

Validation of an international prediction model including the Oxford classification in Korean patients with IgA nephropathy

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Abstract

Background: Recently, a new international risk prediction model including the Oxford classification was published which was validated in a large multi-ethnic cohort. Therefore, we aimed to validate this risk prediction model in Korean patients with IgA nephropathy.

Methods: This retrospective cohort study was conducted with 545 patients who diagnosed IgA nephropathy with renal biopsy in three medical centers. The primary outcome was defined as a reduction in estimated glomerular filtration rate (eGFR) of >50% or incident end-stage renal disease (ESRD). Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were used to validate models.

Results: During the median 3.6 years of follow-up period, 53 (9.7%) renal events occurred. In multivariable Cox regression model, M1 (hazard ratio [HR], 2.22; 95% confidence interval [CI], 1.02–4.82; $p = .043$), T1 (HR, 2.98; 95% CI, 1.39–6.39; $p = .005$) and T2 (HR, 4.80; 95% CI, 2.06–11.18; $p < .001$) lesions were associated with increased risk of renal outcome. When applied the international prediction model, the area under curve (AUC) for 5-year risk of renal outcome was 0.69, which was lower than previous validation and internally derived models. Moreover, cNRI and IDI analyses showed that discrimination and reclassification performance of the international model was inferior to the internally derived models.

Conclusion: The international risk prediction model for IgA nephropathy showed not as good performance in Korean patients as previous validation in other ethnic group. Further validation of risk prediction model is needed for Korean patients with IgA nephropathy.

KEYWORDS

clinical decision-making, glomerulonephritis, IgA, Koreans, validation study

[Correction added on 11 March, after first online publication: Grant numbers have been added for the funders National Research Foundation and Soonchunhyang University.]

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1 | INTRODUCTION

Immunoglobulin A (IgA) nephropathy is the most common type of glomerulonephritis worldwide and is known to be more prevalent in Asia than in the West.¹ Among the types of glomerulonephritis diagnosed with a renal biopsy, IgA nephropathy accounts for 27.5%–28.3% and is gradually increasing in Korea.^{2,3} Patients with IgA nephropathy show diverse clinical features ranging from mild microscopic hematuria to nephrotic syndrome and rapid progressive glomerulonephritis, and also have a heterogeneous risk of renal function decline.⁴

Therefore, risk stratification is an important and challenging issue in the management of patients with IgA nephropathy.⁵ In particular, guidelines recommend assessing the risk of progression and using corticosteroid therapy in high-risk patients.⁶ However, risk stratification with known clinical predictors, such as high blood pressure, proteinuria and decreased baseline kidney function, is still inaccurate. In addition, recent clinical trials failed to show a significant clinical benefit of immunosuppressive treatment in patients with IgA nephropathy.^{7,8} This lack of benefit could be partly due to the failure of screening of the high-risk patients. Thus, precise risk stratification is also needed for future trials on the efficacy of pharmacologic agents for IgA nephropathy.⁹

Accordingly, several researchers have developed risk prediction models that integrate the clinical and histologic features of IgA nephropathy.^{10–17} Although these models showed good performance in each study, they have not been widely used because they were not validated in other ethnic groups and included histologic grading systems not routinely used in clinical practice. The Oxford MEST (mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T]) histologic classification has been validated in many studies over the last decade worldwide and has become a standard histologic grading system for IgA nephropathy.^{18–20} Interestingly, a recent study presented a new international risk prediction model based on clinical predictors and the Oxford MEST histologic classification.²¹ This model was derived and validated in large multi-ethnic cohorts, and provided a model considering ethnic characteristics and a model not considering ethnic characteristics. However, the models have not been verified in the Korean population. Therefore, we aimed to use and validate this international risk prediction model in Korean patients with IgA nephropathy.

2 | METHODS

2.1 | Study population

This retrospective observational study was conducted in patients with IgA nephropathy diagnosed using renal biopsy at three tertiary hospitals in South Korea (Soonchunhyang University Seoul Hospital, Soonchunhyang University Bucheon Hospital and Soonchunhyang University Cheonan Hospital). This cohort consisted of 691 patients who underwent renal biopsy between Jan 2009 and March 2019. Among these, we excluded 47 patients aged <20 years, 53 patients without baseline 24-h proteinuria and medication records, and

SUMMARY AT A GLANCE

Prediction models for IgA nephropathy using clinical variables and the Oxford MEST scores were developed and may be utilised to individualise risk of progression. This study evaluates the performance of these prediction models in an external cohort of Korean patients.

