The initial predictors of death in 153 patients with ANCA-associated vasculitis in a single Korean centre

C.H. Mun, J. Yoo, S.M. Jung, J.J. Song, Y.-B. Park, S.-W. Lee

Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.

Chin Hee Mun, PhD
Juyoung Yoo, MD
Seung Min Jung, MD, PhD
Jason Jungsik Song, MD, PhD
Yong-Beom Park, MD, PhD
Sang-Won Lee, MD, PhD

Please address correspondence to:
dr Sang-Won Lee,
Division of Rheumatology,
Department of Internal Medicine,
Yonsei University College of Medicine,
50-1 Yonsei-ro, Seodaemun-gu,
Seoul, 03722, Republic of Korea.
Email: sangwonlee@yuhs.ac

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ABSTRACT

Objectives. *We estimated the cumulative patient survival rates, the causes of death and the initial predictors of death in Korean patients with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA).*

Methods. *We reviewed the medical records of 153 patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). We collected clinical and laboratory data including ANCA, Birmingham vasculitis activity score (BVAS), five factor score (FFS) (2009), comorbidities, medications and prognosis (death and relapse). The hazard ratio (HR) of variables at diagnosis for death in the disease course was assessed by the Cox hazard model analysis.*

Results. *The mean age of 153 AAV patients (47 men and 106 women) was 55.2 years and the mean follow-up duration was 51.5 months. Fourteen of 153 patients (9.2%) died (7 MPA and 7 GPA patients) during the mean follow-up of 56.9 months. In all patients with AAV, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.1%, 94.8% and 92.8%, respectively. The most common cause of death was infection of various causes. FFS (2009) ≥2 (HR 16.520, p=0.012) and diffuse alveolar haemorrhage (DAH) (HR 3.705, p=0.042) at diagnosis could predict death during the follow-up in AAV patients in multivariate COX regression analysis.*

Conclusion. *The overall mortality rate was 9.2% and 10-year cumulative patient survival rate was 92.8%. At diagnosis, FFS (2009) ≥ 2 and DAH were independent predictors of death during the follow-up in Korean patients with MPA, GPA and EGPA.*

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a very rare autoimmune disease, which often involves small vessels of various organs (1). AAV is composed of 3 variants based on clinical manifestations including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (1). Because AAV can involve almost all the major organs, particularly heart, lung and kidneys, AAV may provoke the poorer prognosis including both disease and treatment drugs-related death than other rheumatic diseases (2). In terms of Western countries, 1 year-, 5 year- and 10 year-cumulative patient survival rates were estimated as 82~95%, 74~97% and 89%, respectively (3). In terms of North-Eastern countries with similar ethnicity, 1 year- and 5 year- cumulative patient survival rates were 79.1% and 63.6% in Japan, and 6 month- cumulative patient survival rate was 78.7% in China (4, 5).

So far, there have been a few retrospective cohort-studies regarding the cumulative patient survival rate in Korean patients with AAV (6-8). However, they included only patients with MPA or GPA, and as far as we know, there was no report regarding the cumulative patient survival rates, the causes of death and predictors of death in Korean patients with all variants of AAV to date. Hence, the purpose of this study was to estimate the cumulative patient survival rates, the causes of death and the initial predictors of death in Korean patients with MPA, GPA and EGPA.

Patients and methods

Patients

We retrospectively reviewed the medical records of 153 AAV patients based on the inclusion criteria as follows: i) patients who had been classified as MPA, GPA and EGPA from October 2000 to April 2017 at Division of Rheumatology, Department of Internal Medicine, Yonsei University College

of Medicine, Severance hospital; ii) those who fulfilled The American College of Rheumatology 1990 criteria for the classification (the 1990 ACR criteria) of GPA and EGPA, the algorithm suggested by the European Medicines Agency (EMA) in 2007 (the 2007 EMA algorithm) and the Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitides proposed in 2012 (the 2012 CHCC definitions) (1, 9-11); iii) those who had been followed up for at least more than 12 weeks to determine relapse (12); iv) those who had the results of myeloperoxidase (MPO)-ANCA or perinuclear (P)-ANCA and proteinase 3 (PR3)-ANCA or cytoplasmic (C)-ANCA tests; v) those who had well-documented medical records to assess the initial clinical manifestations, Birmingham vasculitis activity score (BVAS) or BVAS for GPA and five factor score proposed in 2009 (FFS (2009)) (13-15); vi) those who were not concurrently diagnosed with fatal medical conditions such as malignancies. Medical conditions were searched by the 10th revised International Classification of Diseases (ICD-10) and medications administered were monitored under the Korean Drug Utilization Review (DUR) system. This study was approved by the institutional Review Board of Severance Hospital (4-2017-0673).

