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RESEARCH ARTICLE

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Novel mortality-predicting index at diagnosis can effectively predict all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Background: This study investigated whether the inflammation prognostic index (IPI) and the mortality predicting index (MPI) at diagnosis could predict all-cause mortality in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: We included 223 AAV patients and reviewed their medical records. Clinical and laboratory data and AAV-specific indices at diagnosis were assessed. The IPI was calculated as neutrophil-to-lymphocyte ratio (NLR) × C-reactive protein to albumin ratio (CAR). Here, we newly developed an MPI (NLR × CAR × monocyte counts).

Results: The mean age of 223 patients (122 MPA, 57 GPA and 44 EGPA patients) was 59 years. The rate of mortality was 11.2%. Using the receiver operator characteristic curve for all-cause mortality, the cut-offs were calculated as NLR: 3.22, CAR: 3.25, IPI: 18.53 and MPI: 8367.82. In the univariable Cox hazard analysis, age, gender, smoking history, BVAS, FFS and over the cut-off of each index showed statistical significance. As the indices share at least two mutual variables, the multivariable analysis was conducted four times based on each index. An IPI ≥18.53 (HR 3.162) and MPI ≥8367.82 (HR 3.356) were significantly associated with all-cause mortality.

Conclusions: This study developed a novel indicator, MPI, that uses the existing NLR and CAR indices and proved that it could predict all-cause mortality in AAV patients.

KEYWORDS
all-cause mortality, antineutrophil cytoplasmic antibody, inflammation prognostic index, Mortality-predicting index, vasculitis

1 | INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterised by necrotising vasculitis with few or no immune complex deposits in the small vessels. AAV includes three subtypes such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA), based on clinical, laboratory, radiological and histological features.[1,2] While the clinical progression of AAV varies widely, if appropriate treatment is not provided or AAV is not responsive to treatment, AAV may recur or death may result from fatal complications.[3,4] Therefore, active treatment is required from the time of diagnosis of AAV, and indicators at diagnosis that can predict a poor prognosis during follow-up may be clinically useful.

Various prognosis-predicting indices based on laboratory values at diagnosis have been suggested in tumour patients.[5,6] The indices such as neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) to albumin ratio (CAR) have also shown clinical significance in AAV patients in that they could predict poor outcomes of AAV.[7,8] These prognosis-predicting indices have merit as they use variables derived from the results of routinely performed laboratory tests at AAV diagnosis. Another advantage is that they are more stable and reliable through the mutual buffering effect between variables than a single variable such as ANCA type, gender, age, renal involvement and immunosuppressive agents at diagnosis.[3,9]

A new inflammation prognostic index (IPI) was recently introduced and demonstrated to be useful for predicting the prognosis of non-small-cell lung cancer.[10] The IPI is calculated as the product of two existing indices, NLR and CAR, which are useful for predicting the prognosis of AAV.[7,8] However, no studies have assessed its clinical significance in AAV patients. We recently proved that the systemic immune inflammatory index (SII), which includes platelet counts at diagnosis, and the pan-immune-inflammation value, which includes monocyte counts at diagnosis, could predict the poor outcomes of AAV.[11,12]

Based on these concepts, we developed a novel index, the mortality-predicting index (MPI) which is calculated as NLR × CAR × monocyte counts at diagnosis. This study investigated whether the IPI and MPI at diagnosis could predict all-cause mortality during the follow-up. Furthermore, we compared the predictive potential for all-cause mortality among the NLR, CAR, IPI and MPI in AAV patients.

2 | PATIENTS AND METHODS

2.1 | Study subjects

The medical records of 223 patients with AAV were retrospectively reviewed. All patients fulfilled both the 2007 European Medicines Agency algorithm and the 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides.[1,2] They had well-documented medical records to obtain clinical and laboratory results including the Birmingham Vasculitis Activity Score (BVAS), Five-Factor Score (FFS) and ANCA positivity at diagnosis.[13,14] All patients were followed up for more than 3 months from AAV diagnosis. Patients with concomitant serious medical conditions such as malignancies, serious infections and end-stage organ damages at AAV diagnosis were excluded from this study. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2020-1071), which waived the requirement for patient written informed consent due to the retrospective study design.

