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Clinical perspective on serum periostin in antineutrophil-cytoplasmic antibody-associated vasculitis

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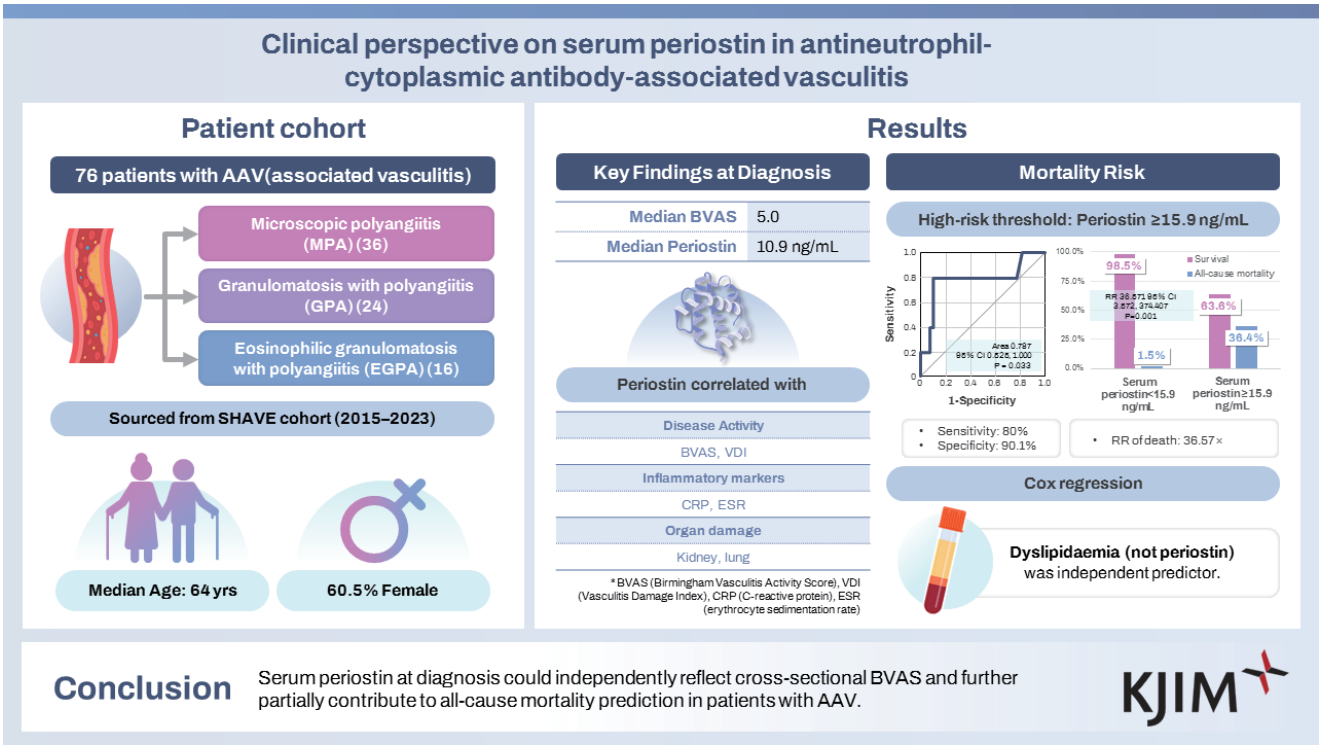

Background/Aims: This study evaluated the clinical utility of serum periostin measured at diagnosis in reflecting activity at diagnosis and predicting all-cause mortality during follow-up in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods: This study included 76 patients with AAV whose serum periostin was measured from sera collected and stored at diagnosis. The correlation of either serum periostin or the Birmingham Vasculitis Activity Score (BVAS) with other variables was evaluated. Cumulative survival rates were compared using Kaplan–Meier survival analysis. The variables at diagnosis were compared between deceased and surviving patients. Hazard ratios were obtained by Cox proportional hazard analysis.

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Results: The median age of the 76 patients was 64.0 years and 60.5% were female. The median BVAS and serum periostin were 5.0 and 10.9 ng/mL, respectively. Five of the 76 patients (6.6%) died. Serum periostin was independently correlated with cross-sectional BVAS, the Vasculitis Damage Index (VDI), white blood cell count, and serum albumin. Patients with serum periostin ≥ 15.9 ng/mL at diagnosis had a significantly lower cumulative survival rate than those without. In addition to high VDI, dyslipidaemia frequency, and C-reactive protein, deceased patients showed higher serum periostin than surviving patients. In multivariable Cox analysis, however, only dyslipidaemia rather than serum periostin was identified as an independent predictor of all-cause mortality.
Conclusions: This study is the first to demonstrate that serum periostin at diagnosis could independently reflect cross-sectional BVAS and further partially contribute to all-cause mortality prediction in patients with AAV.

