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Evaluation of ACR/EULAR 2022 ANCA associated vasculitis classification criteria: The impact of reclassification in a large cohort with long-term follow-up

ACR/EULAR 2022 ANCA ilişkili vaskülit sınıflandırma kriterlerinin değerlendirilmesi ve mevcut kriterler ile karşılaştırılması

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Abstract

Objective: To compare the performance of the EMA (European Medicines Agency) algorithm for classification of necrotizing vasculitis and the new American College of Rheumatology (ACR)/European League of Rheumatology (EULAR) 2022 classification criteria in our single center long-term anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) cohort.

Methods: Patients classified as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) according to EMA algorithm were included into the study. ACR/EULAR 2022 classification criteria were implemented retrospectively. Antibody-based classification (ABC) was performed as a third model, which classify patients either GPA or MPA if anti-proteinase 3 (PR3) or myeloperoxidase (MPO) is positive, respectively. Kappa analysis was used to explore the agreement between criteria sets.

Results: Data of 221 patients classified as GPA (85.6%) and MPA (14.5%) according to EMA algorithm were included. PR3-ANCA and MPO-ANCA was positive in 124 (56.1%) and 79 (35.7%) patients. ACR/EULAR 2022 classified 137 (62%) and 84 (38%) patients as GPA and MPA, respectively. Nine (4%) patients were classified as both GPA and MPA, nine (4%) patients were unclassifiable. The new criteria set was in weak agreement with EMA algorithm (kappa=0.28 for GPA and 0.24 for MPA). On the other hand, strong agreement with ABC was observed (kappa=0.88 for GPA and 0.89 for MPA).

Conclusion: A significant number of patients who classified as GPA could be classified as MPA with the ACR/EULAR 2022 criteria and agreement with EMA algorithm was weak. The new criteria set was indecisive for some AAV patients. Strong agreement with ABC indicated the significant influence of serology in the ACR/EULAR 2022 criteria.

Keywords: ANCA associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, classification criteria

Öz

Amaç: Çalışmamızda tek merkezden uzun dönem takipli antinötrofil sitoplazmik otoantikor (ANCA) ilişkili vaskülit hastalarında nekrotizan vaskülitler için geliştilen Avrupa İlaç Kurumu (EMA) algoritması ve ACR/EULAR 2022 küçük damar vasküliti sınıflandırma kritlerlerinin performasını karşılaştırmayı amaçladık.

Yöntem: Çalışmamıza EMA algoritmasına göre granülomlu polianjiitis (GPA) ve mikroskopik polianjiitis (MPA) olarak sınıflandırılan hastalar dahil edildi. Amerikan Romatoloji Cemiyeti (ACR)/Avrupa Romatizma Birliği (EULAR) 2022 sınıflandırma kriterleri retrospektif olarak uygulandı. Üçüncü model olarak, antikora bağlı sınıflandırma uygulandı ve anti-proteinaz-3 (PR3) pozitif hastalar GPA, anti-myeloperoksidaz (MPO) pozitif hastalar MPA olarak sınıflandırıldı. Kriterler arasındaki uyum Kappa analizi ile değerlendirildi.

Bulgular: Çalışmaya EMA algoritmasına göre GPA (%85,6) ve MPA (%14,5) olarak sınıflandırılan toplam 221 hasta dahil edildi. PR3-ANCA 124 (%56,1) and MPO-ANCA 79 (%35,7) hastada pozitifti. ACR/EULAR 2022 sınıflandırma kriterleriyle 137 (%62) hasta GPA, 84 (%38) hasta MPA olarak sınıflandırıldı. Dokuz (%4) hasta hem GPA hem MPA olarak sınıflandırılırken, dokuz (%4) hasta sınıflandırılamadı. Yeni kriterler ve EMA algoritması arasında zayıf uyum gözlendi (GPA için kappa=0,28 ve MPA için kappa=0,24). Ek olarak, ACR/EULAR 2022 kriterleri ve antikora bağlı sınıflandırma metodu arasında yüksek uyum mevcuttu (GPA için kappa=0,88 ve MPA için kappa=0,89).

