Earliest total vascular damage index scores independently predict all-cause mortality in patients with ANCA-associated vasculitis

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Abstract

Objective

This study investigated whether the earliest total Vasculitis Damage Index (VDI) score could significantly predict all-cause mortality during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods

This study included AAV patients who were first diagnosed at this hospital from 2001 to 2022. The earliest total VDI score was defined as the first VID assessed more than 3 months after AAV diagnosis in 93.5% of patients or after the first AAV presentation in 6.5% of patients. The optimal cut-off of the earliest total VDI score for all-cause mortality was obtained using the receiver operating characteristic curve.

Results

The median age and earliest VDI score were 60.0 years (35.5% men), and 3.0. The most common damaged system in the earliest VDI was the pulmonary (55.3%) system. Among the AAV patients, 39 (13.3%) died. When the optimal cut-off of the earliest total VDI score for all-cause mortality was set at 3.0 (sensitivity 64.1%, specificity 75.2%), AAV patients with the earliest total VDI score ≥3.0 exhibited a significantly higher risk for all-cause mortality than those without (relative risk 6.090). AAV patients with the earliest total VDI score ≥3.0 exhibited a significantly lower cumulative patients' survival rate than those without. In the multivariable Cox hazards model analyses, not only the earliest total VDI score but also the earliest total VDI score ≥3.0 were independently associated with all-cause mortality.

Conclusion

This study was the first to demonstrate that the earliest total VDI score could predict all-cause mortality during follow-up in AAV patients.

Key words

vascular damage index, mortality, predict, antineutrophil cytoplasmic antibody, vasculitis

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Received on April 27, 2023; accepted on July 10, 2023.

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Funding: this work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare (HI14C1324), Handok Inc., Seoul, Republic of Korea (HANDOK 2021-006) and CELLTRION PHARM Inc. Chungcheongbuk-do, Republic of Korea (NCR 2019-6).

Competing interests: none declared.

Introduction

According to the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides (the 2012 CHCC definitions), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is small vessel vasculitis along with immune complex vasculitis (1). AAV has three subtypes based on clinical, laboratory, radiological, and histological features: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatous polyangiitis (EGPA) (2, 3). Since AAV has the potential to primarily affect almost all major organs, resulting in permanent damage, AAV may provoke poor outcomes, particularly death. The overall mortality rate associated with AAV ranges from 24% to 50.2% during the entire follow-up period, and researchers have identified various mortality predictors in addition to traditional risk factors for all-cause mortality in the general population (4, 5).

Among the various predictors of all-cause mortality during follow-up in AAV patients, the Vasculitis Damage Index (VDI) score has drawn attention. A VDI scoring system is composed of 11 systems and 64 items without weighting different points and can be used in all subtypes of AAV (6). For newly diagnosed AAV patients, the VDI score should be 0 because scores regarding organ damage are assigned only when it occurs after the onset of vasculitis. However, exceptionally, it will be accepted only if two conditions are satisfied: One is that more than 3 months have elapsed since the onset of vasculitis, and the other is that the damage has started or worsened since the onset of vasculitis (6, 7). It could be reasonably inferred that VDI may be more closely related to all-cause mortality due to organ damage than other predictors (8) because a VDI score is an index that directly reflects damage to major organs. Previous studies have suggested a cut-off of the total VDI score at 6 months or later after the onset of presentation for fatal disease in patients with vasculitis (9, 10). Nevertheless, in real clinical settings, there is a need for an index assessed earlier than 6 months after AAV diagnosis, and this index may enable us to establish a proper initial treatment strategy and compare its ability to predict all-cause mortality with that of other variables at AAV diagnosis. However, to date, no study has provided information on the clinical implications of the total VDI score assessed earlier than 6 months after the first AAV presentation in predicting all-cause mortality during follow-up in AAV patients. Therefore, in the present study, given two exceptional conditions for VDI assessed within 3 months after AAV diagnosis, we newly defined the earliest total VDI score as the first VID assessed more than 3 months after AAV diagnosis in 274 (93.5%) patients or after the first AAV presentation in 19 (6.5%) patients. And we investigated whether the earliest total VDI score could predict all-cause mortality during follow-up in AAV patients.

Patients and methods

Study population

This study included 293 AAV patients who were first diagnosed at our hospital by three specialised rheumatologists from March 2001 to September 2022. All patients met both the 2012 CHCC definitions and the European Medicine Agency algorithm for AAV (1-3) and could be reclassified as having AAV according to the new classification criteria proposed by the American College of Rheumatology and the European Alliance of Associations for Rheumatology in 2022 (11-13). They had well-written electronic medical records to reclassify them as having AAV based on the new classification criteria, and further, to assess the Birmingham vasculitis activity score (BVAS), the five-factor score (FFS), and the total VDI score (6, 14, 15). All patients were followed up for at least 3 months after AAV diagnosis and had no concomitant serious medical conditions mimicking AAV within 4 weeks before AAV diagnosis.

Ethical disclosure

The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB no. 4-2020-1071), and was conducted according to the Declaration of Hel-

sinki. Given the retrospective design of the study and the use of anonymised patient data, the requirement for written informed consent was waived.

