Outcomes of Immunosuppression in IgA Nephropathy Based on the Oxford Classification

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ABSTRACT. Numerous studies have addressed the predictive value of pathology findings from the Oxford Classification. Whether this influences treatment choice has not been determined. We evaluated patients with IgA nephropathy who were immunosuppressed and correlated our findings with both clinical and histological features as per the Oxford Classification. This was a retrospective observational study of 45 patients who had biopsy-proven IgA nephropathy with a mean follow-up of 2.6 years. Primary outcomes were time to end-stage renal disease (ESRD) or a 50% rise in serum creatinine. Immunosuppression was not associated with lower hazards for both ESRD and 50% rise in serum creatinine. From the Oxford Classification, only T0 was associated with significantly lower hazards for ESRD [hazard ratio (HR), 0.067; confidence interval (CI) 0.01–0.58]. Patients who had crescents and/or necrotizing lesions on biopsy were more likely to be immunosuppressed (odds ratio 9.99; 95% CI 1.99–50.06, P = 0.005) but demonstrated a statistically nonsignificant higher hazard for both renal end points (HR, 1.61; CI 0.19–13.89). Such lesions were also associated with a higher incidence of hypertension (149 vs. 135 mm Hg) and greater proteinuria (2.7 vs. 1.9 g/day) at presentation. The use of the Oxford Classification did not aid decision-making with regard to the use of immunosuppression. Crescents and/or necrosis identified on histology were associated with the use of immunosuppression. Hence, there is a need for these lesions to be evaluated further in large cohorts and incorporated into future disease classifications.

Introduction

IgA nephropathy is the most prevalent form of glomerulonephritis worldwide and is now accepted as an important cause of end-stage renal disease (ESRD) at all ages.¹ There is a significant risk of progressing to ESRD of 15%–20% by 10 years from onset and 40% by 20 years.² Previous studies have explored factors, both clinical and pathological, that predict outcomes in IgA nephropathy. However, risk stratification remains a challenge in patients with IgA nephropathy because the natural history of IgA nephropathy ranges from persistent asymptomatic microscopic...
hematuria to progressive kidney failure. The Oxford Classification was formulated to provide clinicians and pathologists a uniform classification method to assess histological features that would predict the outcome. Numerous studies have addressed the predictive value of pathology findings. Currently, the control of blood pressure and using renin-angiotensin (RAS) blockade remain the cornerstone of management, but the benefit of immunosuppression (IM) remains an unresolved issue. The KDIGO guidelines make no recommendation for the use of immunosuppression with an initial eGFR <50 mL/min/1.73 m² because this is a group that is underrepresented in trials. Hence, there is a dearth of information exploring the associations of the Oxford Classification (which excluded patients with an eGFR <30 mL/min/1.73 m²) with clinical presentation and response to immunosuppression. Our study aims to explore this. We evaluated the influence of the Oxford Classification on the use of immunosuppression, and the respective clinical outcomes.

Materials and Methods

This was a retrospective observational study in patients under active follow-up with the kidney unit. These patients were identified from the patient database CV5. Data were collected from the electronic patient records for all patients labeled with a diagnosis of IgA nephropathy between 2010 and 2015 (Figure 1). Only those patients who had biopsy-proven disease were considered. Patients with a possible secondary cause such as cirrhosis, coeliac disease, HIV, seronegative arthropathies, small-cell carcinoma, lymphomas, disseminated tuberculosis, bronchiolitis obliterans, and inflammatory bowel disease were excluded. Those with more than one diagnosis on biopsy were also excluded. All biopsy specimens had a minimum of eight glomeruli assessed by light microscopy.

This investigation was approved by the institutional review board at the hospital trust and was in accordance with the principle of the Helsinki Declaration II. As the study was retrospective in design and did not include any interventions.

