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Clinical Characteristics and Prognosis of Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis According to Serotype: A Retrospective Study of 349 Chinese Patients

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Abstract

Objective: According to clinical phenotypic classification, there is a significant overlap of clinical features between different anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), and disease classification based on ANCA subtype helps to differentiate clinical phenotypes. We investigated the clinical features and outcomes of patients based on ANCA serotype classification. **Methods:** Clinical and laboratory data were collected retrospectively. We compared clinical manifestations and organ involvement based on serotype. The risk factors for death and renal survival were investigated with univariate and multivariate Cox regression models. **Results:** Patients with MPO-ANCA were predominant, whose median age and lung involvement at diagnosis was higher than that of the PR3-ANCA patients. Compared to the AAV patients without renal involvement, those with renal involvement have older, anemia, low complement C3, and hypoproteinemia, more likely to have cardiovascular and abdominal involvement, and have less lung involvement. Multivariate Cox analysis revealed that age ≥ 65 years (HR = 2.611, $p < 0.001$), serum creatinine (SCR) ≥ 500 μmol/L (HR = 1.546, $p = 0.019$), BVAS ≥ 15 (HR = 1.943, $p = 0.001$), low C3 (HR = 1.696, $p = 0.008$), and hypoproteinemia (HR = 1.438, $p = 0.044$) were associated with mortality. SCR ≥ 500 μmol/L (HR = 13.583, $p < 0.001$), BVAS ≥ 15 (HR = 1.660, $p = 0.020$), low C3 (HR = 1.506, $p = 0.049$) were independent detrimental factors for renal survival, and immunosuppressive treatment was a protective factor for renal survival (HR = 0.523, $p = 0.003$). **Conclusions:** Clinical manifestations varied by AAV categories. Age, SCR, BVAS, low C3 and hypoproteinemia at diagnosis were in-

dependent predictors of mortality. BVAS, low C3, SCR at diagnosis and immunosuppressive treatment were independently related to renal survival in ANCA positive patients.

Keywords

MPO-ANCA, PR3-ANCA, Associated Vasculitis, Characteristics, Renal Involvement, Risk Factors, Survival

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotizing vasculitis that often affects small vessels, leading to multi-system damage throughout the body. Based on clinical manifestations, AAV is commonly divided into three types, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. MPA primarily affects the kidneys and lungs, causing glomerulonephritis, pulmonary capillaritis, and necrotizing vasculitis [2] [3]. GPA frequently involves the upper and lower respiratory tracts; granulomatous inflammation in the upper respiratory tract is a unique feature of GPA patients, and it can also affect the kidneys, leading to necrotizing glomerulonephritis [2] [4]. EGPA often accompanies asthma, eosinophilia, and other allergic features, commonly affecting the lungs and skin. In the latest guidelines, EGPA is considered an independent entity and has been applied in some clinical trials [5]. With the disease definition based on clinical phenotypes, significant overlap in clinical features exists, and due to the difficulty in obtaining sufficient pathological specimens or variations in diagnostic standards, clinical diagnosis of AAV can sometimes be challenging. Classification of AAV based on the ANCA subtype will be a more accessible diagnostic approach in clinical practice. Myeloperoxidase (MPO) and proteinase 3 (PR3) are the main target antigens of ANCA. AAV has been reclassified according to ANCA serological types in recent years into MPO-ANCA positive vasculitis, PR3-ANCA positive vasculitis, and MPO- and PR3-ANCA double-positive vasculitis. ANCA is a useful diagnostic marker, and it may have a specific pathogenic mechanism in vasculitis. MPO- and PR3-ANCA are found in the three clinical phenotypes of AAV, with PR3-positive ANCA often associated with GPA and MPO-positive ANCA associated with MPA [6] [7] [8] [9]. Studies have shown that MPO- and PR3-ANCA vasculitis are genetically different, and disease classification based on the ANCA subtype helps to differentiate clinical phenotypes and better predict AAV recurrence [10]. Until now, few reports have been on the clinical features and outcomes of AAV patients classified by ANCA serotype in China. Therefore, this study aims to explore the clinical characteristics and prognostic factors of the two types of MPO- and PR3-ANCA-positive vasculitis.

2. Patients and Methods

2.1. Patients

We conducted a retrospective study on ANCA-positive AAV patients newly diagnosed at the First Affiliated Hospital of Chongqing Medical University from January 2012 to December 2020. All patients met the AAV standards at the Chapel Hill Consensus Conference [11]. Exclusion criteria: 1) Age < 18, 2) Secondary vasculitis, such as Systemic lupus erythematosus (SLE) and Rheumatoid arthritis (RA), or combined kidney disease (such as IgA nephropathy, Diabetic nephropathy), Hepatitis B Virus or C virus infection, drug-induced vasculitis like Propyl-thiouracil induced AAV, 3) Malignant tumors, 4) PR3- and MPO-ANCA double positive or ANCA negative patients (due to the small sample size), 5) Patients with incomplete baseline information. This study was approved by the local independent ethics committee of the First Affiliated Hospital of Chongqing Medical University (IRB number: 2017-060). This retrospective study is based on case data analysis and does not involve drugs or other intervention measures, so the patients did not sign consent forms.

