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Original contribution

Comparison of the Haas and the Oxford classifications for prediction of renal outcome in patients with IgA nephropathy☆,☆☆

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Summary Pathologic features can provide valuable information for determining prognosis in IgA nephropathy (IgAN). However, it is uncertain whether the Oxford classification, a new classification of IgAN, can predict renal outcome better than previous ones. We conducted a retrospective cohort study in 500 patients with biopsy-proven IgAN between January 2002 and December 2010 to compare the ability of the Haas and the Oxford classifications to predict renal outcome. Primary outcome was a doubling of the baseline serum creatinine concentration (D-SCr). During a mean follow-up of 68 months, 52 (10.4%) and 35 (7.0%) developed D-SCr and end-stage renal disease, respectively. There were graded increases in the development of D-SCr in the higher Haas classes. In addition, the primary endpoint of D-SCr occurred more in patients with the Oxford M and T lesions than those without such lesions. In multivariate Cox regression analyses, the Haas class V (HR, 12.19; $P = .002$) and the Oxford T1 (hazard ratio [HR], 6.68; $P < .001$) and T2 (HR, 12.16; $P < .001$) lesions were independently associated with an increased risk of reaching D-SCr. Harrell's C index of each multivariate model with the Haas and the Oxford classification was 0.867 ($P = .015$) and 0.881 ($P = .004$), respectively. This was significantly higher than that of model with clinical factors only ($C = 0.819$). However, there was no difference in C-statistics between the 2 models with the Haas and the Oxford classifications ($P = .348$). This study suggests that the Haas and the Oxford classifications are comparable in predicting progression of IgAN.

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1. Introduction

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide and the leading cause of end-stage renal disease (ESRD) [1,2]. The clinical course is highly variable, ranging from asymptomatic microscopic hematuria to ESRD [3,4]. IgAN is not entirely a benign condition because approximately 30% to 40% of patients with IgAN develop ESRD within 20 years of apparent disease onset [5-7]. Therefore, identifying risk factors for progression is of paramount importance to improve renal outcomes. To date, a number of studies examining risk stratification for IgAN have been published and reach a general consensus regarding adverse risk factors such as hypertension, heavy proteinuria, and decreased kidney function at the time of diagnosis [1,4,8-10].

In addition to these measurable clinical risk factors, pathologic features of IgAN can also be of aid in risk stratification. During past decades, there have been many histologic classification models for IgAN and their utility in predicting renal outcome have been tested in a number of studies. These classifications are mostly presented using semi-quantitative or single-grade systems [2]. The former is generally well-correlated with renal outcome, but it is a time-consuming process, which limits its clinical utility [11]. The 2 single-grade scoring systems that have been widely used in clinical practice are the Lee classification and the Haas classification. However, both classifications have been criticized because of the use of subjective and vague terminology such as “maybe” and “more than”, which reduces their reproducibility. In fact, in the Lee classification, mesangial sclerosis and segmental glomerulosclerosis were not clearly distinguished [12]. Similarly, the Haas classification did not specify mesangial and endocapillary hypercellularity, but these lesions were incorporated in each class [11,13]. Although pathologic classifications can provide valuable information for determining prognosis, there has been much controversy as to whether histopathologic features are superior to clinical factors in risk stratification of IgAN [11].

With this background in mind, the Oxford classification was proposed by the Working Group of the International IgA Nephropathy Network and the Renal Pathology Society and has gained worldwide acceptance [2,14]. It has a simpler semi-quantitative scoring system that encompasses 4 pathologic lesions associated with progression including mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental sclerosis (S), and tubular atrophy/interstitial fibrosis (T). To date, a number of studies have been conducted to validate this classification, particularly in terms of predicting worse outcome [10,15-18]. However, it is currently unknown whether the Oxford classification can predict future adverse renal outcomes better than previous classifications. Therefore, in this retrospective cohort study, we aimed to compare the ability of the Haas and the Oxford classification systems to predict renal outcome in IgAN.

