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The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

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IgA nephropathy is the most common glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Here a new classification for IgA nephropathy is presented by an international consensus working group. The goal of this new system was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA nephropathy, thus enabling both clinicians and pathologists to improve individual patient prognostication. In a retrospective analysis, sequential clinical data were obtained on 265 adults and children with IgA nephropathy who were followed for a median of 5 years. Renal biopsies from all patients were scored by pathologists blinded to the clinical data for pathological variables identified as reproducible by an iterative process. Four of these variables: (1) the mesangial hypercellularity score, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, and (4) tubular atrophy/interstitial fibrosis were subsequently shown to have independent value in predicting renal outcome. These specific pathological features withstood rigorous statistical analysis even after taking into account all clinical indicators available at the time of biopsy as well as during follow-up. The features have prognostic significance and we recommended they be taken into account for predicting outcome independent of the clinical features both at the time of presentation and during follow-up. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.

Kidney International (2009) **76,** 534–545; doi:10.1038/ki.2009.243; published online 1 July 2009

KEYWORDS: glomerulonephritis; IgA nephropathy; Oxford classification; pathology; renal failure

IgA nephropathy (IgAN) is the commonest glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Nephrologists use clinical information to identify the risk of developing progressive chronic kidney disease in individual patients with IgAN. There is now extensive evidence that a number of clinical features at presentation predict risk of progressive chronic kidney disease. In published series, these consistently include extent of proteinuria, hypertension, and excretory renal function.[1–5] Recent work also indicates the prognostic importance of reduction in proteinuria during follow-up, allowing continuing refinement of the prognostic information given to an individual patient.[6] Pathologists have developed a number of classifications of IgAN over the last 25 years; some are semiquantitative,[7–10] others are single-grade classifications.[11–15] Each of these classifications has been developed from expert opinion, each has strengths and limitations in predicting prognosis, and none has gained pre-eminence. There is continuing debate whether pathological features seen on renal biopsy contribute additional prognostic information beyond that provided by clinical features.[16]

This lack of consensus on classifications based on pathology has weakened a number of areas of investigation into IgAN. It has contributed to slow progress in developing a prognostic system with the sensitivity and specificity to predict outcome for individual patients. It has reduced

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Received 17 November 2008; revised 8 April 2009; accepted 19 May 2009; published online 1 July 2009

the capacity to make international comparisons between different outcome studies, and it has limited opportunities to refine the stratification of risk for the design of clinical intervention trials. This is a major disadvantage in a slowly progressive disease like IgAN where large studies of long duration are needed to evaluate new interventions unless patients with a high risk of progression can be better defined early in the course of the disease.

In 2004, a proposal to develop a consensus clinicopathological classification came from the International IgA Nephropathy Network—an informal network of nephrologists and scientists with representation from the majority of nephrology research groups around the world active in the field of IgAN (www.IgAN-world.org)—and members of the Renal Pathology Society interested in IgAN. A questionnaire among renal pathologists showed support for the development of a consensus classification of IgAN provided it could be shown to have real clinical utility. Therefore, representatives of the International IgA Nephropathy Network and the Renal Pathology Society established a working group to seek agreement on an evidence-based clinicopathological consensus classification for IgAN.[17] From the beginning this was designed as an international consensus aiming to involve nephrologists and pathologists from as many parts of the world as possible, including all areas where IgAN is known to be of high prevalence. Eventually, the consensus group had representation from 10 countries on four continents.

The goal of the new classification was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgAN, which would enable both clinicians and pathologists to improve individual patient prognostication. It was recognized that such a classification may also in the future facilitate the identification of specific features that may predict response to immunosuppression or other specific treatments, and refine recruitment to clinical trials by their capacity to stratify patients by their risk of progression.

The work was approached without preconceptions to test objectively the predictive power of a wide range of pathological features. The consensus work required unity of purpose and a collaborative approach. Organizational challenges included the development of tools allowing consistent data collection, and the need to meet the varying requirements of institutional review boards and ethics committees so that anonymized pathological material and clinical data could be circulated within and beyond its country of origin.

The overall approach used by the working group was the following:

- Agreement on a clinical data set useful for outcome studies in IgAN;
- Identification of centers willing to provide cases with sufficient clinical data and biopsy material available for review, including cohorts varying in age, and in geographical and racial origin;
- Agreement on definitions and scoring of a wide range of pathological features;
- Testing reproducibility between pathologists of scoring these features; and
- Analysis of informative pathological features in the context of clinical outcome to develop a classification.

By this rigor of approach, we aimed to gain the confidence of clinicians and investigators worldwide, so that the new classification will become the norm in routine clinical practice and in future clinicopathological outcome reports of IgAN.

The working group had two consensus meetings in 2005 and 2008, both held in Oxford, UK. It has, therefore, been decided to call the product of our work, the Oxford Classification of IgA Nephropathy.

RESULTS

Clinical data and adequate renal biopsy material from 265 patients with IgAN were collected from eight countries on four continents. Five centers from Asia, six from Europe, two from United States, one from South America, and two multicenter networks (Canada and USA) participated in the study (Table 1). The proportion of children was similar in each continent ($\sim$30%).

Overall pathology findings

Pathology information was complete for each variable in all 265 cases. There were a median number of 18 glomeruli per biopsy (interquartile range 8–24). Distributions of selected pathology findings are shown in Figure 1. In all, 42 and 45% of patients had endocapillary hypercellularity or crescents (but the median numbers of glomeruli involved in each affected patient were only 12 and 9%, respectively). Necrosis

Table 1 | Age and geographical origin of the study cohort of 265 cases of IgA nephropathy

		Adults	Children (age < 18 years at biopsy)
Total	**265**	**206**	**59**
Asia		*48*	*14*
China	Beijing	12	2
	Hong Kong	9	1
	Nanjing	7	1
Japan	Tokyo	19	1
	Wakayama	1	9
Europe		*73*	*21*
France	St Etienne	23	1
Italy	Bari	23	1
	Milano	16	3
	Roma	–	9
	Torino	3	7
United Kingdom	Glasgow	8	–
North America		82	24
Canada	Toronto	32	0
United States	Birmingham	12	1
	Mayo Clinic	14	4
	South West Study Group	24	19
South America		*3*	*0*
Chile	Santiago	3	0