2.2. Data Collection

The clinical data were collected, such as age, gender, and involvement of kidneys, lungs, upper respiratory tract (nose/sinus/ear), skin, peripheral nervous system, central nervous system, and gastrointestinal tract, were collected from medical records at the time of the primary diagnosis. General clinical manifestations include fever, arthritis, muscle pain, fatigue, and weight loss. Ear, nose, and throat (ENT) involvement includes nasal bleeding, sinusitis, subglottic stenosis, mastoiditis, or hearing loss. Skin manifestations include palpable purpura, ulcers, or biopsy-confirmed rash. Laboratory data collected include complete blood count, 24-hour proteinuria, routine urinalysis, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), serum albumin (ALB), and serum creatinine (SCR) levels, glomerular filtration rate (GFR), complement C3 and C4 levels, detection of ANCA subtype (PR3- or MPO-ANCA) using indirect immunofluorescence and immunoblotting, and histopathological and radiological examinations at the date of diagnosis. The Birmingham vasculitis activity score (BVAS) was used to assess the disease activity index [12].

2.3. Renal Histology

Light microscopy, immunofluorescence, and electron microscopy examined all renal biopsy specimens. Renal histopathology was classified as focal (≥50% normal glomeruli), crescentic (≥50% glomeruli with cellular crescents), mixed (<50% normal, <50% crescentic, and <50% global sclerotic glomeruli), or sclerotic (≥50% sclerotic glomerulus). Global glomerulosclerosis was sclerotic changes in a single glomerulus > 80%. Cellular crescents were defined as cellular components of the segmental or annular crescent > 10% [13].

2.4. Definitions

Renal involvement in AAV was defined by one or more of the following criteria: 1) Proteinuria (>300 mg/d) and/or hematuria (>five red cells/high-power field) and/or red blood cell casts, with or without increased serum creatinine levels; 2) Serum creatinine > 100 μmol/L or estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2; 3) Necrotizing glomerulonephritis without immune complexes in kidney biopsy. Pulmonary involvement was defined as respiratory failure, alveolar hemorrhage, interstitial lung disease (ILD), pulmonary granulomatosis (PG), or radiologically confirmed infiltration, nodules, or cavitation, without evidence of infection. Typical ILD manifestations include honeycombing, reticulation, and ground-glass opacity (GGO). Renal remission includes improvement or disappearance of proteinuria or hematuria and decrease or stabilization of serum creatinine. The progression to End-Stage Renal Disease (ESRD) and doubling serum creatinine were used as an endpoint of renal death. ESRD was defined as irreversible kidney function, estimated glomerular filtration rate below 15 ml/min, lasting at least three months. Renal survival was defined as independent renal replacement therapy. All-cause mortality was defined as death due to any causes.

2.5. Treatment

Treatments of AAV include corticosteroids and cytotoxic drugs. In terms of induction therapy, oral prednisone was prescribed at an initial dose of 1 mg/kg/day for 6 - 8 weeks, reducing doses to 12.5 - 15 mg by 3 - 6 months. Cyclophosphamide (CYC) was given daily orally (2 mg/kg/day) or intravenously (15 mg/kg) every month, and azathioprine (AZA) was given 1 to 2 mg/kg/day mg, and mycophenolate mofetil (MMF) 2 g per day. Some patients with rapidly progressive glomerulonephritis or severe alveolar hemorrhage received three pulses of intravenous methylprednisolone (7 - 15 mg/kg/day) and plasma exchange before induction treatment. Oral or intravenous CYC, AZA or MMF were given for maintenance therapy. No patient received rituximab treatment. In our study, 142 patients (40.7%) did not receive immunosuppressive treatment for personal reasons. All patients were followed up until December 30, 2021, or death.

2.6. Statistical Analysis

The continuous data of normal distribution were expressed as mean ± standard and compared by t-test, while the data of non-normal distribution were expressed as median with interquartile interval (IQR) and compared by nonparametric test (Mann Whitney U test). Categorical data were expressed as numbers and percentages, and the Chi-square test was used for comparisons. Risk factors for death and renal survival were investigated with univariate and multivariate Cox regression models, and the results were expressed as hazard ratios (HRs) with a 95% confidence interval (CI). Risk factors for the survival of patients were analyzed by Kaplan-Meier survival curve analysis. We conducted all statistical

analyses using the SPSS package for Windows v. 27 (IBM). *p*-values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline Characteristics

The baseline characteristics are described in Table 1. Of 349 AAV, 258 (73.9%) patients were classified as MPA, 74 (21.2%) as GPA, and 17(4.9%) as EGPA. Also, based on ANCA subtypes, among 349 AAV patients, 316 patients (90.5%) were classified as MPO-ANCA positive AAV and 33 patients (9.5%) were done as PR3-ANCA positive AAV. The mean age was 63.6 years old. At diagnosis, the most common clinical manifestation was renal (82.2%), followed by general (69.3%), pulmonary (47.0%), and Gastrointestinal (28.7%). In our study, 207 patients (59.3%) received immunosuppressive therapy. The median follow-up time was 23.0 months. The 26 (7.4%) patients were lost to follow-up, and 138 (42.7%) patients died during follow-up.

3.2. Comparison of Variables among MPO- and PR3-ANCA-Positive AAV

The mean age of MPO-ANCA positive AAV patients was older than that of PR3-ANCA positive AAV (64.4 ± 12.2 vs 56.4 ± 15.4, $p = 0.007$). Regarding lung involvement, patients with MPO-ANCA positive AAV were higher than those with PR3-ANCA positive AAV (48.7% vs 30.3%, $p = 0.044$). In particular, there were differences in the presentation of ILD between the two groups (31.3% vs. 9.1%, $p = 0.008$). There were no significant differences in the presence of kidney, abdominal, cardiovascular, and nervous system involvement, and the levels of BVAS, SCR, hemoglobin, serum albumin, complement C3 and C4 between those patients with MPO- and PR3-ANCA positive AAV (Table 2).

