ARP Rheumatology 2026;5:90-99
https://doi.org/10.63032/OCTZ5542

ORIGINAL ARTICLES

Serum caspase-1 is correlated with vasculitis activity at diagnosis and associated with all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis

Ha JW[1], Kwon OC[2], Chung J[3], Park MC[2], Park YB[3,4], Lee SW[3,4]

ABSTRACT

Background: Caspase-1, a key protein involved in the inflammasome activation pathway, induces pyroptosis and inflammasome-mediated cytokine activation and release. In this study, we investigated whether serum caspase-1 could guess cross-sectional vasculitis activity and predict future all-cause mortality in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods: This study included 73 patients with AAV. Their clinical data at AAV diagnosis and during follow-up were collected and recorded. Disease activity was assessed using the Birmingham vasculitis activity score (BVAS). Serum caspase-1 was measured from the stored sera collected at AAV diagnosis. The end-point of a poor outcome in this study was set as all-cause mortality.

Results: The median age of the 73 patients was 64.0 years, and 30 and 43 patients were male and female, respectively. The median BVAS was 5.0, and the median levels of serum caspase-1 were 124.2 pg/mL. During follow-up, the rate of all-cause mortality was identified as 8.2%. Serum caspase-1 was positively correlated with BVAS (r = 0.241, P = 0.040). In multivariable Cox proportional analysis, serum caspase-1 (hazard ratio [HR] 1.003, 95% confidence interval [CI] 1.000, 1.006) along with dyslipidaemia (HR 36.610, 95% CI 2.050, 653.701) at AAV diagnosis were significantly and independently associated with all-cause mortality during follow-up in patients with AAV.

Conclusion: This study demonstrated that serum caspase-1 at AAV diagnosis could guess cross-sectional AAV activity, as represented by BVAS and further predict future all-cause mortality during follow-up in patients with AAV.

Keywords: Caspase-1; Antineutrophil cytoplasmic antibody; Vasculitis; Activity; Mortality

KEY MESSAGES

- Serum casepase-1 levels correlate with AAV diseaes activity.
- Higher serum casepase-1 levels are associated with a higher risk of all-cause mortality in patients with AAV.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis characterised by fibrinoid necrotising vasculitis affecting primarily capillaries, arterioles, venules and, occasionally, medium-sized arteries[1,2]. AAV is divided into three subtypes according to clinical, histopathologic and immunologic features: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA)[2-6]. Although the pathogenesis of AAV remains incompletely understood, cytokine-induced priming of neutrophils, subsequent activation of these primed neutrophils by ANCA, and activation of the complement cascade are recognized as central mechanisms driving the development of AAV[7]. In addition to these elements, inflammasome has also been suggested to be potentially involved in the pathogenesis of AAV.8 To date, few studies investigated the clinical role of the inflammasome in AAV, and these were limited to patients with ANCA-associated glomerulonephritis patients. Furthermore, the proposed mechanism has

[1] Division of Rheumatology, Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Gyeonggi-do, Republic of Korea;
[2] Division of Rheumatology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea;
[3] Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;
[4] Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Republic of Korea

Submitted: 14/07/2025
Accepted: 12/11/2025

Correspondence to: Sang-Won Lee
E-mail: sangwonlee@yuhs.ac

mainly been explained by the effects of IL-1β and IL-18 produced and released by the inflammasome activation pathway, which are thought to contribute to the inflammatory processes in AAV[9-11].

Caspases (cysteine-aspartic proteases) are integral to the function of the inflammasome, which is an intracellular multi-protein complex that activate innate immunity in response to inflammatory signals from infection agents and cell damage[12]. To date, fourteen caspases have been discovered, and these are divided into three categories according to their roles in programmed cell death including apoptosis and pyroptosis. Additionally, caspases may be divided into three types according to their response to stimuli such as initiator, executioner, and inflammatory types[13]. Among the 14 caspases, caspase-1, which is composed of a caspase recruitment domain (CARD), p20, and p10 subunits, belongs to the pyroptosis category and to the inflammatory type, and it plays a key role in the pyroptosis process of the inflammasome activation pathway[13,14]. The inflammasome usually consists of three main domains. For example, the Nod-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome has three distinct parts: NLRP3 as a sensor, caspase-1 as an effector, and apoptosis-associated speck-like protein containing a CARD (ASC) as an adaptor[15]. Upon sensing pathogen-associated molecular patterns or damage-associated molecular patterns (DAMPs) by the sensor NLRP3, the adaptor ASC activates caspase-1. Activated casepase-1 subsequently induces pyroptosis through cleavage of gasdermin D and promotes secretion ofinterleukin (IL)-1β, and IL-18. Therefore, caspase-1 executes a critical duty in the process of pyroptosis and inflammatory immune responses of the inflammasome[14-16]. Although caspase-1 is mainly present in cells, it may also be detected in the peripheral blood possibly as a consequence of pyroptosis[16]. To date, the clinical implications of serum caspase-1 have been investigated in several inflammatory diseases including adult-onset Still's disease, autoinflammatory syndromes, and axial spondyloarthritis[17-19]. Additionally, it has generally been demonstrated to be a useful biomarker for guessing the current disease activity by showing its significant positive correlation with the extent of inflammatory burden[17,19].

Previous studies have revealed that neutrophil extracellular traps (NETs) can induce pyroptosis in endothelial cells in small vessels[20,21]. Therefore, it could be reasonably inferred that serum caspase-1, which could be released through the process of pyroptosis, may be significantly correlated with the current activity of AAV. However, no study regarding the clinical significance of serum caspase-1 in patients with AAV has been reported to date. Hence, in this study, we investigated whether serum caspase-1 could guess cross-sectional vasculitis activity or the extent of inflammation at diagnosis and predict all-cause mortality during follow-up in patients with AAV.