Keywords: Periostin; Antineutrophil cytoplasmic antibody; Vasculitis; Activity; Mortality

INTRODUCTION

Periostin is an extracellular matrix protein that belongs to the Fasciclin family because of its homology to Fasciclin 1. Periostin is produced in mesenchymal lineage cells such as osteoblasts, periodontal ligament, and periosteum, and it is secreted into the extracellular space [1]. Periostin plays a role in forming and maintaining cellular structures by interacting with structural matrix proteins, including collagen [2]. Conversely, as a matricellular protein, it may also play other roles in regulating and modulating cellular functions through cross-talk with cell-surface receptors, proteases, and hormones [3,4]. The clinical utility of serum periostin was first reported in allergic diseases because of the induction of periostin gene expression by interleukin (IL)-4 and IL-13 [2,5]. Subsequently, many studies have reported the utility of periostin as a serum biomarker and therapeutic target in various chronic inflammatory and fibrotic diseases, such as liver and lung diseases [6]. In particular, periostin is involved in signalling pathways via nuclear factor kappa-light-chain-enhancer of activated B cells, IL-8, extracellular signal-regulated kinase, and mitogen-activated protein kinase in the pathophysiology of chronic kidney diseases and inflammatory bowel disease [7,8]. The possibility of the clinical utility of periostin in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with a similar pathological mechanism has been proposed [9,10]. To date, only one study that included patients with eosinophilic granulomatosis with polyangiitis (EGPA) has reported the clinical utility of serum periostin in AAV [11]. However, since the pathogenesis of EGPA is also partially based on a well-known allergic immunological mechanism, the previous study could not represent all cases of AAV with vasculitic immunological mechanisms and thus; may not provide new and additional information on pre-existing concepts [12]. To determine the clinical role of serum periostin in AAV, patients with three subtypes of AAV: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and EGPA were included in this study and the clinical utility of serum periostin in patients with AAV was evaluated.

METHODS

Patients

One hundred patients with AAV were randomly selected from the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort, a prospective and observational cohort of Korean patients with AAV, and retrospectively screened by reviewing their medical records. Among the 100 patients, 76 were included in this study based on the inclusion criteria: (1) fulfilment of the following three criteria for or definitions of AAV: the 2007 European Medicines Agency algorithms for AAV, the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, and the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for AAV [13-18]; (2) first classification of AAV at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, and Severance Hospital, from November 2015 to June 2023; (3) completion of sufficiently well-written medical records to collect clinical, laboratory, radiological, and histopathological data for AAV classification at diagnosis and to obtain

Table 1. Characteristics of patients with AAV at diagnosis and during follow-up (N = 76)

Variable	Value
At the time of diagnosis	
Demographic data	
Age (yr)	64.0 (52.0–73.8)
Sex, female	46 (60.5)
Ex-smoker	3 (3.9)
Body mass index (kg/m^2)	22.4 (20.7–24.7)
AAV subtypes	
MPA	36 (47.4)
GPA	24 (31.6)
EGPA	16 (21.1)
ANCA positivity	
MPO-ANCA (or P-ANCA) positive	41 (53.9)
PR3-ANCA (or C-ANCA) positive	12 (15.8)
Both ANCA positive	3 (3.9)
ANCA negative	26 (34.2)
AAV-specific indices	
BVAS	5.0 (3.0–17.0)
FFS	0.0 (0.0–1.0)
SF-36 PCS	52.5 (35.3–67.7)
SF-36 MCS	54.6 (39.7–72.6)
VDI	3.0 (2.0–4.0)
Comorbidities	
Type 2 diabetes mellitus	17 (22.4)
Hypertension	26 (34.2)
Dyslipidaemia	14 (18.4)
Acute-phase reactants	
ESR (mm/h)	18.0 (7.0–68.0)
CRP (mg/L)	3.6 (0.8–27.0)
Laboratory results	
White blood cell count (/mm^3)	7,565.0 (5,937.5–10,490.0)
Neutrophil count (/mm^3)	4,930.0 (3,550.0–8,040.0)
Lymphocyte count (/mm^3)	1,620.0 (1,200.0–2,110.0)
Monocyte count (/mm^3)	470.0 (390.0–590.0)
Eosinophil count (/mm^3)	120.0 (60.0–270.0)
Haemoglobin (g/dL)	12.2 (10.1–13.7)
Platelet count (×1,000/mm^3)	241.0 (190.0–360.0)
Blood urea nitrogen (mg/dL)	18.7 (13.6–29.5)
Serum creatinine (mg/dL)	0.9 (0.6–1.7)
Total serum protein (g/dL)	6.8 (6.4–7.3)
Serum albumin (g/dL)	4.2 (3.7–4.4)
Serum periostin (ng/mL)	10.9 (9.5–14.5)
During follow-up	
Mortality	
All-cause mortality	5 (6.6)
Follow-up duration based on all-cause mortality	26.7 (12.2–44.7)
Medications	
Glucocorticoids	75 (98.7)
Cyclophosphamide	49 (64.5)
Rituximab	16 (21.1)
Mycophenolate mofetil	18 (23.7)
Azathioprine	45 (59.2)
Tacrolimus	7 (9.2)
Methotrexate	3 (3.9)

