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Clinical application of low erythrocyte sedimentation rate/ high C-reactive protein to antineutrophil cytoplasmic antibody-associated vasculitis

Pil Gyu Park[1] 🔘 | Jason Jungsik Song[1,2] 🔘 | Yong-Beom Park[1,2] 🔘 | Sang-Won Lee[1,2] 🔘

[1]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

[2]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea

Correspondence
Sang-Won Lee, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722 Seoul, Korea.
Email: sangwonlee@yuhs.ac

Abstract

Background: This study investigated whether the discordance between erythrocyte sedimentation rate (ESR) and C-reactive protein at diagnosis could estimate the simultaneous clinical and laboratory variables and predict the poor outcomes during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods: The medical records of 254 AAV patients were reviewed. Clinical and laboratory and AAV-specific indices at diagnosis and all-cause mortality, relapse and end-stage renal disease during follow-up were obtained. ESR and CRP levels were categorised as high and low based on the median values. Accordingly, the patients were divided into the following four groups: high ESR/low CRP; low ESR/high CRP; low ESR/low CRP; and high ESR/high CRP.

Results: Of the 254 AAV patients, 51 patients exhibited discordance between ESR and CRP. Among the 51 AAV patients, the median age was 59.0 years, and 20 patients were men (29 MPA, 13 GPA and 9 EGPA). Cardiovascular and nervous systemic manifestations were observed more frequently in AAV patients with low ESR/high CRP than in those with high ESR/low CRP. Six patients from the low ESR/high CRP group died. AAV patients with low ESR/high CRP exhibited significantly lower cumulative patients' survival rates than both those with high ESR/low CRP and those with low ESR/low CRP. Also, AAV patients with low ESR/high CRP exhibited significantly higher simultaneous BVAS than those with low ESR/low CRP.

Conclusions: Low ESR/high CRP at diagnosis could not only estimate the simultaneous high BVAS but also predict all-cause mortality during follow-up in AAV patients.

KEYWORDS
antineutrophil cytoplasmic antibody, C-reactive protein, erythrocyte sedimentation rate, mortality, vasculitis

1 | INTRODUCTION

Currently, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most widely used biomarkers for detecting the inflammatory burden.[1] ESR is determined by the rouleaux formation of the red blood cells (RBCs), which is induced by fibrinogen and it depends on the negative charge repulsion of the RBCs. Therefore, ESR may be altered according to the concentration of fibrinogen, the number, size and shape of the RBCs and immunoglobulins.[2] Moreover, it may be affected by the amount and concentration of inflammation-related proteins. During the acute inflammation period, the levels of ceruloplasmin, haptoglobin, alpha-2-macroglobulin and complement 3 increase, whereas those of albumin and transferrin decrease.[3] ESR begins to rise within 24–48 h from the onset of inflammation and declines slowly in the 2–3 weeks following resolution of inflammation, resulting in the persistent elevation of ESR until 2 or 3 weeks after the onset of inflammation.[4] Therefore, the limitation of ESR as a biomarker is that its sensitivity and specificity are not high enough to detect acute or recent inflammation at the onset of inflammation.

C-reactive protein, known to play a role in the host immunity against infection, is produced by the liver in response to pro-inflammatory cytokines, particularly, interleukin-6 secreted by macrophages and T cells.[1,5] CRP level is primarily affected by the extent of inflammation, but it may also be influenced by malignancies, infections and other serious medical conditions such as cardiovascular diseases.[6,7] CRP begins to rise within several hours from the initiation of inflammation and falls quickly owing to its short half-life of 19 h after the termination of inflammation.[2] Hence, CRP is preferably used as a marker to detect acute and recent inflammation and to evaluate therapeutic efficacy. Despite the discordance between ESR and CRP, they are still widely used for screening acute and recent inflammation.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a typical small-vessel vasculitis that affects capillaries, adjacent arterioles and venules.[8] AAV is categorised into three subtypes according to the clinical, laboratory, radiological and histological features: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA).[8,9] Since AAV may invade almost all the major organs and lead to inflammation and fibrotic changes, both ESR and CRP are currently used to monitor the intensity and extent of inflammation at every visit in actual clinical settings.

