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Birmingham vasculitis activity score at diagnosis is a significant predictor of relapse of polyarteritis nodosa

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Abstract The objective of this study was to investigate whether clinical and laboratory data, Birmingham vasculitis activity score (BVAS) and five factor scores (FFS) at diagnosis could predict relapse in 30 patients with polyarteritis nodosa (PAN) having the follow-up duration for over 12 months. We reviewed the medical charts of 30 patients with PAN. We obtained clinical and laboratory data at diagnosis, and we compared them between the two groups based on relapse. The optimal cut-off values of BVAS and FFS (1996) at diagnosis to predict relapse were extrapolated. The mean age of patients (15 men) was 50.8 years, and the mean follow-up duration was 64.1 months. Nine patients (30.0%) had experience relapse after remission. Patients having relapse showed the higher frequency of weight loss and ocular symptoms and the less frequency of diastolic hypertension than those having not ($p < 0.005$ for all). On multivariate logistic regression analysis, weight loss was the only independent predictor of relapse, but on Cox Hazard model analysis, its statistical significance disappeared. The mean initial BVAS and FFS (1996) of patients in relapse group were higher than those of patients in no relapse group ($p < 0.005$ for all). Patients having initial BVAS over 13.5 and FFS (1996) over 1 exhibited significantly higher risk of relapse than those having not (RR 40.0 and RR 7.0, respectively). However, initial BVAS over 13.5 only remained significant in Kaplan–Meier survival analysis. In conclusion, BVAS over 13.5 at diagnosis was the only independent predictor of relapse of PAN.

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Introduction

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting medium-sized arteries [1, 2]. PAN can also affect small-sized arteries, but it may not target arterioles, venules, and capillaries [1]. The incidence of PAN has been reported to be up to 1.6 cases per million, and its prevalence up to 31 cases per million [3]. PAN can involve diverse organs, but PAN is known not to affect lungs [4, 5]. Medium-sized vessel microaneurysm is the typical feature of PAN and the rupture or occlusion of inflamed arteries can cause haemorrhage or ischemia of affected arteries-feeding tissues in various organs [4]. The aetiology of PAN still remains uncertain, but there are several evidence supporting that PAN might result from endothelial cell activation, leading to endothelial dysfunction and damages provoked by both vasculitis itself and pro-inflammatory cytokines or antibodies [4, 6]. Besides, various adhesion molecules and immune cells, especially T cells, participate in the pathogenesis of PAN [7, 8]. There are three clinical subclasses of PAN; cutaneous PAN, hepatitis B virus (HBV)-associated PAN, and idiopathic generalised PAN. Cutaneous PAN and idiopathic generalised PAN, but not HBV-associated PAN, are placed on a spectrum of clinical presentations, and cutaneous PAN can progress to idiopathic generalised PAN [2]. In the pathogenesis of HBV-associated PAN, distinct mechanism has been elucidated: the direct vascular injury through viral replication and the indirect vascular deposition of circulating immune complex can in turn activate neutrophils and complement system and further

induce extravasation of immune cells and subsequent adjacent tissue damages [8–10].

In contrast with other systemic vasculitis, treatment modalities of PAN mostly depend on its clinical subclasses. Patients with mild PAN or cutaneous PAN are often treated with glucocorticoid alone as an induction as well as a maintenance therapeutic regimen. When they are refractory to glucocorticoid alone, they can be treated with azathioprine, methotrexate or mycophenolate mofetil, but generally cyclophosphamide is not recommended in these cases, due to cytotoxic adverse effects [11–15]. Meanwhile, patients with moderate-to-severe idiopathic generalised PAN should be initially treated with a combination of glucocorticoid and cyclophosphamide [13, 16]: intravenous cyclophosphamide of 600 mg/m^2 every 2 weeks for three doses, and then every 4 weeks for 4 months or intravenous cyclophosphamide of 15 mg/kg at weeks 0, 2 and 4 and then every 3 weeks [16, 17]. Patients who are refractory to cyclophosphamide can receive Rituximab after methylprednisolone pulse therapy [18]. On the other hand, patients with HBV-associated PAN are suggested to be initially treated with antiviral agents rather than immunosuppressive medications after they are treated with glucocorticoid or plasma exchange as an induction therapeutic regimen, until antiviral agents become efficient [19]. Azathioprine, methotrexate, or mycophenolate mofetil is recommended as a remission-maintenance therapeutic regimen [11, 13]. The first year and 5 year relapse rates of cutaneous and idiopathic generalised PAN were reported to be 9.2 and 24%, and the relapse rate of HBV-associated PAN was known to be less than those of others [12].