Values are presented as median (25–75 percentile) or number (%).
ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; SF-36, 36-item short form survey; PCS, physical component summary; MCS, mental component summary; VDI, Vasculitis Damage Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

data for further assessment of the progression to all-cause mortality during follow-up [15-17,19]; (4) a minimum follow-up of six months; (5) completion of written informed consent at diagnosis; (6) availability of sera stored at diagnosis; (7) no concomitant serious medical conditions such as malignancies and severe infectious diseases at the time of AAV diagnosis [18]; (8) no exposure to immunosuppressive drugs within four weeks before AAV diagnosis.

This study was approved by the Institutional Review Board (IRB) of Severance Hospital, Republic of Korea (IRB No. 4-2016-0901). All patients in this study provided written informed consent at the time of being included in the SHAVE cohort (at the time of both AAV diagnosis and blood sampling). The IRB waived the need for additional written informed consent when it had been previously obtained at entry into the SHAVE cohort.

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Clinical information, blood samples, and measurement of serum periostin

Clinical data as described in Table 1 were collected. Explaining several important items, first, perinuclear (P)-ANCA and cytoplasmic (C)-ANCA were accepted as ANCA results in addition to myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA according to the 2022 ACR/EULAR criteria for AAV [15-17]. Second, AAV-specific indices included the Birmingham Vasculitis Activity Score (BVAS), the Five-Factor Score (FFS), the 36-item short form survey physical and mental component summary (SF-36 PCS and SF-36 MCS), and the Vasculitis Damage Index (VDI) [20-23]. Third, type 2 diabetes mellitus, hypertension, and dyslipidaemia were recorded as comorbidities and as a part of the traditional risk factors for mortality [24]. Fourth, we investigated all-cause mortality as a poor outcome in AAV cases [25]. Although almost all patients died of two causes such as disease progression and infection, because it was impossible to clearly distinguish one from the other, we used the term, "all-cause mortality" in this study. We defined the follow-up duration based on all-cause mortality as the period from AAV diagnosis to death for deceased patients and as that from AAV diagnosis to the last visit for surviving patients. Finally, the number of patients who had ever received each medication during follow-up was counted.

Whole blood was obtained from patients with AAV on the day of the completion of written informed consent (the same day of AAV diagnosis). Sera were immediately isolated from whole blood and stored at -80°C. The concentration of serum periostin was measured using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA) from collected and stored sera at diagnosis.

Statistical analyses

All statistical analyses were performed using SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Continuous and categorical variables were expressed as medians (25–75 percentiles), and numbers (percentages). Correlation coefficients (r) between the two variables were obtained using either Pearson correlation analysis or univariable linear regression analysis. The standardised correlation coefficient (β) was obtained by multivariable linear regression analysis using variables with statistical significance in univariable analysis. Significant differences between the two categorical variables were analysed using chi-square and Fisher's exact tests. Significant differences between two continuous variables were compared using Mann–Whitney U test. A multivariable Cox proportional hazard model using variables with $p < 0.1$ in a univariable Cox analysis was performed to obtain a hazard ratio (HR) during follow-up. The significant area under the curve (AUC) was confirmed by performing a receiver operator characteristic (ROC) curve analysis. The optimal cut-off was extrapolated by performing ROC curve analysis and selected as one with the maximum sum of sensitivity and specificity the relative risk (RR) of the

Table 2. Correlation analysis of continuous variables for serum periostin at diagnosis in patients with AAV (N = 76)

Variable	Univariable	
	Correlation coefficient (r)	*p* value
Demographic data		
Age (yr)	0.282	0.013
Body mass index (kg/m^2)	0.265	0.020
AAV-specific indices		
BVAS	0.450	< 0.001
FFS	0.337	0.003
SF-36 PCS	-0.255	0.026
SF-36 MCS	-0.088	0.448
VDI	0.354	0.002
Acute-phase reactants		
ESR (mm/h)	0.361	0.002
CRP (mg/L)	0.425	< 0.001
Laboratory results		
White blood cell count (/mm^3)	0.193	0.094
Neutrophil count (/mm^3)	0.013	0.914
Lymphocyte count (/mm^3)	-0.136	0.244
Monocyte count (/mm^3)	0.038	0.748
Eosinophil count (/mm^3)	-0.026	0.823
Haemoglobin (g/dL)	-0.454	< 0.001
Platelet count (×1,000/mm^3)	-0.105	0.372
Blood urea nitrogen (mg/dL)	0.264	0.021
Serum creatinine (mg/dL)	0.284	0.013
Total serum protein (g/dL)	-0.112	0.346
Serum albumin (g/dL)	-0.447	< 0.001