PATIENTS AND METHODS

Patients

From a single-centre cohort of AAV, consisting of 327 patients who met the predefined inclusion and exclusion criteria, 73 patients were randomly selected for this study. The inclusion criteria were i) patients were newly diagnosed with AAV in the Division of Rheumatology, Department of Internal Medicine of this institute from November 2005 to December 2023; ii) patients met both the algorithm for classifying AAV proposed by the European Medicine Agency in 2007 and the revised nomenclature of systemic vasculitides suggested by the Chapel Hill Consensus Conference in 2012;[1,2] iii) patients also satisfied the newly proposed classification criteria for MPA, GPA, and EGPA proposed by a joint group of the American College of Rheumatology and European Alliance of Associations for Rheumatology in 2022 (the 2022 ACR/EULAR criteria);[3-5] iv) patients had electronic medical records sufficiently detailed to allow collection of clinical, laboratory, radiological, and histological data, including demographics, ANCA type, disease manifestations, AAV-specific indices [the Birmingham vasculitis activity score (BVAS), the five-factor score (FFS), and the vasculitis damage index (VDI)], and treatment information from AAV diagnosis to the last visit; v) patients had results of ANCA tests performed within 2 weeks before or after AAV diagnosis; vi) patients were followed up for at least 6 months after AAV diagnosis; vii) patients provided informed consent for the use of clinical data and stored blood samples for future studies at the time of cohort enrolment. The exclusion criteria were i) patients who had serious medical conditions such as active malignancies, and severe infectious diseases requiring hospital admission, including as pneumonia, meningitis, endocarditis, and sepsis, as well as those with concomitant autoimmune diseases at the time of the diagnosis;[3-5,22] ii) patients who were exposed to medications (eg., prophylthiouracil, methimazole, hydralazine, etc) or had concomitant diseases (eg., human immunodeficiency viral syndrome, monoclonal gammopathy, tuberculosis, etc) affecting ANCA positivity;[23,24] iii) patients who had received immunosuppressive drugs were administered before AAV diagnosis, including cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, and methotrexate.

Ethical approval

The present study was approved by the Institutional Re-

view Board (IRB) of Severance Hospital, Seoul, Republic of Korea (IRB number 4-2016-0901). All patients provided written informed consent upon enrolment in the SHAVE cohort (at the time of AAV diagnosis and blood sampling). The IRB waived the requirements for additional written informed consent as it was obtained upon enrolment into the SHAVE cohort.

Data at AAV diagnosis

Data on age, sex, smoking history, and body mass index were collected as baseline demographic data. With regard to AAV-related data, the following were recorded: AAV subtype, ANCA titres and positivity, and AAV-specific indices. AAV-specific indices included the BVAS, the FFS, and the VDI, as indicators of activity, prognosis, and damage around the time of AAV diagnosis, respectively.25-27 Comorbidities were defined as those conditions that were recognized before AAV diagnosis and included type 2 diabetes mellitus, hypertension, and dyslipidaemia in this study.28 Erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were evaluated as acute-phase reactants.29 Laboratory results included white blood cell count, haemoglobin, platelet count, fasting glucose, total cholesterol, blood urea nitrogen, serum creatinine, total serum protein, and serum albumin.

Tests for ANCA

Myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA titres were quantified by an immunoassay method, whereas, perinuclear (P)-ANCA and cytoplasmic (C)-ANCA were confirmed by an indirect immunofluorescence assay. In this study, MPO-ANCA and PR3-ANCA titres were measured by the novel anchor-coated highly sensitive (hs) Phadia ELiA (Thermo Fisher Scientific/Phadia, Freiburg, Germany) performed on a Phadia250 analyser using human native antigens. Based on the description of ANCA results approved by the 2022 ACR/EULAR criteria[6] both the results of MPO-ANCA/PR3-ANCA and those of P-ANCA/C-ANCA were recognized as the test results for ANCA.

Blood samples and serum caspase-1 measurement

Whole blood was collected from the patients with their permission at the time of AAV diagnosis before immunosuppressive drugs were administered. On the same day, sera were immediately isolated from whole blood and stored at -80°C. Serum caspase-1 was measured from the stored sera using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The sensitivity was <1.24 pg/mL and inter-assay coefficients of variation were 8.3% to 9.4%.

Data during follow-up after AAV diagnosis

The end-point of a poor outcome of this study was set as all-cause mortality.

The follow-up duration based on all-cause mortality was defined as the period from AAV diagnosis to death for deceased patients and as the period from AAV diagnosis to the last visit for surviving patients. The number of patients receiving glucocorticoids and each immunosuppressive drug during follow-up after AAV diagnosis was investigated.

Statistical analyses

All statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). Continuous and categorical variables were expressed as medians (Q1 to Q3), and number (percentage). Correlation coefficients (r) between two variables were determined using Pearson correlation analysis. A multivariable Cox proportional hazards model using variables with $P < 0.1$ in a univariable Cox analysis was performed to obtain a hazard ratio (HR) during follow-up. $P < 0.05$ was considered to be statistically significant.

