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ORIGINAL ARTICLE

Predictors of renal and patient outcomes in anti-neutrophil cytoplasmic antibody-associated vasculitis: Our single-center, tertiary care experience

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ABSTRACT

Objectives: This study aims to assess the different predictors of renal and patient prognosis in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) patients with and without renal involvement.

Patients and methods: A total of 79 patients (51 males, 28 females; mean age: 57.3±14.2 years; range, 18 to 71 years) with AAV between January 2006 and November 2019 were retrospectively analyzed. Demographic and laboratory data including the complement 3 (C3) serum levels and renal biopsy findings were extracted from the electronic and printed medical records of the hospital registry. Survival, renal survival, remission, and relapse outcomes were analyzed.

Results: A total of 35% of the patients with renal involvement progressed to end-stage renal disease (ESRD). The dialysis requirement at the time of admission (hazard ratio [HR]: 21.95 [2.93-164.22]; p=0.003), estimated glomerular filtration rate (eGFR) (HR: 0.97 [0.94-0.99]; p=0.024) and Five-Factor Score (FFS) ≥2 at the time of diagnosis (HR: 3.59 [1.08-11.94]; p=0.037) were the predictors of ESRD. The five-year patient survival rate was 87.1%. The only predictor of mortality was age (HR: 1.07 [1.01-1.14]; p=0.024). The patients with hypocomplementemia (22%) had a lower remission rate (p=0.049), FFS ≥2 at the time of diagnosis (p=0.026), and higher levels of hematuria (p=0.004) and proteinuria (p=0.037). The FFS ≥2 at the time of diagnosis was an independent predictor of relapse (HR: 8.9 [1.02-77.36]; p=0.047).

Conclusion: Our study suggests that the baseline renal function and FFS ≥2 at the time of diagnosis are the major prognostic factors for progression to ESRD in AAV patients. In addition, AAV patients with hypocomplementemia may have a lower remission rate.

Keywords: Anti-neutrophil cytoplasmic antibody-associated vasculitis, end-stage renal disease Five Factor Score, hypocomplementemia, renal survival.

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of small vessel vasculitis that can be life-threatening, if the diagnosis or therapy is delayed. The disease is classified mainly based on the clinical and pathological features: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA), and renal-limited vasculitis (RLV) as defined by the lack of extrarenal manifestations.[1] The first, GPA, is characterized by extravascular necrotizing granulomatous inflammation in the upper and lower respiratory tract with renal involvement, and is more commonly associated with cytoplasmic ANCA (c-ANCA). On the other hand, MPA, EGPA, and RLV are more frequently associated with

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perinuclear ANCA (p-ANCA).[2] Renal involvement occurs in almost 70% of patients with GPA[3] and 100% with MPA.[4] It is associated with poor renal and patient survival.[5,6] Renal replacement therapy (RRT) is often needed at the time of diagnosis, although renal recovery and withdrawal from dialysis may occur during follow-up. Among AAV patients with renal disease, 20 to 25% of them develop end-stage renal disease (ESRD).[7]

Although it is difficult to predict, several studies have investigated different determinants of renal and patient outcomes in AAV.[6,8,9] Baseline renal function and some histopathological parameters have been reported to be major determinants of renal survival.[2] Several studies have also indicated that hypocomplementemia signifies a poor prognosis in AAV.[10,11] There is a growing experimental and clinical evidence supporting the involvement of the alternative complement pathway in AAV.[12] *In vitro* experiments have demonstrated that the neutrophils stimulated by ANCA cause C3 activation (cleavage of C3 into C3a and C3b) and formation of complement 5a (C5a) fragments, inducing neutrophil chemotaxis and maintenance of the inflammatory response.[13] In a recent meta-analysis,[14] compared to controls, patients with active AAV had significantly higher levels of activated complement components, including C5a, C3a, factor B, and membrane attack complex. Therefore, many researchers speculated that a reduction of the serum C3 level could be a consequence of severe AAV at diagnosis. Low serum C3 levels have been reported in 4 to 35% of patients with AAV in previous studies.[10,15-21] Nevertheless, data regarding the prognostic significance of renal complement deposition in patients with AAV are limited. One of the few studies showed that renal C3 deposition correlated with severe renal damage, more significant proteinuria, and overall disease activity.[15]

Despite the recently reduced mortality rates reported in AAV, approximately one-third of patients experience relapse within five years after diagnosis.[22] Relapses can be prevented by developing treatment and monitoring strategies defining the patients at high risk.[23,24]

