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CLINICAL RESEARCH

Validation of 2 Prognostic Models to Predict Renal Allograft Outcome After IgA Nephropathy Recurrence

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Introduction: IgA nephropathy (IgAN) recurrence (IgANr) after kidney transplantation (KTx) is common and contributes to reducing graft survival. Some tools have been developed to predict the patients who are at a higher risk of poor outcomes among the native (international IgAN prediction tool [IIgAN-PT]) and graft (Bednarova's prediction tool [Bednarova-PT]) kidney. We aimed to analyze their performance in a KTx population other than the originally reported.

Methods: We performed a multicenter retrospective study including KTx with biopsy-proven IgANr. IIgAN-PT and Bednarova-PT were used to calculate the risk of death-censored graft loss (DCGL). We assessed the performance of both prediction models using discrimination and calibration metrics and Kaplan-Meier plots.

Results: One hundred twenty KTx with IgANr were included. The time-dependent receiver operating characteristic (ROC) area under the curve (AUC) of Bednarova-PT for predicting DCGL was 83.5 (95% CI: 72.3–94.7) and the calibration slope was 0.96 (95% CI: 0.37–1.49). The time-dependent ROC AUC of IIgAN-PT for predicting DCGL was 87.3 (95% CI: 77.58–97.02) and the calibration slope was 2.49 (95% CI: 0.19–4.13). IIgAN-PT tended to underestimate the graft-loss risk in high-risk individuals. The Kaplan-Meier curve of the highest risk group, defined by using both prediction tools, was clearly separated from the other curves.

Conclusion: Both IIgAN-PT and Bednarova-PT performed well in predicting DCGL after IgANr and should be used to identify those KTx at the highest risk. Both models had good discriminatory ability and were well-calibrated, although the calibration slope was higher for IIgAN-PT, tending to underestimate the risk in high-risk individuals.

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The primary glomerular disease most commonly placed on the waiting list and receiving a kidney transplant is IgAN, accounting for approximately one-third of cases in the Australia and New Zealand Dialysis and Transplant Registry registry.[1,2] After transplantation, the incidence of IgANr in this

registry was 5%, 10%, and 15% at 5, 10, and 15 years, respectively.[2] Thus, IgANr is the primary recurrent glomerular disease most commonly often after KTx in absolute numbers, although it occurs at a lower rate and later than other glomerular diseases such as focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis.[2] IgANr contributes to an increased long-term risk of graft loss beyond 5 to 10 years after KTx.[3-5] In this sense, prevention and therapy of IgANr may help to improve kidney transplant outcomes.

Although initially recognized as a benign disease, a significant proportion of patients with IgAN in their native kidneys are at high risk of poor renal outcomes. According to the UK National Registry of Rare Kidney Diseases, almost all patients with IgAN plus proteinuria of 0.5 g/d or estimated glomerular filtration rate (eGFR) $<$ 60 ml/min per 1.73 m^2 were at risk of progression to renal failure within their expected lifetime.[6] Several specific therapies have been developed and tested in randomized clinical trials to improve the outcome of patients with IgAN.[7,8] It would be of great interest to have an accurate method to identify patients who are at higher risk of poor outcome and who may therefore benefit most from a specific IgAN therapy. Several prognostic tools have been developed to predict the risk of end-stage renal disease in patients with IgAN based on well-identified risk factors. Although some of these tools are based only on clinical variables, the recently developed IIgAN-PT uses both clinical and histologic variables at the time of native kidney biopsy to predict the risk of end-stage kidney disease or a 50% decline in eGFR, allowing for appropriate patient-specific risk stratification.[9] The adequacy of IIgAN-PT has been demonstrated in different populations of patients with IgAN in their native kidneys; however, its performance in KTx recipients with IgANr is not known.[10-21] In addition, Bednarova *et al.*[22] recently developed and validated a kidney transplant-specific nomogram for predicting IgANr outcome. We aimed to analyze and validate the prognostic performance of these tools in a population of KTx recipients with IgANr and to compare both models.

METHODS

We conducted an observational, retrospective study from 11 tertiary medical centers in Spain (Hospital Universitario Marqués de Valdecilla/IDIVAL, Santander; Hospital Clinic, Barcelona; Hospital Universitario Regional, Málaga; Hospital Clínico San Carlos, Madrid; Hospital del Mar, Barcelona; Hospital Universitario Dr. Peset, Valencia; Hospital Universitario Puerta del Mar, Cádiz; Hospital Universitario Son Espases, Mallorca; Hospital Universitario La Fe, Valencia; Hospital Universitario 12 de Octubre, Madrid; and Hospital Universitario La Paz, Madrid). The centers included all adult renal transplant recipients with IgAN in their native kidney who had a biopsy-confirmed diagnosis of IgANr between 1996 and 2021, for whom MEST-C scores were available, and who were recorded in their registries. Clinical data were collected retrospectively from patients' medical records up to 2024. IgANr was defined as the presence of dominant or codominant IgA mesangial deposits in biopsies performed for clinical purposes. The study was conducted according to the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital Marqués de Valdecilla (2019.135).

Recipient race; recipient and donor age and sex; living donation; maximum panel reactive antibody; duration of cold ischemia; retransplantation; duration of renal replacement therapy; A, B, and DR human leukocyte antigen matching, induction type, delayed graft function and acute rejection during the first year were recorded (Table 1). The need for dialysis during the first week after transplantation was used to define delayed graft function. Data collected at graft biopsy included systolic and diastolic blood pressure, immunosuppressive therapy, renin-angiotensin-aldosterone system blockade, number of antihypertensive medications, eGFR, and 24-hour proteinuria (Table 1). There were no missing data. The main end point was progression to DCGL, defined as return to dialysis or retransplantation. All patients were receiving immunosuppressive treatment according to the usual practice of their center.

