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ORIGINAL ARTICLE

Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea

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Abstract The classification system for antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and polyarteritis nodosa had its limitations due to numerous overlapping features of these disease entities. The aim of this study is to investigate the clinical features and outcome of patients diagnosed with microscopic polyangiitis (MPA) according to the newly proposed consensus algorithm of ANCA-associated vasculitides and polyarteritis nodosa. Fifty-five cases of MPA, comprised of 33 men and 22 women, diagnosed according to a new consensus algorithm at a single tertiary hospital were identified for analysis. The main clinical features were constitutional symptoms (78.2%), followed by renal involvement (74.5%), musculoskeletal symptoms (67.3%), skin manifestations (50.9%), neurologic involvement (43.6%), and lung involvement (41.8%). P-ANCA and/or anti-myeloperoxidase antibody were present in 69.1%. Five Factor Score and Birmingham Vasculitis Activity Score (BVAS) at diagnosis were 1.1 ± 0.9 and 10.9 ± 4.9, respectively. Forty-four patients were available for a long-term follow-up, and six patients (13.6%) resulted in death. Mortality was associated with BVAS > 9 at the time of diagnosis, age > 60 years, and presence of cardiomyopathy and interstitial lung disease. The survival rate at 1 and 3 years was 93.9 and 89.2%, respectively. Eight patients (14.5%) required dialysis at the time of diagnosis. This is the first study to demonstrate the clinical features in patients with MPA using a new consensus algorithm. Survival rate was higher than previously reported, and interstitial lung disease was a new risk factor for death in patients with MPA.

Keywords Microscopic polyangiitis · A new consensus algorithm · Interstitial lung disease · Korean

Introduction

Microscopic polyangiitis (MPA) is a systemic vasculitis histologically characterized by necrotizing inflammation of small vessels, such as arterioles, venules, or capillaries. Necrotizing glomerulonephritis is a common clinical feature and diffuse alveolar hemorrhage due to pulmonary capillaritis often occurs [1].

The classification of antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and polyarteritis nodosa (PAN) has been controversial due to the fact that many of the clinical features of these disease entities overlap. In addition, the American College of Rheumatology (ACR) classification criteria do not only include MPA as a disease entity, but also ANCA as a serologic hallmark for ANCA-associated vasculitis (AAV). The Chapel Hill Consensus Conference (CHCC) defined MPA as necrotizing vasculitis with few or no immune deposit affecting relatively small

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blood vessels without granuloma formation [1]. Previous studies may not accurately reflect the clinical characteristics and prognosis of MPA because MPA had been described as a subgroup of PAN and criteria for MPA were also unclear. The development of laboratory tests, such as ANCA, and the introduction of new classification criteria have enabled us to further understand primary vasculitis and facilitated more accurate diagnosis. Nevertheless, there are many points that are yet to be resolved. Recently, a new consensus algorithm using the ACR criteria and the CHCC definitions for classification of AAV had been proposed by Watts et al. [2]. This algorithm provided a useful tool for application in the epidemiological studies for AAV and PAN [2, 3].

Epidemiologic studies reported that there is an inverse relationship between the incidence of Wegener's granulomatosis (WG) and MPA depending on geographical and ethnic differences [4]. In the United Kingdom and New Zealand, more patients with WG than MPA are found, whereas in China, MPA is about threefold to fourfold more frequent than WG [3–5]. Furthermore, the clinical phenotype of MPA seemed to be very different between the Japanese and the Europeans [6–8]. Clearly then, it is important to investigate the different clinical manifestations and outcomes of these vasculitides according to different geographic location and ethnicity. Thus, this study was undertaken to demonstrate the clinical features and prognosis in Korean patients with MPA according to a new algorithm using both the ACR criteria and CHCC definitions.

