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Clinical features and outcomes of elderly patients with antineutrophil cytoplasmic antibody-positive vasculitis: a single-center retrospective study

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Background: We aimed to investigate the clinical characteristics and outcomes of patients aged ≥65 years with antineutrophil cytoplasmic autoantibody (ANCA)-positive ANCA-associated vasculitis (AAV) in Korea.

Methods: Seventy patients diagnosed with ANCA-positive AAV from 2006 to 2019 at a single center were analyzed and categorized into younger (aged <65 years) or elderly (aged ≥65 years) groups. Initial induction treatments were investigated according to age group. All-cause mortality and kidney outcomes were evaluated.

Results: After categorization by age, 34 (48.6%) and 36 patients (51.4%) were in the younger and elderly groups, respectively. In the elderly group, more patients were treated with oral cyclophosphamide (CYC) (30.6%) than with intravenous CYC (19.4%). During a median follow-up of 14.6 months (range, 3.0–53.1 months), 13 patients died (elderly group: 11 patients, 84.6%). In the elderly group, older age (hazard ratio [HR], 1.44; 95% confidence interval [CI], 1.09–1.90; p = 0.01), lower hemoglobin (HR, 0.21; 95% CI, 0.08–0.60; p = 0.003), and higher serum creatinine level (HR 14.17; 95% CI, 1.29–155.84; p = 0.03) were significant risk factors for all-cause mortality after adjustment. Oral CYC + steroid treatment was associated with decreased all-cause mortality compared to untreated induction immunosuppressants (HR, 0.01; 95% CI, 0.001–0.47; p = 0.02). Kidney failure or kidney recovery outcomes were not significantly different between the younger and elderly groups.

Conclusion: Patients aged ≥65 years had higher mortality rates than younger patients, and mortality was associated with older age, lower hemoglobin, higher serum creatinine level, and nontreatment compared to oral CYC + steroids.

Keywords: Aged, Antineutrophil cytoplasmic antibodies, Antineutrophil cytoplasmic antibody-associated vasculitis, Mortality, Vasculitis

Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) comprises granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, previously known as Churg-Strauss syndrome) [1]. A reclassification of AAV into three categories, according to

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the presence of ANCA, was recently suggested as follows: myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA, and ANCA-negative vasculitis [2]. In patients with AAV, renal involvement can often present as rapidly progressive glomerulonephritis (GN), and the upper or lower respiratory tract and the peripheral nervous system may be involved as extrarenal manifestations. Although AAV also occurs in younger patients, it presents more commonly in elderly patients. The peak age of AAV incidence is between 65 and 74 years [3–6]. In a study of 430 Chinese patients aged ≥65 years who underwent renal biopsy, AAV (44%) was the leading cause of secondary GN [7]. In a recent study in Korea, AAV was more prevalent in those aged ≥65 years compared to those aged <65 years (3.9% vs. 0.3%) [8].

Substantial morbidity and mortality occur with AAV, especially in elderly patients. In addition, rapidly progressive GN requires prompt diagnosis and the early initiation of adequate treatment. Although AAV predominantly affects older patients, appropriate treatment strategies have not been established clearly, and it is unclear whether the benefits of immunosuppressants surpass the risks. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend reducing the cyclophosphamide (CYC) dose in patients over 60 years old [9]. Data on the clinical characteristics and outcomes of elderly patients with AAV are scarce, especially in Asia. Therefore, this study aimed to investigate the demographic factors, treatments, and clinical outcomes of patients with AAV in Korea and to compare the characteristics of AAV among elderly and young patients.

Methods

Study design and subjects

The study reviewed patients that were ANCA-positive (MPO/P-ANCA or PR3/C-ANCA) at Pusan National University Hospital from 2006 to 2019. We excluded patients who were ANCA-positive because of non-vasculitis conditions, such as inflammatory bowel disease, primary sclerosing cholangitis, systemic lupus, idiopathic pulmonary fibrosis, and endocarditis. After excluding patients who were ANCA-positive due to non-vasculitis conditions, AAV was diagnosed with findings of necrotizing vasculitis in ANCA-positive patients who underwent biopsy. Patients who could not undergo a biopsy were diagnosed via physician judgment based on clinical characteristics, laboratory findings, and radiographic images. The AAV nomenclature was according to the Chapel Hill Consensus Conference 2012 revised nomenclature [1]. At the time of diagnosis, patients aged ≥65 years were defined as elderly patients with AAV.

