INTRODUCTION

Plasma fibrinogen is produced by the liver, and its expression may be increased along with the inflammatory burden. For this reason, fibrinogen is considered a positive acute-phase protein similar to erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).\(^1,2\) Meanwhile, serum albumin is also produced by the liver but its expression may be decreased in response to the inflammatory burden, unlike fibrinogen. For this reason, serum albumin is categorised to a negative acute-phase protein similar to fibrinogen.
transferrin. Recently, a new concept of an inflammation-related index using these two variables, fibrinogen to albumin ratio (FAR), has been introduced. Theoretically, FAR may maximise the potential of reflecting the inflammatory burden by placing a positive acute-phase protein on the molecule and a negative acute-phase protein on the denominator. A previous study demonstrated that an inverse form of FAR, albumin to fibrinogen, was useful for monitoring the cross-sectional activity of rheumatoid arthritis, which is a typical auto-inflammatory disease. In addition to the ability to reflect the current inflammatory burden, the clinical significance of FAR as a predictor of the prognosis of several cancers has been also reported.

Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) belong to a group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). They share a common feature of small-vessel necrotising vasculitis in pathological findings; however, they present quite different clinical manifestations. MPA frequently induce rapid progressive glomerulonephritis and pulmonary capillaritis, whereas GPA primarily exhibits granulomatous inflammation in both upper and lower respiratory tracts and occasionally necrotising crescentic glomerulonephritis. Unlike MPA and GPA, EGPA has additional clinical features of allergic and eosinophilic components.

Given that FAR is an index, which is composed of reciprocal acute-phase proteins and it is proved to reflect the current inflammatory burden, it can be inferred that FAR will be useful as an index to reflect the cross-sectional activity in AAV patients. However, to our best knowledge, no study has assessed the clinical implication of FAR in patients with AAV to date. Hence, in this study, we investigated whether FAR at diagnosis could reflect the cross-sectional activity and furthermore predict poor outcomes in AAV patients.

2 | PATIENTS AND METHODS

2.1 | Patients

This study included 54 immunosuppressant drug-naïve AAV patients having the results of both plasma fibrinogen and serum albumin at the time of diagnosis. Based on the European Medicine Agency algorithm for AAV and polyarteritis nodosa proposed in 2007 and the revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides suggested in 2012, all patients were initially diagnosed with AAV at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital between October 2000 and March 2020. All patients were followed up for at least, more than 3 months from diagnosis and had no serious medical conditions such as coexisting malignancies and serious infections. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673). The need for patients’ written informed consent was waived, as this was a retrospective study.

2.2 | Clinical and laboratory data

The medical records of 54 AAV patients were retrospectively reviewed. With regard to variables at diagnosis, age, gender, AAV subtype, ANCA positivity, Birmingham vasculitis activity index (BVAS), comorbidities, acute-phase reactants and routine laboratory results were assessed. With regard to variables during follow-up, poor outcomes of AAV, such as all-cause mortality, cerebrovascular accident (CVA), cardiovascular disease (CVD) and end-stage renal disease (ESRD), were assessed. The follow-up duration was defined as the period between the time of diagnosis of AAV and the last visit for patients without poor outcomes, whereas it was defined as the period between the time of diagnosis to the occurrence of each poor outcome.

2.3 | Fibrinogen to albumin ratio

Plasma fibrinogen was measured with ACL TOP 750 CTS analyzer (Werfen, Barcelona, Spain) using clotting method, and serum albumin was measured with Siemens Atellica® CH 930 analyzer (Siemens, Munich, Germany) using Bromocresol green. FAR was calculated by dividing plasma fibrinogen by serum albumin: FAR = plasma fibrinogen (g/dl)/serum albumin (g/dl).

2.4 | 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. The correlation coefficient was obtained using the Pearson correlation analysis. The optimal cut-off was extrapolated by plotting the receiver operator characteristic (ROC) curve and selecting the maximised sum of sensitivity and specificity. Standardised coefficient (β) was determined by the univariable and multivariable linear regression analyses. Comparison of the cumulative survival rates between two groups was performed by the Kaplan-Meier survival analysis with the log-rank test. p-values < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics at diagnosis

The median age was 65.5 years, and 59.3% of patients were women. Of 54 patients, 61.1% of patients had MPA, 24.1% had GPA and 14.8% had EGPA. Forty-six of 54 patients had ANCA. The median BVAS, ESR and CRP were 13.0, 53.5 mm/h and 9.0 mg/l, respectively. The most common comorbidity was hypertension (35.2%), followed by chronic kidney disease (stage 3–5; 33.3%). The median plasma fibrinogen, serum albumin and FAR were 0.38 g/dl, 3.7 g/dl and 0.10, respectively (Table 1).
3.2 Correlation of variables at diagnosis

Fibrinogen to albumin ratio was significantly correlated with BVAS (r = 0.271), ESR (r = 0.668) and CRP (r = 0.638). However, it was not correlated with age (Figure 1).

