Clinical features of Korean elderly patients with antineutrophil cytoplasmic antibody-associated vasculitis

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Background/Aims: We compared the clinical and laboratory data between elderly and non-elderly patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) at diagnosis; further, we investigated the predictors at diagnosis for all-cause mortality and end-stage renal disease (ESRD) occurrence during follow-up in Korean elderly patients with AAV.

Methods: We reviewed the medical records of 191 AAV patients regarding clinical manifestations and laboratory results at diagnosis and during follow-up. The follow-up duration was defined as the period from diagnosis to death for deceased patients or to the time of dialysis for ESRD patients, or to the last visit. Elderly (n = 67) and non-elderly (n = 124) patients were grouped based on an age threshold of 65 years.

Results: At diagnosis, elderly patients exhibited higher median Birmingham Vasculitis Activity Score (BVAS) and higher frequencies of ANCA positivity and pulmonary manifestations than non-elderly patients. Furthermore, elderly patients exhibited increased median white blood cell count, blood urea nitrogen (BUN), alkaline phosphatase, erythrocyte sedimentation rate, and C-reactive protein and decreased median hemoglobin. However, there were no significant differences in all-cause mortality and ESRD occurrence between elderly and non-elderly patients. Meanwhile, elderly patients exhibited lower cumulative patients' and ESRD-free survival rates than non-elderly patients. In the multivariable Cox hazards model, BUN, creatinine and serum albumin at diagnosis were independent predictors for ESRD occurrence, whereas there were no independent predictors at diagnosis for all-cause mortality.

Conclusions: Elderly AAV patients exhibited substantially higher rates of all-cause mortality and ESRD occurrence during follow-up compared than non-elderly AAV patients.

Keywords: Antineutrophil cytoplasmic antibody-associated vasculitis; Aged; All-cause mortality; End-stage renal disease; Predictor

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic vasculitides involving small vessels. On the basis of the 2012 Revised International Chapel Hill Consensus Conference No-

menclature of Vasculitides (the 2012 definitions), AAV is defined as vasculitis predominantly affecting small vessels such as small intraparenchymal arteries, arterioles, capillaries, venules, and occasionally medium-sized arteries and veins [1]. AAV can be further classified into three variants such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) based on clinical manifestations and histological features such as necrotizing vasculitis, granulomas and eosinophilic infiltration [1,2]. Compared to other vasculitis, particularly Takayasu arteritis or immunoglobulin A vasculitis (Henoch-Schonlein), AAV tends to occur in elderly people. Both MPA and GPA mainly occur in 60 to 70-year-old persons, whereas, EGPA often occurs in 40 to 60-year-old persons [3].

To date, there have been several studies comparing the clinical features and outcomes of young and elderly AAV patients: Early classification before advanced chronic kidney disease (CKD) and the use of immunosuppressive drugs improved the prognosis of AAV [4]; moreover, ESRD occurred more frequently in patients who were not treated with immunosuppressive drugs at 1 year after diagnosis. However, the rate of all-cause mortality was not different between the two groups [5]; elderly AAV patients exhibited higher incidence of both all-cause mortality and ESRD occurrence as well as the highest mortality rate within the first 6 months [6].

To the best of our knowledge, however, there is no report yet on the comparative analysis of the clinical and laboratory features and the incidence of all-cause mortality and ESRD occurrence in Korean elderly patients with AAV. Hence, in this study, we compared the clinical and laboratory features of elderly and non-elderly AAV patients at diagnosis and investigated the predictors at diagnosis for all-cause mortality and ESRD occurrence during follow-up in Korean elderly patients with AAV.

METHODS

Patient population

We reviewed the medical records of 191 AAV patients according to the following inclusion and exclusion criteria: (1) patients should have been first classified as AAV at the Division of Rheumatology, Department of

Internal Medicine, Yonsei University College of Medicine, Severance Hospital, between October 2000 and October 2018; (2) patients should have well-documented medical records to confirm their classification as MPA, GPA or EGPA and to assess both clinical manifestations at diagnosis and death during follow-up, and calculate Birmingham Vasculitis Activity Score (BVAS) and five factor score (FFS) at diagnosis. Because BVAS for GPA has a different weight-system from BVAS, we evenly applied BVAS to GPA to unify the scoring system [7-9]; (3) patients should meet the American College of Rheumatology 1990 criteria and should be classified by the 2007 European Medicines Agency algorithm and the 2012 definitions [1,2]; (4) patients should have the results of perinuclear (P)-ANCA and cytoplasmic (C)-ANCA or myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. P-ANCA and C-ANCA were detected using an immunofluorescence assay and the titres of MPO-ANCA and PR3-ANCA were measured using an enzyme-linked immunosorbent assay [10]; (5) patients should have been followed up for 3 months or more; (6) patients should not have any serious medical conditions other than AAV, by which AAV activity and severity might be confused. Comorbidities at diagnosis or during follow-up were identified using the 10th revised International Classification Diseases (ICD-10) and immunosuppressive drugs administered for AAV were verified by the Korean Drug Utilization Review system. We collated a list of 224 AAV patients, who had been classified as AAV and had AAV as the primary diagnosis from October 2000, via the Clinical Data Repository System (CDRS) in November 2016. Of 224 AAV patients, 127 AAV patients fulfilled the inclusion criteria. In addition, from November 2016 to 3 months before the entry of this study, 74 patients were newly classified as AAV and added to this study population. Finally, 191 AAV patients were included in this study. This study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2017-0673), which waived the need for written informed consent from the patients, as this was a retrospective study.

