# ANCA-associated vasculitis: On clinical management and renal outcome

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# HISTOPATHOLOGICAL CLASSIFICATION OF ANCA-ASSOCIATED GLOMERULONEPHRITIS: INTEROBSERVER VARIABILITY AND CLINICAL OUTCOME

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*Submitted for publication*

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## ABSTRACT

**Introduction:** Renal involvement is very common in antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis (AAV). Therefore, a histopathological classification of ANCA-associated glomerulonephritis was developed, which consisted of the classes: focal, crescentic, mixed, and sclerotic. This classification was associated with renal outcome. Subsequent validation studies showed contradiction regarding the crescentic and mixed classes and the association with renal outcome. Here, we present a worldwide validation study and also analysed interobserver variability.

**Methods:** We included 145 patients from 10 centers worldwide with at least five glomeruli in their diagnostic renal biopsy. Seven pathologists scored renal biopsies of patients to determine the histopathological classification and to evaluate tubulointerstitial parameters. In addition, clinical data was collected. The primary outcome of the study was renal function at 5 years ($eGFR_5$). Interobserver variability was a secondary outcome.

**Results:** Renal function at baseline and during follow-up were most favorable in the focal class and worst in the sclerotic class, consistent with primary findings. However, there was no difference between crescentic and mixed class regarding renal function at baseline and during follow-up. A multivariate analysis showed that the best model for predicting $eGFR_5$ included $eGFR_0$, having sclerotic class, age, $proteinuria_0$, and interstitial fibrosis and tubular atrophy. There was a moderate agreement between the pathologists in classifying the diagnostic renal biopsies; kappa (κ) 0.56.

**Conclusions:** Our study showed a difference between focal and sclerotic class regarding renal outcome, but no difference between crescentic and mixed class. These findings show that the histopathologic classification of AAGN is a valuable tool in the management of patients with AAV, but needs further improvement to distinguish biopsies with crescentic and mixed features better.

## INTRODUCTION

The most common primary systemic small-vessel vasculitis in adults is antineutrophil cytoplasmic autoantibody (ANCA) associated vasculitis (AAV).[1] AAV includes granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). There is also a limited disease variant called renal limited vasculitis (RLV), which only affects the kidneys. In GPA around 20 percent of the patients have glomerulonephritis at presentation.[2] ANCA-associated glomerulonephritis (AAGN) occurs in approximately 80 to 90 percent of patients with GPA and MPA during the disease course.[1;2] Renal involvement in EGPA is less frequent and less severe.[3] Renal involvement in AAV has an important impact on morbidity and mortality.[4-8] AAGN can rapidly progress to renal failure, especially if treated inappropriately. Currently, 20 to 40% of patients with AAV develop end stage renal disease (ESRD).[9-11]

The gold standard for establishing a diagnosis of AAGN is a renal biopsy. Light microscopy shows necrotizing and crescentic glomerulonephritis accompanied by a pauci-immune pattern, i.e. a negative or subdued granular pattern for immunoglobulins and complement.[12;13] Electron microscopy shows degranulation of neutrophils and subendothelial edema due to endothelial injury with few or no immune deposits.[14] The amount of acute and chronic lesions in the renal biopsy may vary considerably from patient to patient. Also, patients' outcome varies considerably.[15;16] Several clinicopathologic studies showed substantial prognostic value of specific pathologic lesions –or the absence thereof– in renal biopsies for renal outcome in AAV.

Frequently described associations in the literature are: 1) percentage of normal glomeruli and favorable renal outcome, 2) percentage of sclerotic glomeruli and adverse renal outcome.[16-19] Moreover, the presence of cellular crescents, which indicates active disease, was associated with the probability of renal recovery with immunosuppressive therapy.[16;18] These findings led to the introduction of a histopathological classification of AAGN in 2010.[20] The classification is based on four categories named focal, crescentic, sclerotic and mixed class. Depending on the predominant glomerular phenotype, each renal biopsy with AAGN can be classified into one of these classes. The classification system was shown to be associated with ESRD and renal function at 1- and 5-year follow-up in the original study consisting of 100 patients.[20]

Since 2010, several validations studies in adult and pediatric cohorts worldwide have been published.[21-43] All these studies show that the focal class has the best renal

outcome, while the sclerotic class has the worst outcome.[25] Contradiction exists regarding the crescentic and mixed classes; in some studies, renal function was better in the crescentic class, whereas in others renal outcome was significantly better in the mixed class, and in addition some did not show a difference.[25] Because of this contradiction, a large international validation study consisting of a worldwide cohort was called for. We here present a worldwide validation study, driven by the original investigators, including a collaboration between 10 centers worldwide. In this study, we also analysed interobserver variability to investigate to what extent this could play a role in the hitherto described discrepancies.