Clinical and laboratory data, comorbidities and medications

We collected age, gender and the follow-up duration as demographic data. The follow-up duration was defined as the period from diagnosis to the last visit for survived patients, and that from diagnosis to death for deceased patients with AAV. Clinical manifestations at diagnosis consisted of organ-based items of BVAS or BVAS for GPA. BVAS or BVAS for GPA and FFS (2009) at diagnosis were calculated. We searched chronic kidney disease (CKD) stage ≥ 3 (including end stage renal disease (ESRD)) and diffuse alveolar haemorrhage (DAH) as comorbidities at diagnosis and ESRD, diabetes mellitus (DM), hypertension (HTN), interstitial lung disease (ILD), hyper- and hypothyroidism, ischaemic heart disease (IHD), cerebrovascular accident (CVA) or carotid arterial stenosis, hepatitis B or C virus (HBV or HCV) infection and other rheumatic diseases as comorbidities during the follow-up. Relapse was defined as recurrence or new onset of disease attributable to active vasculitis (12). We reviewed immunosuppressive drugs or procedure including glucocorticoid (GC), cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine (AZA), calcineurin inhibitor (CNI), rituximab (RTX), methotrexate (MTX) and plasma exchange (PE). Perinuclear (P)-ANCA and cytoplasmic (C)-ANCA were detected by immunofluorescent assay. MPO-ANCA and PR3-ANCA had been measured by ELISA kit for anti-PR3 and anti-MPO (Inova Diagnostics, San Diego, USA) before 2013, and by the novel anchor coated highly sensitive (hs) Phadia ELiA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) using human native antigens, performed on a Phadia250 analyser after 2013.

Statistical analyses

All statistical analyses were conducted using SPSS software (v. 23 for windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were done as number and the percentage. Significant differences between survived and deceased patients with AAV were compared using the chi square test and Fisher's extract test for categorical data and the Student's *t*-test or Mann-Whitney U-test for continuous variables. The cumulative patient survival rate was estimated by the Kaplan-Meier analysis and statistical significance was evaluated by Log Rank test. The optimal cut-off of FFS (2009) to presuppose death during the follow-up was extrapolated by computing the area under the receiver operator characteristic curve (AUROC) and choosing the maximised sum of sensitivity and specificity at 2 of FFS (2009) (Area 0.862, 95% confidence interval 0.779, 0.944, $p<0.001$). The odds ratio (OR) of GPA, FFS (2009) ≥2, CDK stage ≥3 and DAH at diagnosis, and hypertension, ILD, hyperthyroidism and relapse during the follow-up for death was analysed by the univariate and multivariate logistic regression analyses. The hazard ratio (HR) of GPA, FFS (2009) ≥2, CKD stage ≥3 and DAH at diagnosis for death during the follow-up was assessed using the univariate and multivariate Cox hazard model analysis. *P*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of all AAV patients were described in Table I. The mean age of 153 AAV patients (47 men and 106 women) was 55.2 years and the mean follow-up duration was 51.5 months. Eight-three patients had MPA, 37 had GPA and 33 had EGPA. Renal manifestation (58.8%) was the most frequent clinical symptoms and signs, followed by pulmonary (52.3%) and general manifestations (44.4%). At diagnosis, 94 patients had MPO-ANCA (or P-ANCA), 26 had PR3-ANCA (C-ANCA) and 7 had both ANCAs, while 40 patients had no ANCA. The initial mean BVAS or BVAS for GPA and FFS (2009) were 12.2 and 1.2. At diagnosis, 64 patients (41.8%) exhibited CKD stage ≥3 and 12 patients (7.8%) presented DAH. Among comorbidities during the follow-up, hypertension (43.8%) was the most commonly observed, followed by interstitial lung disease (41.2%). Sixty-five patients 65 patients (42.5%) had ever received CYC with GC and 15 patients (9.8) had ever received RTX due to refractory activity of AAV to CYC. AZA (27.5%) was the most favoured maintenance therapeutic regimen and plasma exchange was performed in 4 patients (2.6%). Forty-four patients (28.8%) experienced relapse.

