Application of the 2022 ACR/EULAR criteria for microscopic polyangiitis to patients with previously diagnosed microscopic polyangiitis

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Abstract

Objective

This study applied the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (the 2022 ACR/EULAR) criteria for microscopic polyangiitis (MPA) to patients with previously diagnosed MPA as per the 2007 European Medicines Agency algorithm (the 2007 EMA algorithm) and the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides (the 2012 CHCC definitions). The concordance rate between the new and old criteria was investigated.

Methods

This study included 117 patients with MPA, and the new criteria were applied to these patients. MPA can be classified when the total score is ≥5.

Results

The median age was 64.0 years. The concordance rate between the new and old criteria reached 96.6%. Four patients with previously diagnosed MPA were unclassified. Of these, three patients without myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA) (or perinuclear [P]-ANCA) were not reclassified as having MPA according to the new criteria, despite histopathological findings that were suggestive of MPA based on both the 2007 EMA algorithm and the 2012 CHCC definitions. Conversely, three of four patients with both MPO-ANCA (or P-ANCA) and proteinase 3 (PR3)-ANCA (or cytoplasmic [C]-ANCA) were reclassified as having both MPA and granulomatosis with polyangiitis (GPA) simultaneously according to the 2022 ACR/EULAR criteria for MPA and GPA.

Conclusion

In the new criteria, excessively high score was assigned to MPO-ANCA (or P-ANCA) and MPA-specific histopathological findings were not considered. Hence, the 2007 EMA algorithm and the 2012 CHCC definitions can be applied as additional criteria to complex cases.

Key words

microscopic polyangiitis, application, 2022 ACR/EULAR criteria, reclassification

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Introduction

According to the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides (the 2012 CHCC definitions), microscopic polyangiitis (MPA) is defined as necrotising vasculitis with few or no immune deposits in the absence of granulomas. MPA predominantly invades the capillaries, arterioles, venules, and occasionally medium-sized arteries. MPA may provoke necrotising glomerulonephritis and pulmonary capillarities more frequently than other subtypes of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA) and eosinophilic GPA (EGPA) (1).

In 1990, the American College of Rheumatology (ACR) published the classification criteria for vasculitis (the 1990 ACR criteria), which have been widely used in clinical practice and clinical trials (2, 3). However, the 1990 ACR criteria have some limitations. First, the criteria for MPA were not established because MPA was not recognised as an independent disease entity at that time. Second, the ANCA status was not included in the criteria. Finally, when applied to a large contemporary cohort, the sensitivity of the 1990 ACR criteria diminished markedly (4).

In 2007, the European Medicines Agency proposed an algorithm for classifying AAV (the 2007 EMA algorithm), which consists of a flowchart of EGPA, GPA, MPA, polyarteritis nodosa, and unclassifiable vasculitis. Notably, the criteria for MPA can be applied only when the 2017 EMA algorithm for EGPA and GPA is not met. According to the 2007 EMA algorithm, MPA can be diagnosed only in two conditions after excluding EGPA and GPA, which are as follows: (i) in the presence of clinical features compatible with systemic vasculitis, with histopathological findings of necrotising vasculitis in small vessels without granulomas or eosinophil infiltration and (ii) when clinical findings of renal vasculitis, such as haematuria or proteinuria, are confirmed with ANCA positivity and without surrogate markers for GPA, in the absence of biopsy (5). Thus, histopathological findings defined by CHCC play an essential role in diagnosing MPA.