The study was approved by the Institutional Review Board of Pusan National University Hospital (No. H-2008-002-093), which waived the requirement for informed patient consent because of the retrospective design of the study. All clinical investigations were in accordance with the Declaration of Helsinki.

Clinical data collection and laboratory measurements

The following data were retrospectively collected by reviewing the medical charts of patients: age, sex, ANCA specificity, diagnosis date, comorbidities, organ involvement, laboratory findings, induction treatment type, and initial dialysis dependency. ANCA was determined using an indirect immunofluorescence assay for P-ANCA and/or C-ANCA or enzyme-linked immunosorbent assay (ELISA) for MPO and/or PR3. ANCA testing was performed according to the manufacturer's instructions. The indirect immunofluorescence assay was performed using an Immco ANCA kit (Immco Diagnostics, Inc., Buffalo, NY, USA). MPO and/or PR3 was measured using a ZEUS ELISA kit (ZEUS Scientific, Inc., Branchburg, NJ, USA) at the Seoul Clinical Laboratories (Yongin, Korea) until January 20, 2013. An ORGENTEC ELISA kit (ORGENTEC Diagnostika GmbH, Mainz, Germany) was used at our hospital after January 21, 2013. The date of AAV diagnosis was defined as the day of the first positive ANCA test result. Organ involvement, including the kidney, lung, skin, ear, nose, and throat (ENT), nerve, and gastrointestinal tract, was determined. Organ involvement was evaluated from the patients' medical history, laboratory findings, radiographic images, and expert judgment. Kidney involvement was defined as urinary abnormalities, such as hematuria or proteinuria, or by kidney biopsy results that showed (1) no evidence of immune-complex deposition in immunofluorescence staining and electron microscopic examination, and (2) evidence of glomerular crescent but no other explainable pathologic diagnosis, such as lupus nephritis or immunoglobulin A nephropathy. Lung involvement was defined as a lung nodule, cavitation, lung fibrosis, pulmonary

hemorrhage, history of interstitial lung disease, and so on. Skin involvement was defined as purpura, skin ulcer, cutaneous nodule, and so on. ENT involvement was defined as rhinitis, sinusitis, septal perforation, nasal collapse, and so on. Nerve involvement was defined as peripheral neuropathy, mononeuritis multiplex, results of a nerve conduction study and electromyography, and so on. Gastrointestinal tract involvement was defined as bloody diarrhea, ischemic abdominal pain, and so on. The laboratory values reported closest to the date of AAV diagnosis were used for the analysis. Serum creatinine was measured using isotope dilution mass spectrometry (IDMS) reference method [10]. The estimated glomerular filtration rate at the time of AAV diagnosis was calculated using the abbreviated four-variable Modification of Diet in Renal Disease Study equation [11], using IDMS-traceable serum creatinine assay. Severe proteinuria and hematuria were defined as ≥3+ on the dipstick urine test and >100 red blood cells per high-power field in a urine microscopy examination, respectively. The protein quantitation values were investigated in patients with random urinary protein-to-creatinine ratio (UPCR) (g/g) values. Induction treatments were categorized as intravenous CYC + steroids, oral CYC + steroids, steroids only, others (rituximab or mycophenolate mofetil + steroids), or untreated. The usual induction treatment dose was as follows: intravenous CYC 500–750 mg/month, oral CYC 1.0-2.0 mg/kg/day with adjustment based on age and kidney function, starting with oral prednisolone 1 mg/kg/day and then taper down, rituximab 375 mg/m^2, or mycophenolate mofetil 500 mg twice a day. Pulse steroids or plasma exchange treatment were also investigated. The pulse steroid dose was usually methylprednisolone 500–1,000 mg for 3 days. Dosage was adjusted according to the clinical judgment of the physician. Patients with severe kidney injury requiring dialysis at the time of AAV diagnosis were defined as having initial dialysis dependency.

Outcomes

Patients were followed up until April 2020. The primary outcome of the present study was all-cause death during the follow-up period. Causes of death were also investigated. The secondary outcome was kidney failure or kidney recovery. Kidney failure was defined as the need for maintenance dialysis in patients who did not require dialysis at the time of AAV diagnosis. In patients with initial dialysis dependency, kidney recovery with the cessation of dialysis was defined as a kidney outcome.

