Clinical Kidney Journal, 2023, vol. 16, no. 7, 1122–1131

https://doi.org/10.1093/ckj/sfad057
Advance Access Publication Date: 23 March 2023
Original Article

ORIGINAL ARTICLE

A pre-transplantation risk assessment tool for graft survival in Dutch pediatric kidney recipients

Loes Oomen [1], Huib de Jong [2], Antonia H.M. Bouts [3], Mandy G. Keijzer-Veen [4], Elisabeth A.M. Cornelissen [5], Liesbeth L. de Wall [1], Wout F.J. Feitz [1] and Charlotte M.H.H.T. Bootsma-Robroeks [5,6]

[1]Department of Urology, Division of Pediatric Urology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands, [2]Department of Pediatric Nephrology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands, [3]Department of Pediatric Nephrology, Amsterdam University Medical Center, Emma Children's Hospital, Amsterdam, The Netherlands, [4]Department of Pediatric Nephrology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands, [5]Department of Pediatric Nephrology, Radboudumc Amalia Children's Hospital, Nijmegen, The Netherlands and [6]University of Groningen, University Medical Center Groningen, Department of Pediatrics, Pediatric Nephrology, Beatrix Children's Hospital, Groningen, The Netherlands

Correspondence to: Loes Oomen; E-mail: Loes.Oomen@radboudumc.nl

ABSTRACT

Background. A prediction model for graft survival including donor and recipient characteristics could help clinical decision-making and optimize outcomes. The aim of this study was to develop a risk assessment tool for graft survival based on essential pre-transplantation parameters.

Methods. The data originated from the national Dutch registry (NOTR; Nederlandse OrgaanTransplantatie Registratie). A multivariable binary logistic model was used to predict graft survival, corrected for the transplantation era and time after transplantation. Subsequently, a prediction score was calculated from the β-coefficients. For internal validation, derivation (80%) and validation (20%) cohorts were defined. Model performance was assessed with the area under the curve (AUC) of the receiver operating characteristics curve, Hosmer–Lemeshow test and calibration plots.

Results. In total, 1428 transplantations were performed. Ten-year graft survival was 42% for transplantations before 1990, which has improved to the current value of 92%. Over time, significantly more living and pre-emptive transplantations have been performed and overall donor age has increased ($P < .05$).The prediction model included 71 829 observations of 554 transplantations between 1990 and 2021. Other variables incorporated in the model were recipient age, re-transplantation, number of human leucocyte antigen (HLA) mismatches and cause of kidney failure. The predictive capacity of this model had AUCs of 0.89, 0.79, 0.76 and 0.74 after 1, 5, 10 and 20 years, respectively ($P < .01$). Calibration plots showed an excellent fit.

Conclusions. This pediatric pre-transplantation risk assessment tool exhibits good performance for predicting graft survival within the Dutch pediatric population. This model might support decision-making regarding donor selection to optimize graft outcomes.

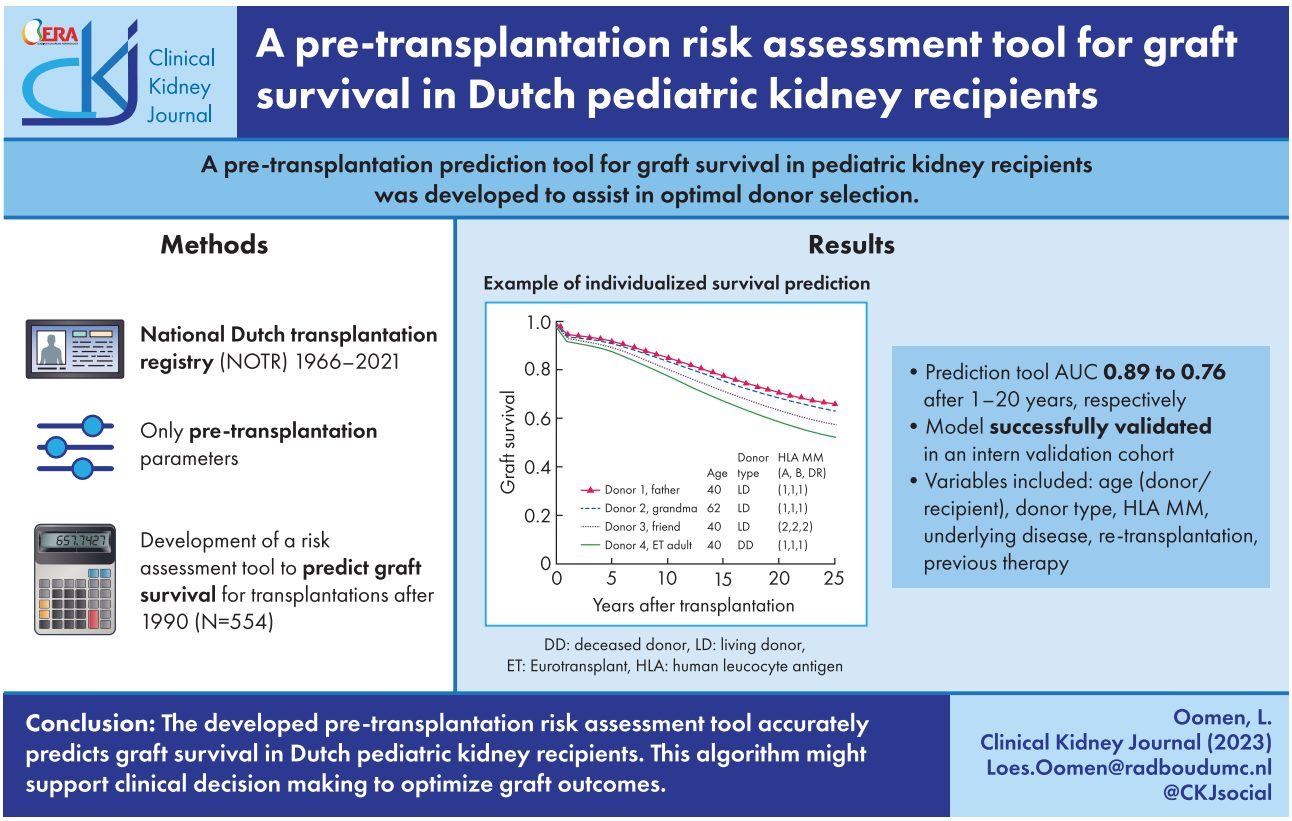
Trial registration. ClinicalTrials.gov Identifier: NCT05388955

