Effect of numbers of metabolic syndrome components on mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis with metabolic syndrome

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Abstract

Objective

This study investigated the effect of the number of metabolic syndrome (MetS) components on all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) with MetS.

Methods

The medical records of 93 AAV patients with MetS were retrospectively reviewed. MetS was diagnosed when three or more the following MetS components for Asians were met: (i) increased waist circumference; ii) high blood pressure; (iii) hypertriglyceridaemia; (iv) low level of high-density lipoprotein (HDL)-cholesterol; and (v) impaired fasting glucose (IFG) or type 2 diabetes mellitus (T2DM). All-cause mortality was defined as death owing to any aetiology.

Results

The median age was 61.4 years and 33 patients were men. Among 93 AAV patients with MetS, as the number of MetS components increased, the cumulative patient survival rate significantly decreased ($p = 0.024$). Compared to surviving AAV patients with MetS, deceased AAV patients with MetS were older, had higher Birmingham vasculitis activity score (BVAS) and Five-factor score (FFS), a lower frequency of IFG or T2DM, and a higher number of MetS components. In the multivariable Cox analysis, AAV patients with MetS who had all five MetS components were approximately 62 times more susceptible to all-cause mortality than those who had only three components. In terms of IFG or T2DM, patients with only IFG exhibited a significantly lower cumulative patients' survival rate than those without.

Conclusion

The presence of many MetS components at the initial diagnosis of AAV was an independent and significant predictor of all-cause mortality in AAV patients with MetS.

Key words

antineutrophil cytoplasmic antibody, vasculitis, metabolic syndrome, components, all-cause mortality

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Introduction

Metabolic syndrome (MetS) refers to a medical condition associated with type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and insulin resistance. It is a cluster of metabolic abnormalities that include impaired glucose metabolism, central obesity, dyslipidaemia, and hypertension (1). So far, several criteria for defining MetS have been proposed, and the 2005 National Cholesterol Education Program Adult Treatment Panel III criteria is the most widely used in clinical practice (2-4). Previous studies have reported that MetS can increase the incidence of CVD as well as all-cause mortality (5, 6). Moreover, a previous study examining a Korean population reported that MetS was an independent risk factor for increased all-cause mortality regardless of the presence or absence of T2DM (7).

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitis that involves the smallest vessels. It comprises three subtypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA) (8, 9). It is a representative systemic autoimmune disease that causes inflammation and can affect almost all major organs, leading to damage and dysfunction (10). Since inflammation is associated with obesity, insulin resistance, cardiovascular risks, and MetS (11, 12), it can be hypothesised that patients with AAV may have an increased incidence of MetS. Furthermore, MetS may increase the all-cause mortality rate in patients with AAV. We recently demonstrated that the prevalence of MetS was significantly higher in Korean patients with AAV than in healthy controls. However, there are limited studies that have investigated the effect of MetS and its severity on all-cause mortality in AAV patients with MetS (13).

Meanwhile, a previous study reported that the severity of MetS, assessed according to the number of MetS components, could predict vascular deaths in a Korean population. The study showed that the risk of atherosclerotic vascular disease, ischaemic heart disease, and stroke significantly increased as the number of MetS components increased (14). Hence, in this study, we investigated the effect of MetS severity, assessed according to the number of MetS components, on all-cause mortality in AAV patients diagnosed with MetS at the time of AAV diagnosis.