46 patients without follow-up data. Consequently, a total of 545 patients were finally included in this study (Figure 1). Patients were followed until Jan 2020. This study was performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review boards of Soonchunhyang University Seoul Hospital, Soonchunhyang University Bucheon Hospital, and Soonchunhyang University Cheonan Hospital.

2.2 | Data collection

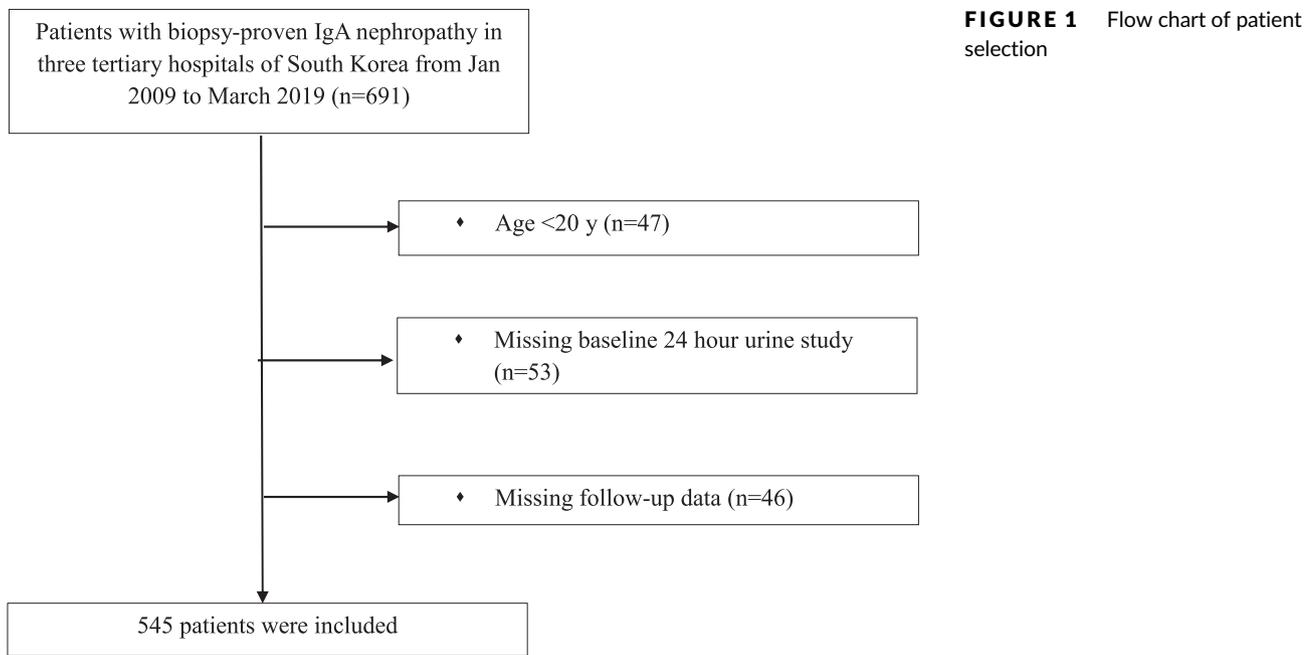
De-identified data including medical history, medications, anthropometric measurements and laboratory findings were extracted from the electronic medical record system of Soonchunhyang University Medical Center. The patients' blood pressure, height and weight were measured on the day of hospitalization for renal biopsy. All blood tests were performed on the day of the biopsy, and proteinuria was assessed using a 24-h urine test. Serum creatinine was measured using the isotope dilution mass spectrometry-traceable method, and the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.²² The pathologic diagnosis was established by pathologists at each center according to the Oxford MEST-C scoring system (MEST and crescent formation [C]).^{23,24} For patients underwent biopsy before the MEST-C score was published in 2017,²⁴ the C score was confirmed by our pathologists based on their previous readings.

2.3 | Primary outcome

The primary outcome was a composite renal outcome defined as a > 50% decrease in eGFR from baseline and/or incident end-stage renal disease (eGFR <15 ml/min/1.73 m², dialysis or transplantation).

