Atherogenic index of plasma predicts cerebrovascular accident occurrence in antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Background: We investigated whether the atherogenic index of plasma (AIP) at diagnosis can predict cerebrovascular accident (CVA) and cardiovascular disease during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: The medical records of 167 immunosuppressive drug-naïve AAV patients and those of 300 age- and gender-matched controls were retrospectively reviewed. AIP was calculated using the following equation: AIP = Log (triglyceride (mmol/L) / high-density-cholesterol (mmol/L)). AAV patients were divided into two groups according to their AIP, AAV patients with AIP < 0.11 (N=115) and AAV patients with AIP ≥ 0.11 (N=52).

Results: The median age and body mass index of AAV patients were 59.0 years and 22.1 kg/m^2, respectively. The median calculated AIP of patients was 0.01 and AAV patients with AIP < 0.11 exhibited a lower Birmingham vasculitis activity score than those with AIP ≥ 0.11 but it was not significant (P = 0.064). AAV patients had a significantly lower body mass index than controls, nevertheless, AAV patients had a significantly higher AIP than controls (0.01 vs. -0.12). Sixteen patients were diagnosed with CVA, and AAV patients with AIP ≥ 0.11 had a significantly lower CVA-free survival rate than those with AIP < 0.11. Multivariable analysis indicated that AIP ≥ 0.11 at diagnosis was significantly associated with CVA during follow-up.

Conclusions: AIP was significantly higher in AAV patients than in controls. Furthermore, AIP at diagnosis could predict CVA occurrence during follow-up in AAV patients.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic necrotising vasculitides involving small vessels including arterioles, venules and capillaries. Based on the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis (the 2012 CHCC definitions) and the 2007 European Medicines Agency algorithm (the 2007 EMA algorithm), AAV consists of three subtypes such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [*1, 2]*.. Pathophysiologically, AAV occurs via neutrophil-priming, ANCA formation, endothelial damage, transmigration of inflammatory cells, degranulation of neutrophils and recruitment of autoreactive immune cells in and beyond vessel-walls, which in turn, induced inflammation and fibrosis [*3, 4]*.. In addition, since the inflammatory process in vessel-walls can also initiate and accelerate the formation of thrombus [*5]*,, serious thromboses such as cerebrovascular accident (CVA) and cardiovascular disease (CVD) are of concern in AAV patients.

Thus far, there have been several studies regarding CVD and CVA in AAV patients. A previous study compared comorbidities between AAV patients and the general population and reported a significantly high incidence of venous thrombosis and an increasing tendency of the incidence of CVD in AAV patients [*6]*.. Another study of a meta-analysis of 7 studies clarified an increase in the risk of CVA in AAV patients

compared with the general population [*7]*.. Moreover, a population-based study revealed that the risk of CVD and CVA in AAV patients were 3- and 8-fold higher than those in matched subjects over the course of a 20-year follow-up, respectively, despite a similar CVD and CVA baseline incidence in both groups [*8]*.. Therefore, it is clinically important to uncover predictors at diagnosis for serious thromboses occurrence during follow-up in AAV patients.

Atherogenic index of plasma (AIP), which is calculated based on serum triglyceride (TG) and high-density lipoprotein (HDL)-cholesterol, is one of the indices for atherogenic status and has been used to assess the extent of dyslipidaemia and predict the potential of CVD and CVA in various medical conditions [*9–11]*.. However, to date, there have been no studies that sought to determine the predictive potential of AIP at diagnosis for CVA and CVD occurrence over the course of the follow-up duration in AAV patients. Hence in this study, we investigated whether AIP in AAV patients might be higher than that in age- and gender-matched controls and whether AIP at diagnosis could predict CVA and CVD during follow-up in AAV patients.

Methods

Patient inclusion

The medical records of 216 immunosuppressive drug-naïve AAV patients in the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort were retrospectively reviewed. All patients were classified as MPA, GPA, or EGPA based on the 2007 EMA algorithm and the 2012 CHCC definition at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital between October 2000 and December 2019 [*1, 2]*.. All patients in the SHAVE cohort had well-documented medical records to collect clinical and laboratory results including Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) at the time of diagnosis [*12, 13]*.. Furthermore, confirmation of ANCA both by an indirect immunofluorescence assay (IFA) for perinuclear (P)-ANCA and cytoplasmic (C)-ANCA and antigen-specific assays for myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA was also included in the medical records. Patients negative by antigen-specific assay but positive for ANCA by IFA were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected due to clinical features or histological confirmation [*14]*.. All study subjects were followed up for at least 3 months until the time of inclusion in this study. At the time of diagnosis, patients had no serious medical conditions similar to that of AAV or that would enable a false-positive ANCA, such as coexisting malignancies and serious infections, as identified by the 10th revised International Classification Diseases and had no history of immunosuppressive drugs. Of the 216 AAV patients, 29 patients were excluded from this study owing to a lack of TG and HDL-cholesterol records and 8 were excluded owing to a lack of either TG or HDL-cholesterol records. Furthermore, 12 patients were also excluded due to exposure to drugs for dyslipidaemia. Finally, 167 were included and analysed in this study (*Fig. 1)*.. In addition, 300 people, who had consecutively visited Severance Executive Healthcare Clinic in Severance Hospital, a university-affiliated tertiary care hospital, for a comprehensive medical health check-up and had no serious medical conditions, were also included in this study as controls. Only

