2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis

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ABSTRACT

Objective To develop and validate classification criteria for microscopic polyangiitis (MPA).

Methods Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in five phases: (1) identification of candidate items using consensus methodology, (2) prospective collection of candidate items present at the time of diagnosis, (3) data-driven reduction of the number of candidate items, (4) expert panel review of cases to define the reference diagnosis and (5) derivation of a points-based risk score for disease classification in a development set using least absolute shrinkage and selection operator logistic regression, with subsequent validation of performance characteristics in an independent set of cases and comparators.

Results The development set for MPA consisted of 149 cases of MPA and 408 comparators. The validation set consisted of an additional 142 cases of MPA and 414 comparators. From 91 candidate items, regression analysis identified 10 items for MPA, 6 of which were retained. The final criteria and their weights were as follows: perinuclear antineutrophil cytoplasmic antibody (ANCA) or anti-myeloperoxidase-ANCA positivity (+6), pauci-immune glomerulonephritis (+3), lung fibrosis or interstitial lung disease (+3), sino-nasal symptoms or signs (−3), cytoplasmic ANCA or anti-proteinase 3 ANCA positivity (−1) and eosinophil count ≥1×10^9/L (−4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having MPA with a cumulative score of ≥5 points. When these criteria were tested in the validation data set, the sensitivity was 91% (95% CI 85% to 95%) and the specificity was 94% (95% CI 92% to 96%).

Conclusion The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for MPA are now validated for use in clinical research.

INTRODUCTION

The first description of 'periarteritis nodosa' was made by Kussmaul and Maier in 1866.[1] In 1948, Davson *et al* described 14 cases at autopsy that fitted the clinical description of periarteritis nodosa.[2] They divided the cases into two groups based on the histological findings in the kidneys. The clinical presentations of both groups were similar, but their pathological features differed: nine patients showed a distinctive pattern of necrotising glomerulonephritis with no arterial aneurysms, whereas the other five patients showed no glomerular lesions in the kidney but had widespread renal arterial aneurysms and renal infarcts. This is the first time that a clear distinction was made between the microscopic form of polyarteritis nodosa (now called microscopic polyangiitis (MPA)) and classic polyarteritis nodosa (PAN). The 1990 American College of Rheumatology (ACR) criteria for the classification of vasculitis did not make this distinction; instead both entities were included under the term 'polyarteritis nodosa'[3] or possibly 'granulomatosis with polyangiitis' (then called Wegener's granulomatosis).

The publication that resulted from the 1994 Chapel Hill Consensus Conference (CHCC) aimed to standardise the nomenclature and commented that 'different names are being used for the same disease and the same name is being used for different diseases'.[4] The distinction between MPA and PAN is recognised in the CHCC definitions. The main discriminating feature between MPA and PAN is the presence in MPA of pauci-immune vasculitis in arterioles, venules or capillaries. PAN is restricted to a medium-vessel disease, and MPA is a predominantly small-vessel vasculitis that can also involve medium-sized vessels.

The resulting inconsistency between disease definitions and existing classification criteria highlights an important need to update the classification criteria and to include MPA as its own entity. Additionally, over time there have been improvements in our understanding of the different forms of vasculitis, which have been informed in part by routine testing for antineutrophil cytoplasmic antibody (ANCA) in patients with vasculitis and increased utilisation of cross-sectional imaging, both of which have occurred since the 1990 ACR criteria were published. Indeed, most investigators regard MPA as part of the group of small-vessel vasculitides related to the presence of ANCA. This article outlines the development and validation of the new ACR/European Alliance of Associations for Rheumatology (EULAR)—endorsed classification criteria for MPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for MPA is provided in online supplemental appendix 1. Briefly, an international

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Steering Committee comprising clinician investigators with expertise in vasculitis, statisticians and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project. The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of six forms of vasculitis.

Stage 1: generation of candidate classification items for the systemic vasculitides

Candidate classification items were generated by expert opinion and reviewed by a group of vasculitis experts across a range of specialties using a nominal group technique.

Stage 2: DCVAS prospective observational study

A prospective, international multisite observational study was conducted (see collaborators for study investigators and sites). Consecutive patients representing the full spectrum of disease were recruited from academic and community practices. Patients were included if they were 18 years or older and had a diagnosis of vasculitis or a condition that mimics vasculitis. Patients with ANCA-associated vasculitis (AAV) could only be enrolled within 2 years of diagnosis. Only data present at diagnosis were recorded.

Stage 3: refinement of candidate items specifically for AAV

The Steering Committee conducted a data-driven process to reduce the number of candidate items of relevance to cases and comparators for AAV. Items were selected for exclusion if they had a prevalence of <5% within the data set and/or they were not clinically relevant for classification criteria (eg, related to infection, malignancy or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.

