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Adjusted Global Antiphospholipid Syndrome Score Is Associated with End-Stage Kidney Disease in Patients with ANCA-Associated Vasculitis: A Single-Centre Pilot Study

Pil Gyu Park[1]*, Hyun Joon Choi[2]*, Yong-Beom Park[3,4], and Sang-Won Lee[3,4]

[1]Division of Rheumatology, Department of Internal Medicine, National Health Insurance Service Ilsan Hospital, Goyang;
[2]Department of Medicine, Yonsei University College of Medicine, Seoul;
[3]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[4]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea.

Purpose: The adjusted Global Antiphospholipid Syndrome (APS) Score (aGAPSS) was developed for assessing the probability of thrombotic events in APS patients. This study investigated whether the aGAPSS at diagnosis was associated with poor outcomes during follow-up in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Materials and Methods: This study included 170 AAV patients who had the results of APS-related antibodies at diagnosis but were not diagnosed with APS. All-cause mortality, end-stage kidney disease (ESKD), cerebrovascular accident, and acute coronary syndrome were considered poor AAV outcomes. The aGAPSS comprises five items, with 5, 4, 4, 3, and 1 points assigned to anticardiolipin antibodies, anti-β2-glycoprotein 1 antibodies, lupus anticoagulants, hyperlipidaemia, and arterial hypertension at AAV diagnosis, respectively.

Results: The median age of the 170 patients [93 microscopic polyangiitis (MPA), 44 granulomatosis with polyangiitis (GPA), and 33 eosinophilic GPA (EGPA)] was 63.0 years. The optimal cut-off of the aGAPSS at diagnosis for ESKD during follow-up was set as two using the receiver operating characteristic curve. AAV patients with an aGAPSS ≥2 at diagnosis exhibited a significantly reduced ESKD-free survival rate compared to those with an aGAPSS <2 at diagnosis (p=0.045). Additionally, MPA and GPA patients, excluding EGPA patients for whom the median aGAPSS at diagnosis was close to 0, also showed similar patterns to the results among the 170 patients with AAV (p=0.021).

Conclusion: This study is the first to demonstrate that the aGAPSS at diagnosis was significantly associated with ESKD during follow-up in AAV patients without APS.

Key Words: Adjusted Global Anti-Phospholipid Syndrome Score, predict, end-stage kidney disease, antineutrophil cytoplasmic antibody, vasculitis

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease that is characterised by typical clinical phenotypes, including thrombotic events and obstetric complications, in the presence of consecutive APS-related antibodies, such as anticardiolipin antibodies (aCL) IgG/IgM, anti-β2-glycoprotein 1 antibodies (aβ2GPI) IgG/IgM, and lupus anticoagulant (LA).[1] To date, various indices have been developed for assessing thrombotic risks in APS patients, among which a Global Antiphospholipid Syndrome Score (GAPSS) was proposed by Sciascia, et al.[2] in 2013. The GAPSS comprises six items, in-

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Corresponding author: Sang-Won Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
E-mail: sangwonlee@yuhs.ac

*Pil Gyu Park and Hyun Joon Choi contributed equally to this work.
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cluding aCL IgG/IgM, aβ2GPI IgG/IgM, LA, antiphosphatidylserine/prothrombin antibody (aPS/PT) complex IgG/IgM, hyperlipidaemia, and arterial hypertension, with a differently weighted point assigned to each item. The highest total score of the GAPSS is 20.[2] In contrast, the adjusted GAPSS (aGAPSS), which does not include an item of the aPS/PT complex IgG/IgM due to its fluctuating and inaccurate levels over time, was introduced. Therefore, the aGAPSS consists of five items, and its highest total score decreased to 17.[3] According to previous studies, the aGAPSS at the time of APS diagnosis has been demonstrated to be associated with thrombotic complications in APS patients.[4,5]

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease that is characterised by necrotising vasculitis in small- and medium-sized vessels.[6,7] AAV has three subtypes based on its clinical features: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA).[8-11] A previous study involving a considerable number of participants reported that the risk of cardiovascular and cerebrovascular thrombotic events in patients with AAV was higher than that of age- and sex-matched healthy controls.[12] Given that the aGAPSS assesses thrombotic risks, it could be theoretically assumed that the aGAPSS may reflect the increased risk of cerebrovascular or cardiovascular thrombotic events in AAV patients without primary or secondary APS. However, no study has investigated the clinical usefulness of the aGAPSS at diagnosis for predicting poor outcomes in AAV patients without APS. Hence, the present study included AAV patients without APS and investigated whether the aGAPSS at diagnosis might be associated with poor outcomes during follow-up in a single-centre cohort of AAV.

