



# Predictor of depressive disorders in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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## Abstract

We investigated the frequency of depressive disorders and determined the predictors of depressive disorders in Korean patients with antineutrophil cytoplasmic antibody-associated vasculitis. Sixty-one patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were enrolled in this study. We assessed the Birmingham vasculitis activity score (BVAS), vasculitis damage index (VDI) and the Korean version of the short form 36-item Health Survey (SF-36). SF-36 consists of the mental component score (MCS) and physical component score (PCS). Depression disorder was identified based on the Korean version of the Center for Epidemiologic Studies Depression Scale-Revised (K-CESD-R)  $\geq 16$ . Mood states including depression were assessed by the Korean edition of the Profile of Mood States (K-POMS) subscales. The mean age was 62.2 years (19 men). Twenty-eight AAV patients (45.9%) had depressive disorders based on K-CESD-R  $\geq 16$ . Both SF-36 MCS and SF-36 PCS were negatively correlated with K-CESD-R ( $r = -0.687$  and  $r = -0.594$ ) and K-POMS depression ( $r = -0.604$  and  $r = -0.480$ ), respectively. The optimal cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders based on K-CESD-R  $\geq 16$  were obtained as 48.07 and 55.63. Patients with SF-36 MCS  $\leq 48.07$  exhibited a significantly high RR for depressive disorders, compared with those without (RR 42.667). Also, patients with SF-36 PCS  $\leq 55.63$  showed a significantly high RR depressive disorder, compared with those without (RR 13.619). We demonstrated that SF-36 could help to estimate the current depressive disorders. We also suggest a method to obtain the optimal cut-offs of SF-36 to predict depressive disorders.

## Key points

- Both SF-36 MCS and SF-36 PCS were negatively correlated with K-CESD-R and K-POMS depression.
- Patients with SF-36 MCS  $\leq 48.07$  exhibited a significantly high relative risk (RR) for depressive disorders, compared with those without (RR 42.667).
- Patients with SF-36 PCS  $\leq 55.63$  showed a significantly high RR depressive disorder, compared with those without (RR 13.619).

**Keywords** Antineutrophil cytoplasmic antibody-associated vasculitis · Depression · Predictor · SF-36

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## Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotising vasculitides involving small vessels such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. In real clinical settings, we occasionally encounter AAV patients complaining of depressive symptoms. However, depressive symptoms are often ignored due to more serious systemic manifestations of AAV and most physicians do not quantify depressive symptoms using several questionnaires at every visit. Nonetheless, previous studies have reported the frequency of depressive disorders as 24.6% to 55% in AAV patients [2–5].

In the Korean general population, a previous study reported the overall prevalence and the point prevalence rates of depressive disorders as 3.3–5.6% and 2% [6]. Recently, self-reported questionnaires are used to assess depressive disorders. Among these self-reported questionnaires, the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale has been widely used for depressive disorders. The cut-off of CES-D  $\geq 16$  is currently the most accepted [7]. Based on CES-D  $\geq 16$ , a previous nationwide study reported the prevalence of depressive disorders in the Korean population as 25.3% to 38.9% [8, 9]. In addition to CES-D, depressive disorders can be evaluated by profile of mood states (POMS). POMS consists of 6 subscales and one of them is depression [10]. As far as we know, there was no study investigating the degree of depression in AAV patients using POMS yet.

Because both CES-D and POMS are self-reported questionnaires, we used the Korean version of Center for Epidemiologic Studies Depression Scale-Revised (K-CESD-R) and the Korean edition of the Profile of Mood States (K-POMS). In this study, we investigated based on the K-CESD-R  $\geq 16$ . We evaluated the correlation of routinely performed AAV-specific indices and laboratory results with K-CESD-R and K-POMS subscales. Also, we determined the cross-sectional predictors of depressive disorders in Korean patients with AAV.

