

# Association Between Body Mass Index and Severe Infection in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Retrospective Cohort in Japan

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## Research article

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# Abstract

**Background:** Although previous studies have evaluated risk factors for the incidence of severe infection in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), the relationship between body mass index (BMI) and severe infection in AAV has not been elucidated. We hypothesized that elderly AAV patients with a low BMI would be at a higher risk of infection. To evaluate this hypothesis, we investigated the association between underweight at AAV diagnosis and subsequent severe infection in elderly AAV patients.

**Methods:** This single-center retrospective cohort study included 98 consecutive elderly AAV patients treated at the Aichi Medical University Hospital in Japan between 2004 and 2018. The relationships between BMI at diagnosis and subsequent first severe infection were assessed using multivariate Cox proportional hazards models.

**Results:** During the entire follow-up period (median, 22 months; interquartile range, 7–52 months), 32 (32.7%) patients developed at least one severe infection. Low BMI ( $< 18.5 \text{ kg/m}^2$  compared with normal BMI [ $18.5\text{--}23.0 \text{ kg/m}^2$ ], adjusted hazard ratio [HR] = 2.70, 95% confidence interval [CI]: 1.18–6.17;  $P = 0.018$ ) and use of methylprednisolone pulse therapy (adjusted HR = 3.09, 95% CI: 1.37–6.99;  $P = 0.007$ ) were the significant predictors of severe infection. Furthermore, an interaction effect between unintentional body weight loss ( $> 10\%$ ) within 6 months before diagnosis and low BMI was observed ( $P < 0.001$ ).

**Conclusions:** Low BMI was associated with a higher risk of severe infection in elderly AAV patients, suggesting that careful management may be required to prevent the development of infection in patients with a low BMI. Further studies are needed to elucidate the optimal treatment strategy for these patients.

## Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by necrotizing vasculitis of the small vessels and high ANCA-positivity; the condition includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1, 2].

Recently, avoidance of fatal organ damage in AAV has been achieved by advances in the treatment strategy for AAV [3–7]. However, patients with AAV have markedly higher rates of severe infection than the general population, and infection is an important complication, associated with morbidity and mortality, that occurs during immunosuppressive treatment for AAV [8].

Previous studies have identified several risk factors for development of infection in AAV; these include the use of high-dose and higher cumulative exposure to glucocorticoids, the use of immunosuppressive agents, older patient age, leukopenia or lymphopenia, and kidney dysfunction [8–18].

Body mass index (BMI) has been regarded as an indicator of nutritional issues; malnutrition can lead to underweight, while overnutrition can lead to overweight [19]. To date, although the association between BMI and the incidence of infection has been evaluated in several general population-based observational studies [19–28], the results, according to the participants' characteristics, were inconsistent. Furthermore, no previous studies have focused on patients who are immunocompromised due to immunosuppressive treatment, including patients with AAV. Therefore, the clinical impact of BMI on the incidence of infection in AAV patients receiving immunosuppressive therapy remained unknown.

In the present study, we hypothesized that elderly AAV patients with a low BMI would be at a higher risk of development of infection. To evaluate this hypothesis, we investigated the association between underweight at the diagnosis of AAV and subsequent severe infection in elderly AAV patients, using a single-center, retrospective cohort from Japan.

## Methods

### Study population

The present study included 126 adult patients who were diagnosed with AAV, including GPA, MPA, and EGPA, based on the classification of the AAV by the European Medicines Agency algorithm [29], at Nephrology and Rheumatology centers in the Aichi Medical University in Japan between 2004 and 2018. After excluding 28 patients (22.2%) who were non-elderly (aged < 65 years; n = 20), were not on immunosuppressive therapy (n = 2), and those with missing BMI data (n = 6), 98 patients (77.8%) who received immunosuppressive therapy were included in the present study (Fig. 1).

The study protocol was approved by the Ethics Committees of Aichi Medical University (approval number 2018-H350, date November 3, 2019). The need to obtain patients' informed consent was waived due to the retrospective nature of the study.