Cumulative patient survival rates

The cumulative patient survival rate using Kaplan-Meier analysis was depicted in Figure 1. First, in terms of 153 AAV patients, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.1%, 94.8% and 92.8%, respectively. Second, in terms of 83 MPA patients, 1 year-, 5 year- and 10

Table I. Baseline characteristics of 153 patients with AAV .

Variables	Values
Demographic data	
Age at diagnosis (year old)	55.2 ± 15.2
Male gender (n, (%))	47 (30.7)
Follow-up duration (months)	51.5 ± 49.4
Variants of AAV at diagnosis (n, (%))*	
MPA	83 (54.2)
GPA	37 (24.2)
EGPA	33 (21.6)
Clinical manifestations at diagnosis (n, (%))	
General manifestation	68 (44.4)
Cutaneous manifestation	36 (23.5)
Mucous membranes/Eyes manifestation	12 (7.8)
Ear Nose Throat manifestation	54 (35.3)
Cardiovascular manifestation	45 (29.4)
Gastrointestinal manifestation	10 (6.5)
Pulmonary manifestation	80 (52.3)
Renal manifestation	90 (58.8)
Nervous systemic manifestation	52 (34.0)
ANCA at diagnosis (n, (%))	
MPO-ANCA (or P-ANCA)	94 (61.4)
PR3-ANCA (or C-ANCA)	26 (17.0)
Both ANCAs	7 (4.6)
ANCA negative	40 (26.1)
BVAS or BVAS for GPA at diagnosis	12.2 ± 7.6
FFS (2009) at diagnosis	1.2 ± 1.0
Comorbidities at diagnosis (n, (%))	
CKD stage ≥ 3	64 (41.8)
DAH	12 (7.8)
Comorbidities during the follow-up (n, (%))	
ESRD	24 (15.7)
DM	34 (22.2)
HTN	67 (43.8)
ILD	63 (41.2)
Hyperthyroidism	11 (7.2)
Hypothyroidism	4 (2.6)
IHD	10 (6.5)
CVA or carotid arterial stenosis	15 (9.8)
HBV or HCV carrier	5 (3.3)
Other rheumatic diseases	15 (9.8)
Medications or procedure during the follow-up (n, (%))	
GC	132 (86.3)
CYC	65 (42.5)
MMF	10 (6.5)
AZA	42 (27.5)
CNI	9 (5.9)
RTX	15 (9.8)
MTX	13 (8.5)
PE	4 (2.6)
Relapse during the follow-up (n, (%))	44 (28.8)

Values are expressed as mean and standard deviation or N (%).
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; CKD: chronic kidney disease; DAH: diffuse alveolar haemorrhage; ESRD: end stage renal disease; DM: diabetes mellitus; HTN: hypertension; ILD: interstitial lung disease; IHD: ischaemic heart disease; CVA: cerebrovascular accident; GC: glucocorticoid; CYC: cyclophosphamide; MMF: mycophenolate mofetil; AZA: azathioprine; CNI: calcineurin inhibitor; RTX: Rituximab; MTX: methotrexate; PE: plasma exchange.

year-cumulative patient survival rates were 96.4%, 94.0% and 91.6%, respectively. Third, in terms of 37 GPA patients, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 91.9%, 91.9% and 89.2%, respectively. Last, in terms of 33 EGPA patients, no patients had deceased during the follow-up. When we compared the cumulative patient survival rates among 3 variants of AAV, we could find no remarkable difference.

Characteristics of 14 deceased patients with AAV

The detailed characteristics of 14 deceased patients with AAV were described in Table II. The mean age at diagnosis of 14 deceased patients with AAV (6 men and 8 women) was 57.9 years and the mean follow-up duration was 59.9 months. Seven patients had MPA and 7 had GPA. Twelve patients (85.7%) exhibited CKD stage ≥3 and 4 patients (28.6%) presented DAH at diagnosis. Among comorbidities during the follow-up, hypertension (78.6%) was the most commonly observed, followed by interstitial lung disease (71.4%). Eight patients (57.1%) experienced relapse. The most common cause of death was pneumonia of various origins in 7 patients (Aspergilosis in 3 patients, bacterial infection in 3 patients and cytomegalovirus infection in 1 patient), followed by bacterial sepsis in 3 patients and cardiac arrest, alveolar haemorrhage, influenza infection and biliary infection in each patient.

