

RESEARCH ARTICLE

Multivariable index for assessing the activity and predicting all-cause mortality in antineutrophil cytoplasmic antibody-associated vasculitis

Minyoung Kevin Kim¹  | Hyeok Choi¹  | Jae Yeon Kim¹  | Jason Jungsik Song^{2,3}  |
Yong-Beom Park^{2,3}  | Sang-Won Lee^{2,3} 

¹Department of Medicine, Yonsei University College of Medicine, Seoul, Korea

²Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

³Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea

Correspondence

Sang-Won Lee, Division of Rheumatology, Department of Internal Medicine, Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Email: sangwonlee@yuhs.ac

Funding information

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2017R1D1A1B03029050) and 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).

Abstract

Background: So far, there has been no tool to estimate activity at diagnosis and predict all-cause mortality in patients with ANCA-associated vasculitis (AAV). Hence, we determined the initial predictors of them in patients with AAV.

Methods: We retrospectively reviewed the medical records of 182 patients with AAV. Severe AAV was defined as Birmingham Vasculitis Activity Score (BVAS) ≥ 16 . The cutoffs were extrapolated by the receiver operator characteristic (ROC) curve. The odds ratio (OR) and the relative risk (RR) were assessed using the multivariable logistic regression analysis and the chi-square test, respectively.

Results: In the comparison analysis, patients with severe AAV exhibited the higher neutrophil and platelet counts, creatinine, erythrocyte sedimentation rate and C-reactive protein, and the lower lymphocyte count, hemoglobin, and serum albumin than those without. In the multivariable logistic regression analysis, creatinine ≥ 0.9 mg/dL (OR 2.264), lymphocyte count $\leq 1430.0/\text{mm}^3$ (OR 1.856), and hemoglobin ≤ 10.8 g/dL (OR 2.085) were associated with severe AAV. We developed a new equation of a multivariable index for AAV (MVIA) = $0.6 \times (\text{Lymphocyte count} \leq 1430.0/\text{mm}^3) + 0.7 \times (\text{Hemoglobin} \leq 10.8 \text{ g/dL}) + 0.8 \times (\text{Creatinine} \geq 0.9 \text{ mg/dL})$. The optimal cutoff of MVIA for severe AAV was set as 1.35. Severe AAV was identified more frequently in patients with MVIA at diagnosis ≥ 1.35 than those without (RR 4.432). Patients with MVIA at diagnosis ≥ 1.35 exhibited the lower cumulative patient survival rate than those without.

Conclusion: Multivariable index for AAV could assess the cross-sectional activity and predict all-cause mortality in patients with AAV.

KEYWORDS

activity, ANCA-associated vasculitis, multivariable index, prognosis

1 | INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of three systemic vasculitides involving small vessels, such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) according to the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis (the 2012 CHCC definitions).¹ On the basis of small-vessel necrotizing vasculitis, MPA mainly provokes necrotizing glomerulonephritis and pulmonary capillaritis and GPA often causes granuloma formation of the upper and lower respiratory tracts and occasionally necrotizing glomerulonephritis. Meanwhile, EGPA is characterized by three typical allergic components including asthma, peripheral eosinophilia, and eosinophil-rich granuloma of the respiratory tracts.^{1,2}

A natural history of AAV was previously reported. The first-year and the second-year mortality rates were 82% and 90%, and the main etiology of mortality was uremia as a result of rapidly progressive glomerulonephritis.³ As various therapeutic regimens were developed and widely used, the first-year mortality rate was remarkably decreased to <10%-20%.^{4,5} Nevertheless, any delayed initiation of induction therapy for severe AAV potentially causes irreversible organ damages, which is eventually jeopardizing the quality of life. Therefore, the early diagnosis and treatment for AAV are required and the proper selection of therapeutic regimens should be carefully chosen based on the stage of the disease and its severity. Furthermore, the first treatment should be targeted for induction of remission.²

Birmingham Vasculitis Activity Score (BVAS) has been used for assessing the activity and severity of AAV, and it was reportedly associated with the poor prognosis of AAV.^{6,7} Five-factor score (FFS; 2009) was also used to predict the poor prognosis.⁸ Besides BVAS and FFS (2009), several other indices have been applied to Korean patients with AAV, in order to estimate AAV activity at diagnosis and predict the poor prognosis. However, there has been no tool to estimate AAV activity at diagnosis and predict all-cause mortality in patients with AAV, and thus, there has been a great need for a new AAV-specific index for assessing the cross-sectional activity at diagnosis and predicting the prognosis during follow-up in patients with AAV. To elucidate these issues, in this study, we screened variables at diagnosis which were associated with severe AAV and determined the initial predictors of the cross-sectional activity at diagnosis and all-cause mortality during follow-up in immunosuppressive drug-naïve patients with AAV.