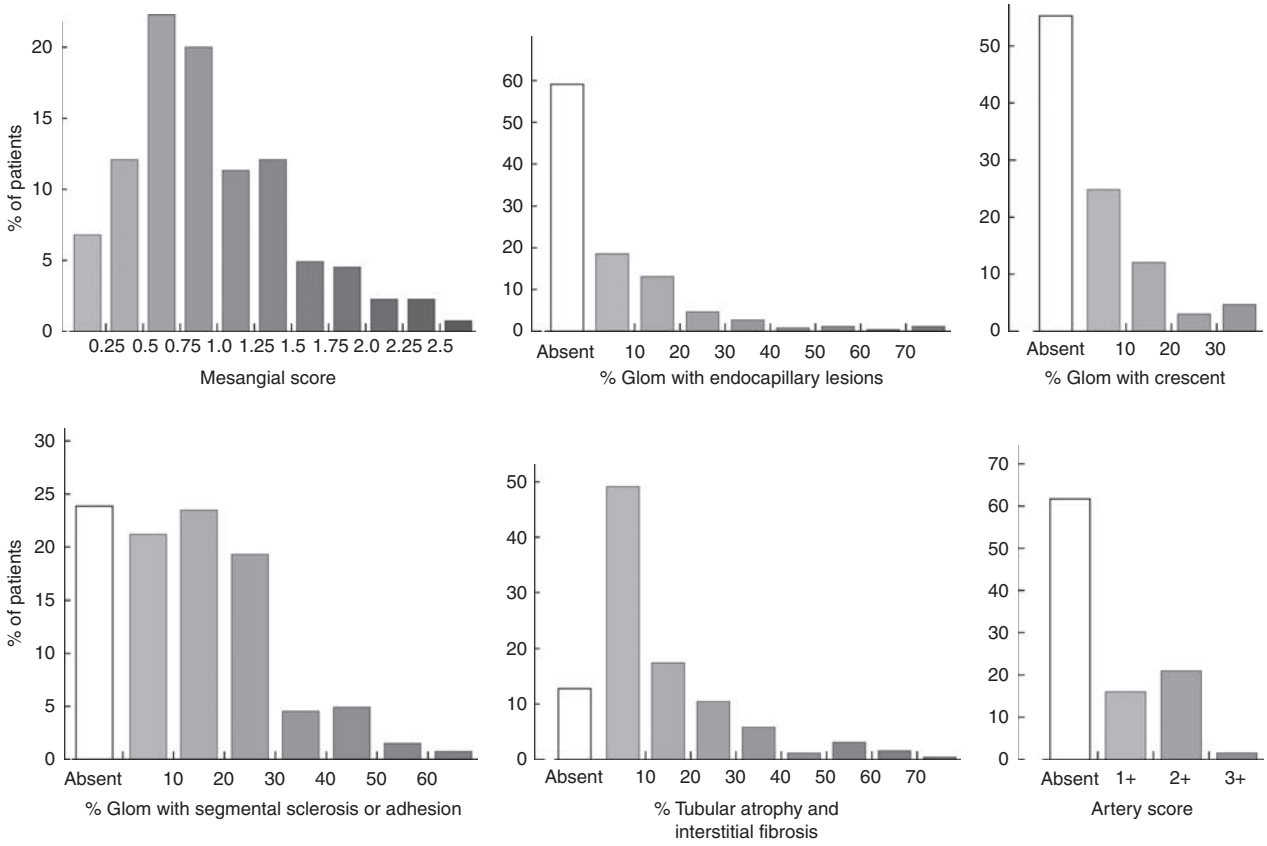

Figure 1 | Frequency of pathological features in 265 renal biopsies. Percentage of patients with each pathological feature. The six pathological features illustrated are those with sufficient reproducibility and frequency to merit evaluation for association with clinical outcome. Glom, glomeruli.

was seen in only six cases and glomerular basement membrane duplication in 30 cases. The majority of patients had no arterial or arteriolar lesions.

Reproducibility of pathology variables

The reproducibility of the various pathological lesions is described in detail in the accompanying paper (Roberts *et al.*, The Oxford Classification of IgA Nephropathy pathology definitions, correlations and reproducibility).[18]

Following refinement of the definitions, those pathological lesions that continued to show poor reproducibility within the working group were not incorporated into the final classification, as even lower reproducibility could be expected in routine practice without the advantage of the iterative processes of the working group. These included the percentage of normal glomeruli as well as the percentage of glomeruli showing adhesions, glomerular basement membrane duplication, necrosis, arteriolar lesions, and interstitial inflammation involving non-fibrotic cortex. Reproducibility of scoring for adhesions increased when combined with segmental sclerosis, suggesting that different pathologists identified the same lesion as either segmental sclerosis or an adhesion. For subsequent analysis, segmental sclerosis and adhesions were summed.

Correlation between pathology variables

Details of the correlations between the different pathology variables are presented in the accompanying paper (Roberts *et al.*). For those variables that displayed considerable correlation ($r > 0.8$), it was decided to include only one variable from each group for further consideration based on reproducibility, ease of identification, and susceptibility to sampling error.

The mesangial hypercellularity score was preferred to the percentage of glomeruli showing severe mesangial hypercellularity as it is more reproducible. A simplification of the mesangial hypercellularity score to <50 or $>50\%$ showing mesangial hypercellularity is described in the accompanying paper. The percentage of glomeruli showing cellular and fibrocellular crescents was preferred to the crescent score, which required a complex calculation including scoring the size of the crescents in each glomerulus. Interstitial fibrosis combined with tubular atrophy was preferred to global glomerulosclerosis, as its quantification is less susceptible to error due to paucity of glomeruli or subcapsular sampling, whichever was the higher value (interstitial fibrosis or tubular atrophy) chosen. The highest arterial score for any size of vessel was preferred to either the arcuate or interlobular artery score as it was less susceptible to sampling error.

Therefore, the selected pathology variables used in the subsequent analysis were the following:
mesangial hypercellularity score;
segmental glomerulosclerosis or adhesion;
endocapillary hypercellularity;
cellular only and cellular or fibrocellular crescents;
tubular atrophy/interstitial fibrosis; and
artery score.

