

## RESEARCH ARTICLE

# Predicting the depressive status using empirical dietary inflammatory index in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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## Abstract

**Background:** This study investigated whether the empirical dietary inflammatory index (eDII) score is associated with the inflammatory burden as well as the depressive status in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

**Methods:** Eighty-four patients with AAV participated in this study. Birmingham vasculitis activity score (BVAS) and short-form 36-item Health Survey mental component summary (SF-36 MCS) were considered as indices assessing the inflammatory burden and depressive status, respectively. The eDII includes 16 food components and consists of three groups: -9 to -2, the low eDII group; -1 to +1, the moderate eDII group; and +2 to +10, the high eDII group. Furthermore, the lower eDII group includes both the low and moderate eDII groups.

**Results:** The median age was 64.5 years (36 men). The eDII scores inversely correlated with SF-36 MCS ( $r = -0.298$ ,  $p = 0.006$ ) but not with BVAS. SF-36 MCS significantly differ between the lower and higher eDII groups (69.7 vs. 56.7,  $p = 0.016$ ), but not among the low, moderate and high eDII groups. Additionally, when patients with AAV were divided into two groups according to the upper limit of the lowest tertile of SF-36 MCS of 55.31, patients in the higher eDII group exhibited a significantly higher risk for the lowest tertile of SF-36 MCS than those in the lower eDII group (RR 3.000).

**Conclusion:** We demonstrated for the first time that the eDII could predict the depressive status by estimating SF-36 MCS without utilising K-CESD-R  $\geq 16$  in patients with AAV.

## KEYWORDS

antineutrophil cytoplasmic antibody-associated vasculitis, depression, empirical dietary inflammatory index, SF-36 MCS

## 1 | INTRODUCTION

Various nutrients and foods have shown an association with the extent or acceleration of inflammation in chronic inflammatory diseases, and habitual dietary patterns may be involved in the modulation of inflammation.<sup>1</sup> The dietary inflammatory index (DII), which is the most widely used index, was developed based on these concepts.<sup>2,3</sup> The DII showed an association with the inflammatory burden based on the levels of high-sensitivity C-reactive protein (CRP) in healthy volunteers in Korea and Japan.<sup>4,5</sup> Moreover, the DII elicited an elevated inflammatory potential in patients with rheumatoid arthritis, as compared to the controls.<sup>6</sup> In addition to the inflammatory potential, the DII could predict depressive disorders in healthy adults as well as patients with chronic diseases,<sup>7-10</sup> suggesting an important role of dietary nutrition in public mental health.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis that primarily affects small-sized vessels, including capillaries and adjacent arterioles and venules and occasionally medium-sized arteries. AAV is characterised by necrotising vasculitis and/or granuloma formation and is composed of three typical subtypes, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) according to clinical, laboratory, imaging and histologic features.<sup>11,12</sup> AAV is a representative chronic inflammatory disease that repeatedly exacerbated and improved over a long period, owing to its autoimmune disease mechanism.<sup>13</sup> In addition to chronic inflammation, AAV is associated with mental health. A previous study revealed that the frequency of depressive disorders in Korean patients with AAV was 45.9% based on the Korean version of centre for epidemiologic studies depression scale-revised (K-CESD-R)  $\geq 16$ , which was negatively correlated with the short-form 36-item Health Survey (SF-36) mental component summary (MCS) scores.<sup>14-16</sup> Therefore, it can be reasonably assumed that the DII may estimate the cross-sectional inflammatory burden as well as the depressive status in patients with AAV. However, there have been no reports regarding the clinical relevance of the DII in patients with AAV.

To overcome the difficulties in using the previous DII due to many items, the empirical dietary inflammatory index (eDII), based on 16 food components was recently developed.<sup>17</sup> Hence, this study used the novel and convenient eDII questionnaire and investigated whether it is associated with the inflammatory burden as well as the depressive status in patients with AAV.

## 2 | PATIENTS AND METHODS

### 2.1 | Study subjects

The participants were randomly selected from those who were enrolled in the Severance Hospital ANCA-associated Vasculitides (SHAVE) cohort and who agreed to participate in the study. The SHAVE cohort is a prospective and observational cohort, which

began in November 2016, and includes patients with MPA, GPA or EGPA. AAV diagnosis in all participants was confirmed at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine and Severance Hospital. All participants fulfilled both the revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides proposed in 2012, and the 2007 European Medicines Agency algorithms for AAV.<sup>11,12</sup> During study enrolment, the patients were followed up for at least 3 months and had no concomitant serious medical conditions resulting in ambiguity in interpreting the results, such as malignancies and infectious diseases requiring hospitalisation.<sup>14,18</sup> Although 89 patients with AAV volunteered to participate and provided informed consent, two patients were excluded due to concomitant serious infectious diseases and three patients due to consent withdrawal. Finally, 84 patients with AAV were included in this study. This study was approved by the Institutional Review Board of Severance Hospital (4-2016-0901) and conducted according to the Declaration of Helsinki. The patients' written informed consent was obtained from all patients.

