Navigating the future with chronic kidney disease: towards patient-centred prognostic modelling

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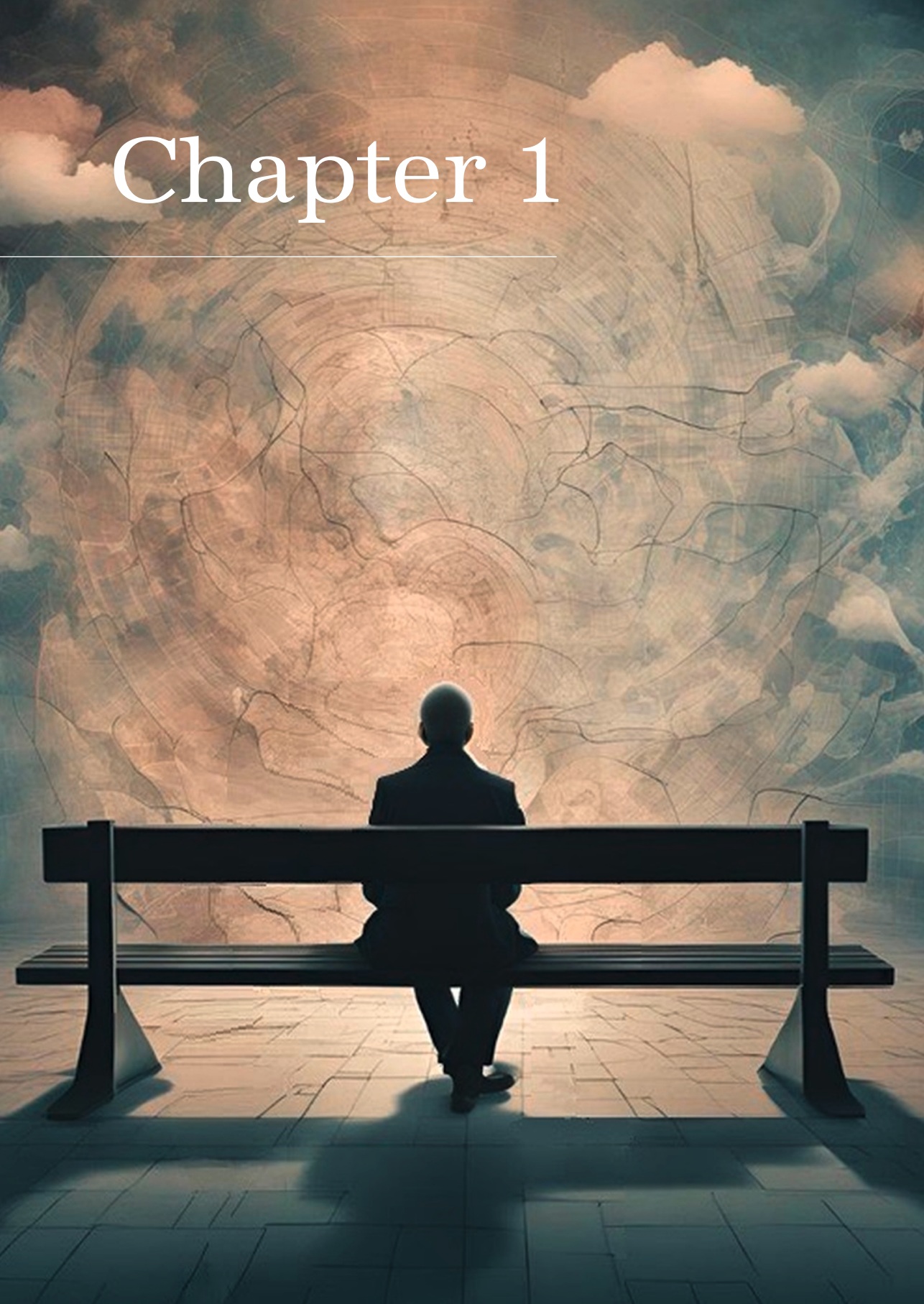
Chapter 1



GENERAL INTRODUCTION AND OUTLINE OF THESIS

General introduction and thesis outline

“I don’t know what lies ahead for me.”

"I fear that the disease will get worse.”

“I really worry about what my life will look like.”

“I wonder what is going to come my way. This makes me feel sad and uncertain.”

These statements, made by patients with chronic kidney disease (CKD), reflect a common experience of those living with the condition: a profound sense of uncertainty about their future. How will the disease progress? How will it affect their daily life, including social activities and personal relationships? What other difficulties will they face along the way? Patients are constantly confronted with prognostic questions, and the unknowns of living with CKD—coupled with its physical symptoms and the emotional difficulties—can become overwhelming. Living with CKD is not only about managing and treating the disease, but also about attempting to regain a sense of control in the face of an uncertain future. Yet, navigating the future is challenging when said future is full of uncertainties, as it is difficult to make plans and prepare for something unknown.

