New index using triglyceride-glucose-body mass index for predicting mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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Article

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Abstract

This study aimed to investigate whether triglyceride-glucose-body mass index (TyG-BMI) and a new index using TyG-BMI (NITGB) could predict all-cause mortality in nonobese patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). The medical records of 78 nonobese AAV patients (BMI < 23.0 kg/m² for Asian) were retrospectively reviewed. TyG-BMI was calculated by the equation: Ln [triglyceride × fasting glucose/2] × BMI. To develop NITGB, we assigned a weight of a number close to an 0.1 decimal integer to each variable according to the slopes for independent variables with P-value < 0.1 in the multivariable Cox analysis. The median age was 54.3 years and five patients died. When nonobese AAV patients were divided into two groups based on TyG-BMI ≥ 187.74, those with TyG-BMI ≥ 187.74 exhibited a significantly higher risk for all-cause mortality than those without (RR 9.450). Since age (HR 1.324), Birmingham vasculitis activity score (BVAS; HR 1.212), and TyG-BMI ≥ 187.74 (HR 12.168) were independently associated with all-cause mortality, NITGB was developed as follow: age + 0.2 × BVAS + 2.5 × TyG-BMI ≥ 187.74. When nonobese AAV patients were divided into two groups based on NITGB ≥ 27.36, those with NITGB ≥ 27.36 showed a significantly higher risk for all-cause mortality than those without (RR 284.000). Both nonobese AAV patients with TyG-BMI ≥ 187.74 and those with NITGB ≥ 27.36 exhibited significantly higher cumulative rates of all-cause mortality than those without. NITGB along with TyG-BMI could predict all-cause mortality in nonobese AAV patients.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a cluster of vasculitides affecting mainly the capillaries, arterioles, and venules, and occasionally small arteries. Its histological features are characterised by typical necrotising vasculitis with few or no immune deposits. AAV is generally classified into microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) but may be categorised according to antigens targeted by ANCA as follows: MPO-ANCA vasculitis, PR3-ANCA vasculitis, and ANCA-negative vasculitis.

A previous study with an inception cohort reported that the overall all-cause mortality rate was 38.4/1000 patient-years, and the standardised mortality ratio was 2.3. The most common cause of mortality was cardiovascular disease (CVD) with a cumulative incidence rate of 7.1%, followed by malignancy and infection, and the predictor of mortality was the presence of MPO-ANCA. Meanwhile, AAV-specific indices for disease activity and prognosis, such as the Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) at AAV diagnosis, have also been reported as independent predictors of CVD or CVD-related mortality in patients with AAV. In addition to these indices, the risk factors for all-cause mortality in patients with systemic necrotising vasculitis should be considered. We previously reported that both old age and male sex were significantly associated with all-cause mortality in patients with AAV. Since the mortality rate of patients with AAV is relatively higher than that of those with other
vasculitides, more careful attention should be paid to patients with risk factors for all-cause mortality at diagnosis.

Recently, a novel index, triglyceride (TG) glucose-body mass index (BMI) (TyG-BMI), was introduced. The equation for calculating TyG-BMI consists of three variables including fasting plasma TG level, fasting plasma glucose level, and BMI. As expected from the constituent variables, TyG-BMI was initially proposed as a predictor of type 2 diabetes mellitus (T2DM) and insulin resistance (IR). In addition to T2DM or IR, TyG-BMI was reported to be useful in identifying non-alcoholic fatty liver disease in both the general population with obesity and those without, which is closely associated with an increased risk for cardiovascular disease (CVD). Also, TyG-BMI has also been demonstrated to be significantly associated with cerebrovascular accidents (CVA; ischaemic stroke) in the general population.

