Clinical Kidney Journal, 2019, vol. 12, no. 3, 348–354

doi: 10.1093/ckj/sfy093
Advance Access Publication Date: 10 October 2018
Original Article

ORIGINAL ARTICLE

Assessment of active tubulointerstitial nephritis in non-scarred renal cortex improves prediction of renal outcomes in patients with IgA nephropathy

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ABSTRACT

Background. The addition of tubulointerstitial inflammation to the existing pathological classification of IgA nephropathy (IgAN) is appealing but was previously precluded due to reportedly wide inter-observer variability. We report a novel method to score percentage of non-atrophic renal cortex containing active tubulointerstitial inflammation (ATIN) in patients with IgAN and assess its utility to predict clinical outcomes.

Methods. All adult patients with a native renal biopsy diagnosis of IgAN between 2010 and 2015 in a unit serving 1.5 million people were identified. Baseline characteristics, biopsy reports and outcome data were collected. ATIN was calculated by subtracting the percentage of atrophic cortex from the percentage of total cortex with tubulointerstitial inflammation, with ≥10% representing significant ATIN. The primary outcome was a composite of requiring renal replacement therapy or doubling of serum creatinine.

Results. In total 153 new cases of IgAN were identified, of which 111 were eligible for inclusion. Of these, 76 (68%) were male and 54 (49%) had ATIN on biopsy. During a median follow-up of 2.3 years, 34 (31%) reached the primary outcome. On univariable Cox regression analysis, ATIN was associated with a five-fold increase in the primary outcome [hazard ratio (HR) (95% confidence interval) 4.9 (95% confidence interval (CI) 2.1–11.3)]. On multivariable analysis, mesangial hypercellularity, tubular atrophy and interstitial fibrosis and ATIN independently associated with renal outcome ($P = 0.02$ for ATIN). Inter-observer reproducibility revealed fair agreement in the diagnosis of ATIN ($\kappa = 0.43$, $P = 0.05$).

Conclusions. Within our centre, ATIN was significantly associated with renal outcome in patients with IgAN, independently of established histological features and baseline clinical characteristics.

Keywords: chronic kidney disease, glomerulonephritis, inflammation, Immunoglobulin A (IgA) nephropathy, renal pathology

Received: 23.4.2018; Editorial decision: 13.8.2018

INTRODUCTION

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide [1]. Diagnosis is confirmed by the presence of IgA dominant or co-dominant immune deposits in glomeruli on immunofluorescence or immunohistochemistry [2]. The spectrum of histological and clinical disease is varied but ~25% progress to end-stage renal disease (ESRD) within 10 years of diagnosis [3]. Histological reporting of IgAN is now standardized following publication of the Oxford Classification of IgA Nephropathy in 2009 [2, 4]. This system was developed by an international working group following rigorous examination of commonly reported histological variables to identify those with robust definitions, reliable inter-observer reproducibility and without collinearity with other variables. Four histopathological features were ultimately included: mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S) and tubular atrophy and interstitial fibrosis (T). The 'MEST' classification system has subsequently been validated in numerous cohorts [5–7] and has been shown to improve significantly the prediction of renal outcomes in patients with IgAN when combined with baseline clinical data [3]. The original working group continue to refine and improve the pathological classification of IgAN with an update in 2016 announcing the addition of crescents (C) to form the MEST-C score [7].

There are, however, limitations to the clinical application of the MEST-C score: not all features are predictive of renal outcome [5, 7, 8] and patients with Henoch–Schonlein purpura (HSP), which is pathologically indistinguishable from IgAN on biopsy, were excluded from validation studies. Furthermore, beyond prognostication of renal outcome, the role of the MEST-C score in guiding management decisions has never been prospectively established. Although it is unsurprising that markers of chronic damage, such as tubular atrophy, interstitial fibrosis and glomerulosclerosis, which are represented in the MEST score as S and T, associate with a poor long-term renal outcome, it is conceivable that the more active glomerular lesions, such as M, E and C, may prove to be better predictors of response to immunosuppressive therapy [4, 7, 9, 10]. Consequently, the absence of a measure of active tubulointerstitial inflammation (ATIN) is a potential criticism of the current MEST-C score. In this paper, we report a novel method to score the percentage of renal cortex containing tubulointerstitial inflammation in unscarred areas (ATIN) in patients with IgAN, similar to that recorded in transplant biopsy reporting [11] and assess its ability to predict clinical outcomes when used in conjunction with the established MEST-C score.

