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Original Article

# Modified Body Mass Index at Diagnosis is a Useful Predictor of Mortality in Patients With Antineutrophil Cytoplasmic Antibody-associated Vasculitis

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**Objective:** We investigated whether modified body mass index (mBMI) at diagnosis could predict all-cause mortality during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

**Methods:** The medical records of 203 AAV patients with BMI ≥18.5 kg/m$^2$ were reviewed. mBMI was calculated using an equation: mBMI=BMI (kg/m$^2$)×serum albumin (g/L). All-cause mortality was considered as a poor outcome, and the follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to death for deceased patients, and the period from AAV diagnosis to the last visit for surviving patients.

**Results:** The median age was 59.0 years (35.5% were male). The median BMI and mBMI were 22.8 kg/m$^2$ and 813.2 kg·g/m$^2$·L. Twenty-five patients (12.3%) died. mBMI was well correlated with age, BVAS, FFS, erythrocyte sedimentation rate and C-reactive protein at diagnosis. Deceased patients exhibited significantly lower mBMI at diagnosis compared to surviving patients. AAV patients mBMI ≤570.1 kg·g/m$^2$·L showed a significantly higher frequency of all-cause mortality (38.5% vs. 8.5%), and furthermore, exhibited a significantly higher risk for all-cause mortality than those with mBMI >570.1 kg·g/m$^2$·L (RR 6.750). mBMI ≤570.1 kg·g/m$^2$·L showed a significantly lower cumulative patients' survival rate than those with mBMI >570.1 kg·g/m$^2$·L. In the multivariable Cox hazards model analysis, either serum albumin or mBMI was significantly associated with all-cause mortality in AAV patients.

**Conclusion:** In conclusion, mBMI ≤570.1 kg·g/m$^2$·L at diagnosis may be a useful predictor of all-cause mortality during follow-up additionally to serum albumin in AAV patients.

**Keywords:** Antineutrophil cytoplasmic antibody, Body mass index, Albumin, Mortality

## INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis that affects small vessels including capillaries and adjacent arterioles and venules [1]. AAV can be divided into three subtypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1,2]. The overall mortality rate in AAV patients may differ by ethnicity and geographical location [3,4]. The overall mortality rate

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in Korean patients with AAV is reported to be about 10% [5]. Previous studies revealed that age at diagnosis, male sex, ANCA type, comorbidities, and damages to major organs are risk factors for all-cause mortality in AAV patients [6].

As for the general population, the association between body mass index (BMI) and all-cause mortality has been studied in various aspects. It is well known that the mortality rate is the lowest in people with normal BMI, and it increases as BMI increases [7]. It is also known that the mortality rate increases in people with BMI <18.5 kg/m$^2$ [8]. The association between BMI and all-cause mortality in the general population forms exhibits a U-shape curve [9]. Moreover, in patients with Takayasu arteritis, a rare systemic vasculitis, lower BMI at diagnosis is reported to be associated with all-cause mortality [10]. However, the direct link between BMI at diagnosis and all-cause mortality during follow-up in AAV patients remains controversial.

Recently, modified BMI (mBMI) has been introduced, which is calculated using an equation consisting of two variables: conventional BMI and serum albumin. In a previous study, mBMI was reported able to predict all-cause mortality within 30 days and 1 year after intensive care unit management but could not surpass the predictive potential of serum albumin [11]. We were curious about the predictability of mBMI for all-cause mortality in AAV patients and the comparison with that of serum albumin. However, there is no study on this issue to date. Hence, in this study, we investigated the predictability of mBMI at diagnosis for all-cause mortality during follow-up in AAV patients and compared it with that of serum albumin.