Given that IR and its related diseases such as CVD and CVA are generally major risk factors for all-cause mortality in the general population, it could be assumed that TyG-BMI could be a robust predictor of all-cause mortality in AAV patients. However, to date, no study has evaluated the predictive potential of TyG-BMI for unwanted outcomes such as all-cause mortality, CVA and CVD in AAV patients. Hence, we included only nonobese AAV patients (BMI < 23.0 kg/m²) in this study to minimise the effect of BMI on mortality, and investigated whether TyG-BMI at AAV diagnosis could predict poor outcomes during follow-up in nonobese AAV patients. In addition, when TyG-BMI and other variables were competitive in predicting all-cause mortality, we attempted to develop a new index for predicting all-cause mortality based on TyG-BMI and evaluated its clinical usefulness in nonobese AAV patients.

**Methods**

**Patients**

One-hundred and forty-one AAV patients who fulfilled the inclusion criteria and did not meet the exclusion criteria were selected from the SHAVE (Severance Hospital ANCA associated VasculitidEs) cohort. Of them, 78 nonobese AAV patients were included in this study and their medical records were retrospectively reviewed. According to the World Health Organization BMI classification for Asian population, nonobese patients were defined as those with BMI < 23.0 kg/m². The inclusion criteria have been previously described elsewhere: 1) initial diagnosis of AAV at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from October 2000 to May 2021; 2) fulfilment of the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and the 2007 European Medicine Agency algorithm for AAV; 3) well-documented medical records sufficient to collect clinical and laboratory data including ANCA results at AAV diagnosis, calculate BVAS and FFS at AAV diagnosis, and analyse unwanted outcomes during follow-up; 4) available data on the variables that compose the equation to calculate TyG-BMI such as fasting plasma TG level, fasting plasma glucose level and BMI at AAV diagnosis; and 5) BMI < 23.0 kg/m². To minimise ethnic differences, only Korean patients with AAV were included in this study. The
exclusion criteria have been previously described elsewhere: \(^{21,22}\) 1) concurrent serious medical conditions such as cancers, infectious diseases that require hospitalisation, and other systemic vasculitides at AAV diagnosis; 2) follow-up duration of < 3 months after the time of AAV diagnosis; and 3) exposure to immunosuppressive drugs for treating suspected AAV in outside hospitals before AAV diagnosis. The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Republic of Korea, IRB No. 4-2020-1071), and conducted in accordance with the Declaration of Helsinki. Given the retrospective design of the study and the use of anonymised patient data, the requirement for written informed consent was waived.

**Variables**

The collected variables are described in Table 1. Patient baseline data, including basic patient characteristics, physical examination findings (e.g. BMI), and laboratory data, were collected by trained research coordinators at each visit. Blood samples for biochemical analysis were obtained after an overnight fasting period of at least 8 hours. All-cause mortality was defined as death from any aetiology. The follow-up duration based on all-cause mortality was defined as the period between AAV diagnosis and the last visit for surviving patients and as the period between AAV diagnosis and death for deceased patients. Medications were defined as those that had been administered from AAV diagnosis to the last visit.
Table 1
Characteristics of nonobese AAV patients (BMI < 23 kg/m²)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Basic clinical data</strong></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.3 (27.8)</td>
</tr>
<tr>
<td>Male sex (N, (%))</td>
<td>16 (20.5)</td>
</tr>
<tr>
<td><strong>AAV subtypes (N, (%))</strong></td>
<td></td>
</tr>
<tr>
<td>MPA</td>
<td>42 (53.8)</td>
</tr>
<tr>
<td>GPA</td>
<td>16 (20.5)</td>
</tr>
<tr>
<td>EGPA</td>
<td>20 (25.6)</td>
</tr>
<tr>
<td><strong>ANCA positivity (N, (%))</strong></td>
<td></td>
</tr>
<tr>
<td>MPO-ANCA (or P-ANCA) positive</td>
<td>50 (64.1)</td>
</tr>
<tr>
<td>PR3-ANCA (or C-ANCA) positive</td>
<td>17 (21.8)</td>
</tr>
<tr>
<td><strong>AAV-specific indices</strong></td>
<td></td>
</tr>
<tr>
<td>BVAS</td>
<td>13.0 (12.0)</td>
</tr>
<tr>
<td>FFS</td>
<td>1.0 (2.0)</td>
</tr>
<tr>
<td><strong>Comorbidities (N, (%))</strong></td>
<td></td>
</tr>
<tr>
<td>T2DM</td>
<td>14 (17.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (21.8)</td>
</tr>
<tr>
<td><strong>Acute phase reactants</strong></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>48.0 (60.0)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.6 (27.6)</td>
</tr>
<tr>
<td><strong>TyG-BMI index-related variables</strong></td>
<td></td>
</tr>
<tr>
<td>TyG</td>
<td>8.6 (0.7)</td>
</tr>
</tbody>
</table>