Categorization of the selected pathology variables

The independent predictive value of the continuous glomerular variables could not be easily studied using multivariate linear analysis in light of severely skewed distributions. Therefore, receiver operating characteristic curves were drawn for each variable to determine the optimal cutoffs predicting a worse outcome (the most clinically relevant outcome was the rate of renal function decline, which we needed to dichotomize to perform this analysis). The optimal cutoff for the mesangial hypercellularity score was 0.71. This number was approximated to 0.5 (without significant loss of sensitivity) to facilitate scoring. Segmental glomerulosclerosis, endocapillary hypercellularity, and extracapillary proliferation were categorized as either present or absent as determined by receiver operating characteristic curve. Tubular atrophy/interstitial fibrosis was classified as absent (0%), mild (1–25%), moderate (26–50%), or severe (>50%), because this straightforward reproducible classification is widely used in clinical practice.

Clinical features and outcome of the cohort

Clinical features at the time of biopsy and during follow-up are shown in Table 2 and are typical of IgAN. At the time of renal biopsy, the median age was 32 years (4–73 years), with male predominance. The mean arterial pressure (MAP) was 98 ± 18 mm Hg (63% of adult patients had blood pressure above the value of 130/80 mm Hg and 31% were taking antihypertensive medication). Nine children (15%) had adjusted blood pressure >130/80 mm Hg (MAP s.d. score >1) or were taking antihypertensive medication. The estimated glomerular filtration rate (eGFR) values were evenly distributed within stages 1, 2, and 3 of the Kidney Disease Outcomes Quality Initiative (KDOQI) classification of chronic kidney disease, although most children had stage 1 chronic kidney disease (77%). Median proteinuria was 1.7 g per 24 h (1.95 g per 24 h per 1.73 m^2 in children). Median follow-up was 5 years (range: 1–22 years, with 90% followed for more than 3 years). Twenty-nine percentage of the patients enrolled (47% of children and 23% of adults) received immunosuppressive therapy, consisting of variable dosages of corticosteroids with additional immunosuppressive agents in only 9% of the cases. Patients with segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and arterial lesions were more likely to have been treated with renin-angiotensin system blockade (RAS) blockade (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). Conversely, those with endocapillary or extracapillary lesions received more immunosuppressive treatment (Table 3). Fish oil was prescribed for 16% and statins for 13% of the patients. No patient had a tonsillectomy during the follow-up.

The mean rate of renal function decline was −3.5 ± 8.4 ml/min per 1.73 m^2 per year (–3.7 ± 6.6 in adults and –2.7 ± 1.05 in children, $P>0.1$). The end point of 50% decline in eGFR was reached in 22% of the cases and end-stage renal disease (ESRD) was reached in 13%.

Correlations between pathological lesions and clinical presentation at renal biopsy

This was a typical cohort of patients with IgAN as indicated by the strong association observed between initial eGFR,

Table 2 | Clinical characteristics at the time of biopsy and follow-up in 265 patients with IgA nephropathy

At time of biopsy		Follow-up	
Age (years)	30 (4–73)	Duration of follow-up (months)	69 (12–268)
Female	28%		
Pediatric at time of biopsy (<18 years)	22%		
Ethnicity (Caucasian/African/Asian/Other)	66, 3, 27, and 4%		
BMI	25 ± 6		
MAP (mm Hg)	98 ± 17	MAP (mm Hg)	95 ± 10
Taking antihypertensive medication	31%	No. of antihypertensive medications	0.9 (0–4.7)
Treated with RAS blockade	20%	Treated with RAS blockade (ACEi and ARB)	74% (68 and 22%)
eGFR (ml/min per 1.73 m^2)	83 ± 36	Rate of renal function decline (ml/min per 1.73 m^2 per year)	−3.5 ± 8.4
Stage 1, 2, 3 CKD (KDOQI)	36, 38, and 26%	50% Decline in renal function	22%
		End-stage renal disease (<15 ml/min per 1.73 m^2)	13%
Proteinuria (g/day)	1.7 (0.5–18.5)	Proteinuria (g/day)	1.1 (0.1–9.3)
Previous macroscopic hematuria	34%		
Previous immunosuppression	14%	Immunosuppression	29%
		Prednisone	29%
		Other (cyclophosphamide)	9% (6%)
Previous use of fish oil	6%		
Known previous tonsillectomy	6%		

ACEi, angiotensin-converting inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; RAS, renin-angiotensin system.
Values are expressed as mean ± s.d. or median (range). Calculation of MAP, eGFR, and proteinuria is detailed in the text.
eGFR, MAP, and proteinuria at onset were missing in 12% of cases. The median numbers of BP, GFR, and proteinuria measurements per patient were 7, 7, and 6, respectively.

MAP, and proteinuria as well as follow-up MAP and proteinuria and the outcomes measured (data not shown). Mesangial score, segmental glomerulosclerosis, endocapillary hypercellularity, and extracapillary proliferation were strongly associated with proteinuria at the time of biopsy. Segmental glomerulosclerosis was associated with reduced eGFR and higher MAP at the time of biopsy. Tubular atrophy/interstitial fibrosis was associated with a reduced initial eGFR and higher initial MAP and proteinuria. Arterial disease was strongly associated with initial blood pressure and eGFR but had no relation with initial proteinuria (Table 4).

Table 3 | Therapy received during follow-up in relation to pathological features

	% RAS blockade	*P*-value	% Immuno-suppression	*P*-value
Mesangial hypercellularity score				
⩽0.5	71		21	
>0.5	75	>0.1	30	>0.1
Segmental glomerulosclerosis				
Absent	54	<0.001	28	>0.1
Present	81		29	
Endocapillary hypercellularity				
Absent	76		17	
Present	72	>0.1	45	<0.001
Extracapillary hypercellularity				
Absent	72		20	0.002
Present	78	>0.1	39	
Tubular atrophy/interstitial fibrosis				
Absent	48	0.003	31	>0.1
1–25%	76		28	
26–50%	84		24	
>50%	85		50	
Artery score				
Absent	68	0.04	32	>0.1
Mild	83		24	
Moderate	86		19	
Severe	75		50	

Percentage of patients with each pathological feature receiving renin–angiotensin system blockade or immunosuppressive therapy.

