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Evaluating a New International Risk-Prediction Tool in IgA Nephropathy

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IMPORTANCE Although IgA nephropathy (IgAN) is the most common glomerulonephritis in the world, there is no validated tool to predict disease progression. This limits patient-specific risk stratification and treatment decisions, clinical trial recruitment, and biomarker validation.

OBJECTIVE To derive and externally validate a prediction model for disease progression in IgAN that can be applied at the time of kidney biopsy in multiple ethnic groups worldwide.

DESIGN, SETTING, AND PARTICIPANTS We derived and externally validated a prediction model using clinical and histologic risk factors that are readily available in clinical practice. Large, multi-ethnic cohorts of adults with biopsy-proven IgAN were included from Europe, North America, China, and Japan.

MAIN OUTCOMES AND MEASURES Cox proportional hazards models were used to analyze the risk of a 50% decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease, and were evaluated using the R^2_D measure, Akaike information criterion (AIC), C statistic, continuous net reclassification improvement (NRI), integrated discrimination improvement (IDI), and calibration plots.

RESULTS The study included 3927 patients; mean age, 35.4 (interquartile range, 28.0-45.4) years; and 2173 (55.3%) were men. The following prediction models were created in a derivation cohort of 2781 patients: a clinical model that included eGFR, blood pressure, and proteinuria at biopsy; and 2 full models that also contained the MEST histologic score, age, medication use, and either racial/ethnic characteristics (white, Japanese, or Chinese) or no racial/ethnic characteristics, to allow application in other ethnic groups. Compared with the clinical model, the full models with and without race/ethnicity had better R^2_D (26.3% and 25.3%, respectively, vs 20.3%) and AIC (6338 and 6379, respectively, vs 6485), significant increases in C statistic from 0.78 to 0.82 and 0.81, respectively (ΔC, 0.04; 95% CI, 0.03-0.04 and ΔC, 0.03; 95% CI, 0.02-0.03, respectively), and significant improvement in reclassification as assessed by the NRI (0.18; 95% CI, 0.07-0.29 and 0.51; 95% CI, 0.39-0.62, respectively) and IDI (0.07; 95% CI, 0.06-0.08 and 0.06; 95% CI, 0.05-0.06, respectively). External validation was performed in a cohort of 1146 patients. For both full models, the C statistics (0.82; 95% CI, 0.81-0.83 with race/ethnicity; 0.81; 95% CI, 0.80-0.82 without race/ethnicity) and R^2_D (both 35.3%) were similar or better than in the validation cohort, with excellent calibration.

CONCLUSIONS AND RELEVANCE In this study, the 2 full prediction models were shown to be accurate and validated methods for predicting disease progression and patient risk stratification in IgAN in multi-ethnic cohorts, with additional applications to clinical trial design and biomarker research.

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Supplemental content

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The most common type of glomerulonephritis, IgA nephropathy (IgAN) has a worldwide incidence exceeding 1.5 per 100 000 persons/y and is a frequent causes of end-stage renal disease (ESRD) in Asian countries.[1] A significant challenge in IgAN is the extremely heterogeneous risk of progressive kidney function decline, with a 10-year risk of ESRD varying between 5% and 60%.[2] Although guidelines recommend risk stratifying patients with IgAN so that immunosuppressive treatment can be targeted to high-risk patients, there is currently no tool available to accurately predict kidney disease progression.[3] Instead, risk stratification and treatment decisions rely on broad categories of clinical risk factors which can be highly inaccurate. A significant proportion of patients who qualify for immunosuppression therapy have nonprogressive disease, while many patients who do not qualify for treatment nonetheless experience kidney function decline.[4-8] Several clinical trials in IgAN have failed efficacy end points partly owing to inadvertently recruiting low-risk patients, and future trials will continue to be limited by unreliable methods of risk stratification.[9-14] This indicates a clear need for an accurate tool to predict disease progression in IgAN.