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

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BMI: body mass index; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; T2DM: type 2 diabetes mellitus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TyG: triglyceride-glucose; TyG-BMI: triglyceride-glucose-body mass index.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>19.9 (3.0)</td>
</tr>
<tr>
<td>TyG-BMI</td>
<td>171.1 (26.6)</td>
</tr>
<tr>
<td>During follow-up</td>
<td></td>
</tr>
<tr>
<td>Poor prognosis (N, (%))</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5 (6.4)</td>
</tr>
<tr>
<td>Follow-up period based on all-cause mortality</td>
<td>36.6 (68.6)</td>
</tr>
<tr>
<td>Medications (N, (%))</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>74 (94.9)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>39 (50.0)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>9 (11.5)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>15 (19.2)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>41 (52.9)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>8 (10.3)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>7 (9.0)</td>
</tr>
<tr>
<td>Plasma exchange</td>
<td>6 (7.7)</td>
</tr>
</tbody>
</table>

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

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BMI: body mass index; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; T2DM: type 2 diabetes mellitus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TyG: triglyceride glucose; TyG-BMI: triglyceride glucose-body mass index.

Equations of TyG-BMI and a new index using TyG-BMI for all-cause mortality

TyG-BMI is calculated as follows: Ln [TG (mg/dL) × FPG (mg/dL)/2] × BMI. To develop an equation of a new index using TyG-BMI and other variables for predicting all-cause mortality, we assigned a weight of a number close to an 0.1 decimal integer to each variable according to the slopes for independent variables with P-value < 0.1 in the multivariable Cox analysis as described in our previous study.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as medians (interquartile ranges) and
categorical variables as numbers (percentages). The correlation coefficient \( r \) between the two variables was obtained using Pearson correlation analysis. The area under the curve (AUC) was calculated using receiver operating characteristic (ROC) curve analysis. Further, the optimal cut-off value was extrapolated by performing ROC curve analysis, and one value with the maximum sum of sensitivity and specificity was selected. The multivariable Cox hazard model using variables with statistical significance in the univariable Cox hazard model was used to obtain the hazard ratios (HRs) during follow-up. The relative risk (RR) of the cut-off value for high AAV activity was analysed using contingency tables and the chi-square test. The cumulative survival rates between the two groups were compared using Kaplan–Meier survival analysis with the log-rank test. Statistical significance was set at \( P < 0.05 \) in the overall analyses and \( P < 0.1 \) in the ROC curve and univariable and multivariable Cox analyses.

**Ethics statement**

This study was approved by the Institutional Review Board of Severance Hospital (Seoul, Korea; approval no. 4-2020-1071). The requirement for written informed consent was waived owing to the retrospective study design and use of anonymised patient data.

**Results**

**Patient characteristics**

At AAV diagnosis, the median age was 54.3 years and 20.5% of the patients were men. Forty-two, sixteen, and twenty patients were classified as having MPA, GPA, and EGPA, respectively. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were positive in 50 (64.1%) and 17 patients (21.8%), respectively. Fourteen patients had T2DM and 17 had hypertension. The median BVAS, FFS, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level were 13.0, 1.0, 48.0 mm/hr, and 3.6 mg/L, respectively. Also, the median TyG, BMI, and TyG-BMI were 8.6, 19.9 kg/m², and 171.1, respectively. During follow-up, five patients died within an average follow-up duration of 36.6 months. Glucocorticoids, cyclophosphamide, and azathioprine were administered to 74 (94.9%), 39 (50.0%), and 41 patients (52.9%), respectively (Table 1).