Patients and methods

Patient selection

Fifty-five patients, diagnosed with MPA according to the Watts' algorithm in a single tertiary medical center between 1994 and 2009, were identified for this study. Patients were diagnosed and followed by nephrologists and/or rheumatologists at our hospital. All patients fulfilled the following three entry criteria required by the Watts' algorithm and were older than 16 years of age [2]. First, a patient must have symptoms and signs compatible with the diagnosis of AAV or PAN. Second, at least one of the following must be fulfilled: histological proof of vasculitis and/or granuloma formation, positive serology for ANCA (proteinase 3-ANCA or myeloperoxidase-ANCA), specific investigations strongly suggestive of vasculitis and/or granuloma, and eosinophilia (>10% or >1.5 $\times$ 10^9/l). Last, the followings must be specifically excluded: malignancy, infection (including hepatitis B and C, HIV, tuberculosis, subacute bacterial endocarditis), drugs (including hydralazine, propylthiouracil, cocaine and allopurinol), secondary vasculitis (rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, connective tissue disease), Behcet's disease, Takayasu's arteritis, giant cell arteritis, Kawasaki's disease, essential mixed cryoglobulinaemia, Henoch Scho¨nlein purpura, anti-GBM disease, vasculitis mimics (cholesterol embolism, calciphylaxis, catastrophic antiphospholipid antibody syndrome, atrial myxoma), sarcoidosis, and other non-vasculitic granulomatous diseases [2].

Demographic and clinical data

From the medical records, we recorded the gender, age at the time of MPA diagnosis, duration of disease, clinical symptoms and signs, cause of death, types and medication dosage, and organ involvement at presentation and during follow-up for all patients. Organ involvement was defined as the presence of one or more items within each category of the Birmingham Vasculitis Activity Score (BVAS) form (constitutional or general, cutaneous, mucous membrane, eye, otorhinolaryngeal, chest, cardiovascular, abdominal, nervous system) [9]. Respiratory involvement was diagnosed on the basis of chest X-rays and computed tomography (CT) scan. Renal involvement was defined as the presence of proteinuria, hematuria associated with red cell casts, or renal insufficiency (defined as serum creatinine value >1.36 mg/dl). Laboratory data for analysis included white blood cell (WBC) and platelet counts, hemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine (Cr), estimated creatinine clearance (Ccr), liver enzymes, and hematuria and proteinuria on urinalysis. The following immunologic parameters were also recorded: the presence and titer of antinuclear antibody (ANA), rheumatoid factor (RF), ANCA, complement components C3 and C4, hepatitis B virus surface antigen (HBs Ag) and antibody (anti-HBs), and anti-hepatitis C virus antibody (anti-HCV). To evaluate disease activity and prognostic factors, we measured the five factor score (FFS) and BVAS at the time of MPA diagnosis. Five factor score is comprised of proteinuria (>1 g/day), renal insufficiency (serum creatinine >1.58 mg/dl), severe GI tract involvement (defined as bleeding, perforation, infarction, and/or pancreatitis), cardiomyopathy (defined as significant impairment of cardiac function due to poor ventricular wall motion, confirmed by echocardiography), and/or central nervous system (CNS) involvement. The presence of each factor was accorded 1 point [10]. The BVAS is a clinical tool to quantify disease activity in systemic vasculitis, which is based on symptoms and signs in 9 separate organ systems [11].

Clinical remission was defined when there was stabilization or improvement of kidney function, as measured by serum Cr level and resolution of hematuria, and other manifestations of systemic vasculitis for more than 1 month.

Treatment resistance was defined as progressive decline in kidney function with persistent active urine sediment, or persistent or new appearance of any extra-renal manifestations of active vasculitis despite immunosuppressive therapy. Relapse was defined as new systemic manifestations of vasculitis or deterioration of one or several initial manifestations of the disease—occurrence of at least one of the followings: (1) rapid rise in serum Cr concentration accompanied by active urine sediment; (2) renal biopsy demonstrating active necrosis or crescent formation; (3) hemoptysis, pulmonary hemorrhage, or new or expanding nodules without the evidence of infection; (4) active vasculitis of the respiratory or gastrointestinal tracts as demonstrated by endoscopy with biopsy; (5) iritis or uveitis; (6) new mononeuritis multiplex; or (7) necrotizing vasculitis identified by biopsy [12].

Statistical analysis

All data are expressed as mean ± standard deviation (SD). The normality of data was tested by Shapiro–Wilk test. To compare continuous variable distributions and categorical variables between groups, we used Student's t test or Mann–Whitney U test and the χ^2-test or Fisher's exact test, respectively. A P value less than 0.05 was considered statistically significant. We performed a stepwise logistic regression model for multivariate analysis of the predictive power of baseline variables for mortality. Only variables significantly associated with death or end-stage renal disease (ESRD) by univariate analysis were utilized. Survival was analyzed according to the Kaplan–Meier survival analysis. The PASW statistics 17.0 (Predictive Analytics Software, SPSS Inc.0, Chicago, IL, USA) was used for all analyses.