3.3 High BVAS

Since BVAS is a continuous variable, we could not obtain the optimal cut-off of FAR at diagnosis for reflecting the high activity of AAV based on BVAS. For this reason, we arbitrarily defined the highest tertile of BVAS as high BVAS (BVAS at diagnosis ≥16).

3.4 Optimal cut-off of FAR for reflecting the cross-sectional high BVAS

Based on high BVAS, we conducted the ROC curve (area 0.639, 95% confidence interval (CI) 0.483, 0.795) and could obtain the cut-off of FAR for reflecting high BVAS at diagnosis at 0.118. When the optimal cut-off of FAR for the cross-sectional high BVAS was set as FAR at diagnosis ≥0.118, the sensitivity was 59.1% and the specificity was 71.9% (Figure 2A). When we classified AAV patients into two groups based on FAR at diagnosis ≥0.118, the cross-sectional high BVAS was identified more frequently in AAV patients with FAR at diagnosis ≥0.118 than those with FAR at diagnosis <0.118 (59.1% vs. 28.1%). Furthermore, AAV patients with FAR at diagnosis ≥0.118 had a significantly higher risk for the cross-sectional high BVAS than those with FAR at diagnosis <0.118 (RR 3.361, 95% CI 1.172, 11.626; Figure 2B).

3.5 Linear regression analysis of variables based on BVAS at diagnosis

In the univariable linear regression analysis, CRP (β = 0.383) and FAR (β = 0.297) were significantly correlated with BVAS at diagnosis. However, in the multivariable analysis, both CRP (β = 0.328) and FAR (β = 0.476) were not independently associated with BVAS at diagnosis (Table 2). Therefore, we conclude that FAR, in particular FAR at diagnosis ≥0.118, could reflect the cross-sectional the activity of AAV; however, FAR at diagnosis could not reflect independently by surpassing other variables, such as CRP, in reflecting the cross-sectional BVAS.

3.6 Comparison of the cumulative patients’ survival rate during follow-up

Since we could not obtain the cut-off of FAR at diagnosis for predicting all-cause mortality, CVA, CVD and ESRD using the ROC curve, we applied the cut-off values of FAR at diagnosis for the cross-sectional high BVAS (FAR at diagnosis ≥0.118) to the Kaplan-Meier survival analysis. When applying FAR at diagnosis ≥0.118, there was no significant difference in the cumulative patients’, CVA-free, CVD-free and ESRD-free survival rates between patients with FAR at diagnosis ≥0.118 and those without. (Figure 3).

| TABLE 1 Characteristics of 54 patients with AAV at diagnosis |
|---------------------------------------------------------------|
| **Variables** | **All patients** |
| Demographic data | |
| Age (years) | 65.5 (19.8) |
| Female gender (N, %) | 32 (59.3) |
| AAV subtypes (N, %) | |
| MPA | 33 (61.1) |
| GPA | 13 (24.1) |
| EGPA | 8 (14.8) |
| ANCA positivity (N, %) | |
| MPO-ANCA (or P-ANCA) positivity | 46 (85.2) |
| PR3-ANCA (or C-ANCA) positivity | 3 (5.6) |
| Both ANCA positivity | 1 (1.9) |
| ANCA positivity | 48 (88.9) |
| BVAS | 13.0 (9.3) |
| Organ involvement (N, %) | |
| Systemic | 26 (48.1) |
| Cutaneous | 9 (16.7) |
| Mucous membranes/eyes | 1 (1.9) |
| ENT | 23 (42.6) |
| Chest | 41 (75.9) |
| Cardiovascular | 1 (1.9) |
| Abdominal | 2 (3.7) |
| Renal | 38 (70.4) |
| Nervous system | 14 (25.9) |
| Comorbidities at diagnosis (N, %) | |
| Chronic kidney disease (stage 3–5) | 18 (33.3) |
| Diabetes mellitus | 10 (18.5) |
| Hypertension | 19 (35.2) |
| Dyslipidaemia | 7 (13.0) |
| Acute-phase reactant at diagnosis | |
| ESR (mm/h) | 53.5 (93.0) |
| CRP (mg/L) | 9.0 (96.0) |
| FAR-related variables | |
| Plasma fibrinogen (g/dl) | 0.382 (0.153) |
| Serum albumin (g/dl) | 3.7 (1.4) |
| FAR | 0.10 (0.081) |

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; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FAR, fibrinogen to albumin ratio; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3.
**FIGURE 1** Correlation between FAR and variables at diagnosis. FAR at diagnosis was significantly correlated with BVAS, ESR and CRP but not age at diagnosis. FAR, fibrinogen to albumin ratio; BVAS, Birmingham vasculitis activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