### 2.2 | Clinical data

All data were collected at the time of informed consent provision, filling out the eDII and SF-36 questionnaires, assessing AAV-specific indices and performing blood tests. The demographic data included age and sex. Regarding the AAV-related variables, the AAV subtype, ANCA positivity status, AAV-specific indices and clinical manifestations were recorded. In terms of acute-phase reactants reflecting the inflammatory status, erythrocyte sedimentation rate (ESR) and CRP levels were investigated along with routine laboratory tests.<sup>14,18</sup> Medications which were currently administered at the time of this study were also assessed.

### 2.3 | AAV-specific indices

The SF-36 MCS and SF-36 physical component summary (PCS) scores were considered as a functional status index,<sup>16</sup> Birmingham vasculitis activity score (BVAS) as a vasculitis activity index,<sup>19</sup> and vasculitis damage index (VDI) as a damage index.<sup>20</sup> In particular, SF-36 MCS and BVAS were considered as indices assessing the inflammatory burden and depressive status, respectively.

### 2.4 | ANCA measurement

Myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA were measured using the novel anchor-coated highly sensitive Phadia Elia (Thermo Fisher Scientific/Phadia, Freiburg, Germany) and human native antigens, using Phadia250 analyser. Immunoassays were used as the primary screening method for ANCA; however, when patients tested negative for ANCA by an antigen-specific assay but positive for perinuclear (P)-ANCA or cytoplasmic (C)-ANCA by an indirect

immunofluorescence assay, they were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected based on the clinical and laboratory features.<sup>21</sup>

## 2.5 | Empirical dietary inflammation index

In the eDII, red meat, processed meat, organ meat, other fish, eggs, sugar-sweetened beverages, tomatoes, white rice and bread/noodles are considered pro-inflammatory foods. On the contrary, leafy green vegetables, dark yellow vegetables, fruit juices, oily fish, coffee, tea, wine, beer or other alcoholic beverages are considered anti-inflammatory foods. Differentiated scores are assigned from 0 to +2 and from -2 to 0 according to the frequency of consumption of pro-inflammatory foods and anti-inflammatory foods, respectively. The higher eDII score, the greater the inflammation.<sup>17</sup>

## 2.6 | Stratification

Patients were divided into three groups according to the eDII scores: -9 to -2, the low eDII group; -1 to +1, the moderate eDII group; and +2 to +10, the high eDII group.<sup>17</sup>

## 2.7 | Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows version 26 (IBM Corp.). Continuous variables are expressed as medians with interquartile ranges, whereas categorical variables are expressed as numbers (percentages). The correlation coefficient (*r*) between the two variables was obtained using either the Pearson correlation analysis. Significant differences between two continuous variables were compared using the Mann-Whitney U test. Significant differences among more than three continuous variables were investigated using the Kruskal-Wallis test. The relative risk (RR) was analysed using contingency tables and the chi-square test. *p*-values less than 0.05 were considered statistically significant.<sup>14</sup>

# 3 | RESULTS

## 3.1 | Characteristics of participants

The median age of the participants was 64.5 years, and 36 patients were men. MPA was noted in 44 patients, GPA in 25 and EGPA in 15. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 31 (36.9%) and 7 patients (8.3%), respectively, whereas ANCA was not detected in 47 patients (56.0%). The median scores of SF-36 PCS, SF-36 MCS, BVAS and VDI were 66.7, 62.3, 4.0 and 3.0, respectively. The most common clinical manifestation was pulmonary (54.8%), followed by otorhinolaryngological (46.4%) and renal (39.3%) manifestations. The median eDII score was 1.0. The

laboratory results and medications being currently administered are described in [Table 1](#).