**Correlations of TyG-BMI with the continuous variables at AAV diagnosis**

TyG-BMI was not significantly correlated with age \( (r = 0.168) \), BVAS \( (r = -0.184) \), FFS \( (r = -0.071) \), ESR \( (r = 0.138) \), and CRP level \( (r = -0.073) \).

**Comparison of the AUCs of TyG-BMI for predicting all-cause mortality according to BMI**

The AUC of TyG-BMI in all 141 patients regardless of BMI was 0.611. For 63 patients with a BMI \( \geq 23 \) kg/m², the AUC was 0.431. However, this difference was not significant. Meanwhile, the AUC of TyG-BMI in the 78 nonobese AAV patients was significant \( (AUC = 0.729, P = 0.088) \) (Fig. 1).
Comparison of the AUCs of TyG-BMI for predicting other poor outcomes

Poor outcomes other than all-cause mortality, including relapse, end-stage renal disease (ESRD), CVA and CVD, were also analysed. The follow-up duration based on each poor outcome was defined as the period between AAV and each poor outcome occurrence. Conversely, for patients who had no poor outcome, it was defined as the period between AAV diagnosis and the last visit. In this study, the AUCs of TyG-BMI for relapse, ESRD, CVA, and CVD showed no statistical significance in nonobese AAV patients (Suppl Fig. S1).

Optimal cut-off value of TyG-BMI and RR for predicting all-cause mortality

When the cut-off value of TyG-BMI for all-cause mortality was set as 187.74 in the ROC curve analysis, the sensitivity and specificity were 60.0% and 86.3%, respectively. When nonobese AAV patients were divided into two groups based on this cut-off value, 13 patients were assigned as a group with TyG-BMI $\geq$ 187.74. All-cause mortality was identified in nonobese AAV patients with TyG-BMI $\geq$ 187.74 more frequently than those with TyG-BMI < 187.74 (23.1% vs. 3.1%, P = 0.007). Furthermore, nonobese AAV patients with TyG-BMI $\geq$ 187.74 exhibited a significantly higher risk for all-cause mortality than those with TyG-BMI < 187.74 (RR 9.450, 95% confidence interval [CI] 1.400, 63.787) (Fig. 1, Fig. 2).

Cox hazards analyses based on TyG-BMI $\geq$ 187.74

In the univariable analysis, age (HR 1.359), male sex (HR 7.656), and TyG-BMI $\geq$ 187.74 (HR 6.264) were significantly associated with all-cause mortality, and BVAS (HR 1.116) tended to be associated with all-cause mortality in nonobese AAV patients (P = 0.060). As described in the methods section, variables with a P-value < 0.1 were included in the multivariable Cox analysis. In the multivariable analysis, none of the variables were statistically significant. However, age (HR 1.324, P = 0.089), BVAS (1.212, P = 0.095), and TyG-BMI $\geq$ 187.74 (HR 12.168, P = 0.056) tended to be associated with all-cause mortality meaningfully in nonobese AAV patients (Table 2).
Table 2
Cox hazards model analysis of variables at diagnosis for all-cause mortality during follow-up in nonobese AAV patients (BMI < 23.0 kg/m²)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.359</td>
<td>1.041, 1.773</td>
</tr>
<tr>
<td>Male sex</td>
<td>7.656</td>
<td>1.239, 46.191</td>
</tr>
<tr>
<td>MPA</td>
<td>58.987</td>
<td>0.044, 79750.522</td>
</tr>
<tr>
<td>GPA</td>
<td>0.035</td>
<td>0.000, 397.710</td>
</tr>
<tr>
<td>MPO-ANCA (or P-ANCA) positive</td>
<td>3.504</td>
<td>0.345, 35.604</td>
</tr>
<tr>
<td>PR3-ANCA (or C-ANCA) positive</td>
<td>0.034</td>
<td>0.000, 335.249</td>
</tr>
<tr>
<td>BVAS</td>
<td>1.116</td>
<td>0.995, 1.250</td>
</tr>
<tr>
<td>FFS</td>
<td>1851</td>
<td>0.803, 4.268</td>
</tr>
<tr>
<td>T2DM</td>
<td>3.063</td>
<td>0.507, 18.499</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.923</td>
<td>0.315, 11.723</td>
</tr>
<tr>
<td>ESR</td>
<td>1.005</td>
<td>0.982, 1.028</td>
</tr>
<tr>
<td>CRP</td>
<td>1.002</td>
<td>0.984, 1.020</td>
</tr>
<tr>
<td>TyG-BMI index ≥ 187.74</td>
<td>6.264</td>
<td>1.038, 37.785</td>
</tr>
</tbody>
</table>