Chronic kidney disease

CKD is a condition that is characterized by a decline in kidney function over time, measured by a reduction in the estimated glomerular filtration rate (eGFR) and/or the presence of markers of kidney damage, such as albuminuria. CKD is diagnosed when the eGFR is consistently below 60 mL/min per 1.73 m^2 or when albuminuria is present for at least three months. (1,2) Currently, CKD affects approximately 10% of the global population, and the multifaceted burden of the disease is continuously growing, with its prevalence expecting to rise due to aging of the population and an accompanying increase in common causes of CKD like hypertension and diabetes mellitus. (3, 4)

In the early stages of CKD, management of the disease focuses on two main aspects: 1) treating the underlying cause of CKD, when possible (e.g. lupus nephritis), and 2) managing risk factors for cardiovascular disease, like hypertension and obesity, to prevent deterioration of kidney function and lower the significantly increased cardiovascular risk in CKD patients. When treating the underlying cause is not possible, the focus shifts to slowing down disease progression and preventing complications through lifestyle changes such as dietary restrictions (e.g. decreased sodium and protein intake), weight management, and increased physical activity. As the kidney disease progresses, the kidneys are no longer able to sufficiently eliminate waste from the body, regulate fluid balance, and maintain other essential functions like the production of hormones such as erythropoietin. To compensate, medical interventions are introduced progressively.

The final stage of CKD, also known as kidney failure or end-stage kidney disease (ESKD), is characterized by a eGFR below 15 mL/min per 1.73 m^2. At this point, patients require medical intervention for survival. Several treatment strategies exist for patients with kidney failure, namely kidney replacement therapy (KRT)—consisting of either dialysis treatment or kidney transplantation—or conservative management. With dialysis treatment, the kidneys' functions are mimicked, and toxins, waste products and excess fluids are removed from the bloodstream artificially. (5) Two main types of dialysis treatment exist: haemodialysis and peritoneal dialysis, with haemodialysis being the most commonly used type of the two. (6,7) During haemodialysis the blood is filtered through an external dialysis machine. Blood is typically drawn through an arteriovenous fistula, graft, or catheter, as a regular intravenous line cannot provide the flow that is required for effective dialysis. The blood then circulates through a dialyzer in which waste and excess fluids are extracted, before it is returned to the body. (8) Contrarily, for peritoneal dialysis, the patient's peritoneal membrane is used as a natural filter. Through a catheter, a dialysate is introduced into the abdominal cavity, where it absorbs waste and excess fluids. After, the dialysate is drained and substituted by fresh fluid. (9) Although both dialysis types come with their own advantages and disadvantages, dialysis treatment significantly impacts patients' lives, and treatment-related burden is high. (10, 11) Haemodialysis is usually performed three times per week at the hospital, a dialysis centre or sometimes at home, and sessions usually last three to four hours, or eight hours if performed at night. (5) Despite advances in haemodialysis technology since its invention, the treatment remains burdensome. Patients experience many treatment-related symptoms, and it takes them on average five to seven hours to recover from each session. (12-15) Furthermore, patients may encounter issues with vascular access and treatment-related complications like intradialytic hypotension. (16, 17) In contrast to haemodialysis, peritoneal dialysis is usually performed at the patients' homes, and sessions are performed every day or night. Although daily treatment may seem like a greater burden, peritoneal dialysis can offer patients more independence and more flexibility in planning their treatment around their daily activities as opposed to haemodialysis, enabling them to better maintain their work, social life, and to travel more easily. However, this flexibility is highly patient-dependent, and some individuals may find that haemodialysis offers them more independence or a structured routine that better fits their lifestyle. In addition, peritoneal dialysis comes with other disadvantages, such as the risk of peritonitis and peritoneal membrane failure. (5, 18, 19) Despite dialysis being an important lifeline to many CKD patients, mortality rates remain high, with up to 20% of patients dying within a year after dialysis initiation. (20, 21) Kidney transplantation is often seen as the most favourable treatment for many patients with kidney failure, as it offers the best chances of improved survival and health-related quality of life. Furthermore, a successful kidney transplantation allows patients to avoid the burdensome dialysis treatment and its accompanying complications. (22-24) Kidney transplantation, however, comes with its own challenges. First, not all patients are eligible for a transplantation, and there is a global shortage of donor kidneys, leading to waiting times that can range from months up to several years. (25, 26) Some waitlisted patients may never receive a kidney transplant.

