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

Word count: 2,163

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 eosinophilic granulomatosis with polyangiitis (then named Churg Strauss Syndrome) 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 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 eosinophilic 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 eosinophilic granulomatosis with polyangiitis (EGPA).

Methods: Patients with vasculitis or comparator diseases were recruited into an international cohort. The study proceeded in five phases: i) Identification of candidate criteria items using consensus methodology; ii) Prospective 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 EGPA consisted of 107 cases of EGPA and 450 comparators. The validation set consisted of an additional 119 cases of EGPA and 437 comparators. From 91 candidate items, regression analysis identified 11 items for EPGA, seven of which were retained. The weighting of final criteria items was: i) Maximum eosinophil count ≥ $1x10^9$/L (+5), ii) Obstructive airway disease (+3), iii) Nasal polyps (+3), iv) cANCA or anti-PR3 ANCA positivity (-3), v) Extravascular eosinophilic predominant inflammation (+2), vi) Mononeuritis multiplex/motor neuropathy not due to radiculopathy (+1), and vii) Hematuria (-1). After excluding mimics of vasculitis, a patient with a diagnosis of small- or medium-vessel vasculitis could be classified as EGPA with a cumulative score of ≥ 6 points. When these criteria were tested in the validation dataset, the sensitivity was 85% (95% confidence interval [95% CI] 77-91%) and the specificity was 99% (95% CI 98-100%).

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

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a form of vasculitis that is histologically defined by eosinophil-rich, necrotizing granulomatous inflammation primarily involving the respiratory tract along with necrotizing vasculitis of small- to medium-sized arteries (1). EGPA is considered a form of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), along with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). ANCA are detected in approximately 40-60% of patients with EGPA and are typically directed against myeloperoxidase (MPO) (2, 3).

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 (4). In 1990, the American College of Rheumatology (ACR) published classification criteria for EGPA (5). By current standards, these criteria have never been validated because they were developed using data from only 20 patients with EGPA without independent test and validation sets. Furthermore, the criteria were derived by comparing clinical data from patients with EGPA to 787 patients with other forms of vasculitis. Many of these comparators were patients with giant cell arteritis (GCA), a form of large-vessel vasculitis that is typically not difficult to readily distinguish from EGPA based on obvious clinical differences. Despite these methodologic weaknesses, the 1990 ACR criteria for EGPA have existed unchanged for several decades and have been useful to advance clinical research in these diseases.

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

METHODS

A detailed and complete description of the methods involved in the development and validation of the classification criteria for EGPA 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 (6). 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 subset 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 EGPA.* The DCVAS AAV dataset was randomly split into development (50%) and validation (50%) sets. Comparisons were performed between cases of EGPA and a comparator group randomly selected from the DCVAS cohort in the following proportions: another type of AAV (including GPA and MPA) – 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. Comparison was also made between the measurement properties of the new classification criteria for EGPA and the 1990 ACR Classification Criteria for EGPA 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 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. 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, 226/315 cases of EGPA were retained for subsequent analysis. Compared to patients who were retained, patients who were excluded from further analysis had significantly higher serum creatinine (102.8 ±88.7 vs 85.0 ±53.6, p=0.03), lower rates of MPO-ANCA positivity (22 vs 43%, p<0.01), and were less likely to have maximum eosinophil counts >$1x10^9$/L (62 vs 92%, p<0.01). There were 887 comparators randomly selected for analysis. **Table 1** describes the demographic and disease features of the 1113 cases included in this analysis (226 EGPA and 887 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 eosinophilic granulomatosis with polyangiitis

Lasso regression of the previously selected 91 items yielded 11 independent items for EGPA, **Supplementary Materials 9A**. Each item was then adjudicated by the DCVAS steering committee for inclusion based on clinical relevance and specificity to EGPA, resulting in 7 final items. Weighting of an individual criterion was based on logistic regression fitted to the 7 selected items (see **Supplementary Materials 10A**).

Model performance

Using a cut-off of ≥6 in total risk score **(see Supplementary Materials 11A for different cut-points)**, the sensitivity was 84.9% (95% confidence interval [95% CI] 77.2-90.8%) and the specificity was 99.1% (95% CI 98.3-99.8%) in the validation set. The area under the curve for the model was 0.98 (95% CI 0.97-1.00) in the development set and 0.99 (95% CI 0.97-1.00) in the validation set for the final EGPA classification criteria **(Supplementary Materials 12A).** The final classification criteria for EGPA are presented in **Figure 1**.

Sensitivity analyses

The classification criteria for EGPA were applied to 2871 patients in the DCVAS database using the original physician submitted diagnosis (EGPA=315; randomly-selected comparators=2556).

Using the same cut-point of ≥6 points for the classification for EGPA, there was a similar specificity of 99% but a lower sensitivity of 75%. This upheld the *a priori* hypothesis that specificity would remain unchanged but sensitivity would be reduced in a population of patients that included fewer clear-cut diagnoses of EGPA (i.e. cases that did not pass expert panel review).

When the 1990 ACR classification criteria for EGPA were applied to the DCVAS dataset, the criteria performed poorly due to low sensitivity (44%) but retained excellent specificity (99%), with an area under the curve of 0.72 (95% CI 0.68-0.75).

