Modification of 2022 ACR/EULAR ANCA-associated vasculitis classification criteria in a Japanese cohort (J-CANVAS)

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Abstract

Objective

The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria (the 2022 ACR/EULAR criteria) for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were recently published. This study aimed to evaluate the accuracy of these criteria in Japanese patients with AAV using data from the Japan Collaborative Registry of ANCA-associated Vasculitis (J-CANVAS).

Methods

This multicentre retrospective cohort study analysed patients with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). The 2022 ACR/EULAR criteria were applied to J-CANVAS participants to determine diagnostic performance, including sensitivity and specificity. A modified version of the 2022 ACR/EULAR criteria (the modified criteria) was subsequently developed, and its performance was compared with that of the 2022 ACR/EULAR criteria.

Results

In the J-CANVAS cohort, sensitivity values for MPA, GPA, and EGPA using the 2022 ACR/EULAR criteria were 96.1%, 48.5%, and 84.6%, respectively, while specificity values were 70.0%, 95.9%, and 98.0%, respectively. The modified criteria improved sensitivity to 90.7%, 83.8%, and 96.2% for MPA, GPA, and EGPA, respectively, and specificity to 86.7%, 99.0%, and 95.8%, respectively, with consistently higher AUC values.

Conclusion

The modified criteria improved the accuracy of AAV classification in Japanese patients.

Key words

ANCA-associated vasculitis, classification criteria, Japanese cohort, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, MPO-ANCA, PR3-ANCA, vasculitis, validation

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an ANCA-mediated small- and medium-vessel vasculitis that includes eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA) (1, 2). Historically, the diagnosis of AAV relied primarily on clinical experience and disease definition. In 1990, the American College of Rheumatology (ACR) published the first standardised classification criteria to distinguish individual vasculitic diseases and facilitate their use in epidemiological research (3). However, the absence of clinical, radiological, and serological markers such as ANCA, combined with the low specificity of these criteria, limited their application in routine clinical practice. In 1994, the Chapel Hill Consensus Conference (CHCC), convened by experts across multiple medical fields, proposed standardised definitions of vasculitis (4). Within the small-vessel vasculitides, AAV was defined as pauci-immune vasculitis, characterised by minimal or absent immunoglobulin staining of vessel walls on immunohistology. Subsequently, in 2007, Watts *et al*. developed a stepwise algorithm that incorporated the 1990 ACR criteria. However, owing to its limited specificity, the algorithm often permitted multiple overlapping diagnoses (4, 5). The algorithm also incorporated the CHCC definition, which emphasised histopathology, but still left some patients without a definitive diagnostic label. In 2012, a second CHCC was convened, revising the 1994 vasculitis definitions. By then, the widespread availability of ANCA serological testing and improved physician awareness had markedly increased diagnostic rates, underscoring the need for updated classification criteria (1). In response, the Diagnostic and Classification Criteria for Vasculitis (DCVAS) project was initiated, enrolling 6,991 patients with vasculitis or vasculitis-like conditions (6). Findings from this international effort informed the development of the 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria (the 2022 ACR/EULAR criteria), which have since gained wide acceptance owing to their high sensitivity and specificity (7-9).

However, regional and ethnic differences in AAV epidemiology have been reported (10, 11). For example, GPA has a high incidence in Northern Europe but a low incidence in Asian countries. A prospective study comparing AAV epidemiology in Japan and the UK demonstrated that MPA and myeloperoxidase (MPO)-ANCA were more prevalent in Japan, whereas GPA and proteinase 3 (PR3)-ANCA were more prevalent in the UK; however, the overall incidence of AAV did not differ significantly between the two countries (12). Because approximately 80% of patients enrolled in the DCVAS were Caucasian, verifying the accuracy of the 2022 ACR/EULAR criteria in Asian populations, including Japanese patients, is essential. Nevertheless, only two studies have addressed this issue to date (13, 14).

Classification criteria are intended to promote homogeneity in research settings, whereas diagnostic criteria are designed for clinical practice to guide patient care. The present study does not aim to establish a new diagnostic standard but rather to validate and assess potential refinements to the 2022 ACR/EULAR classification criteria in a Japanese cohort, considering this population's unique epidemiological features.

Methods

Registry and patients

This multicentre, retrospective cohort study was conducted using the Japan Collaborative Registry of ANCA-associated Vasculitis (J-CANVAS), a nationwide registry involving 24 university and core regional hospitals across Japan, with participation from the rheumatology, nephrology, and respiratory medicine departments. The registry consecutively enrolled adult patients (≥20 years) with newly diagnosed AAV or severe relapse between January 2017 and June 2020. A total of 680 patients were registered in J-CANVAS, of whom 558 had new-onset disease. All patients were classified as having MPA, GPA, or EGPA according to the 2012

International CHCC nomenclature and the European Medicines Agency (EMA) algorithm, with final diagnoses confirmed by experienced specialists (rheumatologists, nephrologists, or pulmonologists) at each site. Patients with overlapping features between different AAV subtypes were excluded from the registry. Clinical, laboratory, and treatment data were collected using a standardized case report form through a secure, web-based electronic data capture system (Viedoc; PCG Solutions, Uppsala, Sweden). To ensure consistency, definitions were harmonised across all sites, and the coordinating centre performed centralised checks for missing or inconsistent data, with queries returned to investigators for resolution. The study was approved by the institutional review boards of all participating centres and conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. All data were anonymised and de-identified prior to analysis (15-23).