**FIGURE 2** Relative risk of FAR at diagnosis ≥0.118 for high BVAS. When the optimal cut-off of FAR for the cross-sectional high BVAS was set as FAR at diagnosis ≥0.118, AAV patients with FAR at diagnosis ≥0.118 had a significantly higher risk for the cross-sectional high BVAS than those with FAR at diagnosis <0.118 (RR 3.691). FAR, fibrinogen to albumin ratio; BVAS, Birmingham vasculitis activity score, RR, relative risk. CI, confidence interval.
**TABLE 2** Linear regression analysis of variables at diagnosis based on BVAS in patients with AAV

| Variables                              | Univariable       |                      | Multivariable     |                      |
|----------------------------------------|-------------------|----------------------|-------------------|----------------------|
|                                        | Standardized     | 95% CI               | p value           | Standardized        | 95% CI               | p value           |
|                                        | coefficient (β)   |                      |                   | coefficient (β)     |                      |                   |
| Age                                    | 0.283             | -0.001, 0.243        | 0.051             |                      |                      |                   |
| Female gender                          | -0.099            | -5.178, 2.578        | 0.503             |                      |                      |                   |
| ANCA positivity                        | 0.251             | -0.720, 10.529       | 0.086             |                      |                      |                   |
| Chronic kidney disease (stage 3-5)     | 0.183             | -1.542, 6.769        | 0.212             |                      |                      |                   |
| Diabetes mellitus                      | 0.032             | -4.603, 5.703        | 0.831             |                      |                      |                   |
| Hypertension                           | -0.084            | -5.138, 2.869        | 0.571             |                      |                      |                   |
| Dyslipidaemia                          | 1.014             | -3.086, 9.356        | 0.316             |                      |                      |                   |
| ESR                                    | 0.177             | -0.017, 0.070        | 0.229             |                      |                      |                   |
| CRP                                    | 0.383             | 0.001, 0.066         | 0.007             | 0.328                | -0.003, 0.069        | 0.074             |
| FAR                                    | 0.297             | 1.434, 61.095        | 0.040             | 0.476                | -29.072, 47.081      | 0.636             |

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham vasculitis activity score; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FAR, fibrinogen to albumin ratio; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

**FIGURE 3** Comparison of poor outcome-free survival rates. When the cut-off of FAR at diagnosis for the cross-sectional high BVAS (FAR at diagnosis ≥0.118) was applied to the Kaplan-Meier survival analysis, there was no significant difference in the cumulative patients', CVA-free, CVD-free and ESRD-free survival rates between patients with FAR at diagnosis ≥0.118 and those without. FAR, fibrinogen to albumin ratio; CVA, cerebrovascular accident; CVD, cardiovascular disease; ESRD, end-stage renal disease.
4 | DISCUSSION

In this study, we demonstrated that FAR at diagnosis could reflect the cross-sectional BVAS, as well as the inflammatory burden in patients with AAV. The advantage of this study is that a new concept indicator was applied to AAV patients for the first time, and the laboratory results that can be easily performed was used. Also, we provided the cut-off of FAR at diagnosis good enough to estimate BVAS as high as the upper tertile.

With regard to reflecting the cross-sectional activity of AAV, plasma fibrinogen and serum albumin are also well known as acute-phase proteins. Although plasma fibrinogen itself was not proved to be significantly correlated with BVAS, it was inversely correlated with serum albumin \( r = -0.304, p = 0.025 \). That is, the direct correlation between BVAS and plasma fibrinogen is not clear; however, it can be inferred that plasma fibrinogen indirectly reflects the inflammatory burden through its correlation with serum albumin. Then, why a new index called FAR was selected in this study instead of using fibrinogen or albumin itself as an index to reflect the inflammatory burden? First, in terms of fibrinogen, comparing the correlation coefficient between fibrinogen and FAR for BVAS shows that FAR has a more statistical power than fibrinogen. Therefore, FAR can be recommended and applied as a better index if only one has to be selected.

Next, in terms of albumin, in rheumatic diseases where glomerulonephritis (an increase in excreting albumin) or liver disease (a decrease in producing albumin) is not a major clinical manifestation, such as rheumatoid arthritis or ankylosing spondylitis, serum albumin may more directly reflect the inflammatory burden. However, in patients with AAV, where proteinuria is one of the main clinical signs, serum albumin may not directly reflect inflammation, and it is difficult to interpret serum albumin on inflammation because of confounding factors. Therefore, for these reasons, FAR can be a better index to reflect the inflammatory burden than each plasma fibrinogen or serum albumin. In addition, an index, which is composed of two variables that show significant correlations with BVAS, may be more flexible and reliable to reflect the inflammatory burden than only either fibrinogen or albumin is used. Moreover, FAR was not significantly different between patients with or without renal involvement \( p = 0.051 \), which means that renal involvement is not the only factor that can affect FAR of AAV patients. This result is not surprising since albumin itself is affected not only by proteinuria but also by nutritional or inflammatory status of AAV patients. Thus, in general AAV patients, FAR can still be a useful marker that is significantly correlated with the cross-sectional BVAS at diagnosis.