Correlations between pathological lesions and outcome

By univariate analysis, the rate of renal function decline as well as survival without ESRD or 50% reduction in initial eGFR were significantly associated with a mesangial hypercellularity score >0.5, presence of segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis. As the outcome in patients with absent tubular atrophy/interstitial fibrosis was identical to the 1–25% group, we merged these two categories to maximize statistical power (Table 5).

In the whole patient group, endocapillary and extracapillary proliferative lesions were not significantly predictive of the rate of renal function decline, nor of survival from a combined event. Patients with endocapillary hypercellularity deteriorated at a rate of -3.8 ± 10.6 ml/min per 1.73 m^2 per year compared with -3.3 ± 6.4 in those without these lesions ($P > 0.1$) and those with extracapillary proliferation deteriorated by -4.4 ± 10.4 ml/min per 1.73 m^2 per year compared with -2.8 ± 6.3 in those without ($P > 0.1$, with similar results when addressing cellular crescents alone). However, there was a significant interaction between endocapillary hypercellularity and immunosuppression (see below). The rate of renal function decline was almost identical in the different artery score groups (data not shown).

Two models of multivariate analysis were calculated. The first model was designed to address whether the

Table 4 | Correlations between pathological features and clinical features at the time of renal biopsy

	MAP mm Hg	*P*-value	GFR ml/min per 1.73 m^2	*P*-value	Proteinuria g/day	*P*-value
Mesangial hypercellularity score⩽0.5	100 ± 18	>0.1	84 ± 28	>0.1	1.4 (0.6–9.2)	0.001
Mesangial hypercellularity score >0.5	98 ± 17		82 ± 38		2.0 (0.5–18.5)	
No endocapillary hypercellularity	101 ± 19	0.008	76 ± 31	0.001	1.5 (0.5–11.3)	0.01
Any endocapillary hypercellularity	95 ± 15		92 ± 40		2.0 (0.5–18.5)	
No extracapillary proliferation	98 ± 17	>0.1	84 ± 37	>0.1	1.5 (0.5–18.5)	0.002
Any extracapillary proliferation	98 ± 18		80 ± 35		2.2 (0.5–12.0)	
No segmental glomerulosclerosis	94 ± 16	0.04	95 ± 40	0.003	1.5 (0.5–7.2)	0.004
Any segmental glomerulosclerosis	100 ± 18		79 ± 34		1.9 (0.6–18.5)	
Tubular atrophy and interstitial fibrosis						
None (0%)	91 ± 17	0.03	109 ± 35	<0.001	1.5 (0.5–7.2)	0.03
Mild (1–25%)	99 ± 18		86 ± 35		1.7 (0.5–18.5)	
Moderate (26–50%)	100 ± 12		59 ± 17		1.8 (0.6–7.5)	
Severe (⩾51%)	105 ± 24		46 ± 27		3.0 (1.1–9.0)	
Artery score						
Absent	96 ± 17	0.02	92 ± 40	<0.001	1. 8 (0.5–18.5)	>0.1
Mild	104 ± 15		67 ± 19		1.5 (0.6–4.6)	
Moderate	101 ± 20		70 ± 25		1.6 (0.8–7.3)	
Severe	102 ± 7		72 ± 33		1.7 (1.1–2.2)	

GFR, glomerular filtration rate; MAP, mean arterial pressure.
Mean ± s.d., median (range).

Table 5 | Correlations between pathological features and outcomes: univariate and multivariate pathologic determinants of slope

	Rate of renal function decline (linear regression)			Survival from renal failure or a 50% drop in GFR (Cox regression)		
	Univariate slope (ml/min per 1.73 m^2 per year)	Multivariate[a]		Univariate hazard ratio (95% CI)	Multivariate[a]	
		Model A β (s.d.)	Model B β (s.d.)		Model A	Model B
Mesangial hypercellularity score						
⩽0.5	−0.5 ± 3.3	−2.2 (1.3)	−0.8 (1.2)	0.06 (0.01–0.45)	0.07 (0.01–0.53)	0.11 (0.01–0.80)
>0.5	−4.2 ± 9.0			1	1	1
	$P<0.001$	$P=0.10$	$P>0.1$	$P=0.006$	$P=0.01$	$P=0.03$
Segmental glomerulosclerosis						
Absent	−0.5 ± 7.5			1	1	1
Present	−4.4 ± 8.4	−3.6 (1.3)	−2.5 (1.1)	3.1 (1.4–7.3)	1.8 (0.6–5.3)	2.5 (0.9–7.3)
	$P=0.001$	$P=0.005$	$P=0.03$	$P=0.009$	$P>0.1$	$P=0.09$
Tubular atrophy/interstitial fibrosis[b]						
0–25%	−2.5 ± 7.6	−5.2 (1.1)	−3.7 (1.0)	1	1	1
26–50%	−5.7 ± 8.8			3.5 (1.9–6.5)	6.0 (2.7–13.9)	5.0 (2.3–11.1)
>50%	−11.1 ± 12.6			15.5 (7.5–31.9)	17.3 (5.9–50.9)	8.8 (2.9–26.4)
	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$

CI, confidence interval; GFR, glomerular filtration rate; MAP, mean arterial pressure.
Endocapillary, extracapillary, and arterial lesions were not associated with the rate of renal function decline or survival from renal failure or a 50% drop in GFR (see text, Correlations between pathological lesions and outcome).
[a]Model A: multivariate with three pathological features + initial GFR, MAP, proteinuria. Model B: multivariate with three pathological features + initial GFR and follow-up MAP and proteinuria.
[b]Outcomes with 0% tubular atrophy/interstitial fibrosis were identical to 1–25% tubular atrophy/interstitial fibrosis, hence the two categories were combined to maximize statistical power.

