
doi: 10.1093/ndt/gfu237
Advance Access publication 12 July 2014

Long-term outcome of anti-neutrophil cytoplasm antibody-associated glomerulonephritis: evaluation of the international histological classification and other prognostic factors

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ABSTRACT

Background. Anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis with renal involvement requires treatment with potentially toxic drugs to reduce morbidity and mortality, and there is a major challenge to determine clinical and histological features predictive of renal prognosis. The aim of our study was to evaluate the use of the 2010 international histological classification for ANCA-associated glomerulonephritis (AAGN) as a predictor of renal outcome when used in conjunction with other prognostic factors.

Methods. One hundred and four patients with AAGN treated at our centre were included: 23 were classified as focal, 26 as crescentic, 48 as mixed and 7 as sclerotic. Renal outcomes were based on estimated glomerular filtration rate (eGFR) at 1 and 5 years, and on renal survival.

Results. By univariate analysis, patients in the focal class had the best renal outcome, those in the sclerotic class the worst outcome, and those in the mixed and crescentic classes had intermediate renal survival. There was no significant difference in outcome between the mixed and crescentic classes. In multivariate models, histological class did not improve model fit or associate with renal outcome after adjusting for established prognostic factors. Lower percentage of normal glomeruli, greater degree of tubular atrophy (TA), MPO-ANCA positivity, increasing age and lower starting eGFR, all correlated with poorer renal outcomes.

Conclusions. We conclude that, in our cohort of patients, the international histological classification is predictive of renal outcome in AAGN, but did not appear to be additionally informative over other established prognostic factors in multivariate analysis. However, it may be of value to combine the current histological classification with other established parameters, such as TA and percentage normal glomeruli.

Keywords: ANCA, clinical outcome, glomerulonephritis, renal pathology, vasculitis
INTRODUCTION

The anti-neutrophil cytoplasm antibody (ANCA) associated vasculitides (AAV) are a group of multisystem disorders characterized by necrotizing inflammation of small blood vessels [1]. These include granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss syndrome) and renal limited vasculitis [2]. Renal manifestations, in particular rapidly progressive glomerulonephritis (GN), are a major cause of both morbidity and mortality. Rapidly progressive GN results in end-stage renal disease (ESRD) or death in over 50% of patients with AAV at 5 years, even with current treatment [4]. Renal biopsy remains the gold standard for diagnosis of renal vasculitis. Biopsies are characterized by necrotizing inflammation of small blood vessels [1]. These include granulomatosis with polyangiitis (GPA, formerly Wegener’s granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss syndrome) and renal limited vasculitis [2]. There is a reported untreated mortality of 80–90% [3].

Renal manifestations, in particular rapidly progressive glomerulonephritis (GN), are a major cause of both morbidity and mortality. Rapidly progressive GN results in end-stage renal disease (ESRD) or death in over 50% of patients with AAV at 5 years, even with current treatment [4]. Renal biopsy remains the gold standard for diagnosis of renal vasculitis. Biopsies are classically described as ‘pauci immune’, with a variety of histological features including extracapillary proliferation and fibrinoid necrosis, as well as varying degrees of glomerular sclerosis and tubular atrophy (TA).

One of the challenges of ANCA-associated glomerulonephritis (AAGN) is to ascertain clinical and histological features of prognostic value, including identification of pathological features in patients who may respond to immunotherapy. Previous studies have demonstrated a correlation between the proportion of normal glomeruli on biopsy and renal outcome [5-8] and shown that patients with biopsies demonstrating active inflammatory lesions, such as crescents, have an increased probability of response to immunosuppressive therapy [5]. The degree of glomerular sclerosis has also been shown to be predictive of renal outcome, with a higher degree of sclerosis correlating with a worse renal prognosis [9]. TA on presenting biopsy has been associated with poor renal outcome in a number of renal diseases, including AAV [10].

Treatment for AAV includes potentially toxic immunosuppressive agents, such as cyclophosphamide (CyP), and has been reported as being responsible for one-third of deaths in the first year following diagnosis [11], as well as conferring a long-term risk of malignancy. Immunosuppression is currently not tailored to biopsy findings. This is in contrast to lupus nephritis, for which treatment is adjusted according to histological classification [12]. A histological classification also exists for IgA nephropathy [13] and diabetic nephropathy [14], enabling not only the personal tailoring of therapy but also appropriate stratification and uniformity of reporting outcomes of clinical trials.

