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Prognostic Models in Nephrology: Where Do We Stand and Where Do We Go from Here? Mapping Out the Evidence in a Scoping Review

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ABSTRACT

Prognostic models can strongly support individualized care provision and well-informed shared decision making. There has been an upsurge of prognostic research in the field of nephrology, but the uptake of prognostic models in clinical practice remains limited. Therefore, we map out the research field of prognostic models for kidney patients and provide directions on how to proceed from here. We performed a scoping review of studies developing, validating, or updating a prognostic model for patients with CKD. We searched all published models in PubMed and Embase and report predicted outcomes, methodological quality, and validation and/or updating efforts. We found 602 studies, of which 30.1% concerned CKD populations, 31.6% dialysis populations, and 38.4% kidney transplantation populations. The most frequently predicted outcomes were mortality ($n=129$), kidney disease progression ($n=75$), and kidney graft survival ($n=54$). Most studies provided discrimination measures (80.4%), but much less showed calibration results (43.4%). Of the 415 development studies, 28.0% did not perform any validation and 57.6% performed only internal validation. Moreover, only 111 models (26.7%) were externally validated either in the development study itself or in an independent external validation study. Finally, in 45.8% of development studies no useable version of the model was reported. To conclude, many prognostic models have been developed for patients with CKD, mainly for outcomes related to kidney disease progression and patient/graft survival. To bridge the gap between prediction research and kidney patient care, patient-reported outcomes, methodological rigor, complete reporting of prognostic models, external validation, updating, and impact assessment urgently need more attention.

A personalized approach is needed to tailor care to the variable disease trajectory and personal preferences. Prognostic models can be powerful tools to enhance patient-centered care provision in nephrology because they can provide individualized prognostic information. Previous research has shown that most patients with CKD and RRT patients have an explicit wish to receive more information about their future with the disease. Prognostic models can help patients gain more knowledge on the course of their disease, which in turn may help them regain a sense of control and help them cope with living with the disease.^{7,8}

Moreover, patients with CKD and their health care professionals have to make many decisions over the course of the disease. Prognostic models can be used to support this process of shared decision making and its timing by

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INTRODUCTION

Individuals with CKD and those receiving RRT experience numerous symptoms and are confronted with an increased risk of mortality and a multitude of comorbidities, such as cardiovascular disease and kidney failure.^{1–3}

Unsurprisingly, quality of life (QoL) is reported to be lower in patients with CKD compared with that of the general population, and treatment-related burden is often high.^{4–6} The disease trajectory varies across individuals, causing patients to go through many phases of uncertainty regarding their prognosis.

identifying patients at high risk of certain outcomes and by providing both the clinician and the patient with more information on the individual disease trajectory.^{8–10}

Despite the potential of these prognostic models, their clinical use and impact in nephrology lag behind other medical fields.^{11–13} Only a handful of models are actually implemented in clinical practice, and it is unclear how many prognostic models exist for the CKD population, which outcomes they predict, and what the status of these models is in terms of methodological robustness. Several systematic reviews of prognostic studies have previously been conducted, but all were aimed at specific outcomes, such as mortality and kidney failure or specific populations, and a broad overview of all studies dedicated to developing, validating, or updating a prognostic model has not yet been presented.^{14–17} The aim of this scoping review was to map out existing studies that develop, validate, or update a prognostic model for patients with CKD or RRT patients, detailing their methodological rigor and their range in populations and outcomes. This comprehensive overview of the entire field is needed to see where we currently stand, where knowledge gaps remain, and how to progress from here to bridge the gap between promising prognostic models and their implementation in clinical care.

METHODS

This study was conducted in line with the methodological framework for scoping reviews as proposed by Arksey and O'Malley in 2005.¹⁸ In addition, the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews was adhered to, to ensure transparent reporting (Supplemental Table 1).^{19,20} Scoping reviews are aimed at mapping the body of literature on a particular research topic and generally concern a broader research question than those that are used in systematic reviews.²¹

Study Selection

To identify studies that describe prognostic prediction models for all outcomes relevant for patients with CKD at any stage and RRT populations, a literature search was performed in PubMed and Embase. All studies published before January 1, 2022, were considered. Studies were included if they met the following criteria: (1) The study must aim to develop, validate, or update at least one formal multivariable prognostic model and (2) the study population must consist of adults with CKD, patients receiving chronic dialysis, or kidney transplantation patients (waitlisted patients, recipients, and donors). Studies concerning patients undergoing a combined transplantation procedure (e.g., combined liver–kidney transplantation or pancreas–kidney transplantation) or patients with AKI were excluded. Furthermore, studies with a methodological or statistical aim, diagnostic models, pharmacokinetic explanatory models, studies solely testing for associations, and prognostic finding studies were excluded. Only English language studies were included, and no date limit was set. The complete search strategy is presented in the Supplemental Material. All identified studies were screened for relevance by J. Milders and independently by a second reviewer (C.L. Ramspek, R.J. Janse, or M. van Diepen). Discrepancies on study inclusion were resolved by consulting a third reviewer (M. van Diepen). Reference lists of the included studies and relevant reviews were manually screened to identify any additional studies for inclusion.

Data Extraction

Relevant data were extracted from the included studies by J. Milders using a data extraction form. First, general characteristics of all studies were extracted, including year of publication, continent of publication, study type (development, validation, update, or a combination), the prognostic model of interest, the study population (CKD, dialysis, or kidney transplantation), and the predicted outcome. Second, data were extracted on sample size, whether the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Di-

agnosis (TRIPOD) guideline was referenced, and whether discrimination, calibration, or reclassification measures were reported.^{22,23} In addition, for the studies in which a prognostic model was developed, data on how the prognostic model was presented (e.g., full regression formula or risk score), whether internal and/or external validation was performed, and model derivation method (conventional regression modeling (e.g., linear regression, logistic regression, or Cox proportional hazards regression) or machine learning) were extracted. In the Supplemental Material, elaboration on extracted data and choices made regarding classification of studies is available.

Analysis

All findings were summarized using descriptive statistics. Continuous variables are presented as mean values with SDs or median values with interquartile ranges, depending on their distribution. Categorical variables are presented as numbers with percentages. R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses and figures included in this study.