## METHODS

### Study cohort

Patients from 10 centers worldwide were included. Inclusion criteria were: histopathologically proven AAGN, available diagnostic renal biopsy with at least five glomeruli and a follow-up of at least 3 years (including patients that developed ESRD or died within the first 3 years). Exclusion criteria were: age under 18 years, overlap syndrome (e.g., AAGN combined with anti-glomerular basement membrane disease), and participation in a previous validation study. This study was conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments.

### Diagnostic renal biopsies

Biopsy slides were collected at Leiden University Medical Center. All biopsies with at least five glomeruli were considered sufficient for this study, based on recent findings that biopsies containing three to nine glomeruli were also valid for the prognostic capability of the classification.[22] The biopsies were scanned with the Ultra-Fast Scanner (UFS) at a magnification of 40x. The scanned biopsy were uploaded on a highly secured website, where they were accessible only for a group of seven pathologists (FF, KJ, YO, SW, LHN, JAB and IMB). These pathologists, blinded to the clinical data, scored the biopsies independently. The scoring form (S Document 1 in the supplementary material) was a modified version of the original scoring form for AAGN that was published in 1996.[44] In short, the scoring consisted of the histopathological class, inflammatory infiltrates, interstitial fibrosis and tubular atrophy (IFTA), and tubulitis. Each case was scored by two pathologists. In case of disagreement between these two pathologists, a third pathologist (IMB or JAB) made the final decision on the case. For analytic purposes, tubulointerstitial scores from two pathologists were averaged and categorized as: inflammatory infiltrate in <25% or ≥25% of unscarred parenchyma; IFTA in <25% or ≥25% of cortical area; and tubulitis foci with <5 or ≥5 cells/tubular cross section.

### Clinical data

For each patient we retrieved the following data from the clinical records at participating centers: patient demographics, diagnosis (GPA, MPA, EGPA, or RLV), serum and urine laboratory values, and details on induction and maintenance therapy. Renal function was expressed as eGFR, calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, adjusted for race/ethnicity (Caucasian/Asian or other).[45-47] eGFR was calculated at the time of biopsy ($eGFR_0$) and at 1- and 5-year follow-up ($eGFR_1$ and $eGFR_5$, respectively). The eGFR calculation was omitted, when patients reached ESRD; in that case, eGFR was considered 0 for analytic purposes.

### Outcomes

The primary outcome of the study was renal function at 5 years ($eGFR_5$). Secondary outcomes were: renal function at 1 year ($eGFR_1$), renal relapse, ESRD, death and interobserver variability. A renal relapse was defined as a rise in serum creatinine of >30% or a fall in estimated glomerular filtration rate >25% and/or new hematuria or proteinuria (all attributable to active vasculitis), as indicated by the Birmingham Vasculitis Activity Score.[48-50] ESRD was defined as a need for renal replacement therapy (dialysis for at least three months or transplantation) or as an eGFR value below 15 mL/min that persisted for at least three months. Renal survival was expressed as the time between diagnosis and ESRD.

### Statistical analyses

Continuous variables were expressed as mean±SD. Categorical variables were expressed as numbers (%). Numerical data of groups were compared with the student's t-test or one-way analysis of variance. Categorical data of groups were compared with Fisher's exact test or the chi-square test. Renal survival was analyzed with the Kaplan Meier survival analysis and log-rank test. Pearson's correlation coefficients were calculated to identify variables correlating with $eGFR_5$. Stepwise multiple linear regression analysis was performed to find the best model for predicting $eGFR_5$. Interobserver agreement was investigated by calculating the κ for the histopathological classification, and the ICC for tubulointerstitial parameters. Values of κ or ICC were interpreted as following: >0.75, excellent agreement; 0.40-0.75, fair to good agreement; and <0.40, poor agreement.[51;52] All analyses were performed with SPSS version 23 (IBM Corp., Armonk, NY, USA). *P* values <0.05 were considered significant.