Data collection

All clinical data were obtained from medical records at each participating site. Baseline characteristics collected prior to the initiation of treatment or management of relapse included demographic information (age, sex), disease type (MPA, GPA, or EGPA), disease status (newly diagnosed or relapsed), ANCA serotype (MPO-ANCA or PR3-ANCA), and organ involvement (Birmingham Vasculitis Activity Score [BVAS] 3.0, interstitial lung disease, and hypertrophic pachymeningitis) (24).

Statistical analysis

Data from 558 patients with new-onset disease among the 680 patients enrolled in J-CANVAS were analysed. Patients with severe relapse (n=122) were excluded to focus on the performance of the classification criteria in newly diagnosed cases. Baseline characteristics of patients with MPA, GPA, and EGPA were compared. The 2022 ACR/EULAR criteria were then applied to evaluate diagnostic accuracy, including sensitivity and specificity. Next, the positivity of each individual item in the 2022 ACR/EULAR criteria was calculated, and multivariate logistic regression models were used to assign weights for classifying MPA, GPA, and EGPA. The dependent variable was the presence or absence of each disease subtype, and the independent variables included all ACR/EULAR items (nasal involvement, MPO-ANCA positivity, interstitial pneumonia, pauci-immune glomerulonephritis, PR3-ANCA positivity, blood eosinophil count ≥ 1×10^9/L, cartilaginous involvement, hearing loss, granulomatous lesion, rhinosinusitis, pulmonary nodule, obstructive airway disease, nasal polyps, mononeuritis multiplex, extravascular eosinophilic-predominant inflammation on biopsy, and haematuria). Statistically significant variables were identified, and their regression coefficients were rounded to one decimal place. The sum of coefficients was considered the modified score.

Cut-off values were determined using receiver operating characteristic (ROC) analysis. Two-sided *p*-values <0.05 were considered statistically significant. A new weighted score was then constructed to generate the modified criteria, and its diagnostic accuracy was compared with that of the original 2022 ACR/EULAR criteria. Patients diagnosed with the other two AAV subtypes served as the control group. All analyses were performed using SPSS software (v. 27.0; IBM Japan, Tokyo, Japan).

Ethical approval

This study was approved by the Ethics Committee of the University of Yamanashi (reference number: 2422). Written informed consent from patients was not required under local regulations for retrospective observational studies. Patient information was handled in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Participants in Japan.

Table I. Baseline demographics and patient characteristics.

Clinical characteristics (n=558)	MPA (n=355)	GPA (n=99)	EGPA (n=104)
Age, mean (SD), years	74.0 (11.7)	70.1 (13.0)	61 (10.9)
Sex, female, n (%)	193 (54.4)	54 (54.5)	57 (54.8)
Types of ANCA, n (%)			
MPO-ANCA	342 (96.3)	57 (57.6)	36 (34.6)
PR3-ANCA	10 (2.8)	39 (39.4)	3 (2.9)
Negative	3 (0.8)	3 (3.0)	65 (62.5)
eGFR, median (IQR), ml/min/1.73m^2	43.1 (22.7-66.4)	70.2 (53.3-87.6)	81.9 (68.5-100.6)
Serum CRP, median (IQR), mg/dL	7.8 (2.4-12.6)	7.9 (2.1-13.9)	4.0 (1.6-7.6)
Clinical features, n (%)			
BVAS score, median (IQR)	15 (12-20)	15 (10-20)	15 (11-21)
General symptoms, n (%)	235 (66.2)	59 (59.6)	52 (50.0)
Renal, n (%)	299 (84.2)	59 (59.6)	33 (31.7)
Pulmonary, n (%)	153 (43.1)	58 (58.6)	51 (49.0)
ENT, n (%)	51 (14.4)	60 (60.6)	37 (35.6)
Nervous, n (%)	96 (27.0)	34 (34.3)	83 (79.8)
Skin, n (%)	70 (19.7)	17 (17.2)	51 (49.0)
Eye, n (%)	24 (6.8)	25 (25.3)	4 (3.8)
Cardiovascular, n (%)	21 (5.9)	2 (2.0)	19 (18.3)
Gastrointestinal, n (%)	6 (1.7)	3 (3.0)	12 (11.5)
Hypertrophic pachymeningitis, n (%)	10 (2.8)	10 (10.1)	0 (0.0)
Interstitial pneumonia, n (%)	191 (53.8)	19 (19.2)	15 (14.4)

ANCA: antineutrophil cytoplasmic antibody; BVAS: Birmingham vasculitis activity score; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; EGPA: eosinophilic granulomatosis with polyangiitis; ENT: ear, nose and throat; GPA: granulomatosis with polyangiitis; IQR: interquartile range; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; SD: standard deviation.

Results

Patient characteristics

Table I presents the baseline demographics and clinical characteristics of the 558 patients included in the study. MPA was diagnosed in 355 patients (63.6%), GPA in 99 (17.7%), and EGPA in 104 (18.6%). Diagnoses were established by experienced rheumatologists,

Table II. Comparison of 2022 ACR/EULAR criteria and modified criteria.