MATERIALS AND METHODS

Study population

We retrospectively screened the medical records of 195 patients with AAV enrolled in the Severance Hospital ANCA-associated vasculitides cohort. The inclusion criteria for the present study were as follows: 1) patients who were diagnosed with AAV for the first time at the Division of Rheumatology, the Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from October 2000 to March 2023; 2) patients who met the 2007 European Medicine Agency algorithm for AAV and polyarteritis nodosa, the revised 2012 Chapel Hill Consensus Conference Nomenclature of Vasculitides, and the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for MPA, GPA, and EGPA;[6-11] 3) patients who had the medical records from which sufficient clinical, laboratory, radiological, and histological data could be obtained, particularly regarding AAV-specific indices such as the Birmingham Vasculitis Activity Score (BVAS), and the Five-Factor Score (FFS),[13,14] and variables to calculate the aGAPSS at AAV diagnosis; 4) patients who had the results of tests for myeloperoxidase (MPO)-ANCA [or perinuclear (P)-ANCA] and proteinase 3 (PR3)-ANCA [or cytoplasmic (C)-ANCA] as well as those for aCL IgG/IgM, aβ2GPI IgG/IgM, and LA at diagnosis; 5) patients who had been followed up for 3 months or more; 6) patients who had never been diagnosed with APS before or at AAV diagnosis; 7) patients who had no concomitant serious medical conditions mimicking AAV, such as infectious disease requiring hospitalisation or malignancies at AAV diagnosis; and 8) patients who had not been exposed to immunosuppressive drugs or glucocorticoids (≥10 mg equivalent to prednisolone) within 3 months before AAV diagnosis. Co-existing serious medical conditions and immunosuppressive drugs administered were identified by the 10th revised International Classification Diseases and the Korean Drug Utilization Review system, respectively. Of the 195 patients, six patients were excluded as they had been diagnosed with APS before or at AAV diagnosis. Additionally, 19 patients were further excluded as they had no results of tests for aCL IgG/IgM, aβ2GPI IgG/IgM, and LA at AAV diagnosis. Finally, 170 patients were included and analysed in the present study.

Ethical disclosure

The present study was approved by the Institutional Review Board (IRB) of Severance Hospital, Seoul, Republic of Korea (IRB No. 4-2020-1071), and conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective design of the study and use of anonymised patient data.

Clinical and laboratory data at diagnosis

Demographic data included age, sex, body mass index, and smoking history. Additionally, data including AAV subtype, ANCA positivity, and AAV-specific indices (BVAS for AAV activity and FFS for prognosis), and acute-phase reactants, such as erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), were also collected. Comorbidities, such as type 2 diabetes mellitus, arterial hypertension, and hyperlipidaemia, were investigated.

Measurement of ANCA and APS-related antibodies

MPO-ANCA and PR3-ANCA levels were measured using immunoassays, whereas the presence of P-ANCA and C-ANCA was confirmed using indirect immunofluorescence assays.[15] APS-related antibodies, including aCL IgG/IgM and anti-β2GPI IgG/IgM, were tested using automated immunoassay with a fluorescence enzyme immunoassay method. LA was screened and confirmed using diluted Russell viper venom time.[16,17]

Calculation of the aGAPSS

The aGAPSS comprises five items with 5, 4, 4, 3, and 1 points assigned to aCL IgG/IgM, aβ2GPI IgG/IgM, LA, hyperlipidaemia, and arterial hypertension, respectively. The total score of

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the aGAPSS ranges from 0 to 17.[3]

Clinical data during follow-up

In the present study, all-cause mortality, end-stage kidney disease (ESKD), cerebrovascular accident (CVA), and acute coronary syndrome (ACS) were considered poor AAV outcomes. The follow-up duration based on each poor outcome was defined as the period from AAV diagnosis to the occurrence of each poor outcome in AAV patients with who experienced it, and from AAV diagnosis to the last visit for those who did not. The number of patients who received glucocorticoids, cyclophosphamide, rituximab, azathioprine, mycophenolate mofetil, tacrolimus, or methotrexate during follow-up was recorded.

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 with 25–75 percentiles and numbers (percentages), respectively. Significant differences between two categorical variables were analysed using the chi-square and Fisher's exact tests. Significant differences between two and three continuous variables were compared using the Mann–Whitney U and Kruskal–Wallis tests, respectively. Correlation coefficients (r) between the two variables were obtained using the Pearson correlation analysis. The optimal cut-offs were extrapolated by performing receiver operating characteristic (ROC) curve analysis, and one value with the maximum sum of sensitivity and specificity was selected. Relative risk (RR) of the cut-off for each poor outcome was analysed using contingency tables and the chi-square test. Comparison of the cumulative survivals rates between the two groups was analysed by Kaplan–Meier survival analysis with a log-rank test. Multivariable Cox hazard model using variables with statistical significance in univariable Cox hazard model was conducted to appropriately obtain the hazard ratios (HRs) during follow-up. Statistical significance was set at $p<0.05$.

RESULTS

Characteristics of AAV patients

Regarding variables at diagnosis, the median age of the patients was 63.0 years and 39.4% were males. Of the 170 patients, 93, 44, and 33 were diagnosed with MPA, GPA, and EGPA, respectively. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 124 and 26 patients, respectively. The median BVAS, FFS, ESR, and CRP were 12.0, 1.0, 61.0 mm/h, and 12.9 mg/L, respectively. Of the 170 patients, 41, 61, and 32 had type 2 diabetes mellitus, arterial hypertension, and hyperlipidaemia, respectively. Among the five APS-related antibodies, aCL IgG, aCL IgM, aβ2GPI IgG, aβ2GPI IgM, and LA were positive in 10, 6, 5, 4, and 39 patients, respectively. The median aGAPSS was calculated as 3.0. Regarding variables during follow-up, among the 170 patients, 20 died, and 34, 17, and 4 develped ESKD, CVA, and ACS, respectively. Glucocorticoids were prescribed for 168 patients. The most frequently administered immunosuppressive drug was cyclophosphamide (60.0%), followed by azathioprine (57.6%) (Table 1).

