Histopathological Classification and Renal Outcome in Patients with Antineutrophil Cytoplasmic Antibodies-associated Renal Vasculitis: A Study of 186 Patients and Metaanalysis

Yong-Xi Chen, Jing Xu, Xiao-Xia Pan, Ping-Yan Shen, Xiao Li, Hong Ren, Xiao-Nong Chen, Li-Yan Ni, Wen Zhang, and Nan Chen

ABSTRACT. Objective. Renal vasculitis is one of the most common manifestations of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and renal histology is a key predictor of the outcome. A new histopathologic classification was proposed and validated, but the results are still debated.

Methods. We performed a retrospective analysis to validate the histopathologic classification and performed a metaanalysis to evaluate its predictive value. There were 186 patients with ANCA-associated renal vasculitis diagnosed at Ruijin Hospital who were enrolled in the retrospective study. The metaanalysis considered the data for 1601 patients.

Results. In our retrospective study, patients with focal class had the best renal outcome while patients with mixed class had the worst (p < 0.001). Metaanalysis showed that patients with focal class had better renal outcome than did those with crescentic class [risk ratio (RR) 0.23, 95% CI 0.16–0.34, p < 0.00001], with no evidence of heterogeneity (I² = 0%, p = 0.96). Patients with crescentic class had better renal outcome than did those with sclerotic class (RR 0.52, 95% CI 0.41–0.64, p < 0.00001), with no evidence of heterogeneity (I² = 2%, p = 0.43). We did not find statistical significance regarding renal outcome between mixed and crescentic classes (RR 1.14, 95% CI 0.91–1.43, p = 0.27), with no evidence of heterogeneity (I² = 23%, p = 0.19). The retrospective study showed that lung and upper respiratory tract involvement were the most common extrarenal manifestations.

Conclusion. We demonstrated the clinical utility of histopathologic classification in determining renal outcome in patients with AAV. Metaanalysis showed that patients with focal class had the best outcome while sclerotic class had the worst. (First Release December 15 2016; J Rheumatol 2017;44:304–13; doi:10.3899/jrheum.160866)

Key Indexing Terms: ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES HISTOPATHOLOGIC CLASSIFICATION RENAL VASCULITIS OUTCOME METAANALYSIS

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) constitutes a group of life-threatening diseases including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Renal involvement is one of the most common manifestations of AAV and an important factor in a patient’s prognosis. The characteristic of renal involvement is the so-called pauci-immune glomerulonephritis, which often presents as necrotizing or crescentic glomerulonephritis without deposition of immunoglobulins. Apart from the pauci-immune glomerulonephritis, immune complex deposition...
could also be found in the kidneys of some patients with AAV.4,5.

The prognostic value of renal biopsy is widely known in patients with AAV because specific renal pathologic lesions, either absence or presence, are important factors in renal outcome6. Studies point out that renal histology is much more accurate than baseline glomerular filtration rate (GFR) at entry alone to predict renal outcome. Apart from reflecting the kidney function at disease onset, renal biopsy specimens provide evidence to predict renal outcome.7,8. To further determine the patterns of renal injuries in patients with AAV and to investigate its correlation with patients’ prognosis, a new histopathologic classification of ANCA-associated renal vasculitis was proposed. The classification consists of 4 categories: focal, mixed, sclerotic, and crescentic classes depending on the percentage of globally sclerotic glomeruli or crescentic in the renal specimens.50. Though the classification has been validated in many studies9–18,19,20,21,22,23, the results are still debated partly because of the small sample size or the low number of endpoints observed, which limits the statistical power to draw firm conclusions. In our study, we retrospectively analyzed our patients with the newly proposed histopathologic classification and then performed a metaanalysis to evaluate the predictive value of the histopathologic classification of ANCA-associated glomerulonephritis.

MATERIALS AND METHODS

Patient selection. For the histopathological study, we performed a retrospective, observational cohort study to analyze patients with newly diagnosed AAV with renal involvement who underwent renal biopsy at the Department of Nephrology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine between 1997 and 2014.