## MATERIALS AND METHODS

### Patients

Initially, the electronic medical records of 257 patients with AAV were screened. The medical records of 244 patients with AAV, in which BMI at diagnosis was clearly documented, were retrospectively reviewed. The inclusion criteria were as follows: i) patients who were diagnosed with AAV at this institute between October 2000 and January 2021; ii) patients who were reclassified as AAV based on the classification algorithm for AAV and polyarteritis nodosa proposed by the European Medicine Agency in 2007 (the 2007 algorithm) [2], and the revised nomenclature of vasculitides suggested by the Chapel Hill Conference Consensus in 2012 (the 2012 definitions) [1]; iii) patients who were followed up for more than 3 months; iv) patients whose medical records were well documented and include AAV-specific indices and clinical and laboratory data recorded at diagnosis and during follow-up; and v) patients who had BMI at diagnosis ≥18.5 kg/m$^2$. The exclusion criteria were as follows: i) patients who had serious medical conditions such as malignancy, severe infection, and autoimmune diseases other than AAV [12,13]; and ii) patients who had ever received immunosuppressive drugs for AAV treatment of prior to the diagnosis of AAV. Of 244 patients, to avoid the effect of underweight on all-cause mortality and to minimise the effects of confounding factors [9], 41 patients with BMI at diagnosis <18.5 kg/m$^2$ were excluded. Finally, 203 patients with BMI ≥18.5 kg/m$^2$ were included in this study and analysed. This study was approved by the Institutional Review Board of this institute, which waived the need for patients' written informed consent, as this was a retrospective study (IRB protocol number 4-2020-1071).

### Variables at diagnosis

Information regarding age, BMI and sex was collected as the demographic data. Further, information on AAV subtypes, ANCA types and positivity, and AAV-specific indices including Birmingham vasculitis activity score (BVAS, version 3), and five-factor score (FFS) was also obtained [14,15]. Patients in whom the ANCA results were negative by antigen-specific assay but were positive by immunofluorescence assay, were considered to have ANCA when AAV was strongly suspected based on the clinical and laboratory features [16]. Clinical manifestations based on BVAS, comorbidities, and acute-phase reactants were reviewed. Diabetes mellitus, hypertension, chronic kidney disease (stages 3, 4, and 5), hyperlipidaemia, and interstitial lung disease were assessed as comorbidities [17].

### Modified body mass index at diagnosis

mBMI was calculated using the following equation: mBMI (kg·g/m$^2$·L)=BMI (kg/m$^2$)×serum albumin (g/L) [or 10×serum albumin (g/dL)] [11].

### Variables during follow-up

All-cause mortality, which was defined as death by any cause, was considered as a poor outcome in this study. The follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to death for deceased patients, and the period from AAV diagnosis to the last visit for surviving patients. Medicines that were administered during the follow-up period

**Table 1.** Characteristics of AAV patients with at diagnosis and during follow-up (n=203)

| Variables | Values |
|---|---|
| At the time of diagnosis | |
| Demographic data | |
| Age (yr) | 59.0 (18.5)* |
| Male sex | 72 (35.5) |
| AAV subtypes | |
| MPA | 112 (55.2) |
| GPA | 54 (26.6) |
| EGPA | 37 (18.2) |
| ANCA positivity | |
| MPO-ANCA (or P-ANCA) positivity | 136 (67.0) |
| PR3-ANCA (or C-ANCA) positivity | 34 (16.7) |
| Both ANCA positivity | 8 (3.9) |
| ANCA negativity | 41 (20.2) |
| AAV-specific indices | |
| BVAS | 12.0 (10.5)* |
| FFS | 1.0 (1.0)* |
| Clinical manifestations at diagnosis | |
| Generalized symptoms | 88 (43.3) |
| Skin | 44 (21.7) |
| Mucous membrane and eyes | 11 (5.4) |
| Ear nose throat | 92 (45.3) |
| Lungs | 120 (59.1) |
| Heart | 43 (21.2) |
| Gastrointestine | 9 (4.4) |
| Kidneys | 127 (62.6) |
| Central or peripheral nervous systems | 61 (30.0) |
| Comorbidities at diagnosis | |
| Diabetes mellitus | 52 (25.6) |
| Hypertension | 78 (38.4) |
| Chronic kidney disease (stages 3~5) | 58 (28.6) |
| Hyperlipidaemia | 35 (17.2) |
| Interstitial lung disease | 56 (27.6) |
| Acute-phase reactants | |
| ESR (mm/hr) | 54.0 (68.0)* |
| CRP (mg/L) | 11.7 (60.5)* |
| BMI (kg/m$^2$) | 22.8 (3.6)* |
| Serum albumin (g/dL) | 3.7 (1.1)* |
| mBMI (kg·g/m$^2$·L) | 813.2 (270.7)* |
| During the follow-up period | |
| Mortality during follow-up | |
| All-cause mortality | 25 (12.3) |
| Follow-up duration based on all-cause mortality (mo) | 36.6 (66.1)* |
| Medications administered during follow-up | |
| Glucocorticoids | 189 (93.1) |
| Cyclophosphamide | 101 (49.8) |
| Rituximab | 33 (16.3) |
| Azathioprine | 113 (55.7) |
| Mycophenolate mofetil | 24 (11.8) |
| Tacrolimus | 10 (4.9) |
| Methotrexate | 21 (10.3) |