biopsy findings predicted long-term outcome independently of the initial assessment; it considered the pathology variables in addition to the initial clinical data set (eGFR, MAP and proteinuria). The second model was designed to address which of the selected pathology variables were independent predictors of outcome even when clinical follow-up data were taken into account; this model included pathology data, initial eGFR, and follow-up data (MAP and proteinuria). Linear regression of rate of renal function decline correlated with segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis in both models. The mesangial hypercellularity score failed to attain independent significance in both models. When the end points of ESRD or 50% reduction in eGFR was considered as the outcome, the Cox regression showed for both models significant associations for mesangial hypercellularity score and tubular atrophy/interstitial fibrosis, whereas the association for segmental glomerulosclerosis failed to reach statistical significance in both models. There was a marked reduction in the mean hazard ratio from 1 (with mesangial hypercellularity score >0.5) to 0.11 (an 89% reduction) when the score was ⩽0.5. There was a rapid escalation of the hazard ratio as tubular atrophy/interstitial fibrosis increased: mean hazard ratio 5 (when 26–50%) and 8.8 (when >50%). The presence of endocapillary and extracapillary lesions, and the severity of arterial lesions were not statistically associated with a decreased survival from a combined event (data not shown).

There was a highly significant association by univariate analysis between follow-up proteinuria and the mesangial hypercellularity score, the presence of segmental glomerulosclerosis or adhesions, and tubular atrophy/interstitial fibrosis; their association with follow-up proteinuria persisted even when adjusted for the initial proteinuria, GFR, or MAP (data not shown).

Table 6 | Examples of associations between pathological variables and rapid rate of renal function decline

	Odds ratio	95% confidence intervals		*P*-value
Tubular atrophy or interstitial fibrosis				
0–25%	1	(Reference)		
26–50%	3.0	1.3	7.4	0.01
51–100%	21.8	2.3	206.2	0.007
Segmental glomerulosclerosis present	2.8	1.2	6.2	0.01
Mesangial hypercellularity score >0.5	2.1	0.9	4.7	0.08

GFR, glomerular filtration rate.
Decline defined by the worst half of the rate of renal function decline (slope > −1.6 ml/min per 1.73 m^2 per year). This model is adjusted for the initial GFR and the follow-up blood pressure and proteinuria.

Finally, odds ratios were also derived for a more rapid rate of decline in renal function. Odds ratios were determined after splitting the rate of renal function decline into two halves and adjusting for both initial GFR and follow-up blood pressure and proteinuria (Table 6).

Our analyses included 43 patients with less than 2 years of observation, a relatively brief period for a condition as slowly progressive as IgAN. To be sure this did not introduce unforeseen bias, we recalculated all the multivariate models

using only patients with greater than 24 months of follow-up (222 patients) and found the same statistically significant pathology variables shown in Table 5 (data not shown).

Interaction of pathological features with therapy

In this retrospective study, it is possible therapy could confound correlations between pathology and clinical outcome. Therefore, the use of two major treatments, RAS blockade and immunosuppression, was assessed in relation to the selected pathological lesions (Table 3). Those with endocapillary or extracapillary lesions were more likely to receive immunosuppressive treatment. The relationship between each pathology variable and the rate of renal function decline was not influenced by immunosuppression except for endocapillary lesions ($P = 0.006$). In patients who received no immunosuppression, the rate of renal function decline in those with endocapillary lesions was -5.4 ± 11.1 ml/min per $1.73\,m^2$ per year, compared with -2.6 ± 5.1 ml/min per $1.73\,m^2$ per year in those without endocapillary proliferation ($P = 0.02$). There was no such difference in patients treated with immunosuppression, providing indirect evidence that endocapillary lesions are responsive to immunosuppressive therapy. Finally, we confirmed this significant interaction using survival from a combined event for outcome and expressing immunosuppressive therapy as a time-dependant variable (time to start of therapy) to address immortal time bias (data not shown).

We found no statistically significant interactions between any of selected pathological features and RAS blockade.

Interaction of pathological features with age and ethnicity

There were marked differences in the pathology findings between children and adults. Younger patients presented with significantly less segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and fewer vascular lesions, but had significantly more endocapillary lesions (data not shown). However, the predictive value of each pathology variable on the rate of renal function decline was not influenced by the age at the time of biopsy ($P > 0.1$ for interaction term).

Finally, we studied whether ethnicity influenced the predictive value of the biopsy. We only considered Caucasian and Asian patients as there were too few subjects from other racial groups for analysis. For each pathology variable, the interaction term with ethnicity was not statistically significant except for endocapillary lesions ($P = 0.02$); the rate of renal function decline associated with this finding in Asian subjects was significantly better compared with that in Caucasians. However, Asian patients were significantly more likely to receive immunosuppressive therapy during follow-up (42% compared with 22% in Caucasians, $P = 0.002$) and, in light of the interaction between endocapillary lesions and immunosuppressive therapy outlined above, this finding requires cautious interpretation.

In summary, our analysis shows that the following features are independently predictive of clinical outcome: a mesangial hypercellularity score > 0.5, endocapillary hypercellularity, segmental glomerulosclerosis, and the extent of tubular atrophy/interstitial fibrosis.

Recommendations for renal biopsy reporting

These results would indicate that the renal biopsy report in IgAN should specifically report on these four features, for which brief definitions are shown in Table 7. We suggest that these should be summarized and scored as shown in (Table 8).

The biopsy report in IgAN should include a detailed description of the features present on light microscopy, immunohistochemistry, and electron microscopy. A diagnostic statement giving the diagnosis and listing and scoring of the four features above that are present in the biopsy should then follow. Thus, an example of a diagnostic summary would be as follows:

IgAN with mesangial proliferation, segmental sclerosis, and 40% tubular atrophy/interstitial fibrosis (M1 E0 S1 T1).

In addition, to give a quantitative assessment of glomerular inflammation and scarring, there should be a summary of the total number of glomeruli and the number with endocapillary proliferation, necrosis, cellular/

Table 7 | Definitions of pathological variables used in the classification of IgA nephropathy

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 ⩽ 0.5 M1 > 0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 >50% – T2

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Table 8 | Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on
Light microscopy
Immunohistochemistry
Electron microscopy
Summary of four key pathological features
Mesangial score $\leqslant$0.5 (M0) or $>$0.5 (M1)
Segmental glomerulosclerosis absent (S0) or present (S1)
Endocapillary hypercellularity absent (E0) or present (E1)
Tubular atrophy/interstitial fibrosis $\leqslant$25% (T0), 26–50% (T1), or $>$50% (T2)
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

fibrocellular crescents, global glomerulosclerosis, and segmental glomerulosclerosis.