2. Methods

2.1. Study subjects

A flow diagram of participants is presented in Fig. 1. Between 2002 and 2010, there were 644 patients with biopsy-proven IgAN in Yonsei University Severance Hospital and National Health Insurance Service Ilsan Hospital. Patients with Henoch-Schonlein purpura were considered ineligible for the study. We excluded patients if they were aged <18 years (n = 22) or had a follow-up duration of <12 months (n = 89). Patients with an inadequate biopsy sample ≤7 glomeruli (n = 13), secondary causes of mesangial IgA deposition such as IgA-dominant acute post-infectious glomerulonephritis (n = 4), systemic lupus erythematous (n = 4), liver cirrhosis (n = 7), or malignancy (n = 5) were also excluded. Thus, a total of 500 patients were included in this study. This study was approved by the institutional review board of Yonsei University Health System Clinical Trial Center. This study was a retrospective medical record–based study, and the institutional review board waived the requirement for written consent from the patients.

2.2. Clinical and biochemical data collection

All data were obtained from the databases of the 2 institutions. Baseline data were collected at the time of renal biopsy. These included gender, age, systolic and diastolic blood pressure, presence of comorbid conditions, date of renal biopsy, pathologic findings on renal biopsy, and laboratory parameters including serum blood urea nitrogen, creatinine, albumin, total cholesterol, triglyceride, hemoglobin, random urine protein-to-creatinine ratio (UPCR), and 24-hour urinary protein excretion. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In addition, medications including anti-hypertensives, renin-angiotensin system (RAS) blocker (either angiotensin converting enzyme inhibitors or angiotensin type II receptor blockers), steroids, and other immunosuppressants were recorded. In this study, we presented pathologic findings using the Haas and the Oxford classification criteria [2,14,19]. Briefly, Haas grading systems are classified from I (minimal lesion) to V (advanced chronic lesion) according to the severity of pathologic findings. These histologic variables consist of mesangial matrix expansion, glomerular hypercellularity, focal or global glomerular sclerosis, crescents, and tubular atrophy/interstitial fibrosis [19]. Oxford classification is a semi-quantitative scoring system that includes four pathologic variables. Mesangial hypercellularity (M), segmental glomerulosclerosis (S), and endocapillary hypercellularity (E) are categorized as either present or absent and tubular atrophy/interstitial fibrosis (T) are divided into T0 (≤25%), T1 (26%-50%) and T2 (>50%) [2].

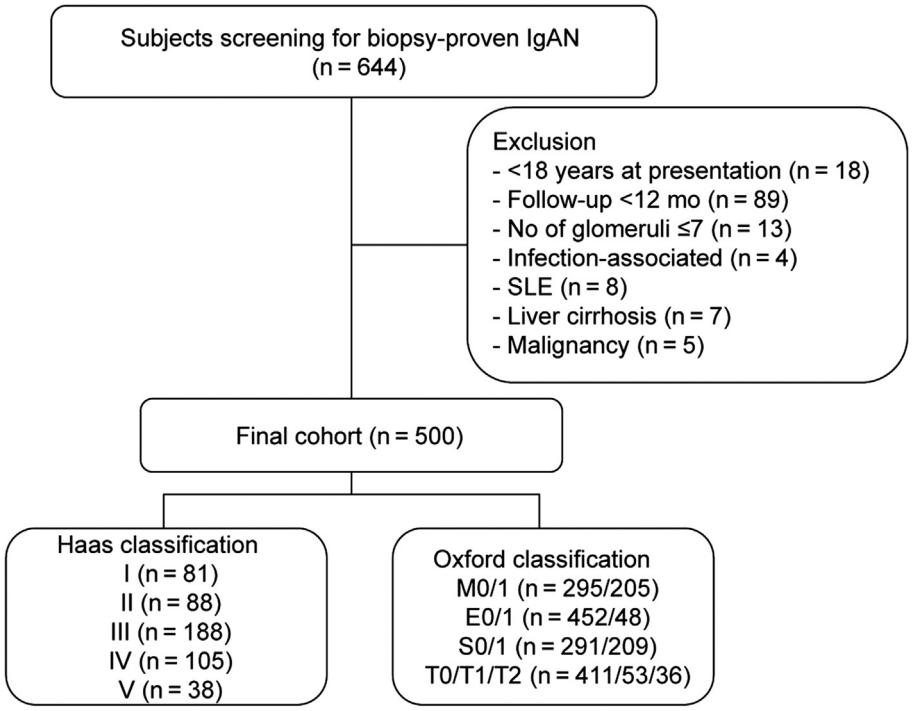

Fig. 1 Flow diagram of the study.