Values are expressed as a median (interquartile range)* or number (%). AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, BMI: body mass index, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, EGPA: eosinophilic GPA, MPO: myeloperoxidase, P: perinuclear, PR3: proteinase 3, C: cytoplasmic, BVAS: Birmingham vasculitis activity score, FFS: five-factor score, CRP: C-reactive protein, mBMI: modified body mass index.

were recorded.

## Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25. (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as median with the interquartile range, whereas categorical variables are expressed as numbers (%). Significant differences between the two categorical variables were analysed using the Chi-square and Fisher's exact tests. The correlation coefficient (r) between the two variables was obtained using either the Pearson correlation analysis or the univariable linear regression analysis. Also, multicollinearity was evaluated using the univariable linear regression analysis. The optimal cut-off was extrapolated by performing the receiver operator characteristic (ROC) curve analysis and one value having the maximised sum of sensitivity and specificity was selected. Comparison of the cumulative survivals rates between the two groups was analysed by the Kaplan–Meier survival analysis with the log-rank test. The multivariable Cox hazard model using variables with statistical significance in the univariable Cox hazard model was conducted to appropriately obtain the hazard ratios (HRs) during the considerable follow-up duration. p-values less than 0.05 were considered statistically

significant.

## RESULTS

### Variables at diagnosis

The median age of the included patients was 59.0 years (35.5% were male) and the median BMI was 22.8 kg/m$^2$. Of the 203 patients with AAV, 112 had MPA, 54 had GPA and 37 had EGPA. One hundred thirty-six patients had MPO-ANCA (P-ANCA), while 41 patients did not have ANCA. The median BVAS and FFS were 12.0 and 1.0, respectively. The most commonly involved organ was the kidneys (62.6%), followed by the lungs (59.1%), and the common comorbidity was hypertension (38.4%). The median serum albumin level was 3.7 g/dL and the median mBMI was 813.2 kg·g/m$^2$·L (Table 1).

### Variables during follow-up

Of the 203 patients, 25 patients (12.3%, 16 MPA, and 9 GPA patients) died during follow (median, 36.6 months). Glucocorticoids were administered to 189 patients (93.1%). In addition, 101 patients received cyclophosphamide and 113 patients received azathioprine (Table 1).

### Correlation between variables at diagnosis

mBMI was significantly correlated with age (r=–0.248), BVAS (r=–0.333), FFS (r=–0.270), erythrocyte sedimentation rate (ESR) (r=–0.476) and C-reactive protein (CRP) (r=–0.555) (Supplementary Figure 1).

### mBMI at diagnosis between surviving and deceased patients

There were no significant differences between surviving and deceased patients in terms of medications administered during follow-up (Supplementary Table 1). BMI at diagnosis did not significantly differ between surviving and deceased patients. However, deceased patients exhibited significantly lower serum albumin (p<0.001) and mBMI (p=0.001) at diagnosis than surviving patients (Figure 1).

### Optimal cut-off of mBMI for all-cause mortality

When the cut-offs of mBMI for all-cause mortality were obtained using the ROC curve (area 0.702, 95% confidence interval [CI] 0.598~0.807), mBMI of 570.1 was chosen for the optimal one due to the maximised sum of sensitivity and specificity. The sensitivity and specificity were 91.0% and 40.0% as the cut-off was set as mBMI ≤570.1 kg·g/m$^2$·L (Figure 2).