In this study, we aimed to assess different variables including hypocomplementemia and renal C3 deposition in predicting prognosis in AAV patients with and without renal involvement.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Celal Bayar University, Faculty of Medicine, Department of Nephrology and Rheumatology between January 2006 and November 2019. We retrospectively searched the medical records of our hospital registry to identify the patients who were diagnosed with AAV. All patients fulfilled either the 1990 American College of Rheumatology (ACR) criteria or the 2012 Chapel Hill Consensus Conference Nomenclature of GPA, MPA, EGPA, or RLV.[25] Renal-limited vasculitis was defined as idiopathic, biopsy-proven, pauci-immune glomerulonephritis without systemic disease manifestations. Patients with comorbid renal diseases, secondary vasculitis such as Henoch-Schönlein purpura, lupus vasculitis, cryoglobulinemia, and infection were excluded from the study. Finally, a total of 79 patients (51 males, 28 females; mean age: 57.3±14.2 years; range, 18 to 71 years) with AAV were included. A written informed consent was obtained from each patient. The study protocol was approved by the Celal Bayar University, Faculty of Medicine Ethics Committee (20.478.486/15.01.2020). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

The medical records of the patients were examined and clinical data including demographic details, clinical and laboratory findings, histopathological findings of the biopsies, treatment, and follow-up data were obtained. Details of treatment and clinical outcomes (including renal function, proteinuria, hematuria, dialysis requirement, inflammatory markers (erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) were collected at admission and during follow-up. Anti-neutrophil cytoplasmic and perinuclear antibodies (c-ANCA and p-ANCA) were determined by indirect immunofluorescence (IIF). Hypocomplementemia was defined as having C3 values lower than 90 mg/dL and/or C4 values below 10 mg/dL.

At the time of presentation, skin (palpable purpura, ulcers, or rashes confirmed by biopsy), eyes (retinal vasculitis, uveitis, episcleritis, scleritis, conjunctivitis, or orbital mass), musculoskeletal (arthralgia, or arthritis), ear-nose-throat (ENT) (bloody nasal discharge, sinusitis, subglottic stenosis, otomastoiditis, or hearing loss), pulmonary (alveolar hemorrhage, parenchymal lung nodules, or other vasculitis-specific chest findings), cardiovascular (pericarditis, myocarditis, or conduction system abnormalities), gastrointestinal (infarct, ischemia, or perforation), renal, and neurological (hemorrhage, infarct or brain lesions confirmed by computed tomography or magnetic resonance imaging, or peripheral nerve abnormalities) involvements were recorded. Organ involvement was defined as the organ-specific findings characteristic of vasculitis.

Renal involvement was defined as the presence of proteinuria, active urinary sediment (leukocyturia, hematuria or red blood or white blood cell casts), and/or an increase in serum creatinine values over 1.4 mg/dL. Rapidly progressive glomerulonephritis (RPGN) was defined as the presence of hematuria, proteinuria, or urinary casts associated with a decline in renal function within weeks or months. Hematuria and proteinuria were defined as ≥2+ hemoglobin or protein in urinalysis using a testing strip. We used 24-h proteinuria in the analysis. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation (MDRD) formula.[26] The eGFR of the patients were the values at the time of the diagnosis. Renal biopsy histology was classified into four categories as focal, crescentic, mixed-type, or sclerosing groups according to the 2010 Berden's histological classification of AAV.[27]

We evaluated the factors to predict the relapse and prognosis using the Five Factor Score (FFS) revised (2009) form, which was identified and proposed by the French Vasculitis Study Group (FVSG). It includes the following five items: *(i)* age >65 years, *(ii)* cardiac insufficiency, *(iii)* gastrointestinal involvement, *(iv)* renal insufficiency (stabilized peak plasma creatinine concentration >1.7 mg/dL [150 μmol/L]), and *(v)* absence of ENT manifestations (otherwise associated with a better prognosis). The presence of each factor is one point. The FFS score ranges from 0 to 2; a score of 0 is given when none of the factors are present, a score of 1 for one factor, and a score of 2 for two or more factors. This scoring system has been shown to be correlated with prognosis.[28]

Death from any cause was noted. Relapse was defined as the reactivation of vasculitis in any organ system, while ESRD was defined as an eGFR of <15 mL/min/1.73 m^2 or requirement of RRT for >3 months. Remission on or off therapy required the absence of dysmorphic urinary red blood cells and no evidence of vasculitic lesions or symptoms in any organ.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY., USA). Descriptive statistics were expressed in mean ± standard deviation (SD) and median (interquartile range [IQR]) for continuous normal and non-normally distributed variables, respectively. Categorical variables were expressed in number and frequency. Clinical and laboratory variables were compared using the analysis of variance (ANOVA), Mann-Whitney, Chi-square, or Fisher's test, where applicable. Survival curves were calculated using the Kaplan-Meier estimates, and differences were tested with the log-rank test. The Cox proportional hazard analysis for each outcome parameter was done. The results were expressed in hazard ratio (HR) with 95% confidence interval (CI). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Initially, 79 consecutive patients were diagnosed with AAV in our hospital. There were only two patients with EGPA and, due to this small number, they did not undergo further analysis. All patients had a biopsy-proven diagnosis. The distribution of biopsies was as follows: renal in 57 (79%), lung in eight (11%), ENT in four (6%), and skin in three (4%). The mean follow-up time was 50 months. Of the patients, 59 (77%) had renal involvement. Demographic and clinical data of the patients are presented in Table 1.