RESULTS

Study Selection

In total, 4169 potentially relevant studies were identified through PubMed and Embase, and their titles and abstracts were screened. Of these, 776 studies were selected for full-text review. Through screening of the references of included studies, 36 additional studies were identified. Finally, 602 studies met the inclusion criteria and were included in the scoping review. A Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram of the study selection process is presented in Figure 1, and an overview of all included studies and their extracted data is included in the Supplemental Material.

General Characteristics of Included Studies

Of the included studies, the first study was published in 1982.²⁴ Since then,

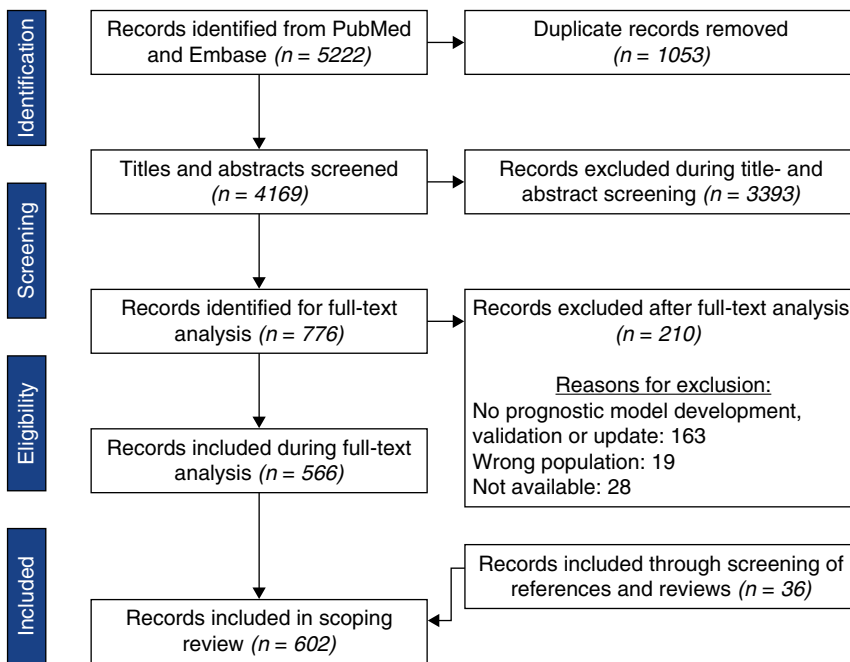


Figure 1. PRISMA flow diagram of the study selection process. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

there has been a steep increase in the amount of prognostic modeling studies published per year, with a record of 96 studies in the year 2021 (Figure 2). Moreover, there has been an increase in all types of prediction studies (development, validation, and update).

Studies included mainly patients from Europe ($n=221$, 34.2%), North America ($n=210$, 32.5%), and Asia ($n=181$, 28.0%). Very few studies included patients from South America ($n=17$, 2.6%) and Australia ($n=15$, 2.3%), and only three studies (0.5%) included patients from Africa. The world map in Supplemental Figure 1 shows the distribution of the included studies over the continents. Of the 602 included studies, 181 (30.1%) concerned a CKD population, 190 (31.6%) a dialysis population, and 231 (38.4%) a kidney transplantation population. Figure 3 shows how many development, validation, update, or combination studies were published. In short, 415 studies developed a prognostic model, 205 studies externally validated an already existing model, and 62 studies updated a model. Studies with multiple aims were counted in all applicable study type categories (e.g., a study in which a model was developed and

also an existing model was externally validated was counted in both the development and the validation category).

In the 415 development studies, 447 prognostic models were proposed, covering a wide variety of predicted outcomes. To provide a comprehensible overview, the outcomes were divided into 22 categories. In Supplemental Table 2, an explanation of the outcome categories can be found. Overall, outcomes that were most often predicted were mortality ($n=129$), kidney disease progression ($n=75$), and kidney graft survival ($n=54$) (Figure 4).

Methodology and Reporting of Studies

Sample sizes of the included studies varied highly, with a median (interquartile range [IQR]) of 746 (262–3180) (Figure 5). A total of 141 (23.4%) studies used a sample size of <250 participants, and 112 studies (18.6%) included more than 5000 participants.

Of the studies published after the TRIPOD publication date in 2015 ($n=399$), only 56 (14.0%) referred to the reporting guideline. In 2021, there was a steep increase, and nearly 30% of the studies referenced it (Supplemental Figure 2).

In our sample of studies, 484 (80.4%) studies presented a measure of discrimination, and only 261 (43.4%) studies presented a measure of calibration. Over time, more studies reported measures of discrimination while reporting of calibration did not increase (Supplemental Figure 3). Examples of alternative performance measures that were presented include the likelihood ratio test, mean absolute/squared error, and sensitivity and specificity for a specific cutoff (mainly for artificial intelligence-based models). Of the 62 studies that reported on the updating of a model, 27 (43.5%) reported the net reclassification index and/or the integrated discrimination improvement. Update studies that did not include a net reclassification index and/or integrated discrimination improvement usually did include performance measures, such as c-statistics, calibration plots, and likelihood ratio tests.

Most development studies ($n=312$, 75.2%) used conventional regression modeling techniques, and 59 (14.2%) studies used a form of machine learning. The remaining studies ($n=44$, 10.6%) developed both types of models and generally aimed to compare the performance of the newer machine learning techniques with that of a conventional logistic regression model.

Finally, of the 415 development studies, only 120 (28.9%) reported their full model formulas so that absolute risks could be calculated from the model. Furthermore, 71 (17.1%) studies presented a risk score, and 34 (8.2%) presented both. The remainder studies ($n=190$, 45.8%) did not report a useable version of their models, meaning that they neither reported an intercept with the regression coefficients nor any information on how to calculate risks on the basis of the developed model. Of the 59 studies in which machine learning techniques were used to develop a model, only 10 (16.9%) studies provided a useable format of the model. The data of this section are summarized in Table 1.

