

**2021 American College of Rheumatology / European League Against Rheumatism
Classification Criteria for Granulomatosis with 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 of 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, Insmmed, 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, granulomatosis with polyangiitis, anti-neutrophil cytoplasm antibody, classification

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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 granulomatosis with polyangiitis (GPA, then named Wegener's granulomatosis) have proven to be quite useful in research and clinical practice. However, in the last 30 years the recognition of the key diagnostic importance of testing for anti-neutrophil cytoplasmic antibody, the increased use of advanced imaging, and the introduction of separate classification of microscopic polyangiitis makes revision of the criteria an important undertaking.

What does this study add?

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

How might this impact on clinical practice or future developments?

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

ABSTRACT

Objective: To develop and validate revised classification criteria for granulomatosis with polyangiitis (GPA).

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 collection of candidate items present at time of diagnosis; iii) Data-driven reduction of candidate items; iv) Expert review to define the reference diagnosis; and 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 GPA consisted of 578 GPA cases and 652 comparators. The validation set consisted of an additional 146 cases of GPA and 161 comparators. From 91 candidate items, regression analysis identified 26 items for GPA, 10 of which were retained. The weighting of final criteria items was: i) Bloody nasal discharge, nasal crusting, or sino-nasal congestion (+3), ii) Cartilaginous involvement (+2), iii) Conductive or sensorineural hearing loss (+1), iv) cANCA or anti-PR3 ANCA positivity (+5), v) Pulmonary nodules, mass, or cavitation on chest imaging (+2), vi) Granuloma or giant cells on biopsy (+2), vii) Inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1), viii) Pauci-immune glomerulonephritis (+1), ix) pANCA or anti-MPO ANCA positivity (-1), and x) Eosinophil count ≥ 1 ($\times 10^9/L$) (-4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as GPA with a cumulative score of ≥ 5 points. When these criteria were tested in the validation dataset, the sensitivity was 93% (95% confidence interval [95% CI] 87-96%) and the specificity was 94% (95% CI 89-97%).

Conclusion: The 2021 ACR-EULAR GPA Classification Criteria demonstrate strong performance characteristics and are validated for use in research.

INTRODUCTION

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are multisystem disorders involving inflammation of the small blood vessels and include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) (1). GPA is characterized by necrotizing granulomatous inflammation involving the ears, nose, and upper and lower respiratory tracts, and necrotizing vasculitis affecting predominantly small- to medium-sized vessels, often including necrotizing glomerulonephritis (1).

Unlike diagnostic criteria, the purpose of classification criteria is to ensure that a homogenous population is selected for inclusion into clinical trials and other research studies (2). In 1990, the American College of Rheumatology (ACR) published criteria for the classification of GPA (then named Wegener's granulomatosis) (3-5). The 1990 criteria were effective and widely accepted, facilitating coordinated approaches to international, randomized controlled trials (6, 7). In 2011 it was proposed to change the name "Wegener's granulomatosis" to "granulomatosis with polyangiitis" with subsequent wide adoption of the new terminology (8-10). The 1994 and 2012 publications of the international Chapel Hill Consensus Conference (CHCC) Nomenclature of Vasculitis clarified and standardized the nomenclature of the systemic vasculitides (11) (1). The CHCC is a nomenclature system based on expert consensus rather than a classification system (1).

There are several important reasons for the development of revised classification criteria for the vasculitides, including: i) a decline in the sensitivity of the 1990 ACR Classification Criteria, particularly for AAV (12); ii) a consensus that any such criteria must now incorporate testing for ANCA; iii) increased and widespread use, since 1990, of cross-sectional diagnostic imaging tools, including magnetic resonance imaging and computerized tomography (13, 14); and iv) the introduction and adoption of classifying patients with microscopic polyangiitis, a term not in use in the 1990 ACR Classification Criteria.

There have been methodological advances in the derivation of classification criteria, moving from the “number of criteria” rule, as used in the ACR 1990 criteria (4), towards weighted criteria with threshold scores, as demonstrated in the 2010 Classification Criteria for rheumatoid arthritis (15). Weighted criteria improve measurement properties of classification criteria because certain items within a criteria list may be more discriminative. The previous 1990 criteria for vasculitis collected retrospective data from patient files, without specification between items relevant at time of diagnosis compared to those important later in the disease process. Criteria based on prospectively-collected data sets of newly-diagnosed patients should have higher face validity as inclusion criteria for future clinical trials of early-stage disease.

This paper outlines the development and validation of the revised ACR-EULAR-endorsed classification criteria for GPA.

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for GPA 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 (16). 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 GPA. The DCVAS AAV dataset was randomly split into development (80%) and validation (20%) sets. Comparisons were performed between cases of GPA confirmed by expert review and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including MPA and EGPA) – 40%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis) or medium-vessel vasculitis (e.g., polyarteritis nodosa) – 60%. 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. Comparison was also made between the measurement properties of the new classification criteria for GPA and the 1990 ACR Classification Criteria for GPA using pooled data from the development and validation sets.

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 study participants is 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.

Supplementary Materials 6 lists the final candidate items used for the derivation of the classification criteria for GPA, MPA and EGPA.

Stage Four: Expert review methodology 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**. 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 review, 724/843 cases retained a reference diagnosis of GPA. There were 813 comparators randomly selected for analysis. **Table 1** describes the demographic and disease

features of the 1,537 cases included in this analysis (724 GPA and 813 comparators), of which 1230 (80%) were in the development dataset, and 307 (20%) in the validation set.