Correlation analysis

Among the continuous variables at diagnosis, FFS (r=0.175, $p=0.022$), ESR (r=0.267, $p<0.001$), CRP (r=0.164, $p=0.033$), haemoglobin (r=-0.276, $p<0.001$), platelet count (r=0.163, $p=0.033$), serum creatinine (r=0.170, $p=0.027$), serum albumin (r=-0.237, $p=0.002$), and estimated glomerular filtrate rate (eGFR) (r=-0.219, $p=0.004$) were significantly correlated with the aGAPSS (Table 2).

Comparative analysis

Among the variables at diagnosis, the median aGAPSS in EGPA patients was significantly lower than that in MPA and GPA patients (0 vs. 3.0, and 3.0, $p=0.014$). Additionally, AAV patients with MPO-ANCA (or P-ANCA) exhibited a significantly higher median aGAPSS compared to those without (3.0 vs. 0, $p=0.029$). However, there were no significant differences in the aGAPSS between the two groups according to PR3-ANCA (or C-ANCA) positivity or sex. Among the four poor outcomes during follow-up, only AAV patients with ESKD exhibited a significantly higher median aGAPSS at diagnosis compared to those without ESKD (3.5 vs. 3.0, $p=0.017$) (Fig. 1). Contrary to initial expectations, the aGAPSS at diagnosis was associated with neither CVA nor ACS during follow-up in AAV patients.

Optimal cut-off of the aGAPSS for ESKD and RR

Using ROC curve analysis, the area under the curve (AUC) of the aGAPSS at AAV diagnosis for ESKD was found to be statistically significant [AUC 0.628, 95% confidence interval (CI) 0.523–0.732]. When the cut-off of the aGAPSS at diagnosis was set as 2, the sensitivity and specificity were 73.5% and 49.3%, respectively. When AAV patients were divided into two groups according to the aGAPSS ≥2 at diagnosis, ESKD was observed more frequently in patients with an aGAPSS ≥2 at diagnosis than in those with an aGAPSS <2 at diagnosis (26.6% vs. 11.8%, RR 2.697, 95% CI 1.173–6.203) (Fig. 2A). Meanwhile, since the median aGAPSS at diagnosis in EGPA patients was close to 0, and only six patients with EGPA had ESKD during follow-up, we included only 93 patients with MPA and 44 with GPA in these analyses. We found that a cut-off of an aGAPSS ≥2 at diagnosis was still optimal for predicting ESKD (AUC 0.671, 95% CI 0.562–0.781), with a sensitivity and specificity of 82.1% and 45.0%, respectively. Similarly, patients with an aGAPSS ≥2 at diagnosis exhibited a higher frequency of ESKD compared to those with an aGAPSS <2 at diagnosis (27.7% vs. 9.3%, RR 3.757, 95% CI 1.330–10.609) (Fig. 2B).

Table 1. Characteristics of AAV Patients (n=170)

Variables	Values
At the time of AAV diagnosis	
Demographic data	
Age (yr)	63.0 (50.0–70.33)
Male sex	67 (39.4)
Body mass index (kg/m^2)	22.7 (20.3–24.2)
Smoking history	9 (5.3)
AAV subtypes	
MPA	93 (54.7)
GPA	44 (25.9)
EGPA	33 (19.4)
ANCA positivity	
MPO-ANCA (or P-ANCA) positivity	124 (72.9)
PR3-ANCA (or C-ANCA) positivity	26 (15.3)
Both ANCA positivity	7 (4.1)
ANCA negativity	27 (15.9)
AAV-specific indices	
BVAS	12.0 (7.0–18.0)
FFS	1.0 (0–2.0)
Acute-phase proteins	
ESR (mm/h)	61.0 (23.0–101.8)
CRP (mg/L)	12.9 (1.6–63.9)
Comorbidities at diagnosis	
Type 2 diabetes mellitus	41 (24.1)
Arterial hypertension	61 (35.9)
Hyperlipidaemia	32 (18.8)
Laboratory results	
White blood cell (×1000/mm^3)	9180.0 (6692.5–12882.5)
Haemoglobin (g/dL)	11.3 (9.6–13.2)
Platelet count (×1000/mm^3)	304.5 (221.0–400.3)
Blood urea nitrogen (mg/dL)	18.2 (13.8–29.9)
Serum creatinine (mg/dL)	0.9 (0.6–1.8)
Serum total protein (g/dL)	6.8 (6.1–7.2)
Serum albumin (g/dL)	3.7 (3.2–4.2)
eGFR (mL/min/1.73m^2)	88.0 (33.5–101.3)
APS-related antibodies	
aCL IgG	10 (5.9)
aCL IgM	6 (3.5)
aCL (IgG+IgM)	16 (9.4)
aβ2GPI IgG	5 (2.9)
aβ2GPI IgM	4 (2.4)
aβ2GPI (IgG+IgM)	9 (5.3)
LA	39 (22.9)
aGAPSS	3.0 (0–4.0)
During follow-up period	
Poor outcomes during follow-up	
All-cause mortality	20 (11.8)
Follow-up duration based on all-cause mortality (months)	37.9 (13.6–60.9)
ESKD	34 (20.0)
Follow-up duration based on ESKD (months)	33.0 (8.8–58.5)
CVA	17 (10.0)
Follow-up duration based on CVA (months)	32.1 (10.6–59.2)
ACS	4 (2.4)
Follow-up duration based on ACS (months)	35.4 (12.4–61.2)
Medications administered during follow-up	
Glucocorticoid	168 (98.8)
Cyclophosphamide	102 (60.0)
Rituximab	34 (20.0)
Azathioprine	98 (57.6)
Mycophenolate mofetil	43 (25.3)
Tacrolimus	13 (7.6)
Methotrexate	11 (6.5)