Received: 31.10.2022; Editorial decision: 19.2.2023

LAY SUMMARY

Kidney transplantation in children is rare and therefore relatively little research has been done in this population. We do know that the success of a kidney transplantation is influenced by a combination of multiple factors. In order to support clinical decision-making in pediatric kidney transplantation, we developed a risk assessment tool based on 554 pediatric kidney transplantations in the Netherlands. The tool predicts graft survival after transplantation using only information that is available prior to transplantation such as donor age and underlying disease. In this way, this tool could help to make a trade-off between different donors and determining the transplantation strategy to optimize the outcomes of kidney transplantation.

GRAPHICAL ABSTRACT



Keywords: donor allocation, graft survival, pediatric kidney transplantation, prediction model

INTRODUCTION

Kidney transplantation is the treatment of choice for children with kidney failure, and both patient and graft survival have greatly improved over time [1, 2].

The success of individual transplants is influenced by a combination of multiple factors. Whereas living donation (LD) and pre-emptive transplantation are considered preferable [3, 4], expanding the donor pool with suboptimal donors is controversial and the risks must be evaluated in the context of further increasing waiting lists [5, 6]. Early transplantation might be beneficial regarding clinical conditions, whereas the use of suboptimal donors might reduce graft survival. Furthermore, a higher number of human leucocyte antigen (HLA) mismatches might lead to sensitization and increase the waiting time for a re-transplantation [7]. This balance is further complicated since the parameters of a successful transplant depend on the individual recipient and their clinical scenario. Hence, every future transplantation must be carefully evaluated regarding the specific donor and recipient details.

With the above background, predicting graft survival from pre-transplantation donor and recipient parameters would be of great value for making these complicated decisions [8].

Although several pre-transplantation parameters are known to independently affect graft survival, little is known about their weights and combined effect.

In adults, multiple prediction models are available to predict graft survival after either LD or deceased donation (DD) [8–13]. However, the process of pediatric kidney transplantation (PKT) differs significantly from that of adults, and most prediction models for both adults [10] and children [14] include post-transplantation parameters such as allograft histopathology and post-transplantation renal function. To assist in donor selection

for PKT recipients, a pre-transplantation prediction model in which only commonly available pre-transplantation factors are incorporated is needed.

In the Netherlands there are multiple options for donor allocation: LD or DD, direct or cross-over donation, and ABO-compatible or ABO-incompatible donors. This variety allows the analysis of donor characteristics within a cohort and underlines the complexity of donor–recipient matching.

The aim of this study is to develop and validate a pre-transplantation risk assessment tool for PKT outcomes to assist decision-making on the optimal donor and transplantation strategy. In addition, this tool is expected to improve personalized healthcare and optimize the counseling of patients and their parents.

MATERIALS AND METHODS

Data and study population

This cohort study (ClinicalTrials.gov Identifier: NCT05388955) was performed using de-identified patient data from the Dutch organ transplantation registry NOTR (Nederlandse OrgaanTransplantatie Registratie; Dutch Organ Transplantation registry). All patients and/or their parents provided written informed consent for data collection and data use. The study population included all Dutch PKT recipients between 1966 and 2021.

Data collection within NOTR started at the time of transplantation. Follow-up data were collected yearly until graft loss occurred or a patient died with a functioning graft. Graft loss was defined as the start of dialysis or re-transplantation. When a patient died with a functioning graft, this was considered as graft survival since the death was not due to renal problems.

Extensive recipient, donor and transplantation-related data were collected such as donor age, HLA mismatches and underlying disease causing kidney failure (Supplementary data, Table S4). Administrative censoring was performed on 31 December 2021.

Underlying diseases causing kidney failure were classified as congenital anomalies of the kidney and urinary tract (CAKUT), ciliopathy, glomerulopathy, metabolic nephropathy, rare cause of hypertension, tubulopathy or other (Supplementary data, Table S7).

In the Netherlands, the first living related transplantation was performed in 1966, the first pre-emptive transplantation was performed in 1980 and the first living unrelated transplantation was performed in 2005. The Dutch protocols are developed and implemented on a national level and the three PKT centers collaborate closely and evaluate provided care on a regular basis. National protocols regarding HLA matching changed over time, along with the advancements in HLA identification and insights, such as the influence of HLA-DR (mis)matching on graft outcome [15, 16]. The aim is to pursue a maximum of 4 HLA mismatches whereas no HLA-DR mismatches are accepted for patients <12 years old, and 1 mismatch for those between 12 and 18 years old. In addition, exceptions (<1%) could be made in living donations (e.g. cross-over program), in which 6 mismatches might be accepted.

Tacrolimus was introduced in 1986 and the immunosuppression protocol without steroids (TWIST protocol) was implemented in 2012. These developments are comparable to international literature [2, 17].

Statistical analysis

Predictive model

Variable selection was knowledge driven: literature review and expert opinion were used to select possible predictors for graft function [18]. These predictors were included in a final multivariable logistic regression model with the time after transplantation modeled using restricted cubic splines (Supplementary data, Table S6 and Table S8) [19, 20]. In the model, the following parameters were included:

Recipient age, donor age, LD, pre-emptive transplantation, re-transplantation, number of HLA mismatches, number of HLA-DR mismatches, and primary disease causing kidney failure, and the model was corrected for the decade (era) of transplantation. Parameters such as sex mismatches, duration of dialysis, HLA-DQ mismatches and donor health were excluded because of missing data, and ABO incompatibility was excluded because of its low incidence. Complete-case analysis was performed, with transplantations with missing data for these parameters excluded for this model.