MATERIALS AND METHODS

Patient population

All adult patients with a first native renal biopsy diagnosis of IgAN between 2010 and 2015 in the Glasgow Renal & Transplant Unit were identified. This unit serves a defined population of 1.5 million, with the predominant ethnic group being white. Baseline serum creatinine (sCr), serum albumin (sAlb) and urine protein:creatinine ratio (uPCR) were recorded. Data from biopsy reports were recorded including date of biopsy, number of glomeruli, number of globally sclerosed glomeruli, individual M, E, S, T and C scores, and cumulative MEST-C score. Patients with fewer than eight glomeruli on biopsy were excluded in line with existing literature [2, 7]. In addition, patients with a T score of 2 were excluded on the basis that our method of scoring ATIN using an estimated percentage of viable cortex would be inappropriate and irrelevant in the presence of extensive tubular atrophy. Clinical correspondence was reviewed to determine if patients had a coexisting clinical diagnosis of HSP. Data were collected regarding immunosuppressive therapy during follow-up, date of doubling of sCr, date of first renal replacement therapy (RRT) and date of death (where applicable). The primary outcome was a composite of doubling of sCr or requiring RRT.

Pathological technique

ATIN was calculated by subtracting the percentage of cortex with tubular atrophy from the percentage of total cortex with tubulointerstitial inflammation in order to make an indirect assessment of the percentage of renal cortex in the biopsy in which there was inflammation in non-scarred areas (Figure 1). A binary threshold of $\geq$10% was deemed to represent significant ATIN (score of 0 or 1). Biopsies were reported by a single pathologist, but inter-observer reproducibility was assessed by selection of a random sample of 14 cases representing >10% of the total cohort, which were rescored by a second independent pathologist for percentage of renal cortex with tubular atrophy and percentage of renal cortex with tubulointerstitial inflammation. Additional guidance with regard to the pathological criteria used to define the presence or absence of tubular atrophy and interstitial inflammation for the purposes of calculating ATIN is included in Supplementary data, Table S1.

Statistical analysis

Descriptive statistics are reported as mean and SD or median and interquartile range (IQR) for normally distributed and non-parametric variables, respectively. Time from renal biopsy to the primary composite outcome was analysed using Cox proportional hazards model with censoring at time of death or last recorded blood result. Baseline variables were entered into the multivariable analysis and excluded in a stepwise manner until only variables that retained independent statistical significance ($P < 0.05$) remained. Overall model fit was assessed using binary logistic regression with an increase in Nagelkerke's R^2 suggesting a better model fit. The frequency of immunosuppression in those with and without different clinical and pathological features was compared using Pearson's chi-squared test, Fisher's exact test (when expected cell count was <5), two-sample t-test or Mann–Whitney U test as appropriate. Correlation between ATIN and other pathological variables was assessed using Spearman's rank correlation. Inter-observer reproducibility was measured using (i) kappa statistic (κ) for ATIN and (ii) intraclass correlation co-efficient (ICC) (two-way random) for scores of the percentage of cortex containing either inflammation or tubular atrophy [12]. All analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA) and a conventional significance level of <0.05 was used. Figures were generated using SPSS 22.0 (IBM, NY), Microsoft PowerPoint® 2011 and GNU Image Manipulation Programme© (version 2.10.4).

RESULTS

Demographics

A total of 153 new cases of biopsy-proven IgAN were identified over 6 years. Of these, 42 cases were excluded: 24 had fewer than eight glomeruli on biopsy, 6 had inadequate biopsy for