So far, there have been several previous studies reporting the associated factors of prognosis of PAN such as five factor scores (FFS) or the use of immunosuppressive drugs as induction therapeutic regimens [5, 6, 16]. There was only a previous report regarding the prognosis of polyarteritis nodosa in Korea, which commented that testicular tenderness and a high FFS were associated with a poor prognosis, such as mortalities or co-morbidities [20]. In daily clinical settings, a majority of rheumatologists are interested in relapse as much as mortalities and co-morbidities of systemic vasculitis, and further predictors of their relapse, if possible. However, there were few reports regarding predictors of relapse of PAN, especially, there was no report in Korea. Hence, in this study, we investigated whether clinical manifestations, a specified organ involvement, ANCA positivity, Birmingham vasculitis activity score (BVAS), and FFS at diagnosis could predict relapse in 30 patients with PAN having the follow-up duration for at least more than 12 months [6, 16, 21].

Methods

Patients

We reviewed the medical charts of 42 patients, who had been classified as PAN from January 2000 to September 2015 according to the inclusion criteria for PAN as follows: (1) patients who had been first classified as PAN on the basis of American College of Rheumatology (ACR) 1990 criteria for the classification of PAN [22]; (2) patients who had been classified as PAN at Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance hospital; (3) patients who had been followed up for more than 12 months after diagnosis; (4) patients who had the baseline results of myeloperoxidase (MPO)-antineutrophil cytoplasmic antibodies (ANCA) and proteinase 3 (PR3)-ANCA conducted by the enzyme-linked immunosorbent assay at diagnosis, but not by immunofluorescent assay; (5) patients who had never had systemic illness or received medications affecting the false positivity of MPO-ANCA or PR3-ANCA; (6) patients whose medical charts contained the contents qualified enough to fill up the forms of BVAS and FFSs (1996 and 2009) [6, 16, 21]; (7) patients whose medical charts clearly commented the status of remission or relapse; and (8) patients who had achieved remission at least once during the follow-up. Among 42 patients with PAN, 12 patients were excluded: three patients had also been classified as other connective tissue diseases, two patients did not have the results of MPO-ANCA nor PR3-ANCA, and seven patients did not have medical charts which clearly described clinical features at diagnosis or commented remission or relapse during the follow-up. This study was approved by the institutional Review Board of Severance hospital.

Baseline clinical features, specified organ involvements, prognosis, ANCA measurement, and medications

We collected baseline age, gender, and the follow-up duration. We set the follow-up duration as the period from diagnosis to the last visit to hospital for patients in no relapse group and we set it as the period from diagnosis to relapse for those in relapse group. We counted the number of items of ACR 1990 criteria for the classification of PAN which patients had fulfilled [22]. We obtained variables of clinical manifestations and specified organ involvements based on BVAS version 3 and FFSs (1996 and 2009) [6, 16, 21]. In addition, we collected histopathological results and biopsy-performed sites, and we searched induction and maintenance therapeutic regimens. Remission was defined as the absence of disease activity attributable to active disease qualified by the need for on-going stable maintenance

immunosuppressive therapy. In addition, relapse was defined as recurrence or new onset of disease attributable to active vasculitis [23, 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. In addition, we reviewed medications which had been administered as both induction and maintenance therapeutic regimens.

Statistical analysis

Mann–Whitney *U* test was used to compare continuous variables between no relapse and relapse groups, which were expressed as the mean ± standard deviation. Chi-Square test and Fisher's extract test were used to analyse significant differences in categorical variables between the two groups. The odds ratio (OR) was assessed using multivariate logistic regression of variables with significance on univariate analysis. We also conducted Cox Hazard model analysis using the same variables with significance due to the small number of subjects in this study. 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 maximize 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 according to the Kaplan–Meier survival analysis. We conducted all statistical analysis using the SPSS package for Windows version 23 (IBM). *p* values less than 0.05 were considered statistically significant.