3.3. The Clinical Characteristics of ANCA Positive Patients with and without Renal Involvement

Of 349 newly diagnosed ANCA-positive AAV patients, 287 patients with and 62 patients without renal involvement. The patients with renal involvement were older than those without renal impairment (64.2 ± 12.2 vs 60.7 ± 14.8, $p = 0.045$). Compared with patients without renal involvement, patients with renal involvement had more abdominal and heart involvement ($p = 0.002$, $p < 0.001$) and higher BVAS score ($p < 0.001$). By contrast, Patients without renal impairment were more likely to develop interstitial lung disease ($p = 0.034$). General manifestations, ENT symptoms, and Pulmonary involvement were less commonly documented in the Patients with renal involvement than those without ($p = 0.033$, $p = 0.008$ and 0.027, respectively). However, the levels of Hb, serum albumin, complement C3 ($p < 0.001$), general clinical manifestations, and survival rate ($p = 0.033$) in patients with renal involvement were significantly lower than those in patients without renal involvement. There were no statistical differences

in gender, serum type, complement C4, skin, and ENT organ involvement in patients with and without renal involvement (Table 3).

Table 1. Baseline characteristics of 349 patients with ANCA positive AAV.

Variables	Values
Variants of AAV (n, %)	
MPA	258 (73.9)
GPA	74 (21.2)
EGPA	17 (4.9)
Serotype of AAV (n, %)	
MPO-ANCA positive	316 (90.5)
PR3-ANCA positive	33 (9.5)
Age (years)	63.6 ± 12.7
Male gender (n, %)	165 (47.3)
General manifestations (n, %)	242 (69.3)
Skin involvement (n, %)	22 (6.3)
ENT involvement (n, %)	15 (4.3)
Cardiovascular involvement (n, %)	112 (32.1)
Abdominal involvement (n, %)	100 (28.7)
Nervous systemic involvement (n, %)	39 (11.2)
Pulmonary involvement (n, %)	164 (47.0)
Alveolar hemorrhage (n, %)	48 (13.8)
Interstitial lung disease (n, %)	102 (29.2)
Kidney involvement (n, %)	287 (82.2)
Proteinuria and /or hematuria (n, %)	258 (73.9)
SCR (μmol/L)	223 (77, 575.5)
Hemoglobin (g/L)	91 (75.5, 109.0)
Serum albumin (g/L)	30 (26, 35)
Complement C3 (g/L) (0.8 - 1.52 g/L)	0.79 (0.66, 0.93)
Complement C4 (g/L) (0.16 - 0.38 g/L)	0.22 (0.17, 0.27)
BVAS	15 (10, 18)
Immunosuppressive treatment (n, %)	207 (59.3)
Death (n, %)	138 (42.7)
Infection	73 (52.9)
Follow-up time (months)	23.0 (7.5, 45.7)

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat. SCR, serum creatinine, BVAS: Birmingham vascular activity score.

Table 2. The clinical characteristics of patients with MPO-and PR3-ANCA positive AAV.

Variables	MPO-positive (n = 316)	PR3-positive (n = 33)	*p*-value
Age (years)	64.4 ± 12.2	56.4 ± 15.4	0.007
Gender (M/F)	148/168	17/16	0.608
Variants of AAV			
MPA	238 (75.3%)	20 (60.6%)	0.173
GPA	63 (19.9%)	11 (33.3%)	
EGPA	15 (4.8%)	2 (6.1%)	
General manifestation	220 (69.6%)	22 (66.7%)	0.726
Skin involvement	17 (5.4%)	5 (15.2%)	0.069
ENT involvement	14 (4.4%)	1 (3.0%)	1.000
Cardiovascular involvement	105 (33.2%)	7 (21.2%)	0.159
Abdominal involvement	90 (28.5%)	10 (30.3%)	0.826
Nervous system involvement	37 (11.7%)	2 (6.1%)	0.490
Pulmonary involvement	154 (48.7%)	10 (30.3%)	0.044
Alveolar hemorrhage	44 (13.9%)	4 (12.1%)	0.984
Interstitial lung disease	99 (31.3%)	3 (9.1%)	0.008
Kidney involvement	262 (82.9%)	25 (75.8%)	0.306
Proteinuria and/or Hematuria	237 (75.0%)	21 (63.6%)	0.157
SCR (μmol/L)	239 (80.5, 602.5)	145 (68.0, 474.5)	0.153
Hemoglobin (g/L)	90.5 (75.0, 108.0)	97.0 (84.0, 120.5)	0.134
Serum albumin (g/L)	30.0 (26.0, 35.0)	31.0 (25.0, 36.0)	0.895
Complement C3 (g/L)	0.79 (0.66,0.93)	0.80 (0.62, 1.00)	0.883
Complement C4 (g/L)	0.22 (0.17,0.27)	0.23 (0.19, 0.29)	0.368
BVAS	15.0 (11.0,18.0)	15.0 (9.0, 17.5)	0.663
Survival	168 (57.5%)	17 (54.8%)	0.773
Death	124 (42.5%)	14 (45.2%)	

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; M: male F: female; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat, SCR: serum creatinine, BVAS: Birmingham vascular activity score.