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; 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; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; eGFR, estimated glomerular filtrate rate; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-glycoprotein 1 antibodies; LA, lupus anticoagulant; aGAPSS, adjusted Global Antiphospholipid Syndrome Score; ESKD, end-stage kidney disease; CVA, cerebrovascular accident; ACS, acute coronary syndrome.
Values are expressed as a median (25–75 percentiles) or n (%).

Table 2. Correlation of aGAPSS with Continuous Variables at the Time of AAV Diagnosis

Continuous variables	Correlation coefficient (r)	*p* value
Age	0.121	0.116
Body mass index	0.147	0.057
BVAS	0.085	0.271
FFS	0.175	0.022
ESR	0.267	<0.001
CRP	0.164	0.033
White blood cell	0.026	0.737
Haemoglobin	-0.276	<0.001
Platelet count	0.163	0.033
Blood urea nitrogen	0.113	0.144
Serum creatinine	0.170	0.027
Serum total protein	-0.106	0.168
Serum albumin	-0.237	0.002
eGFR	-0.219	0.004

aGAPSS, adjusted Global Antiphospholipid Syndrome Score; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; eGFR, estimated glomerular filtrate rate.

Comparative analysis of cumulative ESKD-free survival rates

Among the 170 patients, patients with an aGAPSS ≥2 at diagnosis exhibited a significantly reduced ESKD-free survival rate compared to those with an aGAPSS <2 at diagnosis (p=0.045) (Fig. 3A). Additionally, among the 137 patients with MPA and GPA, patients with an aGAPSS ≥2 at diagnosis also showed a

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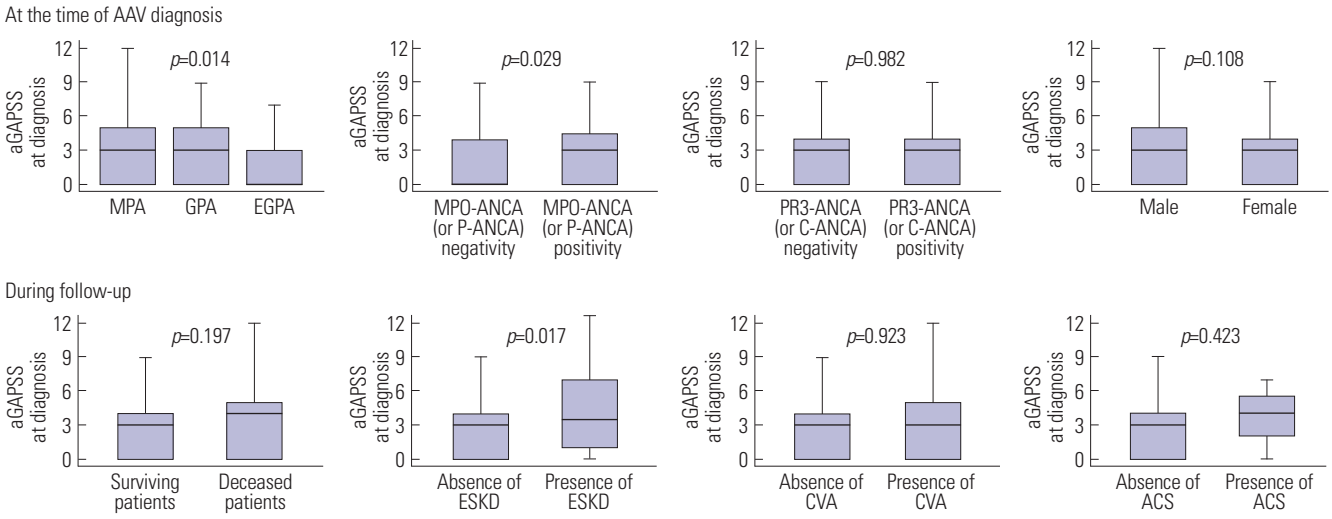

Fig. 1. Comparative analysis of the aGAPSS at diagnosis among groups. AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; aGAPSS, adjusted Global Antiphospholipid Syndrome Score; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; ESKD, end-stage kidney disease; CVA, cerebrovascular accident; ACS, acute coronary syndrome.