One way to reduce waiting times is through living donor kidney transplantations, where a healthy individual (e.g. a family member) donates a kidney to the patient with CKD. Second, kidney transplantation involves the risk of intraoperative complications, such as bleeding, and patients have to commit to a lifetime of post-operative care and medication regimes. (27) Recipients have to take immunosuppressive medication to prevent rejection of the donor kidney. Besides coming with a variety of burdensome side effects, immunosuppressives also increase the risk of certain cancer types and infections. (28-30) For those that cannot or do not want to receive KRT, conservative kidney management exists. Although KRT is also aimed at symptom reduction and preservation of quality of life, it primarily aims to prolong life. Contrarily, conservative management primarily focuses on symptom management, slowing down disease progression, and preserving health-related quality of life through medication and lifestyle modifications. (31, 32)

In addition to the treatment burden, CKD in itself is a burdensome disease, as patients experience numerous debilitating symptoms, including severe itch, pain and fatigue. (33) Beyond these physical symptoms, mental health issues like depression and anxiety are also prevalent in this population, further adding to the burden. (34) These symptoms impact many aspects of patients' lives, such as their ability to work, their life participation and overall quality of life. (35, 36) Besides CKD, patients often face a multitude of comorbidities like cardiovascular disease, hypertension and diabetes mellitus. (37) Unsurprisingly, quality of life is considerably lower in CKD patients when compared to that of the general population. (38) Finally, CKD patients are at an increased risk of adverse outcomes, such as cardiovascular events, progression to kidney failure, initiation of KRT, and death. (39, 40)

Prognostic uncertainty in patients with chronic kidney disease

Confronted with all these challenges, patients with CKD often struggle with uncertainty regarding their prognosis. The course of CKD varies greatly per individual, making it even harder for patients to foresee what the future has in store for them. The uncertain nature of the disease trajectory, together with the increased risk of many different adverse outcomes and burdensome symptoms, causes patients to experience feelings of hopelessness and fear upon being diagnosed with CKD. (41) The asymptomatic nature of the disease in the early stages can further add to this uncertainty. As patients may not yet experience many symptoms early on, there is often a certain scepticism regarding their diagnosis, and they are largely unaware of the major impact the disease will most likely have on their life. (41-43)

Prognostic uncertainty is thus a recurring and important theme in nephrology and is closely related to patients' mental health. Having to cope with this plethora of uncertainties can contribute to the risk of mental health issues like depression and anxiety, and may cause patients to feel like they are not in control over their own lives and health. (41, 44, 45) In addition to the emotional toll this prognostic uncertainty may take on patients, it can also act as an important barrier to self-management. For effective self-management, patients need to actively engage by closely monitoring their health, and by adhering to prescribed medication regimens and recommended lifestyle modifications. However, a lack of knowledge on the trajectory of the disease or the potential benefit of their efforts may limit patients' motivation to engage in these activities. (46, 47)

Prognostic information provision in nephrological care

Addressing this prognostic uncertainty is crucial in nephrological care, and patients with CKD have often expressed a need to be informed about their prognosis. (41, 44, 45, 48) Due to the complex and variable nature of CKD, accurate and individualized prognostic information is often not easily available. Yet, engaging in open and patient-centred discussions about the future can be of great benefit to patients. Even when healthcare providers cannot provide answers or solutions, patients report that discussing topics that matter to them is very relevant, as it makes them feel heard and understood. (49, 50) Beyond discussing potential outcomes, these discussions should focus on the individual's concerns and preferences in regard to their future with CKD.

Providing patients with more individualized prognostic information can benefit them in several ways. First, over the course of the disease patients have to make multiple difficult treatment decisions in consultation with their healthcare provider. To support these discussions and to empower patients to actively engage in this process of shared-decision making, it is important that they feel well-informed about the complex treatment options and their potential benefits, challenges, and the impact each option may have on their future. Moreover, with more knowledge, patients can make choices that better align with their values and life preferences. Second, knowledge is a key facilitator of self-management, as understanding their prognosis allows patients to adopt proactive self-management strategies, and to prioritize activities, treatments, and lifestyle changes that could help delay disease progression. (47, 51) Finally, by simply informing patients on *what* they can expect in the future, and *when* to expect certain outcomes, patients can regain a sense of autonomy and control after being diagnosed with CKD, allowing them to better cope with the disease. Besides, gaining more knowledge about the future may support patients in fostering a sense of hope, and may aid in preparing for the future with CKD. (52)

Even so, patients' prognostic information needs and preferences may vary significantly. Where some patients may actively search for as much information as possible to prepare for what is to come, others may prefer not knowing what lies ahead. Beyond every individual's personality and personal characteristics, these preferences may also depend on the topic of concern or the context in which they arise; for instance, patients might be specifically interested in receiving prognostic information on preventable outcomes, or information that supports them in their treatment decisions. Individual patient characteristics, such as age, gender, disease stage or cultural background can further shape patients' preferences. Acknowledging and taking this individuality in preferences into consideration is crucial in providing patient-centred care.