Data on methodology and reporting of the included studies did not differ between the three populations (CKD,

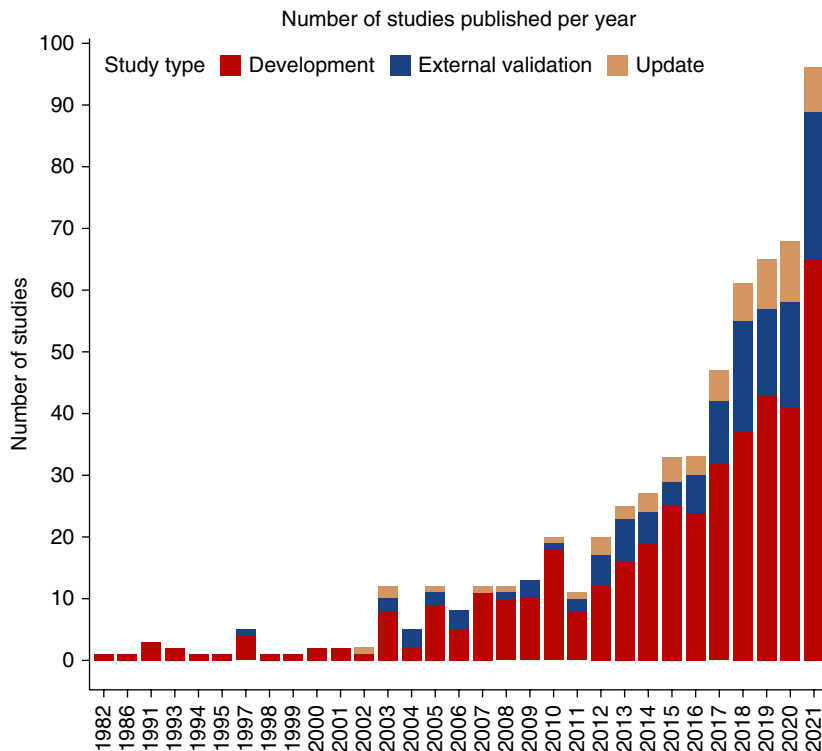


Figure 2. Number of studies published per year. Development=studies of which the main aim is to develop a novel prognostic model. This category may also include studies that, besides developing a model, also externally validate an existing model. External validation=studies that solely externally validate an already existing model. Update=studies of which the main aim is to update an existing model. This category may also include studies that, besides updating a model, also externally validate that same model.

dialysis, and kidney transplantation) (Supplemental Table 3).

In Supplemental Figure 4, we present a flowchart that shows how many models were presented in a useable format, how many were accompanied by a measure of discrimination and calibration, how many models were validated internally and externally, and how many models were developed in a sample size larger than 250 patients. In the end, only 49 (11.0%) models remain for which all the abovementioned steps were completed.

Validation and Updating

Within-Study Validation

In the 415 development studies, most researchers only performed internal validation ($n=239$, 57.6%), and in more than a quarter of these studies, no validation steps were undertaken at all ($n=116$, 28.0%). A small number of studies performed external validation

of their developed models within the same study ($n=60$, 14.5%), of which 37 (8.9%) performed both internal and external validations. Over the past 15 years, no clear increase in validation efforts was observed (Supplemental Figure 5).

External Validation and Updating

From the development studies that were included in this review, we identified which models were repeatedly validated and updated. Of the 415 development studies and their models, only 111 (26.7%) were externally validated either in the development study itself or in subsequent independent external validation studies. Of these, 43 (38.7%) were solely validated externally within the development study itself (Supplemental Table 4). If validated at all, most models were externally validated only once ($n=70$). The remainder ($n=41$) was validated more

often, with a median (IQR) of 3.0 (2.0–4.0). The number of models that were externally validated once, two to five times, and more than five times, stratified by population, is presented in Figure 6. Moreover, 17 development studies and their corresponding models were updated in a separate study. Most models ($n=11$) were updated only once, and the remainder ($n=6$) was updated with a median (IQR) of 2.5 (2.0–4.5). By far, the most validated and updated model was the kidney failure risk equation (KFRE) with 34 external validation studies and eight update studies.²⁵

Validation of Prognostic Models from Other Populations

39.0% of included validation studies and 48.4% of update studies concerned prognostic models that were not originally intended for a CKD/RRT population, such as general comorbidity scores and so on. The model that was validated ($n=19$) and updated ($n=14$) the most was the Framingham risk score for cardiovascular events.²⁶

Comparative External Validation Studies

We identified 35 comparative external validation studies in which the predictive abilities of more than two prognostic models were compared through validation within the same cohort. Two main types of comparative external validation studies were identified: (1) studies in which a newly developed model is compared with multiple already existing models and (2) studies which aimed to systematically search and externally validate all or the most widely used models for a certain outcome. Three (8.6%) studies were of the first type, and the remaining 32 (91.4%) studies were of the second type. The number of models that were compared per study varied, with a median (IQR) of 4.0 (3.0–5.0) models. In three of the found studies, more than ten models were validated.^{14,15,27}

CKD Models

In total, 124 studies were included that presented models developed in a CKD population; most of these ($n=75$)

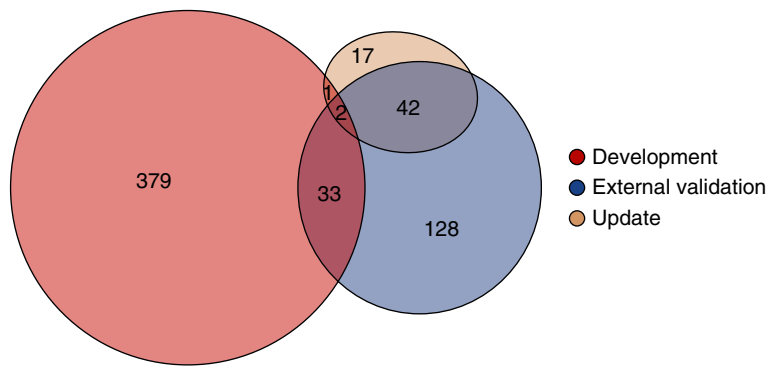


Figure 3. Euler diagram of study types (development, validation, and update). Development studies in which a model was also externally validated are only counted in the development group. The external validation category consists of independent external validation studies in which an existing model is validated.

predicted kidney disease progression, which encompasses outcomes, such as dialysis initiation, eGFR decline, or an increase in serum creatinine. The second and third largest outcome categories for patients with CKD were mortality ($n=18$) and cardiovascular events/death ($n=13$). Two studies included patients receiving conservative care, of which one aimed to predict cardiovascular events and the other mortality.^{28,29}

Of the 75 CKD models predicting kidney disease progression, most ($n=47$, 62.7%) were never externally validated. Of 18 models predicting mortality, 5 (27.7%) models were externally validated once within the development study itself, and of the cardiovascular event models, 2 (15.4%) were externally validated within the development study. For CKD populations, the most validated and updated model was the aforementioned KFRE with 34 external validations and eight update studies, followed by the Framingham risk score which was externally validated in eight studies and updated in ten.