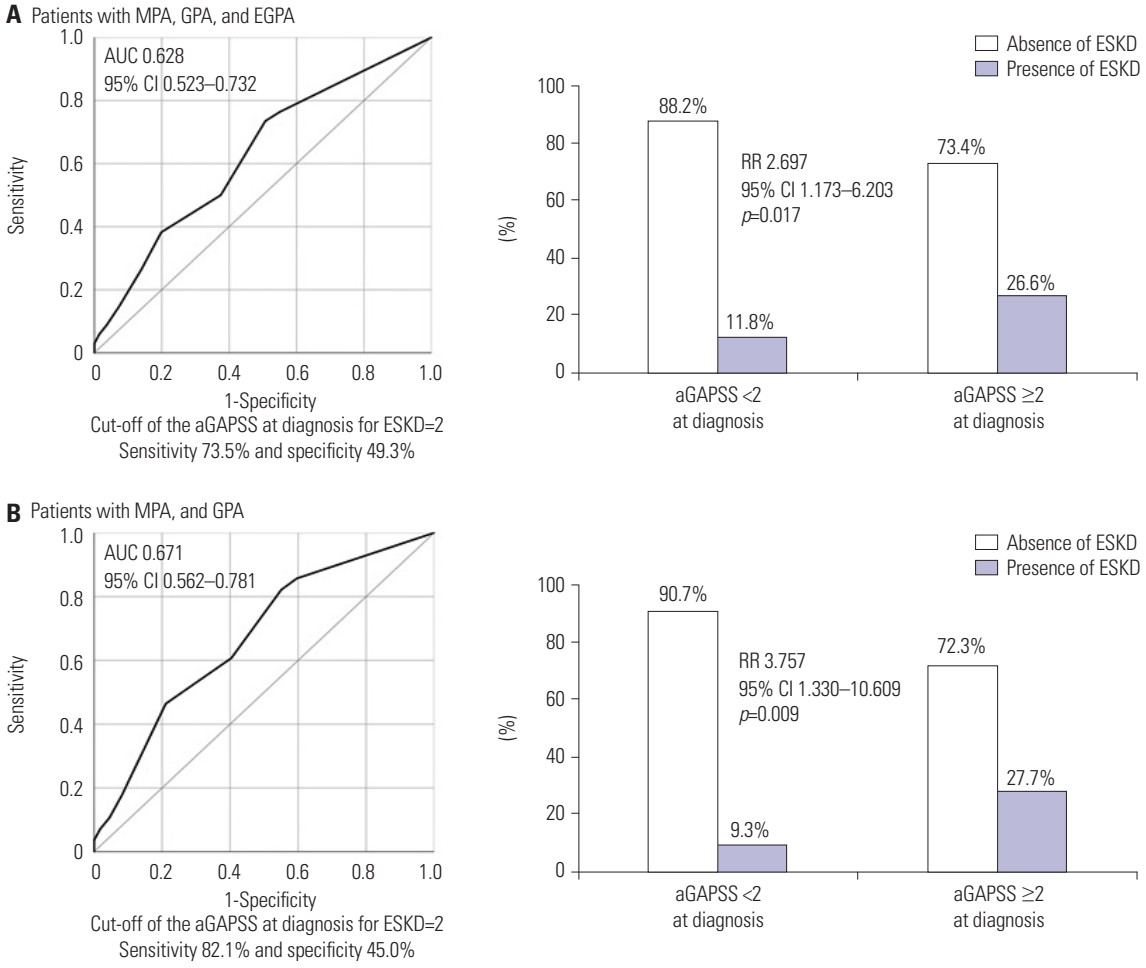

Fig. 2. Optimal cut-offs of the aGAPSS at diagnosis for ESKD during follow-up and RR. (A) Among MPA, GPA, and EGPA patients, ESKD was observed more frequently in patients with an aGAPSS ≥2 at diagnosis than in those with an aGAPSS <2 at diagnosis. (B) Among MPA, and GPA patients, patients with an aGAPSS ≥2 at diagnosis exhibited a higher frequency of ESKD than those with an aGAPSS <2 at diagnosis. aGAPSS, adjusted Global Antiphospholipid Syndrome Score; ESKD, end-stage kidney disease; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; AUC, area under the curve; CI, confidence interval; RR, relative risk.