ANCA measurement

Both ANCAs detected using an indirect immunofluorescence assay (perinuclear [P]-ANCA and cytoplasmic [C]-ANCA) and those measured using an immunoassay (myeloperoxidase [MPO]-ANCA and proteinase 3 [PR3]-ANCA) were considered ANCA positivity according to the new classification criteria (11-15).

Variables at diagnosis

Demographic variables included age, sex, body mass index (BMI), and smoking history. AAV-specific variables included the AAV subtype, ANCA type, the Birmingham vasculitis activity score (BVAS), and the five-factor score (FFS) (16, 17). Laboratory results including erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels, were also collected. Type 2 diabetes mellitus (T2DM), hypertension, and dyslipidaemia before the first presentation of AAV were considered co-morbidities.

The earliest VDI

Based on the mandatory conditions of VDI assessment (6), the total VDI score should be assessed more than 3 months after AAV diagnosis. Meanwhile, exceptionally, the total VDI within 3 months after AAV diagnosis will be accepted only if two conditions are satisfied: One is that more than 3 months have elapsed since the onset of vasculitis, and the other is that the damage has started or worsened since the onset of vasculitis. Therefore, in the present study, we newly defined the earliest total VDI score as the first VID assessed more than 3 months after AAV diagnosis in 274 (93.5%) patients or after the first AAV presentation in 19 (6.5%) patients (Fig. 1). The total VDI score was assessed based on 64 items, and organ-based damaged systems among the 11 systems were counted (6).

Variables during follow-up

Poor outcomes included all-cause mortality relapse, end-stage kidney disease (ESKD), cerebrovascular accident (CVA), and acute coronary syndrome (ACS). The number of patients with each poor outcome was counted. The follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to death for deceased patients or the last visit for survivors. The follow-up duration based on each poor outcome was defined as the period from AAV diagnosis to each poor outcome for patients with a poor outcome or the last visit for those without. Medications administered during follow-up were also investigated.

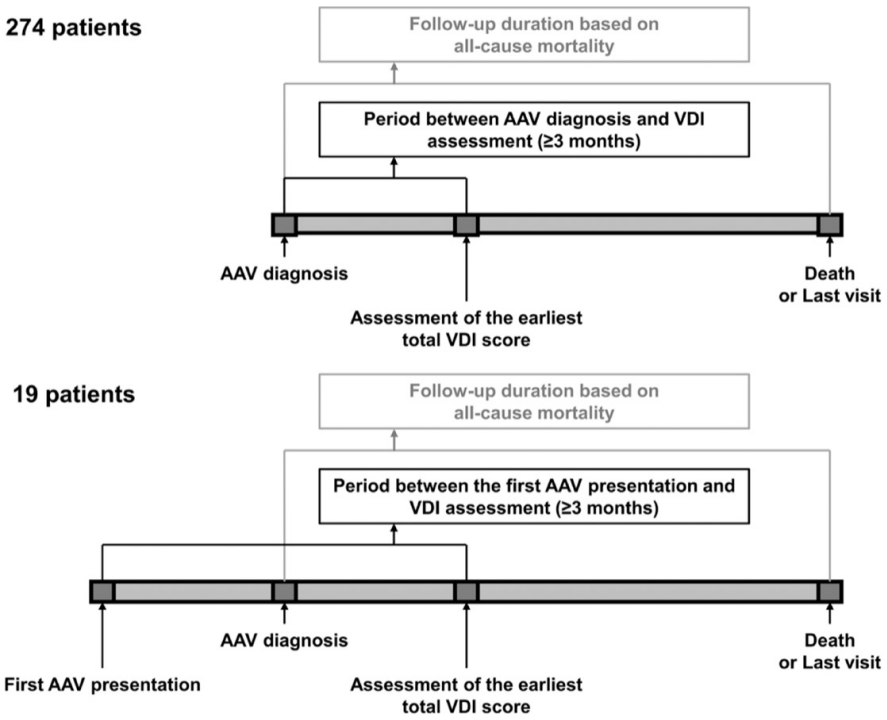

Fig. 1. Concept of the time of the assessment the earliest total VDI score in AAV patients.
VDI: vasculitis damage index; AAV: antineutrophil cytoplasmic antibody-associated vasculitis.

Statistical analyses

SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Continuous and categorical variables are expressed as medians (25–75 percentiles) and numbers (percentages), respectively. The ability to predict poor outcomes was first evaluated using the receiver operating characteristic (ROC) curve and area under the curve (AUC). The optimal cut-off of the earliest total VDI score for all-cause mortality was extrapolated by performing the ROC curve analysis and one value having the maximised sum of sensitivity and specificity was selected. The relative risks (RRs) of the cut-off for all-cause mortality were analysed using contingency tables and the chi-square test. A comparison of the cumulative survivals rates between the two groups was performed using the Kaplan-Meier survival analysis with the log-rank test. The univariable and multivariable Cox hazards model analyses for each poor outcome were performed using variables at diagnosis and the total VDI scores to appropriately obtain the hazard ratios (HRs) during the considerable follow-up duration. $p<0.05$ was considered statistically significant.