Comparison of variables between survived and deceased patients

Comparison of variables between survived and deceased patients was described in Supplementary Table I. We divided 153 patients with AAV into 2 groups according to death, and we compared variables between 139 survived and 14 deceased patients. There were no differences in demographic data and ANCA positivity at diagnosis between the two groups. At diagnosis, deceased patients exhibited cardiovascular and pulmonary manifestations more frequently than survived patients. Furthermore, deceased patients showed the higher mean FFS (2000) at diagnosis than survived patients (2.5 *vs*. 1.1, $p<0.001$), but not BVAS or BVAS for GPA. Deceased patients showed the increased rates of CKD stage ≥3 and DAH at diagnosis compared to survived patients (85.7% *vs*. 37.4%, $p<0.001$, and 28.6% *vs*. 5.8%,

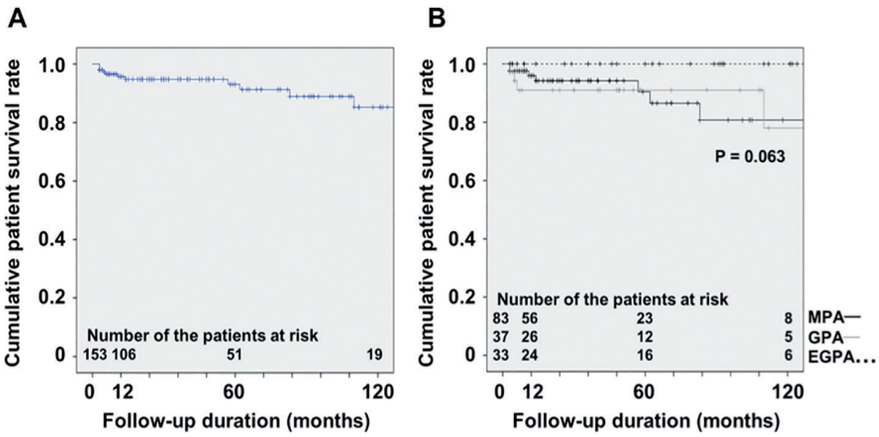

Fig. 1. The cumulative patient survival rates in all patients with AAV and patients with each variant. (**A**) In all AAV patients, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.1%, 94.8% and 92.8%, respectively. (**B**) In 83 MPA, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.4%, 94.0% and 91.6%, respectively and in 37 GPA patients, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 91.9%, 91.9% and 89.2%, respectively. AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis.

p=0.002). Among comorbidities during the follow-up, deceased patients exhibited hypertension and hyperthyroidism more frequently than survived patients. Immunosuppressive drugs had been evenly administered to the two groups. Deceased patients experienced relapse more often than survived patients (57.1% *vs*. 25.9%, p=0.014).

Univariate and multivariate logistic regression analysis

To assess the factors related to death, we performed univariate logistic regression analysis with variables having statistical significance in comparison analysis. We excluded cardiovascular manifestation, because a considerable number of patients had both cardiovascular manifestation and an item of cardiomyopathy in FFS (2009). Univariate logistic analysis revealed GPA, FFS (2009) ≥2, CDK stage ≥3 and DAH at diagnosis, and hypertension, ILD, hyperthyroidism and relapse during the follow-up were associated with death in AAV patients (Table III). Multivariate logistic regression analysis unveiled that only GPA (OR 29.652, p=0.001), FFS (2009) at diagnosis ≥2 (OR 45.993, p=0.006), and relapse (OR 9.729, p=0.018) were associated with death (Table III).

Predictors of death during the follow-up of AAV

To determine the initial predictor of death in the disease course, we performed Kaplan-Meier analysis and COX regression model analysis using GPA, FFS (2009) ≥2, CKD stage ≥3 and DAH at diagnosis. Variables during the follow-up or before diagnosis with significance in Table III including hypertension, ILD, hyperthyroidism and relapse were not analysed, because the time-gap from the initiation of event to death was difficult to be determined. In Kaplan-Meier analysis with Log Rank

Table II. Characteristics of 14 deceased patients with AAV.