Although there are well-established clinical and histologic risk factors for kidney function decline, when used individually they are unable to accurately identify high-risk patients.[4,5,15,16] Previous efforts to integrate multiple risk factors into a prediction model have been limited by predictor variables that are not clinically meaningful; the use of histological scoring systems that have not been validated and are not routinely available in clinical practice; and lack of external validation, especially in different ethnic groups.[5,17-23] This last limitation is particularly relevant given the highly variable incidence and severity of disease related to ethnicity.[24] Although the Oxford MEST histologic score (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S] and interstitial fibrosis/tubular atrophy [T]) in IgAN has been internationally validated, is widely available, and is independently associated with the risk of kidney progression, to our knowledge it has not been included in a risk prediction model validated in multiple ethnic groups.[24-26] Owing to these substantial limitations, none of the existing prediction models in IgAN are sufficiently robust for use in clinical practice.

We therefore used a large international collaboration of data sets with diverse ethnic representation to derive and externally validate a comprehensive risk prediction model in IgAN using readily available clinical and laboratory risk factors and the MEST histologic score.

Key Points

Question How can we better predict, at the time of kidney biopsy, the risk of a 50% decline in kidney function or end-stage renal disease in patients with IgA nephropathy?

Findings Large international multiethnic cohorts including 3927 patients were enrolled to both derive and externally validate 2 prediction models, one that included patient race/ethnicity, and one that did not. Both models outperformed clinical measures for prediction of kidney disease progression and patient risk stratification.

Meaning The 2 prediction models were shown to be accurate and validated methods to help clinicians improve management and treatment of IgA nephropathy in multi-ethnic cohorts and may aid international researchers in trial recruitment.

Methods

Study Population

The study population comprised cohorts that were collected independently for research purposes from Europe (VALIGA, n = 1406); Europe, Asia, and North and South America (Oxford derivation, n = 265); North America (Oxford validation, n = 187); China (Beijing, n = 410; Nanjing, n = 1026); and Japan (Fukuoka, n = 702) (**Figure 1**A). Details have been previously described.[15,27-31] An additional Japanese cohort (Tokyo, n = 635) was collected from Juntendo University in Tokyo. All of these cohorts included only patients with biopsy-proven idiopathic IgAN, available MEST scores, and long-term follow-up after biopsy. Further details are provided in eMethods in the Supplement. The *derivation cohort* comprised the VALIGA, Nanjing, and Tokyo cohorts, and the *validation cohort* comprised the Beijing, Fukuoka, and both Oxford cohorts. We included patients in our analysis 18 years or older who did not have ESRD at the time of biopsy and who had available estimated glomerular filtration rate (eGFR) data. This project was approved by the University of British Columbia research ethics board, waiving patient written informed consent for de-identified data.