Results

Characteristics at diagnosis

The median age was 60.0 years (35.5% men), and the median BMI was 22.5 kg/m^2. Nine patients had a history of smoking cigarettes. Among the 293 AAV patients, 160, 74, and 59 were diagnosed with MPA (54.6%), GPA (25.3%), and EGPA (20.1%), respectively. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 199 and 48 patients, respectively; 58 patients had no ANCA. The median BVAS, FFS, ESR,

and CRP levels were 12.0, 1.0, 59.0 mm/hr, and 13.4 mg/L, respectively. Before AAV diagnosis, 116, 77, and 59 patients had hypertension, T2DM, and dyslipidaemia, respectively (Table I).

The earliest VDI

The median earliest VDI score was 3.0. The most common damaged system in the earliest VDI was the pulmonary system (55.3%), followed by the renal (51.5%) and ENT (43.0%) systems (Table I).

Poor outcomes and medications during follow-up

Among the 293 AAV patients, 39 (13.3%) died during a median follow-up duration based on all-cause mortality of 46.9 months. In addition, 84 patients experienced relapse after remission, and 62, 21, and 10 patients had end-stage kidney disease (ESKD; 21.2%), cerebrovascular accidents (CVA; 7.2%), and acute coronary syndrome (ACS; 3.4%) during follow-up, respectively. Among the 293 AAV patients, 277 (94.5%) received glucocorticoids, and the most frequently administered immunosuppressive drug during follow-up was cyclophosphamide (55.3%), followed by azathioprine (52.9%). There were no significant differences in the uses of cyclophosphamide and rituximab between surviving and deceased patients (54.3% *vs*. 61.5%, p=0.399, and 15.8% *vs*. 25.6%, p=0.126, respectively). In addition, we calculated the cumulative doses of glucocorticoids and compared them between surviving and deceased patients. The median cumulative dose of glucocorticoids was 7,558.2 mg with 25 and 75 percentiles of 2,154.6 mg and 13,346.6 mg, respectively. The median cumulative doses of glucocorticoids in surviving and deceased patients were 7,994.3 mg and 2,567.9 mg, respectively. There was no significant difference in the cumulative doses of glucocorticoids administered after AAV diagnosis between the two groups (p=0.099) (Table I).

Optimal cut-off and relative risks for all-cause mortality

When the optimal cut-off of the earliest total VDI score for all-cause mor-

Table I. Characteristics of AAV patients (n=293).

Variables	Values
Variables at AAV diagnosis	
Demographic data	
Age (years)	60.0 (49.5-69.0)
Male sex (n, (%))	104 (35.5)
BMI (kg/m^2)	22.5 (20.3-24.6)
Ex-smoker (n, (%))	9 (3.1)
AAV subtype (n, (%))	
MPA	160 (54.6)
GPA	74 (25.3)
EGPA	59 (20.1)
ANCA type and positivity (n, (%))	
MPO-ANCA (or P-ANCA) positivity	199 (67.9)
PR3-ANCA (or C-ANCA) positivity	48 (16.4)
Both ANCA positivity	12 (3.8)
ANCA negativity	58 (19.1)
AAV-specific indices	
BVAS	12.0 (7.0-18.0)
FFS	1.0 (0-2.0)
Laboratory results	
White blood cell count (/mm^3)	9,180.0 (6,410.0-12,895.0)
Haemoglobin (g/dL)	11.4 (9.5-13.2)
Platelet count (× 1000/mm^3)	295.0 (227.5-393.0)
Fasting glucose (mg/dL)	101.0 (90.0-122.8)
Blood urea nitrogen (mg/dL)	17.7 (12.5-31.0)
Serum creatinine (mg/dL)	0.9 (0.7-1.8)
Serum total protein (g/dL)	6.8 (6.0-7.3)
Serum albumin (g/dL)	3.7 (3.1-4.2)
Acute phase reactants	
ESR (mm/hr)	59.0 (22.0-96.0)
CRP (mg/L)	13.4 (1.6-64.5)
Comorbidities (n, (%))	
Hypertension	116 (39.6)
T2DM	77 (26.3)
Dyslipidaemia	59 (20.1)
The earliest VDI*	
The earliest total VDI scores	3.0 (2.0-4.0)
Damaged systems of the earliest VDI (n, (%))	
Musculoskeletal	26 (8.9)
Skin/mucous membranous	44 (15.0)
Ocular	14 (4.8)
ENT	126 (43.0)
Pulmonary	162 (55.3)
Cardiovascular	76 (25.9)
Peripheral vascular	6 (2.0)
Gastrointestinal	6 (2.0)
Renal	151 (51.5)
Neuropsychiatric	90 (30.7)
Other	27 (9.2)
Variables during AAV follow-up	
Poor outcomes (n, (%))	
All-cause mortality	39 (13.3)
Relapse	84 (28.7)
ESKD	62 (21.2)
CVA	21 (7.2)
ACS	10 (3.4)
Follow-up duration based on each poor outcome (months)	
All-cause mortality	46.9 (15.3-81.9)
Relapse	26.7 (8.3-59.6)
ESKD	37.7 (8.8-71.8)
CVA	40.5 (12.0-77.1)
ACS	46.1 (13.5-77.4)
Medications (n, (%))	
Glucocorticoids	277 (94.5)
Cumulative dose of glucocorticoids (mg, equivalent to prednisolone)	7,558.2 (2,154.6-13,346.6)
Cyclophosphamide	162 (55.3)
Rituximab	50 (17.1)
Mycophenolate mofetil	55 (18.8)
Azathioprine	155 (52.9)
Tacrolimus	24 (8.2)
Methotrexate	24 (8.2)