Sonuç: Önemli sayıda ANCA asosiye vaskülitler (AAV) hastasının dahil edildiği çalışmamızda daha önce GPA olarak sınıflandırılan yüksek sayıda hastanın MPA olarak sınıflandırıldığı gözlendi. ACR/EULAR 2022 ve EMA algoritması arasındaki uyum düşüktü. Yeni kriterlerle daha önce AAV olarak sınıflandırılan hastaların bir bölümü sınıflandırılamadı. Antikora bağlı sınıflandırma ve yeni kriterler arasındaki yüksek uyum yeni kriterlerde antikorların ciddi oranda etkili olduğu şeklinde yorumlanabilir.

Anahtar Kelimeler: ANCA ilişkili vaskülit, mikroskopik polianjiitis, granülomlu polianjiitis, sınıflandırma kriterleri

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises an important subset of small vessel vasculitis and includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic microscopic polyangiitis (EGPA).[1] ANCAs raise against the myeloperoxidase (MPO) and proteinase-3 (PR3) antigens in neutrophil and monocyte cytoplasm. Clinical phenotypes of GPA and MPA are highly correlated with anti-PR3 and anti-MPO antibodies. Granulomatous inflammation is the hallmark of GPA and ear, nose, throat and orbital involvement in addition to pulmonary nodules are characteristic clinical features.[2] These involvements are seldom observed in MPA, and patients often present with pulmonary-renal syndrome, defined by concurrent presence of glomerulonephritis and alveolar bleeding.[3,4]

The first classification criteria for systemic vasculitis were published by American College of Rheumatology (ACR) in 1990 and included seven different types of vasculitis including Wegener's granulomatosis (GPA) and Churg-Strauss syndrome (EGPA).[5,6] MPA was defined as a separate disease entity and AAV subgroup in 1994 and revised 2012 Chapel Hill Consensus Conference (CHCC) definitions. The substantial role of ANCAs in the pathogenesis and emergent clinical features of AAV was also highlighted.[7] To overcome the high rate of overlapping and unclassifiable cases in ACR 1990 and CHCC, Watts et al. developed a classification algorithm [European Medicine Association (EMA) classification] with a step-by-step approach in 2007 using ANCA serotype, histopathologic features and surrogate markers for Wegener's granulomatosis which previously described by Sorensen et al.[8,9] It has been extensively used in recent years for epidemiological studies on AAV.

In 2022, a new criteria set was established by ACR and European League of Rheumatology (EULAR) through Diagnostic and Classification Criteria in Vasculitis (DCVAS) project for systemic vasculitis.[10,11] These criteria set is a product of a multinational collaboration and includes the analysis of approximately 7000 patients with clinical, laboratory, histopathologic and imaging findings. The most noticeable change for the classification AAV in these criteria is the significant weight of ANCA-serotype. Emphasizing the crucial importance of serology is a novelty consistent with current knowledge, however, this approach also has raised questions about the need to classification into two different clinical phenotypes due to presence of shared clinical characteristics and treatment options.[12]

In this study, we aim to evaluate the performance of different criteria in our single centre long-term cohort of AAV patients.

