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Evaluation of body composition using computed tomography in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis

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Background/Aims: Measures of body composition, including visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA), are considered important prognostic factors in chronic diseases. The association of these measures with auto-inflammatory disorders, such as anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), remains unclear. We investigated the clinical significance of VAT, SAT, and SMA in patients with AAV.

Methods: Patients with AAV subjected to chest computed tomography (CT), abdominal CT, or positron emission tomography-CT on diagnosis of AAV were evaluated. Quantitative assessment of VAT, SAT, and SMA was performed at the third lumbar vertebral level and computed by summing the pixel attenuation for tissue-specific Hounsfield units in the corresponding region. Associations of VAT, SAT, and SMA with clinical and laboratory data and clinical outcome measures were evaluated.

Results: Of the 117 patients, 61 (52.1%) were classified as having microscopic polyangiitis, 28 (23.9%) as granulomatosis with polyangiitis, and 28 (23.9%) as eosinophilic granulomatosis with polyangiitis. VAT significantly correlated with age, weight, body mass index (BMI), and Birmingham Vasculitis Activity Score, whereas SAT correlated with weight, BMI, and creatinine levels. A significant association was found between SMA and age, height, weight, BMI, and the Five-Factor Score. Cox proportional hazards analysis showed that creatinine levels (odds ratio [OR], 1.346; 95% confidence interval [CI], 1.034 to 1.753; $p = 0.027$) and high VAT (OR, 7.137; 95% CI, 1.343–37.946; $p = 0.021$) were independently associated with all-cause mortality during follow-up.

Conclusions: Evaluation of VAT using CT is useful for estimating disease activity and all-cause mortality in patients with AAV.

Keywords: Body composition; Computed tomography; Prognosis; Anti-neutrophil cytoplasmic antibody-associated vasculitis; Visceral adipose tissue

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an auto-inflammatory disorder characterized by the production of pathogenic ANCAs and necrotizing inflammation in the vessels [1]. Three

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different diseases, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), comprise this disease entity, which is differentiated by the different organs affected and the pathologic findings [2]. Although improvements in therapeutic approaches in recent decades have led to significant favorable clinical outcomes, substantially higher mortality has been still reported in patients with AAV. In the European Vasculitis Society cohort data, the 1- and 5-year survival rates for patients with AAV were 88% and 78%, respectively [3], and a population based study performed in southern Sweden showed that 1-, 5-, and 10-year survival rates for patients with AAV were 87%, 70%, and 55%, respectively [4]. Moreover, a recent meta-analysis has demonstrated that the risk of mortality estimates was over 2.7-fold in comparison to the general population [5]. In particular, clinical factors such as age, sex, and impaired kidney function, and higher disease activity has been suggested to be associated with mortality, but with discordant results [4,6]. In this context, much attention has been persistently given to the discovery of predictive factors of prognosis in patients with AAV.

Body composition refers to the distribution of fat and lean mass within the body, which could be measured by various methods including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) [7,8]. While it was previously understood that body composition is a merely a measure of physical fitness, a growing body of evidence now suggests that changes in body composition are associated with alterations of the immune response and are associated with health outcomes of patients [9,10]. Among various measures to assess body composition, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA) are now considered important prognostic factors in chronic diseases. Typically, VAT was reported to be associated with excessive risk of mortality in patients with cancer, while an inverse correlation between SAT and SMA with patient prognosis has also been shown [11]. Nevertheless, the clinical significance of VAT, SAT, and SMA in patients with auto-inflammatory disorders, especially AAV has not been well described. Therefore, the aims of the present study were to (1) evaluate the association of VAT, SAT, and SMA with clinical and laboratory data and (2) elucidate the prognostic significance of VAT, SAT, and SMA in patients with AAV.

METHODS

Patient selection

The medical records of patients who were diagnosed as AAV between October 2000 and December 2018 were retrospectively reviewed. The inclusion criteria were as follows: (1) patients who were diagnosed with AAV at Severance Hospital in Seoul, Korea; (2) patients with had no serious comorbidities that could mimic AAV at diagnosis as identified in the 10th revised International Classification of Diseases; (3) patients who had undergone either chest CT, abdominal CT, and positron emission tomography (PET)-CT to determine the site of inflammation when the diagnosis of AAV was made. All patients were reclassified into AAV subtypes as per the 2007 European Medicines Agency algorithm for AAV and the descriptions provided by the 2012 Chapel Hill Consensus Conference definitions [2,12]. Ultimately, 117 patients with AAV were included in the study. Age-, sex-, and body mass index (BMI)-matched healthy controls (n = 50) included for comparison were recruited from those who had undergone abdominal CT for a regular health check up at the Hospital's health examination center. This study was approved by the Institutional Review Board of Severance Hospital (IRB No. 4-2017-0673) and performed in accordance with the principles set by the Declaration of Helsinki, and the requirement for written informed consent was waived because of the retrospective nature of the study.

Collection of clinical information

The clinical information collected included AAV variants, ANCA types, demographic data, clinical manifestations, comorbidities, and laboratory data, which were assessed at the date when the diagnosis of AAV was made. Demographic data consisted of age, sex, height, weight, BMI, and the Birmingham Vasculitis Activity Score (BVAS), and Five-Factor Score (FFS) (2009), which were calculated from the medical records of patients [13,14]. The clinical manifestations were collected as per the items in the BVAS and FFS (2009). Owing to the difference in weights between the revised BVAS/GPA

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and BVAS 3.0, the BVAS for patients with GPA was also calculated using BVAS 3.0 [15]. Comorbidities included the presence of hypertension, diabetes mellitus, and dyslipidemia prior to the diagnosis of AAV. Patients were defined as having the following medical condition previously when they were currently on medications or clearly stated that they were diagnosed for the corresponding comorbidities. As for laboratory data, the results of white blood cell, neutrophil, and platelet counts; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); serum albumin, total cholesterol, fasting blood glucose, and creatinine levels were obtained.