Dialysis Models

For dialysis populations, we identified 151 models, of which most predicted the outcomes mortality ($n=80$), cardiovascular events ($n=20$), and vascular access-related outcomes, such as arteriovenous fistula failure or maturation ($n=16$).

Of the models predicting mortality, cardiovascular events, and vascular

access-related outcomes, 72.2%, 90.0%, and 87.5% were never externally validated, respectively. Furthermore, 6.3%, 5.0%, and 0.0%, respectively, were externally validated solely within the development study itself. Three models predicting mortality were updated, one model predicting cardiovascular events, and one model for vascular access-related outcomes.

In the dialysis population, the Geriatric Nutritional Risk Index (GNRI) and the Charlson Comorbidity Index (CCI) were validated most often. The GNRI and the CCI were validated in ten and nine separate studies, respectively. Both models were originally developed in different populations to predict long-term mortality.^{30,31} In addition, the GNRI and CCI were both updated once.

Kidney Transplantation Models

Of the 178 models that were made for kidney transplantation populations, the majority predicted graft survival ($n=54$), recipient mortality ($n=31$), and delayed graft function ($n=24$).

Most models for graft survival, recipient mortality, and delayed graft function were never externally validated, 64.2%, 74.2%, and 66.7%, respectively. Moreover, 18.9%, 12.9%, and 8.3%, respectively, were only externally validated within their development study. Four models for graft survival, one model for mortality, and one model for delayed graft function were updated.

The model that was most often validated and updated was the Kidney Do-

nor Risk Index (KDRI) with a total of 26 external validation studies and five update studies. The KDRI was originally developed by Rao *et al.* in 2009 to predict recipient and graft survival after kidney transplantation.³² A nomogram to predict delayed graft function after kidney transplantation by Irish *et al.* and its updated version was externally validated in 11 separate external validation studies.^{33,34} Three other models predicting patient and graft survival and delayed graft function were externally validated and updated relatively frequently.^{35–37}

DISCUSSION

This scoping review provides a comprehensive overview of 602 studies describing the development, validation, or updating of prognostic models in patients with CKD and/or RRT, including information on their reporting and methodology, predicted outcome definitions and external validation, and updating of existing models.

Populations

Many prediction models exist for a wide variety of patients with CKD. However, certain patient groups are currently severely underrepresented. For example, only two studies included patients receiving conservative care as opposed to RRT. Moreover, very few studies include patients from South America, Australia, and Africa. Relevant predictors and model performance vary highly on the basis of differences in populations and their health care system. It, therefore, remains unknown whether any of the existing prediction models are generalizable to patients from these underrepresented continents.

Outcomes

From our findings it becomes apparent that current prognostic research mainly focuses on traditional clinical outcomes, such as kidney disease progression, mortality, graft survival, and cardiovascular events. These outcomes are instinctively of great importance to both clinicians and patients themselves, and they have

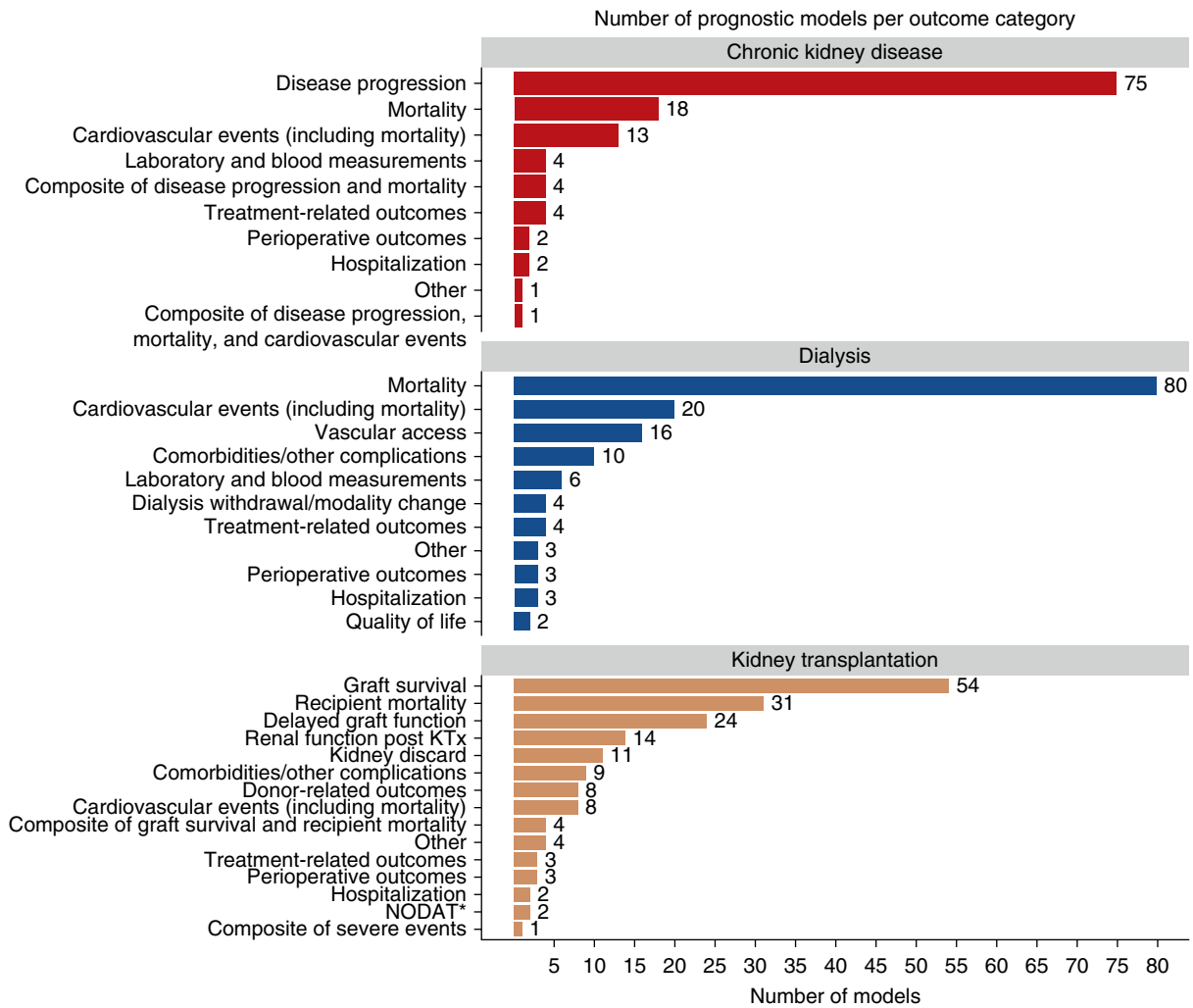


Figure 4. Number of prognostic models per outcome category. Studies in which multiple outcomes were predicted were counted in all applicable outcome categories. For example, a study in which both kidney disease progression and mortality were predicted was included in both outcome categories. Therefore, the total number of models adds up to more than the total number of development studies. *New-onset diabetes mellitus after transplantation. KTx, kidney transplantation.

