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Application of the International IgA Nephropathy Prediction Tool one or two years post-biopsy

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OPEN

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The International IgA Nephropathy (IgAN) Prediction Tool is the preferred method in the 2021 KDIGO guidelines to predict, at the time of kidney biopsy, the risk of a 50% drop in estimated glomerular filtration rate or kidney failure. However, it is not known if the Prediction Tool can be accurately applied after a period of observation post-biopsy. Using an international multi-ethnic derivation cohort of 2,507 adults with IgAN, we updated the Prediction Tool for use one year after biopsy, and externally validated this in a cohort of 722 adults. The original Prediction Tool applied at one-year without modification had a coefficient of variation (R^2) of 55% and 54% and four-year concordance (C statistic) of 0.82 but poor calibration with under-prediction of risk (integrated calibration index (ICI) 1.54 and 2.11, with and without race, respectively). Our updated Prediction Tool had a better model fit with higher R^2 (61% and 60%), significant increase in four-year C-statistic (0.87 and 0.86) and better four-year calibration with lower ICI (0.75 and 0.35). On external validation, the updated Prediction Tool had similar R^2 (60% and 58%) and four-year C-statistics (both 0.85) compared to the derivation analysis, with excellent four-year calibration (ICI 0.62 and 0.56). This updated Prediction Tool had similar prediction performance when used two years after biopsy. Thus, the original Prediction Tool should be used only at the time of biopsy whereas our updated Prediction Tool can be used for risk stratification one or two years post-biopsy.

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KEYWORDS: disease progression; end-stage kidney disease; IgA nephropathy; prediction tool; risk prediction

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IgA nephropathy (IgAN) has a very heterogeneous risk of kidney function decline to end-stage kidney disease (ESKD) that ranges between less than 10% to over 60%.[1] Until recently, there has not been a method to predict individual-patient risk of disease progression that has been externally validated in different ethnic groups and uses predictor variables readily available in clinical practice and histology scoring systems that are reproducible and validated.[2] As a result, it was not possible to accurately inform patients of their long-term kidney prognosis or to develop personalized-medicine approaches to the treatment of IgAN that are based on individual risk of disease progression.[3] In 2019, the International IgAN Prediction Tool (IIgAN-PT) publication addressed these limitations.[4] The IIgAN-PT comprises 2 models that use clinical predictor variables and the MEST (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], and interstitial fibrosis/tubular atrophy [T]) histology scores at the time of biopsy, with or without race/ethnicity, to accurately predict the risk of a 50% decline in estimated glomerular filtration rate (eGFR), or ESKD. The IIgAN-PT has subsequently undergone additional external validation analyses, has been updated for use in children, is available for clinical use online and in a mobile-app calculator (qxmd.com/calculate-by-qxmd), and is now the recommended method of risk stratification for IgAN in the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) glomerulonephritis guidelines.[5–8]

The original IIgAN-PT was designed to be used around the time of biopsy; however, this limits application of the tool to re-evaluate individual patient risk after a period of observation with supportive care. The 2021 KDIGO guidelines recommend blood pressure control and the use of medications that block the renin-angiotensin system (RASB) in all patients with proteinuria >0.5 g/day, and that supportive therapies be optimized before using proteinuria to risk-stratify patients for treatment with corticosteroids.[8,9] The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) trial confirmed the benefit of rigorous implementation of supportive therapies in reducing the risk of disease progression.[10] Most current clinical trials in IgAN aim to enroll patients that

remain at high risk for kidney function decline after a period of optimal blood pressure control and RASB.[11–14] The need is clear for reassessment of individual patient risk months to years post biopsy, so that it can be used to guide subsequent treatment decisions. Thus, evaluation of whether the original IIgAN-PT needs to be updated for use after biopsy is necessary.

We therefore used the large international multiethnic databases from the original IIgAN-PT analysis to update and externally validate the IIgAN-PT models so that they can be used at a time point 1 year or 2 years after biopsy to predict the subsequent risk of a 50% decline in eGFR, or ESKD.

METHODS

Study population

The study population comprised the cohorts used for the original IIgAN-PT analysis as previously described, with separate derivation and validation cohorts.[4] Details are provided in the Supplementary Methods. All cohorts included only those patients with biopsy-proven IgAN, available MEST-crescent (C) scores, who were age ≥18 years, did not have ESKD at the time of biopsy, and had available eGFR data. We additionally excluded patients who progressed to ESKD within the first year after biopsy, those who had less than 1 year of follow-up, and those who did not have at least one eGFR measurement before and after the new landmark time of 1 year after biopsy, in order to ensure adequate baseline and longitudinal follow-up eGFR data.

Variable definitions

Definitions for predictor variables at biopsy were the same as those used in the IIgAN-PT analysis. In addition, predictor variables were redefined relative to a landmark time of 1 year after biopsy. Details are provided in the Supplementary Methods. The primary outcome was a composite of the first occurrence of ESKD (eGFR < 15 ml/min per 1.73 m^2, dialysis, or transplantation) or a permanent reduction in eGFR to below 50% of the value at the 1-year landmark time.