Values are expressed as a median (25-75 percentile) 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; VDI: vascular damage index; DM: diabetes mellitus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; T2DM: type 2 diabetes mellitus; ENT: ear, nose, and throat; ESKD: end-stage kidney disease; CVA: cerebrovascular accident; ACS: acute coronary syndrome.

tality was set at 3.0 (AUC 0.747, 95% confidence interval [CI] 0.673, 0.821) using the ROC curve, the sensitivity, and specificity were 64.1% and 75.2%, respectively (Fig. 2A). When the 293 AAV patients were divided into two groups based on the optimal cut-off of the earliest total VDI score of 3.0, AAV patients with the earliest total VDI score ≥3.0 died at a higher rate than those with the earliest total VDI score <3.0 (20.2% *vs*. 4.0%, $p<0.001$). Furthermore, AAV patients with the earliest total VDI score ≥3.0 exhibited a significantly higher risk for all-cause mortality than those without (RR 6.090, 95% CI 2.307, 16.073) (Fig. 2B).

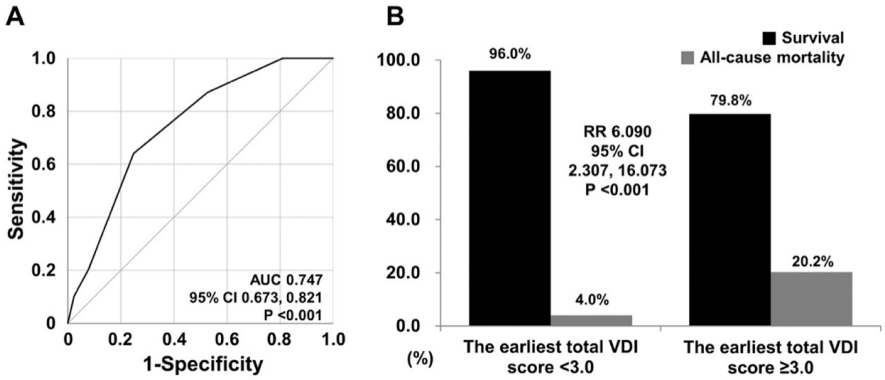

Fig. 2. Optimal cut-off of the earliest total VDI score for all-cause mortality and relative risk.
A) The optimal cut-off of the earliest total VDI score for all-cause mortality was set as ≥3.0 (sensitivity = 64.1%, and specificity = 75.2%); **B**) AAV patients with the earliest total VDI score ≥3.0 exhibited a significantly higher risk for all-cause mortality than those without.
VDI: vasculitis damage index; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; AUC: area under the curve; RR: relative risk.

Comparison of cumulative patients' survival rates according to the earliest total VDI scores ≥3.0

Given the concept of the follow-up duration based on all-cause mortality, a comparative analysis of the cumulative patients' survival rates between AAV patients with the earliest total VDI score ≥3.0 and those without was conducted using the Kaplan-Meier survival analysis. AAV patients with the earliest total VDI scores ≥3.0 exhibited a significantly lower cumulative patients' survival rate than those with the earliest total VDI score <3.0 ($p<0.001$) (Fig. 3).