	MPA			GPA			EGPA		
	2022A/E score	Modified score	*p*-value	2022A/E score	Modified score	*p*-value	2022A/E score	Modified score	*p*-value
Sensitivity (%)	96.1	90.7		48.48	83.8		84.62	96.2	
Specificity (%)	70	86.7		95.86	99		98.02	95.8	
PPV (%)	84.8	92.4		71.6	64.3		71.6	84.0	
NPV (%)	91.0	81.5		89.6	96.3		96.5	99.1	
AUC	0.8962	0.951	<0.001	0.8462	0.9269	<0.001	0.972	0.9942	0.0293
Cut-off value	5	1.23		5	1.22		6	1.85	

Sensitivity, specificity, positive predictive value, negative predictive value and AUC were analysed for the 2022ACR/EULAR criteria score, and the modified criteria score, respectively. A chi-square test was performed to compare the areas under the receiver operating characteristic curves. Statistical significance was defined as a *p*-value of less than 0.05.
ACR: American College of Rheumatology; AUC: area under the curve. EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; GPA: granulomatosis with polyangiitis; J-CANVAS: Japan Collaborative registry of ANca-associated VAScultis; Modified score: J-CANVAS modified criteria score; MPA: microscopic polyangiitis; 2022A/E score: 2022ACR/EULAR criteria score; PPV: positive predictive value; NPV: negative predictive value.

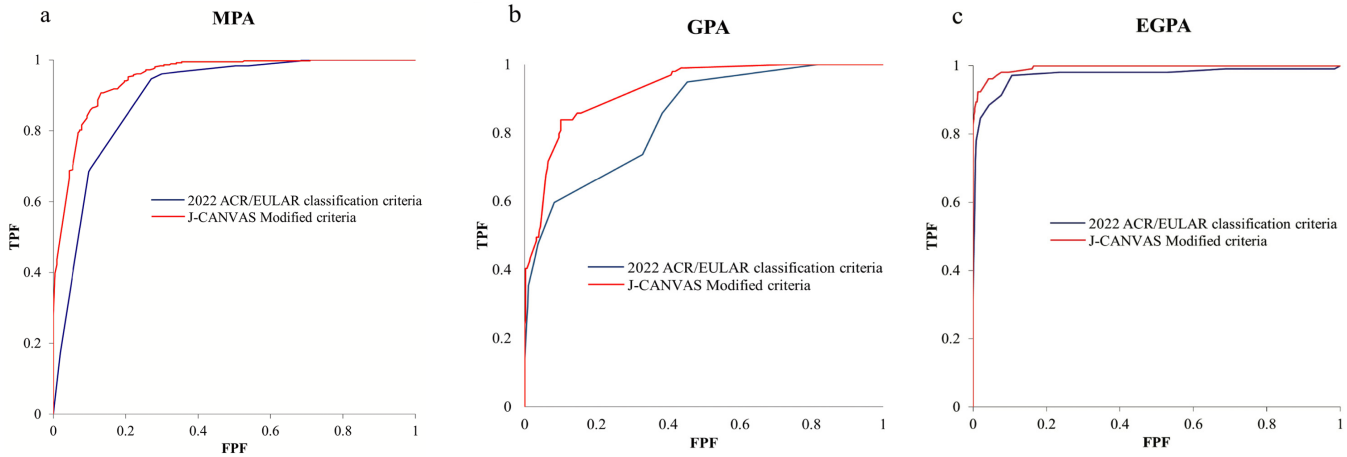

Fig. 1. Comparison of ROC curves between 2022 ACR/EULAR criteria, the modified criteria.
The blue line indicates the 2022 ACR/EULAR criteria, and the red line indicates the modified criteria. A chi-square test was performed to compare the areas under the receiver operating characteristic curves. Statistical significance was defined as a *p*-value of less than 0.05.
a. Comparison of ROC curves between 2022 ACR/EULAR criteria, the modified criteria for MPA. The AUC for 2022 ACR/EULAR criteria was 0.8962 (95%CI 0.866-0.926, *p*-value <0.001) the AUC for the modified criteria was 0.951 (95%CI 0.933-0.969, *p*-value <0.001). There was a significant difference between the 2 ROC curves (*p*-value<0.001).
b. Comparison of ROC curves between 2022 ACR/EULAR criteria, the modified criteria for GPA. The AUC for 2022 ACR/EULAR criteria was 0.8462 (95%CI 0.805-0.887, *p*-value <0.001) the AUC for the modified criteria was 0.9269 (95%CI 0.901-0.953, *p*-value <0.001). There was a significant difference between the 2 ROC curves (*p*-value<0.001).
c. Comparison of ROC curves between 2022 ACR/EULAR criteria, the modified criteria for EGPA. The AUC for 2022 ACR/EULAR criteria was 0.972 (95%CI 0.949-0.995, *p*-value <0.001) the AUC for the modified criteria was 0.9942 (95%CI 0.989-0.999, *p*-value <0.001). There was a significant difference between the 2 ROC curves (*p*-value 0.0293).
ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; EGPA: eosinophilic granulomatosis with polyangiitis; FPR: false positive rate; GPA: granulomatosis with polyangiitis; J-CANVAS: Japan Collaborative registry of ANca-associated VAScultis; Modified score: J-CANVAS modified criteria score; MPA: microscopic polyangiitis; ROC curve: receiver operating characteristic curve; TPR: true positive rate; 2022A/E score: 2022 ACR/EULAR criteria score; 95% CI: 95% confidence interval.

