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ORIGINAL ARTICLE

Performance of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for antineutrophil cytoplasmic antibody-associated vasculitis in previously diagnosed adult patients from Türkiye

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ABSTRACT

Objectives: This study aimed to evaluate the applicability of the new 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria in Turkish adult patients previously diagnosed with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Patients and methods: One hundred sixty-four patients (96 males, 68 females; mean age: 49.6±14.4 years; range, 18 to 87 years) diagnosed with AAV by experienced rheumatologists between July 2016 and May 2022 were included in this retrospective cross-sectional study and reclassified based on the 1990 ACR criteria, the European Medicines Agency (EMEA) algorithm, and the 2022 ACR/EULAR criteria. For external validation, 83 patients (48 males, 35 females; mean age: 47.3±17.5 years; range, 19 to 81 years) diagnosed with immunoglobulin (Ig)A vasculitis were included.

Results: One hundred twenty-six (76.8%) patients had granulomatosis with polyangiitis (GPA), 13 (7.9%) patients had eosinophilic granulomatosis with polyangiitis (EGPA), and 25 (15.2%) patients had microscopic polyangiitis (MPA). According to the criteria, the number of unclassified patients was nine (5.5%) for both the 2022 ACR/EULAR AAV classification criteria and the EMEA algorithm. The new criteria had an almost perfect agreement with the clinician's diagnosis (Cohen's kappa coefficient [κ]=0.858 for GPA, κ=0.820 for EGPA, and κ=0.847 for MPA). The kappa statistics for agreement of 2022 ACR/EULAR classification criteria with the EMEA algorithm were found 0.794 for GPA, 0.820 for EGPA, and 0.700 for MPA. None of the 83 patients diagnosed with IgA vasculitis could be classified as GPA, EGPA, or MPA using the new ACR/EULAR AAV classification criteria.

Conclusion: The 2022 ACR/EULAR classification criteria for AAV showed substantial or perfect agreement with the clinical diagnosis and the EMEA algorithm.

Keywords: Antineutrophil cytoplasmic antibody-associated vasculitis, classification criteria, eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, microscopic polyangiitis.

Vasculitis is a pathological process that characterizes an inflammatory disease of blood vessels of different types, sizes, and histology.[1] Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease characterized by necrotizing small vessel vasculitis. It consists of three distinct diseases: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[2]

Until recently, there were two classification criteria with different sensitivity and specificity levels: the 1990 American College of Rheumatology (ACR) criteria and the European Medicines Agency (EMEA) algorithm.[3,4] Although the 1990 ACR criteria have been widely used to date, there is widespread controversy regarding the use of these criteria. An international survey of experts in vasculitis reported that 43% of professionals were dissatisfied with the 1990 ACR criteria for GPA, and 76%

were discontent with the 1990 ACR criteria for EGPA.[5] The most important limitation of these criteria was not incorporating an ANCA test, which is the most characteristic feature of these vasculitides. Furthermore, as advances in diagnostic techniques allowed better distinction between vasculitis types, the sensitivity of these criteria has been reduced.[6] The EMEA algorithm uses a stepwise hierarchical approach, starting with EGPA, as the ACR 1990 EGPA criteria have high specificity and sensitivity. Next, GPA, MPA, and polyarteritis nodosa are considered, respectively.[4]

Recently, the 2022 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for GPA, MPA, and EGPA were presented.[7-9] The development and validation of these new AAV criteria were carried out in a patient cohort of DCVAS (Diagnostic and Classification Criteria in Vasculitis Study), which was a multinational prospective observational study. The data set of DCVAS was randomly split into a development set and a validation set. This may cause the independence of the validation set from the development set to be questioned.[10] The validation of disease classification criteria must be tested in independent cohorts consisting of patients who are not included in the development cohort. In this study, we aimed to evaluate the classification performance of these new criteria in AAV-diagnosed adult patients from Türkiye and to compare previously used criteria.