## RESULTS

### Patient characteristics

Histopathological and clinical data of 157 patients were collected. Twelve cases were excluded, because of missing clinical data or an insufficient number of glomeruli in the biopsy (i.e. less than five glomeruli). The baseline characteristics of the 145 included patients, all diagnosed between 1991 and 2011, are shown in Table 1.

**Table 1 | Characteristics of the total cohort**

| | **Total (*n*=145)** |
|---|---|
| Age at biopsy, year, mean±SD | 61.2±12.7 |
| Male (%) | 83 (57.2) |
| Diagnosis (%)[a] | |
| GPA | 63 (45.0) |
| MPA | 71 (50.7) |
| EGPA | 2 (1.4) |
| RLV | 4 (2.9) |
| Diagnostic delay, months, mean±SD | 3.1±9.0 |
| ANCA specificity (%)[b] | |
| PR3 | 50 (37.0) |
| MPO | 73 (54.1) |
| Negative | 6 (4.4) |
| Double positive | 6 (4.4) |
| Center | |
| Cochin Hospital, Paris | 6 (4.1) |
| General University Hospital in Prague | 38 (26.2) |
| Leiden University Medical Center, Leiden | 36 (24.8) |
| Medical University of Innsbruck | 7 (4.8) |
| Medical University of Vienna | 9 (6.2) |
| Necker Hospital, Paris | 4 (2.8) |
| Rigshospitalet Copenhagen | 7 (4.8) |
| Teinekeijnkai Hospital Sapporo | 7 (4.8) |
| JCHO Sendai Hospital, Sendai | 24 (16.6) |
| Weill Cornell Medical College New York | 7 (4.8) |

ANCA, antineutrophil cytoplasmic autoantibody; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RLV, renal-limited vasculitis; SD, standard deviation.
[a] The AAGN diagnosis was not further specified in 5 patients.
[b] ELISA test results were available in 135 patients.

### Histopathological classes and clinical parameters

Of the diagnostic biopsies, 52 (35.9%) were focal class, 37 (25.5%) crescentic class, 39 (26.9%) mixed class, and 17 (11.7%) were sclerotic class (Table 2). GPA predominated in the focal class, while MPA predominated in the mixed class. There was no difference between the crescentic and sclerotic class regarding the diagnosis. Although there was no significant difference in the prevalence of myeloperoxidase (MPO-)ANCA and proteinase-3 (PR3-)ANCA specificity among the classes, the crescentic and mixed class showed a predominance of MPO-ANCA, while the focal class showed a slight predominance of PR3-ANCA. MPO- and PR3-ANCA were found in equal numbers in the sclerotic class.

### Histopathological classes and renal function

Focal class had the highest eGFR at baseline (Table 2). After one and five year follow-up, focal class still had the highest eGFR. Sclerotic class had the lowest eGFR at baseline and during follow-up. Renal functions at baseline and during follow-up were not significantly different between the crescentic and mixed classes. Proteinuria at the time of the biopsy was lowest in the focal class, and comparable between the crescentic, mixed, and sclerotic class.