Results

Baseline characteristics of patients with polyarteritis nodosa

Baseline characteristics of patients with PAN were described in Table 1. The mean age of patients with PAN (15 men and 15 women) was 50.8 years, and the mean follow-up duration was 64.1 months. Among items of ACR 1990 criteria for the classification of PAN, myalgia or weakness or leg tenderness (60.0%) and histopathological abnormalities (60.0%) were the most frequently fulfilled items, followed by diastolic BP over 90 mmHg (50.0%). Six patients (20.0%) had cutaneous PAN, 14 (46.7%) had HBV-associated PAN, and 10 (33.3%) had idiopathic generalised PAN. The most common clinical feature at

Table 1 Baseline characteristics of patients with PAN ($N = 30$)

Variables	Values
Demographic data	
Age (year old)	50.8 ± 15.5
Male gender [*N*, (%)]	15 (50.0)
Follow-up duration (months)	64.1 ± 62.0
ACR 1990 criteria for the classification	
Weight loss ≥ 4 kg	7 (23.3)
Myalgia, weakness or leg tenderness	18 (60.0)
Livedo reticularis	3 (10.0)
Mono- or polyneuropathy	6 (20.0)
Testicular pain and tenderness	2 (6.7)
Diastolic BP > 90 mmHg	15 (50.0)
Elevated BUN (>40 mg/dL) or Cr (>1.5 mg/dL)	5 (16.7)
Positivity for hepatitis B virus infection	14 (46.7)
Arteriographic abnormality	14 (46.7)
Histopathological abnormality	18 (60.0)
Subclasses of PAN [*N*, (%)]	
Cutaneous PAN	6 (20.0)
Hepatitis B virus-associated PAN	14 (46.7)
Idiopathic generalised PAN	10 (33.3)
Clinical manifestations [*N*, (%)]	
General manifestations	24 (80.0)
Myalgia	18 (60.0)
Arthralgia/arthritis	11 (36.7)
Fever ≥ 38 °C	6 (20.0)
Weight loss ≥ 2 kg	7 (23.3)
Cutaneous manifestations	16 (53.3)
Infarct (digital ischemia)	0 (0)
Purpura	7 (23.3)
Others	9 (30.0)
Mucous membranes/eyes manifestations	2 (6.7)
Scleritis/episcleritis	2 (6.7)
Ear nose throat manifestations	1 (3.3)
Paranasal sinus involvement	1 (3.3)
Chest manifestations	7 (23.3)
Massive hemoptysis/alveolar haemorrhage	0 (0)
Others	7 (23.3)
Cardiovascular manifestations	5 (16.7)
Cardiomyopathy or congestive heart failure	4 (13.3)
Others (pericarditis)	1 (3.3)
Abdominal manifestations	4 (13.3)
Bloody diarrhea	3 (10.0)
Peritonitis	1 (3.3)
Renal manifestations	9 (30.0)
Proteinuria > 1 g/day	5 (16.7)
Renal insufficiency	5 (16.7)
Hematuria	8 (26.7)
Nervous systemic manifestations	11 (36.7)
Central nervous system involvement	5 (16.7)
Peripheral neuropathy or mononeuritis multiplex	6 (20.0)

Table 1 (continued)

Variables	Values
BVAS and FFS	
BVAS	10.1 ± 9.5
FFS (1996)	0.8 ± 1.1
FFS (2009)	1.6 ± 0.9
Antineutrophil cytoplasmic antibody [*N*, (%)]	
MPO-ANCA	7 (23.3)
PR3-ANCA	3 (10.0)
Pathological diagnosis site (biopsy) [*N*, (%)]	
Skin	13 (43.3)
Nerve	2 (6.7)
Muscle	2 (6.7)
Others	3 (10.0)
No biopsy	10 (33.3)
Medications	
Induction therapeutic regimens	
Cyclophosphamide[a]	4 (13.3)
Azathioprine[a]	4 (13.3)
Methotrexate[a]	1 (3.3)
Mycophenolate mofetil[a]	1 (3.3)
Antiviral agents	5 (16.7)
Colchicine[a]	1 (3.3)
Glucocorticoid monotherapy	14 (46.7)
Maintenance therapeutic regimens	
Azathioprine[a]	8 (26.7)
Methotrexate	1 (3.3)
Mycophenolate mofetil[a]	1 (3.3)
Antiviral agents	5 (16.7)
Non-steroidal anti-inflammatory drugs	2 (6.7)
Colchicine	1 (3.3)
Glucocorticoid monotherapy	6 (20.0)
No medication	6 (20.0)
Prognosis [*N*, (%)]	
Remission and no relapse	21 (70.0)
Remission and relapse	9 (30.0)

Values are expressed as mean ± standard deviation and number (%)

ACR American College of Rheumatology, *BP* blood pressure, *BUN* blood urea nitrogen, *Cr* creatinine, *BVAS* Birmingham vascular activity score, *FFS* five factor score, *MPO* myeloperoxidase, *PR3* proteinase 3, *ANCA* antineutrophil cytoplasmic antibody