PATIENTS AND METHODS

This retrospective cross-sectional study was conducted on patients recruited from the rheumatology departments of two different academic centers Gülhane Training and Research Hospital and Gazi University Faculty of Medicine. Medical records of patients diagnosed with AAV between July 2016 and May 2022 were retrospectively scanned. A total of 171 AAV patients were identified, and seven of them were excluded due to incomplete data. Finally, 164 AAV patients (96 males, 68 females; mean age: 49.6±14.4 years; range, 18 to 87 years) were included in the study. Patients were diagnosed with AAV by rheumatologists with a minimum of five years of experience. For external validation, patients diagnosed with immunoglobulin (Ig)A vasculitis based on European League Against Rheumatism/ Paediatric Rheumatology International Trials Organisation/Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) IgA vasculitis classification criteria were used as comparators.[11,12] Initially, 87 patients with IgA vasculitis were included, of whom four were excluded due to missing data, resulting in 83 IgA vasculitis patients (48 males, 35 females; mean age: 47.3±17.5 years; range, 19 to 81 years) being included in the final analysis. Patients with missing clinical or laboratory data and patients younger than 18 years of age were excluded. Demographic data, clinical characteristics, ANCA status determined by enzyme-linked immunosorbent assay (myeloperoxidase [MPO], proteinase 3 [PR3], or negative) and indirect immunofluorescence (perinuclear, cytoplasmic, or negative), and the type of diagnosis were recorded. To evaluate the performance of the 2022 ACR/EULAR AAV classification criteria, we classified all patients using the 1990 ACR criteria for GPA and EGPA, the EMEA algorithm, and the 2022 ACR/EULAR AAV classification criteria.

Statistical analysis

All data were analyzed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. Normally distributed continuous values were expressed as mean ± standard deviation and categorical variables as number and percentage. Clinical diagnosis confirmed by two independent, experienced rheumatologists was accepted as the standard criterion in all cases. The values for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, and Cohen's kappa coefficient (κ) were calculated. κ values were interpreted as follows: 0-0.20, very poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; 0.81-1.0, perfect agreement.

RESULTS

One hundred twenty-six (76.8%) patients had GPA, 13 (7.9%) patients had EGPA, and 25 (15.2%) patients had MPA. Cytoplasmic-ANCA (c-ANCA) or anti-PR3 antibody was positive in 116 (70.7%) of patients, and perinuclear-ANCA (p-ANCA) or anti-MPO antibody was positive in 37 (22.6%) of patients. The patients' clinical and laboratory characteristics at disease presentation are presented in Table 1.

The performance of criteria according to the type of AAV was presented in Table 2. When patients with the clinical diagnosis of AAV were evaluated according to the criteria, the number of unclassified patients was nine (5.5%) for both the 2022 ACR/EULAR AAV classification criteria and the EMEA algorithm. The demographic and clinical characteristics of unclassified patients according to the 2022 ACR/EULAR AAV criteria were summarized in Table 3. Among the nine unclassified patients according to the EMEA algorithm, one patient with clinically diagnosed GPA met the 2022 ACR/EULAR GPA criteria, and two patients with clinically diagnosed EGPA met the 2022 ACR/EULAR EGPA criteria.

Of the 126 clinically diagnosed GPA patients, 88 (69.8%) patients met the 1990 ACR criteria for GPA, 121 (96%) patients met the EMEA algorithm, and 117 (92.9%) met the 2022 ACR/EULAR GPA classification criteria. One patient classified as GPA according to the 2022 ACR/EULAR GPA classification criteria also met the 2022 ACR/EULAR MPA

Table 1. Clinical and laboratory characteristics of adult patients diagnosed with AAV