A previous study investigated the clinical implications of the discordance between ESR and CRP in various diseases such as rheumatoid arthritis, systemic lupus erythematosus and infections, and reported that cases with the highest tertile of ESR and the lowest tertile of CRP were associated with infection and renal insufficiency.[10] The Birmingham vasculitis activity score (BVAS) is a standardised system for assessing the activity of AAV. Since it takes into consideration the newly developed, worsened or persistent clinical and laboratory data from the last 4 weeks,[11] it may correlate better with either ESR or CRP, depending on the time of the onset of inflammation. In other words, it is expected that the discordance between the two acute-phase reactants may be observed in AAV patients. However, there

has been no study on the clinical implications of the discordance between ESR and CRP in AAV patients. Hence, in this study, we investigated whether the discordance between ESR and CRP, such as high ESR/low CRP and low ESR/high CRP at diagnosis could estimate the simultaneous clinical and laboratory variables and predict the poor outcomes during follow-up in patients with AAV.

2 | PATIENTS AND METHODS

2.1 | Study subjects

We reviewed the medical records of 256 AAV patients who fulfilled the inclusion and exclusion criteria of this study. The inclusion criteria were as follows: i) diagnosis of MPA, GPA or EGPA at the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital between October 2000 and March 2021; ii) fulfilment of both the classification algorithm for AAV and polyarteritis nodosa proposed by the European Medicine Agency in 2007 (the 2007 algorithm) and the revised nomenclature of vasculitides suggested by the Chapel Hill Conference Consensus in 2012 (the 2012 definitions)[8,9]; iii) availability of medical records containing clear information for collecting clinical and laboratory data including perinuclear (P) or myeloperoxidase (MPO)-ANCA and cytoplasmic (C)- or proteinase 3 (PR3)-ANCA positivity and for assessing AAV-specific indices, BVAS and five-factor score (FFS) at diagnosis[11,12]; and iv) availability of both ESR and CRP results at diagnosis. The exclusion criteria were as follows: i) the follow-up duration <3 months; ii) presence of serious medical conditions to affect ANCA positivity or mimic AAV at the time of diagnosis of AAV, such as malignancies, infections and systemic vasculitides other than AAV; and iii) treatment with immunosuppressive drug at diagnosis.

Of the 256 AAV patients, 2 were excluded from this study due to the absence of ESR and CRP results. Finally, 254 AAV patients were included. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4–2020–1071). Given the retrospective design of the study and the use of anonymised patient data, the requirement for written informed consent was waived.

2.2 | Data at diagnosis

The demographic data collected included age, sex and smoking history. The data regarding AAV subtypes, ANCAs, AAV-specific indices, and clinical manifestations based on the BVAS system and comorbidities were collected. The results of ESR, CRP and routine laboratory tests were also obtained (Table 1). Immunoassays were used as the primary screening method for ANCA. However, when patients tested negative for ANCA by an antigen-specific assay but positive for perinuclear (P)-ANCA or cytoplasmic (C)-ANCA by an indirect immunofluorescence assay, they were considered to have MPO-ANCA or PR3-ANCA, especially when AAV was strongly suspected based on the clinical and laboratory features.[13]