Clinical and laboratory data at diagnosis

At the time of AAV diagnosis, age and sex were compiled as demographic data. We calculated BVAS and FFS at diagnosis as AAV-specific indices. Clinical manifestations at diagnosis were recorded based on the items of

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BVAS and FFS: general, cutaneous, muco-membranous/ocular, ear nose throat, pulmonary, cardiovascular, gastrointestinal, renal, and nervous manifestations [7,9]. Routine laboratory data included positive ANCA types, white blood cell and platelet count, hemoglobin, fasting glucose, blood urea nitrogen (BUN), creatinine, total serum protein, serum albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). At diagnosis, the results of tests for autoantibodies were also reviewed to exclude autoimmune diseases other than AAV.

Data during follow-up

During follow-up, all-cause mortality and ESRD were considered dependent variables in the prognosis analysis. In this study, patients, who received renal replacement therapy before diagnosis, were not counted as ESRD during follow-up. The follow-up duration based on either all-cause mortality or ESRD was defined as the period between the date of the diagnosis of AAV and the date of the last visit for surviving patients or those without renal replacement. In the case of deceased patients, the follow-up duration based on all-cause mortality was defined as the period between the diagnosis of AAV and the time of death. For patients who had ESRD, the follow-up duration for ESRD was defined as the period starting from the diagnosis of AAV until the initiation of renal replacement therapy. Comorbidities during follow-up included CKD (stage 3 to 5), diabetes mellitus, hypertension, interstitial lung disease (ILD), diffuse alveolar hemorrhage, ischemic heart disease, and cerebrovascular accident [3]. We also reviewed immunosuppressive drugs for AAV such as glucocorticoid, cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, tacrolimus, methotrexate, and plasma exchange.

Definition of an elderly AAV patient and severe AAV

The median age at diagnosis of study population (n = 191) was 56.1 years with an interquartile range (IQR) of 21.0. We chose 65 years at diagnosis rather than 75 years could be a better cut-off age for elderly AAV patients. When we defined an elderly AAV patient as a patient aged 65 years and above at the time of diagnosis [9], 124 patients comprised the non-elderly AAV pa-

tient-group and 67 patients comprised the elderly AAV patient-group. Additionally, we classified AAV patients aged 65 years or below at diagnosis as non-elderly AAV patients. We stratified AAV patients into three groups based on the tertile of BVAS and defined the lower limit of the highest tertile as the cut-off for severe AAV in the study (BVAS at diagnosis ≥ 18).

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics software version 23 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median and IQR, and categorical variables were expressed as number and percentage. We divided AAV patients into the two groups using the age of 65 years and above or below as the criterion and compared variables between two groups. Significant differences in categorical variables between the two groups were analyzed using the chi-square and Fisher's exact tests. Significant differences in continuous variables between the two groups were compared using the Mann-Whitney U test. Comparison of the cumulative patients' and ESRD-free survival rate between the two groups were analyzed by the Kaplan-Meier survival analysis. In 67 patients with age ≥ 65 years, the multivariable Cox hazard model using variables with p value less than 0.05 and clinically relevant the hazard ratio (HR) in univariable Cox hazard model was conducted to appropriately obtain HRs and determine the predictors for all-cause mortality and ESRD occurrence during the considerable follow-up duration. The p values less than 0.05 were considered statistically significant.

RESULTS

Comparison of variables at diagnosis of elderly and non-elderly AAV patients based on an age cut-off of 65 years

The median ages of elderly and non-elderly AAV patients were 71.0 and 50.0 years, respectively. The proportion of each AAV variant was evenly distributed in the two groups. MPO-ANCA (or P-ANCA) was detected more often in elderly AAV patients, whereas ANCA negative was observed more frequently in non-elderly AAV patients. Since FFS includes the age of 65 years or above

as one item of five factors, the median FFS in elderly AAV patients at diagnosis was inevitably larger than that in non-elderly AAV patients. Meanwhile, age is not a sub-item of BVAS. Nonetheless, the median BVAS in elderly AAV patients at diagnosis was higher than that in non-elderly AAV patients (14.0 vs. 11.5, p = 0.037). Among clinical manifestations at diagnosis, only the frequency of pulmonary manifestation meaningfully differed between elderly and non-elderly AAV patients (73.1% vs. 48.4%, p = 0.001). Compared to non-elderly AAV patients, both elderly MPA patients and elderly GPA patients showed higher frequencies of pulmonary manifestation. However, elderly EGPA patients showed a frequency of pulmonary manifestation similar to that of non-elderly EGPA patients. In this study, we counted five types of lung lesions at diagnosis: ILD, ground glass opacity, lung nodules, cavitary lesion, and migratory lung infiltration. There were no significant differences in five types of pulmonary manifestation between elderly and non-elderly AAV patients. Among routine laboratory results at diagnosis, elderly AAV patients exhibited higher median white blood cell count, fasting glucose, BUN, ALP, ESR, and CRP than non-elderly AAV patients. In contrast, elderly AAV patients had lower median hemoglobin and serum albumin than non-elderly AAV patients (Table 1). There were no significant differences in the presence of autoantibodies between the two groups.

