

# The Novel Fibrosis Index at Diagnosis May Predict All-cause Mortality in Patients With Antineutrophil Cytoplasmic Antibody-associated Vasculitis Without Substantial Liver Diseases.

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## Research article

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# Abstract

**Objectives:** Antineutrophil cytoplasmic antibody associated vasculitis (AAV) is a fatal disease. Currently, predictors of mortality of AAV are based on distribution of organ involvement. Novel fibrosis index (NFI) is an index, which is composed of laboratory results, that reflects the degree of liver fibrosis. The aim of this study is to evaluate whether NFI can predict poor outcomes among patients with AAV without substantial liver diseases.

**Methods:** 210 immunosuppressive drug-naïve AAV patients were retrospectively reviewed. NFI was calculated as follows:  $NFI = [\text{serum bilirubin} \times (\text{alkaline phosphatase})^2] / [\text{platelet count} \times (\text{serum albumin})^2]$ . Cut-off of NFI was set at 1.24, and patients were divided into two groups. Poor outcomes were defined as all-cause mortality, relapse, and end-stage renal disease (ESRD).

**Results:** During the median 34.5 months of follow up, twenty-one patients (10%) died, 72 patients (34.3%) relapsed, and 38 patients (18.1%) reached ESRD due to AAV progression. The median calculated NFI was 0.61, and it was higher in AAV patients with all-cause mortality than those without mortality, but it didn't reach the statistical significance (1.26 vs. 0.59). AAV patients with NFI at diagnosis  $\geq 1.24$  exhibited a significantly lower cumulative patients' survival rate than those with NFI at diagnosis  $< 1.24$  ( $P = 0.002$ ). Multivariate Cox hazard model analysis showed that NFI at diagnosis  $\geq 1.24$  was an independent predictor of all-cause mortality in AAV (HR 2.850, 95% CI 1.026, 7.910).

**Conclusions:** NFI at diagnosis  $\geq 1.24$  may be an independent predictive marker for all-cause mortality in AAV patients without substantial liver diseases.

## Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is one of the systemic vasculitides and characterised by necrotising vasculitis in small-sized vessels including arterioles, venules and capillaries and occasionally arteries. AAV has three subtypes based on the histological and clinical features such as microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [1]. So far various classification criteria and definitions have been suggested and currently, the 2007 European Medicine Agencies algorithm for AAV and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides are widely used for the diagnosis of AAV [1, 2]. The disease activity of AAV is assessed and expressed by Birmingham vasculitis activity score (BVAS), which consists of nine items [3]. In addition, vasculitis damage index (VDI) is used to assess the irreversible damage caused by AAV and five-factor score (FFS) is used to predict the prognosis [4, 5].

The details of BVAS or VDI include several major organs, but they do not contain the symptoms or damages pertaining to liver involvement of AAV. In a similar context, a previous study reported that the progression of liver involvement or autoimmune hepatitis was rarely observed in AAV patients [6]. Meanwhile, other previous studies have reported that the indices for liver fibrosis were associated with all-

cause mortality in patients AAV [7] and those with rheumatoid arthritis [8]. With regard to AAV, a hypothesis is more persuasive that these results might have resulted from the association of the variables, which compose the formulae of the indices for liver fibrosis, with the cross-sectional inflammatory burden and its related poor outcomes of AAV rather than the direct association between the indices for liver fibrosis and liver involvement of AAV.

Recently, two similar indices for liver fibrosis have been introduced such as fibrosis cirrhosis index (FCI) and novel fibrosis index (NFI). NFI is a modified formula by squaring both alkaline phosphatase in the molecule of FIC and serum albumin in the denominator of a formula of FCI. That is, NFI is an amplification of the reflected contribution of alkaline phosphatase, which shows a positive correlation with liver fibrosis, and serum albumin, which shows a negative correlation [9]. Among the variables of NFI, there have been few previous reports on the association of AAV prognosis with bilirubin or alkaline phosphatase at diagnosis, but the association of AAV prognosis and either platelet count or serum albumin at diagnosis have already been demonstrated [10, 11]. For these reasons, it can be reasonably speculated that NFI at diagnosis could predict the poor outcomes of AAV during follow-up in AAV patients. However, there has been no report on the clinical significance of NFI at diagnosis in the disease course of AAV to date. Hence, in this study, we investigated whether NFI at diagnosis might be associated with the cross-sectional activity of AAV and furthermore could predict the poor outcomes of AAV, particularly all-cause mortality, during follow-up in immunosuppressive drug-naïve patients AAV patients without substantial chronic liver diseases.