2 | MATERIALS AND METHODS

2.1 | Patients

We retrospectively screened the medical records of 209 patients with AAV and reviewed those of 182 patients with AAV, who met the conditions as follows: (a) the first classification as AAV at the Division of Rheumatology, the Department of Internal Medicine,

Yonsei University College of Medicine, Severance Hospital from October 2000 to April 2018; (b) the fulfillment of the American College of Rheumatology 1990 criteria for GPA and EGPA and then the reclassification as AAV by the 2007 European Medicines Agency algorithm and the 2012 CHCC definitions^{1,9-11}; (c) the follow-up duration of at least three months or greater; (d) the well-documented medical records precise enough to assess calculate BVAS and FFS (2009)^{6,8}; (e) the presence of the results of perinuclear (P)-ANCA and cytoplasmic (C)-ANCA or myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA at diagnosis¹²; (f) no other medical conditions at diagnosis to confuse the classification of AAV, which were identified by the 10th revised International Classification of Diseases (ICD-10)¹³; and (g) no history of immunosuppressive drugs prior to or at diagnosis of AAV, which was verified by the Korean Drug Utilisation Review (DUR) system. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), and the patient's written informed consent was waived by the approving IRB, as this was a retrospective study.

2.2 | Data at diagnosis of AAV

We obtained age at diagnosis and gender in patients with AAV. We reviewed clinical manifestations and laboratory data at diagnosis and then calculated BVAS and FFS (2009). We collected laboratory results at diagnosis, such as white blood cell, neutrophil, lymphocyte and platelet counts, hemoglobin, prothrombin time (international normalized ratio, INR), fasting glucose, blood urea nitrogen, creatinine, total protein, serum albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

2.3 | Data during follow-up

We defined the follow-up duration as the period from diagnosis to the last visit for patients with remission and/or survived patients, and we defined it as the period from diagnosis to death for deceased patients. Since chronic kidney disease, end-stage renal disease, ischemic heart disease, congestive heart failure, interstitial lung disease, and cerebrovascular disease belong to items of BVAS, we also counted the number of patients with diabetes mellitus and hypertension among comorbidities. We reviewed the administration of immunosuppressive drugs during follow-ups such as glucocorticoid, cyclophosphamide, azathioprine, rituximab, methotrexate, mycophenolate mofetil, and tacrolimus. Death was defined as all-cause mortality.

2.4 | Severe AAV

We stratified patients with AAV into three groups based on the tertile of BVAS and defined the lower limit of the highest tertile as the cutoff for the current severe AAV (BVAS at diagnosis ≥ 16).

2.5 | Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp). Continuous variables were expressed as a median (interquartile range, IQR), and categorical variables were expressed as number and the percentage. Significant differences in categorical variables between the two groups were analyzed using chi-square and Fisher's exact tests. Significant differences in continuous variables between the two groups were compared using the Mann-Whitney test. The optimal cutoffs of laboratory variables at diagnosis for severe AAV were extrapolated by calculating the area under the receiver operator characteristic curve (AUROC) and selecting the point to maximize the sum of sensitivity and specificity. The odds ratio (OR) was assessed using the multivariable logistic regression analysis of variables with P values $< .05$ on the univariable logistic regression analysis. The relative risk (RR) of the optimal cutoff was analyzed using contingency tables and the chi-square test. Comparison of cumulative patient survival between the two groups was analyzed by the Kaplan-Meier survival analysis. In this study, P values less than 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics of patients with AAV

Demographic, clinical, and laboratory data at diagnosis of AAV were described in Table 1. The most common clinical manifestation at diagnosis was renal involvement (58.2%), followed by pulmonary involvement (56.0%). The median BVAS and FFS (2009) at diagnosis were 12.0 (11.0) and 1.0 (1.0), respectively. The median values of laboratory results were shown in Table 1. During the follow-up of the median duration of 39.5 (72.0) months, 36 patients (19.8%) had diabetes mellitus and 76 patients (41.8%) had hypertension. The most frequently administered immunosuppressive drug was glucocorticoid (86.8%), followed by cyclophosphamide (41.8%) and azathioprine (53.3%). Fifteen patients (8.2%) died of all etiologies during follow-up (Table 1).

3.2 | Comparison of laboratory variables at diagnosis between AAV patients with and without severe AAV

Sixty-three patients had BVAS more than 16 and were classified as severe AAV. There were no differences in age and gender between the two groups. Because clinical manifestations at diagnosis were based on all items of BVAS, as was expected, patients with BVAS at diagnosis ≥ 16 exhibited the higher frequencies of renal, pulmonary, general, cardiovascular, and gastrointestinal manifestations than those without. Compared with non-severe AAV patients, patients with severe AAV had the increased median neutrophil count, platelet count, blood urea nitrogen, creatinine, ESR, and CRP than those without. On the other hands, patients with severe AAV exhibited the lower median lymphocyte count, hemoglobin, and serum albumin than those

without (Table 2). As there was collinearity between blood urea nitrogen and creatinine, we excluded it in the following analyses.