**Table 2 | Patient characteristics according to histopathological class**

| | Focal (*n*=52) | Crescentic (*n*=37) | Mixed (*n*=39) | Sclerotic (*n*=17) | P - value |
|---|---|---|---|---|---|
| Age at biopsy, year, mean±SD | 59.7±12.6 | 61.6±11.4 | 60.6±14.4 | 65.9±11.7 | 0.37 |
| Male (%) | 33 (63.5) | 24 (64.9) | 18 (46.2) | 8 (47.1) | 0.22 |
| Diagnosis (%)[a] | | | | | 0.005 |
| GPA | 33 (63.5) | 14 (40.0) | 8 (21.6) | 8 (50.0) | |
| MPA | 17 (32.7) | 19 (54.3) | 27 (73.0) | 8 (50.0) | |
| EGPA | 1 (1.9) | 0 (0.0) | 1 (2.7) | 0 (0.0) | |
| RLV | 1 (1.9) | 2 (5.7) | 1 (2.7) | 0 (0.0) | |
| ANCA specificity (%)[b] | | | | | 0.13 |
| PR3 | 23 (47.9) | 13 (37.1) | 7 (19.4) | 7 (43.8) | |
| MPO | 19 (39.6) | 21 (60.0) | 25 (69.4) | 8 (50.0) | |
| Negative | 3 (6.3) | 0 (0.0) | 3 (8.3) | 0 (0.0) | |
| Double positive | 3 (6.3) | 1 (2.9) | 1 (2.8) | 1 (6.3) | |
| Diagnostic delay, months, mean±SD | 4.7±12.9 | 1.4±2.7 | 2.4±3.2 | 3.6±11.5 | 0.39 |
| $eGFR_0$, ml/min/1.73 $m^2$, mean±SD | 49.9±29.3 | 18.0±15.7 | 26.7±18.6 | 19.4±11.8 | <0.001 |
| Proteinuria class at biopsy (%)[c] | | | | | 0.005 |
| Normal | 4 (8.7) | 1 (3.1) | 2 (5.3) | 0 (0.0) | |
| Moderately increased | 18 (39.1) | 4 (12.5) | 3 (7.9) | 3 (18.8) | |
| Severely increased | 24 (52.2) | 27 (84.4) | 33 (86.8) | 13 (81.3) | |
| $eGFR_1$, ml/min/1.73 $m^2$, mean±SD | 61.4±23.9 | 37.3±20.6 | 37.7±21.1 | 20.3±16.0 | <0.001 |
| $eGFR_5$, ml/min/1.73 $m^2$, mean±SD | 59.7±21.1 | 34.9±20.4 | 37.3±23.7 | 19.3±20.0 | <0.001 |
| Renal relapse during follow-up (%) | 20 (40.0) | 14 (40.0) | 11 (28.9) | 3 (18.8) | 0.33 |
| ESRD during follow-up (%) | 1 (1.9) | 9 (24.3) | 6 (15.4) | 8 (47.1) | <0.001 |
| Death during follow-up (%) | 15 (28.8) | 15 (40.5) | 9 (23.1) | 6 (35.3) | 0.40 |

ANCA, antineutrophil cytoplasmic autoantibody; $eGFR_{0/1/5}$, estimated glomerular filtration rate at baseline, at 1 year and at 5 years respectively; EGPA, eosinophilic granulomatosis with polyangiitis; ESRD, end-stage renal disease; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3; RLV, renal-limited vasculitis; SD, standard deviation.

[a] The AAGN diagnosis was not further specified in 5 patients.

[b] ELISA test results were available in 135 patients.

[c] In accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines, normal level of proteinuria was defined as protein excretion of <0.15 g/day, or as a negative protein dipstick test; moderately increased proteinuria was defined as a protein excretion rate of 0.15–0.50 g/day, or as trace on protein dipstick test; severely increased proteinuria was defined as total protein excretion >0.50 g/day, or as + or more on protein dipstick. The proteinuria class could be determined in 132 patients.

### Predictors of renal function in time

Variables significantly associated with $eGFR_5$ were: age, clinical diagnosis (MPA or GPA), ANCA serology (MPO-ANCA or PR3-ANCA), $eGFR_0$, the amount of proteinuria at time of biopsy, the histopathological classification, the extent of interstitial infiltrate, the amount of interstitial fibrosis and tubular atrophy (IFTA), and the amount of tubulitis. When performing a stepwise multivariate regression analysis, the best predicting model for $eGFR_5$ included $eGFR_0$, having sclerotic class, age, $proteinuria_0$, and IFTA (Table 3).

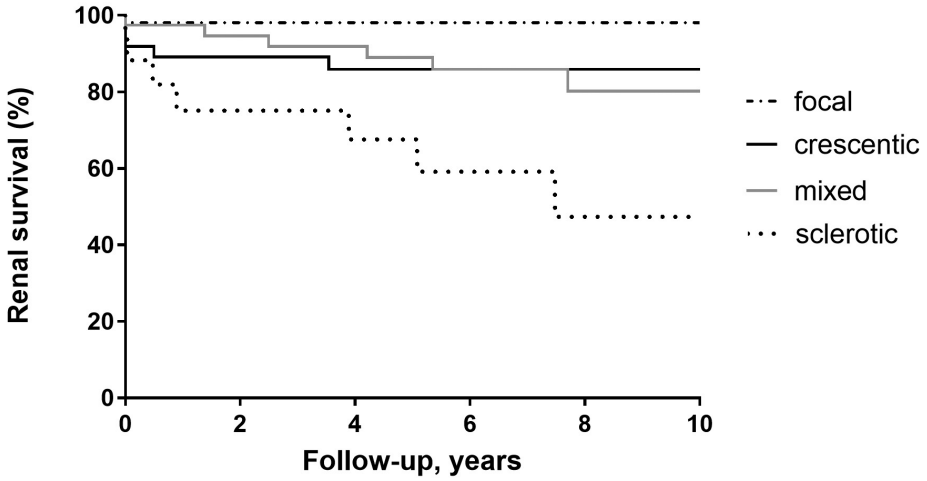
**Table 3 | Multivariate prediction models of $eGFR_5$**