Because of the significant changes in protocols over time, a separate analysis was executed for transplantations that were performed after 1990. Eventually, two models were developed. Model 1 including the data from all transplantations with complete data, and Model 2 including the data from all transplantations with complete data transplanted after 1990.

A person period file was created in which each month of follow-up was used as an individual observation point [21]. The probability of graft loss was predicted for every patient for every month after transplantation.

The effects of the variable "months after transplantation" were fitted using restricted cubic splines to allow for nonlinear relationships. Natural splines were used with five knots placed at the quantiles 0.05, 0.275, 0.5, 0.725 and 0.95, as suggested by Harrel [20]. We examined model calibration using smoothed plots of observed versus predicted values (Supplementary data, Fig. S5). As a result, six time-related variables were created, which were used to estimate how graft failure probability develops over the months following transplantation (V1–V6).

The hazard for graft failure was calculated for each patient at a given time point after transplantation according to the β-regression coefficients estimated from this final logistic model. These hazards were used to calculate the predicted survival, which was used to draw a survival curve for each patient based on the available parameters.

Model performance

For internal validation we used a derivation cohort, which consisted of a random sample of 80% of the datapoints, to develop the model. This model was then validated using the remaining datapoints, the validation cohort. As recommended by Steyerberg *et al.*, the performance of the prediction model was assessed using both discrimination and calibration [22].

The discrimination performance was evaluated using the area under the curve (AUC) of the time-dependent receiver operating characteristics (ROC) curve for each year after transplantation [23]. AUC curves derived from the derivation cohort were compared with those of the validation cohort. Calibration was assessed using both the Hosmer–Lemeshow test and calibration plots.

The prediction model was reported in accordance with the TRIPOD statement [24]. Continuous baseline characteristics were described as means and standard deviations or medians

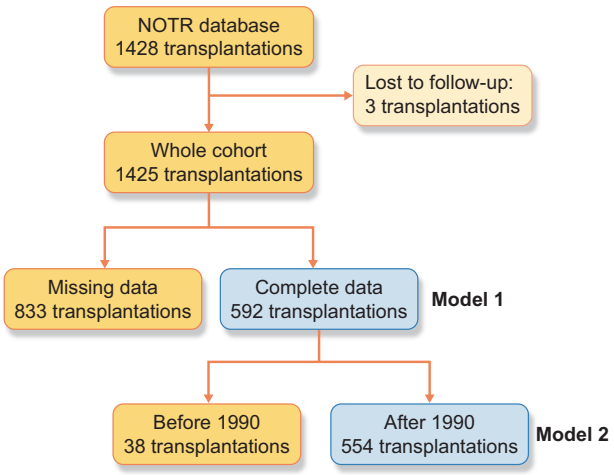


Figure 1: Flowchart of transplantations included in analysis.

and interquartile ranges. Differences between groups were analyzed using chi-square tests and independent sample T-tests, with the Mann–Whitney U test used for data that were not distributed normally. Data were analyzed using SPSS Statistics 25.0 and R 4.1.3. Differences were considered significant at $P < .05$.

RESULTS

A total of 1428 PKT were executed between 1966 and 2021. Three transplantations were excluded because of loss to follow-up. In total, complete data were available on 592 transplantations (Model 1), of which 554 were performed after 1990 (Model 2) (Fig. 1). Incomplete data were mainly due to missing data on donor age (308), pre-emptive transplantation (436) or HLA-mismatches (458) (Table 1).

Characteristics whole cohort (N = 1425 transplantations)

The follow-up time ranged from 0 to 52 years with an interquartile range of 2–16 years. The majority of patients received a kidney from a DD (Table 1). Over time, the use of LD increased significantly, as did the number of pre-emptive transplantations. Appendix 2 shows the characteristics of different cohorts (Supplementary data, Table S4).

Over the 55 years, graft loss occurred in 715 (51%) of the patients, and 84 (6%) patients died with a functioning graft. Graft survival significantly improved over time ($P < .01$) (Fig. 2): 10-year graft survival was 42% for transplantations before 1990, compared with the current value of 92%. In the early days, the percentual graft loss was highest in the first year after transplantation; however, this is less clear for the most recent cohorts (Supplementary data, Fig. S5).

Characteristics Model 1 (N = 592 transplantations 1968–present)

Characteristics of the transplantations included in Model 1 are shown in Table 1. In this cohort 39 patients (7%) were under the age of 4 years with a mean weight of 14.2 kg. No patients under 10 kg were transplanted and 30 patients weighed <15 kg.

Table 1: Patient characteristics.

	Total, N = 1425	Model 1, N = 592	Model 2, N = 554	Missing data, N = 833
Age recipient (years), mean ± SD	12 ± 5	11 ± 5	11 ± 5	12 ± 5
Age donor (years), median (IQR)	39 (19–46)	39 (21–47)	40 (24–49)	41 (31–48)
Missing, *n* (%)	308 (22)			308 (48)
Donor type, *n* (%)				
Living donor	498 (35)	170 (29)	176 (33)	328 (39)
Deceased donor	927 (65)	422 (71)	368 (66)	505 (61)
Underlying disease, *n* (%)				
CAKUT	326 (23)	154 (26)	132 (24)	172 (21)
Ciliopathy	88 (6)	42 (7)	38(7)	46 (6)
Glomerulopathy	357 (25)	152 (26)	144 (27)	205 (25)
Metabolic nephropathy	81 (6)	39 (7)	35 (6)	42 (5)
Rare cause of hypertension	8 (1)	3 (1)	3 (1)	5 (1)
Tubulopathy	7 (1)	5 (1)	5 (1)	2 (0)
Other	531 (37)	197 (33)	187(34)	334 (40)
Missing	27 (2)			27 (4)
Pre-emptive transplantation, *n* (%)	255 (18)	107 (18)	101 (19)	148 (18)
Missing, *n* (%)	436 (31)			436 (52)
HLA mismatches, (*n*) median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (1–3)
Missing, *n* (%)	458 (32)			458 (71)
First transplantation, *n* (%)	1197 (84)	484 (82)	441 (81)	713 (86)
Era of transplantation, *n* (%)				
1966–1990	467 (33)	38 (6)		429 (52)
1991–2000	336 (24)	158 (27)	158 (29)	178 (21)
2001–2010	346 (24)	217 (37)	217 (40)	129 (15)
2011–2021	276 (19)	169 (29)	169 (31)	107 (13)

The column "total" represents all pediatric kidney transplantations between 1966 and 2021; Model 1 are all kidney transplantations between 1966 and 2021, of which complete data were available; Model 2 are all pediatric kidney transplantation after 1990 of which complete data were available; missing data are all pediatric kidney transplantation between 1966–2021, of which at least one parameter was missing.
IQR: interquartile range; SD: standard deviation.