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BMI: body mass index; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; T2DM: type 2 diabetes mellitus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TyG-BMI: triglyceride glucose-body mass index.

New index using TyG-BMI (NITGB) for all-cause mortality
According to the description in the methods section, three variables, age, BVAS, and TyG-BMI ≥ 187.74 were included in an equation of NITGB for all-cause mortality, their slopes were modified as 0.3 (0.281), 0.2 (0.193), and 2.5 (2.499), and eventually, an equation was developed as follows: NITGB for all-cause mortality in nonobese AAV patients at AAV diagnosis = 0.3 × age + 0.2 × BVAS + 2.5 × TyG-BMI ≥ 187.74 (yes = 1 and no = 0).

**Optimal cut-off value of NITGB and RR for predicting all-cause mortality**

Using the ROC curve, when the cut-off value of NITGB was set as 27.36, the sensitivity and specificity were 80.0% and 98.6%. When nonobese AAV patients were divided into two groups based on the cut-off value of 27.36, all-cause mortality was observed in nonobese AAV patients with NITGB ≥ 27.36 more frequently than those with NITGB < 27.36 (80.0% vs. 1.4%, P < 0.001). Furthermore, nonobese AAV patients with NITGB ≥ 27.36 showed a significantly higher risk for all-cause mortality than those with NITGB < 27.36 (RR 284.000, 95% CI 14.877, 5421.390) (Fig. 3A).

**Comparison of the AUCs between TyG-BMI and NITGB for all-cause mortality**

The AUC of NITGB (area 0.925, P = 0.002) was significantly higher than that of TyG-BMI (area 0.731, P = 0.088) for predicting all-cause mortality in nonobese AAV patients (Fig. 3B).

**Comparison of the cumulative rates of all-cause mortality**

In the comparison based on the cut-off value of TyG-BMI, nonobese AAV patients with TyG-BMI ≥ 187.74 exhibited a significantly higher cumulative rate of all-cause mortality than those with TyG-BMI < 187.74 (P = 0.022). In the comparison according to the cut-off value of NITGB, the cumulative rate of all-cause mortality in nonobese AAV patients with NITGB ≥ 27.36 was significantly higher than that in those with NITGB < 27.36 (P < 0.001) (Fig. 4). Both the cut-off values showed a possibility of predicting all-cause mortality in nonobese AAV patients properly.

**Discussion**

Herein, we investigated the ability of TyG-BMI to predict all-cause mortality, developed a new index for predicting mortality using TyG-BMI, and evaluated its clinical usefulness in nonobese AAV patients. We obtained several interesting findings. Firstly, the AUC of TyG-BMI for all-cause mortality in the 78 nonobese AAV patients, tended to be statistically significant but those of all or obese AAV patients showed no similar trend of significance. Secondly, when the cut-off value of TyG-BMI for all-cause mortality was set as 187.74, all-cause mortality was more frequently identified in AAV patients with TyG-BMI ≥ 187.74 than those with TyG-BMI < 187.74. Thirdly, a new index using TyG-BMI for all-cause mortality (NITGB) was developed using variables that were with a P-value < 0.1 in the Cox hazards model analyses for predicting all-cause mortality. Fourthly, when the cut-off value of NITGB for predicting all-
cause mortality was set as 27.36, the cumulative mortality rate in nonobese AAV patients with NITGB ≥ 27.36 was significantly higher than that in those with NITGB < 27.36. Therefore, it is concluded that TyG-BMI and NITGB at AAV diagnosis could be useful in predicting all-cause mortality, and furthermore, the predictive ability of NITGB is greater than that of TyG-BMI in nonobese AAV patients.