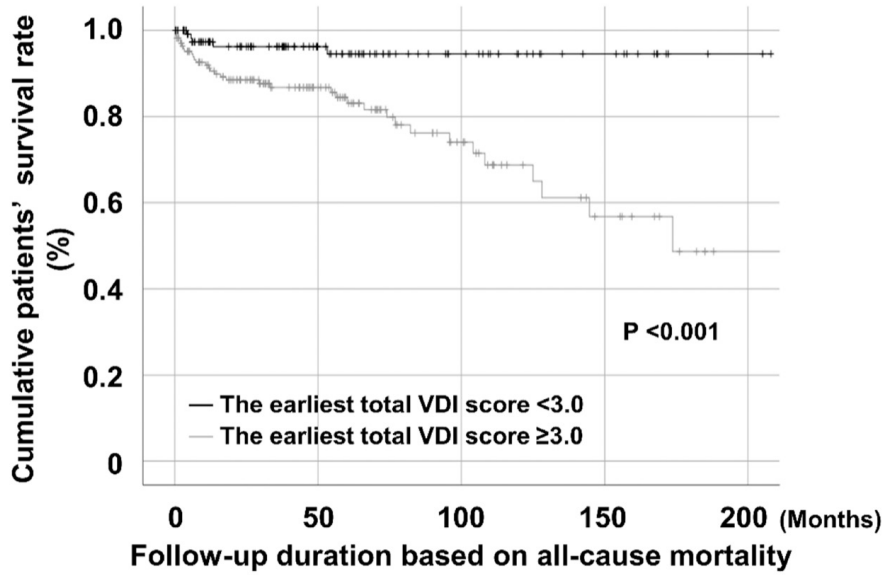

Fig. 3. Comparison of cumulative survival rates according to the earliest total VDI scores ≥3.0.
AAV patients with the earliest total VDI scores ≥3.0 exhibited a significantly lower cumulative patients' survival rate than those without.
AAV: antineutrophil cytoplasmic antibody-associated vasculitis; VDI: vasculitis damage index.

Cox hazards model analyses for all-cause mortality

In the univariable Cox analysis, age, male sex, BMI, BVAS, FFS, white blood cell count, haemoglobin, blood urea nitrogen, serum creatinine, serum total protein, serum albumin, ESR, and CRP at diagnosis were significantly associated with all-cause mortality during follow-up. In the multivariable Cox analysis with the earliest total VDI score, male sex (HR 2.777, 95% CI 1.265, 6.096), FFS (HR 1.556, 95% CI 1.020, 2.374), and serum albumin (HR 0.368, 95% CI 0.188, 0.722) at diagnosis were independently associated with all-cause mortality. The earliest total VDI score (HR 1.392, 95% CI 1.040, 1.863) was also independently associated with all-cause mortality. In the multivariable Cox analysis with the earliest total VDI score ≥3.0, male sex (HR 3.104, 95% CI 1.458, 6.608), BMI (HR 1.114, 95% CI 1.002, 1.238), FFS (HR 1.689, 95% CI 1.111, 2.569), and serum albumin (HR 0.361, 95% CI 0.185, 0.706) at diagnosis were independently associated with all-cause mortality. The earliest total VDI score ≥3.0 (HR 3.436, 95% CI 1.233, 9.573) was also independently associated with all-cause mortality (Table II).

Comparison of AUCs of variables with significance in the multivariable Cox analysis for all-cause mortality

When the AUCs of the four variables with significance in the multivariable Cox analysis with the earliest total VDI score were compared, the AUC of the earliest total VDI score (0.747, $p<0.001$) was the highest, followed by that of serum albumin (0.734, $p<0.001$) and FFS (0.714, $p<0.001$) at diagnosis. As serum albumin was inversely associated with all-cause mortality, the adjusted AUC of serum albumin was calculated as 0.734 (1. 0 minus 0.266) (Supplementary Fig. S1).

Comparison of cumulative patients' survival rates according to each damaged system of VDI

Among the 11 VDI systems, AAV patients with musculoskeletal, pulmo-

Table II. Cox hazards model analyses of the earliest VDI with variables at diagnosis for all-cause mortality during follow-up in AAV patients.

Variables	Univariable			Multivariable (The earliest total VDI scores)			Multivariable (The earliest total VDI scores ≥3.0)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	1.063	1.031, 1.095	<0.001	1.028	0.995, 1.062	0.096	1.025	0.992, 1.060	0.134
Male sex (n, (%))	2.691	1.425, 5.080	0.002	2.777	1.265, 6.096	0.011	3.104	1.458, 6.608	0.003
BMI (kg/m^2)	1.122	1.028, 1.225	0.010	1.108	0.997, 1.230	0.057	1.114	1.002, 1.238	0.045
Ex-smoker (n, (%))	1.694	0.407, 7.047	0.468						
MPO-ANCA (or P-ANCA) positivity	1.453	0.720, 2.930	0.297						
PR3-ANCA (or C-ANCA) positivity	0.679	0.265, 1.737	0.419						
BVAS	1.082	1.037, 1.128	<0.001	0.995	0.931, 1.063	0.880	0.995	0.932, 1.061	0.871
FFS	1.968	1.453, 2.665	<0.001	1.556	1.020, 2.374	0.040	1.689	1.111, 2.569	0.014
T2DM	1.061	0.536, 2.100	0.866						
Hypertension	1.174	0.624, 2.208	0.619						
Dyslipidaemia	1.809	0.915, 3.575	0.088						
White blood cell count (/mm^3)	1.000	1.000, 1.000	0.034	1.000	1.000, 1.000	0.795	1.000	1.000, 1.000	0.694
Haemoglobin (g/dL)	0.788	0.681, 0.913	0.002	1.008	0.794, 1.280	0.948	1.028	0.812, 1.301	0.819
Platelet count (× 1000/mm^3)	1.000	0.998, 1.002	0.943						
Fasting glucose (mg/dL)	1.005	0.999, 1.010	0.108						
Blood urea nitrogen (mg/dL)	1.012	1.004, 1.019	0.004	1.006	0.991, 1.021	0.447	1.006	0.990, 1.021	0.466
Serum creatinine (mg/dL)	1.144	1.018, 1.286	0.024	0.977	0.790, 1.207	0.829	0.989	0.799, 1.224	0.918
Serum total protein (g/dL)	0.561	0.384, 0.818	0.003	0.986	0.881, 1.102	0.799	0.982	0.876, 1.101	0.753
Serum albumin (g/dL)	0.378	0.247, 0.580	<0.001	0.368	0.188, 0.722	0.004	0.361	0.185, 0.706	0.003
ESR (mm/hr)	1.009	1.001, 1.017	0.032	0.994	0.982, 1.006	0.310	0.995	0.983, 1.007	0.423
CRP (mg/L)	1.008	1.003, 1.012	0.001	1.000	0.992, 1.008	0.935	1.000	0.993, 1.008	0.905
The earliest total VDI scores	1.694	1.344, 2.135	<0.001	1.392	1.040, 1.863	0.026			
The earliest total VDI scores ≥3.0	5.061	1.978, 12.947	0.001				3.436	1.233, 9.573	0.018

