2021~~0~~ American College of Rheumatology / European League Against Rheumatism Classification Criteria for Microscopic Polyangiitis

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Collaborators: We propose to list and designate all the site investigators and key personnel as "collaborators" as per Medline designation. This means their names are searchable on Medline. This is an important method to appropriately recognize the work of the many co-investigators o this study and is consistent with approaches taken by major journals for such work. A full list of collaborators will be provided for publication per each journal's format.

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Conflicts of Interest

A.J. has received personal fees from Freshfields Bruckhaus Deringer, and is a member of the Data Safety and Monitoring Board (which involved receipt of fees) from Anthera Pharmaceuticals, INC. PAM has received consulting fees from AbbVie, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, ChemoCentryx, CSL Behring, Genzyme/Sanofi, GlaxoSmithKline, Genentech/Roche, InflaRx, Insmed, Janssen, Kiniksa, Sanofi, and Sparrow, and research funds from Boehringer Ingelheim, Bristol-Myers Squibb, CaridianBCT, Celgene, ChemoCentryx, Genentech/Roche, GlaxoSmithKline, Kypha, American College of Rheumatology, European League Against Rheumatism, US National Institutes of Health, US Food and Drug Administration, The Patient-Centered Outcomes Research Institute, and The Vasculitis Foundation, and royalties from UpToDate. RL has received grants from Arthritis Research UK, GSK, MRC, University of Oxford Innovation Fund, Canadian Institutes of Health Research, The Vasculitis Foundation, Celgene, and Vifor; consultancy fees and honoraria from Grunenthal, GSK, InflaRx, Medpace, MedImmune, Roche. JR has received honorarium from Roche and Chemocentryx. RAW has received honoraria from Roche.

Key words

Vasculitis, microscopic polyangiitis, anti-neutrophil cytoplasm antibody, classification

Word count: 2,126

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Key messages: Please summarize the key points of your article in a total of up to 5 bullet points, structured under the following question headings:

What is already known about this subject?

- The 1990 ACR Classification Criteria for vasculitis did not include a separate classification criteria for microscopic polyangiitis.

What does this study add?

- This study provides comprehensively data-driven classification criteria that represent the current state of clinical medicine and utilized newer statistical approaches to develop the criteria.

How might this impact on clinical practice or future developments?

- These new classification criteria for microscopic polyangiitis will be useful to researchers evaluating therapeutic effectiveness for patients with vasculitis.

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: i) Identification of candidate items using consensus methodology; ii) Prospective data collection of candidate items present at the time of diagnosis; iii) Data-driven reduction of candidate items; iv) Expert panel review of cases to define the reference diagnosis; v) Derivation of a points-based risk score for disease classification in a development set using lasso 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 409 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 weighting of final criteria items was: i) pANCA or anti-MPO ANCA positivity (+6), ii) Pauci-immune glomerulonephritis (+3), iii) Lung fibrosis or interstitial lung disease (+3), iv) Sino-nasal symptoms or signs (-3), v) cANCA or anti-PR3 ANCA positivity (-1), and vi) Eosinophil count ≥ $1x10^9$/L (-4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as MPA with a cumulative score of ≥ 5 points. When these criteria were tested in the validation dataset, the sensitivity was 91% (95% confidence interval [95% CI] 85-95%) and the specificity was 94% (95% CI 92-96%).

Conclusion: The 2021~~0~~ ACR-EULAR MPA Classification Criteria are now validated for use in clinical research.

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INTRODUCTION

The first description of 'periarteritis nodosa' was made by Kussmal and Meier 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 pathologically nine patients showed a distinctive pattern of necrotizing glomerulonephritis with no arterial aneurysms whereas the other five patients showed no glomerular lesions in the kidney; however, they 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 classical polyarteritis nodosa. The 1990 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 from the 1994 Chapel Hill Consensus Conference (CHCC) aimed to standardize 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 polyarteritis nodosa (PAN) is recognized in the CHCC definitions. The main discriminating feature between MPA compared to polyarteritis nodosa 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 which can also involve medium sized vessels.

The resulting inconsistency between disease definitions and existing classification criteria highlight 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~~ the understanding of the different forms of vasculitis, which has been informed in part by the routine testing of antineutrophil cytoplasmic antibody (ANCA) for patients with vasculitis, and increased utilization 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 paper outlines the development and validation of the new ACR-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 located in the **Supplementary Materials 1**. Briefly, an international Steering Committee comprised of 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 five-stage plan using data-driven and consensus methodology to develop the criteria for each of the six forms of vasculitis:

Stage One: *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 nominal group technique.

Stage Two: *DCVAS prospective observational study.* A prospective, international multisite observational study was conducted. Ethical approval was obtained by national and local ethics committees. 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 AAV could only be enrolled within 2 years of diagnosis. Only data present at diagnosis was recorded.