Centre pathologists reviewed biopsies with sufficient sample size according to the Oxford Classification of IgAN updated in 2016 and the Banff 2017 classification.[23,24] Briefly, M1 was characterized by the presence of $>$ 3 cells in a mesangial area in at least half of the glomeruli; E1 was defined as the presence of endocapillary hypercellularity; S1 was defined as the presence of segmental glomerulosclerosis; T1 and T2 were defined when tubular atrophy/interstitial fibrosis were between 26% and 50% or $>$ 50%, respectively; cellular or fibrocellular crescents in at least 1 glomerulus was defined as C1; and crescents in $>$ 25% of glomeruli was defined as C2.[24] The Banff 2017 categorization system was used to define concurrent T-cell-mediated rejection and antibody-mediated rejection, which was updated by the center pathologist as required (Table 1). Tubulointerstitial inflammation was defined when "t" or "i" was $\geq$ 2 as previously reported.[25] The pathologists were blinded to clinical data and graft outcomes.

Table 1. Patient characteristics of our cohort and comparison with de IIgANPT and Bednarova derivation cohorts

Characteristics	Validation cohort	IIgANPT	Bednarova
Number of IgAN recurrent patients	120	2781	83
Recipient age at recurrence (yrs)	45.6 ±13.9	35.6	40
Median time to IgAN recurrence (yrs)	2.9		2.3
Recipient sex (male)	79.2%	57.8%	70%
Race (Caucasian/Other)	90.0%/10.0%	42.0%/58.0%	
Donor age (yrs)	43.9 ± 15.7		51
Donor sex (male)	72.5%		16.8%
Median dialysis vintage (mos)	25.0 (IQR: 9.8–48.9)		16.0
Living donation	17.5%		28.9%
Peak PRA	11.7 ± 26.2%		8%
Cold ischemia time (h)	14.0 ± 7.7		14.0
Retransplant	14.2%		25.3%
Mismatches A-B-DR	3.6 ± 1.2		3
Thymoglobulin induction	41.7%		
Basiliximab induction	28.3%		
Delayed graft function	25.0%		
First year acute rejection	9.2%		
Number of antihypertensive drugs	1.9 ± 1.1		
RAAS blockade at biopsy	70.8%	32.4%	
Estimated GFR at biopsy (ml/min per 1.73 m^2)	47.2 ± 17.8	83.0	
24-h proteinuria (g/d)	1.5 ± 1.6	1.2	
Proteinuria > 1 g/d at biopsy	60.8%	57.9%	42.2%
Systolic blood pressure (mm Hg)	135 ± 14		
Steroid use at biopsy	83.3%		
Daily prednisone dose at biopsy (mg)	5.5 ± 6.2		
Tacrolimus use at biopsy	86.7%		
Cyclosporine use at biopsy	8.3%		
Azathioprine use at biopsy	3.3%		
Mycophenolate/mycophenolic use at biopsy	88.3%		
mTOR inhibitor at biopsy	10.8%		
g 0/1/2/3	55.0%/28.3%/15.0%/1.7%		
i 0/1/2/3	48.3%/40.0%/11.7%/0.0%		
t 0/1/2/3	58.3%/32.5%/8.3%/0.8%		
TII	17.5%		
v 0/1/2/3	94.2%/5.0%/0.8%/0.0%		
cg 0/1/2/3	80.0%/10.0%/5.8%/4.2%		
ptc 0/1/2/3	79.2%/14.2%/6.7%/0.0%		
ci 0/1/2/3	24.2%/50.0%/23.3%/2.5%		
ct 0/1/2/3	25.8%/49.2%/22.5%/2.5%		
ptc C4d deposition positivity	13.3%		
ptc or glomerular C4d Deposition positivity	28.3%		16.9%
AbMR	10.8%		
TCMR	5.8%		
M 1	68.3%	38.0%	
E 1	35.8%	17.3%	
S 1	56.7%	77.0%	
T 1/2	55.0%/5.0%	24.7%/4.6%	
C 0/1/2	76.7%/20.8%/2.5%		
MEST-C	2.5 ± 1.5		
IIgANPT	9.1 ± 8.9%		
Bednarova's model	32.5 ± 23.3%		
3-year DCGL	15.0%		

AbMR, antibody-mediated rejection; DCGL, death-censored graft loss; GFR, glomerular filtration rate; IgAN, IgA nephropathy; IIgAN-PT, international IgAN prediction tool; IQR, interquartile range; mTOR, mammalian target of rapamycin; PRA, panel reactive antibody; RAAS, renin-angiotensin-aldosterone system; TCMR, T-cell–mediated rejection; TII, tubulointerstitial inflammation.

The risk of a 50% decline in eGFR or end-stage kidney disease at 3 years after transplant biopsy was calculated according to IIGAN-PT on the website https://qxmd.com/calculate/calculator_499/international-igan-prediction-tool-at-biopsy-adults. Variables used to calculate the IIGAN-PT risk were eGFR at biopsy,

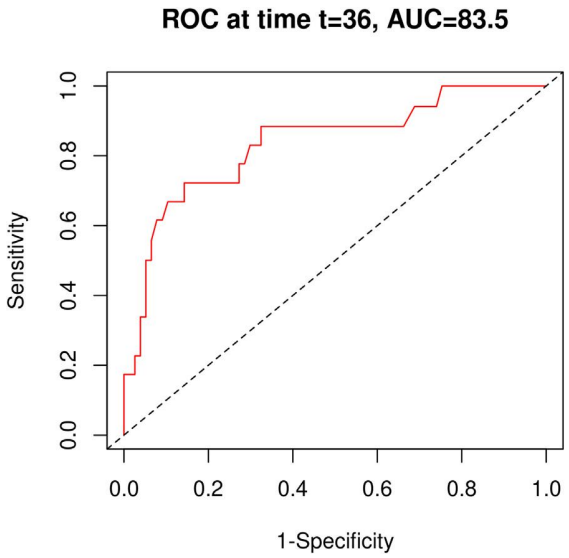

Figure 1. ROC curve of the Bednarova's model for predicting death censored graft loss. AUC, area under the curve; ROC, receiver operating characteristic.

systolic and diastolic blood pressure, proteinuria (g/d), age, race (Caucasian vs. other), use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and some variables of the Oxford Score (M, E, S, and T).[9] All patients were receiving immunosuppression at the time of biopsy.

Bednarova's probability of graft failure at 3 years after IgANr biopsy was calculated using the website reported in the original manuscript ("Graft survival after reIgAN (shinyapps.io)"). The variables used to calculate this risk were recipient age, years to recurrence, eGFR, proteinuria, peritubular capillary or glomerular C4d positivity, and number of antihypertensive medications.[22] The risk of graft loss was estimated using both models blinded to the primary end point.