Estimation of VAT, SAT, SMA, and sarcopenia

Acquired chest CT, abdominal CT, and PET-CT images were used for the quantitative assessment of the VAT, SAT, and SMA. All analyses were performed at the third lumbar vertebral (L3) level using the Aquarius iNtuition Viewer version 4.4.12 (TeraRecon Inc., Fremont, CA, USA). The L3 level was defined as the slice including the middle of the third lumbar vertebrae. VAT, SAT, and SMA were computed identically by summing the pixel attenuation for tissue-specific Hounsfield unit: (1) adipose tissue, –190 to –30 and (2) skeletal muscle, –29 to +150 [16]. VAT was manually separated from SAT at the identical slice using the boundary inner to the abdominal muscle wall. Representative images were used to estimate VAT, SAT, and SMA are shown in Fig. 1. Sarcopenia was defined as a L3 skeletal muscle index of ≤ 49 cm^2/m^2 for men and ≤ 31 cm^2/m^2 for women based on a previous study [17]. All measurements were performed by an experienced radiology technician who was blinded to the clinical information.

Definition of obesity, clinical outcome measures, and immunosuppressive medications

Patients with and without obesity were divided in accordance with the Asian-Pacific cut-off values of BMI ≥ 25 kg/m^2 [18]. For the clinical outcome measures, all-cause mortality, end-stage renal disease (ESRD), disease relapse, acute coronary syndrome (ACS), and stroke were investigated during follow-up. We defined all-cause mortality as death attributable to any reason during follow-up, and ESRD as an impairment of renal function requiring dialysis. Disease relapse was defined as recurrence or new onset of disease with active vasculitis, as described previously [19]. The definition of ACS was set as either myocardial infarction or unstable angina and stroke as either hemorrhagic or ischemic [20,21]. Immunosuppressive medications that were used to the patients after diagnosis was counted by using the Hospital's electronic medical record system.

Statistical analysis

All statistical analyses were conducted using MedCalc software version 19 (MedCalc Software, Ostend, Belgium). Continuous variables are expressed as medians (interquartile ranges) and categorical variables as numbers (percentages). Significant differences between the two groups were analyzed using the Mann-Whitney *U* test for continuous variables and chi-square or Fisher's exact tests for categorical variables. High VAT, SAT, SMA, and VAT-to-SAT ratio was defined as the respective values over the median values, and the correlation between continuous variables was estimated by Pearson's correlation analysis. Comparison of the cumulative survival rate between groups was analyzed using the Kaplan-Meier survival analysis and the log-rank test. Multivariable Cox proportional hazards analysis using variables with significance in univariable analysis was used to identify predictive factors associated with all-cause mortality and ESRD. The p values < 0.05 were considered statistically significant in all analyses.

RESULTS

Baseline characteristics of patients

Baseline characteristics of the patients that were included in the study are described in Table 1. Sixty-one (52.1%) patients were classified as MPA, 28 (23.9%) as GPA, and 28 (23.9%) as EGPA. Seventy-nine (67.5%), 18 (15.4%), and 25 (21.4%) patients had myeloperoxidase-ANCA (or perinuclear ANCA), proteinase 3-ANCA (or cytoplasmic ANCA), and negative ANCAs, respectively. The median age of the patients was 61 years and 74 (63.2%) patients were female. The median height, weight, and BMI of the patients were 1.6 m, 56.0 kg, and 22.0 kg/m^2, respectively. Based on the cut-off BMI of ≥ 25 kg/m^2, a total of 20 (17.1%) and 97 (82.9%) patients were assigned to the obese group and non-obese groups, respectively. Patients were followed up for a median duration of 27.3 months after

Table 1. Baseline characteristics of patients with AAV

Characteristic	Value (n = 117)
AAV variants	
MPA	61 (52.1)
GPA	28 (23.9)
EGPA	28 (23.9)
ANCA types	
MPO-ANCA (or P-ANCA) positivity	79 (67.5)
PR3-ANCA (or C-ANCA) positivity	18 (15.4)
ANCA negativity	25 (21.4)
Demographic data	
Age, yr	61.0 (51.0–70.3)
Female sex	74 (63.2)
Height, m	1.6 (1.5–1.7)
Weight, kg	56.0 (50.0–65.0)
BMI, kg/m^2	22.0 (19.9–24.3)
BVAS	12.0 (8.0–19.0)
FFS (2009)	1.0 (1.0–2.0)
Follow-up duration, mon	27.3 (10.3–67.9)
Clinical manifestations	
General manifestation	58 (49.6)
Cutaneous manifestation	22 (18.8)
Mucous membrane and eye manifestation	5 (4.3)
Ear, nose, and throat manifestation	44 (37.6)
Pulmonary manifestation	77 (65.8)
Cardiovascular manifestation	31 (26.5)
Abdominal manifestation	8 (6.8)
Renal manifestation	71 (60.7)
Nervous system manifestation	41 (35.0)
Comorbidities	
Hypertension	46 (39.3)
Diabetes mellitus	23 (19.7)
Dyslipidemia	8 (6.8)
Laboratory data	
White blood cell count, /mm^3	9,800.0 (6,615.0–13,657.5)
Neutrophil count, /mm^3	7,160.0 (4,257.5–10,315.0)
Platelet count, × 10^3/mm^3	331.0 (241.0–418.3)
ESR, mm/hr	68.0 (31.8–102.0)
CRP, mg/L	24.0 (2.2–95.2)
Serum albumin, g/dL	3.3 (2.6–3.8)
Total cholesterol, mg/dL	165.0 (133.5–190.3)
Fasting blood glucose, mg/dL	106.0 (92.0–129.3)
Creatinine, mg/dL	0.9 (0.7–2.0)
Body composition indices, cm^2	
VAT	98.9 (56.7–145.5)
SAT	106.9 (69.5–158.6)
SMA	107.7 (90.9–132.2)

Values are presented as number (%) or median (interquartile range).
AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area.

the diagnosis of AAV. Among clinical manifestations, pulmonary events (65.8%) were the most common, followed by renal and general manifestations (60.7% and 49.6%). The comorbidities of hypertension, diabetes mellitus, and dyslipidemia were found in 39.3%, 19.7%, and 6.8% of patients, respectively. Concerning laboratory data, the median white blood cell, neutrophil, and platelet counts, ESR, and CRP levels were 9,800/mm^3, 7,160/mm^3, 331 × 10^3/mm^3, 68.0 mm/hr, and 24.0 mg/L, respectively. The median total cholesterol, fasting blood glucose, and creatinine levels were 165, 106, and 0.9 mg/dL, respectively.