Stage Three: *Refinement of candidate items specifically for ANCA-associated vasculitis.* 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 i) prevalence of <5% within the data set, and/or ii) they were non-clinically relevant for classification criteria (e.g., related to infection, malignancy, or demography). Low-frequency items of clinical importance could be combined, when appropriate.

Stage Four: *Expert review to derive a gold standard-defined set of cases of ANCA-associated vasculitis.* Experts in vasculitis from a wide range of geographical locations and specialties reviewed all submitted cases of vasculitis and a random selection of mimics of vasculitis. Each reviewer was asked to review approximately 50 submitted cases to confirm the diagnosis and to specify certainty of their diagnosis as follows: very certain, moderately certain, uncertain, or very uncertain. Only cases agreed upon with at least moderate certainty were retained for further analysis.

Stage Five: *Derivation and validation of the final classification criteria for MPA.* The DCVAS AAV dataset 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 GPA and EGPA) – 60%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel vasculitis (e.g., polyarteritis nodosa) – 40%. Lasso (least absolute shrinkage and selection operator) logistic regression was used to identify items from the dataset 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 was identified for classification, which best balanced sensitivity and specificity.

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

RESULTS

Stage One: Generation of candidate classification items for the systemic vasculitides

The Steering Committee identified over 1000 candidate items for the DCVAS CRF (see **Supplementary Materials 2**).

Stage Two: 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 are listed in **Supplementary Materials 3, 4, and 5**.

Stage Three: Refinement of candidate items specifically for ANCA-associated vasculitis

Following a data-driven and expert consensus process, 91 items from the DCVAS CRF 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 favor 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 **Supplementary Materials 6** for the final candidate items used within the derivation of the classification criteria for GPA, MPA and EGPA.

Stage Four: Expert review to derive a gold standard-defined final set of cases of ANCA-associated vasculitis

Fifty-five independent experts reviewed vignettes derived from the CRFs of 2871 cases submitted with a diagnosis of either small-vessel vasculitis (90% of CRFs), another type of vasculitis, or a mimic of vasculitis (10% of CRFs). The characteristics of the expert reviewers are shown in **Supplementary Materials 7**. The flow chart reporting results of the expert review process is shown in **Supplementary Materials 8**. A total of 2072 (72%) cases passed the process and were designated as cases of vasculitis; these cases were used for the Stage Five analyses.

After expert panel review by 55 investigators, 269/404 of the cases retained a submitting physician diagnosis of MPA, and 22 additional cases were re-classified as MPA by consensus of 2 expert reviewers. Compared to the 291 patients with a reference diagnosis of MPA, the 135 cases that were excluded had lower rates of pANCA or 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 >$1x10^9$/L (12 vs 6%, p=0.02), and were more likely to be cANCA- or PR3-ANCA-positive (20 vs 4%, p<0.01). There were 822 comparators randomly selected for analysis. **Table 1** describes the demographic and disease features of the 1113 cases included in this analysis (291 MPA and 822 comparators), of which 557 (50%) were in the development dataset, and 556 (50%) in the validation set.

Stage Five: Derivation and validation of the final classification criteria for microscopic polyangiitis

Lasso regression of the previously selected 91 items resulted in 10 independent items for MPA (see **Supplementary Materials 9C)**. Each item was then adjudicated by the DCVAS Steering Committee for inclusion based on clinical relevance and specificity to MPA, resulting in 6 final items. Weighting of individual criterion was based on logistic regression fitted to the 6 selected items (see **Supplementary Materials 10C**).

Model performance

Using a cut-off of ≥ 5 in total risk score **(see Supplementary Materials 11C for different cut-points)**, the sensitivity was 90.8% (95% confidence interval [95% CI] 84.9-95.0%) and the specificity was 94.2% (95% CI 91.5-96.3%) in the validation set. The area under the curve for the model was 0.98 (95% CI 0.97-0.99) in the development set and 0.97 (95% CI 0.95-0.98) in the validation set for the final MPA classification criteria **(Supplementary Materials 12C).** The final classification criteria for MPA are shown in **Figure 1**.

Sensitivity analysis

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The classification criteria for MPA was applied to 2871 patients in the DCVAS database using the original physician submitted-diagnosis: all 404 cases of MPA and 2467 randomly selected comparators. Using the same cut-point of ≥ 5 points for the classification for MPA, there was 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 clear-cut diagnoses of MPA (i.e., cases that did not pass expert panel review).

DISCUSSION

Presented here are the 20219 ACR-EULAR MPA Classification Criteria. These are the first formal criteria for MPA. A five-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 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 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 (5). The aim of the classification criteria is to differentiate cases of MPA from similar types of vasculitis in research settings (6). Therefore, the criteria should only be applied when a diagnosis of small- or medium-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 (7) and rheumatoid arthritis (8). The 1990 ACR Classification Criteria for vasculitis perform poorly when used for diagnosis (i.e., when used to differentiate between cases of vasculitis versus mimics without vasculitis) (9) and it is expected that the 20219 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 weighting 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.