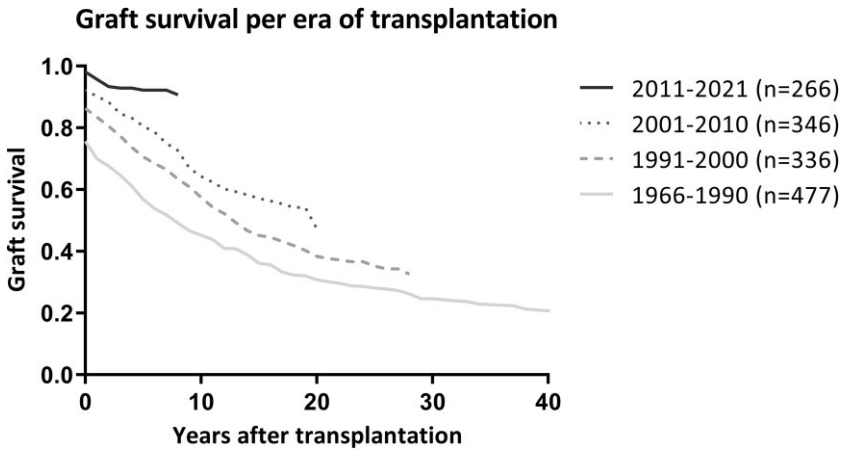


Figure 2: Kidney graft survival over time for each transplantation era.

Table 2: Patient characteristics by cohort (Model 2).

	Total, $N = 554$	Derivation cohort, $N = 435$	Validation cohort, $N = 109$	P-value
Age recipient (years) mean ± SD	11 ± 5	11 ± 5	11 ± 5	.89
Age donor (years) median (IQR)	40 (24–49)	40 (23–49)	40 (24–48)	.75
Donor type*, *n* (%)				.02
Living donor	176 (33)	131 (30)	45 (41)	
Deceased donor	368 (66)	304 (70)	64 (59)	
Underlying disease, *n* (%)				.62
CAKUT	132 (24)	112 (26)	20 (18)	
Ciliopathy	38 (7)	32 (7)	6 (6)	
Glomerulopathy	144 (27)	112 (26)	32 (29)	
Metabolic nephropathy	35 (6)	29 (7)	6 (6)	
Rare cause of hypertension	3 (1)	2 (1)	1 (1)	
Tubulopathy	5 (1)	4 (1)	1 (1)	
Other	187 (34)	144 (33)	43 (39)	
Pre-emptive transplantation, *n* (%)	101 (19)	78 (18)	23 (21)	.26
HLA mismatches, (*n*) median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	1.00
First transplantation, *n* (%)	441 (81)	354 (81)	87 (80)	.40
Era of transplantation, *n* (%)				.55
1991–2000	158 (29)	131 (30)	27 (25)	
2001–2010	217 (40)	171 (39)	46 (42)	
2011–2021	169 (31)	133 (31)	36 (33)	

Derivation cohort is random 80% ($N = 435$) sample of whole cohort, validation cohort is random 20% ($N = 109$) sample of whole cohort.
IQR: interquartile range; SD: standard deviation.
*Significant difference between groups ($P < .05$).

Characteristics were comparable to the whole cohort, although the percentage of deceased donors was higher in this cohort (71%).

Characteristics Model 2 ($N = 554$ transplantations 1990–present)

The majority of transplantations was performed after 2000 (71%) and had a DD (66%). Characteristics were comparable to those of the whole cohort. As in Model 1, in this cohort 39 patients (7%) were under the age of 4 years. In total 25 patients weighted <15 kg. Because this model was most representative for current care, outcome of this model will be described in the following paragraphs. More detailed descriptions of Model 1 can be found in Appendix 5 (Supplementary data, Table S9).

Prediction Model 2

In total, 958 transplantations were performed after 1990, of which 554 had complete data. Therefore 71 829 datapoints for 554 transplantations were used to create a derivation and validation cohort (Table 2) and develop the multivariate binary logistic model. The exponents of the β-coefficients are shown in Table 3. These values were used to develop the risk assessment tool described in the next paragraphs. The total significance of the model was $P < .01$.

Model performance

The discrimination ability of the model was assessed by calculating the AUC of the ROC curve for every year after transplanta-

Table 3: Independent determinants of graft loss in derivation cohort: multivariable binary logistic analysis.

Predictor	Exp B	95% CI Exp B
Re-transplantation	1.214	0.81–1.20
Pre-emptive transplantation	0.995	0.61–1.62
Underlying disease		
CAKUT	1.383	0.94–2.04
Ciliopathy	1.644	0.88–3.06
Glomerulopathy	1.590	1.09–2.31
Metabolic nephropathy	1.481	0.86–2.55
Rare cause of hypertension	0.000	0.000
Tubulopathy	0.587	0.08–4.34
Other	Ref	N/A
Recipient age at transplantation (years)	1.003	0.97–1.04
Donor age at transplantation (years)	1.006	0.99–1.01
Living donor	0.709	0.46–1.09
HLA mismatches (*n*)	1.106	0.96–1.27
HLA-DR mismatches (*n*)	0.981	0.81–1.20

The exponent B is the odds ratio for graft loss for every 1 unit of change in the predictor variable. Era of transplantation was included to test the model for earlier transplantations.
CI: confidence interval; N/A: not applicable.

tion (Fig. 3A) for up to 25 years after transplantation (Fig. 3B) for the validation cohort.