Patients and methods

Patients

This study included 93 AAV with MetS and retrospectively reviewed their medical records. All patients were enrolled in the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort, which is a prospective and observational cohort of patients with AAV established in November 2016. The inclusion criteria were as follows: (i) AAV diagnosed at Severance Hospital by specialised rheumatologists with consensus by a vasculitis team; (ii) AAV diagnosis based on both the classification algorithm for AAV and polyarteritis nodosa proposed by the European Medicines Agency in 2007 and the revised nomenclature of vasculitides suggested by the Chapel Hill Conference Consensus in 2012 (8, 9); (iii) sufficient medical records for collecting clinical and laboratory data, particularly AAV-specific indices such as Birmingham vasculitis activity score (BVAS) (15, 16) and five-factor score (FFS) (17). Because BVAS for GPA has a differently weighted scoring system compared to BVAS, we evenly applied BVAS v3 to GPA to unify the scoring system; and (iv) a clear description of MetS components in medical records and the fulfilment of the classification criteria of MetS at AAV diagnosis (2, 4). The exclusion criteria were as follows: (i) serious concomitant medical conditions affecting MetS components or AAV diagnosis, such as malignancies, infectious diseases, and systemic vasculitides other than AAV; (ii) use of immunosuppressive drugs for AAV treatment before AAV diagnosis; or (iii) follow-up ≤3 months. Coexisting serious medical conditions and administered immunosuppressive drugs were identified according to the International Classification of Diseases (10th revision) and the Korean Drug Utilization

Review (DUR) system, respectively. 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.

Variables

Age, sex, smoking history, and body mass index (BMI) were collected as variables at AAV diagnosis. Data on AAV subtypes, ANCA type, AAV-specific indices, MetS components, and MetS diagnosis were also obtained. Physical examination was performed by measuring the height, weight, waist circumference, and blood pressure of patients according to standard methods. Trained examiners measured patients' waist circumference at the midpoint between the lower border of the rib cage and the iliac crest. Blood pressure was measured in triplicate, and the mean value of the second and third measurements was used for the analysis. BMI was calculated as weight in kilograms divided by height in square metres (kg/m^2). Blood samples to determine fasting glucose and lipid levels were obtained in the morning after an overnight fast. All-cause mortality rate and follow-up duration based on all-cause mortality were assessed as follow-up variables. Medications administered during the follow-up period were also reviewed.

All-cause mortality

All-cause mortality was defined as death owing to any aetiology. The follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to death in deceased patients and as the period from AAV diagnosis to the last visit in surviving patients. In patients transferred to other hospitals, death was confirmed based on data from the Korean National Health Insurance Corporation.

MetS diagnosis

MetS was diagnosed when three or more of the following five MetS components for Asians were present (2, 4): (i) increased waist circumference (90 cm in men, 80 cm in women); ii) high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or antihypertensive medication use); (iii) hypertriglyceridaemia (triglyceride ≥150 mg/dl); (iv) low level of high-density lipoprotein (HDL)-cholesterol (<40 mg/dl in men, <50 mg/dl in women); and (v) impaired fasting glucose (IFG) (fasting plasma glucose ≥100 mg/dl) or T2DM (fasting plasma glucose level ≥126 mg/dl or use of medication for high blood glucose).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 25; IBM Corp., Armonk, NY, USA). Continuous variables are

Table I. Characteristics of 93 AAV patients with MetS.

Variables	Values
At diagnosis	
Demographic data	
Age (years)	61.4 (15.5)
Sex (N, (%))	
Male	33 (35.5)
Female	60 (64.5)
Ex-smoker (N, (%))	9 (9.7)
Body mass index (kg/m^2)	23.3 (3.2)
AAV Subtypes (N, (%))	
MPA	49 (52.7)
GPA	24 (25.8)
EGPA	20 (21.5)
ANCA positivity (N, (%))	
MPO-ANCA (or P-ANCA) positivity	70 (75.3)
PR3-ANCA (or C-ANCA) positivity	12 (12.9)
Both ANCA positivity	1 (1.1)
ANCA positivity	81 (87.1)
AAV-specific indices	
BVAS	14.0 (11.0)
FFS	1.0 (1.0)
MetS components (N, (%))	
Increased waist circumference (Waist circumference 90 cm in men and 80 cm in women)	65 (69.9)
High blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or antihypertensive medication	43 (46.2)
Hypertriglyceridaemia (triglyceride ≥ 150 mg/dL)	70 (75.3)
Low high-density lipoprotein (HDL)-cholesterol (men <40 mg/dL and women < 50 mg/dL)	48 (51.6)
IFG (impaired fasting glucose) (fasting plasma glucose ≥ 100 mg/dL) or T2DM (fasting plasma glucose ≥ 126 mg/dL or on medication for high blood glucose)	75 (80.6)
Number of fulfilled MetS components (N, (%))	
3	56 (60.2)
4	30 (32.3)
5	7 (7.5)
During follow-up	
All-cause mortality (N, (%))	9 (9.7)
Follow-up duration based on all-cause mortality (months)	28.1 (58.8)
Medications administered during follow-up (N, (%))	
Glucocorticoid	88 (94.6)
Cyclophosphamide	50 (53.8)
Rituximab	16 (17.2)
Mycophenolate mofetil	11 (11.8)
Azathioprine	47 (50.5)
Tacrolimus	3 (2.2)
Methotrexate	5 (5.4)