TABLE 1 Characteristics of 51 AAV patients with discordance between ESR and CRP

Variables	Values
At the time of diagnosis	
Demographic data	
Age (years)	59.0 (27.0)
Male sex (N, (%))	20 (39.2)
Smoking history (N, (%))	3 (5.9)
AAV subtypes (N, (%))	
MPA	29 (56.9)
GPA	13 (25.5)
EGPA	9 (17.6)
ANCA positivity (N, (%))	
MPO-ANCA (or P-ANCA) positive	33 (64.7)
PR3-ANCA (or C-ANCA) positive	10 (19.6)
Both ANCA positive	3 (5.9)
ANCA negative	11 (21.6)
AAV-specific indices	
BVAS	15.0 (10.0)
FFS	1.0 (1.0)
Clinical manifestations (N, (%))	
General manifestations	23 (45.1)
Cutaneous manifestations	12 (23.5)
Mucous and ocular manifestations	3 (5.9)
Otorhinolaryngologic manifestations	26 (51.0)
Pulmonary manifestations	33 (64.7)
Cardiovascular manifestations	9 (17.6)
Gastrointestinal manifestations	3 (5.9)
Renal manifestations	35 (68.6)
Nervous systemic manifestations	18 (35.3)
Comorbidities (N, (%))	
Chronic kidney disease without RRT	16 (31.4)
Diabetes mellitus	14 (27.5)
Hypertension	22 (43.1)
Dyslipidaemia	9 (17.6)
Acute phase reactants	
ESR (mm/hr)	58.0 (49.0)
CRP (mg/L)	14.0 (23.0)
Laboratory results	
White blood cell count (/mm^3)	8660.0 (6862.5)
Haemoglobin (g/dl)	11.5 (3.5)
Platelet count (×1000/mm^3)	265.5 (129.3)
Fasting glucose (mg/dl)	101.0 (43.0)
Blood urea nitrogen (mg/dl)	18.6 (28.2)
Creatinine (mg/dl)	1.0 (2.2)
Total protein (g/dl)	6.6 (1.3)
Serum albumin (g/dl)	3.8 (0.8)

TABLE 1 (Continued)

Variables	Values
Alkaline phosphatase (IU/L)	75.5 (46.5)
Aspartate aminotransferase (IU/L)	18.0 (8.5)
Alanine aminotransferase (IU/L)	16.0 (16.3)
During the follow-up duration	
Poor outcomes (N, (%))	
All-cause mortality	6 (11.8)
Relapse	20 (39.2)
ESRD	11 (21.6)
Follow-up duration based on each poor outcomes (months)	
All-cause mortality	26.7 (63.8)
Relapse	11.2 (31.2)
ESRD	17.3 (36.0)
Medications (N, (%))	
Glucocorticoids	50 (98.0)
Cyclophosphamide	29 (56.9)
Rituximab	11 (21.6)
Mycophenolate mofetil	9 (17.6)
Azathioprine	25 (49.0)
Tacrolimus	6 (11.8)
Methotrexate	3 (5.9)
Plasma exchange	10 (19.6)

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

Abbreviations: AAV, ANCA-associated vasculitis; ACS, acute coronary syndrome; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham vasculitis activity score; C, cytoplasmic; CRP, C-reactive protein; CVA, cerebrovascular accident; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; ESRD, end-stage renal disease; FFS, five-factor score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; RRT, renal replacement therapy.

2.3 | Data during follow-up

The poor outcomes of AAV include all-cause mortality, relapse and end-stage renal disease (ESRD). All-cause mortality is defined as death of any aetiology, and relapse is defined as the increased activity after the achievement of remission. ESRD is defined as a medical condition requiring renal replacement therapy. The follow-up duration based on mortality in this stud was defined as the period from AAV diagnosis to death in deceased patients. The follow-up durations based on relapse and ESRD were defined as the periods from AAV diagnosis to the time of relapse and the initial renal replacement therapy in patients with relapse and ESRD respectively. For patients without the poor outcomes, the follow-up duration was defined as the period from AAV diagnosis to the last visit in surviving patients. The medications that were administered were also reviewed.

2.4 | Stratification based on ESR and CRP at diagnosis

Due to the small sample size in this study, tertile stratification was not allowed; hence, the ESR and CRP levels were categorised as high and low based on the median values. Accordingly, the patients were divided into the following four groups: high ESR/low CRP; low ESR/high CRP; low ESR/low CRP; and high ESR/high CRP. Of the 254 AAV patients, 51 exhibited the discrepancies between ESR and CRP, of which 25 and 26 patients presented high ESR/low CRP and low ESR/high CRP, respectively, at diagnosis.