Stage 4: expert review to derive a gold standard—defined set of cases of AAV

Experts in vasculitis from a wide range of geographic locations and specialties reviewed all submitted cases of vasculitis and a random selection of mimics of vasculitis. Each reviewer was asked to review ~50 submitted cases to confirm the diagnosis and to specify the certainty of their diagnosis as follows: very certain, moderately certain, uncertain or very uncertain. Only cases agreed on with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for MPA

The DCVAS AAV data set was randomly split into development (50%) and validation (50%) sets. Comparisons were performed between cases of MPA and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA)), 60%; another form of small-vessel vasculitis (eg, cryoglobulinaemic vasculitis) or medium-vessel vasculitis (eg, PAN), 40%. Least absolute shrinkage and selection operator (Lasso) logistic regression was used to identify items from the data set and create a parsimonious model including only the most important items. The final items in the model were formulated into a clinical risk-scoring tool with each factor assigned a weight based on its respective regression coefficient. A threshold that best balanced sensitivity and specificity was identified for classification.

In sensitivity analyses, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS data set based on the submitting physician diagnosis.

RESULTS

Generation of candidate classification items for the systemic vasculitides

The Steering Committee identified >1000 candidate items for the DCVAS case report form (see online supplemental appendix 2.

DCVAS prospective observational study

Between January 2011 and December 2017, the DCVAS study recruited 6991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators and participants is listed in online supplemental appendices 3–5.

Refinement of candidate items specifically for AAV

Following a data-driven and expert consensus process, 91 items from the DCVAS case report form were retained for regression analysis, including 45 clinical (14 composite), 18 laboratory (2 composite), 12 imaging (all composite) and 16 biopsy (1 composite) items. Some clinical items were removed in favour of similar but more specific pathophysiological descriptors. For example, 'Hearing loss or reduction' was removed, and the composite item 'Conductive hearing loss/sensorineural hearing loss' was retained. See online supplemental appendix 6 for the final candidate items used in the derivation of the classification criteria for GPA, MPA and EGPA.

Expert review to derive a gold standard—defined final set of cases of AAV

Fifty-five independent experts reviewed vignettes derived from the case report forms for 2871 cases submitted with a diagnosis of either small-vessel vasculitis (90% of case report forms) or another type of vasculitis or a mimic of vasculitis (10% of case report forms). The characteristics of the expert reviewers are shown in online supplemental appendix 7. A flow chart showing the results of the expert review process is shown in online supplemental appendix 8. A total of 2072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert panel review by 55 investigators, 269 of 404 of the cases retained the submitting physician diagnosis of MPA and 22 additional cases were reclassified as having MPA by consensus of two expert reviewers. Compared with the 291 patients with a reference diagnosis of MPA, the 135 cases that were excluded had lower rates of perinuclear ANCA (pANCA) or anti-myeloperoxidase-ANCA (anti-MPO-ANCA) positivity (76% vs 98%; p<0.01), were less likely to have pauci-immune glomerulonephritis (16% vs 49%; p<0.01), were more likely to have maximum eosinophil counts $\geq 1\times10^9$/L (12% vs 6%; p=0.02), and were more likely to be cytoplasmic ANCA positive or proteinase 3-ANCA-positive (20% vs 4%; p<0.01). There were 822 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1113 cases included in this analysis (291 patients with MPA and 822 comparators), of which 557 (50%; 149 patients with MPA and 408 comparators) were in the development set and 556 (50%; 142 patients with MPA and 414 comparators) were in the validation set.

Table 1 Demographic and disease features of cases of MPA and comparators*

	MPA (n=291)	Comparators (n=822)*	P value
Age, mean±SD years	65.5±13.2	52.0±16.9	<0.001
Sex, no. (%) female	164 (56.4)	394 (47.9)	0.016
Maximum serum creatinine, mean			<0.001
μmoles/L	126.4	185.2	
mg/dL	1.4	2.1	
cANCA positive, no. (%)	11 (3.8)	257 (31.3)	<0.001
pANCA positive, no. (%)	236 (81.1)	136 (16.5)	<0.001
Anti-PR3-ANCA positive, no. (%)	6 (2.1)	265 (32.2)	<0.001
Anti-MPO-ANCA positive, no. (%)	279 (95.9)	142 (17.3)	<0.001
Maximum eosinophil count ≥1×10^9/L, no. (%)	15 (5.2)	244 (29.7)	<0.001

*Diagnoses of comparators for the classification criteria for microscopic polyangiitis (MPA) included granulomatosis with polyangiitis (n=300), eosinophilic granulomatosis with polyangiitis (n=226), polyarteritis nodosa (n=51), non-ANCA-associated small-vessel vasculitis that could not be subtyped (n=51), Behçet's disease (n=50), IgA vasculitis (n=50), cryoglobulinaemic vasculitis (n=34), ANCA-associated vasculitis that could not be subtyped (n=25), primary central nervous system vasculitis (n=19) and anti-glomerular basement membrane disease (n=16). ANCA, antineutrophil cytoplasmic antibody; anti-MPO-ANCA, anti-myeloperoxidase-ANCA; anti-PR3-ANCA, anti-proteinase 3-ANCA; cANCA, cytoplasmic antineutrophil cytoplasmic antibody; pANCA, perinuclear ANCA.