Among the patients with renal involvement, 42 patients performed renal biopsy: 38 patients with MPO-ANCA positive AAV and four patients with PR3-ANCA positive AAV. The glomerulosclerosis ratio was higher in patients with MPO-ANCA positive AAV than those with PR3-ANCA positive AAV (28.6% vs. 6.7%, $p = 0.032$). There were no significant differences in the proportions of pathological types, crescent ratio, or glomerular capillary necrosis between the two groups (Table 4).

Table 3. Comparison of patients with or without features of renal involvement at diagnosis.

Variables	Patients with renal involvement (n = 287)	Patients without renal involvement (n = 62)	*p*-value
Age (years)	64.2 ± 12.2	60.7 ± 14.8	0.045
Gender (M/F)	133/154	32/30	0.451
MPO-positive AAV	262 (91.3%)	54 (87.1%)	0.306
PR3-positive AAV	25 (8.7%)	8 (12.9%)	
General manifestation	192 (66.9%)	50 (80.7%)	0.033
Skin involvement	17 (5.9%)	5 (8.1%)	0.733
ENT involvement	8 (2.8%)	7 (11.3%)	0.008
Cardiovascular involvement	105 (36.6%)	7 (11.3%)	<0.001
Abdominal involvement	92 (32.1%)	8 (12.9%)	0.002
Nervous system involvement	28 (9.8%)	11 (17.7%)	0.07
Pulmonary involvement	127 (44.3%)	37 (59.7%)	0.027
Alveolar hemorrhage	41 (14.3%)	7 (11.3%)	0.535
Interstitial lung disease	77 (26.8%)	25 (40.3%)	0.034
Hemoglobin (g/L)	87.0 (73.0, 105.0)	108.5 (95.8, 121.3)	<0.001
Serum albumin (g/L)	29.0 (26.0, 35.0)	33.0 (29.8, 37.0)	<0.001
Complement C3 (g/L)	0.78 (0.64, 0.89)	0.92 (0.79, 1.14)	<0.001
Complement C4 (g/L)	0.22 (0.17, 0.27)	0.23 (0.16, 0.28)	0.963
BVAS	15.0 (12.0, 19.0)	9.0 (8.0, 12.0)	<0.001
Survival	147 (54.7%)	38 (70.4%)	0.033
Death	122 (45.4%)	16 (29.6%)	

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; M: male F: female; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat, BVAS: Birmingham vascular activity score.

Table 4. Renal pathological features of different ANCA associated glomerulonephritis (AAGN).

Variables	MPO-AAGN (n = 38)	PR3-AAGN (n = 4)	*p*-value
Pathological type			
Sclerotic class	13 (34.2%)	0 (0.0%)	0.401
Focal class	5 (13.2%)	1 (25.0%)	0.474
Crescentic class	9 (23.7%)	2 (50.0%)	0.589
Mixed class	11 (28.9%)	1 (25.0%)	1.000
Pathological changes			
Cellular crescent ratio (%)	25.7 (12.3, 57.9)	36.5 (5.8, 72.5)	0.764
Fibrous crescent ratio (%)	0 (0, 12.4)	0 (0, 23.1)	0.803
Glomerulosclerosis ratio (%)	28.6 (13.3, 60.6)	6.7 (1.3, 19.4)	0.032
Glomerular capillary necrosis	16 (42.1%)	2 (50.0%)	1.000

3.4. The Clinical Characteristics of ANCA-Positive Patients with and without ILD

Of the 349 newly diagnosed ANCA-positive AAV patients, 102 developed ILD, and 247 did not. The mean age of patients with ILD was older than that of non-ILD patients (69.9 ± 9.7 vs 61.0 ± 12.9, $p < 0.001$). The rate of MPO-ANCA positive in patients with ILD was higher than that in patients without ILD (97.1% vs 87.9%, $p = 0.008$). The mortality rate of AAV with ILD was significantly higher than that in the non-ILD group (51.0% vs 39.1%, $p = 0.047$). Renal involvement in patients without ILD happened more frequently than in patients with ILD (85.0% vs. 75.5%, $p = 0.034$). However, other organ involvement and the serum levels of Hb, ALB, complement C3 and C4 in patients had no statistical difference between those two groups (Table 5).

Table 5. Comparison of patients with or without ILD characteristics at diagnosis.

Variables	Patients with ILD (n = 102)	Patients without ILD (n = 247)	*p*-value
Age (years)	69.9 ± 9.7	61.0 ± 12.9	<0.001
Gender (M/F)	55/47	110/137	0.110
MPO-positive AAV	99 (97.1%)	217 (87.9%)	0.008
PR3-positive AAV	3 (2.9%)	30 (12.2%)	
General manifestation	69 (67.7%)	173 (70.0%)	0.659
Skin involvement	3 (2.9%)	19 (7.7%)	0.097
ENT involvement	5 (4.9%)	10 (4.1%)	0.946
Cardiovascular involvement	25 (24.5%)	87 (35.2%)	0.051
Abdominal involvement	27 (26.5%)	73 (29.6%)	0.562
Nervous system involvement	11 (10.8%)	28 (11.3%)	0.882
Kidney involvement	77 (75.5%)	210 (85.0%)	0.034
Hemoglobin (g/L)	94.5 (79.8, 116.3)	90.0 (74.0, 107.0)	0.105
Serum albumin (g/L)	31.0 (26.8, 35.3)	30.0 (26.0, 35.0)	0.293
Complement C3 (g/L)	0.77 (0.65, 0.93)	0.81 (0.66, 0.92)	0.245
Complement C4 (g/L)	0.24 (0.17, 0.29)	0.21 (0.17, 0.26)	0.109
BVAS	14.5 (10.0, 17.3)	15.0 (11.0, 18.0)	0.666
Survival	48 (48.9%)	137 (60.9%)	0.047
Death	50 (51.0%)	88 (39.1%)	

AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; M: male F: female; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat, BVAS: Birmingham vascular activity score.