2.3. Study endpoints

The study endpoints were a doubling of the baseline serum creatinine concentration (D-SCr) and the onset of ESRD. D-SCr was defined as a sustained, greater than 2-fold increase in serum creatinine for at least three consecutive measurements. The first of these consecutive measurements was retrospectively designated as the endpoint. ESRD was defined as initiation of dialysis or receiving transplantation.

2.4. Statistical analyses

Data analyses were performed using SPSS software for Windows, version 20 (SPSS, Chicago, IL). All variables with normal distribution were expressed as mean ± SD. Comparisons were made using the Student *t* test or 1-way ANOVA for continuous variables and by the χ^2 test for categorical variables as required. The Kolmogorov-Smirnov test was used to determine the normality of the distribution of parameters. If data did not have a normal distribution, they were expressed as median and interquartile range and were compared using the Mann–Whitney test or Kruskal–Wallis test. The cumulative renal survival rates were estimated by the Kaplan–Meier method, and differences between survival curves were compared with the log-rank test. Renal survival time was defined as the interval between the time of biopsy and last follow-up. Cox proportional hazards models were constructed to identify independent variables associated with reaching D-SCr. The results were expressed as a hazard ratio (HR) and 95% confidence interval (CI). Using Stata software (version 11.0, StataCorp, www.stata.com), Harrell's *C* index of each Cox model was calculated to investigate its discriminatory utility. Using this index, we determined whether there was a difference in predicting renal outcome between the Haas and the Oxford classification. All *P* values were 2 tailed, and $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics according to the Haas and the Oxford classifications

Baseline characteristics of the patients are presented in Table 1. Mean age was 37.1 ± 12.0 years, and 43.0% were male. Mean arterial pressure (MAP) was 94.2 ± 11.7 mmHg, and 122 (24.4%) patients were diagnosed with hypertension (HTN) before renal biopsy. Mean eGFR was 87.3 ± 28.5 mL/min per 1.73 m^2 and mean 24-hour proteinuria was 1.06 ± 1.48 g per day. Clinical and laboratory parameters were compared by the Haas and the Oxford classifications. In terms of the Haas classification, there were 81 (16.2%), 88 (17.6%), 188 (37.6%), 105 (21.0%), and 38 (7.6%) patients in classes I, II, III, IV, and V, respectively. Age, sex, and MAP did not differ across the classes of the Haas system. However, eGFR was lower and proteinuria was higher in the higher Haas classes (*P* for trend <.001). RAS blockers were most commonly prescribed in patients with class IV. In addition,

Table 1 Baseline characteristics and comparison of clinical and laboratory parameters by Haas classification

	All (n = 500)	I (n = 81)	II (n = 88)	III (n = 188)	IV (n = 105)	V (n = 38)	*P* for trend
Age (years)	37.1 ± 12.0	33.8 ± 12.6	40.2 ± 11.8	37.2 ± 11.4	35.9 ± 11.9	40.8 ± 12.0	.298
Sex (male, n %)	215 (43.0%)	40 (19.4%)	36 (40.9%)	79 (42.0%)	50 (42.7%)	10 (38.5%)	.773
MAP (mmHg)	94.2 ± 11.7	94.0 ± 9.652	93.1 ± 10.84	94.3 ± 12.4	67.8 ± 11. 9	96.1 ± 14.0	.307
Hypertension (n,%)	122 (24.4%)	12 (14.8%)	22 (25.0%)	44 (23.4%)	30 (25.6%)	14 (53.8%)	.002
S-Cr (mg/dL)	1.04 ± 0.37	0.90 ± 0.22	0.98 ± 0.31	1.01 ± 0.37	1.11 ± 0.38	1.50 ± 0.54	<.001
eGFR (mL/min per 1.73 m^2)	87.3 ± 28.5	96.5 ± 24.6	89.3 ± 24.9	89.4 ± 28.6	81.7 ± 29.5	62.1 ± 29.5	<.001
Serum albumin (g/dL)	4.0 ± 0.6	4.3 ± 0.7	4.1 ± 0.6	4.0 ± 0.5	3.8 ± 0.6	3.7 ± 0.5	<.001
T- chol (mg/dL)	189.9 ± 49.9	179.0 ± 53.1	190.4 ± 50.7	188.6 ± 52.4	196.1 ± 42.5	203.1 ± 46.8	.013
Proteinuria UPCR (g/g)	1.45 ±1.76	1.06 ± 2.20	1.16 ± 1.34	1.29 ± 1.50	1.97 ± 1.95	2.5 ± 1.53	<.001
24-h protein (g/day)	1.06 ± 1.48	0.45 ± 0.84	0.68 ± 0.83	1.01 ± 1.68	1.41 ± 1.50	2.05 ± 1.75	<.001
Treatment (n, %)							
RAS blocker	388 (77.6%)	42 (51.9%)	68 (77.3%)	147 (78.2%)	98 (93.3%)	33 (86.8%)	<.001
Steroid	55 (11.0%)	5 (6.2%)	8 (9.1%)	25 (13.3%)	11 (10.4%)	6 (15.7%)	.127

