

Validating the Oxford Classification of IgA Nephropathy

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The evolution of patients with IgA nephropathy (IgAN) varies greatly, and predictive tools are needed to assess confidently the risk for progression. Although in many studies clinical risk factors such as hypertension and proteinuria have consistently been linked to outcome, the independent value of pathology remains debated. Pathologists have developed a number of classifications over the years, at times with seemingly conflicting results. In 2009, the International IgA Nephropathy Network Group, working in collaboration with the Renal Pathology Society, proposed a set of four predictive renal biopsy findings independent of clinical assessment, the MEST score (M, mesangial hypercellularity; E, endocapillary proliferation; S, segmental glomerulosclerosis/adhesion; T, tubular atrophy/interstitial fibrosis) (1,2). This study differed from previous classification by using a stepwise methodology initially considering all plausible variables, subsequently eliminating those with poor reproducibility, avoiding highly collinear biopsy findings, testing their univariate predictive value and, finally, adjusting for clinical risk factors of progression. It also simultaneously considered two important, albeit different, outcomes: The rate of renal function decline and the survival from a 50% reduction of renal function or renal failure. Despite this meticulous approach, certain limitations were unavoidable. Its retrospective design and uncontrolled treatment allocation could have influenced the results. Validation of the Oxford classification has been carried out in children as well as adults (3,4). Verification is necessary because premature implementation of biased conclusions can harm patients and mislead future research.

It has been emphasized repeatedly that a validation study should consist of an adequate sample of different but related patients compared with the derivation population (5). “Relatedness” is defined by patients at risk for the same event. Whether a decision rule can be extrapolated to a population at different risk can never be confidently answered from the initial study, regardless of its quality. The original Oxford study excluded patients with an (1) initial estimated GFR (eGFR) <30 ml/min per 1.73 m², (2) proteinuria <0.5 g/d, and (3) follow-up period of less than 12 months. On the basis of these criteria, one can argue that three important subgroups of patients with IgAN were disregarded from the classification: Patients with ad-

vanced disease, patients with low-grade proteinuria unlikely to progress over a few years, and, finally, the rare but important patient presenting with a rapidly progressive form of IgAN.

In this issue of *CJASN*, Alamartine *et al.* (6) carried a validation endeavor in 183 adult patients who had IgAN and were followed for an average of 77 months. Pathologic assessment was assessed and covariates gathered identically to the original study. The authors stated that very mild and very severe forms of the disease were not *a priori* excluded. Many wished the original study had included them, and addressing these groups is clinically relevant. Consequently, differences in the study populations have surfaced. Mesangial and endocapillary hypercellularity was present in 81% and 42% in the Oxford cohort, respectively, as opposed to 21% and 14% in this study. The validation cohort was 13 years older without children, and the initial proteinuria was 1.24 g/d as opposed to 1.7 g/d originally. Finally, 13 and 12 patients presented with stages 4 and 5 chronic kidney disease (CKD), respectively. Treatment allocation seemed similar.

Clinicopathologic correlations mirrored those found in the Oxford study with the notable exception of the M lesion showing no relation with proteinuria. The E, S, and T lesions also predicted the survival from a combined event by univariate analysis, but none remained significant when adjusting for clinical variables. In the multivariate model, only baseline eGFR was a positive predictive factor for doubling of serum creatinine or ESRD. Interestingly, proteinuria and BP also failed to predict survival independently from a combined event when factoring in the initial eGFR. Both were strongly associated with outcome univariately, as expected. Table 3 offers a glimpse of the important collinearity between tubulointerstitial disease and eGFR when the hazard ratio for the T lesion jumps from 1.24 to 5.11 when eGFR is removed from the equation. The original study also showed this attenuation, to a lesser extent, perhaps having excluded patients with stages 4 and 5 CKD. Using the rate of renal function decline (slope) as an outcome allows the impact of the initial eGFR that weights strongly on renal survival analyses to be distinguished. However, estimating the slope can be difficult and biased by a single outlier. Consistency using both outcomes offers reassurance.

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The lack of independent value of the E, S, and T lesions must be carefully interpreted. Validation studies typically include fewer patients and are expected to show a similar signal compared with the original study without necessarily duplicating every result (5). Two additional features here may have influenced statistical power. The initial eGFR varied considerably, and patients included in the Oxford study presented with more frequent mesangial and endocapillary hypercellularity than in the present one. This study does offer interesting insight as to whether the Oxford classification can be extrapolated to those with more advanced CKD, with fewer proliferative lesions and lower proteinuria. In this study, 25 patients had an eGFR <30 ml/min per 1.73 m² and perhaps in such patients, the M, E, S, and T lesions offer less predictive value. Interestingly, the M lesion also was questioned in a recent validation study (7). It is the only variable that must be calculated and for which disagreement is more likely to appear among pathologists. Interesting also are the differences in clinical practice: In the Oxford study, endocapillary hypercellularity was most commonly associated with the use of and response to corticosteroids, whereas in the study by Alamartine *et al.* (6), endocapillary hypercellularity was the lesion that was less frequently associated with this form of treatment.

The inability to produce a classification that applies to every individual may seem disappointing. However, when examined closely, the excluded patients from the Oxford study do present unique distinguishing features. Those with consistently low proteinuria do not progress, patients with advanced scarring and little proliferation rarely benefit from immunosuppression and, finally, crescentic IgAN is approached clinically like a vasculitis. Such is the diversity of IgAN. A close parallel can be drawn with lupus nephritis. Coincidentally, multiple pathologic classifications in lupus have been proposed and debated, but none have been derived using a stepwise approach, yet.

Disclosures

None.

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See related article, "The Use of the Oxford Classification of IgA Nephropathy to Predict Renal Survival," on pages 2384–2388.