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; SF-36, 36-item short form survey; PCS, physical component summary; MCS, mental component summary; VDI, Vasculitis Damage Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 3. Linear regression analysis of continuous variables at diagnosis for cross-sectional BVAS in patients with AAV

Variable	Univariable			Multivariable (without AAV-specific indices)			Multivariable (with AAV-specific indices)		
	Beta	95% CI	*p* value	Beta	95% CI	*p* value	Beta	95% CI	*p* value
Age (yr)	0.020	-0.119 to 0.142	0.862						
Body mass index (kg/m^2)	0.277	-0.657 to 0.869	0.783						
FFS	0.375	1.724–6.338	0.001				-0.133	4.011–0.766	0.179
SF-36 PCS	-0.626	-0.325 to -0.179	< 0.001				-0.029	-0.154 to 0.132	0.874
SF-36 MCS	-0.541	-0.293 to -0.138	< 0.001				-0.212	-0.211 to 0.048	0.214
VDI	0.566	1.920–3.897	< 0.001				0.213	0.139–1.976	0.025
ESR (mm/h)	0.424	0.043–0.135	< 0.001	-0.164	-0.099 to 0.030	0.289	-0.274	-0.124 to 0.009	0.087
CRP (mg/L)	0.573	0.095–0.193	< 0.001	0.231	-0.004 to 0.143	0.062	0.164	-0.028 to 0.127	0.206
White blood cell count (/mm^3)	0.585	0.809–1.576	< 0.001	0.362	0.495–1.645	< 0.001	0.324	0.397–1.511	0.001
Neutrophil count (/mm^3)	0.147	-0.070 to 0.319	0.207						
Lymphocyte count (/mm^3)	-0.092	-2.734 to 1.185	0.434						
Monocyte count (/mm^3)	0.028	-3.704 to 4.709	0.812						
Eosinophil count (/mm^3)	0.178	-1.049 to 8.345	0.126						
Haemoglobin (g/dL)	-0.553	-2.942 to -1.419	< 0.001	0.015	-0.951 to 1.079	0.900	0.018	-0.954 to 1.102	0.885
Platelet count (×1,000/mm^3)	0.263	0.002–0.031	0.023	0.077	-0.008 to 0.018	0.461	0.109	-0.006 to 0.020	0.293
Blood urea nitrogen (mg/dL)	0.161	-0.041 to 0.237	0.165						
Serum creatinine (mg/dL)	0.218	-0.052 to 2.926	0.058						
Total serum protein (g/dL)	-0.384	-6.978 to -1.915	0.001	-0.018	-3.583 to 3.149	0.898	0.104	-2.029 to 4.565	0.444
Serum albumin (g/dL)	-0.720	-12.264 to -7.737	< 0.001	-2.392	-9.800 to -0.867	0.020	-0.343	-9.640 to -0.567	0.028
Serum periostin (ng/mL)	0.450	0.473–1.277	< 0.001	0.205	0.008–0.737	0.045	0.246	0.083–0.812	0.017

BVAS, Birmingham Vasculitis Activity Score; ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; CI, confidence interval; FFS, Five-Factor Score; SF-36, 36-item short form survey; PCS, physical component summary; MCS, mental component summary; VDI, Vasculitis Damage Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

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cut-off for all-cause mortality was analysed using contingency tables and chi-square test. A comparison of the cumulative survival rates between the two groups was performed using Kaplan–Meier survival analysis with the log-rank test. *p* values < 0.05 were considered statistically significant.

RESULTS

Characteristics

The median age of the 76 patients (36 with MPA, 24 with GPA, and 16 with EGPA) was 64.0 years and, 46 patients (60.5%) were female. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 41 (53.9%), and 12 patients (15.8%), respectively. The median BVAS, FFS, SF-36 PCS, SF-36 MCS, and VDI were 5.0, 0.0, 52.5, 54.6, and 3.0, respectively. In addition, the median erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were 18.0 mm/h, and 3.6 mg/L, respectively. The median serum periostin was 10.9 ng/mL. Regarding variables during follow-up, five of the 76 patients (6.6%) died during a median follow-up of 26.7 months. Almost all patients (98.7%) received glucocorticoids; the most commonly administered immunosuppressive drug was cyclophosphamide (64.5%),

Table 4. Comparative analysis of variables at diagnosis between surviving and deceased patients with AAV