3.3 | Optimal cutoffs of laboratory variables for severe AAV at diagnosis

We obtained the optimal cutoffs of laboratory variables at diagnosis for severe AAV, which were significant in the comparative analysis between patients with and without severe AAV. The optimal cutoffs of variables are as below: neutrophil count $\geq 7570.0/\text{mm}^3$; lymphocyte count $\leq 1430.0/\text{mm}^3$; hemoglobin $\leq 10.8 \text{ g/dL}$; platelet count $\geq 352\ 500.0/\text{mm}^3$; creatinine $\geq 0.9 \text{ mg/dL}$; serum albumin $\leq 3.5 \text{ g/dL}$; ESR $\geq 83.5 \text{ mm/h}$; and CRP $\geq 20.0 \text{ mg/L}$ (Table S1). Although platelet count exhibited no statistical significance (area 0.568, 95% confidence interval (CI) 0.475, 0.661), we included platelet count $\geq 352\ 500.0/\text{mm}^3$ in the logistic regression analyses, because it significantly differed between patients with and without severe AAV in the comparison analysis.

3.4 | Univariable and multivariable logistic regression analyses for severe AAV at diagnosis

Since there were no significant differences in age at diagnosis and gender between the two groups, we did not include them in the univariable and multivariable logistic regression analyses. In the univariable logistic regression analysis of laboratory variables at diagnosis for severe AAV, all laboratory variables with significance in the comparative analysis exhibited significant ORs: neutrophil count $\geq 7570.0/\text{mm}^3$ (OR 2.499); lymphocyte count $\leq 1430.0/\text{mm}^3$ (OR 2.664); hemoglobin $\leq 10.8 \text{ g/dL}$ (OR 4.348); platelet count $\geq 352\ 500.0/\text{mm}^3$ (OR 2.325); creatinine $\geq 0.9 \text{ mg/dL}$ (OR 3.536); serum albumin $\leq 3.5 \text{ g/dL}$ (OR 2.770); ESR $\geq 83.5 \text{ mm/h}$ (OR 3.051); and CRP $\geq 20.0 \text{ mg/L}$ (OR 2.770; Table 3). In the multivariable logistic regression analysis of laboratory variables at diagnosis for severe AAV, only creatinine $\geq 0.9 \text{ mg/dL}$ was significantly associated with severe AAV at diagnosis (OR 2.264, 95% CI 1.107, 5.040). In addition, lymphocyte count $\leq 1430.0/\text{mm}^3$ and hemoglobin $\leq 10.8 \text{ g/dL}$ also tended to be associated with severe AAV at diagnosis (OR 1.856, 95% CI 0.906, 3.804 and OR 2.085, 95% CI 0.917, 4.737, respectively; Table 3). We derived an equation of a multivariable index for AAV (MVIA) using lymphocyte count, hemoglobin, and creatinine with P value $< .01$ in the multivariable logistic regression analysis.

3.5 | Equation of MVIA

We assigned a weight of a number close to an integer to each variable according to the slopes for independent variable with P value $< .1$ in the multivariable logistic regression analysis: $B = 0.6$ for Lymphocyte $\leq 1430.0/\text{mm}^3$, $B = 0.7$ for Hemoglobin $\leq 10.8 \text{ g/dL}$, and $B = 0.8$ for Creatinine $\geq 0.9 \text{ mg/dL}$ (Table 3). And we developed a new equation as follows: a multivariable index for AAV (MVIA) = $0.6 \times (\text{Lymphocyte} \leq 1430.0/\text{mm}^3: \text{yes} = 1 \text{ or no} = 0) + 0.7 \times (\text{Hemoglobin} \leq 10.8 \text{ g/dL}: \text{yes} = 1 \text{ or no} = 0) + 0.8 \times (\text{Creatinine} \geq 0.9 \text{ mg/dL}: \text{yes} = 1$

TABLE 1 Characteristics of 182 patients with AAV at diagnosis and during follow-up

Variables	Values
At diagnosis	
Demographic data at diagnosis	
Age (year old)	58.5 (21.0)
Male gender (N, [%])	55 (30.2)
Variants of AAV	
MPA	97 (53.3)
GPA	45 (24.7)
EGPA	40 (22.0)
ANCA at diagnosis (N, [%])	
MPO-ANCA (or P-ANCA)	117 (64.3)
PR3-ANCA (or C-ANCA)	30 (16.5)
MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)	9 (4.9)
ANCA negativity	44 (24.2)
Clinical manifestations at diagnosis (N, [%])	
Renal	106 (58.2)
Pulmonary	102 (56.0)
General	80 (44.0)
Ear Nose Throat	68 (37.4)
Nervous system	56 (30.8)
Cardiovascular	47 (25.8)
Cutaneous	41 (22.5)
Mucous membranes/eyes	12 (6.6)
Gastrointestinal	10 (5.5)
Vasculitis activity and prognostic factors at diagnosis	
BVAS or BVAS for GPA	12.0 (11.0)
FFS (2009)	1.0 (1.0)
Laboratory results at diagnosis	
White blood cell (/mm ³)	9260.0 (6425.0)
Neutrophil (/mm ³)	6510.0 (6000.0)
Lymphocyte (/mm ³)	1480.0 (980.0)
Hemoglobin (g/dL)	11.6 (3.7)
Platelet (×1000/mm ³)	307.5 (164.5)
Prothrombin time (INR)	1.0 (0.2)
Fasting glucose (mg/dL)	101.0 (34.0)
Blood urea nitrogen (mg/dL)	17.4 (19.4)
Creatinine (mg/dL)	1.0 (1.3)
Total protein (g/dL)	6.6 (1.3)
Serum albumin (g/dL)	3.6 (1.1)
Alkaline phosphatase (IU/L)	68.5 (37.3)
Aspartate aminotransferase (IU/L)	18.0 (8.0)
Alanine aminotransferase (IU/L)	15.0 (14.0)
Total bilirubin (mg/dL)	0.5 (0.2)
ESR (mm/h)	57.5 (70.0)