Clinical data and definitions

Clinical and laboratory variables were extracted from medical records from the time of the renal biopsy to the last available follow-up visit and/or initiation of RRT. eGFR was calculated using the Modification of Diet in Renal Disease Study group equation. Quantification of daily protein excretion was based on a spot urinary protein-to-creatinine ratio. There was no restrictive eGFR or proteinuria entry criteria.

![Figure 1. Study flow diagram.](image-url)
Risk factor profile

Hypercholesterolemia, diabetes, and history of ischemic heart disease were recorded when there was a previous documented history or when patients were receiving treatment for these conditions. The presence of arterial hypertension was defined as a systolic BP ≥140 mm Hg and/or diastolic ≥90 mm Hg. Cigarette smoking was classified as either current or nonsmoker. Each risk factor was evaluated at baseline.

Medication history

The medications taken at the time of inception into the study were included. These included the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blockers, calcium channel blockers, statin therapy, and the use of fish oil. Immunosuppressive therapy was recorded if a patient was started on treatment. From available follow-up data, an estimate of the duration of therapy was made. Patients prescribed immunomodulatory treatment were considered as treated, regardless of duration. Patients who were given glucocorticoids, 1 mg/kg or ≥20 mg/day were considered treated with glucocorticoids.

Histological definition

The MEST score consisted of mesangial hypercellularity (M) with the presence of more than three cells in most cellular mesangial area on more than 50% of glomeruli (M1; M0 absent), Endocapillary hypercellularity (E0 absent; E1 present), segmental glomerulosclerosis (S0 absent; S1 present), and tubular atrophy/interstitial fibrosis (T0 <25%; T1 25%–50%; T2 .50%). Although this is not part of the Oxford Classification, KDIGO GN treatment guidelines suggest that the presence of crescents or necrosis are associated with a worse prognosis.5

Study endpoints

Primary outcomes were recorded during follow-up and were also noted by hospital admission in subsequent review of the CV5 patient nephrology database. Outcomes included (1) those who reached ESRD, which was defined as patients who reached Stage V CKD (eGFR ≤15 mL/min/1.73 m²), and/or (2) 50% percent rise in serum creatinine. Adverse outcomes were identified if reported in the medical notes by the attending nephrologist.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The data are presented as frequencies and percentages for categorical variables. Continuous variables with normal distribution are indicated as mean ± standard deviation and nonnormally distributed variables as median and inter-quartile range. Comparison between variables was done using t-tests and Chi-squared or Fisher’s exact tests (two-tailed) respectively. Statistical significance was considered as a two-tailed probability of P ≤0.05. Logistic regression analysis was used to evaluate the factors associated with the use of immunosuppressive therapy. Kaplan–Meier survival curves were used to visually evaluate the relationship between immunosuppressive therapy and renal endpoints. Comparisons were made using log-rank testing. Cox-proportional hazard models were built to analyze the association between clinical, histological, and medication factors with renal outcomes. Adjustment variables were chosen if the factor was not on the causal pathway between presentation and the outcome and were felt clinically likely to influence the outcome. These results were expressed as hazard ratios (HR) with 95% confidence intervals (CIs).

Results

During the study period, 109 patients were identified to have a diagnosis of IgA nephropathy. Exclusion criteria resulted in 64 patients being omitted. The main reason for exclusion was that these 57 patients did not have a histologically proven diagnosis. This study included 45 patients, of whom 25 were men and 91% were Caucasians. At the time of the biopsy, their mean age was 48 ± 15 years with
and eGFR of 45 ± 24 mL/min/1.73 m² and an average proteinuria of 2.3 ± 1.8 g/day. Arterial hypertension was present in 62% of patients with more than half these patients requiring two or more agents for blood pressure control. Only 64% of the study population were on either an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB). In addition, 16% of patients were on fish oils. The mean follow-up time was 2.6 ± 1.7 years.