Statistical analyses

Continuous variables are presented as means ± standard deviations and were compared using t tests. Non-normally distributed variables are expressed as the medians (interquartile ranges) and were compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test or Fisher exact test, and the results are presented as frequencies and percentages. Log transformation was used to normalize variables with a skewed distribution. The Kaplan-Meier method was used to evaluate patient survival and kidney failure outcome, and statistical significance was determined using the log-rank test. Cox proportional hazards regression analyses were conducted. In the multivariable analysis, clinically relevant variables were chosen as covariates according to previous studies [8,12,13]. The logarithm of serum creatinine was used in the Cox regression analyses. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The p-values of <0.05 were considered statistically significant. All analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of the patients

Seventy patients diagnosed with ANCA-positive AAV were analyzed. Table 1 presents the characteristics of all patients at baseline and after categorization by age. The mean age of patients was 62.8 ± 13.3 years and 64.3% were male. For ANCA-specific types, 52 (74.3%), 15 (21.4%), and three of the patients (4.3%) were MPO/P-ANCA, PR3/C-ANCA, and double-positive, respectively. The kidneys (70.0%) and lungs (70.0%) were the organs most commonly involved. The initial serum creatinine was 2.0 mg/dL (0.9–5.2 mg/dL). Eighteen (25.7%) and 25 patients (35.7%) had severe proteinuria and hematuria, respectively. The UPCR measured in 56 patients was 1.6 g/g (0.8–3.8 g/g). Among patients with renal involvement, 33 patients underwent kidney biopsy. The specific results of the kidney biopsy are

Table 1. Baseline clinical characteristics and initial treatment of patients with ANCA-positive AAV

Characteristic	Total	Younger group	Elderly group	p-value
No. of patients	70	34	36	
Age (yr)	62.8 ± 13.3	52.9 ± 12.0	72.2 ± 5.4	<0.001
Male sex	45 (64.3)	23 (67.6)	22 (61.1)	0.57
Comorbidities				
Diabetes mellitus	20 (28.6)	12 (35.3)	8 (22.2)	0.23
Hypertension	24 (34.3)	11 (32.4)	13 (36.1)	0.74
ANCA subtype				0.16
MPO/P-ANCA	52 (74.3)	23 (67.6)	29 (80.6)	
PR3/C-ANCA	15 (21.4)	8 (23.5)	7 (19.4)	
Double-positive	3 (4.3)	3 (8.8)	0 (0)	
Organ involvement				
Kidney	49 (70.0)	23 (63.6)	26 (72.2)	0.68
Lung	49 (70.0)	22 (64.7)	27 (75.0)	0.35
Skin	14 (20.0)	8 (23.5)	6 (16.7)	0.47
ENT	21 (30.0)	12 (35.3)	9 (25.0)	0.35
Nerve	22 (31.4)	11 (32.4)	11 (30.6)	0.87
Gastrointestinal	2 (2.9)	1 (2.9)	1 (2.8)	0.97
Laboratory findings				
WBC ($\times 10^3/mm^3$)	11,759 ± 6,466	11,803 ± 7,147	11,718 ± 5,853	0.96
Platelet ($\times 10^3/mm^3$)	287 ± 120	293 ± 120	282 ± 122	0.73
Hemoglobin (g/dL)	10.0 ± 2.1	10.6 ± 2.5	9.4 ± 1.6	0.02
Albumin (g/dL)	3.1 ± 0.7	3.3 ± 0.7	2.9 ± 0.6	0.02
Total cholesterol (mg/dL)	149.5 ± 51.5	161.3 ± 46.1	138.4 ± 54.5	0.08
CRP (mg/L)	3.3 (0.8–7.2)	1.3 (0.4–5.4)	4.8 (1.8–11.4)	0.004
BUN (mg/dL)	31.3 (16.9–56.3)	24.8 (13.1–50.0)	38.9 (19.5–62.7)	0.25
Creatinine (mg/dL)	2.0 (0.9–5.2)	1.5 (0.8–5.1)	2.5 (0.9–5.2)	0.64
eGFR (mL/min/1.73 m^2)	29.6 (10.6–88.0)	47.5 (12.3–107.7)	24.6 (10.1–73.2)	0.39
Severe proteinuria[a]	18 (25.7)	10 (29.4)	8 (22.2)	0.49
Severe hematuria[a]	25 (35.7)	10 (29.4)	15 (41.7)	0.29
UPCR (g/g)[b]	1.6 (0.8–3.8)	1.4 (0.8–3.6)	1.7 (0.9–4.0)	0.85
Induction treatment				0.11
Intravenous CYC + steroids	19 (27.1)	12 (35.3)	7 (19.4)	
Oral CYC + steroids	15 (21.4)	4 (11.8)	11 (30.6)	
Steroids only	23 (32.9)	14 (41.2)	9 (25.0)	
Others[c]	3 (4.3)	1 (2.9)	2 (5.6)	
Untreated	10 (14.3)	3 (8.8)	7 (19.4)	
Plasmapheresis	5 (7.1)	3 (8.8)	2 (5.6)	0.60
Pulse steroids	35 (50.0)	18 (52.9)	17 (47.2)	0.63
Initial dialysis dependency	22 (31.4)	9 (26.5)	13 (36.1)	0.39