### Relative risk of mBMI ≤570.1 kg·g/m$^2$·L. for all-cause mortality

When we divided patients into two groups based on mBMI ≤570.1 kg·g/m$^2$·L, 26 of 203 patients were assigned to the group with mBMI ≤570.1 kg·g/m$^2$·L.

All-cause mortality was identified more frequently in AAV patients with mBMI ≤570.1 kg·g/m$^2$·L than those with mBMI >570.1 kg·g/m$^2$·L (38.5% vs. 8.5%, p<0.001).

Furthermore, AAV patients with mBMI ≤570.1 kg·g/m$^2$·L exhibited a significantly higher risk for all-cause mortality than those with mBMI >570.1 kg·g/m$^2$·L (relative risk [RR] 6.750, 95% CI 2.608~17.468) (Figure 2).

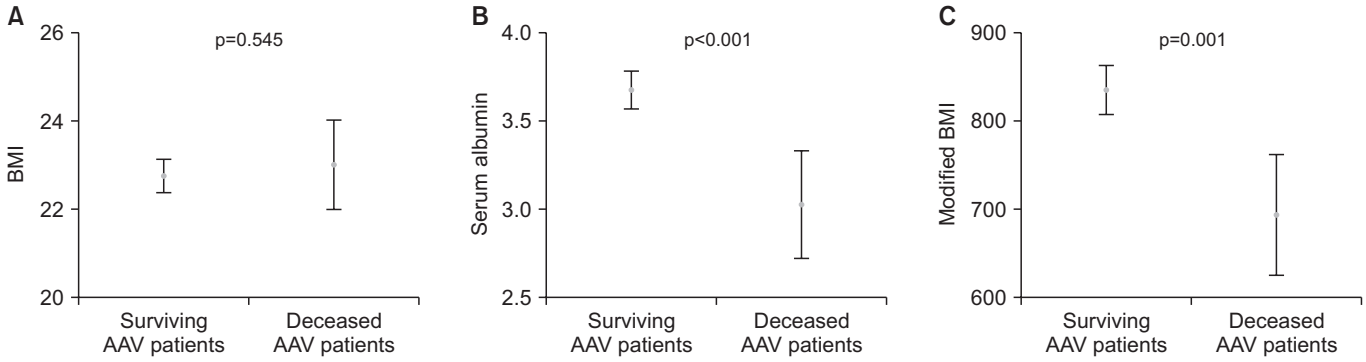


**Figure 1.** Comparison between surviving and deceased patients. (A) BMI at diagnosis did not differ between the two groups. (B, C) However, deceased patients exhibited significantly lower serum albumin and mBMI at diagnosis. mBMI: modified body mass index, BMI: body mass index, AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody.