2.5 | Statistical analyses

All statistical analyses were performed using IBM Statistical Product and Service Solutions Statistics for Windows, version 25 (IBM Corp.). Continuous variables are expressed as medians with interquartile ranges, whereas categorical variables are expressed as numbers (percentages). Significant differences between the two categorical variables were analysed using the chi-square and Fisher exact tests. The Mann-Whitney U test was used to compare significant differences between two continuous variables. Significant differences among more than three continuous variables were investigated using the Kruskal-Wallis test. Comparison of the cumulative survival rates between the two groups was performed using the Kaplan-Meier survival analysis with the log-rank test. p values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of AAV patients with the discordance between ESR and CRP (N = 51)

The characteristics of the AAV patients with the discordance between ESR and CRP are described in Table 1. At diagnosis, the median age of the patients was 59.0 years, and 20 patients were men. Of the 51 patients, 29, 13 and 9 were diagnosed with MPA, GPA and EGPA respectively. The median values of BVAS, FFS, ESR and CRP were 15.0, 1.0, 58.0 mm/h and 14.0 mg/L respectively. During an average follow-up of 26.7 months, 6 patients died of any cause.

3.2 | Comparison of variables between AAV patients with high ESR/low CRP and high ESR/low CRP

There were no significant differences in the demographic data, AAV subtypes, ANCA positivity and AAV-specific indices at diagnosis between the groups with the discordance in ESR and CRP. Particularly, AAV patients with low ESR/high CRP at diagnosis tended to have a higher simultaneous BVAS than those with high

ESR/low CRP, although the difference was not statistically significant. Regarding the clinical manifestations based on the BVAS system at diagnosis, cardiovascular and nervous systemic manifestations were observed more frequently in AAV patients with low ESR/high CRP than in those with high ESR/low CRP (30.8% vs. 4.0% and 50.0% vs. 20.0% respectively). Regarding the laboratory test results at diagnosis, AAV patients with high ESR/low CRP had a significantly higher level of total protein than those with low ESR/high CRP (6.8 g/dl vs. 6.3 g/dl). The analysis of the poor outcomes during follow-up revealed that only 6 patients from the low ESR/high CRP group died (Table 2).

3.3 | Comparison of cumulative each poor outcome-free survival rates between AAV patients with high ESR/low CRP and those with high ESR/low CRP

Associated vasculitis patients with low ESR/high CRP exhibited a significantly lower cumulative patients' survival rate than those with high ESR/low CRP (p = 0.034). However, there were no significant differences in the cumulative relapse-free and ESRD-free survival rates between the two groups (Figure 1).

3.4 | Comparison of cumulative patients' survival rates among 254 AAV patients with the discordance or concordance between ESR and CRP

Associated vasculitis patients were divided into four groups according to high or low levels of ESR and CRP, and in whom cumulative patients' survival rates were compared among four groups. AAV patients with low ESR/high CRP exhibited significantly lower cumulative patients' survival rates than both those with high ESR/low CRP and those with low ESR/low CRP (Figure 2).

3.5 | Comparison of BVAS among the four groups

Among the four groups, AAV patients with low ESR/high CRP (group 2) exhibited significantly higher simultaneous BVAS than those with low ESR/low CRP (18.0 vs. 9.0) (Figure 3). The high CRP level seemed to contribute to the high BVAS in this study.