the potential to positively contribute to patient care by identifying high-risk patients and treatment opportunities and by supporting prognostic information provision. However, the patient perspective remains rather unexplored in prognostic research. The importance of patient-reported outcomes (PROs), such as health-related QoL (HRQoL) and symptom burden, and their potential for use in clinical practice is increasingly recognized. Although this is a relatively novel take on prognostic research in all medical fields, some models have been developed for PROs like HRQoL in other populations, proving

that it is feasible to predict outcomes other than mortality and treatment initiation.^{38,39} In 2018, a Kidney Disease Improving Global Outcomes (KDIGO) report also urged prognostic model development for outcomes other than kidney failure, such as functional status and hospitalizations.⁴⁰ However, on the basis of our findings, we can conclude that methodologically robust, validated models for such outcomes currently do not exist in the field of nephrology. An important barrier to the development of prognostic models to predict PROs is the limited uptake of such outcomes in data sets. Therefore, we recommend

increasing the inclusion of PROs in novel data sources.

Methodology and Reporting of Studies

Methodology and reporting of prediction studies is often inadequate, and from this review we can conclude that prognostic research for kidney patients is no exception to this.^{41,42} First, many studies included a relatively small sample of patients. When developing a prognostic model, it is crucial to use a sufficient sample size to reduce the risk of overfitting and consequently inaccurate risk predictions.⁴³ Recently,

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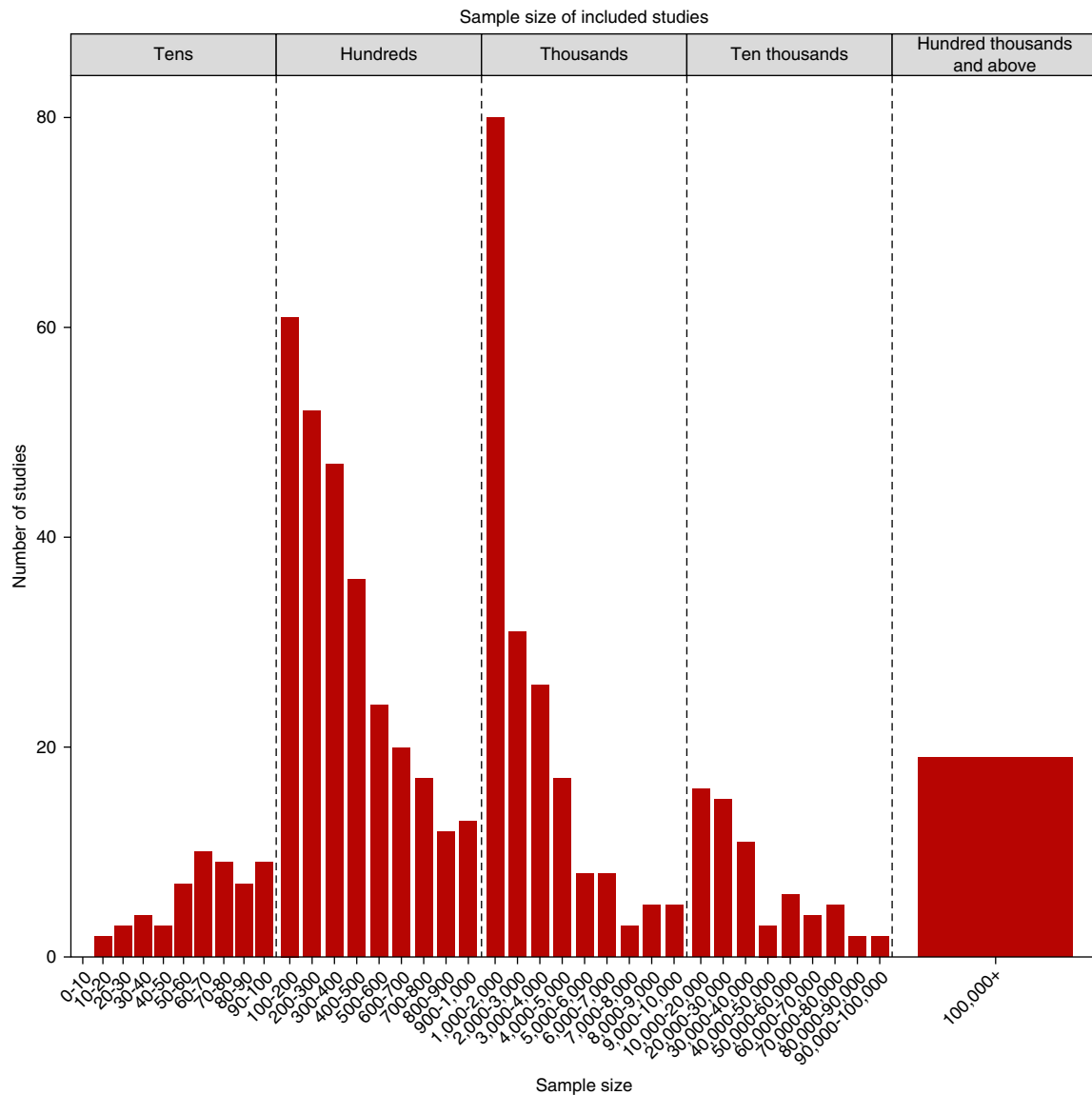


Figure 5. Sample size of included studies.