#### Data collection

Baseline characteristics, at the start of immunosuppressive therapy, were collected retrospectively from patients' medical records and included the following: age; sex; BMI; body weight loss > 10% within 6 months before diagnosis; serum creatinine level; serum albumin level; C-reactive protein level; serum IgG level; presence of diabetes mellitus; Birmingham Vasculitis Activity Score (BVAS) 2003 [30]; organ involvement; anti-myeloperoxidase (MPO) and anti-proteinase 3 (PR3) ANCA levels; use of immunosuppressive treatment, such as induction immunosuppressive therapy; methylprednisolone pulse therapy (0.5 or 1.0 g/day for 3 consecutive days); intravenous cyclophosphamide (CYC) or rituximab (RTX) use, and maintenance therapy; oral CYC use, azathioprine (AZA) use, methotrexate use, and RTX use.

All serum samples were tested by direct antigen-specific enzyme-linked immunosorbent assays for MPO and PR3-ANCA, using serial serum dilutions, as previously described [31]. The samples were diluted 1:500

(Nipro Medical Corporation, Osaka, Japan) or 1:101 (Medical and Biological Laboratories Co., Ltd., Nagoya, Japan).

## Outcomes

The primary exposure of interest was the BMI at the diagnosis of AAV. BMI was defined according to the World Health Organization Asian Standard [32]; underweight was defined as BMI < 18.5 kg/m<sup>2</sup>, normal weight as BMI 18.5–22.9 kg/m<sup>2</sup>, overweight as BMI 23.0–24.9 kg/m<sup>2</sup>, obesity I (moderate obesity) as BMI 25.0–29.9 kg/m<sup>2</sup>, and obesity II (severe obesity) as BMI ≥ 30 kg/m<sup>2</sup>. Because of the small number of overweight, obesity I and II patients, we combined these three groups into a “high BMI” group. Accordingly, we stratified patients into three BMI categories: low BMI (BMI < 18.5 kg/m<sup>2</sup>), normal BMI (BMI 18.5–23 kg/m<sup>2</sup>), and high BMI (BMI > 23 kg/m<sup>2</sup>).

The main outcome of interest was the development of severe infection, which was defined as infection requiring hospitalization for any causes. Remission was defined as the absence of clinical signs and symptoms of active vasculitis (BVAS = 0) for more than 2 months. Relapse was defined as clinical signs of vasculitic activity in any organ system, followed by an increase in corticosteroid dosing and/or add-on use of immunosuppressive agents after development of remission, as previously described [33]. Other outcome data, including information about end-stage renal disease (ESRD) requiring dialysis, death, and hospitalization due to causes other than infection, was collected. Patients were followed up until December 2019 and data were censored at death or on the last day of attending examination in our hospital before December 2019.

## Statistical analyses

Baseline patient characteristics were summarized according to the three BMI categories, and are presented as a percentage for categorical variables and as median (interquartile range) for continuous variables with both normal and skewed distributions.

The associations of BMI with outcomes were assessed using univariate and multivariate Cox proportional hazards (CPH) models. The multivariate models were adjusted for the following potential confounding factors; age, sex, lung involvement, diabetes mellitus, serum creatinine level, use of methylprednisolone therapy, and BMI (low, normal, and high BMI), based on the clinical experience and theoretical considerations.

Furthermore, we assessed the effect of changes in body weight loss (> 10%) within 6 months before diagnosis and low BMI for the primary outcome in a multivariate model, adjusted for age, sex, lung involvement, diabetes mellitus, serum creatinine level, and use of methylprednisolone therapy.

The proportional hazard assumption for covariates was tested using scaled Schoenfeld residuals. For continuous variables, the Wilcoxon rank-sum test was used to evaluate the significance of intergroup differences. Categorical variables are expressed as percentages and were compared using the Fisher's exact test. The cumulative probability of the development of a first severe infection was calculated using the Kaplan–Meier method and log-rank test.

The level of statistical significance was set at  $P < 0.05$ . All statistical analyses were performed using JMP, version 14.0.0 (SAS Institute, Cary, NC, USA) and STATA version 13.0 (StataCorp LP, College Station, TX, USA).

## Results

### Clinical characteristics

The baseline characteristics stratified by three BMI categories are shown in Table 1. The present cohort included 23 (23.5%) patients with BMI  $< 18.5 \text{ kg/m}^2$ , 56 (57.1%) patients with BMI  $18.5\text{--}23.0 \text{ kg/m}^2$ , and 19 (19.4%) patients with BMI  $> 23.0 \text{ kg/m}^2$ . On comparing the baseline characteristics among the three groups, the proportion of patients with unintentional body weight loss  $> 10\%$  within 6 months before diagnosis was significantly higher in the low BMI group than those in the high BMI group ( $P = 0.003$ ). For other baseline characteristics, no significant difference was observed among the three groups.