Beyond creating more space and awareness for patients' concerns regarding their future with CKD, healthcare providers have several other opportunities to provide their patients with more prognostic information. A first, and commonly used approach is to explain the expected course of the disease based on clinical expertise and experience. For instance, in the early stages of CKD, healthcare providers often discuss prognostic information to inform patients for treatment decisions. Several decision aid tools and dashboards with disease-related data exist to support healthcare providers and patients in obtaining relevant information. (53) Furthermore, a large body of literature exists on the evolution of many CKD-related outcomes, such as changes in symptom burden and health-related quality of life before and after dialysis initiation. (54, 55) While this information is not fully tailored to an individual's unique characteristics, it is often stratified into broader patient groups based on important clinical factors like age and kidney function. This stratified information offers patients a general idea of what to expect in the future, but the more personalized prognostic information becomes, the more relevant it may be for individual patients.

Prognostic prediction models

Prognostic prediction models take this a step further by providing more individualized information. Prognostic models are aimed at estimating an individual's risk of specific outcomes, based on a selection of patient characteristics (i.e. predictors). By doing so, patients and their healthcare providers can better understand the expected disease trajectory of that individual. Thus, prognostic models and the individualized predictions they provide hold great potential to improve prognostic information provision in nephrology for a number of reasons. First, prognostic models may support patients in navigating the future by diminishing some of the prognostic uncertainty they experience, and may help them regain a sense of control. Second, the prognostic information obtained from models can empower patients to actively take part in shared-decision making and help them make treatment decisions. (56) For example, when healthcare providers inform patients on treatment decisions, they often indirectly perform a risk assessment of that individual. Although it is not a formal risk calculation, it is a type of prediction based on the intuition and expertise of the healthcare provider. This risk assessment is often also based on extrapolations of patient characteristics, such as the GFR slope or the patient's age, similar to what prognostic models do. Prognostic models can be valuable in supporting this process and can reduce uncertainty

in risk estimations. While experienced clinicians base their risk assessments on clinical intuition and experience that was built over years of working in clinical practice, newer clinicians, in particular, may benefit even more from the specific and individualized predictions these models provide. However, even experienced healthcare providers may struggle to estimate individual risks as it usually depends on a multitude of factors. Prognostic models can thus complement clinical expertise by systematically incorporating a broad range of patient characteristics, offering more accurate and individualized risk predictions. Finally, prognostic models play an important role in referral strategies and planning of healthcare. Currently, prognostic models are used to guide referral to a nephrologist or to timely plan vascular access for KRT by predicting the risk of disease progression in patients with early CKD. (57-59) Moreover, prognostic models are used to support kidney allocation in the United States by predicting the risk of kidney graft failure and mortality in recipients, highlighting the importance of the accuracy of these models. (60-62) A few models are currently endorsed in clinical guidelines for abovementioned purposes, such as the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. (63, 64) Examples of recommended models are the kidney failure risk equation (KFRE) and the Kidney Donor Risk Index (KDRI). (57, 60)

A specific example of the use of prognostic models in nephrology concerns the prediction of mortality risk in patients starting dialysis treatment. In this case, models can be used to identify those that are at an increased of risk of dying after dialysis initiation. By identifying these patients, a different approach in treatment strategy can be considered. For instance, these patients can be monitored more closely, or treatment can be intensified if needed. Conversely, for high-risk patients, a strategy focused on quality of life can be considered instead, and strategies like decremental dialysis or earlier transition from dialysis treatment to palliative care can be chosen. (65, 66)

However, despite their potential, so far the use of such models in nephrological practice remains limited, and lags behind other medical fields. (67-69) Many models already exist, and new models are continuously being developed for a wide range of populations and outcomes. Yet, their uptake is limited, and multiple reasons can be thought of to explain this gap between prognostic research and clinical practice, including poor performance, poor methodology, a lack of external validation and impact assessment, limited uptake in clinical guidelines, and a lack of recognition and trust from healthcare providers. (56)