(Continues)

TABLE 1 (Continued)

Variables	Values
CRP (mg/L)	14.5 (60.2)
During follow-up	
Follow-up duration (mo)	39.5 (72.0)
Comorbidities (N, [%])	
Diabetes mellitus	36 (19.8)
Hypertension	76 (41.8)
Immunosuppressive drugs (N, [%])	
Glucocorticoid	158 (86.8)
Cyclophosphamide	76 (41.8)
Azathioprine	97 (53.3)
Rituximab	19 (10.4)
Methotrexate	13 (7.1)
Mycophenolate mofetil	10 (5.5)
Tacrolimus	9 (4.9)
Prognosis (N, [%])	
All-cause mortality	15 (8.2)

Note: Values are expressed as a median (interquartile range [IQR]) or N (%). Abbreviations: AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; C-ANCA, cytoplasmic ANCA; CRP, C-reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; FFS, five-factor score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P-ANCA, perinuclear ANCA; PR3, proteinase 3; WBC, white blood cell.

or no = 0). For instance, if a patient had lymphocyte $\leq 1430.0/\text{mm}^3$, hemoglobin ≤ 10.8 g/dL, and creatinine ≥ 0.9 mg/dL, that patient would have MVIA of 2.1 ($0.6 \times 1 + 0.7 \times 1 + 0.8 \times 1$).

3.6 | Optimal cutoff of MVIA for severe AAV

The median calculated MVIA was 0.8 with IQR of 1.5. The maximum and minimum MVIA were 2.1 and 0, respectively. MVIA was positively correlated with BVAS at diagnosis ($r = 0.370$, $P < .001$). We also obtained the optimal cutoff of MVIA for severe AAV as 1.35 (sensitivity 0.667 and specificity 0.689) using the AUROC curve (area 0.727, 95% CI 0.648, 0.805; Figure 1A). When we divided patients with AAV into the two groups based on the optimal cutoff of MVIA for severe AAV, 79 patients belonged to the group of MVIA at diagnosis ≥ 1.35 . The cross-sectional severe AAV appeared more frequently in patients with MVIA at diagnosis ≥ 1.35 than those without (53.2% vs 20.4%, $P < .001$). In addition, patients with MVIA at diagnosis ≥ 1.35 exhibited a significantly high RR for severe AAV at diagnosis, compared to those without (RR 4.432, 95% CI 2.309, 8.507; Figure 1B).

3.7 | Cumulative patient survival rate

We investigated the cumulative patient survival rate during follow-up between patients with and without MVIA at diagnosis ≥ 1.35 .

TABLE 2 Comparison of laboratory variables at diagnosis between AAV patients with and without BVAS at diagnosis ≥ 16