Table 1  
Clinical characteristics of 98 patients with AAV

	Low BMI (< 18.5) (n = 23)	Normal BMI (18.5– 23.0) (n = 56)	High BMI (> 23) (n = 19)	P value
<b>Baseline characteristics</b>				
Age (years)	78 (68–80)	73 (69–78)	75 (68–78)	0.540
Male sex	15 (65.2)	29 (51.8)	8 (42.1)	0.314
BMI (kg/m <sup>2</sup> )	17.9 (17.1–18.3)	21.0 (19.9–22.1)	24.2 (23.4–26.2)	< 0.001
Body weight loss > 10% within 6 months before diagnosis	13 (56.5)	26 (46.4)	4 (21.1)	0.003
Serum creatinine level (mg/dL)	1.4 (1.0–6.4)	1.6 (0.8–3.6)	1.2 (0.6–2.2)	0.213
Serum albumin level (mg/dL)	3.0 (2.6–3.2)	2.8 (2.4–3.3)	3.2 (2.5–3.5)	0.569
Serum IgG level (mg/dL)	1812 (1564–1958)	1814 (1538–2019)	1734 (1407–2002)	0.508
CRP level (mg/dL)	6.1 (2.6–10.7)	3.5 (1.1–9.2)	3.9 (0.3–12.7)	0.370
Diabetes mellitus	7 (30.4)	9 (16.1)	4 (21.1)	0.350
Diagnosis				< 0.001
MPA	22 (95.7)	53 (94.6)	18 (94.7)	0.982
GPA	0 (0.0)	0 (0.0)	0 (0.0)	
EGPA	1 (4.4)	3 (5.4)	1 (5.3)	
Antibody				0.122
MPO-ANCA	23 (100)	56 (100)	18 (94.7)	

Continuous data are presented as a median (interquartile range), and categorical data are expressed as a number (proportion).

Abbreviations: BMI, body mass index; MPO, myeloperoxidase; PR3, proteinase-3 ANCA; ANCA, anti-neutrophil cytoplasmic antibody; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; mPSL, methylprednisolone; HD, hemodialysis;

	Low BMI ( $< 18.5$ ) (n = 23)	Normal BMI (18.5– 23.0) (n = 56)	High BMI ( $> 23$ ) (n = 19)	<i>P</i> value
PR3-ANCA	0 (0)	0 (0)	1 (5.2)	
BVAS	15 (12– 17)	14 (11–16)	14 (11–14)	0.437
Organ involvement				
General	23 (100)	56 (100)	18 (94.7)	0.122
Cutaneous	3 (13.0)	1 (1.8)	2 (10.5)	0.111
Ear nose and throat	7 (30.4)	9 (16.1)	5 (26.3)	0.316
Chest	6 (26.1)	22 (39.3)	6 (31.6)	0.508
Cardiovascular	0 (0)	0 (0)	0 (0)	0.000
Abdominal	1 (4.4)	1 (1.8)	0 (0)	0.599
Renal	19 (82.6)	42 (75.0)	14 (73.7)	0.729
Nervous system	5 (21.7)	11 (19.6)	5 (26.3)	0.828
Induction immunosuppressive therapy				
mPSL pulse therapy	12 (52.2)	27 (48.2)	8 (42.1)	0.808
Intravenous cyclophosphamide	3 (13.0)	4 (7.1)	1 (5.2)	0.600
Rituximab	1 (4.4)	4 (7.1)	2 (10.5)	0.741
Maintenance immunosuppressive therapy				0.336
Glucocorticoid monotherapy	17 (73.9)	39 (69.6)	14 (73.7)	
Oral cyclophosphamide	0 (0)	1 (1.8)	1 (5.3)	
Azathioprine	5 (21.7)	14 (25.0)	2 (10.5)	
Methotrexate	0 (0)	0 (0)	0 (0)	
Mizoribine	1 (4.4)	0 (0)	0 (0)	

Continuous data are presented as a median (interquartile range), and categorical data are expressed as a number (proportion).