Patient number	Gender	Age at diagnosis	Age at death	AAV variant	Cause of death	Time-gap from diagnosis to death (months)	Relapse	Comorbidities	Immunosuppressive agents
1	Female	46	53	MPA	CMV pneumonia	83	Yes	CKD, HTN, ILD, Hyperthyroidism	GC+CYC
2	Male	68	69	MPA	Aspergilosis pneumonia	11	Yes	ESRD, DM, HTN, ILD	GC+CYC
3	Male	62	67	MPA	Cardiac arrest	57	Yes	CKD, DAH, HTN, ILD, Hyperthyroidism, IHD	GC+AZA
4	Female	65	65	MPA	Sepsis	3	No	ESRD, DM, HTN	GC
5	Female	59	64	MPA	Sepsis	62	Yes	CKD, DM, HTN, ILD, CVA	GC+CYC → CG+MMF
6	Male	70	70	MPA	Sepsis	3	No	CKD, DAH, HTN, ILD, HBV carrier	GC+CYC
7	Female	79	80	MPA	Aspiration pneumonia	14	Yes	ESRD, DM, HTN, ILD, CVA	GC+CYC → GC
8	Female	75	75	GPA	Aspergilosis pneumonia	5	No	DAH, DM, HTN, ILD, Hyperthyroidism, CVA	GC
9	Male	46	46	GPA	Alveolar haemorrhage	3	No	CKD, DAH, ILD	GC+CYC → GC+PE
10	Female	42	54	GPA	Pneumonia	146	Yes	ESRD, HTN, ILD	GC
11	Male	55	64	GPA	Aspergilosis Pneumonia	110	No	CKD, DM, HTN, ILD	GC+CYC → GC+RTX
12	Male	15	29	GPA	Pneumonia	164	Yes	CKD	GC+CYC → GC+MMF → GC+CYC → GC+RTX
13	Female	57	68	GPA	H1N1 influenza	129	Yes	None	GC
14	Female	71	72	GPA	Biliary infection	6	No	CKD, HTN, IHD	GC+CYC → GC+RTX

AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; CMV: cytomegalovirus; CKD: chronic kidney disease stage ≥ 3 at diagnosis; HTN: hypertension; ILD: interstitial lung disease; ESRD: end stage renal disease; DM: diabetes mellitus; DAH: diffuse alveolar haemorrhage at diagnosis; IHD: ischaemic heart disease; CVA: cerebrovascular accident.

Table III. Univariate and multivariate logistic regression analysis of the association of variables with death in patients with AAV.

Variables	Univariate			Multivariate		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Demographic data						
Age at diagnosis (year old)	1.014	0.976, 1.053	0.486			
Male gender (N, (%))	0.558	0.182, 1.709	0.307			
Follow-up duration (months)	1.002	0.992, 1.013	0.671			
*Variants of AAV at diagnosis (n, (%))**						
MPA compared to Other AAV variants	0.829	0.276, 2.489	0.738			
GPA compared to Other AAV variants	3.633	1.182, 11.168	0.024	29.652	3.809, 230.799	0.001
Clinical manifestations at diagnosis (n, (%))						
General manifestation	1.279	0.426, 3.841	0.661			
Cutaneous manifestation	0.515	0.110, 2.416	0.400			
Mucous membranes/Eyes manifestation	2.150	0.422, 10.966	0.357			
Ear Nose Throat manifestation	1.020	0.324, 3.214	0.972			
Cardiovascular manifestation	19.273	4.103, 90.539	<0.001			
Gastrointestinal manifestation	2.729	0.520, 14.331	0.235			
Pulmonary manifestation	3.720	0.994, 13.914	0.051			
Renal manifestation	2.785	0.744, 10.425	0.128			
Nervous systemic manifestation	0.758	0.226, 2.546	0.654			
ANCA at diagnosis (n, (%))						
MPO-ANCA (or P-ANCA)	0.822	0.270, 2.499	0.729			
PR3-ANCA (or C-ANCA)	2.127	0.612, 7.394	0.235			
ANCA double positive	1.705	0.190, 15.270	0.633			
ANCA negative	0.752	0.199, 2.845	0.674			
BVAS or BVAS for GPA at diagnosis	1.020	0.950, 1.094	0.590			
FFS (2009) ≥ 2 at diagnosis	29.023	3.679, 228.972	0.001	45.993	2.964, 713.758	0.006
Comorbidities at diagnosis (n, (%))						
CKD stage ≥ 3	10.038	2.161, 46.632	0.003	3.500	0.234, 52.307	0.364
DAH	6.550	1.678, 25.562	0.007	1.768	0.205, 15.262	0.604
Comorbidities during the follow-up (n, (%))						
ESRD	2.380	0.680, 8.328	0.175			
DM	2.973	0.954, 9.266	0.060			
HTN	5.435	1.451, 20.361	0.012	2.818	0.266, 29.865	0.390
ILD	4.057	1.211, 13.590	0.023	1.338	0.216, 8.288	0.754
Hyperthyroidism	4.466	1.034, 19.280	0.045	7.229	0.488, 107.016	0.150
Hypothyroidism	N/A					
IHD	2.729	0.520, 14.331	0.235			
CVA or carotid arterial stenosis	2.886	0.707, 11.789	0.140			
HBV or HCV carrier	2.596	0.270, 24.979	0.409			
Other rheumatic diseases	N/A					
Medications or procedure during the follow-up (n, (%))						
GC	2.185	0.271, 17.636	0.463			
CYC	2.668	0.849, 8.380	0.093			
MMF	2.729	0.520, 14.331	0.235			
AZA	0.184	0.023, 1.452	0.108			
CNI	N/A					
RTX	2.886	0.707, 11.789	0.140			
MTX	N/A					
PE	3.487	0.338, 35.970	0.294			
Relapse during the follow-up (n, (%))	3.815	1.239, 11.744	0.020	9.729	1.489, 63.566	0.018