The classification of GN in AAV described by Berden et al. [15] in 2010, was the first histopathological classification for this disease. An international working group of renal pathologists divided biopsies into four subgroups: focal, crescentic, mixed and sclerotic, based on histological features on light microscopy. All biopsies were characterized as pauci-immune and included at least 10 glomeruli for analysis. The focal group was defined as those biopsies with ≥50% normal glomeruli. Biopsies in the crescentic group contained ≥50% crescents and those in the sclerotic group ≥50% globally sclerotic glomeruli. The mixed category included biopsies with <50% normal, <50% crescentic and <50% sclerotic glomeruli.

A validation study was carried out on 100 biopsies from patients recruited in various European Vasculitis Study Group (EUVAS) clinical trials to assess the prognostic value of this classification system [15]. Biopsies for this validation study were obtained from patients with at least 1 year of follow-up data, recruited at 32 centres across nine European countries. Results confirmed the prognostic value of the classification system over a 1- and 5-year-follow-up period, with patients in the sclerotic category experiencing the worst renal outcome with regard to both estimated glomerular filtration rate (eGFR) and renal survival, followed in order by the mixed, crescentic and focal groups.

Chang et al. [16] carried out a validation of this classification system in 121 AAV patients at a single centre in China [16]. This study confirmed the poorest prognosis in patients in the sclerotic group and the best outcome in the focal group; however, there were poorer outcomes in the crescentic group than in the mixed group, in contrast to the European cohort [15], perhaps related to differences in treatment.

Hilhorst et al. [17] also carried out a validation study in 164 patients from the Limburg renal registry. This study included only one patient in the sclerotic category, but confirmed the best prognosis in the focal group. In contrast with previous studies, there was no significant difference between the mixed and crescentic categories. There was poorer renal survival in both these categories when biopsies showed <25% normal glomeruli and the authors suggested that the prognostic value of the classification system could be improved by adding percentage normal glomeruli. Ellis et al. [18] also carried out a validation study at a single American centre. Seventy-six patients were included, 20 classified as focal, 18 crescentic, 27 mixed and 11 sclerotic. Histological class was found to be predictive of renal survival.

These studies have confirmed the use of the classification system as a predictor of renal outcome and progression to ESRD, but their differences highlight variation in different population groups and the need for further validation. We have a large and diverse population of AAV patients under follow-up in the vasculitis clinic. The aim of this study was to identify potential prognostic factors, including the international histological classification, for patient and renal outcomes at our centre.

MATERIALS AND METHODS

Patients

The study sample comprised 104 consecutive patients with renal biopsy proven GN due to AAV recruited from the vasculitis clinic between 1997 and 2011. All patients met the criteria for the Chapel Hill Consensus Conference definition of AAV [2]. Exclusion criteria were as follows: fewer than 10 glomeruli on biopsy, lost to follow-up within 1 year or additional renal diagnosis such as anti-glomerular basement antibody nephritis, IgA nephropathy or diabetic nephropathy. Patients who died within a year of follow-up were included in the study. If patients were lost to follow-up or died in the study period, their status at last available follow-up was recorded.
Data collection

Patient records and electronic data were reviewed retrospectively for age, gender, ethnicity, ANCA type, presenting renal function and renal function at 1 year, 5 years and last follow-up. Biopsy reports were obtained and classified using the algorithm described by Berden et al. [15]. There was a central read of patients’ biopsies by one experienced renal histopathologist who was blinded to outcome. Patients were divided into four groups according to this classification: focal, crescentic, mixed and sclerotic. Biopsies were categorized as crescentic based on the percentage of cellular crescents. In addition, the mixed group was subdivided according to percentage of normal glomeruli, those containing crescents, and sclerotic glomeruli in an attempt to investigate this subgroup further. Patents were also classified according to percentage TA into three groups: <20%, 20–50% and >50%. The eGFR was calculated using the four-variable Modification of Diet in Renal Disease study equation (MDRD4) [19]. Renal death was defined as the development of ESRD. We defined dialysis dependence at presentation if patients required dialysis within 48 h of their biopsy.

Treatment and outcomes

Patients were treated according to local vasculitis protocols. For patients treated between 1997 and 2006, treatment was as per established published protocols [20] and included induction with either oral or intravenous CyP in addition to oral prednisolone, followed by maintenance therapy with azathioprine and prednisolone from 3 months. Ninety-five per cent of our patients received CyP induction. All patients with life or organ threatening involvement, including pulmonary haemorrhage, cerebral vasculitis or serum creatinine >500 μmol/(5.7 mg/dL), also received plasmapheresis at induction. Overall, 28 of 104 patients underwent plasmapheresis. In 2006, a new protocol was introduced, incorporating the addition of the anti-CD20 agent rituximab as induction therapy in an attempt to reduce cumulative CyP and steroid exposure [21]. Thus, 41 patients received rituximab at induction. The clinical endpoints assessed were the development of ESRD and the eGFR at 1 and 5 years (calculated by MDRD4).