Results

Clinical characteristics and treatment

Fifty-five patients were diagnosed with MPA according to the Watts' algorithm (33 men and 22 women with a mean age of 59.3 years). The demographic data and clinical manifestations are detailed in Table 1. Renal insufficiency was present in 32 patients (78.0%). Eight patients (14.5%) required dialysis at the time of diagnosis, and none of these patients died. During treatment, 1 patient was able to be taken off dialysis. Interstitial lung disease (ILD) was seen in 13 (23.6%), of whom usual interstitial pneumonia (UIP) was the most frequent in 84.6%. One patient had cryptogenic organizing pneumonia and 2 patients nonspecific interstitial pneumonia. Eye involvement and orchitis were not found. Of patients with gastrointestinal involvement, abdominal pain was found in 6 patients, cholecystitis in 3, hematochezia, superior mesentery artery rupture, melena, and bowel perforation in 1, respectively. Two patients experienced cardiomyopathy, who complained of dyspnea at the time of diagnosis. Echocardiographic and chest radiographic findings of these patients revealed decreased left ventricular ejection fraction and cardiomegaly.

Table 1 Demographic data and clinical manifestations observed in Korean patients with microscopic polyangiitis (n = 55)

Demographics	
Age at the time of diagnosis (years)	59.29 ± 13.60
Male	33 (60.0)
Follow-up duration (months)	46.07 ± 39.98
Clinical manifestations	
Constitutional symptoms	43 (78.2)
Weight loss	24 (43.6)
Fever	32 (58.2)
Fatigue	17 (30.9)
Musculoskeletal	37 (67.3)
Arthralgia	21 (38.2)
Myalgia	26 (47.3)
Skin manifestations	28 (50.9)
Purpura	6 (10.9)
Livedo reticularis	8 (14.5)
Nodules	3 (5.5)
Skin rash	14 (25.5)
Orchitis	0 (0)
Digital ischemia	4 (7.5)
Renal involvement	41 (74.5)
Neurologic	24 (43.6)
CNS involvement	5 (9.1)
Peripheral neuropathy	22 (40.0)
Mononeuritis multiplex	20 (36.4)
Eye involvement	0 (0)
Sinusitis	15 (27.3)
Cardiovascular	10 (18.2)
Hypertension	9 (16.4)
Cardiac failure or cardiomyopathy	2 (3.8)
Pericarditis	2 (3.6)
Myocardial infarct	1 (1.8)
Respiratory	23 (41.8)
Alveolar hemorrhage	4 (7.3)
Pneumonitis	1 (1.8)
Pleuritis	7 (12.7)
Infiltration	7 (12.7)
Interstitial lung disease	13 (23.6)
Gastrointestinal involvement	11 (20.0)

Unless otherwise indicated, values are frequencies (percentages) or means ± SD (standard deviation). *CNS* central nervous system

The mean FFS and BVAS at the time of diagnosis was 1.1 ± 0.9 and 10.7 ± 4.8, respectively. The mean FFS score and BVAS of patients with renal manifestations were 1.4 ± 0.9 and 12.7 ± 4.2, respectively. The coefficient for FFS and BVAS was 0.753 ($P < 0.001$) and that for BVAS and CRP or ESR were 0.315 ($P = 0.021$) and 0.276 ($P = 0.043$), respectively.

Forty-seven patients (85.5%) were treated with a combination of steroids and/or cyclophosphamide, and seven patients (12.7%) were treated with a combination of steroids and azathioprine or mycophenoate mofetil. Thirty remissions (58.8%) occurred, and 10 patients (18.2%) experienced relapse during the follow-up period available. Of 10 patients relapsed, 5 patients showed rapid rise in serum creatinine concentration, accompanied by an active urine sediment.