Statistical analysis

The analysis strategy was based on changing the "baseline" time point from the biopsy date, as was done for the original IIgAN-PT, to a new landmark time 1 year after biopsy. The time from the new baseline to the primary outcome censored at either death or the end of follow-up was modeled using Cox proportional hazards models. In the derivation analysis, the original IIgAN-PT models (with and without race/ethnicity) were applied directly to the analytic cohort.[4] This process was done to determine if the original IIgAN-PT could be used without modification 1 year after biopsy. In addition, new updated IIgAN-PT models were refit in the derivation cohort specifically derived to be applied at the new baseline time point. Model fit was evaluated using R^2_D and the Akaike information criterion (AIC).[15] Discrimination was assessed using the C-statistic adapted for censoring.[16] Reclassification was assessed using the continuous net reclassification improvement and the integrated discrimination improvement adapted for censoring.[16] Calibration for a specific time horizon was evaluated using smoothed calibration plots of predicted versus observed risk, and using the integrated calibration index, which is a weighted difference between predicted and observed risk that quantifies the amount of miscalibration.[17] The validation analysis followed the methodology proposed by Royston and Altman for external validation of survival prediction models.[15] To determine if the updated IIgAN-PT could be used at time points beyond 1 year after biopsy, the updated models were applied without modification in the combined derivation and validation cohorts at a new landmark time 2 years after biopsy.

Results are presented according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (see Supplementary Table S1).[18] Additional details regarding the statistical analysis are provided in the Supplementary Methods.

RESULTS

Derivation analysis

The derivation cohort comprised 2507 patients (Supplementary Figure S1) and is described in Table 1. At the time of biopsy, 31.2% of patients were on RASB, and 8.5% had received prior immunosuppression. By 1 year after biopsy, both percentages had increased, with 80.1% of patients on RASB, and 32.5% previously treated with immunosuppression (of whom 94.5% received corticosteroids alone and 5.5% received other types of immunosuppression). Proteinuria and mean arterial blood pressure (MAP) at biopsy were 1.2 g/d (interquartile range [IQR] 0.7, 2.2) and 96.7 mm Hg (IQR 89.3, 106.7), respectively, both of which had decreased

Table 1 | Description of the derivation and validation cohorts

Characteristic	Derivation cohort	Validation cohort
Number of patients	2507	722
Follow-up, yr	3.9 (2.1, 6.5)	4.5 (2.4, 7.0)
Year of biopsy	2005 (2003, 2008)	2004 (1999, 2006)
Age, yr	36 (29, 46)	36 (29, 46)
Male sex	1474 (58.8)	398 (55.1)
Race/ethnicity:		
White	1112 (44.4)	187 (25.9)
Japanese	390 (15.6)	197 (27.3)
Chinese	983 (39.2)	288 (39.9)
Other	22 (0.9)	49 (6.8)
eGFR at biopsy, ml/min per 1.73 m^2	83 (57, 108)	80 (60, 103)
eGFR at 1 yr, ml/min per 1.73 m^2	84 (58, 108)	78 (60, 101)
MAP at biopsy, mm Hg	96.7 (89.3, 106.7)	94.5 (85.8, 103.3)
MAP at 1 yr, mm Hg	93.3 (86.7, 101.7)	91.2 (83.3, 100.0)
Proteinuria at biopsy, g/d	1.2 (0.7, 2.2)	1.3 (0.8, 2.3)
Proteinuria at 1 yr, g/d	0.5 (0.2, 1.0)	0.7 (0.3, 1.5)
Pathology		
M1	941 (37.5)	476 (65.9)
E1	399 (15.9)	303 (42)
S1	1925 (76.8)	546 (75.6)
T1	589 (23.5)	142 (19.7)
T2	101 (4)	46 (6.4)
Crescents	809 (32.3)	377 (52.2)
Medication use for RASB at biopsy	781 (31.2)	337 (46.7)
Medication use for RASB at 1 yr	2008 (80.1)	510 (70.6)
Immunosuppression use before biopsy	214 (8.5)	109 (15.1)
Immunosuppression use before 1 yr	804 (32.1)	245 (33.9)
Immunosuppression use after 1 yr	288 (11.5)	53 (7.3)
Outcome events		
50% Decline in eGFR	306 (12.2)	112 (15.5)
ESKD	236 (9.4)	88 (12.2)
Primary outcome	385 (15.4)	123 (17)

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; MAP, mean arterial blood pressure; MEST, mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], and interstitial fibrosis/tubular atrophy [T]; RASB, block of the renin–angiotensin system.

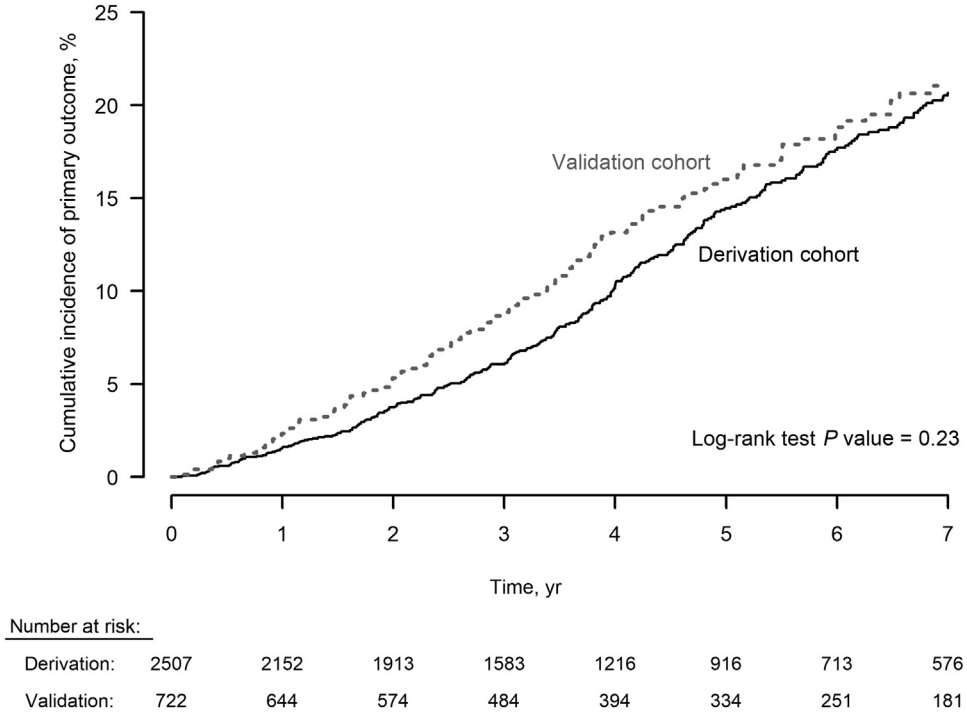


Figure 1 | The cumulative incidence of the primary outcome in the derivation and validation cohorts. Time at risk starts at a baseline landmark time point 1 year after biopsy. The primary outcome was a 50% decline in estimated glomerular filtration rate from the value at baseline, or end-stage kidney disease.

