The MEST score provides earlier risk prediction in IgA nephropathy

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The Oxford Classification of IgA nephropathy (IgAN) includes four histologic components: mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S) and interstitial fibrosis/tubular atrophy (T). These combine to form the MEST score and are independently associated with renal outcome. Current prediction and risk stratification in IgAN requires clinical data over 2 years of follow-up. Using modern prediction tools, we examined whether combining MEST with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than current best methods that use 2 years of follow-up data. We used a cohort of 901 adults with IgAN from the Oxford derivation and North American validation studies and the VALIGA study followed for a median of 5.6 years to analyze the primary outcome (50% decrease in eGFR or ESRD) using Cox regression models. Covariates of clinical data at biopsy (eGFR, proteinuria, MAP) with or without MEST, and then 2-year clinical data alone (2-year average of proteinuria/MAP, eGFR at biopsy) were considered. There was significant improvement in prediction by adding MEST to clinical data at biopsy. The combination predicted the outcome as well as the 2-year clinical data alone, with comparable calibration curves. This effect did not change in subgroups treated or not with RAS blockade or immunosuppression. Thus, combining the MEST score with cross-sectional clinical data at biopsy provides earlier risk prediction in IgAN than our current best methods.

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Until recently, there has not been a reproducible and validated histologic classification of IgA nephropathy (IgAN). The MEST score as part of the Oxford Classification overcomes these obstacles, and various components of its score have been validated in multiple studies worldwide to be associated with hard renal outcomes independent of kidney function, blood pressure, and proteinuria both at presentation and over time.[1–5] However, it remains largely unknown whether the MEST score can quantitatively improve the prediction of individual patient prognosis and guide management decisions at the time of biopsy.

The current approach to determining the risk of renal progression in IgAN using clinical data alone is challenging owing to the highly variable nature of the disease. Previous studies suggest that 2 years or longer of follow-up proteinuria and blood pressure data is needed before clinically meaningful prediction can be achieved.[6–11] This approach has limited utility in clinical practice given current guidelines that recommend treatment decisions based mostly on clinical features near the time of biopsy.[12] We hypothesize that by adding the MEST score from the Oxford Classification to clinical data available at the time of biopsy, we can improve risk stratification earlier in the course of disease and predict the risk of renal outcome to the same degree as using longitudinal blood pressure and proteinuria over 2 years of follow-up. If the MEST score can achieve accurate risk stratification 2 years sooner than methods used in current clinical practice, it would allow earlier modification of patient treatment, which in turn may help preserve functioning nephron mass.

To address our hypothesis, we pooled cohorts from the VALIGA, Oxford, and North American validation studies in IgAN to compare the prediction of a hard renal outcome using the combination of renal function, blood pressure, and proteinuria at biopsy with and without the MEST score versus using only renal function and longitudinal changes in blood pressure and proteinuria over 2 years.[1,3,4] Because the use of renin-angiotensin system blockade (RASB) prior to biopsy and immunosuppression use during follow-up have the

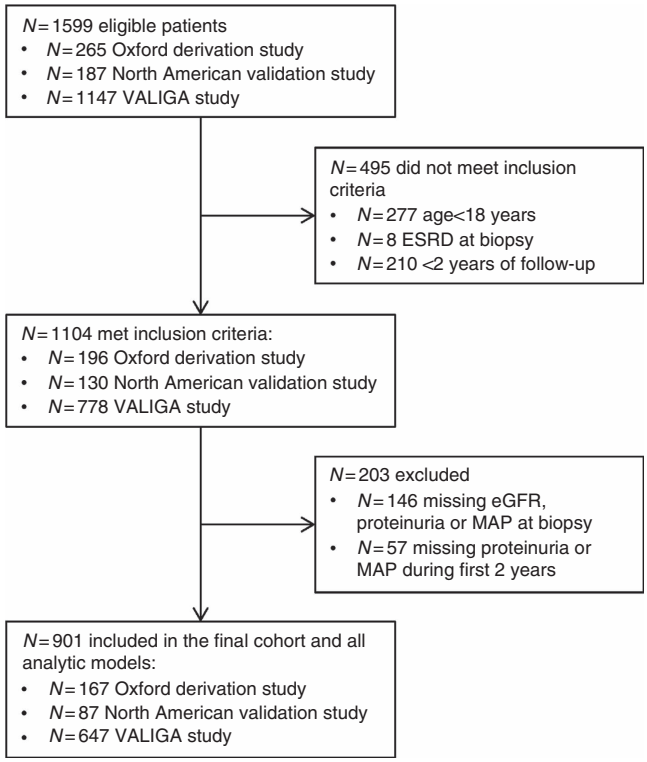

Figure 1 | Derivation of the cohort.

potential to impact the relationship between pathology and renal outcome, we repeated our analyses in *a priori* defined subgroups on the basis of the use of these medications.