RESULTS

Characteristics of patients

At AAV diagnosis, the median age of the 73 patients was 64.0 years, and 30 (41.1%) patients were male and 43 (58.9%) patients were female. Regarding disease subtype, 35 (47.9%) patients were diagnosed with MPA, 23 (31.5%) with GPA, and 15 (20.5%) with EGPA. MPO-ANCA (or P-ANCA) were detected in 40 (54.8%) patients and PR3-ANCA (or C-ANCA) in 12 (16.4%) patients. Among AAV-specific indices, median BVAS was assessed as 5.0, FFS as 0, and VDI as 3.0. The median ESR was 27.0 mm/h and CRP levels 5.5 mg/L. The median serum caspase-1 was 124.2 pg/mL. The remaining results of routinely performed laboratory tests are described in Table I. In terms of data during follow-up, 6 of the 73 patients (8.2%) died after a median follow-up duration of 26.3 months based on all-cause mortality. Seventy-two of the 73 patients (98.6%) received glucocorticoids, and the most commonly administered immunosuppressive drug was cyclophosphamide (63.0%) followed by azathioprine (58.9%) (Table I).

Correlation analysis

Serum caspase-1 was positively correlated with BVAS ($r = 0.241$, $P = 0.040$), CRP ($r = 0.291$, $P = 0.014$) (Supplementary Figure 1), white blood cell count ($r = 0.313$,

TABLE I. Characteristics of patients with AAV at diagnosis and during follow-up (N=73)

Variables	Values
At diagnosis	
Demographic data	
Age (years)	64.0 (52.0–74.0)
Male sex (N, (%))	30 (41.1)
Female sex (N, (%))	43 (58.9)
Ex-smoker (N, (%))	2 (2.7)
Body mass index (kg/m^2)	22.4 (20.8–24.8)
AAV subtypes (N, (%))	
MPA	35 (47.9)
GPA	23 (31.5)
EGPA	15 (20.5)
ANCA titres and positivity (N, (%))	
MPO-ANCA titre	0 (0–33.0)
PR3-ANCA titre	0 (0–0)
MPO-ANCA (or P-ANCA) positive	40 (54.8)
PR3-ANCA (or C-ANCA) positive	12 (16.4)
Both ANCA positive	3 (4.1)
ANCA negative	24 (32.9)
AAV-specific indices	
BVAS	5.0 (3.0–17.0)
FFS	0 (0–1.0)
VDI	3.0 (2.0–4.0)
Comorbidities (N, (%))	
Type 2 diabetes mellitus	17 (23.3)
Hypertension	25 (34.2)
Dyslipidaemia	13 (17.8)
Acute-phase reactants	
ESR (mm/hr)	27.0 (8.5–83.8)
CRP (mg/L)	5.5 (0.9–32.8)
Laboratory results	
White blood cell count(/mm^3)	7,610.0 (5,945.0–10,530.0)
Haemoglobin (g/dL)	12.0 (10.1–13.7)
Platelet count (x1,000/mm^3)	247.0 (190.8–364.3)
Fasting glucose (mg/dL)	93.5 (85.5–109.8)
Total cholesterol (mg/dL)	171.5 (136.8–211.3)
Blood urea nitrogen (mg/dL)	19.2 (13.3–28.7)
Serum creatinine (mg/dL)	0.8 (0.6–1.7)
Total serum protein (g/dL)	6.8 (6.4–7.3)
Serum albumin (g/dL)	4.2 (3.6–4.4)
Serum caspase-1 (pg/mL)	124.2 (97.3–278.0)

continues on the next column

TABLE I. Continuation

Variables	Values
During follow-up	
Mortality	
All-cause mortality (N, (%))	6 (8.2)
Follow-up period based on all-cause mortality (months)	26.3 (11.8–46.1)
Medications	
Glucocorticoids	72 (98.6)
Cyclophosphamide	46 (63.0)
Rituximab	14 (19.2)
Mycophenolate mofetil	18 (24.7)
Azathioprine	43 (58.9)
Tacrolimus	6 (8.2)
Methotrexate	2 (2.7)

Values are expressed as a median (25~75 percentile) or N (%).
ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: the Birmingham vasculitis activity score; FFS: the five-factor score; VDI: vasculitis damage index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

P = 0.007), and platelet count (r = 0.332, P = 0.004). Whereas, serum caspase-1 was also inversely correlated with haemoglobin (r = -0.266, P = 0.023), total serum protein (r = -0.328, 0.006), and serum albumin (r = -0.374, P = 0.001) (Table II). We also investigated which of the nine items of BVAS was associated with serum caspase-1 at diagnosis. First, we performed a correlation analysis and found that serum caspase-1 was significantly correlated with the sum scores of the items of general (r = 0.234, P = 0.046), cutaneous (r = 0.320, P = 0.006), mucous/ocular (r = 0.310, P = 0.008), and pulmonary (r = 0.235, P = 0.045) manifestations, respectively. Next, we compared serum caspase-1 between patients with each item and those without and found that two items, cutaneous and pulmonary manifestations, exhibited significant differences between the two groups. Patients with cutaneous (226.3 vs. 117.7 pg/mL, P = 0.025), pulmonary (140.9 vs. 105.5 pg/mL, P = 0.005), and nervous systemic (155.4 vs. 115.3 pg/mL, P = 0.041) manifestations exhibited higher median serum caspase-1 concentrations than those without, respectively (Supplementary Table I). Among them, only cutaneous and pulmonary items showed statistical significance in the two analyses. Thus, we concluded that serum caspase-1 may contribute to reflecting BVAS through its significant association with cutaneous and pulmonary manifestations. On the other hand, among the subitems of cutaneous and pulmonary items, serum caspase-1 was significantly correlated with the score

TABLE II. Correlation analysis of serum caspase-1 with cross-sectional continuous variables at diagnosis in patients with AAV (N=73)