The patients who had an organ- or a life-threatening disease were treated with an induction regimen consisting of glucocorticoids

Table 1. Demographic and clinical characteristics of patients

	Total (n=77)			With renal involvement (n=59)			Without renal involvement (n=18)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			57.3±14.2			58.6±14.6			52.7±11.8	0.024
Sex										
Female	28	36.4		19	32.2		9	50		0.262
Duration of vasculitis (month)			49.7±46.5			56.8±46.9			27.1±18.1	0.048
Clinical classification										<0.001
MPA	18	23.4		18	31.0		0	0		
GPA	39	50.6		23	39.7		18	100		
RLV	19	24.7		18	29.3		0	0		
Extra-renal involvement										
Pulmonary	41	53.2		29	49.2		12	66.7		0.281
ENT	29	37.7		15	25.4		14	77.8		<0.001
Musculoskeletal	21	27.3		8	13.6		13	72.2		<0.001
Skin	12	15.6		8	13.6		4	22.2		0.459
Gastrointestinal	2	2.6		2	3.4		0	0		0.428
Neurological	7	9.1		5	8.5		2	11.1		0.663
Clinical presentation and outcomes										
Hypertension	31	40.3		30	51.7		1	5.9		0.001
Initial RRT	31	40.3		31	52.5		0	0		
ESRD	21	27.3		21	35.6		0	0		
Remission	46	59.7		28	47.4		18	100		<0.001
Relaps	21	27.3		21	35.6		0	0		0.05
Death	10	12.9		10	16.9		0	0		0.016
FFS										
FFS<2	30	38.9		12	20.3		18	100		<0.001
FFS≥2	47	61.0		47	79.6		0	0		<0.001
Induction therapy										<0.001
CYC + GC	58	75.3		55	93.2		3	16.6		
RTX + GC	10	12.9		5	8.4		5	27.7		
MTX + GC	10	12.9		0	0		10	55.5		
Plasmapheresis	1	1.3		1	1.7		0	0		
IVIG	1	1.3		0	0		1	5.5		
Maintenance therapy										<0.001
AZA ± GC	62	80.5		56	95		6	33.3		
RTX ± GC	5	6.5		3	5		2	11.1		
MTX ± GC	10	12.9		0	0		10	55.5		

SD: Standard deviation; MPA: Microscopic polyangiitis; GPA: Granulomatous polyangiitis; RLV: Renal-limited vasculitis; ENT: Ear, nose, throat; RRT: Renal replacement therapy; ESRD: End stage renal disease; FFS: Five factor score, CYC: Cyclophosphamide; GC: Glucocorticoids; RTX: Rituximab; MTX: Methotrexate; IVIG: Intravenous immunoglobulin; AZA: Azathioprine.

(GCs) in combination with either rituximab (RTX) or cyclophosphamide (CYC). We preferred a CYC-based regimen, particularly in patients presenting with more severe renal disease and/or pulmonary hemorrhage. We treated one patient with GCs in combination with both RTX and CYC. One patient with alveolar hemorrhage received intravenous immunoglobulin (IVIG) in addition to the standard treatment regimen due to central nervous system infection. The plasmapheresis was required in a patient with severe alveolar hemorrhage in association with CYC plus GC therapy for the first 14 days. The maintenance regimen was low-dose GC with RTX/methotrexate/azathioprine. The induction and maintenance treatment regimens of the patients are given in Table 1.

The patients with renal involvement had lower hemoglobin, albumin, and C3 levels than those without renal involvement. The laboratory data of the patients at admission are given in Table 2.

AAV classification systems

Clinical classification

We classified all patients into clinical diagnostic groups: GPA, n=39 (50.6%); MPA,

Table 2. Laboratory data of patients at admission

	Total (n=77)			With renal involvement (n=59)			Without renal involvement (n=18)			
Variable	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
WBC (×10³/μL)			10.6±4.6			10.6±4.0			10.9±4.0	0.413
Hemoglobin (g/dL)			10.4±2.0			9.7±1.6			12.5±1.8	<0.001
Platelet			300.2±122.1			288.4±105.4			338.4±162.8	0.278
CRP (mg/L)			58.0±56.5			62.3±45.5			46.8±29.4	0.062
ESR (mm/h)			59.0±33.0			64.2±32.2			44.3±31.6	0.010
Serum creatinine (mg/dL)			3.4±2.6			4.3±2.4			0.7±0.1	<0.001
eGFR (mL/min/1.73 m²)			43.3±39.7			25.4±23.6			101.0±17.3	<0.001
Serum albumin (g/L)			3.2±0.8			2.9±0.7			4.0±0.7	<0.001
C3 (mg/dL)			118.7±39.8			114.6±37.9			138.3±44.7	0.042
C4 (mg/dL)			27.4±11.0			27.8±11.7			25.3±7.3	0.334
Hypocomplementemia	15	19		15	27		0	0		0.042
MPO-ANCA	23	29.9		18	52.9		5	38.5		0.288
PR3-ANCA	24	31.2		16	47.1		8	61.5		
p-ANCA	33	42.9		27	44.8		6	33		0.323
c-ANCA	30	38.8		21	36.2		9	50		
ANCA (-)	14	18.3		11	19		3	17		
ANA	19	24.7		15	36.6		4	28.6		0.420
Proteinuria (g/24 h)			2.6±2.2			3.5±3.3			0.008±0.035	<0.001
Hematuria (Urinary erythrocytes/HPF)			105.4±68.9			139.1±82.6			0	<0.001
C3 deposits in renal biopsy specimens				9	18		0	0		