4 | DISCUSSION

There are three differences between the clinical implications of a previous study and this study.[10] First, the previous study identified the discordance between ESR and CRP in 87 out of 2069 patients with various medical conditions. In contrast, our study included 254 patients with AAV and identified the discordance between ESR and CRP in 51 of them. Therefore, it can be said our study has an

TABLE 2 Comparison of variables between AAV patients with high ESR/low CRP and those with low ESR/high CRP

Variables	AAV patients with high ESR/low CRP (N = 25)	AAV patients with low ESR/high CRP (N = 26)	p-value
At the time of diagnosis			
Demographic data			
Age (years)	59.0 (25.5)	57.0 (29.5)	0.925
Male sex (N, (%))	8 (32.0)	12 (46.2)	0.301
Smoking history (N, (%))	0 (0)	3 (11.5)	0.235
AAV subtypes (N, (%))			
MPA	15 (60.0)	14 (53.8)	0.664
GPA	5 (20.0)	8 (30.8)	
EGPA	5 (20.0)	4 (15.4)	
ANCA positivity (N, (%))			
MPO-ANCA (or P-ANCA) positive	19 (76.0)	14 (53.8)	0.098
PR3-ANCA (or C-ANCA) positive	2 (8.0)	8 (30.8)	0.075
Both ANCA positive	0 (0)	3 (11.5)	0.235
ANCA negative	4 (16.0)	7 (26.9)	0.499
AAV-specific indices			
BVAS	13.0 (6.0)	18.0 (13.3)	0.113
FFS	1.0 (2.0)	1.0 (1.0)	0.402
Clinical manifestations (N, (%))			
General manifestations	9 (36.0)	14 (53.8)	0.224
Cutaneous manifestations	7 (28.0)	5 (19.2)	0.460
Mucous and ocular manifestations	0 (0)	3 (11.5)	0.235
Otorhinolaryngologic manifestations	13 (52.0)	13 (50.0)	0.886
Pulmonary manifestations	17 (68.0)	16 (61.5)	0.629
Cardiovascular manifestations	1 (4.0)	8 (30.8)	0.024
Gastrointestinal manifestations	0 (0)	3 (11.5)	0.235
Renal manifestations	19 (76.0)	16 (61.5)	0.266
Nervous systemic manifestations	5 (20.0)	13 (50.0)	0.025
Comorbidities (N, (%))			
Chronic kidney disease without RRT	7 (28.0)	9 (34.6)	0.611
Diabetes mellitus	7 (28.0)	7 (26.9)	0.931
Hypertension	10 (40.0)	12 (46.2)	0.657
Dyslipidaemia	3 (12.0)	6 (23.1)	0.465
Laboratory results			
White blood cell count (/mm^3)	8470.0 (4690.0)	8760.0 (7690.0)	0.396
Haemoglobin (g/dl)	11.5 (3.4)	10.8 (4.3)	0.391
Platelet count (×1000/mm^3)	274.0 (122.0)	227.0 (139.0)	0.194
Fasting glucose (mg/dl)	97.0 (50.5)	101.0 (42.5)	0.877
Blood urea nitrogen (mg/dl)	19.0 (27.8)	17.6 (29.8)	0.799

(Continues)

TABLE 2 (Continued)

Variables	AAV patients with high ESR/low CRP (N = 25)	AAV patients with low ESR/high CRP (N = 26)	p-value
Creatinine (mg/dl)	1.0 (2.0)	1.0 (2.3)	0.970
Total protein (g/dl)	6.8 (1.0)	6.3 (1.6)	0.025
Serum albumin (g/dl)	3.8 (0.8)	3.6 (1.3)	0.135
Alkaline phosphatase (IU/L)	71.0 (29.5)	85.0 (75.5)	0.246
Aspartate aminotransferase (IU/L)	18.0 (7.0)	17.0 (15.5)	0.792
Alanine aminotransferase (IU/L)	15.0 (13.5)	19.0 (23.0)	0.540
During the follow-up duration			
Poor outcomes (N, (%))			
All-cause mortality	0 (0)	6 (23.1)	0.023
Relapse	10 (40.0)	10 (38.5)	0.910
ESRD	5 (20.0)	6 (23.1)	0.789
Follow-up duration based on each poor outcomes (months)			
All-cause mortality	35.5 (45.3)	17.3 (92.9)	0.200
Relapse	16.9 (39.4)	8.3 (22.4)	0.144
ESRD	22.1 (43.7)	9.6 (33.8)	0.175
Medications (N, (%))			
Glucocorticoids	24 (96.0)	26 (100.0)	0.490
Cyclophosphamide	13 (52.0)	16 (61.5)	0.492
Rituximab	4 (16.0)	7 (26.9)	0.499
Mycophenolate mofetil	4 (16.0)	5 (19.2)	1.000
Azathioprine	13 (52.0)	12 (46.2)	0.676
Tacrolimus	2 (8.0)	4 (15.4)	0.668
Methotrexate	3 (12.0)	0 (0)	0.110
Plasma exchange	3 (12.0)	7 (26.9)	0.291