	Correlation Coefficient (r)	P value
Age	0.214	0.068
Body mass index	0.133	0.261
BVAS	0.241	0.040
FFS	0.122	0.304
VDI	0.132	0.270
ESR	0.203	0.096
CRP	0.291	0.014
White blood cell count	0.313	0.007
Haemoglobin	–0.266	0.023
Platelet count	0.332	0.004
Fasting glucose	0.191	0.131
Total cholesterol	–0.068	0.588
Blood urea nitrogen	0.205	0.082
Serum creatinine	0.127	0.286
Total serum protein	–0.328	0.006
Serum albumin	–0.374	0.001

s: soluble; R: receptor; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; BVAS: the Birmingham vasculitis activity score; FFS: the five-factor score; VDI: vasculitis damage index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

assigned to the subitems of purpura (r = 0.288, P = 0.013), and massive alveolar haemorrhage (r = 0.447, P < 0.001). Additionally, patients with purpura (333.0 vs. 122.4 pg/mL, P = 0.027) and massive alveolar haemorrhage (472.7 vs. 120.1 pg/mL, P = 0.005) exhibited higher median serum caspase-1 concentrations than those without, respectively (Supplementary Figure 2).

Cox proportional hazards analyses for all-cause mortality

In univariable Cox proportional analysis, VDI (HR 1.561), dyslipidaemia (HR 11.204), white blood cell count (HR 1.126), haemoglobin (HR 0.621), serum albumin (HR 0.162), and serum caspase-1 (HR 1.002) at AAV diagnosis were significantly associated with all-cause mortality during follow-up. Age, body mass index, BVAS, and total serum protein at AAV diagnosis tended to be correlated with all-cause mortality during follow-up. However, they were not statistically significant. In multivariable Cox proportional analysis, dyslipidaemia (HR 36.610, 95% confidence interval [CI] 2.050, 653.701), and serum caspase-1 (HR 1.003, 95% CI 1.000, 1.006) at AAV diagnosis were significantly and independently associated with all-cause mortality during follow-up (Table III). Additionally, we performed bootstrapping for the internal validation and found that similar to the main analysis, dyslipidaemia (P = 0.021) and serum caspase-1 (P = 0.037) were still significantly and independently associated with all-cause mortality, increasing the robustness of the model.

DISCUSSION

To date, it has been found that caspase-1, which is involved in programmed cell death, can be detected in the peripheral blood by pyroptosis[14,15] and may be a useful biomarker for guessing the current disease activity in several inflammatory diseases[9-11]. Therefore, in this study, we investigated whether serum caspase-1 might be correlated with cross-sectional vasculitis activity or the extent of inflammation at diagnosis. We also investigated if it was associated with poor outcomes during follow-up in patients with AAV and finally obtained several interesting findings. First, serum caspase-1 at diagnosis exhibited a significant correlation with the cross-sectional activity represented by BVAS and inflammation severity expressed by CRP in patients with AAV. Second, serum caspase-1 at diagnosis could independently predict all-cause mortality during follow-up in patients with AAV, together with the presence of dyslipidaemia at diagnosis. Therefore, we concluded that this study provided the opportunity to discover the clinical potential of serum caspase-1 as a new biomarker for the current activity and future mortality in patients with AAV.

By what mechanism could serum caspase-1 have reflected cross-sectional AAV activity in patients with AAV? Once the inflammasome activation pathway is turned on, the cell undergoes two distinct processes. One is IL-1β and IL18 activation and release. The other is pyroptosis, one of the types of programmed cell death[14,15]. First, in terms of IL-1β and IL-18 activation and release, these inflammasome-mediated proinflammatory cytokines contribute to AAV activation through three mechanisms. The first mechanism is that IL-1β may enhance cytoplasmic MPO and PR3 exposure to antigen-presenting cells[7,30]. The second mechanism is that IL-18 may participate in priming neutrophils[8,31]. The third mechanism is that both IL-1β and IL-18 provoke endothelial dysfunction and augment leukocyte recruitment by increasing the production of adhesion molecules by endothelial cells[14]. Therefore, it could be inferred that the extent of inflammasome activation leading to IL-1β and IL-18 activation and release may be closely associated with and reflect cross-sectional AAV activity.

Next, in terms of pyroptosis, caspase-1 plays a role in promoting the inflammasome activation pathway

TABLE III. Cox proportional hazards model analyses of serum caspase-1 and variables at diagnosis for all-cause mortality during follow-up in AAV patients (N=73)

Variables	Univariable			Multivariable		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)	1.093	0.996, 1.200	0.061			
Male sex (N, (%))	2.489	0.522, 15.558	0.227			
Ex-smoker (N, (%))	0.047	0.000, 26,419,937.13	0.767			
Body mass index (kg/m^2)	0.768	0.567, 1.040	0.088			
MPO-ANCA (or P-ANCA) positive	4.850	0.565, 41.645	0.150			
PR3-ANCA (or C-ANCA) positive	0.037	0.000, 366.720	0.483			
BVAS	1.078	0.995, 1.167	0.066			
FFS	2.193	0.862, 5.580	0.100			
VDI	1.561	1.046, 2.331	0.029	1.505	0.721, 3.141	0.277
Type 2 diabetes mellitus	3.590	0.724, 17.800	0.118			
Hypertension	1.003	0.184, 5.477	0.998			
Dyslipidaemia	11.204	2.046, 61.349	0.005	36.610	2.050, 653.701	0.014
ESR (mm/hr)	1.016	0.996, 1.036	0.120			
CRP (mg/L)	1.014	0.997, 1.031	0.102			
White blood cell count	1.126	1.019, 1.243	0.020	1.238	0.934, 1.641	0.138
Haemoglobin	0.621	0.402, 0.960	0.032	1.345	0.526, 3.442	0.537
Platelet count	1.002	0.997, 1.006	0.405			
Fasting glucose	1.006	0.997, 1.016	0.195			
Total cholesterol	0.989	0.968, 1.010	0.307			
Blood urea nitrogen	1.022	0.986, 1.059	0.231			
Serum creatinine	1.238	0.836, 1.835	0.287			
Total serum protein	0.402	0.158, 1.024	0.056			
Serum albumin	0.162	0.050, 0.520	0.002	0.221	0.008, 5.899	0.368
Serum caspase-1	1.002	1.000, 1.003	0.010	1.003	1.000, 1.006	0.045

ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; HR: hazard ratio; CI: confidence interval; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: the Birmingham vasculitis activity score; FFS: the five-factor score; VDI: vasculitis damage index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

inside the cell mainly, but it is not a protein that is doomed to be produced and released out of the cell[12-15]. Accordingly, caspase-1 detected in peripheral blood outside the cell is likely to have been cleaved and released active caspase-1, a product of programmed cell death, especially pyroptosis. As infectious or auto-inflammatory signals increase, pyroptosis may progress and active caspase-1 present in the cell may be released out of the cell. Therefore, it could be inferred that serum caspase-1 is active caspase-1 which can serve as a biomarker for the extent of inflammasome activation which may reflect cross-sectional AAV activity[14,15]. In summary, it can be concluded that serum caspase-1 may be useful in guessing cross-sectional AAV activity associated with the extent of inflammasome activation that mediates not only IL-1β and IL-18 activation and release but also pyroptosis.

Given IL-1β and IL-18 activation and release as the distinct consequences of inflammasome activation, it could be assumed that serum both IL-1β and IL-18 may have the clinical utility in reflecting cross-sectional AAV activity. However, several previous studies investigating the role of inflammatory cytokines and chemokines in AAV pathogenesis or clinical practice have provided inconsistent and controversial evidence supporting this assumption. Regarding IL-1β, serum IL-1β concentration was reported to exhibit no significant differences between patients with active AAV and those in remission or controls[32] or its levels were too labile to be sufficiently analysed due to the issue of detection efficiency[33]. In contrast, serum IL-18 was reported to be meaningfully higher in patients with GPA compared with controls,[34,35] and further, correlated with BVAS in patients with AAV[36]. Given that the serum IL-1β and IL-

18, the downstream immunologic consequences of the caspase-1 containing inflammasome activation pathway, show different patterns in AAV patients, it could be concluded that measuring serum caspase-1, which may directly reflect the extent of inflammasome activation-mediated pyroptosis, would be more effective in understanding the relationship between inflammasome activation and AAV activity.

In multivariable Cox analysis including serum caspase-1, the independent predictive potential for all-cause mortality in patients with AAV was proven to be significant in only serum caspase-1 and dyslipidaemia at AAV diagnosis. We wondered how serum caspase-1 measured at AAV diagnosis could predict future mortality during follow-up in patients with AAV. Therefore, we inferred its predictive mechanism according to the three categories for risk factors of all-cause mortality at the time of AAV diagnosis in patients with AAV[30,37,38]. First of all, among the traditional risk factors, serum caspase-1 tended to be positively correlated with age ($r = 0.214$, $P = 0.068$) but not body mass index. Additionally, no significant differences in serum caspase-1 according to sex ($P = 0.147$), type 2 diabetes mellitus ($P = 0.695$), hypertension ($P = 0.443$), or dyslipidaemia ($P = 0.846$) were observed. Next, among the inflammation-related risk factors, serum caspase-1 was significantly correlated with CRP ($r = 0.291$, $P = 0.014$) and it tended to be positively correlated with ESR ($r = 0.203$, $P = 0.096$). Also, it was inversely correlated with serum albumin ($r = -0.374$, $P = 0.001$), which is one of the acute-phase reactants. Last, among the AAV-related risk factors, serum caspase-1 was significantly correlated with BVAS ($R = 0.241$, $P = 0.040$) (Table II). In summary, we carefully concluded that serum caspase-1 at the time of AAV diagnosis may have the potential to predict future all-cause mortality by reflecting the initial risk factors for mortality at AAV diagnosis such as age, the acute-phase reactants, and the activity of AAV.

Secondly, we also inferred its predictive mechanism by means of the concept of NETs formation. In the process of neutrophil priming and activation in AAV, the interaction between circulating ANCAs and neutrophils promotes the formation of NETs, which may release the cytoplasmic antigens of ANCAs such as MPO, and PR3[39]. Subsequently, these molecules may be recognized by pattern recognition receptors (PRRs), leading to the activation of the NLRP3 inflammasome[9,40]. NETs, which are composed of DNA, histones, and antimicrobial proteins, may trap pathogens and act as potent DAMPs. When recognized by PRRs, they may initiate a signalling cascade that activates the NLRP3 inflammasome, leading to caspase-1 activation and related pro-inflammatory cytokine release[14,41]. This suggests that a feedback loop may be formed, in which inflammasome activation is driven by NET formation, leading to an intensified inflammatory state. Additionally, NETs may induce pyroptosis which is one of the programmed cell death processes that can inherently result in inflammation, and thus, they may directly damage epithelial and endothelial cells[41]. Therefore, we carefully concluded that serum caspase-1 at the time of AAV diagnosis can reflect the consequences that these NETs formation-mediated factors may contribute to intensifying AAV progression and increasing the rate of all-cause mortality in patients with AAV.