Values are expressed as mean and standard deviation or N (%).

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; CKD: chronic kidney disease; DAH: diffuse alveolar haemorrhage; ESRD: end stage renal disease; DM: diabetes mellitus; HTN: hypertension; ILD: interstitial lung disease; IHD: ischaemic heart disease; CVA: cerebrovascular accident; HBV: hepatitis B virus; HCV: hepatitis C virus; GC: glucocorticoid; CYC: cyclophosphamide; MMF: mycophenolate mofetil; AZA: azathioprine; CNI: calcineurin inhibitor; RTX: Rituximab; MTX: methotrexate; PE: plasma exchange.

test, FFS (2009) ≥2 (p<0.001), CKD stage ≥3 (p=0.033) and DAH (p<0.001) at diagnosis were associated with death in AAV patients (Fig. 2). However, GPA did not influence the cumulative patient survival rate, compared to MPA or EGPA. In multivariate COX regression model analysis, FFS (2009) at diagnosis ≥2 (OR 16.520, p=0.012) and DAH (OR 3.705, p=0.042) at diagnosis could predict death in the disease course of AAV (Table IV).

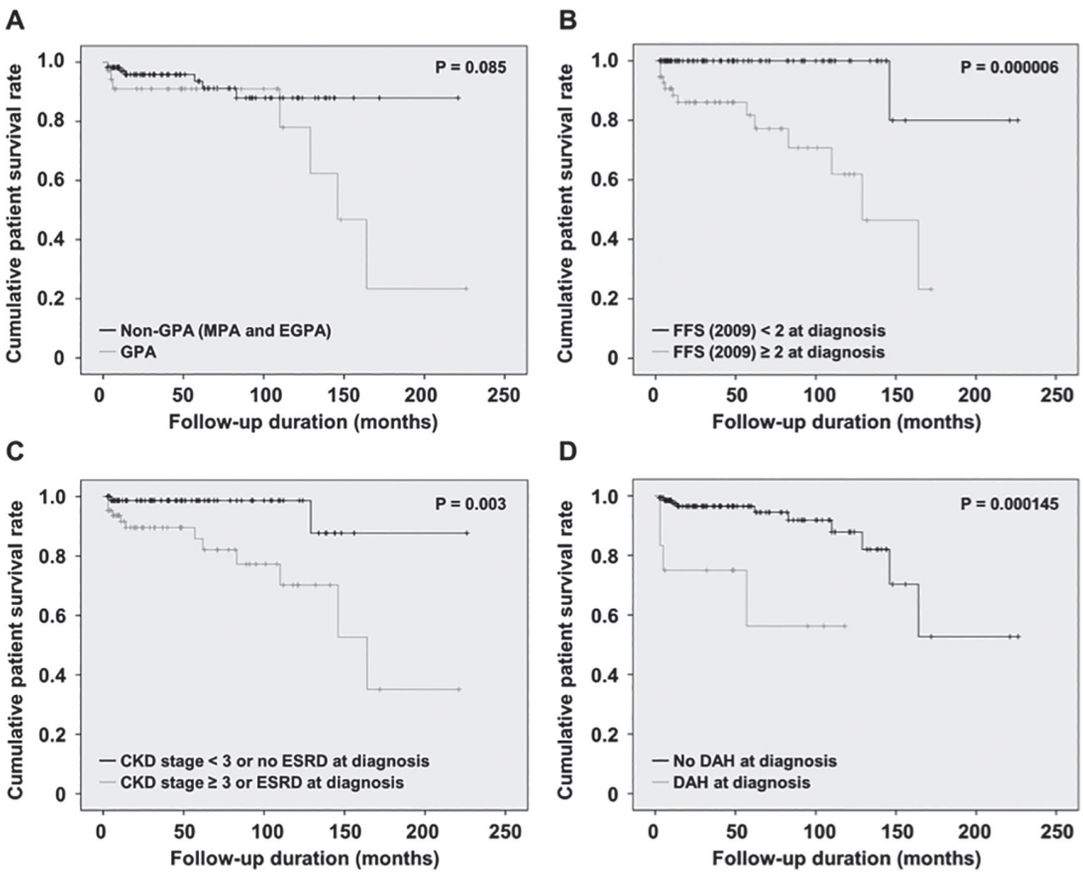

Fig. 2. The cumulative patient survival rates based on variables with significance in univariate COX regression model analysis in all AAV patients. (**A**) GPA vs. MPA and EGPA. (**B**) FFS (2009) ≥2 vs. FFS (2009) <2 at diagnosis. (C) CKD stage ≥3 vs. CKD stage <3 at diagnosis (D) DAH vs. no DHA at diagnosis. AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; FFS: five factor score; CKD: chronic kidney disease; DAH: diffuse alveolar haemorrhage.

Table IV. Univariate and multivariate COX regression model analysis of the association of variables with death in patients with AAV.

Variables	HR	95% CI	*p*-value
FFS (2009) ≥2 at diagnosis	16.520	1.833, 148.858	0.012
CKD stage ≥3 at diagnosis	1.543	0.293, 8.128	0.609
DAH at diagnosis	3.705	1.049, 13.085	0.042

AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; FFS: five factor score; CKD: chronic kidney disease; DAH: diffuse alveolar haemorrhage; HR: hazard ratio; 95% CI: 95% confidence interval.

Discussion

In this study, we estimated the cumulative patient survival rates, the causes of death and predictors of death in 153 Korean patients with MPA, GPA and EGPA. First, in terms of the cumulative patient survival rates, 14 of 153 patients (9.2%) died (7 MPA and 7 GPA patients). In all patients with AAV, 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.1%, 94.8% and 92.8%, respectively. GPA patients exhibited a slightly reduced cumulative patient survival rate compared to MPA patients without significance. Second, in terms of the causes of death, the most common cause of death was pneumonia of