Variable	Surviving patients (n = 71)	Deceased patients (n = 5)	*p* value
Demographic data			
Age (yr)	63.0 (22.0)	74.0 (16.0)	0.087
Sex, female	44 (62.0)	2 (40.0)	0.378
Ex-smoker	3 (4.2)	0 (0.0)	> 0.999
Body mass index (kg/m^2)	22.3 (3.9)	24.5 (13.4)	0.516
AAV subtypes			0.278
MPA	32 (45.1)	4 (80.0)	
GPA	23 (32.4)	1 (20.0)	
EGPA	16 (22.5)	0 (0.0)	
ANCA positivity			
MPO-ANCA (or P-ANCA) positive	37 (52.1)	4 (80.0)	0.366
PR3-ANCA (or C-ANCA) positive	12 (16.9)	0 (0.0)	> 0.999
AAV-specific indices			
BVAS	5.0 (14.0)	18.0 (16.0)	0.074
FFS	0.0 (1.0)	2.0 (2.0)	0.050
VDI	3.0 (2.0)	5.0 (4.0)	0.013
Comorbidities			
Type 2 diabetes mellitus	14 (19.7)	3 (60.0)	0.071
Hypertension	24 (33.8)	2 (40.0)	> 0.999
Dyslipidaemia	10 (14.1)	4 (80.0)	0.003
Acute-phase reactants			
ESR (mm/h)	17.0 (62.0)	120.0 (N/A)	0.072
CRP (mg/L)	2.7 (12.5)	65.7 (N/A)	0.024
Serum periostin (ng/mL)	10.8 (4.4)	16.4 (11.4)	0.033

Values are presented as median (interquartile range) or number (%).
ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; VDI, Vasculitis Damage Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; N/A, not applicable.

followed by azathioprine (59.2%) (Table 1).

Correlation analysis among variables at diagnosis

Age and body mass index at diagnosis were significantly correlated with cross-sectional serum periostin. Moreover, BVAS (r = 0.450), FFS (r = 0.337), SF-36 PCS (r = -0.255), VDI (r = 0.354), ESR (r = 0.361), and CRP (r = 0.425) at diagnosis were significantly correlated with cross-sectional serum periostin. Among the laboratory results at diagnosis, serum periostin was positively correlated with cross-sectional blood urea nitrogen (r = 0.264), and serum creatinine (r = 0.284), and inversely correlated with haemoglobin (r = -0.454), and serum albumin (r = -0.447) (Table 2).

Linear regression analyses for BVAS among variables at diagnosis

In univariable linear regression analysis, FFS, SF-36 PCS, SF-36 MCS, VDI, ESR, white blood cell count, haemoglobin, platelet count, total serum protein, serum albumin, and serum periostin at diagnosis were significantly correlated with cross-sectional BVAS. In multivariable analysis without AAV-specific indices, white blood cell count (standardised β 0.362, 95% confidence interval [CI] 0.495–1.645), serum albumin (standardised β -2.392, 95% CI -9.800 to -0.867), and serum periostin (standardised β 0.205, 95% CI 0.008–0.737) at diagnosis were independently correlated with cross-sectional BVAS. In addition, in multivariable analysis including AAV-specific indices with statistical significance in univariable analysis, VDI (standardised β 0.213, 95% CI 0.139–1.976), white blood cell count (standardised β 0.324, 95% CI 0.397–1.511), serum albumin (standardised β -0.343, 95% CI -9.640 to -0.567), and serum periostin (standardised β 0.246, 95% CI 0.083–0.812) at diagnosis were independently correlated with cross-sectional BVAS (Table 3).

Table 5. Cox proportional hazard analyses of variables at diagnosis for all-cause mortality during follow-up in patients with AAV

Variable	Univariable			Multivariable		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Conventional risks						
Age	1.084	0.982–1.197	0.110			
Sex, male	2.234	0.373–13.372	0.379			
Ex-smoker	0.046	0.000–5,254,314.439	0.745			
Body mass index	1.302	1.028–1.650	0.029	1.155	0.813–1.641	0.421
Type 2 diabetes mellitus	5.673	0.948–33.969	0.057			
Hypertension	1.390	0.232–8.321	0.719			
Dyslipidaemia	20.840	2.323–186.921	0.007	185.496	1.914–17,973.586	0.025
AAV-specific risks						
MPA and GPA vs. EGPA	30.212	0.004–224,326.581	0.454			
MPO-ANCA (or P-ANCA) positive	4.006	0.446–35.951	0.215			
PR3-ANCA (or C-ANCA) positive	0.038	0.000–1,055.457	0.530			
BVAS	1.102	1.010–1.203	0.029	0.965	0.786–1.185	0.735
FFS	3.125	0.997–9.793	0.051			
VDI	1.789	1.157–2.765	0.009	1.772	0.868–3.619	0.116
Inflammation-related risks						
ESR	1.027	0.998–1.056	0.064			
CRP	1.019	1.002–1.036	0.029	1.039	0.983–1.099	0.174
Serum periostin	1.189	1.063–1.329	0.002	0.880	0.669–1.157	0.361

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; HR, hazard ratio; CI, confidence interval; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; VDI, Vasculitis Damage Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

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Comparison of variables at diagnosis according to all-cause mortality