NOTE. All data are expressed as mean ± SD.
Abbreviations: MAP, mean arterial pressure; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate; T-chol, total cholesterol; UPCR, urine protein-to-creatinine ratio; RAS, renin-angiotensin system.

patients with classes III, IV, and V were more treated with corticosteroids than those with classes I and II, but there were no significant differences in corticosteroid use between patients with classes III, IV, and V (Table 1).

We also compared clinical and laboratory parameters according to Oxford-MEST score (Supplementary Table 1 and 2). There were 205 (41.0%), 48 (9.6%), 209 (41.8%), 53 (10.6%), and 36 (7.2%) patients with M1, E1, S1, T1, and T2 lesions, respectively. Patients with a high score for M, E, and T lesions had greater proteinuria and lower eGFR. In addition, these patients were more treated with RAS blockers than those without these lesions. However, there was no overall difference in corticosteroids use based on the presence of Oxford-M, -S, and -T lesions. Corticosteroids were significantly more prescribed for patients with E1 than for those with E0 (P = .006).

3.2. Renal outcome according to the 2 pathologic classifications

During a mean follow-up of 68 months, 52 (10.4%) and 35 (7.0%) patients developed D-SCr and ESRD. In this study, no patients progressed to ESRD before reaching D-SCr. D-SCr was reached in 2 (2.5%), 0 (0.1%), 16 (8.5%), 20 (17.1%), and 13 (50.0%) patients with the Haas classes I, II, III, IV, and V, respectively (P < 0.001). ESRD did not occur in patients with classes I and II compared with 9 (4.8%), 17 (14.5%), and 9 (34.6%) in classes III, IV, and V. Kaplan-Meier plots with respect to the Haas classification also showed that renal survival rates were worse in higher Haas classes; survival rate was the lowest in class V (Fig. 2). In addition, D-SCr and ESRD occurred more in patients with higher score M and T lesions by the Oxford classification and so confirmed that renal survival rates were higher in patients without M or T lesions (Fig. 3).

3.3. Comparison of the predictive abilities of the Haas and Oxford classifications

To compare renal survival prediction between the 2 classifications, we constructed three multivariate Cox regression models (Table 2). Model 1 included only clinical factors, while the Haas and Oxford classifications were added to model 1 in models 2 and 3, respectively. In all three models, higher proteinuria and lower eGFR were consistently associated with an increased risk of reaching D-SCr. In addition, risk of progression was highest in patients with Haas class V lesions in model 2 (HR, 12.91; 95% CI, 2.61-63.84; P = .002). In model 3, T1 (HR, 6.68; 95% CI, 2.86-