2.4 | Statistical analysis

Continuous variables are expressed as median and interquartile ranges, and categorical variables are expressed as numbers and percentages. Comparisons between variables were performed using the *t* test, chi-square test, and Mann–Whitney U-test, as appropriate. Predictors were selected according to a previous multi-ethnic international cohort study.²¹ Among the international models in the study, the model

**TABLE 1** Baseline characteristics of patients with IgA nephropathy

Variables	Without outcome	With outcome ^a	Total	p-value
Participants	492	53	545	
Age, median (IQR), year	39.0 (31.0–51.0)	39.0 (31.0–46.0)	39.0 (31.0–50.0)	.886
Male sex, n (%)	265 (53.9)	30 (56.6)	295 (54.1)	.772
HTN, n (%)	149 (30.3)	26 (49.1)	175 (32.1)	.008
DM, n (%)	25 (5.1)	2 (3.8)	27 (5.0)	>.999
BMI, median (IQR), kg/m ²	24.0 (21.5–26.7)	24.0 (22.7–26.9)	24.0 (21.6–26.7)	.323
SBP, median (IQR), mmHg	120 (110–130)	130 (120–140)	120(110–130)	.001
DBP, median (IQR), mmHg	80 (70–80)	80 (70–80)	80 (70–80)	.096
MAP, median (IQR), mmHg	93 (83–100)	95 (90–103)	93 (83–100)	.004
eGFR, median (IQR), ml/min/1.73m ²	91.0 (69.1–111.4)	61.0 (40.8–80.1)	88.0 (66.8–109.4)	<.001
24 h proteinuria, median (IQR), g/day	0.7 (0.3–1.5)	1.9 (1.0–3.3)	0.8 (0.4–1.7)	<.001
RASB use at biopsy, n (%)	209 (42.5)	34 (64.2)	243 (44.6)	.003
RASB use during follow-up, n (%)	412 (83.7)	47 (88.7)	459 (84.2)	.431
Immunosuppressant use at biopsy, n (%)	2 (0.4)	0 (0.0)	2 (0.4)	>.999
Immunosuppressant use during follow-up, n (%)	95 (19.3)	24 (45.3)	119 (21.8)	<.001
Oxford classification (MEST-C), n (%)				
M1	214(43.5)	44 (83.0)	258 (47.3)	<.001
E1	178 (36.2)	17 (32.1)	195 (35.8)	.652
S1	353 (71.7)	42 (79.2)	395 (72.5)	.331
T1	101 (20.5)	19 (35.8)	120 (22.0)	<.001
T2	28 (5.7)	19 (35.8)	47 (8.6)	
C1	120 (24.4)	15 (28.3)	135 (24.8)	.742
C2	6 (1.2)	1 (1.9)	7 (1.3)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; MAP, mean arterial pressure; MEST-C, mesangial (M), endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T) and crescent formation (C.); RASB, renin-angiotensin system blockade; SBP, systolic blood pressure.

^aThe outcome was a composite renal outcome defined as a > 50% decrease in eGFR from baseline and/or incident end-stage renal disease (eGFR <15 ml/min/1.73 m², dialysis, or transplantation).

including race is limited for use in Caucasian, Chinese and Japanese populations. Therefore, in this study, we first applied a model without a race (designed to perform risk prediction regardless of race). Thus, predictors including age, eGFR, proteinuria, mean arterial pressure (MAP), use of renin-angiotensin system blockade (RASB) and

immunosuppression, and the Oxford MEST scores were used for the prediction model. Linear predictors were calculated for each patient, and the beta-coefficients of predictors were derived from the above-mentioned international study.²¹ The predicted probability of the primary outcome was calculated based on the linear predictors, and

TABLE 2 Comparison of baseline characteristics of patients with the original cohorts

Variables	This cohort	Original derivation cohort	Original validation cohort
Participants	545	2781	1146
Age, median (IQR), year	39 (31–50)	36 (28–45)	35 (27–45)
Male sex, <i>n</i> (%)	295 (54.1)	1608 (58)	565 (49)
Follow-up, median (IQR)	3.6 (1.7–6.6)	4.8 (3.0–7.6)	5.8 (3.4–8.5)
MAP, median (IQR), mmHg	93 (83–100)	97 (89–106)	93 (85–103)
eGFR, median (IQR), ml/min/1.73m ²	88.0 (66.8–109.4)	83.0 (56.7–108.0)	89.7 (65.3–112.7)
24 h proteinuria, median (IQR), g/day	0.8 (0.4–1.7)	1.2 (0.7–2.2)	1.3 (0.6–2.4)
RASB use at biopsy, <i>n</i> (%)	243 (44.6)	862 (32.4)	320 (30)
Immunosuppressant use at biopsy, <i>n</i> (%)	2 (0.4)	252 (9.1)	82 (7.1)
Oxford classification (MEST-C), <i>n</i> (%)			
M1	258 (47.3)	1054 (38.0)	481 (42.0)
E1	195 (35.8)	478 (17.3)	476 (41.5)
S1	395 (72.5)	2137 (77.0)	912 (79.6)
T1	120 (22.0)	686 (24.7)	207 (18.1)
T2	47 (8.6)	128 (4.6)	122 (10.6)
C1	135 (24.8)	953 (34.3) ^a	642 (56.1) ^a
C2	7 (1.3)		

Abbreviations: eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; MEST-C, mesangial (M), endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T) and crescent formation (C); RASB, renin-angiotensin system blockade.