The discriminative performance decreased with time after transplantation, with AUCs of 0.89, 0.79, 0.76 and 0.74 after 1, 5, 10 and 20 years, respectively ($P < .01$). In Model 1 these were 0.85, 0.83, 0.80 and 0.75 after 1, 5, 10 and 20 years (Supplementary data, Fig. S7).

In order to test whether this risk model could predict the actual graft survival of our cohort we performed a calibration plot for the whole cohort. Visual inspection of the calibration plot showed good agreement of both mean predicted hazard with mean observed hazard and mean predicted survival with mean observed survival up to 25 years after transplantation (Fig. 4), with both significantly correlated ($P < .01$). The Hosmer–Lemeshow test confirmed a good fit (8.941, $P = .347$).

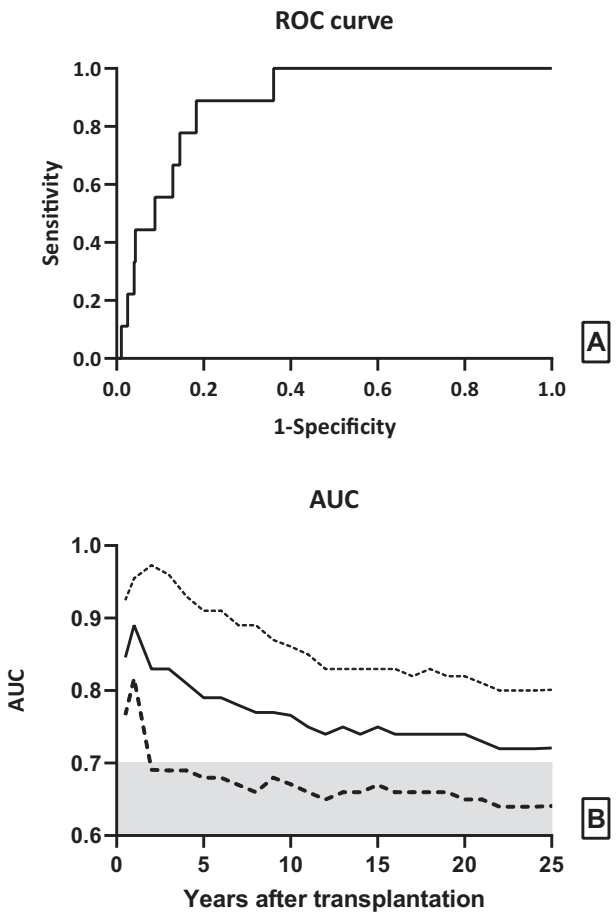


Figure 3: Discrimination ability of risk assessment tool. (**A**) ROC curve for prediction of graft survival 1 year after transplantation in validation cohort. (**B**) AUC of time-dependent ROC curves in validation cohort. Performance of prediction model in validation cohort. Solid lines represent AUC point estimates of time-dependent ROC curves and dotted lines represent 95% confidence intervals.

Implementation

Based on the estimates of the β-coefficients, a risk assessment tool was built for predicting graft survival for each year up to 25 years after transplantation.

A predicted graft survival curve was drawn for individual patients. By changing the donor characteristics, the influence of these parameters on predicted survival can be compared (Fig. 5).

For example, for a 12-year-old recipient with CAKUT as the underlying disease, 25-year graft survival is 66% for LD with 3 HLA mismatches (1,1,1) and 52% for DD with a 3 mismatches (1,1,1).

DISCUSSION

In this large multicenter study, we developed a pre-transplantation risk assessment tool for graft survival in pediatric kidney recipients in the Netherlands. This risk calculator showed good performance for this population. Therefore, this tool is expected to be helpful in daily practice to optimize transplantation outcomes through personalized medicine.

Over recent decades, short-term graft survival has markedly increased and might have reached its plateau. As children who are transplanted nowadays have a graft half time of >15 years [15], it has become more important to focus on long-term effects.

This study underlines the complexity of donor–recipient matching, since the prediction of outcome is based on an interaction of multiple factors rather than single predictors.

In the literature, most studies have concentrated on independent prognostic factors and conflicting findings have been published on the importance of HLA matching. Some authors have stated that fully mismatched LD is preferable to fully matched DD, whereas others stated that proper HLA matching is the strongest predictor for graft survival [15, 16, 25, 26]. In a recent analysis, LD with 4–6 mismatches lost the LD advantage and had similar allograft survival to DD with 0–3 mismatches [25, 26]. Previous research suggested that HLA-DQ mismatching might be a risk factor for graft survival, independent of HLA-ABDR [27, 28]. However, information on HLA-DQ was not available for our population.

Previous studies on the outcomes of re-transplantation are inconclusive [29, 30]. In general, repeat transplantations are considered less successful compared with first transplantations. However, this might be misleading because patients undergoing re-transplantations by definition have failed a previous transplantation.