When we calculated the body composition measures of VAT, SAT, and SMA using CT, the median values of each measure were 98.9, 106.9, and 107.7 cm^2. No significant differences were noted regarding the included measures according to ANCA variants and ANCA types compared to age-, sex-, and BMI-matched healthy controls (Fig. 2).

Comparison of VAT, SAT, and SMA according to the presence of comorbidities

Because body composition could be influenced by metabolic syndrome prior to AAV diagnosis, the presence of comorbidities of hypertension, diabetes, and dyslip-

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Table 2. Correlation of variables with VAT, SAT, and SMA in patients with AAV

	VAT	*p* value	SAT	*p* value	SMA	*p* value
Age	0.311	< 0.001	0.041	0.660	−0.256	0.005
Height	0.075	0.422	−0.154	0.099	0.582	< 0.001
Weight	0.572	< 0.001	0.339	< 0.001	0.624	< 0.001
BMI	0.702	< 0.001	0.593	< 0.001	0.352	< 0.001
BVAS	0.203	0.028	−0.086	0.354	−0.130	0.162
FFS (2009)	0.122	0.192	−0.087	0.350	−0.183	0.048
White blood cell count	0.057	0.543	−0.107	0.253	0.091	0.329
Neutrophil count	0.120	0.197	−0.122	0.190	0.081	0.385
Platelet count	0.097	0.299	0.163	0.080	0.047	0.613
ESR	0.059	0.527	−0.034	0.713	−0.040	0.666
CRP	0.153	0.101	−0.027	0.773	0.040	0.670
Serum albumin	−0.128	0.170	0.013	0.890	0.047	0.614
Total cholesterol	0.065	0.489	0.150	0.108	−0.044	0.641
Fasting blood glucose	0.174	0.060	−0.089	0.342	0.066	0.478
Creatinine	−0.048	0.610	−0.210	0.023	0.136	0.145

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

idemia, which are components of metabolic syndrome, were investigated according to measures of VAT, SAT, and SMA [22]. However, among these comorbidities, only the presence of hypertension was more frequent in patients with high VAT (58.6% vs. 20.3%, $p < 0.001$) (Supplementary Table 1).

Correlation of variables with VAT, SAT, and SMA

We investigated the correlation of VAT, SAT, and SMA measures with different variables. VAT was significantly correlated with age, weight, BMI, and BVAS, whereas SAT was correlated with weight, BMI, and creatinine. A significant correlation was found between SMA and age, height, weight, BMI, and the FFS (2009) (Table 2).

Comparison of clinical outcome measures according to VAT, SAT, and SMA

The clinical outcomes of all-cause mortality, ESRD, disease relapse, ACS, and stroke were compared according to VAT, SAT, and SMA measures. Patients with high VAT more frequently experienced mortality (22.4% vs. 3.4%, $p = 0.002$), while those with high SAT were less likely to develop ESRD (8.6% vs. 25.4%, $p = 0.016$). Disease relapse was less frequent in patients with high SMA (20.7% vs. 37.3%, $p = 0.049$) (Supplementary Table 2). In comparison, when the clinical outcome measures were evaluated according to the presence of sarcopenia, no differences in clinical outcomes were observed between the sarcopenia and non-sarcopenia groups (Supplementary Table 3).

Factors associated with all-cause mortality and ESRD

To exclude the possibility of length bias, Kaplan-Meier curve analysis was performed to compare the overall, renal, and relapse-free survival rates according to VAT, SAT, and SMA. Patients with high VAT and low SAT had lower overall survival and renal survival rates, respectively ($p < 0.001$ and $p = 0.014$) (Supplementary Fig. 1A and 1B). However, there were no differences in the relapse-free survival rate according to SMA ($p = 0.097$) (Supplementary Fig. 1C). In addition, the clinical outcomes showed no significant differences between patients with and without obesity (Supplementary Fig. 2).

We performed Cox proportional hazards analysis to evaluate factors associated with all-cause mortality and ESRD. As shown in Table 3, the diagnosis of MPA, age, BVAS, the presence of hypertension, CRP, serum al-