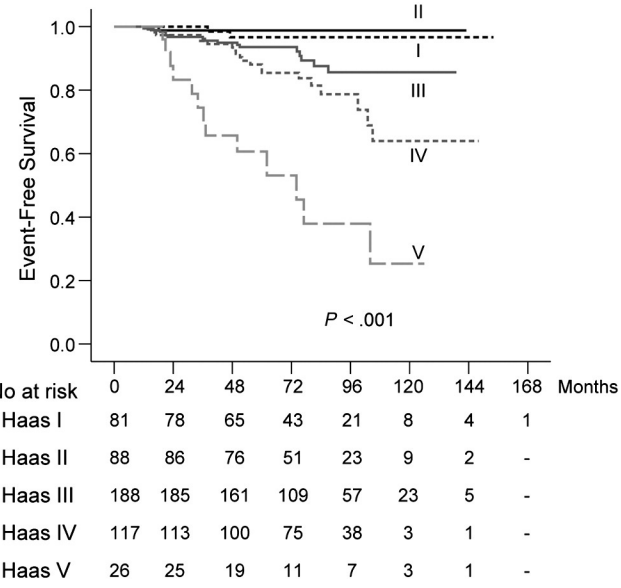

Fig. 2 A Kaplan-Meier plot for primary endpoint according to the Haas classification. Event-free renal survival rates were worse in the higher classes.

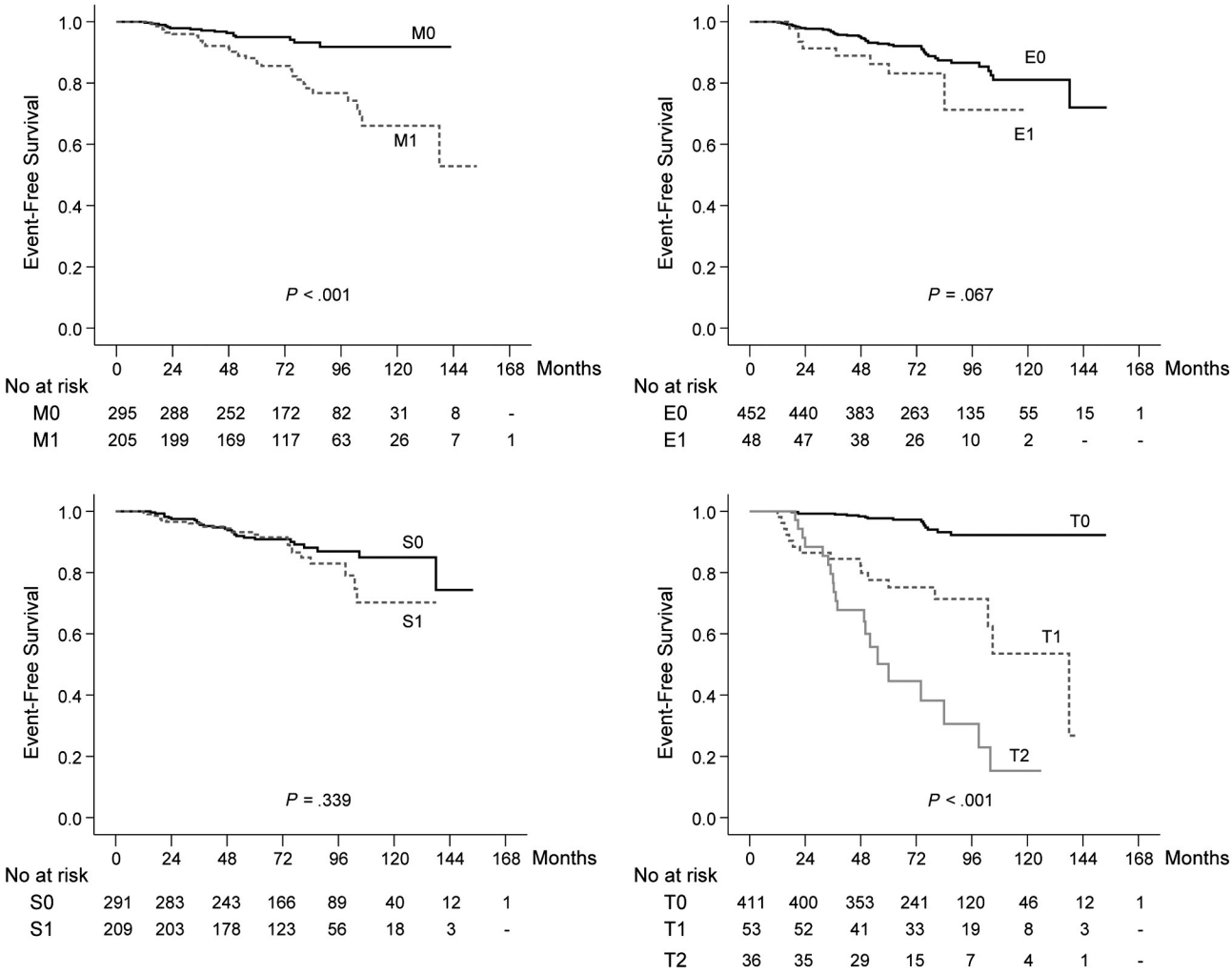

Fig. 3 Kaplan-Meier plots for primary endpoint according to the Oxford classification. Event-free renal survival rates were lower in patients with M0 and T0 than those with M1and T1/2.