nephrologists, or pulmonologists at the time of initial presentation, according to the 2012 CHCC definitions and the EMA algorithm. The mean age of patients with MPA was 74 years, and 193 (54.4%) were female. MPO-ANCA positivity was observed in 342 patients (96.3%), and PR3-ANCA positivity in 10 (2.8%). For GPA, the mean age was 70 years, with 54 patients (54.5%) female; MPO-ANCA positivity was found in 57 (57.6%) and PR3-ANCA positivity in 39 (39.4%). For EGPA, the mean age was 61 years, with 57 patients (54.8%) female; MPO-ANCA positivity was observed in 36 (34.6%) and PR3-ANCA positivity in 3 (2.9%). At diagnosis, the median BVAS was 15 across all three groups. In contrast, the median eGFR differed notably: 43.1 mL/min/1.73 m^2 in the MPA group, 70.2 mL/min/1.73 m^2 in the GPA group, and 81.9 mL/min/1.73 m^2 in the EGPA group. Renal involvement (n=299, 84.2%) and interstitial pneumonia (n=191, 53.8%) were frequent in MPA; ear–nose–throat (ENT) involvement (n=60, 60.6%) was frequent in GPA, and nervous system involvement (n=83, 79.8%) was frequent in EGPA.

Validation of the 2022 ACR/EULAR classification criteria

When the 2022 ACR/EULAR criteria were applied to the 558 patients in J-CANVAS, the sensitivity for classifying MPA, GPA, and EGPA was 96.1%, 48.5%, and 84.6%, respectively, and the corresponding specificity values were 70.0%, 95.9%, and 98.0% (Table II). ROC curves for the 2022 ACR/EULAR criteria for MPA, GPA, and EGPA are shown in blue (Fig. 1a, 1b, and 1c), and the area under the curve (AUC) values are summarised in Table II. To explore the reduced sensitivity for GPA and specificity for MPA, the positivity of each item in the 2022 ACR/EULAR criteria was calculated (Supplementary Tables S1-S3). Among patients classified as MPA, MPO-ANCA positivity was high not only in patients with MPA (96.3%) but also in patients with GPA (57.6%). In addition, interstitial pneumonia (53.8%) and pauci-immune glomerulonephritis (38.3%) were more frequent in MPA than in the other subtypes. Among patients classified as GPA, PR3-ANCA positivity was only 39.4%. Positivity for nasal involvement (26.3%), hearing loss (33.3%), granulomatous lesions (62.6%), and pulmonary nodules (40.4%) was higher than in the other subtypes. For EGPA, positivity for obstructive airway disease (88.5%), mononeuritis multiplex (52.9%), and blood eosinophil count ≥ 1×10^9/L (88.5%) was higher than in the other subtypes, whereas haematuria (23.1%) was less frequent.

Development of novel classification criteria

Multivariate analysis was performed for each AAV subtype to develop the modified criteria for the Japanese population (Tables III-V). The cut-off values for the modified criteria were 1.23 for MPA, 1.22 for GPA, and 1.85 for EGPA.

For MPA, the weights of MPO-ANCA positivity and interstitial pneumonia were lower than in the 2022 ACR/EULAR score, whereas nasal and ear involvement, pulmonary nodules, and obstructive airway disease carried negative scores. Haematuria was also added to the scoring system. For GPA, most weights were similar to those of the original criteria, although PR3-ANCA positivity had a smaller weight, while mononeuritis multiplex and interstitial pneumonia received negative scores. Hearing loss was included as an additive item. For EGPA, pauci-immune glomerulonephritis and MPO-ANCA-positive interstitial pneumonia were given negative scores.

The sensitivity of the modified criteria for classifying MPA, GPA, and EGPA was 90.7%, 83.8%, and 96.2%, respectively, and the corresponding specificity values were 86.7%, 99.0%, and 95.8% (Table II). ROC curves for each AAV subtype were generated based on the sum of modified scores, with the modified criteria, shown in red (Fig. 1a, 1b,

Table III. Modified criteria of MPA by multivariate logistic regression analysis.

	Regression coefficient	Odds ratio	95%CI		*p*-value	2022 A/E score	Modified score
Nasal involvement	-2.337	0.097	0.028	0.331	<0.001	-3	-2.3
Hearing loss	-1.482	0.227	0.103	0.501	<0.001		-1.5
Rhinosinusitis	-1.259	0.284	0.125	0.646	0.003		-1.3
MPO-ANCA positive	2.716	15.121	6.648	34.391	<0.001	6	2.7
Blood eosinophil count ≥ 1×10^9/litre	-3.004	0.05	0.018	0.136	<0.001	-4	-3
Pulmonary nodule	-2.332	0.097	0.045	0.211	<0.001		-2.3
Haematuria	0.756	2.13	1.158	3.917	0.015		0.8
Obstructive airway disease	-1.761	0.172	0.073	0.403	<0.001		-1.8
Interstitial pneumonia	1.577	4.838	2.471	9.474	<0.001	3	1.6

