Chest and renal involvements, Birmingham vascular activity score more than 13.5 and five factor score (1996) more than 1 at diagnosis are significant predictors of relapse of microscopic polyangiitis

Y.-J. Oh, S.S. Ahn, E.S. Park, 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.

Yoon-Jeong Oh, MD
Sung Soo Ahn, MD
Eun Seong Park, 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.
E-mail: sangwonlee@yuhs.ac

Received on November 7, 2016; accepted in revised form on December 20, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S47-S54.

Key words: microscopic polyangiitis, relapse, predictor, organ involvement, BVAS, FFS

Funding: this study was supported by a faculty research grant of Yonsei University College of Medicine (6-2016-0145) and by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI14C1324).

Competing interests: none declared.

ABSTRACT

Objective. *We investigated whether specified organ involvements, antineutrophil cytoplasmic antibody (ANCA) positivity, Birmingham vasculitis activity score (BVAS) and five factor scores (FFS) at diagnosis could predict relapse of microscopic polyangiitis (MPA).*

Methods. *We reviewed the medical records of 90 patients with MPA. We collected clinical and prognostic data, (MPO)-ANCA and proteinase 3 (PR3)-ANCA, BVAS and FFS at diagnosis, and we compared them between the two groups. The optimal cut-off values of BVAS and FFS (1996) for predicting relapse were extrapolated.*

Results. *The mean age of patients (63 women) was 62.3 years and the mean follow-up duration was 41.7 months. At diagnosis, the mean BVAS, FFS (1996) and FFS (2009) of patients in no remission group were higher than those of patients in remission group ($p<0.005$ for all). Patients in relapse group exhibited chest and renal manifestations more frequently than those in no relapse group and the mean BVAS and FFS (1996) of patients in relapse group were significantly higher than those of patients in remission group ($p<0.005$ for all). There were no differences in MPO-ANCA and PR3-ANCA between the two groups. On multivariate logistic regression analysis, chest and renal manifestations were all independent predictors of relapse (OR 2.013 and OR 3.517). Patients who had BVAS ≥13.5 and FFS ≥ 1 exhibited a significantly increased risk of relapse than those who did not (RR 4.408 and RR 3.030).*

Conclusion. *Chest and renal involvements, BVAS ≥13.5 and FFS ≥1 at diagnosis were independent predictors of relapse of MPA.*

Introduction

Microscopic polyangiitis (MPA) is a systemic autoimmune vascular inflammation, which is characterised by necrotising vasculitis with few or no immune complex deposition and which mainly affects small vessels (1, 2). MPA can often provoke crescentric necrotising glomerulonephritis and it can occasionally involve lung, leading to pulmonary capillaritis and alveolar haemorrhage (2, 3). Beyond kidney and lung, MPA can affect various organs from skin to central and peripheral nerve systems (CNS and PNS) (1, 4). The aetiology of MPA seems to be multifactorial including ethnicity, genes, gender and environment. The incidence of MPA is approximately 1-3 per 1 million people per year and it has been gradually increasing (5). Antineutrophil cytoplasmic antibodies (ANCAs) are a group of autoantibodies which can bind cytoplasmic proteins in neutrophils, myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is mostly detected in a majority of MPA patients, but the detection rate of PR3-ANCA is not remarkable along with no-ANCA (6). Although the role of MPO-ANCA in the pathogenesis of MPA still remains unclear, animal experiments using anti-MPO antibody transfer or immunisation by human MPO in nephritis-susceptible rats might support the potential pathogenicity of MPO-ANCA in MPA (7, 8). The treatment modalities in MPA are similar to those in granulomatosis with polyangiitis (GPA): a number of patients may need cyclophosphamide, rituximab or other immunosuppressive agents combined with glucocorticoid as induction therapeutic regimens, because major organ involvements are often observed in MPA patients (9, 10).

Also less toxic immunosuppressive drugs such as azathioprine or mycophenolate mofetil are necessary in most patients to prevent relapse after remission (1, 9). A long-term observational study reported that 5-year survival was 78% with a standardised mortality ratio of 2.6 in comparison with the normal population, and mortality rate had a tendency to increase in patients with MPA having MPO-ANCA positive, compared to those who did not (11). After remission, relapse can occur in up to 34% of patients of MPA, and PR3-ANCA is more likely to correlate with relapse of MPA (12).

So far, there have been only two reports regarding prognosis and clinical outcome of MPA in Korean patients. The previous studies included a relatively small number of patients, and they mainly focused on the mortality and co-morbidities such as end stage renal disease (ESRD), but not relapse. Also, they did not analyse patients with MPA separately according to the presence of MPO-ANCA or PR3-ANCA or they just mentioned ANCA positivity (13, 14). Hence, in this study, we included 90 patients with MPA and investigated whether a specified organ involvement, ANCA positivity, Birmingham vasculitis activity score (BVAS) and five factor scores (FFS) at diagnosis could predict relapse of MPA (15-17).