Only nonobese AAV patients were included herein. BMI is known to be closely associated with mortality in the general population. In particular, it shows a U shape, which is characterised by roughly opposite results between the nonobese and obese people. Since BMI is proportional to the probability of all-cause mortality in individuals with BMI ≥ 23.0 kg/m², the mortality-reflected effect of BMI itself is added to the predictability of all-cause mortality. TyG, which may interfere with interpreting the predictability of all-cause mortality of TyG-BMI and leave its lower reliability. Whereas, since BMI is inversely correlated with the probability of all-cause mortality in individuals with BMI < 23.0 kg/m², BMI may highlight the predictability of all-cause mortality of TyG-BMI in AAV patients. Actually, when all patients were analysed in this study, the AUC of TyG-BMI for all-cause mortality was not significant, whereas it showed a tendency to be statistically significant in 78 non-obese AAV patients in the ROC curve analysis. These results indicated that the risk of all-cause mortality associated with TyG-BMI is meaningful in non-obese people but it is not in overweight and obese people (Fig. 1). This finding is consistent with findings of other studies which showed that non-obese people have a higher risk of TyG-BMI related diabetes and non-alcoholic fatty liver disease than overweight and obese people. However, we were not able to provide evidence regarding whether the presence or absence of a U shape exist in the association between the risk of all-cause mortality and BMI in our data because the number of mortality case was small.

Since TyG-BMI consists of fasting plasma TG, fasting plasma glucose, TyG, and BMI, we assessed the abilities of each component for predicting all-cause mortality and compared them with TyG-BMI in nonobese AAV patients. First, in the ROC curve analysis, the AUCs of fasting plasma TG, fasting plasma glucose, TyG and BMI were 0.547 (P = 0.729), 0.521 (P = 0.878), 0.570 (P = 0.603), and 0.688 (P = 0.162), respectively. There was no trend of the significant association between each component composing an equation of TyG-BMI and all-cause mortality (Suppl Fig. S2). Next, in the univariable Cox hazards model analysis, fasting plasma TG (HR 1.001, P = 0.908), fasting plasma glucose (HR 1.010, P = 0.509), TyG (HR 1.831, P = 0.536), and BMI (HR 1.541, P = 0.186) were not associated with all-cause mortality. Whereas TyG-BMI ≥ 187.74 (HR 6.264, P = 0.045) was independently and significantly associated with all-cause mortality in nonobese AAV patients. Therefore, to cope with the possibility of all-cause mortality during follow-up in nonobese AAV patients, attention should be carefully paid to the predictability of TyG-BMI over the cut-off for predicting mortality at the time of AAV diagnosis.

In this study, in order to meet the clinical need for a new index for predicting all-cause mortality, the cut-off value of TyG-BMI with a P-value < 0.1 was obtained from the ROC curve. To overcome this statistical limitation, we also analysed the implication of TyG-BMI for presupposing all-cause mortality using two more cut-offs, the highest tertile, and quartile, that are frequently and clinically applied. In terms of the
highest tertile of TyG-BMI, the lower limit of the highest tertile was set as 179.28. When nonobese AAV patients were partitioned into two groups, there was no significant difference in the cumulative mortality rates between patients with TyG-BMI ≥ 179.28 and those with TyG-BMI < 179.28 (P = 0.276) (Suppl Fig. S3A). In terms of the highest quartile of TyG-BMI, the lowest value of the highest quartile was calculated as 183.57. When nonobese AAV patients were divided into two groups, patients with TyG-BMI ≥ 183.57 tended to exhibit a significantly higher cumulative mortality rate than those with TyG-BMI < 183.57 but it did not reach statistical significance (Suppl Fig. S3B). Therefore, it is concluded that 187.74 obtained from the ROC curve is the suitable cut-off value for predicting all-cause mortality in nonobese AAV patients.