15.57; $P < .001$) and T2 (HR, 12.16; 95% CI, 4.78-30.94; $P < .001$) lesions were independently associated with an increased risk of reaching D-SCr.

To assess the predictive power of each pathologic classification, we calculated Harrell's *C* index for each Cox model (Table 3). *C*-statistics of models 2 and 3 were 0.867 and 0.881, respectively, which were significantly higher than that of model 1 with clinical factors only ($C = 0.819$). However, there was no significant difference in *C*-statistic between models 2 and 3 containing the Haas and the Oxford systems ($P = .348$).

4. Discussion

In this study, we compared ability of 2 widely–used IgAN pathologic classifications to predict long-term renal outcome. We found that adding either the Haas classification or the Oxford-MEST score to clinical factors improved prediction of renal outcome. However, *C*-statistics of the 2 classifications did not differ significantly, suggesting that the predictive abilities of these 2 classifications are comparable.

To date, a number of pathologic classifications have been developed to identify risk factors associated with progression of IgAN. However, it is uncertain whether pathologic findings confer additional prognostic information over clinical features [20-23]. We clearly showed that, using Harrell's *C* indexes of three multivariate Cox models, *C*-statistics were significantly higher in the models incorporating the Haas classification or the Oxford classification than in a model with clinical factors only. This suggests that prediction of renal outcome was improved after each pathologic classification was added. It should be noted that, in our study, the main pathologic feature that determined prognosis was tubulointerstitial fibrosis. In fact, only the Haas class V lesion (model 2) and T lesion of the Oxford-MEST score (model 3) were independently associated with an increased risk of reaching D-SCr in multivariate analyses after adjustment for clinical factors.

Table 2 Multivariate Cox regression analyses

	Model 1 [a]		Model 2 [b]		Model 3 [c]	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per 1 year increase)	0.98 (0.96-1.01)	.117	0.99 (0.96-1.02)	.412	0.99 (0.96-1.01)	.273
MAP (per 1 mmHg increase)	0.99 (0.97-1.02)	.644	1.00 (0.98-1.02)	.833	1.00 (0.97-1.02)	.788
HTN (*vs* no)	1.39 (0.74-2.59)	.306	1.02 (0.53-1.98)	.952	1.02 (0.53-1.94)	.959
UPCR (per 1 g/g increase)	1.28 (1.17-1.49)	<.001	1.28 (1.16-1.41)	<.001	1.20 (1.09-1.32)	<.001
eGFR (per 1 ml/min per 1.73 m^2 increase)	0.97 (0.96-0.98)	<.001	0.98 (0.97-0.99)	<.001	0.98 (0.97-0.99)	.002
Haas classification						
I	–	–	Reference		–	–
II	–	–	0.45 (0.04-5.01)	.512	–	–
III	–	–	3.49 (0.78-15.75)	.104	–	–
IV	–	–	4.50 (1.01-20.04)	.048	–	–
V	–	–	12.91 (2.61-63.84)	.002	–	–
Oxford-MEST						
M1 (*vs* M0)	–	–	–	–	0.80 (0.37-1.69)	.795
E1 (*vs* E0)	–	–	–	–	0.77 (0.34-1.73)	.525
S1 (*vs* S0)	–	–	–	–	0.77 (0.42-1.39)	.383
T0	–	–	–	–	Reference	
T1	–	–	–	–	6.68 (2.86-15.57)	<.001
T2	–	–	–	–	12.16 (4.78-30.94)	<.001

[a] Sex, age, and baseline clinical variables (MAP, UPCR, and eGFR).
[b] Model 1 + the Haas classification.
[c] Model 2 + the Oxford-MEST.