by the 1-year mark to 0.5 g/d (IQR 0.2, 1.0) and 93.3 mm Hg (IQR 86.7, 101.7). The purpose of this analysis was to predict the risk of the primary outcome (50% decline in eGFR or ESKD) using the IIgAN-PT applied at a baseline landmark time 1 year after biopsy. Over a median 3.9 years of follow-up after this baseline time point (IQR 2.1, 6.5), 385 patients experienced the primary outcome, with a 4-year risk of 10.3% (95% confidence interval [CI] 8.9, 11.7) and a 5-year risk of 14.5% (95% CI 12.7, 16.2; Figure 1).

The original IIgAN-PT models, with and without race/ethnicity, were applied directly to the derivation cohort at the new baseline time point. This process was done to determine if the IIgAN-PT could be used 1 year after biopsy without any modification, with prediction performance shown in Table 2. The IIgAN-PT models with and without race/ethnicity were then refit in the derivation cohort using a baseline landmark time of 1 year after biopsy to generate updated prediction models that were derived specifically to be used at this time point, herein referred to as the time-updated "post-biopsy IIgAN-PT." The post-biopsy IIgAN-PT models are detailed in Supplementary Tables S2 and S3, with prediction performance shown in Table 2.

When the original IIgAN-PT models were applied directly without modification to the derivation cohort, the C-statistic suggested good discrimination for the 4-year risk of the primary outcome (0.82 for both models with and without race/ethnicity; Table 2). However, calibration was poor, with predicted 4-year risk substantially lower than observed risk, especially for patients with predicted risk >10% (Figure 2a). The integrated calibration index was 1.54 and 2.11 for the models with versus without race/ethnicity, respectively, which is a measure of calibration in which higher values indicate worse calibration. The post-biopsy IIgAN-PT models include new beta-coefficients and new baseline survival curves that were generated using the derivation cohort (Supplementary Figure S3). Compared to the original models, the post-biopsy models both with versus without race/ethnicity had better model fit with lower AIC and higher R^2_D, significantly higher C-statistics (0.86–0.87), and better reclassification given by significant event and non-event net reclassification improvement and integrated discrimination improvement results (Table 2). Calibration for the 4-year risk of the primary outcome was also improved substantially using the post-biopsy models, with better agreement between predicted and observed risks and lower integration calibration indices of 0.75 and 0.35 (Figure 2b). The results were similar using the 5-year risk of the primary outcome (Table 2; Supplementary Figure S2A and B). These findings suggest that the post-biopsy IIgAN-PT models are better able to predict the primary outcome, compared with the original models when applied at a baseline time point 1 year after biopsy, and were therefore further assessed in the external validation analysis.

Validation analysis

The validation cohort comprised 722 patients (Supplementary Figure S1) and is described in Table 1. As expected, some differences were seen in patient characteristics compared to those

Table 2 | Prediction performance in the derivation analysis of the original compared to the post-biopsy International IgAN Prediction Tool models applied at a baseline time point 1 year after biopsy

	Prediction Tool model with race/ethnicity		Prediction Tool model without race/ethnicity	
Variable	Original model	Post-biopsy model	Original model	Post-biopsy model
AIC	4701	4637	4727	4662
R^2_D, %	55.0	61.2	54.3	60.0
Prediction performance at 4-yr time horizon				
C-statistic	0.82 (0.81, 0.82)	0.87 (0.86, 0.87)	0.82 (0.81, 0.83)	0.86 (0.85, 0.87)
ΔC-statistic	Ref	0.05 (0.05, 0.06)	Ref	0.04 (0.04, 0.05)
Event NRI	Ref	0.62 (0.44, 0.77)	Ref	0.54 (0.44, 0.64)
Non-event NRI	Ref	0.20 (0.16, 0.25)	Ref	0.05 (0.01, 0.10)
IDI	Ref	0.11 (0.09, 0.13)	Ref	0.10 (0.08, 0.11)
Prediction performance at 5-yr time horizon				
C-statistic	0.82 (0.81, 0.83)	0.87 (0.86, 0.87)	0.82 (0.81, 0.83)	0.86 (0.85, 0.87)
ΔC-statistic	Ref	0.05 (0.04, 0.05)	Ref	0.04 (0.04, 0.05)
Event NRI	Ref	0.55 (0.44, 0.67)	Ref	0.50 (0.39, 0.60)
Non-event NRI	Ref	0.19 (0.15, 0.23)	Ref	0.10 (0.06, 0.15)
IDI	Ref	0.11 (0.10, 0.13)	Ref	0.10 (0.09, 0.11)

Δ, change in C-statistic; AIC, Akaike Information Criterion; CI, confidence interval; IDI, integrated discrimination improvement; IgAN, International IgA Nephropathy; NRI, net reclassification improvement; Ref, reference model for comparison.
95% confidence intervals are given in parentheses. Overall model fit was assessed using R^2_D and the AIC, with an increase in R^2_D and reduction in AIC suggesting better model fit. Discrimination was assessed using the C-statistic, and reclassification using the continuous NRI in subgroups based on experiencing the primary outcome event and the IDI were both adapted for censoring. For ΔC-statistic, NRI, and IDI, statistically significant improvement is indicated by a 95% CI that does not include zero. Time-specific prediction performance was provided for 4 years and 5 years after the baseline time point 1 year after biopsy.