Comparison of variables during follow-up of elderly and non-elderly AAV patients based on an age cut-off of 65 years during follow-up

Nine of 67 elderly AAV patients (13.4%) died, whereas 10 of 124 non-elderly AAV patients (8.1%) died during follow-up based on all-cause mortality. In addition, ESRD occurred in 14.9% of elderly AAV patients and 14.5% of non-elderly AAV patients during follow-up based on ESRD. Among the comorbidities during follow-up, elderly AAV patients exhibited higher frequency of CKD than non-elderly AAV patients (40.3% vs. 21.8%, p = 0.007); however, patients in both groups showed similar frequencies of ESRD. Furthermore, the frequency of concurrent ILD in elderly AAV patients was much higher than that in non-elderly AAV patients (56.7% vs. 37.9%, p = 0.013). Glucocorticoid and immunosuppressive drugs were evenly administered to both groups (Table 2).

Comparison of the cumulative patients' and ESRD-free survival rates of elderly and non-elderly AAV patients based on an age cut-off of 65 years

To closely examine the differences in the cumulative patients' and ESRD-free survival rates between the two groups considering the different median follow-up durations, we conducted the Kaplan-Meier survival analysis. Elderly AAV patients exhibited lower cumulative patients' survival rate than non-elderly AAV patients during follow-up based on all-cause mortality (p = 0.003) (Fig. 1A). Moreover, elderly AAV patients showed higher incidence of ESRD occurrence than non-elderly AAV patients during follow-up based on ESRD (p = 0.049) (Fig. 1B).

Predictors at diagnosis for all-cause mortality during follow-up in elderly AAV patients

To obtain independent predictors at diagnosis for all-cause mortality during follow-up, we conducted the univariable and multivariable Cox hazard model analyses. In the univariable Cox hazards model analysis, severe AAV (BVAS ≥ 18), hemoglobin, BUN, ALP, AST, and ALT at diagnosis were significantly associated with all-cause mortality in elderly AAV patients. However, no significant and independent predictors were found at diagnosis for all-cause mortality in the multivariable Cox hazards model analysis (Table 3).

Predictors at diagnosis for ESRD occurrence during follow-up in elderly AAV patients

We also analyzed the predictors for ESRD occurrence during follow-up using the univariable and multivariable Cox hazard model analysis. In the univariable Cox hazards model analysis, severe AAV, hemoglobin, BUN, creatinine, total serum protein, and serum albumin at diagnosis were significantly associated with all-cause mortality in elderly AAV patients. In general, total serum protein is inversely correlated with renal dysfunction. However, in the univariable analysis, total serum protein exhibited a positive HR, which is not clinically relevant. Thus, we did not include total serum protein in the multivariable analysis despite its statistical significance. In the multivariable Cox hazards model analysis, BUN (HR, 1.073; 95% confidence interval [CI], 1.016 to 1.133), creatinine (HR, 1.642; 95% CI, 1.132 to 2.383), and serum albumin (HR, 0.051; 95% CI, 0.006 to 0.444) were

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Table 1. Comparison of variables at diagnosis between elderly and non-elderly AAV patients based on an age of 65 years

Variable	Elderly AAV patients[a] (n = 67)	Non-elderly AAV patients[a] (n = 124)	p value
Demographic data at diagnosis			
Age, yr	71.0 (67.0–75.0)	50.0 (40.0–58.0)	< 0.001
Female sex	45 (67.2)	85 (68.5)	0.845
Variants at diagnosis			0.110
MPA	40 (59.7)	62 (50.0)	
GPA	18 (26.9)	29 (23.4)	
EGPA	9 (13.4)	33 (26.6)	
ANCA positivity at diagnosis			
MPO-ANCA (or P-ANCA)	53 (79.1)	68 (54.8)	0.001
PR3-ANCA (or C-ANCA)	6 (9.0)	24 (19.4)	0.059
Both ANCAs	1 (1.5)	7 (5.6)	0.172
ANCA negativity	9 (13.4)	39 (31.5)	0.006
AAV-specific indices at diagnosis			
BVAS	14.0 (8.0–20.0)	11.5 (6.3–16.0)	0.037
FFS	2.0 (1.0–3.0)	1.0 (0–1.0)	< 0.001
Clinical manifestations at diagnosis			
General	36 (53.7)	50 (40.3)	0.075
Cutaneous	10 (14.9)	33 (26.6)	0.065
Muco-membranous/ocular	3 (4.5)	9 (7.3)	0.450
Ear nose throat	26 (38.8)	48 (38.7)	0.990
Pulmonary	49 (73.1)	60 (48.4)	0.001
Interstitial lung disease	16 (23.9)	23 (18.5)	0.383
Ground glass opacity	19 (28.4)	24 (19.4)	0.155
Lung nodules	10 (14.9)	13 (10.5)	0.368
Cavitary lung lesions	5 (7.5)	6 (4.8)	0.458
Migratory lung infiltration	6 (9.0)	18 (14.5)	0.269
Cardiovascular	18 (26.9)	30 (24.2)	0.685
Gastrointestinal	3 (4.5)	7 (5.6)	0.730
Renal	45 (67.2)	67 (54.0)	0.079
Nervous	17 (25.4)	44 (35.5)	0.153
Routine laboratory results at diagnosis			
White blood cell count, /mm³	11,130.0 (7,700.0–14,500.0)	8,130.0 (5,912.5–11,392.5)	< 0.001
Hemoglobin, g/dL	10.4 (9.1–12.6)	12.2 (10.1–13.4)	0.001
Platelet count, × 1,000/mm³	333.0 (230.0–433.0)	288.0 (228.3–373.0)	0.075
Fasting glucose, mg/dL	109.0 (93.0–129.0)	97.0 (89.0–115.0)	0.011
BUN, mg/dL	21.0 (15.2–42.6)	15.8 (10.8–25.0)	< 0.001
Creatinine, mg/dL	1.0 (0.7–2.7)	0.9 (0.7–1.4)	0.141
Total serum protein, g/dL	6.4 (5.8–7.0)	6.7 (6.2–7.4)	0.136
Serum albumin, g/dL	3.2 (2.4–3.8)	3.8 (3.2–4.2)	0.036
ALP, IU/L	75.0 (60.0–106.0)	66.0 (50.3–88.8)	0.009