^aOnly information on the presence of crescents was provided.

TABLE 3 The relationship between risk predictors and outcome

Predictors	Hazard ratio	95% confidence interval	<i>p</i> -value
Age (year)	0.97	0.94–0.99	.028
MAP (mmHg)	0.99	0.98–1.02	.890
RASB (vs. nonuser)	1.00	0.54–1.85	.993
Proteinuria ^a (g/day)	1.38	1.01–1.90	.045
eGFR (ml/min/1.73m ²)	0.97	0.96–0.99	<.001
Oxford classification (MEST-C)			
M1 (vs. M0)	2.22	1.02–4.82	.043
E1 (vs. E0)	0.84	0.40–1.74	.636
S1 (vs. S0)	1.54	0.71–3.32	.274
T (vs. T0)			
T1	2.98	1.39–6.39	.005
T2	4.80	2.06–11.18	<.001
C (vs. C0)			
C1	1.90	0.90–3.98	.091
C2	1.12	0.14–9.13	.916

Note: Cox proportional hazard regression was performed with listed predictors.

Abbreviations: eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; MEST-C, mesangial (M), endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T) and crescent formation (C); RASB, renin-angiotensin system blockade.

^aLog-transformed.

calibration plots were generated to compare the predicted risk and the observed risk. The observed risk was derived using Kaplan–Meier analysis. In addition, the relationship between predictors and the primary outcome was analysed using the Cox proportional hazard model in our study. We created two risk prediction models for our cohort. A clinical model was constructed with predictors including age, MAP, eGFR, proteinuria and use of RASB. In addition, a full model was constructed by adding the Oxford MEST scores to the clinical model. There was no severe collinearity among these predictors. A detailed description of internally derived models is presented in Supporting Information S1. The risk prediction of these two models and that of the international model were compared. The prediction performance of the models was examined using receiver operating characteristic (ROC) curve analysis, and the area under the ROC curve (AUC) was evaluated. ROC curves were derived using survival analysis based on the Cox proportional hazard model. In this analysis, we further validated the model with race (Chinese, Japanese, other race) and compared with internally derived models in our cohort. In addition, continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were also used to assess the performance of the prediction model. cNRI and IDI with 95% confidence intervals (CIs) not containing 0 were considered significant. Finally, although the Oxford classification was updated to include the C score as a potential predictor, the C score was not included in the international model.^{21,24} Thus, we examined the prediction performance of the C score in our cohort. All analyses were conducted using SPSS version 23.0 (IBM Corporation) and R language, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Our study used the TRIPOD checklist for prediction model validation as a validation study. (Supporting information S2).

3 | RESULTS

3.1 | Baseline characteristics

The baseline characteristics of the patients are summarised in Table 1. The median age of the patients was 39.0 years, and 54.1% of them were men. Patients with an outcome had a significantly higher prevalence of hypertension and MAP than those without an outcome. In addition, patients with an outcome had a significantly lower baseline eGFR at the time of biopsy and higher 24-h proteinuria levels and RASB use than patients without an outcome. In the Oxford classification, patients with an outcome had significantly higher M1, T1 and T2 scores than those without an outcome; however, the E1, S1, C1 and C2 scores were comparable between the groups. The comparison of the characteristics of our cohort and the original cohorts is presented in Table 2.

3.2 | Predictors and risk of renal outcomes in Korean patients with IgA nephropathy

During the median follow-up of 3.6 years, a 50% or more decline in eGFR and end-stage renal disease occurred in 41 (7.5%) and 37 (6.8%)

patients, respectively. Thereby, 53 (9.7%) primary outcomes occurred during the follow-up period. The median time to event was 3.7 (1.7–6.7) years. We examined the relationship between well-established clinical and histologic risk predictors and the occurrence of the primary outcome using the Cox proportional hazard model (Table 3). With respect to clinical predictors, young age (hazard ratio [HR] per 1-year increase, 0.97; 95% CI, 0.94–0.99; $p = .028$), high level of proteinuria (HR per 1 log increase, 1.38; 95% CI, 1.01–1.90; $p = .045$) and low baseline eGFR (HR per 1 ml/min/1.73 m² increase, 0.97; 95% CI, 0.96–0.99; $p < .001$) were significantly associated with an increased risk of the primary outcome. With respect to the Oxford histologic scores, M1 (HR, 2.22; 95% CI, 1.02–4.82; $p = .043$), T1 (HR, 2.98; 95% CI, 1.39–6.39; $p = .005$) and T2 (HR, 4.80; 95% CI, 2.06–11.18; $p < .001$) were significantly associated with the primary outcome. However, the E1, S1, C1 and C2 scores were not associated with the primary outcome.