[a]Combination therapy with glucocorticoid

diagnosis was general manifestations (80.0%), including myalgia, joint symptoms, fever, and weight loss, followed by cutaneous (53.3%) and nervous systemic manifestations (36.7%). The mean initial BVAS was 10.1, and the mean initial FFSs (1996 and 2009) were 0.8 and 1.6, respectively. MPO-ANCA was detected in seven patients (23.3%), and PR3-ANCA was done in only three patients (10.0%). Skin was the most common site which biopsy was performed (43.3%), and no biopsy was done in ten patients (33.3%). Glucocorticoid monotherapy (46.7%) was the most frequently administered induction therapeutic regimen, followed by antiviral agents for HBV-associated PAN (16.7%), cyclophosphamide (13.3%), and azathioprine (13.3%). In addition, azathioprine was the most common maintenance therapeutic regimen (26.7%), followed by glucocorticoid monotherapy (20.0%) and no treatment (20.0%). Twenty-one patients had achieved remission without relapse, while nine patients had experienced relapse after remission during the follow-up.

Comparison of variables between patients in no relapse and relapse groups

There were no significant differences in age, gender, and the follow-up duration between the two groups. At diagnosis, patients in relapse group had complained of weight loss and scleritis/episcleritis more frequently than those in no relapse group (55.6 vs. 9.5%, $p = 0.006$ and 22.2 vs. 0%, $p = 0.025$, respectively). By contrast, patients in no relapse group showed the higher proportion of diastolic hypertension than those in relapse group (61.9 vs. 22.2%, $p = 0.046$). There were no differences in the number of patients among subclasses of PAN. In addition, abdominal manifestations did exhibited a statistical significance (33.3% for relapse group and 4.8% for no relapse group, $p = 0.035$) (Table 2). Patients in relapse group had the higher mean initial BVAS and FFS (1996) than those in no relapse group (18.6 vs. 6.5, $p = 0.015$ and 1.6 vs. 0.4, $p = 0.010$, respectively). However, patients in both groups showed no significant difference in FFS (2009). MPO-ANCA and PR3-ANCA were evenly detected in the two groups (Table 2). Among induction therapeutic regiments, only azathioprine showed statistically significant differences between no relapse and relapse groups, but the frequency of its use was higher in relapse group than no relapse group. In order not to leave a misunderstanding that the use of azathioprine might be a risk factor for relapse, we did not include azathioprine in multivariate logistic regression analysis. Similar to azathioprine as induction therapeutic regimen, although glucocorticoid exhibited significant difference between the two groups, we excluded it in multivariate analysis.

Independent predictors of relapse of PAN

We performed multivariate logistic regression analysis on variables with statistical significance on univariate analysis: weight loss, diastolic hypertension, and scleritis/episcleritis. Although abdominal manifestations did exhibit a statistically significant difference, since abdomen-related items, including bloody diarrhea, peritonitis, and ischemic abdominal pain, showed no statistical significance, we did not take into account abdominal manifestations in

Table 2 Comparison of variables between patients in no relapse and relapse groups