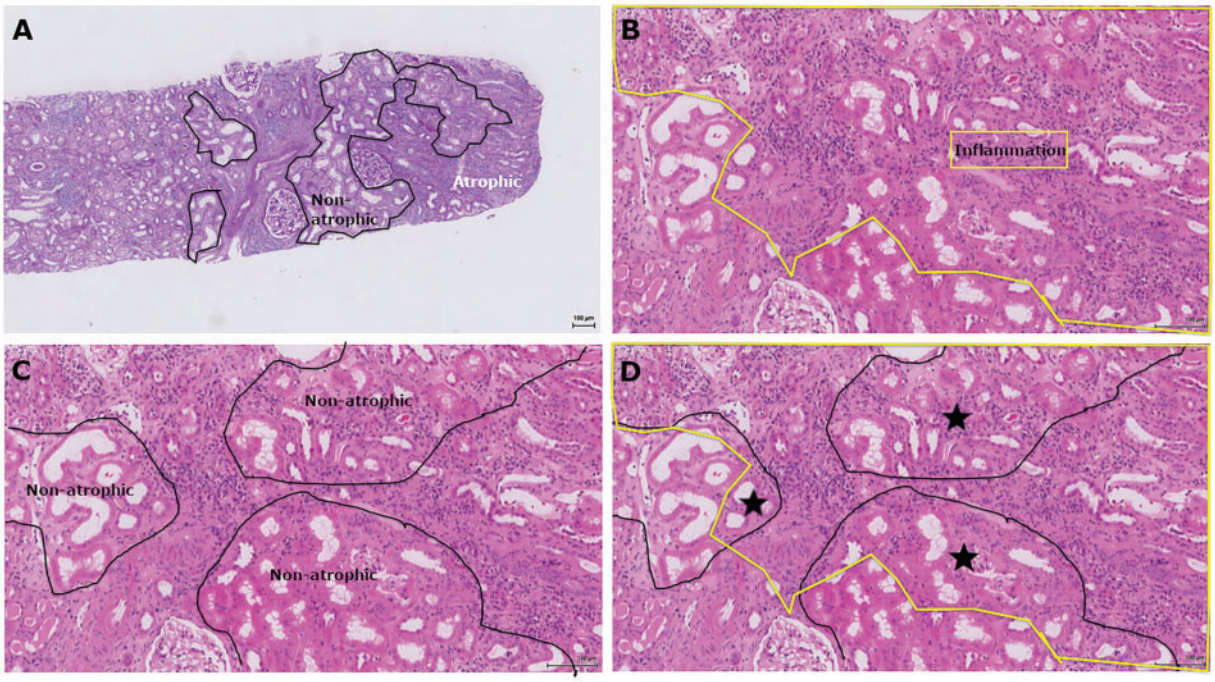

FIGURE 1: Diagrammatic representation of the pathological technique for calculating ATIN. (A) shows a low-powered magnification of a section of renal cortex with areas delineated based on the presence or absence of tubular atrophy. (B), (C) and (D) all show a higher power magnification of the same tissue. To score ATIN, the pathologist first makes an estimation of the total percentage of cortex in which inflammation is present as outlined by the yellow box of panel (B). Next, the pathologist estimates of the percentage of cortex in which there is tubular atrophy as depicted by the black border in panel (C). Finally, the pathologist subtracts these two percentages to produce a surrogate measure of the percentage of non-atrophic cortex in which tubulointersitial inflammation exists as depicted by the asterisks in panel (D). This method is based on the assumption that areas of tubular atrophy and interstitial fibrosis will contain inflammation.

Table 1. Baseline demographics in entire cohort and then subdivided based on whether or not patients had ≥10% ATIN

Variable	All ($n=111$)	No ATIN ($n=57$)	ATIN ($n=54$)	P
Male (%)	76 (68)	35 (61)	41 (76)	0.1
Mean age, years (±SD)	52 (±17)	49 (±16)	55 (±17)	0.056
HSP (%)	18 (16)	7 (12)	11 (20)	0.25
Median sCr, umol/L (IQR)	156 (101–212)	122 (78–187)	165 (133–225)	0.002
uPCR, mg/mmol (IQR)	228 (125–435)	184 (89–288)	340 (180–635)	<0.001
M1 (%)	59 (53)	21 (37)	38 (70)	<0.001
E1 (%)	70 (63)	31 (54)	39 (72)	0.052
S1 (%)	73 (66)	39 (68)	34 (63)	0.545
T1 (%)	24 (22)	8 (14)	16 (30)	0.046
C1 (%)	31 (28)	11 (19)	20 (37)	<0.001
C2 (%)	9 (8)	0 (0)	9 (17)	<0.001
ATIN (%)	54 (49%)	–	–	

P-values relate to Pearson's chi-squared test comparing frequencies based on presence or absence of ATIN, except for age where a two-sample t-test was used, and sCr and uPCR, where Mann–Whitney U tests were performed. Accepted significance level for all variables defined as <0.05.

uPCR, urine protein:creatinine ratio at time of biopsy; M1, mesangial hypercellularity in <50% of glomeruli; E1, presence of endocapillary hypercellularity; S1, presence of segmental glomerulosclerosis; T1, tubular atrophy and interstitial fibrosis in 25–50% of cortex; T2, tubular atrophy and interstitial fibrosis in >50% of cortex (excluded); C1, presence of active crescents in 1–25% of glomeruli; C2, presence of active crescents in >25% of glomeruli; ATIN, presence of ≥10% of non-scarred cortex containing active tubulointerstitial inflammation.