A multivariate logistic regression analysis was performed. The dependent variable was whether the patient was diagnosed as MPA or not, the independent variables were all the items of the 2022ACR/EULAR criteria, of MPA, GPA, and EGPA (nasal involvement, MPO-ANCA positivity, interstitial pneumonia, pauci-immune glomerulonephritis, PR3-ANCA positivity, blood eosinophil count ≥1×10^9/litre, cartilaginous involvement, hearing loss, granulomatous lesion, rhinosinusitis, pulmonary nodule, obstructive airway disease, nasal polyps, mononeuritis multiplex, extravascular eosinophilic-predominant inflammation on biopsy, haematuria). Statistical significance was defined as a *p*-value of less than 0.05. Items with significant differences were extracted. Regression coefficient of the extracted items was rounded off to one decimal place, which sum was regarded as the modified score.
ACR: American College of Rheumatology; ANCA: anti-neutrophil cytoplasmatic antibody; AUC: Area under the curve; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; GPA: granulomatosis with polyangiitis; J-CANVAS: Japan Collaborative registry of ANca-associated VAScultis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; 2022A/E score: 2022 ACR/EULAR criteria score; 95% CI: 95% confidence interval.

Table IV. Modified criteria of GPA by multivariate logistic regression analysis.

	Regression coefficient	Odds ratio	95%CI		*p*-value	2022 A/E	Modified score
Nasal involvement	2.451	11.597	3.710	36.244	<0.001	3	2.5
Hearing loss	1.883	6.572	3.122	13.835	<0.001	1	1.9
PR3-ANCA positive	2.975	19.587	7.849	48.880	<0.001	5	3
Rhinosinusitis	0.947	2.579	1.100	6.047	0.029	1	0.9
Blood eosinophil count ≥ 1×10^9/litre	-3.044	0.048	0.008	0.272	0.001	-4	-3
Pulmonary nodule	2.450	11.593	5.411	24.838	<0.001	2	2.5
Mononeuritis multiplex	-1.805	0.165	0.032	0.855	0.032		-1.8
Interstitial pneumonia	-1.423	0.241	0.115	0.505	<0.001		-1.4

A multivariate logistic regression analysis was performed. The dependent variable was whether the patient was diagnosed as GPA or not, the independent variables were all the items of the 2022ACR/EULAR criteria, of MPA, GPA, and EGPA (nasal involvement, MPO-ANCA positivity, interstitial pneumonia, pauci-immune glomerulonephritis, PR3-ANCA positivity, blood eosinophil count ≥1×10^9/litre, cartilaginous involvement, hearing loss, granulomatous lesion, rhinosinusitis, pulmonary nodule, obstructive airway disease, nasal polyps, mononeuritis multiplex, extravascular eosinophilic-predominant inflammation on biopsy, haematuria). Statistical significance was defined as a *p*-value of less than 0.05. Items with significant differences were extracted. Regression coefficient of the extracted items was rounded off to one decimal place, which sum was regarded as the modified score.
ACR: American College of Rheumatology; ANCA: anti-neutrophil cytoplasmatic antibody; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; GPA: granulomatosis with polyangiitis; J-CANVAS: Japan Collaborative registry of ANca-associated VAScultis; MPA: microscopic polyangiitis; PR3: proteinase 3; 2022A/E score: 2022 ACR/EULAR criteria score; 95% CI: 95% confidence interval.

Table V. Modified criteria of EGPA by multivariate logistic regression analysis.

	Regression coefficient	Odds ratio	95% CI		*p*-value	2022 A/E score	Modified score
Pauci-immune glomerulonephritis	-2.540	0.08	0.008	0.768	0.029		-2.5
MPO-ANCA positive	-1.405	0.25	0.064	0.945	0.041		-1.4
Blood eosinophil count ≥ 1×10^9/litre	5.039	154.26	34.556	688.591	<0.001	5	5
Mononeuritis multiplex	1.963	7.12	1.560	32.526	0.011	1	2
Obstructive airway disease	3.965	52.73	13.480	206.295	<0.001	3	4
Interstitial pneumonia	-1.906	0.15	0.029	0.774	0.024		-1.9

A multivariate logistic regression analysis was performed. The dependent variable was whether the patient was diagnosed as EGPA or not, the independent variables were all the items of the 2022ACR/EULAR criteria, of MPA, GPA, and EGPA (nasal involvement, MPO-ANCA positivity, interstitial pneumonia, pauci-immune glomerulonephritis, PR3-ANCA positivity, blood eosinophil count ≥1×10^9/litre, cartilaginous involvement, hearing loss, granulomatous lesion, rhinosinusitis, pulmonary nodule, obstructive airway disease, nasal polyps, mononeuritis multiplex, extravascular eosinophilic-predominant inflammation on biopsy, haematuria). Statistical significance was defined as a *p*-value of less than 0.05. Items with significant differences were extracted. Regression coefficient of the extracted items was rounded off to one decimal place, which sum was regarded as the modified score.
ACR: American College of Rheumatology; ANCA: anti-neutrophil cytoplasmatic antibody; EGPA: eosinophilic granulomatosis with polyangiitis; EULAR: European Alliance of Associations for Rheumatology; GPA: granulomatosis with polyangiitis; J-CANVAS: Japan Collaborative registry of ANca-associated VAScultis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; 2022A/E score: 2022 ACR/EULAR criteria score; 95% CI: 95% confidence interval.

and 1c). The AUC was 0.951 (95% confidence interval [CI], 0.933–0.969; $p<0.001$) for MPA, 0.927 (95% CI, 0.901–0.953; $p<0.001$) for GPA, and 0.994 (95% CI, 0.989–0.999; $p<0.001$) for EGPA. Compared with the 2022 ACR/EULAR classification criteria, the AUC values improved for all three subtypes (Table II).