## Materials and methods

Sixty-one patients with AAV were enrolled in this study. All 61 patients have been included in the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort from November 2016 to May 2018. All patients were first classified as AAV at the Department of Rheumatology, Yonsei University College of Medicine and Severance Hospital. They all fulfilled the 1990 American College of Rheumatology classification criteria for GPA and EGPA [11, 12], the 2007 European Medicines Agency algorithms for AAV and polyarteritis nodosa [13] and the 2012 CHCC definitions [1]. On the visit day, 3 categories of AAV-specific indices were assessed and patients with serious medical conditions other than AAV, such as malignancy, autoimmune diseases or serious infections, were excluded from this study. Also, we reviewed immunosuppressive drugs administered.

AAV-specific indices include the Birmingham vasculitis activity score (BVAS) [14], vasculitis damage index (VDI) [15] and the Korean version of the short form 36-item Health Survey (SF-36) with both mental component score (MCS) and physical component score (PCS) [16]. We evaluated clinical data using items of both BVAS and VDI.

We measured myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA [17]. Routinely laboratory tests include white blood cell, platelet and haemoglobin counts,

fasting glucose, blood urea nitrogen (BUN), creatinine, uric acid, total cholesterol, total protein, serum albumin, alkaline phosphatase (ALK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and urinalysis. Proteinuria was represented as a protein/creatinine ratio which is calculated by random urine total micro-protein and creatinine, and microscopic haematuria was counted as urine RBC  $> 10$ /high-power field.

Depression disorder was assessed by K-CESD-R and depression disorder was identified based on K-CESD-R  $\geq 16$  [7, 18]. Mood states including depression were assessed by K-POMS, which include 6 subscales and 65 items [10]. On the visit day, K-CESD-R and K-POMS were completed by AAV patients.

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a mean  $\pm$  standard deviation, and categorical variables were expressed as number and percentage. The correlation coefficient between the two variables was obtained using the Pearson correlation analysis. The optimal cut-off was extrapolated by calculating the receiver operator characteristic (ROC) curve and selecting the maximised sum of sensitivity and specificity. The relative risk (RR) was analysed using the contingency tables and the chi-square test. *P* values less than 0.05 were considered statistically significant.

## Results

### Characteristics of patients with AAV

Baseline characteristics of patients with AAV are described in Table 1. The mean BVAS and VDI were 5.26 and 3.18. The mean SF-36 MCS and SF-36 PCS were 60.7 and 56.2. Glucocorticoid (85.2%) was the most frequently administered immunosuppressive drug. The mean K-CESD-R was 19.3, and 28 of 61 AAV patients (45.9%) were identified to have depressive disorders. The mean K-POMS tension, depression, anger, vigour, fatigue, confusion and total were 8.6, 12.8, 6.4, 11.7, 9.0, 7.3 and 55.8, respectively.

### Correlation among AAV-specific indices and acute phase reactants

Among AAV-specific indices and acute phase reactants, SF-36 MCS was significantly correlated only with SF-36 PCS ( $r = 0.773$ ), whereas, SF-36 PCS was inversely correlated with BVAS ( $r = -0.320$ ). BVAS was significantly correlated with VDI ( $r = 0.400$ ), ESR ( $r = 0.418$ ) and CRP ( $r = 0.498$ ) (Table 2).