Patients and methods

Patients

We reviewed the medical records of 128 patients, who had been first diagnosed with MPA from October 2000 to May 2016 on the basis of the inclusion criteria as follows: 1) patients who had been diagnosed with MPA according to the algorithm for the classification of ANCA associated vasculitis and the 2012 revised Chapel Hill Consensus Conference (2, 18); 2) those who had been classified as MPA at Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; 3) those who had ever neither had medical history of other autoimmune and systemic diseases nor received medications affecting the false positivity of MPO-ANCA or PR3-ANCA; 4) those who had the laboratory results of MPO-ANCA and PR3-ANCA measured by the enzyme-linked immunosorbent assay at diagnosis (not perinuclear (P)-ANCA or cytoplasmic (C)-ANCA by immunofluorescent assay); 5) those in whom comments regarding clinical manifestations and specified organ involvements were described in electronic medical charts clearly enough to fill up the forms of BVAS and FFSs (1996 and 2009) (15-17); 6) those whose medical records definitely mentioned the status of remission, relapse or refractory disease; 7) in analysis of relapse-prediction, those who had achieved remission during the follow-up (79 patients in this study).

Among 128 subjects, 38 patients were excluded in this study with reasons as follows: 6 had been diagnosed with MPA outside our institute; 7 had been concurrently classified as autoimmune connective diseases; 1 had ever received propylthiouracil for hyperthyroidism; 9 had only results of ANCA measured by immunofluorescent assay test; 15 did not have clearly-mentioned medical records for clinical forms or disease-prognosis. Finally, we included 90 patients with MPA in this study, and also selected 79 out of 90 patients, who had achieved remission, for statistical analysis of relapse-prediction. This study was approved by the institutional Review Board of Severance Hospital.

Baseline demographic data, clinical manifestations and specified organ involvements

We obtained age, gender and the follow-up duration at diagnosis. We defined the follow-up duration according to each prognosis as follows: 1) as the period from diagnosis to the last visit for subjects in no relapse group; 2) as that from diagnosis to relapse for those in relapse group; 3) as that from diagnosis to death or ESRD for those in no remission group. We collected data of clinical manifestations and specified organ involvement as those described in BVAS version 3 including general, cutaneous, mucous membrane or eyes, ear nose throat, chest, cardiovascular, abdominal, renal and nervous systemic manifestations (15). We also searched clinical and laboratory features belonging to items of FFS (1996), as well as FFS (2009) (16, 17), and we reviewed pathological findings and drugs as both induction and maintenance therapeutic regimens.

MPO-ANCA and PR3-ANCA measurement

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.

Definition of prognosis

Remission was defined as absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy (19). Relapse was defined as recurrence or new onset of disease attributable to active vasculitis (19). Refractory disease was defined as unchanged or increased disease activity in acute vasculitis after 4 weeks of treatment with standard therapy or lack of response or chronic and persistent disease after over 12 weeks of treatment (19). Death and ESRD were counted only when they were directly related to MPA.

Statistical analysis

We conducted all statistical analysis using the SPSS package for Windows version 23 (IBM). We used Student's *t*-test or Mann-Whitney U-test to compare continuous variables between the two groups, and we expressed them as the mean ± standard deviation. We analysed significant differences in variables between the two groups using the chi-square test and Fisher's exact test for categorical variables. The odds ratio (OR) was assessed using multivariate logistic regression of variables with *p*-value less than 0.05 on univariate analysis. The optimal cut-off values of BVAS and FFS (1996) for predicting relapse were extrapolated by calculating the area under the receiver operator characteristic curve (AUROC) and

selection to maximise the sum of sensitivity and specificity. In addition, the relative risk (RR) of BVAS and FFS (1996) for relapse was analysed using contingency tables and the chi-square test. Cumulative relapse free survival was analysed by the Kaplan-Meier survival analysis. *P*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

The baseline characteristics are described in Table I. The mean age of 90 patients (27 men and 63 women) was 62.3 years old and the mean follow-up duration was 41.7 months. At diagnosis, the most common clinical feature was renal manifestations (70.0%), followed by general (60.0%), chest (47.8%), cardiovascular (37.8%) and cutaneous manifestations (35.6%). The mean initial BVAS, FFS (1996) and FFS (2009) were 16.9, 0.8 and 1.9, respectively. MPO-ANCA was detected in 84 patients (93.3%) and PR3-ANCA was done in 4 patients (4.4%). Two patients (2.2%) had neither MPO-ANCA nor PR3-ANCA. Kidney was the common organ where biopsy was performed (53.3%), while biopsy was not done in 24 patients. Forty-eight patients (53.3%) had achieved remission without relapse, 31 patients (34.4%) had ever experience relapse after remission, and 11 patients (12.2%) had not achieved remission during the follow-up. Ten patients had died and 12 patients had started dialysis owing to MPA. Cyclophosphamide (42.2%) was the most frequently administered induction therapeutic regimen, and glucocorticoid monotherapy (55.6%) was a mostly used maintenance therapeutic regimen.

Comparison of variables between patients in remission and no remission groups

The mean age of patients in no remission group was higher than that of patients in remission group, while the mean follow-up duration of the former was much shorter than that of the latter, which might be related to rapid progression or disease-refractoriness

Table I. Baseline characteristics of patients with microscopic polyangiitis (n=90).