Statistical analyses

Variables are presented as mean (SD) or median [interquartile range (IQR)] according to their distribution. One-way analysis of variance, χ² test and Fisher’s exact test were used to compare continuous variables between groups and categorical data as appropriate. The Kaplan–Meier method was used to calculate the probability of renal survival. Log-rank tests were used to assess differences across categories of variables studied. All P-values are two sided, with significance defined as P < 0.05. Analyses were carried out using PRISM (version 4) and SPSS (version 19.0). Multivariable linear regression was used to examine the association between predesignated potential predictors of renal function at follow-up (baseline eGFR, age, ANCA class, degree of TA and histological class as a categorical variable), and eGFR at 1 and 5 years. Variables were retained in the model where there was an improvement in model fit. This was judged to have occurred where there was a significant reduction in the log likelihood (using a likelihood ratio test).

The association between histological classification (as a categorical variable) and renal survival (i.e. death censored renal replacement therapy) was estimated using a Cox proportional hazards model before and after adjustment for baseline eGFR. Departure from the proportional hazards assumption was tested by examining Schoenfeld residuals both globally and for each covariate.

RESULTS

One hundred and four patients with adequate histology and at least 1 year of follow-up, or death within the first year, were included in the study. The average age was 62.2 years (range 17.3–87.2) and 58% were male. There were similar proportions of patients with MPO-ANCA and PR3-ANCA, and the median time of follow-up was 49.9 months (range 0.1–182.4).

Histological classification

According to the classification system proposed by Berden et al. [15, 22] patients were classified as focal, 26 as crescentic, 48 as mixed and 7 as sclerotic. Table 1 illustrates baseline characteristics of patients according to histological classification. Seventy-six per cent of the patients reported their ethnic group as Caucasian, 14% as Indo-Asian and 6% as Afro-Caribbean. Eight patients were dialysis dependent at the time of renal biopsy. These included five patients in the crescentic category, three of whom made a renal recovery, two in the sclerotic group of whom one made a renal recovery and one in the mixed category who did not recover renal function. The percentage of deaths at last follow-up was similar in the focal (17.4%) and the crescentic (17.1%) category, but higher in the mixed (35.4%) and sclerotic (42.9%) category.

Figure 1 (a) demonstrates renal function in the four histological categories at presentation, 1 year and 5 years. A significant difference is demonstrated across the four categories in terms of eGFR at presentation and at 1 year, and in the change in eGFR at 1 year. There remained no statistically significant differences across groups in terms of eGFR at 5 years, although the change in eGFR at 5 years remained significant. Numbers for analysis at this time point were, however, limited to 42 patients.

Figure 1 (b) illustrates renal survival by histological class and shows significantly different survival across classes with the best outcomes in the focal class, followed sequentially by mixed, crescentic and sclerotic classes (log-rank P = 0.01). At 1 year, there was 100% renal survival in the focal class, 85% in the mixed class, 74% in the crescentic class and 50% in the sclerotic class. At 5 years, there remained 100% renal survival in the focal class, with 77% in the mixed, 74% in the crescentic and only 25% in the sclerotic class. However, on longer term follow-up, renal survival was better in the crescentic than the mixed class.

We subdivided the mixed group further by percentage crescents (< or >20%), percentage normal glomeruli (< or >20%) and percentage sclerotic glomeruli (< or >20%). Using these subdivisions, there was significantly lower eGFR at 1 year for...
patients in the mixed class with <20% crescents compared with those with >20% crescents. This is consistent with the finding of greatest overall improvement at 1 year in eGFR in patients in the crescentic class. When dividing the mixed class by percentage sclerotic glomeruli, there was a significantly lower eGFR at 5 years with a greater percentage of sclerotic glomeruli.

**Percentage normal glomeruli**

Figure 2 (a) demonstrates eGFR at presentation, 1 year and 5 years according to the percentage of normal glomeruli at presentation. There was a statistically significant difference across groups at presentation and 1 year with a greater proportion of normal glomeruli correlating with better eGFR. The difference failed to reach significance at 5 years, likely because of the reduced numbers at this time point. There was significantly improved renal survival with increasing proportion of normal glomeruli (log-rank P = 0.005) (Figure 2b).