3.3 | Calibration of the international prediction model in Korean patients with IgA nephropathy

Figure 2 shows the predicted risk and the observed risk for the 5-year risk of the outcome when the international model was applied to Korean patients with IgA nephropathy. When we calculated the predicted risk in tenth-of-risk groups, it was not well calibrated with the observed risk and a significant overestimation was observed, especially in patients with a higher risk of the primary outcome.

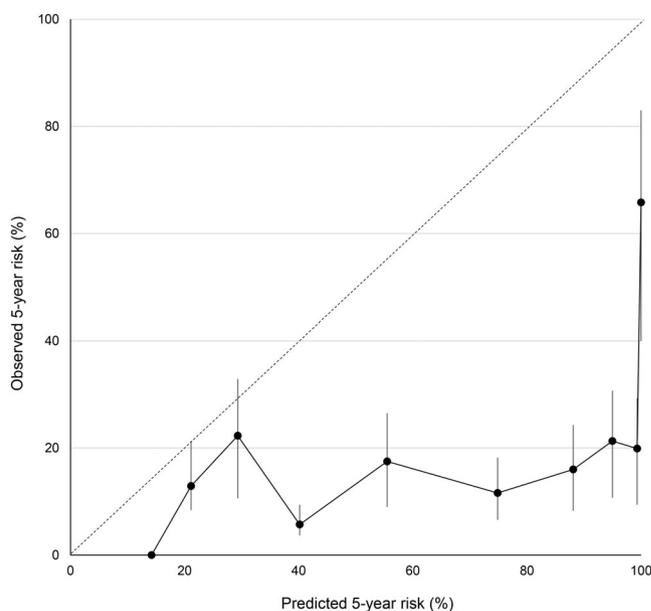


FIGURE 2 Calibration plot of the international prediction model applied to Korean IgA nephropathy patients. Comparison of observed and predicted 5-year risk of the outcome when the international prediction model without race was applied to Korean. The observed risk was derived using Kaplan–Meier analysis. The dashed line represents the perfect calibration, and the vertical line represents 95% confidence interval

3.4 | Performance of the international prediction model in Korean patients with IgA nephropathy

We further validated the performance of the international model according to AUC in Korean patients with IgA nephropathy. The AUC of the international model in Korean patients was 0.69, which was lower than that in the original validation (0.81). The internally derived clinical and full models had AUC values of 0.78 and 0.84, respectively, which were greater than the AUC of the international model (Figure 3A). Because our cohort had a relatively shorter median follow-up period (3.6 years) than the original validation cohort (5.8 years), we further examined the AUCs for 3- and 4-year risks. As a result, the AUCs of the international model for the 3- and 4-year

risks were 0.70 and 0.67, respectively, which were also lower than those of the internally validated models (Figure 3B,C). When we further validated the international model with race in our cohort, all three (Chinese, Japanese and other) race models showed an AUC of 0.67. In the comparison of prediction performance between models based on IDI and cNRI, the clinical model showed significant improvement of risk reclassification compared with the international model based on IDI (0.12; 95% CI, 0.01–0.22), but not based on cNRI (0.36; 95% CI, –0.01–0.58) (Table 4). However, the prediction performance of the internally validated models was greater than that of the international model for the 3- and 4-year risks. Moreover, the full model was better than the international model, with IDI and cNRI of 0.22 (95% CI, 0.1–0.32) and 0.52 (95% CI, 0.33–0.72), respectively. In addition,