Variables	Values
Demographic data	
Age (year old)	62.3 ± 16.5
Male gender (n, (%))	27 (30.0)
Follow-up duration (months)	41.7 ± 51.0
Clinical manifestations (n, (%))	
General manifestations	**54 (60.0)**
Myalgia	22 (24.4)
Arthralgia/arthritis	37 (41.1)
Fever ≥38°C	39 (43.3)
Weight loss ≥2 kg	20 (22.2)
Cutaneous manifestations	**32 (35.6)**
Infarct (digital ischaemia)	1 (1.1)
Purpura	9 (10.0)
Others	32 (35.6)
Mucous membranes/Eyes manifestations	**7 (7.8)**
Scleritis/Episcleritis or Conjunctivitis/Keratitis/Blepharitis	7 (7.8)
Ear Nose Throat manifestations	**7 (7.8)**
Paranasal sinus involvement	7 (7.8)
Chest manifestations	**43 (47.8)**
Massive haemoptysis/alveolar haemorrhage	13 (14.4)
Others	37 (41.1)
Cardiovascular manifestations	**34 (37.8)**
Cardiomyopathy or Congestive heart failure	5 (5.6)
Others	33 (36.7)
Abdominal manifestations	**6 (6.7)**
Bloody diarrhoea	6 (6.7)
Renal manifestations	**63 (70.0)**
Proteinuria >1 g/day	29 (32.2)
Renal insufficiency	27 (30.0)
Others	59 (65.6)
Nervous systemic manifestations	**30 (33.3)**
Central nervous system involvement	2 (2.2)
Peripheral neuropathy or mononeuritis multiplex	28 (31.1)
BVAS and FFS	
BVAS	16.9 ± 7.8
FFS (1996)	0.8 ± 1.0
FFS (2009)	1.9 ± 0.8
Antineutrophil cytoplasmic antibody (n, (%))	
MPO-ANCA	84 (93.3)
PR3-ANCA	4 (4.4)
ANCA-negative	2 (2.2)
Pathological diagnosis site (biopsy) (n, (%))	
Kidney	37 (41.1)
Skin	14 (15.6)
Nerve	10 (11.1)
Lung	4 (4.4)
Nasal cavity	1 (1.1)
No biopsy	24 (26.7)
Prognosis (n, (%))	
Remission and no relapse	48 (53.3)
Remission and relapse	31 (34.4)
No remission	11 (12.2)
Death	10 (11.1)
End stage renal disease	12 (13.3)
Induction therapeutic regimens	
Cyclophosphamide*	38 (42.2)
Glucocorticoid monotherapy	29 (32.2)
Rituximab*	9 (10.0)
Calcineurin inhibitor*	5 (5.6)
Azathioprine*	3 (3.3)
Mycophenolate mofetil*	3 (3.3)
No medication	2 (2.2)
Plasma exchange*	1 (1.1)
Maintenance therapeutic regimens	
Glucocorticoid monotherapy	50 (55.6)
Azathioprine*	25 (27.8)
Methotrexate*	6 (6.7)
Calcineurin inhibitor*	4 (4.4)
Mycophenolate mofetil*	3 (3.3)
No medication	2 (2.2)

Values are expressed as mean ± standard deviation and number (%).
*Combination therapy with glucocorticoid.
Cr: creatinine; BVAS: Birmingham vascular activity score; FFS: five factor score; MPO: myeloperoxidase; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody.

including death and ESRD (Table II). Among clinical manifestations, patients in no remission group showed weight loss and renal insufficiency more frequently than those in remission group. The mean BVAS, FFS (1996) and FFS (2009) of patients in no remission group were remarkably higher than those of patients in remission group ($p<0.005$ for all) (Table II). The detection rate of ANCAs was not significantly different between the two groups. In no remission group, glucocorticoid monotherapy was chosen as an induction therapeutic regimen rather than cyclophosphamide combined with glucocorticoid in a majority of cases, and this might be related to the urgent situation explained by the relatively short follow up duration to death or ESRD (Table II).

Comparison of variables between patients in no relapse and relapse groups

There were no significant differences in demographic data between the two groups.

Patients in relapse group exhibited chest and renal manifestations more frequently than those in no relapse group (61.3% *vs*. 33.3%, $p=0.015$, and 83.9% *vs*. 58.3%, $p=0.017$, respectively). Especially, the rates of proteinuria more than 1 g/day and renal insufficiency in patients with relapse were much higher than those in patients without ($p<0.002$ for all) (Table III). The mean initial BVAS and FFS (1996) of patients in relapse group were significantly higher than those of patients in remission group (19.0 *vs*. 14.3, $p=0.004$, and 1.0 *vs*. 0.5, $p=0.010$, respectively). However, there was no significant difference in initial FFS (2009) between patients in the two groups (Table III). MPO-ANCA and PR3-ANCA at diagnosis did not seem to predict the disease prognosis in patients with MPA. Patients belonging to the two groups had evenly received cyclophosphamide combined with glucocorticoid as an induction therapeutic regimen. Patients in no relapse patients had received glucocorticoid monotherapy more frequently and rituximab and mycophenolate mofetil less frequently than those

Table II. Comparison of variables between patients in remission and no remission groups.

