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
different diseases, microscopic polyangiitis (MPA), granulomatosi
with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA), comprise
this disease entity, which is differentiated by the dif-
ferent 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 Vascu-
litis 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 suggest-
ed 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 alter-
ations of the immune response and are associated with
health outcomes of patients [9,10]. Among various mea-
sures to assess body composition, visceral adipose tissue
(VAT), subcutaneous adipose tissue (SAT), and skeletal
muscle area (SMA) are now considered important prog-
nostic factors in chronic diseases. Typically, VAT was
reported to be associated with excessive risk of mortal-
ity in patients with cancer, while an inverse correla-
tion 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) eval-
uate the association of VAT, SAT, and SMA with clinical
and laboratory data and (2) elucidate the prognostic sig-
nificance 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 Internation-
al Classification of Diseases; (3) patients who had un-
dergone 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 writ-
ten informed consent was waived because of the retro-
spective nature of the study.

Collection of clinical information
The clinical information collected included AAV vari-
ants, ANCA types, demographic data, clinical manifesta-
tions, 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
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 \( \leq 49 \) cm\(^2\)/m\(^2\) for men and \( \leq 31 \) 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 \( \geq 25 \) 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 ANCs, 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 \( \geq 25 \) 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...
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 165.0 mg/dL, 106.0 mg/dL, 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 cm$^2$, 106.9 cm$^2$, and 107.7 cm$^2$, 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$^2$, respectively. The median total cholesterol, fasting blood glucose, and creatinine levels were 165, 106, and 0.9 mg/dL, respectively.

**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-
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 (\( p = 0.697 \)) (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 albumin, and total cholesterol were associated with all-cause mortality and ESRD.

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

| Variable                      | 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   | 0.681 | 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.
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.
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, and dyslipidemia were significantly associated with mortality.

### 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 | 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 | 2.333 (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) | 0.065 |       | 1.271 (0.329–4.901)   | 0.728 |       |
| Diabetes mellitus               | 2.500 (0.846–7.383)  | 0.097 |       |                        |       |       |
| Dyslipidaemam\(^a\)            | 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 (0.153–1.358)   | 0.155 |       |
| Total cholesterol               | 0.990 (0.977–1.004)  | 0.148 |       |                        |       |       |
| Fasting blood glucose           | 1.005 (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.
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,
nally 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 (i.e., 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 obesity, and thus 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 cata-
bolic effects of proinflammatory cytokines, and that it
predicts adverse clinical outcomes by serving as a sur-
rogate marker of systemic inflammation and malnutrition
[34,35]. Interestingly, we found a significant inverse cor-
relation between SMA and FFS (2009), which is an estab-
lished 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 ap-
plied [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 gen-
eralized 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 develop-
ment 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 differenc-
es in definitions of clinical parameters should also be
taken into account. Conversely, there are several advan-
tages in our study. First, all data were collected from a
single center, which makes our study less prone to in-
terobserver or intercenter variability. Second, both CT
and MRI are currently gold standard methods for the
measurement of abdominal adipose tissue [38]. There-
fore, CT could be more accurate for assessing VAT and
SAT. Third, we measured SMA and investigated its clin-
ical significance together with those of VAT and SAT.
Fourth, besides cardiovascular events, other clinical out-
comes 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, be-
cause the study design was retrospective, data were col-
lected 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 inflam-
matory 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 charac-
teristics 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 rep-
resentative 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 pa-
ients with AAV. Additional investigations are warranted
to verify the results of our study and to elucidate the im-
pact 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 mea-
sured by quantitative computed tomography
(CT), visceral adipose tissue (VAT) was asso-
ciated with disease activity in patients with
antibody-associated vasculitis (AAV).
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)     | <.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       |
| Mortality (+)             | 13 (22.4)     | 2 (3.4)       | 0.002         | 8 (13.8)       | 7 (11.9)      | 0.756         |
| Mortality (-)             | 45 (77.6)     | 57 (96.6)     |               | 50 (86.2)      | 52 (88.1)     |               |
| ESRD (+)                  | 8 (13.8)      | 12 (20.3)     | 0.349         | 5 (8.6)        | 15 (25.4)     | 0.016         |
| ESRD (-)                  | 50 (86.2)     | 47 (79.7)     |               | 53 (91.4)      | 44 (74.6)     |               |
| Disease relapse (+)       | 18 (31.0)     | 16 (27.1)     | 0.642         | 17 (29.3)      | 17 (28.8)     | 0.953         |
| Disease relapse (-)       | 40 (69.0)     | 43 (72.9)     |               | 41 (70.7)      | 42 (71.2)     |               |
| Acute coronary syndrome (+)| 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)     |               |
| Stroke (+)                | 4 (6.9)       | 3 (5.1)       | 0.717         | 4 (6.9)        | 3 (5.1)       | 0.717         |
| Stroke (-)                | 54 (93.1)     | 56 (94.9)     |               | 54 (93.1)      | 56 (94.9)     |               |

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.
### 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.
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.