In 2022, the ACR and the European Alliance of Associations for Rheumatology proposed new classification criteria for AAV (the 2022 ACR/EULAR criteria). The most significant difference from the previous classification criteria for MPA is that the 2022 ACR/EULAR criteria for MPA have a scoring system: differently weighted scores are assigned to each item, and MPA can be classified when the total score is ≥ 5. Another important point is that excluding EGPA and GPA is not necessary for classifying MPA in the new criteria (6). The 2022 ACR/EULAR criteria have two entry requirements – evidence of small- or medium-sized vasculitis and exclusion of other diseases mimicking AAV. The 2022 ACR/EULAR criteria for MPA include one criterion on clinical features and five criteria pertaining to laboratory, radiological, and histopathological features. Among the six criteria, positive scores are assigned to myeloperoxidase (MPO)-ANCA (or perinuclear [P]-ANCA) positivity (+6 points), fibrosis or interstitial lung disease (ILD) on chest imaging (+3), and pauci-immune glomerulonephritis on biopsy (+3). Conversely, negative scores are assigned to serum eosinophil count ≥1000/μL (-4), nasal involvement (-3), and proteinase 3 (PR3)-ANCA (or cytoplasmic [C]-ANCA) positivity (-1). MPA can be classified when the total score is ≥5.

As the 2022 ACR/EULAR criteria were only recently introduced, only a few studies have applied them to patients with previously diagnosed MPA that was based on both the 2007 EMA algorithm and the 2012 CHCC definitions (the old criteria). Hence, this study applied the 2022 ACR/EULAR criteria for MPA to reclassify patients who had previously been identified as having MPA based on the old criteria and investigated the concordance rate between the new and old criteria.

Patients and methods

Patients

This study included 117 patients with MPA enrolled in the Severance Hospital ANCA associated VasculitidEs

(SHAVE) cohort. The SHAVE cohort, which began in November 2016, is a prospective and observational cohort of patients with MPA, GPA, and EGPA. Patients classified as having MPA before the initiation of the cohort were reclassified according to the 2007 EMA algorithm and the 2012 CHCC definitions to maximise the accuracy of the classification and the concordance rate of diagnosis. After the initiation of the cohort, all patients were classified as having MPA according to the old criteria. MPA classification was performed or confirmed at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine and Severance Hospital. All patients had sufficient medical records for investigating clinical, laboratory, radiological, and histopathological findings as well as for assessing AAV-specific indices during AAV diagnosis. Although listed in the SHAVE cohort, patients with ambiguous or insufficient medical records for reclassification of AAV status using the 2007 EMA algorithm, 2012 CHCC definitions, and 2022 ACR/EULAR criteria for MPA were excluded from this study. Moreover, patients with concurrent serious medical conditions mimicking AAV at the time of either classification or reclassification, such as malignancies and infectious diseases requiring hospitalisation, were excluded. Patients who received immunosuppressive drugs for the treatment of AAV before classification and reclassification of MPA were also excluded to minimise confusion. Co-existing severe medical conditions and administered immunosuppressive drugs were identified using the International Classification of Diseases 10th revision and the Korean Drug Utilization Review system, respectively (7, 8).

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

Table I. Characteristics patients with previously diagnosed MPA (n=117).

AAV patients	Values
At the time of diagnosis	
Demographic data	
Age (years)	64.0 (18.2)
Male sex (n (%))	43 (36.8)
ANCA positivity (n (%))	
MPO-ANCA (or P-ANCA) positivity	114 (97.4)
PR3-ANCA (or C-ANCA) positivity	4 (3.4)
Both ANCA positivity	4 (3.4)
ANCA negativity	3 (2.6)
AAV-specific indices	
BVAS	16.0 (10.0)
FFS	2.0 (1.0)
Clinical manifestations at diagnosis (n (%))	
General	64 (54.7)
Cutaneous	20 (17.1)
Muco-membranous/ocular	3 (2.6)
Ear nose throat	28 (23.9)
Pulmonary	76 (65.0)
Cardiovascular	31 (26.5)
Gastrointestinal	5 (4.3)
Renal	95 (81.2)
Nervous	32 (27.4)

Values are expressed as median (interquartile range) or number (percentage).
MPA: microscopic polyangiitis; AAV: antineutrophil cytoplasmic antibody-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; BVAS: Birmingham vasculitis activity score; FFS: five-factor score.

Ethics

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea; IRB no. 4-2020-1071) and conducted in accordance with the principles of the Declaration of Helsinki.