Derivation and validation of the final classification criteria for MPA

Lasso regression of the previously selected 91 items yielded 10 independent items for MPA (see online supplemental appendix 9C. Each item was then adjudicated by the DCVAS Steering Committee for inclusion based on clinical relevance and specificity to MPA, resulting in six final items. Weighting of an individual criterion was based on logistic regression fitted to the six selected items (see online supplemental appendix 10C.

Model performance

Use of a cut-off of ≥5 in total risk score (see online supplemental appendix 11C, for different cut points) yielded a sensitivity of 90.8% (95% CI 84.9% to 95.0%) and a specificity of 94.2% (95% CI 91.5% to 96.3%) in the validation set. The area under the curve for the model was 0.98 (95% CI 0.97 to 0.99) in the development set and 0.97 (95% CI 0.95 to 0.98) in the validation set for the final MPA classification criteria (online supplemental appendix 12C). The final classification criteria for MPA are shown in figure 1 (for the slide presentation version, see online supplemental figure 1).

Sensitivity analysis

The classification criteria for MPA were applied to 2871 patients in the DCVAS database using the original physician-submitted diagnosis (n=404 cases of MPA and 2467 randomly selected comparators). Use of the same cut point of ≥5 points for the classification for MPA yielded a similar specificity of 92.5% but a lower sensitivity of 82.4%. This is consistent with the a priori hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population with fewer clearcut diagnoses of MPA (ie, cases that did not pass expert panel review).

DISCUSSION

Presented here are the 2022 ACR/EULAR MPA classification criteria. These are the first formal criteria for MPA. A 5-stage approach has been used, underpinned by data from the multinational prospective DCVAS study and informed by expert review and consensus at each stage. The comparator group for developing and validating the criteria were predominantly patients with other forms of AAV and other small- and medium-vessel vasculitides, the clinical entities where discrimination from MPA is difficult, but important. The new criteria for MPA have excellent sensitivity and specificity and incorporate ANCA testing and modern imaging techniques. The

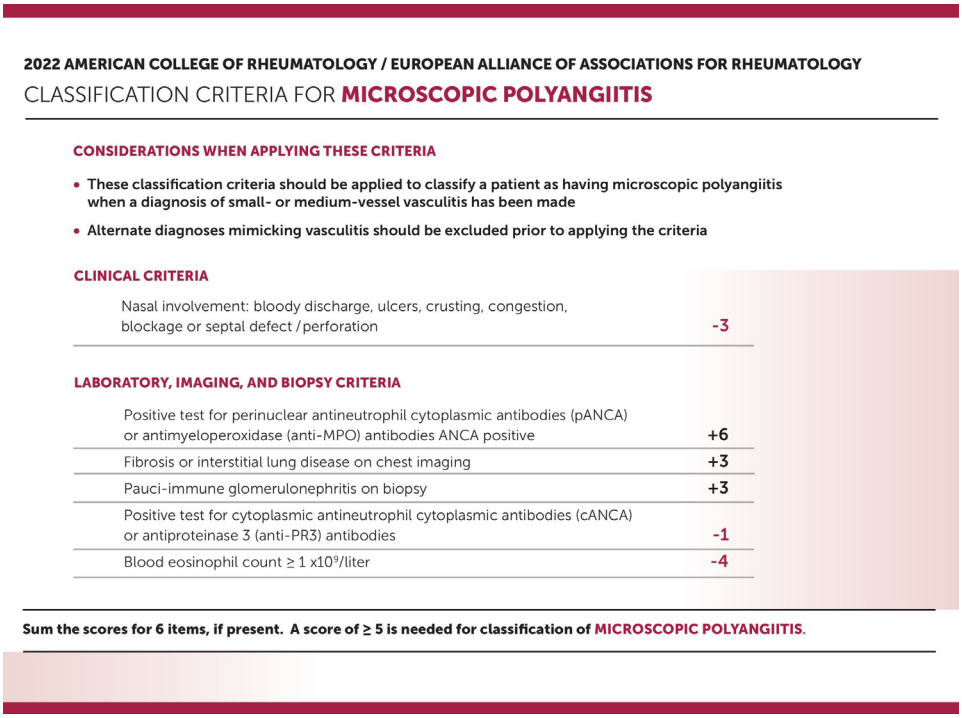

Figure 1 2022 American College of Rheumatology /European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis.

criteria were designed to have face and content validity for use in clinical trials and other research studies.

