Clinical and prognostic features of Korean patients with MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis

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ABSTRACT

Objective. *We reclassified Korean patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) into 3 categories of AAV including MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis, and investigated clinical and prognostic features.*

Methods. *We reviewed the medical records of 133 patients with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA), who had either myeloperoxidase (MPO)-ANCA, proteinase 3 (PR3)-ANCA or no ANCA, and who had ever achieved the first remission. We compared clinical manifestations, initial Birmingham vasculitis activity score (BVAS) and five factor score (FFS), and relapse rates.*

Results. *Patients with ANCA-negative vasculitis had the youngest mean age at diagnosis (50.0 years old) among AAV categories. General, cutaneous and renal manifestations were commonly observed in MPO-ANCA vasculitis, while mucous membrane, eye, ear nose throat (ENT) and renal manifestations were often documented in PR3-ANCA vasculitis. ENT manifestation was also frequently observed in ANCA-negative vasculitis. However, there were no significant differences in pulmonary and nervous system manifestations among 3 AAV categories. There were no significant differences in cumulative relapse free survival according to the presence of MPO-ANCA or PR3-ANCA or no ANCA. Meanwhile, initial BVAS or BVAS for GPA ≥13.5 in MPO-ANCA vasculitis and initial FFS (1996) ≥1 in MPO-ANCA and ANCA-negative vasculitis were significant predictors of relapse of each AAV category.*

Conclusion. *Clinical manifestations varied AAV categories, and neither MPO-ANCA nor PR3-ANCA significantly affected relapse of AAV. Initial BVAS or BVAS for GPA and FFS (1996) helped to predict relapse of specified AAV categories.*

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotising vasculitides, which often involve small vessels, and which leave few or no immune deposits in affected organs (1). AAV has been classified into 3 variants according to clinical manifestations and pathological features including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) (1). GPA and EGPA are identical to what have been called Wegener's granulomatosis and Churg-Strauss syndrome, respectively (1). MPA mainly induces rapid progressive necrotising glomerulonephritis, and it occasionally provokes pulmonary capillaritis or alveolar haemorrhage (1-3). GPA often involves the upper and lower respiratory tracts, and it also affects kidneys, leading to necrotising glomerulonephritis (4). Meanwhile, EGPA is commonly accompanied by allergic features such as asthma and eosinophilia, and it frequently involves lung and skin (5).

Recently, some authors proposed a new concept of the reclassification of AAV into 3 categories based on the presence of ANCA and its types including MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis (6, 7). These movements have been motivated and encouraged by several needs as follows: first, MPA has been classified by the algorithm for the classification of ANCA-associated vasculitis and the 2012 revised Chapel Hill Consensus Conference (1, 8, 9), since MPA does not have the clear classification criteria (10, 11); Second, the American College of Rheumatology 1990 criteria for GPA and EGPA are too old to reflect currently developed AAVs to dates; Third, neither MPO-ANCA nor PR3-ANCA was not included in those criteria, despite its clinical implication in both diagnosis and prognosis (8, 10, 11). Moreo-

ver, recent studies have supported the distinct entities among MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis (12). Even in one AAV variant, patients having MPO-ANCA presented significantly different clinical manifestations from those having PR3-ANCA or no ANCA, and furthermore responses to immunosuppressive drugs exhibited distinguishing results along with ANCA types (13-15).

So far, in Korean patients with AAV, there have been several studies on clinical and prognostic patterns of each AAV variant (16-18). However, to our best knowledge, there was no report on clinical and prognostic features in Korean patients with AAV categories based on the presence of ANCA and its types. We support that there must be ethnic and geographic influence on clinical and prognostic patterns of AAV. Hence in this study, we reclassified patients with AAV into 3 categories according to ANCA types such as MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis. And we investigated clinical and prognostic features among them, who had no medical conditions other than AAV, and who had the follow-up duration for at least more than 12 weeks.