Table 1. Continued

Variable	Elderly AAV patients[a] (n = 67)	Non-elderly AAV patients[a] (n = 124)	p value
AST, IU/L	18.0 (15.0–26.0)	18.0 (15.0–22.0)	0.635
ALT, IU/L	15.0 (10.0–21.0)	17.0 (12.3–26.0)	0.058
Total bilirubin, mg/dL	0.5 (0.3–0.6)	0.5 (0.4–0.6)	0.395
ESR, mm/hr	75.0 (40.0–107.0)	44.5 (20.0–82.5)	< 0.001
CRP, mg/L	50.0 (2.9–112.4)	7.3 (1.0–36.9)	< 0.001

Values are presented as median (interquartile range) or number (%).

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, five factor score; BUN, blood urea nitrogen; ALT, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

[a]Elderly AAV patients was defined as those with an age ≥ 65 years, whereas non-elderly AAV patients was defined as those with an age < 65 years.

Table 2. Comparison of variables during follow-up between elderly and non-elderly AAV patients based on an age of 65 years

Variable	Elderly AAV patients[a] (n = 67)	Non-elderly AAV patients[a] (n = 124)	p value
Prognosis during follow-up			
All-cause mortality	9 (13.4)	10 (8.1)	0.237
Follow-up duration based on all-cause mortality, mon	15.4 (6.2–59.0)	46.1 (13.1–104.2)	< 0.001
ESRD	10 (14.9)	18 (14.5)	0.939
Follow-up duration based on ESRD, mon	15.4 (6.0–59.2)	44.2 (13.1–104.2)	< 0.001
Comorbidities during follow-up			
CKD (stage 3–5)	27 (40.3)	27 (21.8)	0.007
Diabetes mellitus	17 (25.4)	21 (16.9)	0.163
Hypertension	34 (50.7)	48 (38.7)	0.109
ILD	38 (56.7)	47 (37.9)	0.013
Diffuse alveolar hemorrhage	2 (3.0)	7 (5.6)	0.408
Ischemic heart disease	7 (10.4)	6 (4.8)	0.142
Cerebrovascular accident	7 (10.4)	10 (8.1)	0.581
Immunosuppressive drugs			
Glucocorticoid	62 (92.5)	105 (84.7)	0.118
Cyclophosphamide	25 (37.3)	55 (44.4)	0.347
Rituximab	5 (7.5)	15 (12.1)	0.318
Azathioprine	20 (29.9)	43 (34.7)	0.498
Mycophenolate mofetil	2 (3.0)	10 (8.1)	0.167
Tacrolimus	1 (1.5)	8 (6.5)	0.123
Methotrexate	2 (3.0)	12 (9.7)	0.090
Plasma exchange	3 (4.5)	3 (2.4)	0.436

Values are expressed as median (interquartile range) or number (%).

AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ESRD, end-stage renal disease; CKD, chronic kidney disease; ILD, interstitial lung disease.

[a]Elderly AAV patients was defined as those with an age ≥ 65 years, whereas non-elderly AAV patients was defined as those with an age < 65 years.