SD: Standard deviation; WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; eGFR: Estimated glomerular filtration rate; C3: Complement 3; C4: Complement 4; MPO-ANCA: Myeloperoxidase-anti-neutrophil cytoplasmic antibody; PR3-ANCA: Proteinase 3-anti-neutrophil cytoplasmic antibody; p-ANCA: Perinuclear- anti-neutrophil cytoplasmic antibody; c-ANCA: Cytoplasmic-anti-neutrophil cytoplasmic antibody; ANA: Anti-nuclear antibody; HPF: High-power field.

n=18 (23.4%); and RLV n=19 (24.7%). The mean age at diagnosis was 56.8±11.1 years in GPA patients, 64.9±14.6 years in MPA patients, and 53.3±16.1 years in RLV patients (p=0.006). Twenty-three patients with GPA (59%) and all patients in MPA and RLV groups had renal involvement. In addition, ENT involvement was observed in 89% of the GPA patients and 36% of the MPA patients (p<0.001). A total of 66% of the GPA and MPA patients had lung involvement. Joint involvement was noted in 38% of the GPA patients and 11% of the MPA patients (p=0.001). There was a significant relationship between the FFS and clinical classification (p<0.001). Seventeen patients with MPA (94%), 16 patients with RLV (84%), and 16 of GPA patients (41%) had FFS ≥2 at diagnosis. The mean hemoglobin values were lower in MPA (9.5±1.3 g/dL) and RLV (9.6±1.9 g/dL) patients than in GPA (11.2±2.0 g/dL) patients (p=0.006). The mean ESR was higher in the MPA group (79.6±29.1 mm/h) than in the GPA (51.6±31.8 mm/h) and RLV (52.5±34.3 mm/h) groups (p=0.036). The mean creatinine value was similar in the MPA (4.2±2.0 mg/dL) and RLV (4.8±2.7 mg/dL) groups, but higher than in the GPA (2.8±2.6 mg/dL) group (p=0.001). There was a significant difference in the mean eGFR values between the groups (GPA (55.7±42.3 mL/min/1.73 m²), MPA (21.6±17.2 mL/min/1.73 m²), RLV (24.3±27.3 mL/min/1.73 m²), p=0.001). The mean amount of proteinuria at diagnosis was 4,847.33±4,227.97 mg/24 h in RLV patients, 2,898.88±1,634.47 mg/24 h in MPA patients, and 1,524.28±992.65 mg/24 h in GPA

patients (p=0.004). The amount of hematuria (urinary erythrocytes/high-power field [HPF] in microscopy) was higher in the MPA group (p=0.035).

Serological classification

All patients were identified by IIF and 47 patients by enzyme-linked immunosorbent assay (ELISA) for ANCA positivity. According to the IIF test patients were divided into p-ANCA (n=33), c-ANCA (n=30), and negative ANCA (n=14) subgroups. Of note, 30 patients were excluded, since the test was unable to be performed and 47 patients were determined as PR3-ANCA (n=24) and MPO-ANCA (n=23).

Hypocomplementemia

Overall, 68 of the 77 patients (88%) had C3 and C4 complement levels measured at admission. Mean serum C3 level was 118.7±39.8 mg/dL and was significantly lower in the patients with renal involvement (114.6±37.9 mg/dL), compared to those without renal involvement (138.3±44.7 mg/dL) (p=0.042). Hypocomplementemia was detected in 15 patients (22%) with AAV (7 MPA, 3 GPA, and 5 RLV). All these 15 patients had renal involvement. Among the patients with hypocomplementemia, 10 (67%) needed dialysis and 14 (93%) had FFS ≥2 at admission. Four (36%) patients achieved remission, three (20%) patients died, and nine (60%) patients progressed to ESRD during the follow-up in the hypocomplementemic group.

There were statistically significant differences between the patients with and without hypocomplementemia. The patients with hypocomplementemia had a higher rate of hematuria (p=0.004), a lower remission rate (p=0.049), and a higher FFS≥2 at diagnosis (p=0.026). The patients with hypocomplementemia were older (64.3±15.8 *vs.* 56.3±13.9 years, p=0.014), had lower mean hemoglobin levels (9.3±0.9 *vs.* 10.6±2.2 g/dL, p=0.026), lower mean albumin levels (2.6±0.7 *vs.* 3.3±0.7 g/L, p=0.001), higher mean level of proteinuria (4.4 *vs.* 2.5 g/24 h, p=0.037), and higher mean ESR levels (74.1±26.2 *vs.* 57.1±34.0 mm/h, p=0.034). There were no significant differences according to either clinical, serological, or histopathological classification.