## 3.2 | Correlation

The correlation between the eDII scores and the values of the continuous variables was investigated. Among AAV-specific indices, the eDII scores showed a significant inverse correlation with SF-36 MCS ( $r = -0.298$ ,  $p = 0.006$ ). Furthermore, the eDII scores showed a correlation with SF-36 PCS and VDI, but the difference was not statistically significant. Conversely, the eDII scores did not correlate with BVAS ( $r = 0.144$ ,  $p = 0.192$ ). Among the laboratory investigations, neither ESR nor CRP level was correlated with the eDII scores ([Table 2](#)).

## 3.3 | SF-36 MCS among the three groups

The low, moderate and high eDII groups included 5 (6.0%), 40 (47.6%) and 39 (46.4%) patients, respectively. SF-36 MCS of patients with AAV among the low, moderate and high eDII groups did not differ significantly (69.2, 70.1 and 56.7, respectively,  $p = 0.052$ ) ([Figure 1A](#)). However, since these median values were similar between the patients of the low and moderate eDII groups, the patients were then divided into two groups; the lower eDII group, including both the low and moderate eDII groups, and the higher eDII group including the high eDII group. There was a significant difference in the median SF-36 MCS between the lower and higher eDII groups (69.7 vs. 56.7,  $p = 0.016$ ) ([Figure 1B](#)).

## 3.4 | Relative risk

In a previous study, the cut-off score of SF-36 MCS, which can predict the depressive status based on K-CESD-R  $\geq 16$ , was 48.07, which was close to the upper limit of the lowest tertile value of 50.00.<sup>14</sup> Therefore, although K-CESD-R  $\geq 16$  could not be applied, the depressive status could be anticipated from the lowest tertile of SF-36 MCS. Thus, we investigated whether the higher eDII group could predict the lowest tertile of SF-36 MCS. When patients with AAV were divided into two groups according to the upper limit of the lowest tertile of SF-36 MCS of 55.31, there were 28 patients in the lowest tertile of SF-36 MCS. Patients in the higher eDII group exhibited a significantly higher risk for the lowest tertile of SF-36 MCS than those in the lower eDII group (RR 3.000 95% confidence interval 1.168, 7.707) ([Figure 2](#)).

# 4 | DISCUSSION

This study investigated whether the eDII is associated with the inflammatory burden or the depressive status in patients with AAV and obtained several interesting findings. First, the eDII scores are

TABLE 1 Characteristics of participants (N = 84)

Variables	Values
Demographic data	
Age (years)	64.5 (21.8)
Male sex (N, [%])	36 (42.9)
AAV Subtype (N, [%])	
MPA	44 (52.4)
EGPA	25 (29.8)
GPA	15 (17.9)
ANCA positivity (N, [%])	
MPO-ANCA (or P-ANCA) positivity	31 (36.9)
PR3-ANCA (or C-ANCA) positivity	7 (8.3)
Both ANCA positivity	1 (1.2)
ANCA negativity	47 (56.0)
AAV-specific indices	
SF-36 PCS	66.7 (31.9)
SF-36 MCS	62.3 (25.6)
BVAS	4.0 (4.0)
VDI	3.0 (3.0)
Clinical manifestations (N, [%])	
General	4 (4.8)
Cutaneous	9 (10.7)
Mucous membranous/Ocular	6 (7.1)
Otorhinolaryngological	39 (46.4)
Pulmonary	46 (54.8)
Cardiovascular	9 (10.7)
Gastrointestinal	0 (0)
Renal	33 (39.3)
Nervous systemic	25 (29.8)
Laboratory results	
ESR (mm/h)	13.0 (17.0)
CRP (mg/L)	1.3 (3.6)
WBC count (/mm <sup>3</sup> )	6790.0 (2380.0)
Haemoglobin (g/dl)	13.2 (1.9)
Platelet count (×1000/mm <sup>3</sup> )	237.0 (82.0)
Fasting glucose (mg/dl)	95.0 (13.5)
BUN (mg/dl)	19.9 (11.3)
Serum creatinine (mg/dl)	1.1 (0.9)
Total protein (g/dl)	6.8 (0.6)
Serum albumin (g/dl)	4.4 (0.4)
ALP (IU/L)	63.0 (33.0)
AST (IU/L)	19.0 (6.5)
ALT (IU/L)	16.0 (10.0)
Total bilirubin (mg/dl)	0.7 (0.4)
Complements	
C3 (mg/dl)	117.1 (26.7)
C4 (mg/dl)	26.7 (10.1)

TABLE 1 (Continued)