Patients were eligible for inclusion if they met the following criteria: (1) positive for ANCA, (2) fulfilling the criteria of the Chapel Hill Consensus Conference definition for AAV, (3) underwent renal biopsy showing histology consistent with AAV at the time of presentation with ≥ 10 glomeruli found in the renal biopsy specimen, and (4) had been followed up for at least 12 months (including patients who died within the first 12 mos). Patients were excluded if they had secondary vasculitis or comorbid renal diseases, including antiglomerular basement membrane nephritis, lupus nephritis, and membranous nephropathy.

Renal histopathology. Renal specimens were evaluated using light microscopy with direct immunofluorescence for immunoglobulins and complement components, and electron microscopy, Periodic Acid-Schiff, silver methenamine, H&E staining, and Mason’s trichrome staining were used for the light microscope. Biopsies were independently scored by 2 pathologists (XXP and JX) blinded to the clinical data and according to the previously standardized definitions. Differences in scoring between the 2 pathologists were resolved by re-reviewing the biopsies by a third pathologist (QC) and coming to a consensus. The biopsy specimens were assigned to 4 categories according to the definition of the 2010 histological classification6: those with ≥ 50% of globally sclerosed glomeruli were classified as sclerotic class, those with ≥ 50% of normal glomeruli were classified as focal class, those with ≥ 50% of glomeruli with cellular crescents were classified as crescentic class, and those who did not meet these criteria were classified as mixed class. All the specimens met the requirement of a minimum of 10 whole glomeruli6. Tubulo-interstitial lesions such as interstitial fibrosis and tubular atrophy were graded semiquantitatively, as previously reported24–26 (scale 0 to 3: score 0 for absent, 1 for 1–20%, 2 for 21–50%, and 3 for > 50%).

ANCA analysis and clinical data. All patients had been tested for the presence of ANCA by indirect immunofluorescence (Euroimmun AG). ELISA was performed to test antitymelyperoxidase (MPO) and antiproteinase 3 (PR3) antibodies in all sera (Euroimmun AG), as previously reported24,25,26,27,28.

The estimated GFR (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration Creatinine Equation29 while considering the highest serum creatinine at diagnosis. Disease activity at initial clinical presentation was evaluated by the Birmingham Vasculitis Assessment Score (BVAS) 200330. Systemic organ damage was evaluated by the Vasculitis Damage Index (VDI).31

Statistics. Statistical analysis was performed using SPSS 11.0 software (SPSS Inc.). Data were summarized as mean ± SD or otherwise indicated. Baseline differences between different histopathologic groups were assessed using 1-way ANOVA or the chi-squared test for categorical variables when appropriate. We plotted Kaplan-Meier curves and made comparisons by using the log-rank test to analyze patient survival as well as renal survival between patients with different histopathologic groups. A p value < 0.05 was considered statistically significant.

Data source, search strategy, and selection criteria. We performed a systematic review of the published literature according to the approach recommended by the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement for the conduct of metaanalyses.31 Relevant studies were identified by searching MEDLINE, OVID, SCOPUS, and EMBASE (updated to May 31, 2015) for English-language articles by combinations of the following terms: “ANCA,” “antineutrophil cytoplasmic antibody,” “vasculitis,” “vasculitides,” “glomerulonephritis,” “histopathology,” “histopathologic,” “histopathological,” “histology,” “histological,” “kidney,” and “renal”. All eligible articles were retrieved and their references were reviewed to identify additional relevant studies. The search was limited to studies validating the histopathological classification in ANCA-associated glomerulonephritis.

All studies that validated the histopathological classification of ANCA-associated glomerulonephritis were eligible for the inclusion. Study endpoints include endstage renal diseases (ESRD), renal replacement therapy (hemodialysis, peritoneal dialysis, or transplantation), and death.

Data extraction and quality assessment. Data for each eligible study were extracted into a spreadsheet including patients’ baseline character (sex, age), eGFR, level of proteinuria, followup duration, BVAS, ANCA serotype, vasculitis classification, pathology methodology, number of glomeruli, statistical methodology, survival, patient’s survival, endpoint definition, characteristics of the histological classification, and treatment. The literature search, data extraction, and quality assessment were undertaken independently by 2 authors (YXC and WZ) using a standardized approach. Any disagreement about the data were adjusted by a third reviewer (PYS).