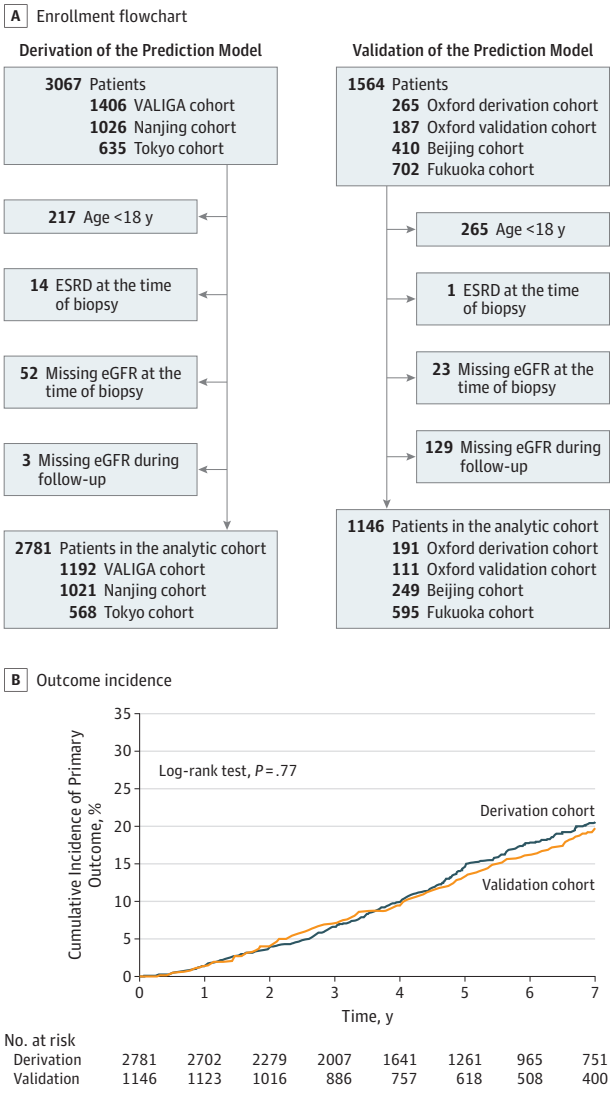
Definitions

Proteinuria, mean arterial blood pressure (MAP), eGFR (using the Chronic Kidney Disease Epidemiology Collaboration formula[32]), body mass index (BMI), age, and prior use of medications that block the renin-angiotensin system (RASBs, including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers) and the use of immunosuppression were determined at the time of biopsy. Race was self-reported by the patient as white, Chinese, Japanese, or other. Kidney biopsies were scored according to established criteria for the Oxford MEST scoring system, with the addition of crescents given recent evidence of their importance.[15,16,33] The primary outcome was a composite of the first occurrence of either ESRD (eGFR <15 mL/min/1.73m^2, dialysis, or transplantation) or a permanent reduction in eGFR to below 50% of the value at biopsy, which is an established kidney-related surrogate end point.[34,35]

Statistical Analysis

Time from kidney biopsy to the primary outcome (censored at death or end of follow-up) was analyzed using Cox proportional hazards models. In the derivation analysis, the *clinical model* contained only data on eGFR, proteinuria, and MAP at biopsy because these are the best recognized clinical predictors of outcome.[4] The *limited model* included the following core predictor variables based on the existing literature: eGFR, MAP

Figure 1. Enrollment Flowchart and Cumulative Incidence of the Primary Outcome in the Derivation and Validation Cohorts



A, Derivation of the analytic cohorts used for the derivation and validation of the risk prediction models. B, The primary outcome was 50% decline in eGFR or ESRD. eGFR indicates estimated glomerular filtration rate; ESRD, end-stage renal disease.

and proteinuria at biopsy, and the MEST score.[4,25] The *full model* included the same core predictor variables, but also considered age, sex, race/ethnicity, crescents, BMI, RASB and immunosuppression at biopsy, and interaction terms. The additional predictors were determined based on the existing literature and selected for retention in the model using a backward elimination procedure with $P = .20$.[4,24,25,31,36,37] A second *full model* was created in the same manner but without race/ethnicity as a potential predictor variable because the categories for race/ethnicity may not generalize to other populations. Prediction model performance was assessed using measures of model fit (R^2_D,[38] Akaike Information Criterion [AIC]), discrimination (C statistic adapted for censoring[39]), reclassification (continuous net reclassification improvement [NRI] and integrated discrimination improvement [IDI] adapted for censoring[39]), and calibration plots.

Results are presented according to the TRIPOD guidelines for risk-prediction models (see eTable 1 in the Supplement).[40] Two-tailed $P < .05$ findings were considered statistically significant, except where otherwise indicated. Additional details regarding the study methods and statistical analyses are provided in eMethods in the Supplement.

Results

Derivation Analysis

There were 3067 patients in the combined VALIGA, Nanjing, and Tokyo cohorts, of whom 2781 satisfied the inclusion criteria and formed the derivation cohort (Figure 1A). Characteristics of the derivation cohort are detailed in **Table 1**. The 5-year risk of the primary outcome (50% reduction in eGFR or ESRD) was 14.7% (95% CI, 13.1%-16.3%) (Figure 1B).

Results of the clinical, limited, and full prediction models are detailed in eTable 2 in the Supplement. The clinical model contains data on eGFR, MAP, and proteinuria at biopsy. The limited model additionally contains the MEST score. The full model with race/ethnicity additionally contains the MEST score, age, race/ethnicity, RASB and immunosuppression at biopsy, and interactions between proteinuria and each of MAP and the T-score component of MEST. The full model without race/ethnicity contains the same predictors but with an interaction between RASB and proteinuria instead of race/ethnicity (which was selected for retention in the model only when race/ethnicity was removed). Race was categorized as Chinese, Japanese, white, or other. The distribution of predicted 5-year risk of the primary outcome is shown in eFigure 1 in the Supplement.

