with regard to patient-relevant outcomes after kidney transplantation are discussed.

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