Patients and methods

Patients

We retrospectively inquired into the details of the medical records of 150 patients with AAV according to the inclusion criteria as follows: i) patients who had been first classified as MPA, GPA and EGPA from October 2000 to August 2016 at Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; ii) those who had fulfilled the algorithm for the classification of ANCA-associated vasculitis and the 2012 revised Chapel Hill Consensus Conference for MPA, and who had satisfied the ACR 1990 criteria for the classification for GPA and EGPA (8-11); iii) those who had been followed up for at least 12 weeks after diagnosis of AAV; iv) those who had the results of MPO-ANCA and PR3-ANCA by the enzyme-linked immunosorbent assay (ELISA) at diagnosis (not P-ANCA or C-ANCA); v) those who did not have both MPO-ANCA and PR3-ANCA for minimising the confounding factors to interpret the influence of the presence of ANCA and its types on clinical or prognostic features of AAV categories; vi) those who had well-documented medical records for calculating Birmingham vasculitis activity score (BVAS), BVAS for GPA and five factor scores (FFS) (1996 and 2009) at diagnosis (19-22); vii) those of whom medical records included the sufficient contents to determine the disease course of AAV during the follow-up duration; viii) those who had no significant medical history or who had never received medications for diseases other than AAV. In this study, we did not include AAV patients with refractory disease, because AAV patients did not have the even follow-up durations: ≥6 months for MPA, ≥3 months for GPA and ≥24 months for EGPA. With this reason, 11 MPA patients and 6 GPA patients were excluded. Finally, we enrolled 133 patients with AAV including 79 MPA patients, 24 GPA patients and 30 EGPA patients in the present study. This study was approved by the institutional Review Board of Severance Hospital (4-2016-0901).

Clinical and laboratory data

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 AAV patients having achieved remission without relapse. And we defined the follow-up duration in patients having experiencing relapse as the period from AAV diagnosis to the first relapse (23). Clinical data included general, cutaneous, mucous membrane and eye, ear nose throat (ENT), cardiovascular, gastrointestinal, pulmonary, renal and nervous manifestation, which are items of BVAS or BVAS for GPA. Since there are differences in detailed items between BVAS or BVAS for GPA, we decided to set clinical information at the level of each title of involved organ (19, 20). BVAS was assessed for both MPA and EGPA patients, and BVAS for GPA was used for GPA patients. And we calculated FFS (1996) and FFS (2009) using essential clinical and laboratory items for each (21, 22). Since therapeutic regimens have been differently recommended according to AAV variants, and furthermore, there is no standardised recommendation for therapeutic regimens in AAV categories based on ANCA types, we could not simply compare them between patients with remission and relapse in this study (24). 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.

Prognosis

Remission was defined as absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy. Relapse was defined as recurrence or new onset of disease attributable to active vasculitis. We did not include AAV patients with refractory patients as described above (23). Death was considered only when it was related to AAV.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Significant differences between the two groups according to individual variants of AAV as well as ANCA types 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 hazard ratio (HR) was assessed using univariate and multivariate Cox Hazard model. The optimal cut-offs of BVAS or BVAS for GPA and FFS (1996) to presuppose relapse during the follow-up duration were extrapolated by computing the area under the receiver operator characteristic curve (AUROC) and choosing the maximised sum of sensitivity and specificity. In addition, the relative risk (RR) of BVAS or BVAS for GPA and FFS (1996) for relapse was analysed using contingency tables and the chi-square test. Cumulative relapse free survival was analysed

Table I. Baseline characteristics of 133 patients with anti-neutrophil cytoplasmic antibody-associated vasculitis, who had ever achieved remission.

Variables	Values
Variants of AAV (n, (%))	
Microscopic polyangiitis	79 (59.4)
Granulomatosis with polyangiitis	24 (18.0)
Eosinophilic granulomatosis with polyangiitis	30 (22.6)
Categories of AAV based on ANCA types (n, (%))	
MPO-ANCA vasculitis	91 (68.4)
PR3-ANCA vasculitis	21 (15.8)
ANCA negative vasculitis	21 (15.8)
Demographic data	
Age (years)	58.3 ± 16.4
Male gender (n, (%))	43 (32.3)
Follow-up duration (months)	54.0 ± 46.3
Clinical manifestations (n, (%))	
General manifestations	60 (45.1)
Cutaneous manifestations	45 (33.8)
Mucous membranes/Eyes manifestations	12 (9.0)
Ear Nose Throat manifestations	52 (39.1)
Cardiovascular manifestations	35 (26.3)
Gastrointestinal manifestations	9 (6.8)
Pulmonary manifestations	71 (53.4)
Renal manifestations	76 (57.1)
Nervous systemic manifestations	46 (34.6)
BVAS, BVAS for GPA and FFS	
BVAS or BVAS for GPA	13.4 ± 7.5
FFS (1996)	0.7 ± 0.9
FFS (2009)	1.6 ± 0.9
Disease course (n, (%))	
Remission and no relapse	82 (61.7)
Relapse	51 (38.3)