MEST scoring, 3 were on RRT at the time of biopsy and 9 patients had a T score of 2. Of the remaining 111 patients, 76 (68%) were male. Mean age at biopsy was 52 years (±16.7) and 18 (16%) had a coexisting clinical diagnosis of HSP. Median sCr was 156 μmol/L (IQR 103–214) and median uPCR 228 mg/mmol (125–435). 54 (49%) had ATIN on biopsy (Table 1). All patients were managed to established blood pressure targets [13] and with maximal dosing of inhibitors of the renin–angiotensin system, where possible.

Outcomes

During a median follow-up of 2.3 years, 34 (31%) patients reached the primary outcome and 16 (14%) died. Of those that died nine reached the primary outcome prior to death. Cause of death was cancer ($n=5$), sepsis ($n=3$), ESRD ($n=3$), myocardial infarction ($n=2$), other ($n=2$) and no data available ($n=1$).

Univariable analysis

On univariable cox regression survival analysis, pathological features that associated with the primary outcome included MEST (cumulative), M, E, T, C and ATIN (Table 2). M and ATIN had the greatest individual predictive impact and were associated with a near five-fold increase in the primary outcome [hazard ratio (HR) (95% CI) 4.8 (95% CI 2.0–11.7) and 4.9 (95% CI 2.1–11.3), respectively] (Figure 2). When compared with established pathological variables, ATIN significantly correlated with M, T and C. The strength of the correlation was comparable with that seen between M and C (Supplementary data, Table S2). Clinical features that were predictive of outcome included baseline sCr and uPCR >100 mg/mmol (Table 2). There was an inverse relationship between sAlb and the primary outcome (Table 2).

Table 2. HR for primary composite outcome (doubling of sCr or RRT) based on a 1-unit increment in each individual pathological or biochemical variable

Variable	HR	95% CI	P
M	4.8	2.0–11.7	<0.001
E	2.5	1.1–5.8	0.03
S	1.6	0.7–3.6	0.24
T	2.6	1.3–5.3	<0.001
C	1.9	1.2–3.1	0.007
MEST-C	1.9	1.5–2.5	<0.001
ATIN	4.9	2.1–11.3	<0.001
Baseline sCr (μmol/L)	1.004	1.001–1.006	0.008
uPCR ≥100 mg/mmol	4.9	1.2–20.4	0.03
sAlb (g/dL)	0.9	0.9–1.0	0.006

Cox proportional hazards model with accepted significance level of <0.05.
95% CI, 95% confidence interval; M, mesangial hypercellularity; E, endocapillary hypercellularity; S, segmental glomerulosclerosis; T, tubular atrophy and interstitial fibrosis; C, crescents, ordinal variable based on percentage of glomeruli containing crescents (C0 = 0%, C1 = 125%, C2 = >25%); MEST-C, cumulative of M, E, S, T, C; ATIN, presence of ≥10% of non-scarred cortex containing active tubulointerstitial inflammation; baseline sCr, serum creatinine at time of biopsy; sAlb, serum albumin at time of biopsy.

Multivariable analysis

On multivariable analysis of pathological features, M, T and ATIN independently contributed to the prediction model of renal outcome whereas E, S and C did not (Table 3). When baseline sCr (continuous), baseline sCr >150 (binary) or uPCR >100 were added to the model, ATIN retained independent significance, but the clinical parameters themselves did not. Overall model fit improved with the addition of ATIN to M and T, with R^2 increasing from 0.29 to 0.37.

ATIN and response to immunosuppression

A total of 20 (18%) patients received immunosuppression, all of which were steroid-based regimens (prednisolone 1 mg/kg, median dose 60 mg and median duration 7 months). Only six patients received additional induction with oral cyclophosphamide (1.5–2 mg/kg/day, duration 3 months), of whom four patients progressed to maintenance azathioprine therapy. Baseline variables that associated with an increased frequency of immunosuppression usage included M, E, C, ATIN, sCr, uPCR and a clinical diagnosis of HSP (Supplementary data, Table S3). Patients who received immunosuppression had a more severe clinical phenotype as evidenced by higher sCr and uPCR at baseline (Supplementary data, Table S3). Out of 20 patients, 18 patients received immunosuppression had ATIN on biopsy, of whom 9 reached the primary outcome and 9 did not (Figure 3). Conversely, 36 patients with ATIN did not receive immunosuppression of whom 18 reached the primary outcome and 18 did not. On subgroup analysis of the 91 patients who did not receive immunosuppression, M, T and ATIN all remained independent predictors on multivariable analysis (data not shown).