Variables	Remission (n=79)	No remission (n=11)	*p*-value
Demographic data			
Age (year old)	60.4 ± 16.4	75.9 ± 8.9	0.003
Male gender (n, (%))	22 (27.8)	5 (45.5)	0.233
Follow-up duration (months)	52.2 ± 5.9	1.5 ± 0.4	0.006
Clinical manifestations (n, (%))			
General manifestations	43 (54.4)	11 (100)	0.004
Myalgia	19 (24.1)	3 (27.3)	0.816
Arthralgia/arthritis	35 (44.3)	2 (18.2)	0.099
Fever ≥ 38°C	32 (40.5)	7 (63.6)	0.147
Weight loss ≥ 2 kg	12 (15.2)	8 (72.7)	0.001
Cutaneous manifestations	30 (38.0)	2 (18.2)	0.199
Infarct (digital ischaemia)	1 (1.3)	0 (0)	0.706
Purpura	9 (11.4)	0 (0)	0.238
Others	30 (38.0)	2 (18.2)	0.199
Mucous membranes/Eyes manifestations	7 (8.9)	0 (0)	0.304
Scleritis/Episcleritis or Conjunctivitis/Keratitis/ Blepharitis	7 (8.9)	0 (0)	0.304
Ear Nose Throat manifestations	7 (8.9)	0 (0)	0.304
Paranasal sinus involvement	7 (8.9)	0 (0)	0.304
Chest manifestations	35 (44.3)	8 (72.7)	0.077
Massive haemoptysis/alveolar haemorrhage	10 (12.7)	3 (27.3)	0.196
Others	30 (38.0)	7 (63.6)	0.105
Cardiovascular manifestations	30 (38.0)	4 (36.4)	0.918
Cardiomyopathy or Congestive heart failure	4 (5.1)	1 (9.1)	0.585
Others	30 (38.0)	3 (27.3)	0.490
Abdominal manifestations	5 (6.3)	1 (9.1)	0.731
Bloody diarrhoea	5 (6.3)	1 (9.1)	0.731
Renal manifestations	54 (68.4)	9 (81.8)	0.361
Proteinuria > 1 g/day	23 (29.1)	6 (54.5)	0.091
Renal insufficiency	19 24.1)	8 (72.7)	0.001
Others	50 (63.3)	9 (81.8)	0.226
Nervous systemic manifestations	24 (30.4)	6 (54.5)	0.111
Central nervous system involvement	1 (1.3)	1 (9.1)	0.099
Peripheral neuropathy or mononeuritis multiplex	23 (29.1)	5 (45.5)	0.273
BVAS and FFS			
BVAS	16.1 ± 7.3	22.8 ± 8.8	0.007
FFS (1996)	0.9 ± 0.1	1.4 ± 0.4	0.001
FFS (2009)	0.8 ± 0.1	1.0 ± 0.3	0.025
Antineutrophil cytoplasmic antibody (n, (%))			
MPO-ANCA	75 (94.9)	9 (81.8)	0.102
PR3-ANCA	3 (3.8)	1 (9.1)	0.425
ANCA-negative	1 (1.3)	1 (9.1)	0.099
Induction therapeutic regimens			
Cyclophosphamide*	36 (45.6)	2 (18.2)	0.085
Glucocorticoid monotherapy	22 (27.8)	7 (63.6)	0.017
Rituximab*	9 (11.4)	0 (0)	0.238
Calcineurin inhibitor*	4 (5.1)	1 (9.1)	0.585
Azathioprine*	3 (3.8)	0 (0)	0.511
Mycophenolate mofetil*	3 (3.8)	0 (0)	0.511
Plasma exchange*	0 (0)	1 (9.1)	0.007
No medication	2 (2.5)	0 (0)	0.594
Maintenance therapeutic regimens			
Glucocorticoid monotherapy	39 (49.4)	11 (100)	0.002
Azathioprine*	25 (31.6)	0 (0)	0.028
Methotrexate*	6 (7.6)	0 (0)	0.344
Calcineurin inhibitor*	4 (5.1)	0 (0)	0.445
Mycophenolate mofetil*	3 (3.8)	0 (0)	0.511
No medication	2 (2.5)	0 (0)	0.594

Values are expressed as mean ± standard deviation and number (%).
*Combination therapy with glucocorticoid.
Cr: creatinine; BVAS: Birmingham vascular activity score; FFS: five factor score; MPO: myeloperoxidase; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody.

Table III. Comparison of variables between patients in no relapse and relapse groups.