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range). Younger group, aged <65 years; elderly group, aged ≥65 years.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BUN, blood urea nitrogen; CRP, C-reactive protein; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ENT; ear, nose, and throat; MPO, myeloperoxidase; PR3, proteinase 3; UPCR, urinary protein-to-creatinine ratio; WBC, white blood cells.

[a]Severe proteinuria and hematuria were defined as dipstick urine protein ≥3+ and urine red blood cells ≥100/high-power field, respectively. [b]Measured only in 56 patients. [c]Rituximab or mycophenolate mofetil + steroids.

in Supplementary Table 1 (available online). After categorizing patients by age, 34 (48.6%) and 36 (51.4%) were in the younger and elderly groups, respectively. The number of patients by diagnosis year according to age groups is shown in Supplementary Fig. 1 (available online). More patients were diagnosed with AAV between 2013 and 2019 than between 2006 and 2012, and more of these patients were elderly. The mean age of the elderly group was 72.2 ± 5.4 years. Ten patients (14.3%) were above 75 years old, and the oldest patient was 83 years old. Comorbidities such as diabetes mellitus and hypertension were similar between the age groups. In the elderly group, MPO/P-ANCA was noted in 80.6% of patients. Hemoglobin (p = 0.015) and serum albumin (p = 0.019) were significantly lower and C-reactive protein (p = 0.004) was significantly higher in the elderly group compared with the younger group. The baseline kidney function which was evaluated using serum creatinine values within 6 months was available only in 45 patients (64.3%), with 22 (64.7%) in the younger group and 23 (63.9%) in the elderly group. The baseline serum creatinine was 0.90 mg/dL (0.75–1.20 mg/dL), and the values were similar between the younger (0.93 mg/dL [0.75–1.21 mg/dL]) and elderly (0.90 mg/dL [0.70–1.20 mg/dL]) groups (p > 0.99). The changes in serum creatinine between baseline and the time of diagnosis are shown in Supplementary Fig. 2 (available online). Initial dialysis dependency was noted in 22 patients (31.4%) and was not significantly different between the younger (26.5%) and elderly (36.1%) groups (p = 0.39). Nineteen patients received conventional hemodialysis and three patients received continuous renal replacement therapy (CRRT). Two of three patients who received CRRT had lung hemorrhage. The cause of dialysis at the time of diagnosis included active AAV (n = 19) and infection (n = 3).

Initial induction treatment

Initial induction treatments were as follows: intravenous CYC + steroids (27.1%), oral CYC + steroids (21.4%), steroids only (32.9%), others (4.3%), and untreated (14.3%) (Table 1). Pulse steroid therapy was administered to 50% of patients. More patients were treated with intravenous CYC (35.3%) than with oral CYC (11.8%) in the younger group. In contrast, more patients were treated with oral CYC (30.6%) than with intravenous CYC (19.4%) in the elderly group. Overall, 19.4% of patients in the elderly group were untreated (vs. 8.8% in the younger group). In the elderly group, the untreated group tended to be slightly older than the treated group, but this was not statistically significant (74.1 ± 5.8 years vs. 71.7 ± 5.3 years, p = 0.23). The numbers of patients treated with plasmapheresis and pulse steroids were similar between the younger and elderly groups.