Of the 45 patients, 27 received no immunosuppression, 17 patients received mycophenolate (MMF) and corticosteroids, and 1 received cyclophosphamide and corticosteroids. At baseline, there was no difference between the mean eGFR and systolic blood pressure between the groups. In total, 17 of the 18 (94%) patients who received immunosuppression >1 g/day of proteinuria compared to only 63% of those not immunosuppressed. The average duration of immunosuppression was 17.9 months (Table 1).

Mesangial hypercellularity was present in 64% and endocapillary proliferation in only 15%. Seventy-one percent of biopsies demonstrated segmental sclerosis and 45% had no evidence of tubular atrophy/interstitial fibrosis (Table 2).

The factors associated with immunosuppressive treatment are summarized in Tables 3 and 4. The odds of receiving immunosuppressive treatment was no different if the presenting eGFR <50 mL/min/1.73 m². Notably, patients who demonstrated the presence of necrotizing lesions or crescents had a very high likelihood of receiving immunosuppression (OR 11.44; 95% CI 2.78–47.17). Following adjustment for proteinuria, mesangial hypercellularity, tubulointerstitial fibrosis, and the presence of crescents or necrosis, this relationship remained (OR 9.99; 95% CI 1.99–50.06, P = 0.005). Those with mesangial hypercellularity also had a higher likelihood of receiving immunosuppressive therapy (OR 4.64; 95% CI, 1.09–19.82) but did not reach statistical significance (OR 2.24; 95% CI, 0.36–14.00) in the adjusted model (Table 4).

In univariate and time-dependent analyses, outcomes did not differ between the two groups (Figure 2).

In both unadjusted and adjusted Cox survival models (Table 5), the use of immunosuppression was not associated with a statistically significant lower hazard for both ESRD (HR, 0.83; CI, 0.24–2.86) and 50% rise in serum creatinine (HR, 0.682; CI, 0.08–5.51). A baseline eGFR <50 mL/min/1.73 m² and the presence of tubulointerstitial fibrosis showed a trend toward a higher risk for both renal outcomes and both remained independently associated with the outcome after adjustment for the other variables.

Oxford Classification criteria of mesangial hypercellularity, segmental sclerosis, and endocapillary proliferation were not significantly associated with renal outcomes. Notably, Kaplan–Meier plots did demonstrate a statistically significant survival benefit in terms of reaching ESRD in those graded as having T0 lesions (Figure 3). Likewise, a similar trend was also observed in the time to a 50% rise in serum creatinine.

The Cox models also showed that those graded with T0 had a lower risk of developing ESRD (HR, 0.067; CI 0.01–0.58).

Although the odds of receiving immunosuppression were high in the presence of necrotizing lesions and/or crescents, there was no statistically significant association between these lesions and the renal end points ESRD (HR, 1.86; CI 0.19–18.26) and 50% rise in serum creatinine (HR, 1.61; CI 0.19–13.89).

Clinicopathological correlations were analyzed and the only MEST lesion to clinical presentation was T0. These patients had a higher presenting eGFR compared to those with T1 or T2 lesions (41 ± 16 vs. 27 mL/min/1.73 m², P = 0.001). The presence of crescents was associated with a higher systolic blood pressure at presentation (149 ± 21 vs. 135 ± 17 mm Hg, P = 0.018). However, the presence of necrotizing lesions was significantly associated with both higher proteinuria (3.5 ± 2.1 vs. 1.9 ± 1.6 g/24h, P = 0.017) and systolic blood pressures (154 ± 21 vs. 137 ± 18, P = 0.013). Neither of these lesions influenced the presenting eGFR (Table 6).
Table 1. Baseline characteristics by immunosuppression status at entry into study.