The present study has an advantage in that this is the first study to demonstrate the clinical utility of serum caspase-1 measured at the time of AAV diagnosis as a biomarker for guessing cross-sectional AAV activity represented by BVAS and further predicting all-cause mortality during follow-up in patients with AAV. Another advantage is that this study suggested the possibility that serum caspase-1 could be a more stable and reliable indicator reflecting the extent of inflammasome activation than inflammasome-mediated proinflammatory cytokines.

The present study has several limitations. The first critical limitation is that this study included only a small number of patients and was conducted retrospectively. The second limitation is that this study had no data regarding the serum concentrations of inflammatory-mediated pro-inflammatory cytokines such as IL-1β and IL-18. This was because unfortunately, the available serum samples for measuring the serum concentrations of IL-1β and IL-18 were all used and none were left. The third limitation is that this study did not measure serum caspase-1 in blood samples collected at different times of AAV activity in the same patients. This would have allowed for demonstrating the dynamic association between serum caspase-1 and cross-sectional AAV activity. The fourth limitation is that the correlation coefficients are modest ($r < 0.4$), and thus, their clinical relevance should be interpreted with caution. The fifth limitation is that the number of events (6 deaths) is low relative to the number of predictors included in the multivariable Cox model. This raises concerns about model overfitting, with a reported HR of 36.610 for dyslipidaemia and marginal HR for caspase-1. In addition, the extremely wide 95% CI (2.050–653.701) for dyslipidaemia is indicative of instability in the model. However, despite these limitations, we believe that this study has clinical implications as a pilot study. Additionally, we believe that a future prospective study including more patients and measurements of serum caspase-1 and inflammatory-mediated pro-inflammatory cytokines, using paired blood samples will provide more dynamic and reliable information on the clinical utility of serum caspase-1 in patients with AAV.

CONCLUSION

In this study, we demonstrated that serum caspase-1 at AAV diagnosis could guess cross-sectional AAV activity represented by BVAS and further predict future all-cause mortality during follow-up in patients with AAV. Based on the results of this study, we would like to propose that serum caspase-1 at AAV diagnosis has the clinical potential to be a useful biomarker in real clinical practice for managing patients with AAV.

FUNDING

This study was funded by Eisai Korea Inc. Seoul, Republic of Korea (4-2024-0700), Yuhan Corporation, Seoul, Republic of Korea, as part of their "2024 Investigator Initiated Translation Research Program" (4-2025-0044), Samsung Bioepis Co., Ltd., Incheon, Republic of Korea (4-2025-1066), and Samil Pharmaceutical Co., Ltd., Seoul, Republic of Korea (4-2025-1087; LFN-26-I01). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication. Therefore, we disclose that these analyses were pre-specified and conducted independently.

REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. Jan 2013;65(1):1-11.
2. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. Feb 2007;66(2):222-7. https://doi.org/10.1136/ard.2006.054593
3. Suppiah R, Robson JC, Grayson PC, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. Mar 2022;81(3):321-326. https://doi.org/10.1002/art.41983
4. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. Mar 2022;81(3):315-320. 5 https://doi.org/10.1002/art.41986
5. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. Ann Rheum Dis. Mar 2022;81(3):309-314. https://doi.org/10.1002/art.41982
6. Pyo JY, Lee LE, Park YB, Lee SW. Comparison of the 2022 ACR/EULAR Classification Criteria for Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Previous Criteria. Yonsei Med J. Jan 2023;64(1):11-17. https://doi.org/10.3349/ymj.2022.0435
7. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers. Aug 27 2020;6(1):71. https://doi.org/10.1038/s41572-020-0204-y
8. Shin JI, Lee KH, Joo YH, et al. Inflammasomes and autoimmune and rheumatic diseases: A comprehensive review. J Autoimmun. Sep 2019;103:102299. https://doi.org/10.1016/j.jaut.2019.06.010
9. Anton-Pampols P, Diaz-Requena C, Martinez-Valenzuela L, et al. The Role of Inflammasomes in Glomerulonephritis. Int J Mol Sci. Apr 11 2022;23(8) https://doi.org/10.3390/ijms23084208
10. Hutton HL, Ooi JD, Holdsworth SR, Kitching AR. The NLRP3 inflammasome in kidney disease and autoimmunity. Nephrology (Carlton). Sep 2016;21(9):736-44. https://doi.org/10.1111/nep.12785
11. Daca A, Storoniak H, Dębska-Ślizień A, Kusztal MA, Krajewska M, Lisowska KA. Chemokines and Cytokines Profiles in Patients with Antineutrophil Cytoplasmic Antibodies-Associated Vasculitis: A Preliminary Study. Int J Mol Sci. Oct 18 2023;24(20) https://doi.org/10.3390/ijms242015319
12. Drynda A, Padjas A, Wójcik K, et al. Clinical Characteristics of EGPA Patients in Comparison to GPA Subgroup with Increased Blood Eosinophilia from POLVAS Registry. J Immunol Res. 2024;2024:4283928. https://doi.org/10.1155/2024/4283928
13. Galluzzi L, López-Soto A, Kumar S, Kroemer G. Caspases Connect Cell-Death Signaling to Organismal Homeostasis. Immunity. Feb 16 2016;44(2):221-31. https://doi.org/10.1016/j.immuni.2016.01.020
14. Mariathasan S, Monack DM. Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. Nat Rev Immunol. Jan 2007;7(1):31-40. https://doi.org/10.1038/nri1997
15. Bai B, Yang Y, Wang Q, et al. NLRP3 inflammasome in endothelial dysfunction. Cell Death Dis. Sep 18 2020;11(9):776. https://doi.org/10.1038/s41419-020-02985-x
16. Wei S, Feng M, Zhang S. Molecular Characteristics of Cell Pyroptosis and Its Inhibitors: A Review of Activation, Regulation, and Inhibitors. Int J Mol Sci. Dec 17 2022;23(24) https://doi.org/10.3390/ijms232416115
17. Matsumoto H, Yoshida S, Koga T, et al. Increased serum caspase-1 in adult-onset Still's disease. PLoS One. 2024;19(7):e0307908. https://doi.org/10.1371/journal.pone.0307908
18. Sharma D, Sharma BR, Vogel P, Kanneganti TD. IL-1β and Caspase-1 Drive Autoinflammatory Disease Independently of IL-1α or Caspase-8 in a Mouse Model of Familial Mediterranean Fever. Am J Pathol. Feb 2017;187(2):236-244. https://doi.org/10.1016/j.ajpath.2016.10.015
19. Kim SH, Lee JH, Jeong HJ, et al. Clinical Significance of Elevated Serum Caspase-1 Levels in Patients With Ankylosing Spondylitis. Ann Lab Med. Mar 1 2022;42(2):293-295. https://doi.org/10.3343/alm.2022.42.2.293
20. Zhao P, Zhu J, Bai L, et al. Neutrophil extracellular traps induce pyroptosis of pulmonary microvascular endothelial cells by activating the NLRP3 inflammasome. Clin Exp Immunol. Jun 20 2024;217(1):89-98. https://doi.org/10.1093/cei/uxae028
21. Ju J, Liu Y, Liang H, Yang B. The role of pyroptosis in endothelial dysfunction induced by diseases. Front Immunol. 2022;13:1093985. https://doi.org/10.3389/fimmu.2022.1093985
22. Do H, Pyo JY, Ahn SS, Song JJ, Park YB, Lee SW. Cancer-associated vasculitides: a single-centre case series. Clin Rheumatol. Jan 2023;42(1):151-158. https://doi.org/10.1007/s10067-022-06363-0
23. Chen M, Gao Y, Guo XH, Zhao MH. Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis. Nat Rev Nephrol. Jun 5 2012;8(8):476-83. https://doi.org/10.1038/nrneph.2012.108
24. Moiseev S, Cohen Tervaert JW, Arimura Y, et al. 2020 international consensus on ANCA testing beyond systemic vasculitis. Autoimmun Rev. Sep 2020;19(9):102618. https://doi.org/10.1016/j.autrev.2020.102618
25. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. Dec 2009;68(12):1827-32.