Variables	No relapse (n=48)	Relapse (n=31)	*p*-value
Demographic data			
Age (year old)	62.4 ± 15.5	57.3 ± 64.6	0.179
Male gender (n, (%))	12 (25.0)	10 (32.3)	0.482
Follow-up duration (months)	39.4 ± 41.3	59.2 ± 64.6	0.099
Clinical manifestations (n, (%))			
General manifestations	23 (47.9)	20 (64.5)	0.148
Myalgia	13 (27.1)	6 (19.4)	0.433
Arthralgia/arthritis	23 (47.9)	12 (38.7)	0.421
Fever ≥ 38 ‘C	17 (35.4)	15 (48.4)	0.252
Weight loss ≥ 2 kg	7 (14.6)	5 (16.1)	0.141
Cutaneous manifestations	19 (39.6)	11 (35.5)	0.714
Infarct (digital ischaemia)	1 (2.1)	0 (0)	0.414
Purpura	6 (12.5)	3 (9.7)	0.700
Others	19 (39.6)	11 (35.5)	0.714
Mucous membranes/Eyes manifestations	5 (10.4)	2 (6.5)	0.545
Scleritis/Episcleritis or Conjunctivitis/ Keratitis/Blepharitis	5 (10.4)	2 (6.5)	0.545
Ear Nose Throat	6 (12.5)	1 (3.2)	0.157
Paranasal sinus involvement	6 (12.5)	1 (3.2)	0.157
Chest manifestations	16 (33.3)	19 (61.3)	0.015
Massive haemoptysis/alveolar haemorrhage	4 (8.3)	6 (19.4)	0.150
Others	15 (31.3)	15 (48.4)	0.125
Cardiovascular manifestations	16 (33.3)	14 (45.2)	0.290
Cardiomyopathy or Congestive heart failure	3 (6.3)	1 (3.2)	0.549
Others	16 (33.3)	14 (45.2)	0.290
Abdominal manifestations	2 (4.2)	3 (9.7)	0.326
Bloody diarrhoea	2 (4.2)	3 (9.7)	0.326
Renal manifestations	28 (58.3)	26 (83.9)	0.017
Proteinuria > 1 g/day	7 (14.6)	16 (51.6)	0.000
Renal insufficiency	7 (14.6)	12 (38.7)	0.014
Others	26 (54.2)	24 (77.4)	0.036
Nervous systemic manifestations	15 (31.3)	9 (29.0)	0.834
Central nervous system involvement	0 (0)	1 (3.2)	0.210
Peripheral neuropathy or mononeuritis multiplex	15 (31.3)	8 (25.8)	0.603
BVAS and Five factor scores (FFS)			
BVAS	14.3 ± 7.2	19.0 ± 6.7	0.004
FFS (1996)	0.5 ± 0.8	1.0 ± 1.0	0.010
FFS (2009)	1.8 ± 0.8	1.8 ± 0.7	0.793
Antineutrophil cytoplasmic antibody (n, (%))			
MPO-ANCA	46 (95.8)	29 (93.6)	0.651
PR3-ANCA	2 (4.2)	1 (3.2)	0.831
ANCA-negative	0 (0)	1 (3.2)	0.210
Induction therapeutic regimens			
Cyclophosphamide*	23 (47.9)	13 (41.9)	0.602
Glucocorticoid monotherapy	18 (37.5)	4 (12.9)	0.017
Rituximab*	1 (2.1)	8 (25.8)	0.001
Calcineurin inhibitor*	3 (6.3)	1 (3.2)	0.549
Azathioprine*	1 (2.1)	2 (6.5)	0.321
Mycophenolate mofetil*	0 (0)	3 (9.7)	0.028
Plasma exchange*	0 (0)	0 (0)	1.000
No medication	2 (4.2)	0 (0)	0.250
Maintenance therapeutic regimens			
Glucocorticoid monotherapy	23 (47.9)	16 (51.6)	0.748
Azathioprine*	18 (37.5)	7 (22.6)	0.164
Methotrexate*	3 (6.3)	3 (9.7)	0.574
Calcineurin inhibitor*	1 (2.1)	3 (9.7)	0.133
Mycophenolate mofetil*	1 (2.1)	2 (6.5)	0.321
No medication	2 (4.2)	0 (0)	0.025

Values are expressed as mean ± standard deviation and number (%).
*Combination therapy with glucocorticoid.
Cr: creatinine; BVAS: Birmingham vascular activity score; FFS: five factor score; MPO: myeloperoxidase; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody.

in relapse group (37.5% *vs*. 12.9% *p*=0.017, 2.1% *vs*. 25.8%, *p*=0.001, and 0% *vs*. 9.7%, *p*=0.028, respectively). As maintenance therapeutic regimens, there were no significant differences in immunosuppressive drugs including azathioprine and methotrexate (Table III). On multivariate logistic regression analysis of these significant variables, chest and renal manifestations were all independent predictors of relapse of MPA (OR 2.013, 95% CI 1.141, 7.954, *p*=0.026, and OR 3.517, 95% CI 1.116, 11.082, *p*=0.032) (Table IV). Since BVAS and FFSs contain items of the duplicated clinical manifestations, we did not include these variables in multivariate logistic regression analysis.

Optimal cut-off values of BVAS and FFS (1996) to predict relapse of MPA

Since BVAS and FFS (1996) at diagnosis showed significant differences between patients in no relapse and relapse groups, we calculated the optimal cut-off values of BVAS and FFS to predict relapse in 79 patients having experiencing remission on the basis of ROC curve analysis. And we found that 13.5 of BVAS (AUROC 0.689, 95% CI 0.571, 0.807, *p*=0.005) and 1 of FFS (1996) (AUROC 0.656, 95% CI 0.053, 0.782, *p*=0.020) were the optimal cut-off values good enough to predict relapse. When we classified 79 patients into two groups according to the calculated optimal cut-off value of BVAS, relapse in patients having BVAS ≥13.5 was identified more frequently than in those having BVAS <13.5 (53.3% *vs*. 20.6%, *p*=0.003). Also when we divided them into two groups based on the optimal cut-off value of FFS, relapse in patients having FFS ≥1 was observed more frequently than in those having FFS <1 (52.6% *vs*. 26.8%, *p*=0.019) (Fig. 1). Furthermore, patients having BVAS more than 13.5 and FFS more than 1 exhibited significantly increased risk of relapse of MPA than those having not (RR 4.408, 95% CI 1.595, 12.187, *p*=0.003, and RR 3.030, 95% CI 1.184, 7.754, *p*=0.019).

