INTRODUCTION

Clusterin is a disulphide-linked heterodimeric protein that plays an anti-apoptotic role in the cells. Clusterin plays the role of a chaperone, which enables proteins to be secreted by folding their structure. Through this mechanism, clusterin facilitates the activity of pro-apoptotic and anti-apoptotic entities.

Additionally, clusterin has been reported to play anti-inflammatory roles by downregulating the transcriptional activity of nuclear factor-kappa B (NF-κB) in several systemic autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Moreover, the concentration of clusterin was reported to be low in both active rheumatoid arthritis and systemic lupus erythematosus due to the regulation of and loss of ability to inactivate lupus-specific complements, respectively.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises vasculitis of two small vessels together with immune complex small-vessel vasculitis. AAV is characterised by necrotising vasculitis in capillaries and adja-
cent arterioles and venules and has three subtypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA).\textsuperscript{5,6} Given that the role of NF-κB in the pathogenesis of AAV is well known,\textsuperscript{7,8} it can be reasonably speculated that the serum level of clusterin might be inversely correlated with the current disease activity of AAV.

A previous study investigated new biomarkers of disease activity among serum proteins in AAV. The previous study, however, could provide no clinical significance of clusterin levels in the comparison analysis between patients with AAV and healthy controls.\textsuperscript{9} Nevertheless, given the lack of information on the relationship between serum clusterin level and the current AAV-specific indices in the previous study, we believe that it may be valuable to reassess the clinical implication of serum clusterin levels in patients with AAV. Hence, in this study, we randomly selected patients from a cohort of patients with AAV in a single centre and investigated whether serum clusterin levels could reflect the current AAV-specific indices.

**MATERIALS AND METHODS**

**Patients**

We randomly selected 57 patients with AAV from the Severance Hospital ANCA-associated Vasculitides (SHAVE) cohort, which is a prospective and observational cohort including patients with MPA, GPA, and EGPA that was established in November 2016. The diagnosis of AAV in all patients was confirmed at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, and Severance Hospital. All AAV patients in the SHAVE cohort met both the 2007 European Medicines Agency algorithms for AAV and polyarteritis nodosa and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides criteria.\textsuperscript{5,6} This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0761). To compare serum clusterin levels between patients with AAV and healthy controls, serum samples were obtained from 40 healthy controls who underwent regular check-ups at the healthcare centre of Severance Hospital. The use of clinical data from healthy controls was approved by the IRB of Severance Hospital (4-2017-0761).

**Blood collection and storage**

Whole blood was collected after obtaining patient consent and sera were isolated and stored at -80°C. All AAV-specific indices were assessed, and tests for acute phase reactants were performed on the day of blood collection.

**High disease activity**

In this study, the highest tertile of BVAS (≥16) was defined as high activity of AAV.

**Measurement of serum clusterin levels**

Serum clusterin levels were measured in stored sera using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s instructions.

**Healthy controls**

To compare serum clusterin levels between patients with AAV and healthy controls, serum samples were obtained from 40 healthy controls who underwent regular check-ups at the healthcare centre of Severance Hospital. The use of clinical data from healthy controls was approved by the IRB of Severance Hospital (4-2017-0761).

**Statistical analyses**

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with interquartile ranges, whereas categorical variables are expressed as numbers (percentages). The correlation coefficient (r) between the two variables was obtained using the Pearson’s correlation analysis. Significant differences between two continuous variables and among the three continuous variables were compared using the Mann-Whitney U test and analysis of variance test, respectively. The standardised correlation coefficient (β) was obtained by multivariable linear regression analysis using variables with statistical significance in the univariable analysis. The optimal cut-off was extrapolated by performing receiver operator characteristic (ROC) curve analysis, and one value with the maximum sum of sensitivity and specificity was selected. The relative risk (RR) of the cut-off for the high activity of AAV was analysed using contingency tables and the chi-square test. Statistical significance was set at $p<0.05$.

**RESULTS**

**Characteristics**

At the time of blood collection, the median age of patients with
AAV was 64.0 years and 19 patients were males. Twenty-nine patients had MPA, 17 had GPA, and 11 had EGPA. The median serum clusterin level was 168.2 μg/mL. AAV-specific indices, as well as clinical and laboratory data are presented in Table 1. Until blood collection, glucocorticoids, azathioprine, cyclophosphamide, and rituximab were administered to 75.9%, 29.3%, 8.6%, and 5.2% of patients with AAV, respectively.