various origins in 7 patients, followed by bacterial sepsis in 3 patients, biliary infection in 1 patient and influenza infection in 1 patient. Cardiac arrest and alveolar haemorrhage were observed in each deceased patient. Third, in terms of predictors of death at diagnosis in the disease course, FFS (2009) ≥2 (HR 16.520, p=0.012) and DAH (HR 3.705, p=0.042) at diagnosis could predict death during the follow-up in AAV patients in multivariate COX regression model analysis. The predictive factors of death at diagnosis have advantages that they can presuppose death according to the relatively regular follow-up durations (16). However, the associated factors with death during the follow-up cannot predict it, because we could not recognise the exact time of their initiation. With these reasons, in the present study, we made an effort to conduct both analyses: multivariate logistic regression analysis for assessing all contributing factors associated with death during the whole follow-up period, and multivariate COX regression model analysis for determining the initial predictive factors of death in the disease course.

So far, there were several reports estimating poor outcome in Korean patients with AAV. However, those studies included patients with only one variant of AAV, for instance, 18 MPA patients, 55 MPA patients or 45 GPA patients. Thus the results of previous studies could not represent the survival patterns in Korean patients with all variants of AAV, particularly in patients with unclassifiable ANCA positive vasculitis. Therefore, in this study, to estimate the overall cumulative survival rates or predictors of death dur-

ing the follow-up in Korean patients with AAV, we included patients with all variants of AAV in this study. The survival rate of our study was higher that of three previous studies: 10 year-cumulative patient survival rate was 92.8% in our study; the overall cumulative patient survival rate was 44% in 18 MPA patients; 3 year-cumulative patient survival rate was 89.2% in 55 MPA patients; and the overall survival rate was 77.8% in 45 GPA patients (6-8). Moreover, previous Korean studies discovered that old age, ANCA-positivity, BVAS over 9, cardiovascular and pulmonary manifestations, particularly DAH could predict mortality in AAV patients (6-8). Meanwhile, in our study, only FFS (2009) and DAH could predict death in patients with AAV. The discrepancies in the cumulative patient survival rates and the initial predictors of deaths among Korean studies might have been due to the different inclusion criteria, the follow-up duration and therapeutic regimens.