age, gender, body mass index and AIP-related variables from 300 controls with identification codes were reviewed. This study was approved by the Institutional Review Board of Severance Hospital (4–2017–0673). The need for patients' written informed consent was waived, as this was a retrospective study.

Clinical data at diagnosis and during follow-up

As for variables at diagnosis, age, gender, body mass index and smoking history were collected as demographic data. AAV subtypes and ANCA positivity and both BVAS and FFS were obtained. Comorbidities, such as chronic kidney disease (CKD) (stage III~V), diabetes mellitus, hypertension and interstitial pneumonia, were assessed. Routine laboratory tests included white blood cell and platelet counts, haemoglobin, fasting glucose, blood urea nitrogen (BUN), creatinine, total serum protein, serum albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Serum total cholesterol, TG, HDL-cholesterol and low-density lipoprotein (LDL)-cholesterol levels were also reviewed to calculate AIP. As for variables during follow-up, all-cause mortality, CVA and CVD were evaluated as poor outcomes. In this study, stroke, transient ischaemic attack and cerebral haemorrhage were defined as CVA and acute coronary syndrome including myocardial infarct and angina pectoris was defined as CVD. The follow-up duration was defined as the duration between the date of AAV diagnosis and the date of the last visit for the survived patients. In cases where the patients were deceased, the follow-up duration was defined as the duration between AAV diagnosis and the time of death. For patients who had poor outcomes, the follow-up duration was defined as the duration starting from AAV diagnosis until each poor outcome appeared. The number of patients who received immunosuppressive drugs during follow-up were also counted.

Equation for AIP

AIP was calculated by the following equation: AIP = Log (TG (mmol/L) / HDL-cholesterol (mmol/L)) [*9*].. Since TG and HDL-cholesterol levels were obtained as a unit of mg/dL, they were transformed into a unit of mmol/L and then applied to the equation. Based on AIP, the risk of CVA and CVD was divided into three ranges: AIP < 0.11, AIP 0.11~0.21 and AIP > 0.21 indicate low, intermediate and high risk, respectively [*15*].. In this study, AAV patients were divided into two groups according to AIP as follows: AAV patients with AIP < 0.11 (N = 115) and AAV patients with AIP ≥ 0.11(N = 52).

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). 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 analysed using the Chi-square and Fisher's exact tests and among more

than three groups using the ANOVA analysis. Significant differences in continuous variables between the two groups were compared using the Mann-Whitney test. The correlation coefficient between A and B was obtained using the Pearson correlation analysis. Comparison of the cumulative survivals rates between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. The multivariable Cox hazards model analysis using variables with statistical significance in the univariable Cox hazards model analysis was conducted to appropriately obtain the hazard ratios (HRs) for the considerable the follow-up duration. A P-values less than 0.05 were considered statistically significant.

Results

Characteristics of AAV patients at diagnosis

The median age and body mass index of the 167 AAV patients included in this study were 59.0 years 22.1 kg/m^2, respectively. Fifty-four patients were men and 6 patients were ex-smokers. The most common AAV subtype was MPA (55.1%) and ANCA was positive in 133 patients (79.6%). The most common clinical manifestation was renal (62.3%), and the most frequent comorbidity was hypertension (53.3%). The median levels of routine laboratory results are shown in *Table 1.* The median calculated AIP was 0.01 and 115 and 52 patients were deemed to have low and intermediate to high risk of serious thromboses, respectively.

Table 1

Characteristics of AAV patients at diagnosis and comparison of variables at diagnosis between AAV patients with AIP < 0.11 and those with AIP ≥ 0.11