Values are expressed as a median (interquartile range, IQR) or N (%).
AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MetS: metabolic syndrome; 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; T2DM: type 2 diabetes mellitus.

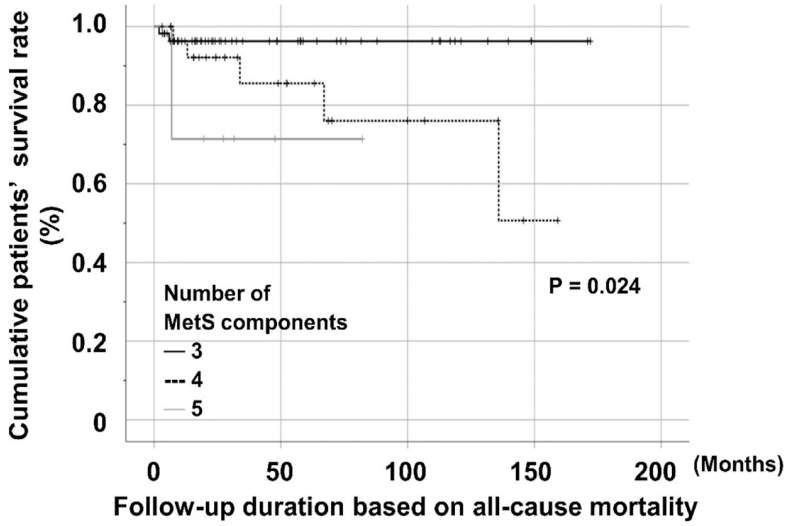

Fig. 1. Comparison of cumulative survival rates in AAV patients with MetS.
As the number of MetS components increased, the cumulative patient survival rate significantly decreased.
AAV: antineutrophil cytoplasmic antibody-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MetS: metabolic syndrome.

expressed as medians with interquartile ranges, and categorical variables are expressed as numbers (percentages). Cumulative survival rates were compared between two groups using Kaplan-Meier survival analysis with the log-rank test. Significant differences between two categorical variables were analysed using the chi-square and Fisher's exact tests. The Mann-Whitney U-test was used to compare significant differences between two continuous variables. A multivariate Cox hazard model using statistically significant variables in the comparison test was used to obtain hazard ratios (HRs) during the follow-up. Statistical significance was set at p values <0.05.

Results

Characteristics of AAV patients with MetS

At AAV diagnosis, the median age was 61.4 years and 33 patients were men. Among 93 AAV patients with MetS, 49 were classified as MPA, 24 as GPA, and 20 as EGPA. ANCA was detected in 81 patients. The median BMI, BVAS, and FFS were 23.3 kg/m^2, 14.0, and 1.0, respectively. Among the MetS components, the most prevalent item was IFG or T2DM, followed by hypertriglyceridaemia. Seven patients had all five MetS components, 30 had four components, and 56 had three components. Nine patients died at a median follow-up of 28.1 months. Glucocorticoids were administered to 88 patients, and cyclophosphamide and rituximab were administered to 50 and 16 patients, respectively, as induction therapy (Table I).