in the derivation cohort. However, similar to the derivation cohort, from the time of biopsy to 1 year later, both the proportion of patients on RASB and of those with prior immunosuppression use increased (from 46.7% to 70.6%, and 15.1% to 33.9%, respectively), and there was a reduction in both proteinuria (1.3 g/d to 0.7 g/d) and MAP (94.5 mm Hg to 91.2 mm Hg). Over a median 4.5 years of follow-up after a baseline time point 1 year after biopsy (IQR 2.4, 7.0), 123 patients experienced the primary outcome. The observed risk of the primary outcome was similar in the derivation and validation cohorts (Figure 1; log-rank *P*-value 0.23), with a 4-year risk of 13.2% (95% CI 10.4, 16.0), and a 5-year risk of 16.0% (95% CI 12.9, 19.1) in the validation cohort. The distribution of predicted risk is shown in Supplementary Figure S4.

When the post-biopsy IIgAN-PT models with versus without race/ethnicity were applied in the validation cohort, the R^2_D results were 60.1% and 58.2%, respectively, which were comparable to those in the derivation analysis (61.2% and 60.0%; Table 2). The calibration slope for both models was not different than 1, suggesting similar discrimination compared to the derivation analysis (1.02, 95% CI 0.86, 1.17, $P = 0.8$; and 1.02, 95% CI 0.86, 1.18, $P = 0.8$).[15] The C-statistics for the 4-year and 5-year risks of the primary outcome for both the models, with versus without race/ethnicity, were all 0.85 (95% CI 0.84, 0.87), which is comparable to the values in the derivation analysis (Table 2) and suggests similar discrimination. Calibration for the 4-year risk of the primary outcome showed good agreement between predicted and observed risk (Figure 2c). The integrated calibration indexes for the model with versus without race/ethnicity were 0.62 and 0.56, respectively, suggesting similar calibration compared to the derivation analysis (Figure 2b). Calibration results were similar using the 5-year risk of the primary outcome (Supplementary Figure S2C).

Ancillary analyses

For the post-biopsy IIgAN-PT models, both with versus without race/ethnicity, a higher predicted risk of the primary outcome was associated with a significantly faster rate of eGFR decline (Table 3). The prediction performance for both models was unchanged when assessed in the subgroup of patients not exposed to immunosuppression after the baseline time point 1 year after biopsy (Supplementary Table S4). When crescents were added to the post-biopsy IIgAN-PT models, no improvement was seen in model fit (R^2_D, AIC) or discrimination (C-statistic) with worse calibration given by higher integrated calibration indices (Supplementary Table S5). The differences in beta-coefficients between the post-biopsy and original IIgAN-PT models were used to determine if the risk of the outcome for any given value of a predictor variable (i.e., the hazard ratio) differed between the 2 models (Figure 3). Compared to both the original IIgAN-PT models, in the post-biopsy models there was a significant decrease in the hazard ratios for eGFR, T1 and T2, and a significant increase in the hazard ratio for Japanese race/ethnicity, and an increase in the hazard ratio for E1 in the model without race/ethnicity. No significant difference was seen in the hazard ratios between the original and post-biopsy models for all other predictor values.

When the landmark time point was changed from 1 year to 2 years after biopsy, 2734 patients in the combined derivation and validation cohorts satisfied updated inclusion