Discussion

In the present study, when patients in J-CANVAS were reclassified using the 2022 ACR/EULAR criteria, the sensitivity for GPA was only 48.5% and the specificity for MPA was 70.0%, both lower than those reported in DCVAS. We consider this to be largely attributable to the fact that approximately 80% of DCVAS participants were Caucasian; although Asian patients were included, the proportion was too small to allow meaningful conclusions regarding Japanese patients.

While PR3-ANCA-positive cases are more common in Europe, MPO-ANCA-positive cases predominate in Japan. Moreover, ANCA specificity is lower in Japan than in Europe, meaning that patients who clinically present with GPA features such as nasal involvement, granulomatous lesions, and pulmonary nodules may test MPO-ANCA positive, and *vice versa*. Because the 2022 ACR/EULAR criteria emphasise ANCA specificity, some clinically diagnosed GPA cases were classified as MPA, leading to lower diagnostic sensitivity and specificity among Japanese patients. To address this issue, we conducted multivariate analysis to develop modified criteria tailored to the Japanese population. These modifications improved, MPA specificity to 86.7% and GPA sensitivity to 83.8%.

Eight studies have validated the 2022 ACR/EULAR criteria in non-DCVAS patient populations (13, 14, 25-30). Although the sensitivity and specificity of the 2022 ACR/EULAR criteria were generally higher than those of the 1990 ACR criteria, one study reported reduced sensitivity and specificity, consistent with our findings (30). Because some cases are classified as having overlapping features or remain unclassifiable, several studies have argued that classification should incorporate previous criteria and algorithms, such as the Watts algorithm (5, 25, 28).

In the present study, some patients also had overlapping or unclassifiable diagnoses. When reclassified by the 2022 ACR/EULAR criteria, 16 patients (2.8%) met both GPA and MPA criteria, 13 (2.3%) met both MPA and EGPA criteria, and none met both EGPA and GPA criteria. A total of 21 patients (3.8%) were unclassifiable (Supplementary Fig. S1). Using the modified criteria, 22 patients (3.9%) met both GPA and MPA criteria, 6 (1.1%) met both the MPA and EGPA criteria, and 9 (1.6%) met both EGPA and GPA criteria, while 6 (1.1%) were unclassifiable (Suppl. Fig. S2). Thus, applying the modified criteria increased the number of overlapping cases but reduced the number of unclassifiable cases. Because these numbers were small, we believe they do not affect our overall conclusions. Sada *et al*. compared the 2022 ACR/EULAR criteria with the Watts algorithm using two Japanese cohort (25). They reported that ENT involvement was significantly less frequent in patients reclassified as MPA than in those reclassified as GPA. By contrast, in J-CANVAS, 46 patients (93.9%) reclassified as MPA and 8 patients (44.4%) reclassified as GPA had ENT involvement, demonstrating contradictory results. This discrepancy may be due to the lower percentage of GPA patients in Sada *et al.'s* cohort (9.9%) compared with J-CANVAS (17.7%). They also noted that four out of 350 patients were reclassified as MPA despite showing granulomatous inflammation histologically, because they were MPO-ANCA positive and lacked ENT involvement. We agree with their interpretation that MPO-ANCA-positive GPA patients may be misclassified under the 2022 ACR/EULAR criteria. Moreover, other studies have emphasised the importance of ANCA-positivity rates over histological findings (29). To our knowledge, no previous studies have attempted to explore potential modifications of the new criteria. In this study, we conducted an exploratory analysis to determine whether minor adjustments to the 2022 ACR/EULAR criteria could improve classification performance in the Japanese population, incorporating conventional histological evaluation and clinical features. These findings should be interpreted cautiously and regarded as a step toward further validation in diverse populations.

In J-CANVAS, biopsies were performed in 163 patients with MPA (45.9%), 62 with GPA (62.6%), and 34 with EGPA (32.7%). Among the 49 patients whose diagnosis changed from GPA to MPA after application

of the 2022 ACR/EULAR criteria, 48 (97.9%) were MPO-ANCA positive, reflecting the high weighting of MPO-ANCA positivity in the 2022 ACR/EULAR criteria. However, within this group, 31 patients (63.3%) had been originally diagnosed with GPA by biopsy, 19 (38.8%) had pulmonary nodules, and 46 (93.8%) had ENT involvement. These findings indicate that the 2022 ACR/EULAR criteria failed to classify patients with classical GPA features who were MPO-ANCA positive. Therefore, because the 2022 ACR/EULAR criteria assign a high weighting to ANCA, some clinically diagnosed GPA cases are reclassified as MPA. The modified criteria reduced the weight of MPO-ANCA and PR3-ANCA positivity and yielded higher specificity and sensitivity compared to the 2022 ACR/EULAR criteria. Thus, the modified criteria may provide more accurate classification of AAV in Japanese patients. ANCA has also been reported to be positive in diseases other than AAV, and in some cases, becomes positive after a long latency, even when negative at onset (31). Hence, ANCA-based classification alone should be applied cautiously, particularly in the Japanese population. Future studies should incorporate the histological evidence of vasculitis and granulomatous inflammation, as well as the site and nature of the lesions (32, 33).

