SUPPLEMENTARY MATERIAL

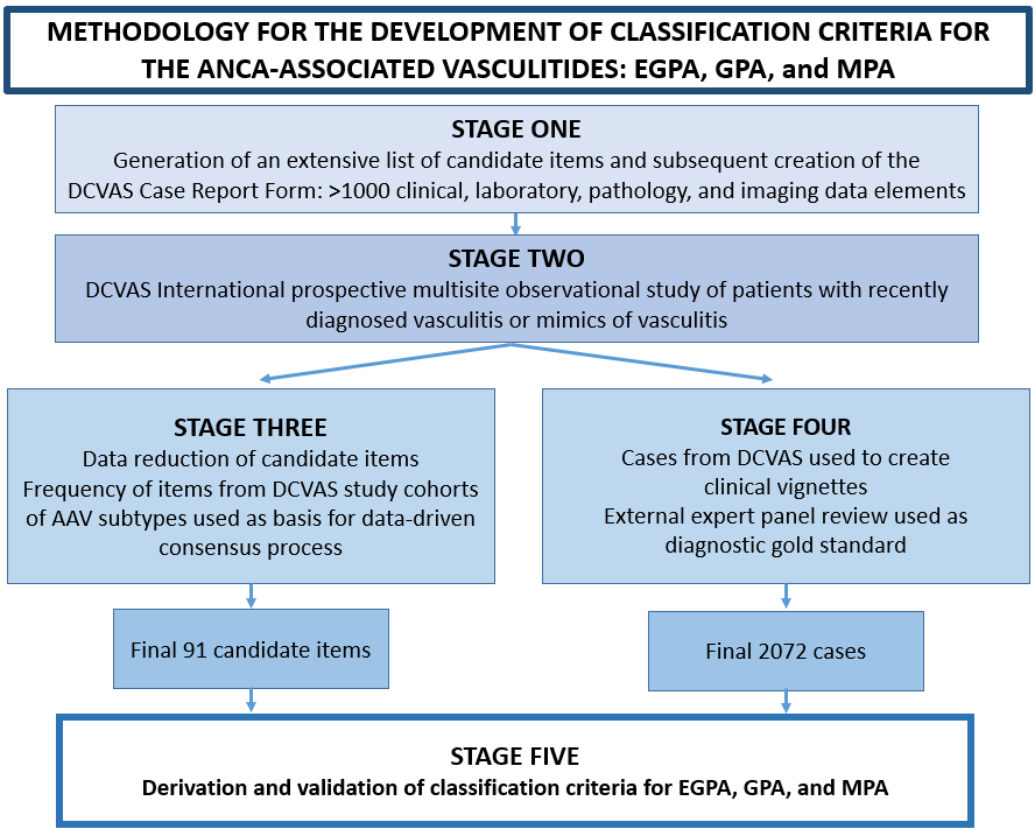
AMERICAN COLLEGE OF RHEUMATOLOGY AND EUROPEAN LEAGUE AGAINST RHEUMATISM 2021 CLASSIFICATION CRITERIA FOR ANCA-ASSOCIATED VASCULITIS [GRANULOMATOSIS WITH POLYANGIITIS, MICROSCOPIC POLYANGIITIS, AND EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS]

1. **Detailed description of the research methods for the development of classification criteria for eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and microscopic polyangiitis**
2. **Diagnosis and Classification of Vasculitis Study Case Report Form**
3. **Diagnosis and Classification of Vasculitis Study Sites and Investigators**
4. **Diagnosis and Classification of Vasculitis Study Sites/Investigators Characteristics**
5. **Study Participant Details**
6. **Final candidate items used within each regression analysis to derive classification criteria for granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis**
7. **Expert reviewer characteristics**
8. **Flow chart of expert review process to create the Diagnosis and Classification of Vasculitis Study dataset for ANCA-associated vasculitis**
9. **Results of regression analysis for each type of ANCA-associated vasculitis**
10. **Data-driven and clinically-selected models for each type of ANCA-associated vasculitis with associated risk scored based off beta coefficient weighting**
11. **Performance characteristics of a points-based risk score for each type of ANCA-associated vasculitis with different thresholds**
12. **Discrimination curves for the classification criteria for each type of ANCA-associated vasculitis**

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 1. Detailed description of the research methods for the development of classification criteria for eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis, and microscopic polyangiitis

An international Steering Committee comprised of clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall DCVAS project. A five-stage process was used to derive each of the classification criteria for granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA). An overview of each stage of the methodology is presented in the figure below.



EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis

Full details of each stage in the process are described below.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

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

Candidate items were generated by expert opinion including items from the 1990 ACR Classification Criteria, the 2012 Chapel Hill Nomenclature, and the major disease activity and damage indices for AAV (1-5). Items were categorized as demographic, symptoms, physician-observed findings, laboratory tests, diagnostic radiology, and biopsy results. Candidate items were reviewed and discussed at a major international vasculitis conference, and nominal group technique was used to modify the potential list of items with input from vasculitis experts across a range of specialties. The full list of items was then reviewed by the Steering Committee to address potential omissions or redundancy in the list with appropriate revisions made. A list of data elements was finalized by the Steering Committee for use in prospective data collection in Stage Two. The resulting DCVAS case report form (CRF) is shown in **Supplementary Materials 2**.

Stage Two: DCVAS prospective observational study

The DCVAS study is an international prospective multisite observational study of patients recently-diagnosed with vasculitis or mimics of vasculitis (6).

The University of Oxford sponsored the study, and ethics approval was given by the UK Berkshire Research Ethics Committee (reference 10/H0505/19) on May 7, 2010. The study was performed in accordance with the 1964 Declaration of Helsinki, ethical approval was obtained by national and local ethics committees in accordance with national legislation.

Site Selection

A wide range of sites were targeted for inclusion to ensure representation from different geographical regions, clinical specialties, and types of sites (including both academic and non-academic clinical practices). To increase the number and types of study sites, the DCVAS study was promoted through national and international presentations, and the DCVAS website (**Supplementary Materials 3 & 4**).

Patient Recruitment

Inclusion criteria for the DCVAS study:

1) Patients aged ≥18 years; 2) Ability to give informed consent or consent via an appropriate surrogate; 3) i) Diagnosis as made by the submitting clinician within the previous two years of GPA, MPA, EGPA, other AAV, giant cell arteritis, anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, Behçet's disease, primary central nervous system vasculitis, IgA vasculitis, isolated aortitis, other large-vessel vasculitis, or a diagnosis within the previous five years of polyarteritis nodosa or Takayasu's arteritis; OR ii) Diagnosis as made by the submitting clinician within the previous two years of a condition which mimics systemic vasculitis, e.g., infection, tumor, other inflammatory conditions (see **Supplementary Materials 5** for the complete details of physician-submitted diagnoses). For patients enrolled six months after diagnosis, only patients for whom the submitting physician had complete records detailing symptoms present at the time of diagnosis were eligible for study inclusion.

Exclusion criteria:
1) Patients < 18 years of age; 2) Inability to provide informed consent.

Submitting-Physician Diagnosis
For patients with vasculitis who were enrolled in the DCVAS study within six months of the initial diagnosis, the submitting physician was asked to confirm the accuracy of the diagnosis at the six-month time point in a separate study form.

Data Collection
Paper and web-based versions of the CRF were used **(Supplementary Materials 2)**. Data from patients with a working diagnosis of systemic vasculitis or mimics of systemic vasculitis were entered. The diagnosis and level of certainty for diagnosis was requested from the submitting physician at time of diagnosis and six months later. Data from all study participants was reviewed at a central location for completeness. Local investigators were contacted to resolve any data discrepancies.

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

The DCVAS CRF included > 1000 data elements. The final statistical analysis to create classification criteria for all subtypes of AAV, including GPA, required approximately 100 predictors to avoid over-fitting of the final model during regression analysis (7).

A data-driven process of reduction of the DCVAS initial items was used to retain candidate items of relevance to cases and comparators for AAV. Seven members of the DCVAS Steering Committee (PG, RL, PM, CP, RS, JR, RW) were split into groups of two to each review a different category of items in terms of frequency across all AAV subtypes, and assess clinical relevance: clinical features, laboratory results, pathology results, and imaging. Data on frequency of items was prepared for review from cases of GPA, MPA and EGPA (physician diagnosis) from the DCVAS dataset. 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 (for example the items for “fever”, “night sweats”, and “rigors”, see **Supplementary Materials 6** for single and composite items). Consensus was reached between the two independent Steering Committee members, who then presented and discussed the items for exclusion to reach agreement across the wider steering committee over the course of four teleconferences.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

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

An online independent Expert Review Process was used to avoid the circularity of applying a previously derived gold standard such as the 1990 ACR Criteria (8). Experts in vasculitis from a wide range of geographical locations and specialties reviewed all cases of vasculitis submitted (see **Supplementary Materials 7** for the expert reviewer characteristics). Fifty-five external expert reviewers reviewed approximately 50 cases each. Reviewers were blinded to the submitting physician's diagnosis**.**

Clinical vignettes of each case, including clinical, laboratory, imaging, and biopsy results were produced using data from the CRFs and presented in a standard clinical vignette form**.** All cases labeled GPA, MPA, EGPA, or a different form of small vessel vasculitis by the submitting physician were reviewed. To ensure a rigorous process, 10% of cases with a submitting physician diagnosis of polyarteritis nodosa, other small-vessel vasculitis, large-vessel vasculitis, or a condition mimicking vasculitis were also randomly included for expert review.