Values are expressed as mean and standard deviation or n (%).
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; BVAS: Birmingham vascular activity score; GPA: granulomatosis with polyangiitis; FFS: five factor score; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3.

by the Kaplan-Meier survival analysis. We conducted all statistical analysis using the SPSS package for Windows v. 23 (IBM). *p*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics are described in Table I. Of 133 AAV, 79 patients had MPA, 24 had GPA and 30 had EGPA. Also, based on the presence of ANCA and its types, among 133 AAV patients, 91 patients (68.4%) were also reclassified as MPO-ANCA vasculitis, 21 patients (15.8%) were done as PR3-ANCA vasculitis, and 21 patients (15.8%) were done as ANCA-negative vasculitis. The mean age was 58.3 years old (43 men) and the mean follow-up duration was 54.0 months. At diagnosis, the most common clinical manifestation was renal manifestation (57.1%), followed by pulmonary (53.4%), general (45.1%) and ENT manifestation (39.1%). The initial mean BVAS or BVAS for GPA was 13.4. The initial mean FFS (1996) and FFS (2009) were 0.7 and 1.6, respectively. All patients achieved remission, and 51 of 133 patients (38.3%) had ever experienced the first relapse during the follow-up duration.

Comparison of variables among variants of AAV

Comparison of variables among variants of AAV is described in Table II. The rate of the reclassification as MPO-ANCA vasculitis in MPA patients was higher than that of both GPA and EGPA patients (94.9% *vs*. 20.8%, $p<0.001$ and 94.9% *vs*. 36.7%, $p<0.001$, respectively). Meanwhile, the rate of the reclassification as PR3-ANCA vasculitis in GPA patients was higher than both MPA and EGPA patients (62.5% *vs*. 3.8%, $p<0.001$ and 62.5% *vs*. 10.0%, $p<0.001$, respectively). And furthermore, a considerable number of EGPA patients (53.35) were reclassified as ANCA-negative vasculitis. The mean age of EGPA patients (50.3 years old) was lower than those of MPA and GPA patients (60.4 and 61.5 years, $p=0.004$ and $p=0.009$, respectively). By contrast, the mean follow-up duration of EGPA patients (72.5 months) was longer than those of MPA and GPA patients (47.1 months, $p=0.015$ and 53.5 months, $p=0.041$). In terms of clinical manifestations, general manifestation was more commonly described in MPA patients than EGPA patients (54.4% *vs*. 30.0%, $p=0.023$). Cutaneous manifestation was less commonly documented in GPA patients than both MPA and EGPA patients (8.3% *vs*. 38.0%, $p=0.006$ and 8.3% *vs*. 43.3%, $p=0.004$). GPA patients (91.7%) showed the highest rate of ENT manifestation among AAV variants. MPA patients presented cardiovascular manifestations more often than GPA and EGPA patients (38.0% *vs*. 4.2%, $p=0.002$ and 38.0% *vs*. 13.3%, $p=0.013$). Pulmonary manifestation was the most frequently counted in EGPA patients, resulting from the detailed item of wheezing belonging to not only BVAS, but also classification criteria for EGPA (76.7% *vs*. 44.3% for MPA, $p=0.002$ and 76.7% *vs*. 54.2% of GPA, $p=0.081$) (10, 18). By contrast, renal manifestations was the least frequently counted in EGPA (33.3% *vs*. 68.4% for MPA, $p=0.001$ and 33.3% *vs*. 50.0% for GPA, $p=0.215$). Nervous systemic manifestation was the most commonly found in EGPA patients (66.7%), followed by MPA (30.4%) and GPA patients (8.3%). The initial mean BVAS or BVAS for GPA of MPA patients was higher than those of EGPA and GPA patients. The initial mean FFS (1996) of EGPA showed the highest score. There were no significant differences in remission and relapse among AAV variants.

Comparison of variables among MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis

Comparison of variables among categories of AAV based on ANCA types

Table II. Comparison of baseline variables among patients with MPA, GPA and EGPA.