## Patients And Methods

### Patients

We retrospectively reviewed the medical records of 210 immunosuppressive drug-naïve AAV patients, who had been classified as AAV based on the 2007 EMA algorithm and the 2012 CHCC definitions at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital between October 2000 and March 2020 [1, 2]. BVAS and FFS were collected and if not available, they were calculated based on clinical and laboratory data documented in the medical records. Confirmation of ANCA both by an indirect immunofluorescence assay (IFA) for perinuclear (P)-ANCA and cytoplasmic (C)-ANCA and antigen-specific assays for myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA was also included in the medical records. Patients negative by antigen-specific assay but positive for ANCA by IFA were considered to have MPO-ANCA or PR3-ANCA when AAV was strongly suspected by the clinical and laboratory features [12]. All patients included in this study had been followed up for at least 3 months or longer. Patients had no serious medical conditions such as coexisting malignancies, serious infections and chronic liver diseases affecting the value of NFI at diagnosis. Also, they had never received immunosuppressive drugs prior to diagnosis. This study was approved by the Institutional Review Board of Severance Hospital (4-2017-0673). The need for patients' written informed consent was waived, as this was a retrospective study.

## Exclusion substantial liver diseases

Substantial liver diseases were identified by blood tests for liver function and viral hepatitis A, B and C and imaging studies such as computed tomography or ultrasonography at diagnosis. In addition, they were also confirmed by the 10th revised International Classification Diseases.

## Clinical data at diagnosis and during follow-up

At diagnosis, age, gender, body mass index and smoking history were obtained. AAV subtypes, ANCA positivity, BVAS and FFS were also collected as AAV-specific indices. Chronic kidney disease (stage 3–5), diabetes mellitus, hypertension and interstitial pneumonia, were assessed. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also reviewed as acute-phase reactants. Medications administered during follow-up including glucocorticoid, cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, tacrolimus and methotrexate, were also counted.

## Poor outcomes

All-cause mortality, relapse and end-stage renal disease (ESRD) were evaluated as the poor outcomes of AAV during follow-up. The follow-up period was defined as the duration between diagnosis and last visit for the survived patients. In cases of the deceased patients, it was defined as the duration between diagnosis and death. For patients who had relapse and ESRD, it was defined as the duration starting from diagnosis until relapse or the initiation of renal replacement therapy, respectively.

## Equation for FCI and NFI

FCI and NFI were calculated by the following formulae:  $FCI = (\text{serum bilirubin} \times \text{alkaline phosphatase}) / (\text{platelet count} \times \text{serum albumin})$ , and  $NFI = [\text{serum bilirubin} \times (\text{alkaline phosphatase})^2] / [\text{platelet count} \times (\text{serum albumin})^2]$

## Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as a median (interquartile range, IQR) and categorical variables were expressed as number and the percentage. Significant differences in categorical variables between the two groups were analysed using the Chi-square and Fisher's exact tests and among more than three groups using the ANOVA analysis. Significant differences in continuous variables between the two groups were compared using the Mann-Whitney test. The correlation coefficient between the two groups was obtained using the Pearson or the Spearman correlation analyses. Comparison of the cumulative survival rates between the two groups was analysed by the Kaplan-Meier survival analysis with the log-rank test. The multivariable Cox hazards model analysis using variables with statistical significance in the univariable Cox hazards model analysis was conducted to appropriately obtain the hazard ratios (HRs) during the considerable follow-up duration. The relative risk (RR) of A for B was analysed using contingency tables and the chi square test. P-values less than 0.05 were considered statistically significant.

## Results

### Characteristics of AAV patients at diagnosis

The median age of patients was 59.0 years and 32.5% were men. The median body mass index (BMI) was 22.2 kg/m<sup>2</sup> and only 7 patients had ever smoked but not current smokers. The most common AAV subtype and detected ANCA type were MPA (55.2%) and MPO-ANCA (or P-ANCA) (66.7%). The median BVAS and FFS were 12.0 and 1.0. The most common comorbidity was hypertension (46.7%), followed by chronic kidney disease (stage 3–5) (28.6%). The median ESR, CRP, NFI and FCI were 60.5 mm/hr, 13.2 mg/L, 0.61 and 0.032, respectively. Twenty-one patients (10%) died, 72 patients (34.3%) relapsed, and 38 patients (18.1%) reached ESRD due to AAV progression. Median follow up duration until each event were 34.5 months, 22.8 months, and 30.5 months, respectively. Glucocorticoid was administered to 91.4% of patients and both cyclophosphamide (48.1%) and azathioprine (47.6%) were most commonly used as induction therapy and maintenance therapy, respectively (Table 1).