This study had some limitations. First, the control group included only patients classified with other AAV subtypes and did not include patients with other vasculitis subtypes or vasculitis-like conditions. This limitation may have contributed to the lower cut-off values of the modified criteria and could have influenced specificity estimates. Therefore, future validation studies incorporating external control cohorts are needed. Second, the study was retrospective, and various biases at the data collection stage cannot be excluded. Because J-CANVAS is a multicentre registry primarily involving university and core referral hospitals, more severe cases may have been preferentially included, while milder or earlier cases may have been underrepresented. The registry enrolled only newly diagnosed and severely relapsing cases, and not all patients underwent histological confirmation, raising the possibility of verification bias. Third, although we proposed modified classification criteria based on J-CANVAS, these were not validated using external data, and future international collaborative validation will be required. Fourth, while the proposed modifications are biologically and epidemiologically plausible in the Japanese population, they may increase the risk of misclassification in patients with dual ANCA positivity or overlapping eosinophilic features suggestive of EGPA. Finally, because this study was conducted exclusively in a Japanese cohort, in which MPO-ANCA-positive MPA was predominant, the proposed modifications may not be directly applicable to non-Japanese populations, such as Western cohorts where PR3-ANCA–positive GPA is more prevalent. Future collaborative validation studies are essential for confirming external validity and broader applicability.

Conclusions

This study suggests that exploratory modifications to the 2022 ACR/EULAR criteria have improved classification performance in our Japanese cohort. As the accuracy of classification criteria may vary between populations and ANCA types, further validation in independent and ethnically diverse cohorts is warranted.