Variables	All AAV patients (N=167)	AAV patients with AIP < 0.11 (N=115)	AAV patients with AIP ≥ 0.11 (N=52)	P-value
At the time of diagnosis				
Demographic data				
Age (years)	59.0 (22.0)	60.0 (24.0)	56.0 (19.8)	0.369
Male gender (N, (%))	54 (32.3)	34 (29.6)	20 (38.5)	0.255
Body mass index (kg/m^2)	22.1 (4.5)	22.0 (4.8)	23.2 (4.3)	0.198
Smoking history (N, (%))	6 (3.6)	3 (2.6)	3 (5.8)	0.310
AAV Subtypes (N, (%))				0.641
MPA	92 (55.1)	64 (55.7)	28 (53.8)	
GPA	38 (22.8)	24 (20.9)	14 (26.9)	
EGPA	37 (22.2)	27 (23.5)	10 (19.2)	
ANCA positivity (N, (%))				
MPO-ANCA (or P-ANCA) positivity	114 (68.3)	79 (68.7)	35 (67.3)	0.858
PR3-ANCA (or C-ANCA) positivity	27 (16.2)	16 (13.9)	11 (21.2)	0.239
Both ANCA positivity	8 (4.8)	6 (5.2)	2 (3.8)	1.000
ANCA negativity	34 (20.4)	26 (22.6)	8 (15.4)	0.283
AAV-specific indices				
BVAS	12.0 (11.0)	12.0 (11.0)	14.0 (10.0)	0.064
FFS	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.656
Clinical manifestations at diagnosis (N, (%))				
General	75 (44.9)	48 (41.7)	27 (51.9)	0.221
Cutaneous	38 (22.8)	29 (25.2)	9 (17.3)	0.259
Muco-membranous /Ocular	10 (6.0)	5 (4.3)	5 (9.6)	0.184
Ear nose throat	75 (44.9)	51 (44.3)	24 (46.2)	0.828

Pulmonary	97 (58.1)	69 (60.0)	28 (53.8)	0.455
Cardiovascular	43 (25.7)	27 (23.5)	16 (30.8)	0.318
Gastrointestinal	9 (5.4)	7 (6.1)	2 (3.8)	0.553
Renal	104 (62.3)	69 (60.0)	35 (67.3)	0.367
Nervous	56 (33.5)	38 (33.0)	18 (34.6)	0.842
Comorbidities at diagnosis (N, (%))				
Chronic kidney disease (stage 3-5)	53 (31.7)	33 (28.7)	20 (38.5)	0.209
Diabetes mellitus	51 (30.5)	35 (30.4)	16 (30.8)	0.965
Hypertension	89 (53.3)	57 (49.6)	32 (61.5)	0.151
Interstitial lung disease	50 (29.9)	36 (31.3)	14 (26.9)	0.567
Routine laboratory results at diagnosis				
White blood cell count (/mm^3)	9,210.0 (6,347.5)	9,180.0 (6,430.0)	10,230.0 (6,000.0)	0.927
Haemoglobin (g/dL)	11.3 (3.7)	11.6 (3.7)	11.0 (3.8)	0.250
Platelet count (× 1,000/mm^3)	308.0 (166.0)	311.0 (158.5)	294.0 (195.0)	0.949
Fasting glucose (mg/dL)	104.0 (36.0)	103.0 (34.0)	106.0 (38.0)	0.466
BUN (mg/dL)	18.4 (22.4)	18.0 (23.0)	24.2 (21.6)	0.078
Creatinine (mg/dL)	1.0 (1.3)	0.9 (1.0)	1.3 (2.0)	0.105
Total serum protein (g/dL)	6.6 (1.3)	6.7 (1.1)	6.4 (1.7)	0.043
Serum albumin (g/dL)	3.6 (1.2)	3.6 (1.1)	3.2 (1.4)	0.072
ALP (IU/L)	72.0 (38.0)	69.0 (36.0)	77.0 (51.0)	0.339
AST (IU/L)	18.5 (9.0)	19.0 (8.0)	17.0 (10.0)	0.121
ALT (IU/L)	16.5 (14.8)	15.0 (13.5)	19.0 (18.0)	0.985
Total bilirubin (mg/dL)	0.5 (0.3)	0.5 (0.3)	0.5 (0.4)	0.620
ESR (mm/hr)	64.0 (69.3)	64.0 (67.0)	64.0 (75.0)	0.406
CRP (mg/L)	17.0 (85.8)	15.0 (69.3)	25.0 (119.3)	0.123
AIP-related variables				

Total cholesterol (mg/dL)	178.0 (58.0)
TG (mg/dL)	113.0 (73.0)
HDL-cholesterol (mg/dL)	51.0 (23.0)
LDL-cholesterol (mg/dL)	104.6 (41.6)
AIP	0.01 (0.31)
Low risk (AIP < 0.11) (N, (%))	115 (68.9)
Intermediate risk (AIP = 0.11~0.21) (N, (%))	20 (12.0)
High risk (AIP > 0.21) (N, (%))	32 (19.2)

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

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; AIP: atherogenic index of plasma; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; BUN: blood urea nitrogen; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Comparison of variables between AAV patients with AIP < 0.11 and those with AIP ≥ 0.11

Based on having low or intermediate to high risk of serious thromboses, AAV patients were divided into the following two groups: AAV patients with AIP < 0.11 and those with AIP ≥ 0.11. Of the variables at diagnosis, AAV patients with AIP < 0.11 exhibited a lower BVAS than those with AIP ≥ 0.11: however, this was not statistically significant (P = 0.064). Whereas, AAV patients with AIP < 0.11 exhibited a significantly higher serum total protein levels than those with AIP ≥ 0.11 (6.7 mg/dL vs. 6.4 mg/dL) (*Table 1)*..