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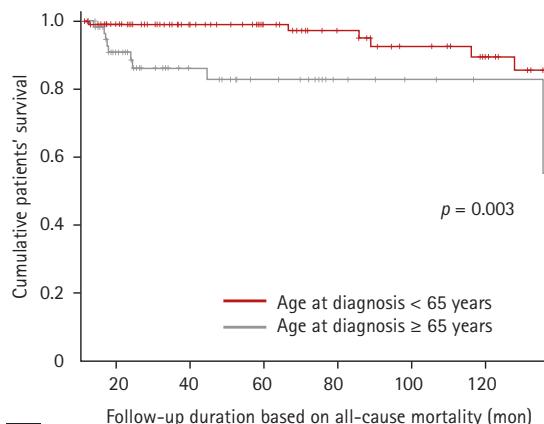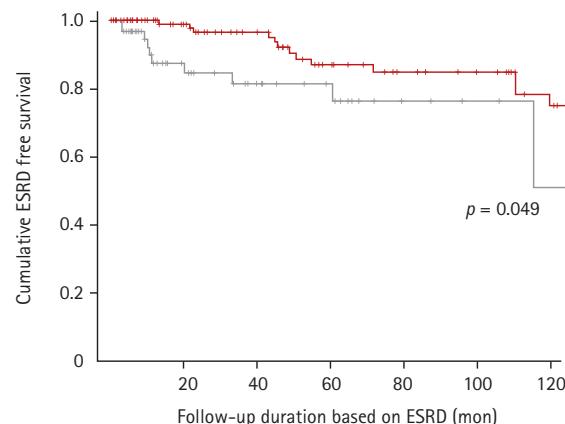
Figure 1. (A, B) Comparison of the cumulative survival rates based on the age cut-off of 65 years. Elderly antineutrophil cytoplasmic antibody-associated vasculitis (AAV) patients (aged ≥ 65 years) exhibited lower cumulative patients' and end-stage renal disease (ESRD)-free survival rates than non-elderly AAV patients (aged < 65 years).

independent predictors at diagnosis for ESRD occurrence during follow-up based on ESRD in elderly AAV patients (Table 4).

DISCUSSION

In this study, we compared clinical and laboratory data between elderly and non-elderly AAV patients. We first investigated the predictors at diagnosis for all-cause mortality and ESRD occurrence during follow-up in elderly AAV patients in a monocentric retrospective cohort in Korea and obtained several interesting findings. In the cross-sectional comparative analysis of variables at AAV diagnosis, elderly AAV patients exhibited higher median BVAS and higher frequencies of MPO-ANCA (or P-ANCA) positivity, ANCA positivity and pulmonary manifestations than non-elderly AAV patients. Furthermore, elderly AAV patients exhibited higher median white blood cell count, BUN, ALP, ESR, and CRP and lower median hemoglobin than non-elderly AAV patients. In the cross-sectional comparative analysis of variables during follow-up, elderly AAV patients exhibited higher frequencies of CKD and ILD than non-elderly AAV patients. However, there were no significant differences in all-cause mortality and ESRD occurrence between elderly and non-elderly AAV patients.

With these results, we could make two assumptions.

The first assumption is that highly active and severe AAV might occur more often in elderly people than in younger ones. The high median BVAS and increased frequencies of MPO-ANCA (or P-ANCA) and ANCA positivity in elderly AAV patients might support this assumption. Alternatively, even AAV, whose activity and severity are similar to those in non-elderly patients, could exaggerate the frequencies of AAV-specific manifestations due to low daily functionality in elderly AAV patients, leading to an increase in BVAS. The second assumption is that ageing itself might provoke enhanced autoimmunity and prolong autoinflammation. The detection rate of MPO-ANCA (or P-ANCA) is increased and the serological markers of chronic inflammation become apparent with age [5,11-14].

The Kaplan-Meier survival analysis revealed that elderly AAV patients exhibited lower cumulative patients' and ESRD-free survival rates than non-elderly AAV patients, which were similar to the results of previous studies [4-6]. In addition, because the incidences of all-cause mortality and ESRD occurrence may gradually increase with age, if the age cut-off for elderly AAV patients is raised, would the difference be greater? The age cut-off for elderly AAV patients was set at 75 years and the cumulative patients' and ESRD-free survival rates were compared between the two groups. Similarly, elderly AAV patients exhibited lower cumulative patients' and ESRD-free survival rates than non-elderly AAV patients

Table 3. Predictors at diagnosis for all-cause mortality during follow-up in elderly AAV patients (n = 67)