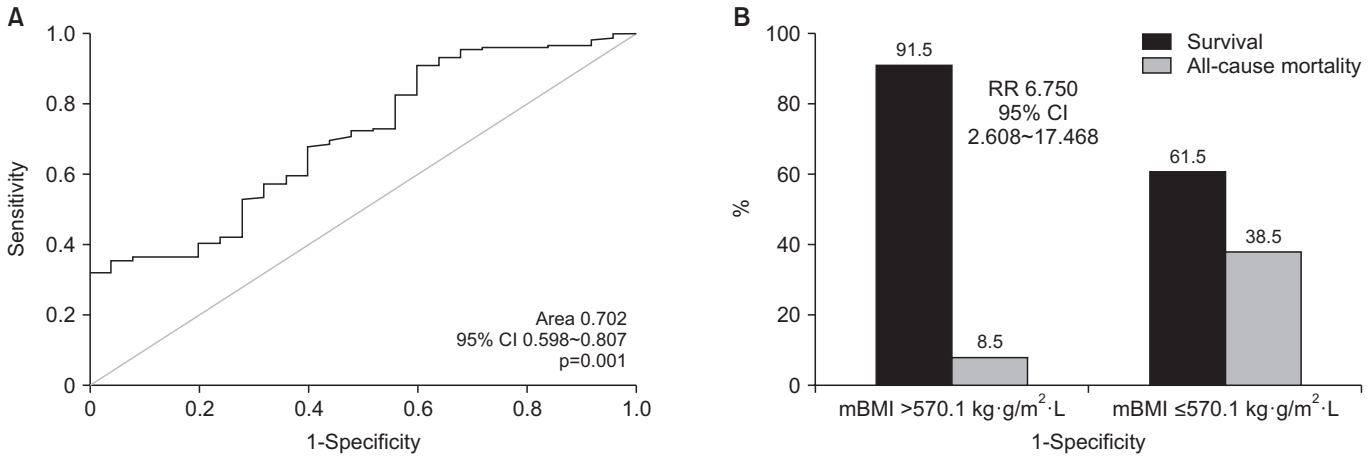


**Figure 2.** (A) When the cut-offs of mBMI for all-cause mortality were obtained using the ROC curve (area 0.702, 95% CI 0.598~0.807), mBMI of 570.1 was chosen for the optimal one due to the maximised sum of sensitivity and specificity. All-cause mortality was identified more frequently in AAV patients with mBMI ≤570.1 kg · g/m$^2$·L than those without. (B) Furthermore, AAV patients with mBMI ≤570.1 kg·g/m$^2$·L exhibited a significantly higher risk for all-cause mortality than those without. mBMI: modified body mass index, ROC: the receiver operator characteristic, CI: confidence interval, AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, RR: relative risk.

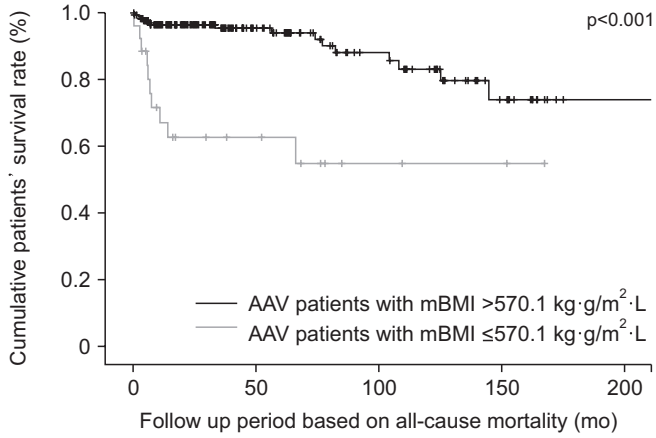


**Figure 3.** AAV patients with mBMI ≤570.1 kg·g/m$^2$·L showed a significantly lower cumulative patients' survival rate than those without. AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, mBMI: modified body mass index.

### Comparison of cumulative survival rates

AAV patients with mBMI ≤570.1 kg·g/m$^2$·L showed a significantly lower cumulative patients' survival rate than those with mBMI >570.1 kg·g/m$^2$·L (p<0.001) (Figure 3).

### Cox hazards model analyses

In the univariable Cox hazards model analysis, age, BVAS, FFS, chronic kidney disease (stage 3, 4, and 5), interstitial lung disease, CRP, serum albumin and mBMI at diagnosis were significantly associated with all-cause mortality during follow-up. However, BMI at diagnosis was not associated with all-cause mortality during follow-up (Table 2). In the multivariable Cox hazards model analysis using variables with statistical significance in the univariable analysis, since there was multicollinearity between serum albumin and mBMI (condition number=22.929), the multivariable analysis was conducted twice with either serum albumin or mBMI. In the multivariable analysis using serum albumin, the independent predictors of all-cause mortality in AAV patients were BVAS (HR 1.086, 95% CI 1.018~1.159), FFS (HR 2.099, 95% CI 1.262~3.491), interstitial lung disease (HR 4.699, 95% CI 1.825~12.097) and serum albumin (HR 0.207, 95% CI 0.087~0.492) at diagnosis. Whereas, in the multivariable analysis using mBMI, the independent predictors of all-cause mortality were BVAS (HR 1.091, 95% CI 1.025~1.162), FFS (HR 1.966, 95% CI 1.198~3.226), interstitial lung disease (HR 4.472, 95% CI 1.721~11.619) and mBMI (HR 0.995, 95% CI 0.992~0.998) at diagnosis (Table 3).