new ways of calculating the required sample size for the development of prognostic models were proposed.^{44–46} Second, in our sample of studies published after the release of the TRIPOD statement in 2015, only about 14% referenced the reporting guideline. The TRIPOD checklist was published to aid researchers in the reporting of their prediction modeling studies and consequently improve the transparency of reporting.²² Besides the reporting aspect, advisory on robust methodology is given in the Explanation and Elaboration document of the TRIPOD.²³ Because

artificial intelligence–based models are gaining popularity rapidly, a TRIPOD guideline specifically for the reporting of artificial intelligence model studies is currently in development.⁴⁷ Third, when validating a prognostic model, both discrimination and calibration are essential performance measures to assess the predictive abilities. Although most of studies in our sample reported on the discriminative abilities of the model, far less also reported a form of calibration. This is in line with previous systematic reviews of non-nephrological studies, which also found that calibration often

receives little attention.^{48,49} Not assessing and reporting measures of calibration imposes risks for clinical practice when a model is used for decision making because a poorly calibrated model can lead to misleading risk predictions and misclassification.⁵⁰ Fourth, only a little more than half of the development studies reported a useable prognostic model, consisting of either a full regression formula or a risk score, making validation or further implementation of the model impossible. Naturally, to combat research waste and to make it possible for a model to be implemented

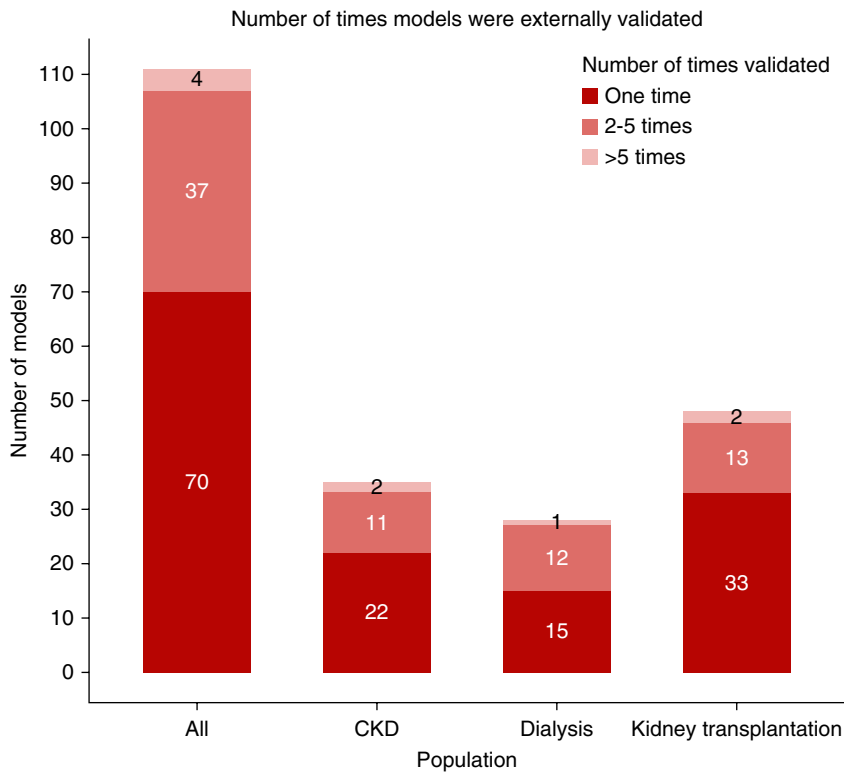


Figure 6. Number of times models were externally validated.

into clinical practice, it is vital to report the necessary information to use the model to estimate risks. Finally, algorithmic bias remains a neglected topic in prediction modeling. Algorithmic bias refers to systematic errors that lead to different prediction performance in different groups of people. Algorithmic bias may arise as a result of systematic and institutional biases represented in data (e.g., people of color are less likely to receive indicated medication) or during the modeling process (e.g., due to biases of the person building the model). Because of reduced human control, artificial intelligence-based models are more prone to algorithmic biases because they may unintentionally represent biases in the data. It is important to take measures to prevent algorithmic bias, for example, by ensuring that the data used to train the algorithm are diverse and representative, to determine whether there is differential model performance between subgroups (e.g., men versus women), and by knowing what variables the model uses to make a prediction.

Over time, an increase in attention for methodology and reporting can be seen: More studies reported measures of discrimination and referenced the TRIPOD guideline. However, reporting of calibration and the performance of external validation still lag behind.

Validation and Updating

To bring prognostic models one step closer to their implementation, external validation is crucial. Not adequately validating prognostic models that are intended to be used in clinical decision making may negatively influence patient outcomes. For example, overpredicting or underpredicting the risk of a certain outcome may lead to erroneous treatment decisions.⁵¹

In this review, we have found that of the 447 of models for kidney patients, the majority have never been tested in a new set of patients or only a few times, meaning that their generalizability and real-world applicability remain unknown. Moreover, the world and the people in it are constantly subject to

change. Therefore, validation, and updating if necessary, in the target population in which the prognostic model is intended to be used is crucial for ensuring their accuracy, reliability, and clinical utility and should be performed more frequently.⁵²

More recently, comparative comprehensive external validation studies have been introduced, in which multiple prognostic models are compared. In this review, we identified 35 comparative external validation studies. This type of study allows for a direct comparison of the performance of different models and can provide insight into the strengths and weaknesses of each model. Besides testing the generalizability of the included models, comparative external validation studies can serve two other major aims: (1) They can help researchers and clinicians to identify the best performing model for a given outcome, allowing us to choose the most promising model for use in clinical practice, and (2) they can help to identify whether a new model is significantly better than already implemented models, making it possible to determine whether the effort and resources required to actually implement the new model are justified. Currently, most comparative external validation studies compare only a few prognostic models. To really be able to identify the best model for a specific clinical question, we recommend performing a systematic search to identify all relevant models for that research question. These models can then be compared in one study, and the best model can be presented. Such comprehensive comparative external validation studies are not often performed yet, but good examples exist also in the field of nephrology.^{14,17,27}

Impact Assessment

After the development, validation and update stages it is time to look into implementation of the prognostic models. An important step in this process is assessment of their impact on patient care by performing so-called impact studies. The aim of an impact study is to quantify the effect of using a

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Table 1. Methodological and reporting quality of all studies