Deceased patients tended to be older than surviving patients (74.0 years vs. 63.0 years, $p = 0.087$). Among the variables regarding AAV-specific indices at diagnosis, VDI in deceased patients was significantly higher than that in surviving patients (5.0 vs. 3.0, $p = 0.013$). BVAS and FFS also exhibited similar patterns but no statistical significance was found. Among comorbidities at diagnosis, deceased patients had dyslipidaemia more frequently than surviving patients (80.0% vs. 14.1%, $p = 0.003$). Type 2 diabetes mellitus also showed a similar pattern but it did not reach significance. Among inflammatory indices, CRP showed a significant difference between deceased and surviving patients (65.7 mg/L vs. 2.7 mg/L, $p = 0.024$). ESR also presented a similar tendency despite no statistical significance. Finally, deceased patients were demonstrated to have significantly higher serum periostin than surviving patients (16.4 ng/mL vs. 10.8 ng/mL, $p = 0.033$). Therefore, we concluded that from a strictly statistical point of view, serum periostin, along with VDI, dyslipidaemia, and CRP, exhibited a significantly elevated value in deceased patients compared to surviving patients at the time of AAV diagnosis (Table 4).

Cox proportional hazard analyses for all-cause mortality

First of all, we divided variables at diagnosis into three categories according to the risk factors adjusted to the disease condition of AAV such as conventional, AAV-specific, and inflammatory-related risks [24,25]. In univariable Cox analysis, among conventional risks, body mass index, and dyslipidaemia were significantly associated with all-cause mortality. Among AAV-specific risks, BVAS, and VDI were significantly associated with all-cause mortality. Among inflammation-related risks, only CRP was significantly associated with all-cause mortality. Finally, serum periostin also exhibited a significant association with all-cause mortality. In multivariable Cox analysis including only variables with significance in univariable analysis, only the presence of baseline dyslipidaemia was identified to be significantly and independently associated with all-cause mortality during follow-up in patients with AAV (Table 5).

Cut-off and RR for all-cause mortality and cumulative survival rates

Using ROC curve analysis, the optimal cut-off of serum periostin at diagnosis for all-cause mortality during follow-up was set as 15.9 ng/mL (AUC 0.787, 95% CI 0.525–1.000, $p = 0.033$). The sensitivity and specificity of this cut-off were 80.0%, and 90.1%, respectively (Fig. 1A). When patients were divided into two groups according to serum periostin at diagnosis of 15.9 ng/mL, all-cause mortality during follow-up was identified more commonly in patients with serum periostin ≥ 15.9 ng/mL at diagnosis in than those with a lower value (36.4% vs. 1.5%, $p = 0.001$). Additionally, they also had a significantly higher risk for all-cause mortality during follow-up than those with serum periostin < 15.9 ng/mL at diagnosis (RR 36.571, 95% CI 3.572–374.407) (Fig. 1B). Patients with serum periostin ≥ 15.9 ng/mL at diagnosis had a significantly lower cumulative patients' survival rate than those with serum periostin < 15.9 ng/mL at diagnosis ($p < 0.001$) (Fig. 1C).

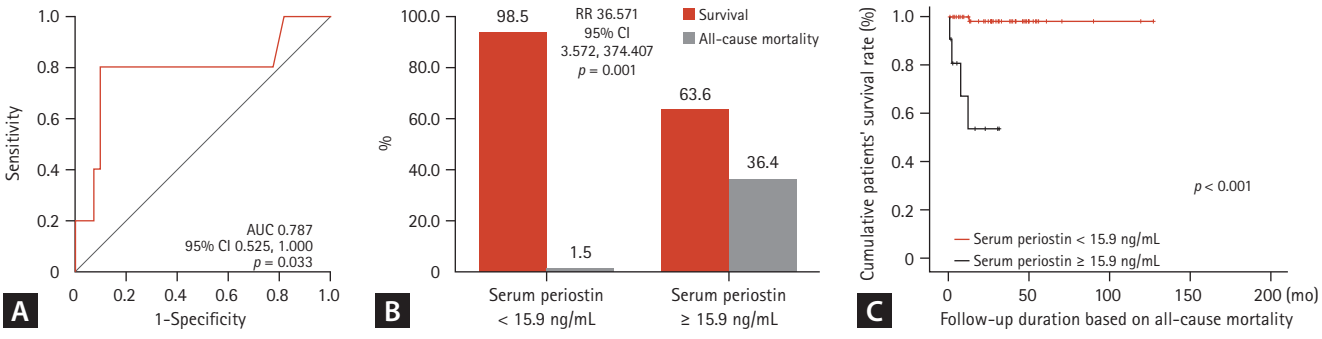

Figure 1. RR for all-cause mortality and cumulative survival rates. (A) Cut-off of serum periostin was set as 15.9 ng/mL. (B) Patients with serum periostin ≥ 15.9 ng/mL at diagnosis exhibited a significantly higher risk for all-cause mortality during follow-up than those without. (C) Patients with serum periostin ≥ 15.9 ng/mL at diagnosis exhibited a significantly lower cumulative patients' survival rate than those without. AUC, area under the curve; CI, confidence interval; RR, relative risk.