2.2 | Clinical and laboratory data

At the time of AAV diagnosis, age, gender, smoking history and body mass index were collected as demographic data, and AAV subtype, ANCA positivity, BVAS and FFS were obtained as AAV-specific variables. Chronic kidney disease without renal replacement therapy, diabetes mellitus, hypertension and dyslipidaemia were also evaluated as the initial comorbidities. During the follow-up, the number of patients who died from any cause was assessed. The follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to the last visit of the surviving patients and the date of death of the deceased patients. The medications administered during the follow-up duration were also investigated (Table 1).

2.3 | Indices for predicting prognosis

(i) NLR = neutrophil counts (/μl) / lymphocyte counts (/μl)[5] ; (ii) CAR = CRP (mg/L) / serum albumin (g/dl)[6] ; (iii) IPI = NLR × CAR[10] ; (iv) MPI = NLR × CAR × monocyte counts (/μl).

2.4 | Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25. (IBM Corp.). Continuous variables are expressed as medians with interquartile ranges and categorical variables as numbers (percentages). Significant differences between the two categorical variables were analysed using the chi-square and Fisher's exact tests. The optimal cut-off of each index for all-cause mortality was extrapolated by performing the receiver operator characteristic (ROC) curve analysis, and one value having the maximised sum of sensitivity and specificity was selected. Comparison of the cumulative survivals rates based on each cut-off between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. The multivariable Cox hazard model analysis using variables with statistical significance in the univariable analysis was conducted to appropriately obtain the hazard ratios (HRs) during the considerable follow-up durations.

3 | RESULTS

3.1 | Characteristics at diagnosis

The mean age of the study subjects (33.2% men) was 59.0 years. Six patients had been exposed to smoking, and the mean body mass index was 22.2 kg/m^2. This study included 122 MPA patients, 57 GPA patients and 44 EGPA patients. Myeloperoxidase (MPO)-ANCA (or perinuclear (P)-ANCA) and proteinase 3 (PR3)-ANCA (or cytoplasmic (C)-ANCA) were detected in 148 and 38 patients, respectively, whereas no ANCA was found in 46 patients. The median BVAS and FFS were 2.0 and 1.0, respectively, and the most common comorbidity was hypertension (40.4%). The mean NLR, CAR, IPI and MPI values were 4.4, 3.2, 15.6 and 4893.2, respectively (Table 1).

TABLE 1 Characteristics of 223 AAV patients at diagnosis and during follow-up

Variables	Values
At diagnosis	
Demographic data	
Age (years)	59.0 (20.0)
Male gender (*N*, (%))	74 (33.2)
Smoking history (*N*, (%))	6 (2.7)
Body mass index (kg/m^2)	22.2 (4.4)
AAV subtypes (*N*, (%))	
MPA	122 (54.7)
GPA	57 (25.6)
EGPA	44 (19.7)
ANCA positivity (*N*, (%))	
MPO-ANCA (or P-ANCA) positivity	148 (66.4)
PR3-ANCA (or C-ANCA) positivity	38 (17.0)
Both ANCA positivity	9 (4.0)
ANCA negativity	46 (20.6)
AAV-specific indices	
BVAS	12.0 (11.0)
FFS	1.0 (2.0)
Comorbidities at diagnosis (*N*, (%))	
Chronic kidney disease without renal replacement therapy[a]	66 (29.6)
Serum creatinine (mg/dl)	0.9 (1.1)
Diabetes mellitus	53 (23.8)
Hypertension	90 (40.4)
Dyslipidaemia	37 (16.6)
Indices for predicting prognosis	
NLR	4.4 (6.1)
CAR	3.2 (22.8)
IPI	15.6 (154.6)
MPI	4893.2 (48264.1)
During follow-up	
Follow-up duration (months)	36.2 (63.3)
Poor outcomes	
All-cause mortality (*N*, (%))	25 (11.2)
Follow-up duration based on mortality (months)	36.5 (66.9)
Medications (*N*, (%))	
Glucocorticoid	207 (92.8)
Cyclophosphamide	112 (50.2)
Rituximab	35 (15.7)
Azathioprine	120 (53.8)
Mycophenolate mofetil	28 (12.6)
Calcineurin inhibitor	12 (5.4)
Methotrexate	22 (9.9)
Plasma exchange	13 (5.8)

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

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; C, cytoplasmic; CAR, C-reactive protein-to-albumin ratio; EGPA, eosinophilic GPA; FFS, Five-Factor Score; GPA, granulomatosis with polyangiitis; IPI, inflammation prognostic index; MPA, microscopic polyangiitis; MPI, mortality-predicting index; MPO, myeloperoxidase; NLR, neutrophil-to-lymphocyte count ratio; P, perinuclear; PR3, proteinase 3.