Clinical, laboratory, radiological and histopathological data

The data collected in this study are presented in Table I. The Birmingham vasculitis activity score (BVAS) version 3 and the five-factor score (FFS) were obtained as AAV-specific indices, and clinical manifestations were collected according to the nine categories of BVAS (9, 10). High-resolution computed tomography was performed when lung abnormalities were suspected. Biopsy was performed according to both the physician's decision and the patient's consent. Renal vasculitis was defined when the following conditions were met: red blood cell (RBC) cast-related haematuria or >10% dysmorphic RBC haematuria or 2+ haematuria and 2+ proteinuria on urine stick testing according to the 2007 EMA algorithm (5). 'Patients with previously diagnosed MPA' referred to patients who were classified as having MPA using the 2007 EMA algorithm and the 2012 CHCC definitions before this study.

ANCA measurement

At our institute, we mainly measured and interpreted MPO-ANCA and PR3-ANCA status using the novel anchor-coated highly sensitive (hs) Phadia Elia (Thermo Fisher Scientific/Phadia, Freiburg, Germany) and human native antigens, performed on a Phadia 250 analyser. Immunoassays were used as the primary screening method for P-ANCA and C-ANCA. Patients who tested negative for antigen-specific assays but were positive for ANCA in indirect immunofluorescence assays were considered to have MPO-ANCA or PR3-ANCA, when AAV was strongly suspected according to clinical and laboratory features (11).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA). Continuous and categorical variables are expressed as medians with interquartile ranges and numbers (percentages), respectively.

Take home messages

- The concordance rate between the 2022 ACR/EULAR criteria and both the 2007 EMA algorithm and 2012 CHCC definitions was 96.6%.
- Three patients without MPO-ANCA (or P-ANCA) were not reclassified as MPA according to the 2022 ACR/EULAR criteria despite histopathologic findings suggestive of MPA.
- Conversely, three of the four patients with both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were reclassified as MPA and GPA simultaneously according to the 2022 ACR/EULAR criteria.

Results

Characteristics of patients with previously diagnosed MPA

The median age was 64.0 years, and 37.3% of the patients were men. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were detected in 114 (97.4%) and 4 (3.4%) patients, respectively. All four patients with PR3-ANCA (or C-ANCA) also had MPO-ANCA (or P-ANCA). Three patients (2.6%) did not have ANCA. The median BVAS and FFS values were 16.0 and 2.0, respectively. The most commonly observed clinical manifestation was renal involvement (81.2%), followed by pulmonary (65.0%) and general (54.7%) manifestations (Table I).

Frequency of each criterion in the 2022 ACR/EULAR criteria for MPA fulfilled by patients with previously diagnosed MPA

We analysed clinical, laboratory, radiological, and histopathological data that had been collected at the time of enrolment. In terms of clinical criteria, only one patient presented with nasal congestion. With respect to laboratory, radiological, and histopathological criteria, 114 patients had a score of +6 because of MPO-ANCA (or P-ANCA) positivity and 4 patients received a score of -1 owing to PR3-ANCA (or C-ANCA) positivity. Fifty-eight (49.6%) and 61 (52.1%) patients exhibited fibrosis or ILD on chest imaging and pauci-immune glomerulonephritis on biopsy, respectively. Although five patients showed serum eosinophilia, none of them were classified as having EGPA according to the 2007 EMA algorithm and the 2012 CHCC definitions (Table II).

Total scores of the 2022 ACR/EULAR criteria for MPA applied to patients with previously diagnosed MPA

Of the 117 patients with previously diagnosed MPA, 113 were reclassified as having MPA according to the 2022 ACR/EULAR criteria, which resulted in a concordance rate of 96.6%. The distribution of the total scores of the 2022 ACR/EULAR criteria for MPA is shown in Table III. Twenty-six patients with previously diagnosed MPA achieved the highest score of 12, and six patients had a total score of 5, which was the lowest cut-off for MPA classification according to the 2022 ACR/EULAR criteria. Conversely, four patients did not achieve a total score of 5 and were not reclassified as having MPA – two patients had a total score of 3, and the other two patients had a total score of 0.