Renal histopathological classification

Fifty-seven patients had a renal biopsy at diagnosis. All biopsies were analyzed by light microscopy and immunofluorescence staining. Forty-seven patients had histopathological classification as follows: focal (n=8), crescentic

Table 3. Data of patients with C3 deposition

	Patients								
	1	2	3	4	5	6	7	8	9
Sex	Male	Female	Male	Male	Female	Male	Male	Female	Male
Age (year)	27	65	54	38	59	67	53	77	66
Follow-up (months)	96	50	154	90	84	6	48	112	8
AAV type	RLV	MPA	RLV	RLV	GPA	GPA	GPA	MPA	RLV
Five Factor Score	2	2	2	1	2	2	2	2	2
Creatinine (mg/dL)	7.2	4.78	4.8	5.8	2.2	5.2	3.5	4.85	2.4
Proteinuria (g/24 h)	3	1.7	1.3	4	2.5	2.4	2.4	3.5	6.4
Hypocomplementemia	No	No	Yes	No	No	No	No	Yes	No
Initial dialysis	Yes	Yes	Yes	No	No	Yes	No	Yes	No
ESRD	Yes	Yes	Yes	No	No	No	No	Yes	No
Remission	No	No	No	Yes	Yes	Yes	Yes	No	No
Death	No	No	No	No	No	Yes	No	No	Yes
Histopathology	Mixed-type	Mixed-type	Crescentic	Crescentic	Mixed-type	Crescentic	Crescentic	Mixed-type	Mixed-type

AAV: ANCA associated vasculitis; RLV: Renal-limited vasculitis; MPA: Microscopic polyangiitis; GPA: Granulomatous polyangiitis; ESRD: End stage renal disease.

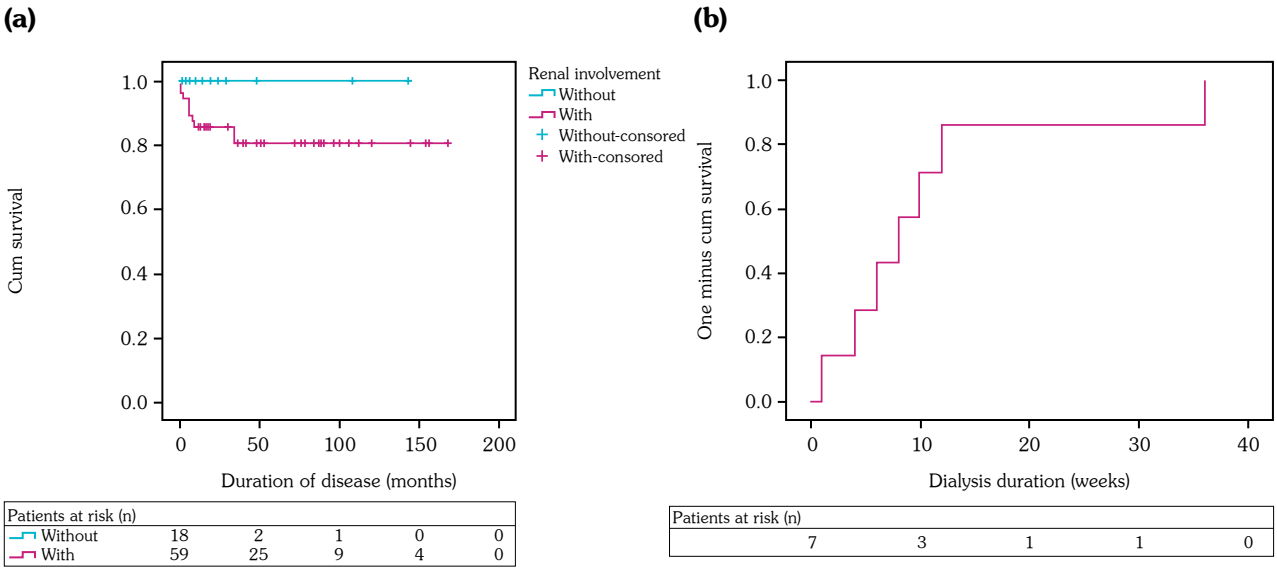

Figure 1. Kaplan-Meier survival curves describing **(a)** patient survival **(b)** renal outcomes: proportion off dialysis. The patient with the longest follow-up came off hemodialysis at the end of 36 weeks.

(n=21), mixed-type (n=18), or sclerosing (n=0) groups. There were statistically significant differences between the groups according to creatinine levels (2.7±1.7; 5.3±2.8; 4.2±1.8 mg/dL respectively, p=0.015), and eGFR (39.9±29.4; 20.4±16.6; 21.5±12.5 mL/min/1.73 m^2 respectively, p=0.045). The dialysis requirement ratios were greater in the crescentic (71%) and mixed-type (61%) groups than the focal (12.5%) group (p=0.015).