[a]Patients who took renal replacement therapy (negative follow-up duration) were not included in this study because end-stage renal disease is one of poor outcomes.

3.2 | Characteristics during follow-up

Twenty-five patients (11.2%) died of any cause during 36.5 months of the median follow-up duration based on all-cause mortality. Glucocorticoids were administered to 207 patients (92.8%). The most frequently administered medication, except for glucocorticoid, was azathioprine (53.8%), followed by cyclophosphamide (50.2%) (Table 1). No significant differences in medications administered were observed between the surviving and deceased patients (Table S1).

3.3 | Areas under the curve and cut-offs for all-cause mortality

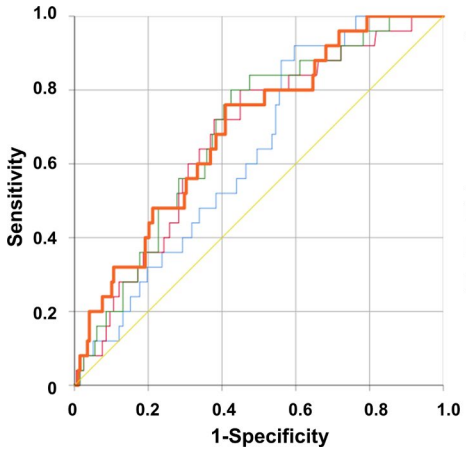
Regarding the ROC curves of the four indices for all-cause mortality, the MPI exhibited the highest area under the curve (AUC) (0.691, 95% confidence interval [CI] 0589, 0.792), followed by the IPI (0.686, 95% CI 0.587, 0.786) (Figure 1). The optimal cut-offs for all-cause mortality were calculated as NLR: 3.22 (sensitivity 92.0%, specificity 40.4%), CAR: 3.25 (sensitivity 80.0%, specificity 55.1%), IPI: 18.53 (sensitivity 80.0%, specificity 57.6%) and MPI: 8367.82 (sensitivity 76.0%, specificity 59.1%).

3.4 | Comparison of the cumulative survival rates

The cumulative patients' survival rates were significantly lower in patients with an NLR ≥3.22 ($p = 0.001$), CAR ≥3.25 ($p = 0.004$), IPI ≥18.53 ($p < 0.001$) and MPI ≥8367.82 ($p = 0.001$) than those without (Figure 2).

3.5 | Hazard ratios of the indices for all-cause mortality during follow-up

In the univariable Cox hazards model analysis, age, gender, smoking history, BVAS, FFS, NLR ≥3.22, CAR ≥3.25, IPI ≥18.53 and MPI ≥8367.82 showed statistical significance (Table S2). As the four



Variables	Area	P-value	95% CI
Indices			
NLR	0.631	0.033	0.534, 0.728
CAR	0.671	0.005	0.567, 0.775
IPI	0.686	0.002	0.587, 0.786
MPI	0.691	0.002	0.589, 0.792

FIGURE 1 Area under the curve of each index for all-cause mortality. Regarding the ROC curves of the four indices for all-cause mortality, the MPI exhibited the highest AUC value, followed by the IPI. AUC, area under the curve; IPI, inflammation prognostic index; MPI, mortality-predicting index; ROC, receiver operator characteristic

