# Pan-immune-inflammation value at diagnosis independently predicts all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis

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## ABSTRACT

**Objective.** *The pan-immune-inflammation value (PIIV), a novel, validated predictor of the prognosis of several diseases, has been recently introduced. We investigated whether PIIV at diagnosis could predict all-cause mortality during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).*

**Methods.** *Medical records of 219 immunosuppressive drug-naïve patients with AAV were reviewed. PIIV was calculated as follows: neutrophil count (x $1000/m^3$) x monocyte count (x $1000/m^3$) x platelet count (x $1000/mm^3$) / lymphocyte count (x $1000/m^3$). Additionally, conventional risk factors of mortality, AAV-specific indices, and acute-phase reactants at diagnosis were evaluated.*

**Results.** *The median age at diagnosis was 59.0 years and 32.9% of the patients were male. During follow-up, 24 patients (11.0%) died due to all causes. When the cut-off of PIIV at diagnosis for all-cause mortality was set at 1011.3, sensitivity and specificity of 52.0% and 71.2%, were attained (p=0.041). When AAV patients were divided into two groups according to the calculated cut-off, those with PIIV ≥1011.3 at diagnosis had a significantly lower cumulative survival rate than those without (p=0.009). In the multivariable Cox hazards model analysis, male gender (HR 2.307), FFS (HR 1.728) and PIIV ≥1011.3 (HR 2.689) were identified as significant and independent risk factors of all-cause mortality.*

**Conclusion.** *PIIV at diagnosis exceeding the optimal cut-off for death could predict all-cause mortality during follow-up in AAV patients comparable to male gender and FFS at diagnosis.*

## Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic vasculitides, that primarily affects small-sized vessels such as capillaries, arterioles, and venules, and occasionally invades medium-sized vessels (1, 2). AAV consists of three subtypes of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA). AAV mainly affects the smallest blood vessels, and furthermore, has a wide variety of clinical features affecting almost all parts of the body ranging from the brain to the peripheral nervous and vascular systems (3). Therefore, the clinical manifestations and outcomes of AAV may vary from patients to patients.

So far, various AAV-specific indices (4-6) and conventional risk factors of death (7) have been introduced for predicting all-cause mortality and are being applied clinically in patients with AAV. However, it is difficult to predict all-cause mortality at the time of diagnosis of AAV, unlike the association between renal involvement at diagnosis and renal relapse during follow-up (8). This is because, besides the AAV-specific and conventional risk factors of all-cause mortality, other factors such as the selection of both induction and maintenance therapeutic regimens and drug-related complications, affect the prognosis of AAV (9-11). Furthermore, because various combinations of risk factors are possible in each individual, the number of risk factor combinations may be larger than expected. Nevertheless, ever since significant clinical implications have been shown with the discovery of new indices that can predict all-cause mortality at diagnosis, it has led to increased research efforts and it should be continued.

As a result of such research, the pan-immune-inflammation value (PIIV), a new indicator that predicts prognosis, has recently been introduced. PIIV has

been proven as a strong predictor of survival outcomes in patients with metastatic colorectal cancer (12). As PIIV is composed of four immune and inflammation-related variables, its ability to predict all-cause mortality is expected to be better and more stable than that of existing prognostic factors of various diseases, including AAV. However, to date, no study has investigated the clinical implication of PIIV in predicting the poor outcomes of AAV. Hence, in this study, we investigated whether PIIV at diagnosis could predict all-cause mortality during follow-up in immunosuppressive drug-naïve patients with AAV. Furthermore, we compared its predictive potential with that of other known AAV-specific and conventional risk factors of all-cause mortality.

## Patients and methods
### Participants
We included 219 immunosuppressive drug-naïve patients with AAV and reviewed their medical records retrospectively. All patients were initially classified as having AAV in our institute between March 2005 and March 2020, in accordance with the 2007 European Medicines Agency algorithm for AAV and polyarteritis nodosa and the 2012 revised Chapel Hill Consensus Conference Nomenclature of Vasculitides (1, 2). They had never been treated with immunosuppressive drugs for AAV treatment nor did they have any medical conditions that influenced the rate of all-cause mortality or initial blood cell counts, such as malignancies, infectious diseases, and haematologic disorders. All patients had well-documented medical records, including those for conventional risk factors, AAV-specific indices, and inflammation-related laboratory results at diagnosis. They were followed up for at least ≥3 months since the time of AAV diagnosis. This study was approved by the Institutional Review Board of Severance Hospital (4-2017-0673), which waived the need for the patients' written informed consent, owing to the retrospective nature of the study.