DISCUSSION

Presented here are the final 2021 ACR-EULAR EGPA 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, which are the clinical entities where discrimination from EGPA is difficult, but important. The new criteria for EGPA have excellent sensitivity and specificity and incorporate ANCA testing. 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 using in establishing a *diagnosis* of vasculitis (4). The aim of the classification criteria is to differentiate cases of EGPA 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 (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 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. Specifically, the criteria were not developed to differentiate patients with EGPA from other related hypereosinophilic syndromes or eosinophilic malignancies (10).

The 2021 ACR/EULAR EGPA Classification Criteria reflect the collaborative effort of the international vasculitis community to delineate the salient clinical features that differentiate EGPA from other forms of vasculitis. The final criteria include seven clinical items that are easily assessed during routine clinical evaluation of patients with EGPA. The criteria highlight the importance of peripheral eosinophilia, asthma, and eosinophilic inflammation to classify EGPA

among other forms of vasculitis and specify additional features (e.g., nasal polyps, mononeuritis multiplex) that function as important disease classifiers. Classification criteria are intended to define a homogeneous group of patients with a particular disease for inclusion into clinical research studies. By maximizing specificity, the revised criteria for EGPA ensure that few cases will inappropriately meet the criteria threshold of ≥6 points, thus these criteria will function to facilitate the conduct of future clinical trials and other studies in EGPA.

The negative items included in the final criteria underscore that these criteria are intended for use as classification, not diagnostic, criteria to differentiate EGPA from other forms of vasculitis in research settings. Both hematuria and anti-PR3-ANCA function as negative items in the new EGPA classification criteria, yet glomerulonephritis and ANCA are features of disease that, when present, can be useful to diagnose EGPA. When compared to other forms of ANCA-associated vasculitis, however, biopsy-proven glomerulonephritis was significantly less common in the DCVAS cohort in patients with EGPA (4.9%) compared to GPA (27.8%) or MPA (48.5%). Similarly, anti-PR3-ANCA have been reported in few patients with EGPA but are much more prevalent in GPA (11). For these reasons, hematuria and anti-PR3-ANCA work against a patient with small vessel vasculitis being classified as EGPA. Although anti-MPO-ANCA can be detected in 40-60% of patients with EGPA, positive anti-MPO-ANCA were not included in the final criteria because these antibodies are significantly more prevalent in diseases like microscopic polyangiitis and thus are not discriminant classifiers for EGPA.

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 EGPA 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.

There are several strengths to the new 2021 ACR/EULAR EGPA Classification Criteria. The criteria were developed within a large cohort reflecting international expertise in systemic vasculitis according to ACR guidance for classification criteria development (12). The criteria represent several important methodologic advancements compared to the original 1990 ACR Classification Criteria for EGPA. Expert review rather than submitting physician diagnosis was used as the diagnostic reference standard to minimize investigator bias. Second, while the 1990 ACR criteria were entirely derived in 20 patients with EGPA and not validated, the new criteria were developed in 107 patients with EGPA and validated in an independent test set which contained an additional 119 patients with EGPA. Third, unlike the 1990 ACR criteria, the new ACR-EULAR EGPA criteria are weighted to reflect the relative importance of specific items (e.g. eosinophil counts). Finally, when both criteria sets were tested within the DCVAS cohort, the performance characteristics of the 1990 ACR criteria were suboptimal when compared to the revised 2021 ACR/EULAR EGPA criteria.

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

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

	EGPA n = 226	Comparators* n = 887	p-value
Mean age, years (SD)	52.9 (14.4)	56.2 (17.6)	0.009
Female sex, n (%)	113 (50.0)	445 (50.2)	1.000
Max creatinine μmol/L (SD)	85.0 (53.6)	205.90 (237.0)	<0.001
mg/dL (SD)	0.96 (0.6)	2.33 (2.7)	
cANCA positive, n (%)	17 (7.5)	251 (28.3)	<0.001
pANCA positive, n (%)	83 (36.7)	289 (32.6)	0.271
Anti-PR3-antibody positive, n (%)	7 (3.1)	264 (29.8)	<0.001
Anti-MPO-antibody positive, n (%)	98 (43.4)	323 (36.4)	0.065
Max eosinophil ≥ $1x10^9$/L, n(%)	208 (92.0)	53 (6.0)	<0.001

*Diagnoses of comparators for the classification criteria for eosinophilic granulomatosis with polyangiitis included granulomatosis with polyangiitis (n=300), microscopic polyangiitis (n=291), 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 eosinophilic granulomatosis with polyangiitis

Considerations when applying these criteria	▪ These classification criteria should be applied to classify a patient as having eosinophilic 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	Obstructive airway disease	**+3**
	Nasal polyps	**+3**
	Mononeuritis multiplex	**+1**
Laboratory and Biopsy Criteria	Serum eosinophil count ≥ 1 ($x10^9$/L)	**+5**
	Extravascular eosinophilic predominant inflammation on biopsy	**+2**
	cANCA or anti-PR3-antibody positive	**-3**
	Hematuria	**-1**

Sum scores for 7 items, if present. A score of ≥ 6 is needed for classification of eosinophilic granulomatosis with polyangiitis.

cANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; PR3: proteinase 3.

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