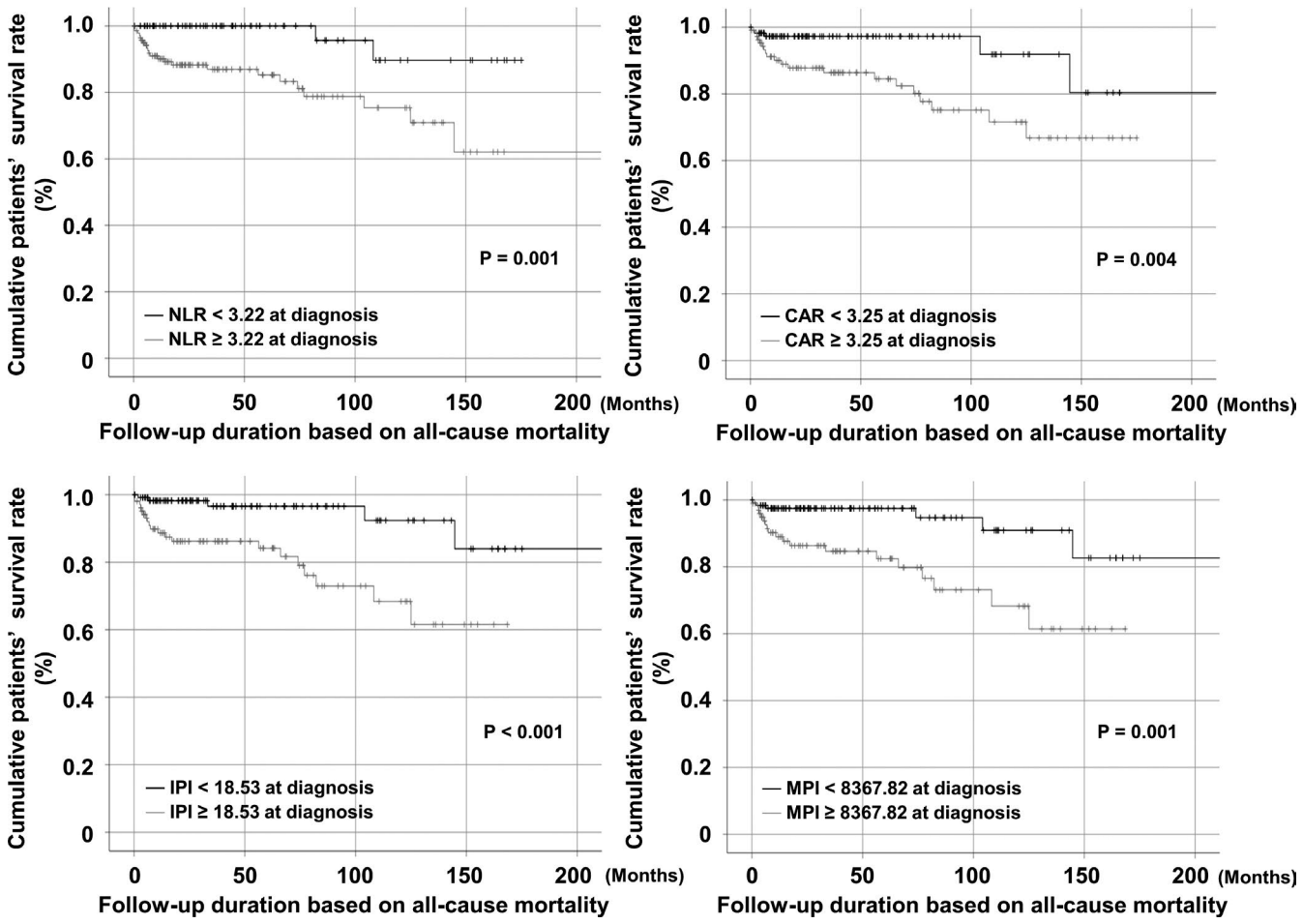


FIGURE 2 Cumulative patient survival rates. The cumulative patient survival rates were significantly lower in patients with an NLR ≥3.22, CAR ≥3.25, IPI ≥18.53 and MPI ≥8367.82 than those without. CAR, C-reactive protein-to-albumin ratio; IPI, inflammation prognostic index; MPI, mortality-predicting index; NLR, neutrophil-to-lymphocyte count ratio

indices share at least two mutual variables, the multivariable analysis included age, gender, smoking history, BVAS, FFS and each of the four prognosis-predicting indices. In the multivariable analysis with the NLR, only an NLR ≥3.22 at diagnosis (HR 5.367, 95% CI 1.188, 24.252) was an independent predictor of all-cause mortality. In the multivariable analysis with the CAR, the CAR was not discovered as an independent predictor of all-cause mortality. Instead, gender and FFS at diagnosis was significantly associated with all-cause mortality. In the multivariable analysis with the IPI, only an IPI ≥18.53 at diagnosis (HR 3.162, 95% CI 1.128, 2.513) was an independent predictor of all-cause mortality. In the multivariable analysis with an MPI ≥8367.82 (HR 3.356, 95% CI 1.290, 8.735), smoking history and FFS at diagnosis were significantly associated with all-cause mortality (Table 2). We confirmed no significant multicollinearity among continuous variables in the multivariable Cox hazard model analysis.