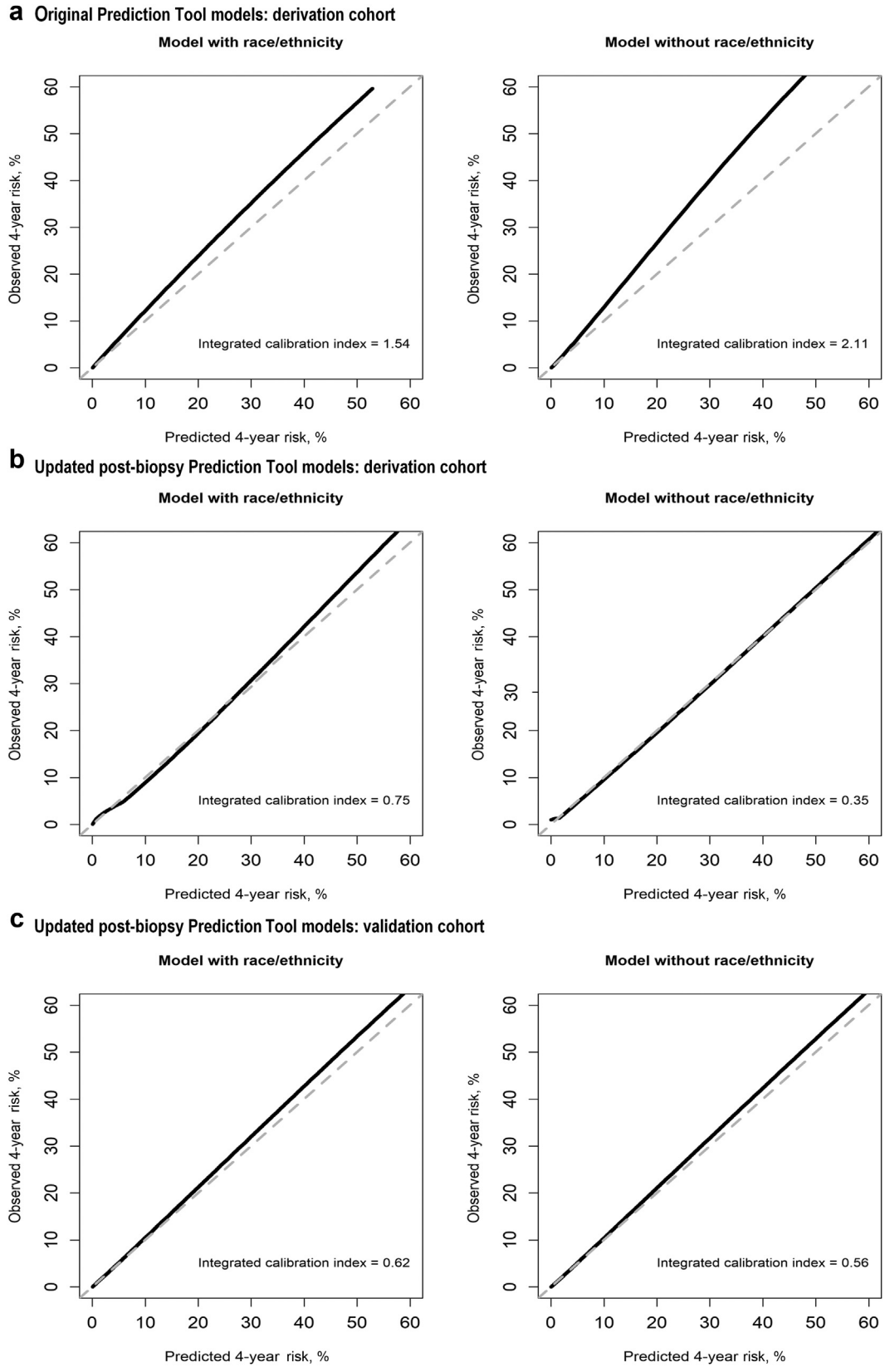


Figure 2 | Calibration curves depicting the predicted versus observed 4-year risks of the primary outcome using the original and post-biopsy International IgAN Prediction Tool (IIgAN-PT) models applied at a baseline time point 1 year after biopsy. The models with race/ethnicity are on the left, and the models without race/ethncity are on the right. (**a**) The original IIgAN-PT models were applied without modification in the derivation cohort. (**b**) The post-biopsy IIgAN-PT models were applied in the derivation cohort, and (**c**) in the (continued)

Table 3 | The rate of kidney function decline in subgroups based on predicted risk from the post-biopsy International IgAN Prediction models applied at a baseline time point 1 year after biopsy

Risk subgroup	Mean predicted 4-yr risk, %	Mean predicted 5-yr risk, %	Rate of eGFR decline, ml/min per 1.73 m^2 per yr	
			Mean (95% CI)	*P*
Model with race/ethnicity				
Lowest risk	0.6	0.8	−1.42 (−1.79, −1.05)	< 0.0001
Low risk	2.2	3.1	−1.84 (−2.09, −1.59)	
Intermediate risk	8.4	11.5	−2.57 (−2.81, −2.33)	
High risk	39.5	48.7	−3.91 (−4.28, −3.54)	
Model without race/ethnicity				
Lowest risk	0.6	0.8	−1.64 (−2.0, −1.26)	< 0.0001
Low risk	2.3	3.2	−1.85 (−2.10, −1.60)	
Intermediate risk	8.9	11.9	−2.56 (−2.79, −2.32)	
High risk	39.6	48.4	−3.67 (−4.04, −3.30)	

CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, International IgA Nephropathy.
Subgroups were based on <16th (lowest risk), 16th–50th (low risk), 50th–84th (intermediate risk), and >84th (high risk) percentiles of the linear predictor from the post-biopsy models with versus without race/ethnicity. The mean predicted risks in each subgroup are provided for the 4-year and 5-year risks of the primary outcome. *P*-values are for the differences in the rates of eGFR decline across risk subgroups.

criteria. Over a median 3.6 years of follow-up after the new landmark time point (IQR 2.0, 6.4), 405 patients experienced the primary outcome. When the post-biopsy IIgAN-PT models were applied without modification at a landmark time point 2 years after biopsy, the R^2_D and C-statistic results were similar to those seen in the validation analysis at the 1-year landmark time point (Supplementary Table S6). Calibration showed good agreement between predicted and observed risk (Supplementary Figure S5). The integrated calibration indices for the models with versus without race/ethnicity were 0.88 and 1.02, respectively, both of which are better than the 4-year calibration results from the original IIgAN-PT applied without modification at the 1-year landmark time point (1.54 and 2.11, as above).

The post-biopsy IIgAN-PT models in Supplementary Tables S2 and S3 have been converted into mobile-app and web-based prediction tools available on Calculate by QxMD for iOS, Android, and the web at https://qxmd.com/calculate-by-qxmd.