Table 1  
 Characteristics of AAV patients with at diagnosis and during follow-up (N = 210)

<b>AAV patients</b>	<b>Values</b>
At the time of diagnosis	
<b>Demographic data</b>	
Age (years)	59.0 (20.3)
Male gender (N, (%))	68 (32.4)
Body mass index (kg/m <sup>2</sup> )	22.2 (4.4)
Smoking history (N, (%))	7 (3.3)
<b>AAV Subtypes (N, (%))</b>	
MPA	116 (55.2)
GPA	52 (24.8)
EGPA	42 (20.0)
<b>ANCA positivity (N, (%))</b>	
MPO-ANCA (or P-ANCA) positivity	140 (66.7)
PR3-ANCA (or C-ANCA) positivity	35 (16.7)
Both ANCA positivity	9 (4.3)
ANCA negativity	44 (21.0)
<b>AAV-specific indices</b>	
BVAS	12.0 (11.0)
FFS	1.0 (2.0)
<b>Comorbidities at diagnosis (N, (%))</b>	
Chronic kidney disease (stage 3–5)	60 (28.6)
Diabetes mellitus	55 (26.2)
Hypertension	98 (46.7)
Interstitial lung disease	55 (26.2)

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; NFI: novel fibrosis index; FCI: fibrosis cirrhosis index; ESRD: end-stage renal disease.

<b>AAV patients</b>	<b>Values</b>
<b>Acute-phase proteins</b>	
ESR (mm/hr)	60.5 (70.3)
CRP (mg/L)	13.2 (70.6)
<b>NFI</b>	0.61 (0.95)
<b>FCI</b>	0.032 (0.037)
During the follow-up period	
<b>Follow-up duration (months)</b>	34.5 (64.6)
<b>Poor outcomes during follow-up (N, (%))</b>	
All-cause mortality (N, (%))	21 (10.0)
Follow-up duration based on all-cause mortality (months)	34.5 (64.7)
Relapse (N, (%))	72 (34.3)
Follow-up duration based on relapse (months)	22.8 (44.0)
ESRD (N, (%))	38 (18.1)
Follow-up duration based on ESRD (months)	30.5 (69.4)
<b>Medications administered during follow-up (N, (%))</b>	
Glucocorticoid	192 (91.4)
Cyclophosphamide	101 (48.1)
Rituximab	31 (14.8)
Azathioprine	100 (47.6)
Mycophenolate mofetil	23 (11.0)
Tacrolimus	11 (5.2)
Methotrexate	19 (0.0)
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; NFI: novel fibrosis index; FCI: fibrosis cirrhosis index; ESRD: end-stage renal disease.	

## Correlation of continuous variables at diagnosis

NFI and FCI tended to be correlated with the cross-sectional activity of AAV based on BVAS but it did not reach statistical significance ( $r = 0.133$ ,  $P = 0.054$  and  $r = 0.133$ ,  $P = 0.055$ , respectively). Furthermore, neither NFI nor FCI was significantly correlated with age, BMI, FFS, ESR and CRP at all (Table 2). Therefore, NFI was not associated with the cross-sectional BVAS.

Table 2  
Correlation of continuous variables with either NFI or FCI at diagnosis in AAV patients

Variables	Based on NFI		Based on FCI	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Age	0.061	0.380	0.063	0.366
BMI	0.046	0.511	0.046	0.503
BVAS	0.133	0.054	0.133	0.055
FFS	0.046	0.508	0.046	0.504
ESR	0.009	0.898	0.010	0.885
CRP	-0.013	0.846	-0.005	0.937

NFI: novel fibrosis index; FCI: fibrosis cirrhosis index; AAV: ANCA-associated vasculitis; BMI: body mass index; BVAS: Birmingham vasculitis activity score; FFS: five-factor score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

## Comparison of FCI and NFI at diagnosis based on each poor outcome

Deceased AAV patients exhibited a higher NFI at diagnosis than survived AAV patients, but it was not statistically significant (1.26 vs. 0.59,  $P = 0.055$ ). However, there were no significant differences in NFI at diagnosis between AAV patients with relapse and those without relapse or AAV patients with ESRD and those without ESRD. On the other hand, FCI at diagnosis did not differ between the three groups classified according to either all-cause mortality or relapse or ESRD occurrence (Fig. 1).

## Cut-offs of NFI and FCI at diagnosis for each poor outcomes

To obtain the cut-offs of NFI and FCI at diagnosis for each poor outcome, we conducted the ROC curve analysis, but could not obtain the cut-offs. Instead, we arbitrarily defined the cut-offs of NFI and FCI as lower limit of the highest quartile at diagnosis:  $NFI \geq 1.24$  and  $FCI \geq 0.057$ .