Not surprisingly, this finding is consistent with many previous studies indicating that advanced chronic lesions such as tubular atrophy and interstitial fibrosis seen on the initial renal biopsy predict a future adverse renal outcome in patients with IgAN [10,24,25]. In this regard, our finding underscores the importance of tubulointerstitial fibrosis in risk stratification of patients with IgAN.

We further compared predictive ability between the 2 classifications using Harrell's C index. However, there was no significant difference in *C*-statistics between the 2 classification systems, suggesting that both were comparable in predicting renal outcome in patients with IgAN. The lack of a difference between the 2 models can in part be explained by the strong impact of tubulointerstitial fibrosis on outcome. In the Haas classification, only class V lesions have advanced glomerulosclerosis, severe tubular atrophy or interstitial fibrosis. Classes III and IV represent focal and diffuse proliferative features without fibrosis. In addition, T lesions of the Oxford-MEST score by definition designate tubular atrophy/interstitial fibrosis. Therefore, most cases with Haas class V lesions or Oxford T2 lesions overlap. We clearly showed that these 2 lesions were powerful predictors of progression in the multivariate Cox models. The presence of tubulointerstitial lesions largely determines prognosis of IgAN. Since these lesions are equally well-reflected in the 2 classifications, it is not surprising that the *C*-statistics of the 2 classifications were not significantly different.

Table 3 *C*-statistics for prediction of primary outcome using multivariate Cox regression models

Model	*C*-statistics (95% CI)	*P* for difference in *C*-statistics between models		
		Model 1 [a]	Model 2 [b]	Model 3 [c]
Model 1	0.819 (0.764-0.875)	NA	–	–
Model 2	0.867 (0.817-0.917)	0.015	NA	–
Model 3	0.881 (0.840-0.923)	0.004	0.348	NA

[a] Sex, age, and baseline clinical variables (MAP, HTN, UPCR, and eGFR).
[b] Model 1 + the Haas classification.
[c] Model 2 + the Oxford-MEST.

Unfortunately, our retrospective analyses were unable to identify such a relationship between pathologic features and treatment modalities. Proteinuria and eGFR are the strongest predictors of clinical outcome. Therefore, the clinical decision on whether to treat or not is entirely based on the amount of proteinuria or deterioration in kidney function, not pathologic features. This is clearly evident in the analyses using the Haas classification. There was no difference in corticosteroid use between patients in the five different Haas classes. Even in patients with diffuse proliferative glomerulonephritis (class IV), who are more likely to be treated with corticosteroids than those with other classes, only 11.1% received corticosteroids. In addition, >50% of patients with

class I were treated with RAS blockers during follow-up although they had pathologic abnormalities at the time of biopsy. This finding suggests that the main determinant used to guide treatment options is clinical features, not pathologic features. However, our finding should be interpreted with caution because the small number of corticosteroid users limits their generalizability.

There are several other shortcomings to this study. First, this retrospective study did not have pre-set indication for the use of immunosuppression although we generally followed the KDIGO guidelines [26]. Accordingly, treatment differed depending on individual physician preferences. In addition, different biopsy practice policies may affect the timing of diagnosis and can thus cause potential lead-time bias in estimating kidney survival [27]. Variation in diagnosis timing may also have an impact on the clinical and pathologic features present when the disease is recognized and thus affect treatment decision, leading to confounding by indication. Second, as aforementioned, there were a small number of corticosteroid users, which may not provide adequate statistical power to see a difference in renal outcome according to pathologic features. Finally, IgAN is known to have geographic variability and ethnic differences in progression [13,28]. Thus, it is unknown whether our findings can be extrapolated to other populations.

In conclusion, our study showed that predictive power of the Haas classification and Oxford classifications with respect to renal outcome are comparable in patients with IgAN. This is largely attributed to the fact that tubulointerstitial fibrosis is a strong indicator of outcome and is reflected well by both classifications. However, detailed analysis on the relationship between pathologic features and responsiveness to immunosuppression are limited by the retrospective nature of our study and the fact that treatment decisions were based on clinical features. The Oxford classification has strengths to help delineate such relationships because four specific pathologic features of IgAN that are associated with progression are specifically recognized within the classification. Further well-designed randomized controlled studies are required to delineate the relationships between pathologic features of the Oxford-MEST lesions and treatment responsiveness.

Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.humpath.2013.08.019.

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