| Variable | Model 1 ($R^2$ = 0.43) | | Model 2 ($R^2$ = 0.48) | | Model 3 ($R^2$ = 0.50) | | Model 4 ($R^2$ = 0.55) | | Model 5 ($R^2$ = 0.56) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | β | P-value | β | P-value | β | P-value | β | P-value | β | P-value |
| $eGFR_0$ | 0.65 | <0.001 | 0.61 | <0.001 | 0.56 | <0.001 | 0.49 | <0.001 | 0.41 | <0.001 |
| Histopathological classification[a] Sclerotic | | | -0.23 | 0.001 | -0.22 | 0.002 | -0.22 | 0.002 | -0.17 | 0.02 |
| Age | | | | | -0.15 | 0.04 | -0.22 | 0.004 | -0.24 | 0.002 |
| $Proteinuria_0$ | | | | | | | -0.27 | 0.001 | -0.27 | <0.001 |
| IFTA category | | | | | | | | | -0.21 | 0.006 |

$eGFR_{0/5}$, estimated glomerular filtration rate at baseline and at 5 years respectively; IFTA, interstitial fibrosis and tubular atrophy.
[a] Focal class as reference.

### Renal relapse and end-stage renal disease

During a mean follow-up duration of 8.0±5.4 years, 48 (33.1%) patients experienced at least one renal relapse. There was no difference between crescentic and mixed class regarding the number of patients who experienced a renal relapse ($P$=0.34; S Table 1 in the supplementary material). Twenty-four (16.6%) patients developed ESRD. At 10 years follow-up renal survival was significantly different between the four histopathological classes, but not between crescentic and mixed class (Figure 1). A total of 45 (31.0%) patients died. When combining death and/or ESRD within 10 years as one outcome, no difference was seen between crescentic and mixed class (S Figure 1 in the supplementary material).




| N at risk | | | | | | |
|---|---|---|---|---|---|---|
| Focal | 52 | 49 | 43 | 27 | 17 | 17 |
| Crescentic | 37 | 29 | 27 | 14 | 10 | 7 |
| Mixed | 39 | 34 | 32 | 23 | 14 | 13 |
| Sclerotic | 17 | 11 | 9 | 7 | 3 | 2 |

**Figure 1 | Renal survival according to histopathological class**.
At 10-year follow-up, renal survival was different between the four classes ($P$<0.001), but not between crescentic and mixed class ($P$=0.98).

## Treatment

The majority of patients received corticosteroids and cyclophosphamide as induction therapy (106 [74.1%] patients; S Table 2 in the supplementary material). Patients receiving corticosteroids and cyclophosphamide had a similar 10-year renal survival rate compared to patients receiving other treatment regimens as induction therapy ($P$=0.17). Maintenance therapy consisted for most patients of corticosteroids together with azathioprine or mycophenolate mofetil (83 [61.5%] patients). Ten-year renal survival rates did not differ between patients with no or minimal maintenance therapy (only corticosteroids) compared to patients with maintenance therapy consisting of multiple immunosuppressive drugs ($P$=0.37). Plasma exchange was more frequently used in patients with crescentic class compared to the other classes (24.3% versus 10.4%, $P$=0.04; S Table 2 in the supplementary material). Within the crescentic class, renal survival at 10 years did not differ between patients that received and patients that did not receive plasma exchange therapy ($P$=0.34).

### Interobserver agreement

Agreement on the histopathological class between the two pathologists was observed in 99 (68.3%) cases; kappa (κ) 0.56 (Figure 2). This agreement rate corresponds to moderate agreement. In seven cases there was complete disagreement between three pathologists. We discovered three possible reasons for disagreement when re-evaluating the cases that lacked agreement (*n*=46); technical (e.g., differences between histological stains), interpretative (e.g., different interpretations of the definitions) and errors (e.g., miscalculations and incomplete scorings). The intraclass correlation coefficient (ICC) between two pathologists was 0.57 for interstitial infiltrate, 0.46 for IFTA, and 0.36 for tubulitis.