Statistical analysis. Metaanalysis was performed using Review Manager Software (RevMan 5.3; The Nordic Cochrane Centre). For the purpose of the metaanalysis, renal outcome from individual studies were combined using risk ratios (RR) and their 95% CI. Heterogeneity of renal outcome between studies was assessed using the chi-squared test statistic and quantified by I2 test. The pooled RR was estimated by a random-effect model. A sensitivity analysis was performed to evaluate stability by sequential omission of individual studies. Overall effects were determined using the Z test. Publication bias was tested by the Egger linear regression test for funnel plot asymmetry by using STATA 12 software (StataCorp LP).

Ethics. Because our study was retrospective and a metaanalysis, ethics approval was not required, in accordance with the policy of our institution.

RESULTS

Demographic features, clinical presentations, and treatment for the histopathological study. We enrolled 186 patients with ANCA-associated glomerulonephritis, including 154 MPA, 10 GPA, 4 EGPA, and 18 renal-limited vasculitis. Mean age...
at presentation was 56.9 years. In our study, 46 biopsy specimens (24.7%) were classified as focal, 36 (19.4%) as crescentic, 36 (19.4%) as sclerotic, and 68 (36.6%) as mixed class (Table 1). No significant differences were found among different groups with regard to sex and age at disease presentation (p > 0.05). Lung and upper respiratory tract involvement were the most common manifestations of the patients at diagnosis (131/186, 70.4%), but no significant differences were seen regarding extrarenal manifestations among patients (p > 0.05). The mean BVAS at diagnosis was 19 and significant difference was found regarding BVAS among the groups (p < 0.001). We also compared the VDI of the patients at 6 months and found no statistical significance within different classes (p > 0.05).

For treatment, most patients (153/186, 82.3%) were treated with corticosteroids in combination with cyclophosphamide (CYC) for the induction therapy, as previously described26,27,28; for those who survived induction therapy, 8.3% (11/132) were treated with azathioprine and 91.7% (121/132) were treated with intravenous CYC every 3 months. Twenty patients were treated with corticosteroids and mycophenolate mofetil (20/186, 10.8%). Plasma exchange was done in 10 patients (10/186, 5.4%). Thirteen patients (13/186, 7%) were treated with corticosteroids alone.

**Kidney injury, renal pathology, and outcome.** As depicted in Table 2, tubulointerstitial injury was present in 176 patients (94.6%). Significant difference was found in tubulointerstitial injury among different classification groups (p < 0.001). Patients in focal class had the least tubulointerstitial injury while patients in sclerotic class had the most severe injury. Further, patients in focal class presented with the highest percentage of normal glomeruli (p < 0.001) and the lowest percentage of cellular crescents (p < 0.001). All these results were consistent with the lower level of serum creatinine and proteinuria (p < 0.001, p = 0.002, respectively), and higher eGFR (p < 0.001) for focal classification at presentation (Table 2).

**Table 1. Demographic and clinical characteristics of the patients among 4 histological classes.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Focal, n = 46</th>
<th>Crescentic, n = 36</th>
<th>Sclerotic, n = 36</th>
<th>Mixed, n = 68</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>19/27</td>
<td>17/19</td>
<td>14/22</td>
<td>31/37</td>
<td>0.87</td>
</tr>
<tr>
<td>Age, yrs, mean ± SD</td>
<td>53.9 ± 17.7</td>
<td>56.3 ± 14.8</td>
<td>58.2 ± 13.7</td>
<td>58.2 ± 12.7</td>
<td>0.43</td>
</tr>
<tr>
<td>MPO-ANCA/PR3-ANCA, n</td>
<td>33/13</td>
<td>32/4</td>
<td>33/3</td>
<td>65/3</td>
<td>0.002</td>
</tr>
<tr>
<td>Extrarenal involvement, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung and upper respiratory tract</td>
<td>27 (58.7)</td>
<td>31 (86.1)</td>
<td>25 (69.4)</td>
<td>48 (70.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>ENT</td>
<td>16 (34.8)</td>
<td>18 (50)</td>
<td>17 (47.2)</td>
<td>19 (27.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Nervous system</td>
<td>7 (15.2)</td>
<td>8 (22.2)</td>
<td>5 (13.9)</td>
<td>6 (8.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cutaneous/mucous membranes/eyes</td>
<td>8 (17.4)</td>
<td>4 (11.1)</td>
<td>3 (8.3)</td>
<td>5 (7.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>BVAS, median</td>
<td>19</td>
<td>25</td>
<td>18</td>
<td>18</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p value applies to the variable across the differing histological classes. ANCA: antineutrophil cytoplasmic antibodies; MPO-ANCA: myeloperoxidase ANCA; PR3-ANCA: proteinase 3 ANCA; BVAS: Birmingham Vasculitis Activity Score.