**Table 1** Characteristics of patients with AAV at survey ( $N=61$ )

Variables	Values
Demographic data	
Age (years old)	62.2 ± 13.2
Age ≥ 65 years ( $N$ , (%))	28 (45.9)
Male gender ( $N$ , (%))	19 (31.1)
AAV variants ( $N$ , (%))	
MPA	33 (54.1)
GPA	19 (31.1)
EGPA	9 (14.8)
ANCA positivity ( $N$ , (%))	
MPO-ANCA	26 (42.6)
PR3-ANCA	4 (6.6)
ANCA negative	31 (50.8)
Anti-GBM	0 (0)
AAV-specific indices	
BVAS	5.26 ± 4.7
VDI	3.18 ± 1.9
SF-36 MCS	60.7 ± 22.6
SF-36 PCS	56.2 ± 21.1
Routine laboratory results	
WBC count (/mm <sup>3</sup> )	7856.6 ± 4680.1
Haemoglobin (g/dL)	12.6 ± 2.0
Platelet count × 10 <sup>3</sup> (/mm <sup>3</sup> )	252.5 ± 70.2
Fasting glucose (mg/dL)	100.8 ± 21.6
BUN (mg/dL)	25.7 ± 18.7
Creatinine (mg/dL)	1.7 ± 2.3
Uric acid (mg/dL)	5.0 ± 1.7
Total cholesterol (mg/dL)	194.0 ± 44.8
Protein (g/dL)	6.7 ± 0.6
Serum albumin (g/dL)	4.0 ± 0.5
ALK (IU/L)	76.3 ± 40.6
AST (IU/L)	19.6 ± 6.8
ALT (IU/L)	20.2 ± 20.7
Total bilirubin (mg/dL)	0.6 ± 0.3
ESR (mm/h)	29.6 ± 28.0
CRP (mg/L)	9.3 ± 25.6
Urine P/Cr ratio	0.6 ± 0.9
Haematuria ( $N$ , (%))	13 (21.3)
Medications	
Glucocorticoid	52 (85.2)
Dose of glucocorticoid (prednisolone-equivalent) (mg)	7.9 ± 10.2
Azathioprine	18 (29.5)
Mycophenolate mofetil	4 (6.6)
Tacrolimus	2 (3.3)
Methotrexate	2 (3.3)
K-CESD-R	
K-CESD-R	19.3 ± 21.6
K-CESD-R ( $N$ , (%))	28 (45.9)
K-POMS	
Tension (anxiety)	8.6 ± 8.4
Depression (dejection)	12.8 ± 14.4
Anger (hostility)	6.4 ± 9.6
Vigour (activity)	11.7 ± 7.6
Fatigue (inertia)	9.0 ± 7.5
Confusion (bewilderment)	7.3 ± 6.2
Total	55.8 ± 41.3

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

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; BVAS, Birmingham vasculitis activity score; VDI, vasculitis damage index; SF-36, the 36-item short form health survey questionnaire; MCS, mental component score; PCS, physical component score; WBC, white blood cell; BUN, blood urea nitrogen; ALK, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; K-CESD-R, the Korean version of the Center for Epidemiologic Studies Depression Scale Revised; K-POMS, the Korean edition of the Profile of Mood States

**Table 2** Correlation among AAV-specific indices and acute phase reactants

Variables	SF-36 MCS	SF-36 PCS	BVAS	VDI	ESR	CRP
SF-36 MCS	1	0.773**	-0.194	-0.021	0.012	-0.188
SF-36 PCS		1	-0.320*	-0.067	-0.034	-0.236
BVAS			1	0.400**	0.418**	0.498**
VDI				1	0.052	0.073
ESR					1	0.518**
CRP						1

\* $P < 0.005$  and \*\* $P < 0.001$

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; SF-36, the 36-item short form health survey questionnaire; MCS, mental component score; PCS, physical component score; BVAS, Birmingham vasculitis activity score; VDI, vasculitis damage index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

### Correlation of AAV-specific indices with K-CESD-R and K-POMS

Both SF-36 MCS and SF-36 PCS were negatively correlated with K-CESD-R ( $r = -0.687$ ,  $P < 0.001$  and  $r = -0.594$ ,  $P < 0.001$ ) as well as K-POMS total ( $r = -0.543$ ,  $P < 0.01$  and  $r = -0.426$ ,  $P = 0.001$ ) with significance. Among K-POMS subscales, SF-36 MCS exhibited the highest negative correlation with depression ( $r = -0.604$ ,  $P < 0.001$ ), followed by fatigue ( $r = -0.570$ ,  $P < 0.001$ ), whereas SF-36 PCS exhibited the strongest inverse correlation with fatigue ( $r = -0.551$ ,  $P < 0.001$ ), followed by depression ( $r = -0.480$ ,  $P < 0.001$ ). By contrast, BVAS was correlated with neither K-CESD-R nor K-POMS (Table 3).