Continuous and categorical variables were expressed as mean ± SD and relative frequencies, respectively. Normality was assessed using the Shapiro-Wilk test. The *t* test and Mann-Whitney test were used to compare normally and nonnormally distributed continuous variables, respectively; and the chi-square test was used to compare qualitative data. We assessed the performance of both prediction models using discrimination and calibration metrics. Both time-dependent ROC (td-ROC) and time-independent ROC (tn-ROC) analyses were used to assess discrimination. Model calibration was analyzed using validation plots and logistic regression with the Hosmer-Lemeshow test for 36-month censored survival data. The calibration slope was then calculated by fitting a linear model of predicted values to observed values. We used 95% CIs of calibration statistics to estimate using 100 bootstrap replicates. Kaplan-Meier plots were constructed to compare time-dependent predicted and observed survival for 4 risk groups. For all analyses, $\alpha = 0.05$ was used. All analyses were performed with the R software package, version 4.4.1 (R Core Team, Vienna, Austria). Time-dependent AUC-ROC curves were compared using EpiDat software. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines (Supplementary Material).[26]

RESULTS

Study Population

The main patient characteristics are shown in Table 1 and compared with the model-development cohorts.[9,22] The median time from transplantation to IgANr was 2.9 (interquartile range: 1.5–6.7) years. The median follow-up after diagnosis of IgAN relapse was 49.1 (interquartile range: 27.1–79.1) months and after KTx was 98.1 (interquartile range: 65.8–143.3) months. Thirty-two patients (26.7%) lost the graft (censoring death) and the median time from IgANr to DCGL was 29.1 (interquartile range: 12.2–67.5) months. 18 patients (15.0%) had graft loss at year 3.

Bednarova-PT

The mean calculated probability of graft failure at 3 years after IgANr biopsy according to Bednarova's prediction tool (Bednarova-PT) was 32.5% ± 23.3%. The td-ROC analysis showed that the AUC for Bednarova's model to predict DCGL for the cohort of this study was 83.5 (95% CI: 72.3–94.7), indicating that this model has a good ability to predict the 3-year risk of graft loss (Figure 1). Similarly, the tn-ROC was 82.7% (95% CI: 71.4%–93.9%, $P < 0.001$). The sensitivity and specificity values according to the Youden index were 72.7% and 72.2% for the td-ROC curve and 72.2% and 86.3% for the tn-ROC curve, respectively. The calibration slope was 0.96 (95% CI: 0.37–1.49), suggesting that discrimination was comparable to the original derivation cohort.

The 3-year calibration plot showed that the Bednarova PT was well-adapted to the observed renal survival (Figure 2). The Bednarova-PT was well-calibrated according to the Hosmer-Lemeshow goodness of fit test ($P = 0.278$). However, the calibration plot showed that the model tended to overestimate the risk of DCGL at year 3, especially for the lower predicted probabilities.

The Kaplan-Meier curves between risk subgroups according to Bednarova PT are shown in Figure 3. The curve for the highest risk was clearly separated from the other curves, suggesting that the model was able to

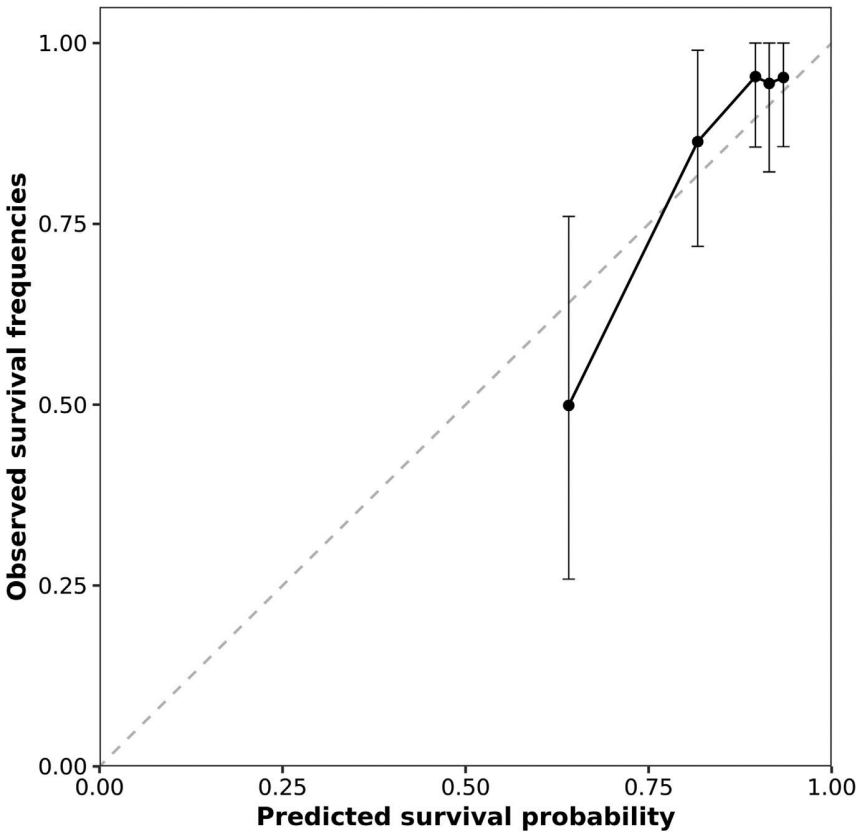

Figure 2. Calibration plot showing the predicted vs. observed 3-year risk of DCGL using the Bednarova-PT. Vertical line represents the 95% CI of the observed risks. Dashed line means whether the observed and predicted risks were identical. Bednarova-PT, Bednarova's prediction tool; DCGL, death-censored graft loss.