TyG is an index composed of fasting plasma TG and fasting plasma glucose and has been well known as an index that effectively reflects IR and overall metabolic status in individuals. However, Er et al. found that the new index of TyG-BMI, which is formed by combining the TyG index with BMI, can better reflect IR status than the TyG index. Our study results provide clinically supporting evidence for the biologically plausible hypothesis that IR plays an important role in the AAV patients. Although the underlying mechanism of the relationship between TyG-BMI and all-cause mortality in AAV patients is unclear, it may be related to IR. TyG as a surrogate marker of IR is associated with metabolic disorders including T2DM. Consequently, it ultimately increases the risk of all-cause mortality by enhancing the possibility of their systemic complications including CVA and CVD. However, when the association between TyG-BMI and CVA or ACS was investigated using the ROC curve and univariable Cox hazards model analysis, the AUCs of TyG-BMI for CVA and CVD were not statistically significant (Suppl Fig. S1), and furthermore, TyG-BMI was significantly associated with neither CVA (HR 1.026, P = 0.315) nor CVD (HR 1.033, P = 0.293).

It is inferred that the pathological association between IR increased by TyG-BMI and the clinically significant occurrence of CVA or CVD in nonobese AAV patients was not as robust as that in AAV patients regardless of BMI. In fact, when the univariable Cox analysis was performed in all 141 AAV patients, TyG-BMI showed a tendency to be associated with the occurrence of CVD but it was not statistically significant (HR 1.014, P = 0.110). Therefore, the mechanism by which TyG-BMI could predict all-cause mortality in nonobese AAV patients could not be explained solely by increased IR and subsequently the augmented possibility of CVA, and CVD.

In Table 2, in the multivariable Cox analysis, in addition to TyG-BMI ≥ 187.74, both age and BVAS were also associated with all-cause mortality in nonobese AAV patients. First of all, variables of age and the male sex are ready-established conventional risk factors for all-cause mortality. In the previous studies, we demonstrated that elderly AAV patients, as well as male AAV patients, had a significantly higher rate of all-cause mortality. However, a variable of age could predict all-cause mortality independently but that of the male sex could not in this study. It is assumed that these results might be owing to a relatively small proportion of male patients compared to females. Furthermore, the inclusion of only AAV patients with BMI < 23.0 kg/m² might have influenced the results by diminishing the effect of obesity on all-cause
mortality. On the other hand, BVAS is the most widely used index for assessing the activity of AAV. In addition to a role to reflect the cross-sectional activity of AAV, BVAS has been considered associated with all-cause mortality, in particular, cardiovascular disease-related mortality in AAV patients.27,28

Given these concepts, in this study, we assigned weights to age, BVAS, and TyG-BMI ≥ 187.74 by referring to the slope of the multivariable Cox analysis, and developed a new index using TyG-BMI for predicting all-cause mortality in nonobese AAV patients. We found two advantages of NITGM compared to TyG-BMI. One is that NITGM exhibited a more robust ability for predicting all-cause mortality than TyG-BMI itself because the abilities of age and BVAS for predicting all-cause mortality were added to that of TyG-BMI. The other is that NITGM includes three risk factors for all-cause mortality in a variety of areas: metabolic disorders-related cardiovascular (TyG-BMI), conventional (age), and AAV-specific (BVAS) risk factors. Finally, we found that the independent ability of NITGM ≥ 27.36 to predict all-cause mortality tended to be stronger than that of TyG-BMI ≥ 187.74 by the comparative analysis of the cumulative rates of all-cause mortality between the two groups (Fig. 4).

For the first time, we demonstrated the abilities of TyG-BMI and a new index using TyG-BMI (NITGB) to predict all-cause mortality in nonobese AAV patients. Our findings provide evidence that these indices are reliable markers for the early identification of individuals at high risk of mortality. Given the relatively high mortality rate of AAV, it is believed that this study has an advantage in that it enabled the development of biomarkers or indices at the time of AAV diagnosis for predicting all-cause mortality during follow-up in nonobese AAV patients. Additionally, the evaluated indices can be flexibly applied to AAV patients with ethnic and geographical differences by applying a method for deriving the cut-offs of TyG-BMI and NITGB rather than suggesting fixed values.