As our data were derived from biopsies containing at least eight glomeruli, we suggest that biopsies with fewer glomeruli should be considered of uncertain value for assessing prognosis.

DISCUSSION

Our objective was to develop a classification for IgAN that would only consider pathological features that had correlation to clinical outcome independent of the clinical data, and would improve our current capacity to predict the outcome of patients with this disease. None of the previously established pathological classifications for IgAN have achieved consensus in our community in part due to the failure to show these correlations.[7–9,11–13,19] One major concern that applies to all pathology classifications is that cross-sectional data, such as those obtained from a renal biopsy specimen, are rarely as powerful a predictor of outcome as longitudinal data obtained by a repeated clinical assessment of patients; this is particularly true in a slowly progressive disease such as IgAN. Such longitudinal data have not been taken into account in the development of previous pathological classifications of IgAN. In our study, the independent value of specific pathology features was assessed after the known relevant initial and follow-up clinical and laboratory data were included in our models. Our objective was to create a template that could integrate the identified pathological parameters into routine renal pathology reports and provide specific and new prognostic information for both the clinician and the patient with IgAN.

The involvement of the International IgA Nephropathy Network and the Renal Pathology Society enabled us to acquire a study cohort that included a wide age spectrum and was geographically and racially diverse. Creation of the standardized platform for the evaluation of renal pathology tissue was critical to our strategy and is reported in the associated paper (Roberts *et al.*). This led to agreed definitions for each pathological feature, which were refined by an iterative assessment based on reproducibility, eliminating features that could not be reconciled or were so infrequent as to be of little use in a general classification of the disease. This was a unique strategy never previously undertaken by a group of renal pathologists, and led to a final pathology data set suitable for routine clinical work comprising pathological variables relatively common in IgAN that were easy to assess, had a high degree of reproducibility, and independently correlated with clinical outcome. The variables identified were mesangial hypercellularity score, and the presence or absence of segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis.

We standardized the estimation of GFR, blood pressure, and proteinuria.[20–23] Standardization of eGFR was limited by the use of different methods for measuring serum creatinine, inevitably the case in such a retrospective multicenter international study. Although this does introduce some additional uncertainty about comparison of baseline eGFR between individuals, accuracy of the calculation of slope of eGFR is not affected, as it is based on serial measurements of serum creatinine in the same institution using the same method.

The majority of patients had significant proteinuria and reasonable preservation of GFR at the time of biopsy, which left us with the potential risk that the extremes of the disorder, that is the most mild and most severe cases, would not be represented. We expected that pathological lesions indicative of progression would be rather infrequent in mild cases, making them less informative and, therefore such cases were best excluded from this study.[24,25] At the other end of the spectrum, rapidly progressive IgAN is rare, and is almost always associated with abundant crescents.[26,27] The requirement for study entry of at least 1 year of follow-up excluded those most likely to have extensive crescent formation. Although 45% of the study cohort had crescents, the median number of glomeruli with crescents was only 9%, and no case had more than 55% of glomeruli with crescents. We recognize that the prognostic significance of crescents may well be confirmed if validation cohorts include more rapidly progressive cases, but based on the evidence obtained in this cohort, we cannot justify their inclusion in this classification. Similarly, we cannot make firm conclusions regarding the significance of necrosis, which was rare in this series. Reproducibility for the identification of necrosis was also poor for the reasons discussed in the accompanying paper. Despite these limitations, we remain confident we have produced pathological criteria that could be applied to most cases of IgAN.

The critical and unique value of the study is that we have shown that these pathological features have a value independent of the patient's clinical parameters in predicting the outcome in IgAN. We used three widely accepted clinical outcomes in the models that assessed the independent relevance of these variables. They include a surrogate outcome—follow-up proteinuria; an outcome using a continuous variable—slope of eGFR; and renal survival—ESRD

or 50% reduction from baseline of eGFR. The latter combined survival estimate can be a misleading end point in patients with an initial severe impairment of GFR, but the observation that those reaching ESRD or a 50% reduction from initial GFR parallel closely those with the most negative slopes of eGFR and those with higher follow-up proteinuria provides reassurance that these pathological parameters correctly identify a poor prognostic cohort.[6] Subsequent multivariate analyses using these outcome variables confirmed that each of the selected pathological features provided added value in estimating prognosis that was independent of both the initial and follow-up clinical data. The correlations between the pathological features and initial clinical presentation were not unexpected, with some exceptions discussed below, and helped to confirm that the cohort was representative of the IgAN population. It is also possible that immunosuppressive therapy is a significant confounding factor. The presence of both endocapillary and extracapillary lesions and crescents was strongly associated with subsequent immunosuppressive treatment. Although we cannot state that there was a cause-and-effect relationship, this retrospective analysis does suggest that endocapillary proliferation may be a lesion more responsive to immunosuppressive therapy, a suggestion supported by the markedly higher rate of decline in renal function in those patients with endocapillary proliferation who did not receive immunosuppressive treatment compared with those who did.

We obtained information on the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (Table 2), which indicated that they were prescribed in 74% of the cohort at some time during follow-up. On account of the retrospective nature of the study, reliable information on duration of treatment or dosing could not be obtained. It is, therefore, not possible to draw conclusions with any confidence from this retrospective study about the influence of renin–angiotensin blockade on outcomes.