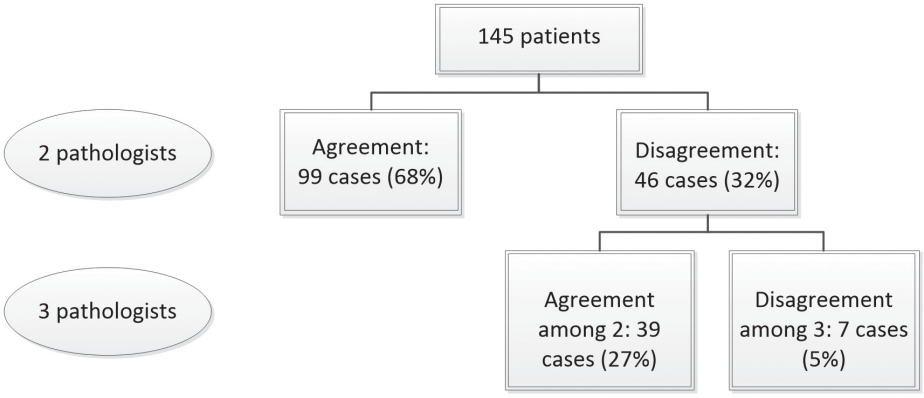



**Figure 2 | Interobserver agreement on histopathological class.**

## DISCUSSION

Our worldwide multicenter study on the histopathological classification of AAGN showed a favorable outcome in the focal class and a poor outcome in the sclerotic class, which is in line with our original study and previous validation studies. There was no difference between renal outcome in the crescentic and mixed class, which is in contrast to findings of the original study, but it is in line with results from a recent meta-analysis.[25]

Overall, our data show that the histopathological classification is associated with renal function and the development of ESRD during follow-up. This association with $eGFR_5$ persists after correcting for other baseline values. However, the crescentic and mixed class were indiscriminate regarding renal function and developing ESRD. Although these findings suggest that a revision of the original classification is called for, we are reluctant to lump the crescentic and mixed class, in particular because

other studies showed that cellular crescents are an important factor for predicting potential reversibility of renal impairment during follow-up.[16;18] This kind of information can be used for therapeutic purposes and tailoring treatment for individual patients. An additional factor not yet incorporated in the current classification, but which have shown some predictive value for long-term renal outcome, are fibrous crescents.[15] Currently it is investigated whether these can be of additive value for predicting renal outcome in the current classification.

There are four possible explanations for the conflicting results regarding crescentic and mixed class: differences in patient populations, differences in treatment, moderate interobserver agreement and insufficiency of the histopathologic classification. Epidemiologic studies showed that there is a difference in distribution of GPA/MPA/EGPA and ANCA-specificity around the globe.[53;54] Since there is an association between the histopathological class and diagnosis, and both variables are associated with renal outcome as shown above, differences in patient population could partly be an explanation for the conflicting results. Unfortunately, our cohort was not large enough to analyze this hypothesis. Regarding treatment, our study showed that patients with crescentic class received plasma exchange more frequently than patients in the other classes. However, a subanalysis showed that the use of plasma exchange did not affect renal survival within the crescentic class. This is an interesting finding, because crescentic class is considered an active and potentially reversible disease state, which could be reversed with the right treatment.[16;18;20] Our study is insufficient for firm conclusions on whether the therapy must be considered in addition to the histopathological classification for predicting outcome. A third explanation is interobserver agreement which was moderate in this study. In addition, the scoring was performed by seven experienced nephropathologists, and therefore we cannot translate this level of agreement to the clinical practice in a one-on-one fashion. This agreement level could influence the observed contradiction in the previous studies.

A fourth explanation is insufficiency of the histopathologic classification. The current histopathologic classification of AAGN is only based on glomerular lesions, not taking tubulointerstitial parameters into account, because these did not have an additional predictive value in the original study and made the classification only more complicated.[20] The importance of tubulointerstitial parameters for renal outcome in AAGN, even when used in addition to the histopathologic classification of AAGN, has been shown in other studies.[15;16;18;29;36;40;42;55-58] In our study, the extents of interstitial infiltrate, IFTA, and tubulitis were significantly associated with $eGFR_5$ in the univariate analysis. In the multivariate analysis, only IFTA remained significantly associated

with $eGFR_5$. These data suggest that including tubulointerstitial parameters in the classification system will lead to refinements for the prognostication of patients at time of diagnosis, although the poor to moderate interobserver agreement regarding tubulointerstitial variables must also be considered.