DISCUSSION

This study investigated the clinical utility of serum periostin in AAV and there were several notable findings. First, serum periostin at diagnosis was significantly correlated with cross-sectional AAV activity and acute-phase reactants. Additionally, serum periostin at diagnosis exhibited the potential as a predictor of all-cause mortality during follow-up in patients with AAV. In particular, clinical implication of this study is that this is the first to elucidate the clinical roles of serum periostin at diagnosis during the disease course of AAV.

We speculated that the mechanistic background enables serum periostin to play a crucial clinical role in patients with AAV. IL-4 and IL-13 have been reported to enhance gene expression and production of periostin, revealing the immunological mechanisms involved in the pathogenesis of asthma [2,5]. In addition, a previous study reported the clinical role of serum periostin in patients with EGPA, including an allergic component [11]. Therefore, based on these prior studies, we divided the patients into two groups; patients with MPA and GPA, and patients with EGPA, and predictions were made by comparing the variables between the two groups. First, the count of eosinophils at diagnosis may be higher in patients with EGPA than in those with MPA and GPA. As expected, patients with EGPA exhibited a higher median eosinophil count than those with MPA and GPA (280.0/mm^3 vs. 90.0/mm^3, $p = 0.003$). Second, serum periostin may be higher in patients with EGPA than in those with MPA and GPA. This is because periostin production is influenced by the eosinophil-specific cytokines, IL-4, and IL-13. However, in contrast to our expectations, patients with EGPA had a significantly lower median serum periostin than those with MPA and GPA (9.3 ng/mL vs. 11.7 ng/mL, $p < 0.001$). Moreover, when serum periostin was adjusted for BVAS, patients with EGPA had a significantly reduced median serum periostin/BVAS ratio compared to those with MPA and GPA (1.1 vs. 2.0, $p = 0.040$). Therefore, based on these results, it can be reasonably concluded that serum periostin in AAV, including EGPA, may be affected by signalling pathways other than those involving IL-4 or IL-13 [2,5,7,8].

Ideally, this issue should be clarified by investigating the intracellular signalling pathways involved in the crosslink between serum periostin and cross-sectional BVAS. However, because the cells that produce and secrete periostin or the tissues with these cells were no obtained from the patients included in this study, this proved impractical. Nevertheless, several inferences are made based on the results of multivariable linear regression analysis of the variables at diagnosis (Table 3). In multivariable linear regression analysis, the ability of serum periostin to independently reflect the current activity of AAV was proved to be comparable to that of VDI. Therefore, the first inference is that serum periostin may reflect cross-sectional BVAS by participating in intracellular signals related to the pathogenesis of AAV, that could induce damage in various major organs [23,26,27]. In addition, multivariable analysis revealed that the potential of serum periostin to independently estimate cross-sectional BVAS was not inferior to white blood cell count and serum albumin. Therefore, the second inference is that serum periostin may indirectly estimate cross-sectional BVAS by facilitating intracellular signals related to general inflammatory reactions [28]. These findings highlight that serum periostin is linked to intracellular signalling pathways directly and indirectly related to AAV, which we believe may represent a great advantage as a biomarker.

In the present study, we found that serum periostin at diagnosis was significantly and independently correlated with cross-sectional BVAS in patients with AAV. We further investigated which of the nine systemic items of BVAS contributed to the observed correlation with serum periostin [20]. Among the items of BVAS, serum periostin was significantly correlated with general ($r = 0.280$, $p = 0.014$), pulmonary ($r = 0.237$, $p = 0.039$), renal ($r = 0.530$, $p < 0.001$), and neurological ($r = 0.245$, $p = 0.033$) manifestations (Supplementary Table 1). Additionally, we identified more detailed correlations between serum periostin and the subitems of each systemic item of BVAS as follows: among the subitems of general manifestations, serum periostin was significantly correlated with arthralgia/arthritis ($r = 0.278$, $p = 0.015$) and high fever ($r = 0.276$, $p = 0.016$). Among the subitems of pulmonary manifestations, serum periostin was significantly correlated with diffuse alveolar haemorrhage ($r = 0.328$, $p = 0.004$). Among the subitems of renal manifestations, serum periostin was significantly correlated with proteinuria > 1+ ($r = 0.501$, $p < 0.001$), haematuria ($r = 0.503$, $p < 0.001$), and serum creatinine ranging from 1.14 to 2.82 mg/dL ($r = 0.315$, $p = 0.006$). However, among the subitems of neurological systemic manifestations, no correlation was observed between serum periostin and the subitems. Although limited information prevented further analysis, given

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that previous studies have reported an association between periostin and central neurological events, lung and kidney diseases, and arthritis [7,8], we believe that this result may be inferred to have some validity and may support the clinical utility of serum periostin in patients with AAV.