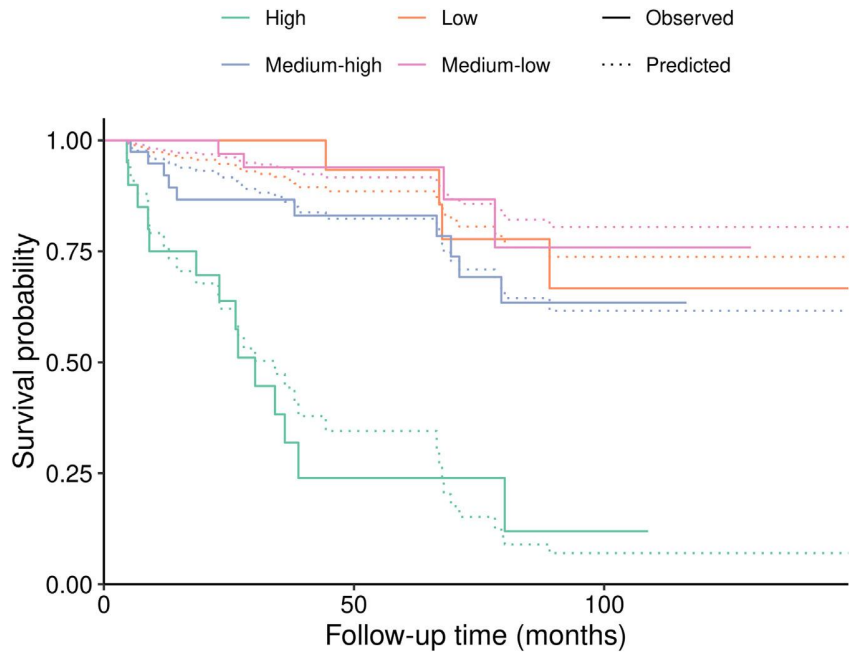

Figure 3. Kaplan-Meier survival curves comparing the observed survival (continuous lines) versus the mean predicted survival (dashed lines) based on the quartiles of risk estimated by using Bednarova-PT. Low risk (orange), Medium-low risk (pink), Medium-high risk (blue) and High risk (green). Bednarova-PT, Bednarova's prediction tool.

Table 2. Predicted and observed death censored graft survival according to Bednarova-PT and IIgAN-PT

Risk Group	Observed (x ± SE)	Predicted (x ± SE)
Bednarova-PT		
Low	100.00 ± 0.00	91.80 ± 4.27
Medium-Low	93.94 ± 4.15	94.08 ± 3.05
Medium-High	86.68 ± 5.55	87.27 ± 4.47
High	38.30 ± 11.90	47.38 ± 10.54
IgAN-PT		
Low	100.00 ± 0.00	97.22 ± 2.78
Medium-Low	93.56 ± 4.45	87.80 ± 4.45
Medium-High	91.67 ± 4.61	89.44 ± 3.97
High	32.00 ± 10.7	42.77 ± 11.09

Bednarova-PT, Bednarova's prediction tool; IIgAN-PT, international IgAN prediction tool.

identify those patients with a worse outcome after IgAN relapse, being the predicted and observed curves similar for all risk groups. Predicted and observed death-censored graft survival according to Bednarova-PT is reported in Table 2.

IIgAN-PT

We used IIgAN-PT, which is designed to calculate the risk of a 50% decline in eGFR or end-stage kidney disease at 3 years after IgAN biopsy in the native kidney, to predict DCGL at 3 years after IgANr. The mean calculated probability of graft failure at 3 years after IgANr biopsy according to IIgAN-PT was 9.1% ± 8.9%. The td-ROC analysis showed that the AUC for the IIGAN-PT model for this study cohort was 87.3 (95% CI: 77.58–97.02) and the tn-ROC was 88.5% (95% CI: 0.795–0.974), indicating that this model has a good ability to discriminate those patients at risk of graft loss

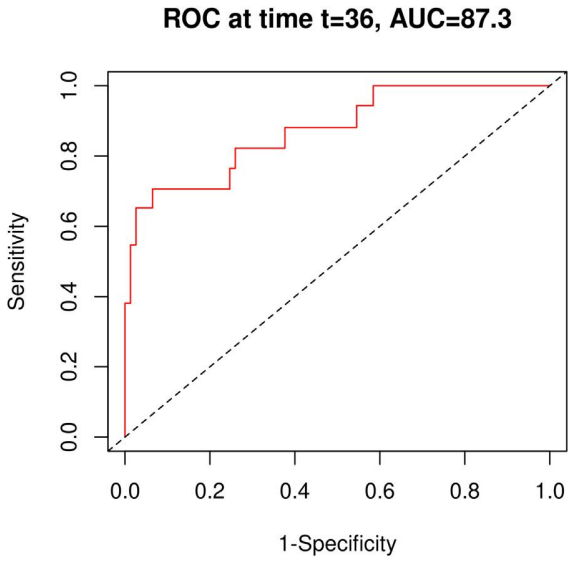

Figure 4. ROC curve of the IIgAN-PT for predicting death censored graft loss. AUC, area under the curve; IIgAN-PT, international IgAN prediction tool; ROC, receiver operating characteristic.

(Figure 4). The sensitivity and specificity values according to the Youden index were 75.3% and 76.5% for the td-ROC curve and 72.2% and 94.1% for the tn-ROC, respectively. However, the calibration slope was high (2.49 [95% CI: 0.19–4.13]), suggesting that the model had some limitations and tended to underestimate the risk for high-risk individuals. For example, the predicted risk for the highest quartile was 16.9%, whereas the observed rate was 43.3%. Notably, there were no significant differences between the Bednarova-PT and IIgANPT tn-ROC curves ($P = 0.374$).

IIgAN-PT showed a nonsignificant Hosmer-Lemeshow goodness of fit test ($P = 0.674$), indicating good calibration. The 3-year calibration plot showed that the IIGAN-PT model fits the observed renal survival well (Figure 5). However, the calibration plot showed that the model tended to overestimate the risk of DCGL at lower predicted probabilities and underestimate it at higher predicted probabilities.

IIgAN-PT predicted and observed Kaplan-Meier survival curves were very similar for each risk group (Figure 6). Predicted and observed death-censored graft survival according to IIgAN-PT is reported in Table 2. Similar to Bednarova-PT, IIgAN-PT identified the at-risk patients with an expected worse survival.