**Tubular atrophy**

The effect of the degree of TA on renal outcome at 1 year and 5 years was assessed and is demonstrated in Figure 3 (a). Biopsies were divided according to degree of TA into three groups: (i) TA < 20%, (ii) 21–50% and (iii) >50%. There was a statistically significant difference in eGFR at both 1 and 5 years when patients were divided by degree of TA. There was also significantly improved renal survival with reducing degrees of TA at presentation (log-rank P = 0.04) (Figure 3b).

**Tubulointerstitial nephritis**

There was no statistically significant difference in renal survival between patients with active tubulointerstitial nephritis on their biopsies when compared with those without.

**ANCA type**

We assessed the impact of ANCA type on outcome and demonstrated a significantly improved renal survival in patients

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**Table 1. Baseline clinical and pathological characteristics according to histological classification**

<table>
<thead>
<tr>
<th></th>
<th>Focal</th>
<th>Crescentic</th>
<th>Mixed</th>
<th>Sclerotic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>26</td>
<td>48</td>
<td>7</td>
<td>104</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>61.2</td>
<td>54.9</td>
<td>66.3</td>
<td>66.6</td>
<td>62.2</td>
</tr>
<tr>
<td>(range)</td>
<td>(28.9–80.4)</td>
<td>(17.3–74.3)</td>
<td>(23.7–87.2)</td>
<td>(51.1–76.9)</td>
<td>(17.3–87.2)</td>
</tr>
<tr>
<td>Male sex n (%)</td>
<td>10 (43)</td>
<td>15 (58)</td>
<td>29 (60)</td>
<td>4 (57)</td>
<td>58 (56)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian n (%)</td>
<td>19 (83)</td>
<td>16 (61)</td>
<td>37 (77)</td>
<td>4 (57)</td>
<td>76 (73)</td>
</tr>
<tr>
<td>Indo-Asian n (%)</td>
<td>2 (9)</td>
<td>6 (23)</td>
<td>5 (10)</td>
<td>1 (14)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Afro-Caribbean n (%)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>2 (4)</td>
<td>1 (14)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>1 (4)</td>
<td>2 (8)</td>
<td>4 (8)</td>
<td>1 (14)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>ANCA status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR3 ANCA (%)</td>
<td>7 (30)</td>
<td>17 (65)</td>
<td>24 (50)</td>
<td>1 (14)</td>
<td>49 (47)</td>
</tr>
<tr>
<td>MPO ANCA (%)</td>
<td>14 (60)</td>
<td>8 (31)</td>
<td>22 (46)</td>
<td>5 (71)</td>
<td>49 (47)</td>
</tr>
<tr>
<td>ANCA negative</td>
<td>2 (9)</td>
<td>1 (4)</td>
<td>2 (4)</td>
<td>1 (14)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>51.5</td>
<td>19.5</td>
<td>28.3</td>
<td>13.5</td>
<td>30.3</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean total glomeruli</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>24.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Normal (%)</td>
<td>65.5</td>
<td>26.9</td>
<td>17.0</td>
<td>2.3</td>
<td>26.8</td>
</tr>
<tr>
<td>Crescents (%)</td>
<td>9.6</td>
<td>67.7</td>
<td>21.6</td>
<td>15.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Sclerotic (%)</td>
<td>15.3</td>
<td>5.0</td>
<td>19.2</td>
<td>59.1</td>
<td>15.7</td>
</tr>
<tr>
<td>TA (%)</td>
<td>18.4</td>
<td>8.8</td>
<td>23.9</td>
<td>46.4</td>
<td>19.5</td>
</tr>
<tr>
<td>Median time of follow in months (range)</td>
<td>38.0 (0.4–182.4)</td>
<td>62.9 (0.3–146.3)</td>
<td>39.4 (0.8–166.7)</td>
<td>64.5 (0.1–149.6)</td>
<td>49.9 (0.07–182.4)</td>
</tr>
</tbody>
</table>

**Figure 1:** (a) eGFR by histological class at presentation, 1 year and 5 years. (b) Kaplan–Meier curve demonstrating renal survival by histological class.
who had PR3-ANCA compared with those with MPO-ANCA (log-rank \( P = 0.03 \)) (Figure 4).

**Age**

The effect of age of the patients was assessed and showed a significantly worse renal survival with increasing age (log-rank \( P = 0.04 \)).