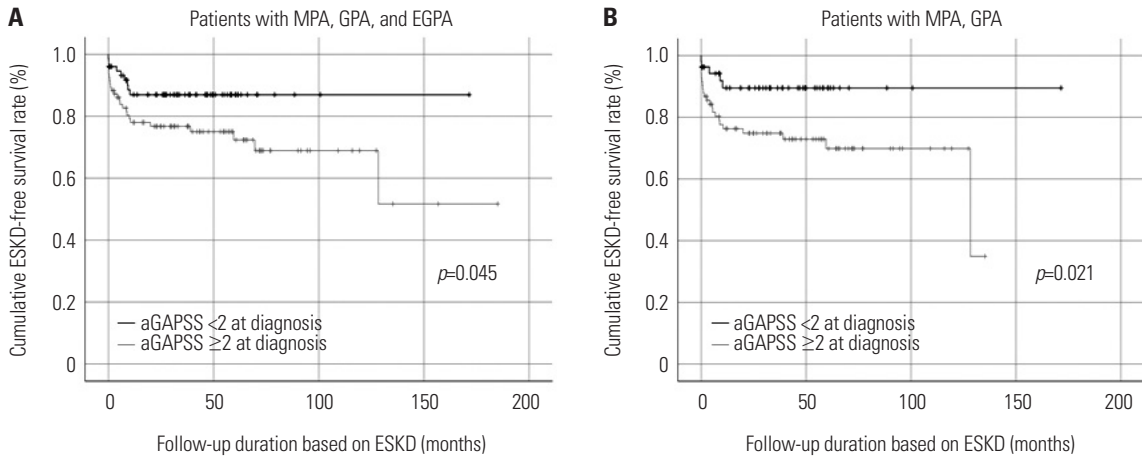

Fig. 3. Comparative analysis of cumulative ESKD-free survival rates. Among both MPA, GPA, and EGPA patients (A), as well as among MPA and GPA patients (B), patients with an aGAPSS ≥2 at diagnosis exhibited a significantly reduced ESKD-free survival rate compared to those with an aGAPSS <2 at diagnosis. ESKD, end-stage kidney disease; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; aGAPSS, adjusted Global Antiphospholipid Syndrome Score.

significantly lower ESKD-free survival rate than those with an aGAPSS <2 at diagnosis (p=0.021) (Fig. 3B).

DISCUSSION

In the present study, despite no association of the aGAPSS with CVA or ACS contrary to initial expectations, we found that the aGAPSS at diagnosis was associated with ESKD during follow-up. We obtained the cut-off of the aGAPSS at diagnosis for ESKD as 2 and demonstrated that ESKD was observed more frequently in patients with an aGAPSS ≥2 at diagnosis than in those with an aGAPSS <2 at diagnosis. We also unveiled that AAV patients with an aGAPSS ≥2 at diagnosis exhibited a significantly reduced ESKD-free survival rate compared to those with an aGAPSS <2 at diagnosis. The results in the analysis, which included only MPA and GPA patients, and excluded EGPA patients, for whom the median aGAPSS at diagnosis was close to 0, showed similar patterns to these results. Therefore, we concluded that the aGAPSS at diagnosis might be associated with progression to ESKD follow-up in AAV patients without APS.

Since there are no controlled studies with sufficient data on AAV patients with APS-related antibodies but without APS diagnosis, it is currently impossible to suggest an exact mechanism for how the aGAPSS at diagnosis might be associated with ESKD based on the results of the present study. However, through a literature review regarding the close link between AAV and APS itself or APS-related antibodies, which mainly comprised the aGAPSS equation, we provided several suggestions. First, a previous study reported a case in which a patient with MPA with APS exhibited P-ANCA positivity and pauci-immune glomerulonephritis (GN) on kidney biopsy. This case suggests two possible explanations: 1) APS-related antibodies may indirectly affect P-ANCA generation and subsequently induce ANCA-associated GN; and 2) APS-related antibodies may directly provoke glomerular endothelial inflammation, with P-ANCA being detected coincidently or falsely.[18] Second, another study reported a case in which ANCA-associated GN and APS occurred simultaneously after COVID-19 infection. The authors of the second case suggested the possibility that ANCA-associated GN and APS occurred as systemic inflammation, such as a cytokine storm produced ANCA and APS-related antibodies, and the pathological mechanism started and progressed.[19]

If the first possibility is correct, then there should be a high incidence of renal involvement at diagnosis in APS antibody-positive patients. In the present study, renal involvement was observed in 38 of 55 patients with APS-related antibodies and in 60 of 115 patients without these antibodies (69.1% vs. 52.2%, p=0.037, RR 2.049, 95% CI 1.039–4.040). These results support the first possibility. If the second possibility is correct, higher ESR and CRP levels should be measured in patients with APS-related antibodies at diagnosis than in those without APS-related antibodies. Additionally, higher ESR and CRP levels were observed in ANCA-positive patients than in ANCA-negative patients. In the present study, patients with APS-related antibodies exhibited higher levels of ESR (82.5 mm/h vs. 50.0 mm/h, p=0.002) and CRP (22.7 mg/L vs. 6.2 mg/L, p=0.009) compared those without APS-related antibodies. Moreover, ANCA-positive patients showed higher levels of ESR (65.0 mm/h vs. 31.0 mm/h, p=0.005) and CRP (14.5 mg/L vs. 2.0 mg/L, p=0.008) than ANCA-negative patients. These results support the second possibility. Similarly, patients with renal involvement at diagnosis had a higher median aGAPSS than those without renal involvement. However, no significant differences were found between two groups according to the presence of cardiovascular or nervous system involvements (Supplementary Fig. 1, only online). Additionally, since the aGAPSS at diagnosis was significantly correlated with not only ESR and CRP but also serum creatinine at diagnosis (Table 2), these results also support the predictive ability of aGAPSS at diagnosis for ESKD follow-up in

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AAV patients.