Measures Pertaining to Methodological and Reporting Quality	All (N=602)	Development (n=415)	Validation (n=205)	Update (n=62)
Sample size, No. (%)				
Median (IQR)	746 (262–3180)	830 (276–3702)	633 (261–2328)	669 (345–3763)
0–250	141 (23.4)	97 (23.4)	46 (22.4)	8 (12.9)
251–1500	242 (40.2)	155 (37.3)	90 (43.9)	34 (54.8)
1501–5000	107 (17.8)	76 (18.3)	40 (19.5)	8 (12.9)
>5000	112 (18.6)	87 (21.0)	29 (14.1)	12 (19.4)
Reference to TRIPOD statement, No. (%)				
Published before TRIPOD	203 (33.7)	150 (36.1)	58 (28.3)	18 (29.0)
Yes	56 (9.3)	36 (8.7)	24 (11.7)	0 (0)
No	343 (57.0)	229 (55.2)	123 (60.0)	44 (71.0)
Performance aspects, No. (%)				
Discrimination	484 (80.4)	335 (80.7)	170 (82.9)	50 (80.6)
Calibration	261 (43.4)	186 (44.8)	90 (43.9)	27 (43.5)
Reclassification measures	N.A.	N.A.	N.A.	
NRI				8 (12.9)
IDI				4 (6.5)
Both				15 (24.2)
Model derivation method, No. (%)	N.A.		N.A.	N.A.
Conventional regression model		312 (75.2)		
Machine learning		59 (14.2)		
Both		44 (10.6)		
Model presentation, No. (%)	N.A.		N.A.	N.A.
Full regression formula		120 (28.9)		
Risk score		71 (17.1)		
Both		34 (8.2)		
Neither		190 (45.8)		

Total No. of development, validation, and update studies adds up to more than the original number of included studies (n=602) because studies that combine multiple aims (e.g., development and external validation) were counted in all applicable categories. IDI, integrated discrimination improvement; IQR, interquartile range; N.A., not applicable; NRI, net reclassification index; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis.

prognostic model in clinical practice on decision making and, consequently, patient outcomes. The preferred setting for an impact study would be a cluster randomized controlled trial (RCT) in which one cluster (e.g., a hospital) will be randomized to using the prognostic model and the other to not using it. However, because an RCT is often not feasible, another option for impact assessment is to compare outcomes before and after the implementation of a model in an observational study.⁵³ Impact studies are currently rarely performed, and it remains an uncharted territory, despite their potential to further support clinical implementation of prognostic models. Although our search was not specifically designed for finding impact studies, we came across five observational studies that performed some sort of impact assessment.^{54–58} In addition, we found two protocols for RCTs of which the results have not yet been published.^{59,60} It is important to note that numerous models may be used in clinical practice without formal

reporting on this usage in the literature. Implementation of prognostic models could thus also be assessed using surveys among nephrologists and/or patients.⁸

Clinical Use of Prognostic Models

We believe prognostic models have the potential to be of significant value in kidney patient care for a number of reasons. First, studies have shown that most patients with CKD experience feelings of uncertainty and anxiety regarding their future and their disease progression.⁶¹ Prognostic uncertainty is a recurring theme in this fragile population, and patients with CKD have explicitly described a wish for more information about their future because they value knowing what to expect when it comes to living with the disease.^{7,61,62} Examples are important clinical end points, such as kidney failure and mortality, and also PROs, such as HRQoL and symptom burden. By providing patients with such information on the expected course of

the disease, these models can foster a sense of control over their condition while also facilitating their active involvement in the process of shared decision making. Second, when nephrologists inform their patient on their expected disease trajectory and advise on treatment options, they are implicitly making a risk assessment for that individual patient. This risk assessment is not a formal calculation but an intuitive assessment or extrapolation of a certain variable, such as the eGFR slope. Prognostic models cannot replace the clinical judgment of a nephrologist, but they may be a valuable addition to it because they provide a formal individualized predicted risk calculation on the basis of a multitude of patient characteristics and can also help less experienced clinicians develop a sense of risk assessment. Third, prediction models have proven to be of value in health care planning and referral strategies. As kidney disease is a chronic illness with a large variety in trajectories and

treatment options and has a large role for shared decision making, many choices may be aided by prognostic models because they help provide patients with a realistic outlook on their journey with CKD. Prognostic models are used to assess risk of progression in early CKD stages and guide nephrologist referral. Subsequently, prognostic models are currently used to support kidney transplant allocation by predicting the risk of kidney graft failure in a specific recipient in the United States. In the future, prognostic models could provide realistic insights into postkidney transplantation QoL, aligning patient expectations with potential outcomes. Other specific examples of the use of prognostic models include predicting kidney failure for timely vascular access surgery referral and mortality risk prediction for different RRT forms, which help make more informed choices between treatment modalities. Finally, it is worth mentioning the concept of counterfactual prediction. Counterfactual prediction aims to predict how a patient might fare on various alternative treatment plans. This entails combining prediction and etiology and ideally provides individualized risks for different treatment options, such as conservative care versus dialysis.²⁹ Counterfactual prediction is still largely uncharted territory and a methodological challenge due to confounding, but an important research area to explore in years to come, particularly for a nephrological population.

Implemented Models for Kidney Patients

Although the uptake of prognostic models in nephrology seems limited compared with other medical fields, such as oncology, a few models have actually been implemented into clinical practice. First, the previously mentioned KFRE has been extensively validated, and previous impact studies have shown benefit of using the model in patient care.^{25,63,64} The model was originally intended to predict kidney failure requiring RRT among patients with CKD stage 3–5 but is now also recommended to be used by general practitioners to help them decide whether patients need to be referred to a nephrologist and for RRT planning. The KFRE is now endorsed in several guidelines, such as the UK National Institute for Health and Care Excellence guidelines, the KDIGO guidelines, and the

Kidney Disease Outcomes Quality Initiative guidelines. Another model that is recommended in one of the KDIGO guidelines is a model proposed by Grams *et al.* which predicts the risk of ESKD in healthy people who consider donating their kidney.^{65,66} Finally, the current US kidney transplant allocation system is partly based on the KDRI, which predicts the quality of kidney grafts and recipient life expectancy.^{32,58,67}

Prognostic models that are endorsed in clinical guidelines, such as the KFRE and the KDRI, are inclined to have a better uptake in clinical practice. The inclusion of a prognostic model in clinical guidelines endorses a model's credibility, enhancing health care providers' trust and adoption of the model.