## Comparison of cumulative survival rates

AAV patients with NFI at diagnosis  $\geq 1.24$  exhibited a significantly lower cumulative patients' survival rate than those with NFI at diagnosis  $< 1.24$  ( $P = 0.002$ ). However, the cumulative relapse-free and ESRD-free

survival rates were not different between AAV patients with NFI at diagnosis  $\geq 1.24$  and those without. Meanwhile, FCI at diagnosis  $\geq 0.057$  was unable to predict any poor outcome of AAV (Fig. 2).

## **Cox hazards model analysis for all-cause mortality**

To clarify whether NFI at diagnosis  $\geq 1.24$  might be an independent predictor of all-cause mortality during follow-up, we conducted the univariable and multivariable Cox hazards model analysis using variables at diagnosis for all-cause mortality. In the univariable analysis, age, male gender, BVAS, hypertension, interstitial lung disease, CRP and NFI at diagnosis  $\geq 1.24$  were significantly associated with all-cause mortality. In the multivariable analysis, age (HR 1.049, 95% confidence interval (CI) 1.05, 1.095), BVAS (HR 1.082, 95% CI 1.010, 1.159), interstitial lung disease (HR 4.728, 95% CI 1.878, 11.901) and NFI at diagnosis  $\geq 1.24$  (HR 2.850, 95% CI 1.026, 7.910) were turned out to be independent predictors of all-cause mortality during follow-up in AAV patients (Table 3).

Table 3

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	1.060	1.019, 1.104	0.004	1.049	1.005, 1.095	0.029
Body mass index	1.115	0.962, 1.293	0.147			
Male gender	2.410	1.021, 5.690	0.045	2.289	0.899, 5.830	0.082
Smoking history	1.964	0.262, 14.734	0.512			
MPO-ANCA (or P-ANCA) positivity	1.784	0.682, 4.664	0.238			
PR3-ANCA (or C-ANCA) positivity	1.036	0.348, 3.088	0.949			
BVAS	1.081	1.002, 1.143	0.007	1.082	1.010, 1.159	0.024
Chronic kidney disease (stage 3–5)	1.985	0.833, 4.733	0.122			
Diabetes mellitus	1.015	0.393, 2.619	0.976			
Hypertension	3.132	1.145, 8.566	0.026	1.414	0.471, 4.241	0.536
Interstitial lung disease	5.614	2.307, 13.663	< 0.001	4.728	1.878, 11.901	0.001
ESR	1.009	0.998, 1.020	0.108			
CRP	1.007	1.001, 1.014	0.022	0.999	0.991, 1.007	0.768
NFI at diagnosis $\geq 1.24$	3.627	1.538, 8.556	0.003	2.850	1.026, 7.910	0.044

AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NFI: novel fibrosis index.

## Relative Risk of NFI at diagnosis $\geq 1.24$ for all-cause mortality

When we classified AAV patients into two groups based on the calculated cut-off of NFI, 54 of 210 patients were partitioned into the group with NFI at diagnosis  $\geq 1.24$ . All-cause mortality was identified more frequently in AAV patients with NFI at diagnosis  $\geq 1.24$  than those with NFI at diagnosis  $< 1.24$  (20.4% vs. 6.3%,  $P = 0.003$ ). Furthermore, AAV patients with NFI at diagnosis  $\geq 1.24$  had a significantly higher risk for all-cause mortality than those with NFI at diagnosis  $< 1.24$  (RR 3.735, 95% CI 1.468, 9.385) (Fig. 3).

## Discussion

In this study, we investigated whether NFI, one of the indices for liver fibrosis, might be associated with the cross-sectional activity of AAV and furthermore could predict the poor outcomes, particularly all-cause mortality in immunosuppressive drug-naïve patients with AAV. We found four valuable results as follows: firstly, NFI could reflect the cross-sectional neither activity of AAV based on BVAS nor acute-phase reactants including ESR and CRP. Secondly, when the cut-off of NFI at diagnosis was defined as the lower limit of the higher quartile, AAV patients with NFI at diagnosis  $\geq 1.24$  exhibited a significantly lower cumulative patients' survival rate than those with NFI at diagnosis  $< 1.24$ . Thirdly, in the multivariable Cox hazards model analysis, NFI at diagnosis  $\geq 1.24$  could independently predict all cause-mortality during follow-up together with age, BVAS and interstitial lung disease at diagnosis. Lastly, AAV patients with NFI at diagnosis  $\geq 1.24$  had a significantly higher risk for all-cause mortality than those with NFI at diagnosis  $< 1.24$  (RR 3.735).