The prediction performance details and all supporting data for the clinical, limited, and full models are reported in **Table 2**. Compared with the clinical model, the limited and full models all had better model fit, as demonstrated by higher R^2_D and lower AIC, better discrimination with significant increases in C statistics (ΔC), and significant improvement in reclassification with NRI and IDI 95% CIs above 0. Compared with the limited model, the full model with race/ethnicity had better model fit with higher R^2_D and lower AIC, better discrimination with a significant increase in C statistic to 0.82 (ΔC 0.02; 95% CI, 0.01-0.02), and significant improvement in reclassification as assessed by the IDI (0.03; 95% CI, 0.02- 0.04), but not the NRI (0.01; 95% CI, −0.08 to 0.16). The full model without race/ethnicity had a similar pattern, but with a significant NRI (0.19; 95% CI, 0.08-0.32). Both full models were well calibrated with very similar predicted and observed risks of the primary outcome 5 years after biopsy (**Figure 2**) and over the duration of follow-up (eFigure 2 in the Supplement). When the full models were compared with each other, there was no consistent trend in the C statistics, NRI, or IDI favoring one model over the other (data not shown). Based on these results, both full models were further assessed in the external validation analysis.

Table 1. Description of the Derivation and Validation Cohorts[a]

Characteristic	Derivation Cohort	Validation Cohort
Patients, No.	2781	1146
Follow up, median (IQR), y	4.8 (3.0-7.6)	5.8 (3.4-8.5)
Death	35 (1.2)	0
Year of biopsy, median (IQR)	2006 (2004-2008)	1998 (1993-2003)
Age, median (IQR), y	35.6 (28.2-45.4)	34.8 (26.9-45.0)
Male sex	1608 (57.8)	565 (49.3)
Race/ethnicity		
White	1167 (42.0)	176 (15.5)
Japanese	569 (20.5)	616 (54.4)
Chinese	1021 (36.7)	292 (25.8)
Other	22 (0.8)	49 (4.3)
Creatinine level at biopsy, median (IQR), μmol/L	92.0 (70.7-123.8)	84.0 (66.2-111.4)
eGFR at biopsy, median (IQR), mL/min/1.73m^2	83.0 (56.7-108.0)	89.7 (65.3-112.7)
<30	142 (5.1)	37 (3.2)
30-60	657 (23.6)	191 (16.7)
60-90	800 (28.8)	350 (30.5)
>90	1182 (42.5)	568 (49.6)
MAP at biopsy, median (IQR), mm Hg	96.7 (88.7-106.3)	93.3 (85.0-103.3)
Proteinuria at biopsy, median (IQR), g/d	1.2 (0.7-2.2)	1.3 (0.6-2.4)
<0.5	383 (13.9)	221 (19.4)
0.5-1	772 (28.1)	209 (18.3)
1-2	817 (29.7)	352 (30.8)
2-3	360 (13.1)	145 (12.7)
>3	415 (15.1)	215 (18.8)
BMI at biopsy, median (IQR)	23.8 (21.3-26.6)	22.8 (20.2-25.3)
MEST histologic score		
M1	1054 (38.0)	481 (42.0)
E1	478 (17.3)	476 (41.5)
S1	2137 (77.0)	912 (79.6)
T1	686 (24.7)	207 (18.1)
T2	128 (4.6)	122 (10.6)
Crescents	953 (34.3)	642 (56.1)
RASB use		
At biopsy	862 (32.4)	320 (30)
During follow-up	2400 (86.7)	708 (66.4)
Time from biopsy to start of RASB, median (IQR), mo	0.3 (0.0-3.6)	0.0 (0.0-4.7)
Immunosuppression use		
At biopsy	252 (9.1)	81 (7.1)
After biopsy	1209 (43.5)	359 (31.3)
Time from biopsy to onset of immunosuppression, median (IQR), mo	1.6 (0.0-5.1)	1.2 (0.0-11.5)
Primary outcome[b]		
50% Decline in eGFR	420 (15.1)	210 (18.3)
ESRD	372 (13.4)	155 (13.5)
Total primary outcomes	492 (17.7)	213 (18.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IQR, interquartile range; MAP, mean arterial blood pressure; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T); RASB, renin-angiotensin system blocker.