Variables	No relapse ($N=21$)	Relapse ($N=9$)	p value
Demographic data			
Age (year old)	53.0 ± 16.6	45.7 ± 11.7	0.241
Male gender [N, (%)]	10 (47.6)	5 (55.6)	0.690
Follow-up duration (months)	56.5 ± 62.1	81.7 ± 61.8	0.316
ACR 1990 criteria for the classification			
Weight loss ≥4 kg	2 (9.5)	5 (55.6)	0.006
Myalgia, weakness or leg tenderness	11 (52.4)	7 (77.8)	0.193
Livedo reticularis	3 (14.3)	0 (0)	0.232
Mono- or polyneuropathy	5 (23.8)	1 (11.1)	0.426
Testicular pain and tenderness	1 (4.8)	1 (11.1)	0.523
Diastolic BP >90 mmHg	13 (61.9)	2 (22.2)	0.046
Elevated BUN or Cr	2 (9.5)	3 (33.3)	0.109
Positivity for hepatitis B virus (HBV) infection	10 (47.6)	4 (44.4)	0.873
Arteriographic abnormality	8 (38.1)	6 (66.7)	0.335
Histopathological abnormality	13 (61.9)	5 (55.6)	0.948
Subclasses of PAN [N, (%)]			0.607
Cutaneous PAN	5 (23.8)	1 (11.1)	
Hepatitis B virus-associated PAN	10 (47.6)	4 (44.4)	
Idiopathic generalised PAN	6 (28.6)	4 (44.4)	
Clinical manifestations [N, (%)]			
General manifestations	15 (71.4)	9 (100)	0.073
Myalgia	11 (52.4)	7 (77.8)	0.193
Arthralgia/arthritis	8 (38.1)	3 (33.3)	0.804
Fever ≥38 °C	3 (14.3)	3 (33.3)	0.232
Weight loss ≥2 kg	2 (9.5)	5 (55.6)	0.006
Cutaneous manifestations	11 (52.4)	5 (55.6)	0.873
Infarct (digital ischemia)	0 (0)	0 (0)	1.000
Purpura	5 (23.8)	2 (22.2)	0.925
Others	6 (28.6)	3 (33.3)	0.794
Mucous membranes/eyes manifestations	0 (0)	2 (22.2)	0.025
Scleritis/episcleritis	0 (0)	2 (22.2)	0.025
Ear nose throat manifestations	0 (0)	1 (11.1)	0.120
Paranasal sinus involvement	0 (0)	1 (11.1)	0.120
Chest manifestations	3 (14.3)	4 (44.4)	0.073
Massive haemoptysis/alveolar haemorrhage	0 (0)	0 (0)	1.000
Others (all pleural effusion)	3 (14.3)	4 (44.4)	0.073
Cardiovascular manifestations	2 (9.5)	3 (33.3)	0.109
Cardiomyopathy or Congestive heart failure	2 (9.5)	2 (22.2)	0.348
Others (pericarditis)	0 (0)	1 (11.1)	0.120
Abdominal manifestations	1 (4.8)	3 (33.3)	0.035
Bloody diarrhea	1 (4.8)	2 (22.2)	0.144
Peritonitis	0 (0)	1 (11.1)	0.120
Renal manifestations	5 (23.8)	4 (44.4)	0.258
Proteinuria >1 g/day	2 (9.5)	3 (33.3)	0.109
Renal insufficiency	2 (9.5)	3 (33.3)	0.109
Haematuria	4 (19.0)	4 (44.4)	0.149
Nervous systemic manifestations	7 (33.3)	4 (44.4)	0.563
Central nervous system involvement	2 (9.5)	3 (33.3)	0.109
Peripheral nervous system involvement	5 (23.8)	1 (11.1)	0.426
BVAS and FFS			
BVAS	6.5 ± 5.7	18.6 ± 11.6	0.015

Table 2 (continued)

Variables	No relapse ($N=21$)	Relapse ($N=9$)	p value
FFS (1996)	0.4 ± 0.8	1.6 ± 1.5	0.010
FFS (2009)	1.5 ± 0.9	1.7 ± 0.9	0.684
Antineutrophil cytoplasmic antibody [*N*, (%)]			
MPO-ANCA	4 (19.0)	3 (33.3)	0.397
PR3-ANCA	2 (9.5)	1 (11.1)	0.894
Medications			
Induction therapeutic regimens			
Cyclophosphamide[a]	4 (19.0)	0 (0)	0.160
Azathioprine[a]	1 (4.8)	3 (33.3)	0.035
Methotrexate[a]	1 (4.8)	0 (0)	0.506
Mycophenolate mofetil[a]	0 (0)	1 (11.1)	0.120
Antiviral agents	4 (19.0)	1 (11.1)	0.593
Colchicine[a]	1 (4.8)	0 (0)	0.506
Glucocorticoid monotherapy	10 (47.6)	4 (44.4)	0.873
Maintenance therapeutic regimens			
Azathioprine[a]	5 (23.8)	3 (33.3)	0.589
Methotrexate	1 (4.8)	0 (0)	0.506
Mycophenolate mofetil[a]	0 (0)	1 (11.1)	0.120
Antiviral agents	4 (19.0)	1 (11.1)	0.593
Non-steroidal anti-inflammatory drugs	2 (9.5)	0 (0)	0.338
Colchicine	1 (4.8)	0 (0)	0.506
Glucocorticoid monotherapy	2 (9.5)	4 (44.4)	0.028
No medication	6 (28.6)	0 (0)	0.073

Values are expressed as mean ± standard deviation and number (%)

ACR American College of Rheumatology, *BP* blood pressure, *BUN* blood urea nitrogen, *Cr* creatinine, *BVAS* Birmingham vascular activity score, *FFS* five factor score, *MPO* myeloperoxidase, *PR3* proteinase 3, *ANCA* antineutrophil cytoplasmic antibody

[a]Combination therapy with glucocorticoid

multivariate analysis (Table 2). Moreover, BVAS and FFSs were not analysed together with clinical features or specified organ involvements on multivariate analysis, because those indices include a considerable number of duplicated clinical variables. On multivariate analysis, only weight loss ≥4 kg was a independent predictor of relapse of PAN (OR 11.066, 95% CI 1.279, 95.719, $p=0.029$) (Table 3). Due to the small number of subjects, we also conducted Cox Hazard model analysis using the same variables on multivariate logistic regression analysis, and we could find no variable with statistical significance (Table 3).