Variable	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Demographic data at diagnosis						
Age	1.127	0.968–1.312	0.122			
Female sex	0.366	0.091–1.469	0.156			
Variants at diagnosis						
MPA	2.53	0.529–12.317	0.243			
GPA	0.894	0.180–4.429	0.890			
EGPA	0.035	0.000–57.698	0.376			
ANCA positivity at diagnosis						
MPO-ANCA (or P-ANCA)	29.554	0.028–31,172.127	0.340			
PR3-ANCA (or C-ANCA)	0.043	0.000–2,396.268	0.573			
AAV-specific indices at diagnosis						
BVAS, ≥ 18	4.305	1.069–17.346	0.040	2.945	0.465–18.643	0.251
FFS, ≥ 2	4.078	0.509–32.685	0.186			
Clinical manifestations at diagnosis						
General	0.501	0.120–2.096	0.344			
Cutaneous	0.567	0.070–4.614	0.596			
Muco-membranous/ocular	0.045	0.000–11,492.194	0.625			
Ear nose throat	0.020	0.000–4.912	0.164			
Pulmonary	3.518	0.402–30.750	0.256			
Cardiovascular	3.279	0.878–12.243	0.077			
Gastrointestinal	3.497	0.650–18.805	0.145			
Renal	3.891	0.476–31.804	0.205			
Nervous	0.833	0.172–4.025	0.820			
Laboratory results at diagnosis						
White blood cell count	1.000	1.000–1.000	0.593			
Hemoglobin	0.663	0.449–0.978	0.038	0.867	0.473–1.589	0.645
Platelet count	1.000	0.995–1.004	0.845			
Fasting glucose	1.005	0.995–1.015	0.357			
BUN	1.058	1.022–1.096	0.001	1.022	0.951–1.098	0.558
Creatinine	1.419	1.094–1.841	0.008	1.561	0.956–2.551	0.075
Total serum protein	0.612	0.263–1.424	0.254			
Serum albumin	0.360	0.129–1.007	0.051			
ALP	1.011	1.005–1.018	0.001	1.011	0.991–1.032	0.285
AST	1.028	1.002–1.005	0.035	1.197	0.985–1.456	0.071
ALT	1.017	1.003–1.032	0.017	0.880	0.761–1.019	0.087
Total bilirubin	3.429	0.604–19.447	0.164			
ESR	1.013	0.994–1.032	0.171			
CRP	1.005	0.994–1.015	0.393			

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; HR, hazard ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, five factor score; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

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Table 4. Predictors at diagnosis for ESRD during follow-up in elderly AAV patients (n = 67)

Variable	Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
Demographic data at diagnosis						
Age	1.033	0.894–1.194	0.657			
Female sex	0.700	0.174–2.809	0.615			
Variants at diagnosis						
MPA	3.235	0.683–15.323	0.139			
GPA	0.743	0.154–3.580	0.711			
EGPA	0.034	0.000–30.337	0.329			
ANCA positivity at diagnosis						
MPO-ANCA (or P-ANCA)	30.314	0.051–18,148.326	0.296			
PR3-ANCA (or C-ANCA)	0.043	0.000–876.777	0.534			
AAV-specific indices at diagnosis						
BVAS, ≥ 18	3.820	1.066–13.694	0.040	0.434	0.077–2.438	0.343
FFS, ≥ 2	42.806	0.201–9,125.277	0.170			
Clinical manifestations at diagnosis						
General	2.862	0.594–13.787	0.190			
Cutaneous	0.460	0.058–3.681	0.464			
Muco-membranous/ocular	1.501	0.186–12.114	0.703			
Ear nose throat	0.334	0.071–1.577	0.166			
Pulmonary	1.091	0.267–4.459	0.903			
Cardiovascular	0.639	0.136–3.016	0.572			
Gastrointestinal	1.142	0.130–9.989	0.905			
Renal	5.576	0.691–45.017	0.107			
Nervous	1.227	0.316–4.762	0.767			
Laboratory results at diagnosis						
White blood cell count	1.000	1.000–1.000	0.230			
Hemoglobin	0.606	0.405–0.905	0.015	1.518	0.788–2.925	0.212
Platelet count	1.002	0.998–1.006	0.325			
Fasting glucose	0.998	0.986–1.011	0.813			
BUN	1.064	1.031–1.099	< 0.001	1.073	1.016–1.133	0.012
Creatinine	1.673	1.286–2.177	< 0.001	1.642	1.132–2.383	0.009
Total serum protein	1.057	1.001–1.117	0.047			
Serum albumin	0.227	0.073–0.710	0.011	0.051	0.006–0.444	0.007
ALP	1.005	0.996–1.013	0.312			
AST	0.939	0.846–1.042	0.234			
ALT	0.950	0.867–1.040	0.266			
Total bilirubin	0.123	0.002–6.110	0.293			
ESR	1.004	0.988–1.021	0.609			
CRP	1.005	0.995–1.015	0.325			

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; HR, hazard ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, five factor score; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

but the statistical power was much higher (Supplementary Fig. 1). However, as mentioned in the Methods section, the small number of elderly AAV patient could not warrant the statistical reliability. Therefore, we adopted the results of the comparative analysis of the cumulative survival rates between patients aged 65 years and above and those aged 65 years and below.

Regarding the predictors for ESRD occurrence during follow-up based on ESRD, BUN, creatinine and serum albumin at diagnosis were significant in the multivariable analysis. Because BUN and creatinine are variables directly associated with renal function, it could easily be accepted that the initial BUN and creatinine levels could predict the development of ESRD occurrence during AAV follow-up. Reduced serum albumin might be associated with persistent proteinuria, which can, in turn, accelerate renal function deterioration and finally provoke ESRD. Therefore, BUN, creatinine, and serum albumin at diagnosis could predict ESRD occurrence during follow-up based on ESRD regardless of the relationship between these variables and the concurrent activity of AAV [15].