### Formula for PIIV
PIIV was calculated using the following formula (12): PIIV = neutrophil count ($\times 1000/m^3$) $\times$ monocyte count ($\times 1000/m^3$) $\times$ platelet count ($1000/mm^3$) / lymphocyte count ($\times 1000/m^3$). The results of the tests that were performed for AAV diagnosis were used to calculate PIIV in patients visiting the outpatient office. On the other hand, results of the initial tests that were performed for AAV diagnosis and before the administration of any drug for relieving symptoms during admission, were used to calculate PIIV in hospitalised patients.

### Conventional risk factors of all-cause mortality at diagnosis
The conventional risk factors of all-cause mortality were including age, male gender, smoking history (or current smoker) and body mass index were collected as demographic data. In addition, diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease were identified as comorbidities. Patients with other medical conditions that could affect the mortality rate were excluded from this study.

### AAV-specific indices at diagnosis
Information on the AAV subtypes and ANCA positivity (myeloperoxidase [MPO]-ANCA, perinuclear [P]-ANCA, proteinase 3 [PR3]-ANCA and cytoplasmic [C]-ANCA) was collected from the patients' medical records. Patients who tested negative in the antigen-specific assay but positive in the indirect immunofluorescence assay were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected based on clinical and laboratory features (13). Additionally, Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) were assessed (3, 14).

### Inflammation-related laboratory results at diagnosis
In addition to the four variables, data on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were collected as acute-phase proteins.

### Follow-up period and medications
The follow-up period based on all-cause mortality for the surviving patients was defined as the period from the date of AAV diagnosis to the date of their last visit, while that for deceased patients was defined as the period from the initial AAV diagnosis to the time of death. The number of medications administered during follow-up was counted.

### Statistical analyses
All statistical analyses were conducted using SPSS software (version 25 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median (interquartile

**Table I.** Characteristics of 219 patients with AAV at diagnosis.

| Variables | Values |
|---|---|
| *Conventional risk factors at diagnosis for all-cause mortality* | |
| Age (years) | 59.0 (20.0) |
| Male gender (n, (%)) | 72 (32.9) |
| Smoking history (n, (%)) | 6 (2.7) |
| Body mass index (kg/m²) | 22.1 (4.4) |
| Diabetes mellitus | 52 (23.7) |
| Hypertension | 88 (40.2) |
| Dyslipidaemia | 36 (16.4) |
| Cardiovascular disease | 4 (1.8%) |
| | |
| *AAV-specific indices* | |
| AAV subtypes (n, (%)) | |
| MPA | 121 (55.3) |
| GPA | 55 (25.1) |
| EGPA | 43 (19.6) |
| ANCA positivity (n, (%)) | |
| MPO-ANCA (or P-ANCA) positivity | 144 (65.8) |
| PR3-ANCA (or C-ANCA) positivity | 38 (17.4) |
| Both ANCA positivity | 9 (4.1) |
| ANCA negativity | 46 (21.0) |
| FFS | 1.0 (2.0) |
| BVAS | 12.0 (11.0) |
| | |
| *Inflammation-related laboratory results* | |
| ESR (mm/hr) | 56.0 (69.0) |
| CRP (mg/L) | 11.9 (60.0) |
| White blood cell count (/mm³) | 8940.0 (6050.0) |
| Neutrophil count (/mm³) | 6110.0 (5540.0) |
| Monocyte count (/mm³) | 440.0 (290.0) |
| Lymphocyte count (/mm³) | 1470.0 (1010.0) |
| PIIV | 525.6 (1055.2) |

Values are expressed as a median (interquartile range, IQR) or N (%).
AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; 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; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PIIV: pan-immune-inflammatory value.

range), and categorical variables were expressed as number (%). The optimal cut-off of PIIV for all-cause mortality was extrapolated by calculating the receiver operator characteristic (ROC) curve and selecting the maximised sum of sensitivity and specificity. Comparison of the cumulative survivals rates between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. The multivariable Cox hazard model using variables with statistical significance in the univariable Cox hazard model was conducted to appropriately obtain the hazard ratios (HRs) during the considerable follow-up duration. *p*-values less than 0.05 were considered statistically significant.