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

Abbreviations: AAV, ANCA-associated vasculitis; ACS, acute coronary syndrome; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham vasculitis activity score; C, cytoplasmic; CRP, C-reactive protein; CVA, cerebrovascular accident; EGPA, eosinophilic granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate; ESRD, end-stage renal disease; FFS, five-factor score; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; RRT, renal replacement therapy.

advantage in identifying the clinical significance of discordance between ESR and CRP in a uniform target disease.

Second, the previous study classified ESR and CRP by tertile and categorised the patient with the highest tertile as having elevated ESR and CRP and the patient with the lowest tertile as having low ESR and CRP. On the other hand, due to the limitation of the small number of patients, our study stratified ESR and CRP according to the median values and defined the patients with values higher and lower than the median as high ESR and CRP and low ESR and CRP respectively. If only the clinical significance is to be determined, then the median value is more convenient than the tertile for application in actual clinical situations. Third, the previous study concluded that infection was associated with elevated ESR/low CRP. However, since serious infection was specified in the exclusion criteria of this study, AAV patients with infectious diseases at the time of the study were not included.

Generally, ESR and CRP levels rise or fall together in most rheumatic diseases, but sometimes they may present changes differently. If the CRP level is remarkably elevated but ESR is within normal or slightly elevated, given that the peak time of CRP level is earlier than that of ESR level in response to inflammation, recent inflammation rather than chronic or remote inflammation is usually considered and differentiated.[2] Thus, low ESR/high CRP might represent the acute and recent inflammation, whereas high CRP/low ESR might reflect relatively chronic inflammation.

Why did low ESR/high CRP reflect the current high BVAS better? The BVAS is calculated based on the results of clinical symptoms, imaging tests and blood or urine test results for the last 4 weeks. Some items included in the BVAS system reflect recent inflammation, whereas others reflect relatively chronic inflammation. Therefore, even two patients with the same BVAS may show differences in the rates of recent or chronic inflammation.[4] Hence,
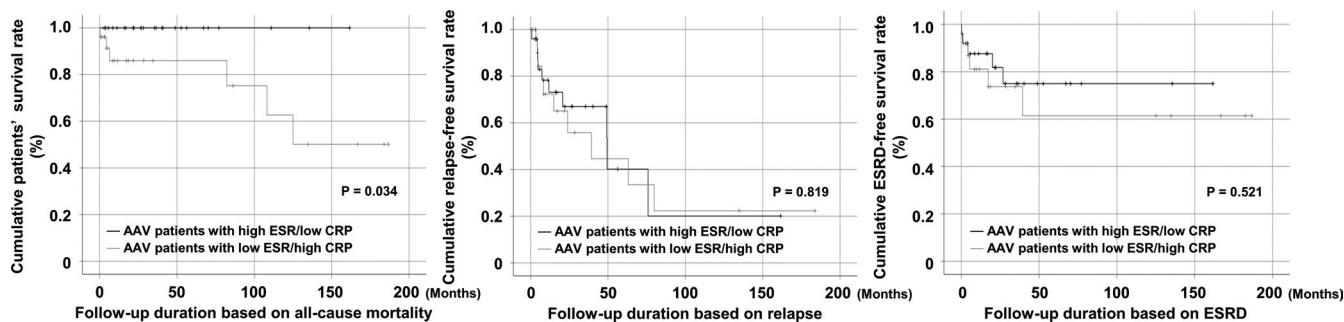
FIGURE 1 Poor outcomes of AAV during follow-up. AAV patients with low ESR/high CRP exhibited a significantly lower cumulative patients' survival rate than those with high ESR/low CRP ($p = 0.034$) but not a cumulative relapse-free or ESRD-free survival rates. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ESRD, end-stage renal disease