Variables	Values
eDII score	1.0 (3.0)
Medications being currently administered	
Glucocorticoids	82 (97.6)
Cyclophosphamide	0 (0)
Rituximab	2 (2.4)
Mycophenolate mofetil	14 (16.7)
Azathioprine	43 (51.2)
Tacrolimus	10 (11.9)
Methotrexate	11 (13.1)
Plasma exchange	0 (0)

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

Abbreviations: AAV, ANCA-associated vasculitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; BVAS, Birmingham vasculitis activity score; C, cytoplasmic; C3, complement 3; C4, complement 4; CRP, C-reactive protein; eDII, empirical dietary inflammatory index; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; GPA, granulomatosis with polyangiitis; MCS, mental component summary; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P, perinuclear; PCS, physical component summary; PR3, proteinase 3; SF-36, short-form 36-item Health Survey; VDI, vasculitis damage index; WBC, white blood cell.

inversely correlated with only SF-36 MCS with a statistically significant difference. Second, when the patients with AAV were divided into two groups according to the eDII scores, those in the higher eDII group exhibited significantly lower median SF-36 MCS than those in the lower eDII group. Third, patients in the higher eDII group exhibited a significantly higher risk for the lowest tertile of SF-36 MCS than those in the lower eDII group (RR 3.000). Therefore, we can conclude that the eDII scores can predict the current depressive status based on SF-36 MCS scores.

The depressive status should be defined based on K-CESD-R  $\geq 16$ .<sup>15</sup> However, at the start of this study, a correlation between the eDII scores and BVAS or the values of acute-phase reactants was expected; thus, we did not fill out the K-CESD-R form in this study. Nevertheless, we replaced the lowest tertile of SF-36 MCS with the cut-off of SF-36 MCS based on K-CESD-R  $\geq 16$  to determine the depressive status. This was done because the cut-off of SF-36 MCS, which can predict the depressive status based on K-CESD-R  $\geq 16$ , was close to the upper limit of the lowest tertile value of 50.0 in a previous study.<sup>14</sup> In this study, the upper limit of the lowest SF-36 MCS was 55.31. If K-CESD-R had been used to assess the study participants, the cut-off of SF-36 MCS for the depressive status based on K-CESD-R would be close to 55.31, because the patients were selected from the same cohort as of the previous study. It is believed that the eDII scores are clinically significant in patients with AAV in the higher eDII group, who may be more susceptible to the depressive status based on the lowest tertile of SF-36 MCS than those in the lower eDII group.

There is a temporal difference between the eDII and SF-36 MCS questionnaires. SF-36 MCS assesses the mental health and emotional state over the past month, while the eDII scores assess

**TABLE 2** Correlation of the eDII scores with the values of continuous variables in patients with AAV

Variables	Correlation coefficient (r)	p-value
Demographic data		
Age (years)	-0.004	0.968
AAV-specific indices		
SF-36 PCS	-0.191	0.082
SF-36 MCS	-0.298	0.006
BVAS	0.144	0.192
VDI	0.202	0.066
Laboratory results		
ESR (mm/hr)	-0.063	0.590
CRP (mg/L)	-0.077	0.520
WBC count (/mm <sup>3</sup> )	0.090	0.440
Haemoglobin (g/dl)	0.158	0.173
Platelet count (×1000/mm <sup>3</sup> )	0.049	0.677
Fasting glucose (mg/dl)	0.077	0.488
BUN (mg/dl)	0.089	0.444
Serum creatinine (mg/dl)	0.124	0.285
Total protein (g/dl)	0.095	0.412
Serum albumin (g/dl)	0.144	0.214
ALP (IU/L)	0.057	0.623
AST (IU/L)	-0.043	0.715
ALT (IU/L)	0.008	0.946
Total bilirubin (mg/dl)	-0.056	0.633
Complements		
C3 (mg/dl)	0.095	0.417
C4 (mg/dl)	0.134	0.249

Abbreviations: AAV, ANCA-associated vasculitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; BVAS: Birmingham vasculitis activity score; C3, complement 3; C4, complement 4. CRP, C-reactive protein; eDII, empirical dietary inflammatory index; ESR, erythrocyte sedimentation rate; MCS, mental component summary; PCS, physical component summary; SF-36, short-form 36-item Health Survey; VDI, vasculitis damage index; WBC, white blood cell.