During followup, 2 patients (4.3%) with focal, 12 (33.3%) with crescent, 16 (44.4%) with sclerotic, and 19 (27.9%) with mixed class developed ESRD. The 1- and 2-year renal survival were both 97.8% for focal class, 72.2% and 68.9% for crescentic class, 69.3% and 52.1% for sclerotic class, and 85.3% and 80.5% for mixed class, respectively. Patients with focal presented with the best renal outcome in comparison with other groups (p < 0.001; Figure 1A).

In all, 69 patients (10 in focal class, 17 in sclerotic class, 18 in crescentic class, and 24 in mixed class) died during followup. The 1-year cumulative survival was 90.8% for focal class, 73.7% for crescentic class, 71.5% for sclerotic class, and 86.3% for mixed class. The cumulative survival of the patients in different groups were mixed, sclerotic, focal, and crescentic in descending order (Figure 1B), with significant difference (p < 0.05).

**Metaanalysis of the histological classification on renal outcome.** Of the 519 publications initially identified in different databases, 17 studies6,9–18,19,20,21,22,23 were enrolled in our metaanalysis, including our current study; the flow diagram is presented in Figure 2. Six studies were from Asia (China, Japan, and India), 5 from Europe, 4 from North America (United States and Canada), 1 from South America (Argentina), and 1 from Australia. There were 1601 patients in the metaanalysis, including 61 pediatric patients and 1540 adults (Table 3A and Table 3B). Details of the included studies are listed in Supplementary Table 1 (available from the authors on request).

**Applicability of the histopathological classification.** Sixteen studies reported kidney failure events and/or patient’s survival separately within different histopathologic classifications, and one11 combined the data. Because the study by Ford, et al11 did not separate patients with ESRD from the deaths, it was not included in our metaanalysis. With a total of 1481 patients and 335 kidney failure events from 16 studies, the renal outcome between focal and crescentic classes showed statistically significant difference in favor of focal class (RR 0.23, 95% CI 0.16–0.34, p < 0.00001; Figure 3A).
3A), with no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.96$). Renal outcome between crescentic and sclerotic classes reported the association of sclerotic class with progression to kidney failure (RR 0.52, 95% CI 0.41–0.64, $p < 0.00001$; Figure 3B), with no evidence of heterogeneity ($I^2 = 2\%$, $p = 0.43$). For the renal outcome of mixed and sclerotic classes, the results showed the statistically significant difference that was in favor of mixed class (RR 0.42, 95% CI 0.33–0.54, $p < 0.00001$; Figure 3C), with no evidence of heterogeneity ($I^2 = 33\%$, $p = 0.10$). However, there was no statistically significant difference in the risk of developing ESRD between the mixed and crescentic classes (RR 1.14, 95% CI 0.91–1.43, $p = 0.27$; Figure 3D), with no evidence of heterogeneity ($I^2 = 23\%$, $p = 0.19$).

Sensitivity analysis and publication bias. No significant change in pooled RR was found by sequential omission of individual studies, which suggests that our results are stable and reliable. Further, inclusion of the study of Ford, et al11 did not lead to any changes to our results. For publication bias, funnel plots and Egger tests were used to evaluate publication bias. The results showed no obvious funnel plot asymmetry. All the p values of Egger tests were > 0.05, suggesting that publication bias was not evident in our metaanalysis (Supplementary Figures 1–4 are available from the authors on request).