Comparison of cumulative survival and poor outcome-free survival rates in AAV patients with MetS

As the number of MetS components increased, the cumulative patient survival rate significantly decreased (Fig. 1). We further investigated the effect of the number of MetS components at diagnosis on poor outcomes other than all-cause mortality during follow-up including end-stage renal disease (ESRD), cerebrovascular accident (CVA), and acute coronary syndrome (ACS) in 93 AAV patients, using the same analytical method. However, the

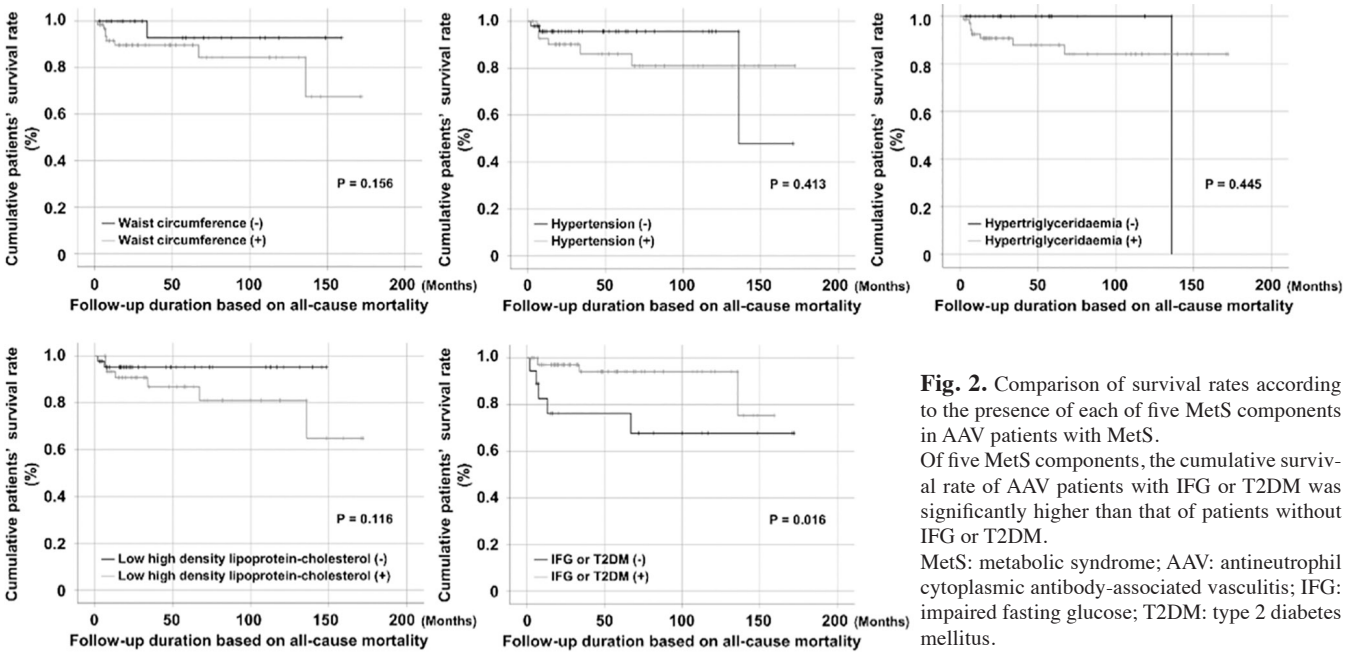

Fig. 2. Comparison of survival rates according to the presence of each of five MetS components in AAV patients with MetS.
Of five MetS components, the cumulative survival rate of AAV patients with IFG or T2DM was significantly higher than that of patients without IFG or T2DM.
MetS: metabolic syndrome; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; IFG: impaired fasting glucose; T2DM: type 2 diabetes mellitus.

cumulative relapse-free, ESRD-free, CVA-free, and ACS-free survival rates did not significantly differ among AAV patients with MetS according to the number of MetS components (Supplementary Fig. S1). In addition, among five MetS component, the cumulative survival rate of AAV patients with IFG or T2DM was significantly higher than those without (Fig. 2).