## Results
### *Characteristics of the patients at diagnosis*
The median age of the participants was 59.0 years. In this study, 32.9% of the patients were male and six patients were ex-smokers. The median body mass index was 22.1 kg/m$^2$. Hypertension (40.2%) was the most common comorbidity at diagnosis, followed by diabetes mellitus (23.7%). MPA was determined in 121 patients and MPO-ANCA (or P-ANCA) was detected in 144 patients. The median BVAS and FFS were 12.0 and 1.0, respectively. The median PIIV at diagnosis was 525.6 (Table I).

### *Comparison of medications administered during follow-up*
Twenty-four patients (11.0%) died of all causes during follow-up. No significant difference was observed between the patients who survived and those who did not in terms of the number of patients receiving medications (Table II).

### *Cut-off of PIIV at diagnosis for all-cause mortality during follow-up*
Using the ROC curve, when the optimal cut-off of PIIV at diagnosis for all-cause mortality was set at 1011.3, sensitivity of 52.0% and specificity of 71.2% were attained (area 0.625, 95% confidence interval [CI] 0.511, 0.740, *p*=0.041) (Fig. 1).

**Table II.** Comparison of medications for AAV administered during follow-up between survived and deceased patients with AAV.

| Variables | Survived patients (n=174) | Deceased patients (n=24) | *p*-value |
|---|---|---|---|
| *Medications for AAV (n, (%))* | | | |
| Cyclophosphamide | 95 (54.6) | 14 (58.3) | 0.508 |
| Rituximab | 30 (17.2) | 4 (16.7) | 0.944 |
| Azathioprine | 105 (60.3) | 13 (54.2) | 0.841 |
| Mycophenolate mofetil | 24 (13.8) | 3 (12.5) | 1.000 |
| Tacrolimus | 10 (5.7) | 2 (8.3) | 0.632 |
| Methotrexate | 20 (11.5) | 1 (4.2) | 0.480 |

Values are expressed as n (%).
ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis.



**Fig. 1.** Cut-off of PIIV for all-cause mortality.
When the optimal cut-off of PIIV at diagnosis for all-cause mortality was set at 1011.3, the sensitivity was 52.0% and the specificity was 71.2%.
PIIV: pan-immune-inflammation value; CI: confidence interval.

Area 0.625
95% CI 0.511, 0.740
P = 0.041



P = 0.009

— PIIV at diagnosis < 1011.3
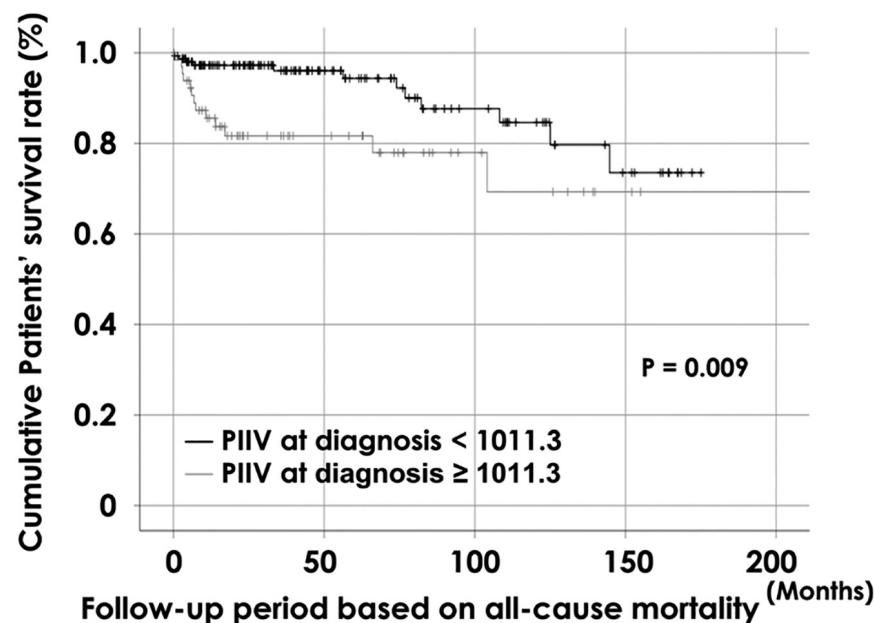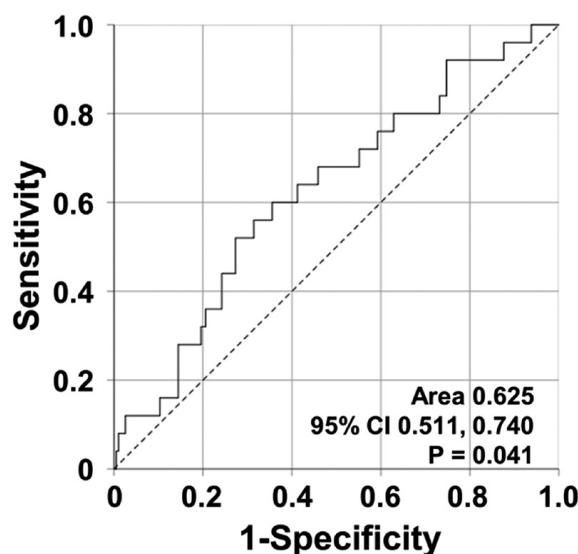— PIIV at diagnosis ≥ 1011.3