Table 3 Multivariate logistic regression analysis and Cox Hazard model using variables with statistical significance between no relapse and relapse groups

Variables	Odds ratio	95% confidence interval	p value
Multivariate logistic regression analysis			
Weight loss ≥4 kg	11.066	1.279, 95.719	0.029
Diastolic BP >90 mmHg	0.305	0.038, 2.455	0.265
Scleritis/Episcleritis	N/A	N/A	0.999
Cox hazard model analysis			
Weight loss ≥4 kg	2.173	0.512, 9.233	0.293
Diastolic BP >90 mmHg	0.594	0.108, 3.284	0.551
Scleritis/episcleritis	0.688	0.110, 4.316	0.690

Optimal cut-off values of BVAS and FFS (1996) for predicting relapse of PAN and prognosis

We calculated the optimal cut-off values of BVAS and FFS (1996) for predicting relapse of PAN, which showed significant difference between the two groups, using ROC curve analysis. We found that 13.5 of BVAS (AUROC 0.854, 95% CI 0.713, 0.996, $p=0.002$, sensitivity 0.952 and specificity

0.667) and 1 of FFS (AUROC 0.772, 95% CI 0.575, 0.970, $p=0.020$, sensitivity 0.778 and specificity 0.667) were the best cut-off values to predict relapse during the follow-up. When we assigned 30 patients into two groups based on the optimal cut-off value of BVAS, 7 patients belonged to BVAS ≥13.5 group and 23 patients belonged to BVAS <13.5 group. The proportion of relapse in patients having BVAS ≥13.5 was much greater than that in patients having BVAS <13.5 (85.7% vs. 13.0%, $p<0.001$). In addition, when we classified all patients in two groups according to the optimal cut-off value of FFS (1996), 14 patients were allocated to FFS ≥1 group and 16 patients were done to FFS < 1 group. The rate of relapse in patients having FFS ≥1 was higher than that in patients having FFS <1 (50.0% vs. 12.5%, $p=0.025$) (Fig. 1). Furthermore, patients having BVAS ≥13.5 and FFS ≥1 were discovered to have significantly increased risk of relapse of PAN, compared to those having not (RR 40.0, 95% CI 3.486, 458.984, and RR 7.0, 95% CI 1.140, 42.969) (Fig. 1).

We depicted cumulative relapse-free survival rates in terms of BVAS and FFS (1996) as predictors of relapse in Fig. 2, using Kaplan–Meier survival analysis. There was remarkable difference in cumulative relapse-free survival between BVAS ≥13.5 and BVAS <13.5 ($p=0.033$); however, there was no significant difference in that between FFS ≥ (1996) and FFS (1996) <1 ($p=0.377$). With these results, we concluded that BVAS ≥13.5 was the only independent predictor of relapse of PAN during the follow-up.

Discussion

In this study, when we compared variables between patients in no relapse and relapse groups, we found that patients having relapse showed the higher frequency of weight loss and ocular symptoms and the less frequency of diastolic hypertension than those having not. Interestingly, compared to ocular symptoms and diastolic hypertension, weight loss more than 4 kg showed a great difference between patients