## DISCUSSION

This study investigated the predictability of mBMI at diagnosis for all-cause mortality during follow-up in AAV albumin in AAV patients with BMI at diagnosis ≥18.5 kg/m$^2$ and compared it with that of serum. Our study has several new findings. First, at diagnosis, mBMI was well correlated with age, BVAS, FFS, ESR, and CRP. Second, deceased patients exhibited significantly lower mBMI at diagnosis compared to surviving patients, however, no difference in BMI was observed. Third,

**Table 2**. Univariable Cox hazards model analysis of variables at diagnosis for predicting all-cause mortality in AAV patients

| Variables | Univariable | | |
|---|---|---|---|
| | HR | 95% CI | p-value |
| Age (yr) | 1.052 | 1.016~1.090 | 0.005 |
| Male sex | 1.728 | 0.782~3.820 | 0.176 |
| MPO-ANCA (or P-ANCA) positivity | 1.469 | 0.623~3.464 | 0.380 |
| PR3-ANCA (or C-ANCA) positivity | 0.961 | 0.357~2.585 | 0.937 |
| BVAS | 1.101 | 1.046~1.159 | <0.001 |
| FFS | 2.752 | 1.783~4.246 | <0.001 |
| Chronic kidney disease (stages 3~5) | 2.269 | 1.032~4.988 | 0.041 |
| Diabetes mellitus | 0.854 | 0.341~2.143 | 0.737 |
| Hypertension | 1.160 | 0.526~2.557 | 0.713 |
| Interstitial lung disease | 2.546 | 1.151~5.630 | 0.021 |
| ESR | 1.004 | 0.994~1.014 | 0.395 |
| CRP | 1.007 | 1.001~1.013 | 0.017 |
| BMI | 1.070 | 0.920~1.244 | 0.382 |
| Serum albumin | 0.308 | 0.175~0.544 | <0.001 |
| mBMI | 0.996 | 0.994~0.998 | 0.001 |

AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, HR: hazard ratio, CI: confidence interval, MPO: myeloperoxidase, P: perinuclear, PR3: proteinase 3, C: cytoplasmic, BVAS: Birmingham vasculitis activity score, FFS: five factor score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein: BMI: body mass index, mBMI: modified body mass index.

**Table 3**. Multivariable Cox hazards model analysis of variables at diagnosis with statistical significance in the univariable analysis for predicting all-cause mortality in AAV patients

| Variables | HR | 95% CI | p-value |
|---|---|---|---|
| Multivariable with serum albumin | | | |
| Age (yr) | 1.008 | 0.975~1.042 | 0.637 |
| BVAS | 1.086 | 1.018~1.159 | 0.012 |
| FFS | 2.099 | 1.262~3.491 | 0.004 |
| Chronic kidney disease (stages 3~5) | 1.546 | 0.639~3.743 | 0.334 |
| Interstitial lung disease | 4.699 | 1.825~12.097 | 0.001 |
| CRP | 0.994 | 0.984~1.003 | 0.179 |
| Serum albumin | 0.207 | 0.087~0.492 | <0.001 |
| Multivariable with mBMI | | | |
| Age (yr) | 1.022 | 0.990~1.055 | 0.180 |
| BVAS | 1.091 | 1.025~1.162 | 0.007 |
| FFS | 1.966 | 1.198~3.226 | 0.007 |
| Chronic kidney disease (stages 3~5) | 1.438 | 0.587~3.521 | 0.427 |
| Interstitial lung disease | 4.472 | 1.721~11.619 | 0.002 |
| CRP | 0.998 | 0.989~1.006 | 0.579 |
| mBMI | 0.995 | 0.992~0.998 | 0.003 |

AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, HR: hazard ratio, CI: confidence interval, BVAS: Birmingham vasculitis activity score, FFS: five factor score, CRP: C-reactive protein, mBMI: modified body mass index.

AAV patients mBMI ≤570.1 kg·g/m$^2$·L showed a significantly higher frequency of all-cause mortality, and furthermore, exhibited a significantly higher risk for all-cause mortality than those with mBMI >570.1 kg·g/m$^2$·L (RR 6.750). Fourth, AAV patients with mBMI ≤570.1 kg·g/m$^2$·L showed a significantly lower cumulative patients' survival rate than those with mBMI >570.1 kg·g/m$^2$·L. Last, in the multivariable Cox analysis, either serum albumin or mBMI was significantly associated with all-cause mortality. Therefore, we concluded that mBMI could be clinically used as a significant and additional predictor of all-cause mortality to serum albumin in AAV patients with BMI at diagnosis ≥18.5 kg/m$^2$.