Variables	Patients with BVAS at diagnosis ≥ 16 (N = 63)	Patients with BVAS at diagnosis < 16 (N = 119)	P value
Demographic data at diagnosis			
Age (year old)	62.0 (23.0)	56.0 (21.0)	.057
Male gender (N, [%])	16 (25.4)	39 (32.8)	.303
Clinical manifestations at diagnosis (N, [%])			
Renal	55 (87.3)	51 (42.9)	<.001
Pulmonary	42 (66.7)	60 (50.4)	.036
General	39 (61.9)	41 (34.5)	<.001
Ear Nose Throat	21 (33.3)	47 (39.5)	.414
Nervous system	23 (36.5)	33 (27.7)	.222
Cardiovascular	28 (44.4)	19 (16.0)	<.001
Cutaneous	16 (25.4)	25 (21.0)	.500
Mucous membranes/ eyes	4 (6.3)	8 (6.7)	.923
Gastrointestinal	7 (11.1)	3 (2.5)	.016
Laboratory results at diagnosis			
White blood cell (/mm ³)	10 470.0 (7210.0)	9040.0 (5600.0)	.097
Neutrophil (/mm ³)	7640.0 (6000.0)	5440.0 (5000.0)	.025
Lymphocyte (/mm ³)	1210.0 (780.0)	1580.0 (980.0)	.033
Hemoglobin (g/dL)	9.9 (3.2)	12.3 (3.1)	<.001
Platelet ($\times 1000/\text{mm}^3$)	337.0 (256.5)	301.0 (143.5)	.032
Prothrombin time (INR)	1.0 (0.2)	1.0 (0.2)	.310
Fasting glucose (mg/dL)	100.0 (33.0)	101.0 (34.0)	.896
Blood urea nitrogen (mg/dL)	24.6 (23.8)	15.2 (11.8)	.002
Creatinine (mg/dL)	1.4 (2.1)	1.2 (0.7)	.010
Total protein (g/dL)	6.4 (1.2)	6.8 (1.1)	.910
Serum albumin (g/dL)	3.3 (1.4)	3.8 (1.1)	<.001
Alkaline phosphatase (IU/L)	68.0 (40.0)	69.0 (35.0)	.745
Aspartate aminotransferase (IU/L)	17.0 (9.0)	18.0 (8.0)	.468
Alanine aminotransferase (IU/L)	14.0 (16.0)	17.0 (13.3)	.751
Total bilirubin (mg/dL)	0.4 (0.3)	0.5 (0.2)	.361
ESR (mm/h)	69.0 (88.0)	49.0 (59.0)	.005
CRP (mg/L)	27.2 (90.0)	7.5 (41.7)	.015

Note: Values are expressed as a median (interquartile range [IQR]) or N (%).

Abbreviations: AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

^aBecause blood urea nitrogen is closely related to creatinine, we included only creatinine in the analysis.

Patients with MVIA at diagnosis ≥ 1.35 exhibited the lower cumulative patient survival rate than those with MVIA <1.35 ($P = .006$). We also applied the Kaplan-Meier survival analysis to all laboratory variables having optimal cutoffs and found only hemoglobin at diagnosis ≤ 10.8 g/dL was significantly associated with all-cause mortality in patients with AAV ($P = .006$; Figure 2).

4 | DISCUSSION

In this study, we derived a new equation of MVIA using laboratory variables significantly associated with severe AAV at diagnosis and successfully documented that MVIA could assess the cross-sectional activity and severity at diagnosis and predict all-cause mortality during follow-up in immunosuppressive drug-naïve patients with AAV. First, our findings suggest that patients with severe AAV exhibited the higher median neutrophil count, platelet count, creatinine, ESR, and CRP, and showed the lower median lymphocyte count, hemoglobin, and serum albumin than those without. Second, we obtained the optimal cutoff of each variable with significance in the comparative analysis using the AUROC curve. Third, in the univariable and multivariable logistic regression analysis, we found that lymphocyte count $\leq 1430.0/\text{mm}^3$, hemoglobin ≤ 10.8 g/dL, and creatinine ≥ 0.9 mg/dL were meaningfully associated with the cross-sectional severe AAV. Using these three variables at diagnosis, we derived a new equation of MVIA. The optimal cutoff of MVIA for severe AAV was identified as 1.35. Fourth, the cross-sectional severe AAV was identified more frequently in patients with MVIA at diagnosis ≥ 1.35 than those without (RR 4.432, 95% CI 2.309, 8.507). Fifth, in the survival analysis, MVIA at diagnosis ≥ 1.35 was significantly associated with all-cause mortality during follow-up.

Among variables routinely measured at each visit in the clinics, in the univariable analysis, eight variables were associated with severe AAV, and furthermore, in the multivariable analysis, creatinine at diagnosis ≥ 0.9 mg/dL alone was statistically highly associated with severe AAV. In addition, lymphocyte count $\leq 1430.0/\text{mm}^3$ and hemoglobin ≤ 10.8 g/dL also tended to be associated with severe AAV at diagnosis. We explored an index with more than two variables including lymphocyte count $\leq 1430.0/\text{mm}^3$, hemoglobin ≤ 10.8 g/dL, and creatinine ≥ 0.9 mg/dL to offset against the high variability in one variable, which eventually could be more stable and reliable. For these reasons, MVIA showed the highest area for severe AAV in the multivariable AUROC curve (area 0.678, 95% CI 0.595, 0.761), compared with other eight variables at diagnosis (Figure S1).

Why did we need to calculate MVIA at diagnosis, in addition to BVAS at diagnosis? We wondered whether patients with AAV in the present study received the proper induction and maintenance therapies based on the cross-sectional activity.^{2,14} When we divided patients with AAV into the two groups based on MVIA at diagnosis ≥ 1.35 , 79 patients belonged to the group of MVIA at diagnosis ≥ 1.35 . We compared the use of cyclophosphamide, rituximab,