**Baseline eGFR**

When the effect of eGFR at baseline was assessed, there was significantly improved renal survival with higher baseline eGFR, (log-rank \( P = 0.0001 \)).

**Treatment**

There was no difference in outcome when dividing patients into those treated before and after the introduction of rituximab as an induction agent in 2006.

Multivariate analysis

Results of multivariable models of eGFR at 1 year and at 5 years (Table 2) demonstrate that after adjustment for age,
baseline eGFR and TA, the association between histological class and renal function at follow-up was no longer significant. Furthermore, inclusion of the histological class variable did not improve the model fit. In a sensitivity analysis, addition of the histological class variable to the model before the inclusion of TA did not result in a significant improvement in model fit in either the 1- or 5-year outcome models. Although histological class predicted renal survival in the Kaplan–Meier survival model, this association was no longer apparent after adjustment for baseline GFR in a Cox proportional hazards model (Table 3). Models were also constructed to predict eGFR at 1 and 5 years including baseline eGFR, age and the histological classification without TA. Using these models, histological class was not found to be a significant contributor to renal outcome at either 1 or 5 years (Supplementary Table 1).

Table 2. Multivariable models of eGFR at 1 and 5 years

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>1 year</th>
<th>P-value for LR test versus previous model</th>
<th>5 years</th>
<th>P-value for LR test versus previous model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \beta )</td>
<td>95% CI</td>
<td></td>
<td>( \beta )</td>
</tr>
<tr>
<td>1</td>
<td>Baseline eGFR</td>
<td>0.73</td>
<td>0.53–0.92</td>
<td>&lt;0.005</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>Baseline eGFR</td>
<td>0.67</td>
<td>0.49–0.85</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>–0.58</td>
<td>–0.83–0.32</td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>3</td>
<td>Baseline eGFR</td>
<td>0.62</td>
<td>–16.55 to –2.85</td>
<td>0.005</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>–0.52</td>
<td>–0.77–0.26</td>
<td></td>
<td>–0.67</td>
</tr>
<tr>
<td></td>
<td>TA (per tertile)</td>
<td>–9.70</td>
<td>–16.55–2.85</td>
<td></td>
<td>–9.11</td>
</tr>
<tr>
<td>4</td>
<td>Baseline eGFR</td>
<td>0.64</td>
<td>0.42–0.85</td>
<td>0.43</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>–0.49</td>
<td>–0.77 to –0.26</td>
<td></td>
<td>–0.56</td>
</tr>
<tr>
<td></td>
<td>Histological class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sclerotic</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crescentic</td>
<td>13.38</td>
<td>5.01–31.77</td>
<td></td>
<td>19.01</td>
</tr>
</tbody>
</table>

Table 3. Cox proportional hazards model for predicted renal survival

<table>
<thead>
<tr>
<th>Sclerotic (reference)</th>
<th>HR</th>
<th>SE</th>
<th>( Z )</th>
<th>( P &gt; Z )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sclerotic (reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crescentic</td>
<td>0.55</td>
<td>0.40</td>
<td>–0.82</td>
<td>0.412</td>
<td>0.13–2.29</td>
</tr>
<tr>
<td>Mixed</td>
<td>0.65</td>
<td>0.44</td>
<td>–0.64</td>
<td>0.523</td>
<td>0.17–2.45</td>
</tr>
<tr>
<td>Focal</td>
<td>0.66</td>
<td>0.83</td>
<td>–0.33</td>
<td>0.742</td>
<td>0.06–7.59</td>
</tr>
<tr>
<td>eGFR at presentation</td>
<td>0.92</td>
<td>0.02</td>
<td>–3.20</td>
<td>0.001</td>
<td>0.87–0.97</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; CI, confidence interval.

DISCUSSION

This large single-centre study was carried out with the aim of assessing the long-term prognostic value of the 2010 international histological classification [15], together with other prognostic factors, in our cohort of patients with AAGN. By univariate analysis, we found a significant difference in renal outcome by histological category. The poorest prognosis was in patients in the sclerotic class at all time points and the best prognosis was in the focal class. This is in accordance with the validation studies carried out by Berden et al. [15] and Chang et al. [16]. The recent validation paper from Hilhorst et al. [17] did not comment on the sclerotic category as there was only one patient in this group. Similarly to their study, we found no significant difference in outcome between mixed and crescentic categories.