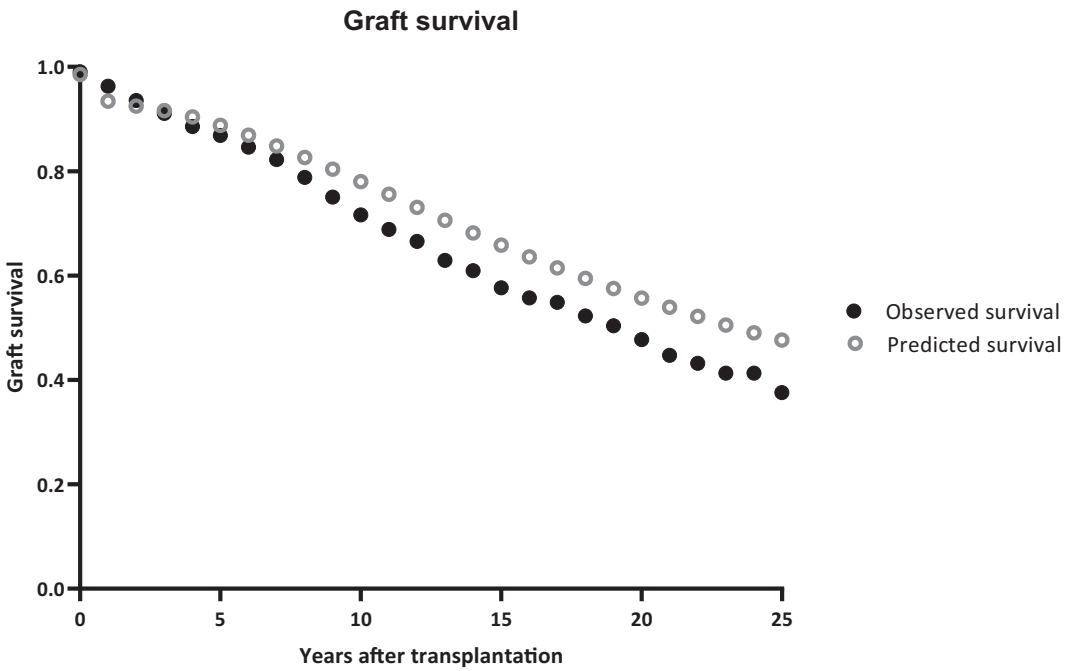


Figure 4: Calibration plot of mean predicted graft survival and mean observed graft survival after kidney transplantation in 554 transplantations. Solid dots represent mean actually observed survival in this cohort ($N = 554$), open dots represent mean survival as predicted by the prediction model ($N = 554$).

It is known that pre-emptive transplantation is beneficial for cognitive development and reducing long-term cardiovascular complications [31, 32]. In addition, pre-emptive transplantation might be undervalued due to the relatively short time on dialysis in children compared with adults [33]. The duration of dialysis was not incorporated in the model, since this information was not available and because of the relatively short of time on dialysis in children the influence of being on dialysis was expected to be more important than the duration.

Whereas Chesnaye *et al.* showed that the risk of graft failure for older LD (50–75 years old) was similar to that for younger LD [34], other authors showed that an increased age difference between donor and recipient was associated with decreased graft survival [16].

Over recent decades conflicting results have been published on the outcome in very young children [33, 35, 36]. In our cohort, small children had comparable outcomes to older recipients. However, this might be due to the limited number of very small children (no patients under 10 kg were included) in our cohort and therefore the applicability of this model for these patients might be limited.

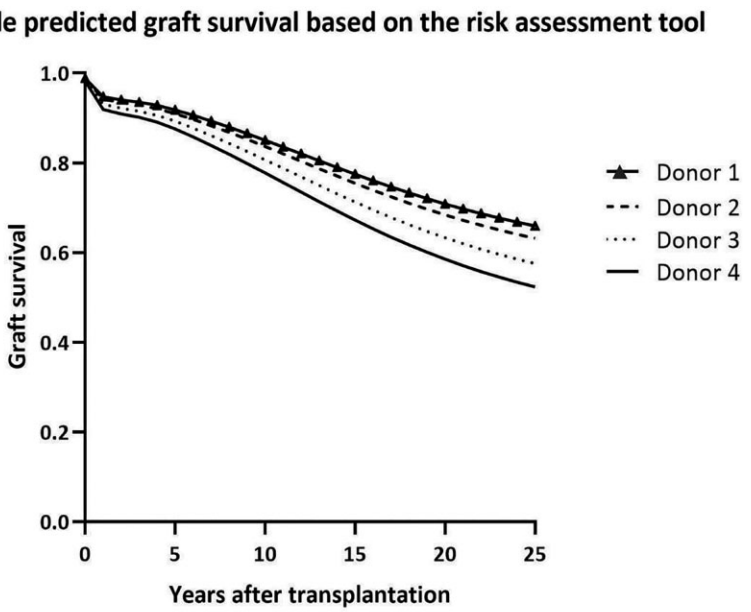
Comparing existing prediction models is complicated because of the large heterogeneity between studies [8], in which multiple predicting factors and definitions for graft loss were used and follow-up time varied widely [9, 10, 14, 37]. As we aim to help decision-making in donor and recipient selection, we included only pre-transplantation parameters rather than post-transplantation information such as biopsy results, proteinuria and graft function.

Moreover, in literature different methods are used to predict graft survival such as Cox regression analysis, decision tree methodology or Bayesian belief [8–10, 37–40]. However, these continuous-time models are based on the unrealistic assumption that the effect of a predictor is constant over time. In reality, these effects vary over time [41]. Hence, we used binary logistic regression analysis to model the influence of time after transplantation with time as a discrete value, allowing us to clarify the influence of the different parameters over time [20, 21, 42]. Clinical practice is continuously evolving and influenced by new knowledge and innovations. Proper registration and prospective data collection will help in developing future clinical tools.

The risk calculator assesses the risk for a given time point after transplantation and predicts the course of graft survival over time. Although many factors are unchangeable (such as the recipient age and underlying disease), this prediction model can be used in the context of (shared) decision-making regarding donor selection prior to transplantation. Therefore, it should also be made available to parents or caregivers to help them to better understand the impact of different donor choices on the predicted graft survival. We are currently developing an online tool that can be freely accessed by both patients and healthcare professionals.

Strengths and limitations

An important strength of this study is the detailed database. We used a large population-based prospective data set which is unique in the field of PKT. Secondly, all the required variables for the prediction model are definite, objective and commonly available to clinicians at the time of transplantation. Finally, we assessed the discrimination and accuracy of our model with a second separate group of patients (validation cohort) to avoid biased conclusions from overfitting. The model showed good performance, especially when compared with earlier models in adults [8]. Moreover, two models were developed to determine whether the transplantations that were performed before 1990 could be excluded from the analysis to make to model more accurate for current healthcare patients, since it is less affected by the many changes in care that were implemented over the years in the early period.