TABLE 2 Multivariable Cox hazards model analysis of variables at diagnosis statistical significance in univariable analysis for all-cause mortality during follow-up in AAV patients

Variables at diagnosis	Univariable			Multivariable (NLR ≥3.22)			Multivariable (CAR ≥3.25)		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (years)	1.055	1.018, 1.093	0.003	1.031	0.995, 1.067	0.093	1.029	0.994, 1.066	0.108
Male gender (*N*, (%))	2.264	1.029, 4.978	0.042	0.575	0.242, 1.366	0.210	0.406	0.179, 0.919	0.031
Smoking history (*N*, (%))	6.052	1.787, 20.498	0.004	0.285	0.070, 1.158	0.079	2.774	0.739, 10.417	0.131
BVAS	1.096	1.040, 1.155	0.001	1.052	0.992, 1.115	0.090	1.037	0.978, 1.101	0.226
FFS	2.142	1.468, 3.126	<0.001	1.483	0.945, 2.326	0.086	1.716	1.086, 2.713	0.021
NLR ≥3.22	7.525	1.773, 31.945	0.006	5.367	1.188, 24.252	0.029			
CAR ≥3.25	3.872	1.451, 10.336	0.007				2.317	0.836, 6.421	0.106
IPI ≥18.53	4.967	1.860, 13.263	0.001						
MPI ≥8367.82	4.378	1.746, 10.979	0.002						

Variables at diagnosis	Multivariable (IPI ≥18.53)			Multivariable (MPI ≥8367.82)		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (years)	1.028	0.993, 1.064	0.114	1.024	0.989, 1.061	0.183
Male gender (*N*, (%))	2.181	0.947, 5.022	0.067	1.995	0.859, 4.633	0.108
Smoking history (*N*, (%))	3.910	0.984, 15.529	0.053	4.116	1.021, 16.596	0.047
BVAS	1.039	0.980, 1.102	0.196	1.041	0.983, 1.102	0.170
FFS	1.575	0.988, 2.513	0.056	1.861	1.134, 3.054	0.014
NLR ≥3.22						
CAR ≥3.25						
IPI ≥18.53	3.162	1.128, 8.861	0.029			
MPI ≥8367.82				3.356	1.290, 8.735	0.013

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CAR, CRP-to-albumin ratio; CI, confidence interval; CRP, C-reactive protein; FFS, Five-Factor Score; HR, hazard ratio; IPI, inflammation prognostic index; MPI, mortality-predicting index; NLR, neutrophil-to-lymphocyte ratio.

4 | DISCUSSION

The motive for performing this study was the question of whether the IPI, which has been reported to predict survival-related prognosis in tumour patients, could predict all-cause mortality in AAV patients.[10] As the IPI is calculated as the product of the NLR and CAR, which have been reported to predict poor outcomes in AAV patients, positive conclusions were expected from the start of the study. In addition, we modified the IPI (NLR × CAR) to develop a new index, MPI, using monocyte counts, which were closely associated with all-cause mortality in previous studies.[7,8]

In the ROC curve analysis performed to obtain the cut-offs for all-cause mortality, all four indices showed statistically significant AUC values, although the follow-up duration based on mortality was not considered. Interestingly, the IPI, which is the product of the NLR and CAR, showed a higher AUC value than that of either NLR or CAR alone. In particular, the MPI, which includes monocyte counts combined with IPI, showed the highest AUC value. The addition of monocyte counts completed the three lineages of white blood cells and increased the predictability of the mortality rate. There are several possible mechanisms of how monocytes could predict all-cause mortality through the relationship between the early inflammatory burden and mortality in AAV patients.[15] ANCAs stimulate the production of monocyte chemoattractant portien-1, pro-inflammatory cytokines and reactive oxygen species (ROS), which subsequently drive monocytes to persist local inflammation around small vessel walls.[16-18]