Abbreviations: BMI, body mass index; MPO, myeloperoxidase; PR3, proteinase-3 ANCA; ANCA, anti-neutrophil cytoplasmic antibody; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; mPSL, methylprednisolone; HD, hemodialysis;

	Low BMI ( $< 18.5$ ) (n = 23)	Normal BMI (18.5– 23.0) (n = 56)	High BMI ( $> 23$ ) (n = 19)	P value
Rituximab	0 (0)	2 (3.6)	2 (10.5)	
Outcomes				
Remission	19 (82.6)	51 (91.1)	17 (89.5)	0.553
Relapse	8 (42.1)	19 (37.3)	7 (41.2)	0.916
Severe infection	15 (65.2)	15 (26.8)	2 (10.5)	$< 0.001$
HD	8 (34.8)	11 (19.6)	4 (21.1)	0.340
Death	7 (30.4)	13 (23.2)	2 (10.5)	0.030
Infection	7 (100)	6 (46.2)	1 (50.0)	
Vasculitis	0 (0)	3 (23.1)	0 (0)	
Malignancy	0 (0)	2 (15.4)	0 (0)	
Cardiovascular	0 (0)	0 (0)	1 (50.0)	
Unknown	0 (0)	2 (15.4)	0 (0)	
Observation period (months)	11 (2– 51)	17 (5–43)	28 (7–53)	0.489
Continuous data are presented as a median (interquartile range), and categorical data are expressed as a number (proportion).				
Abbreviations: BMI, body mass index; MPO, myeloperoxidase; PR3, proteinase-3 ANCA; ANCA, anti-neutrophil cytoplasmic antibody; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; mPSL, methylprednisolone; HD, hemodialysis;				

## BMI and severe infection

During the study period, 39 severe infections occurred in 32 (32.7%) patients. The low BMI category was significantly associated with development of severe infection ( $P < 0.001$ ). The cumulative probabilities of severe infection within 1, 2, and 5 years were, respectively, 0.55, 0.59, and 0.65 for those with low BMI; 0.23, 0.31, and 0.35 for those with normal BMI; and 0.06, 0.06, and 0.16 for those with high BMI. Severe infection differed significantly according to BMI category (log rank,  $P < 0.001$ ; Fig. 2). Causes of infection were tuberculosis pleuritis (n = 1), millitary tuberculosis (n = 1), cytomegalovirus pneumonia (n = 1), influenza pneumonia (n = 1), bacterial pneumonia (n = 12), fungal pneumonia (n = 4), *Pneumocystis*

*jiroveci* pneumonia (n = 2), acute colitis (n = 1), soft tissue infection (n = 1), infectious endocarditis (n = 1), vertebral osteomyelitis (n = 1), methicillin-resistant *Staphylococcus aureus* bacteremia (n = 1), fungemia (n = 1), and acute pyelonephritis (n = 4).

## Predictors of severe infections

Predictors of severe infection were evaluated using the clinical data, including age, sex, BMI, serum creatinine level, and use of methylprednisolone pulse therapy on the basis of previous reports [15–18]. Univariate CPH analyses identified several statistically significant predictors of increased infection risk, namely, older age, use of methylprednisolone pulse therapy, and low BMI (Table 2). Using the multivariate CPH model, adjusted for age, sex, serum creatinine level, use of methylprednisolone pulse therapy, and BMI, low BMI (< 18.5 kg/m<sup>2</sup> compared with normal BMI [18.5–23.0 kg/m<sup>2</sup>], adjusted hazard ratio [HR] = 2.70, 95% confidence interval [CI]: 1.18–6.17; *P* = 0.018) and use of methylprednisolone pulse therapy (adjusted HR = 3.09, 95% CI: 1.37–6.99; *P* = 0.007) were identified as the significant predictors of severe infection (Table 2). Furthermore, an interaction effect between unintentional body weight loss (> 10%) within 6 months before diagnosis and low BMI was observed (*P* < 0.001).