DISCUSSION

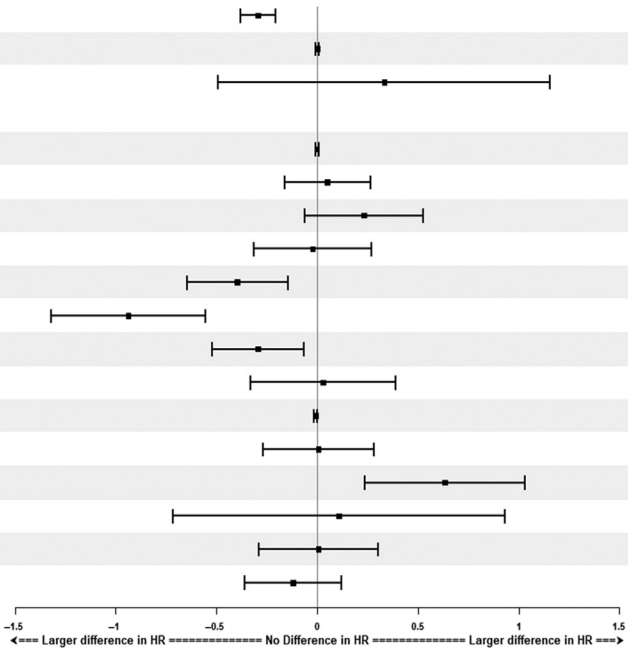
We have used a large international and ethnically diverse cohort of patients with IgAN to derive and externally validate updated post-biopsy versions of the IIgAN-PT models that contain the same predictor variables as in the original tool but can be used at a landmark time point 1 year after biopsy to accurately predict the subsequent risk of a 50% decline in eGFR or ESKD. This approach was necessary because the original IIgAN-PT models that were developed to be used at the time of biopsy did not predict outcome as accurately when used 1 year after biopsy. The post-biopsy IIgAN-PT models also can accurately predict risk when used at a landmark time point of 2 years after biopsy, and they have been converted into mobile-app and web-based calculators to facilitate their clinical implementation.

Our results have important implications for the clinical management of patients with IgAN. By the 1-year landmark time point, most patients in both the derivation and validation cohorts had been treated with RASB (80.1% and 70.6%), and MAP at 1 year was lower compared to that at biopsy, indicating better blood pressure control (Table 1). This pattern is consistent with KDIGO guideline recommendations that most patients with IgAN initially should be treated with optimal supportive care.[8,9] The majority of RASB (81.9%) and immunosuppression (68.0%) that was started after biopsy occurred within the first year. Although the datasets did not contain details on the dose and duration of therapy, accurate ascertainment of the presence of medication use was nonetheless possible. The high frequency of exposure to RASB and immunosuppression in the first year may explain why the post-biopsy IIgAN-PT had excellent prediction performance when applied at the 2-year landmark time and suggests that the post-biopsy models may also be applicable at later time points beyond 2 years, although this possibility needs to be confirmed in independent data sets with longer follow-up. Thus, the post-biopsy IIgAN-PT models support the implementation of KDIGO guideline recommendations by providing the tool necessary to re-evaluate the risk of disease progression after a period of observation and supportive care. Those patients who remain at higher risk can be considered for other therapies such as immunosuppression, whereas those who have responded to supportive care

Figure 2 | (continued) validation cohort. Predicted 4-year risks are from the prediction models, and observed 4-year risks are estimated using a flexible adaptive hazard regression model with the complementary log–log of the predicted 4-year risk as the covariate, as proposed by Austin *et al.*[17] The dotted line represents perfect calibration in which predicted and observed risks are identical.

a Model with race/ethnicity

Predictors	Hazard ratio original model at biopsy	Hazard ratio post-biopsy model	P value for difference in beta-coefficients
Estimated GFR (per square-root unit)	0.7	0.52	<0.0001
MAP (per 10 mm Hg)	0.96*	0.99*	0.81
Proteinuria (per g/d)	1.57 (at T0)* 1.75 (at T1)* 1.12 (at T2)*	1.92 (at T0)* 1.62 (at T1)* 1.45 (at T2)*	0.43
MAP*Proteinuria	--	--	0.76
M1	1.17	1.25	0.64
E1	0.88	1.1	0.12
S1	1.1	1.06	0.88
T1	1.78*	1.27*	0.002
T2	3.64*	1.34*	<0.0001
Proteinuria*T1	--	--	0.01
Proteinuria*T2	--	--	0.87
Age (per year)	0.98	0.97	0.07
Chinese (vs. White) ethnicity	2.27	1.56	0.96
Japanese (vs. White) ethnicity	1.5	2.94	0.002
Other (vs. White) ethnicity	0.65	0.71	0.8
Use of RASB	1.28	1.26	0.97
Prior use of immunosuppression	0.8	0.75	0.32



b Model without race/ethnicity

Predictors	Hazard ratio original model at biopsy	Hazard ratio post-biopsy model	P value for difference in beta-coefficients
Estimated GFR (per square-root unit)	0.73	0.56	<0.0001
MAP (per 10 mm Hg)	0.99*	0.95*	0.45
Proteinuria (per g/d)	1.70 (at T0)* 1.89 (at T1)* 1.24 (at T2)*	1.81 (at T0)* 1.52 (at T1)* 1.32 (at T2)*	0.89
MAP*Proteinuria	--	--	0.55
M1	1.24	1.32	0.65
E1	0.97	1.28	0.04
S1	1.09	1	0.54
T1	1.95*	1.46*	0.003
T2	3.79*	1.68*	<0.0001
Proteinuria*T1	--	--	0.02
Proteinuria*T2	--	--	0.84
Age (per year)	0.98	0.98	0.2
Use of RASB	1.07*	1.33*	0.14
Use of RASB * Proteinuria	--	--	0.09
Prior use of immunosuppression	0.77	0.72	0.31