FIGURE 2 Comparison of cumulative patients' survival rates among four groups. AAV patients with low ESR/high CRP exhibited significantly lower cumulative patients' survival rates than those with high ESR/low CRP and low ESR/low CRP. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein
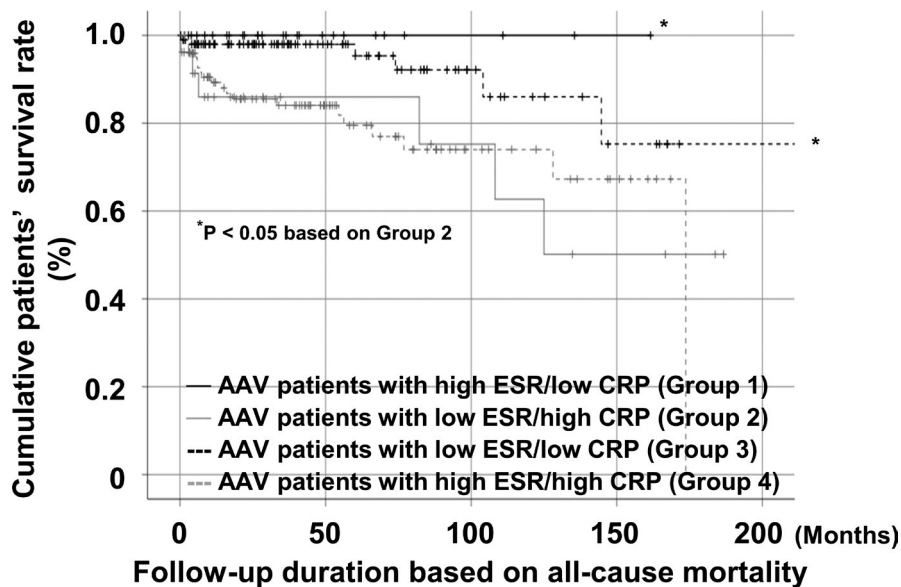
among the four combinations of high/low ESR and CRP, the low ESR/high CRP combination would effectively reflect the degree of high acute inflammatory burden despite presenting the same BVAS.

Conversely, compared with the last 4 weeks, the BVAS may decrease even if there is no clinical improvement. This is because, in BVAS version 3, newly developed/worsening symptoms and persistent symptoms are assigned different scores. For example, a new occurrence of proteinuria on urine stick of score >1+ or worsening from a score 2+ to 3+ will receive a BVAS of 4, but persistent symptoms without improvement or deterioration will receive a BVAS of only 2.[11]

In the comparative analysis, cardiovascular and nervous systemic manifestations were more frequent in the AAV patients with low ESR/high CRP than in those with high ESR/low CRP (Table 2). Previous studies have reported that the elevated CRP levels could predict cardiovascular diseases, such as coronary arterial diseases and cardiomyopathy or pericarditis.[14,15] As for nervous systemic manifestations, several previous studies demonstrated that the elevated CRP levels were associated with peripheral and central

nervous systemic symptoms.[16,17] However, since the association between ESR and cardiac or neural involvement in patients with systemic vasculitis has been accepted, it remains controversial whether high CRP/low ESR clearly reflects cardiovascular and nervous systemic manifestations.