TABLE 3 Logistic regression analyses for severe AAV at diagnosis

Variables at diagnosis	Univariable			Multivariable			
	OR	95% CI	P value	B	OR	95% CI	P value
Neutrophil $\geq 7570.0/\text{mm}^3$	2.499	1.334, 4.681	.004	0.332	1.394	0.627, 3.099	.416
Lymphocyte $\leq 1430.0/\text{mm}^3$	2.664	1.418, 5.007	.002	0.619	1.856	0.906, 3.804	.091
Hemoglobin ≤ 10.8 g/dL	4.348	2.272, 8.320	.001	0.735	2.085	0.917, 4.737	.079
Platelet $\geq 352\ 500.0/\text{mm}^3$	2.325	1.236, 4.374	.009	0.448	1.566	0.624, 3.931	.340
Creatinine ≥ 0.9 mg/dL	3.536	1.805, 6.926	<.001	0.817	2.264	1.107, 5.040	.045
Serum albumin ≤ 3.5 g/dL	2.770	1.475, 5.202	.002	0.035	1.036	0.457, 2.348	.933
ESR ≥ 83.5 mm/h	3.051	1.578, 5.898	.001	0.507	1.660	0.682, 4.045	.264
CRP ≥ 20.0 mg/L	2.770	1.475, 5.202	.002	0.023	1.023	0.427, 2.452	.960

Abbreviations: AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

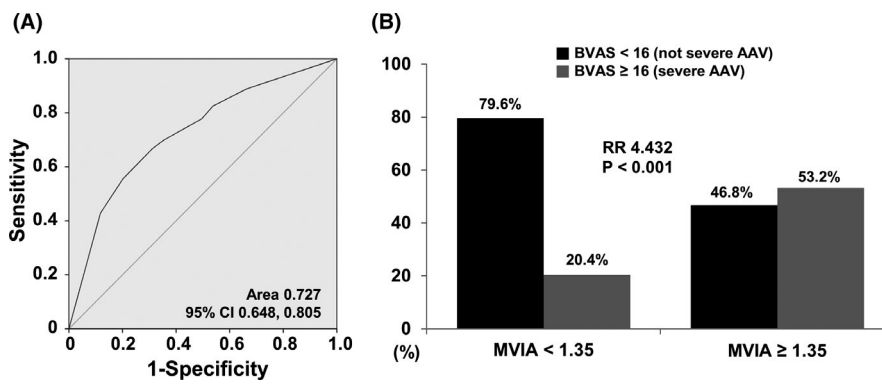


FIGURE 1 Optimal cutoff of MVIA for severe AAV. A, The optimal cutoff of MVIA at diagnosis for severe AAV was obtained as 1.35 (sensitivity 0.667 and specificity 0.689). B, Patients with MVIA at diagnosis ≥ 1.35 exhibited a significantly high RR for severe AAV at diagnosis, compared to those without (RR 4.432, 95% CI 2.309, 8.507). AAV, antineutrophil cytoplasm antibody (ANCA)-associated vasculitis; CI, confidence interval; MVIA, a multivariable index for AAV; RR, relative risk

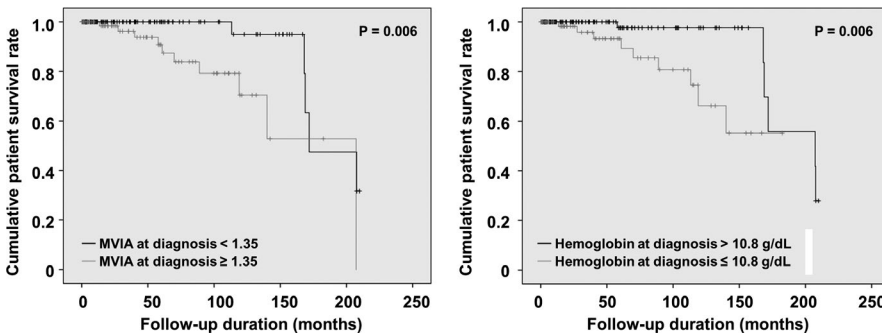


FIGURE 2 All-cause mortality rate. Patients with MVIA at diagnosis ≥ 1.35 ($P = .006$) and hemoglobin at diagnosis ≤ 10.8 g/dL ($P = .006$) were significantly associated with all-cause mortality in AAV patients. AAV, antineutrophil cytoplasm antibody (ANCA)-associated vasculitis; MVIA, a multivariable index for AAV

and azathioprine between patients with MVIA at diagnosis ≥ 1.35 and those without. Cyclophosphamide was administered to patients with MVIA at diagnosis ≥ 1.35 more frequently than those without (44.7% vs 29.1%, $P < .001$). Rituximab was evenly administered to both groups. Because only one cycle of rituximab in the whole life can be covered by the Korean National Health Insurance, rituximab might be administered as an induction therapeutic regimen. Azathioprine was also administered to patients with MVIA at diagnosis ≥ 1.35 more frequently than those without (64.6% vs 44.7%, $P < .001$). If we had serially noticed the severity of AAV, more aggressive therapies could

have been applied to patients with the high severity of AAV. This further highlights our study that MVIA at diagnosis could be used as a supplementary index for severe AAV. In the clinical settings, BVAS might be affected by subjective complaints, such as myalgia or arthralgia, and it needs more tests including echocardiography in a patient suspected of myocarditis. However, since MVIA consists of only laboratory variables, which are routinely measured at every visit, it is more convenient to evaluate the severity of AAV. And furthermore, if we develop an automatic calculator of MVIA, severe AAV based on BVAS may be rapidly and promptly assessed.

