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Validation Study of the Oxford Classification for IgA Nephropathy in Korean Adults

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Many pathologists have developed a number of classifications for immunoglobulin A (IgA) nephropathy. However, the critical limitations are a lack of reproducibility among pathologists and the complexity of using the classifications routinely [1]. To overcome these limitations, many pathologists or nephrologists have continued to investigate new pathological classifications. In 2004, a proposal to develop a consensus clinicopathological classification came from the International IgA Nephropathy Network and the Renal Pathology Society [2]. Six variables were initially selected based on acceptable reproducibility. Among the six variables, four were independent values for predicting renal outcomes. The Oxford classification was developed in 2009 as a new predictor of clinical findings for IgA nephropathy. This classification uses a stepwise methodology that initially considers all plausible variables and subsequently eliminates those with poor reproducibility while avoiding highly collinear biopsy findings; it also tests the variables' univariate predictive value and, finally, adjusts for clinical risk factors of progression. Two important outcomes were also considered: the rate of renal function decline and survival from a 50% reduction in renal function or renal failure [3]. Many validation studies have been carried out since the development of the Oxford classification.

In this issue of the Korean Journal of Internal Medicine, Lee et al. [4], who conducted one of the validation studies in Korean adults, validated 69 adult patients who had IgA nephropathy and were followed for > 36 months. The validation cohort was > 18 years. Initial proteinuria concentration was 1.2 g/day, and serum creatinine was 0.9 ± 0.3 mg/dL. They showed that endocapillary hypercellularity (E; E0/E1 lesions) and tubular atrophy/interstitial fibrosis (T; T0/T1/T2 lesions) predicted renal outcomes. Kang et al. [5] showed slightly different results in a similar validation study in Korean adults. Their cohort was 197 adult patients followed for an average of 56.8 ± 29.8 months. Initial proteinuria concentration was 2.07 g/day, and serum creatinine was 1.09 ± 0.72 mg/dL (Table 1). Kang et al. [5] showed that gial hypercellularity (M; M0/M1 lesions), segmental glomerulosclerosis (S; S0/S1 lesions), and T are associated with proteinuria at the time of initial biopsy but that only T predicted the decline in renal function, not E.

This said, the relationship between E and prognosis is controversial, as the prognosis depends on immunosuppressive therapy, age, and ethnicity. E has been discussed as part of glomerular hypercellularity (including mesangial hypercellularity, M) rather than as a single

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Table 1. Comparison of the Lee and Kang cohorts

	Kang et al. [5] cohort	Lee et al. [4] cohort
No. of patients	197	69
Age, yr	32.4 ± 12	34 (range, 27-45)
Male:Female	116:85	40:29
Proteinuria, g/day	2.07 ± 2.81	1.2 (range, 0.4-1.9)
Creatinine, mg/dL	1.09 ± 0.72	
eGFR, mL/min/1.73 m²	87.1 ± 29.2	90.8 ± 38.0
Rate of renal function decline, mL/min/1.73 m²/yr	-2.20 ± 7.60	
50% decline in renal function or ESRD during follow-up	16 (0.8)	16 (23)
Taking antihypertensive drug	164 (83.2)	65 (94)
Taking RAS blocking drug	163 (82.7)	62 (90)
Immunosuppression	75 (38.1)	13 (18.3)
Histological lesion, %		
M0/1	73.6/26.4	40/60
S0/1	43.7/56.3	21/79
E0/1	88.8/11.2	69/31
T0/1/2	66.5/25.9/7.6	50/24/26

Values are presented as number (%) or mean ± SD.
eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; RAS, rennin-angiotensin system; M, mesangial hypercellularity; S, segmental glomerulosclerosis; E, endocapillary hypercellularity; T, tubular atrophy/interstitial fibrosis.

prognostic factor and is generally correlated with active lesions [5]. In the Oxford classification, E1 was indicated by the presence of E and was defined as a single predictor [2,6,7]. Two studies have shown that this variable is correlated with clinical findings [2,6]; Working Group of the International IgA Nephropathy Network and the Renal Pathology Society et al. [2] showed that E1 correlates with initial presentation but not with follow-up findings (such as rate of renal function decline). They suggested that more immunosuppressive treatment in patients with E1 lesions may influence renal outcome. In Lee et al. [4], E lesions had a significant value for predicting the reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease, independently of clinical parameters and other pathological variables, even though patients with E lesions received more immunosuppressive agents. In the Kang et al. [5] cohort, too small a number of patients with E1 were enrolled to discuss a correct conclusion about E lesions in renal outcomes.

In the other validation study in East Asians, Katafuchi et al. [8] demonstrated that S and T are associated with end-stage renal failure. They found no significant association between E and renal outcome in the analysis, which included not only all cases but also those that met the Oxford classification inclusion criteria. In that study, a multivariate model, including M, E, S, and T, and clinical parameters with extra-capillary proliferation, revealed that T and extracapillary proliferation, but not S, were significantly associated with the development of end stage renal failure. They suggested that extracapillary proliferation should be included in the next version of the IgA nephropathy Oxford classification, which would create a more comprehensive system.

Most validation studies have shown that T is associated with renal outcome. The Kang et al. [5] cohort also showed that serum creatinine and renal function at the time of initial biopsy correlated with T. At the end of follow-up, time average proteinuria (TAP) and renal function correlated with T. Proteinuria at the end point of the follow-up was substantially lower in the three groups, but eGFR decreased with increasing T grade. This demonstrates that T is an independent predictor of TAP and decreased renal function.

We still have not identified the pathological variables correlated with renal outcome. However, clinical characteristics using the IgA nephropathy classification according to each pathological variable are different. The

Oxford classification is a simple method for predicting renal outcome and distinguishing between active and chronic lesions. We suggest that the Oxford classification offers an advantage for determining treatment strategy in patients with IgA nephroapthy. Further large scale and controlled studies in different races are needed to demonstrate the overall superiority of the Oxford classification.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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