Correlation of AIP with continuous variables at diagnosis

At diagnosis, AIP was found to be positively correlated with both ESR (r = 0.213, P = 0.006) and CRP (r = 0.232, P = 0.003) and negatively correlated with serum albumin (r = −0.209, P = 0.007). However, AIP was not significantly correlated with age, body mass index, BVAS or FFS.

Comparison of AIP between AAV patients and controls

Of the demographic data, there were no significant differences in age (59.0 vs. 58.0 years) and male gender (32.3% vs. 27.3%). AAV patients had a significantly lower body mass index than controls (22.1 vs. 23.3 kg/m^2). Nevertheless, AAV patients exhibited a significantly higher AIP than controls (0.01 vs. −0.12, $P < 0.001$) (*Fig. 2)*..

Poor outcomes and medications during follow-up

The median follow-up duration was 33.7 months. Eighteen patients died of all-causes, 16 patients were diagnosed with CVA and 14 patients experienced CVD. The most frequently administered immunosuppressive drugs were cyclophosphamide (52.1%) and azathioprine (49.1%) (*Table 2)*..

Table 2
Characteristics of AAV patients during follow-up (N=167)

AAV patients	**Values**
Follow-up duration (months)	33.7 (65.6)
Poor outcomes during follow-up (N, (%))	
All-cause mortality (N, (%))	18 (10.8)
Follow-up duration based on all-cause mortality (months)	33.7 (65.6)
CVA (N, (%))	16 (9.6)
Follow-up duration based on CVA (months)	30.5 (64.0)
CVD (N, (%))	14 (8.4)
Follow-up duration based on CVD (months)	32.8 (63.6)
Medications administered during follow-up (N, (%))	
Glucocorticoid	15 (92.8)
Cyclophosphamide	87 (52.1)
Rituximab	29 (17.4)
Azathioprine	82 (49.1)
Mycophenolate mofetil	22 (13.2)
Tacrolimus	11 (6.6)
Methotrexate	12 (7.2)

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

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; CVA: cerebrovascular accident; CVD: cardiovascular disease.

Comparison of poor outcome-free survival analysis between AAV patients with AIP < 0.11 and those with AIP ≥ 0.11

During the follow-up duration, AAV patients with AIP ≥ 0.11 exhibited a significantly lower CVA-free survival rate than those with AIP < 0.11 based on CVA occurrence. However, there were no significant differences in patients' and CVD-free survival rates between the two groups (*Fig. 3)*..

Cox hazards model analysis for CVA

To investigate whether AIP ≥ 0.11 at diagnosis could independently predict CVA occurrence during follow-up, we compared the predictive potential of conventional risk factors for CVA, AAV-specific indices, acute phase reactants and AIP using the univariable and multivariable Cox hazards model analyses. In the univariable analysis, both AIP ≥ 0.11 (HR 3.391, 95% confidence interval (CI) 1.075, 10.695) and CRP (HR 1.008, 95% CI 1.001, 1.016) were significantly associated with CVA during follow-up. However, in the multivariable analysis, only AIP ≥ 0.11 at diagnosis was significantly associated with CVA during follow-up (*Table 3)*..

Table 3

Predictors at diagnosis for CVA occurrence during follow-up in AAV patients

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Conventional risk factors for thrombosis						
Age	1.027	0.982, 1.074	0.243			
Male gender	0.862	0.259, 2.874	0.809			
Body mass index	0.991	0.826, 1.190	0.924			
Smoking	0.047	0.000, 32787.590	0.656			
Chronic kidney disease (stage 3-5)	1.069	0.322, 3.551	0.914			
Diabetes mellitus	1.527	0.484, 4.810	0.470			
Hypertension	1.636	0.492, 5.442	0.422			
AAV-specific indices						
MPO-ANCA (or P-ANCA) positivity	0.678	0.215, 2.142	0.508			
PR3-ANCA (or C-ANCA) positivity	1.041	0.228, 4.760	0.958			
BVAS	1.074	0.995, 1.160	0.066			
FFS	1.476	0.851, 2.559	0.165			
Acute phase reactants						
ESR (mm/hr)	1.001	0.986, 1.017	0.860			
CRP (mg/L)	1.008	1.001, 1.016	0.035			
AIP ≥ 0.11	3.391	1.075, 10.695	0.037	3.392	1.076, 10.696	0.037

CVA: cerebrovascular accident; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five factor score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein: AIP: atherogenic index of plasma.