We detected C3 deposition in nine (16%) of 57 renal biopsy specimens. Among them, five patients needed initial dialysis, four patients developed ESRD, while all had proteinuria levels above 1 g/day and were classified into the crescentic or mixed-type groups. Eight of nine patients had FFS ≥2 at presentation. However, only two of our patients with C3 deposition had hypocomplementemia (Table 3).

Survival analysis

Ten patients died during follow-up. Among these patients, three died in the first month, three in the sixth, one in the ninth, and two patients in the 34th month. While the main cause of death was infection (pulmonary infection, n=5), intracerebral bleeding, neurological involvement, and acute myocardial infarction were the other causes. The survival rates were 92.2%, 90.9%, 87.1%, and 87.1% at 6, 12, 36, and 60 months of follow-up, respectively (Figure 1a). The estimated median survival time was 143 (range, 129 to 157) months. No mortality was observed among the patients without renal involvement.

In the Cox regression analysis, only age was significantly associated with mortality (HR: 1.07 [1.01-1.14]; p=0.024). There was no significant association between mortality and sex, comorbid conditions, smoking, clinical, and serological classification.

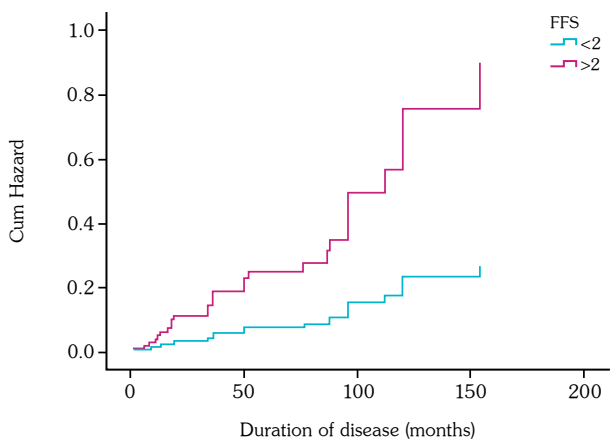

Figure 2. Cox proportional hazard regression analysis of FFS with ESRD.

FFS: Five-Factor Score; ESRD: End-stage renal disease.

According to mortality analysis, lower eGFR (17.3±9.6 *vs.* 48.0±41.2 mL/min/1.73 m^2; p=0.047), higher proteinuria (4,416.22±1,575.59 *vs.* 2,356.15±1,006.98 g/24 h; p=0.044) and hematuria (169.55±30.58 *vs.* 95.00±31.59 HPF; p=0.016) levels were significantly associated with mortality. While there was no death in the group with FFS <2, and the mortality rate was 21% in the group with FFS ≥2 at diagnosis (p=0.005).

Renal outcomes: Renal survival and dialysis-free survival

Of 59 patients with renal involvement, 31 (53%) needed dialysis at admission, and seven of them came off dialysis (all treated with CYC-based regimen). The patient with the longest follow-up came off hemodialysis at the end of 36 weeks (Figure 1b). Among the patients who came off hemodialysis, the median time of

Table 4. Cox-regression analysis for progression to end-stage renal disease

	HR (95% CI) Univariate	*p*
Predictor		
Age (year)	1.02 (0.99-1.04)	0.143
Sex Male	1.51 (0.67-3.42)	0.321
Mean arterial pressure (mmHg)	1.02 (0.99-1.04)	0.183
RRT at presentation	21.95 (2.93-164.22)	0.003
eGFR	0.97 (0.94-0.99)	0.024
FFS	3.59 (1.08-11.94)	0.037
Serology		
Negative	1.00 (ref)	Ref
p-ANCA serology	0.82 (0.33-2.08)	0.678
c-ANCA serology	0.53 (0.18-1.58)	0.253
Clinical diagnosis		
GPA	1.00 (ref)	Ref
MPA	1.01 (0.43-2.40)	0.978
RLV	0.46 (0.17-1.25)	0.127
Histopathological class		
Focal class	1.00 (ref)	Ref
Crescentic class	4.71 (0.60-36.48)	0.138
Mixed class	5.83 (0.73-46.12)	0.095
Laboratory		
Hypocomplementemia	0.72 (0.32-1.64)	0.436
ESR (mm/h)	1.00 (0.99-1.01)	0.648
CRP (mg/L)	0.99 (0.99-1.00)	0.514
Serum creatinine (mg/dL)	1.08 (0.96-1.22)	0.188
Hemoglobin (g/dL)	0.98 (0.78-1.23)	0.856
Albumin (g/dL)	1.07 (0.62-1.84)	0.800
Ferritin (ng/mL)	0.99 (0.99-1.00)	0.112
Hematuria (HPF)	1.00 (0.99-1.00)	0.826
Proteinuria at presentation (mg/24 h)	1.00 (1.00-1.00)	0.730

HR: Hazard ratio; RRT: Renal replacement therapy; eGFR: Estimated glomerular filtration rate; FFS: Five Factor Score; p-ANCA: Perinuclear-anti-neutrophil cytoplasmic antibody; c-ANCA: Cytoplasmic- anti-neutrophil cytoplasmic antibody GPA: Granulomatous polyangiitis; MPA: Microscopic polyangiitis; RLV: Renal-limited vasculitis; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

renal recovery was 8 (range, 1 to 36) weeks (95% CI: 2.86 to 13.13). Twenty-one patients with renal involvement (35%) developed ESRD during follow-up.