Prognosis

Cumulative relapse free survival rates regarding each predictor of relapsewere

Table IV. Multivariate logistic regression analysis of the independent predictive variable for relapse of microscopic polyangiitis at baseline (n=79).

Variables	Odds ratio	95% Confidence Interval	*p*-value
Clinical manifestations			
Chest manifestations	3.013	1.141, 7.954	0.026
Renal manifestations	3.517	1.116, 11.082	0.032

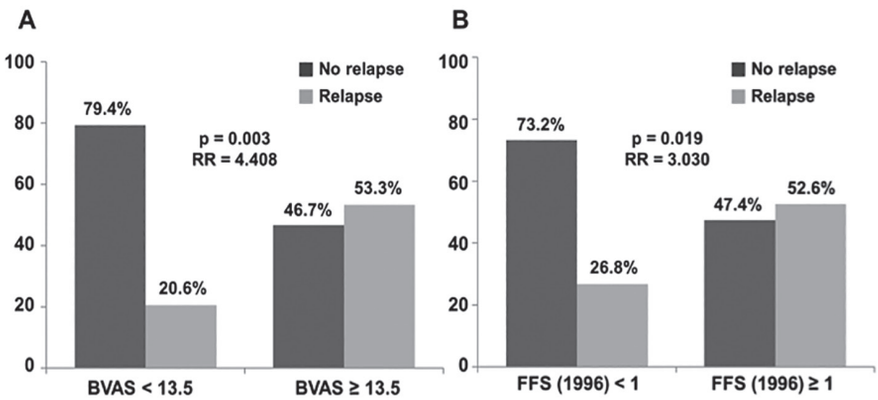

Fig. 1. Optimal cut-off values of Birmingham vasculitis activity score (BVAS) and five factor scores (FFS) (1996) to predict relapse of microscopic polyangiitis (MPA).
A: Relapse in patients having BVAS ≥ 13.5 was identified more frequently than in those having BVAS <13.5, and relapse in patients having FFS ≥ 1 was observed more frequently than in those having FFS <1.
B: Patients having BVAS more than 13.5 and FFS more than 1 exhibited significantly increased risk of relapse of MPA than those not having (RR 4.408 and RR 3.030).

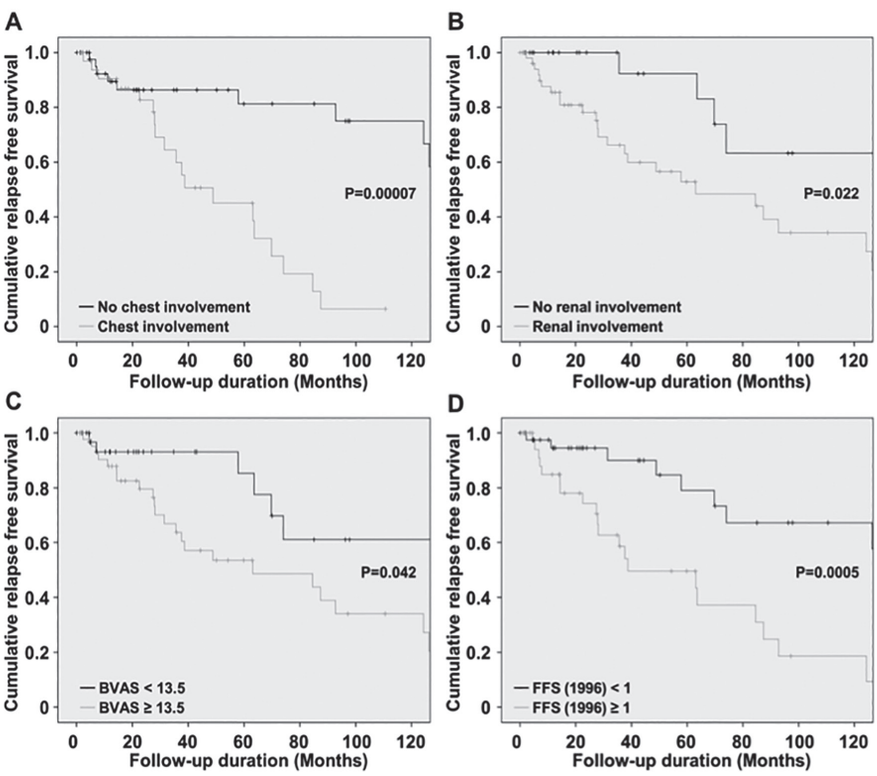

Fig. 2. Cumulative relapse free survival rates regarding each predictor of relapse of microscopic polyangiitis.
A-**B**: There were significant differences in cumulative relapse free survival according to presence of chest and renal involvement.
C-D: Patients having Birmingham vascular activity score (BVAS) <13.5 and five factor scores (FFS) <1 showed significantly higher cumulative relapse free survival rates than those having BVAS ≥13.5 and FFS ≥1.

depicted in Figure 2. There were significant differences in cumulative relapse free survival according to presence of chest involvement (p=0.00007) and renal involvement (p=0.022). Furthermore, patients having BVAS <13.5 and FFS <1 showed significantly higher cumulative relapse free survival rates than those having BVAS ≥13.5 and FFS ≥1, (p=0.042 and p=0.0005, respectively).