Comparison of variables at AAV diagnosis between surviving and deceased AAV patients with MetS

Deceased AAV patients with MetS were significantly older (70.8 *vs*. 60.6 years) and had significantly higher BVAS (19.0 *vs*. 13.5) and FFS (2.0 *vs*. 1.0) than surviving AAV patients with MetS. Interestingly, fewer deceased AAV patients with MetS had IFG or T2DM than surviving AAV patients with MetS (44.4% *vs*. 84.5%). In terms of the number of MetS components, deceased AAV patients with MetS had a higher number of MetS components than surviving AAV patients with MetS (Table II).

Hazard ratio of the number of MetS components for all-cause mortality

In the multivariate Cox hazard analysis using the significant variables in the comparison analysis, IFG or T2DM showed an inverse association with all-cause mortality in AAV patients with MetS (HR 0.031). In addition, AAV patients with MetS who had all five MetS components were approximately 62 times more susceptible to all-cause mortality than those who had only three components (HR 62.098) (Table III).

Table II. Comparison of variables at AAV diagnosis between surviving and deceased AAV patients with MetS.

Variables	Surviving AAV patients with MetS (N = 84)	Deceased AAV patients with MetS (N = 9)	*p*-values
At diagnosis			
Demographic data			
Age (years)	60.6 (15.9)	70.8 (9.8)	0.008
Sex (n, (%))			1.000
Male	30 (35.7)	3 (33.3)	
Female	54 (64.3)	6 (66.7)	
Ex-smoker (n, (%))	9 (10.7)	0 (0)	0.592
Body mass index (kg/m^2)	23.4 (3.4)	23.1 (3.0)	0.943
AAV Subtypes (n, (%))			0.065
MPA	41 (48.8)	8 (88.9)	
GPA	23 (27.4)	1 (11.1)	
EGPA	20 (23.8)	0 (0)	
ANCA positivity (N, (%))			
MPO-ANCA (or P-ANCA) positivity	61 (72.6)	9 (100)	0.106
PR3-ANCA (or C-ANCA) positivity	12 (14.3)	0 (0)	0.599
Both ANCA positivity	1 (1.2)	0 (0)	1.000
ANCA positivity	72 (85.7)	9 (0)	0.599
AAV-specific indices			
BVAS	13.5 (12.0)	19.0 (7.0)	0.008
FFS	1.0 (1.0)	2.0 (2.0)	0.044
MetS components (n, (%))			
Increased waist circumference (Waist circumference 90 cm in men and 80 cm in women)	57 (67.9)	8 (88.9)	0.269
High blood pressure: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or antihypertensive medication	37 (44.0)	6 (66.7)	0.294
Hypertriglyceridaemia (triglyceride ≥ 150 mg/dL)	62 (73.8)	8 (88.9)	0.443
Low high-density lipoprotein (HDL)-cholesterol (men < 40 mg/dL and women < 50 mg/dL)	41 (48.8)	7 (77.8)	0.160
IFG (impaired fasting glucose) (fasting plasma glucose ≥100 mg/dL) or T2DM (fasting plasma glucose ≥126 mg/dL or on medication for high blood glucose)	71 (84.5)	4 (44.4)	0.012
Number of MetS components (n, (%))			0.031
3	54 (64.3)	2 (22.2)	
4	25 (29.8)	5 (55.6)	
5	5 (6.0)	2 (22.2)	
During follow-up			
Medications administered during follow-up (n, (%))			
Glucocorticoid	79 (94.0)	9 (100)	1.000
Cyclophosphamide	45 (53.6)	5 (55.6)	1.000
Rituximab	14 (16.7)	2 (22.2)	0.650
Mycophenolate mofetil	10 (11.9)	1 (11.1)	1.000
Azathioprine	41 (48.8)	6 (66.7)	0.486
Tacrolimus	2 (2.4)	1 (11.1)	0.266
Methotrexate	5 (6.0)	0 (0)	1.000

Values are expressed as a median (interquartile range, IQR) or N (%).
AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MetS: metabolic syndrome; 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; T2DM: type 2 diabetes mellitus.