In the Cox regression analysis, dialysis requirement at admission (HR 21.95 [2.93-164.22]; p=0.003), lower eGFR at detection of renal involvement (HR 0.97 [0.94-0.99]; p=0.024), and FFS ≥2 at diagnosis (HR 3.59 [1.08-11.94]; p=0.037) (Figure 2) were significantly associated with progression to ESRD (Table 4). In the multivariable Cox regression analysis, initial dialysis requirement was the only (HR 5.83 [1.25-27.24]; p=0.025) parameter related to ESRD.

Relapse

Relapse occurred in 21 patients (27%), and three of them experienced more than one relapse. According to the clinical classification, 14 patients had GPA, five had MPA, and two patients had RLV. The relapse-free survival rates were 89.3%, 85.3%, 67.7%, 54.1%, and 37.8% at 6, 12, 24, 36, and 60 months of follow-up, respectively. The estimated mean relapse-free survival time was 34 (range, 21.4 to 46.6) months. Totally, 60% of the patients were on AZA and low-dose steroid maintenance treatment at the time of relapse occurrence.

The patients with relapse showed higher creatinine (p=0.027) and lower eGFR (p=0.017) values at the time of admission, compared to those without relapse. Relapses were observed in the patients with renal involvement only (p=0.05). In the Cox regression analysis, FFS ≥2 at diagnosis predicted an increased relapse rate (HR 8.9 [1.02-77.36]; p=0.047).

Remission

Of 77 patients, only 46 (56%) achieved disease remission with induction immunosuppressive treatments at diagnosis primarily on CYC plus corticosteroid (n=55). There was a significant correlation between remission and the clinical classification status (p=0.020). While there was 74% remission in GPA, this rate was 33% and 44% in MPA and RLV patients, respectively. Complete remission rates were 100% in patients with FFS=0, 69% in patients with FFS=1, and 53% in patients with FFS=2 (p<0.001).

DISCUSSION

In this study, we described clinical, serological, and histopathological characteristics of AAV patients with and without renal involvement in our tertiary care center. There were no statistically significant differences in renal or patient survival between clinical and serological classifications. We found that the baseline renal function and FFS ≥2 at diagnosis were the main predictors for renal outcome. Although there was no correlation between hypocomplementemia and renal and patient outcomes in the Cox regression analysis, the patients with hypocomplementemia at admission had higher levels of proteinuria and hematuria with a lower remission rate.

In our cohort, we found GPA (50.6%) more frequently than MPA (23.4%) and RLV (24.7%), consistent with an epidemiological report from our country.[29] The patients diagnosed with MPA were older, needed more RRT at presentation, and had higher levels of creatinine and proteinuria at admission as previously reported.[30] Despite the similarities in renal pathology and function, FFS was higher in MPA and RLV than GPA. This result indicates a better GPA prognosis for patients with ENT involvement.

Furthermore, 77% of AAV patients had renal involvement and these patients were older in our study, consistent with recent reports.[31,32] This group of patients had lower hemoglobin, albumin, C3 levels, and higher ESR. These results extend support for the argument that the inflammation is more prominent in case of renal involvement, as discussed in the study by Fukui et al.[31] Half of our patients with renal involvement needed dialysis at admission, and most of them presented with rapidly progressive glomerulonephritis. However, other studies reported the need for dialysis at admission in 32 to 47% of the patients.[21,33] Since we are the only tertiary health center in our region, patients with severe renal involvement are referred to our hospital.

Theoretically, the complement was not accepted to play an important role in AAV due to the normal serum complement levels and the absence of complement deposition in renal biopsy specimens. However, recent studies have shown that neutrophil stimulation induced by ANCA leads to activation of the alternative complement

pathway[34] and that lower C3 levels are associated with poor patient and renal survival.[10]

In the present study, 15 (22%) patients had hypocomplementemia at disease onset, and most of them (47%) were classified as MPA. Fukui et al.[15] and Molad et al.[16] also reported the prevalence of hypocomplementemia as 20% in AAV. García et al.[18] demonstrated that the predominant type of vasculitis with hypocomplementemia was MPA. In our study, complement levels were significantly lower in patients with renal involvement in line with previous studies.[15,18,19] The association of the hypocomplementemia at admission with poor patient and renal prognosis in patients with AAV has been previously demonstrated.[10,16,17,19] We found that the prevalence of ESRD (60%) and the rate of dialysis requirement at admission (67%) were higher in the hypocomplementemic group without a statistical significance. Due to our small sample size, these findings were not translated into a significant effect in renal survival. The patients with hypocomplementemia had higher rates of proteinuria, active urinary sediment, and elevated creatinine levels with an increased dialysis requirement in previous studies.[15,18,20] Similarly, our patients with lower complement levels exhibited higher rates of proteinuria and hematuria. Furthermore, we showed that the hypocomplementemic group had a higher rate of FFS ≥2 at diagnosis. This relationship was due to impaired renal function and advanced age. Choi et al.[35] also showed that FFS was higher in patients with low serum C3 levels. In the present study, increased ESR and lower albumin levels which indicated the active disease were found to be significantly associated with hypocomplementemia. This is the first study to show the relationship between hypocomplementemia at diagnosis and lower remission rate.