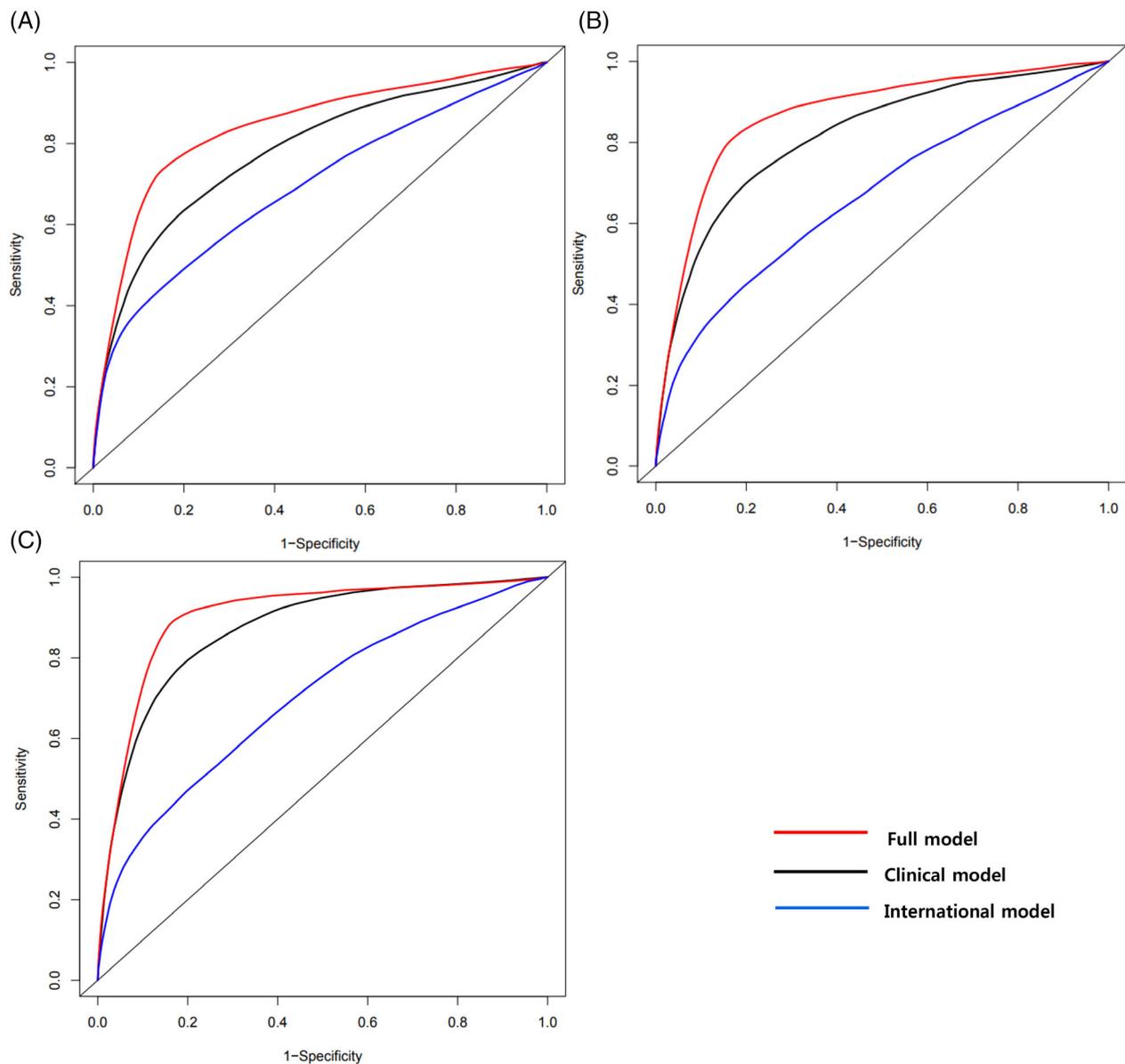


FIGURE 3 Comparison of 3-, 4- and 5-year risk predictions of three risk prediction models through AUC of ROC curve analysis. The prediction performance of the three models was compared using receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was evaluated. (A) ROC curves for the 5-year risk prediction, (B) ROC curves for the 4-year risk prediction and (C) ROC curves for the 3-year risk prediction

TABLE 4 Comparisons of prediction performance among models

	5-year risk		4-year risk		3-year risk	
	IDI (95% CI)	cNRI (95% CI)	IDI (95% CI)	cNRI (95% CI)	IDI (95% CI)	cNRI (95% CI)
Compared with the international model without race						
Clinical model ^a	0.12 (0.01–0.22)	0.36 (–0.01–0.58)	0.12 (0.02–0.22)	0.46 (0.13–0.70)	0.13 (0.01–0.25)	0.54 (0.10–0.76)
Full model ^b	0.22 (0.10–0.32)	0.52 (0.33–0.72)	0.20 (0.07–0.33)	0.62 (0.26–0.81)	0.20 (0.07–0.35)	0.64 (0.21–0.83)
Compared with the clinical model ^a						
Full model ^b	0.10 (0.02–0.17)	0.44 (0.15–0.62)	0.08 (0.01–0.14)	0.39 (0.11–0.62)	0.07 (0.02–0.15)	0.38 (0.16–0.69)

Note: The prediction performance of the models was compared with cNRI and IDI. For cNRI and IDI, statistically significant improvement is indicated by a 95% confidence interval that does not include zero.