Discussion

In this study, when we compared variables between patients in remission and no remission groups, patients in no remission group were older and showed the higher frequency of general manifestation and renal insufficiency at diagnosis, and the shorter follow-up duration than those in remission group. Moreover, patients in no remission group had the higher mean initial BVAS and FFSs (1996 and 2009) than those in remission group. In fact, 8 of 11 patients in no remission group died and the rest of them progressed to ESRD. This result might reflect that patients in no remission group had more severe and rapidly progressive disease than those in remission group, and thus they had no opportunity to timely receive immunosuppressive drugs as induction therapeutic regimens. One case of plasma exchange and no case of rituximab in no remission group could also support this assumption.

We found that patients in relapse group exhibited the higher frequency of chest (p=0.015) and renal (p=0.017) involvements at diagnosis than those in no relapse group. And we clarified that baseline chest and renal involvements could increase the risk of relapse of MPA, three and 3.5 times as high as no involvement (p=0.026 and p=0.032, respectively). We confirmed this result using Kaplan-Meier survival analysis in Figure 2 (p=0.00007 and p=0.0.002, respectively). Especially, proteinuria >1g/day, renal insufficiency and other symptoms including haematuria evenly contributed to renal manifestations in relapse group, while variables in chest manifestation did not. A retrospective previous study similarly reported chest involvement as the only predictor of re-

lapse in dialysis-dependent patients of MPA, irrespective of massive proteinuria or renal insufficiency (20). Another retrospective study also reported that age of 60–69 years, chest involvement and renal insufficiency were significant predictors of death in 824 ANCA-positive rapid progressive glomerulonephritis patients (21), similar to our results. In addition, a retrospective study recently reported that disease severity and both FFS (1996) and FFS (2009) at diagnosis were prognostic factor for relapse-free survival (22). But pulmonary and renal involvements were not significant predictors of relapse in contrast with our results. In this study, patients in no relapse group had the higher mean BVAS and mean FFS (1996) at diagnosis than those in relapse group. However, there was no significant difference in FFS (2009). Discrepancies between the two studies might result from the new item of age >65 years in FFS (2009), because their study population was mainly confined to elderly patients.

We first extrapolated the optimal cut-off values of BVAS and FFS (1996) to predict relapse using AUROC and we set them as 13.5 of BVAS and 1 of FFS (1996). We discovered that patients having BVAS more than 13.5 (RR 4.408) and FFS (1996) more than 1 (RR 3.030) exhibited the significantly higher risk of relapse of MPA than those not having. We confirmed this result using Kaplan-Meier survival analysis in Figure 2 (p=0.042 and p=0.0005, respectively). The optimal cut-off of BVAS in our study, 13.5, is slight high compared to that in a previous study on Korean patients with MPA, 9 (13). The difference can be explained by the aim of each study: relapse and mortality.

We analysed and interpreted the association of medications as induction as well as maintenance therapeutic regimens with relapse of MPA. In terms of induction therapeutic regimens, cyclophosphamide plus glucocorticoid seemed not to prevent relapse of MPA, but was it true that glucocorticoid monotherapy could prevent it (37.5% for no relapse and 12.9% for relapse groups, p=0.017)? The higher frequency of glucocorticoid monotherapy might result from milder disease activity in no relapse group than relapse group. Both the higher mean BVAS and FFS (1996) and higher frequency of rituximab and mycophenolate mofetil could support this hypothesis. Two patients provided with no induction therapy in no relapse group also indirectly proved milder disease activity in no relapse group. In terms of maintenance therapeutic regimens, primarily, there were no significant differences in immunosuppressive drugs between the two groups. Basically, in generalised or severe cases, the concomitant administration of glucocorticoid plus immunosuppressive drugs such as azathioprine, methotrexate, mycophenolate mofetil, leflunomide and rituximab have been strongly recommended (9, 23-25). Therefore, we counted the numbers of patients who had received immunosuppressive drugs as maintenance therapeutic regimens and compared them among groups divided by the optimal cut-off values of BVAS and FFS (1996). Twelve of 24 (50.0%) patients with relapse in 45 patients having BVAS ≥13.5 and 9 of 20 (45.0%) patients with relapse in 38 patients having FFS (1996) ≥1 had not received immunosuppressive drugs after induction therapy. It must be impossible to uniformly apply immunosuppressive drugs to MPA patients as maintenance therapeutic regimens owing to diverse affected organs, various disease severity and multifarious medical situations. However, supposed that immunosuppressive drugs combined with glucocorticoid had been administered to more patients having BVAS and FFS (1996) more than each optimal cut-off after remission, similar to azathioprine recommended as a maintenance therapeutic regimen in eosinophilic granulomatosis with polyangiitis (9, 10), we could have reduced the rate of relapse in patients with MPA.