Table 2  
Predictors of first severe infection in AAV

	Univariate model		Multivariate model	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Age (per 10 years)	1.79 (1.03–3.10)	0.036	1.39 (0.89–1.16)	0.246
Male (vs. female)	1.03 (0.51–2.07)	0.929	1.21 (0.39–1.74)	0.620
Lung involvement	0.77 (0.36–1.62)	0.488	1.11 (0.47–2.59)	0.814
Serum creatinine (per 1.0 mg/dL)	1.09 (0.96–1.21)	0.150	1.02 (0.89–1.16)	0.767
Diabetes mellitus	1.10 (0.49–2.47)	0.815	0.44 (0.18–1.12)	0.085
mPSL pulse therapy	2.81 (1.33–5.94)	0.007	3.09 (1.37–6.99)	0.007
BMI groups				
Low BMI (< 18.5 kg/m <sup>2</sup> )	2.76 (1.34–5.66)	0.006	2.70 (1.18–6.17)	0.018

Data are the HR, 95% CI, and *P* value from Cox proportional hazard regression analyses.

The multivariate model was adjusted for the baseline characteristics, including age, sex, lung involvement, serum creatinine level, diabetes mellitus, use of mPSL pulse therapy, and BMI groups (low, normal, and high BMI). “Normal BMI” was used as the reference category.

Abbreviations: BMI, body mass index; mPSL, methylprednisolone, ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; HR, hazard ratio; CI, confidence interval

	Univariate model		Multivariate model	
Normal BMI (18.5–23.0 kg/m <sup>2</sup> )	Reference		Reference	
High BMI (> 23.0 kg/m <sup>2</sup> )	0.36	0.176	0.37	0.192
	(0.08–1.58)		(0.08–1.65)	
Data are the HR, 95% CI, and <i>P</i> value from Cox proportional hazard regression analyses.				
The multivariate model was adjusted for the baseline characteristics, including age, sex, lung involvement, serum creatinine level, diabetes mellitus, use of mPSL pulse therapy, and BMI groups (low, normal, and high BMI). “Normal BMI” was used as the reference category.				
Abbreviations: BMI, body mass index; mPSL, methylprednisolone, ANCA, anti-neutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; HR, hazard ratio; CI, confidence interval				

## Other outcomes

During the observation period, 19 (82.6), 51 (91.1), and 17 (89.5) patients in the low, normal, high BMI groups achieved remission, respectively (*P* = 0.553). After achieving remission, 8 (42.1), 19 (37.3), and 7 (41.2) patients in the low, normal, high BMI groups developed relapse, respectively (*P* = 0.916). During the observation period, 8 (34.8), 11 (19.6), and 4 (21.1) patients in the low, normal, high BMI groups required permanent dialysis therapy (*P* = 0.340). A total of 22 patients died, including 7 (30.4), 13 (23.2), and 2 (10.5) patients in the low, normal, and high BMI groups, respectively. In terms of the cause of death, 14 (63.6%) patients died due to infection, including 7 (100), 6 (46.2), 1 (50.0) in the low, normal, high BMI groups, respectively.

## Discussion

The present study revealed that low BMI at diagnosis is significantly associated with subsequent development of severe infection in elderly AAV patients in a single-center, retrospective cohort from Japan. Our results suggested that malnutrition at diagnosis might increase vulnerability to infection during immunosuppressive treatment in elderly patients, in particular. No previous study has focused on the clinical impact of underweight on infection risk in elderly AAV patients, and our results may provide a basis for identifying elderly AAV patients requiring more careful management to reduce severe infection risk.

Previously, the relationship between BMI and infection risk has been evaluated in several general population-based cohort studies; however, these studies did not yield consistent results according to the participant’s characteristics [20]. First, in children and adolescents, underweight is considered a significant risk factor for infection in developing countries, probably reflecting malnutrition and poor

hygiene standards [21]. On the other hand, data from industrialized countries suggest that infection rate is increased in obese children and adolescents [22]. For adults, several studies have suggested a U-shaped increase in the infection rate for both underweight and obese participants, in industrialized countries [23–25].

In terms of elderly populations, Thomas et al. studied 619 inpatient geriatric patients ( $\geq 75$  years) and showed that both underweight (BMI  $< 20$  kg/m<sup>2</sup>) and overweight (BMI  $> 28$  kg/m<sup>2</sup>) increased the risk for overall infection, including pneumonia, urinary tract infection (UTI), diarrhea, and others (incidence risk ratios: 1.84 [95% CI 1.40–2.42] for BMI  $< 20$  kg/m<sup>2</sup>, 1.54 [95% CI 1.07–2.22] for BMI  $> 28$  kg/m<sup>2</sup>) [26]. However, their study showed that men experienced UTIs more frequently than did women, although, among the older adults, women are usually more susceptible to UTIs than are men [27]. Although the study ascribed this to the fact that more men than women were supplied with urinary catheters, their study participants might not reflect the general population and the results should be interpreted with caution.