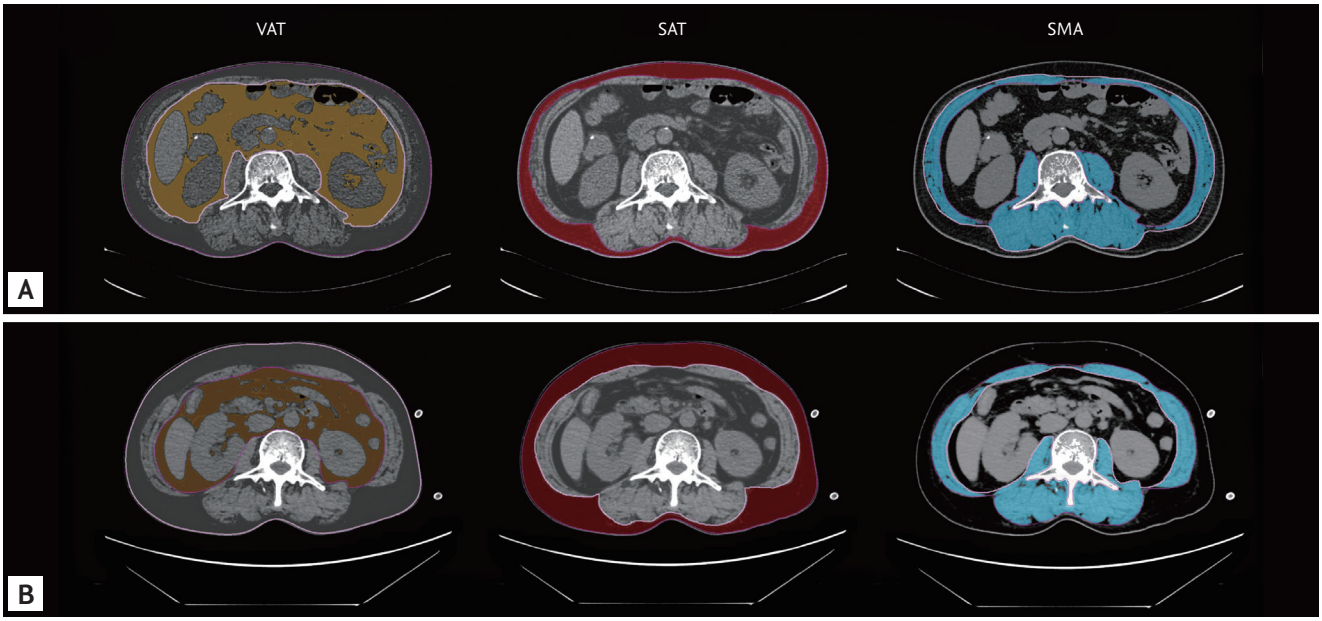

Figure 1. Measurement of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA) using computed tomography in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. Representative images used to measure VAT, SAT, and SMA. Images were obtained from a 72-year-old man (A) and a 56-year-old woman (B).

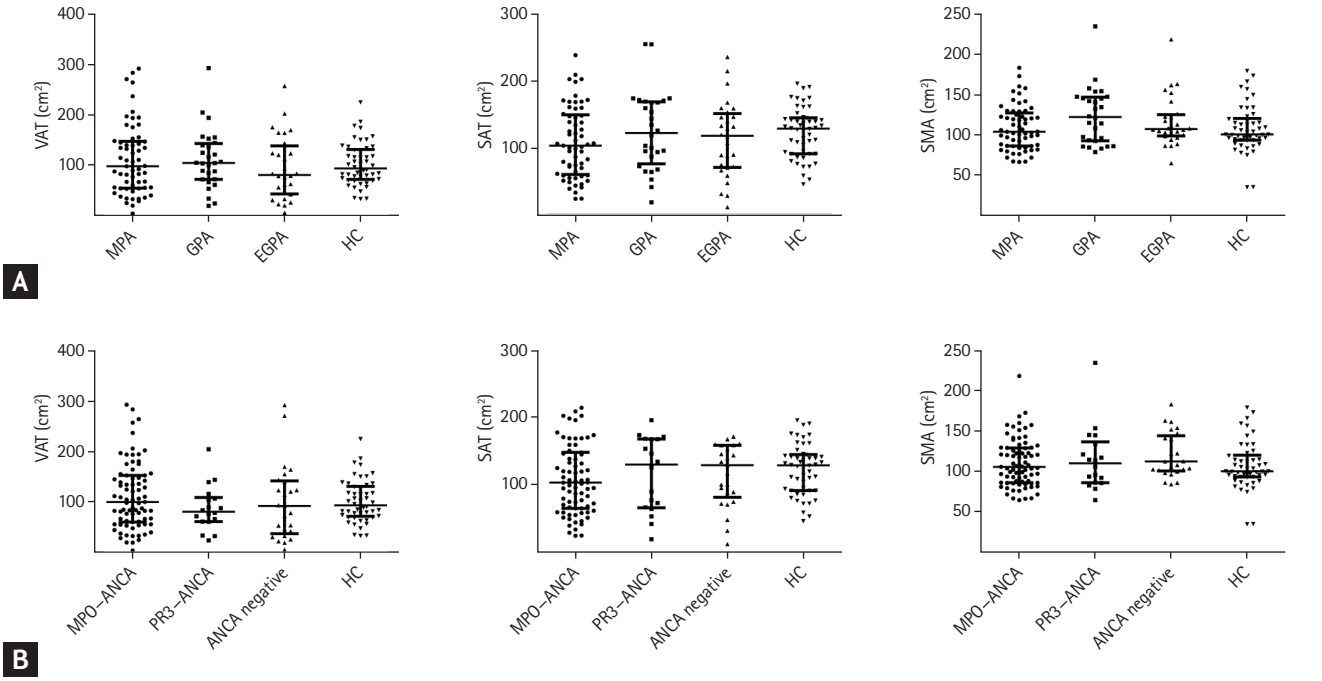

Figure 2. Comparison of visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA) according to diagnosis and anti-neutrophil cytoplasmic antibody (ANCA) serotype in patients with ANCA-associated vasculitis. VAT, SAT, and SMA measures were compared according to diagnosis (A) and ANCA serotype (B) including healthy controls. MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; HC, healthy control; MPO, myeloperoxidase; PR3, proteinase 3.