**Correlations**
Among AAV-specific indices and acute phase reactants, SF-36 PCS score (r=0.328), SF-36 MCS score (r=0.289), BVAS (r= -0.404), ESR (r=-0.336), and CRP levels (r=-0.421) were significantly correlated with serum clusterin levels (Table 2).

**Linear regression for BVAS**
Among AAV-specific indices and serum clusterin levels, in the univariable linear regression analysis, SF-36 PCS score, SF-36 MCS score, FFS, and serum clusterin were significantly correlated with BVAS. In the multivariable analysis, both FFS $[\beta=0.412; 95\% \text{ confidence interval (CI)} 1.258, 4.910]$ and serum clusterin level ($[\beta=-0.250; 95\% \text{ CI} -0.056, -0.001]$) were significantly associated with BVAS in patients with AAV (Table 3).

**Comparison of serum clusterin levels between patients with AAV and BVAS≥16 and those with BVAS<16**
Serum clusterin levels were compared between patients with AAV and BVAS<16 and those with BVAS≥16. Patients with high AAV activity exhibited significantly lower serum clusterin levels than did those with low AAV activity (159.3 μg/mL vs. 185.0 μg/mL, $p=0.017$) (Fig. 1A). However, there was no significant difference in serum clusterin levels among AAV subtypes.

**Comparison of serum clusterin levels among three AAV subtypes**
The median serum clusterin levels were 167.9 μg/mL, 191.1 μg/mL, and 165.7 μg/mL in MPA, GPA, and EGPA patients, respectively. There were no significant differences among the three groups (Supplementary Fig. 1, only online).

**Comparison of serum clusterin levels based on organ involvement**
Patients with AAV who had general manifestations exhibited a significantly lower serum clusterin level than did those without general manifestations (162.0 μg/mL vs. 185.3 μg/mL; $p=0.031$). Additionally, patients with AAV who had pulmonary manifestations showed a significantly lower serum clusterin level than did those without pulmonary manifestations (164.6 μg/mL vs. 205.1 μg/mL; $p=0.038$) (Supplementary Table 1, only online).

**Optimal cut-off of serum clusterin level**
Using the ROC curve (area 0.704; 95% CI 0.559, 0.849; $p=0.017$),

### Table 1. Characteristics of 57 Patients with AAV

| Variables at the time of blood collection | Values |
|------------------------------------------|--------|
| **Demographic data**                     |        |
| Age (yr)                                 | 64.0 (21.0) |
| Male sex                                 | 19 (33.3) |
| **AAV subtypes**                         |        |
| MPA                                      | 29 (50.9) |
| GPA                                      | 17 (29.8) |
| EGPA                                     | 11 (19.3) |
| **ANCA positivity**                      |        |
| MPO-ANCA (or P-ANCA) positivity          | 33 (57.9) |
| PR3-ANCA (or C-ANCA) positivity          | 6 (10.5) |
| Both ANCA                                | 1 (1.8) |
| ANCA negativity                          | 14 (24.6) |
| No results                               | 5 (8.8) |
| **AAV-specific indices**                 |        |
| SF-36 PCS                                 | 50.9 (36.6) |
| SF-36 MCS                                 | 54.5 (36.1) |
| BVAS                                     | 11.0 (11.0) |
| FFS                                      | 0 (2.0) |
| VDI                                      | 3.0 (2.0) |
| **Clinical manifestations**              |        |
| General                                   | 25 (43.9) |
| Cutaneous                                 | 9 (15.8) |
| Mucous/eye                                | 1 (1.8) |
| Otorhinolaryngologic                     | 24 (42.1) |
| Pulmonary                                 | 41 (71.9) |
| Cardiovascular                            | 4 (7.0) |
| Gastrointestinal                          | 2 (3.5) |
| Renal                                     | 32 (56.1) |
| Nervous                                   | 18 (31.6) |
| **Acute phase reactants**                |        |
| ESR (mm/hr)                               | 29.0 (67.0) |
| CRP (mg/L)                                | 3.0 (36.7) |
| Serum clusterin (μg/mL)                  | 168.2 (65.7) |
| **Until blood collection**               |        |
| Disease duration (months)                 | 0.6 (6.7) |
| Immunosuppressive drugs administered     |        |
| Glucocorticoids                           | 44 (75.9) |
| Cyclophosphamide                          | 5 (8.6) |
| Rituximab                                 | 3 (5.2) |
| Azathioprine                              | 17 (29.3) |
| Mycophenolate mofetil                     | 0 (0) |
| Tacrolimus                                | 0 (0) |
| Methotrexate                              | 1 (1.7) |

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; SF-36, short-form 36-item; PCS, physical component summary; MCS, mental component summary; BVAS, Birmingham vasculitis activity score; FFS, five-factor score; VDI, vasculitis damage index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Values are expressed as median (interquartile range) or n (%).
130.45 μg/mL was identified as the optimal serum clusterin cut-off level for high activity of AAV (sensitivity 90.2% and specificity 43.7%) (Fig. 1B).