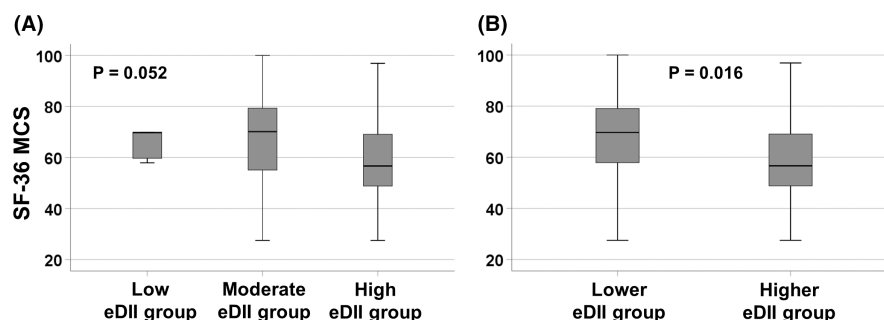
the food intake over the past week.<sup>16,17</sup> Given the time gap, this study investigated whether the eDII score directly predicted the lowest tertile of SF-36 and indirectly predicted the depressive status. As food intake patterns are more of habit than taste, they tend to persist over a relatively long period of time rather than change over a short period. Therefore, we can conclude that the results of this study are reliable. Moreover, the eDII score is more suitable for predicting SF-36 MCS with relatively small changes in the long term than BVAS or CRP levels with large changes in the short term.

Additionally, although the eDII score did not significantly correlate with the AAV-specific indices other than SF-36 MCS and acute-phase reactants, we compared their median values between the higher and lower eDII groups (Figure 1B). Among the measures of SF-36 PCS, BVAS, VDI, ESR and CRP, patients in the higher eDII score group exhibited a higher median BVAS than those in the lower group (5.0 vs. 4.0,  $p = 0.099$ ) (Figure S1). However, this difference was not statistically significant. We conclude that the eDII score may not be useful in estimating the cross-sectional inflammatory burden based on BVAS or acute-phase reactants.

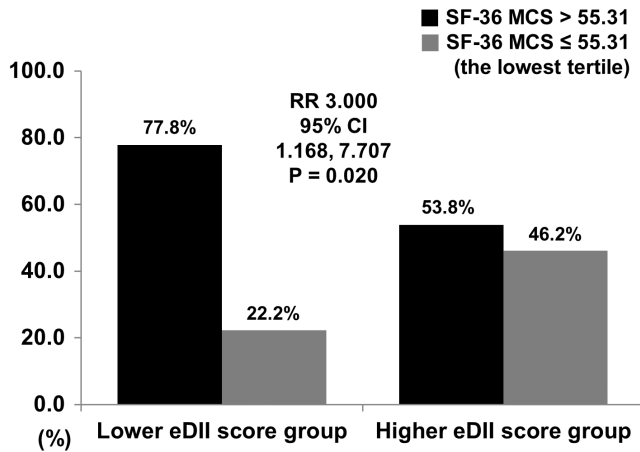
The strength of this study is that for the first time, the inverse correlation between the conveniently revised eDII scores based on the DII and the cross-sectional SF-36 MCS score was revealed. However, this study also has several limitations that should be considered. The number of patients with AAV participating in this study was not adequate to generalise the results to all Korean patients with AAV. Furthermore, this study was designed to compare both the eDII scores and the AAV-specific indices at two different time points. However, the follow-up eDII score could not be completed, because a significant number of patients did not respond to the eDII and SF-36 questionnaires due to the SARS-CoV-2 pandemic. Since this study was conducted during the pandemic, it is unclear whether the study accurately reflected the situation before or after the pandemic. Therefore, if future studies with a large number of patients with AAV that involve completing the DII and SF-36 MCS questionnaires at two or more different times after the pandemic are warranted, they could provide dynamic and more reliable information regarding the clinical implications of the eDII for managing patients with AAV in actual clinical practice.

In conclusion, we demonstrated for the first time that the eDII scores inversely correlated with the cross-sectional score of SF-36 MCS in patients with AAV. Given that the lowest tertile of SF-36 MCS and K-CESD-R  $\geq 16$  were similar in a previous study,<sup>14</sup> the eDII

**FIGURE 1** (A) SF-36 scores among the low, moderate and high eDII groups. (B) SF-36 scores between the lower and higher eDII groups. SF-36: short-form 36-item Health Survey; eDII: empirical dietary inflammatory index







**FIGURE 2** Relative risk of the higher eDII group for the lowest tertile of SF-36 MCS. eDII: empirical dietary inflammatory index; SF-36: short-form 36-item Health Survey; MCS: mental component summary

score may be useful in predicting the depressive disorder without utilising K-CESD-R  $\geq 16$  in patients with AAV.

#### CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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