Impact of HSP

Excluding the 18 patients with a coexistent clinical diagnosis of HSP did not change the variables with independent predictive significance on multivariable analysis. No pathological variable was predictive of outcome in the 18 patients with HSP on univariable or multivariable analysis (data not shown), although these patients were more likely to receive immunosuppression (Supplementary data, Table S3).

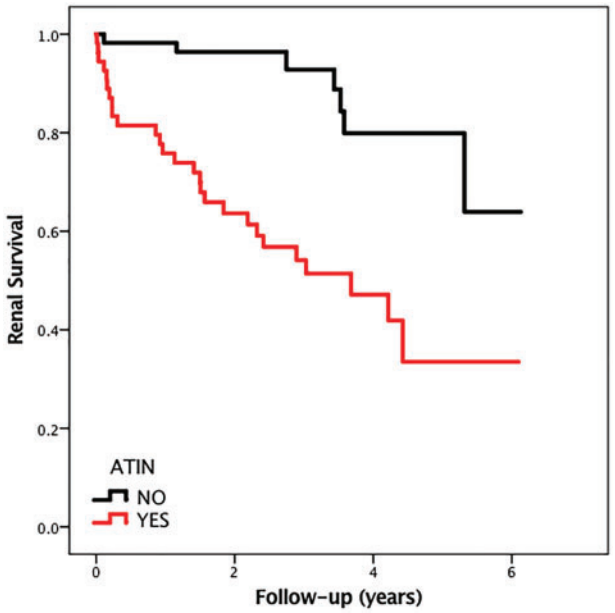

FIGURE 2: Kaplan–Meier survival curve showing time until primary composite outcome (doubling of sCr or RRT) based on the presence or absence of ATIN on renal biopsy. Patients without events were censored at time of death or last recorded blood result.

Table 3. HRs for primary composite outcome (doubling of sCr or RRT) based on multivariable analysis including all significant pathological variables—only significant variables reported (A). Multivariable model of independently significant pathological features, with the addition of univariable significant baseline clinical parameters (B)

(A)

Variables in analysis	HR	95% CI	P
M	3.4	1.3–8.7	0.02
T	2.4	1.2–4.8	0.02
ATIN (binary)	3.0	1.2–7.4	0.02

(B)

Variables in analysis	HR	95% CI	P
M	3.3	1.3–8.1	0.02
T	1.9	0.9–4.1	NS
ATIN (binary)	2.6	1.0–6.3	0.04
Baseline sCr (μmol/L)	1.002	0.999–1.005	NS
uPCR ≥100 mg/mmol	2.7	0.6–11.5	NS

Cox proportional hazards model with accepted significance level of <0.05.
95% CI, 95% confidence interval; M, mesangial hypercellularity; T, tubular atrophy and interstitial fibrosis; ATIN (binary), presence of ≥10% of non-scarred cortex containing active tubulointerstitial inflammation; baseline sCr, serum creatinine at time of biopsy; NS, non-significant.

Inter-observer reproducibility

The reliability between the two raters in scoring the percentage of cortex containing tubular atrophy and interstitial inflammation was 'good' (ICC 0.88; P = 0.001) and 'excellent' (ICC 0.91; P < 0.001), respectively. Inter-observer reproducibility for the