Relative risk
When we divided the patients with AAV into two groups based on the cut-off of serum clusterin level, 16 of 57 patients with AAV were included in the group with serum clusterin level ≤130.45 μg/mL. High AAV activity was identified more frequently in patients with serum clusterin level ≤130.45 μg/mL than in those with serum clusterin level >130.45 μg/mL (43.8% vs. 9.8%; p=0.003). Furthermore, patients with serum clusterin level ≤130.45 μg/mL had a significantly higher risk for high activity of AAV than did those with serum clusterin level >130.45 μg/mL (RR 7.194; 95% CI 1.725, 30.010) (Fig. 1C).

Comparing serum clusterin levels between patients with AAV and healthy controls
Patients with AAV exhibited significantly lower serum clusterin levels than did healthy controls (168.2 μg/mL vs. 230.5 μg/mL; p<0.001) (Fig. 2).

DISCUSSION
In this study, we investigated whether serum clusterin level could reflect the current AAV-specific indices in patients with AAV and obtained several important findings: 1) serum clusterin level was significantly correlated with SF-36 PCS score, SF-36 MCS score, and BVAS among AAV indices; 2) patients with AAV who had the highest tertile of BVAS exhibited a lower serum clusterin than did those without the highest tertile of BVAS; 3) patients with AAV who had serum clusterin levels ≤130.45 μg/mL had a significantly higher risk for high activity of AAV than did those with serum clusterin levels >130.45 μg/mL (RR 7.194); 4) patients with AAV exhibited a significantly lower serum clusterin levels than did healthy controls (168.2 μg/mL vs. 230.5 μg/mL; p<0.001) (Fig. 2).

Table 2. Correlation between Serum Clusterin and Continuous Variables at Blood Collection in AAV Patients

| Variables at the time of blood collection | Correlation coefficient (r) | p value |
|-----------------------------------------|-----------------------------|---------|
| Demographic data                        |                             |         |
| Age (yr)                                | 0.037                       | 0.787   |
| AAV-specific indices                    |                             |         |
| SF-36 PCS                               | 0.328                       | 0.013   |
| SF-36 MCS                               | 0.289                       | 0.029   |
| BVAS                                    | -0.404                      | 0.002   |
| FFS                                     | -0.214                      | 0.110   |
| VDI                                     | -0.180                      | 0.180   |
| Acute phase reactants                   |                             |         |
| ESR (mm/hr)                             | -0.336                      | 0.013   |
| CRP (mg/L)                              | -0.421                      | 0.001   |

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; SF-36, short-form 36-item; PCS, physical component summary; MCS, mental component summary; BVAS, Birmingham vasculitis activity score; FFS, five-factor score; VDI, vasculitis damage index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 3. Linear Regression Analysis of AAV-Specific Indices and Serum Clusterin for the Current BVAS in Patients with AAV

| Variables | Univariable | Multivariable |
|-----------|-------------|---------------|
|           | Beta        | 95% CI        | p value | Beta        | 95% CI        | p value |
| SF-36 PCS | -0.375      | -0.183, -0.037| 0.004   | -0.133      | -0.143, 0.065 | 0.454   |
| SF-36 MCS | -0.306      | -0.189, -0.017| 0.019   | -0.077      | -0.138, 0.087 | 0.648   |
| FFS       | 0.490       | 1.916, 5.408  | <0.001  | 0.412       | 1.258, 4.910  | 0.001   |
| VDI       | 0.144       | -0.492, 1.661 | 0.282   | 0.003       | -0.962, 0.989 | 0.978   |
| Clusterin | -0.343      | 0.000, 0.000  | 0.008   | -0.250      | -0.056, -0.001| 0.043   |

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; BVAS, Birmingham vasculitis activity score; SF-36, short-form 36-item; PCS, physical component summary; MCS, mental component summary; FFS, five-factor score; VDI, vasculitis damage index; CI, confidence interval.
lower serum clusterin level than did healthy controls. Based on these results, we concluded that serum clusterin level could reflect the current SF-36 score and BVAS and serum clusterin level below the optimal cut-off might indicate high activity of AAV.