Itemised analysis of patients not reclassified as having MPA according to the 2022 ACR/EULAR criteria for MPA

Notably, all three patients without MPO-ANCA (or P-ANCA) were not reclassified as having MPA according to the 2022 ACR/EULAR criteria for

Table II. Frequency of each criterion in the 2022 ACR/EULAR criteria for MPA fulfilled by patients with previously diagnosed MPA (n=117).

Variables		Values
At the time of enrolment in the cohort	Score	
Items for the 2022 ACR/EULAR criteria for MPA and assigned scores to each item (n (%))		
Clinical criteria		
Nasal involvement (discharge, ulcers, crusting, congestion, septal defect/perforation)	**-3**	1 (0.9)
Laboratory, imaging and biopsy criteria		
MPO-ANCA (or P-ANCA) positivity	**+6**	114 (97.4)
Fibrosis or interstitial lung disease on chest imaging	**+3**	58 (49.6)
Pauci-immune glomerulonephritis on biopsy	**+3**	61 (52.1)
PR3-ANCA (or C-ANCA) positivity	**-1**	4 (3.4)
Serum eosinophil count ≥1000/μL	**-4**	5 (4.3)
Total score for 6 items above		9.0 (3.0)
Patients with total score ≥5 (n (%))		113 (96.6)

Values are expressed as number (percentage).
ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MPA: microscopic polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; C: cytoplasmic; ANCA: antineutrophil cytoplasmic antibody.

Table III. Total scores of the 2022 ACR/EULAR criteria for MPA applied to patients with previously diagnosed MPA.

	Score for the 2022 ACR/EULAR criteria for MPA													
	0	1	2	3	4	**5***	6	7	8	9	10	11	12	Total
Number of patients with previously diagnosed MPA	2	0	0	2	0	6	21	0	2	57	0	1	26	117

*The cut-off of the total score for MPA classification based on the 2022 ACR/EULAR criteria for MPA.
ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MPA: microscopic polyangiitis.

Table IV. Itemised analysis of patients with previously diagnosed MPA who did not meet the 2022 ACR/EULAR criteria for MPA (n=4).

Patient's number	Scores based on the 2022 ACR/EULAR criteria for MPA (<5)	1 (-3)	2 (+6)	3 (+3)	4 (+3)	5 (-1)	6 (-4)
1	3	1	1	0	0	0	0
2	3	0	0	1	0	0	0
3	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0

1: nasal involvement (discharge, ulcers, crusting, congestion, septal defect/perforation); 2: MPO-ANCA (or P-ANCA) positivity; 3: fibrosis or interstitial lung disease on chest imaging; 4: pauci-immune glomerulonephritis on biopsy; 5: PR3-ANCA (or C-ANCA) positivity; 6: serum eosinophil count ≥ 1000/μL.
MPA: microscopic polyangiitis; ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody; C: cytoplasmic.

Table V. Itemised analysis of patients who met the 2022 ACR/EULAR criteria for both MPA and GPA (n=3).

Patient number	Scores based on the 2022 ACR/EULAR criteria for MPA	1 (-3)	2 (+6)	3 (+3)	4 (+3)	5 (-1)	6 (-4)
A	11	0	1	1	1	1	0
B	8	0	1	0	1	1	0
C	8	0	1	0	1	1	0

1: nasal involvement (discharge, ulcers, crusting, congestion, septal defect/perforation); 2: MPO-ANCA (or P-ANCA) positivity; 3: fibrosis or interstitial lung disease on chest imaging; 4: pauci-immune glomerulonephritis on biopsy; 5: PR3-ANCA (or C-ANCA) positivity; 6: serum eosinophil count ≥ 1000/μL

Patient number	Scores based on the 2022 ACR/EULAR criteria for GPA	1 (+3)	2 (+2)	3 (+1)	4 (+5)	5 (+2)	6 (+2)	7 (+1)	8 (+1)	9 (-1)	10 (-4)
A	5	0	0	0	1	0	0	0	1	1	0
B	5	0	0	0	1	0	0	0	1	1	0
C	5	0	0	0	1	0	0	0	1	1	0