Risk Factors Related to 3-Year DCGL

Both Bednarova-PT (odds ratio [OR]: 1.052, 95% CI: 1.027–1.077, $P < 0.001$) and IIgAN-PT (OR: 1.280, 95% CI: 1.146–1.429, $P < 0.001$) were associated with a higher risk of DCGL when analyzed as continuous variables. As dichotomous variables, the fourth quartiles of both Bednarova-PT (OR: 16.343, 95% CI: 5.044–52.948, $P < 0.001$) and IIgAN-PT (OR: 13.000, 95% CI: 4.094–41.279, $P < 0.001$) were associated with a significant risk of graft loss. The relationships between variables not included in the prediction tools and 3-year DCGL are shown in Table 3. Bednarova-PT fourth quartile (OR: 12.979, 95% CI: 3.626–46.460, $P < 0.001$), C Oxford score (3.941, 95% CI: 1.260–12.325, $P = 0.018$), and tubulointerstitial inflammation (5.132, 95% CI: 1.301–20.250, $P = 0.020$) remained independently associated with a higher risk of 3-year DCGL after multivariate analysis. Similarly, IIgAN-PT fourth quartile (OR: 8.105, 95% CI: 2.372–27.687, $P = 0.001$) was associated with a higher risk of 3-year DCGL independently of C Oxford Score (3.415, 95% CI: 1.174–9.932, $P = 0.024$) and tubulointerstitial inflammation (3.429, 95% CI: 0.887–13.257, $P = 0.074$).

After recurrence, immunosuppression was increased in 44 patients (36.7%) with high-dose steroid (prednisone > 20 mg/d) being used in 35 patients (29.2%) and baseline immunosuppression being optimized (with prednisone being restarted, switched to mycophenolate

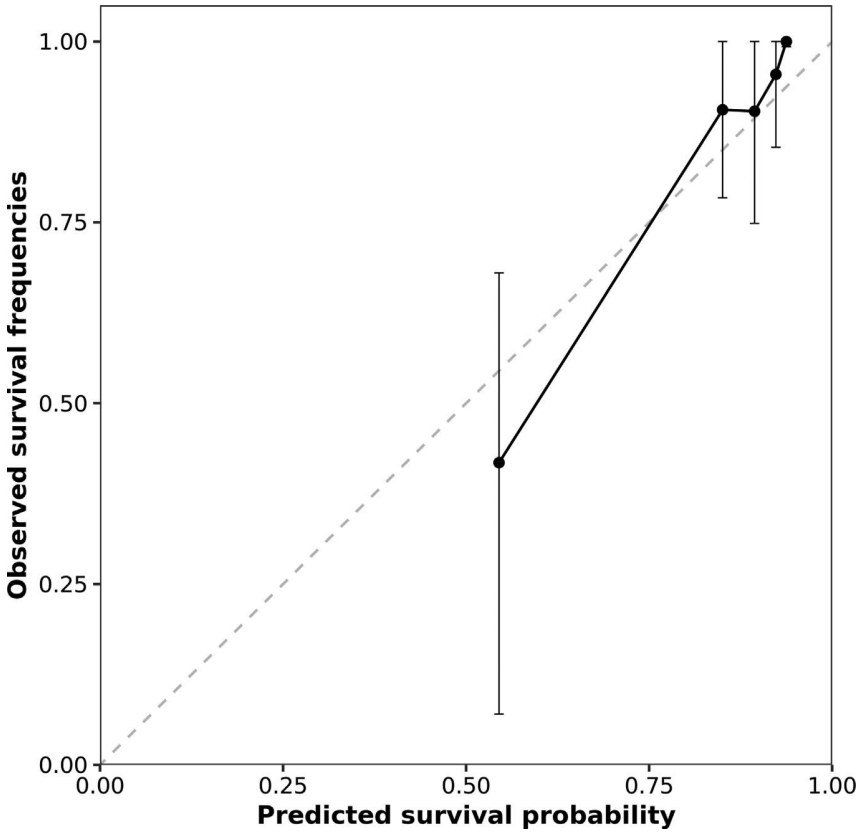

Figure 5. Calibration plot showing the predicted vs. observed 3-year risk of DCGL using the IIgAN-PT. Vertical line represents the 95% CI of the observed risks. Dashed line means whether the observed and predicted risks were identical. DCGL, death-censored graft loss; IIgAN-PT, international IgAN prediction tool.

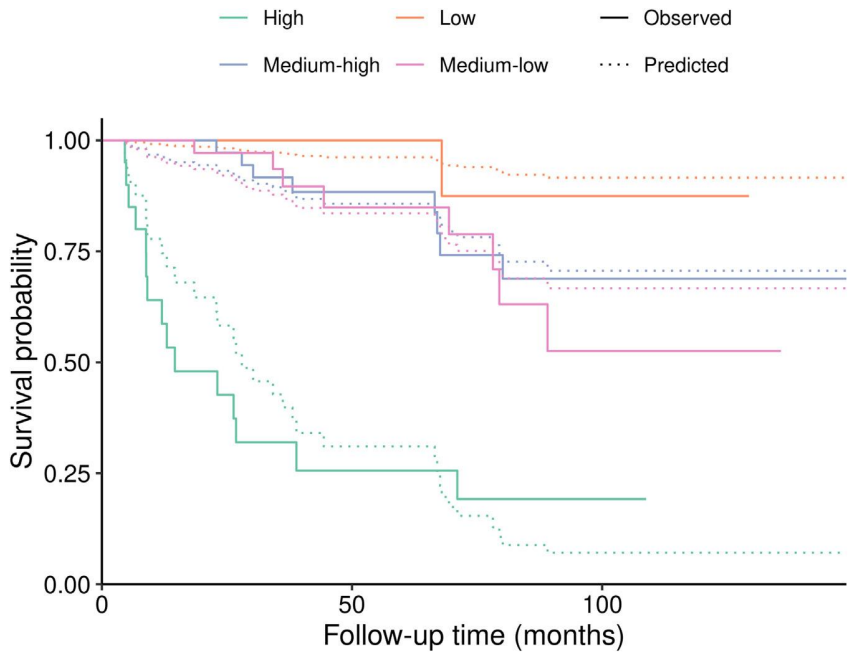

Figure 6. Kaplan-Meier survival curves comparing the observed survival (continuous lines) versus the mean predicted survival (dashed lines) based on the quartiles of risk estimated by using IIgAN-PT. Low risk (orange), Medium-low risk (pink), Medium-high risk (blue), and High risk (green). IIgAN-PT, international IgAN prediction tool.