Materials and Methods

Patients diagnosed with AAV in a single tertiary referral center between 1998 and 2021 were evaluated and patients classified as GPA and MPA according to EMA classification were included in this study. Patient data were collected using a predefined protocol consisted of demographic information, clinical features, laboratory, histopathologic and imaging findings. Four researchers (Bİ, NK, MB and DA) collected the data from all available patient records. In cases where there was uncertainty about the data, the researchers who followed up the patients (LO, MI, AG, YY) were contacted. Clinical diagnoses determined by clinicians who followed up the patients were obtained from patient records. Borderline cases were re-evaluated by BI and final classification of these cases was performed by senior researcher (MI). ANCA testing was performed with indirect immunofluorescence (IIF) and enzyme linked immunosorbent assay (ELISA), ELISA results were considered as true positivity in case of discrepancy.[13]

For classification purposes, ACR/EULAR 2022 classification criteria for GPA and MPA were implemented retrospectively. A final classification was performed according to ANCA-serotype, anti-PR3 and anti-MPO patients were classified GPA and MPA, respectively. The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (decision no: 75926, date: 06.07.2020).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA), was used for statistical analyses. For descriptive analysis categorical variables were presented as a number and percentage, whereas the continuous variables were presented as the mean (standard deviation) or median (inter quantile range). For categorical comparisons, the chi-square test and logistic regression analysis were used. Kappa analysis was used to explore the agreement between criteria sets. A p-value less than 0.05 was accepted as statistically significant.

Results

In this study, data of 241 patients were evaluated and 221 patients were classified as GPA and MPA according to EMA algorithm. Mean age at diagnosis was 54.6±14.2 and 117 (52.9%) patients were female. PR3-ANCA and MPO-

ANCA was positive in 124 (56.1%) and 79 (35.7%) patients, respectively. Only 18 (8.1%) patients were ANCA negative. Clinical diagnosis was GPA in 165 (74.7%) patients and MPA in 56 (25.3%) patients. Table 1 provides a summary of clinical features of patients with AAV.

According to EMA algorithm, 189 (85.6%) patients were classified as GPA and 32 (14.5%) patients were classified as MPA. Classification flowchart for EMA algorithm was shown in Figure 1. One hundred twenty seven (57.5%) patients were classified as GPA (formerly Wegener's granulomatosis) according to ACR 1990 classification criteria and fulfilled the EMA algorithm step 2a. Surrogate markers for GPA were present in 185 (83.7%) patients. A total of 60 (27.1%) patients who did not meet the ACR 1990 criteria were classified as having GPA using the EMA algorithm steps 2c and 2d, based on surrogate markers.

Implementation of ACR/EULAR 2022 Classification Criteria

After implementation of ACR/EULAR 2022 criteria to our cohort, 137 (62%) and 84 (38%) patients met the criteria for GPA and MPA, respectively. Nine (4%) patients met both GPA and MPA criteria. Nine (4%) patients were unclassifiable with the new criteria. A total of 58 patients switched to other AAV subgroup with the new criteria (Figure 2).

Of the 189 patients classified as GPA with the former criteria, 130 (68.8%) fulfilled the new criteria for GPA. Eight (4.2%) of these patients met both GPA and MPA criteria. Fifty-two of 189 (27.5%) patients classified as GPA only met the new criteria for MPA.

Twenty-four of 32 patients (75%) classified as MPA with the former criteria met the ACR/EULAR 2022 criteria for MPA and one of these patients met both GPA and MPA criteria. Six of 32 (18.8%) patients classified as MPA only met the new GPA criteria (Figure 2). Three patients with histopathological examination that revealed granulomatous inflammation only met the MPA criteria. All of these patients were anti-MPO positive and had pauci-immune glomerulonephritis, one had pulmonary nodules and mononeuritis multiplex, two had pulmonary infiltrations revealed granulomatous inflammation. Interstitial lung disease (ILD) was present in 42 patients, and 28 (66%) of these patients were classified as MPA.

In eighteen patients with negative ANCA, seven and three patients met the criteria for GPA and MPA, respectively. Eight patients were unclassifiable.

