2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Granulomatosis With Polyangiitis

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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 5 phases: 1) identification of candidate criteria 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 GPA consisted of 578 cases of GPA 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 final criteria and their weights were as follows: bloody nasal discharge, nasal crusting, or sino-nasal congestion (+3); cartilaginous involvement (+2); conductive or sensorineural hearing loss (+1); cytoplasmic antineutrophil cytoplasmic antibody (ANCA) or anti–proteinase 3 ANCA positivity (+5); pulmonary nodules, mass, or cavitation on chest imaging (+2); granuloma or giant cells on biopsy (+2); inflammation or consolidation of the nasal/paranasal sinuses on imaging (+1); pauci-immune glomerulonephritis (+1); perinuclear ANCA or anticytoplasmic oxidase ANCA positivity (−1); and eosinophil count ≥1 × 10^9/liter (−4). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as having GPA if the cumulative score was ≥5 points. When these criteria were tested in the validation data set, the sensitivity was 93% (95% confidence interval [95% CI] 87–96%) and the specificity was 94% (95% CI 89–97%).

Conclusion. The 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for GPA demonstrate strong performance characteristics and are validated for use in research.


INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (AAV) are multisystem disorders involving inflammation of the small blood vessels and include granulomatosis with polyangitis (GPA), microscopic polyangitis (MPA), and eosinophilic granulomatosis with polyangitis (EGPA) (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 homogeneous population is selected for inclusion in clinical trials and other research studies of GPA. In 1990, the American College of Rheumatology (ACR) published criteria for the classification of GPA (then named Wegener’s granulomatosis) (2–4). The 1990 criteria were effective and widely accepted, facilitating coordinated approaches to international randomized controlled trials (5,6). In 2011 it was proposed to change the name “Wegener’s granulomatosis” to “granulomatosis with polyangiitis” with subsequent wide adoption of the new terminology (7–9). The 1994 and 2012 publications of the international Chapel Hill Consensus Conference (CHCC) nomenclature for vasculitis clarified and standardized the nomenclature of the systemic vasculitides (1,10). 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 a decline in the sensitivity of the 1990 ACR classification criteria, particularly for AAV (11); a consensus that any such criteria must now incorporate testing for ANCA; increased and widespread use, since 1990, of cross-sectional diagnostic imaging tools, including magnetic resonance imaging and computed tomography (12,13); and the introduction and adoption of the classification of patients with MPA, a term not in use in the 1990 ACR classification criteria.

There have been methodologic advances in the derivation of classification criteria, moving from the “number of criteria” rule, as used in the ACR 1990 criteria (3), toward weighted criteria with threshold scores, as demonstrated in the 2010 classification criteria for rheumatoid arthritis (14). 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 of which items were relevant at the time of diagnosis compared to those that were important later in the disease process. Criteria based on prospectively collected data sets from newly diagnosed patients should have higher face validity as inclusion criteria for future clinical trials of early-stage disease. This article outlines the development and validation of the revised ACR/European Alliance of Associations for Rheumatology (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 provided in Supplementary Appendix 1, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. Briefly, an international 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 (15). The Steering Committee established a 5-stage plan using data-driven and consensus methodology to develop the criteria for each of 6 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 Appendix A for study investigators and sites). Ethical approval was obtained from 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 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 (e.g., related to infection, malignancy, or demographic characteristics). Low-frequency items of clinical importance could be combined, when appropriate.


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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 upon with at least moderate certainty were retained for further analysis.

Stage 5: derivation and validation of the final classification criteria for GPA. The DCVAS AAV data set 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), 64%; another form of small-vessel vasculitis (e.g., cryoglobulinemic vasculitis), 36%. 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 a threshold that best balanced sensitivity and specificity. ACR/EULAR classification criteria were validated in a prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and study participants is listed in Supplementary Appendices 2, 3, 4, and 5, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract.

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. 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. Comparisons were performed between cases of GPA confirmed by expert review and a random selection of mimics of vasculitis and a random selection of cases of GPA and comparators included in the DCVAS prospective observational study. Between January 2011 and December 2017, the DCVAS study recruited 6,991 participants from 136 sites in 32 countries. Information on the DCVAS sites, investigators, and study participants is listed in Supplementary Appendices 3, 4, and 5, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract.