Deposition of complement has been reported in renal biopsy specimens of patients with AAV[36] and has been demonstrated to be correlated with the severity of renal damage.[37,38] We detected C3 deposition in nine of 57 renal biopsy specimens (16%), and half of them needed initial dialysis and progressed to ESRD. There was no significant difference between the groups with and without C3 deposition according to initial dialysis requirement and progression to ESRD. The potential reasons for this result can be the small sample size of patients and the fact that the majority of histopathological classification were crescentic and mixed-type in both groups. In line with recent studies, we observed no association between serum C3 levels and complement deposits.[10] Since AAV is not an immune-complex mediated vasculitis, low serum C3 level may simply not be associated with C3 deposits in biopsy specimens.

Decreased GFR at admission is a well-known predictor of ESRD.[9,39-43] We also found that the need for dialysis at presentation predicted ESRD, as well as low GFR at baseline. The former was also correlated with the initial disease severity as assessed by FFS. In our study, crescentic and mixed-type glomerulonephritis were closely associated with dialysis requirement and lower GFR at admission. Probably, the small sample size of other histopathological groups in the study is the reason why histopathological class was not identified as a predictor of renal outcome in the Cox regression analysis.

Recent studies have shown that the survival rates of AAV patients have improved continually over the last decades[44] with a five-year survival rate increasing from 72 to 88%.[43,44] In our study, the five-year survival rate was 87%. Several studies have identified advancing age and various markers of renal impairment as predictors of early mortality.[6,45] Although we found an association of mortality with decreased eGFR and higher levels of proteinuria and hematuria, age was the only significant predictor of mortality. Treatment-related complications including infections account for the majority of deaths within the first year.[6] Seven of 10 AAV patients in our study died within the first year, and the majority died from lung infection. All deaths occurred in the patients with renal involvement.

Despite an improvement in patient survival rates, the relapse rates are still high.[44] In line with previous studies,[46,47] we reported a relapse-free survival of 37.8% at five years. In our study, the five-year relapse rate was 27% which is comparable to a recent study finding from Japan.[48] We found a significant association between lower GFR at diagnosis and relapse rate consistent with other cohorts.[49,50] Somewhat surprisingly, but in harmony with a recent clinical long-term follow-up study, 60% of the patients in our study were

on immunosuppressive medication, primarily on low-dose steroid and AZA, when they relapsed.[43]

We also assessed the prognostic role of baseline FFS in predicting mortality, ESRD, relapse, and remission. The patients with FFS ≥2 at diagnosis have been shown to have increased all-cause mortality and relapse rates.[51-53] Renal involvement was detected in all of our patients with FFS ≥2 at diagnosis. In our study, FFS ≥2 at diagnosis was a good predictor of ESRD and relapse. No study has previously shown that this scoring system has a predictive value for developing ESRD. Although it did not reach any statistical significance in the Cox-regression analysis, all of our deaths occurred in the group of FFS ≥2 at diagnosis. Furthermore, our patients with FFS <2 at admission had a higher remission rate. While the FFS is based upon mortality and not designed to predict either remission or relapse, it is found to be closely associated with remission and relapse in our study. As a result, baseline FFS can stratify individuals to make a treatment decision that patients with a worse prognosis may receive a more aggressive treatment than those with a better prognosis. In the present study, the patients with life-threatening organ involvements had FFS ≥2 and were treated with initial treatment consisting of GC in combination with either CYC or RTX.

Nonetheless, this study has several limitations. It is a retrospective study with a small sample size. The lack of a standardized follow-up protocol during the study period, which may have complicated the interpretation of data, is another limitation. While the single-center nature of our study can be considered as a weakness, it can be seen as a strength, since it ensures consistency in patient management and diagnosis. A long follow-up of up to 13 years may be also seen as one of the main strengths of our study. However, further large-scale, prospective studies are needed to confirm the predictors of renal and patient outcomes.

In conclusion, our results indicate that dialysis requirement, lower GFR, and FFS ≥2 at diagnosis are predictors of worse renal survival. Although there has been some evidence in the literature that hypocomplementemia may be a predictor of worse prognosis in patients with AAV, we found no significant relationship between hypocomplementemia at presentation and ESRD and mortality in our cohort. This study is also valuable, as it is the first to show lower remission rates in patients with hypocomplementemia. The FFS ≥2 at diagnosis is also a good predictor of long-term renal survival, relapse risk and, therefore, may be useful in deciding the optimal induction treatment and monitoring strategies in AAV.

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