The international patient cohort from three different continents was a strength of this study. Only one previous validation study included patients from more than two countries.[40] In addition, our study included a large group of different pathologists for scoring the renal biopsies, which made it possible to investigate interobserver agreement. Our study also has some limitations. Due to the international character there was a wide variety of therapeutic regimens and the study had a retrospective design. Therefore, there was some missing data; but less than 7% of data were missing on renal function, diagnosis, serology, and therapy.

In conclusion, our study showed a significant difference between focal and sclerotic class regarding renal outcome, but no difference between crescentic and mixed class. This last observation was also described by a number of previous studies. These findings show that the histopathologic classification of AAGN is a valuable tool in the management of patients with AAV, but in the near future, adjustments are needed to improve its prognostic value, especially for the crescentic and mixed class. Currently, we are performing a study to evaluate a more detailed scoring system for both glomerular and interstitial variables. Results from that study will determine how to adjust the histopathological classification for AAGN for more sophisticated prognostic value.

## ACKNOWLEDGEMENTS

E.E.vD. is a PhD student supported by the Kolff Student Researcher Grant (number 16OKK53) from the Dutch Kidney Foundation.
Part of this study was presented at the American Society of Nephrology Kidney Week 2016, in Chicago, IL, United States of America (abstract FR-PO681; *JASN Abstract Suppl.* 2016; 27); at the 18th International Vasculitis and ANCA Workshop, March 25-28 2017 in Tokyo, Japan (WS9_1; *Rheumatology [Oxford]* 2017; 56: Suppl 3); and at the American Society of Nephrology Kidney Week 2017 in New Orleans, LA, United States of America (abstract FR-PO720; *JASN Abstract Suppl.* 2017; 28).

## DISCLOSURES

None to declare.

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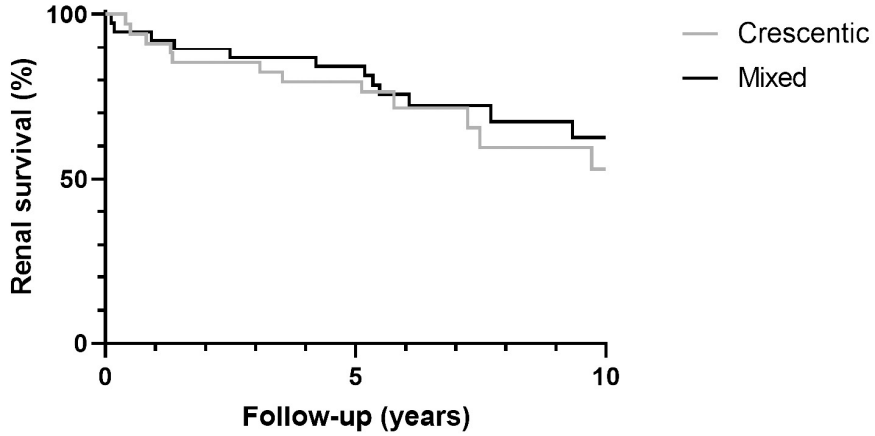
## SUPPLEMENTARY MATERIAL

### Histopathological classification of ANCA-associated glomerulonephritis: interobserver variability and clinical outcome

**S Table 1 | Subanalyses for outcomes in the crescentic and mixed classes**

| | Crescentic (*n*=37) | Mixed (*n*=39) | P-value |
|---|---|---|---|
| Follow-up, yrs | 7.3 ± 5.2 | 8.3 ± 5.3 | 0.41 |
| Renal relapses | 14 (40.0) | 11 (28.9) | 0.34 |
| ESRD within 10 yrs | 9 (24.3) | 6 (15.4) | 0.40 |
| Time to ESRD, yrs | 6.2 ± 6.7 | 3.5 ± 2.8 | 0.31 |
| Death | 15 (40.5) | 9 (23.1) | 0.14 |
| Time to death, yrs | 6.6 ± 5.5 | 4.6 ± 4.5 | 0.39 |
| Death within 10 yrs | 11 (29.7) | 7 (17.9) | 0.29 |