[a] Unless otherwise indicated, data are reported as number (percentage) of patients.

[b] The primary outcome was the first occurrence of either a permanent 50% decline in eGFR from that at biopsy or ESRD.

Validation Analysis

There were 1564 patients in the Oxford derivation, Oxford validation, Beijing, and Fukuoka cohorts, of whom 1146 satisfied the inclusion criteria and formed the validation cohort (Figure 1A). There were some differences, as expected, in patient characteristics compared with the derivation cohort (Table 1). Both the 5-year risk of the primary outcome (13.3%; 95% CI, 11.1%-15.5%) (Figure 1B) and the distribution of predicted 5-year risk (eFigure 1 in the Supplement) were similar to those in the derivation analysis.

The R^2_D for the full models with and without race/ethnicity when applied to the validation cohort were both 35.3%, which were better than the R^2_D for the models applied to the derivation cohort (26.3% and 25.3%, respectively). The

Table 2. Prediction Performance in the Derivation Cohort for the Clinical, Limited, and Full Models[a]

Variable	Clinical Model[b]	Limited Model[b]	Full Model[b]	
			With Race/Ethnicity	Without Race/Ethnicity
AIC	6485	6397	6338	6379
R^2_D, %	20.3	23.6	26.3	25.3
C statistic	0.78 (0.77 to 0.78)	0.80 (0.79 to 0.81)	0.82 (0.81 to 0.82)	0.81 (0.80 to 0.81)
Model Performance Compared With the Clinical Model				
ΔC statistic		0.02 (0.02 to 0.03)	0.04 (0.03 to 0.04)	0.03 (0.02 to 0.03)
NRI		0.55 (0.42 to 0.67)	0.18 (0.07 to 0.29)	0.51 (0.39 to 0.62)
NRI (events)		0.21 (0.10 to 0.32)	0.12 (0.04 to 0.22)	0.26 (0.14 to 0.36)
NRI (nonevents)		0.34 (0.30 to 0.37)	0.05 (0.01 to 0.09)	0.24 (0.20 to 0.28)
IDI		0.04 (0.03 to 0.05)	0.07 (0.06 to 0.08)	0.06 (0.05 to 0.06)
Model Performance Compared With the Limited Model				
ΔC statistic			0.02 (0.01 to 0.02)	0.01 (0.003 to 0.01)
NRI			0.01 (−0.08 to 0.16)	0.19 (0.08 to 0.32)
NRI (events)			0.03 (−0.07 to 0.16)	0.11 (0.01 to 0.23)
NRI (nonevents)			−0.02 (−0.06 to 0.03)	0.08 (0.04 to 0.12)
IDI			0.03 (0.02 to 0.04)	0.02 (0.01 to 0.02)

Abbreviations: AIC, Akaike Information Criterion; eGFR, estimated glomerular filtration rate; IDI, integrated discrimination improvement; MAP, mean arterial blood pressure; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T); NRI, net reclassification improvement.

[a] Unless otherwise indicated, data are reported as measure (95% CI).

[b] The clinical model contains eGFR, MAP, and proteinuria at biopsy; the limited model additionally contains the MEST histologic score; and the full models contain all predictor variables with and without race/ethnicity. Overall model fit was assessed using R^2_D and the AIC, with an increase in R^2_D[38] and reduction in AIC suggesting better model fit. Discrimination was assessed using the C statistic, and reclassification using the IDI and the continuous NRI overall and in subgroups based on experiencing the primary outcome event. For the change (Δ) in C statistic, NRI, and IDI, statistically significant improvement is indicated by a 95% confidence interval (CI), that does not include 0.