The Features of Unclassifiable Patients

There was a total of nine (4%) patients who did not meet ACR/EULAR 2022 criteria. Five patients were ANCA negative patients with surrogate markers and were classified

Table 1. Selected features of patients with AAV (n=221)

	n	%		n	%
Ear nose throat involvement			Kidney involvement		
Nasal crusting	77	34.8	Asymptomatic hematuria	23	10.4
Septal perforation	29	13.1	Proteinuria	50	22.6
Saddle nose deformity	3	1.4	Nephritic syndrome	145	65.6
Tracheal stenosis	6	2.7	Glomerulonephritis in renal biopsy	133	60.2
Otitis	50	22.6	Skin involvement		
Conductive hearing loss	19	8.6	Palpable purpura	41	18.6
Sensorineural hearing loss	25	11.3	Skin ulcer	9	4
Sinusitis	94	42.5	Gangrene/infarction	1	0.5
Lung involvement			Peripheral nerve involvement		
Hemoptysis	67	30.3	Polyneuropathy	30	13.6
Nodules	104	47.1	Mononeuritis multiplex	22	10
Cavitations	44	14.9	Central nervous system involvement	14	6.3
Infiltration	74	33.5	Cardiac involvement	16	7.2
Interstitial lung disease	42	19	Urogenital involvement	6	2.7
Diffuse alveolar bleeding	30	13.6	Granulomatous inflammation in biopsy	18	8.1
Pleurisy	12	5.4	Giant cells in biopsy	2	0.9
Mucosal and eye involvement					
Oral ulcer	21	9.5			
Scleritis	37	16.7			

AAV: Associated vasculitis

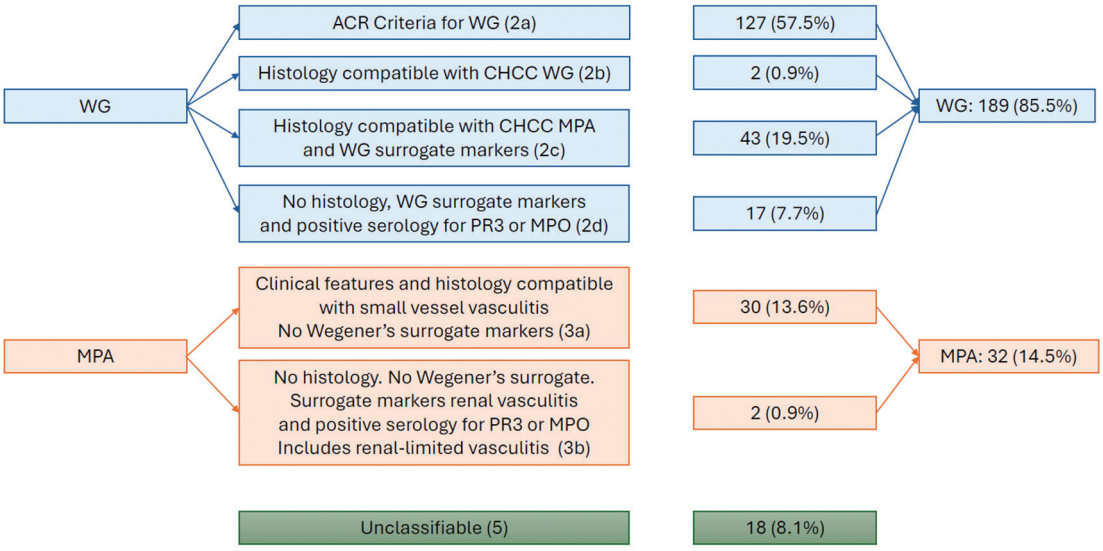

Figure 1. Classification of AAV patients with EMA algorithm
ACR: American College of Rheumatology, AAV: Associated vasculitis, CHCC: Chapel Hill Consensus Conference, EMA: European Medicine Agency, MPA: Microscopic polyangiitis, MPO: Myeloperoxidase, PR3: Proteinase-3, WG: Wegener's granulomatosis