Our study has two features that we consider to be strength: first, we excluded patients who had only immunofluorescent assay results of ANCA (P-ANCA and C-ANCA), leading to increase in reliability of diagnosis of MPA. Second, we first proposed the optimal cut-off values of both BVAS and FFS as predictors of relapse of MPA. But our study also had several limitations: first, this study is the first trial to propose the optimal cut-off values of BVAS and FFS to predict relapse of MPA, so the validation of our data should be conducted by further studies. Second, since we excluded patients who had other concurrent medical conditions to affect the interpretation of our results and who had only immunofluorescent assay results, the number of subjects was not large enough to increase statistical power. Last, this study has a limitation of a retrospective study. In fact, 15 patients definitely classified as MPA were excluded due to unclear medical documents. Thus, future prospective studies with larger number of subjects will provide a more reliable data regarding predictors of relapse of MPA.

In conclusion, chest and renal involvements were independent predictors of relapse of MPA during follow-up. And BVAS more than 13.5 and FFS (1996) more than 1 at diagnosis were significant predictors of relapse of PAN as well. Thus, we suggest that physicians should pay more attention to patients having predictors of relapse, and they should consider initiating immunosuppressive drugs as maintenance therapeutic regimens after remission, as long as there is no contraindication of those drugs in patients with MPA.

References

1. GRECO A, DE VIRGILIO A, RIZZO MI *et al*.: Microscopic polyangiitis: Advances in diagnostic and therapeutic approaches. *Autoimmun Rev* 2015; 14: 837-44.
2. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11.
3. KALLENBERG CG: The diagnosis and classification of microscopic polyangiitis. *J Autoimmun* 2014; 48-49: 90-3.
4. SUN L, WANG H, JIANG X *et al*.: Clinical and pathological features of microscopic polyangiitis in 20 children. *J Rheumatol* 2014; 41: 1712-9.
5. SCOTT DG, WATTS RA: Systemic vasculitis: epidemiology, classification and environmental factors. *Ann Rheum Dis* 2000; 59: 161-3.
6. WEINER M, SEGELMARK M: The clinical presentation and therapy of diseases related to anti-neutrophil cytoplasmic antibodies (ANCA). *Autoimmun Rev* 2016; 15: 978-82.
7. CORNEC D, CORNEC-LE GALL E, FERVENZA FC, SPECKS U: ANCA-associated vasculitis - clinical utility of using ANCA specificity to

classify patients. *Nat Rev Rheumatol* 2016; 12: 570-9.
8. LITTLE MA, SMYTH L, SALAMA AD *et al*.: Experimental autoimmune vasculitis: an animal model of anti-neutrophil cytoplasmic autoantibody-associated systemic vasculitis. *Am J Pathol* 2009; 174: 1212-20.
9. MILLET A, PEDERZOLI-RIBEIL M, GUILLEVIN L, WITKO-SARSAT V, MOUTHON L: Antineutrophil cytoplasmic antibody-associated vasculitides: is it time to split up the group? *Ann Rheum Dis* 2013; 72: 1273-9.
10. ELEFANTE E, TRIPOLI A, FERRO F, BALDINI C: One year in review: systemic vasculitis. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S1-6.
11. FLOSSMANN O, BERDEN A, DE GROOT K *et al*.: Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; 70: 488-94.
12. LIONAKI S, BLYTH ER, HOGAN SL *et al*.: Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. *Arthritis Rheum* 2012; 64: 3452-62.
13. AHN JK, HWANG JW, LEE J, JEON CH, CHA HS, KOH EM: Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea. *Rheumatol Int* 2012; 32: 2979-86.
14. OH JS, LEE CK, KIM YG, NAH SS, MOON HB, YOO B: Clinical features and outcomes of microscopic polyangiitis in Korea. *J Korean Med Sci* 2009; 24: 269-74.
15. MUKHTYAR C, LEE R, BROWN D *et al*.: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32.
16. GAYRAUD M, GUILLEVIN L, LE TOUMELIN P *et al*.: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; 44: 666-75.
17. GUILLEVIN L, PAGNOUX C, SEROR R, MAHR A, MOUTHON L, LE TOUMELIN P: The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90: 19-27.
18. WATTS R, LANE S, HANSLIK T *et al*.: Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66: 222-7.
19. MUKHTYAR C, HELLMICH B, JAYNE D, FLOSSMANN O, LUQMANI R: Remission in antineutrophil cytoplasmic antibody-associated systemic vasculitis. *Clin Exp Rheumatol* 2006; 24 (Suppl. 43): S-93-8.
20. HASEGAWA M, HATTORI K, SUGIYAMA S *et al*.: A retrospective study on the outcomes of MPO-ANCA-associated vasculitis in dialysis-dependent patients. *Mod Rheumatol* 2016; 26: 110-4.
21. YAMAGATA K, USUI J, SAITO C *et al*.: ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes. *Clin Exp Nephrol* 2012; 16: 580-8.
22. ABE Y, TAMURA N, YANG KS *et al*.: Predictive factors for mortality in elderly Japanese patients with severe microscopic polyangiitis: A retrospective single-center study. *Mod Rheumatol* 2016:1-5. [Epub ahead of print]
23. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80.
24. MCADOO SP, PUSEY CD: Should rituximab be used to prevent relapse in patients with ANCA-associated vasculitis? *Clin J Am Soc Nephrol* 2014; 9: 641-4.
25. HIEMSTRA TF, WALSH M, MAHR A *et al*.: Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; 304: 2381-8.