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Table 3. Multivariable Cox proportional hazards analysis for factors associated with all-cause mortality in patients with AAV

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
MPA	3.188 (1.006–10.100)	0.049	2.501 (0.645–9.693)	0.185
GPA	1.238 (0.392–3.905)	0.716		
EGPA[a]	NA			
MPO-ANCA (or P-ANCA) positivity	2.233 (0.626–7.967)	0.216		
PR3-ANCA (or C-ANCA) positivity	0.709 (0.159–3.156)	0.652		
ANCA negativity	0.218 (0.029–1.669)	0.143		
Age, yr	1.069 (1.031–1.165)	0.004	1.051 (0.978–1.130)	0.176
Female sex	0.734 (0.261–2.067)	0.558		
Height	0.533 (0.001–224.598)	0.839		
Weight	1.027 (0.980–1.077)	0.270		
BMI	1.123 (0.960–1.314)	0.146		
BVAS	1.098 (1.017–1.185)	0.017	0.974 (0.862–1.099)	0.664
Hypertension	5.291 (1.660–16.868)	0.005	1.271 (0.329–4.901)	0.728
Diabetes mellitus	2.500 (0.846–7.383)	0.097		
Dyslipidaemia[a]	NA			
White blood cell count	1.000 (0.999–1.000)	0.474		
Neutrophil count	1.089 (0.986–1.204)	0.094		
Platelet count	1.000 (0.997–1.004)	0.707		
ESR	1.014 (0.999–1.028)	0.054		
CRP	1.007 (1.000–1.014)	0.047	1.002 (0.990–1.013)	0.799
Serum albumin	0.260 (0.111–0.610)	0.002	0.454 (0.153–1.348)	0.155
Total cholesterol	0.990 (0.977–1.004)	0.148		
Fasting blood glucose	1.003 (0.993–1.013)	0.536		
Creatinine	1.341 (1.126–1.597)	0.001	1.346 (1.034–1.753)	0.027
High VAT	8.657 (1.940–38.639)	0.005	7.137 (1.343–37.946)	0.021
High SAT	1.150 (0.417–3.174)	0.787		
High SMA	1.761 (0.626–4.960)	0.284		

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; OR, odds ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; NA, not applicable; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area.

[a]The odds ratio was not obtainable because no death was observed in patients with EGPA and dyslipidemia.

bumin, creatinine, and high VAT was associated with all-cause mortality in univariable analysis. However, in multivariable analysis, only creatinine (odds ratio [OR], 1.346; 95% confidence interval [CI], 1.034 to 1.753; $p = 0.027$) and high VAT (OR, 7.137; 95% CI, 1.343 to 37.946; $p = 0.021$) were independently associated with all-cause mortality. Furthermore, patients with mortality and those without mortality showed no differences in terms of the administration of immunosuppressive medications (Supplementary Table 4). In terms of the factors related to ESRD, a diagnosis of MPA, BVAS, the presence of hypertension, total cholesterol, creatinine levels,

Table 4. Multivariable Cox proportional hazards analysis for factors associated with end-stage renal disease in patients with AAV

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
MPA	3.133 (1.134–8.653)	0.028	1.266 (0.367–4.365)	0.709
GPA	0.822 (0.275–2.460)	0.726		
EGPA	0.136 (0.018–1.018)	0.052		
MPO-ANCA (or P-ANCA) positivity	2.155 (0.719–6.459)	0.171		
PR3-ANCA (or C-ANCA) positivity	0.852 (0.248–2.923)	0.799		
ANCA negativity	0.366 (0.085–1.577)	0.177		
Age	1.017 (0.982–1.054)	0.344		
Female sex	1.288 (0.495–3.354)	0.604		
Height	0.108 (0.000–18.515)	0.396		
Weight	0.960 (0.915–1.006)	0.085		
BMI	0.884 (0.760–1.029)	0.112		
BVAS	1.092 (1.027–1.163)	0.005	0.995 (0.909–1.090)	0.917
Hypertension	3.261 (1.296–8.206)	0.012	1.616 (0.521–5.020)	0.406
Diabetes mellitus	1.938 (0.743–5.056)	0.176		
Dyslipidaemia	0.785 (0.105–5.875)	0.813		
White blood cell count	1.000 (0.999–1.000)	0.450		
Neutrophil count	1.066 (0.966–1.175)	0.203		
Platelet count	0.998 (0.995–1.002)	0.390		
ESR	1.004 (0.993–1.015)	0.533		
CRP	1.002 (0.995–1.009)	0.628		
Serum albumin	0.638 (0.345–1.182)	0.153		
Total cholesterol	0.985 (0.973–0.997)	0.016	0.983 (0.967–0.999)	0.039
Fasting blood glucose	1.000 (0.991–1.010)	0.893		
Creatinine	1.784 (1.527–2.085)	< 0.001	1.712 (1.432–2.047)	< 0.001
High VAT	0.697 (0.284–1.709)	0.430		
High SAT	0.303 (0.110–0.836)	0.021	0.518 (0.167–1.606)	0.255
High SMA	2.167 (0.864–5.438)	0.099		

AAV, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; OR, odds ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area.

and high SAT was associated with ESRD. Multivariable analysis revealed that total cholesterol (OR, 0.983; 95% CI, 0.967 to 0.999; $p = 0.039$) and creatinine (OR, 1.712; 95% CI, 1.432 to 2.047; $p < 0.001$) were independent factors for the development of ESRD (Table 4).

DISCUSSION

While measures of body composition, such as adipose tissue and muscle are increasingly accepted as important prognostic factors in various diseases, the relationship between body composition and the prognosis of AAV is still largely uncertain. In the present study, we estimated three different body composition indices,

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namely VAT, SAT, and SMA, using CT in patients with AAV. Among the estimated body composition measures, VAT was associated with disease activity in patients with AAV, and high VAT was independently associated with all-cause mortality along with serum creatinine levels, which is a well-known prognostic factor in AAV. The findings of our study imply that assessment of VAT may aid in assessing disease activity and identifying subjects with increased risk of mortality in patients with AAV.