When we assessed the frequency of affected organs based on the nine items of BVAS in our study population, the most common affected item was renal manifestation (60.0%), followed by pulmonary manifestation (57.1%) and ear nose throat (ENT) manifestation (44.8%). We wondered which specific organ involvement was associated with NFI, and found that only the frequency of ENT manifestation among nine manifestations exhibited a significant difference in NFI. Ninety-four AAV patients with ENT manifestation exhibited a significantly higher median NFI than 116 AAV patients without (0.74 vs. 0.50,  $P = 0.024$ ). So, what mechanism made NFI higher in patients with ENT manifestation compared to those without? Although it has been controversial whether sinusitis might be a typical surrogate marker for GPA or not, it is clear that sinusitis is the most common symptom of ENT involvement of AAV [13]. We conducted the literature review on the association of sinusitis with the four variables that compose a formula of NFI and found a previous study reporting that serum albumin was reported to be statistically lower in patients with chronic rhinosinusitis compared to those without [14]. However, in this study serum albumin did not differ between AAV patients with ENT manifestation and those without. Also, since serum albumin is more clinically linked to renal manifestation, it is difficult to explain the difference in NFI between AAV patients with and those without ENT manifestation by the results of this previous study alone.

The cut-off of NFI or FCI that predict the all-cause mortality was not obtained by using the ROC curve that does not include the period in the analysis. For this reason, the cut-offs of NFI and FCI at diagnosis for all-cause mortality were inevitably set as the lower limit of the highest quartile for each. In the Kaplan Meier

survival analysis, in addition to all-cause mortality which showed a statistically significant difference based on NFI at diagnosis  $\geq 1.24$ , ESRD also showed a trend of significance with a P value of 0.1 or less ( $P = 0.072$ ). Therefore, although statistical significance was not reached, the areas of NFI and FCI at diagnosis for all-cause mortality and ESRD using the ROC curve were qualitatively compared. First of all, in the ROC curve analysis based on all-cause mortality, NFI at diagnosis showed a wider area under the curve than FCI at diagnosis. Moreover, in the ROC curve analysis based on ESRD, NFI at diagnosis also showed a wider area under the curve than FCI at diagnosis (**Supplementary Fig. 1**). Therefore, although the statistical significance was low and the follow-up period was not taken into account, NFI at diagnosis tended to better predict the occurrence of all-cause mortality and ESRD during follow-up than FCI at diagnosis.

The exact mechanism of how NFI at diagnosis independently predict all-cause mortality during follow-up in AAV patients is unclear, however, we made some assumptions. Firstly, with regard to serum albumin, hypoalbuminemia is well-known major risk factor for poor prognosis including all-cause mortality and ESRD occurrence in AAV patients [15]. Since serum albumin is located in the denominator in the formula of NFI, NFI and serum albumin theoretically show an inverse correlation. Therefore, it can be inferred that the smaller the albumin, the higher the NFI, so the highest quartile of NFI at diagnosis, which indicates the lower level of serum albumin, could predict all-cause mortality in AAV patients. The Pearson correlation analysis performed in our study data did not reach statistical significance, but showed a tendency of a negative correlation ( $r = -0.119$ ,  $P = 0.084$ ). In fact, using the Spearman correlation analysis, serum albumin was significantly and inversely correlated with NFI ( $r^2 = -0.322$ ,  $P < 0.001$ ). These results support our assumption that NFI can predict all-cause mortality through serum albumin.

Secondly, with regard to platelet count, there have been studies demonstrating that platelet counts reflect the inflammatory burden of AAV, correlate with BVAS, and may predict the poor outcomes in AAV patients [10, 16]. Since platelet count is also located in the denominator of the formula of NFI, theoretically, the larger the platelet counts, the smaller the NFI. However, the results from our data were not. When we focus on two variables located in the denominator, serum albumin can be considered to have a direct effect on the increase in NFI more than platelet count. Therefore, we concluded that the highest quartile of NFI at diagnosis made a more direct contribution to predicting all-cause mortality through reduced serum albumin which could reflect the high degree of inflammation and malnutrition.

In the Kaplan Meier survival analysis, the cumulative ESRD-free survival rate in AAV patients with NFI at diagnosis  $\geq 1.24$  was lower than that in AAV patients with NFI at diagnosis  $< 1.24$  ( $P = 0.072$ ), although it was not statistically significant. This result may suggest that analysing a larger number of patients can yield statistically significant results.

How can NFI at diagnosis, which belongs to the highest quartile, show a tendency to predict ESRD during follow-up in AAV patients? Firstly, with regard to comorbidity of chronic kidney disease, AAV patients with chronic kidney disease at diagnosis showed higher NFI than those without (0.86 vs. 0.55,  $P = 0.060$ ).