DISCUSSION
Renal vasculitis is the most common manifestation of AAV. It presents in more than half of the patients at diagnosis, and renal biopsy is the gold standard for establishing the diagnosis6. Studies have demonstrated that glomerular lesions are associated with renal outcome7,8,32. Given the background of important prognostic value of renal histopathology, a new histopathological classification was proposed and has been validated ever since.

In our present retrospective study, our results demonstrated that patients with focal class had the best renal outcome in comparison with patients with other classes. Our results were consistent with the results of the histological classification6. Further, metaanalysis confirmed the predictive value of focal class as the best renal outcome among patients with ANCA-associated renal vasculitis. As proposed by the new histological classification, focal class contains biopsies wherein ≥ 50% of glomeruli are normal. The results indicate that the number of normal glomeruli could be an important predictive factor in determining renal outcome in the patients. In addition to our current study, de Lind van Wijngaarden, et al performed a clinical and histological analysis of patients with AAV that showed normal glomeruli be a positive predictor of dialysis independence and improved renal function7. All the studies then confirmed the predictive value of normal glomeruli in determining renal outcome in patients with ANCA-associated renal vasculitis. Another interesting finding in our study was that more patients with PR3-ANCA presented with focal class, which suggested less severe renal involvement in those patients. Our results were consistent with current findings that showed that patients with PR3-ANCA had less severe renal involvement than did those with MPO-ANCA33.

Crescentic lesion is one of the characteristics of ANCA-associated renal vasculitis. The high percentage of cellular crescents indicated active vasculitis lesions in the kidney and those patients might respond to adequate and timely immunosuppressive therapy. In this sense, active lesions were associated with renal function recovery and could be reversible when the patients received timely and proper treatment8. Apart from histologic lesions, ANCA serology may be another important factor that affects treatment response in active vasculitis because most studies suggest that patients with MPO-ANCA have poorer renal outcome than those with PR3-ANCA in different populations33. It has been reported that global sclerotic glomeruli

Table 2. Renal involvement and histological characteristics of the patients among 4 histological classes.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Focal, n = 46</th>
<th>Crescentic, n = 36</th>
<th>Sclerotic, n = 36</th>
<th>Mixed, n = 68</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal involvement, median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>93 (42–620)</td>
<td>383 (60–1363)</td>
<td>432.5 (91–952)</td>
<td>231 (44–1096)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eGFR, ml/min × 1.73m²</td>
<td>72 (5.6–156.4)</td>
<td>11.2 (3.0–134.7)</td>
<td>9.8 (3.3–74.7)</td>
<td>20.6 (3.6–156.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proteinuria, mg/day</td>
<td>446.0 (60–9806)</td>
<td>1514 (125–6720)</td>
<td>1916 (179–5729)</td>
<td>1292(160–8957)</td>
<td>0.002</td>
</tr>
<tr>
<td>Glomerular injury, %, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>75.8 ± 15.5</td>
<td>9.0 ± 11.8</td>
<td>6.7 ± 10.4</td>
<td>14.6 ± 16.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cellular crescents</td>
<td>4.8 ± 7.5</td>
<td>63.8 ± 10.7</td>
<td>8.2 ± 15.7</td>
<td>19.1 ± 15.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tubulointerstitial injury, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 0</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Score 1</td>
<td>34</td>
<td>20</td>
<td>3</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Score 2</td>
<td>4</td>
<td>9</td>
<td>8</td>
<td>20</td>
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</tr>
<tr>
<td>Score 3</td>
<td>2</td>
<td>3</td>
<td>25</td>
<td>13</td>
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</tbody>
</table>