VDI: vascular damage index; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; BMI: body mass index; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; DM: diabetes mellitus; DM: diabetes mellitus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

nary, cardiovascular, and renal damage exhibited significantly reduced cumulative patients' survival rates during follow-up compared to those without damage (Fig. 4).

Discussion

In the present study, we provided a total VDI score ≥3 as the optimal cut-off for poor outcomes of AAV, particularly all-cause mortality during AAV follow-up, and demonstrated its use in predicting all-cause mortality during follow-up in AAV patients. On the other hand, Exley *et al*. proposed a higher cut-off for severe fatal diseases with a total VDI score ≥5 (9, 10). We suggest three hypotheses to explain this inconsistency. The first reason is the time required to assess the total VDI score. In previous studies, the total VDI was assessed at 6 and 24 months after AAV diagnosis. Whereas in the present study, the new concept of the earliest total VDI score, which was assessed earlier than that in previous studies, was provided: we newly defined the earliest total VDI score as the first VID assessed more than 3 months after AAV diagnosis in 274 (93.5%) patients or after the first AAV presentation in 19 (6.5%) patients (Fig. 1). Given that the total VDI score in the early phase is primarily related to AAV itself rather than to treatment drugs, the earliest total VDI score is more useful for identifying the causal relationship between damage due to AAV itself and all-cause mortality during follow-up. The second reason is the type of vasculitides. The previous study included various systemic vasculitis in addition to AAV; however, this study included only AAV patients. The third reason is ethnic and geographical differences. Previous studies have collected clinical data from clinics located in the UK, which included diverse ethnicities. However, this study included only Korean patients with AAV.

Among the 11 damaged systems, the cases with damage in the musculoskeletal, pulmonary, cardiovascular, and renal systems exhibited lower cumulated patients' survival rates than those without (Fig. 4). This result signifies that these four damaged systems might contribute to the ability of the earliest total VDI score to predict all-cause mortality during follow-up in AAV patients. A previous study investigated the proportion of damaged systems in patients with severe fatal diseases and unveiled the four high-ranked damaged systems as renal, neurological, pulmonary, and cardiovascular system (10), whereas, a previous study reported the changes in the proportion of damaged systems composing the early total VDI score in patients with severe fatal vasculitis to date (9). Therefore, given the time points to assess the total VDI scores in previous studies, this is the first to compare the cumulative patients' survival rates according to the presence of each damage system comprising the earliest total VDI score.

The ability of the cut-off of the earliest total VDI score to predict poor outcomes of AAV other than all-cause mortality was investigated using the ROC curve analysis. The earliest total VDI score was not associated with ESKD, CVA, or ACS during follow-up in AAV patients (Suppl. Fig. S2).