Therefore, it can be assumed that NFI reflected the accompanying chronic kidney disease at diagnosis, which could have the potential to predict ESRD occurrence in AAV patients [17].

Secondly, with regard to serum albumin, high NFI means reduced serum albumin at diagnosis as described above. Reduced serum albumin, in turn, is associated with renal manifestation and increased BVAS, and furthermore is another important risk factor for ESRD [3, 18]. Using the univariable Cox hazards model analysis, serum albumin at diagnosis was significantly associated with ESRD during the follow-up period based on ESRD occurrence (HR 0.585, 95% CI 0.384, 0.890). These results support our assumption that NFI can predict ESRD through serum albumin.

Thirdly, NFI is originally an index for liver fibrosis. Nevertheless, how can it predict ESRD? Although the cells involved in liver fibrosis and renal fibrosis are different, biological factors such as cytokine and chemokine that ultimately induce and promote collagen deposition in organs may share common signal pathways in the two different fibrosis-process [9, 20]. Therefore, although it is difficult to explain the exact mechanism, it is expected that the index of liver fibrosis can predict the process of renal fibrosis to some extent.

To our best knowledge, this is the first study to demonstrate that NFI at diagnosis could independently predict all-cause mortality in immunosuppressive drug-naïve AAV patients without chronic liver diseases. The discovery of a new predictor of all-cause mortality in AAV patients is an important advantage of our research. In addition, our study was conducted in a single institution, which may be a drawback, but it is also an advantage in that chronic liver diseases at the time of diagnosis and during the follow-up period were strictly excluded from this study. However, our study has several limitations. First, although chronic liver diseases were excluded from this study, there was no information on liver fibrosis examined by transient elastography or ultrasonography in patients with high NFI. In particular, the disadvantage is that there was no serial information on liver fibrosis in deceased patients with AAV. Second, due to the limitations of a retrospective single institutional study, there is a possibility of selection bias, and missing data among clinical data could not be completely excluded.

## Conclusions

NFI at diagnosis was not associated with the cross-sectional BVAS, whereas the highest quartile of NFI at diagnosis could independently predict all-cause mortality during follow-up in immunosuppressive drug-naïve AAV patients without substantial liver diseases.

## Abbreviations

ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; BMI: body mass index; BVAS: Birmingham vasculitis activity score; C: cytoplasmic; CI: confidence interval; CRP: C-reactive protein; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear nose throat; ESR: Erythrocyte sedimentation rate; ESRD: end-stage renal disease; FCI: fibrosis cirrhosis index; FFS: five-factor score;

GPA: granulomatosis with polyangiitis; HR: hazard ratio; IFA: immunofluorescence assay; MPA: microscopic polyangiitis; MPO: myeloperoxidase; NFI: novel fibrosis index; P: perinuclear; PR3: proteinase 3; RR: relative risk; VDI: vasculitis damage index. ;

## **Declarations**

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Not applicable

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### **Availability of data and materials**

The data used and analysed in this study are available from the corresponding author on reasonable request.

### **Author's contributions**

JYP and SWL participate in research design, the writing of the final version of manuscript, and the performance of the research. JYP, SSA, LEL and SWL contributed to the acquisition of data, interpretations of data. JYP, SSA and SWL participate in the preparation of the draft manuscript. GMC conducted the statistical analyses and validate the interpretation. In particular, LEL helped with English editing. All authors read and approved the final revision of the manuscript.

### **Ethics approval**

This study was approved by the Institutional Review Board of Severance Hospital (4-2017-0673), who waived the need for patient written informed consent, as this was a retrospective study.