	GPA (n=126)			EGPA (n=13)			MPA (n=25)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Age at diagnosis (year)			47.8±13.5			54.2±16.5			56.5±15.7
Sex Female	47	37.3		8	61.5		13	52.0	
c-ANCA or anti-PR3 positivity	115	91.3		1	7.7		0	0	
p-ANCA or anti-MPO positivity	7	5.5		6	46.2		24	96.0	
Nasal involvement	60	47.6		0	0		0	0	
Cartilaginous involvement	6	4.8		0	0		0	0	
Hearing loss	27	21.4		0	0		2	8	
Pulmonary nodules, mass, or cavitation on chest imaging	86	68.3		1	7.7		5	20	
Granuloma or giant cells on biopsy	24	19		1	7.7		0	0	
Inflammation or consolidation of the nasal/paranasal sinuses on imaging	53	42.1		0	0		1	32.9	
Pauci-immune glomerulonephritis	47	37.3		2	15.4		21	84	
Eosinophil count ≥1×10^9/L	2	1.6		12	92.3		1	3.8	
Obstructive airway disease	7	5.6		11	84.6		4	16	
Nasal polyps	5	4		2	15.4		0	0	
Mononeuritis multiplex, motor neuropathy	6	4.8		6	46.2		2	8	
Extravascular eosinophilic predominant inflammation on biopsy	0	0		4	30.8		0	0	
Hematuria	77	61.1		2	15.4		22	88.0	
Lung fibrosis or interstitial lung disease	3	2.4		0	0		3	12.0	

AAV: Antibody-associated vasculitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; SD: Standard deviation.

Table 2. Performance of the different criteria in adult patients diagnosed with AAV

Clinical diagnosis	Criteria	Sensitivity (%)	Specificity (%)	PLR	NLR	PPV	NPV	Accuracy	κ
GPA									
	1990 ACR GPA criteria	69.84	86.84	5.31	0.35	94.62%	46.48%	73.78%	0.435
	EMEA algorithm	96.03	86.84	7.30	0.05	96.03	86.84	93.90%	0.829
	2022 ACR/EULAR GPA criteria	92.86	100	ND	0.07	100%	80.85%	94.51%	0.858
EGPA									
	1990 ACR EGPA criteria	61.54	100	ND	0.38	100%	96.79%	96.95%	0.747
	EMEA algorithm	61.54	100	ND	0.38	100%	96.759%	96.95%	0.747
	2022 ACR/EULAR EGPA criteria	76.92	99.33	116.15	0.23	90.91%	98.04%	97.56%	0.820
MPA									
	EMEA algorithm	80	99.28	116.20	0.20	95.24%	96.50%	96.34%	0.848
	2022 ACR/EULAR MPA criteria	96	95.68	22.24	0.04	80.00%	99.25%	95.73%	0.847

AAV: Antibody-associated vasculitis; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; ACR: American College of Rheumatology; EMEA: European Medicines Agency; EULAR: European Alliance of Associations for Rheumatology, ND: Not determined.

classification criteria, due to both anti-PR3 antibody and anti-MPO antibody positivity. Four clinically diagnosed GPA patients, who also met 1990 ACR criteria for GPA, were reclassified as MPA according to the 2022 ACR/EULAR MPA classification criteria due to anti-MPO antibody positivity. None of the clinically diagnosed GPA patients met the 2022 ACR/EULAR EGPA classification criteria.

Of the 13 clinically diagnosed EGPA patients, eight (61.5%) patients met the 1990 ACR criteria for EGPA, eight (61.5%) patients met the EMEA algorithm, and 10 (76.9%) met the 2022 ACR/EULAR EGPA classification criteria. One EGPA patient classified according to the 2022 ACR/EULAR EGPA classification criteria also met the 2022 ACR/EULAR MPA classification criteria due to anti-MPO antibody positivity. None of the clinically diagnosed EGPA patients met the 2022 ACR/EULAR GPA classification criteria.

Of the 25 clinically diagnosed MPA patients, 21 (84.0%) patients met the EMEA algorithm, and 24 (96%) patients met the 2022 ACR/EULAR MPA classification criteria. One patient classified as MPA according to the 2022 ACR/EULAR MPA classification criteria also met the 2022 ACR/EULAR EGPA classification criteria due to eosinophilia and obstructive airway disease. None of the clinically diagnosed MPA patients met the 2022 ACR/EULAR GPA classification criteria.

