Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis

In patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) and renal involvement, the development of end-stage renal disease (ESRD) remains an undesired issue. To date, reported predictors of renal outcome are mainly patients' age, severe renal dysfunction and histopathological findings at presentation.[1 2] Histopathological classification as defined by Berden *et al* was proposed to be helpful with the highest renal survival rates in the focal group and the poorest in the sclerotic group.[3 4] Recently, Brix *et al* suggested the antineutrophil cytoplasmic antibody renal risk score (ARRS) to predict ESRD in patients with AAV.[5] Unlike Berden's classification, ARRS combines histopathological findings (the percentage of normal glomeruli, tubular atrophy and interstitial fibrosis) with baseline glomerular filtration rate (GFR). Here, we aimed to assess the prognostic factors for renal survival and to evaluate the performances of Berden's histopathological classification and ARRS for predicting ESRD.

We reviewed the medical records of all patients diagnosed with AAV according to biopsy and/or antineutrophil cytoplasmic antibody (ANCA) serology. Patients with renal involvement and categorised according to the 2012 Chapel Hill consensus nomenclature were included. Renal-limited vasculitis (RLV) was considered as a separate group. We reviewed renal biopsies in order to calculate ARRS and according to Berden's classification. Renal survival was defined as the time between diagnosis and the development of ESRD (GFR<15 mL/min/1.73 m^2 or the start of a permanent dialysis programme).

Patients' of two centres were treated similarly, starting with cyclophosphamide or rituximab in conjunction with high-dose glucocorticoids for induction or major relapses, and maintenance treatment was composed of a combination of oral methylprednisolone and azathioprine, rituximab or mycophenolate mofetil for at least 24 months after remission had been achieved. Factors predictive of renal survival were evaluated by the Kaplan-Meier method and the Cox proportional hazard model.

In total, 167 patients with AAV (90 with granulomatosis with polyangiitis (54%), 39 with microscopic polyangiitis (23%), 30 with RLV (18%) and 8 with eosinophilic granulomatosis with polyangiitis (5%)) (95 men (57%), median age at diagnosis of 55 (IQR 19) years, median serum creatinine level at diagnosis of 3.74 (IQR 5.32 mg/dL) with renal involvement at presentation were analysed. ANCAs were detected in 87% (141/163) of the patients with indirect immunofluorescence (IIF) and/or ELISA. ESRD developed in 52 patients (34%) over a median follow-up of 39.6 (IQR 65) months, and the median renal survival was 31 (IQR 65) months. In 72 patients (46%), haemodialysis was performed at presentation. Of the 106 kidney biopsies which were available for the final analysis, 14 (13%) were sclerotic, 41 (39%) were crescentic, 33 (31%) were mixed and 18 (17%) were focal, and among them, ESRD developed in 79%, 51%, 32% and 18%, respectively (p=0.003). Among our patients, 14% were at low risk, 63% were at medium risk and 23% were at high risk group according to ARRS, and ESRD developed in 8%, 42% and 67%, respectively (p=0.005). In univariate analysis, age at diagnosis (HR 1.02, 95% CI 1.00 to 1.04, p=0.045), AAV subgroups (p=0.01), Berden's classification (p=0.009), ARRS (p=0.01), serum creatinine level (HR 1.14, 95% CI 1.09 to 1.19, p<0.001) and GFR (HR 0.92, 95% CI 0.89 to 0.95, p<0.001) were the baseline characteristics associated with renal survival. In multivariate analysis (table 1), Berden's classification predicted renal survival in model 1, but when GFR at diagnosis was included (model 2) in the model, it lost its significance. However, the ARRS was found to be an independent prognostic factor for renal survival (model 3) with the same characteristics in the model.

In baseline evaluation, the prediction of the development of ESRD in patients with AAV may be important for treating physicians. Histopathological findings are proposed to be helpful; however, it does not consider baseline renal function. In the present study, ARRS seems to be more advantageous than Berden's classification, and the possible explanation might be the incorporation of baseline GFR to the histopathological findings. The main limitations of the present study are being retrospective and the absence of interobserver reliability.

In conclusion, high ESRD development rates in AAV emphasises the importance of identifying patients at risk. At this point, our results support the usage of both clinical and histopathological findings to predict the renal outcome.

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Table 1 Multivariate analysis models which predict renal survival

	Model 1			Model 2			Model 3		
Parameters	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age at diagnosis	1.01	0.98 to 1.03	0.39	0.98	0.96 to 1.01	0.41	1.01	0.99 to 1.04	0.18
AAV subgroups			0.36			0.21			0.06
GPA versus MPA	2.10	0.87 to 5.08	0.09	2.72	1.07 to 6.92	0.03	4.07	1.45 to 11.39	0.007
EGPA versus MPA	0	0 n/A	0.98	0.02	0 n/A	0.99	0	0 n/A	0.98
RLV versus MPA	2.22	0.86 to 5.75	0.09	2.20	0.80 to 6.05	0.12	2.92	0.99 to 8.60	0.05
Histopathological classification	–	–	**0.04**	–	–	0.08	–	–	–
Focal versus sclerotic	0.20	0.05 to 0.75	0.01	0.31	0.07 to 1.27	0.10	–	–	–
Mixed versus sclerotic	0.32	0.11 to 0.87	0.02	0.25	0.08 to 0.76	0.01	–	–	–
Crescentic versus sclerotic	0.57	0.23 to 1.41	0.22	0.53	0.21 to 1.29	0.16	–	–	–
GFR at diagnosis	–	–	–	0.90	0.86 to 0.95	**<0.001**	–	–	–
ANCA renal risk score	–	–	–	–	–	–	–	–	**0.04**
Moderate versus low	–	–	–	–	–	–	5.62	0.74 to 42.35	0.09
High versus low	–	–	–	–	–	–	10.48	1.32 to 82.88	0.02

Bold indicates statistically significant values at group level.
AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatosis with polyangiitis; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; N/A, not applicable; RLV, renal-limited vasculitis.

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