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

Lasso logistic regression analysis using all 91 items resulted in a model of 26 independent items (see **Supplementary Materials 9B**). The variables “positive test for cANCA” and “positive test for anti-PR3 antibody” and the variables “positive test for pANCA” and “positive test for anti-MPO antibody” were strongly co-linear and were combined within the model as “positive test for cANCA or positive test for anti-PR3 antibody” and “positive test for pANCA or positive test for anti-MPO antibody”, respectively. Each item was scrutinized for inclusion based on statistical significance, clinical relevance, and specificity to GPA, resulting in 10 final items. Weighing of individual criterion was based on logistics regression fitted to the 10 selected items (see **Supplementary Materials 10B**).

Model performance

Using a cut-off of ≥ 5 in total risk score (see **Supplementary Materials 11B** for different cut-off points), the sensitivity was 92.5% (95% confidence interval [95% CI] 86.9-96.2%) and the specificity was 93.8% (95% CI 88.9-97.0%) in the validation set. The area under the curve for the model was 0.98 (95% CI 0.98-0.99) in the development set and 0.99 (95% CI 0.98-1.00) in the validation set (**Supplementary Materials 12B**). The final classification criteria for GPA are shown in **Figure 1**.

Sensitivity analyses

The classification criteria for GPA were applied to 2511 patients randomly selected from the DCVAS database using the original physician-submitted diagnosis (GPA=483; comparators=2028). Using the same cut-off point of ≥ 5 points for the classification for GPA, there was a similar specificity of 94.6% but a lower sensitivity of 83.8%. This upheld the *a priori*

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hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population with fewer clear-cut diagnoses of GPA (i.e., cases that did not pass expert review).

When the 1990 ACR Classification Criteria for GPA were applied to the DCVAS dataset, the criteria performed poorly due to low sensitivity (69.3%), and moderate specificity (75.8%), with an AUC of 0.73 (95%CI 0.70-0.75).

DISCUSSION

Presented here are the final 2021 ACR-EULAR GPA Classification Criteria. 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 other forms of AAV and other small- and medium-vessel vasculitides, the clinical entities where discrimination from GPA is difficult, but important. The new criteria for GPA 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 (2). The aim of the classification criteria is to differentiate cases of GPA from similar types of vasculitis in research settings. 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 (17) and rheumatoid arthritis (15). 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) (18) and it is expected that the 2021 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 GPA, glomerulonephritis is common among patients with either GPA or MPA and thus does not function as a strong classifier between these conditions.

These criteria differ from the previous 1990 ACR Criteria in that they have been developed using cases presenting prospectively at the start of their disease process. This approach is different from the methods used to generate the 1990 ACR Criteria in which prevalent case

records were utilized, potentially including items related to irreversible damage accrued over time. Inclusion of newly-diagnosed cases in these criteria should improve their accuracy within the context of early intervention trials as well as refractory disease. The comparators used for these new criteria are also more appropriate and closer mimics of GPA; for example, comparators with predominantly small-vessel vasculitis rather than predominantly GCA were included. The new criteria perform better than previous criteria within this dataset (12). ANCA is a major discriminator within these criteria, although patients can be classified as GPA without having a positive test for ANCA if they have a sufficient number of other features. These new criteria were validated in an independent dataset and are weighted with threshold scores (15, 17) to maximize predictive ability.

There are some 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 GPA 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.

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A key strength of this study is the use of an independent expert review process to confirm cases of GPA and comparators to avoid the circularity of using pre-defined criteria to define the gold standard. Approximately a quarter of cases were excluded via this process either due to lack of consensus on exact diagnosis, or insufficient data available to make the diagnosis. A limitation of this approach, however, could be the exclusion of true, but less clear-cut cases submitted by the original physicians. It is important that cases are classified accurately for inclusion in clinical trials; therefore, some loss of sensitivity may be appropriate. Importantly, this study also demonstrated that applying the new criteria for GPA to the whole unselected DCVAS dataset resulted in a reduction in sensitivity while maintaining specificity. Thus, the criteria should also be useful in a more generalized, “real-world” population.

The 2021 ACR-EULAR Classification Criteria for Granulomatosis with 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 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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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 reviewers in a similar fashion in the online supplementary material.

Table 1. Demographic and disease features of cases of granulomatosis with polyangiitis and comparators*

	Granulomatosis with polyangiitis n = 724	Comparators* n = 813	p-value
Mean age, years (SD)	53.6 (16.2)	56.4 (17.1)	0.001
Female sex, n (%)	340 (47.0)	424 (52.2)	0.048
Creatinine $\mu\text{mol/L}$	168.3	185.2	0.077
mg/dL	1.9	2.1	
cANCA positive, n (%)	531 (73.3)	40 (4.9)	<0.001
pANCA positive, n (%)	40 (9.8)	342 (42.1)	<0.001
Anti-PR3 ANCA positive, n (%)	595 (82.2)	21 (2.6)	<0.001
Anti-MPO ANCA positive, n (%)	59 (8.1)	399 (49.1)	<0.001
Max eosinophil $\geq 1 \times 10^9/\text{L}$, n (%)	196 (27)	366 (45)	<0.001

*Diagnoses of comparators for the classification criteria for granulomatosis with polyangiitis included microscopic polyangiitis (n=291), 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).

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

Figure 1. 2021 American College of Rheumatology / European League Against Rheumatism Classification criteria for granulomatosis with polyangiitis

Considerations when applying these criteria	<ul style="list-style-type: none"> ▪ These classification criteria should be applied to classify a patient as having granulomatosis with 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
	Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Laboratory, Imaging, and Biopsy Criteria	cANCA or anti-PR3 ANCA positive	+5
	Pulmonary nodules, mass, or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
	Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune glomerulonephritis on biopsy	+1
	pANCA or anti-MPO ANCA positive	-1
	Serum eosinophil count ≥ 1 ($\times 10^9/L$)	-4

Sum scores for 10 items, if present. A score of ≥ 5 is needed for classification of granulomatosis with polyangiitis.

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

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