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MPA was not recognized as a separate entity in the 1990 ACR Classification Criteria for vasculitis, although the disease was recognized as pathologically distinct from polyarteritis nodosa over 40 years earlier. This omission of MPA caused difficulties in defining clear homogenous 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, 10-13). This approach resulted in heterogeneity between patients enrolled in therapeutic trials and epidemiological studies (14). Due to inconsistent methods employed by researchers when applying the 1990 ACR criteria and the CHCC definitions in parallel, the European Medicines Agency (EMEA) convened meetings to develop a consensus on how to utilize the two systems, leading to the publication of the EMEA algorithm in 2007 (15). 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 2021~~0~~ ACR-EULAR Classification Criteria for MPA and other vasculitides provide validated criteria that can replace the EMEA interim solution and should harmonize 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 homogenous 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 just on the basis of a positive test for MPO-ANCA. 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 had 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 pANCA- 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 to which these Criteria were tested against are not known to substantially differ 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 with 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 maximize 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 2021~~0~~ ACR-EULAR Classification Criteria for Microscopic Polyangiitis are the product of a rigorous methodologic process that utilized an extensive dataset 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 with 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.

ACKNOWLEDGEMENTS

We acknowledge the patients and clinicians who provided data to the DCVAS project.
It is our strong request to name and designate all of the clinical investigators and data science staff as “collaborators” per Medline’s process for this term. This is the appropriate approach to acknowledge their work and now a standard practice for large groups of investigators.

We are including the names of all the investigators and key study staff, including country and name of site institution, in online supplementary material common to the papers on classification of GPA, MPA, and EGPA. We are acknowledging the expert panel reviewers in a similar fashion in the online supplementary material.

Table 1. Demographic and disease features of cases of microscopic polyangiitis and comparators

	Microscopic polyangiitis n = 291	**Comparators* n = 822**	**p-value**
Mean age, years (SD)	65.5 (13.2)	52.0 (16.9)	<0.001
Female sex, n (%)	164 (56.4)	394 (47.9)	0.016
Max creatinine μmol/L mg/dL	126.4 1.4	185.2 2.1	<0.001
cANCA positive, n (%)	11 (3.8)	257 (31.3)	<0.001
pANCA positive, n (%)	236 (81.1)	136 (16.5)	<0.001
Anti-PR3 ANCA positive, n (%)	6 (2.1)	265 (32.2)	<0.001
Anti-MPO ANCA positive, n (%)	279 (95.9)	142 (17.3)	<0.001
Max eosinophil ≥1 x10^9/L, n (%)	15 (5.2)	244 (29.7)	<0.001

*Diagnoses of comparators for the classification criteria for microscopic polyangiitis included granulomatosis with polyangiitis (n=300), eosinophilic granulomatosis with polyangiitis (n=226), polyarteritis nodosa (n=51), non-ANCA-associated vasculitis small-vessel vasculitis that could not be subtyped (n=51), Behçet's disease (n=50), IgA vasculitis (n=50), cryoglobulinemic vasculitis (n=34), ANCA-associated vasculitis that could not be subtyped (n=25), primary central nervous system vasculitis (n=19), anti-glomerular basement membrane disease (n=16).

ANCA: anti-neutrophil cytoplasmic antibody; cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; pANCA: perinuclear anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; SD: standard deviation.

Figure 1: 2021~~0~~ American College of Rheumatology / European League Against Rheumatism classification criteria for microscopic polyangiitis

~~These classification criteria should be applied when a diagnosis of small or medium vessel vasculitis has been made, to classify a patient as having microscopic polyangiitis. Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria.~~

Considerations when applying these criteria	▪ These classification criteria should be applied to classify a patient as having microscopic polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made ▪ Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria	
Clinical Criteria	Nasal bloody discharge, ulcers, crusting, congestion or blockage, or nasal septal defect /perforation	**-3**
Laboratory, Imaging, and Biopsy Criteira	pANCA or anti-MPO ANCA positive	**+6**
	Fibrosis or interstitial lung disease on chest imaging	**+3**
	Pauci-immune glomerulonephritis on biopsy	**+3**
	cANCA or anti-PR3 ANCA positive	**-1**
	Serum eosinophil count ≥ 1 ($x10^9$/L)	**-4**

Sum scores for 6 items. A score of ≥ 5 is needed for classification of MPA

ANCA: anti-neutrophil cytoplasmic antibody; cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; pANCA: perinuclear anti-neutrophil cytoplasmic antibody; PR3: proteinase 3

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