There is abundant evidence in the literature supporting the association between high VAT and all-cause mortality found in the present study. Obesity is characterized by an increase in adipose tissue in the body, which is a condition of impaired immunity leading to chronic inflammation [23]. In obesity, the expression of proinflammatory cytokines and chemoattractants is increased in the adipose tissue and VAT is regarded as the major source [24]. Moreover, adipose tissue is composed of different cell types such as adipocytes, fibroblasts, vascular endothelial cells, and immune cells. Changes that occur in the adipose tissue microenvironment found in obesity could lead to the polarization of immune cells into an inflammatory phenotype (ie., the expansion of M1 macrophages and inflammatory helper T cells), which further amplify and perpetuate the immune response [23]. Furthermore, considering the fact that a higher degree of inflammation is associated with increased mortality in the general population [25], it can be speculated that higher VAT is associated with a lower survival rate in patients with auto-inflammatory disorders, particularly AAV. Of note, VAT was correlated with BVAS, which is the most widely used measure to assess disease activity in AAV, rather than with ESR and CRP, suggesting that VAT could play a role in the inflammatory process in AAV independent of conventional acute phase reactants.

In contrast to VAT, SAT is considered to possess a protective effect on patient prognosis in various cancers [26,27]. Although the precise physiological mechanism by which SAT regulates inflammation is largely unclear, the opposite effect of SAT compared to that of VAT can be partly explained by the "adipose tissue overflow hypothesis," which explains that the accumulation of VAT increases when energy storage in SAT exceeds the normal limit [28]. In line with this finding, we found that SAT was inversely associated with ESRD in univariable Cox proportional hazards analysis, although its significance was not evident in multivariable analysis. Meanwhile, the total cholesterol level was found to be an independent protective factor of ESRD along with creatinine levels. Because dyslipidemia is associated with adverse renal outcomes in general [29], this finding might be considered rather counterintuitive. However, this paradoxical association seems to be relevant to the malnutrition induced by inflammation, as several epidemiologic studies have demonstrated that lower total cholesterol levels are inversely correlated with the incidence of ESRD [30].

As expected, when we evaluated the correlation between body composition measures with different variables, a strong association was found between VAT and SAT with weight and BMI. These findings are in line with the understanding that weight and BMI, which are the most commonly used methods to assess obesity, are increased with the accumulation of corporal adipose tissue. On the other hand, obesity is strongly associated with metabolic syndrome [31]. However, on investigating the medical comorbidities comprising metabolic syndrome, we found that only the presence of hypertension, but not diabetes mellitus or dyslipidemia, was significantly different between patients with high and low VAT. In addition, when we divided our patients into obese and non-obese groups and compared the clinical outcomes, no difference in the patient prognosis was found. These findings suggest that the interplay between adiposity and the pathogenesis of AAV may be complex and may not be exclusively accounted for altered metabolism.

Recently, it has been suggested that patients with AAV exhibit several different characteristics according to the variants and ANCA types [32]. However, in our subgroup analysis based on AAV variants and ANCA types, there was no difference in specific body composition variables between groups, even in comparisons with age-, sex-, and BMI-matched healthy controls. Therefore, it could be suggested that VAT, SAT, and SMA have limited clinical value for differentiating patients with AAV subtypes from healthy controls.

Sarcopenia refers to a condition of decreased skeletal muscle mass, which is closely associated with anthropometric measures as well as the aging process [33]. Consistently, in this study, an inverse correlation was

found between age and SMA and a positive correlation was identified between height, weight, BMI, and SMA. However, recent studies have shown that sarcopenia could also be influenced by inflammation via the catabolic effects of proinflammatory cytokines, and that it predicts adverse clinical outcomes by serving as a surrogate marker of systemic inflammation and malnutrition [34,35]. Interestingly, we found a significant inverse correlation between SMA and FFS (2009), which is an established prognostic factor in AAV, although SMA was not significantly correlated with ESR or CRP. Nevertheless, high SMA was not associated with lower relapse-free survival on Kaplan-Meier analysis. Moreover, when the definition of sarcopenia, derived by the Korean National Health and Nutritional Examination Surveys was applied [17], it was not associated with any of the clinical outcome measures. Thus, it seems that the definition and clinical significance of sarcopenia may not be generalized and should be cautiously adopted depending on the underlying medical condition.

Obesity, especially high VAT levels, has previously been reported to be a relevant factor in the development of cardiovascular events in the general population [36]. Interestingly, a recent publication by Briot et al. [37] evaluated VAT and SAT by DXA and demonstrated that a high VAT-to-SAT ratio predicts major cardiovascular events in patients with systemic necrotizing vasculitis. In contrast, there were no differences in the outcomes of ACS and stroke according to VAT or SAT, as well as the VAT-to-SAT ratio, in our study. Notably, the values of VAT and SAT in the study by Briot et al. [37] were much higher (mean VAT, 121.6 and SAT, 281.0), and the mean BMI value was also higher than that in our cohort. Considering the differences in baseline values of body composition and the patients' ethnic groups, this might have influenced the discrepant result from our study with that of Briot et al. [37]. In addition, the relatively short follow-up duration in our study and the differences in definitions of clinical parameters should also be taken into account. Conversely, there are several advantages in our study. First, all data were collected from a single center, which makes our study less prone to interobserver or intercenter variability. Second, both CT and MRI are currently gold standard methods for the measurement of abdominal adipose tissue [38]. Therefore, CT could be more accurate for assessing VAT and SAT. Third, we measured SMA and investigated its clinical significance together with those of VAT and SAT. Fourth, besides cardiovascular events, other clinical outcomes including all-cause mortality, ESRD, and disease relapse were evaluated, further emphasizing the value of assessing body composition measures in AAV.