### **Consent to publication**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

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## Figures

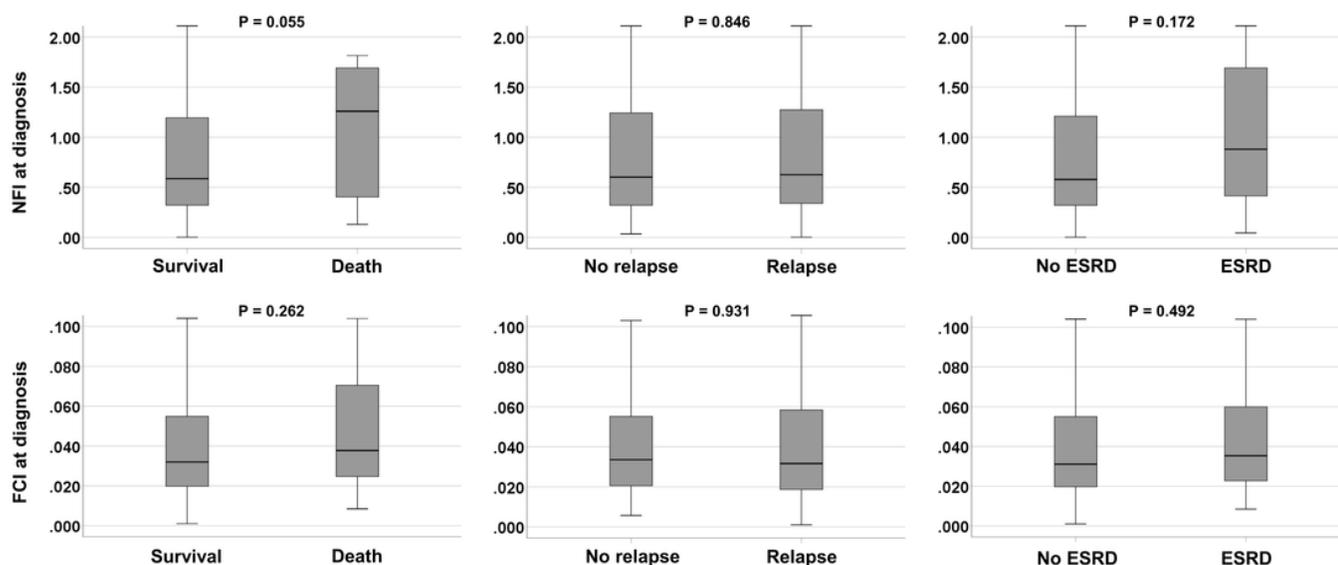
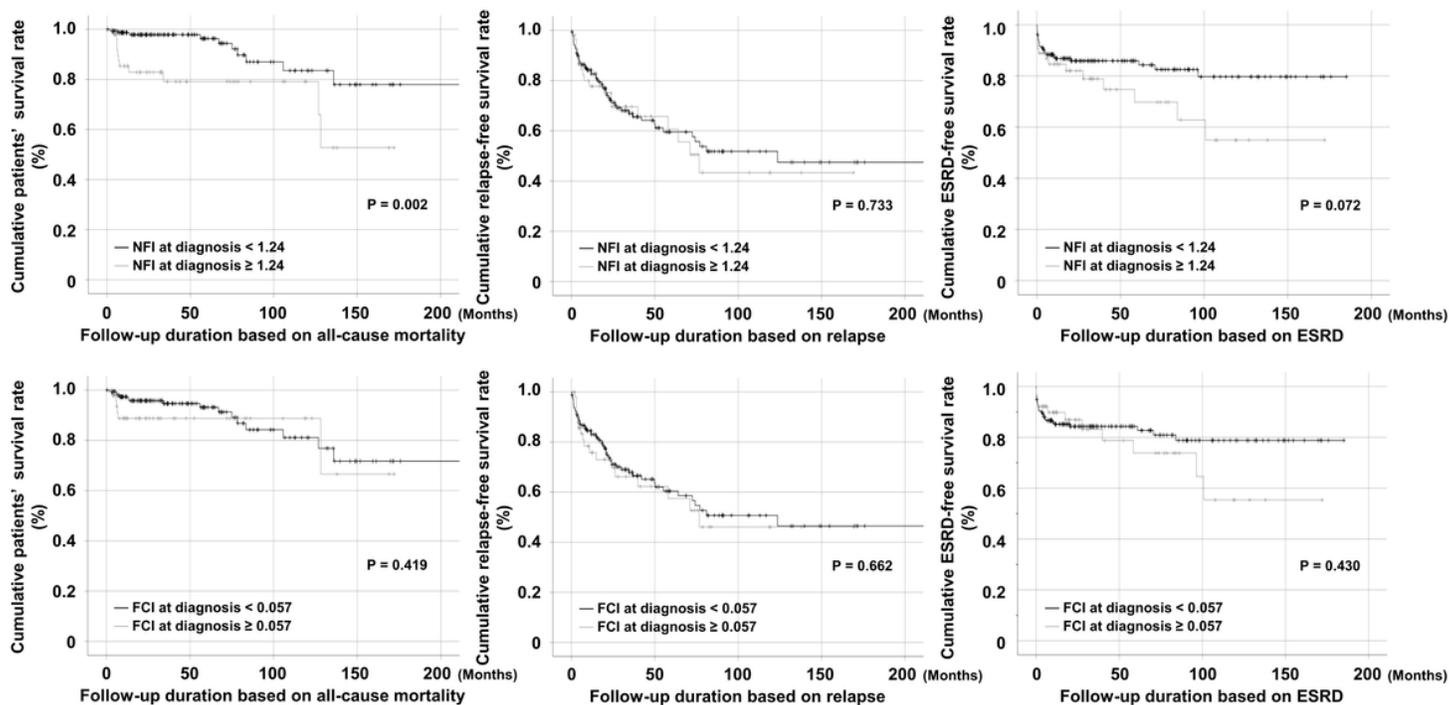