3.5. Risk Factors for the Progression to ESRD and All-Cause Mortality in Patients with ANCA Positive AAV

During follow-up, a total of 106 patients reached the doubling of serum creatinine or ESRD, including 68 (47.9%) of 142 patients who did not receive immunosuppressive therapy and 38 (18.4%) of 207 patients who did receive immunosuppressive therapy. 106 patients had a serum creatinine level above 500 μmol/L at initial diagnosis, and 53 patients had progressed to ESRD at their first visit. Multiple Cox regression analysis showed that BVAS ≥ 15 scores (HR = 1.660, 95% CI 1.083 - 2.543, p = 0.020), Low complement C3 (HR = 1.506, 95% CI 1.001 - 2.264, p = 0.049) and serum creatinine ≥ 500 μmol/L at diagnosis (HR = 13.583, 95% CI 7.646 - 24.128, p < 0.001) were independent risk factors for ESRD, and immunosuppressive treatment was a protective factor for renal survival (HR = 0.523, 95% CI 0.340 - 0.803, p = 0.003) (Table 6).

Table 6. Univariate and multivariate Cox proportional hazard regression analysis for ESRD.

Variables	Univariate		Multivariate	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Age ≥ 65 y (vs. <65 y)	1.248 (0.849 - 1.834)	0.259		
Male gender (Y/N)	0.897 (0.611 - 1.318)	0.581		
MPO-ANCA (vs. PR3-ANCA)	1.155 (0.583 - 2.286)	0.679		
General manifestation (Y/N)	0.796 (0.537 - 1.182)	0.258		
ENT involvement (Y/N)	0.628 (0.199 - 1.979)	0.427		
Cardiovascular involvement (Y/N)	2.575 (1.757 - 3.774)	<0.001	1.174 (0.783 - 1.760)	0.438
Abdominal involvement (Y/N)	3.291 (2.241 - 4.833)	<0.001	1.415 (0.910 - 2.199)	0.123
Nervous system involvement (Y/N)	1.214 (0.692 - 2.131)	0.499		
Pulmonary involvement (Y/N)	1.284 (0.877 - 1.881)	0.199		
ILD (Y/N)	1.126 (0.746 - 1.700)	0.571		
Hematuria or Proteinuria	1.894 (1.127 - 3.183)	0.016	1.027 (0.596 - 1.770)	0.922
Alveolar hemorrhage	1.492 (0.917 - 2.427)	0.107		
SCR ≥ 500 μmol/L (vs. <500 μmol/L)	20.935 (12.266 - 35.732)	<0.001	13.583 (7.646 - 24.128)	<0.001
C3 ≤ 0.8 g/L (vs. >0.8 g/L)	1.769 (1.193 - 2.625)	0.005	1.506 (1.001 - 2.264)	0.049
Hemoglobin ≤ 90 g/L (vs. >90 g/L)	2.836 (1.882 - 4.274)	<0.001	1.090 (0.698 - 1.701)	0.705
ALB < 30 g/L (vs. ≥30 g/L)	1.070 (0.729 - 1.570)	0.731		
BVAS ≥ 15 (vs. <15)	3.577 (2.391 - 5.351)	<0.001	1.660 (1.083 - 2.543)	0.020
Immunosuppressive treatment (Y/N)	0.314 (0.211 - 0.467)	<0.001	0.523 (0.340 - 0.803)	0.003

ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat, SCR: serum creatinine, ILD: interstitial lung disease; ALB: Albumin; BVAS: Birmingham vascular activity score.

During follow-up, 138 (42.7%) patients died; among these, 75(23.2%) patients died within the first six months, and the first-year mortality was 30.3% (98/323). The peak mortality was within the first six months after diagnosis (Figure 1(a)). The main cause of death was infection. The mortality of patients with MPO- and PR3-ANCA positive AAV were 42.5% (124/292) and 45.2% (14/31), with no difference between the two subgroups (p = 0.773) (Table 2, Figure 1(b)). While patients with renal involvement or ILD had a higher mortality rate than those without renal involvement (45.4% vs. 29.6%, p = 0.033) or ILD (51.0% vs. 39.1%, p = 0.047) (Table 3). Kaplan-Meier survival curve analysis suggested that there was a significant difference in survival rate among AAV patients with and without renal involvement (p = 0.037) or ILD (p = 0.018) (Figure 1(c), Figure 1(d)). Multivariate Cox analysis revealed that at diagnosis the age ≥ 65 years (HR: 2.611; 95% CI: 1.739 - 3.920, p < 0.001), serum creatinine ≥ 500 μmol/L at diagnosis (HR: 1.546; 95% CI: 1.075 - 2.224, p = 0.019), Low complement C3 (HR: 1.696; 95% CI: 1.148 - 2.507, p = 0.008), hypoalbuminemia (HR: 1.438; 95% CI: 1.010 - 2.047, p = 0.044), and BVAS ≥ 15 scores (HR: 1.943; 95% CI: 1.317 - 2.866, p = 0.001) were independent risk factors for mortality (Table 7).