Laboratory findings

The mean serum Cr level and estimated Ccr at the time of diagnosis was 2.8 ± 3.0 mg/dl and 45.8 ± 35.3 ml/min, respectively. The mean serum Cr level and estimated Ccr of patients with renal manifestations at the time of MPA diagnosis were 3.44 ± 3.20 mg/dl and 31.6 ± 25.7 ml/min, respectively. Proteinuria (>1 g/day) was found in 38.2%, with a mean 24 h urine protein of 1,486.5 mg/day. Hematuria was present in 73.6% and leukocytouria was noted in 24.5%. Perinuclear ANCA determined by immunofluorescence and/or antibody to myeloperoxidase (MPO) by enzyme linked immunosorbent assay were present in 69.1% at the time of diagnosis. Cytoplasmic ANCA or anti-proteinase 3 (PR3) was not present. Among patients with renal involvement, ANCA were detected in 29 patients (72.5%). Also, ANCA was detected in all four patients with alveolar hemorrhage. Among the autoantibodies tested, RF was found in 26 of 42 patients (61.9%) with a mean value of 90.7 IU/ml, and antinuclear antibody was detected in 6 of 53 patients (11.3%). Hepatitis B surface antigen was found in 3 patients (5.5%) and anti-HCV antibody in 1 patient (1.9%).

Prognosis and predictors for adverse outcomes

The survival rates at 1 and 3 years were 93.9 and 89.2%, respectively. Six of the 44 patients (13.6%) whose long-term follow-up data were available died, 2 from lung cancer, 1 from cholangiocarcinoma, 1 from multi-organ failure and diffuse alveolar hemorrhage, 1 from pneumonia, and 1 from unknown cause. Five of 6 patients who died experienced relapse or treatment resistance. The risk factors that predict death were shown in Table 2. The mean BVAS at the time of the diagnosis and the presence of cardiomyopathy and ILD were the significant markers in predicting mortality. The mean age at the time of diagnosis in the mortality group was higher than those who were alive, although a statistical significance was not reached (70.8 vs. 60.3 years, $P = 0.057$). There were no differences in other clinical manifestations and laboratory findings between the survivors and the deceased. Survival analysis was performed using these risk factors. As shown in Fig. 1, death was associated with BVAS > 9 ($P = 0.034$), age > 60 years ($P = 0.013$) at the time of diagnosis, and the presence of cardiomyopathy ($P = 0.002$) and ILD ($P = 0.006$).

Next, we assessed the risk for ESRD development in patients with MPA. In univariate analysis, ESRD developed more frequently in those with higher serum Cr, CRP, ESR, BVAS, FFS and lower hemoglobin level, albumin and estimated Ccr, C4 level at the time of diagnosis, and in those who experienced pleuritis ($P < 0.05$ for all, table 3). Unfortunately, we could not find significant risk factors for developing ESRD in multivariate logistic regression analysis.

Discussion

There have been considerable disputes in the clinical characteristics, natural course, and mortality of MPA, because of the lack of MPA classification criteria. Since the CHCC provided definitions for MPA, to some extent, it presented a homogeneous disease entity in the studies on MPA. There are many points that are yet to be solved, due to difficulties in using the CHCC definitions for the purpose of MPA classification. Watts et al. [2] recently proposed a new consensus algorithm for the classification of primary systemic vasculitis, and Liu et al. [3] reported that this algorithm was a useful method for classification in epidemiologic studies for AAV. They asserted that one of the strong values of this algorithm is that one could easily make a diagnosis of AAV and PAN by clinical information without histological data. Also, the concept of surrogate markers in vasculitis and ANCA as a diagnostic utility was first introduced. Thus, in our study, patients were selected based on Watts' new algorithm redefined by the ACR and CHCC classification criteria.

The demographic and laboratory data are similar to those in previously published series. A slight predominance in men has been reported, ranging from 1 to 1.8 [10, 13, 14]. In previous studies, the male to female sex ratio was 1.67. P-ANCA, and the anti-MPO antibody has been found in about 50–80% of patients with MPA [10, 15], similar to our study. The overall clinical manifestations were similar, with an exception of a few important differences. Compared to data from earlier studies [14, 16–18], there was more neurologic involvement but less purpura, renal, and pulmonary involvement in our study. While the frequency of DAH was shown to be high in previous studies with higher

Table 2 Comparison of characteristics in patients with microscopic polyangiitis who died and are alive