Abbreviations: cNRI, continuous net reclassification improvement; IDI, integrated discrimination improvement.

^aThe clinical model contains age, mean arterial pressure, eGFR, proteinuria, and use of RASB.

^bThe full model constructed by adding the Oxford MEST scores to the clinical model.

	IDI (95% CI)	p-value	cNRI (95% CI)	p-value
Whole cohort				
5 year risk	0.01 (–0.02–0.04)	.465	0.36 (–0.09–0.53)	.140
4 year risk	0.01 (–0.02–0.04)	.505	0.35 (–0.15–0.55)	.140
3 year risk	0.01 (–0.03–0.03)	.764	0.17 (–0.27–0.45)	.319
Subgroup without immunosuppressive agent				
5 year risk	0.03 (–0.01–0.07)	.126	0.38 (0.08–0.64)	.020
4 year risk	0.01 (–0.03–0.06)	.605	0.25 (–0.19–0.55)	.133
3 year risk	0.01 (–0.05–0.05)	>.999	0.17 (–0.21–0.47)	.385
Subgroup with immunosuppressive agent				
5 year risk	0.01 (–0.02–0.04)	.445	0.20 (–0.34–0.52)	.339
4 year risk	0.02 (–0.02–0.05)	.405	0.30 (–0.25–0.65)	.206
3 year risk	0.02 (–0.03–0.05)	.465	0.16 (–0.40–0.58)	.385

Note: The prediction performances of the full model and the full model plus C score were compared. The prediction performance of the models was compared with cNRI and IDI. For cNRI and IDI, statistically significant improvement is indicated by a 95% confidence interval that does not include zero.

Abbreviations: CI, confidence interval; cNRI, continuous net reclassification improvement; IDI, integrated discrimination improvement.

when the internally validated models were compared, the full model showed better predictive performance than the clinical model.

3.5 | Role of crescents as a predictor

Finally, we examined the prediction performance of crescents in our cohort. When we added the C score (C1 or C2) to the full model, the predictive ability of the model with crescents as a predictor was not superior to that of the full model for the 3-, 4- and 5-year risks (Table 5). A total of 119 patients were treated with immunosuppressive agents at biopsy and during the follow-up period. In a subgroup of 426 patients who were not treated with immunosuppressive agents, adding crescents to the full model showed improved reclassification only in the 5-year risk prediction based on cNRI (0.38; 95% CI, 0.08–0.64; $p = .02$), but not based on IDI. In a subgroup of 119 patients with immunosuppression, all models with crescents did not show improved risk reclassification.

TABLE 5 Prediction performance of crescents in IgA nephropathy

4 | DISCUSSION

In this study, we validated the newly designed international risk prediction model in Korean patients with IgA nephropathy. Contrary to expectations, the prediction performance of the international model without race was lower than that in the original validation, and the model overestimated the risk in Korean patients. The predictive ability of the international model was inferior to that of the internally derived clinical model, which included only clinical parameters but not the Oxford classification. Moreover, the internally derived full model with the Oxford classification had a better prediction performance than the clinical model.

Several risk prediction models have been proposed for predicting the prognosis of IgA nephropathy.^{10–17} However, these models have not been widely used in real clinical practice because they were derived from relatively small cohorts, were not externally validated in multiple races, and did not include widely accepted histologic scoring systems. Therefore, the use of these models for determining

treatment options and predicting prognosis in Korean patients is limited. Recently, the International IgA Nephropathy Network, including cohorts from Europe, North/South America, China and Japan, developed new risk prediction models for patients with IgA nephropathy.²¹ These models were derived from a cohort comprising 2781 multi-ethnic patients and were validated in 1146 patients of various races. Moreover, these models were externally validated in another Chinese cohort of IgA nephropathy patients and showed remarkable prediction performance.²⁵ In addition, these models included well-known clinical predictors of IgA nephropathy and the Oxford classification. Because the Oxford classification is a well-validated histologic scoring system for IgA nephropathy worldwide, including Korea,^{19,20,26,27} we expected these new international risk prediction models to be useful for predicting prognosis in Korean patients with IgA nephropathy.