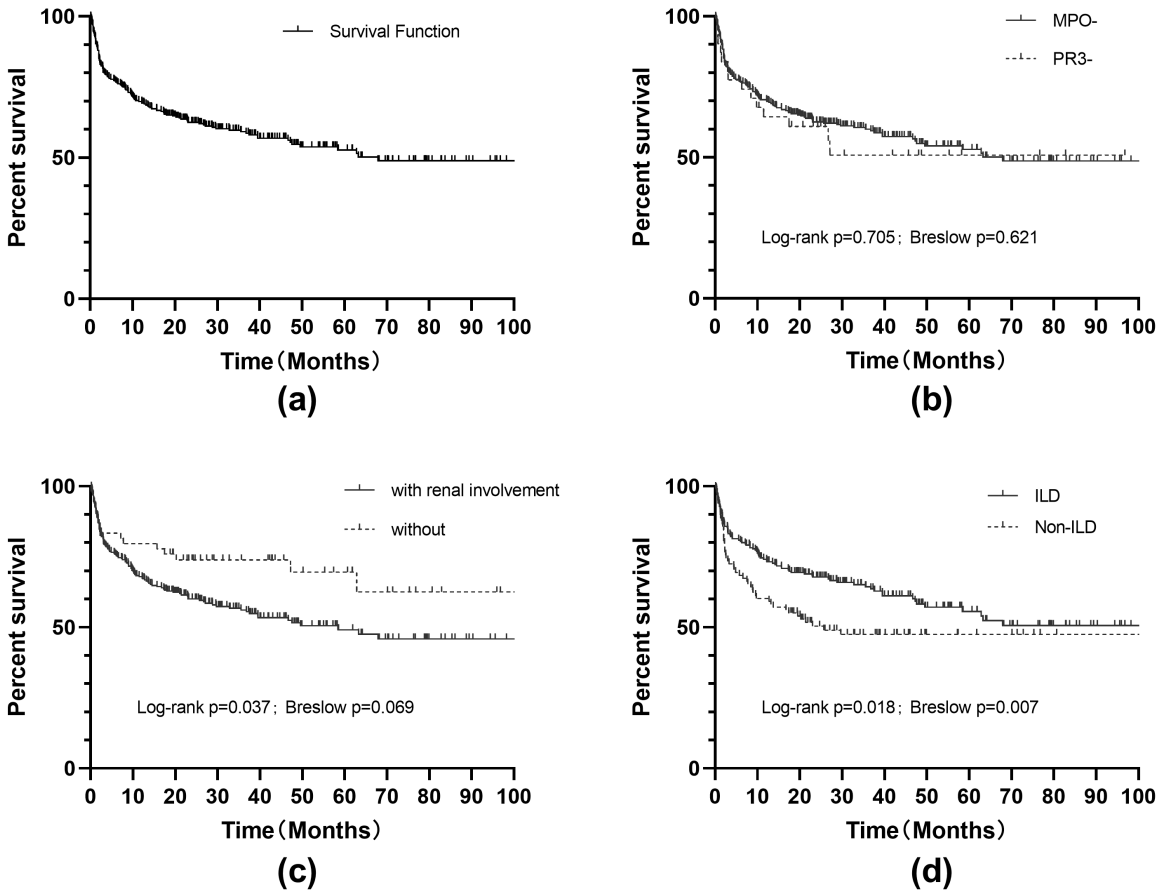

Figure 1. (a) Kaplan-Meier survival curve of 323 patients with ANCA-positive AAV; (b) Kaplan-Meier survival curve of patients with MPO- and PR3-ANCA positive AAV; (c) Kaplan-Meier survival curve of AAV with and without renal involvement; (d) Kaplan-Meier survival curve of AAV with and without ILD.

Table 7. Univariate and multivariate Cox proportional hazard regression analysis for mortality.

Variables	Univariate		Multivariate	
	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Age ≥ 65 y (vs. <65 y)	3.162 (2.152 < 4.644)	<0.001	2.611 (1.739 < 3.920)	<0.001
Male gender (Y/N)	1.230 (0.880 < 1.718)	0.226		
MPO-ANCA (vs. PR3-ANCA)	0.899 (0.517 < 1.562)	0.705		
General manifestation (Y/N)	1.002 (0.701 < 1.430)	0.993		
ENT involvement (Y/N)	0.860 (0.352 < 2.1)	0.740		
Cardiovascular involvement (Y/N)	1.187 (0.839 < 1.680)	0.334		
Abdominal involvement (Y/N)	1.536 (1.086 < 2.171)	0.015	0.935 (0.619 < 1.413)	0.751
Nervous system involvement (Y/N)	0.934 (0.546 < 1.598)	0.804		
Pulmonary involvement (Y/N)	1.432 (1.024 < 2.004)	0.036	1.156 (0.718 < 1.860)	0.551
ILD (Y/N)	1.515 (1.07 < 2.145)	0.019	1.042 (0.622 < 1.747)	0.875
Alveolar hemorrhage (Y/N)	1.298 (0.829 < 2.031)	0.254		
Kidney involvement (Y/N)	1.728 (1.026 < 2.912)	0.040	0.826 (0.453 < 1.503)	0.531
SCR ≥ 500 μmol/L (vs. <500 μmol/L)	1.935 (1.376 < 2.721)	<0.001	1.546 (1.075 < 2.224)	0.019
C3 ≤ 0.8 g/L (vs. >0.8 g/L)	2.554 (1.779 < 3.667)	<0.001	1.696 (1.148 < 2.507)	0.008
Hemoglobin ≤ 90 g/L (vs. >90 g/L)	1.998 (1.419 < 2.813)	<0.001	1.322 (0.893 < 1.959)	0.163
ALB < 30 g/L (vs. ≥30 g/L)	1.843 (1.316 < 2.580)	<0.001	1.438 (1.010 < 2.047)	0.044
BVAS ≥ 15 (vs. <15)	2.979 (2.114 < 4.197)	<0.001	1.943 (1.317 < 2.866)	0.001
Immunosuppressive treatment (Y/N)	0.757 (0.541 < 1.058)	0.103		

ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3. General manifestation includes myalgia, arthritis, fever ≥ 38˚C, weight loss ≥ 2 kg. ENT means ear, nose, and throat, SCR: serum creatinine, ILD: interstitial lung disease; ALB: Albumin; BVAS: Birmingham vascular activity score.

4. Discussion

We retrospectively analyzed and compared the clinical characteristics and potential risk factors for the prognosis of 349 newly diagnosed ANCA-positive patients based on ANCA serological typing and whether AAV was associated with ILD or kidney involvement. This study shows that MPO-ANCA-positive patients have an absolute advantage in the Chinese AAV population, and compared to PR3-ANCA-positive patients, MPO-ANCA-positive patients were older, with lung and kidney damage being the most common.

AAV is a systemic disease affecting the ears, nose, throat, skin, joints, lungs, kidneys, and cardiovascular system. Our study found that compared to PR3-ANCA positive patients, MPO-ANCA positive patients have a higher average age at diagnosis, increased lung involvement, especially a significantly higher proportion of ILD ($p = 0.008$), but no difference in kidney, heart, digestive tract, and other organ involvement. In clinical typing, previous reports have shown that MPA often involves the kidneys and lungs, while GPA mainly involves the upper and lower respiratory tracts. We found that MPA patients mainly show

MPO-ANCA positivity (75.3%), while GPA often presents as PR3-ANCA positive (33.3%) in Chongqing. Studies by Zhao Ming Hui [14] found that in northern China, MPO-ANCA-positive patients mainly present as MPA, GPA. The incidence of ANCA was closely related to regional and environmental factors. It was speculated that the difference was not significant in Western China, but more clinical studies were needed to confirm it.

The kidney was one of the main organs involved in ANCA-associated vasculitis, often manifested as proteinuria, hematuria, and kidney failure, progressive renal function impairment. This study found that 82.2% (287/349) of ANCA-positive AAV patients had kidney involvement at the initial diagnosis. Compared to ANCA patients without kidney involvement, those with kidney involvement were more likely to have gastrointestinal symptoms, possibly related to hypoalbuminemia after kidney damage. In AAV patients with renal involvement, the incidence of non-specific manifestations such as fever, weight loss, muscle pain, and ENT involvement were low, suggesting that AAV patients with non-specific manifestations and ENT involvement may have a lower likelihood of renal involvement.

In our research, older patients tend to have more renal involvement. Those with kidney involvement exhibit higher disease activity, a greater tendency toward anemia, and reduced serum albumin levels, which could be attributed to decreased erythropoietin, protein loss in urine, insufficient nutritional intake, and inflammatory states. Concurrently, patients with renal implications showed reduced complement C3 levels. AAV had previously been categorized as pauci-immune glomerulonephritis. Recent studies [14] [15] had highlighted the significant role of complement system activation (especially the alternative pathway) in the pathogenesis of AAV. Low-intensity deposition of complement components in tissues was prevalent, particularly at sites of inflammation and necrosis [16], leading to decreased circulating C3 levels. These correlate with pronounced proteinuria and impaired renal function. AAV patients frequently experience renal dysfunction, potentially culminating in ESRD, making renal replacement therapy indispensable.

Multivariable Cox regression analysis confirmed that SCR ≥ 500 μmol/L at diagnosis, low complement C3, and BVAS (≥15 scores) were risk factors for ESRD progression. At the same time, immunosuppressive treatment acted as a protective factor for renal survival, and findings emphasized the importance of early diagnosis and timely immunosuppressive treatment in ANCA-positive vasculitis patients for better renal outcomes and potentially favorable prognosis. Further analyzing 42 biopsy-proven cases, we observed that compared to PR3-ANCA-positive patients, those positive for MPO-ANCA exhibited a higher rate of glomerular sclerosis, which suggests that MPO-ANCA-positive patients harbor more chronic lesions and interstitial fibrosis, which was consistent with previous studies [17]. This disparity might be because PR3-ANCA-positive patients experience a more rapid deterioration of renal function than MPO-ANCA counterparts before treatment. The latter's renal function progression was slow-

er, presenting more insidiously, leading to potentially later recognition of these patients. Some research indicates that both ANCA type and titer were independent risk factors for the progression to ESRD in AAV patients [18] [19] [20]. However, our study did not find a correlation between ANCA type and ESRD progression, potentially due to our smaller sample size. The predictive value of ANCA titer for renal outcomes in AAV patients requires verification with a larger sample.