Variables	MPA (n=79)	GPA (n=24)	EGPA (n=30)	*p*-value (MPA *vs*. GPA)	*p*-value (MPA *vs*. EGPA)	*p*-value (GPA *vs*. EGPA)
Categories of AAV based on ANCA types (n, (%))						
MPO-ANCA vasculitis	75 (94.9)	5 (20.8)	11 (36.7)	**<0.001**	**<0.001**	0.205
PR3-ANCA vasculitis	3 (3.8)	15 (62.5)	3 (10.0)	**<0.001**	0.205	**<0.001**
ANCA negative vasculitis	1 (1.3)	4 (16.7)	16 (53.3)	**0.002**	**<0.001**	**0.006**
Demographic data						
Age (year old)	60.4 ± 16.4	61.5 ± 14.0	50.3 ± 15.8	0.766	**0.004**	**0.009**
Male gender (n, (%))	22 (27.8)	9 (37.5)	12 (40.0)	0.367	0.221	0.851
Follow-up duration (months)	47.1 ± 52.2	53.5 ± 30.9	72.5 ± 34.6	0.570	**0.015**	**0.041**
Clinical manifestations (n, (%))						
General manifestations	43 (54.4)	8 (33.3)	9 (30.0)	0.070	**0.023**	0.793
Cutaneous manifestations	30 (38.0)	2 (8.3)	13 (43.3)	**0.006**	0.609	**0.004**
Mucous membranes/Eyes manifestations	7 (8.9)	5 (20.8)	0 (0)	0.109	0.092	**0.009**
Ear Nose Throat manifestations	7 (8.9)	22 (91.7)	23 (76.7)	**<0.001**	**<0.001**	0.142
Cardiovascular manifestations	30 (38.0)	1 (4.2)	4 (13.3)	**0.002**	**0.013**	0.248
Gastrointestinal manifestations	5 (6.3)	1 (4.2)	3 (10.0)	0.692	0.512	0.416
Pulmonary manifestations	35 (44.3)	13 (54.2)	23 (76.7)	0.396	**0.002**	0.081
Renal manifestations	54 (68.4)	12 (50.0)	10 (33.3)	0.101	**0.001**	0.215
Nervous systemic manifestations	24 (30.4)	2 (8.3)	20 (66.7)	**0.029**	**0.001**	**<0.001**
BVAS, BVAS for GPA and FFS						
BVAS or BVAS for GPA	16.1 ± 7.3	4.5 ± 2.5	13.2 ± 4.7	**<0.001**	**0.016**	**<0.001**
FFS (1996)	0.7 ± 0.9	0.4 ± 0.7	0.9 ± 1.0	**0.040**	0.283	**0.018**
FFS (2009)	1.8 ± 0.8	0.8 ± 0.6	1.6 ± 0.9	**<0.001**	0.156	**<0.001**
Disease course (n, (%))						
Remission and no relapse	48 (60.8)	16 (66.7)	18 (60.0)	0.601	0.942	0.614
Relapse	31 (39.2)	8 (33.3)	12 (40.0)	0.601	0.942	0.614

Values are expressed as mean and standard deviation or n (%).
MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; BVAS: Birmingham vascular activity score; GPA: granulomatosis with polyangiitis; FFS: five factor score; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: proteinase 3.

is described in Table III. MPO-ANCA was detected in 82.4% of MPA patients, PR3-ANCA was done in 71.4% of GPA patients, and no ANCA was found in 76.2% of EGPA patients. Patients with ANCA-negative vasculitis had the youngest mean age at diagnosis (50.0 years old) among AAV categories according to the presence of ANCA and its types. In terms of clinical manifestations, general manifestation was more frequently described in patients with MPO-ANCA vasculitis than both those with PR3-ANCA and ANCA-negative vasculitis (52.7% *vs*. 28.6%, p=0.046 and 52.7% *vs*. 28.6%, p=0.046, respectively). Cutaneous manifestation was more commonly documented in patients with MPO-ANCA vasculitis than those with PR3-ANCA vasculitis (41.8% *vs*. 9.5%, p=0.005). Patients with PR3-ANCA vasculitis showed the higher rate of mucous membranes or eye manifestation than those with ANCA-negative vasculitis (19.0% *vs*. 0%, p=0.035). On the other hands, both patients with PR3-ANCA and ANCA-negative vasculitis presented ENT manifestation more often than those with MPO-ANCA vasculitis (81.0% *vs*. 20.9%, p<0.001 and 76.2% *vs*. 20.9%, p<0.001). Patients with MPO-ANCA vasculitis had renal manifestation more frequently than those with ANCA-negative vasculitis (65.9% *vs*. 28.6%, p=0.002), but not those with PR3-ANCA vasculitis. However, unlike previous studies, there were no significant differences in the presence of pulmonary and nervous system manifestations among patients with MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis.