In general, except for underweighted patients, an increase in BMI is associated with a higher mortality rate [18]. Since we only included AAV patients with BMI ≥18.5 kg/m$^2$ in this study, in theory, it was expected that BMI could predict mortality [9]. However, in the univariable Cox hazards model analysis, the association between BMI at diagnosis and all-cause mortality during follow-up was not significant. This discrepancy might be because the distribution of BMI in AAV patients included in this study was not normal. Of 203 patients with AAV, 165 patients (81.3%) were assigned to the normal BMI group, 37 (18.2%) to the overweight BMI group, and only one to the obese BMI group. No patients were assigned to the extremely obese BMI group. For this reason, the cumulative patients' survival rates did not differ among the three groups (Supplementary Figure 2). This pattern of BMI distribution in AAV patients could be explained based on the hypothesis that AAV patients are more cachexic than the general population due to the chronic inflammatory burden [19]. Therefore, we concluded that BMI alone has little clinical significance in predicting all-cause mortality in AAV patients.

Since there was multicollinearity between mBMI and serum albumin, we could not include these two variables together in the multivariable Cox hazards model analysis. However, despite the condition number ≥15 in the multicollinearity analysis, when the multivariable analysis including both serum albumin and mBMI was conducted, serum albumin was independently associated with all-cause mortality (HR 0.223, 95% CI 0.055~0.897), whereas, mBMI was not associated with all-cause mortality (HR 0.894). In addition, even when the cut-off of mBMI for all-cause mortality instead of mBMI was included in the multivariable Cox analysis with serum albumin, mBMI ≤570.1 kg·g/m$^2$·L (HR 2.875, 95% CI 0.742~11.148) could not surpass the independent association with all-cause mortality of serum albumin (HR 0.346, 95% CI 0.120~0.995). Therefore, we conclude that both mBMI and mBMI ≤570.1 kg·g/m$^2$·L had the potential for predicting all-cause mortality in patients with AAV, however, they might play an additional and supplementary clinical role to serum albumin. Nevertheless, the use of mBMI rather than serum albumin along has important clinical implications. Serum albumin is a variable that is affected by various factors other than inflammation such as nutritional impairment, albuminuria, and protein losing enteropathy, which could alter the predictive potential of serum albumin for all-cause mortality in AAV patients. While, since mBMI includes two variables, serum albumin and BMI [11], it may provide a more stable predictive potential by buffering and complementing the change in each variable.

Our study is the first to show the predictive potential of mBMI at diagnosis for all-cause mortality during follow-up in AAV patients. Further, we proposed a method to obtain the cut-off of mBMI for predicting all-cause mortality, and generalised it in AAV patients with different characteristics and conditions. Nevertheless, our study has several limitations such as small sample size, being a single centre study, and a retrospective study design. Despite the limitations, we believe that our study has clinical significance as it provides a novel and clinically useful biomarker for predicting all-cause mortality in AAV patients. We believe that a future prospective study with a large number of AAV patients will validate the results of this study and increase the reliability.

## CONCLUSION

mBMI is significantly associated with all-cause mortality and the lowest quartile or tertile of mBMI at diagnosis is useful in predicting all-cause mortality during follow-up in AAV patients with BMI ≥18.5 kg/m$^2$. We suggest that physicians should consider the characteristics of AAV patients when selecting the lowest quartile or tertile of mBMI as a cut-off for predicting all-cause mortality in each AAV cohort.

## SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2022.29.3.154

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## CONFLICT OF INTEREST

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

## AUTHOR CONTRIBUTIONS

J.Y.P., S.S.A., and S.W.L. designed the study. J.Y.P. and S.W.L. drafted the manuscript. J.Y.P., S.S.A., J.J.S., and S.W.L. contributed to the acquisition and analysis of data. J.J.S. and Y.B.P. validated and reviewed the drafted manuscript. All authors approved the final manuscript.

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