1: Nasal involvement (discharge, ulcers, crusting, congestion, septal defect/perforation); 2: cartilaginous involvement; 3: conductive or sensorineural hearing loss; 4: PR3-ANCA (or C-ANCA) positivity; 5: pulmonary nodules, mass, or cavitation; 6: granuloma, granulomatous inflammation, or giant cells on biopsy; 7: nasal/paranasal sinusitis or mastoiditis on imaging; 8: pauci-immune glomerulonephritis on biopsy; 9: MPO-ANCA (or P-ANCA) positivity; 10: serum eosinophil count ≥ 1000/μL.
ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; MPO: myeloperoxidase; P: perinuclear; PR3: proteinase 3; ANCA: antineutrophil cytoplasmic antibody; C: cytoplasmic.

MPA. Furthermore, all four patients with typical histopathological features of necrotising vasculitis in small vessels without granulomas were not reclassified as having MPA.

Patient 1 exhibited nasal mucosal thickening with congestion and underwent biopsy, which showed histopathological findings of necrotising vasculitis in small vessels without granulomas or eosinophil infiltration. Although nasal congestion is a typical symptom of GPA, the patient did not meet the 2022 ACR/EULAR criteria for GPA (12). This patient also had MPO-ANCA (or P-ANCA) and was unequivocally classified as having MPA according to the 2007 EMA algorithm and the 2012 CHCC definitions. However, the patient did not meet the 2022 ACR/EULAR criteria for MPA because the total score was only 3.

Patient 2 presented with serious diffuse alveolar haemorrhage and underwent a lung transbronchial lung biopsy, which showed clear evidence of necrotising capillaritis without granulomas or eosinophil infiltration. Therefore, this patient was classified as having MPA despite the absence of ANCA, based on typical histopathological features according to the 2007 EMA algorithm and the 2012 CHCC definitions. Nevertheless, this patient could not be reclassified as having MPA owing to the total score of 3, although the sequelae of diffuse alveolar haemorrhage were considered to be indicative of ILD.

Patients 3 and 4 presented with sensory and motor neuropathy in the lower extremities and underwent a nerve conduction velocity study, which confirmed isolated peripheral neuropathy. Nerve biopsy was performed in both patients, which showed necrotising vasculitis without granulomas or eosinophil infiltration in vessels of various sizes, ranging from capillaries to arteries. No symptoms suggestive of Behçet's disease were found. Particularly, patient 4 had proteinuria and haematuria, which satisfied the conditions of renal vasculitis according to the EMA 2007 algorithm. Although these patients were classified as having MPA according to the 2007 EMA algorithm and the 2012 CHCC definitions despite the absence of ANCA, they did not fulfil the new criteria for MPA owing to the total score of 0 (Table IV).

Itemised analysis of patients reclassified as having both MPA and GPA based on the 2022 ACR/EULAR criteria

Of the four patients with both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA), three were reclassified as having both MPA and GPA according to the 2022 ACR/EULAR criteria for MPA and GPA. First, in terms of MPA classification, because these three patients had both types of ANCA, they were given a score of +5 by default when the new criteria were applied. Patients A, B, and C also exhibited pauci-immune glomerulonephritis on biopsy, which added a score of +3, resulting in a total score of +8. Because of ILD, patient A received an additional score of +3, resulting in a total score of +11. All patients achieved total scores above the cut-off for MPA classification. In terms of GPA classification, a score of +4 was assigned to these three patients with both types of ANCA. Patients A, B, and C also exhibited pauci-immune glomerulonephritis on biopsy, which added a score of +1, resulting in a total score of +5. All patients achieved total scores above the cut-off score for classifying GPA (Table V).

Discussion

This study applied the 2022 ACR/EULAR criteria for MPA to patients with previously diagnosed MPA according to the 2007 EMA algorithm and the 2012 CHCC definitions. Several meaningful findings were obtained. First, the concordance rate in classifying MPA between the 2022 ACR/EULAR criteria and both the 2007 EMA algorithm and the 2012 CHCC definitions reached 96.6%. Second, four patients who did not meet the new crite-

ria, achieved total scores of <3, which implied the clinical utility of the new criteria by showing a considerable difference from the classification cut-off score of 5. Third, all three patients without MPO-ANCA (or P-ANCA) were not reclassified as having MPA according to the 2022 ACR/EULAR criteria, which may reflect the importance of MPO-ANCA (or P-ANCA) in MPA classification. Fourth, three of the four patients with both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were reclassified as having both MPA and GPA according to the 2022 ACR/EULAR criteria for MPA and GPA. However, for patients with both types of ANCAs, no one was reclassified as having only GPA. Therefore, we conclude that the new criteria for MPA have a critical power of discrimination in classifying MPA.