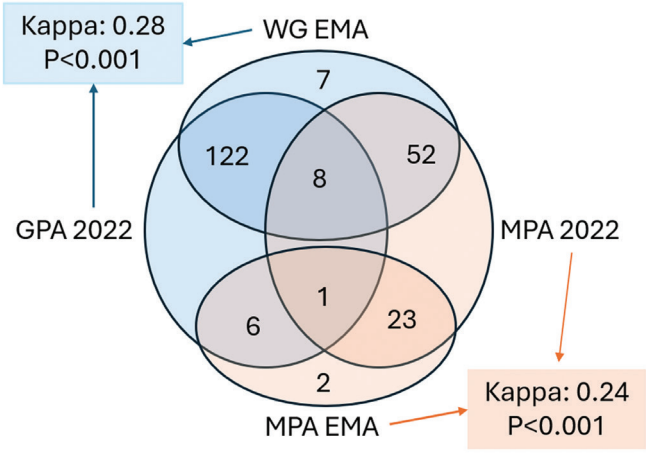

Figure 2. Venn of diagram of distribution of patients with AAV with the EMA algorithm and ACR/EULAR 2022 criteria. Significant inter-class change from WG to MPA with the new criteria could be observed. New criteria also caused overlap in 4% of patients in contrast to EMA algorithm. There was statistically significant but low level of agreement between EMA algorithm and ACR/EULAR 2022 criteria
GPA 2022: ACR/EULAR 2022 classification criteria for granulomatosis with polyangiitis, MPA 2022: ACR/EULAR 2022 classification criteria for microscopic polyangiitis
AAV: Associated vasculitis, ACR: American College of Rheumatology, EULAR: European League of Rheumatology, EMA: European Medicine Agency, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis, WG: Wegener's granulomatosis

as GPA according to EMA algorithm. A single patient was MPO-ANCA positive with nasal involvement and sinusitis. Remaining three patients were ANCA negative renal limited vasculitis. Detailed features of unclassified patients are provided in Table 2. None of the patients had a history of asthma, nasal polyposis, eosinophilia, eosinophilic inflammation in biopsy or mononeuritis multiplex, therefore none of them could be classified as EGPA.

Kappa analysis between the EMA algorithm and ACR/EULAR 2022 criteria for GPA and MPA were both significant (p<0.001), but agreement was low (kappa=0.28 for GPA and 0.24 for MPA) (Figure 2).

Implementation of Antibody-Based Classification to the Cohort

Patients with anti-PR3 and anti-MPO positivity were classified as GPA and MPA according to antibody-based classification (ABC), respectively. A total of 124 (56.1%) patients with anti-PR3 and 79 (35.7%) patients with anti-MPO positivity were classified according to this method. Eighteen (8%) patients were unclassified. The ABC was in perfect agreement with ACR/EULAR 2022 criteria [kappa=0.89 (p<0.001)] for MPA 2022 criteria, 0.88 (p<0.001) GPA 2022 criteria. After the exclusion of double-classified patients with the ACR/EULAR 2022 criteria, two patients classified as GPA with ACR/EULAR 2022 criteria were MPO-ANCA positive, and none of the patients classified as MPA were anti-PR3 positive.

When clinical diagnosis is accepted as reference in our cohort composed of GPA and MPA patients, sensitivity and specificity of EMA algorithm for GPA is 95.2% and 42.9%, ACR/EULAR 2022 criteria for GPA is 82.5% and 100% and ABC for GPA is 75.2% and 100%, respectively. Sensitivity and specificity of EMA algorithm for MPA is 42.9% and 95.2%, ACR/EULAR 2022 criteria for MPA is 98.2% vs. 82.4%, ABC for MPA is 96.4% and 84.8%, respectively.