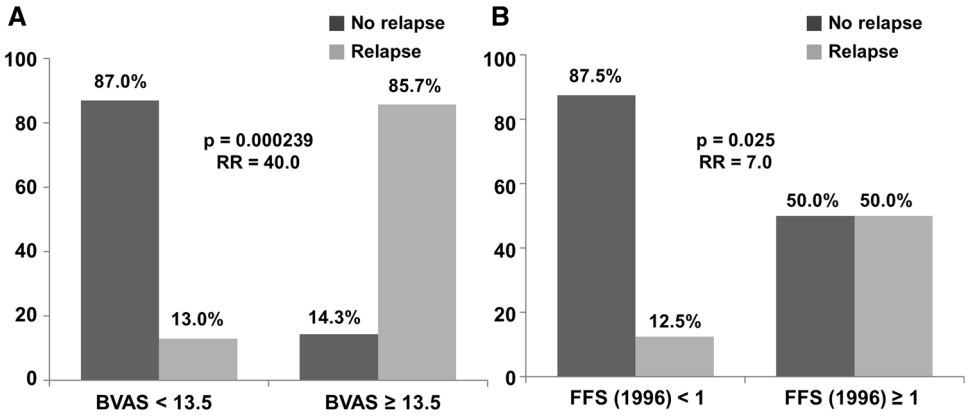

Fig. 1 Optimal cut-off values of Birmingham vasculitis activity score (BVAS) and fiver factor scores (FFS) (1996) for predicting relapse of polyarteritis nodosa (PAN). **a** Proportion of relapse in patients having BVAS ≥13.5 was much greater than that in patients having BVAS <13.5 (85.7% vs. 13.0%, $p<0.001$). **b** Rate of relapse in patients having FFS ≥1 was higher than that in patients having FFS <1 (50.0% vs. 12.5%, $p=0.025$). Furthermore, patients having BVAS ≥13.5 and FFS ≥1 were discovered to have significantly increased risk of relapse of PAN, compared to those having not (RR 40.0, 95% CI 3.486, 458.984, and RR 7.0, 95% CI 1.140, 42.969)

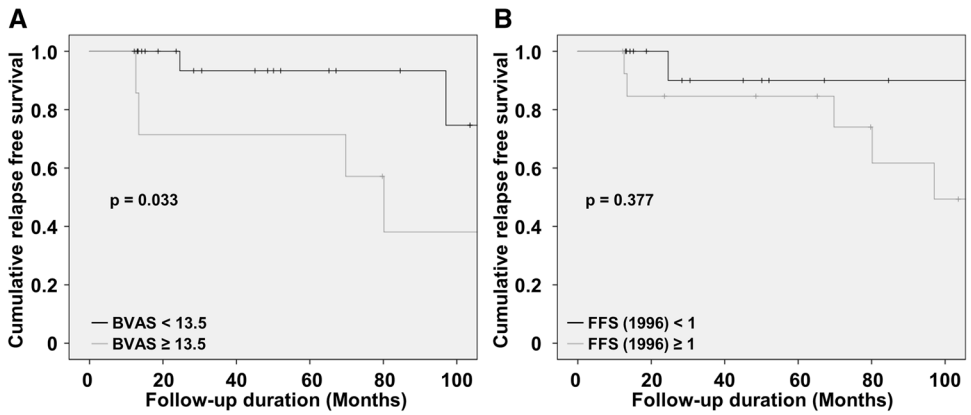

Fig. 2 Cumulative relapse free survival rates regarding each predictor of relapse of polyarteritis nodosa (PAN). **a** There was remarkable difference in cumulative relapse-free survival between BVAS ≥13.5 and BVAS <13.5 ($p=0.033$). **b** However, there was no significant difference in that between FFS ≥ (1996) and FFS (1996) <1 ($p=0.377$)

of the two groups. In addition, on multivariate analysis, only weight loss was an independent predictor of relapse of PAN. Although we could find no significant differences in subclasses of PAN between the two groups in this study, we assumed that patients had presented weight loss at diagnosis had a tendency to be classified as idiopathic generalised PAN. When we conducted a subgroup analysis regarding the correlation between weight loss and subclasses of PAN, weight loss more than 4 kg was observed in only one of 6 patients (16.7%) with cutaneous PAN and 2 of 14 patients (14.3%) with HBV-associated PAN. By contrast, four of ten patients (40.0%) with idiopathic generalised PAN had ever presented weight loss as an initial manifestation at diagnosis. However, when we investigated the effect of clinical manifestations on relapse of PAN by Cox Hazard model analysis, due to the small number of subjects, the statistical significance of weight loss disappeared (Table 3).

Moreover, we found that patients in relapse group had the higher mean initial BVAS and FFS (1996) than those in no relapse group. Furthermore, we analysed and compared the mean of BVAS and FFS (1996) among subclasses of PAN using ANOVA analysis, but we could recognise no significant differences in the mean BVAS and FFS (1996) among them [$p=0.100$ for BVAS and $p=0.051$ for FFS (1996)]. However, we could confirm the tendency of increase in BVAS and FFS (1996) from cutaneous and HBV-associated PAN to idiopathic generalised PAN [3.8, 9.9, and 14.3 for BVAS and 0, 0.6, and 1.4 for FFS (1996)]. Furthermore, we first calculated the optimal cut-off values of BVAS and FFS (1996) to predict relapse of PAN using AUROC and we set them 13.5 for BVAS and 1 for FFS (1996). We elucidated that patients having BVAS over 13.5 (RR 40.0) and FFS (1996) over 1 (RR 7.0) showed the significantly higher risk of relapse of PAN that those having below them. To confirm the follow-up time-dependent statistical significance of BVAS and FFS (1996), we conducted Kaplan–Meier survival analysis, as depicted in Fig. 2. In addition, we knew that only initial BVAS can predict relapse of PAN during the follow-up.