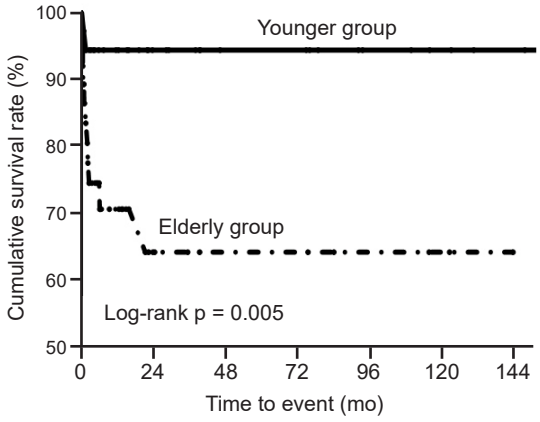
All-cause mortality

Mortality outcomes are shown in Table 2. The median follow-up duration was 14.6 months (3.0–53.1 months). During the follow-up period, 13 patients (18.6%) died: two (5.9%) in the younger group (follow-up duration, 28.5 months [6.9–92.3 months]) and 11 (30.6%) in the elderly group (follow-up duration, 6.0 months [1.6–23.3 months]). Infection (61.5%) was the major cause of death, and all the patients that died had pneumonia. The number of deaths was significantly higher in the elderly group than in the younger group, and the major cause of death in the elderly group was infection (54.5%). In the elderly group, three out of seven patients who did not receive initial induction treatment died, in all of these the cause was pneumonia and all died within 75 days. Fig. 1 presents the Kaplan-Meier curves for all-cause mortality according to age group. The elderly group showed a significantly lower survival rate than the younger group (p = 0.005). The 2-year survival rate was 94% in the younger group and 64% in the elderly group. The Cox regression analysis for all-cause mortality in all the patients and the elderly patients is presented in Table 3.

Table 2. Mortality outcomes and cause of death according to age group

Outcome	Total	Younger group	Elderly group	p-value
No. of participants	70	34	36	
Death[a]	13 (18.6)	2 (5.9)	11 (30.6)	0.008
Cause of death[b]				0.69
Active vasculitis	1 (7.7)[c]	0 (0)	1 (9.1)	
Infection	8 (61.5)[d]	2 (100)	6 (54.5)	
Cardiovascular disease	2 (15.4)	0 (0)	2 (18.2)	
Others	2 (15.4)[e]	0 (0)	2 (18.2)	

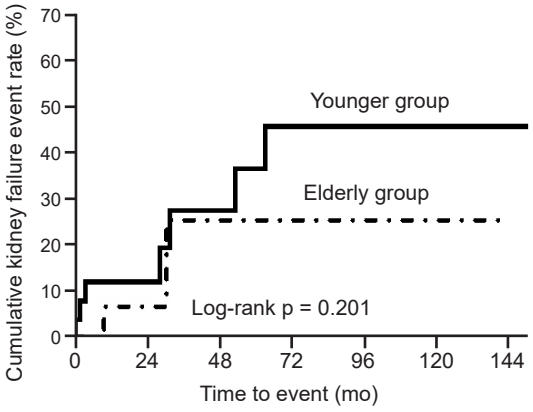
Data are expressed as number only, [a]number (% of patients), or [b]number (% of total deaths).
Younger group, aged <65 years; elderly group, aged ≥65 years.
[c]Pulmonary hemorrhage. [d]All patients had pneumonia. [e]Gastrointestinal bleeding or cancer.



Number at risk

Younger group	34	19	13	12	8	6	3
Elderly group	36	9	6	6	4	3	1

Figure 1. All-cause mortality according to age group. The younger group was aged <65 years and the elderly group was aged ≥65 years. Elderly patients exhibited a significantly lower survival rate than younger patients (p = 0.005).



Number at risk

Younger group	25	12	8	6	5	4	2
Elderly group	23	6	3	3	2	2	0

Figure 2. Kidney failure outcomes rate according to age group. Forty-eight patients who did not require dialysis at the time of antineutrophil cytoplasmic antibody-associated vasculitis diagnosis were analyzed. The younger group was aged <65 years and the elderly group was aged ≥65 years. The cumulative kidney failure event rate was not significantly different according to age group (p = 0.201).