Furthermore, we also found that AAV patients without kidney involvement were more likely to have lung involvement, particularly ILD, possibly accompanied by milder kidney damage. Zhou *et al.* [21] found that in AAV with lung involvement, 80% - 97% had kidney involvement, including 24% - 42% of patients had renal dysfunction, but kidney injury was the lightest in the ILD group, significantly lower than the hemoptysis group, granuloma group. Previous studies have shown that respiratory distress and pulmonary fibrosis negatively correlate with kidney involvement. This negative correlation may be related to different disease characteristics caused by different mechanisms of complex autoimmune diseases [22] [23]. Patients with lung involvement, such as pulmonary interstitial fibrosis, can occur at the same time or before other symptoms of ANCA vasculitis. Therefore, patients may have relatively milder kidney injury when they seek medical treatment early due to lung involvement and the disease had not yet progressed. In terms of lung involvement, this study showed that older patients were more likely to have ILD, with an average age difference of 9 years, suggesting that interstitial lung lesions develop slowly and insidiously. Early intervention may reduce the possibility of interstitial lung lesions. We found that compared to PR3-ANCA positive, MPO-ANCA positive patients have a higher incidence of ILD; This may be due to MPO-ANCA causing the production of oxidation products, thus activating the proliferation of lung fibroblasts, extracellular matrix deposition, and promoting pulmonary fibrosis [24]. However, Zhou *et al.* reported that MPO-ANCA negative patients have the most common ILD, while PR3-ANCA negative patients have the least common ILD [21]. Pulmonary fibrosis was more common in MPO-ANCA positive patients, and they were more likely to suffer from ILD, and there have been reports that the incidence of ILD in ANCA-positive patients in Asian countries such as China and Japan were higher than in Europe [25]. These may be due to the higher incidence of MPO-ANCA positive in the Asian population, and when diagnosing AAV, it should be closely monitored for ILD by regularly performing chest imaging examinations on patients with MPO-ANCA.

During the follow-up period of this study, 138 (42.7%) patients died. Research reports that the mortality rate of AAV patients ranges from 11% to 40% [26] [27] [28]. The mortality rate in our study was significantly higher than in other studies. Further multivariate COX regression analysis found that age over 65, SCR ≥ 500 μmol/L at initial diagnosis, hypoalbuminemia, low complement C3, and BVAS (≥15 scores) were independent risk factors for all-cause death in patients. Therapeutic strategies using cyclophosphamide or rituximab have been

proven to improve the overall survival rate of AAV patients. The use of steroids combined with immunosuppressants and plasma exchange has increased the survival rate of patients [29], and infection was still the leading cause of death in AAV patients. In this study, infection was the leading cause of death (52.9%), consistent with previous research results [30] [31]. We also found that the mortality rate was the highest in the early stages of disease treatment (within the first six months), possibly due to patients receiving immunosuppressive treatment early or having high disease activity and hypoalbuminemia, leading to infection. Additionally, a recent study reported that AAV patients have IFN (Type I interferon) system dysfunction, leading to patients being prone to long-term infections [32]. Patients with kidney involvement were more likely to have other system injuries, with a higher risk of patient death. These suggest that early detection, early intervention, kidney function protection, and proteinuria control were crucial for patient prognosis.

The BVAS was reliable for assessing disease activity and severity and strongly correlates with disease activity. COX multivariate regression analysis found that a high BVAS score at diagnosis was an independent risk factor for all-cause death and ESRD progression in ANCA-positive AAV patients. In our cohort, ANCA-positive AAV patients had worse baseline kidney function and higher BVAS scores at diagnosis, indicating high disease activity, suggesting a worse prognosis.

In recent years, more and more studies have proposed the role of the complement alternative pathway in the pathogenesis of ANCA-related vasculitis [33]. We found that low complement C3 level was an independent factor for all-cause mortality and a risk factor for ESRD progression, consistent with previous reports [34] [35]. Reduced circulating complement C3 may reflect the severity of the disease, and targeting the suppression of the complement system was a promising strategy for inducing AAV remission.

Our study has limitations: Firstly, this was a retrospective study, and the period of the enrolled patients was relatively large, which may lead to management bias. Secondly, the patients in this study all come from a single center and were limited to individuals in mainland China. Thirdly, the sample size of PR3-ANCA patients was small, which may affect the statistical power of the differences between MPO- and PR3-ANCA AAV. Fourthly, only 42 kidney biopsy examinations were performed, which may weaken the ability to demonstrate the correlation between renal pathological changes and prognosis.

In conclusion, we systematically described the clinical manifestations and prognosis of ANCA-positive AAV. MPO-ANCA-positive vasculitis was the most common. The SCR ≥ 500 μmol/L, low complement C3, and BVAS ≥ 15 scores at initial diagnosis were identified as independent risk factors for ESRD progression and all-cause mortality in ANCA-positive AAV patients. At the initial diagnosis, age over 65 and hypoalbuminemia were independent risk factors for ANCA-positive AAV patients, while immunosuppressive treatment was a protective factor for renal survival. To improve the prognosis of AAV patients, we

should identify these risk factors for ESRD and mortality as early as possible and strengthen treatment and prognostic management.

Author Contributions

H.X. designed the clinical trial, analyzed the data, and completed the manuscript. M.F., X.L. and D.Z. collected and organized the data and followed up with patients. L.C. undertook data collection, oversight of analysis, and modified the manuscript. All authors read and approved the final manuscript.

Institutional Review Board Statement

This study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (IRB number: 2017-060).

Informed Consent Statement

The data are anonymous, and the requirement for informed consent was therefore waived.

Availability of Data and Materials

The datasets used and or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Financial/Other Relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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