This study had several limitations. Firstly, the number of patients was too small to derive statistically sufficient significance. Thus, we adjusted the significance level (P-value < 0.05 to < 0.1) in the ROC curve and the Cox analyses. Secondly, because of the retrospective study design, we could not fully control for subclinical confounding factors that could affect not only TyG-BMI and NITGB at diagnosis but also all-cause mortality during follow-up. Moreover, we could not provide the serial data regarding TyG-BMI and NITGB from the time of AAV diagnosis to either the date of death or the last visit. We believe that a future prospective study with a larger number of nonobese AAV patients will validate our results and suggest the possibility of applying them to AAV patients in real clinical practice by showing the dynamic information on the association between either TyG-BMI or NITGB and all-cause mortality.

Conclusion

We demonstrated the clinical implication of TyG-BMI for predicting all-cause mortality, developed a new index for predicting mortality using TyG-BMI and demonstrated that NITGB at AAV diagnosis along with TyG-BMI could predict all-cause mortality during follow-up in nonobese AAV patients. In addition, the predictive ability of NITGB seemed greater than that of TyG-BMI for all-cause mortality in nonobese AAV patients. Based on these results, in addition to several known initial predictors of all-cause mortality in
AAV patients, we suggest deriving the cut-off value of NITGB at diagnosis in each AAV cohort with racial and geographical characteristics and applying it to newly diagnosed nonobese AAV patients.

**Declarations**

**Availability of data and materials**

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

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**Author contributions**

P.P. carried out the statistical analysis. P.P., S.L. and J.H. wrote the first draft of the manuscript. J.P., S.A., J.S. and Y.P. collated data. All authors corrected and approved the revisions and final version of the manuscript. S.L. is responsible for funding for the study. S.L. and J.H. are responsible for the conception and design of the study. S.L. and J.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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**Competing interests**

The Authors declare no competing interests.

**References**


Figure 1

Comparison of area under the curves of TyG-BMI for all-cause mortality based on BMI of 23 kg/m²

The AUC of TyG-BMI for all-cause mortality in nonobese AAV patients tended to be statistically significant compared to all patients and those with BMI ≥ 23 kg/m².

TyG: triglyceride glucose; BMI: body mass index; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody.
Figure 2

Relative risk of TyG-BMI for all-cause mortality

When the cut-off of TyG-BMI was set as 187.74 using the ROC curve, all-cause mortality was identified in nonobese AAV patients with TyG-BMI $\geq$ 187.74 more frequently than those with TyG-BMI < 187.74 (23.1% vs. 3.1%, relative risk 9.450, $P = 0.007$).

TyG: triglyceride glucose; BMI: body mass index; ROC: receiver operator characteristic; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody.

Figure 3
Relative risk of NITGB for all-cause mortality and comparison between TyG-BMI and NITGB

(A) When the cut-off value of NITGB was set as 27.36 using the ROC curve, all-cause mortality was found in nonobese AAV patients with NITGB ≥ 27.36 more frequently than those with NITGB < 27.36 (80.0% vs. 1.4%, relative risk 284.000, P < 0.001); (B) The AUC of NITGB (line) was significantly higher than that of TyG-BMI (dotted) for predicting all-cause mortality in nonobese AAV patients.

NITGB: new index using TyG-BMI; TyG: triglyceride glucose; BMI: body mass index; ROC: receiver operator characteristic; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody.

Figure 4

Comparison of the cumulative rates of all-cause mortality

Both nonobese AAV patients with TyG-BMI ≥ 187.74 and those with NITGB ≥ 27.36 exhibited higher the cumulative rates of all-cause mortality than those with TyG-BMI < 187.74 and those with NITGB < 27.36.

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; TyG: triglyceride glucose; BMI: body mass index; NITGB: new index using TyG-BMI.

Supplementary Files

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

- SUPPLEMENTARYFIGURES1TyGBMIAAV.tif
- SUPPLEMENTARYFIGURES2TyGBMIAAV.tif
- SUPPLEMENTARYFIGURES3TyGBMIAAV.tif