We contemplated how serum clusterin levels reflect the current BVAS in patients with AAV (Table 3 and Fig. 1C) and why it was lower in patients with AAV compared to healthy controls (Fig. 2). Although the function of secreted clusterin is not fully understood, it is known that secreted clusterin has an anti-apoptotic role in the regulation of cell proliferation and extracellular tissue remodelling.14 We drew the following three hypotheses for low serum clusterin levels in patients with AAV and their reflection to BVAS. The first hypothesis is that intracellular signal transduction is inhibited during inflammation. Clusterin may stabilise IκB, which in turn reduces transcription of the NF-κB genes, increasing in the anti-inflammatory process.15

On the other hand, in the introduction section, we described that clusterin has been reported to play anti-inflammatory roles by downregulating the transcriptional activity of NF-κB in several autoimmune inflammatory diseases. However, due to the limitation of the one-time cross-sectional study being designed as a pilot study, we could not additionally measure the serum concentration of the biomarker that can directly reflect the expression level of the NF-κB downstream gene. Meanwhile, a previous study reported that the over-expression of NF-κB could the production of endogenous CRP.16 Based on these results, it may be inferred that serum CRP could indirectly reflect the degree of activation of NF-κB. In summary, it can be hypothesized that clusterin may reduce the transcriptional activity of NF-κB, which leads to a decrease in the production of endogenous CRP. The result that serum clusterin showed a significant inverse correlation with serum CRP ($r=-0.336$, $p=0.013$) may support this hypothesis (Table 2).

The second hypothesis was based on the repolarisation of macrophages. Clusterin may repolarise M1 macrophages (pro-inflammatory) to M2 macrophages (anti-inflammatory). Therefore, low serum clusterin level may lead to inflammatory microenvironments with diminished phagocytic activity, and thereby reducing the clearance of dead cells.17 The last hypothesis was based on the interaction between clusterin and the complement pathway. A low level of clusterin activates the complement pathway, and therefore, more C5b is required by splitting C5.18 This status leads to an increase in C5a, which could form a vicious circle of accelerating the inflammatory process in the pathogenesis of AAV.19

Additionally, we contemplated how serum clusterin level was significantly correlated with the current SF-36 PCS and SF-36 MCS scores. In this study, serum clusterin levels were significantly correlated with BVAS, SF-36 PCS score, and SF-36 MCS score (Table 2). Additionally, BVAS was significantly correlated with both SF-36 PCS and SF-36 MCS scores (Table 3). That is, a triangular correlation was formed among serum clusterin, BVAS, as well as SF-36 PCS and SF-36 MCS scores. To elucidate the relationship between serum clusterin level, BVAS, and SF-36 scores, we conducted univariable and multivariable linear regression analyses with AAV-specific indices and serum clusterin level for the current SF-36 PCS score.

In the univariable analysis, BVAS ($r=-0.374$) and serum clusterin level ($r=0.328$) were significantly correlated with SF-36 PCS score. FFS tended to be correlated with serum clusterin level; however, it did not reach statistical significance ($p=0.063$). Given its $p$-value and clinical significance, we performed the multivariable analysis twice. In the multivariable analysis without FFS, only BVAS ($β=-0.289$, 95% CI -1.914, -0.061) was significantly associated with SF-36 PCS score. However, in another multivariable analysis with FFS, none of the variables were associated with SF-36 PCS score (Supplementary Table 2, only online). Based on these results, we concluded that unlike the direct correlation between serum clusterin level and BVAS, serum clusterin level is thought to have an indirect relationship with SF-36 PCS score.

A previous study known as the “the Rituximab in ANCA-Associated Vasculitis (RAVE)” trial, compared the serum levels of 28 proteins in patients with AAV with an active status, those in remission, and healthy controls, and found no difference in serum clusterin levels between them.3 However, our cross-sectional observational study revealed that serum clusterin levels in patients with AAV were significantly lower than those in healthy controls. We attribute this discrepancy to ethnic and geographical differences; only one Asian patient with AAV was included in the RAVE study.20 Therefore, we think that the discrepancy between the results of the RAVE study and our study does not necessarily mean that our study is less convincing. Rather, considering the racial and geographic situation in which Korean AAV patients need to be treated, we view this discrepancy as valuable information that provides insight to a new phenomenon.