Donor		Donor age (years)	Donor type	HLA-MM (A, B, DR)
1	Father	40	LD	(1,1,1)
2	Grandmother	62	LD	(1,1,1)
3	Friend	40	LD	(2,2,2)
4	ET adult	40	DD	(1,1,1)

Figure 5: Example of risk assessment of various hypothetical donors for 12-year-old recipient; first pre-emptive transplantation, CAKUT as origin of kidney failure.

Several limitations of this study can be identified. First, expected donor selection criteria (especially for DD) might have changed over time. Second, detailed information, such as duration of dialysis and cold ischemia, ethnicity, socioeconomic status and the medical history of the donor, was not included in this model. However, a lower number of variables increases the precision and usability of the model. Third, a large amount of missing data caused the exclusion of 833 transplantations from analysis. Because of the multiple parameters that were missing, imputation would result in cumulative bias. Therefore, a complete case analysis was chosen. Although the transplantations that were included in Model 2 had characteristics comparable to the whole cohort, this might bias outcome. On the other hand, the majority of excluded transplantations were before 1990 and therefore less suited for this model. These missing data underline the importance of proper, complete data collection for which registries might be of great additional value. Last, it is unknown whether this exact model is suitable outside the Netherlands since it is based on a Dutch population. However, it provides a valuable example to which other countries can apply their own data. Nevertheless, we believe that our cohort is of great value because of the high percentage of LD and pre-emptive transplantations.

New research is needed to investigate whether the model is strengthened by including data from other countries. Since there are (slight) differences in daily practice among countries, the model might be most accurate when separately developed for each country. Analyses of large, (inter)national cohorts could answer this question. Therefore, future research could benefit from international collaboration as well as the standardization of data and linking between the different registries.

Conclusion

In conclusion, our proposed pre-transplantation risk assessment tool exhibits very good performance for predicting long-term graft survival in this cohort of Dutch pediatric kidney recipients and might be of clinical use for comparing suitability of different potential donors. In addition, the tool can be used in shared decision-making and to educate and manage the expectations of patients. In the future this model needs to be validated in a completely independent large cohort.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

The authors thank Ben Pelzer for assistance with the statistical analysis.

AUTHORS' CONTRIBUTIONS

L.O.: conceptualization, methodology, formal analysis, investigation, writing—original draft, project administration; H.d.J.: methodology, resources, writing—review and editing, supervision; A.H.M.B.: resources, writing—review and editing;

M.G.K.-V.: resources, writing—review and editing; E.A.M.C.: resources, writing—review and editing; L.L.d.W.: methodology, resources, writing—review and editing, supervision; W.F.J.F.: methodology, resources, writing—review and editing, supervision; C.M.H.H.T.B.-R.: conceptualization, methodology, resources, writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

All the authors declared no competing interests.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

REFERENCES

1. Van Arendonk KJ, Boyarsky BJ, Orandi BJ *et al*. National trends over 25 years in pediatric kidney transplant outcomes. *Pediatrics* 2014;**133**:594–601. https://doi.org/10.1542/peds.2013-2775.
2. Verghese PS. Pediatric kidney transplantation: a historical review. *Pediatr Res* 2017;**81**:259–64. https://doi.org/10.1038/pr.2016.207.
3. Sigurjonsdottir VK, Grimm PC. Living or deceased donor kidney transplantation in children. *Curr Opin Pediatr* 2019;**31**:232–6. https://doi.org/10.1097/MOP.0000000000000740.
4. North American Pediatric Renal Transplant Cooperative Study (NAPRTCS): 2014 Annual Report. 2014. Available from: www.naprtcs.org (11 October 2022, date last accessed).
5. Hernández D, Alonso-Titos J, Armas-Padrón AM *et al*. waiting list and kidney transplant vascular risk: an ongoing unmet concern. *Kidney Blood Press Res* 2020;**45**:1–27. https://doi.org/10.1159/000504546.
6. Ojo AO, Hanson JA, Meier-Kriesche H-U *et al*. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol* 2001;**12**:589–97. https://doi.org/10.1681/ASN.V123589.
7. Rees L, Kim JJ. HLA sensitisation: can it be prevented? *Pediatr Nephrol* 2015;**30**:577–87. https://doi.org/10.1007/s00467-014-2868-6.
8. Riley S, Zhang Q, Tse W-Y *et al*. Using information available at the time of donor offer to predict kidney transplant survival outcomes: a systematic review of prediction models. *Transpl Int* 2022;**35**:10397. https://doi.org/10.3389/ti.2022.10397.
9. Kaboré R, Haller MC, Harambat J *et al*. Risk prediction models for graft failure in kidney transplantation: a systematic review. *Nephrol Dial Transplant* 2017;**32**:ii68–76. https://doi.org/10.1093/ndt/gfw405.
10. Loupy A, Aubert O, Orandi BJ *et al*. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. *BMJ* 2019;**366**:l4923. https://doi.org/10.1136/bmj.l4923.
11. Young A, Knoll GA, McArthur E *et al*. Is the kidney donor risk index a useful tool in non-US patients? *Can J Kidney Health Dis* 2018;**5**:205435811879114. https://doi.org/10.1177/2054358118791148.
12. Rao PS, Schaubel DE, Guidinger MK *et al*. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. *Transplantation* 2009;**88**:231–6. https://doi.org/10.1097/TP.0b013e3181ac620b.
13. Prunster J, Wong G, Larkins N *et al*. Kidney Donor Profile Index and allograft outcomes: interactive effects of estimated post-transplant survival score and ischaemic time. *Clin Kidney J* 2022;**16**:473–83.
14. Kaboré R, Ferrer L, Couchoud C *et al*. Dynamic prediction models for graft failure in paediatric kidney transplantation. *Nephrol Dial Transplant* 2021;**36**:927–35. https://doi.org/10.1093/ndt/gfaa180.
15. Kim JJ, Fuggle SV, Marks SD. Does HLA matching matter in the modern era of renal transplantation? *Pediatr Nephrol* 2021;**36**:31–40. https://doi.org/10.1007/s00467-019-04393-6.
16. Trnka P, McTaggart SJ, Francis A. The impact of donor/recipient age difference and HLA mismatch on graft outcome in pediatric kidney transplantation. *Pediatr Transplant* 2018;**22**:e13265. https://doi.org/10.1111/petr.13265.
17. Pape L. State-of-the-art immunosuppression protocols for pediatric renal transplant recipients. *Pediatr Nephrol* 2019;**34**:187–94. https://doi.org/10.1007/s00467-017-3826-x.
18. Roy J, Shou H, Xie D *et al*. Statistical methods for cohort studies of CKD: prediction modeling. *Clin J Am Soc Nephrol* 2017;**12**:1010–7. https://doi.org/10.2215/CJN.06210616.
19. Lusa L, Ahlin Č. Restricted cubic splines for modelling periodic data. *PLoS One* 2020;**15**:e0241364. https://doi.org/10.1371/journal.pone.0241364.
20. Harrel FE. *Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. *Springer Series in Statistics*, Vol. **2**. Springer International Publishing Ag, 2015.
21. Steele F. Multilevel discrete-time event history models with applications to the analysis of recurrent employment transitions. *Aus N Z J Stat* 2011;**53**:1–20.
22. Steyerberg EW, Vickers AJ, Cook NR *et al*. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010;**21**:128–38. https://doi.org/10.1097/EDE.0b013e3181c30fb2.
23. Kamarudin AN, Cox T, Kolamunnage-Dona R. Time-dependent ROC curve analysis in medical research: current methods and applications. *BMC Med Res Method* 2017;**17**:53. https://doi.org/10.1186/s12874-017-0332-6.
24. Collins GS *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med* 2015;**13**:1. https://doi.org/10.1186/s12916-014-0241-z.
25. Williams RC, West LJ, Opelz G. The risk of failure with HLA mismatch and recipient age in first pediatric (<18 years) kidney transplants. *Transplant Direct* 2018;**4**:e365.
26. Opelz G, Döhler B, Middleton D *et al*. HLA matching in pediatric kidney transplantation: HLA poorly matched living donor transplants versus HLA well-matched deceased donor transplants. *Transplantation* 2017;**101**:2789–92. https://doi.org/10.1097/TP.0000000000001811.
27. Leeaphorn N, Pena JRA, Thamcharoen N *et al*. HLA-DQ mismatching and kidney transplant outcomes. *Clin J Am Soc Nephrol* 2018;**13**:763–71. https://doi.org/10.2215/CJN.10860917.
28. Tambur AR, Kosmoliaptsis V, Claas FHJ *et al*. Significance of HLA-DQ in kidney transplantation: time to reevaluate human leukocyte antigen-matching priorities to improve transplant outcomes? An expert review and recommendations. *Kidney Int* 2021;**100**:1012–22. https://doi.org/10.1016/j.kint.2021.06.026.