Table 3. Variables related to 3-year DCGL by univariate logistic regression analysis

Variable	OR	95% CI	*P*
Donor age (yrs)	0.989	0.958-1.020	0.470
Donor sex (male)	1.389	0.474-4.066	0.549
Median dialysis vintage (mos)	0.981	0.962-1.000	0.054
Living donation	0.933	0.244-3.565	0.920
Peak PRA	0.965	0.918-1.014	0.162
Cold ischemia time (h)	1.037	0.967-1.112	0.308
Mismatches A-B-DR	0.733	0.495-1.086	0.122
Thymoglobulin induction	0.487	0.162-1.468	0.201
Basiliximab induction	1.768	0.622-5.025	0.285
Delayed graft function	0.835	0.252-2.765	0.768
g 0/1/2/3	1.689	0.942-3.027	0.078
TII	4.000	1.328-12.050	0.014
v 0/1/2/3	1.705	0.392-7.406	0.477
cg 0/1/2/3	0.983	0.509-1.899	0.960
ptc 0/1/2/3	1.211	0.539-2.723	0.643
AbMR	1.840	.0453-7.468	0.394
TCMR	4.900	0.997-24.089	0.050
C 0/1/2	4.787	1.927-11.893	0.001
IIgAN-PT fourth quartile	13.000	4.094-41.279	<0.001
Bednarova-PT fourth quartile	16.343	5.044-52.948	<0.001

AbMR, antibody-mediated rejection; Bednarova-PT, Bednarova's prediction tool; IIgAN-PT, international IgAN prediction tool; OR, odds ratio; PRA, panel reactive antibody; TCMR, T-cell–mediated rejection; TII, tubulointerstitial inflammation.

or tacrolimus) in 15 patients (12.5%). Two patients were also treated with cyclophosphamide. This immunosuppression enhancement was related to a higher DCGL risk at 3 years in univariate analysis (OR: 4.375, 95% CI: 1.507–12.698, $P = 0.007$). However, this effect did not reach statistical significance (OR: 2.892, 95% CI: 0.887–9.424, $P = 0.078$) when adjusted for Bednarova-PT.

DISCUSSION

As reported in the introduction, IIgAN-PT was found to be useful for predicting renal outcome in different populations of patients with IgAN in their native kidneys.[10–21] First, this predictive tool showed a good discriminatory ability with a c-statistic of 0.820 in the original full model[9] and ranging from 0.700 to 0.907 in other populations.[10–21] Similarly, we found that the c-statistic for predicting DCGL by time-dependent and time-independent ROC analyses in our renal transplant population was 0.873 and 0.885, respectively. In general, because AUC values between 0.8 and 0.9 can be interpreted as good in clinical studies,[27] we can state that the discriminatory ability of IIgAN-PT for predicting renal failure was good and similar for both native and transplanted kidneys. Second, IIgAN showed good calibration in most populations,[16,17,19] although some reports found that the prediction tool underestimated the risk in some Asian populations[13,15] or overestimated the risk in low-risk patients and underestimated the risk in high-risk patients in an American Indian and Hispanic population.[18]

The performance of IIgAN-PT in our KTx recipients with recurrent IgAN showed good calibration according to the Hosmer-Lemeshow goodness of fit test and the calibration plot (Figure 5), although it tended to overestimate the risk in low-risk patients and underestimate the risk in the high-risk group. This finding suggests that there are specific variables inherent to the transplant population that may influence the risk of graft loss that were not included in the prediction tool. Correct identification of these variables would allow the model to be recalibrated and improve its performance, although we have shown for the first time that the IIgAN-PT has a good overall performance to know the risk of DCGL in KTx recipients with IgAN relapse. Our KTx recipients were older and more often Caucasian, more often received renin-angiotensin-aldosterone system blockers, their eGFR was significantly worse (47 vs. 83 ml/min per 1.73 m^2), and the histologic damage according to the MEST score was more severe than in the population in which the IIgAN-PT was developed.[9] Therefore, some of these differences between the 2 populations may partly explain the differences in calibration. In addition, variables not included in IIgAN-PT may have a greater influence on the graft outcome.

The percentage of crescents was not included in the original full IIgAN-PT because it was highly correlated with race or ethnicity and use of immunosuppression after biopsy and did not meet the *P*-value threshold for selection in the prediction model.[9] Furthermore, only the presence or absence of crescents was analyzed, not the percentage of glomeruli with crescents.[9] In our KTx population, the percentage of crescentic glomeruli classified by MEST-C was a strong risk factor for DCGL, independent of IIgAN-PT. Previous studies have reported the independent influence of crescents on the risk of graft loss after IgANr, accordingly.[3,5,28] Interestingly, the development and influence of crescents in KTx recipients already on immunosuppressive therapy suggests that the current drugs used to prevent alloimmune reactions are not able to prevent their appearance. In this sense, the percentage of crescents should be included in the model to improve the calibration of the IIgAN-PT in renal transplant recipients. Alternatively, a variable specific to renal allografts, such as the alloimmune response, contributes to increasing the risk of censored graft loss. Among other authors, we found that tubulointerstitial inflammation was a risk factor for DCGL, independent of IIgAN-PT.[25,29] The inclusion of tubulointerstitial inflammation should be considered to improve IIgAN-PT calibration in renal transplant recipients.