How did low ESR/high CRP at diagnosis predict all-cause mortality during follow-up? We suggest the two most probable hypotheses. First, CRP reflects the high inflammatory burden of ANCA at the time of diagnosis, highlighting the widespread and rapid progression of major organ damage occurring in the early phase of the pathology.[18] Second, cardiovascular and other vascular inflammations are accelerated by the increased CRP levels at the time of diagnosis,[19] resulting in significantly more frequent cardiovascular manifestations at the time of diagnosis were in AAV patients with low ESR/high CRP than in those with high ESR/low CRP.

Meanwhile, the Cox hazards model analysis was performed to evaluate the predictive potential of BVAS, ESR and CRP at diagnosis for all-cause mortality. In the univariable analysis, BVAS (hazard ratio [HR] 1.105, 95% confidence interval [CI] 1.055–1.157, $p < 0.001$)
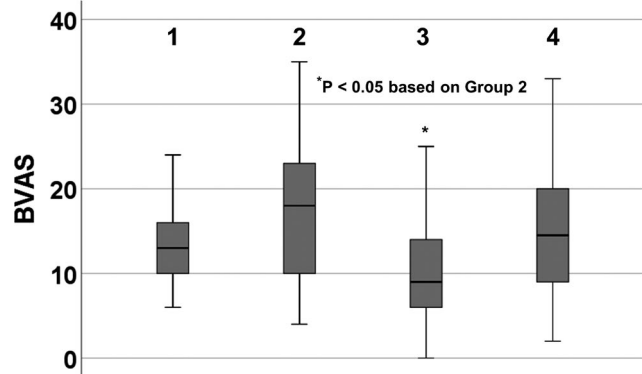
Group 1: AAV patients with high ESR/low CRP (13.0 [6.0])*
Group 2: AAV patients with low ESR/high CRP (18.0 [13.3])*
Group 3: AAV patients with low ESR/low CRP (9.0 [8.0])*
Group 4: AAV patients with high ESR/high CRP (14.5 [11.0])*
*(Median [interquartile range])

FIGURE 3 Comparison of BVAS among the four groups. AAV patients with low ESR/high CRP (group 2) exhibited significantly higher simultaneous BVAS than those with low ESR/low CRP. AAV, antineutrophil cytoplasmic antibody-associated vasculitis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

and CRP (HR 1.008, 95% CI 1.003–1.013, $p = 0.003$) were significantly associated with all-cause mortality, but ESR (HR 1.008, 95% CI 0.999–1.017, $p = 0.067$) was not. Therefore, although it is difficult to present any direct proof, CRP at diagnosis has a high predictive power to presuppose the development of all-cause mortality during follow-up in AAV patients.

This study has several limitations. The study design was retrospective, and the number of AAV patients was not large enough to generalise the results of this study to all patients with AAV. Furthermore, because of the small sample size, we could not stratify the AAV patients into tertile and perform subgroup analysis based on AAV subtypes and ANCA types. However, this pilot study is clinically significant in its use of ESR and CRP, which are the two most widely used markers for detecting inflammation. This study showed that low ESR/high CRP at diagnosis could not only estimate the simultaneous high BVAS but also predict all-cause mortality during follow-up in AAV patients. Future prospective and observational studies with a larger sample size could validate our results and provide reliable evidence to use low ESR/high CRP as a mortality predictor in AAV patients.

In conclusion, this study demonstrated that low ESR/high CRP at diagnosis could not only estimate the simultaneous high BVAS but also predict all-cause mortality during follow-up in AAV patients. Therefore, when discordant patterns of changes in ESR and CRP are observed at the time of AAV diagnosis, physicians might consider applying the methods and results of this study to AAV patients.

ORCID
Pil Gyu Park https://orcid.org/0000-0002-2788-6580
Jason Jungsik Song https://orcid.org/0000-0003-0662-7704
Yong-Beom Park https://orcid.org/0000-0003-4695-8620
Sang-Won Lee https://orcid.org/0000-0002-8038-3341

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