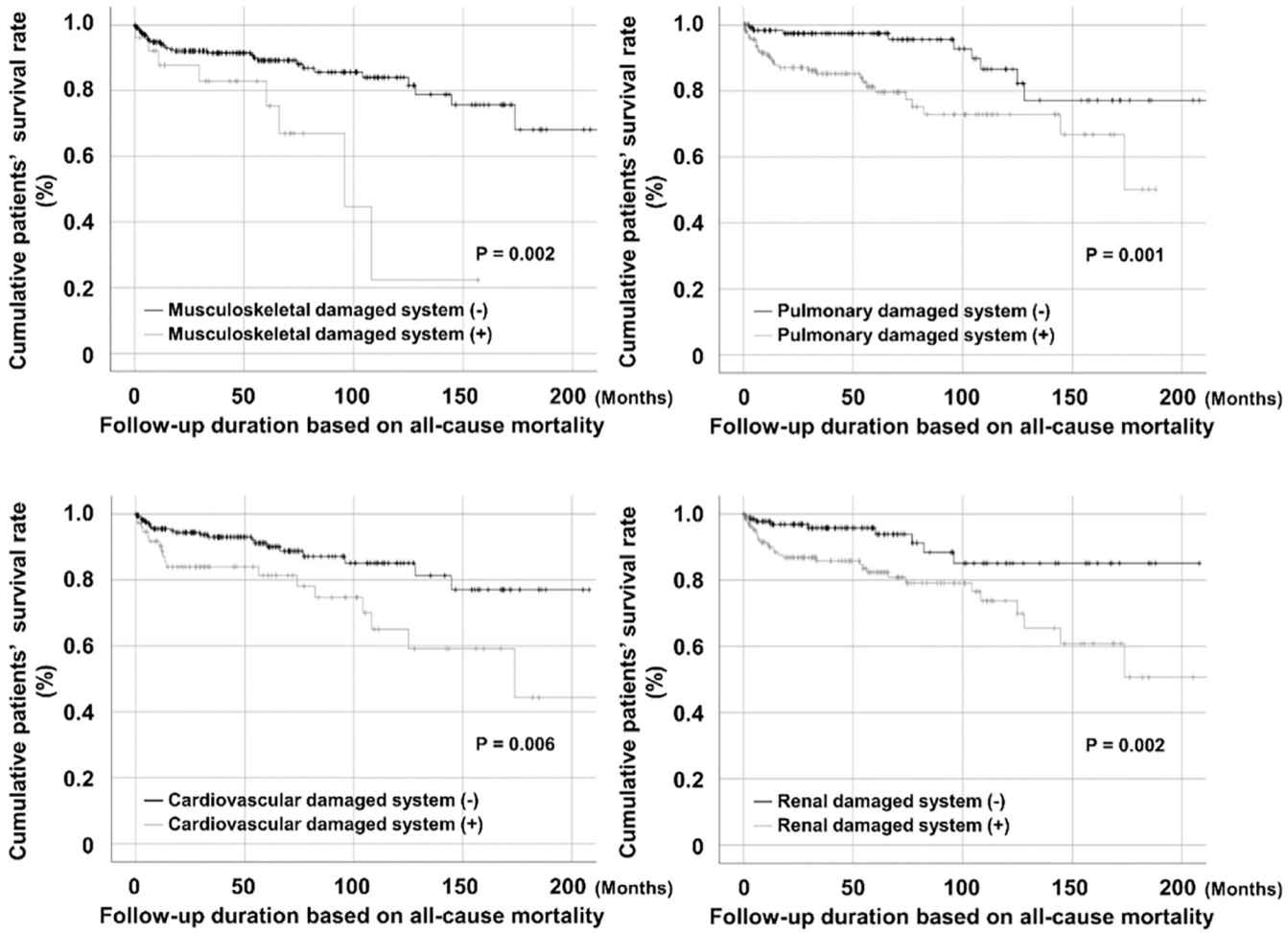

Fig. 4. Comparison of cumulative survival rates according to each damaged system comprising total VDI score.
AAV patients with musculoskeletal, pulmonary, cardiovascular, and renal damaged systems exhibited significantly reduced cumulative patients' survival rates during follow-up compared to those without each damaged system.
VDI: vasculitis damage index; AAV: antineutrophil cytoplasmic antibody-associated vasculitis.

The earliest total VDI score was significantly associated with relapse during AAV follow-up. When the optimal cut-off of the earliest total VDI score for all-cause mortality was set at 3.0 (AUC 0.586, 95% CI 0.518, 0.660) using the ROC curve, the sensitivity, and specificity were 39.3% and 73.7%, respectively (Suppl. Fig. S3A). AAV patients with the earliest total VDI score ≥3.0 exhibited a significantly higher risk for relapse than those without (RR 1.732, 95% CI 1.021, 2.939) (Suppl. Fig. S3B). In addition, AAV patients with the earliest total VDI score ≥3.0 showed a significantly lower cumulative relapse-free survival rate than those without in the Kaplan-Meier survival analysis (Suppl. Fig. S4). However, unlike the association between the earliest total VDI score and all-cause mortality, the earliest total VDI score was not independently associated with relapse in the multivariable Cox analysis (Suppl. Table S1). Therefore, we suggest that the earliest total VDI score should be used to predict all-cause mortality among poor outcomes of AAV in real clinical practice.

On the other hand, the renal, neuropsychiatric, and cardiovascular damage systems of the general VDI score are meaningfully associated with the occurrence of ESKD, CVA, and ACS, respectively. Nevertheless, we wondered whether the renal, neuropsychiatric, and cardiovascular damaged systems of the earliest total VDI score could anticipate the occurrence of each damaged system-related complication during follow-up in AAV patients. We conducted the Kaplan Meier survival analysis and found that AAV patients with renal, neuropsychiatric, and cardiovascular damage systems comprising the earliest total VDI score exhibited significantly lower cumulative ESRD-free, CVA-free, and ACS-free survival rates than those without each damaged system (Suppl. Fig. S5). Therefore, we suggest that the presence of each damaged system comprising the earliest total VDI score should be noted to predict each damaged system-related complication during AAV follow-up along with the earliest total VDI score.