There are several limitations in this study. First, because the study design was retrospective, data were collected by reviewing electronic medical records. Second, although identical criteria were used to estimate VAT, SAT, and SMA, differences in imaging modalities might have influenced the calculation of body composition measures. Third, because CT is not an essential imaging study for AAV, it may have been performed in patients with severe clinical manifestations or uncertain inflammatory foci at the initial presentation. Furthermore, patients with renal involvement might have been less likely to undergo CT. Thus, the characteristics of our study population may not represent the general characteristics of all AAV patients. Fourth, there are concerns regarding the poor level of agreement between skeletal mass measured using CT and other parameters such as BIA findings and the mid-arm muscle circumference; furthermore, it is uncertain whether SMA in L3 is representative of the skeletal mass for defining sarcopenia. Finally, it is still unknown whether measures to reduce VAT (i.e., exercise and diet control) are beneficial in patients with AAV. Additional investigations are warranted to verify the results of our study and to elucidate the impact of body composition in AAV.

In conclusion, our study demonstrated that among body composition measures, VAT was associated with disease activity and high VAT levels were independently associated with all-cause mortality in patients with AAV. Estimation of VAT could aid in estimating the disease activity and identifying subjects with an increased risk of mortality in patients with AAV.

KEY MESSAGE

1. Among the body composition indices measured by quantitative computed tomography (CT), visceral adipose tissue (VAT) was associated with disease activity in patients with antibody-associated vasculitis (AAV).

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2. In addition, high VAT was an independent predictor of all-cause mortality in patients with anti-neutrophil cytoplasmic AAV.
3. Estimation of VAT using CT could aid in estimating disease activity and identifying subjects with an increased risk of mortality in patients with AAV.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Comparison of VAT, SAT, and SMA according to the presence of comorbidities in patients with AAV

Variable	VAT (n = 117)			SAT (n = 117)			SMA (n = 117)		
	High (n = 58)	Low (n = 59)	*p* value	High (n = 58)	Low (n = 59)	*p* value	High (n = 58)	Low (n = 59)	*p* value
HTN (+)	34 (58.6)	12 (20.3)	< 0.001	26 (44.8)	20 (33.9)	0.228	26 (44.8)	20 (33.9)	0.228
HTN (–)	24 (41.4)	47 (79.7)		32 (55.2)	39 (66.1)		32 (55.2)	39 (66.1)	
DM (+)	15 (25.9)	8 (13.6)	0.096	14 (24.1)	9 (15.3)	0.229	12 (20.7)	11 (18.6)	0.782
DM (–)	43 (74.1)	51 (86.4)		44 (75.9)	50 (84.7)		46 (79.3)	48 (81.4)	
Dyslipidemia (+)	6 (10.3)	2 (3.4)	0.163	5 (8.6)	3 (5.1)	0.490	2 (3.4)	6 (10.2)	0.272
Dyslipidemia (–)	52 (89.7)	57 (96.6)		53 (91.4)	56 (94.9)		56 (96.6)	53 (89.8)	

Values are expressed as number (%).

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; HTN, hypertension; DM, diabetes mellitus.

Supplementary Table 2. Comparison of clinical outcome measures according to VAT, SAT, and SMA in patients with AAV

Clinical outcome	VAT (n = 117)			SAT (n = 117)			SMA (n = 117)		
	High (n = 58)	Low (n = 59)	*p* value	High (n = 58)	Low (n = 59)	*p* value	High (n = 58)	Low (n = 59)	*p* value
Mortality (+)	13 (22.4)	2 (3.4)	0.002	8 (13.8)	7 (11.9)	0.756	9 (15.5)	6 (10.2)	0.389
Mortality (–)	45 (77.6)	57 (96.6)		50 (86.2)	52 (88.1)		49 (84.5)	53 (89.8)	
ESRD (+)	8 (13.8)	12 (20.3)	0.349	5 (8.6)	15 (25.4)	0.016	13 (22.4)	7 (11.9)	0.131
ESRD (–)	50 (86.2)	47 (79.7)		53 (91.4)	44 (74.6)		45 (77.6)	52 (88.1)	
Disease relapse (+)	18 (31.0)	16 (27.1)	0.642	17 (29.3)	17 (28.8)	0.953	12 (20.7)	22 (37.3)	0.049
Disease relapse (–)	40 (69.0)	43 (72.9)		41 (70.7)	42 (71.2)		46 (79.3)	37 (62.7)	
Acute coronary syndrome (+)	2 (3.4)	2 (3.4)	0.999	2 (3.4)	2 (3.4)	0.999	2 (3.4)	2 (3.4)	0.999
Acute coronary syndrome (–)	56 (96.6)	57 (96.6)		56 (96.6)	57 (96.6)		56 (96.6)	57 (96.6)	
Stroke (+)	4 (6.9)	3 (5.1)	0.717	4 (6.9)	3 (5.1)	0.717	3 (5.2)	4 (6.8)	0.999
Stroke (–)	54 (93.1)	56 (94.9)		54 (93.1)	56 (94.9)		55 (94.8)	55 (93.2)	

Values are expressed as number (%).

VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; SMA, skeletal muscle area; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ESRD, end-stage renal disease.

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Supplementary Table 3. Comparison of clinical outcome measures according to the presence of sarcopenia in patients with AAV

Clinical outcome	Sarcopenia group (n = 30)	Non-sarcopenia group (n = 87)	*p* value
Mortality (+)	5 (16.7)	10 (11.5)	0.467
Mortality (–)	25 (83.3)	77 (88.5)	
ESRD (+)	6 (20.0)	14 (16.1)	0.625
ESRD (–)	24 (80.0)	73 (83.9)	
Disease relapse (+)	9 (30.0)	25 (28.7)	0.896
Disease relapse (–)	21 (70.0)	62 (71.3)	
Acute coronary syndrome (+)	0	4 (4.6)	0.571
Acute coronary syndrome (–)	30 (100.0)	83 (95.4)	
Stroke (+)	1 (3.3)	6 (6.9)	0.676
Stroke (–)	29 (96.7)	81 (93.1)	

Values are expressed as number (%).
AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ESRD, end-stage renal disease.