The strongest support for the value of the mesangial hypercellularity score, segmental glomerulosclerosis, and extent of tubular atrophy/interstitial fibrosis as independent markers of prognosis comes from the modeling in Table 5.[8,9,28–31] Whether the rate of decline in eGFR or renal survival is used as the outcome, each of the factors remained strongly positive by univariate analysis in the slope analysis and by univariate hazard ratio in the renal survival model. When the models were assessed by multivariate analysis with initial eGFR, as well as when including follow-up blood pressure and proteinuria, the selected pathology features remained significant in one or both of the models. The odds ratios determined after splitting the rate of renal function decline into two halves and adjusting for both initial GFR and follow-up blood pressure and proteinuria (Table 6) further support the strong independent relevance of these pathological features to outcome. The odds ratio for having a faster rate of progression was highest with the greatest degree of tubular atrophy/interstitial fibrosis and lowest with mesangial hypercellularity. This is not unexpected given the limitations of current therapy in modifying tubular atrophy/interstitial fibrosis compared with the potential that antihypertensive and/or immunosuppressive therapy may modify mesangial hypercellularity. There were differences related to pathology and clinical findings in our pediatric cohort. Most were expected, that is there were fewer pathological indicators of chronic disease.[19] However, it is less obvious why there were significantly more endocapillary proliferative lesions in this age group; this has been previously reported and it can be speculated that this represents a more vigorous response to injury than in an older population. This might explain the unexpected finding that endocapillary proliferation was associated with a higher eGFR and lower blood pressure. However, an important observation is that, despite these differences related to age, the predictive value of each of the specific pathological variables was maintained across the age spectrum. Regarding ancestry, there were no significant differences in the predictive value of any pathology variables comparing Caucasians and Asians in our cohort except that the presence of endocapillary proliferation had less impact on outcome in the Asian subjects. This exception may relate to the higher percentage of Asians receiving immunosuppressive therapy than Caucasians, possibly indicating an association between treatment response and endocapillary proliferation, rather than with ethnicity.

Previous classifications of glomerular disease (for example, the World Health Organization/ISN classification of lupus nephritis) have typically assigned four to six to different classes or grades, with multiple pathological features incorporated in each class. However, in our judgment, our approach using individual specific pathological features is easier to understand and apply, both at the individual patient level and as part of a predictive algorithm. Each of the four pathological variables that have been identified by our rigorous methodology is independently associated with outcome, and it is therefore recommended that routine pathology reports in IgAN should be modified to specifically report on these four pathological features without artificial clustering into different 'classes' (Table 8). When offering a prognosis to a patient with IgAN, the nephrologist should now interpret the four pathology features, adding this to the clinical features previously shown to be of prognostic value.

Table 9 gives examples of the way in which different combinations of the pathological variables affected clinical outcome in this cohort of patients. Although the risks are cumulative, caution is required on the evidence available so far; hazard ratios for each pathological variable cannot be directly summed to quantify the risk of progression.

The limitations of this study must be recognized. It is a retrospective observational review. In addition, the original material was not uniformly collected at source and, by design, comes from a wide variety of countries and centers, each with their own laboratory methods of measuring renal function parameters, that is serum creatinine and urine protein. Despite these limitations, the specific pathological features identified withstood rigorous statistical analysis confirming

Table 9 | (a) Combinations of glomerular features—examples of impact on deterioration in renal function; (b) combinations of glomerular and tubulointerstitial features—examples of impact on deterioration in renal function

Glomerular lesions		Criteria	No. of patients	Slope: ml/min per 1.73 m^2 per year
(a)				
Minimal mesangial hypercellularity	Without segmental sclerosis	M0, S0, E0	13	0.7 ± 2.5
	With segmental sclerosis	M0, S1, E0	22	-1.5 ± 2.7
Mesangial hypercellularity	Without segmental sclerosis	M1, S0, E0	31	-2.2 ± 4.3
	With segmental sclerosis	M1, S1, E0	88	-4.7 ± 7.6
Endocapillary proliferation	Without segmental sclerosis	M0/1, S0, E1	21	1.2 ± 1.2
	With segmental sclerosis	M0/1, S1, E1	90	-4.9 ± 10.0

(b) Glomerular lesions	Tubular atrophy/interstitial fibrosis	Criteria	No. of patients	Slope: ml/min per 1.73 m^2 per year
Minimal mesangial hypercellularity	$\leqslant$25%	M0, E0, T0	30	-0.6 ± 3.0
	>26%	M0, E0, T1–2	5	-1.0 ± 1.2
Mesangial hypercellularity	$\leqslant$25%	M1, E0, T0	89	-2.7 ± 5.5
	>26%	M1, E0, T1–2	30	-7.9 ± 9.1
Endocapillary proliferation	$\leqslant$25%	M0/1, E1, T0	88	-3.0 ± 1.9
	>26%	M0/1, E1, T1–2	23	-6.9 ± 1.2

Note that certain combinations are very uncommon, for example, tubular atrophy/interstitial fibrosis (T1, T2) occurring with minimal glomerular lesions (M0, E0).

their value in predicting prognosis independent of both the initial and follow-up laboratory data.

These results will need validation on an independent data set that has been collected prospectively and in a uniform manner. Validation may also lead to a further refinement of these findings, for example whether the number of glomeruli with evidence of endocapillary hypercellularity is important, rather than simply the overall presence or absence of this lesion in the biopsy. In the meantime, however, it is our contention that these pathological features can reliably and consistently be evaluated, using the definitions provided and that both pathologists and nephrologists will benefit by integration of these features into their standard evaluations of the renal tissue in patients with IgAN. In addition, this added value appears to transcend both the age of the patient at biopsy and their ancestry and is derived from a database that is generalizable to most patients with IgAN.

MATERIALS AND METHODS

Pathology definitions

By an iterative process, pathological lesions were defined, lesions with poor reproducibility among pathologists were excluded, and a simplified set of pathology variables was agreed that was suitable for further evaluation in IgAN. (This rigorous process is described in more detail in the paper by Roberts *et al.*)

In brief, the final, simplified pathological variables were selected based on reproducibility among pathologists, least susceptibility to sampling error, ease of scoring in routine practice, and independent correlation with outcome. Selection followed a pre-specified step-by-step methodology, which is as follows:

a. Agreement between pathologists was first assessed and variables were eliminated that showed poor reproducibility or were too infrequently represented in the study cohort to be reliably assessed.
b. Colinearity was measured between the remaining pathology variables and identified different groups of variables with a high correlation coefficient ($r \geqslant 0.8$). Only one variable from each group of highly correlated pathology variables was chosen.
c. Continuous pathology variables were then categorized to facilitate scoring in the final proposed classification. Cutoffs for each variable were determined by sensitivity analysis (using the rate of renal function decline as the outcome).
d. Definitions were also modified where appropriate to reflect ease of use and established conventions (for example, tubular atrophy and interstitial fibrosis have usually been classified as absent, mild, moderate, or severe).
e. Finally, the selected variables were tested in the study cohort for independence from other pathological lesions and from known clinical variables that impact on outcome at onset and during follow-up.