RESULTS

Description of the cohort

There were 901 patients included in the analysis (Figure 1), and a description of the cohort is provided in Table 1. Overall, RASB was used in 38.4% at the time of biopsy and in 85.8% during follow-up starting a median of 0.6 months after biopsy (interquartile range 0, 11.5). Immunosuppression was used in 35.7% starting a median of 1.9 months after biopsy (interquartile range 0.1, 7.2). The primary renal outcome was a composite of end-stage renal disease (ESRD) or a 50% reduction in estimated glomerular filtration rate (eGFR) compared with baseline. This occurred in 18% ($N=162$) of patients and was composed of 21.6% ($N=36$) from the Oxford study, 16.1% ($N=14$) from the North American validation study, and 17.3% ($N=112$) from the VALIGA study. The 5- and 10-year risks of the composite renal outcome were 11.2% and 26.8%, respectively, as shown in the Kaplan–Meier curves in Figure 2.

Using MEST for risk prediction at the time of biopsy

The risks of the composite renal outcome associated with the combination of MEST plus clinical data at biopsy (eGFR, mean arterial blood pressure (MAP), and proteinuria) or with 2-year clinical data alone (eGFR at biopsy and 2-year averages of MAP and proteinuria) are shown in Table 2. MEST as a group ($P<0.0001$) and T1, T2 and M1 scores individually ($P<0.0001$ and 0.018) were significantly associated with the renal outcome independent of clinical data at biopsy.

When MEST was added to clinical data at biopsy, there was improvement in the prediction of the composite renal outcome compared with using clinical data alone. There was an increase in R^2 by 5.5% (12.6 vs. 18.1%) and a reduction in Akaike Information Criterion (AIC) by 41 (1777 down to 1736), demonstrating better model fit. There was also significant improvement in the ability to discriminate between those who did or did not experience the composite renal outcome 5 years after biopsy as measured by the change (Δ) in C-statistic (0.05), continuous net reclassification improvement (cNRI) (0.28), and integrated discrimination improvement (IDI) (0.06) with 95% confidence interval (CI) that were greater than the null value (see Table 3). Consistent with previous studies, 2-year clinical data predicted the composite renal outcome better than clinical data at the time of biopsy.[10,11] This was demonstrated by an increase in R^2 by 6.5% (12.6 vs. 19.1%), reduction in AIC by 60 (1777 down to 1717), and significant improvements in the ΔC-statistic (0.05), cNRI (0.38), and IDI (0.06) (see Table 3). The equations for each regression model that were used to calculate the probability of surviving 5 years without the composite renal outcome are provided in Table 3.

In addition, when MEST was added to the clinical data at biopsy, prediction of the composite renal outcome was similar to that using 2-year clinical data alone. This was evident by similar model fit with a difference in R^2 of only 1.0% (18.1 vs. 19.1%) and a difference in AIC of only 19 (1736 vs. 1717), and no significant changes in the ΔC-statistic (−0.007), cNRI (−0.08), and IDI (0.001) in Table 3 with 95% CI that included the null value. The receiver operating curves in Figure 3 demonstrate near superimposable curves for the two models. The calibration curves in Figure 4 show that there was similar and good calibration in both models, in that the observed and predicted risks were close to each other within the spectrum of predicted survival observed in the cohort (>80%). These results demonstrate that compared with using 2-year clinical data alone, the combination of MEST with clinical data at biopsy predicts the composite renal outcome with similar model fit and discrimination, and no loss in calibration.

Sensitivity analyses within subgroups based on the use of RASB and immunosuppression

We performed sensitivity analyses in separate subgroups on the basis of RASB exposure at the time of biopsy, and on the basis of immunosuppression use during follow-up (see Supplementary Tables S1 and S2 online). In multivariable models that included clinical data at biopsy, the MEST score, and interaction terms between each MEST component and either RASB or immunosuppression exposure as appropriate,