### Correlation of variables other than SF-36 with K-CESD-R and K-POMS

K-CESD-R and K-POMS total and subscales exhibited no significant correlations with routine laboratory results except for fasting glucose. However, the association between fasting glucose and CESD still remains unclear [19, 20]. We also examined the differences in demographic or clinical data and immunosuppressive drugs administered between patients with and without K-CESD-R  $\geq 16$  but there were no significant differences between the two groups.

### Optimal cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders

Since SF-36 MCS and SF-36 PCS were negatively correlated with K-CESD-R, the dependent variable of the ROC curve analysis was set as K-CESD-R  $< 16$ . The optimal cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders based on K-CESD-R  $\geq 16$  were 48.07 and 55.63, respectively (Fig. 1). Patients with SF-36 MCS  $\leq 48.07$  exhibited a significantly high RR for depressive disorders, compared with those without (RR 42.667). Also, patients with SF-36 PCS  $\leq 55.63$

showed a significantly high RR depressive disorder, compared to those without (RR 13.619) (Fig. 1).

## Discussion

In this study, we first report the frequency of depressive disorders based on K-CESD-R  $\geq 16$  in Korean patients with AAV as 45.9%. A previous study reported that 55% of AAV patients had a score of CESD  $\geq 16$  [5]. Compared with that previous study, AAV patients in this study exhibited a slightly lower rate of depressive disorders. But compared with the Korean general population, the frequency of depressive disorders was higher in AAV patients [9]. Therefore, we conclude that the frequency of depressive disorders in Korean patients with AAV is estimated at 45.9%, which is higher than that in the Korean general population.

It is well known that depressive symptoms are closely linked to systemic complications of chronic diseases [21, 22]. Thus, we assumed that SF-36 MCS might be correlated with BVAS, VDI and acute phase reactants. SF-36 PCS exhibited a significantly inverted correlation with BVAS. However, SF-36 MCS showed no significant correlation with BVAS, VDI and acute phase reactants in Korean patients with AAV. Therefore, we conclude that the current mental states might not dependent on AAV activity, damage and inflammatory burden.

We evaluated the correlation of AAV-specific indices with K-CESD-R and K-POMS subscales and found that both SF-36 MCS and SF-36 PCS exhibited significant correlation coefficients with K-CESD-R and K-POMS depression, although K-POMS subscales showed a different pattern. With these results, therefore, we conclude that both SF-36 MCS and SF-36 PCS may reflect the cross-sectional degree of depression and fatigue in AAV patients. Furthermore, SF-36 MCS may be more closely linked to depression mood than SF-36 PCS. We, for the first time, provided the optimal cut-offs of SF-36 MCS and SF-36 PCS for predicting depressive