Relapse according to the presence of ANCA and its types

Cumulative relapse free survival rates were analysed by Cox Hazard model and are depicted in Figure 1. There were no significant differences in cumulative relapse free survival according to MPO-ANCA (p=0.256) and PR3-ANCA positivity (p=0.722) in this study. ANCA negativity showed a tendency to increase cumulative relapse free survival, in comparison with ANCA positivity, but there was no statistical significance (p=0.113).

Discussion

In this study, we first reclassified patients with Korean patients with MPA, GPA and EGPA into 3 AAV categories according to the presence of ANCA and its types including MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis, and we compared clinical and prognostic features among them. Generally, patients with MPO-ANCA vasculitis commonly presented general and cutaneous manifestations compared to those with PR3-ANCA vasculitis, while patients with PR3-ANCA vasculitis often showed ENT manifestation compared to those with MPO-ANCA

Table III. Comparison of baseline variables among patients with MPO-ANCA positive, PR3-ANCA positive and ANCA negative AAV.

Variables	MPO-ANCA vasculitis (n=91)	PR3-ANCA vasculitis (n=21)	ANCA negative vasculitis (n=21)	*p*-value (MPO-ANCA *vs*.. PR3-ANCA vasculitis)	*p*-value (MPO-ANCA *vs*. ANCA negative vasculitis)	*p*-value (PR3-ANCA *vs*. ANCA negative vasculitis)
Type of AAV				**0.046**	**<0.001**	**<0.001**
Microscopic polyangiitis	75 (82.4)	3 (14.3)	1 (4.8)			
Granulomatosis with polyangiitis	5 (5.5)	15 (71.4)	4 (19.0)			
Eosinophilic granulomatosis with polyangiitis	11 (12.1)	3 (14.3)	16 (76.2)			
Demographic data						
Age (year old)	60.0 ± 16.2	59.1 ± 14.4	50.0 ± 17.1	0.817	**0.013**	0.068
Male gender (n, (%))	26 (28.6)	10 (47.6)	7 (33.3)	0.092	0.666	0.346
Follow-up duration (months)	50.4 ± 50.4	52.3 ± 34.8	71.3 ± 33.9	0.865	0.073	0.082
Clinical manifestations (n, (%))						
General manifestations	48 (52.7)	6 (28.6)	6 (28.6)	**0.046**	**0.046**	1.000
Cutaneous manifestations	38 (41.8)	2 (9.5)	5 (23.8)	**0.005**	0.127	0.214
Mucous membranes/Eyes manifestations	8 (8.8)	4 (19.0)	0 (0)	0.171	0.159	**0.035**
Ear Nose Throat manifestations	19 (20.9)	17 (81.0)	16 (76.2)	**<0.001**	**<0.001**	0.707
Cardiovascular manifestations	28 (30.8)	4 (19.0)	3 (14.3)	0.284	0.128	0.679
Gastrointestinal manifestations	6 (6.6)	2 (9.5)	1 (4.8)	0.638	0.755	0.549
Pulmonary manifestations	45 (49.5)	13 (61.9)	13 (61.9)	0.303	0.303	1.000
Renal manifestations	60 (65.9)	10 (47.6)	6 (28.6)	0.118	**0.002**	0.204
Nervous systemic manifestations	31 (34.1)	5 (23.8)	10 (47.6)	0.364	0.245	0.107
BVAS, BVAS for GPA and FFS						
BVAS and BVAS for GPA	15.3 ± 7.3	8.1 ± 7.4	10.2 ± 4.7	**<0.001**	**<0.001**	0.268
FFS (1996)	0.8 ± 0.9	0.7 ± 0.9	0.5 ± 0.8	0.679	0.276	0.583
FFS (2009)	1.7 ± 0.8	1.1 ± 0.9	1.3 ± 0.9	**0.002**	**0.021**	0.495
Disease course (n, (%))						
Remission and no relapse	54 (59.3)	13 (61.9)	15 (71.4)	0.829	0.305	0.513
Relapse	37 (40.7)	8 (38.1)	6 (28.6)	0.829	0.305	0.513