Implementation Barriers

Besides the abovementioned shortcomings of current prediction research for kidney patients, there are other barriers that hinder the implementation of prognostic models. First, the potential of prognostic models is not yet widely recognized by clinicians. A recent study has shown that almost half of the nephrologists did not use prognostic models. Reasons for this included not knowing how to use such models, not knowing where to find them, and thinking that current models are not reliable enough. In addition, nephrologists worried that prediction models may give patients false expectations, do not give enough information about the individual in front of them, and require too much time.⁸ Instead of the continuous development of novel models, more attention needs to be paid to these barriers and how to overcome them. Second, novel models or updates to existing models frequently introduce the use of predictors that are hard to obtain in routine clinical practice, such as specialized biochemical markers or complex imaging techniques, which may pose practical difficulties for integration into standard clinical workflows. This limitation underscores the need for the development of prognostic models that rely on readily accessible predictors, facilitating their implementation into everyday patient care. Finally, another perceived barrier to the implementation of prognostic models that deserves more attention is the classification of prognostic models as a medical device according to the Medical Devices Regulations.⁶⁸

Implementation Opportunities and Future Suggestions

There are various opportunities to further implement prognostic models in kidney patient care. In Box 1, these suggestions, as described below, are summarized.

First, researchers should focus on rigorous methodology and reporting when conducting a

prediction study. To do so, we recommend adherence to the TRIPOD guideline. Second, to combat research waste and to make use of the knowledge we have obtained from previous studies, promising models should be externally validated and, if necessary, updated to improve their predictive abilities in the CKD and RRT population. Third, to reduce the gap between research and clinical practice, two important steps should be undertaken: (1) comparative comprehensive external validation studies to guide clinicians and researchers in choosing the most appropriate prognostic model and facilitating direct comparison between existing models and (2) impact studies in which the effect of such prognostic models on patient care is evaluated. Fourth, prognostic models with good predictive abilities and positive impact on clinical practice should be endorsed in clinical guidelines. For example, the use of prognostic models to predict kidney disease progression for timely referral to a nephrologist is currently encouraged in the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD and three prognostic models are referred to.^{25,69–71} In addition, in the KDIGO guideline on the evaluation and care of living kidney donors, the use of a publicly available online risk calculator to predict the risk of end-stage renal disease in healthy people that consider donating their kidney is advised.⁶⁵ Fifth, even models that perform well and have been extensively validated are often not used in clinical practice because of limited trust and other experienced barriers of nephrologists. To overcome these barriers, more research is needed into why these barriers exist and what is needed for nephrologists to feel ready to use prognostic models. Sixth, new models should be developed for PROs. By doing so, these new models can be used to improve information provision in clinical consultations and ultimately to support the shared decision-making process and patient-centered care provision. And finally, well-performing models should be used in clinical practice to inform patients and to support treatment decisions. Guidance on how risk predictions should be communicated exists.⁷²

Strengths and Limitations

This scoping review has several strengths, including its broad systematic search and thorough screening process with two independent reviewers. Although the large scale of this study is a major strength, it also comes with some potential drawbacks. First, the vast amount of studies that were screened may have led to some unjust inclusions or exclusions because studies were mainly

Box 1. Implementation opportunities and future suggestions.

Opportunities to further implement prognostic models in kidney patient care exist. In this review, several approaches are described.

- (1) More focus on rigorous methodological and reporting quality when conducting a prediction study. To do so, we recommend adherence to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis guideline.
- (2) New models should be developed for patient-reported outcomes.
- (3) Instead of continuously developing new models for the same outcomes, existing models can be externally validated and updated to improve their predictive abilities in the CKD and RRT population.
- (4) Two important steps should be undertaken more: (1) comparative external validation studies and (2) impact studies.
- (5) Promising models with good predictive abilities and positive impact on clinical practice should be endorsed in clinical guidelines.
- (6) Barriers to the implementation of prognostic models, such as limited trust from nephrologists, and ways to overcome them should be further investigated.

included on the basis of their abstract. However, owing to the large number of included studies, it is unlikely that these potentially could have influenced the results and conclusions in a significant manner. Second, formal risk of bias assessment of the included studies using for example the Prediction model Risk of Bias Assessment Tool was not feasible because of the scope of this review.⁷³ Thus, despite our efforts to report on the methodological and reporting quality of the studies, this information is limited. Finally, although most papers are published in English, the restriction to include only English language studies may have inadvertently led to underrepresentation of research from non-English-speaking regions.

In conclusion, the body of literature on prognostic modeling in the field of nephrology has grown immensely, and to achieve more cohesion within the field, it is crucial that we take inventory of the work that has been done over the past 40 years. In this scoping review, we have provided the reader with a comprehensive overview of all prognostic modeling studies for kidney patients, their reporting and methodology, predicted outcome definitions, and potential implementation opportunities. A plethora of prognostic models now exist for patients with CKD, of which a small part is promising for

clinical uptake. Using this review, we can reflect on what has and has not been achieved so far and more harmonious plans for the future can be made. This could not only include setting up large consortia to carry out validation of models on a larger structural scale with attention for representation of various patient groups and ethnicities but also policy on which outcomes are missing in available models and how we can make a joint effort to give patients the individualized prognostic information that is essential to furthering shared decision making and their own disease understanding.

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DATA SHARING STATEMENT

An Excel file with all extracted data accompanied by a data dictionary is publicly available on <https://github.com/jmilders>.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://links.lww.com/JSN/E564>.

Detailed description of the search strategies for the scoping review.

Search string for PubMed.

Search string for Embase.

Supplemental Table 1. Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) checklist.

Explanation of the definitions that were used during the data extraction process.

Supplemental Figure 1. Continents from which patient populations were derived.

Supplemental Table 2. Outcome categories identified per population.

Supplemental Figure 2. Number of studies that referenced the TRIPOD statement.

Supplemental Figure 3. Percentage of studies that reported measures of discrimination and calibration over time.

Supplemental Figure 4. Flow chart depicting how many models were presented in a useable format, how many were accompanied by a measure of discrimination and calibration, how many models were validated internally and externally, and how many models were developed in a sample size larger than 250 patients.

Supplemental Figure 5. Percentage of studies that performed internal and external validations within the same study over time.

Supplemental Table 3. Methodological and reporting quality of included studies per population.

Supplemental Table 4. External validation of models proposed in the development studies.

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