Data are presented as mean ± SD or as number (percentage).
ESRD, end-stage renal disease




**S Figure 1 | Combined outcome of ESRD/death in the crescentic and mixed classes over time.**
P-value (log-rank) = 0.57

**S Table 2 | Treatment according to histopathological class**

| Induction therapy | Total (*n*=143)[a] | Focal class (*n*=51) | Crescentic class (*n*=37) | Mixed class (*n*=39) | Sclerotic class (*n*=16) |
|---|---|---|---|---|---|
| Plasma exchange | 20 (14.0) | 5 (9.8) | 9 (24.3) | 4 (10.3) | 2 (12.5) |
| Corticosteroids only | 19 (13.3) | 4 (7.8) | 4 (10.8) | 6 (15.4) | 5 (31.3) |
| Corticosteroids and cyclophosphamide | 106 (74.1) | 43 (84.3) | 30 (81.1) | 23 (59.0) | 10 (62.5) |
| Corticosteroids and azathioprine or MMF | 8 (5.6) | 2 (3.9) | 1 (2.7) | 4 (10.3) | 1 (6.3) |
| Corticosteroids and mizoribine | 5 (3.5) | 1 (2.0) | 0 (0.0) | 4 (10.3) | 0 (0.0) |
| Corticosteroids and rituximab[b] | 5 (3.5) | 1 (2.0) | 2 (5.4) | 2 (5.2) | 0 (0.0) |

| Maintenance therapy | Total (*n*=136)[c] | Focal class (*n*=49) | Crescentic class (*n*=35) | Mixed class (*n*=36) | Sclerotic class (*n*=16) |
|---|---|---|---|---|---|
| Initially none | 5 (3.7) | 2 (4.1) | 1 (2.9) | 2 (5.6) | 0 (0.0) |
| Corticosteroids only | 27 (19.9) | 8 (16.3) | 4 (11.4) | 7 (19.4) | 8 (50.0) |
| Corticosteroids and cyclophosphamide | 8 (5.9) | 5 (10.2) | 1 (2.9) | 2 (5.6) | 0 (0.0) |
| Corticosteroids and azathioprine or MMF | 83 (61.0) | 29 (59.2) | 25 (71.4) | 21 (58.3) | 8 (50.0) |
| Azathioprine or MMF | 5 (3.7) | 3 (6.1) | 2 (5.7) | 0 (0.0) | 0 (0.0) |
| Corticosteroids and mizoribine | 8 (5.9) | 2 (4.1) | 2 (5.7) | 4 (11.1) | 0 (0.0) |

MMF, mycophenolate mofetil.

[a] Data on induction therapy was missing in 2 patients.

[b] One of these patients also received 2 doses of intravenous cyclophosphamide.

[c] Data on maintenance therapy was available in 142 patients. Six patients did not receive maintenance therapy due to death or dialysis dependency.

**S Document 1 | Scoring questionnaire**

*Overall*

1 Total number of glomeruli:

2 AAGN class

a) Focal

b) Crescentic

c) Mixed

d) Sclerotic

*Inflammatory infiltrate present in:*

3 Infiltrates

a) <10% of unscarred parenchyma

b) 10 to 25% of unscarred parenchyma

c) 26 to 50% of unscarred parenchyma

d) >50% of unscarred parenchyma

4 Dominant cell type of infiltrate

a) Neutrophils

b) Mononuclear cells

c) Eosinophils

5 Interstitial fibrosis and tubular atrophy

a) No interstitial fibrosis and tubular atrophy

b) Mild interstitial fibrosis and tubular atrophy (<25% of cortical area)

c) Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)

d) Severe interstitial fibrosis and tubular atrophy/loss (>50% of cortical area)

6 Intra-epithelial infiltrate

a) No mononuclear cells in tubules

b) Foci with 1 to 4 cells/tubular cross section or 10 tubular cells

c) Foci with 5 to 10 cells/tubular cross section

d) Foci with >10 cells/tubular cross section

*Vessels*

7 Is vasculitis present in the small vessels (arterioles and/or arteries)?

a) Yes

b) No

8 Are large vessels present in the biopsy?

a) Yes (please answer question 9)

b) No (proceed to question 10)

9 Is vasculitis present in the large vessels?

a) Yes

b) No

*Granulomas*

10 Are granulomas present?

a) Yes

b) No

*Conclusion*

11 Do you have any comments?