Additionally, a meta-analysis that included a large number of cohort studies, including 19538 nursing home residents (median age 84.3 years) revealed a higher risk of infection-related mortality (hazard ratio, HR = 1.47 [95% CI 1.12–1.92]) in underweight individuals (BMI  $< 18.5$  kg/m<sup>2</sup>), and a lower risk in overweight individuals (BMI 25–29.9 kg/m<sup>2</sup>; HR = 0.70 [95% CI = 0.58–0.84]) and obese individuals (BMI  $\geq 30$  kg/m<sup>2</sup>; HR = 0.63 [95% CI = 0.45–0.88]) than the normal weight participants (BMI 18.5–25 kg/m<sup>2</sup>) [19].

A retrospective analysis of 66820 clients (aged  $> 65$  years) from Elderly Health Centres in Hong Kong revealed a U-shaped relationship between BMI and influenza-associated mortality in individuals stratified by BMI groups: HR of 1.081 (95% CI 1.013–1.154), 1.047 (1.012–1.084), 0.981 (0.936–1.028), 1.018 (0.980–1.058), and 1.062 (0.972–1.162), for underweight (BMI  $< 18.5$  kg/m<sup>2</sup>), normal weight (BMI 18.5–22.9 kg/m<sup>2</sup>), overweight (BMI 23.0–24.9 kg/m<sup>2</sup>), obese I (BMI 25.0–29.9 kg/m<sup>2</sup>), and obese II (BMI  $\geq 30$  kg/m<sup>2</sup>) groups, respectively [28].

However, no previous studies had focused on the association between BMI and incidence of infection in immunocompromised patients who are on immunosuppressive treatment. Therefore, it is essential to assess the clinical effect of BMI on infection risk in patients receiving immunosuppressive treatment. In the present study, we focused on elderly AAV patients who are at high risk for infection due to immunosuppressive therapy, and found that underweight at diagnosis was a significant predictor of the risk of severe infection.

Furthermore, previous studies [19, 26, 27] did not assess body weight change as an important factor for diagnosing malnutrition [34]. We here assessed the impact of body weight loss in the 6 months preceding diagnosis on subsequent severe infection. We found a significant effect interaction between unintentional body weight loss exceeding 10% in the 6 months prior to diagnosis and of low BMI ( $< 18.5$  kg/m<sup>2</sup>) on the development of severe infection, suggesting that patients who were severely malnourished due to

unintentional weight loss might be more vulnerable to immunosuppressive treatment, increasing their risk for developing severe infection.

Although the precise mechanism of the influence of BMI on the immune system is unresolved, in undernourished subjects, depleted leucocyte, lymphocyte, and T-cell counts, increased CD4/CD8 ratios, and decreased CD2/CD19 ratios have been found [35, 36]. In addition, several factors with immunomodulatory effects, including physical activity [37], nutritional aspects (dietary composition or supplements) [38], and well-being [39] might modulate the infection risk.

The present study had several limitations. First, because of the retrospective, observational nature of the present study, evaluation of the clinical consequences of an altered immune response could not fully adjust for confounding factors, such as the underlying immune condition or co-morbidities of each patient. In addition, the various immunomodulatory factors mentioned above could not be assessed in the present study. Further studies should investigate the impact of these factors. Second, most of our patients were elderly MPA patients from Japan; hence, the results may not be generalizable to young or middle-aged or GPA patients from other geographic areas. Third, we were unable to assess the effect of the lifetime duration of BMI and its status over the entire follow-up period on the outcomes; hence, the impact of change in BMI after starting immunosuppressive treatment could not be assessed. We believe that the potential preventive measures focusing on improving the nutritional intake of these high-risk patients should be evaluated in further studies.

In conclusion, the present study identified a lower BMI as a significant predictor of the risk of severe infection in AAV patients. This suggests that physicians should pay particular attention to AAV patients with low BMI to monitor the development of infection.