* p value applies to the variable across the differing histological classes. eGFR: estimated glomerular filtration rate.
Figure 1. Survival of the patients among different histological classes. A. Renal survival, as shown by different histopathologic classes, suggests that renal survival decreased with the descending order of focal, crescentic, sclerotic, and mixed classes (log-rank analysis, p < 0.001). B. Cumulative survival, as shown by different histopathologic classes, suggests that total survival decreased with the descending order of mixed, sclerotic, focal, and crescentic classes (log-rank analysis, p = 0.012).
are not the typical histological lesions in patients with ANCA-associated renal vasculitis. They usually represent chronic lesions in the kidneys and are associated with adverse renal outcomes. This finding is supported by our metaanalysis, which suggests that chronic glomerular injuries might be associated with negative renal outcome. We are aware that the kidney function of AAV at disease onset as well as the renal outcome might be associated with the severity of acute lesions such as crescents and fibrinoid necrosis, rather than chronic damage such as global sclerotic. Patients with sclerotic lesions, therefore, had more severe chronic glomerular injuries and might not respond to active treatment of vasculitis. In our retrospective study, patients with mixed class had worse outcome than those in sclerotic class, while the metaanalysis showed differently. However, if we take a deep look into our retrospective data, we would find better renal outcome in mixed class when we compared renal outcome with sclerotic class at the same interval during followup. As shown in our study that the followup was longer in mixed class, the overall renal survival seemed better in sclerotic class. Therefore the followup period might be a factor that contributed to the discrepancy between our study and the literature.

Mixed glomerular lesion, according to its definition, contains both active and chronic glomerular injuries. In the histological classification, patients with mixed class had worse renal outcome in comparison with crescentic class, but better renal outcome than those in sclerotic class. In our current metaanalysis, patients with mixed class had better renal outcome than those in sclerotic class. The different renal outcome could be due to treatment response between active and chronic glomerular lesions because patients with mixed class had a lower proportion of sclerotic glomeruli and a higher proportion of crescentic lesions. Though more than half of the studies in our metaanalysis supported better renal outcomes in mixed class, the difference was not statistically significant. As the results varied among the studies, further modifications might be necessary to current histological classification to make it reflect histological lesions on renal outcome.

In our retrospective study, total survival ranked differently from renal survival by histopathological classes. Our results were not contradictory because kidney injury was only one of the factors that affected total survival in patients with AAV. Side effects of longterm immunosuppressive therapy, vasculitis organ damage, and many others could also be involved in determining patients’ prognosis. Therefore, the clinical application of histological classification should be narrowed in renal manifestations and further studies might be necessary to investigate its correlation with extrarenal involvement.

Our study has several limitations that should be addressed. First, the studies included in our metaanalysis used different eGFR equations, which could affect patient baseline characteristics. Second, all the studies included were retrospective, which made our study not an individual-patient data...
Further, BVAS and treatment protocols were unavailable in some studies. Therefore, we could not evaluate the interaction between active vasculitis lesions and immunosuppressive therapy. Third, the quality of studies included were variable. Because we lack robust tools to evaluate risk of bias in nonrandomized studies, effects of study quality on the pooled results were not evaluated in our current study. Finally, data regarding renal tubulointerstitial injuries were unavailable in some studies. Therefore, we could not evaluate the interaction between active vasculitis lesions and immunosuppressive therapy. Third, the quality of studies included were variable. Because we lack robust tools to evaluate risk of bias in nonrandomized studies, effects of study quality on the pooled results were not evaluated in our current study. Finally, data regarding renal tubulointerstitial injuries were
extremely sparse, which limits our ability to draw further conclusions with renal histology.

Despite these limitations, to our knowledge, our current metaanalysis represents the largest and most comprehensive effort to evaluate histological classification on renal outcome in patients with ANCA-associated renal vasculitis. Our study demonstrates that focal class is strongly associated with better renal outcome while sclerotic class is associated with worse outcome. Our findings support the use in clinical practice of the histopathological classification in patients with ANCA-associated renal vasculitis.

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Figure 3. Forest plots of risk ratio of renal outcome measures between different classes. A. Comparing focal versus crescentic class. B. Comparing crescentic versus sclerotic class. C. Comparing mixed versus sclerotic class. D. Comparing mixed versus crescentic class. ESRD: endstage renal disease; M-H: Mantel-Haenszel test.
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