Bowman's capsule rupture on renal biopsy improves the outcome prediction of ANCA-associated glomerulonephritis classifications

We read the published article by Gercik *et al*[1] with great interest. In their retrospective study, they tested the existing classification systems to predict the progression to end-stage renal disease of patients with renal involvement by anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), demonstrating a better performance of the AAV renal risk score (ARRS) proposed by Brix *et al*[2] as compared with the 4-tiered glomerulocentric histological Berden's classification.[3] They suggested that the employment of baseline glomerular filtration rate in the ARRS can partly represent a possible explanation for these results. However, the evaluation of extra-glomerular histological parameters that strongly correlate with the renal outcome[4] (eg, interstitial fibrosis/tubular atrophy (IFTA)), can play a further role in the improvement of the ARRS performance. In this setting, many other classifications demonstrated the putative role of disparate histological features to predict the outcome of patients with primary (eg, IgA nephropathy[5]) and secondary (eg, lupus nephritis[6]) renal diseases, suggesting the possibility to further increase the prognostic role of the existing classification for AAV.

We retrospectively evaluated the performances of the currently used systems and investigated whether additional histological features can improve prognostic workflow of AAV. For this purpose, a retrospective, multicentric series of AAV cases have been reviewed. Each case has been independently evaluated by two renal pathologists, and classified according to the Berden's scheme and ARRS. Additional glomerular, tubulointerstitial and vascular lesions have been recorded for each case, following the previously provided definitions.[7 8] The outcome of interest was time to need for renal replacement therapy (RRT) or death, whatever occurred first. Cox proportional hazards regression models were constructed with time to composite event, loss to follow-up or censoring (30 June 2019). Time at risk started at the date of renal biopsy. The histological features, collapsed into binary variables (0 to 1=low; 2 to 3=high) and subdivided as 'active' (cellular/fibrocellular crescents, endocapillary hypercellularity, fibrinoid necrosis and Bowman's capsule rupture (BCR)) and 'chronic' (global glomerulosclerosis, fibrous crescents, segmental glomerulosclerosis, IFTA and arteriosclerosis) have been evaluated individually and in association with the currently proposed systems to assess their ability to predict the outcome. Univariate and multivariate models (HRs and 95% CIs) have been used to assess the prognostic performance of Berden's class/ARRS alone and with additional predictors (Harrell's c-statistic).

After the selection of cases with available renal biopsy, complete clinical data (at least 6 months of follow-up) and positive anti-neutrophil cytoplasmic antibody (ANCA), 52 patients have been analysed (30 (58%) males, median age 68 years (IQR 58 to 75)). ANCA showed myeloperoxidase (MPO) specificity in 31 (60%) and PR3 in 21 (31%), with a median titre of 101 U/mL (IQR 55 to 264). Six patients (12%) required dialysis at the time of the diagnosis. After the biopsy, 47 (90%) patients were treated with corticosteroids, 34 (66%) with additional immunosuppression and/or plasmapheresis (8 (15%)). During a median follow-up of 31 months (1828 person-months), 13 composite events developed (8 deaths, 5 RRT). Sixteen (31%) cases were classified as Focal, 8 (15%) as Crescentic, 24 (46%) as Mixed and 4 (8%) as Sclerotic. Patients were grouped as low (n=21, 40%), medium (n=24, 46%) and high risk (n=7, 13%) based on ARRS. Among the histological predictors tested (table 1), only BCR was significantly associated with the outcome at the univariate analysis (p=0.023). Its addition (figure 1) to the model, which included only Berden's class (c=0.67) or ARRS (c=0.62), significantly improved the prognostic performance (c=0.76 and

Table 1 Statistical analysis.

Predictor	HR (95% CI)	p-value
Univariate analysis		
Active lesions		
Endocapillary hypercellularity	1.47 (0.32 to 6.72)	0.62
Cellular/fibrocellular crescents	1.68 (0.55 to 5.15)	0.36
Glomerular fibrinoid necrosis	0.62 (0.14 to 2.78)	0.53
Bowman's capsule rupture	3.71 (1.20 to 11.44)	**0.023**
Chronic lesions		
Global glomerulosclerosis	1.49 (0.50 to 4.45)	0.47
Fibrous crescent	2.08 (0.63 to 6.84)	0.23
Segmental sclerosis	2.45 (0.79 to 7.58)	0.12
Interstitial fibrosis/tubular atrophy	1.26 (0.27 to 5.88)	0.77
Arteriosclerosis	2.79 (0.91 to 8.56)	0.07

Univariate analysis on the active/chronic lesions with reported HR and 95% CIs. Statistically significant differences are reported with a bold p-value.