Compared with the 2007 EMA algorithm and the 2012 CHCC definitions, four distinct differences of the 2022 ACR/EULAR criteria for MPA were found (1, 5, 6). First, histopathological findings of necrotising vasculitis without granulomas, which are suggestive of MPA according to the 2012 CHCC definitions, may have only a small contribution to MPA classification, except for renal biopsy-proven pauci-immune glomerulonephritis. The second distinction is that a considerable weight of scores was assigned to MPO-ANCA (or P-ANCA) positivity and negative scores were assigned to PR3-ANCA (or C-ANCA) positivity, thus increasing the clinical significance of the ANCA type in differentiating among AAV subtypes. This is in line with recent studies showing the effects of ANCA specificity (MPO-ANCA or PR3-ANCA) on clinical implications and outcomes (13, 14). However, the pathological and clinical significance of the histological findings of the presence or absence of granuloma cannot be ignored, and warrants further investigation. The third difference is that fibrosis or ILD on chest imaging was included for the first time. The GPA surrogate markers in the lower respiratory tract specified in the 2007 EMA algorithm included fixed, nodular, and cavitary lesions of the lungs; however, the algorithm did not include descriptions of lung lesions associated with MPA. This item is expected to serve as a helpful clue in MPA classification, when MPA is strongly suspected but biopsy cannot be performed. Moreover, a stricter definition has been introduced to determine renal involvement in patients with MPA. The 2007 EMA algorithm classifies MPA according to (i) renal vasculitis defined as haematuria and/or proteinuria, (ii) the presence of any ANCA, and (iii) no evidence of GPA surrogate markers, even though renal biopsy cannot not be performed. However, on the basis of the 2022 ACR/EULAR criteria, only pauci-immune glomerulonephritis histology was included as an indicator of renal involvement.

In this study, four patients had both PR3-ANCA (or C-ANCA) and MPO-ANCA (or P-ANCA), and three of them were reclassified as having both MPA and GPA. Conversely, the remaining one patient was reclassified as having MPA, because this patient had both MPO-ANCA (or P-ANCA) (+6) and PR3-ANCA (or C-ANCA) (-1), resulting in a total score of +5. Although the condition was the same because a score of +5 was assigned to PR3-ANCA (or C-ANCA), the patient was not reclassified as having GPA because of a total score of +4. Nevertheless, this patient demonstrated the clinical significance of PR3-ANCA (or C-ANCA) for the possibility of GPA classification in patients with MPA. Therefore, we recommend applying the 2022 ACR/EULAR criteria for GPA to patients with both MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA), even when they had already been reclassified as having MPA.

Three patients with previously diagnosed MPA were reclassified as having both MPA and GPA, which is ambiguous. This highlights the need for distinction of MPA from GPA as they are significantly different entities. In terms of genetic background and pathogenesis, MPO is encoded by chromosome 17q23.1, stored in primary granules, and not expressed on the surface of resting neutrophils. In contrast, PR3 is encoded by chromosome 19p13.3; stored in primary, secretory, and specific granules; and may be expressed on the surface of resting neutrophils (15). Additionally, MPA can be induced by propylthiouracil and its histopathological feature is necrotising vasculitis without granulomas, whereas GPA may be provoked by *Staphylococcus aureus* and is characterised by necrotising vasculitis with granulomas (16). Moreover, in terms of treatment strategy, the 2021 ACR/Vasculitis Foundation Guideline for the management of AAV recommends the same treatment strategy for active MPA and GPA, but suggests an independent algorithm for non-severe GPA separate from that for MPA (17). These findings support the notion that MPA and GPA should be classified differently. Therefore, when a patient is classified as having both MPA and GPA, a consensus on which disease should be named first needs to be established.