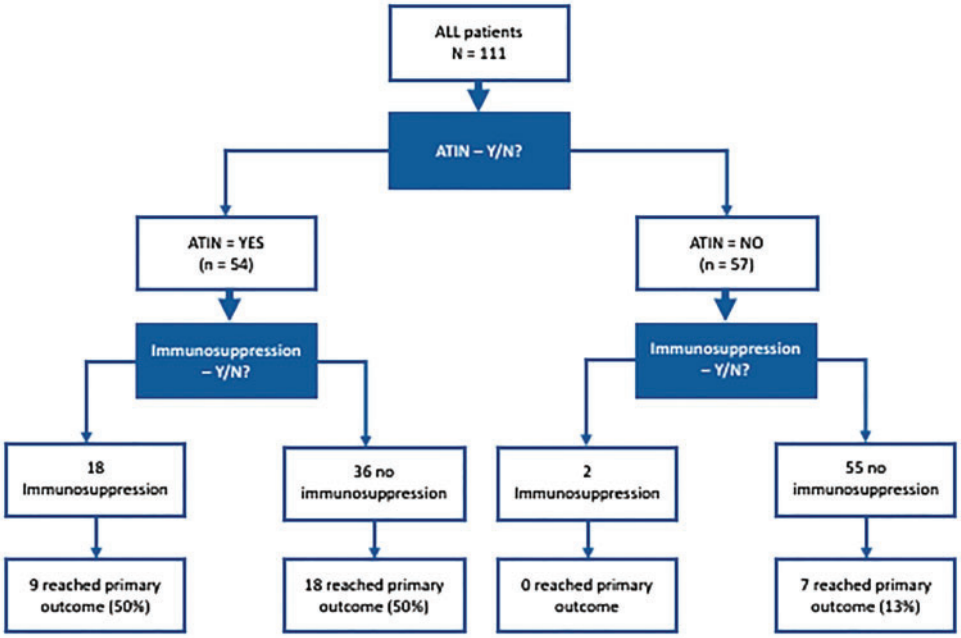

FIGURE 3: Flow chart showing the number of patients who reached the primary outcome based on the presence or absence of ATIN and immunosuppression. Patients who received immunosuppression had a more severe clinical phenotype, with higher sCr and proteinuria at baseline (Table 1).

diagnosis of ATIN was assessed by kappa statistic and revealed a 'fair' agreement (κ=0.43, P = 0.05).

DISCUSSION

Our data show that the presence of >10% active tubulointerstitial nephritis within the viable cortex in patients with IgA nephropathy was independently associated with renal outcome and performed equivalent to, or better than, established MEST-C variables. Further study is required to assess the plausible role of ATIN in predicting response to immunosuppression in IgA nephropathy.

The Oxford Classification of IgA Nephropathy [4] was a significant step forward in providing a framework to diagnose a diverse pathological condition and, commendably, the authors continue to evolve and improve it [7]. An assessment of tubulointerstitial inflammation would be an appealing addition to the current scoring system. Myllymäki *et al.* found parameters of tubulointerstitial inflammation predicted deterioration in renal function in 204 patients with IgA nephropathy [14]. They found significant interstitial inflammation in 25% of biopsies and the grade of interstitial inflammation (normal, mild or marked) correlated with disease progression. Similarly, Freese *et al.* evaluated 67 biopsies from native kidneys of subsequent kidney transplant patients whose primary diagnosis was IgA nephropathy [15]. Cellular infiltrates in the interstitium were more common in their study group of patients and they were associated with shorter progression to ESRD. However, in both studies the authors did not specify if the interstitial inflammation recorded was present in non-fibrotic interstitium, in fibrotic interstitium or both. Interstitial inflammation was considered for the Oxford classification system but was excluded on the basis that the percentage of the total cortex with interstitial inflammation correlated too closely with the degree of interstitial fibrosis ($r = 0.9$), whereas the assessment of interstitial inflammation in non-atrophic areas displayed unacceptably poor ICC at only 0.03 [2]. Our technique overcomes both of these problems. First, by focussing on the percentage of inflammation in non-atrophic cortex we overcome the correlation with interstitial fibrosis. Secondly, the two surrogate histological data items that we use to calculate ATIN displayed acceptable ICC in the original Oxford paper with tubular atrophy scoring 0.79 and total interstitial inflammation at 0.58. This is confirmed on our intra-cohort validation, with 'fair' inter-observer reproducibility as assessed by kappa statistic.

ATIN does exhibit significant correlations with some of the existing pathological variables; however, the strongest of these correlations at $r = 0.39$ is well below the previously defined threshold of $r = 0.8$ [4]. Furthermore, the independent significance of ATIN was maintained in the multivariable analysis with an 8% improvement in overall model fit as represented by R^2 rising from 0.29 to 0.37. This implies that 63% of the variation in outcome is still unexplained by our model. Nevertheless, our results are comparable with previous reports: validation of MEST in the VALIGA cohort had a maximum R^2 of 0.19 [3]. Patients with ATIN had a higher sCr and uPCR at baseline (Table 1), however, ATIN maintained independent significance even when these factors were adjusted for (Table 3).