So why does MVIA at diagnosis reflects severe AAV based on BVAS at diagnosis? We guessed that MVIA may estimate severe AAV well because its parameters could reflect severe AAV (the high activity of AAV) better than other laboratory values. First, lymphocyte count may also be affected by general health and stress or various autoimmune diseases and we previously proved the lower number of lymphocyte in severe AAV compared with non-severe AAV.¹⁵ Second, the reduced hemoglobin was reported to be one of systemic complication of AAV.¹⁶ Third, serum creatinine level is already included in BVAS as one item, and thus, it is naturally accepted that the serum level of creatinine might be correlated with BVAS well.⁶

We found that MVIA at diagnosis ≥ 1.35 was significantly associated with all-cause mortality. Although the poor prognosis includes various clinical situations such as relapse, renal survival, and all-cause mortality, we assessed only all-cause mortality in this study. For, in our retrospective AAV cohort, the clinical significance of BVAS at diagnosis exhibited the difference patterns according to AAV variants: BVAS was associated with relapse of MPA and refractory disease of GPA, but not with the prognosis of EGPA. In this study, BVAS at diagnosis ≥ 16 could not predict all-cause mortality in patients with AAV. Whereas, patients with FFS (2009) at diagnosis ≥ 2 exhibited the higher all-cause mortality rate than those without during follow-up ($P = .001$), which is compatible with our previous study.¹⁷⁻¹⁹ On the other hand, MVIA at diagnosis ≥ 1.35 was significantly associated with all-cause mortality. In fact, the cutoff of MVIA at diagnosis was derived from severe AAV based on BVAS at diagnosis ≥ 16 but not based on all-cause mortality. Nevertheless, MVIA at diagnosis ≥ 1.35 indeed predicted all-cause mortality. We assumed that during follow-up, the effects of each of BVAS items and MVIA variables on all-cause mortality might have been different. It is assumed that the variables of MVIA may have been essential parameters for predicting all-cause mortality compared with all items of BVAS. As a result, MVIA at diagnosis could assess the cross-sectional activity and predict all-cause mortality better than BVAS at diagnosis.

We also focused on FFS at diagnosis ≥ 2 , developed another new equation of MVIA based on FFS at diagnosis and the predictive value for all-cause mortality between MVIA based on BVAS and that based on FFS at diagnosis. We obtained the optimal cutoffs of laboratory variables at diagnosis for FFS at diagnosis ≥ 2 . The optimal cutoffs of variables are as below: neutrophil count $\geq 7570.0/\text{mm}^3$; lymphocyte count $\leq 1475.0/\text{mm}^3$; hemoglobin $\leq 10.8 \text{ g/dL}$; creatinine $\geq 1.16 \text{ mg/dL}$; serum albumin $\leq 3.65 \text{ g/dL}$; and CRP $\geq 39.35 \text{ mg/L}$ (Table S2). In the univariable logistic regression analysis, significant ORs for FFS at diagnosis ≥ 2 were found in all variables with the significant cutoffs. In the multivariable logistic regression analysis, neutrophil $\geq 7570.0/\text{mm}^3$, hemoglobin $\leq 10.8 \text{ g/dL}$, and creatinine $\geq 1.16 \text{ mg/dL}$ were significantly associated with FFS at diagnosis ≥ 2 (Table S3). We assigned a weight to each variable according to the slopes and expressed another new MVIA based on FFS at diagnosis = $1.2 \times (\text{Neutrophil} \geq 7570.0/\text{mm}^3: \text{yes} = 1 \text{ or no} = 0) + 1.6 \times (\text{Hemoglobin} \leq 10.8 \text{ g/dL}: \text{yes} = 1 \text{ or no} = 0) + 1.9 \times (\text{Creatinine} \geq 1.16 \text{ mg/dL}: \text{yes} = 1 \text{ or no} = 0)$. In

addition, we obtained the optimal cutoff of MVIA for FFS at diagnosis ≥ 2 as 1.75 (sensitivity 0.667 and specificity 0.689) using the AUROC curve (area 0.850; Figure S2). We found that MVIA based on FFS at diagnosis ≥ 1.75 exhibited no significant difference in patient survival rate from MVIA based on FFS at diagnosis < 1.75 ($P = .072$; Figure S3). Therefore, we conclude that MVIA based on BVAS at diagnosis ≥ 1.35 could predict all-cause mortality during follow-up in patients with AAV than MVIA based on FFS at diagnosis ≥ 1.75 .