| Variables                      | No immunosuppression | Any immunosuppression | P  |
|--------------------------------|----------------------|-----------------------|----|
| Total                          | 27                   | 18                    |    |
| Age (years)                    | 47.6±13              | 49.4 ± 18             | 0.699 |
| Female                         | 12 (44%)             | 8 (44%)               | 0.619 |
| Ethnicity (white)              | 25 (93%)             | 16 (89%)              | 0.529 |
| Follow-up (years)              | 2.66 (IQR, 1.39 – 4.65) | 1.91 (IQR, 0.88 -2.91) | 0.126 |
| Proteinuria                    |                      |                       |    |
| <1 g/day                       | 10 (37%)             | 1 (5%)                | 0.033 |
| >3 g/day                       | 7 (26%)              | 7 (40%)               | 0.512 |
| Histology                      |                      |                       |    |
| M                              | 14 (52%)             | 15 (83%)              | 0.055 |
| E                              | 3 (11%)              | 3 (17%)               | 0.670 |
| S                              | 18 (67%)             | 14 (78%)              | 0.514 |
| T0                             | 15 (55%)             | 5 (28%)               | 0.078 |
| T1                             | 6 (22%)              | 9 (50%)               | 0.105 |
| T2                             | 6 (23%)              | 4 (22%)               | 0.647 |
| Necrotizing lesions            | 2 (7%)               | 8 (44%)               | 0.008 |
| Crescents                      | 5 (19%)              | 12 (67%)              | 0.002 |
| Necrotizing lesions and/or crescents | 5 (19%)          | 13 (72%)              | 0.001 |
| Comorbidity                    |                      |                       |    |
| HTN                            | 18 (67%)             | 10 (56%)              | 0.537 |
| DM                             | 1 (4%)               | 2 (11%)               | 0.555 |
| Smoker                         | 3 (11%)              | 2 (11%)               | 0.691 |
| CVS                            | 1 (4%)               | 2 (11%)               | 0.555 |
| Medications                    |                      |                       |    |
| ACE                            | 13 (48%)             | 10 (56%)              | 0.763 |
| ARB                            | 4 (15%)              | 2 (11%)               | 0.544 |
| Calcium                        | 13 (48%)             | 8 (44%)               | 0.525 |
| Diuretic                       | 7 (26%)              | 6 (33%)               | 0.417 |
| Other                          | 7 (26%)              | 4 (22%)               | 0.594 |
| 2 or more antihypertensives    | 15 (56%)             | 10 (56%)              | 0.619 |
| Fish Oil                       | 3 (11%)              | 4 (22%)               | 0.412 |
| Statin                         | 7 (26%)              | 1 (6%)                | 0.119 |
| Creatinine (µmol/L)            | 154±85               | 194±107               | 0.184 |
| eGFR (mL/min/1.73m²)           | 49±23                | 40±25                 | 0.228 |
| <50 mL/min/1.73m²              | 15 (56%)             | 12 (67%)              | 0.543 |
| Systolic (mm Hg)               | 138±19               | 144±20                | 0.267 |
| Diastolic (mm Hg)              | 83±10                | 82±13                 | 0.873 |
| Proteinuria (g/day)            | 1.9±1.6              | 2.8±2.0               | 0.101 |

Table 2. Frequency of pathological features in the 45 biopsies.

| M | E | S | T |
|---|---|---|---|
| 0 | 16 (36%) | 39 (85%) | 13 (29%) | 20 (45%) |
| 1 | 29 (64%) | 6 (15%) | 32 (71%) | 15 (33%) |
| 2 | - | - | - | 10 (22%) |
Table 3. Univariate analysis – Factors associated with treatment with immunosuppressive therapy.

| Variables                      | OR   | 95% CI       |
|-------------------------------|------|--------------|
| Ethnicity                     | 0.64 | 0.082–5.01   |
| eGFR <50 mL/min/1.73 m²       | 1.6  | 0.46–5.53    |
| Proteinuria                   |      |              |
| More than 1g                  | 10.0 | 1.15–86.95   |
| Histology                     |      |              |
| M                             | 4.64 | 1.09–19.82   |
| E                             | 1.60 | 0.29–8.98    |
| S                             | 1.75 | 0.45–6.88    |
| T0                            | 0.31 | 0.09–1.10    |
| T1                            | 3.5  | 0.96–12.78   |
| T2                            | 1.0  | 0.24–4.20    |
| Necrotizing lesions           | 10.0 | 1.81–55.5    |
| Crescents                     | 8.80 | 2.22–34.96   |
| Necrotizing and/or crescents  | 11.44| 2.78–47.17   |

eGFR: estimated glomerular filtration rate.