Table 3. Multivariable Cox regression analysis for all-cause mortality in the entire study population and elderly patients with ANCA-positive AAV

Variable	Total		Age ≥65 yr	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)	1.31 (1.12–1.52)	0.001	1.44 (1.09–1.90)	0.01
ANCA type				
MPO/P-ANCA	Reference	-	Reference	-
PR3/C-ANCA	2.44 (0.58–10.23)	0.22	3.02 (0.63–14.32)	0.17
Double-positive	15.72 (1.12–220.58)	0.04	-	-
Hemoglobin(g/dL)	0.31 (0.17– 0.58)	<0.001	0.21 (0.08–0.60)	0.003
Creatinine[a] (mg/dL)	3.75 (0.64–21.95)	0.14	14.17 (1.29– 155.84)	0.03
Induction treatment				
Untreated	Reference	-	Reference	-
Intravenous CYC + steroids	2.46 (0.43–14.20)	0.31	2.89 (0.30–28.05)	0.36
Oral CYC + steroids	0.05 (0.003– 0.75)	0.03	0.01 (0.0003–0.47)	0.02
Steroids only	0.60 (0.12– 3.08)	0.54	0.21 (0.03–1.77)	0.15
Others[b]	1.81×10^{-6} (0.00–NA)	0.99	4.08×10^{-7} (0.00–NA)	0.99

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; CYC, cyclophosphamide; HR, hazard ratio; MPO, myeloperoxidase; PR3, proteinase 3; NA, not available

[a]Log transformation of serum creatinine. [b]Rituximab or mycophenolate mofetil + steroids.

In the multivariable Cox regression analysis, older age (HR, 1.31; 95% CI, 1.12–1.52; p = 0.001) and lower hemoglobin (HR, 0.31; 95% CI, 0.17–0.58; p < 0.001) were significant risk factors for all-cause mortality. ANCA double-positivity (HR, 15.72; 95% CI, 1.12–220.58; p = 0.04) was associated with increased all-cause mortality compared to MPO/P-ANCA positivity. Oral CYC + steroid treatment (HR, 0.05; 95% CI, 0.003–0.75; p = 0.03) was associated with decreased all-cause mortality compared to nontreatment. Similar results were noted in the elderly group. In the elderly group, older

age (HR, 1.44; 95% CI, 1.09–1.90; p = 0.01) and lower hemoglobin (HR, 0.21; 95% CI, 0.08–0.60; p = 0.003) were significant risk factors for all-cause mortality. In addition, higher serum creatinine (HR, 14.17; 95% CI, 1.29–155.84; p = 0.03) was a significant risk factor for all-cause mortality. The elderly group also showed decreased all-cause mortality with oral CYC + steroid treatment (HR, 0.01; 95% CI, 0.0003–0.47; p = 0.02) compared to nontreatment.

Kidney outcomes

During the follow-up period, nine patients (18.8%) developed kidney failure among 48 patients who did not require dialysis at the time of AAV diagnosis. The cause of kidney failure development included active AAV (n = 3), infection (n = 1), and CKD progression after AAV (n = 5). The Kaplan-Meier curves for kidney failure events according to age group are presented in Fig. 2. The event rates for kidney failure were not significantly different between the younger and elderly groups (p = 0.20). Table 4 presents the Cox regression analysis for kidney failure outcomes. In the multivariable Cox regression analysis, higher serum creatinine (HR, 101.29; 95% CI, 3.25–3,159.70; p = 0.03) at the time of AAV diagnosis was a significant risk factor for kidney failure outcomes. In addition, oral CYC + steroid treatment (HR, 0.02; 95% CI, 0.0009–0.56; p = 0.021) was associated with decreased kidney failure events compared to nontreatment. Kidney recovery outcomes were evaluated for 22 patients who required dialysis at the time of AAV diagnosis. Four out of the 22 patients (18.2%) stopped dialysis. Two of the four were in the younger group and two were in the elderly group. In the elderly group, three out of seven of the untreated patients initially needed dialysis, all of whom were unable to stop dialysis.

Table 4. Cox regression analysis for kidney failure outcomes in all patients with ANCA-positive AAV

Variable	Multivariable analysis for total[a]	
	HR (95% CI)	p-value
Age (yr)	1.00 (0.93–1.08)	0.93
Creatinine[b] (mg/dL)	101.29 (3.25–3,159.70)	0.009
Induction treatment		
Untreated	Reference	-
Intravenous CYC + steroids	0.03 (0.0006–1.26)	0.07
Oral CYC + steroids	0.02 (0.0009–0.56)	0.02
Steroids only	0.22 (0.01–3.43)	0.28
Others[c]	8.8×10-6 (0.00–NA)	0.99
Severe proteinuria[d]	2.65 (0.29–24.35)	0.39
Severe hematuria[d]	0.57 (0.07–4.50)	0.59

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; CYC, cyclophosphamide; HR, hazard ratio; NA, not available.
[a]Forty-eight patients who did not require dialysis at the time of AAV diagnosis were analyzed, [b]Log transformation of serum creatinine, [c]Rituximab or mycophenolate mofetil + steroids, [d]Severe proteinuria and hematuria were defined as dipstick urine protein ≥3+ and urine red blood cells ≥100/high-power field, respectively.