Table 2. Scoring of ACR/EULAR 2022 classification criteria in unclassified patients

	Nasal involvement or septal perforation (+3)	Sinusitis and mastoiditis (+1)	Hearing loss (+1)	Pulmonary nodules and cavitations (+2)	Pauci-immune GN (+1 for GPA, +3 for MPA)	Granuloma or giant cells in biopsy (+2)	ANCA	GPA criteria points	MPA criteria points
Patient 1	+	+					MPO-ANCA	3	3
Patient 2	+	+					Negative	4	-3
Patient 3				+		+	Negative	4	0
Patient 4			+	+	+		Negative	4	3
Patient 5	+						Negative	3	-3
Patient 6	+	+					Negative	4	-3
Patient 7					+		Negative	1	3
Patient 8					+		Negative	1	3
Patient 9					+		Negative	1	3

ACR: American College of Rheumatology, ANCA: Anti-neutrophil cytoplasmic antibody, EULAR: European League of Rheumatology, GN: Glomerulonephritis, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis

Discussion

In this study, we applied the new ACR/EULAR 2022 classification criteria to patients previously classified as GPA and MPA with the EMA algorithm and observed acceptable agreement between criteria sets. High agreement between ABC and new ACR/EULAR 2022 criteria was remarkable. Another important finding was significant inter-class change between subgroups, especially from GPA to MPA.

Most rheumatological disorders, including AAV, have a multifactorial pathogenesis which is considered to be associated with the interaction of genetic and environmental factors and does not have a "gold standard" clinical, laboratory, histopathological or radiological feature for a consensus diagnosis. Therefore, development of criteria for use in clinical care and research is an important issue. Main objective of disease classification criteria is to provide a standard method to include homogenous groups of patients in clinical and epidemiological studies.[14] We included only the patients classified as AAV according to EMA algorithm to ensure the homogeneity of analysis in our cohort. In a previous study from our group, it was reported that only 1% of cases diagnosed as necrotizing vasculitis were unclassified according to EMA algorithm, which demonstrated the strength and practicality of this method.[15]

GPA and MPA are two clinical subphenotypes of AAV with significant differences in geographical distribution, genetic background, clinical features, and prognostic outcomes. In epidemiological studies, a higher prevalence of GPA and MPA was reported in Caucasian and Asian populations, respectively. This finding can be largely explained by diverse genetic background of these two subsets which lead to either anti-PR3 or anti-MPO positivity.[16,17] Therefore, the dichotomous classification of these clinical subgroups against each other has significant importance for such studies. In our cohort, 85% and 62% of cases were classified as GPA according to EMA algorithm and ACR/EULAR Classification criteria, respectively. These results were similar to the previous studies from Germany, France, and the United Kingdom, which reported a doubling prevalence of GPA compared to MPA.[18-20] As surrogate markers were detected in over 80% of patients, a greater number of patients were categorized as GPA based on the EMA algorithm in our study.

Implementation of the updated criteria led to a reclassification of 27.5% of patients initially labelled as GPA into the MPA subgroup in our cohort. 56 of 189 (29.6%) patients with anti-MPO positivity classified as GPA with former criteria due to presence of surrogate markers and this relatively high anti-MPO positivity in GPA might explain this finding. Similarly, a South Korean study that included 65 patients with GPA, 28 of whom tested positive for anti-MPO, reported 16 (24.5%) patients to be reclassified as MPA.[21] This change was thought to result from higher sensitivity of EMA algorithm for GPA, which may have contributed to the low agreement between the criteria sets. Upper airway involvement, which is the main component of surrogate markers, is not an exclusive finding to GPA. It was reported as high as 25.8% in 325 patients with MPA in a study from DCVAS group.[22] In this regard, we believe that including antibodies in the criteria is a significant improvement.

Another reason for the low agreement may be the underemphasis of specific clinical findings in the new criteria. Three patients with granulomatous inflammation on biopsy were classified as MPA in our cohort. This subgroup of patients is contradictory to 2012 Chapel-Hill consensus criteria which underlined the importance of granulomatous pathology in GPA and should be approached with caution.[7] Additionally, one third of patients with ILD could not

be classified as MPA in our cohort, due to PR3-ANCA positivity. With regard to pathogenesis, we believe that these specific histopathological and radiological findings should be adequately emphasized in the new criteria, regardless of antibody status.