**Table 3** Correlation of AAV-specific indices with K-CESD-R and K-POMS

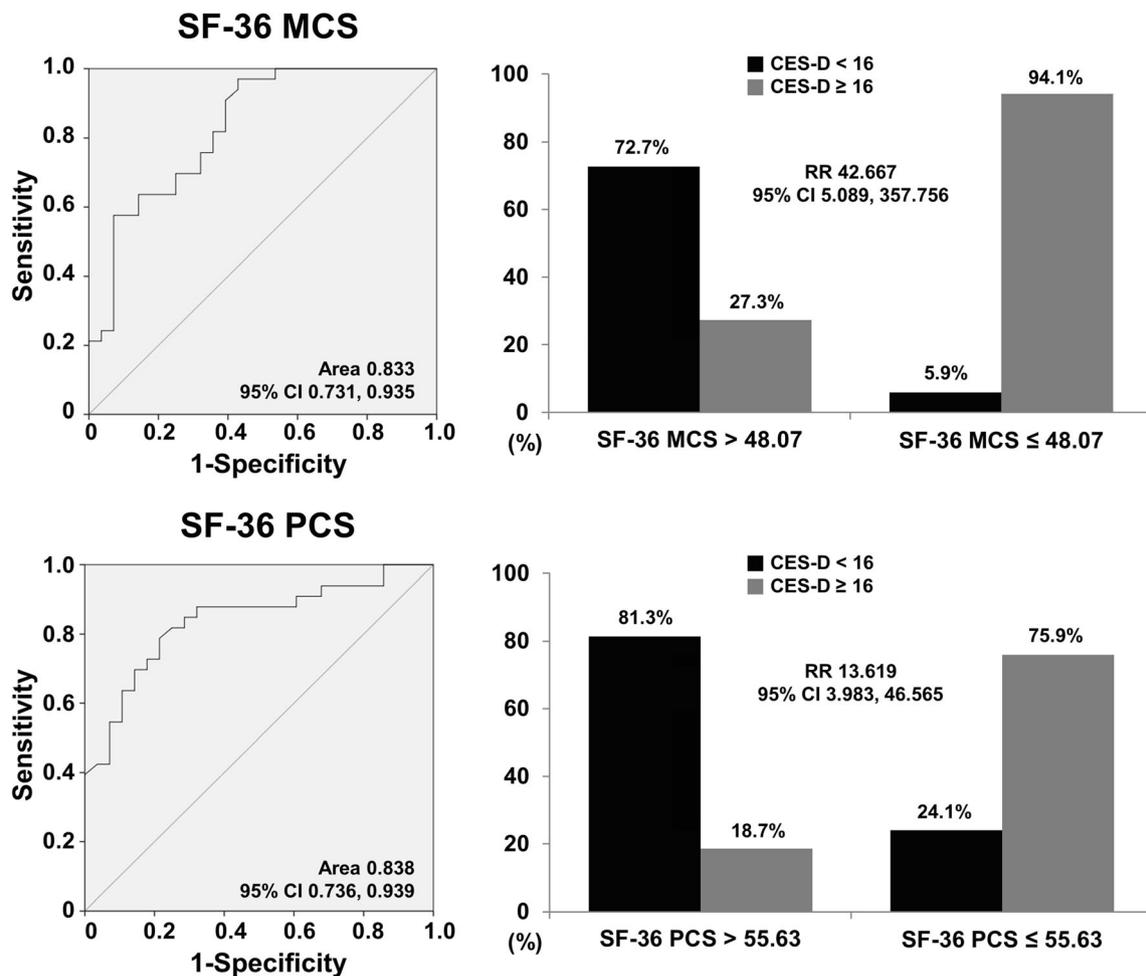
Variables	K-CESD-R	K-POMS						
		Tension	Depression	Anger	Vigour	Fatigue	Confusion	Total
SF-36 MCS	-0.687**	-0.484**	-0.604**	-0.529**	0.379**	-0.570**	-0.522**	-0.543**
SF-36 PCS	-0.594**	-0.379**	-0.480**	-0.335**	0.323*	-0.551**	-0.427**	-0.426**
BVAS	0.097	0.051	0.028	0.001	0.034	0.076	0.137	0.061
VDI	-0.020	-0.100	-0.090	-0.008	0.292**	-0.050	0.051	-0.001

\* $P < 0.005$  and \*\* $P < 0.001$

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; K-CESD-R, the Korean version of the Center for Epidemiologic Studies Depression Scale-Revised; K-POMS, the Korean edition of the Profile of Mood States; SF-36, the 36-item short form health survey questionnaire; MCS, mental component score; PCS, physical component score; BVAS, Birmingham vasculitis activity score; VDI, vasculitis damage index

disorders based on K-CESD-R  $\geq 16$  in AAV patients. Depressive disorders occurred in patients with SF-36 MCS  $\leq 48.07$  43 times as frequent as those without. Moreover, depressive disorders were observed in patients with SF-36 PCS