The above four differences are the advantages of the 2022 ACR/EULAR criteria, along with the cut-off values for MPA classification in the scoring system. However, three issues expected in actual clinical practice cannot be ignored. The first issue is that the weighted score assigned to MPO-ANCA (or P-ANCA) positivity is too high compared with that assigned to histological findings that suggest MPA in major organs other than the kidneys. In this study, despite the histopathological findings of necrotising vasculitis without granuloma on nasal mucosal, lung parenchymal, and peripheral nerve biopsies based on the 2022 ACR/EULAR criteria, the absence of MPO-ANCA (or P-ANCA) was the critical reason for the inability to classify three patients as having MPA. The second issue is whether the diagnosis and treatment strategies in patients previously classified as having MPA or renal-limited vasculitis without biopsy should be changed or maintained. Even if patients were classified as having unclassifiable vasculitis according to the new diagnostic criteria, biopsy to confirm the presence or type of renal vasculitis would be less reliable in proportion to the duration of immunosuppressant administration. In such cases, consensus

should be reached on the basis of the discontinuation of immunosuppressive treatment. The final issue is that the scope of the definition and causes of ILD is too broad and ambiguous. For example, if ILD is incidentally found in an elderly patient with P-ANCA but not MPO-ANCA, who exhibits symptoms of cutaneous leucocytoclastic vasculitis (evidence of small-vessel vasculitis), it is uncertain whether this patient be classified as having MPA. A consensus on the specific scope of ILD also needs to be established.

With the histopathological findings of MPA according to the 2012 CHCC definitions in four patients not reclassified as having MPA and the ambiguous clinical criterion of ILD, the dilemma that arises is whether these patients can be defined as having unclassifiable vasculitis and treated conservatively, or classified as having MPA using the 2007 EMA algorithm and the 2012 CHCC definitions and treated based on the strategies for treating MPA. Particularly, it is unethical to exclude patients with peripheral neuropathy and diffuse alveolar haemorrhage as having unclassifiable vasculitis. Therefore, we recommend applying the 2007 EMA algorithm and the 2012 CHCC definitions as additional diagnostic criteria in patients with unclassifiable vasculitis according to the 2022 ACR/EULAR criteria, for whom active treatment is required because of major organ involvement.

Given the different clinical situations according to the ethnic and geographical differences, this study has the advantage that we, for the first time, applied the 2022 ACR/EULAR criteria for MPA to Korean patients with previously diagnosed MPA according to the 2007 EMA algorithm and the 2012 CHCC definitions and investigated the concordance rate between the old and new criteria. However, this study also had several limitations, including the small sample size and retrospective design. Nevertheless, as this pilot study included patients belonging to a single cohort that had been recruited by the same three rheumatologists using a singular protocol, these limitations can be overcome to some extent. A future study with a larger number of patients from more centres will provide more reliable information on the concordance rate between the old and new criteria, and on the classification of complex cases in which the diagnosis is obscure.

In conclusion, the concordance rate between the 2022 ACR/EULAR criteria and the old criteria was 96.6%. The 2022 ACR/EULAR criteria have several issues, particularly the excessively high score assigned to MPO-ANCA (or P-ANCA) and lack of consideration of MPA-specific histopathological findings. Therefore, we recommend applying the 2007 EMA algorithm and the 2012 CHCC definitions as additional diagnostic criteria in complex cases.

Take home messages

- The concordance rate between the 2022 ACR/EULAR criteria for microscopic polyangiitis (MPA) and both the 2007 EMA algorithm and the 2012 CHCC definitions was 96.6%.
- The excessively high weighted score assigned to MPO-ANCA (or P-ANCA) and the non-consideration of histopathological findings of organs other than the kidneys were considered limitations of the 2022 ACR/EULAR criteria for MPA.
- Therefore, we recommend applying the 2007 EMA algorithm and the 2012 CHCC definitions as additional diagnostic criteria in complex cases.

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