In the present study, the aGAPSS ≥2 at diagnosis showed clinical significance as a predictor of the progression to ESKD in AAV patients or MPA and GPA patients during the follow-up period. Accordingly, we wondered whether the aGAPSS ≥2 at diagnosis could maintain its independent predictive ability of ESKD in interactions with other variables at diagnosis, and performed univariable and multivariable Cox hazard model analyses to answer these questions. Among 170 patients with AAV, in univariable Cox analysis, haemoglobin (HR 0.783), blood urea nitrogen (HR 1.038), serum creatinine (HR 1.349), eGFR (HR 0.976), and the aGAPSS ≥2 (HR 2.149) at diagnosis were significantly associated with ESKD during follow-up. Owing to the concern about the multicollinearity between serum creatinine and eGFR, we performed multivariable Cox analyses including each variable separately. First, in multivariable Cox analysis including serum creatinine, only serum creatinine at diagnosis was independently associated with ESKD during follow-up (HR 1.294, 95% CI 1.094–1.531). Similarly, in multivariable Cox analysis including eGFR, only eGFR at diagnosis was independently associated with ESKD during follow-up (HR 0.981, 95% CI 0.956–0.996). However, this study failed to demonstrate that an aGAPSS ≥2 at diagnosis is an independent predictor of future progression to ESKD in patients with AAV (Supplementary Table 1, only online).

Among 134 patients with MPA and GPA, in univariable Cox analysis, haemoglobin (HR 0.704), blood urea nitrogen (HR 1.038), serum creatinine (HR 1.428), eGFR (HR 0.970), and an aGAPSS ≥2 (HR 2.963) at diagnosis were significantly associated with ESKD during follow-up. Additionally, BVAS (HR 1.052) was also associated with ESKD in patients with MPA and GPA. As mentioned above, multivariable Cox analyses including serum creatinine or eGFR were conducted separately. In multivariable Cox analysis including serum creatinine, only serum creatinine at diagnosis was independently associated with ESKD during follow-up (HR 1.440, 95% CI 1.134–1.829). Also, in multivariable Cox analysis including eGFR, only eGFR at diagnosis was independently associated with ESKD during follow-up (HR 0.974, 95% CI 0.955–0.993). An aGAPSS ≥2 at diagnosis tended to predict ESKD but its independent predictive ability did not reach statistical significance (Supplementary Table 2, only online). Therefore, we concluded that although the aGAPSS at diagnosis showed a strong association with ESKD during follow-up, it could not surpass the predictive power for the progression to ESKD of serum creatinine at diagnosis in AAV patients.

Unlike patients with MPA and GPA, patients with EGPA tended to show little significant relationship between the aGAPSS at diagnosis and future progression to ESKD during follow-up. To clarify this issue, we included only 33 patients with EGPA and conducted Cox analyses of variables at AAV diagnosis for ESKD during follow-up. We found that in univariable Cox analysis, the aGAPSS ≥2 at diagnosis was not significantly associated with future ESKD during follow-up (p=0.682). As described in Supplementary Tables 1 and 2 (only online), the major conclusion of this study seemed to be confined only to patients with MPA and GPA, and did not extent to those with EGPA. However, in actual clinical situations, there are cases where the two subtypes of AAV are confused at the time of AAV diagnosis, and rare cases where one subtype changes to another during the follow-up period. In addition, AAV subtypes may change as new diagnostic classification criteria are suggested. Therefore, it may be appropriate to apply the results of this study to patients with all subtypes including EGPA, rather than only to those with MPA or GPA in real clinical practice. Furthermore, it would be reasonable to find universal principles that can be applied to all three AAV subtypes in future studies.

We previously reported that repeated APS-related antibodies positivity at diagnosis could predict thrombotic events among AAV patients without APS who were enrolled in the same cohort despite a smaller number of patients.[20] Nevertheless, in the present study, we failed to demonstrate that an initial GAPSS, which consisted of three types of APS-related antibodies, was associated with CVA and ACS during follow-up. We attributed this discrepancy to the following three reasons. First, unlike the present study, the previous study did not consider the follow-up duration based on thrombotic events, which is essentially necessary to perform Kaplan–Meier survival analysis. Second, unlike the previous study in which APS-related antibodies continuously detected at 12-week intervals were recognized as positive, the present study recognized antibodies detected once at the time of diagnosis as positive. APS-related antibodies detected as positive in only a single test at diagnosis may carry the potential for false positivity. Therefore, antibodies detected as positive in two consecutive tests with an interval of at least 12 weeks may have clinical significance. However, we consider them to have clinical significance for three reasons. First, the purpose of this study was not to diagnose APS or investigate how confirmed APS affects the disease course of AAV. Second, the purpose of this study was to investigate whether the aGAPSS value calculated using APS-related antibodies positivity or negativity obtained through a single test at diagnosis might be associated with thrombotic poor outcomes of AAV such as CVA or ACS. Contrary to expectations, the results of this study suggested the clinical potential of the aGAPSS at diagnosis as a predictor of future progression of ESKD. Finally, although patients confirmed as having APS were excluded from this study, in general, when APS-related antibodies are detected positively, the tests are repeated 3–4 months later. However, the reliability of the APS-related antibodies test was not sufficient due to the initiation of immunosuppressant treatment just after AAV diagnosis. Therefore, although there are limitations to describing the exact reasons due to the retrospective study design of this study, it could be presumed that the re-test rate was low for these three reasons.