Discussion

In the present study, 36 elderly patients (51.4%) with ANCA-positive AAV were enrolled over 14 years. During the study period, more elderly patients were diagnosed with AAV between 2013 and 2019 than between 2006 and 2012. In the follow-up period, 13 patients died, and most of these patients (11, 84.6%) were in the elderly group. Older age, lower hemoglobin, and higher serum creatinine were significant risk factors for all-cause mortality in the elderly group. Similar to our study, previous studies have also demonstrated that advancing age and impaired renal function are significant risk factors for mortality [14,15]. Kidney outcomes were not significantly different between the younger and elderly groups in the present study.

In elderly patients, decreased immunity and the increased risk of infection are of great concern in immunosuppressant treatment. Elderly patients are particularly vulnerable to the adverse effects of disease and the immunosuppressants used for treatment. In the present study, there was decreased all-cause mortality in the oral CYC + steroids treatment group compared to the untreated group at all ages. This demonstrates the effect of immunosuppressants even in the elderly. In addition, the mortality rate may have been lower because the immunosuppressants were more likely to be used in stronger patients. Infection was the main cause of death, and six patients (54.5%) died of an infection in the elderly group, three of who were treated with immunosuppressants (1 patient each was treated with intravenous CYC + steroids, oral CYC + steroids, or steroids alone) and the other three underwent only supportive treatment. The three patients who received immunosuppressant treatment were relatively older compared to those who received supportive treatment (73, 83, and 83 years vs. 65, 73, and 73 years). In the present study,

there was no significant difference in mortality by infection in the elderly group, regardless of treatment with immunosuppressants. However, the small number of patients precludes a definite conclusion regarding this finding. In a previous retrospective study, patients that were older and receiving immunosuppressants had an increased risk of infection, particularly in the presence of leukopenia [3]. However, other studies have shown that elderly patients with AAV receiving immunosuppressants had a better prognosis (lower mortality and/or lower frequency of end-stage renal disease [ESRD]) than those untreated or not treated via the standard method [16,17]. Overall, immunosuppressants can be used with caution in elderly patients with AAV, with careful monitoring for adverse events.

In our study, there were not many patients who underwent rituximab induction treatment. In previous studies, rituximab was not inferior compared to CYC as an induction treatment [18,19], and rituximab was more efficacious than CYC in patients with relapsing disease [18]. Adverse events were comparable between the two treatments and there was no trend toward reduced infection rates [20]. However, rituximab induction may be preferred in frail older adults according to the expert recommendation in the draft of the 2020 KDIGO clinical guideline on glomerular disease. Therefore, appropriate immunosuppressants in elderly patients can improve the prognosis of the patient. Further study is needed on the outcome of elderly AAV patients using rituximab.

In the present study, oral CYC was prescribed more often than intravenous CYC in older patients. The CYCLOPS study showed that intravenous pulse and oral continuous CYC were equally efficacious and pulse intravenous therapy had lower side effects, including leukopenia [21]. The long-term follow-up of the CYCLOPS study demonstrated that pulse CYC was not associated with increased mortality or long-term morbidity; however, it was associated with a higher risk of relapse than oral CYC [22]. In the present study, the reasons for the greater use of oral CYC compared to intravenous CYC in the elderly could be the following. First, patients from before the CYCLOPS study era were also included in the study, and because of concerns about relapse, which would have required repeat high-dose immunosuppressants, oral CYC may have been prescribed more often than intravenous CYC. Furthermore, intravenous CYC may have been less prescribed in the elderly because the administration method is more cumbersome than oral therapy and occasionally needs short-term admission. In a previous study, oral CYC was prescribed more often than intravenous CYC in very elderly AAV patients (oral vs. intravenous: 58% vs. 24%) [17]. In another observational study, patients receiving oral CYC were older than those receiving intravenous CYC (72 years [65–78 years] vs. 55 years [44–68 years], $p < 0.001$) [23].