Comparison of AIP according to age-ranges and AAV subtypes

Male patients with AAV had significantly higher AIP than female patients with AAV (P = 0.026). However, there were no significant differences in body mass index (underweighted, normal weighted, overweighted and obese patients) (P = 0.131) [*16*],, age of < 50, 50–59, 60–69 and ≥ 70 years (P = 0.236) or those with each AAV subtypes (P = 0.518) (*Supplementary Fig. 1)*..

Discussion

In this study, we investigated for the first time the clinical effectiveness of AIP for predicting thrombotic events in AAV patients. We demonstrated that AAV patients with AIP ≥ 0.11 exhibited the significantly reduced cumulative CVA-free survival rate compared to those with AIP < 0.11 over 20.2 months. Our findings indicate that AIP at diagnosis is an independent predictor for CVA during follow-up among various conventional risk factor for serious thromboses as well as AAV-specific indices and acute phase reactants.

We compared AIP in AAV patients with control subjects who had no serious medical conditions including malignancies, fatal infectious disease, and chronic inflammatory diseases, particularly vasculitis. We found that AIP of AAV patients was significantly elevated compared to that of controls (0.01 vs. −0.12, P < 0.001). In previous studies, AIP of non-obese controls was found to be −0.04 ± 0.28 [*17*],, that of post-menopausal women controls without CVD was assessed as 0.10 ± 0.27 [*9]* and that of non-systemic lupus erythematosus controls was reported to be 0.24 ± 0.21 [*18]*.. Meanwhile, AIP in patients the end-stage renal disease was reported to be 0.47 (interquartile range 0.26–0.66). Moreover, AIP in patients with ankylosing spondylitis receiving anti-tumour necrosis factor-α inhibitor and that in those with AS not receiving were reported to be −0.085 ± 0.378 and −0.119 ± 0.343, respectively. Therefore, the range of AIP in patients and controls appear to vary based on ethnicity, geographical factors and medical conditions. For this reason, we believe that it was clinically significant to determine AIP of Korean patients with AAV as 0.01 for the first time.

In the cross-sectional comparative analysis of variables at diagnosis between patients with AIP < 0.11 and those with AIP ≥ 0.11, only serum total protein levels showed a statistically significant difference between the two groups. However, this difference was not clinically significant because there was no correlation between AIP and serum total protein (r = −0.072, P = 0.356). Furthermore, reduced serum total protein level has not been reported to directly associated with thrombotic events except nephrotic syndrome.

In this study, we chose AIP of 0.11 as the cut-off for predicting CVA for three reasons. First, we investigated the cumulative poor outcome-free survival rate according to low (< 0.11), intermediate (0.11–0.21) and high risk (≥ 0.21) based on AIP using the Kaplan-Meier survival analysis. In terms of death, the cumulative patients' survival rate in AAV patients with AIP < 0.11 was lower than that in those with AIP of 0.11–0.21 and in terms of CVD, the cumulative CVD-free survival rate for patients with AIP 0.11–0.21 was the lowest among three groups. However, in terms of CVA, although statistical significance was not

reached, it can be apparently seen that the frequency of CVA increased as the risk of thromboses based on AIP increases (*Supplementary Fig. 2)*..

Second, if an AAV-specific cut-off of AIP to predict CVA in AAV patients was defined, we could determine the high-risk group and apply close monitoring for CVA occurrence during follow-up by shortening the interval duration or recommending a regular check-up for CVA. For this reason, the AAV-specific cut-off of AIP for CVA occurrence was extrapolated by calculating the receiver operator characteristic (ROC) curve and selecting the maximised sum of sensitivity and specificity. However, no significant cut-off was obtained (area 0.585, 95% CI 0.418, 0.752) owing to no consideration of the follow-up duration in this method (*Supplementary Fig. 3)*.. Third, when AAV patients were divided into groups based on AIP of 0.21, only 32 of 167 patients were assigned to the AIP ≥ 0.21 group. In this case, the specificity of thrombosis is high, but it is not suitable for screening or monitoring because of the low sensitivity. Therefore, we suggest that physicians should inform all AAV patients with AIP ≥ 0.11 that they are of high risk of CVA occurrence and actively recommend a regular check-up for CVA.

Of the medications administered during follow-up, both cyclophosphamide (63.5% vs. 47.0%) and rituximab (26.9% vs. 13.0%) were administered more commonly to AAV patients with AIP ≥ 0.11 than to those with AIP < 0.11 %. Based on the latest recommendations for the management of AAV proposed by the European League Against Rheumatism and the European Renal Association-European Dialysis and Transplant Association, either cyclophosphamide or rituximab together with glucocorticoid should be applied to newly diagnosed patients with life-threatening AAV [*19]*.. Therefore, it can be reasonably speculated that the sum of the inflammatory burden in AAV patients with AIP ≥ 0.11 might be significantly higher than that of patients with AIP < 0.11 during follow-up, leading to an increased risk for CVA. Furthermore, it should be noted that the sum of the inflammatory burden could not simply be estimated by BVAS at diagnosis and rather, it might be reflected by the frequency of the exposure to cyclophosphamide and rituximab.