Our study includes 48 patients in the mixed category, compared with 16 in the Berden study [15, 23] and in the Chang study [16] and 39 in the Hilhorst study [17]. In contrast to the Dutch cohort [17], there were no differences seen when subdividing the mixed group by percentage normal glomeruli. However, we observed better renal function at 1 year in patients with >20% crescents, perhaps reflecting response to treatment and worse renal function at 5 years with >20% sclerotic glomeruli, consistent with the poor outcome in the sclerotic class.

The EUVAS cohort [15] demonstrated better outcomes in the crescentic class than the mixed class, while the Chinese validation cohort [16] showed better outcome in the mixed class. It is difficult to directly compare the results of these groups, however, as there are known differences in disease manifestations in AAV patients in different ethnic groups. European and Chinese patients with AAV have been shown to have different human leucocyte antigen associations [24]. AAV patients who are positive for antibodies to myeloperoxidase have also been demonstrated to experience poorer renal outcomes than those with antibodies to PR3 [22]. The Chinese cohort [16] included 89% of patients who were MPO ANCA positive and this may have impacted upon results. Variations in treatment may also have affected outcomes in these studies.

Despite these differences in univariate analysis, when included in multivariate models histological category did not improve model fit or associate with renal outcome after adjustment for established prognostic factors such as age, baseline eGFR and TA. This suggests that the histological classification alone does not provide additional clinically useful information in our cohort, and is in contrast to the results of the EUVAS validation cohort.

Possible reasons for the differences between our study and the validation study by Berden et al. [15] include: (i) the use of a categorical rather than continuous variable to examine associations of the classification system, (ii) the use of formal
likelihood tests to judge model fit and (iii) examination of histology in a different group of patients receiving different management. In our study, although the sclerotic class predicted outcome in univariate analyses examining follow-up eGFR and ESRD, this lesion also had a strong association with lower baseline GFR and increased TA on biopsy. In multivariable models, it was one or both of these latter measures, rather than the international histological classification, that was independently associated with the outcomes we observed.

In terms of other prognostic factors, age, eGFR and percentage of normal glomeruli were found to be important in our study. Patients presenting with an eGFR of <15 mL/min or who were dialysis dependent experienced a markedly reduced renal survival over the entire study, and elderly patients also experienced poorer outcomes. There was improved renal outcome in patients with a greater percentage of normal glomeruli at presentation. These findings are in accordance with previous publications [7, 23, 25].

The majority of the literature on AAGN focuses on the evolution of glomerular pathology. We found a significant association between the degree of TA and renal outcome. This observation supports the findings of Berden et al. who found TA to be a significant predictor of renal outcome at 1 year in patients treated with rituximab [10]. We also divided patients by ANCA type and demonstrated improved renal survival in patients with PR3-ANCA compared with MPO-ANCA positivity. Patients with PR3-ANCA positivity have previously been reported as having a better long-term renal outcome [26], and PR3-ANCA and MPO-ANCA positive AAV are increasingly considered as genetically distinct disease subsets [27].

This study has the advantage of being from a single centre, with unselected patients, uniformity of treatment and processing of samples, but has the limitation of being a retrospective analysis. Our analysis of eGFR at follow-up is not ideal due to the use of only two time-points for each analysis. Patients who did not have follow-up at these points were excluded and may have been additionally informative. Although a mixed-model approach would account for missing data, and would likely increase the power of such an analysis, we used a simple linear regression approach in an attempt to replicate the analysis by Berden et al. [15]. Further validation in different populations would be of value, and larger numbers are needed, particularly in the mixed category.

In conclusion, although univariate analysis of our study, showed a difference in terms of renal outcome according to histological class, this was not confirmed on multivariate analysis including clinical and histological parameters such as baseline eGFR and TA. In addition, we confirm the effect of ANCA type on renal outcome. However, our cohort included only 104 patients, so numbers in each category and particularly in the sclerotic category were limited. Further validation studies in large varied populations need to be carried out in order to determine the histological classification’s overall clinical utility.

SUPPLEMENTARY DATA
Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS
We acknowledge support from the NIHR Imperial Biomedical Research Centre. We would like to thank all colleagues and patients attending the vasculitis clinic. F.W.K.T. is supported by the Diamond Fund from Imperial College Healthcare Charity. R.M.T. is supported by a Clinician Scientist Fellowship from Arthritis Research UK. This work has been presented in part at the Annual Meeting of the American Society for Nephrology 2012, USA, and the International ANCA and Vasculitis Workshop 2013, Paris, France.

CONFLICT OF INTEREST STATEMENT
None declared.

REFERENCES

Received for publication: 7.11.2013; Accepted in revised form: 10.6.2014