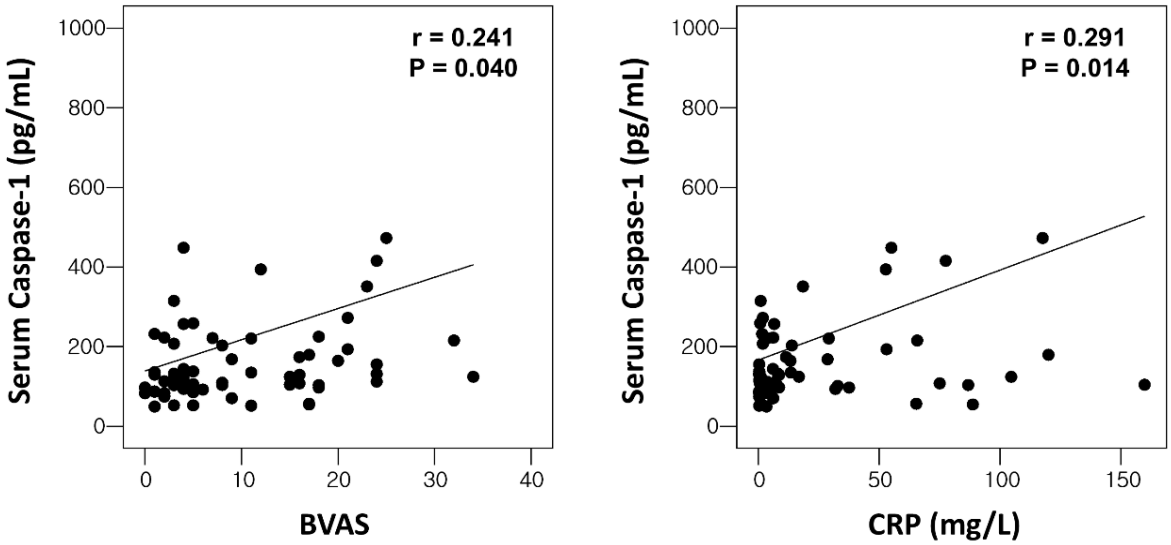
https://doi.org/10.1136/ard.2008.101279
26. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Toumelin PL. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore). Jan 2011;90(1):19-27. https://doi.org/10.1097/MD.0b013e318205a4c6
27. Flossmann O, Bacon P, de Groot K, et al. Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis. Mar 2007;66(3):283-92.
28. Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. Jama. Aug 14 2013;310(6):591-608. https://doi.org/10.1001/jama.2013.13805
29. Mantovani A, Garlanda C. Humoral Innate Immunity and Acute-Phase Proteins. N Engl J Med. Feb 2 2023;388(5):439-452. https://doi.org/10.1056/NEJMra2206346
30. Choi CB, Park YB, Lee SW. Antineutrophil Cytoplasmic Antibody-Associated Vasculitis in Korea: A Narrative Review. Yonsei Med J. Jan 2019;60(1):10-21. https://doi.org/10.3349/ymj.2019.60.1.10
31. Hewins P, Morgan MD, Holden N, et al. IL-18 is upregulated in the kidney and primes neutrophil responsiveness in ANCA-associated vasculitis. Kidney Int. Feb 2006;69(3):605-15. https://doi.org/10.1038/sj.ki.5000167
32. Nogueira E, Hamour S, Sawant D, et al. Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis. Nephrol Dial Transplant. Jul 2010;25(7):2209-17. https://doi.org/10.1093/ndt/gfp783
33. Hoffmann JC, Patschan D, Dihazi H, et al. Cytokine profiling in anti neutrophil cytoplasmic antibody-associated vasculitis: a cross-sectional cohort study. Rheumatol Int. Nov 2019;39(11):1907-1917. https://doi.org/10.1007/s00296-019-04364-y
34. Amsler J, Everts-Graber J, Martin KR, et al. Dysregulation of neutrophil oxidant production and interleukin-1-related cytokines in granulomatosis with polyangiitis. Rheumatology (Oxford). Aug 1 2024;63(8):2249-2258. https://doi.org/10.1093/rheumatology/kead578
35. Hultgren O, Andersson B, Hahn-Zoric M, Almroth G. Serum concentration of interleukin-18 is up-regulated in patients with ANCA-associated vasculitis. Autoimmunity. Nov 2007;40(7):529-31. https://doi.org/10.1080/08916930701622783
36. Liu C. Detection of serum interleukin-18 level and neutrophil/lymphocyte ratio in patients with antineutrophil cytoplasmic antibody-associated vasculitis and its clinical significance. Open Life Sci. 2024;19(1):20220823. https://doi.org/10.1515/biol-2022-0823
37. Tan JA, Dehghan N, Chen W, Xie H, Esdaile JM, Avina-Zubieta JA. Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies. Ann Rheum Dis. Sep 2017;76(9):1566-1574. https://doi.org/10.1136/annrheumdis-2016-210942
38. Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis. Jul 2008;67(7):1004-10. https://doi.org/10.1136/ard.2007.071936
39. Kessenbrock K, Krumbholz M, Schönermarck U, et al. Netting neutrophils in autoimmune small-vessel vasculitis. Nat Med. Jun 2009;15(6):623-5. https://doi.org/10.1038/nm.1959
40. Bauernfeind FG, Horvath G, Stutz A, et al. Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression. J Immunol. Jul 15 2009;183(2):787-91. https://doi.org/10.4049/jimmunol.0901363
41. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. Nat Rev Immunol. Feb 2018;18(2):134-147. https://doi.org/10.1038/nri.2017.105