In the present study, the detection rate of MPO-ANCA or PR3-ANCA in our study-population was relatively high, compared to previous reports, and serologic markers of ANCA are usually suggestive of ANCA-associated vasculitis. Seven patients had MPO-ANCA and three patients had PR3-ANCA, and furthermore, three patients turned out to have both MPO-ANCA and PR3-ANCA. However, all seven patients having either MPO-ANCA or PR3-ANCA or both ANCA were not classified as AAV at all. Of seven patients having ANCA, five patients underwent biopsy: four of five patients exhibited histologic findings compatible to PAN, and one of five patients showed typical small aneurysm of a celiac artery, despite no histologic abnormality. Two of seven patients having ANCA, who had not taken tissue biopsy, also showed arterial abnormality on CT angiography. With these results, seven patients having ANCA were finally classified as PAN.

In general, the strategy of treatment of PAN depends on subclasses of PAN: (1) non-steroidal anti-inflammatory drugs or colchicine with or without glucocorticoid, dapsone, and other immunosuppressive agents are recommended for cutaneous PAN; (2) antiviral agents and glucocorticoid are recommended for HBV-associated PAN; (3) either glucocorticoid monotherapy or combination therapy with immunosuppressive agents are recommended for non-severe idiopathic generalised PAN; and (4) glucocorticoid combination therapy with cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil, are currently recommended for moderate-to-severe idiopathic generalised PAN. Medications can be shifted to others having relatively low risk of adverse effects for maintenance therapy after the achievement of remission [2, 25]. When we compared both induction and maintenance therapeutic regimes between no relapse and relapse groups, we found that azathioprine as induction therapy and glucocorticoid monotherapy as maintenance therapy significantly differed. However, the frequencies of both medications administered were higher in relapse group than no relapse group, so we did not include those medications in multivariate analysis for discovering the independent predictor of relapse of PAN regardless of its subclasses.

Previous studies reported the differences in the relapse rates among subclasses of PAN: relapses can occur in less than 10% of HBV-associated PAN and up to 24% of idiopathic generalised PAN patients [12, 26, 27]. In our study, 4 of 14 (28.6%) patients with HBV-associated PAN had experienced relapse and 4 of 10 (40%) patients with idiopathic generalised PAN had done it. The relapse rates in our study were higher than those in the previous studies. We assumed that this discrepancy might result from the two reasons: First, only four of ten patients with idiopathic generalised PAN had received cyclophosphamide as an induction therapeutic regimen and they all had not experienced relapse during the follow-up. On the contrary, four patients having relapse had refused cyclophosphamide for its serious adverse effects, and they had ever received azathioprine or mycophenolate mofetil rather than cyclophosphamide as induction therapeutic regimens. Despite the absence of the standardised treatment principle to manage from cutaneous to idiopathic generalised PAN, cyclophosphamide should be recommended as the first line induction therapy in patients with moderate and severe idiopathic generalised PAN if there is no contraindication of its use [13, 16, 17]. Second, only 5 of 14 patients with HBV-associated PAN had received antiviral agents, and 4 of them had never suffered from relapse during the follow-up. One of five patients having received antiviral agents had experienced relapse. On the other hands, three of four HBV-associated

PAN patients with relapse had not been treated with antiviral agents before or during the administration of immunosuppressive drugs. For, the Korean medical insurance could not cover antiviral agents when HBV load is lower than the reference range. Given that Korea is an endemic nation of HBV infection and the increased viral load and its immune complex can aggravate PAN, antiviral agents should be primarily considered in patients with HBV-associated PAN.

This study has two features that we consider to be strength: first, we included only patients having the follow-up duration for more than 12 months. At least 12 month-follow-up duration might be a long period enough to observe relapse of PAN. Second, we first proposed the optimal cut-off value of initial BVAS as a predictor of relapse of PAN. Our study also had several issues: first, the number of patients included in this study was too small to perform subgroup analysis among three clinical variants of PAN. Second, this study was designed as a retrospective study. And last, since this study is the first trial to propose the optimal cut-off value of initial BVAS as a predictor of relapse of PAN, the reliability should be tested by the validation studies. Therefore, future prospective studies with larger number of subjects will provide a more reliable data regarding predictors of relapse of PAN.

In conclusion, BVAS over 13.5 at diagnosis was the only independent predictor of relapse of PAN in this study. We suggest that physicians should consider cyclophosphamide as an induction therapeutic regimen in patients with idiopathic generalised PAN having initial BVAS more than 13.5. Furthermore, antiviral agents should be considered in patients with HBV-associated PAN before the administration of immunosuppressive drugs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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