The κ statistics for agreement of 2022 ACR/EULAR classification criteria with the EMEA algorithm were 0.794 for GPA, 0.820 for EGPA, and 0.700 for MPA. The concordance rate between the new criteria and the EMEA algorithm was 91.3% for GPA, 100% for EGPA, and 90.5% for MPA.

All patients with IgA vasculitis had petechiae or purpura, 24 (28.9%) had arthritis, 27 (32.5%) had gastrointestinal system involvement, and 16 (19.28%) had renal involvement. None of them could be classified as GPA, EGPA, or MPA using the new ACR/EULAR AAV classification criteria.

DISCUSSION

In this study, we evaluated the performance of the 2022 ACR/EULAR Criteria for AAV in patients from Türkiye. The new criteria had an almost perfect agreement with the clinician's diagnosis. Furthermore, agreement of new ACR/EULAR classification criteria with the EMEA algorithm was perfect for EGPA

Table 3. The demographic and clinical characteristics of unclassified patients according to the 2022 ACR/EULAR AAV criteria

	GPA					EGPA			MPA
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (year)/sex	19/F	47/F	44/M	35/F	58/M	76/F	34/F	73/M	30/M
Clinical criteria									
Nasal involvement	+	–	–	+	–	–	–	–	–
Cartilaginous involvement	+	–	–	–	–	–	–	–	–
Conductive or sensorineural hearing loss	–	–	–	–	–	–	–	–	–
Obstructive airway disease	–	–	–	–	–	+	–	–	–
Nasal polyps	–	–	–	–	–	–	–	–	–
Mononeuritis multiplex	–	–	–	–	–	–	–	–	–
Laboratory criteria									
PR3-ANCA (or c-ANCA) positivity	–	–	–	–	–	+	–	+	–
MPO-ANCA (or p-ANCA) positivity	–	–	–	+	–	+	–	–	–
Blood eosinophil count ≥1×10^9/L	+	–	–	–	–	+	+	+	–
Hematuria	+	–	–	+	+	+	–	+	+
Biopsy criteria									
Granuloma, extravascular granulomatous inflammation, or giant cells	–	+	–	–	+	–	–	–	–
Pauci-immune glomerulonephritis	+	–	–	–	+	–	–	–	+
Extravascular eosinophilic-predominant inflammation	–	–	–	–	–	–	–	–	–
Imaging criteria									
Pulmonary nodules, mass, or cavitation on chest imaging	–	+	+	–	–	–	–	–	–
Fibrosis or interstitial lung disease on chest imaging	–	–	–	–	–	–	–	–	–
Nasal/paranasal sinusitis or mastoiditis on imaging	+	–	+	+	–	–	–	–	–
Total score									
GPA score	3	4	3	3	3	0	–4	–5	1
EGPA score	4	0	0	–1	–1	4	5	4	–1
MPA score	–4	0	0	3	3	–1	–4	2	3

ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; AAV: Antibody-associated vasculitis; PR3: Proteinase 3; ANCA: Antineutrophil cytoplasmic antibody; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPA: Microscopic polyangiitis.

and substantial for GPA and MPA. The 1990 ACR criteria for GPA and EGPA had the worst agreement with the clinician's diagnosis, with the lowest sensitivity.

AAVs are a heterogeneous group of systemic disorders characterized by necrotizing inflammation of predominantly small blood vessels, few or no immune deposits on histopathological analysis, and the presence of antibodies directed at leukocyte PR3-ANCA and MPO-ANCA.[13] The clinical manifestations of AAV largely depend on the affected vascular bed and can be organ or life-threatening.[14] Early diagnosis and individualized therapy depending on the clinical manifestations reduce the morbidity and mortality rate.[15] The new treatment options for remission induction and optimal use of available drugs are still being investigated.[16] Therefore, diagnostic and classification criteria are needed to facilitate their identification and distinction and to ensure the homogeneity of the study population for research.