Predictor	Harrell's c-statistic	HR (95% CI)	Pp-value
Multivariate analysis			
Berden's class only	0.67	3.61 (1.15 to 11.34)	**0.028**
Berden's class + BCR	0.76		
Renal risk score (Brix) only	0.62	5.25 (1.53 to 18.08)	**0.009**
Renal risk score + BCR	0.73		

Prognostic performance (with relative Harrell's c-statistic) of Berden's classes and Brix risk groups with/without the Bowman's capsule rupture (BCR) assessment and relative multivariate analysis. Statistically significant differences are reported with a bold p-value.

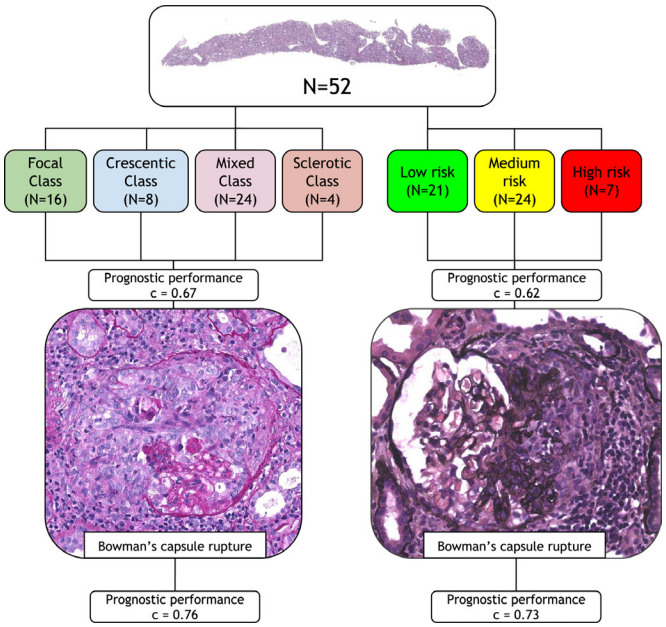

Figure 1 Panel depicting the improvement in prognostic performance of both the Berden's classification system (c=0.67) and the renal risk groups system proposed by Brix *et al* (c=0.62) after the addition of Bowman's capsule rupture as an ancillary parameter of acute renal damage (c=0.76 and c=0.73, respectively).

0.73, respectively). This has been confirmed in the multivariate model which includes Berden's class (HR 3.61, 95% CI 1.15 to 11.34; p=0.028) and ARRS (HR 5.25, 95% CI 1.53 to 18.08; p=0.009). The present study demonstrates an improved performance of prognostic systems in predicting AAV outcome after the implementation of BCR, the additional predictive role of which can partly lie in the irreversible loss of nephrons consequent to the segmental glomerulosclerosis caused by BCR.[9] Further investigations on a larger prospective cohort are required to confirm these results.

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REFERENCES

1 Gercik O, Bilgin E, Solmaz D, *et al*. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. *Ann Rheum Dis* 2020;79:675–6.
2 Brix SR, Noriega M, Tennstedt P, *et al*. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int* 2018;94:1177–88.
3 Berden AE, Ferrario F, Hagen EC, *et al*. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol* 2010;21:1628–36.
4 Hauer HA, Bajema IM, Van Houwelingen HC, *et al*. Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney Int* 2002;62:1732–42.
5 Trimarchi H, Barratt J, Cattran DC, *et al*. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int* 2017;91:1014–21.
6 Bajema IM, Wilhelmus S, Alpers CE, *et al*. Revision of the International Society of Nephrology/Renal pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of health activity and chronicity indices. *Kidney Int* 2018;93:789–96.
7 Working Group of the International IgA Nephropathy Network and the Renal Pathology Society, Roberts ISD, Cook HT, *et al*. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int* 2009;76:546–56.
8 Haas M, Loupy A, Lefaucheur C, *et al*. The Banff 2017 kidney meeting report: revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials. *Am J Transplant* 2018;18:293–307.
9 Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. *Kidney Int* 2005;67:404–19.