Table 4. Multivariate analysis* – Factors associated with initiation of treatment with immunosuppression.

| Variables                                    | OR   | 95% CI     |
|----------------------------------------------|------|------------|
| More than 1 g/day proteinuria                 | 6.513| 0.52–80.88 |
| Mesangial hypercellularity                   | 2.247| 0.361–14.00|
| Absence of tubulointerstitial fibrosis       | 0.323| 0.60–1.728 |
| Necrotizing and/or crescent lesions           | 9.99 | 1.993–50.06|

*Adjusted for more than 1 g/day proteinuria, Mesangial hypercellularity, Absence of tubulointerstitial fibrosis (T0), and presence of either crescent and/or necrosis

Figure 2. Kaplan–Meier (K-M) curves of time to ESRD and time to 50% rise in serum creatinine, by immunosuppression status.

ESRD: End-stage renal disease.
Table 5. Factors associated with primary outcomes.

| Variables                                      | Hazard Ratio | 95% CI       |
|------------------------------------------------|--------------|--------------|
| **Factors associated with ESRD**              |              |              |
| Unadjusted                                     |              |              |
| Not immunosuppressed                           | 1.0          |              |
| Immunosuppressed                              | 0.829        | 0.241–2.86   |
| Adjusted<sup>a</sup>                           |              |              |
| Immunosuppressed                              | 0.832        | 0.226–3.07   |
| eGFR <50 mL/min/1.73 m<sup>2</sup> (start)     | 9.39         | 0.95–92.40   |
| More than 1 g/day proteinuria                  | 2.71         | 0.496–14.753 |
| Mesangial hypercellularity                    | 0.379        | 0.100–1.441  |
| T0 (compared to T1/T2)                        | 0.067        | 0.008–0.578  |
| Necrotizing lesions and/or crescents           | 1.857        | 0.189–18.257 |
| **Factors associated with a 50% rise in serum creatinine** | | |
| Unadjusted                                     |              |              |
| Not immunosuppressed                           | 1.0          |              |
| Immunosuppressed                              | 0.842        | 0.208–3.40   |
| Adjusted<sup>*<sup>  |              |              |
| Immunosuppressed                              | 0.682        | 0.084–5.510  |
| eGFR <50 mL/min/1.73 m<sup>2</sup>             | 7.733        | 0.908–65.85  |
| >1 g/day proteinuria                           | 5.989        | 0.463–19.48  |
| Mesangial hypercellularity                    | 0.671        | 0.087–5.201  |
| T0                                            | 0.064        | 0.004–1.162  |
| Necrotizing lesions and/or crescents           | 1.610        | 0.187–13.897 |

<sup>*Cox regression adjusted for immunosuppression, baseline EGFR, proteinuria, mesangial hypercellularity, tubulointerstitial fibrosis, and presence of necrotizing and/or crescents.</sup>

ESRD: End-stage renal disease, eGFR: estimated glomerular filtration rate.

Figure 3. Kaplan–Meier (K-M) curves of time to ESRD and 50% rise in serum creatinine in those with T0 lesions.

ESRD: End-stage renal disease.
Nine of the 18 immunosuppressed patients suffered an adverse event with three patients having two complications. Adverse events included lower respiratory tract infections, urinary tract infections, diarrhea, shingles, and two individuals required alteration of immunosuppression due to leukopenia. There were no fatalities. Only one person from the non-immunosuppressed group had an adverse event which was a fatal cardiac arrest.