Discussion

In this study, we first demonstrated that the number of MetS components could have a positive influence on the prediction of all-cause mortality in AAV patients with MetS. These results could be explained in two aspects. First, in terms of AAV, AAV itself already has been known as a high risk of all-cause mortality which may result from chronic vascular inflammation, oxidative stress, and cellular dysfunction, leading to CVA and CVD (18-20). Therefore, it can be reasonably assumed that a more severe form of MetS presented by the number of MetS components met may be more closely associated with all-cause mortality and thus, increase its frequency in AAV patients with MetS. Next, in terms of MetS, the number of MetS components was reported to provide an additional risk prediction of all-cause mortality beyond its individual component (14). Therefore, the identification of AAV

Table III. Multivariable Cox hazards model analysis of variables for all-cause mortality during follow-up in AAV patients with MetS.

Variables	Multivariable		
	HR	95% CI	*p* value
Age	1.139	0.984, 1.318	0.082
BVAS	1.126	0.950, 1.335	0.170
FFS	1.370	0.553, 3.393	0.496
IFG or T2DM	0.031	0.003, 0.293	0.002
Number of MetS components			
5 and 4 *vs*. 3	5.042	0.449, 50.925	0.170
5 *vs*. only 3	62.098	3.293, 1171.121	0.006

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MetS: metabolic syndrome; HR: hazard ratio; CI: confidence interval; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; IFG: impaired fasting glucose; T2DM: type 2 diabetes mellitus.

patients with a more severe form of MetS at AAV diagnosis and the early aggressive intervention with newly validated therapeutic regimens might improve the prognosis of AAV patients who were diagnosed with MetS during follow-up (21).

On the other hand, when analysing the effect on all-cause mortality according to the presence of each of the five components, all were expected to show a positive correlation with all-cause mortality. However, IFG or T2DM showed an inverse correlation with all-cause mortality despite the well-established association between them in the general population (22). To find the reason for this discrepancy, we compared the prevalence of abnormal glucose metabolism again by stratifying IFG or T2DM. In terms of IFG, 35 of 84 surviving AAV patients with concurrent MetS (41.7%) had IFG, whereas, none of 9 deceased ones had it (p=0.013). In terms of T2DM, however, 36 of 84 surviving AAV patients with MetS (42.9%) had T2DM, and 4 of 9 deceased ones (44.4%) had it at AAV diagnosis, which did not show the statistical difference (p=1.000). Moreover, when Kaplan Meier survival analysis was performed based on T2DM, the cumulative patients' survival rates were not different between AAV patients with concurrent MetS having T2DM and those not having it (p=0.997). By contrast, there was a significant difference in the cumulative patients' survival rates between AAV patients with concurrent MetS having IFG and those not having it (p=0.031) (Suppl. Fig. S2). With these results, we conclude that IFG rather than T2DM was misleading as if abnormal glucose abnormality was a protective factor for all-cause mortality. Therefore, T2DM should be applied to minimize the misunderstanding, but since IFG and T2DM are defined as one component of MetS (2, 4), it should be applied as it is, but the above results should be kept in mind. Moreover, patients with slightly high glucose levels tend to be placed under stricter surveillance and be received more aggressive management including lifestyle changes for lowering their glucose levels and consequently those factors may lead to more beneficial health outcomes in these subjects.