Additionally, we assessed predictors at diagnosis for all-cause mortality and ESRD in non-elderly AAV patients using the univariable and multivariable Cox hazards model analysis; then we compared the differences between independent predictors for all-cause mortality and ESRD between elderly AAV patients and non-elderly AAV patients. Both elderly and non-elderly AAV patients showed no independent predictor for all-cause mortality (Supplementary Table 1). On the other hand, elderly AAV patients exhibited three independent predictors, such as BUN, creatinine, and serum albumin, whereas non-elderly AAV patients showed four independent predictors, FFS ≥ 2, nervous manifestation, fasting glucose, and creatinine (Supplementary Table 2). Although it is difficult to determine the exact mechanism of the differences between the two groups, we hypothesize that the current activity of AAV at diagnosis may influence the progression to ESRD in non-elderly AAV patients, whereas advanced renal disease with low serum albumin at diagnosis may accelerate progression to ESRD in elderly AAV patients.

We believe that our study will contribute to understanding ethnic features in Korean elderly patients with AAV. We first demonstrated the cross-sectional differences in the clinical and laboratory features at diagnosis and prognosis as well as the comorbidities during follow-up between elderly and non-elderly AAV patients in Korea. Additionally, we provided information on the differences between the cumulative patients' and ESRD-free survival rates based on the age cut-off of 65 years and the initial independent predictors for all-cause mortality and ESRD occurrence during follow-up based on each outcome in Korean patients with AAV. However, our study also has several limitations. First, since we reviewed medical records of AAV patients retrospectively, we could not control the initial variables at AAV diagnosis and prevent missing data such as autoantibodies related to other autoimmune connective tissue diseases, despite searching the concurrent diseases of each patient by ICD-10. Additionally, we could not collate the conventional risk factors for all-cause mortality at the time of diagnosis, such as medical history and duration of diabetes mellitus, hypertension and dyslipidemia, smoking history, alcohol intake, and occupational factors. Concerning medications, the limitations of detailed content in the medical records discouraged the authors from calculating the cumulative dose of each medication administered owing to the retrospective study design and patients' compliance and adherence to the oral immunosuppressive drugs. For this reason, we had to count the number of patients who received each drug. Second, the number of patients in this study was not large enough to provide more validated and stronger evidence on the features of Korean elderly patients with AAV. Third, the number of AAV patients aged 75 years and above was only 20; therefore, we could not clearly analyze the clinical and laboratory features at diagnosis and prognosis as well as the comorbidities during follow-up between patients aged 75 years and above and below. Given that previous studies conducted in Western countries selected the age for elderly AAV patients as 75 or 80 years, we could not compare the results of those previous studies with our results. Future multi-centric prospective studies with a large number of AAV patients, particularly more patients aged 75 years and above, will overcome these issues and provide more information on the features of Korean elderly patients with AAV.

In conclusion, elderly AAV patients exhibited substantially higher rates of all-cause mortality and ESRD occurrence during follow-up than non-elderly AAV pa-

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tients. Furthermore, BUN, creatinine and serum albumin at diagnosis were independent predictors for ESRD during follow-up in Korean elderly patients with AAV.

KEY MESSAGE

1. Based on an age of 65 years, 67 of 191 antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients (35.1%) were classified as elderly patients.
2. Elderly AAV patients exhibited lower cumulative patients' and end-stage renal disease (ESRD) free survival rates than non-elderly AAV patients.
3. Haemoglobin, blood urea nitrogen, creatinine, total protein and serum albumin at diagnosis were the independent predictors for ESRD in elderly AAV patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Predictors at diagnosis for all-cause mortality during follow-up in non-elderly AAV patients (n = 124)

Variable	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Demographic data at diagnosis						
Age	1.052	0.987–1.121	0.121			
Female sex	0.508	0.146–1.771	0.288			
Variants (MPA vs. GPA or EGPA) at diagnosis	0.473	0.121–1.854	0.283			
ANCA positivity at diagnosis						
MPO-ANCA (or P-ANCA)	0.748	0.188–2.974	0.680			
PR3-ANCA (or C-ANCA)	2.766	0.783–9.767	0.114			
AAV-specific indices at diagnosis						
BVAS, ≥ 18	1.063	0.219–5.147	0.943			
FFS, ≥ 2	5.994	1.526–23.543	0.010	3.596	0.429–30.100	0.238
Clinical manifestations at diagnosis						
General	2.263	0.636–8.058	0.208			
Cutaneous	0.122	0.015–1.022	0.052			
Muco-membranous/ocular	1.092	0.213–5.592	0.916			
Ear nose throat	1.973	0.546–7.120	0.300			
Pulmonary	3.508	0.897–13.709	0.071			
Cardiovascular	5.144	1.314–20.137	0.019	1.934	0.230–16.274	0.544
Gastrointestinal	1.084	0.134–8.735	0.940			
Renal	9.993	1.221–81.807	0.032			
Nervous	0.363	0.076–1.727	0.203			
Laboratory results at diagnosis						
White blood cell count	1.000	1.000–1.000	0.458			
Hemoglobin	0.945	0.713–1.251	0.691			
Platelet count	0.999	0.994–1.004	0.689			
Fasting glucose	1.002	0.984–1.021	0.795			
BUN	1.000	0.981–1.019	0.999			
Creatinine	0.946	0.735–1.218	0.667			
Total serum protein	0.755	0.380–1.499	0.422			
Serum albumin	0.651	0.271–1.568	0.339			
ALP	1.000	0.992–1.009	0.937			
AST	0.924	0.819–1.043	0.202			
ALT	0.999	0.974–1.024	0.914			
Total bilirubin	1.139	0.081–16.043	0.923			
ESR	0.995	0.978–1.013	0.592			
CRP	1.007	0.995–1.020	0.251			