These criteria are validated and intended for the purpose of *classification* of vasculitis and are not appropriate for use in establishing a *diagnosis* of vasculitis. The aim of the classification criteria is to differentiate cases of MPA from similar types of vasculitis in research settings. Therefore, the criteria should only be applied when a diagnosis of small- or medium-vessel vasculitis has been made and all potential 'vasculitis mimics' have been excluded. The exclusion of mimics is a key aspect of many classification criteria, including those for Sjögren's syndrome[5] and rheumatoid arthritis.[5] The 1990 ACR classification criteria for vasculitis perform poorly when used for diagnosis (ie, when used to differentiate between cases of vasculitis vs mimics without vasculitis),[6] and it is expected that the 2022 criteria would also perform poorly if used inappropriately as diagnostic criteria in people in whom alternative diagnoses, such as infection or other non-vasculitis inflammatory diseases, are still being considered. The relatively low weight assigned to glomerulonephritis in these classification criteria highlights the distinction between classification and diagnostic criteria. While detection of kidney disease is important to diagnose MPA, glomerulonephritis is common among patients with either GPA or MPA and thus does not function as a strong classifier between these conditions.

MPA was not recognised as a separate entity in the 1990 ACR classification criteria for vasculitis, although the disease was recognised as pathologically distinct from PAN over 40 years earlier. This omission of MPA caused difficulties in defining clear homogeneous populations for research; thus, over the last two decades, investigators have often relied on the disease definitions of the CHCC nomenclature for eligibility criteria when enrolling patients with MPA into clinical trials.[4 7–10] This approach resulted in heterogeneity between patients enrolled in therapeutic trials and epidemiological studies.[11] Due to inconsistent methods employed by researchers when applying the 1990 ACR criteria and the CHCC definitions in parallel, the European Medicines Agency (EMA) convened meetings to develop a consensus on how to use the two systems, leading to the publication of the EMA algorithm in 2007.[12] The algorithm works by first excluding EGPA and GPA, and then relying on the CHCC histological descriptions to discriminate between MPA and PAN. The new 2022 ACR/EULAR classification criteria for MPA and other vasculitides provide validated criteria that can replace the EMA interim solution and should harmonise future research studies.

A potential limitation of these new criteria is that, through the expert panel consensus methodology, only the most definite cases were included in the analyses. However, the purpose of these criteria is to enable homogeneous groupings so that individual diseases can be studied. Overall, the use of more definitive cases is consistent with the purpose of classification criteria. Additionally, positive testing for MPO-ANCA is weighted heavily in the criteria, and it is theoretically possible to classify a patient as having MPA on the basis of a positive test for MPO-ANCA only. However, the criteria are intended to only be applied to patients with an established diagnosis of small- or medium-vessel vasculitis; in this setting, the criteria sets should result in a reduction of the score away from a classification of MPA if the patient has features of another form of AAV. When criteria were tested in a much less clearly defined population using the submitting physician diagnosis as the gold standard, the sensitivity of the criteria fell substantially despite 91% of this group being pANCApositive or MPO-ANCA positive, which supports the contention that ANCA positivity is not overly dominant for the classification. Nonetheless, ANCA testing is obviously a key discriminator between the different forms of AAV and other small- and medium-vessel vasculitides.

There are some additional study limitations to consider. Although this was the largest international study ever conducted in vasculitis, most patients were recruited from Europe, Asia and North America. The performance characteristics of the criteria should be further tested in African and South American populations, which may have different clinical presentations of vasculitis. These criteria were developed using data collected from adult patients with vasculitis. Although the clinical characteristics of MPA and the other vasculitides which these criteria were tested against are not known to differ substantially between adults and children, these criteria should be applied to children with some caution. The scope of the criteria is intentionally narrow and applies only to patients who have been diagnosed as having vasculitis. Diagnostic criteria are not specified. The criteria are intended to identify homogenous populations of disease and, therefore, may not be appropriate for studies focused on the full spectrum of clinical heterogeneity in these conditions. To maximise relevance and face validity of the new criteria, study sites and expert reviewers were recruited from a broad range of countries and different medical specialties. Nonetheless, the majority of patients were recruited from academic rheumatology or nephrology units, which could have introduced referral bias.

The 2022 ACR/EULAR classification criteria for MPA are the product of a rigorous methodological process that used an extensive data set generated by the work of a remarkable international group of collaborators. These are the first classification criteria for this disease. The criteria can now be applied to patients who have been diagnosed as having a small- or medium-vessel vasculitis. These criteria have been endorsed by the ACR and EULAR and are now ready for use to differentiate one type of vasculitis from another to define populations in research studies.

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