The clinical potential of FAR to reflect the cross-sectional BVAS was apparently proved; however, the risk of the association between FAR and BVAS could not be quantified because BVAS is a continuous variable. In this study, we quantified the effectiveness of FAR to reflect the cross-sectional BVAS via four steps: we firstly set the highest tertile of BVAS as high BVAS \( \geq 16 \) and secondly determine the cut-off of FAR for reflecting high BVAS based on BVAS. And then we thirdly obtained the cut-off FAR for high BVAS as FAR of 0.118, and finally, we revealed that AAV patients with FAR higher than 0.118 had a probability of having high BVAS 6.7 times. With these results, we concluded that FAR could effectively reflect the cross-sectional activity of AAV.

For the comparison of FAR with other inflammatory markers, we also examined the relationship of CRP and ESR with BVAS. CRP was significantly correlated with BVAS \( r = 0.296, p = 0.030 \), while ESR was independent of BVAS \( p = 0.429 \). Though CRP is one of the inflammation markers that can predict the cross-sectional BVAS, we suggest that FAR is another useful marker that is significantly correlated with BVAS. FAR can be particularly helpful when there is a discrepancy between CRP and FAR; among 22 patients with FAR \( \geq 0.118 \) at diagnosis, 4 patients had normal CRP values at diagnosis. FAR can be complementary to CRP and possibly to other inflammatory markers.

In terms of all-cause mortality, the mechanism of FAR to predict the prognosis of various cancers still remains unclear; however, several hypotheses have been provided: (a) fibrinogen may enhance cancer cell proliferation, angiogenesis and haematogenous metastasis; (b) reduced serum albumin may indicate malnutrition leading to reduced anti-cancer immunity; (c) both fibrinogen and serum albumin may reflect the link between progressive cancer entity and inflammatory microenvironment. Of the three hypotheses, by the concept of microenvironmental inflammation, FAR at diagnosis was thought to predict all-cause mortality in AAV patients; however, the results of this study concluded that it could not predict all-cause mortality.

In term of CVA and CVD, the fibrinogen is converted into fibrin fibre by thrombin and calcium ion, resulting in participating in the coagulation process. That is, it may be assumed that the fibrin fibre production might be augmented as much as fibrinogen decreased, which might accelerate the coagulation system, leading to an increase in the development of CVA and CVD during follow-up. Although FAR at diagnosis showed a pattern to predict CVA during follow-up, it did not reach statistical significance \( p = 0.185 \). The results of this study concluded that it could not predict CVA or CVD at all.

In terms of ESRD, plasma fibrin reflected the inflammatory burden well, whereas serum albumin might both reflect the inflammation and result from the persistent proteinuria owing to glomerulonephritis. Therefore, theoretically, since FAR contains serum albumin, and the initial albumin level can reflect the amount of initial proteinuria to some extent, FAR at diagnosis was expected to predict the occurrence of chronic kidney disease (stage 3–5) or ESRD during follow-up. However, the results of this study concluded that it could not predict ESRD during follow-up.

The advantage of this study is that we, for the first time, identified the clinical significance of FAR in AAV patients. In particular, in the absence of BVAS, the results of this study are meaningful in that it was the cornerstone of an attempt not to miss the high activity of AAV through close observation and monitoring by selecting patients vulnerable to the aggravation of AAV. However, there are several limitations in this study. Since this study is a single
centre retrospective study, the number of patients involved was not large enough, the confounding variables were not strictly controlled and the exact cause of the high activity of AAV could not be fully considered. Since our institution is currently managing the prospective cohort consisting of about 150 AAV patients and the Korean vasculitis study group is establishing a nationwide prospective cohort together, it will be possible to achieve the result of overcoming these limitations in the near future. In conclusion, FAR at diagnosis could reflect the cross-sectional BVAS but could not predict poor outcomes in patients with AAV.

5 | COMPETING INTEREST

No potential competing interest was reported by the authors.

DISCLOSURE STATEMENT
No potential conflict of interest was reported by the authors.

DATA AVAILABILITY STATEMENT
All data generated or analysed during this study are included in this published article and its supplementary information files.

ORCID
Sung Soo Ahn https://orcid.org/0000-0002-9002-9880
Sang-Won Lee https://orcid.org/0000-0002-8038-3341

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

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