$\leq 55.63$  14 times as often as those without. These cut-offs are not fixed but changeable according to patients' ethnicity and populations. Accordingly, we believe that SF-36 MCS and SF-36 PCS can be a potent substitute for K-CESD-R to



**Fig. 1** Optimal cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders. The optimal cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders based on K-CESD-R  $\geq 16$  were 48.07 and 55.63. Patients with SF-36 MCS  $\leq 48.07$  exhibited a significantly high RR for depressive disorders, compared with those without. Also, patients with SF-36 PCS  $\leq$

55.63 showed a significantly high RR depressive disorder, compared with those without. SF-36, the 36-item short form health survey questionnaire; MCS, mental component score; PCS, physical component score; K-CESD-R, the Korean version of the Center for Epidemiologic Studies Depression Scale-Revised; RR, relative risk

identify depressive disorders and furthermore, our study is clinically meaningful in suggesting a method to set the cut-offs of SF-36 MCS and SF-36 PCS for depressive disorders.

The determination of depressive disorders was based on K-CESD-R  $\geq 16$  in this study. If so, it may be more reasonable to use K-CESD-R rather than SF-36 to identify AAV patients with depressive disorders. However, we have 2 reasons why to use SF-36. First, both SF-36 MCS and SF-36 PCS exhibited a good correlation with all K-POMS subscales; thus, SF-36 may be a more comprehensive indicator for various mood states beyond depression than K-CESD-R. Second, SF-36 includes PCS system as well as MCS system [16]. In this study, SF-36 PCS showed a significant correlation with the current BVAS. Thus, SF-36 has additional merit to estimate the current AAV activity together with the presence of depressive disorder in AAV patients.

In this study, we first reported the frequency of depressive disorders in Korean patients with AAV using K-CESD-R and we provided the predictive potential of SF-36 MCS and SF-36 PCS for depressive disorders. Furthermore, we suggested a method to obtain their optimal cut-offs to identify AAV patients with depressive disorders based on K-CESD-R (or the validated each language's version of CES-D)  $\geq 16$  (or other cut-offs of CES-D for depressive disorders based on ethnicity or populations). However, our study has several issues. The number of patients was too small to generalise these results to all Korean patients with AAV. Furthermore, our study is a cross-sectional study, so we could not clarify the changes in the associations among SF-36 MCS, SF-36 PCS, K-CESD-R and K-POMS subscales, and thus, we could not provide information on the alterations in the severity or activity of AAV by intervention during the disease course. In addition, there is another limitation of discordance in the assessment periods between SF-36 and K-CESD-R: SF-36 is a questionnaire during the last 1 month, whereas K-CESD-R is a questionnaire during the last 1 week. Nonetheless, our study has clinical meanings in that we suggest the usefulness of SF-36 in screening and estimating the cross-sectional depressive disorder in AAV patients. Future studies with follow-up data and a larger number of patients will provide dynamic and more clear information on the predictive value of SF-36 for depressive disorders in AAV patients.

## Conclusions

Twenty-eight of 61 AAV patients (45.9%) were identified to have depressive disorders based on K-CESD-R  $\geq 16$  and depressive disorders may be predicted by the current SF-36 MCS and SF-36 PCS in Korean patients with AAV. We believe that only early detection and aggressive treatment are the best strategies to cope with depressive disorders in AAV

patients. We also suggest a method to obtain the optimal cut-offs of SF-36 to predict depressive disorders.

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## Compliance with ethical standards

This study was approved by the Institutional Review Board of Severance Hospital (4-2016-0901) and the patients' written informed consent was obtained.

**Disclosures** None.

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