In relation to Bednarova-PT, the reported c-statistic in the development and validation cohorts was 0.736 and 0.807, respectively; whereas our cohort showed a slightly better discriminatory ability with td-ROC-AUC of 0.835 and tn-ROC-AUC of 0.827%. Furthermore, the model was well-calibrated (Figure 2), although it tended to overestimate the 3-year risk of DCGL in the lower-risk patients. Thus, we confirm the good performance of Bednarova-PT in predicting the outcome of posttransplant IgANr in a population different from that originally reported. This good performance of Bednarova-PT in our group of KTx recipients may be because of the similarities between the 2 populations. Recipient age, sex, and race; time to recurrence; human leukocyte antigen sensitization; cold ischemia time; number of mismatches; and percentage of patients with proteinuria $>$ 1 g/d were very similar. Conversely, there were striking differences in the percentage of living donors and donor sex. We also found that the percentage of crescents was related to DCGL independently of Bednarova-PT. In the Bednarova model, crescents did not influence graft outcome, but only 4 biopsies (5%) with crescents were included in the study, whereas 28 KTx recipients (23%) in our study group had crescents. Interestingly, tubulointerstitial inflammation was no longer significantly associated with DCGL after adjustment for Bednarova-PT. Although inflammation was not included in this model, we can speculate that a significant proportion of KTx recipients in the Bednarova population had subclinical inflammation that influenced graft outcome, similar to our patient group.[22]

Kaplan-Meier predicted and observed survival curves were very similar when both models were applied, suggesting good risk stratification capabilities. Interestingly, both survival curves allowed the precise identification of the highest risk population that could potentially benefit most from a specific therapy. Unfortunately, the identification of these high-risk patients with IgAN relapses did not prove that they could benefit from a specific therapy without further steps. It would be necessary to know not only the likelihood and degree of response to therapy, weighed against the side effects of therapy, but also the risk of disease progression without therapy. In 3299 patients with IgAN in the native kidney, Barbour *et al.*[30] performed a simulated allocation of hypothetical immunosuppressive therapy for IgAN, comparing the decision based on proteinuria $\geq$ 1 g/d or using IIgAN-PT. They found that IIgAN-PT allowed up to a 35% reduction in treatment in patients with a low risk of progression, whereas 23% of patients with a high risk of progression benefited from specific therapy compared to using a single biomarker such as proteinuria alone.[30] In the field of renal transplantation, we propose to use IgAN-PT or Bednarova-PT to identify patients with IgANr at higher risk of DCGL in whom clinical trials with new drugs specifically targeting IgA can be designed and conducted, considering that they may also benefit from an increase in conventional immunosuppressive treatment to improve the cellular inflammation that contributes to their worsening prognosis.

Our study has several limitations. First, the study is retrospective, so there may be confounding factors that have not been considered. For instance, we did not collect information about the presence of donor-specific antibodies at IgANr diagnosis because a significant number of biopsies were performed at a time when routine donor-specific antibody measurement was not available in most centers. Donor-specific antibodies have been previously related to a higher IgANr risk and could affect graft outcome.[4] Second, the number of biopsies with recurrent IgAN may be low to validate these models developed in a native kidney population, but it is a relevant number in the field of KTx in which most studies include a smaller number of recurrences, including the Bednarova's model. Third, although the end point of the Bednarova study was predicting the risk of graft loss, as in our population, the end point in the IIgAN-PT model was the risk of a 50% decline in eGFR or end-stage kidney disease.[9,22] In addition, with regard to graft loss, we did not differentiate between patients who returned to dialysis or those who received a new kidney transplant. This may partially explain the slightly better performance of the Bednarova's model. Fourth, our population was predominantly Caucasian, so the extension of our results to other KTx populations should not be done without further studies. Fifth, as a limitation of multicenter studies, interobserver differences in the scoring of MEST-C criteria between local pathologists may limit the prognostic value of the Oxford Classification.[31] Finally, the indications for renal biopsy may differ not only between centers but also between native and transplanted kidneys, which may explain the differences between our population and that of IIgAN-PT and may also influence the subsequent outcome.

CONCLUSION

In this study, we validated IIgAN-PT for the first time in a transplant population and validated Bednarova's model in a population independent of the one in which it was originally described. Both models had good discriminatory ability and were well-calibrated, although the calibration slope was higher for IIgAN-PT, which tended to underestimate the risk for high-risk individuals. To improve the calibration of both

models, it would be interesting to include some variables such as the percentage of crescents and the degree of tubulointerstitial inflammation. Both IIgAN-PT and Bednarova-PT can be used to identify patients at high risk of kidney graft loss who may benefit from targeted treatment with the new IgAN therapies. However, the usefulness of this strategy should be demonstrated in trials specifically designed for KTx recipients with IgANr.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

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

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AUTHOR CONTRIBUTIONS

ER, LFQ, ASF, EG, SC, MJPS, AM, and DH participated in the research design. ER and DH participated in the writing of the paper. ER, LFQ, TVS, ASF, AB, EG, JMC, SC, IB, AMS, MLO, FD, JMGO, NCR, MJPS, AS, AM, JER, HT, CJ, and DH participated in the performance of the research. ER and DH participated in data analysis.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

TRIPOD Checklist.