C statistics for both full models were 0.82 (95% CI, 0.81-0.83) and 0.81 (95% CI, 0.80-0.82), respectively, and were similar to the C statistics from the derivation analysis. The calibration slopes were 1.12 (95% CI, 0.98-1.25) and 1.19 (95% CI, 1.04-1.34) for the full models with and without race/ethnicity, respectively, indicating similar or better discrimination than was found in the derivation analysis.[38] Both full models were well calibrated in the validation cohort, with good agreement between predicted and observed risk of the primary outcome at 5 years after biopsy (Figure 2) and over the duration of follow-up (eFigure 2 in the Supplement)

As detailed in **Table 3**, for both full models, a higher predicted risk of the primary outcome was associated with a significantly faster rate of eGFR decline. The formulas for both full prediction models are listed in eTable 3 in the Supplement, and 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.

The Role of Crescents

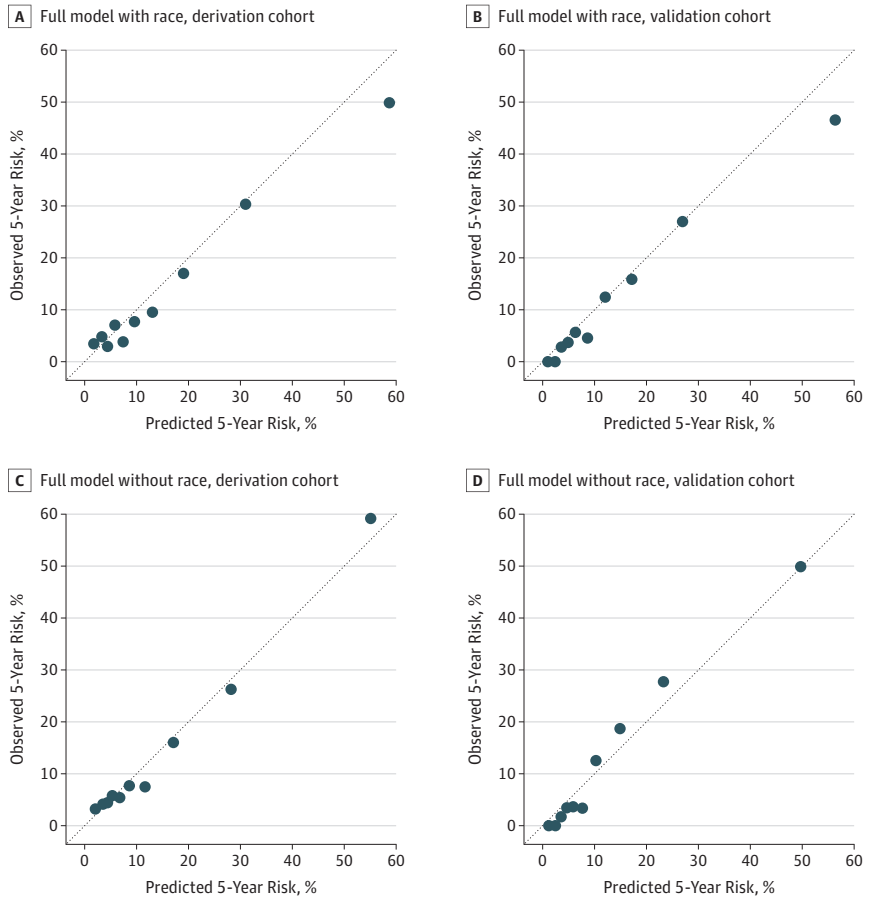
Because crescents have been implicated as an important histologic risk factor, we explored reasons they were not selected in either full prediction model. Crescents were highly correlated with race/ethnicity (see eTable 4 in the Supplement) and with immunosuppression use after biopsy (56% vs 36% of those with and without crescents, $P < .001$). Even when crescents were added to the full model without race/ethnicity, they did not meet the P value threshold for selection in the prediction model ($P < .20$) without also including immunosuppression after biopsy, which was not a candidate predictor variable in our primary analysis (see eTable 5 in the Supplement).