EGPA has different pathogenesis and treatment strategies
compared to MPA and GPA. For this reason, large-scale clinical studies are sometimes conducted with only MPA and GPA patients. Therefore, we included only 29 MPA patients and 17 GPA patients and analysed them again. In the correlation analysis, serum clusterin was significantly correlated with BVAS (r=−0.399, p=0.006), ESR (r=−0.384, p=0.010), and CRP (r=−0.478, p=0.001). In the ROC curve of serum clusterin for BVAS ≥16 (area 0.723; 95% CI 0.572, 0.874; p=0.014), 130.45 μg/mL was also identified as the optimal serum clusterin cut-off level for high activity of MPA and GPA (sensitivity 93.3% and specificity 43.7%). MPA and GPA patients with serum clusterin level ≤130.45 μg/mL had a significantly higher risk for high activity of MPA and GPA than did those with serum clusterin level >130.45 μg/mL (RR 10.889; 95% CI 1.908, 62.144). This result implies that the RR of the cut-off of serum clusterin in patients with MPA and GPA was statistically more convincing than that in patients with all subtypes of AAV. Lastly, we compared serum clusterin levels between MPA and GPA patients and healthy controls. Similar to the comparison analysis between AAV patients and healthy controls, MPA and GPA patients exhibited significantly lower serum clusterin levels compared to healthy controls (168.2 μg/mL vs. 230.5 μg/mL; p=0.003).

Overall, the results of this additional analysis were not different from those in all AAV patients. In addition, the discovery of biomarkers for AAV patients, not limited to MPA and GPA, has two clinical advantages. One is that it can be applied clinically even if the subtype has not yet been finalized in the course of AAV diagnosis. The other is that, albeit rare, there may be a case of alteration of the AAV subtype during follow-up. Even in this case, it can be continuously applied to clinical trials. For this reason, we believe the results of our study, which included all AAV patients, are convincing enough, compared to those including only patients with MPA and GPA.

Among the nine clinical items of BVAS, general manifestations and pulmonary manifestations were associated with low levels of serum clusterin in the same pattern of correlation as BVAS. In addition, when the correlation between the sum of each clinical item and serum clusterin level was investigated, the sum of general manifestations (r=−0.333, p=0.011) and pulmonary manifestations (r=−0.262, p=0.049) showed significant inverse correlations with serum clusterin level. Therefore, although it is challenging to elucidate the exact mechanism, it can be predicted that general manifestations and pulmonary manifestations contribute to the inverse correlation between BVAS and serum clusterin level.

The immunological roles of the NK-κB signalling and the complement pathway in the pathogenesis of renal involvement of AAV are well established. Therefore, according to the hypothesis of an anti-inflammatory action to reduce NF-κB signalling by stabilizing IκB, serum clusterin levels in AAV patients with renal involvement should have been lower than those without renal involvement; however, there was no significant difference between the two groups. Here, we raise two questions. First, would the results be different if only MGA and GPA patients were included? Similar to the results of the analysis including all subtypes of AAV patients, serum clusterin levels in MPA and GPA patients with renal involvement were higher than those without renal involvement, but it did not reach statistical significance (184.8 μg/mL vs. 163.1 μg/mL, p=0.319). Second, should NF-κB signalling, which determines serum clusterin levels, only be associated with renal involvement? The mechanisms of NF-κB signalling and renal injury are well established. On the other hand, like kidney injury through NF-κB, NF-κB signalling is known to play an important role in lung injury. In this study, the frequency of pulmonary involvement was higher than that of renal involvement (71.9% vs. 56.1%). This difference may be the reason for the discrepancy between the expected association between renal invasion and serum clusterin levels by NF-κB signalling and the results of this study.

The primary limitations of the current study are its cross-sectional design and the small number of patients included in the study. In this study, the longitudinal and serial measurement of serum clusterin was not performed. We believe that a future prospective study that measures serum clusterin levels using paired samples before and after treatments and includes a larger number of patients with AAV will provide more valuable clinical information on the implications of serum clusterin levels for patients with AAV.

In conclusion, serum clusterin levels were detected at a lower concentration in the sera of patients with AAV than in those of healthy controls and could reflect the current disease activity in patients with AAV. We believe that serum clusterin level will be a useful biomarker for assessing the current activity of AAV and expect that it will help elucidate the pathophysiology of AAV.

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