In this study, there was no significant difference in BMI values between surviving and deceased AAV patients with MetS. Traditionally, BMI and all-cause mortality are correlated with each other. However, it is popularly believed that there is a J-shaped association, rather than a linear association, between BMI and all-cause mortality; that is, all-cause mortality is the lowest at BMI 21–25 kg/m^2 and gradually increases at BMI <21 or >25 kg/m^2 (23). In the general Korean population, all-cause mortality was the lowest among those with a BMI of 23.0–24.9 kg/m^2 (24). The median BMI value of the study subjects was 23.3 kg/m^2, and 58.1% of AAV patients included in this study had 21 kg/m^2 ≤BMI ≤25 kg/m^2. Therefore, we conclude that these values correspond to the interval with the lowest mortality rate mentioned above, and thus, BMI might have been assumed not to become an independent predictor of all-cause mortality in this study.

In this study, we did not separately analysed MPA, GPA, and EGPA patients, AAV subtypes, but analysed them as AAV patients. It is believed that this analysis has two advantages in real clinical settings. First, even in the process of accurately classifying AAV subtypes before the final classification, if a patient suspected of having AAV meets the diagnostic criteria of MetS, all-cause mortality can be predicted according to the number of MetS components at the time of AAV diagnosis. Second, the results of this study can be applied to patients whose AAV subtype changed after the initial AAV subtype determination.

Nevertheless, we investigated only MPA and GPA patients, because none of EGPA patients died in this study. When the cumulative survival rates were compared according to the number of MetS components, there were no significant differences among AAV patients with three, four, and all five MetS components. Moreover, when only the 24 GPA patients with MetS were analysed, it was not statistically significant either. Meanwhile, when only the 49 MPA patients with MetS were analysed, the cumulative survival rates were significantly associated with the number of MetS components (Suppl. Fig. S3). Based on these results, we can carefully conclude that patients with MPA have a higher risk of all-cause mortality proportional to the number of MetS components unlike patients with GPA or EGPA.

This study has the advantage of being the first study to analyse the number of MetS components in AAV patients with MetS at AAV diagnosis. We demonstrated that a high number of MetS components could be an independent predictor of all-cause mortality. However, some limitations exist. First, because AAV itself is a very rare disease and furthermore, only AAV patients who could be diagnosed with MetS at AAV diagnosis were included in this study, the number of AAV patients with MetS and the number of deceased AAV patients with MetS were not sufficiently large to generalise the results. This limitation also reduced the power

of this study on the reliability of the results of subset analyses such as the mortality rate according to each component of MetS diagnosis criteria. Second, as this was a retrospective study, fasting glucose levels, which define IFG, were not repeatedly measured with suggested accurate intervals at the time of AAV diagnosis. Third, although the DUR system was used to search for medications taken before AAV diagnosis, it was impossible to search for any drugs not currently registered in the DUR system, such as previously prescribed glucocorticoids that could affect fasting glucose levels in this system. Since MetS diagnosis was evaluated only at the time of diagnosis, and furthermore, AAV patients who had ever received glucocorticoids for the treatment of AAV before AAV diagnosis were tried to be excluded from this study, the effect of glucocorticoid or the cumulative dose of glucocorticoid administered before AAV diagnosis on the presence of MetS at diagnosis might be negligible. However, the use of HMG-CoA Reductase Inhibitors, which could affect not only MetS diagnosis but also all-cause mortality, was not fully evaluated before, at the time of, and after AAV diagnosis. Therefore, the results of this study should be validated in future prospective multicentre clinical studies involving more patients. In conclusion, the presence of many MetS components at the initial diagnosis of AAV is an independent and significant predictor of all-cause mortality in AAV patients with MetS. Therefore, the presence or absence of MetS should be confirmed in all patients diagnosed with AAV for the first time. In particular, being aware of higher mortality is important in AAV patients with MetS who fulfil all items of the MetS diagnostic criteria.

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