	Dead (n = 6)	Alive (n = 38)	P value
Age at the time of diagnosis (years)	70.8 ± 7.9	60.3 ± 12.6	0.057
Male (n, %)	5 (83.3)	19 (52.6)	0.213
Follow-up duration (months)	24.0 ± 37.6	54.5 ± 41.0	0.095
Dialysis	0 (0)	5 (13.2)	1.000
Laboratory findings			
White cell counts (/mm^3)	11,268.3 ± 5,121.8	12,044.1 ± 4,168.0	0.683
Hemoglobin (g/dl)	10.4 ± 1.2	9.7 ± 2.1	0.453
CRP (mg/dl)	11.9 ± 8.5	9.4 ± 8.2	0.497
ESR (mm/h)	77.5 ± 15.6	76.4 ± 36.7	0.941
Creatinine	2.67 ± 3.04	2.74 ± 3.02	0.953
Estimated creatinine clearance	45.47 ± 38.31	44.30 ± 34.56	0.940
Albumin	2.60 ± 0.54	2.83 ± 0.71	0.450
p-ANCA	6 (100)	27 (71.1)	0.311
BVAS	14.8 ± 3.7	10.3 ± 4.9	0.032
FFS	1.3 ± 0.5	1.0 ± 0.90	0.399
Constitutional symptoms	6 (100.0)	30 (78.9)	0.573
Weight loss	2 (33.3)	17 (44.7)	0.684
Fever	5 (83.3)	22 (57.9)	0.380
Musculoskeletal	3 (50.0)	25 (65.8)	0.652
Arthralgia	1 (16.7)	14 (36.8)	0.647
Myalgia	3 (50.0)	18 (47.4)	1.000
Skin manifestations	2 (33.3)	18 (47.4)	0.673
Purpura	1 (16.7)	3 (7.9)	0.456
Livedo reticularis	0 (0)	7 (18.4)	0.568
Nodules	0 (0)	2 (5.3)	1.000
Digital ischemia	0 (0)	2 (5.3)	1.000
Neurologic	3 (50.0)	14 (36.8)	0.662
CNS involvement	1 (16.7)	4 (10.5)	0.538
Peripheral neuropathy	2 (33.3)	13 (34.2)	1.000
Mononeuritis multiplex	1 (16.7)	12 (31.6)	0.652
Sinusitis	2 (33.3)	12 (31.6)	1.000
Cardiovascular	0 (0)	9 (23.7)	0.319
Hypertension	1 (16.7)	7 (18.4)	1.000
Cardiomyopathy	2 (33.3)	0 (0)	0.016
Pericarditis	0 (0)	2 (5.3)	1.000
Respiratory	5 (83.3)	15 (39.5)	0.077
Alevolar hemorrhage	1 (16.7)	2 (5.3)	0.363
Pneumonitis	0 (0)	1 (2.6)	1.000
Pleuritis	1 (16.7)	5 (13.2)	1.000
Interstitial lung disease	4 (66.7)	8 (21.1)	0.039
Renal involvement	0 (0)	12 (31.6)	0.167
Gastrointestinal involvement	1 (16.7)	7 (18.4)	1.000

Unless otherwise indicated, values are frequencies (percentages) or means ± SD (standard deviation)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *p-ANCA* perinuclear antineutrophil cytoplasmic antibody, *FFS* five factor score, *BVAS* Birmingham vasculitis activity score

proportion of renal involvement [9, 10, 13], its frequency was low in our report with less renal involvement. A possible explanation for these discrepancies in cases of MPA with glomerulonephritis may be due to the lack of definite classification of MPA. Moreover, many studies reported that ILD is an important and common complication of AAV, and ILD usually occurs in patients whose clinical phenotypes favor MPA [19–22]. Our study showed that ILD is a relatively common pulmonary manifestation of MPA, and UIP was the most common type of ILD. Therefore, MPA should be considered as one of the underlying diseases in patients with UIP.