SUPPLEMENTARY MATERIAL

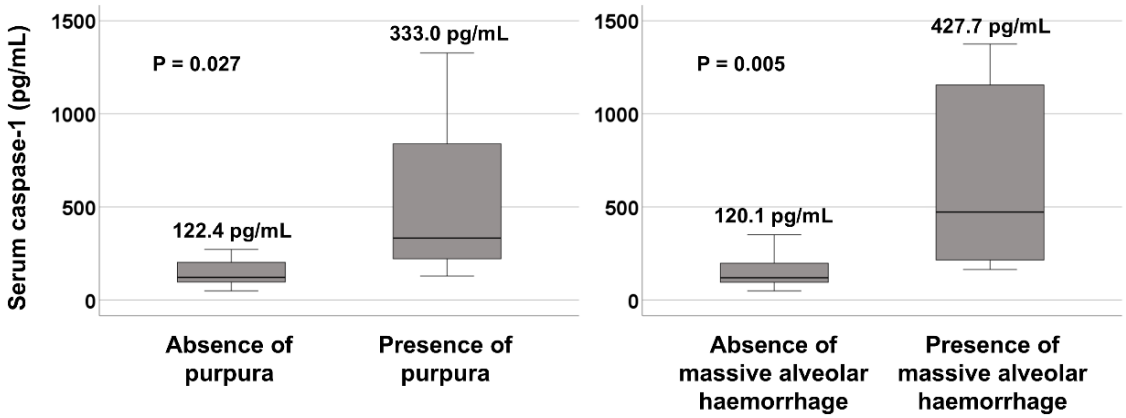
SUPPLEMENTARY TABLE I. Correlation of serum caspase-1 with each of the nine items of BVAS and comparison of its median concentrations between patients with each item and those without

	Correlation Coefficient (r)	P value	Median serum caspase-1 (pg/mL)		P value
			Absence	Presence	
General manifestation	0.234	0.046	120.1	164.4	0.212
Cutaneous manifestation	0.320	0.006	117.7	226.3	0.025
Mucous/ocular manifestation	0.310	0.008	123.3	152.9	0.630
Ear nose and throat manifestation	-0.130	0.273	129.1	122.9	0.719
Pulmonary manifestation	0.235	0.045	105.5	140.9	0.005
Cardiovascular manifestation	0.074	0.553	122.9	225.0	0.101
Gastroenterological manifestation	N/A	N/A	N/A	N/A	N/A
Renal manifestation	0.148	0.211	114.7	129.1	0.508
Nervous systemic manifestation	0.073	0.537	115.3	155.4	0.041

BVAS: the Birmingham vasculitis activity score; N/A: not applicable.



Supplementary Figure 1. Correlation of serum caspase-1 with BVAS and CRP. BVAS: the Birmingham vasculitis activity score; CRP: C-reactive protein.



Supplementary Figure 2. Comparison of serum caspase-1. Patients with purpura and massive alveolar haemorrhage exhibited higher median serum caspase-1 concentrations than those without.