**Fig. 2.** Cumulative patients' survival rate.
AAV patients with PIIV at diagnosis ≥ 1011.3 exhibited a significantly lower cumulative patients' survival rate compared to those without.
AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; PIIV: pan-immune-inflammatory value.

**Table III.** Cox hazards model analysis of variables at diagnosis for all-cause mortality during follow-up in AAV patients.

| Variables | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p*-value | HR | 95% CI | *p*-value |
| Age | 1.056 | 1.020, 1.094 | 0.002 | 1.029 | 0.992, 1.067 | 0.125 |
| Male gender | 2.346 | 1.067, 5.162 | 0.034 | 2.307 | 1.015, 5.247 | 0.046 |
| Smoking history | 5.933 | 1.752, 20.094 | 0.004 | 2.831 | 0.742, 10.800 | 0.128 |
| Body mass index | 1.097 | 0.958, 1.255 | 0.182 | | | |
| Diabetes mellitus | 0.921 | 0.367, 2.312 | 0.861 | | | |
| Hypertension | 1.057 | 0.480, 2.331 | 0.890 | | | |
| Dyslipidaemia | 1.564 | 0.624, 3.921 | 0.340 | | | |
| Cardiovascular disease | 0.048 | 0.000, 3558.285 | 0.595 | | | |
| MPA *vs.* GPA and EGPA | 2.014 | 0.866, 4.684 | 0.104 | | | |
| GPA *vs.* MPA and EGPA | 1.444 | 0.622, 3.354 | 0.393 | | | |
| MPO-ANCA (or P-ANCA) positivity | 1.501 | 0.638, 3.530 | 0.352 | | | |
| PR3-ANCA (or C-ANCA) positivity | 0.938 | 0.349, 2.523 | 0.900 | | | |
| ANCA positivity | 1.892 | 0.643, 5.565 | 0.247 | | | |
| BVAS | 1.095 | 1.039, 1.153 | 0.001 | 1.061 | 1.000, 1.126 | 0.050 |
| FFS | 2.165 | 1.482, 3.162 | <0.001 | 1.728 | 1.074, 2.780 | 0.024 |
| ESR | 1.004 | 0.994, 1.014 | 0.466 | | | |
| CRP | 1.006 | 1.000, 1.012 | 0.037 | 0.999 | 0.992, 1.007 | 0.873 |
| PIIV ≥1011.3 | 2.750 | 1.252, 6.041 | 0.012 | 2.689 | 1.156, 6.254 | 0.022 |

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; 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; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PIIV: pan-immune-inflammatory value.

*Comparison of cumulative survival rate*

When AAV patients were divided into two groups according to the calculated cut-off of PIIV, those with PIIV at diagnosis ≥1011.3 had a significantly lower cumulative patients' survival rate as compared to those with PIIV at diagnosis <1011.3 (*p*=0.009) (Fig. 2).

*Cox hazards model analysis*

A Cox hazards model analysis was conducted too assess the independent predictive potential of PIIV at diagnosis for all-cause mortality during follow-up compared to AAV-specific and conventional risk factors for all-cause mortality and acute-phase proteins at diagnosis. In the univariable analysis, age (HR 1.056), male gender (HR 2.346), smoking history (HR 5.933), BVAS (HR 1.095), FFS (HR 2.165), CRP (HR 1.006) and PIIV ≥1011.3 (HR 2.750) at diagnosis were significantly associated with all-cause mortality. In the multivariable analysis, male gender (HR 2.307, 95% CI 1.015, 5.247), FFS (HR 1.728, 95% CI 1.074, 2.780) and PIIV ≥1011.3 at diagnosis (HR 2.689, 95% CI 1.156, 6.254) were identified as significant and independent risk factors of all-cause mortality (Table III).