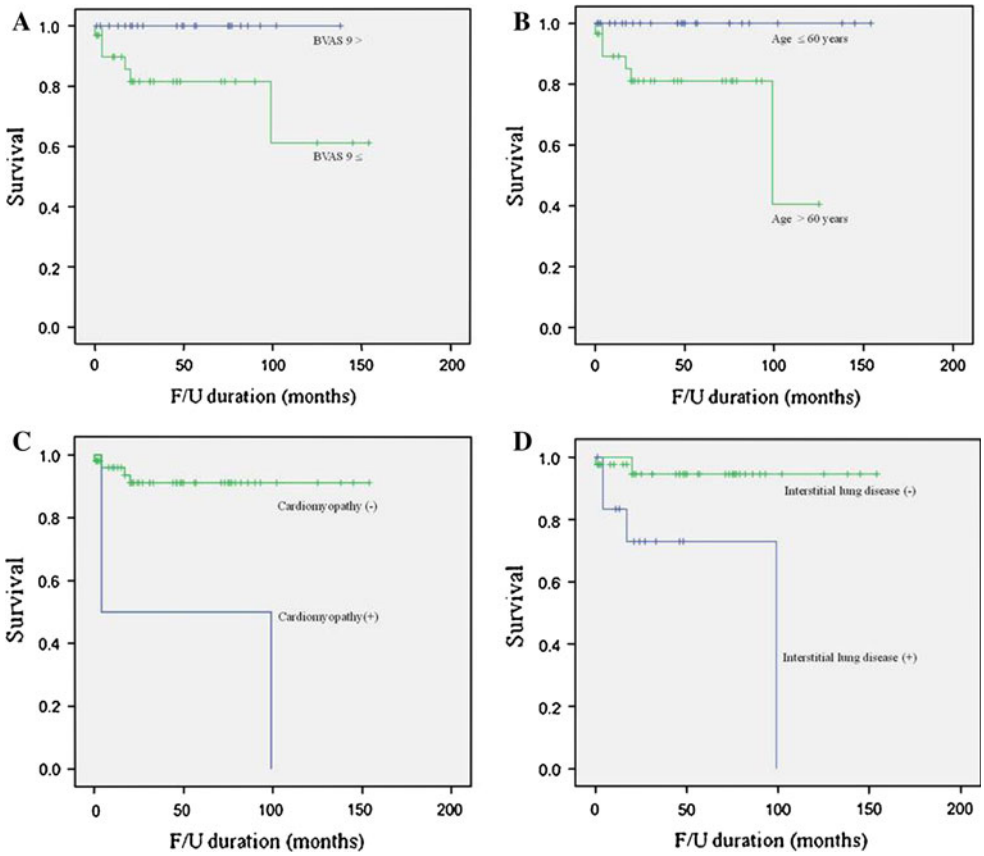

Fig. 1 Survival analysis in Korean patients with microscopic polyangiitis, according to Birmingham Vasculitis Activity Score (BVAS) ($P = 0.034$) (**a**) and age ($P = 0.013$) (**b**) at the time of diagnosis and the presence of cardiomyopathy ($P = 0.002$) (**c**) and interstitial lung disease ($P = 0.006$) (**d**). Data were analyzed using the log-rank test

Causes of death were mainly due to vasculitis-related etiologies or infections in other studies. Unexpectedly, many patients died from malignancy in the present study. A recent report suggests that AAV or Henoch-Schonlein purpura is associated with increased risks of malignancy [23]. However, careful interpretation of these observations is necessary because 5 of 6 patients who died were treated with a combination of steroids and cyclophosphamide, and the cumulative dose of cyclophosphamide administered was more than 20 gram in 3 patients who died of cancer.

In our study, the survival rate at 1 and 3 years was 93.9 and 89.2%, respectively. Other studies reported that the 1 year survival rate was 82–92%, and the 5 year survival rate was 45–76% [6, 9, 24–26]. The outcome of the present study, especially 3 year survival, appeared to be better than that in other studies. The patient population in the present study had lower BVAS than previous studies, reflecting lower disease activity than patients enrolled in previous studies. These differences may be due to ethnic/geographic difference or due to the early detection and early treatment of MPA in our center. Age, renal insufficiency, and renal histology at the time of diagnosis are important adverse predictors for ESRD and/or death in AAV [22, 25, 27]. FFS and BVAS are known to be associated with disease activity, and BVAS was an important risk factor for mortality. Cardiomyopathy as an adverse factor for survival in our study is in concordance with a previous report that suggested renal, cardiovascular, or central venous involvement as importance prognostic factor for mortality [28]. In addition to these traditional risk factors such as BVAS, old age at the time of diagnosis, and cardiomyopathy, we found ILD to be a new adverse predictor for survival. Interstitial fibrosis in MPA may be due to recurrent episodes of DAH for many years [21]. Subclinical alveolar hemorrhage was reported to be relatively common in patients with AAV, and patients with DAH had more extensive disease [29]. From these reports, it seems reasonable to conclude that ILD is the significant risk factors of mortality in our study. Furthermore, patients with ILD may be in need of more aggressive therapy on the basis of these results. In univariate analysis, prognostic factors for renal outcome were similar to previous studies. Unfortunately, in multivariate analysis, we could not find significant risk factors. Only 7 patients eventually had ESRD, thus limiting the statistical power for such a model to be performed. Also, differences in mortality and adverse risk factors among studies may be explained by a rapidly deteriorating course in series reported by nephrologists and overlapping classification system of AAV.