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; HR, hazard ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, five factor score; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

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Supplementary Table 2 Predictors at diagnosis for ESRD during follow-up in non-elderly AAV patients (n = 124)

Variable	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Demographic data at diagnosis						
Age	1.028	0.985–1.073	0.207			
Female sex	1.321	0.429–4.067	0.628			
Variants (MPA vs. GPA or EGPA) at diagnosis	2.647	0.926–7.562	0.069			
ANCA positivity at diagnosis						
MPO-ANCA (or P-ANCA)	4.644	1.554–13.872	0.006	3.697	0.577–23.680	0.168
PR3-ANCA (or C-ANCA)	0.929	0.301–2.867	0.898			
AAV-specific indices at diagnosis						
BVAS, ≥ 18	2.725	1.025–7.242	0.044	0.626	0.114–3.421	0.589
FFS, ≥ 2	3.349	1.269–8.839	0.015	6.875	1.168–40.470	0.033
Clinical manifestations at diagnosis						
General	1.066	0.405–2.804	0.898			
Cutaneous	0.389	0.123–1.234	0.109			
Muco-membranous /Ocular	0.036	0.000–14.645	0.278			
Ear nose throat	0.281	0.080–0.984	0.047	0.289	0.054–1.534	0.145
Pulmonary	2.676	0.980–7.305	0.055			
Cardiovascular	2.197	0.842–5.729	0.108			
Gastrointestinal	0.552	0.073–4.171	0.565			
Renal	23.159	2.891–185.545	0.003	4.746	0.349–64.592	0.242
Nervous	0.211	0.048–0.930	0.040	0.084	0.007–0.964	0.047
Laboratory results at diagnosis						
White blood cell count	1.000	1.000–1.000	0.261			
Haemoglobin	0.685	0.539–0.870	0.002	0.752	0.450–1.257	0.277
Platelet count	0.998	0.993–1.002	0.316			
Fasting glucose	1.013	1.005–1.021	0.001	1.028	1.009–1.046	0.003
BUN	1.017	1.008–1.025	< 0.001	0.979	0.953–1.006	0.119
Creatinine	1.333	1.170–1.518	< 0.001	2.093	1.275–3.435	0.004
Total serum protein	0.650	0.380–1.115	0.118			
Serum albumin	0.970	0.504–1.869	0.929			
ALP	0.998	0.989–1.008	0.687			
AST	0.921	0.842–1.007	0.069			
ALT	0.955	0.903–1.010	0.106			
Total bilirubin	0.165	0.010–2.799	0.212			
ESR	1.004	0.992–1.016	0.497			
CRP	1.003	0.993–1.014	0.539			

AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; HR, hazard ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, five factor score; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; ESR, erythrocyte sedimentation rate; CRP C-reactive protein.
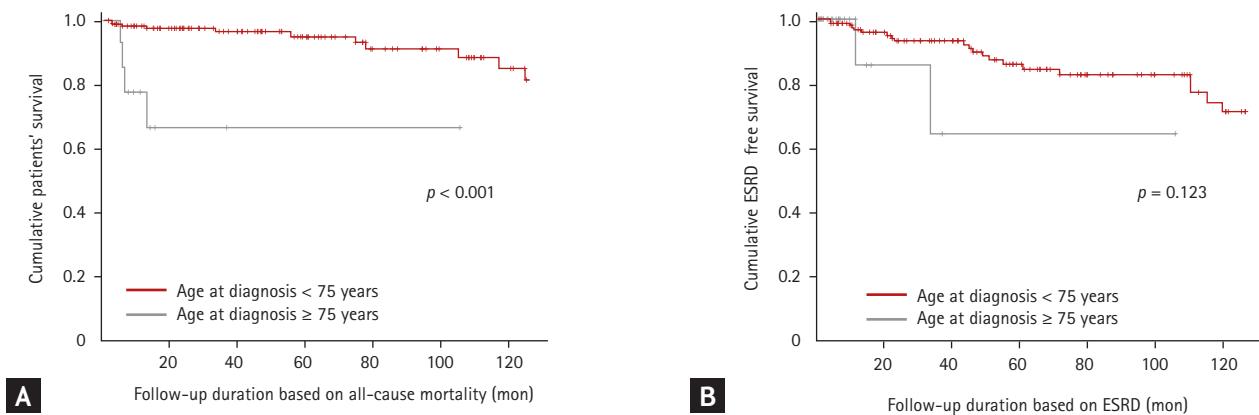
Supplementary Figure 1. (A, B) Comparison of the cumulative survival rates based on the age of 75 years. Elderly antineutrophil cytoplasmic antibody-associated vasculitis (AAV) patients (aged ≥ 75 years) exhibited the lower cumulative patients' and end-stage renal disease (ESRD)-free survival rates than non-elderly AAV patients (aged < 75 years), similar to the comparative analysis based on the age of 65 years.