Discussion

We derived and externally validated 2 risk-prediction models capable of accurately predicting a 50% decline in eGFR or ESRD in biopsy-proven IgAN using large international and ethnically diverse data sets of patients with a broad spectrum of disease and clinical predictor variables readily available at the time of biopsy, including the MEST score. We generated 2 prediction models, one that includes white, Chinese, or Japanese race/ethnicity, and one without race/ethnicity that can be used in other racial groups or if race/ethnicity is not available. An increase in predicted risk was associated with a more rapid rate of eGFR decline, demonstrating that the models robustly capture patients with more aggressive disease. Both prediction models have been converted into mobile-app and web-based calculators to facilitate clinical implementation.

Our risk-prediction models are suitable for implementation worldwide and can potentially improve clinical treatment decisions and future research in IgAN. Risk stratification to determine immunosuppression treatment is currently based on simplistic categorization of clinical variables, which is highly inaccurate.[3] Clinical trial data suggest that up to 75% of patients are unnecessarily treated because they have low-risk nonprogressive disease.[6-8] Conversely, 33% of patients who do not meet clinical treatment criteria but have high-risk MEST

Figure 2. Calibration Curves Depicting the Predicted vs Observed 5-Year Risks of the Primary Outcome Using the Full Prediction Models With and Without Race/Ethnicity



Results from the derivation cohort are on the left, and from the validation cohort on the right. Predicted 5-year risks are from the prediction model, and observed 5-year risks are from Kaplan-Meier estimates within deciles of predicted risk. The dotted line represents perfect calibration in which predicted and observed risks are identical.

Table 3. Rate of Kidney Function Decline and the Mean Predicted 5-Year Risk of the Primary Outcome in Subgroups Based on the Linear Predictor

Risk Subgroup[a]	Mean Predicted 5-Year Risk, %	Rate of eGFR Decline, Mean (95% CI), mL/min/1.73 m^2/y	*P* Value[b]
Full Model With Race/Ethnicity			
Low risk	1.5	−1.24 (−1.63 to −0.85)	<.001
Intermediate risk	4.7	−1.76 (−2.01 to −1.50)	
Higher risk	13.9	−2.35 (−2.35 to −2.10)	
Highest risk	46.5	−3.43 (−3.80 to −3.06)	
Full Model Without Race/Ethnicity			
Low risk	1.6	−1.64 (−2.01 to −1.27)	<.001
Intermediate risk	4.5	−1.82 (−2.07 to −1.57)	
Higher risk	12.0	−2.12 (−2.36 to −1.87)	
Highest risk	40.9	−3.54 (−3.91 to −3.16)	

Abbreviation: eGFR, estimated glomerular filtration rate.

[a] Subgroups were based on the 16th (lowest risk), 16th to 50th (intermediate risk), 50th to 84th (higher risk) and higher than 84th (highest risk) percentiles of the linear predictor from the full models with or without race/ethnicity.

[b] *P* values are for the differences in the rates of eGFR decline across risk subgroups.

scores eventually experience kidney function decline but are denied therapy.[25] Our prediction models can now provide more accurate risk stratification early after a patient's diagnosis, although further research is required to determine the optimal risk threshold for treatment that accounts for both the risks and benefits of immunosuppression. Previous clinical trials in IgAN, including the recent STOP-IgAN trial,[9] have failed to achieve their primary end points partly due to inadvertently recruiting low-risk patients who did not experience kidney outcome events.[9-14] The prediction models can overcome this limitation, improve study power, and facilitate future clinical trial design by allowing targeted recruitment of high-risk patients. The models can also be used in translational research to test the prediction benefit of adding biomarkers to the fully specified models detailed in eTable 3 in the Supplement. This will allow the use of smaller cohorts than would ordinarily be

required for de novo model derivation, thus providing a critical tool for biomarker validation in the clinical domain.