## Abbreviations

AAV, antineutrophil cytoplasmic antibody-associated vasculitis

ANCA, antineutrophil cytoplasmic antibody

AZA, azathioprine

BMI, body mass index

BVAS, Birmingham Vasculitis Activity Score

CI, confidence interval

CYC, cyclophosphamide

EGPA, eosinophilic granulomatosis with polyangiitis

GPA, granulomatosis with polyangiitis

HD, hemodialysis

HR, hazard ratio

MPA, microscopic polyangiitis

MPO, myeloperoxidase

mPSL, methylprednisolone

PR3, proteinase 3

RTX, rituximab

## Declarations

### *Ethics approval and consent to participate:*

The study protocol was approved by the Ethics Committees of Aichi Medical University (approval number 2018-H350, date November 3, 2019). The need to obtain patients' informed consent was waived due to the retrospective nature of the study

### *Consent for publication:*

*Not applicable*

### *Availability of data and material:*

All data were fully anonymized (Table S1).

### *Competing interests:*

There are no conflicts of interest to declare.

### *Funding:*

No fund.

### *Authors' contributions:*

Conceptualization: HS, MY, TK, and SB; Methodology: HS, MY, TK, and YI; Formal analysis and investigation: MY, and TK; Writing – original draft preparation: HS, MY, HN, and SI; Writing – review and editing: MY, TK, SB, YI, HN, SI, HK, and TI; Supervision: MY, TK, SB, YI, HN, HK, SI, and TI. All authors read and approved the final manuscript.