Values are expressed as mean and standard deviation or N (%).
AAV: anti-neutrophil cytoplasmic antibody-associated vasculitis; MPO: myeloperoxidase; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham vascular activity score; GPA: granulomatosis with polyangiitis; FFS: five factor score.

vasculitis, which was compatible with previous results (25, 26). In the meantime, previous studies reported that renal manifestation such as haematuria and necrotising glomerulonephritis, and pulmonary manifestation such as lung fibrosis and alveolar haemorrhage, prevailed in patients having MPO-ANCA than those having PR3-ANCA (27, 28). Moreover, the rate of nervous system manifestation in patients with MPO-ANCA vasculitis was reported to relatively increase compared to those with PR3-ANCA vasculitis (29). But we found discrepancies between results of previous studies and this study. Although patients with MPO-ANCA vasculitis showed an increased frequency of renal manifestation compared to those with PR3-ANCA vasculitis, they had no statistical significance (65.9% *vs*. 47.6%, p=0.118). Also there were no significant differences in pulmonary and nervous systemic manifestations between patients with MPO-ANCA and PR3-ANCA vasculitis. Compared to ANCA-positive vasculitis, ANCA-negative vasculitis occurred at younger age (50.0 years). Patients with ANCA-negative vasculitis initially more commonly presented ENT manifestation, while less commonly general and renal manifestations than those with MPO-ANCA vasculitis. Interestingly, none of them showed cutaneous manifestation. We provided no detailed items of each clinical manifestation due to differences in assessment methods for each phenotypic AAV, but we believed that our results might provide interesting ethnic and geographic features among MPO-ANCA, PR3-ANCA and ANCA-negative vasculitis in Korean patients.

So for, PR3-ANCA positivity has been considered independent predictor of relapse or low response to immunosuppressive treatment: AAV patients having PR3-ANCA tended to relapse 1.9 times as likely as those having MPO-ANCA, and PR3-ANCA could expect relapse in AAV patients with renal disease (25); therapeutic efficacy of both rituximab and cyclophosphamide plus azathioprine in patients having PR3-ANCA was significantly lower than all patients (15). In addition, a recent study including 105 Japanese patients with AAV (88 MPA and 17 GPA) elucidated the predictive value of PR3-ANCA for relapse (26). However, our results showed no contribution of PR3-ANCA or MPO-ANCA to predicting relapse during the follow-up duration. We supposed that this discrepancy might result from different study populations. Most previous studies did not include all AAV variants. Moreover, a considerable number of studies on both patients with MPA and GPA excluded ANCA negative subjects, although studies regarding patients with one phenotypic variant of AAV analysed the gap be-