Lower hemoglobin was a significant risk factor for all-cause mortality in the entire study population, including the elderly group. Anemia-related markers, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), ferritin, iron, total-iron binding capacity (TIBC), and transferrin saturation (TSAT) were evaluated. MCV was 88.6 ± 4.8 fL and MCHC was 33.4 ± 1.7 g/dL. Serum ferritin, iron, TIBC, and TSAT values were available only in 42 patients. Serum ferritin was 552.0 ng/mL (251.8–837.3 ng/mL) and serum iron was 29.0 μg/dL (22.0–51.5 μg/dL). Serum ferritin was significantly higher in the elderly group than in the younger group (younger vs. elderly: 308.2 ng/mL [168.6–646.9 ng/mL] vs. 571.1 ng/mL [375.6–1,092.5 ng/mL]; $p = 0.04$). Iron ($p = 0.428$) and TSAT ($p = 0.35$) were not significantly different between the younger and elderly groups. The presence of anemia is known to increase with age, and anemia is common in the elderly [24]. In one study, anemia was prevalent in >10% of people aged ≥65 years and in >20% of those aged ≥85 years in the United States [24]. In a recent study, 13.8% of people aged ≥65 years who participated in a Korean national survey had anemia [25]. Aging is a proinflammatory condition that may cause altered iron handling or the suppression of erythroid progenitors [26]. Anemia in the elderly is related to various adverse outcomes, including hospitalization, morbidity, and mortality [27]. In our study, ferritin was higher in the elderly, which may reflect inflammatory conditions and lower hemoglobin associated with patient death.

The presence of kidney involvement or impaired renal function is a common negative prognostic factor for elderly patients [14,15]. In the present study, higher serum creatinine was a significant risk factor for all-cause mortality in the elderly group. AAV-associated kidney involvement often presents as rapidly progressive GN [28] and can cause poor morbidities and mortality. Therefore, if elderly patients with AAV have kidney involvement or impaired renal function, meticulous care and close follow-up and

monitoring are needed.

In the present study, ANCA-positive AAV was not classified as GPA, MPA, or EGPA. AAV classification according to clinical phenotype, especially GPA or MPA, has significant overlap in clinical features and often ambiguous distinctions, adding to the controversial issues in AAV classification [29]. A classification system according to ANCA specificity (MPO-ANCA vs. PR3-ANCA disease) has been proposed. Relapse rates and clinical outcomes are better associated with ANCA specificity [29]. Therefore, in the present study, ANCA-positive AAV was classified as MPO/P-ANCA, PR3/C-ANCA, or double-positive AAV. In a previous study, there were no differences in mortality or time to remission between MPO-positive and PR3-positive patients, but PR3-positive patients had a higher rate of relapse and relapsed earlier than MPO-positive patients [30]. In the present study, there were no significant differences in mortality between MPO/P-ANCA and PR3/C-ANCA; however, further large-scale studies are needed to clarify our findings.

The strength of our study is that we investigated the outcomes of patients with AAV, especially elderly patients. In previous randomized controlled trials of induction immunosuppressant in AAV, the mean ages of patients were 57 years [10], 53 years [18], and 60 years [31], and in another study, elderly patients aged above 75 years were excluded [15]. In previous studies, similar responses to immunosuppressive treatment were found in elderly AAV patients compared to younger people [3], and one study found that they did not respond well [32]. Bomback et al. [17] showed that immunosuppressants were associated with a lower risk of ESRD or combined ESRD or death risk at 1 year in very elderly patients over 80 years of age. In a recent study, older age and infection were major risk factors for 1-year mortality in AAV patients over 65 years but failed to show a statistical significance between therapeutic strategy and mortality [33]. In our study, we investigated outcomes according to immunosuppressant use in elderly AAV patients and entire study patients, which is an advantage in our study. However, our study also has several limitations. First, we could not exclude the possibility of residual confounders because of the retrospective nature of the study. Moreover, we could not conduct a multivariable analysis for all-cause mortality in the younger group because mortality events (only two patients [2.9%]) were low during the follow-up period. In addition, this was a single-center study in Korea; thus, caution is required when generalizing our findings to other ethnicities.

In conclusion, patients aged 65 years or older had higher mortality rates than younger patients, which was associated with older age, lower hemoglobin, higher serum creatinine, and nontreatment compared to oral CYC + steroids.

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors' contributions

Conceptualization, Data curation, Formal analysis: HJK, EYS
Investigation: All authors
Methodology: All authors
Project administration: EYS
Writing–original draft: HJK, EYS
Writing–review & editing: HJK, EYS
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