Following recent randomized trials, the role of immunosuppression for the treatment of IgAN remains uncertain. There remains some signal that immunosuppression may be beneficial, for instance, proteinuria reduced in STOP-IgA [16] and renal outcomes improved in TESTING [17], but these minor benefits are outweighed by more significant risks for the majority of patients. IgAN is a heterogeneous disease with variable clinical phenotype. Given the robust pathological classification of IgAN as a result of the Oxford classification system, it is disappointing that current trials have not stratified patients on this basis and future trials would benefit from doing so. There is plausibility that ATIN could be a useful addition in this regard; however, the numbers were too small in this study to address this, with only 20 patients receiving immunosuppression of which 18 had ATIN. That said, given that patients who received

immunosuppression had a more severe clinical phenotype, the fact that 50% of the ATIN group reached the primary outcome regardless of immunosuppression or not, means that immunosuppression may have attenuated the primary outcome rates in the more severe group. Further research in larger cohorts is required. Similarly, we intend to examine the relationship between immunosuppression and ATIN as an ordinal variable, with a score of <10%, 10–24% and ≥25% corresponding to ATIN values of 0, 1 and 2, respectively, in future studies in larger cohorts.

There are limitations to this study, primarily that it is a retrospective series from a single centre and requires validation. There is wide variation in the incidence of biopsy-proven IgAN, attributed to varying clinical practices with regard to the indication for biopsy. We have previously reported our results in comparison to other centres and found that our biopsy rate (and our rate of IgAN diagnosis) lies within the middle of the range compared with 10 countries worldwide [18]. The rates of immunosuppression within our cohort are lower than previously reported [19], and the regimens used were not standardized, meaning any confounding influence is likely to be non-uniform. A single pathologist scored ATIN; however, assessment of inter-observer reproducibility was found to be acceptable and we are reassured by acceptable reproducibility of other scores that rely on similar estimations of inflammation, such as the Banff criteria for reporting renal transplant biopsies [20]. Further research is required to test more rigorously the inter-observer reproducibility of ATIN. Aside from our novel reporting of ATIN, our results are consistent with previous reports validating MEST in clinical cohorts suggesting a reliability to our data. Consistent with previous reports we found M, T and C to associate with renal outcome [4, 5, 7]. E is variably reported to associate with renal outcome in the absence of immunosuppression [5], and so the weak association we observe may be explained by the lower prevalence of immunosuppression in our cohort [7, 9]. In contrast to other reports [4, 7, 8, 21], S did not associate with renal outcome within our cohort; however, this observation is by no means unique [9, 22, 23]. The role of HSP remains to be clarified but we believe there is value in including these patients in studies which examine an indistinguishable histological appearance. The Oxford Classification of IgAN has previously been shown to predict renal outcome in patients with HSP [24]. Furthermore, amongst patients with HSP who undergo renal biopsy, renal outcome is similar to IgAN with 11–25% of patients reaching ESRD within 10 years [25–27]. The exclusion of patients with T2 has a minimal impact on the generalizability of our results as it represented <6% of our biopsy population, with similar figures reported previously [4]. A total of 16 patients died during follow-up, but only 7 did so prior to reaching the primary outcome and so death is unlikely to represent a significant competing risk.

Our method for scoring ATIN relies on the assumption that areas of tubular atrophy and interstitial fibrosis will always contain inflammation. This assumption is contested in transplant literature where differentiating bland, versus inflamed, areas of fibrosis have prognostic significance [28, 29]. However, our assumption remains valid in the majority of cases, with one study showing only 65 out of 337 biopsies had no inflammation in fibrotic areas [28]. Furthermore, in the original Oxford paper, interstitial fibrosis and interstitial inflammation had a correlation coefficient of 0.90, which was deemed 'so close to 1 that to include both in a classification would provide no additional value' [2].

In conclusion, within our centre ATIN was significantly associated with renal outcome in patients with IgAN, independently of established histological features and baseline clinical characteristics. Further assessment of inter-observer reproducibility and validation in other cohorts is still required but these results suggest our method of assessing ATIN could be a worthwhile addition to current pathological scoring systems for IgAN.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

ACKNOWLEDGEMENTS

Preliminary results from this study were presented as an oral presentation at the Scottish Renal Association Annual Conference, October 2017. The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS' CONTRIBUTIONS

All authors contributed to the concept, design or analysis of this project and have been actively involved in drafting this manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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