Of the conventional risk factors for thrombosis, AAV-specific indices, acute phase reactants and AIP [*12–14, 20, 21]*,, CVA occurrence was significantly associated with both AIP ≥ 0.11 and CRP in the univariable Cox hazards analysis and with only AIP ≥ 0.11 in the multivariable Cox model hazards analysis. BVAS at diagnosis tended to be associated with CVA but it did not get to statistical significance (P = 0.066). Also, it was beyond expectation that FFS at diagnosis, which is a prognostic factor in AAV patients, was not associated with CVA occurrence. Therefore, we concluded that AIP ≥ 0.11 at diagnosis can be used as an independent predictor of CVA during follow-up in AAV patients.

However, we expected the synergistic effect of AIP ≥ 0.11 with hypertension and diabetes mellitus which are strong conventional risk factors for thrombosis [*21]*,, and, they were not associated with CVA during the follow-up period per Cox hazards model analysis. Moreover, smoking is well known to be closely related to CVA [*22]*,, however, it was not associated with CVA in this study. We assumed that the influence of smoking on CVA occurrence was underestimated owing to the small number of former smokers (a total six patients).

A previous study suggested the major factors to increase AIP such as male gender, obesity and increased age [*23]*.. Similarly, male patients with AAV exhibited significantly elevated AIP compared to female ones (*Supplementary Fig. 1)*,, however; AIP was not affected by obesity based on body mass index and age in this study. With regard to body mass index, there was a tendency of AIP to decrease along with decreased body mass index-range among normal weighed, overweighted and obese patients. However, it was rebounded up in underweighted patient with AAV. We could not explain exactly about this phenomenon, but we tried to understand this pattern by the U-shape pattern of cholesterol based on body mass index [*24]*.. With regard to age, age was positively correlated with body mass index with a statistical significance (r = 0.213, P = 0.006). however, AIP based on age apparently showed the opposite pattern from AIP based on body mass index. With these results, it is believed that AIP in vasculitis patients exhibits a different movement from AIP in the general population. AAV subtype did not seem to contribute to AIP levels.

This study has merit in that we determined that AIP at diagnosis is an independent predictor for CVA during follow-up in a considerable number of patients with AAV for the first time. However, our study has several issues such as a retrospective study design, a monocentric study and not a large number of AAV patients included. in addition, since AIP does not include other subtypes of cholesterols, such as LDL-cholesterol, total cholesterol and non-LDL cholesterol, we could not clarify the relationship between these cholesterol subtypes and CVA occurrence through AIP in this study. We expect that future prospective studies with a larger number of AAV patients and plenty of laboratory data related to thrombosis will provide better and dynamic information of AIP in predicting thrombotic events as serious complications of AAV.

Conclusions

AIP in AAV patients was significantly higher than that in controls. Also, AIP at diagnosis could predict for CVA occurrence during follow-up in AAV patients.

Abbreviations

AIP: atherogenic index of plasma; ALP: alkaline phosphatase; ALT: alanine aminotransferase; ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; AST: aspartate aminotransferase; BUN: blood urea nitrogen; BVAS: Birmingham vasculitis activity score; C: cytoplasmic; CHCC: Chapel Hill Consensus Conferences; CI: confidence interval; CKD: chronic kidney disease; CRP: C-reactive protein; CVA: cerebrovascular accident; CVD: cardiovascular disease; EGPA: eosinophilic granulomatosis with polyangiitis; EMA: European Medicines Agency; ESR: erythrocyte sedimentation rate;

FFS: five-factor score; GPA: granulomatosis with polyangiitis; HDL: high-density lipoprotein

HR: hazard ratio; IFA: immunofluorescence assay; LDL: low-density lipoprotein; MPA: microscopic polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; ROC: receiver operator characteristic; SHAVE: Severance Hospital ANCA-associated VasculitidEs; TG: triglyceride.

Declarations

Acknowledgement

Not applicable.

Authors’ contributions

SSA and SWL conceived the study. SSA, LEL, JYP and SWL participated in the design. SSA performed statistical analyses, SSA, LEL and SWL drafted the manuscript. JJS, YBP and SWL edited and checked the manuscript. All of the authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Severance Hospital (4–2017–0673). The need for patients’ written informed consent was waived, as this was a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