The strength of this study is that this is the first to introduce the concept of the earliest total VDI score, and to demonstrate that the earliest total VDI score among traditional and AAV-specific risk factors for mortality could independently predict all-cause mortality during follow-up in AAV patients. Moreover, this study was also the first to propose the optimal cut-off of the earliest total

VDI score ≥3.0 for predicting all-cause mortality in AAV patients. This study has several limitations. First, this study was based on a retrospective design; therefore, we acknowledge that there may have been an unavoidable error of accuracy in the process of determining the time of the first AAV presentation because the onset of AAV was based on the medical records completed by the statement of some patients with AAV. Second, since the total VDI scores were not assessed serially and regularly, although, in principle, the total VDI score could not be reduced, it was impossible to investigate the association between the extent of accelerated alterations in the total VDI scores and all-cause mortality. Finally, even though the number of patients was not small given a single-centre study, it was not large enough to generalise the results of this study and apply them to all AAV patients. Additionally, the relatively low sensitivity and specificity of the cut-off for all-cause mortality might be due to the limited number of patients included in the present study. If more AAV patients had been included, the sensitivity and specificity of the cut-off of the earliest total VDI score for predicting all-cause mortality could have been higher. However, this study has clinical significance as a pilot study as it proved, for the first time, the ability of the earliest total VDI score to predict all-cause mortality in AAV patients. A prospective future study with more patients will provide more reliable and dynamic information on the clinical implication of the earliest total VDI score in AAV patients.

In conclusion, this study was the first to demonstrate that the earliest total VDI score assessed could predict all-cause mortality during follow-up in AAV patients. We believe that the earliest total VDI score will help physicians to predict poor outcomes during follow-up and cope with them by establishing an appropriate treatment strategy earlier in addition to AAV-specific clinical and serological biomarkers (18, 19).

References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65: 1-11. https://doi:10.1002/art.37715
2. WATTS R, LANE S, HANSLIK T *et al*.: Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. *Ann Rheum Dis* 2007; 66: 222-7. https://doi:10.1136/ard.2006.054593
3. PYO JY, LEE LE, PARK YB, LEE SW: Comparison of the 2022 ACR/EULAR classification criteria for antineutrophil cytoplasmic antibody-associated vasculitis with previous criteria. *Yonsei Med J* 2023; 64: 11-7. https://doi:10.3349/ymj.2022.0435
4. DAGOSTIN MA, NUNES SLO, SHINJO SK, PEREIRA RMR: Mortality predictors in ANCA-associated vasculitis: experience of a Brazilian monocentric cohort of a rheumatology center. *Medicine* (Baltimore) 2021; 100: e28305. https://doi:10.1097/md.0000000000028305
5. MURRAY CJ, ATKINSON C, BHALLA K *et al*.: The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA* 2013; 310: 591-608. https://doi:10.1001/jama.2013.13805
6. EXLEY AR, BACON PA, LUQMANI RA *et al*.: Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997; 40: 371-80. https://doi:10.1002/art.1780400222
7. FLOSSMANN O, BACON P, DE GROOT K *et al*.: Development of comprehensive disease assessment in systemic vasculitis. *Ann Rheum Dis* 2007; 66: 283-92. https://doi:10.1136/ard.2005.051078
8. BHAMRA K, LUQMANI R: Damage assessment in ANCA-associated vasculitis. *Curr Rheumatol Rep* 2012; 14: 494-500. https://doi:10.1007/s11926-012-0291-1
9. EXLEY AR, CARRUTHERS DM, LUQMANI RA *et al*.: Damage occurs early in systemic vasculitis and is an index of outcome. *QJM* 1997; 90: 391-9. https://doi:10.1093/qjmed/90.6.391
10. EXLEY AR, BACON PA, LUQMANI RA, KITAS GD, CARRUTHERS DM, MOOTS R: Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). *Br J Rheumatol* 1998; 37: 57-63. https://doi:10.1093/rheumatology/37.1.57
11. SUPPIAH R, ROBSON JC, GRAYSON PC *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81: 321-6. https://doi:10.1136/annrheumdis-2021-221796
12. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81: 315-20. https://doi:10.1136/annrheumdis-2021-221795
13. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81: 309-14. https://doi:10.1136/annrheumdis-2021-221794
14. LA ROCCA G, DEL FRATE G, DELVINO P *et al*.: Systemic vasculitis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40: 673-87. https://doi:10.55563/clinexprheumatol/ozhc85
15. MORETTI M, TREPPO E, MONTI S *et al*.: Systemic vasculitis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41: 765-73. https://doi:10.55563/clinexprheumatol/zf4daj
16. MUKHTYAR C, LEE R, BROWN D *et al*.: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32. https://doi:10.1136/ard.2008.101279
17. GUILLEVIN L, PAGNOUX C, SEROR R *et al*.: The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90: 19-27. https://doi:10.1097/md.0b013e318205a4c6
18. AHN SS, HA JW, PARK YB, LEE SW: BVAS version 3 and BVAS/GPA: standing on the same line? *Clin Rheumatol* 2022; 41: 3429-37. https://doi:10.1007/s10067-022-06267-z
19. AHN SS, PARK YB, LEE SW: Serological biomarkers and indices for the current activity and prognosis of ANCA-associated vasculitis: experience in a single centre in Korea. *Yonsei Med J* 2021; 62: 279-87. https://doi:10.3349/ymj.2021.62.4.279