However, when we validated the international model in our cohort, the prediction performance was not as good as we expected. Several possible explanations for this result can be proposed. First, it can be attributed to the differences in patient characteristics between our cohort and the original cohorts. When comparing the baseline characteristics, our cohort showed a lower level of proteinuria (0.8 g/day in our cohort, 1.2 g/day in the original derivation cohort, and 1.3 g/day in the original validation cohort) and less immunosuppressant use (0.4%, 9.1% and 7.1%, respectively) at the time of biopsy. Also, the primary outcome occurred less in our cohort than in the original cohorts (9.7% in our cohort, 18% in the original derivation cohort and 19% in the original validation cohort). Taken together, these results suggest that our cohort included patients with an earlier stage of IgA nephropathy than the original cohorts, which might be caused by the clinical practice of early biopsy in our centers. Thus, it can be presumed that the international model derived from cohorts with more advanced stages of IgA nephropathy could overestimate the renal progression risk in patients with less severity. Second, because our cohort had a relatively shorter follow-up period than the original cohorts, the international model may not be suitable for predicting the 5-year risk of renal outcome in our cohort. However, a recent external validation of the international model in a Chinese cohort with a median follow-up period of 2.4 years showed excellent prediction performance.²⁵ Third, an inter-observer variability could exist among pathologists in scoring using the Oxford classification. A previous study reported that differences in the scoring of MEST-C had a significant impact on the prognostic value of the Oxford classification.²⁸ Finally, the treatment during the follow-up in our study may be different from that in the original study. We included patients who underwent renal biopsy from 2009, but the original cohorts included patients who underwent renal biopsy before 2009. Thus, differences in treatment strategies over time might have resulted in differences in patient prognosis. In particular, there is still no international consensus on the use of immunosuppressant in patients with IgA nephropathy. Therefore, the use of immunosuppressant may differ among studies. Because the international model that we used included only baseline predictors at the time of biopsy, different treatments during the follow-up period may have weakened the prediction performance of the model. Therefore, further validation of the model with various treatment strategies is needed in the future.

However, despite the above-mentioned differences among cohorts, a possibility remains that the international model is not suitable for Koreans because of racial differences. A clear West-to-East prevalence gradient exists in IgA nephropathy, with the highest frequency in some Asian populations (40%–50%), moderate frequency in European populations (20%–30%), and the lowest frequency in African populations (< 5%).²⁹ Furthermore, the genetic susceptibility, clinical presentation, histologic features and disease progression of IgA nephropathy widely vary among different ethnic populations.³⁰ In the aforementioned validation study conducted in China,²⁵ both international models (with and without race) showed good prediction performance in Chinese patients with IgA nephropathy. However, when the 5-year risk prediction was compared between the two models, the risk prediction power of the model with race was better than that of the model without race. Furthermore, the original cohorts of the international model did not include Korean patients. Therefore, further external validation of the international model should be implemented in various Korean cohorts before its wide use in real clinical practice.

The presence of crescents has been reported to be an important histologic risk factor in IgA nephropathy and has been added to the Oxford classification system.²⁴ However, in a recent large international cohort study on IgA nephropathy, crescents improved the risk discrimination performance only in patients without immunosuppression.³¹ Meanwhile, the international model that we used did not include crescents in all models because crescents could not meet the qualifications for selection in the models.²¹ In Korea, Park et al. reported that the presence of crescents significantly improved the discrimination performance of the prediction model for IgA nephropathy, thereby demonstrating the clinical significance of crescents.³² However, they did not use the Oxford classification for histologic presentation. In our study, crescents were not associated with an increased risk of outcome and improved the risk reclassification only for 5-year risk based on cNRI, but not in other models. Therefore, further large studies are needed to examine the exact role of crescents in predicting prognosis and determining treatment methods in patients with IgA nephropathy.

This study had several limitations. First, because of the retrospective nature of this study, we collected patient information from medical records and some data were missing. Therefore, the exclusion of patients may have led to a selection bias. Second, the follow-up period of our study was relatively shorter than that of the original cohorts of the international model, and loss to follow-up might have influenced the prediction performance of the models, and it may be related to our cohort's relatively low occurrence of renal outcomes. However, all prediction analyses, including AUC, cNRI and IDI determinations, were conducted based on survival analysis, and right-censored data were considered. Third, we could not externally validate our internally derived models because the number of patients included in our cohort was relatively small. Therefore, further validation in a large Korean cohort is needed to confirm our findings.

In conclusion, the international risk prediction model for IgA nephropathy devised for multi-racial applications did not show the same good performance in Korean patients as in the previous validation in other ethnic groups. Therefore, additional validation of the

international model in a large cohort or the development of a new prediction model may be needed for Korean patients with IgA nephropathy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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