**Discussion**

This study investigated whether PIIV at diagnosis could predict all-cause mortality during follow-up in immunosuppressive drug-naïve patients with AAV and revealed the three new findings described below. First, 21 of 219 patients (11.0%) died of any cause during follow-up regardless of medications administered. Second, when the cut-off of PIIV at diagnosis for all-cause mortality was set as 1011.3, AAV patients with PIIV at diagnosis ≥1011.3 exhibited a significantly lower cumulative patients' survival rate as compared to those with PIIV at diagnosis <1011.3 (*p*=0.009). Third, in the multivariable Cox hazards model analysis with conventional risk factors, AAV-specific indices and acute-phase reactants at diagnosis, male gender (HR 2.307, 95% CI 1.015, 5.247), FFS (HR 1.728, 95% CI 1.074, 2.780) and PIIV ≥1011.3 at diagnosis (HR 2.689, 95% CI 1.156, 6.254) were identified as significant and independent risk factors of all-cause mortality. Therefore, we proved that PIIV at diagnosis beyond the optimal cut-off for death of any cause could predict all-cause mortality during follow-up in AAV patients.

In this study, we obtained the cut-off of PIIV at diagnosis for all-cause mortality using the ROC curve. However, a time-gap error occurred when using the ROC curve of PIIV at diagnosis based on all-cause mortality during follow-up. This is because the concept of a follow-up period was not included or adjusted in the calculation of the cut-off of PIIV. Hence, when the lower limit of the highest tertile of PIIV at diagnosis was arbitrarily set as the cut-off, the patients with the highest tertile of PIIV at diagnosis showed a lower cumulative patients' survival rate than those with the middle or lowest tertile of PIIV (*p*=0.040). Furthermore, when sequential significance based on the tertile order was investigated, a trend toward statistical significance was observed with a *p*-value of 0.077, but statistical significance was not reached (Supplementary Fig. S1). This result has two clinical implications. First, it revealed that the higher PIIV at diagnosis has the higher the potential for predicting all-cause mortality during follow-up becomes. Second, if the cut-off of PIIV acquisition fails using the ROC curve, it suggests the possibility of applying the highest tertile.

To date, several formulas using blood cell counts at the time of diagnosis that can predict poor prognosis in AAV during follow-up have been proposed

and proven. With regard to neutrophil-to-lymphocyte ratio (NLR), Huang et al. demonstrated that NLR at diagnosis could predict all-cause mortality during follow-up in Chinese patients with MPO-ANCA vasculitis (15). In contrast, Ahn *et al*. reported that NLR could not predict all-cause mortality during independently follow-up in Korean patients with AAV (16). We believe that these differences can be attributed to the differences in the target disease and ethnicities. In addition, Park *et al*. reported that the platelet-to-lymphocyte ratio (PLR) was associated with the cross-sectional activity of AAV based on BVAS, but it did not indicate the predictive potential of PLR for all-cause mortality (17).

Meanwhile, Kim *et al*. reported that the systemic immune-inflammation index (SII) at diagnosis, a new indicator composing of three variables that combine NLR and PLR, showed a tendency to predict all-cause mortality in AAV patients but it did not reach statistical significance ($p$=0.125) (18). Among the many existing formulas, SII, which is composed of neutrophil, platelet and lymphocyte counts, is the most similar to PIIV. Additionally, the concept of the clinical significance of monocytes in AAV has been gradually expanding (19). Therefore, as a formula of PIIV using the counts of four types of blood cells, namely, neutrophils, platelets, monocytes, and lymphocytes, it is thought to enable a more stable and reliable prediction of poor prognosis as compared to the previously suggested indices.