In summary, this is the first study to demonstrate the clinical features of Korean patients diagnosed with MPA using the new consensus algorithm. No distinguished differ-

Table 3 Comparison of clinical characteristics in patients who did and did not develop end-stage renal disease (ESRD)

	With ESRD ($n = 7$)	Without ESRD ($n = 48$)	P value
Age at the time of diagnosis (years)	59.0 ± 12.6	59.3 ± 13.9	0.952
Male	4 (57.1)	28 (60.4)	1.000
Follow-up duration (months)	40.4 ± 50.1	46.9 ± 38.9	0.693
Dead	0 (0)	6 (15.4)	1.000
Laboratory findings			
White cell counts (/mm^3)	12,830.0 ± 6,408.8	12,028.4 ± 4,006.2	0.757
Hemoglobin (g/dl)	8.3 ± 1.46	10.3 ± 2.2	0.027
CRP (mg/dl)	16.9 ± 8.7	8.3 ± 7.1	0.005
ESR (mm/hr)	107.7 ± 35.1	70.8 ± 35.6	0.013
Creatinine	8.93 ± 3.18	1.88 ± 1.58	0.001>
Estimated Creatinine clearance	7.08 ± 2.71	51.46 ± 34.28	0.001>
Albumin	2.39 ± 0.42	2.89 ± 0.69	0.021
p-ANCA	5 (83.3)	33 (68.8)	0.657
Complement 4	38.9 ± 16.6	24.4 ± 12.1	0.021
BVAS	14.6 ± 2.8	10.4 ± 5.0	0.002
FFS	1.9 ± 0.4	0.9 ± 0.9	0.001>
Constitutional symptoms	6 (85.7)	37 (77.1)	1.000
Weight loss	2 (28.6)	22 (45.8)	0.451
Fever	5 (71.4)	27 (56.3)	0.686
Fatigue	4 (57.1)	13 (27.1)	0.185
Musculoskeletal	4 (57.1)	33 (68.8)	0.671
Arthralgia	2 (28.6)	19 (39.6)	0.696
Myalgia	4 (57.1)	22 (45.8)	0.696
Skin manifestations	1 (14.3)	27 (56.3)	0.051
Purpura	0 (0)	6 (12.5)	1.000
Livedo reticularis	0 (0)	8 (16.7)	0.577
Nodules	0 (0)	3 (6.3)	1.000
Digital ischemia	0 (0)	4 (8.3)	1.000
Neurologic	1 (14.3)	23 (47.9)	0.122
CNS involvement	0 (0)	5 (10.4)	1.000
Peripheral neuropathy	1 (14.3)	21 (43.8)	0.223
Mononeuritis multiplex	1 (14.3)	19 (39.6)	0.402
Sinusitis	3 (42.9)	12 (25.0)	0.376
Cardiovascular	2 (28.6)	8 (16.7)	0.599
Hypertension	1 (14.3)	8 (16.7)	1.000
Cardiomyopathy	0 (0)	2 (4.2)	1.000
Pericarditis	1 (14.3)	1 (2.1)	0.240
Respiratory	6 (85.7)	17 (35.4)	0.017
Alveolar hemorrhage	1 (14.3)	3 (6.3)	0.429
Pneumonitis	1 (14.3)	0 (0)	0.127
Pleuritis	3 (42.9)	4 (8.3)	0.037
Interstitial lung disease	2 (28.6)	11 (22.9)	0.664
Gastrointestinal involvement	1 (14.3)	10 (20.8)	1.000

Unless otherwise indicated, values are frequencies (percentages) or means ± SD (standard deviation)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *p-ANCA* perinuclear antineutrophil cytoplasmic antibody, *FFS* five factor score, *BVAS* Birmingham vasculitis activity score

ences in clinical manifestations were found compared with previous studies, according to ethnics and geographical area. The clinical outcomes in our study appeared to be higher than that reported previously. Our findings confirm earlier published results that older age, higher BVAS, and cardiac involvement were important risk factors for death. Furthermore, we identified ILD to be the new risk factor for death in this study.

Conflicts of interest No conflict of interest has been declared by the authors.

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