Supplementary Table 4. Immunosuppressive medications administered to patients with AAV with and without mortality

Immunosuppressive medications	Patients with mortality (n = 15)	Patients without mortality (n = 102)	*p* value
Glucocorticoid	14 (93.3)	92 (90.2)	0.999
Cyclophosphamide	6 (40.0)	53 (52.0)	0.389
Mycophenolate mofetil	2 (13.3)	8 (7.8)	0.615
Azathioprine	4 (26.7)	37 (36.3)	0.571
Tacrolimus	2 (13.3)	4 (3.9)	0.170
Rituximab	3 (20.0)	8 (7.8)	0.149
Methotrexate	1 (6.7)	5 (4.9)	0.569

Values are expressed as number (%).
AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis.

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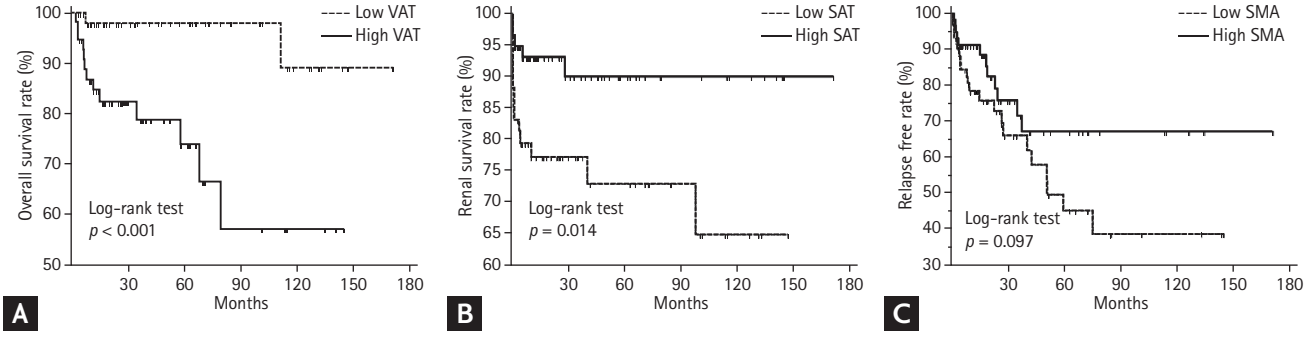
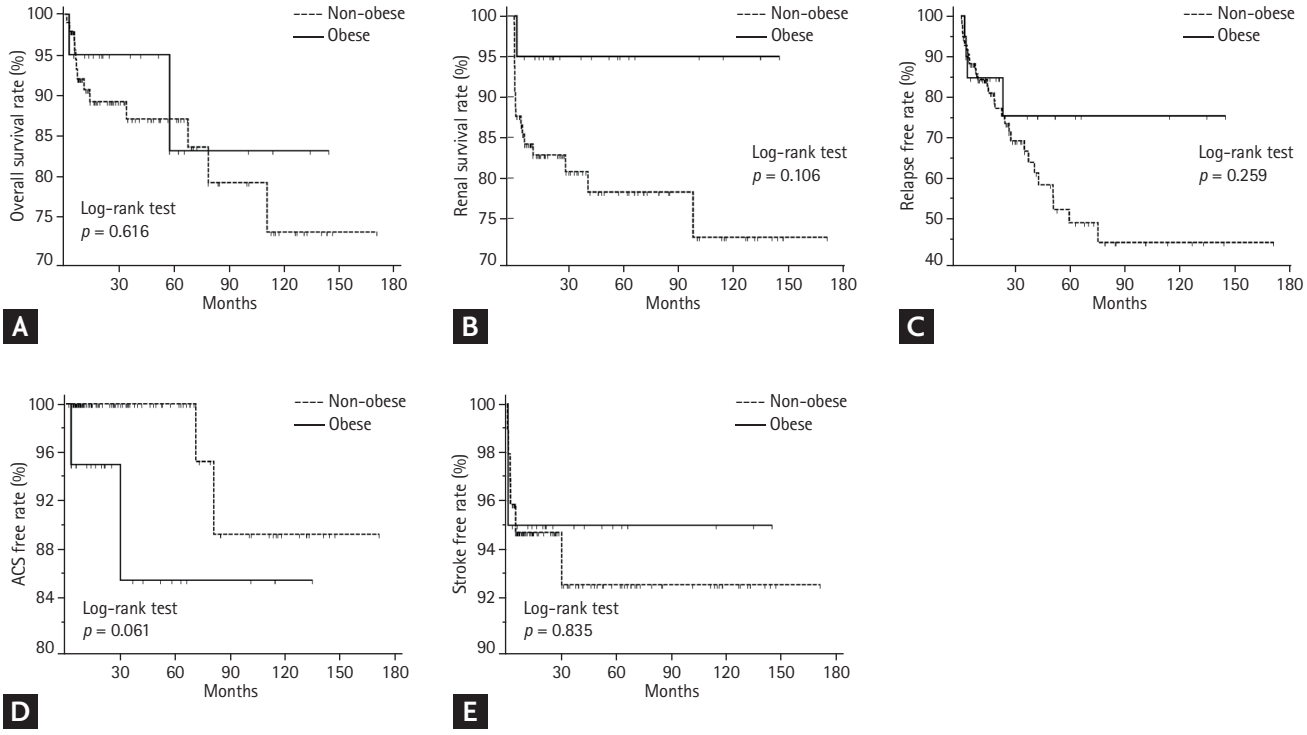


Supplementary Figure 1. Kaplan-Meier curve analysis for overall, renal, and relapse-free survival rates according to visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and skeletal muscle area (SMA) in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. The overall survival rate (A), renal survival rate (B), and relapse-free survival rate (C) are compared according to VAT, SAT, and SMA.



Supplementary Figure 2. Comparison of clinical outcome measures between obese and non-obese patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV). The overall survival rate (A), renal survival rate (B), relapse-free survival rate (C), acute coronary syndrome (ACS)-free rate (D), and stroke-free rate (E) are compared between obese and non-obese patients with AAV.

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