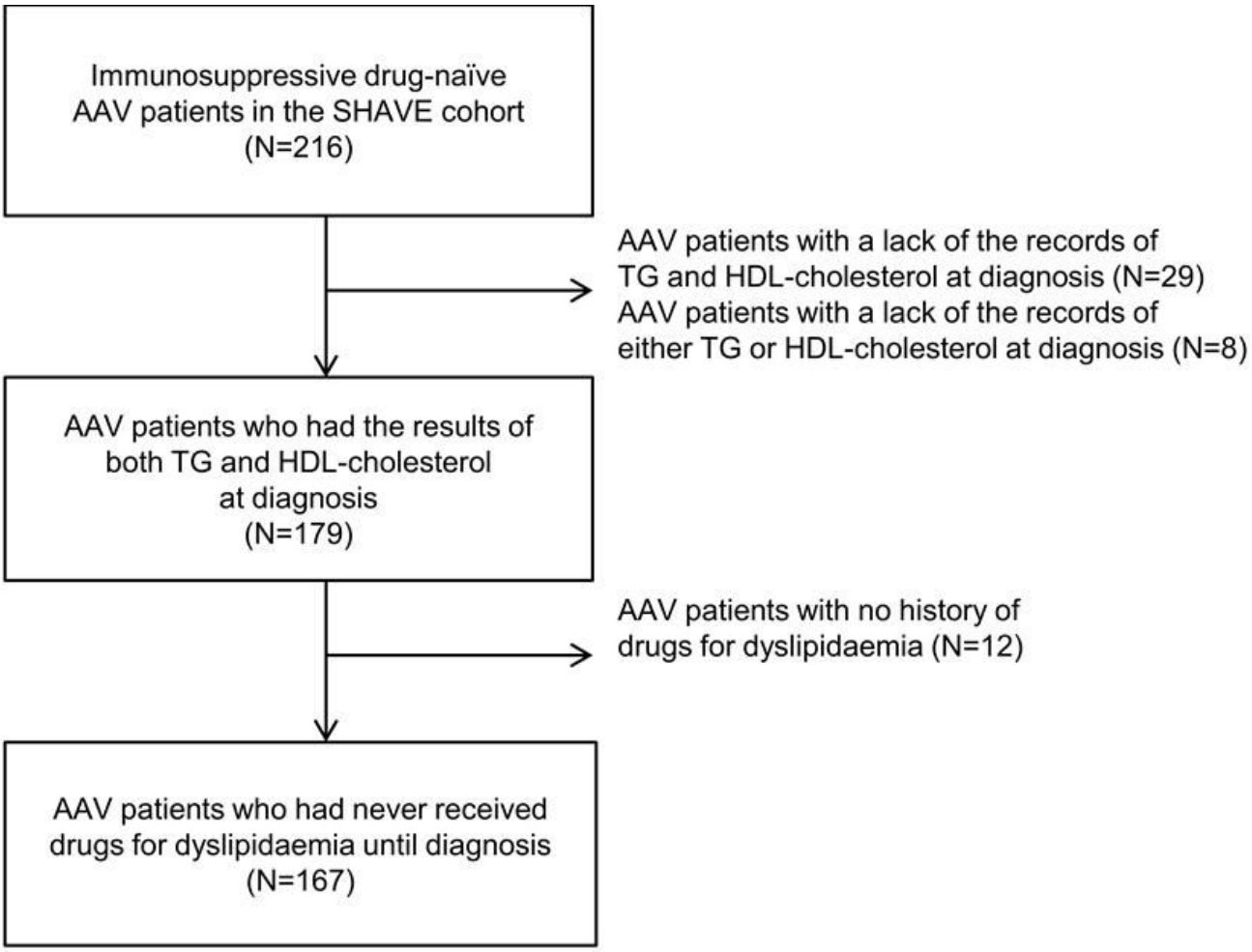

Figure 1

Algorithm for including study subjects. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; SHAVE: Severance Hospital ANCA-associated VasculitidEs; TG: triglyceride; HDL: high-density lipoprotein.