Selection of patient cohorts for testing

Inclusion criteria. Cases were biopsy-proven IgAN (defined by the predominant mesangial deposition of IgA) with an initial eGFR $\geqslant$30 ml/min per 1.73 m^2, and initial proteinuria >0.5 g per 24 h in adults and $\geqslant$0.5 g per 24 h per 1.73 m^2 in children. It was necessary to ensure that selected cases included some in whom there was significant deterioration in GFR over 5 years to maximize the opportunity to identify discriminatory pathological variables of independent importance in predicting outcome. Patients who had received a range of different antihypertensive agents and different immunosuppressive treatment schedules were included.

Exclusion criteria. Cases with an initial eGFR <30 ml/min per 1.73 m^2 were excluded to minimize use of data from cases with advanced disease likely to be beyond a 'point of no return';

it was recognized that this approach had the potential disadvantage of excluding cases with the most acute course. Cases with <12 months of follow-up were excluded to minimize unreliability in the estimation of the rate of renal function decline calculated over a short time, recognizing this was likely to exclude the most acute and rapidly progressive cases. Those with proteinuria <0.5 g per 24 h were excluded to ensure the inclusion of patients at risk of progression. Finally, those with secondary causes of mesangial IgA deposits such as Henoch–Schönlein purpura or those with comorbid conditions such as diabetes mellitus were excluded.

Clinical data set

Demographics were date of birth, gender, ethnicity, and age at the time of biopsy. Children were subjects aged <18 years at biopsy. Clinical parameters collected within 3 months of date of biopsy and during follow-up included systolic and diastolic blood pressure, weight, height, serum creatinine, and 24 h urine protein or urine protein:creatinine ratio. To provide consistency between measurements in adults and children, proteinuria was expressed in g per 24 h per 1.73 m^2 in children and in g per 24 h in adults. Blood pressure was adjusted for gender and age. Treatment modalities were recorded including immunosuppressive agents, fish oil, statins, tonsillectomy, and a number of antihypertensive medications including angiotensin-converting enzyme inhibitor and angiotensin receptor blockers. Data verification occurred by communication between two of the lead authors (ST and RC) and contributing centers.

Definitions

eGFR was estimated using the four-variable MDRD formula in adults and the Schwartz formula in children (using the constant 0.55). ESRD was defined as GFR <15 ml/min per 1.73 m^2. MAP was defined as diastolic pressure plus a third of the pulse pressure. For each child, the s.d. score for MAP was calculated[19] and used to normalize MAP to adult values. For each patient, an average MAP and proteinuria were determined for each year of observation. Follow-up MAP and proteinuria represent the average of these values for MAP and proteinuria. Immunosuppressive treatment is reported as intent to treat regardless of the type or duration of therapy. RAS blockade indicates any exposure to either angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, or both.

Statistical methods

No available data could inform a calculation of the necessary number of cases to allow confident exclusion of type 1 statistical errors in subsequent analyses. A pragmatic recruitment goal was set of 300 cases comprising 250 adults and 50 children. Centers were asked to contribute between 5 and 50 cases with at least 5 years of follow-up and a complete clinical data set.

Normally distributed variables were expressed as mean $\pm$ s.d. and were compared using Student's *t*-test, one-way analysis of variance, or Pearson test. Non-parametric variables were expressed as median and range and compared using either Mann–Whitney, Kruskal–Wallis, or Spearman test. Categorical variables were expressed in percentages and compared using the Pearson χ^2 test.

Reproducibility was assessed for each variable of the extended pathology data set using intraclass correlation coefficient, a measure of reproducibility applicable to multiple raters.[32] By convention, intraclass correlation coefficient of 0.40–0.59 is moderate inter-rater reliability, 0.60–0.79 substantial, and 0.80 outstanding.[33,34]

Continuous pathological variables were categorized to facilitate the applicability of the proposed classification. The relationship between continuous pathological variables and the rate of renal function decline (dichotomized in two groups using the median value) was depicted with receiver operating characteristic curves, and the optimal cutoff predicting a worse outcome was determined from these curves.

Three different clinical outcomes were studied to address the predictive value of pathology variables, which are as follows: (a) the rate of renal function decline (slope of eGFR); (b) survival from a 50% reduction in renal function, or ESRD; and (c) proteinuria during follow-up (as a surrogate outcome measure). The rate of renal function decline was determined by fitting a straight line through available data for eGFR using the principle of least squares. This was plotted and visually examined in each patient. Obvious outliers were censored.

Univariate followed by multiple linear regression was used to determine independent predictors of slope and follow-up proteinuria. Different relevant multivariate models were tested obeying the standard statistical rules. Only pathology variables significantly associated with outcome were further considered. As the follow-up proteinuria was skewed, its square root was used to respect the linear regression assumptions. Slope was also categorized into two halves to derive odds ratios of a more rapid rate of renal function decline using logistic regression. Survival analysis using Cox regression was performed to test the association between each pathological finding and a combined event (50% reduction in renal function or ESRD, to increase the rate of events and permit a valid multivariate analysis). The same models described above were studied through multivariate Cox regression.

Three pre-specified interactions were studied: whether age at biopsy, ethnicity, and immunosuppressive treatment influenced the relation between pathology and the rate of renal function decline using general linear models.

All *P*-values were two-tailed and values less than 0.05 were considered statistically significant. Confidence intervals included 95% of predicted values. Analyses were carried out using SPSS software (version 11; SPSS Inc., Chicago, IL, USA).

DISCLOSURE

The work reported here was supported by an unrestricted educational grant from Vifor Aspreva Pharma. All the authors declared no competing interests.

ACKNOWLEDGMENTS

The Working Group acknowledges the generous support of the International Society of Nephrology, Kidney Research UK, and Vifor Pharma Aspreva.

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