**Discussion**

The Oxford Classification of IgA nephropathy has demonstrated the importance of MEST lesions as important pathological variables predicting renal outcomes. Its use has also been validated in other population groups. However, the impact of this classification method on treatment choice has not been clearly determined. In this study, the use of the Oxford Classification did not aid decision-making process in meriting the use of immunosuppression. This may be explained by a few key differences.

First, compared to the Oxford study, our population was slightly older (48 vs. 38 years), more hypertensive patients (62% vs. 31%) with greater proteinuria (2.3 vs. 1.7 g/day) and lower eGFRs (45 vs. 83 mL/min/1.73 m²). This difference may partly be explained by patients in this cohort being older with age-related glomerular functional changes and having more advanced kidney at the time of their renal biopsy. This also raises the question if the reason for the biopsy was triggered by a recent precipitous decline in renal function, following a prolonged period of monitoring. The natural history of IgA nephropathy is difficult to appreciate due to the variation created by different biopsy practices. This introduces potential lead-time bias in estimates of kidney survival. Ideally, a prospective study of an independent population will allow more meaningful conclusions to be made. However, given the slow progression of IgA disease, such a study will take long time. In addition, only 64% of our population were treated with RAAS inhibition. Forty-six percent of patients were on calcium channel blockers for blood pressure control at the time of biopsy, and these patients were allowed to continue with its use if blood pressure was adequately controlled. RAS blockade was introduced thereafter if patients tolerated the additional antihypertensive effects. Although there is no definitive evidence of RAS inhibition reducing the incidence of ESRD, it has been shown to reduce proteinuria and delay the rate of eGFR decline. Thus, it remains

| Proteinuria (g/day) | P    | eGFR (mL/min/1.73 m²) | P    | Systolic BP (mm Hg) | P    |
|--------------------|------|----------------------|------|--------------------|------|
| M0                 | 1.8±1.5 | 0.158 | 49±25 | 0.516 | 138±19 | 0.469 |
| M1                 | 2.6±1.9 | 0.076 | 44±23 | 0.034 | 141±20 | 0.936 |
| E0                 | 2.1±1.7 | 0.757 | 42±22 | 0.559 | 140±19 | 0.950 |
| E1                 | 3.5±2.2 | 0.685 | 47±25 | 0.001 | 138±18 | 0.696 |
| S0                 | 2.4±2.1 | 0.409 | 41±16 | 0.017 | 141±19 | 0.018 |
| S1                 | 2.2±1.7 | 0.017 | 47±25 | 0.821 | 142±15 | 0.013 |
| T0                 | 2.4±1.9 | 0.017 | 33±16 | 0.675 | 135±19 | 0.012 |
| T1                 | 2.2±1.9 | 0.685 | 41±16 | 0.675 | 135±19 | 0.675 |
| T2                 | 2.5±1.6 | 0.409 | 43±27 | 0.586 | 149±21 | 0.173 |
| Crescents          | 2.6±1.9 | 0.409 | 43±27 | 0.586 | 149±21 | 0.173 |
| No crescents       | 2.1±1.7 | 0.017 | 47±22 | 0.821 | 154±21 | 0.013 |
| Necrotizing        | 3.5±2.1 | 0.017 | 42±22 | 0.821 | 137±18 | 0.013 |
| No necrosis        | 1.9±1.6 | 0.017 | 45±24 | 0.675 | 149±20 | 0.012 |
| Necrosis and/or crescents | 2.7±2.0 | 0.173 | 44±26 | 0.675 | 135±19 | 0.173 |
| Neither            | 1.9±1.6 | 0.173 | 47±23 | 0.675 | 135±19 | 0.173 |
the mainstay of treatment and physicians should strive to replace existing antihypertensive agents with a RAS inhibitor.