Towards patient-centred prognostic modelling

Besides the abovementioned limitations of current prognostic research in nephrology, another aspect plays an important role: the patient perspective is mostly ignored in nephrological prediction models. Most existing prognostic models focus on traditional clinical outcomes like mortality and disease progression, and are primarily designed for use by healthcare providers, rather than being patient-centred. Although said clinical outcomes are relevant to patients too, they often prioritize other outcomes, such as quality of life, fatigue, and other symptoms. (70) The value of these so-called patient-reported outcomes (PROs) is increasingly recognized in nephrology, as they have the potential to improve patient outcomes and quality of care. (50, 71) Yet, the use of PROs as outcomes of prognostic models remains unchartered territory. In other medical fields, prognostic models for PROs like health-related quality of life have been developed, proving that it is possible to predict outcomes beyond mortality and disease progression. (72, 73) In 2018, the development of models for PROs other than kidney failure, such as hospitalizations and functional status, was also urged in a KDIGO conference report. (74) In addition, the predictors used in prognostic models are mostly clinical predictors like age, gender, laboratory measurements, comorbidities and treatment-specific variables, such as dialysis modality. However, evidence from other medical fields (e.g. oncology) suggests that PROs can provide valuable prognostic information beyond the standard clinical predictors. (75) It seems plausible that patients have a good intuitive understanding of their own health and its current status. The incorporation of PROs as predictors in prognostic models could potentially improve their predictive performance and accuracy. However, despite the growing recognition and use of PROs in nephrological patient care, their potential as outcomes and predictors for prognostic models remains largely unexplored.

Objective

The primary objective of this thesis is to improve patient-centred prognostic information provision in nephrology. To do so, we first explore patients' perspectives on their future with CKD, their individual needs and preferences for prognostic information provision, and which prognostic topics matter most to patients themselves. We uncover current gaps in the provision of prognostic information and propose ways to better meet patients' needs. Second, while prognostic models show great potential to provide both healthcare professionals and patients with more individualized prognostic information, they are sparsely used in nephrology care. Therefore, we map out the field of prognostic modelling research in nephrology to see where it currently stands, and where knowledge gaps remain. Furthermore, by finding common pitfalls in prediction research and by identifying novel, and more patient-centred ways to develop and improve prognostic models, we take a first step to bridge the gap between promising prognostic models and their implementation in nephrological care.

Outline of this thesis

Chapter 2 describes a survey study in which we aim to assess whether patients with CKD want to know more about their future, and if so, which topics matter most to them in terms of prognosis. Additionally, we evaluated differences between several subgroups [CKD stage (CKD without KRT, dialysis and kidney transplantation), gender and age]. To do so, we distributed a survey, created together with patient representatives, amongst CKD patients of various disease stages. By identifying the prognostic topics that patients prioritise, more attention can be paid to these topics in both clinical practice and future research. For instance, prognostic models can then be developed for a broader spectrum of outcomes, especially those that matter to patients themselves.

In **Chapter 3** we build on the findings of the first survey study, and aim to explore how patients with CKD perceive their future and what their prognostic needs are. Responses to open-ended questions from the same survey are analysed using thematic qualitative analysis, providing in-depth insights into patients' perspectives and informational needs regarding their future with CKD. This chapter, together with Chapter 2 sets the groundwork for understanding what patients' needs and preferences are for prognostic information provision, and how tailored prognostic discussions can improve patient-centred care in nephrology.

In **Chapter 4,** we present a scoping review in which we map out all existing studies that develop, validate, or update a prognostic prediction model for CKD or KRT patients. By giving a comprehensive overview of the field, including the methodological rigour and the range of populations and outcomes that were used, we aim to take a first step in bridging the gap between promising prognostic models and their implementation in nephrological care. This overview can be used to see where we currently stand and where knowledge gaps remain when it comes to nephrological prognostic models.

Chapter 5 describes whether PROs can improve the prediction of two-year mortality in patients starting dialysis. Using data from the NECOSAD and EQUAL cohorts, we build a base prognostic model using traditional clinical predictors (e.g. demographics, laboratory measurements and comorbidities), and assess the predictive value of various PROs by adding these to the base model. A wide variety of performance measures, including the area under the curve (AUC), measures of calibration, Brier score, likelihood ratio tests, reclassification tables, net reclassification indices, integrated discrimination improvements, and decision curve analyses are used to evaluate the added predictive value of the PROs. In addition, we assess different combinations of predictors, and each PRO individually. This chapter provides insights into the potential of PROs to enhance prognostic models in nephrology.

In the final chapter of this thesis, **Chapter 6**, we summarize and discuss our results. Additionally, we describe the clinical implications of our work, and provide suggestions for future research regarding prognostic information provision in nephrological care.

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