In addition, we compared our results with those of previous studies, which included patients with at least more than 2 variants of AAV and were conducted in North-Eastern countries with similar ethnicity. They reported that older age, pulmonary manifestations including haemorrhage and ILD, and cardiovascular events were predictors of death in AAV patients (5, 17-19). In terms of age, in our study, age showed no potential to predict death. We suppose that this was due to the wide range of age at diagnosis (from 15 to 79 years) and age at death (from 29 to 80 years). In terms of pulmonary manifestations, DAH at diagnosis was significant predictor of death in Korean patients with AAV, but not ILD. We suppose that this is due to the relatively complicated conditions of ILD including type of ILA, extent of involvement, histological features and respiratory functions, compared to DAH. In terms of cardiovascular manifestation, meanwhile, cardiovascular manifestation at diagnosis was observed in deceased patients more frequently than survived patients (85.7% vs. 23.7%), and furthermore it showed significant OR in univariate logistic regression analysis (19.273). However, because a considerable number of the detailed clinical symptoms of cardiovascular manifestation were overlapped with the item of cardiac insufficiency of FFS (2009), we did not include cardiovascular manifestation in multivariate analysis. Thus, we believed that the initial cardiovascular involvement of AAV might contribute to the predictive potential of FFS (2009) of death during the follow-up.

In this study, although organs, which infection occurred, are different, almost all the direct cause of death was the infection. Only two patients died of non-infectious aetiologies, alveolar haemorrhage and sudden cardiac arrest. When we compared immunosuppressive drugs between survived and deceased patients, two medications, CYC (p=0.083) and AZA (p=0.074), reciprocally exhibited differences with p-value below 0.010. With these results, could we assert that immunosuppressive drugs were not related to infectious causes of death in AAV patients? It can be theoretically speculated that high vasculitis activity might enhance the need for immunosuppressive drugs, which in turn, might increase the infection rate in AAV patients. Therefore, we suggest that physicians should pay more attention to the balance between AAV activity-control and infection-control, when they choose induction or maintenance therapeutic regimens.

We wonder whether the associated factors with death in all variants of AAV can still affect the cumulative survival rates in each variant of AAV, because no EGPA patients died in our study. In 83 MPA and 37 GPA patients, we also conducted univariate log rank test in Kaplan-Meier analysis and multivariate COX regression model analysis using variables with significance in 153 patients with AAV. In univariate analysis, FFS (2009) at diagnosis ≥2 (p=0.000034), CKD stage ≥ 3 at diagnosis (p=0.005) and DAH at diagnosis (p=0.002 could predict death in MPA patients, but in multivariate analysis, only FFS (2009) at diagnosis ≥2 can predict death in MPA and GPA patients. Thus we suggest that FFS (2009) ≥2 and DAH at diagnosis should be applied to patients who are not clearly classified as one variants of AAV or who are suspected of AAV without asthma history, or patients with all variants of AAV. And we suggest that only FFS (2009) ≥2 at diagnosis should be applied to patients with definitely classified MPA and GPA

This study has a merit that as far as we know, we first estimated the cumulative survival rates, the causes of death and the initial predictors of death during the follow-up in a considerable number of Korean patients with all AAV variants, MPA, GPA and EGPA. However, our study has several limitations: First, we designed and conducted a retrospective and cross-sectional study. Second, to focus on the effect of AAV and its related immunosuppressive drugs on the cumulative patient survival rate, we excluded malignancies or other fatal diseases, which can affect the survival rate in clinical settings. If future studies can serially and prospectively enrol the larger number of AAV patients in multi-centres, they can provide more valuable and dynamic information on the cumulative survival rates, the causes of death and the predictors of death during the follow-up in Korean patients with AAV.

In conclusion, 14 of 153 patients with AAV died during the follow-up and 1 year-, 5 year- and 10 year-cumulative patient survival rates were 96.1%, 94.8% and 92.8%, respectively. The most common cause of death was infection. FFS (2009) ≥2 (HR 16.520) at diagnosis and DAH (HR 3.705) at diagnosis could predict death during the follow-up in Korean patients with MPA, GPA and EGPA.

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