The biggest difference between PIIV and the previous indicators is that PIIV includes a monocyte count. This leads to the question of how the added monocyte count at diagnosis affects all-cause mortality. First, quiescent monocytes become primed monocytes by triggering factors and subsequent inflammatory cytokines and primed monocytes are converted into activated monocytes by binding with circulating ANCA (19). Activated monocytes secrete reactive oxygen species and inflammatory cytokines and chemokines. They also show an enhanced response to ligands of pattern recognition receptors. The augmented expression of the autoantigens of ANCA on monocyte surfaces may increase interleukin (IL)-1 beta, IL-6, and IL-8 levels (20), leading to the acceleration of AAV activity. In addition, infiltrated CD68^{+} monocytes/macrophages are often found in damaged organ tissues (21). These could be involved in the increased activity of AAV and organ damage based on BVAS and FFS at diagnosis, which were proven to be associated with all-cause mortality during follow-up (Table III). However, monocyte count alone was not significantly associated with all-cause mortality in the univariable Cox hazards model analysis ($p$=0.122). It can be assumed that the monocyte count might affect the predictive potential of PIIV for all-cause mortality in AAV patients along with the other blood cell types, as four parameters are more reliable and flexible than only one parameter of monocyte count.

CRP could be one of the important serum markers to estimate the current activity of AAV, and it may be associated with all-cause mortality in AAV (20). The ROC curve (area 0.662, 95% CI 0.560, 0.765) set the cut-off of CRP for death as 12.7 mg/L (sensitivity 80.0% and specificity 55.2%). When CRP ≥12.7 mg/L was included in the multivariable Cox hazards model analysis instead of CRP (continuous variable), the factors of age, BVAS, FFS, ESR, CRP ≥12.7 mg/L and PIIV ≥1011.3 were significantly associated with all-cause mortality. On the other hand, when the multivariable Cox hazards model analysis was performed using continuous variables of CRP and PIIV with other continuous variables, we found that male gender, BVAS, FFS, ESR and PIIV were significantly associated with all-cause mortality. CRP was not statistically significant in predicting all-cause mortality in patients with AAV (Supplementary Table 1). The aim of this study was not to compare the predictive potentials of CRP and PIIV, but to discover a new index to predict all-cause mortality in AAV patients in order to help physicians cope with poor outcomes of AAV in clinical practice. Therefore, we believe that our study has clinical significance as an attempt to discover new indices.

In addition, we wondered whether PIIV would still exhibit a significant association with all-cause mortality in the Cox hazards model analysis depending on the administration of either cyclophosphamide or rituximab. Of 219 patients, 109 received cyclophosphamide and 34 received rituximab. Furthermore, 24 patients were administered with rituximab after cyclophosphamide. Thus, 85 patients took cyclophosphamide alone, 24 patients took rituximab after cyclophosphamide, and only 10 patients took rituximab alone. When the cumulative patients' survival rates among these three groups were compared using the Kaplan Meier survival analysis with the log-rank test, the rate of all-cause mortality did not significantly differ among them ($p$=0.070). Next, variables of 'cyclophosphamide alone' and 'rituximab alone' without 'rituximab after cyclophosphamide' were included in the univariable Cox hazards model analysis to avoid the confusing effect of the administration of both cyclophosphamide and rituximab. Compared to 'cyclophosphamide alone', 'rituximab alone' did not exhibit a significant association with all-cause mortality in AAV patients (HR 2.637, 95% CI 0.729, 9.534). Therefore, the variable reflecting treatment modality was not included in the multivariable analysis along with PIIV.

Our study presented three advantages. First, the predictive potential of PIIV at diagnosis for all-cause mortality during follow-up in AAV patients was investigated for the first time. Second, we included only immunosuppressive drug-naïve patients and excluded those with haematologic disorders that affect the initial blood cell counts. Third, we provided information on the method to obtain the proper cut-off of PIIV for predicting all-cause mortality in patients of various AAV cohorts. However, our study had several limitations. As this was a monocentric study, the number of patients was not large enough to represent all AAV patients and to generalise these. Moreover, missing data are usually additional concerns in retrospective studies. The fact that we applied a uniform predictive index of the progno-

sis to heterogeneous patients with AAV and that variables that were not directly related to disease were used should be carefully considered. Nevertheless, given that our institute manages the biggest AAV cohort in Korea and that the concern regarding the inter-observer variation and missing data could be reduced by the monocentric design of this study, we believe that these limitations were overcome. Furthermore, the cut-off value of PIIV had relatively low sensitivity. However, in the absence of a widely used serum biomarker for predicting all-cause mortality, our study has relevant clinical implications with respect to efforts in discovering new serum biomarkers, even though the sensitivity was not high. For this purpose and as a pilot study, we believe our results will be the cornerstone of a new beginning. In conclusion, 11.0% of AAV patients died in this study, and PIIV at diagnosis beyond the optimal cut-off for death could predict all-cause mortality during follow-up in AAV patients, and was comparable to male gender and FFS at diagnosis.

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