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References

1. JENNETTE JC, FALK RJ, BACON PA *et al*.: 2012 Revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum* 2013; 65: 1-11. https://doi.org/10.1002/art.37715.
2. KRONBICHLER A, BAJEMA IM, BRUCHFELD A, KIRSZTAJN GM, STONE JH: Diagnosis and management of ANCA-associated vasculitis. *Lancet* 2024; 403: 683-93. https://doi.org/10.1016/S0140-6736(23)01736-1
3. FRIES JF, HUNDER GG, BLOCH DA *et al*.: The American College of Rheumatology 1990 criteria for the classification of vasculitis. Arthritis Rheum 1990; 33: 1135-36. https://doi.org/10.1002/art.1780330812.
4. 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* 2007; 66: 222-27. https://doi.org/10.1136/ard.2006.054593.
6. LUQMANI RA, SUPPIAH R, GRAYSON PC, MERKEL PA, WATTS R: Nomenclature and classification of vasculitis - update on the ACR/EULAR Diagnosis and Classification of Vasculitis Study (DCVAS). *Clin Exp Immunol* 2011; 164: 11-13. https://doi.org/10.1111/j.1365-2249.2011.04358.x
7. 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* 2022; 81: 321-26. https://doi.org/10.1136/annrheumdis-2021-221796
8. 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* 2022; 81: 315-20. https://doi.org/10.1136/annrheumdis-2021-221795
9. 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* 2022; 81: 309-14. https://doi.org/10.1136/annrheumdis-2021-221794
10. MOHAMMAD AJ: An update on the epidemiology of ANCA-associated vasculitis. *Rheumatology* (Oxford) 2020; 59: iii42-iii50. https://doi.org/10.1093/rheumatology/keaa089
11. FURUTA S, CHAUDHRY AN, ARIMURA Y *et al*.: Comparison of the phenotype and outcome of granulomatosis with polyangiitis between UK and Japanese cohorts. *J Rheumatol* 2017; 44: 216-22. https://doi.org/10.3899/jrheum.160005
12. FUJIMOTO S, WATTS RA, KOBAYASHI S *et al*.: Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. *Rheumatology* (Oxford) 2011; 50: 1916-20. https://doi.org/10.1093/rheumatology/ker205
13. NANKI T, TSUBOI N, AMANO K *et al*.: Evaluation of Ministry of Health, Labour and Welfare diagnostic criteria for antineutrophil cytoplasmic antibody–associated vasculitis compared to ACR/EULAR 2022 classification criteria. *Mod Rheumatol* 2024; 34: 551-58. https://doi.org/10.1093/mr/road052
14. IMAI Y, OTA Y, MATSUMOTO K, AKIYAMA M, SUZUKI K, KANEKO Y: Performance of the 2022 ACR/EULAR classification criteria in comparison with the European Medicines Agency algorithm in ANCA-associated vasculitis. *J Rheumatol* 2024; 51: 1102-10. https://doi.org/10.3899/jrheum.2024-0335
15. KIDOGUCHI G, YOSHIDA Y, WATANABE H *et al*.: Effectiveness and safety of rituximab in severely relapsed antineutrophil cytoplasmic antibody-associated vasculitis: a retrospective analysis of a Japanese multicentre cohort from the J-CANVAS. *Clin Rheumatol* 2024; 43: 3195-204. https://doi.org/10.1007/s10067-024-07096-y
16. YOSHIDA Y, NAKAMOTO N, OKA N *et al*.: Seasonal influence on development of anti-neutrophil cytoplasmic antibody-associated vasculitis: a retrospective cohort study conducted at multiple institutions in Japan (J-CANVAS). *J Rheumatol* 2023; 50: 1152-8. https://doi.org/10.3899/jrheum.2023-0040
17. SHIMOJIMA Y, KISHIDA D, ICHIKAWA T *et al*.: Hypertrophic pachymeningitis in ANCA-associated vasculitis: a cross-sectional and multi-institutional study in Japan (J-CANVAS). *Arthritis Res Ther* 2022; 24: 204. https://doi.org/10.1186/s13075-022-02898-4
18. OMURA S, KIDA T, NOMA H *et al*.: Association between hypogammaglobulinaemia and severe infections during induction therapy in ANCA-associated vasculitis: from J-CANVAS study. *Rheumatology* (Oxford) 2023; 62: 3924-31. https://doi.org/10.1093/rheumatology/kead138
19. OMURA S, KIDA T, NOMA H *et al*.: Effectiveness of intravenous methylprednisolone pulse in patients with severe microscopic polyangiitis and granulomatosis with polyangiitis. *Rheumatology* (Oxford) 2024; 63: 2484-93. https://doi.org/10.1093/rheumatology/keae219
20. SOFUE H, KIDA T, HIRANO A *et al*.: Optimal dose of intravenous cyclophosphamide during remission induction therapy in ANCA-associated vasculitis: A retrospective cohort study of J-CANVAS. *Mod Rheumatol* 2024; 34: 767-74. https://doi.org/10.1093/mr/road099
21. NISHIOKA R, OMURA S, NAKAGOMI D *et al*.: Glucocorticoid tapering pace in microscopic polyangiitis and granulomatosis with polyangiitis in Japanese real-world practice: A propensity score-matched retrospective cohort study from the J-CANVAS registry. *Mod Rheumatol* 2025; 35: 469-504. https://doi.org/10.1093/mr/roae112
22. KAWAMORI K, OGURO N, SHIMIZU K *et al*.: Risk factors for cytomegalovirus reactivation during the treatment of ANCA-associated vasculitis: A retrospective cohort study of the J-CANVAS study. *Mod Rheumatol* 2025; 35: 691-96. https://doi.org/10.1093/mr/roaf008
23. OGITA C, NOGUCHI K, TAKEUCHI J *et al*.: Effectiveness for remission maintenance rate and safety of different rituximab regimens for treating anti-neutrophil cytoplasmic antibody-associated vasculitis in Japan: a J-CANVAS study. *Immunol Med* 2025; 48: 203-10. https://doi.org/10.1080/25785826.2024.2448912
24. MUKHTYAR C, LEE R, BROWN D *et al*.: Modification and validation of the Birmingham vasculitis activity score (version 3). *Ann Rheum Dis* 2009; 68: 1827-32. https://doi.org/10.1136/ard.2008.101279
25. SADA KE, KANAME S, HIGUCHI T *et al*.: Validation of new ACR/EULAR 2022 classification criteria for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Mod Rheumatol* 2024; 34: 144-50. https://doi.org/10.1093/mr/road017
26. 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* 2023; 64: 11-17. https://doi.org/10.3349/ymj.2022.0435
27. PYO JY, AHN SS, SONG JJ, PARK YB, LEE SW: The reclassification of patients with previously diagnosed eosinophilic granulomatosis with polyangiitis based on the 2022 ACR/EULAR criteria for antineutrophil cytoplasmic antibody-associated vasculitis. *J Rheumatol* 2023; 50: 213-18. https://doi.org/10.3899/jrheum.220560
28. PYO JY, AHN SS, SONG JJ *et al*.: Application of the 2022 ACR/EULAR criteria for microscopic polyangiitis to patients with previously diagnosed microscopic polyangiitis. *Clin Exp Rheumatol* 2023; 41(4): 792-99. https://doi.org/10.55563/clinexprheumatol/vmrk76
29. RATHMANN J, SEGELMARK M, MOHAMMAD AJ: Evaluation of the ACR/EULAR 2022 criteria for classification of ANCA-associated vasculitis in a population-based cohort from Sweden. *Rheumatology* (Oxford) 2024; 63: 1965-72. https://doi.org/10.1093/rheumatology/kead516
30. PIMENTEL-QUIROZ VR, UGARTE-GIL MF, ALARCÓN GS: Correspondence on "2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis" by Joanna C Robson *et al* and "2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis." *Ann Rheum Dis* 2023; 82: e197. https://doi.org/10.1136/annrheumdis-2022-222317
31. NOCENTE R, GENTILONI SILVERI N, BERTAZZONI G *et al*.: Delayed ANCA positivity in pulmonary-renal syndrome. *Panminerva Med* 2002; 44: 73-75
32. RADICE A, BIANCHI L, SINICO RA: Anti-neutrophil cytoplasmic autoantibodies: methodological aspects and clinical significance in systemic vasculitis. *Autoimmun Rev* 2013; 12: 487-95. https://doi.org/10.1016/j.autrev.2012.08.008
33. TAKEDA R, TAKAHASHI K, KRONBICHLER A *et al*.: Development of a kidney prognostic score in a Japanese cohort of patients with antineutrophil cytoplasmic autoantibody vasculitis. *Kidney Int Rep* 2024; 9: 611-23. https://doi.org/10.1016/j.ekir.2024.01.007