REFERENCES

1. O'Shaughnessy MM, Liu S, Montez-Rath ME, Lafayette RA, Winkelmayer WC. Kidney transplantation rates across glomerulonephritis subtypes in the United States. *Transplantation*. 2017;101:2636–2647. https://doi.org/10.1097/TP.0000000000001657
2. Allen PJ, Chadban SJ, Craig JC, et al. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. *Kidney Int*. 2017;92:461–469. https://doi.org/10.1016/j.kint.2017.03.015
3. Moroni G, Longhi S, Quaglini S, et al. The long-term outcome of renal transplantation of IgA nephropathy and the impact of recurrence on graft survival. *Nephrol Dial Transplant*. 2013;28:1305–1314. https://doi.org/10.1093/ndt/gfs472
4. Uffing A, Pérez-Saéz MJ, Jouve T, et al. Recurrence of IgA nephropathy after kidney transplantation in adults. *Clin J Am Soc Nephrol*. 2021;16:1247–1255. https://doi.org/10.2215/CJN.00910121
5. Alachkar N, Delsante M, Greenberg RS, et al. Evaluation of the modified Oxford Score in recurrent IgA nephropathy in North American kidney transplant recipients: the Banff Recurrent Glomerulonephritis Working Group Report. *Transplantation*. 2023;107:2055–2063. https://doi.org/10.1097/TP.0000000000004640
6. Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18:727–738. https://doi.org/10.2215/CJN.0000000000000135
7. Mathur M, Barratt J, Chacko B, et al. A phase 2 trial of Sibeprenlimab in patients with IgA nephropathy. *N Engl J Med*. 2024;390:20–31. https://doi.org/10.1056/NEJMoa2305635
8. Barratt J, Liew A, Yeo SC, et al. Cemdisiran Phase 2 study investigators and collaborators. Phase 2 trial of Cemdisiran in adult patients with IgA nephropathy: a randomized controlled trial. *Clin J Am Soc Nephrol*. 2024;19:452–462. https://doi.org/10.2215/CJN.0000000000000384
9. Barbour SJ, Coppo R, Zhang H, et al. Evaluating a new international risk-prediction tool in IgA nephropathy. *JAMA Intern Med*. 2019;179:942–952. https://doi.org/10.1001/jamainternmed.2019.0600
10. Zhang Y, Guo L, Wang Z, et al. External validation of international risk-prediction models of IgA nephropathy in an Asian-Caucasian cohort. *Kidney Int Rep*. 2020;5:1753–1763. https://doi.org/10.1016/j.ekir.2020.07.036
11. Papasotiriou M, Stangou M, Chlorogiannis D, et al. Validation of the international IgA nephropathy prediction tool in the Greek registry of IgA nephropathy. *Front Med (Lausanne)*. 2022;9:778464. https://doi.org/10.3389/fmed.2022.778464
12. Barbour SJ, Coppo R, Zhang H, et al. Application of the International IgA Nephropathy Prediction Tool one or two years post-biopsy. *Kidney Int*. 2022;102:160–172. https://doi.org/10.1016/j.kint.2022.02.042
13. Joo YS, Kim HW, Baek CH, et al. External validation of the international prediction tool in Korean patients with immunoglobulin A nephropathy. *Kidney Res Clin Pract*. 2022;41:556–566. https://doi.org/10.23876/j.krcp.22.006
14. Ebbestad R, Sanaei Nurmi M, Lundberg S. Long-term outcomes of patients with IgA nephropathy categorized by the international IgAN risk prediction tool and by the degree of hematuria at diagnosis. *Nephron*. 2022;146:573–583. https://doi.org/10.1159/000525001
15. Bagchi S, Upadhyay AD, Barwad A, et al. The international IgA nephropathy network prediction tool underestimates disease progression in Indian patients. *Kidney Int Rep*. 2022;7:1210–1218. https://doi.org/10.1016/j.ekir.2022.03.016
16. Haaskjold YL, Lura NG, Bjørneklett R, Bostad L, Bostad LS, Knoop T. Validation of two IgA nephropathy risk-prediction tools using a cohort with a long follow-up. *Nephrol Dial Transplant*. 2023;38:1183–1191. https://doi.org/10.1093/ndt/gfac225
17. Bon G, Jullien P, Masson I, et al. Validation of the international IgA nephropathy prediction tool in a French cohort beyond 10 years after diagnosis. *Nephrol Dial Transplant*. 2023;38:2257–2265. https://doi.org/10.1093/ndt/gfad048

18. Shaffi SK, Fischer EG, Argyropoulos CP, Wagner B. Validation of the international IgAN risk-prediction tool in American Indians and Hispanics. *Clin Nephrol*. 2024;101:43–45. https://doi.org/10.5414/CN111110

19. Hu L, Fang Y, Huang J, Liu J, Xu L, He W. External validation of the international prognosis prediction model of IgA nephropathy. *Ren Fail*. 2024;46:2313174. https://doi.org/10.1080/0886022X.2024.2313174

20. Zhang Q, Zhang Q, Duan Z, et al. External validation of the international IgA nephropathy prediction tool in older adult patients. *Clin Interv Aging*. 2024;19:911–922. https://doi.org/10.2147/CIA.S455115

21. Lim RS, Yeo SC. EXternal validation of international IgA nephropathy prediction tool in a Singapore CohorT (EXIST Study). *J Nephrol*. 2024;37:2409–2412. https://doi.org/10.1007/s40620-024-01985-w

22. Bednarova K, Mjøen G, Hruba P, et al. A novel prognostic nomogram predicts premature failure of kidney allografts with IgA nephropathy recurrence. *Nephrol Dial Transplant*. 2023;38:2627–2636. https://doi.org/10.1093/ndt/gfad097

23. Haas M, Loupy A, Lefaucheur C, et al. The Banff 2017 Kidney Meeting Report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant*. 2018;18:293–307. https://doi.org/10.1111/ajt.14625

24. Trimarchi H, Barratt J, Cattran DC, et al. Network and the Renal Pathology Society; conference participants. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017;91:1014–1021. https://doi.org/10.1016/j.kint.2017.02.003

25. Rodrigo E, Quintana LF, Vázquez-Sánchez T, et al. Tubulointerstitial inflammation increases the risk of graft loss after the recurrence of IgA nephropathy. *Clin Kidney J*. 2023;17:sfad259. https://doi.org/10.1093/ckj/sfad259

26. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD). *Ann Intern Med*. 2015;162:735–736. https://doi.org/10.7326/L15-5093-2

27. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med*. 1978;8:283–298. https://doi.org/10.1016/s0001-2998(78)80014-2

28. Park S, Go H, Baek CH, et al. Clinical importance of the updated Oxford classification in allograft IgA nephropathy. *Am J Transplant*. 2019;19:2855–2864. https://doi.org/10.1111/ajt.15400

29. Agrawal V, Singh A, Kaul A, Verma R, Jain M, Pandey R. Utility of Oxford classification in post-transplant immunoglobulin A nephropathy. *Transplant Proc*. 2017;49:2274–2279. https://doi.org/10.1016/j.transproceed.2017.10.002

30. Barbour SJ, Canney M, Coppo R, et al. Improving treatment decisions using personalized risk assessment from the International IgA Nephropathy Prediction Tool. *Kidney Int*. 2020;98:1009–1019. https://doi.org/10.1016/j.kint.2020.04.042

31. Bellur SS, Roberts ISD, Troyanov S, et al. Reproducibility of the Oxford classification of immunoglobulin A nephropathy, impact of biopsy scoring on treatment allocation and clinical relevance of disagreements: evidence from the VALidation of IGA study cohort. *Nephrol Dial Transplant*. 2019;34:1681–1690. https://doi.org/10.1093/ndt/gfy337