In 1990, the ACR published classification criteria for GPA and EGPA with a sensitivity and specificity of 88.2% and 92% for GPA and 85% and 99.7% for EGPA.[17,18] Although these criteria have been widely used to date, they have several major limitations. First, since there was little information about MPA in the 1980s, classification criteria for MPA were not included in these criteria.[3] Second, the ANCA test, which has an important role in the pathogenesis of AAV and is widely used for diagnosis in daily clinical practice, is not included in these criteria.[13] Third, cross-sectional imaging tools, such as magnetic resonance imaging and computed tomography, were not incorporated. Fourth, the application of the ACR criteria alone can result in considerable overlap between the classification of diagnoses.[19] Furthermore, the necessity of a minimum number of criteria for classifying a patient with each type of vasculitis is a methodological disadvantage since some items in a criteria list may be more distinctive. As advances in diagnostic techniques have led to a better distinction between types of vasculitis, the sensitivity of the 1990 ACR criteria has decreased.[6] Similarly, in our study, the sensitivity of the 1990 ACR criteria was 69.84% for GPA and 61.54% for EGPA. In addition, the 1990 ACR criteria showed the worst agreement with the clinician's diagnosis.

Due to the limitations mentioned above, EMEA stepwise algorithm was developed to classify patients into a single category of AAV and to minimize the number of unclassifiable patients.[5] ANCA status was included in this algorithm. In the first step, the patient is evaluated for whether they fulfill the ACR or Lanham criteria for EGPA.[18,20] If the patient cannot be classified as EGPA, the next steps are taken, and the patient is evaluated for categorization as GPA, MPA, and polyarteritis nodosa, respectively. However, due to this hierarchical approach of EMEA, some patients diagnosed with clinical GPA, particularly those with eosinophilia, may be classified as EGPA. In our study, compared to the 1990 ACR criteria for GPA, the EMEA algorithm had better agreement with the clinician's diagnosis.

In 2007, a draft of the new AAV classification criteria was published and showed good sensitivity (93% for GPA, 88% for EGPA, and 87% for MPA) and specificity (94% for GPA, 98% for EGPA, and 96% for MPA).[21] This weighted criteria provided the highest score for c-ANCA or PR3-antibody positivity for GPA and p-ANCA or MPO-antibody positivity for MPA. Pimentel-Quiroz et al.[22] applied these criteria to their patients clinically diagnosed with AAV and found a similar level of sensitivity and specificity for MPA. Moreover, although they found that the specificity of these new criteria for GPA and EGPA was similar to the previously reported value, the sensitivity of these criteria in these types of AAV was lower.

In 2022, the final version of ACR/EULAR classification criteria for GPA, MPA, and EGPA was published.[7-9] Compared to the draft version, only the EGPA criteria were changed, and the cumulative score required to classify a patient as EGPA was increased from five to six.[9,21] The concordance rate was 73.8% for GPA, 96.6% for MPA, and 86.3 for EGPA between the new and previous criteria.[23-25] In our study, the concordance rate between new criteria and the EMEA algorithm was 91.3% for GPA, 100% for EGPA, and 90.5% for MPA. Although the new AAV criteria were not able to reduce the number

of unclassified patients, they showed almost perfect agreement with the clinician's diagnosis.

Five clinically diagnosed GPA patients were not classified according to the 2022 ACR/EULAR AAV criteria. Although two patients had granulomatous inflammation and giant cells on biopsy, which is a typical histologic feature of GPA, they were not classified as GPA due to anti-PR3 or c-ANCA negativity. On the other hand, four clinically diagnosed GPA patients who had granulomatous inflammation on biopsy and met the 1990 ACR criteria for GPA were reclassified as MPA according to the 2022 ACR/EULAR MPA classification criteria due to anti-MPO antibody positivity. It should be kept in mind that up to 20 to 30% of GPA patients have anti-PR3 antibody positivity, and ANCA negativity can be seen in up to 10% of GPA patients.[14] Increasing the point of granulomatous inflammation or giant cells on biopsy may improve the performance of the 2022 ACR/EULAR MPA criteria.