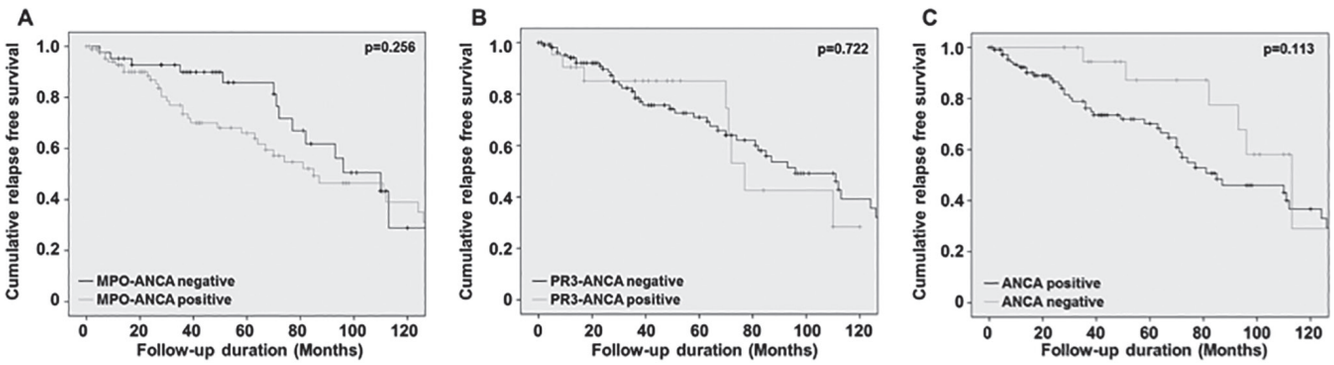

Fig. 1. Cumulative relapse free survival rates according to the presence of MPO-ANCA and PR3-ANCA.
(A, B, C) There were no significant differences in cumulative relapse free survival according to the presence of MPO-ANCA (p=0.256), PR3-ANCA (p=0.722) and the absence of ANCA (p=0.113).

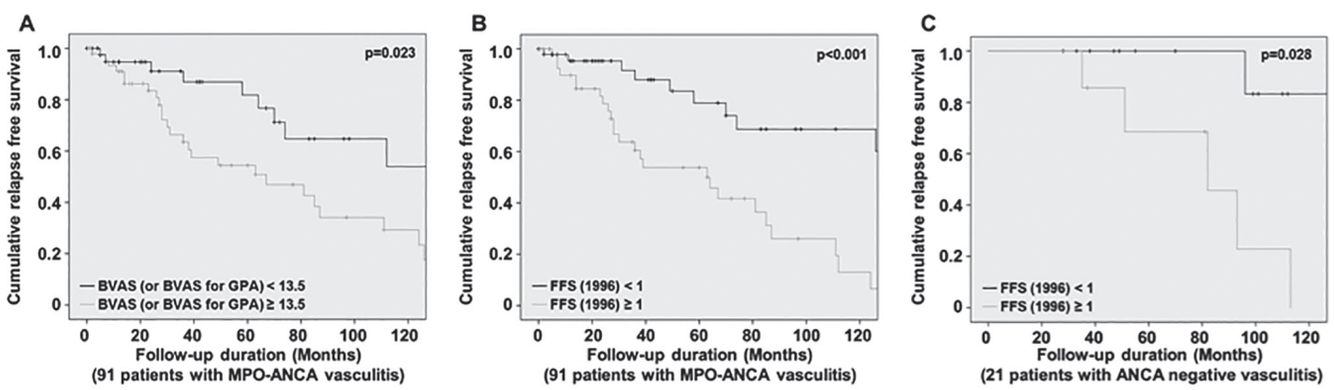

Fig. 2. Cumulative relapse free survival rates according to the optimal cut-offs of BVAS or BVAS for GPA and FFS (1996).
(A, B) Patients with MPO-ANCA vasculitis having BVAS or BVAS for GPA ≥ 13.5 and FFS (1996) ≥1 showed higher cumulative relapse free survival rates than those having not (p=0.023 and p<0.001, respectively). (C) Patients with ANCA negative vasculitis having FFS (1996) ≥1 also had higher cumulative relapse free survival rates than those having not (p=0.028).

tween MPO-ANCA, PR3-ANCA and ANCA negative vasculitis (15, 26, 27, 30, 31). By contrast, our study included all patients with MPA, GPA and EGPA, and furthermore all patients with MPO-ANCA, PR3-ANCA and ANCA negative vasculitis. In addition, we assumed that this discrepancy might be derived from different inclusion criteria: i) we excluded AAV patients with refractory disease, who had never achieved remission at all. When we added 11 MPA and 6 GPA patients with refractory disease to 133 patients, and analysed the link between ANCA and relapse plus refractory disease using Cox hazard model, we found that PR3-ANCA positivity showed a tendency to increase HR, despite no statistical significance (HR 1.663, p=0.089); ii) we excluded AAV patients, who simultaneously had MPO-ANCA and PR3-ANCA, because these patients could not be classified as MPO-ANCA, PR3-ANCA and ANCA negative vasculitis; iii) last, we speculated that discrepancies might be from ethnic difference, because PR3-ANCA as well as MPO-ANCA may be affected by different genetic background (6).