29. Van Arendonk KJ, Wang JMG, Deshpande NA *et al*. Practice patterns and outcomes in retransplantation among pediatric kidney transplant recipients. *Transplantation* 2013;**95**:1360–8. https://doi.org/10.1097/TP.0b013e31828c6d64.
30. Heaphy E, Poggio ED, Flechner SM *et al*. Risk factors for retransplant kidney recipients: relisting and outcomes from patients' primary transplant: retransplant kidney risk factors. *Am J Transplant* 2014;14:1356–67.
31. Cozzolino M, Mangano M, Stucchi A *et al*. Cardiovascular disease in dialysis patients. *Nephrol Dial Transplant* 2018;**33**:iii28–34. https://doi.org/10.1093/ndt/gfy174.
32. Falconi CA, da Cruz Junho CV, Fogaça-Ruiz F *et al*. Uremic toxins: an alarming danger concerning the cardiovascular system. *Front Physiol* 2021;12:686249.
33. Oomen L, Bootsma-Robroeks CMHHT, Cornelissen EAM *et al*. Pearls and pitfalls in pediatric kidney transplantation after 5 decades. *Front Pediatr* 2022;**10**:856630.
34. Chesnaye NC, van Stralen KJ, Bonthuis M *et al*. The association of donor and recipient age with graft survival in paediatric renal transplant recipients in a European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplantation Association Registry study. *Nephrol Dial Transplant* 2017;**32**:1949–56. https://doi.org/10.1093/ndt/gfx261.
35. Chiodini B, Herman J, Lolin K *et al*. Outcomes of kidney transplantations in children weighing 15 kilograms or less: a retrospective cohort study. *Transpl Int* 2018;**31**:720–8. https://doi.org/10.1111/tri.13108.
36. Herthelius M, Celsi G, Halling SE *et al*. Renal transplantation in infants and small children. *Pediatr Nephrol* 2012;**27**:145–50. https://doi.org/10.1007/s00467-011-1962-2.
37. Hemke AC, Heemskerk MBA, van Diepen M *et al*. Survival prognosis after the start of a renal replacement therapy in the Netherlands: a retrospective cohort study. *BMC Nephrol* 2013;**14**:258. https://doi.org/10.1186/1471-2369-14-258.
38. Greco R, Papalia T, Lofaro D *et al*. Decisional trees in renal transplant follow-up. *Transplant Proc* 2010;**42**:1134–6. https://doi.org/10.1016/j.transproceed.2010.03.061.
39. Tang H, Hurdle JF, Poynton M *et al*. Validating prediction models of kidney transplant outcome using single center data. *ASAIO J* 2011;**57**:206–12. https://doi.org/10.1097/MAT.0b013e3182121bc5.
40. Brown TS, Elster EA, Stevens K *et al*. Bayesian modeling of pretransplant variables accurately predicts kidney graft survival. *Am J Nephrol* 2012;**36**:561–9. https://doi.org/10.1159/000345552.
41. Singer JD, Willett JB. It's about time: using discrete-time survival analysis to study duration and the timing of events. *J Educ Stat* 1993;**18**:155–95.
42. Harrell FE, Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**:361–87. https://doi.org/10.1002/(SICI)1097-0258(19960229)15:4%3c361::AID-SIM168%3e3.0.CO;2-4.