The present study also investigated whether serum periostin at diagnosis has a predictive potential for all-cause mortality during follow-up in patients with AAV. We have provided a method to obtain the cut-off of serum periostin for all-cause mortality and demonstrated that patients with serum periostin exceeding the cut-off had a significantly increased risk of death and a decreased cumulative survival rate compared to those without (Fig. 1). However, we failed to demonstrate the independent ability of serum periostin at diagnosis for predicting all-cause mortality in patients with AAV in multivariable Cox proportional hazard analysis (Table 5). Nonetheless, since we found the clinical potential of serum periostin for mortality, we inferred how periostin could predict all-cause mortality through the results that serum periostin, along with the frequency of dyslipidaemia and the levels of VDI and CRP, was significantly higher in deceased patients than in surviving patients described in Table 4. First, in terms of dyslipidaemia as a conventional risk for mortality, in this study, patients having dyslipidaemia had a significantly higher serum periostin than those without (14.0 ng/mL vs. 10.7 ng/mL, $p = 0.044$). Therefore, it is inferred that serum periostin at diagnosis might have the predictive ability for all-cause mortality by interacting with the presence of dyslipidaemia [24]. Second, in terms of VDI as an AAV-specific risk for mortality, serum periostin exhibited a highly close correlation with cross-sectional VDI (Table 2). In the present study, VDI at diagnosis was defined as the first VDI assessing the items lasting for at least 3 months after the first clinical manifestation related to AAV. A recently published study demonstrated the independent predictive potential of the earliest VDI for all-cause mortality in patients with AAV [29]. Therefore, it is also inferred that serum periostin at diagnosis might have the predictive ability for death by borrowing the earliest VDI's ability to predict all-cause mortality during follow-up in patients with AAV. Third, in terms of CRP as an inflammation-related risk for mortality, serum periostin was also significantly correlated with cross-sectional CRP levels (Table 2). Therefore, it is inferred that serum periostin at diagnosis might have the predictive ability for all-cause mortality during follow-up by being affected by the inflammatory burden at diagnosis [30].

The advantage of the present study is that this is the first to investigate the clinical perspectives involving serum periostin in patients with AAV and to demonstrate further that serum periostin at diagnosis could not only reflect cross-sectional AAV activity but also help to foresee all-cause mortality during follow-up. Therefore, as a pilot study, this study is believed to provide valuable information surrounding the clinical significance of serum periostin as a biomarker for AAV activity and prognosis.

The present study had certain limitations. First, although all study subjects were selected from the prospective and observational cohort of AAV patients, their clinical data were analysed retrospectively, and thus, posed difficulties in further analysis of several variables not included in this study. Owing to the characteristics of a pilot study, the number of enrolled patients was insufficient to generalise the results of this study and apply them to real-world clinical practice immediately. The most critical issue regarding this study might be the absence of mechanistic research and analysis of the intracellular signalling pathways linking serum periostin and both AAV activity at diagnosis and AAV-associated mortality during follow-up. Cross-sectional measurement of serum periostin at diagnosis might also be another limitation. We believe that a prospective future study that includes more patients and serially measures serum periostin will provide more reliable and dynamic information concerning the clinical perspective of serum periostin in patients with AAV not only at diagnosis but also during monitoring and follow-up periods.

In conclusion, this study is the first to demonstrate that serum periostin measured at diagnosis could independently reflect cross-sectional vasculitis activity at diagnosis and further contribute to the prediction of all-cause mortality during follow-up in patients with AAV. Additionally, this study also suggested that mechanisms underpinning the clinical roles of serum periostin might be linked to both intracellular signalling pathways directly and indirectly related to AAV, which may represent a great advantage as a biomarker.

KEY MESSAGE

1. Serum periostin at diagnosis was significantly correlated with cross-sectional AAV activity and acute-phase reactants.
2. Serum periostin at diagnosis was independently correlated with cross-sectional BVAS.
3. Serum periostin at diagnosis exhibited the potential as a predictor of all-cause mortality during follow-up in patients with AAV.

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Conflict of interest
The authors disclose no conflicts.

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Supplementary Table 1. Correlation analysis of systemic items of BVAS at diagnosis for cross-sectional serum periostin in patients with AAV (N = 76)

Variable	Univariable	
	Correlation coefficient	*p* value
Systemic items of BVAS		
General manifestation	0.280	0.014
Cutaneous manifestation	0.013	0.909
Mucous and ocular manifestation	-0.166	0.151
Otorhinolaryngologic manifestation	-0.155	0.183
Pulmonary manifestation	0.237	0.039
Cardiovascular manifestation	0.004	0.972
Gastrointestinal manifestation	N/A	N/A
Renal manifestation	0.530	< 0.001
Neurological manifestation	0.245	0.033

BVAS, Birmingham Vasculitis Activity Score; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; N/A, not applicable.