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 favor of similar but more specific pathophysiologic descriptors. Supplementary Appendix 6, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract, lists 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 2,871 cases submitted with a diagnosis of either small-vessel vasculitis

| Table 1. Demographic and disease features of cases of GPA and comparators* |
|-----------------|-----------------|-----------------|
| **GPA** (n = 724) | **Comparators** (n = 813) | **P** |
| Age, mean ± SD years | 53.6 ± 16.2 | 56.4 ± 17.1 | 0.001 |
| Sex, no. (%) female | 340 (47.0) | 424 (52.2) | 0.048 |
| Maximum serum creatinine, mean µmole/liter | 168.3 | 185.2 | 0.077 |
| mg/dl | 1.9 | 2.1 | |
| cANCA positive, no. (%) | 531 (73.3) | 40 (4.9) | <0.001 |
| pANCA positive, no. (%) | 79 (10.4) | 342 (42.1) | <0.001 |
| Anti–PR3-ANCA positive, no. (%) | 595 (82.2) | 21 (2.6) | <0.001 |
| Anti–MPO-ANCA positive, no. (%) | 59 (8.1) | 399 (49.1) | <0.001 |
| Maximum eosinophil count ≥1 x 109/liter, no. (%) | 196 (27) | 366 (45) | <0.001 |

* cANCA = cytoplasmic antineutrophil cytoplasmic antibody; pANCA = perinuclear ANCA; anti–PR3-ANCA = anti–myeloperoxidase-ANCA.
† Diagnoses of comparators for the classification criteria for granulomatosis with polyangiitis (GPA) included microscopic polyangiitis (n = 291), eosinophilic granulomatosis with polyangiitis (n = 226), polyarteritis nodosa (n = 51), non–ANCA-associated small-vessel vasculitis that could not be subtyped (n = 25), 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), and anti–glomerular basement membrane disease (n = 16).
(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 Supplementary Appendix 7, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. A flow chart showing the results of the expert review process is shown in Supplementary Appendix 8, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract. A total of 2,072 cases (72%) passed the process and were designated as cases of vasculitis; these cases were used for the stage 5 analyses.

After expert review, 724 of 843 cases retained a reference diagnosis of GPA. There were 813 comparators randomly selected for analysis. Table 1 shows the demographic and disease features of the 1,537 cases included in this analysis (724 patients with GPA and 813 comparators), of which 1,230 (80%, 578 patients with GPA and 652 comparators) were in the development set, and 307 (20%, 146 patients with GPA and 161 comparators) were in the validation set.

**Derivation and validation of the final classification criteria for GPA.** Lasso logistic regression analysis using all 91 items resulted in a model of 26 independent items (see Supplementary Appendix 9B, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract). The variables “positive test for cytoplasmic ANCA (cANCA)” and “positive test for anti–proteinase 3 (anti-PR3)
antibody” and the variables “positive test for perinuclear ANCA (pANCA)” and “positive test for antimonyeloperoxidase (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. Weighting of an individual criterion was based on logistic regression fitted to the 10 selected items (see Supplementary Appendix 10B, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract).

Model performance. Use of a cutoff of ≥5 for total risk score (see Supplementary Appendix 11B, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract, for different cut points) yielded a sensitivity of 92.5% (95% confidence interval [95% CI] 86.9–96.2%) and a specificity of 93.8% (95% CI 88.9–97.0%) in the validation set. The area under the curve (AUC) 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 Appendix 12B, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract). The final classification criteria for GPA are shown in Figure 1 (for the slide presentation version, see Supplementary Figure 1, available on the Arthritis & Rheumatology website at http://onlinelibrary.wiley.com/doi/10.1002/art.41986/abstract).

Sensitivity analyses. The classification criteria for GPA were applied to 2,511 patients randomly selected from the DCVAS database using the original physician-submitted diagnosis (n = 483 GPA and 2,028 comparators). Use of the same cut point of ≥5 points for the classification of GPA yielded a similar specificity of 94.6% but a lower sensitivity of 83.8%. This upheld the a priori 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 data set, 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 2022 ACR/EULAR GPA classification criteria. 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 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. 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-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 (16) and rheumatoid arthritis (14). 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) (17), 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 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 are closer mimics of GPA; for example, comparators with predominantly small-vessel vasculitides rather than predominantly giant cell arteritis were included. The new criteria perform better than previous criteria within this data set (11). ANCA is a major discriminator within these criteria, although patients can be classified as having GPA without having a positive test result for ANCA if they have a sufficient number of other features. These new criteria were validated in an independent data set and are weighted with threshold scores (14,16) 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 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 homogeneous 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.

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 predefined criteria to define the gold standard. Approximately one-quarter of cases were excluded via this process, due to either a 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 clearcut, 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 data set resulted in a reduction in sensitivity while maintaining specificity. Thus, the criteria should also be useful in a more generalized, “real-world” population.

The 2022 ACR/EULAR classification criteria for GPA are the product of a rigorous methodologic process that utilized an extensive data set 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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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Robson, Grayson, Ponte, Suppiah, Craven, Judge, Khalid, Hutchings, Watts, Merkel, Luqmani.

REFERENCES

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