Our study has several limitations. This study is based on study population that was not large enough to represent the clinical data of all-Korean patients with AAV. Also, due to the retrospective study design, the usefulness of MVIA was not explored for assessing the serially changing the cross-sectional activity and severity of AAV under the administration of immunosuppressive drugs. However, we hope that future nationwide prospective studies with a larger number of patients with AAV could overcome all of these issues.

Our study has several merits. We have first developed an AAV-specific index for assessing the cross-sectional activity and severity and predicting all-cause mortality in patients with AAV. Because we included patients, who had been classified as AAV at the same department of one tertiary hospital, our study was able to minimize the inter-centric variation. Also, our institute is one of the biggest tertiary university hospitals in Korea, and furthermore, our AAV cohort is the only one in Korea. So, almost all the patients are transferred to our institute when a situation occurs requiring consideration of death in patients with AAV. In addition, we tried to contact patients with AAV, who were not followed up, by phone and so we could precisely confirm all-cause mortality, although the causes of death were not known in all patients. Lastly, given that the clinical features and the prognosis of AAV may vary based on geographical and ethnic differences, this study first demonstrated the clinical implication of MVIA in Korean patients with AAV.

5 | CONCLUSION

A new AAV-specific MVIA could assess the cross-sectional activity and severity and predict all-cause mortality in immunosuppressive drug-naïve patients with AAV during follow-up.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICAL APPROVAL

For this retrospective type of study, formal consent is waived.

ORCID

Minyoung Kevin Kim  <https://orcid.org/0000-0003-4826-3232>
 Hyeok Choi  <https://orcid.org/0000-0001-5944-4413>
 Jae Yeon Kim  <https://orcid.org/0000-0003-0208-3121>
 Jason Jungsik Song  <https://orcid.org/0000-0003-0662-7704>
 Yong-Beom Park  <https://orcid.org/0000-0003-4695-8620>
 Sang-Won Lee  <https://orcid.org/0000-0002-8038-3341>

REFERENCES

- Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.
- Kallenberg CG. Key advances in the clinical approach to ANCA-associated vasculitis. *Nat Rev Rheumatol*. 2014;10(8):484-493.
- Berden A, Goceroglu A, Jayne D, et al. Diagnosis and management of ANCA associated vasculitis. *BMJ*. 2012;344:e26.
- Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. *Ann Rheum Dis*. 2017;76(9):1566-1574.
- Mun CH, Yoo J, Jung SM, Song JJ, Park YB, Lee SW. The initial predictors of death in 153 patients with ANCA-associated vasculitis in a single Korean centre. *Clin Exp Rheumatol*. 2018;36:65-72.
- Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham vasculitis activity score (version 3). *Ann Rheum Dis*. 2009;68(12):1827-1832.
- Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis*. 2011;70(3):488-494.
- Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. 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(1):19-27.
- Leavitt RY, Fauci AS, Bloch DA, et al. The American college of rheumatology 1990 criteria for the classification of Wegener's granulomatosis. *Arthritis Rheum*. 1990;33(8):1101-1107.
- Masi AT, Hunder GG, Lie JT, et al. The American college of rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum*. 1990;33(8):1094-1100.
- 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(2):222-227.
- Csernok E, Moosig F. Current and emerging techniques for ANCA detection in vasculitis. *Nat Rev Rheumatol*. 2014;10(8):494-501.
- Noel N, André C, Bengoufa D, et al. Performance evaluation of three assays for the detection of PR3-ANCA in granulomatosis with polyangiitis in daily practice. *Autoimmun Rev*. 2013;12(12):1118-1122.
- 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(8):1273-1279.
- Ahn SS, Jung SM, Song JJ, Park YB, Lee SW. Neutrophil to lymphocyte ratio at diagnosis can estimate vasculitis activity and poor prognosis in patients with ANCA-associated vasculitis: a retrospective study. *BMC Nephrol*. 2018;19(1):187.
- Kawamura T, Usui J, Kaneko S, et al. Anaemia is an essential complication of ANCA-associated renal vasculitis: a single center cohort study. *BMC Nephrol*. 2017;18(1):337.
- Oh YJ, Ahn SS, Park ES, et al. 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. *Clin Exp Rheumatol*. 2017;35:47-54.
- Yoo J, Kim HJ, Jung SM, Song JJ, Park YB, Lee SW. Birmingham vasculitis activity score of more than 9.5 at diagnosis is an independent predictor of refractory disease in granulomatosis with polyangiitis. *Int J Rheum Dis*. 2017;20:1593-1605.
- Kim DS, Song JJ, Park YB, Lee SW. Five factor score of more than 1 is associated with relapse during the first 2 year-follow up in patients with eosinophilic granulomatosis with polyangiitis. *Int J Rheum Dis*. 2017;20(9):1261-1268.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Kim MK, Choi H, Kim JY, Song JJ, Park Y-B, Lee S-W. Multivariable index for assessing the activity and predicting all-cause mortality in antineutrophil cytoplasmic antibody-associated vasculitis. *J Clin Lab Anal*. 2020;34:e23022. <https://doi.org/10.1002/jcla.23022>