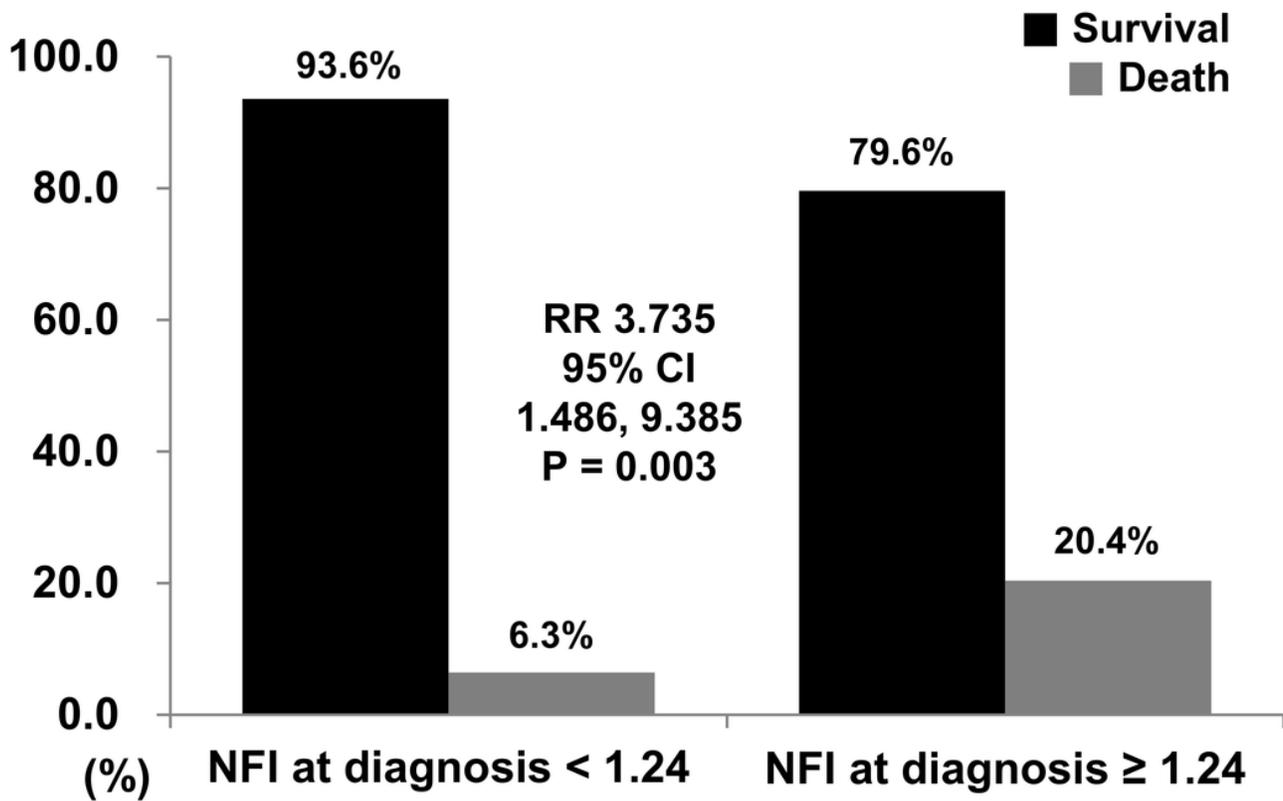
Figure 1

Comparison of FCI and NFI at diagnosis based on each poor outcome. Among six conditions, only NFI at diagnosis in deceased AAV patients tended to be increased compared to survived AAV patients but it did not reach a statistical significance. NFI: novel fibrosis index; ESRD: end-stage renal disease; FCI: fibrosis cirrhosis index.



**Figure 2**

Comparison of the cumulative survival rates. Among six conditions, it was only found that AAV patients with NFI at diagnosis  $\geq 1.24$  exhibited a significantly lower cumulative patients' survival rate than those without. NFI: novel fibrosis index; ESRD: end-stage renal disease; FCI: fibrosis cirrhosis index.



**Figure 3**

Relative Risk for all-cause mortality. AAV patients with NFI at diagnosis  $\geq 1.24$  had a significantly higher risk for all-cause mortality than those with NFI at diagnosis  $< 1.24$  (RR 3.735). NFI: novel fibrosis index; RR: relative risk; CI: confidence interval.

## Supplementary Files

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