This study addresses the limitations of previous prediction models in IgAN related to (1) the use of smaller, single-ethnicity cohorts with comparatively few patients across the spectrum of disease severity, (2) the use of predictor variables requiring prolonged periods of follow-up thus limiting clinical utility, and (3) the use of histologic scoring systems that have not been validated.[5,17-23,26,41] The large size of the present study cohorts from different international centers with few exclusion criteria ensured that the full spectrum of low- and high-risk disease was captured, with 36% to 44% of patients having 5-year predicted risks above 10%. This provides confidence that the prediction models can be applied to a diverse population of patients with IgAN. Because of known differences in the incidence and severity of IgAN across ethnic groups, we specifically assembled international cohorts to reflect this ethnic diversity and included race/ethnicity as a predictor variable.[24,42] Since individual patients may not be adequately represented by the available race/ethnicity categories, we generated a second model without race/ethnicity but with similar overall prediction performance in multiethnic cohorts. We used the MEST histologic scoring system because it has been validated in multiple ethnic groups and is now a recommended component of kidney biopsy reports for IgAN.[33] The other predictor variables are routinely used in clinical practice and are available at the time of kidney biopsy, making the present prediction models easy to implement.

External validation using separate and autonomous data sets from those used to derive the prediction models is a strength of the present analysis and is missing from most previously developed prediction tools in IgAN.[17-23,41] The derivation cohorts were specifically chosen because of their large size with sufficient outcome events, the availability of candidate predictors, and their multi-ethnic representation reflecting the diversity of IgAN. The validation cohort was from an older era, with less frequent use of RASB and immunosuppression, and different racial composition and frequency of histologic lesions. This strengthens the analysis because, in general, prediction models that perform well in a validation cohort that differs substantially from the derivation cohort provide greater generalizability to other populations with IgAN.[43] Most of the patients (86.7%) in the derivation cohort were treated with RASB starting at or shortly after biopsy. The prediction models are thus likely best applied to similarly treated patients, which is consistent with KDIGO guideline recommendations for routine use of RASB in IgAN.[3] The fully specified prediction models in eTable 3 in the Supplement can be used by other researchers for additional validation in more contemporary cohorts or different ethnic and age groups.

The present results highlight the importance of different prognostic factors in IgAN. Despite varying statistical significance of the individual MEST components, the overall MEST score accounts for the improvement in prediction performance between the clinical and limited models. Crescents were not selected as a predictor variable for either full model likely because they were highly correlated with race/ethnicity, which was more strongly associated with the primary outcome, and because the association between crescents and the primary outcome was confounded by the subsequent use of immunosuppression consistent with the findings of several other studies.[31,44] The addition of the MEST score, age, medication use at biopsy, and interaction terms with or without race/ethnicity account for the numerically small but statistically significant improvement in all the prediction performance metrics between the full and clinical models. Because these variables require no additional measurements beyond what is routinely available in clinical practice, the full models can be easily implemented to achieve this improvement in prediction performance. Chinese patients were at lower risk of the primary outcome during the first 3 years after biopsy, but at higher risk thereafter. This was not a finding unique to the derivation cohort; the same effect was observed when the full model with race/ethnicity was refit using the validation data. This highlights the importance of considering the time horizon when investigating ethnic differences in kidney outcome in IgAN.

Limitations

There are several limitations to our results. We included Chinese, Japanese, and white patients whose diagnosis and follow-up were within their countries of origin. Further research applying the models in other ethnic groups, or in countries with multi-ethnic populations or different biopsy practices, will be required. The prediction models apply only to biopsy-proven IgAN and are not applicable to other types of kidney disease. We included only adults in our analysis; therefore, the prediction models may not apply in children. Histologic data were only available for the presence or absence of crescents, and not the percentage of glomeruli involved, as proposed for the updated MEST-C score.[33] Although the models can generate predicted risks at any time point after biopsy, we suggest using 5 years and no more than 7 years because these are the 50th and 75th percentiles of follow-up duration. This time horizon should be considered in the context of a lifelong, slowly progressive disease. Finally, the prediction models were designed to be applied near the time of biopsy, and additional research is needed to determine if they can be used at other time points in the trajectory of the disease.

Conclusions

This project was a large international research collaboration that derived and externally validated prediction models for kidney outcome in IgAN that use readily available clinical and histologic predictor variables and are suitable for clinical implementation in multiple ethnic groups worldwide.

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