In our study, only patients graded with mesangial hypercellularity (M1), as defined by the Oxford Classification, was the only criteria that was associated with a higher likelihood of being treated with immunosuppression. Although the Oxford study demonstrated it was independently associated with GFR loss, our findings were not congruent.\(^4\) Similarly, the other lesions of endocapillary proliferation and segmental sclerosis were not identified as being associated with either primary endpoints. Notably, there was a marked reduction in the risk of reaching the renal endpoints in the absence of tubular atrophy/interstitial fibrosis (T0) compared to those graded as T1 or T2. This is in keeping with previous studies which have identified tubulointerstitial lesions as an important prognostic factor in the long-term prognosis of this disease.\(^7\)

Seventeen of 18 patients immunosuppressed received a combination of prednisolone and MMF. The use of MMF has produced heterogeneous results.\(^11\) The lack of benefit demonstrated in our study may be due to the relatively advanced disease in our group with similar eGFR to those in Frisch G’s study (45 vs. 38 mL/min/1.73 m\(^2\)).\(^11\) Furthermore, mycophenolic acid levels were not measured to assess if patients were adequately dosed. Conversely, Tang S showed benefit in Chinese patients with IgA by producing a significant and sustained reduction in proteinuria, though no difference was observed in creatinine clearance. These contrasting results may be explained by this group having less advanced disease with a mean eGFR of 69 mL/min/1.73 m\(^2\) and/or raises the prospect of racial differences influencing response to treatment.\(^12\)

Patients who were immunosuppressed were more likely to have >1 g/day of proteinuria, have crescents and/or necrotic lesions and more mesangial hypercellularity on histology. Thus, these patients are clinically and pathologically more severe than those who did not receive immunosuppression. However, renal outcomes were similar between the two groups suggesting that the use of immunosuppression may have augmented their clinical course favorably.

Shen study showed in a repeat biopsy based observation study of 60 patients that crescents and necrosis are reversible with immunosuppression.\(^13\) These lesions also demonstrated a higher hazard for both renal end points, similar to findings from a Japanese study.\(^14\) Likewise, in a retrospective study by Walsh M of 146 patients, the presence of any crescents (cellular or fibrocellular) was identified as a predictor of composite end point of ESRD and/or doubling of serum creatinine.\(^15\) Although some authors have reported crescents can be seen in benign disease, as they can also occur in those with isolated microhematuria.\(^16\) Crescents were excluded from the Oxford Classification. Equally, due to the low incidence of necrosis, necrotic lesions too were also excluded.\(^4,14\)

Consistent with several other studies, the presence of crescents and/or necrosis was also shown to be associated with a higher incidence of hypertension (149 vs. 135 mm Hg) and greater proteinuria (2.7 vs. 1.9 g/day) at presentation suggesting that their prognosis may be worse. Currently, the lack of a uniform nomenclature and meaningful definitions of proliferative subsets of disease hampers future trial designs and investigations into the natural history of such disease subsets. Our findings suggest that the presence of extracapillary proliferation needs to be incorporated into future histological grading systems as this carries prognostic significance and influences the decisions to commence immunosuppressive therapy.

A relevant observation in our study was the relative high number of adverse events observed in the immunosuppressive group, especially the incidence of infective complications. Although there were no fatalities, these findings further re-enforce the risks of undertaking such treatment options.

Our study has several limitations. The dataset had small numbers and was obtained retrospectively. Almost all participants were Caucasian and thus cannot extrapolate these findings
to other ethnic populations. In addition, the compliance with treatment is unclear. Finally, due to the small sample size and relatively short follow-up, the small difference in outcomes could have been due to chance alone.

Conclusion

The use of the Oxford Classification did not aid decision-making with regard to the use of immunosuppression. Although the presence of T0 was associated with a lower risk of developing ESRD or a 50% rise in serum creatinine, the use of immunosuppression did not alter the trajectory of the disease. Necrotizing lesions and/or crescents increased the likelihood of being prescribed immunosuppression, but the benefit is unclear. Given their influence on physician decision making, there is a need for such lesions to be evaluated further in large cohorts and incorporated into future disease classifications.

Research Involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

Conflicts of interest: None declared.

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