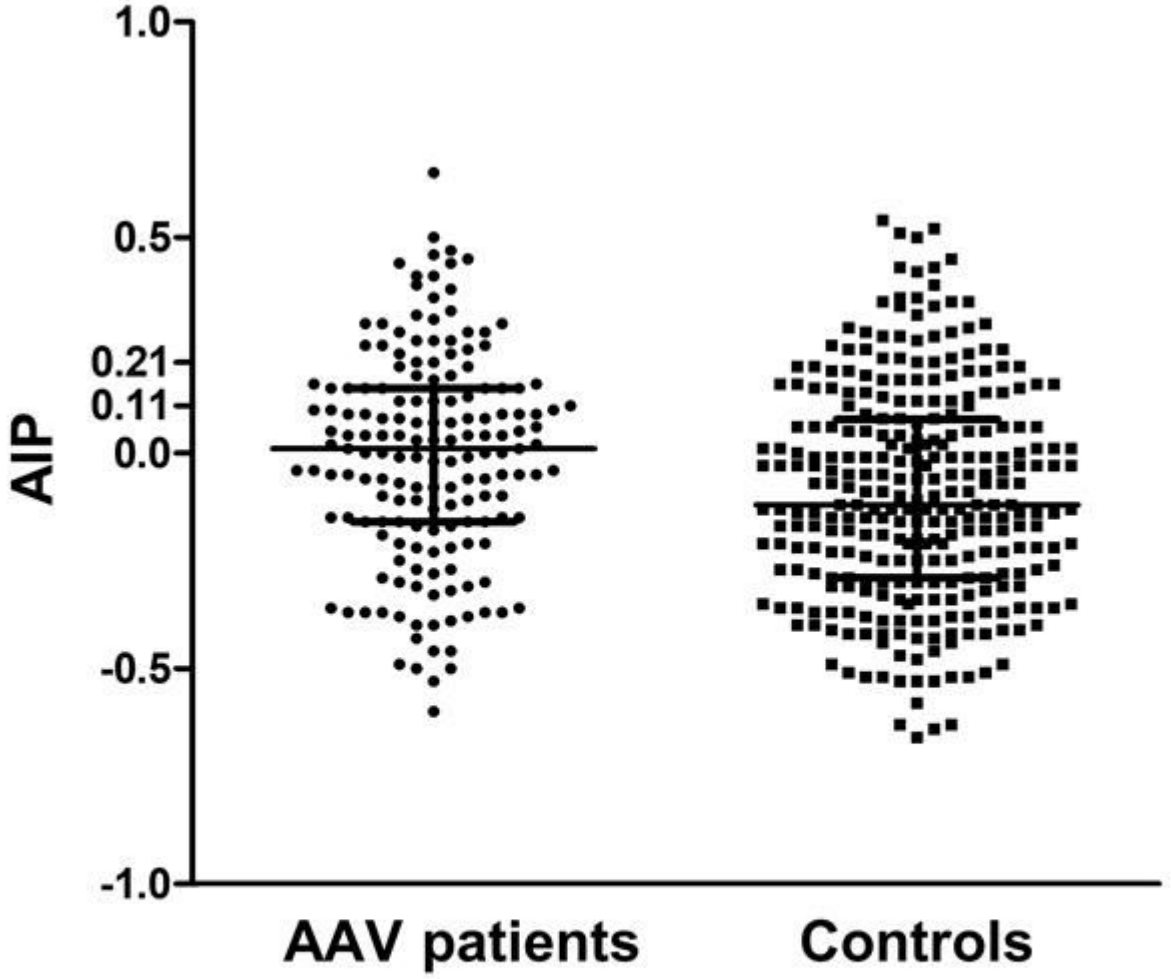

Figure 2

Comparison of AIP between AAV patients and controls. AAV patients exhibited a significantly higher AIP than controls (0.01 vs. -0.12, P < 0.001). AIP: atherogenic index of plasma; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody.

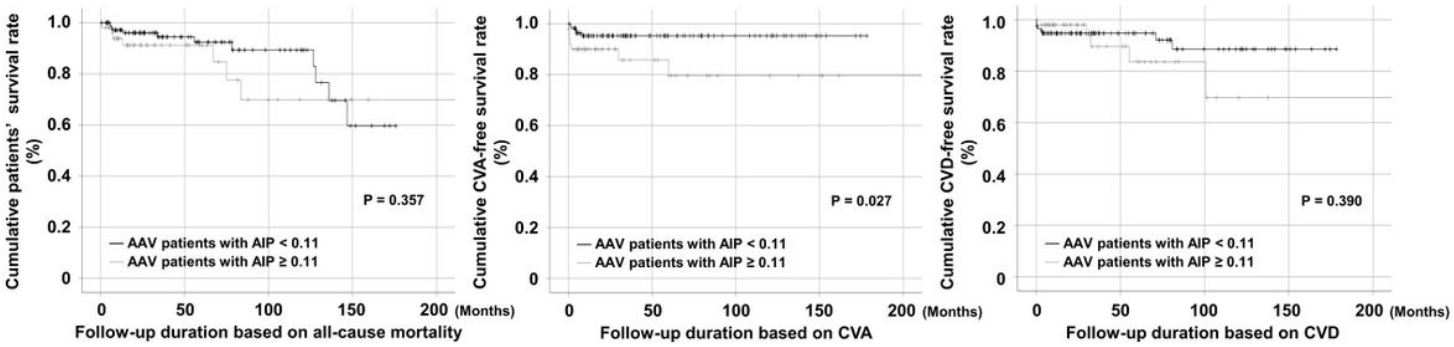

Figure 3

Comparison of the cumulative survival rates of poor outcomes. Among three poor outcomes, AAV patients with AIP ≥ 0.11 exhibited a significantly lower cumulative CVA-free survival rate than those with AIP < 0.11. AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; AIP: atherogenic index of plasma; CVA: cerebrovascular accident; CVD: cardiovascular disease.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPLEMENTARYFIGURE3AIPAAV.jpg
- SUPPLEMENTARYFIGURE1AIPAAV.jpg
- SUPPLEMENTARYFIGURE2AIPAAV.jpg