The mortality predictabilities of the four indices based on the follow-up duration were compared in two univariable variable analyses. In the Kaplan-Meier analysis, the predictive power for all-cause mortality was best for an IPI ≥18.53 ($p < 0.001$) for all-cause mortality was found to be the best, followed by an NLR ≥3.22 ($p = 0.001$) and MPI ≥8367.82 ($p = 0.001$). In addition, in the univariable Cox hazard model analysis, the predictive potential of an IPI ≥18.53 (HR 4.976, $p = 0.001$) was the highest, followed by an MPI ≥8367.82 (HR 4.378, $p = 0.002$). In both univariable analyses, the mortality predictability of the IPI was statistically the most significant.

Meanwhile, to be recognised for clinical significance as an independent predictor for all-cause mortality, the multivariable analysis must show superior or similar mortality predictive ability compared with the conventional risk factors. In this respect, in the multivariable analysis, although all four indices except CAR ≥3.25 showed

significant significance, MPI ≥8367.82 showed the most statistically significant association (p = 0.013), making it the most valid measure for clinical application.

The conventional risk factors for all-cause mortality not only in the general population[19] but also in AAV patients may differ according to ethnic and geographical factors. In addition, the clinical implications of the laboratory results constituting the four indices may be influenced by environmental factors. Therefore, two points should be kept in mind when selecting and applying the most significant mortality-predicting index for AAV patients based on the results of the multivariable analysis of this study. First, an index should be selected, in which the mortality predictability is independently equal to or superior to the conventional risk factors for all-cause mortality with statistical significance in the multivariable Cox hazards model analysis.[19] Second, the cut-off of each index for all-cause mortality suggested in this study should not be used directly, and new cut-offs suitable for each ethnic group or region should be determined according to the described method.

For these reasons, we added several variables with clinical significance to the multivariable Cox analysis such as AAV-specific risk factors and comorbidities at diagnosis, despite no statistical significance in the univariable Cox analysis. In the multivariable Cox analysis, MPO-ANCA, PR3-ANCA, chronic kidney disease without renal replacement therapy, diabetes mellitus, hypertension and dyslipidaemia did not independently predict all-cause mortality. However, an MPI ≥8367.82 (HR 4.698, 95% CI 1.657, 13.315) was proved to be an independent predictor of all-cause mortality during the follow-up in AAV patients along with the FFS (HR 2.219, 95% CI 1.187, 3.818) (Table S3).

What is the clinical significance of the efforts to develop new mortality-predicting indices? The overall mortality rate in this study was 11.2%, which is a much higher value than other rheumatic diseases.[20-22] It was not possible to accurately assess how drug selection and the follow-up duration were determined due to the retrospective study design. However, if AAV patients were classified into a group with a high probability of mortality, more care would likely have been put into these decisions. Therefore, the continued development of various mortality-predicting indices is needed.

This study has three strengths. First, we conducted a multivariable Cox hazards model analysis using the candidate indices with the conventional risk factors for mortality. Second, we developed and proposed new indices with higher predictability than previously reported mortality-predicting indices. Third, to overcome the ethnic and geographical differences, we suggested a method of determining a cut-off for predicting mortality for each index. However, this study also has three limitations. First, due to the retrospective nature of this study, the cause of death was not definitely provided in all patients with AAV. Second, the number of patients was not large enough to represent all Korean patients with AAV. Third, our results were not validated by another cohort of Korean patients with AAV because, in terms of the number of patients and the collection of clinical data and specimen data, there is no cohort of Korean patients with AAV as large, specific and robust as our cohort. Nationwide data on the prognosis of Korean patients with AAV are being collected and will provide more informative evidence regarding the clinical significance of each index for predicting all-cause mortality during the follow-up.

In conclusion, this study developed a novel indicator, MPI, that uses the existing NLR and CAR indices and proved they could predict all-cause mortality in AAV patients. New prognosis-predicting indices at diagnosis are expected to improve the prognosis of AAV.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article and its Supplementary Information files.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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