One clinically diagnosed MPA patient was not classified according to the new criteria. Although this patient presented with diffuse pulmonary hemorrhage, hematuria, and pauci-immune crescentic necrotizing glomerulonephritis on biopsy, the patient could not be classified as AAV due to anti-MPO or p-ANCA negativity. We suggest that adding a new item regarding the absence of granulomatous inflammation on biopsy as a positively weighted criterion and reducing the point assigned to the MPO-ANCA or p-ANCA positivity may improve the applicability of the 2022 ACR/EULAR MPA criteria.

One clinically diagnosed EGPA patient met both the 2022 ACR/EULAR EGPA classification criteria and the 2022 ACR/EULAR MPA classification criteria. This patient had obstructive airway disease, eosinophilia, anti-MPO antibody positivity, and extravascular eosinophilic-predominant inflammation on biopsy. The presence of anti-MPO antibody also caused this patient to be classified as MPA according to new MPA criteria. However, MPA seldom develops eosinophilia or upper respiratory tract features.[26] Additionally, ANCA, mainly anti-MPO, is found in up to 30% of EGPA patients, and a growing body of evidence suggests that clinical phenotypes of EGPA tend to differ according to the ANCA status.[27] Adding the key manifestation of EGPA as negatively weighted items to the new MPA criteria may prevent misclassification. Three clinically EGPA-diagnosed patients were not classified according to the new AAV criteria. The absence of an item for anti-MPO or p-ANCA positivity and the presence of anti-PR3 antibody or p-ANCA positivity as a negatively weighted item in the EGPA criteria caused the patients not to be classified as EGPA. Furthermore, the absence of an item of migratory pulmonary infiltration, which is a typical radiographic feature of EGPA, the absence of an item of cardiac involvement, which is associated with ANCA negativity, eosinophilia, and poor prognosis, and the presence of hematuria, which can be caused by renal involvement of EGPA, as a negatively weighted item were the important factors in the failure to classify EGPA.[26]

Patients with IgA vasculitis based on EULAR/PRINTO/PRES classification criteria were included in this study to test the diagnostic specificity of the 2022 ACR/EULAR AAV classification criteria. IgA vasculitis is a small vessel vasculitis and is clinically characterized by skin, joint, gastrointestinal tract, or renal involvement.[2] AAV should be considered as one of the differential diagnoses of IgA vasculitis. When the new AAV criteria were applied to these patients, none of the patients could be classified as GPA, EGPA, or MPA.

This study has some limitations. The retrospective design of this study was a major limitation. The data were obtained through the hospital's electronic database; therefore, patient selection bias could not be eliminated, and some data on clinical features, images, laboratory, or biopsy results could be missing. However, the number of patients who were not included in our study due to missing data was very small. The second limitation may be the relatively small number of EGPA and MPA patients. Using physician diagnosis as the gold standard may be another limitation. However, it should be kept in mind that the previous 1990 ACR criteria for GPA and EGPA were developed for the classification of patients, not for the diagnosis, and the EMEA algorithm was developed for reducing the unclassified patient number. Therefore, physician diagnosis was used as a gold standard to test whether

the unclassified patient number was reduced. Moreover, we examined the concordance of the new criteria with EMEA, which is a more standardized method.

In conclusion, the 2022 ACR/EULAR Classification Criteria for GPA, MPA, and EGPA were not able to reduce the number of unclassified patients. The new criteria showed the best agreement with the clinical diagnosis in adult patients from Türkiye. However, the diagnostic performance of these new criteria in patients with new onset of AAV-related symptoms is unknown. In addition, it is still unknown whether the 2022 ACR/EULAR EGPA criteria can distinguish EGPA from other hypereosinophilic syndromes.

Ethics Committee Approval: The study protocol was approved by the Committee on the Human Research Ethics of Health Sciences University, Gulhane School of Medicine (date: 2022, number: 68). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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