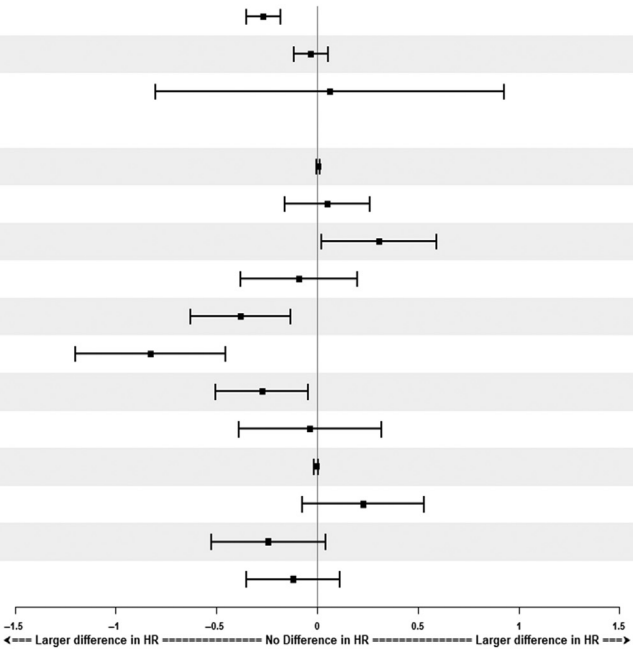


Figure 3 | The hazard ratios (HRs) and difference in beta-coefficients for each predictor variable in the post-biopsy compared to the original International IgAN Prediction Tool (IIgAN-PT) models. Because beta-coefficients in the prediction models determine individual patient risk, the difference in beta-coefficients between the post-biopsy and original IIgAN-PT models were used to determine if the risk of the outcome for any given value of a predictor variable (i.e., HR) was different between the 2 models. A 95% confidence interval (CI) that does not include 0 implies a significant difference between the 2 models. The corresponding hazard ratios (HRs) for the beta-coefficients in each model are also provided. Compared to the original IIgAN-PT models, in the post-biopsy models, there was a significant decrease in the HRs for estimated glomerular filtration rate (GFR), T1 and T2, and a significant increase in the HR for Japanese race/ethnicity and an increase in the HR for E1 in the model without race/ethnicity. *Because of interaction terms in the models, the beta-coefficients for main (continued)

and whose risk remains low can continue without immunosuppression and avoid unnecessary drug toxicity effects. Very few patients in the derivation and validation cohorts were treated with immunosuppression after the 1-year landmark time point (11.5% and 7.3%). Given this, the output of the post-biopsy IIgAN-PT is best interpreted as the predicted risk in the absence of subsequent immunosuppression treatment, which is consistent with the excellent prediction performance seen in the subgroup of untreated patients (Supplementary Table S4). In contrast, 32%–34% of the cohorts were treated with immunosuppression prior to the 1-year landmark time point, which is accounted for as a predictor variable in the models. This implies that the post-biopsy IIgAN-PT could be used to re-evaluate risk in those patients who are treated with immunosuppression within the first few years after kidney biopsy using updated clinical predictor values after treatment.

Substantial progress has been made in the development of personalized risk-prediction in IgAN over the past several years. Previous efforts in this regard were limited by predictor variables that were not clinically meaningful, histology scoring systems that are not clinically available and have not been validated, or the absence of adequate external validation, especially in different ethnic groups.[19–28] In 2019, the International IgAN Network assembled an international collaboration of investigators to create a large multiethnic database to address these limitations. This resulted in the derivation of the IIgAN-PT to predict the risk of disease progression at the time of biopsy in adults with IgAN, with several external validation analyses in multiple different ethnicity groups.[4,6,7] Subsequently, the Prediction Tool has been demonstrated to improve risk-based treatment allocation, has been updated for use in children, and has been used to validate biomarker research in the clinical domain.[5,29–31] As a result, the IIgAN-PT is now the preferred method for patient risk-stratification in IgAN according to the 2021 KDIGO guidelines.[8] Our results build upon this prior work by creating versions of the IIgAN-PT that can be used 1 and 2 years post-biopsy to re-evaluate individual patient risk after either immunosuppression treatment or a period of observation with supportive care. The original and post-biopsy IIgAN-PT constitute the first steps in creating the analytic infrastructure necessary to support future research on precision-medicine in IgAN in the context of multiple new drugs being developed with different toxicity profiles. The long-term goal is to develop personalized treatment decisions that integrate individual risk of disease progression from the various IIgAN-PT models at clinically relevant time points with clinical trial data on drug efficacy, drug toxicity, and the impact on quality of life.

Several reasons account for the improved prediction performance of the post-biopsy IIgAN-PT, compared with that of the original models. The original IIgAN-PT was designed to be used at the time of biopsy. When it was instead applied without modification at the 1-year landmark time point, there was good discrimination, with C-statistics at 0.82, but the models systematically underpredicted risk, resulting in poor calibration (Figure 2a). Because adequate calibration is a minimum requirement for a clinically useful prediction tool, the models were updated for use at the 1-year landmark time point, resulting in better discrimination with C-statistics of 0.86 and 0.87, and better calibration (Figure 2b and c).[32] There are two explanations for this improvement in prediction performance. First, the baseline survival from the original IIgAN-PT systematically underpredicted risk compared to the observed baseline survival (Supplementary Figure S3). This is an expected consequence of moving the baseline time point from biopsy to 1 year later, so the predicted risk for any given time horizon relative to biopsy is 1 year too early, compared to the same time horizon relative to the new baseline time point. Second, small changes in the beta-coefficients for the post-biopsy, compared with the original IIgAN-PT models, collectively resulted in different prediction estimates. These were most significant for eGFR, T1, T2, E1, and Japanese race/ethnicity (Figure 3). Each unit increase in eGFR was associated with a *lower* risk of the primary outcome in the post-biopsy model, compared to the original IIgAN-PT—for example, the hazard ratio decreased from 0.73 to 0.56 for the model without race/ethnicity. This implies that any given value of eGFR at 1 year confers a lower risk of disease progression than the same value at biopsy. This may be because eGFR after 12 months of observation is likely to subsequently be more stable compared to eGFR at biopsy that has a larger potential to change in the first year. The presence of E1 and Japanese race/ethnicity were both associated with a *higher* risk of the primary outcome in the post-biopsy compared to that in the original IIgAN-PT; for example, the hazard ratio for E1 increased from 0.97 to 1.28 in the model without race/ethnicity, and the hazard ratio for Japanese race/ethnicity increased from 1.50 to 2.94. This change suggests that E1 and Japanese race/ethnicity confer a larger risk of disease progression when they are used for risk stratification at 1 year compared to when they are used at biopsy. This difference may relate to immunosuppression use after biopsy, which was more frequent in those with E1 compared to E0 (54% vs. 38%) and in Japanese compared to White patients (64% vs. 38%). Conversely, after the 1-year landmark time point, the use of immunosuppression was similar between groups (E1 vs. E0: 9% vs. 11%; Japanese vs. White: 8% vs. 6%). Thus, the effects of E1 and Japanese race/ethnicity in the original Prediction Tool models at biopsy were confounded by the subsequent use of immunosuppression, which may have spuriously lowered the risk of the primary