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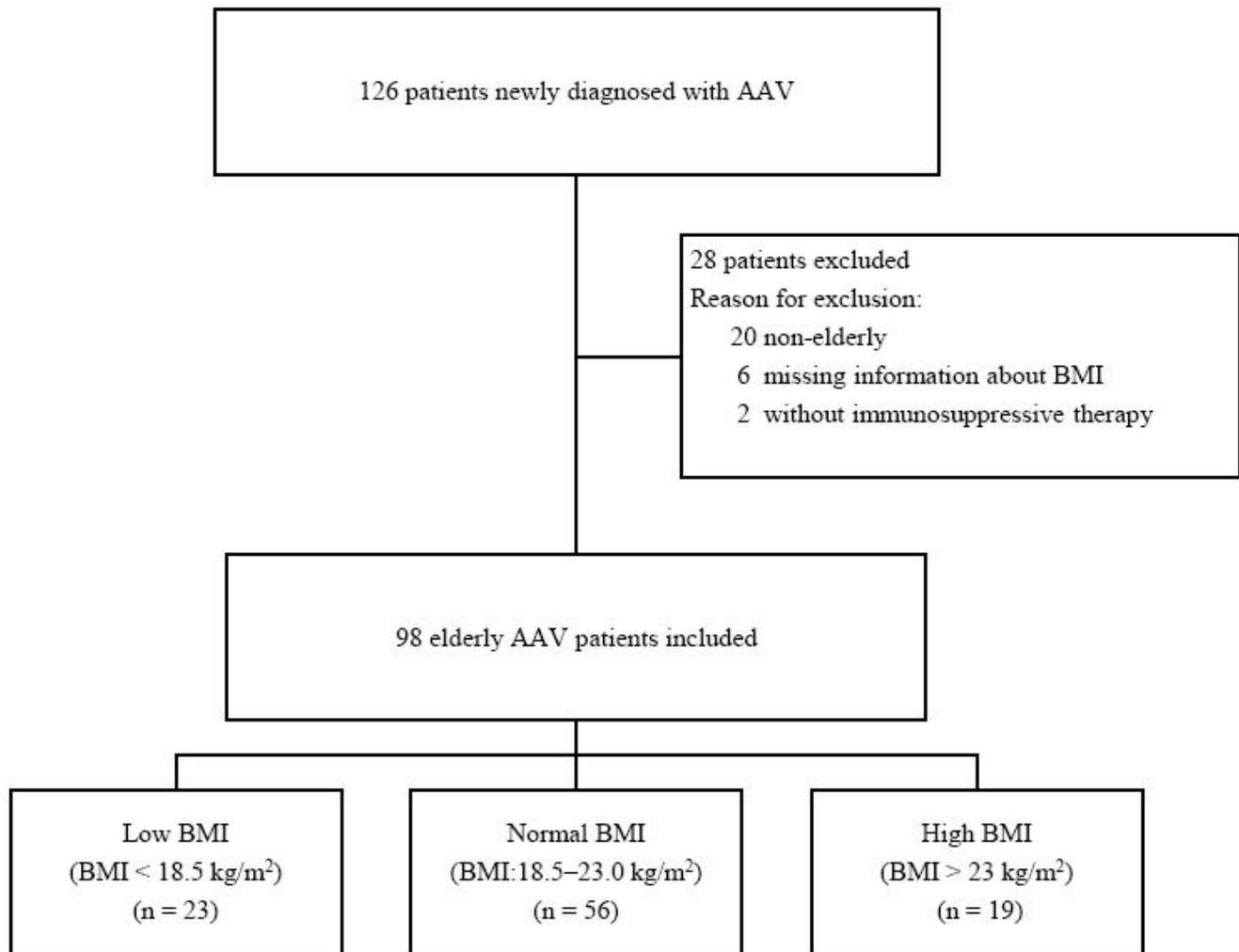
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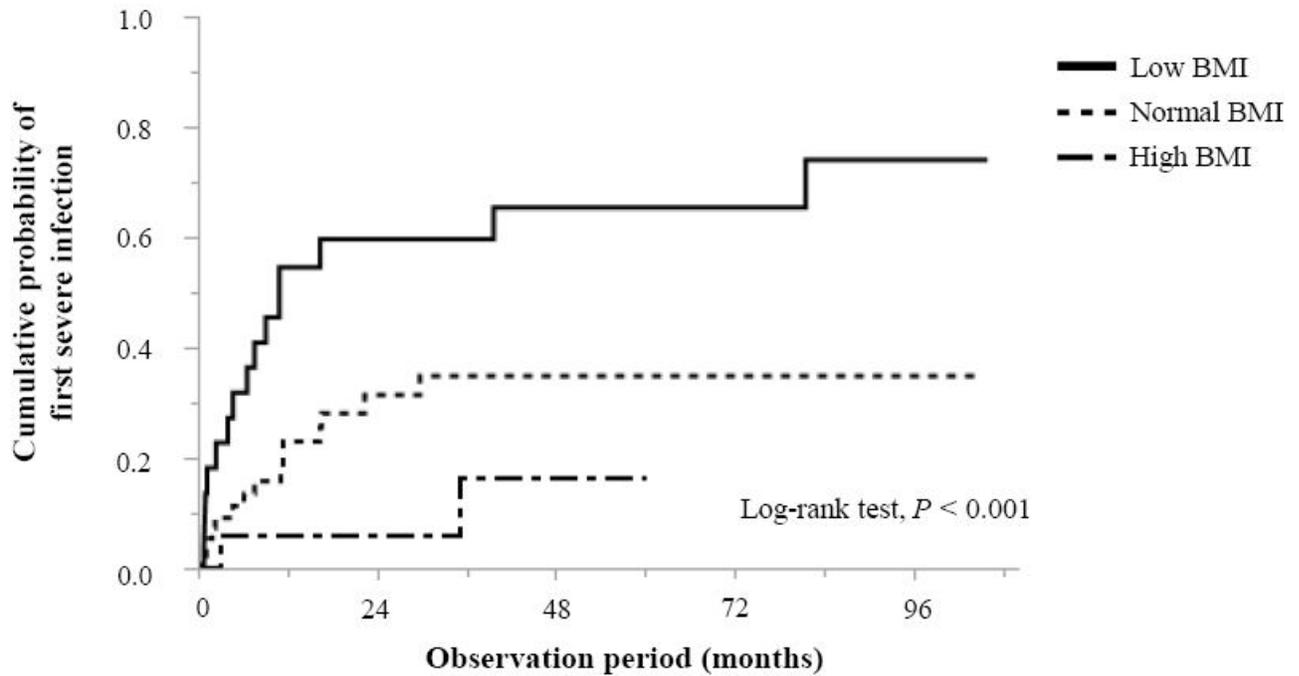
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# Figures



**Figure 1**

Flow diagram of the patient selection



Number at risk						
Low BMI	23	8	7	6	3	
Normal BMI	56	21	11	6	3	
High BMI	19	11	9	0	0	

**Figure 2**

Cumulative probability of the first severe infection

## Supplementary Files

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