When we divided 133 AAV patients into remission and relapse groups, patients with relapse showed the higher mean initial BVAS or BVAS for GPA (16.1 *vs*. 11.7, p=0.001) and FFS (1996) (1.1 *vs*. 0.5, p<0.001), but not FFS(2009) than those without. Furthermore, we directed our attention to the link between relapse and initial BVAS or BVAS for GPA and FFS (1996) in patients with MPO-ANCA, PR3-ANCA and ANCA negative vasculitis. In 91 patients with MPO-ANCA vasculitis, we also found that patients with relapse showed the higher mean initial BVAS or BVAS for GPA (18.3 *vs*. 13.3, p=0.001) and FFS (1996) (1.1 *vs*. 0.5, p=0.001) than those without. We calculated the optimal cut-offs of BVAS or BVAS for GPA and FFS (1996) to predict relapse. We found that 13.5 of BVAS or BVAS for GPA (AUROC 0.700, p=0.001) and 1 of FFS (1996) (AUROC 0.686, p=0.003) were the optimal cut-offs. Furthermore, when we classified 91 patients with MPO-ANCA vasculitis into two groups according to the each optimal cut-off, patients having BVAS or BVAS for GPA ≥13.5 and FFS (1996) ≥1 showed significantly enhanced risk of relapse of AAV than those not having (RR 4.243, p=0.001 for BVAS or BVAS for GPA and HR 3.838, p=0.002). In 21 patients with ANCA negative vasculitis, we also found that patients with relapse showed the higher mean initial FFS (1996) (1.3 *vs*. 0.2, p<0.001) than those without. We calculated the optimal cut-off of FFS (1996) to predict relapse by the same statistical method. We found that 1 of FFS (1996) (AUROC 0.867, p=0.010) were the optimal cut-off. When we divided 21 patients with ANCA negative vasculitis into two groups according to the optimal cut-off, patients having FFS (1996) ≥1

showed significantly enhanced risk of relapse of AAV than those not having (RR 20.000, p=0.007). In 21 patients with PR3-ANCA vasculitis, there were no significant differences in the mean initial BVAS (or BVAS for GPA), FFS (1996) and FFS (2009) between those with relapse or not. In 21 patients with PR3-ANCA vasculitis, there were no significant differences in the mean initial BVAS or BVAS for GPA, FFS (1996) and FFS (2009) between those with relapse or not. Cumulative relapse free survival rates regarding each predictor of relapse are introduced in Figure 2. Patients with MPO-ANCA vasculitis having BVAS or BVAS for GPA ≥13.5 and FFS (1996) ≥1 showed higher cumulative relapse free survival rates than those having not (p=0.023 and p<0.001, respectively). Furthermore, patients with ANCA negative vasculitis having FFS (1996) ≥1 also had higher cumulative relapse free survival rates than those having not (p=0.028).

Our study has three strong advantages: first, we included not only all patients with MPA, GPA and EGPA, but also patients with MPO-ANCA, PR3-ANCA and ANCA negative vasculitis, which could provide more comprehensive information. Second, we excluded AAV patients having both MPO-ANCA and PR3-ANCA simultaneously, which helped to deeply understand the entities of each category of AAV based on ANCA types. Third, we first suggested the optimal cut-off of BVAS or BVAS for GPA and FFS as predictors of relapse of MPO-ANCA vasculitis and ANCA negative vasculitis. Our study also had several issues: first, since there are differences in items between BVAS and BVAS for GPA, we could not analyse the detailed items of them. Second, due to the limitation of retrospective study-design, we could not serially measure the titre of MPO-ANCA and PR3-ANCA to investigate the link between the alteration in their titres and prognosis. Third, due to the different the minimal follow-up duration among AAV variants, we could not patients with refractory diseases, resulting in relatively milder subjects in this study. Last, the accurate rate of ESRD or mortality could not be analysed in this pilot study, because 13 of 51 patients (25.5%) with relapse had not been followed up at the cross-sectional study point after the first relapse. Future prospective studies with larger patients, sub-item analysis, serial measurement of ANCA titres and the same minimal follow-up duration will provide more reliable data on clinical and prognostic features of Korean patients with MPO-ANCA, PR3-ANCA and ANCA negative vasculitis, reflecting the ethnic and geographic diversity. In conclusion, clinical manifestations varied AAV categories based on ANCA types and neither MPO-ANCA nor PR3-ANCA significantly affected relapse of AAV. Furthermore, initial BVAS or BVAS for GPA ≥ 13.5 in MPO-ANCA vasculitis and initial FFS (1996) ≥1 in MPO-ANCA and ANCA negative vasculitis were significant predictors of relapse of each AAV category.

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