Figure 3 | (continued) effects are provided at specified values of proteinuria, mean arterial blood pressure (MAP), T-scores, and block of the renin-angiotensin system (RASB) exposure. The values that were used for proteinuria (0.5 g/d), MAP (93.3 mm Hg), and RASB (exposed) are from the median or mode values in the derivation cohort shown in Table 1. HRs are not provided for interaction terms. MEST, mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], and interstitial fibrosis/tubular atrophy [T].

outcome. However, differences in treatment were largely accounted for in the post-biopsy models using the prior immunosuppression variable, which may explain the increase in hazard ratios. The presence of T1 and T2 were associated with a *lower* risk of the primary outcome in the post-biopsy compared to the original IIgAN-PT; for example, the hazard ratio for T2 in the model without race/ethnicity decreased from 3.79 to 1.68. This does not imply that T1 and T2 are not important predictors of disease progression at 1 year, but instead implies that they confer less risk compared to when they are used for risk stratification at the time of biopsy. RASB after biopsy was used more frequently in those with T0 compared to T1 or T2 (86% vs. 28% or 6%), the majority of which (88%) was started in the first year. The T1 and T2 effects in the models at biopsy were therefore confounded by the subsequent use of RASB, which may have spuriously lowered the risk of the primary outcome in the group with T0. This was accounted for in the post-biopsy models using the prior RASB variable, which may explain the reduction in hazard ratios. These differences between the models likely reflect changes in care that occurred during the 1-year observation period after biopsy.

Our results have several limitations. Controversy remains regarding the net reclassification improvement for variable selection in prediction models.[32,33] However, no new variables were selected in this analysis, and prediction performance was evaluated using a variety of other metrics for model fit, discrimination, and calibration, all of which showed consistent results. Only one Japanese cohort had sufficient follow-up data, so these data were randomly split between the derivation and validation analyses, whereas separate and autonomous cohorts were used for other ethnic groups. This approach was taken in order to ensure adequate multiethnic representation in the validation cohort, which is a strength of our analysis. However, external validation using separate datasets from those used for model derivation is important to ensure generalizability of results.[34] This underscores the need for additional validation of the post-biopsy IIgAN-PT, especially in Japanese patients and other ethnic groups that are not adequately represented by our cohorts. The analytic cohorts do not contain data on the duration or amount of RASB or immunosuppression that was used. This lack of data limits our capacity to assess whether treatment had been used according to current guideline recommendations. The follow-up (median 3.6 years) after the 2-year landmark time point was limited, resulting in a slight reduction in calibration in the range of high predicted risk above 30%, compared to the analysis at the 1-year landmark time point (Supplementary Figure S5). This reduction is because very few patients are at this high level of risk over a short 3-year time horizon. Further validation is required in cohorts with additional follow-up that can evaluate longer clinically relevant time horizons. We suggest using the post-biopsy IIgAN-PT models to predict risk 4 or 5 years, but not more than 7 years, after a new baseline time point 1 year after biopsy, because these correspond to the 50th and 75th percentiles of follow-up duration for the derivation and validation cohorts (Table 1).

In conclusion, we used a large international multiethnic cohort to update the IIgAN-PT models so that they can be used 1 or 2 years after biopsy to predict long-term kidney outcome. This approach allows re-evaluation of individual patient risk after a period of observation, supportive care, or immunosuppression treatment.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist.

Table S2. Details of the post-biopsy International IgAN Prediction Tool models with and without race/ethnicity that can be applied at a baseline time point one year after biopsy.

Table S3. The formulae to calculate the predicted probability of the primary outcome using the post-biopsy International IgAN Prediction Tool models applied at a baseline time point one year after biopsy.

Table S4. The prediction performance of the post-biopsy International IgAN Prediction Tool models applied at a baseline time point one year after biopsy evaluated in the subgroup of patients not exposed to immunosuppression during follow-up.

Table S5. Prediction performance in the derivation cohort of the post-biopsy International IgAN Prediction Tool models applied at a baseline time point one year after biopsy with or without crescents as a predictor variable.

Table S6. The prediction performance of the post-biopsy International IgAN Prediction Tool models applied at a baseline time point two years after biopsy.

Table S7. The values of predictor variables before (complete case) and after multiple imputation with chained equations.

Figure S1. Derivation of the analytic cohorts used for the derivation and validation of the post-biopsy International IgAN Prediction Tool models.

Figure S2. The predicted baseline survival curves from the original International IgAN Prediction Tool models compared to the observed baseline survival in the derivation cohort at a baseline time point one year after biopsy.

Figure S3. Calibration curves depicting the predicted versus observed 5-year risks of the primary outcome using the original and post-biopsy International IgAN Prediction Tool models applied at a baseline time point one year after biopsy.

Figure S4. The distribution of predicted 4-year and 5-year risks of the primary outcome.

Figure S5. Calibration curves depicting the predicted versus observed 3-year risks of the primary outcome using the post-biopsy International IgAN Prediction Tool models applied at a baseline time point two years after biopsy.

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