Nine patients (4%) did not meet the new criteria in our cohort. Among these patients, one MPO-ANCA positive and three ANCA-negative patients with limited upper airway disease and sinusitis couldn't be classified as AAV. Granulomatous involvement in the upper airway is recognized as a significant predictor of treatment resistance.[23] Therefore, we suggest that more inclusive enrolment of patients with upper airway vasculitis in clinical trials may be necessary, particularly those with positive ANCA. Additional 3 unclassifiable patients had ANCA-negative renal limited disease. More than 20% of patients with AAV and glomerulonephritis were reported to have negative ANCA in cohort studies.[20] Due to the high rate of end-stage kidney disease and death in these patients, careful application of treatment recommendations are important.[24] We believe that the failure to categorize these patients, diagnosed with small vessel vasculitis and classifiable under previous criteria, is an important drawback.

Our attempt to explore ABC in our cohort disclosed strong agreement with the new criteria, along with close sensitivity and specificity. When the two methods were compared, the new criteria classified only 4% more patients than ABC and a change from GPA to MPA was observed in three patients. Therefore, ABC might have similar sensitivity for inclusion in both epidemiological studies and clinical trials. The authors of the criteria also concluded that this criteria set is only useful for the discrimination between AAV subgroups rather than making differential diagnoses or discrimination from potential mimickers.[10] This warning should be considered cautiously in the routine clinical practice as the excessive weight of ANCA in the criteria might be misleading due to non-vasculitic conditions that can cause ANCA positivity, such as inflammatory bowel disease, infective endocarditis, and malignancies.[25-27] Rathmann et al.[28] reported a concordance of 98% for GPA and 84% for MPA between ACR/EULAR 2022 criteria and ABC in a study from Sweden similar to our study, showing that our results are applicable to diverse patient cohorts as well.

Study Limitation

The main limitation of our study is the collection of the data retrospectively, in a large patient group extending to 25 years in some patients. The inclusion of patients in the study over a long time period may have led to missing information in the patient data and patient selection bias. To overcome these issues, we used predefined protocol to collect the patient data and included the patients only classifiable according to the EMA algorithm in our study. We believe that exclusion of patients who are unclassifiable according to EMA algorithm ensured consistency on the results. Additionally, the exclusion of EGPA patients could be considered a limitation and caused a decrease in patient count. The rationale for the exclusion was the distinct clinical features and relatively low ANCA positivity of EGPA patients. Unclassifiable patients in our cohort also did not meet ACR/EULAR 2022 EGPA criteria. A final important concern is the possible usage of IIF for ANCA testing in the early years of our cohort. However, we think that long-term follow-up in a single-center cohort with the same investigators ensured homogenization in data collection.

Conclusion

In conclusion, our findings suggest that while the new criteria introduce novelty regarding the cohorts eligible for inclusion in clinical research but may fail to change the approach in drug trials due to collective enrolment in these studies. Also, the fact that ANCA positivity can manifest in mimicking conditions such as chronic infections, drug reactions, and malignancies might pose challenges in clinical practice and patient selection for trials. Adequate differentiation also may not be reached in the presence of disease-specific findings such as granulomatous inflammation in histopathology and interstitial lung disease. Further studies on the validation of the criteria and review of scoring in diverse patient groups may be needed.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (decision no: 75926, date: 06.07.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.İ., N.K., M.B., D.A., Y.Y., A.G., M.L.Ö., M.İ., Concept: B.İ., M.B., Design: B.İ., N.K., M.B., Data Collection or Processing: B.İ., N.K., M.B., D.A., Analysis or Interpretation: B.İ., N.K., M.B., Y.Y., A.G., M.L.Ö., M.İ., Literature Search: B.İ., D.A., Writing: B.İ., M.B., Y.Y., A.G., M.L.Ö., M.İ.

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