There was concern that a medical history of CVA or ACS

might have a significant influence on the results of this study investigating the impact of the initial value of the aGAPSS on poor outcomes of AAV. Among the 170 patients, 18 had a medical history of CVA or ACS before AAV diagnosis. Among the 18 patients with CVA or ACS history, 10 patients experienced newly developed or recurred CVA or ACS after AAV diagnosis and during the disease course. Conversely, the remaining eight patients were not exposed to CVA or ACS. First, among the 18 patients with CVA or ACS history, there was no significant difference in the aGAPSS values between patients with newly developed or recurred CVA or ACS during follow-up and those without (3.0 vs. 4.0, p=0.259). Second, among the 152 patients without CVA or ACS history before AAV diagnosis, patients with an aGAPSS ≥2 at diagnosis still exhibited a significantly lower ESKD-free survival rate than those without (p=0.033). Also, among the 152 patients without CVA or ACS history before AAV diagnosis, an aGAPSS ≥2 at diagnosis was not meaningfully associated with CVA (p=0.654) or ACS (p=0.182) during follow-up, similar to the results in the 170 patients. Therefore, although a medical history of CVA or ACS is a well-established established risk factor for future CVA or ACS occurrence, it was not likely a significant factor influencing the clinical significance of the initial aGAPSS in predicting poor outcomes in patients with AAV. Also, in terms of venous thrombosis, we found that three patients without APS-related antibodies at AAV diagnosis had deep vein thrombosis that was fully resolved before AAV diagnosis. However, we did not find any cases of renal vein thrombosis.

The initial presence of GN and its histopathological pattern have been suggested as important predictors of ESKD in AAV patients with GN.[21] Therefore, it could be reasonable to assume that the frequency of progression to ESKD would be higher in AAV patients with GN confirmed by kidney biopsy in than those without strong clinical implications. To clarify this, we divided the 195 patients with AAV into two groups based on the presence of GN confirmed by kidney biopsy and compared the frequency of progression to ESKD between the two groups. Among the 62 patients with GN, 13 (21.0%) progressed to ESKD, whereas, among the 108 patients without GN, 21 (19.4%) developed ESKD during follow-up. No significant difference in the frequency of ESKD was observed (p=0.811). We suggest two hypotheses to explain the discrepancy between the theory and practice regarding why not all patients with GN progressed to ESKD. The first hypothesis is that if patients with GN responded effectively to AAV treatment, they could sufficiently avoid the risk of progression to ESKD. The second hypothesis suggests counter-evidence that renal involvement of AAV or APS may have a subclinical and persistent influence on GN development during the disease course, regardless of the presence of GN at diagnosis.

The present study has a merit of being the first to demonstrate that the aGAPSS, which comprises five types of APS-related antibodies, arterial hypertension, and dyslipidaemia, at diagnosis was significantly associated with ESKD during follow-up in AAV patients without APS. However, the present study had several limitations. The first limitation is that the present study was conducted as a retrospective study. Therefore, we might have missed the risk of thrombotic events beyond the factors included in the aGAPSS equation, such as a family history of thrombosis or comorbidities not documented in the medical records. The second limitation is that the number of patients was not sufficient to generalise the findings to all patients with AAV or MPA and GPA. Particularly, if the number of patients with MPA and GPA had been included, the independent predictive ability of the aGAPSS at diagnosis for ESKD might have been as statistically significant in multivariable Cox analysis as serum creatinine. The third limitation is that the present study recognized antibodies detected once at diagnosis. Therefore, we might have not only overlooked the possibility of an APS diagnosis in patients positive for APS-related antibodies as mentioned above but also ignored the possibility of positive seroconversion among patients negative for APS-related antibodies. However, we believe that the present study has clinical significance as a pilot study to try to discover additional clinical biomarkers or indices to predict poor outcomes in AAV patients. Moreover, we expect that a future study with a larger number of AAV patients and the serial results of APS-related antibodies will validate the results of the present study and enhance its reliability.

In conclusion, the present study is the first pilot study to demonstrate that the aGAPSS at diagnosis was significantly associated with ESKD during follow-up in AAV patients without APS. Therefore, we suggest that APS-related antibodies should be measured at the time of AAV diagnosis, and if positive, more attention should be given to the occurrence of thrombotic events and renal function deterioration when the GAPSS at diagnosis is calculated to be ≥2.

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AUTHOR CONTRIBUTIONS

Conceptualization: Pil Gyu Park, Hyun Joon Choi, and Sang-Won Lee. Data curation: Pil Gyu Park, Hyun Joon Choi, and Sang-Won Lee. Formal analysis: Pil Gyu Park, Hyun Joon Choi, and Sang-Won Lee. Funding acquisition: Sang-Won Lee. Investigation: Pil Gyu Park, Hyun Joon Choi, and Sang-Won Lee. Methodology: all authors. Project administration: Pil Gyu Park, Hyun Joon Choi, and Sang-Won Lee. Resources: Sang-Won Lee. Software: Pil Gyu Park and Hyun Joon Choi. Supervision: Sang-Won Lee. Validation: Yong-Beom Park. Visu-

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ORCID iDs

Pil Gyu Park https://orcid.org/0000-0002-2788-6580
Hyun Joon Choi https://orcid.org/0000-0001-6138-1861
Yong-Beom Park https://orcid.org/0000-0003-4695-8620
Sang-Won Lee https://orcid.org/0000-0002-8038-3341

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