For each case vignette, the expert reviewer indicated:

(i) whether or not the diagnosis was vasculitis
(ii) which category of vasculitis was present, based on vessel size (small, medium, large, or not categorizable)
(iii) if a type of vasculitis was chosen in (ii) then which subtype of vasculitis was present (for example, if AAV was selected, then a choice of GPA, MPA, EGPA, or uncertain sub-type was provided).

Reviewers were asked about their certainty for each of (i)-(iii) as follows: very certain, moderately certain, uncertain, or very uncertain.

A case was considered to be agreed in full if the Expert Reviewer's assessment matched the submitting physician's assessment at each level, with at least moderate certainty. Cases that were not agreed on expert review were submitted for a blinded second review by a member of the Steering Committee. If the Steering Committee member agreed with either the submitting physician's assessment or the initial expert reviewer with moderate certainty, then the case was agreed upon in full. Cases that were not agreed upon in full were rejected from further analysis. The panel review process was conducted in 2016 using all available data to date. Since study enrollment continued through 2017, additional cases of AAV were submitted to the DCVAS cohort that were not used for analysis.

A flow diagram depicting the results from the expert review process is provided in **Supplementary Materials 8**.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Stage Five: Derivation and validation of the final classification criteria for the ANCA-associated vasculitides

A similar process for the derivation of each of the three final classification criteria for GPA, MPA and EGPA was followed. There were two methodological differences between the three criteria due to a higher proportion of GPA cases available for analysis than the other two types of AAV (as expected in line with known prevalence of the individual subtypes of AAV).

All cases with small or medium vessel vasculitis agreed by the expert review process in Stage 4 were included within the derivation of the GPA classification criteria as either cases (GPA) or comparators (See Table 1 GPA manuscript for subdivision of comparators). For the derivation of the MPA and EGPA criteria, only a proportion of the available GPA cases were included within the comparator groups. This was to avoid over-representation of GPA cases within each comparator group due to higher overall prevalence in the DCVAS dataset. GPA cases were chosen randomly for inclusion as comparators for EGPA and MPA. Exact numbers are shown in Table 1 of each manuscript.

For the GPA criteria, due to a high availability of GPA cases, the development and validation sets were derived from the DCVAS dataset of approved cases (Stage 4) on an 80:20 basis in order to maximize descriptive power of the resultant criteria. In contrast, the derivation of the MPA and EGPA sets split the DCVAS dataset into development and validation sets on a 50:50 basis.

For each criteria, the cases were comprised of one of either GPA, EGPA or MPA cases depending on the criteria, and the comparators made up of the two other forms of AAV plus other small and medium vessel vasculitides (exact numbers given in Table 1 of each manuscript). This process resulted in the generation of a binary outcome (AAV type or comparators) and the following steps were then followed for each criteria using the same 91 candidate item predictors identified from Stage Three.

The candidate predictors from Stage Three were included in a logistic regression model. Fractional polynomial regression modeling was used to assess evidence of linearity with outcome for continuous predictor variables (9). Multiple imputation was used to overcome potential bias from missing data (10). Lasso (least absolute shrinkage and selection operator) logistic regression was used to identify predictors from the dataset and create a parsimonious model including only the most important predictors (7,11,12). To extract the non-zero coefficients and, therefore, the significant predictors, a single model was fitted and adjusted for all potential variables with a 10-fold cross-validation and the minimum average mean-squared error (**Supplementary Materials 9**).

For each criterion, an iterative process within the Steering Committee was followed, with the clinician researchers and expert biostatisticians working collaboratively, to ensure face and content validity and acceptability of the resultant criteria. Most items were excluded because they were not significant predictors within the final model, i.e they did not differentiate between cases and comparators (for example for GPA, “presence of cutaneous infarcts or purpura”, or “maximum ESR”). Some predictors were statistically significant (i.e.

p<0.05) but were either redundant to other items in the final model or thought to be of low clinical significance (for example for GPA, "morning stiffness for >1 hour", or "unspecified tissue inflammation on biopsy"). These items were then removed from the model with the reduced item model tested in turn for discrimination, area under the curve (AUC) sensitivity and specificity to check there was no reduction in predictive value of the model. In this way, the final criteria were based on the most parsimonious models available including only the most important predictors.

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 (13) (**Supplementary Materials 10**). A threshold was identified for classification, which best balanced sensitivity and specificity (**Supplementary Materials 11 & 12**).

Sensitivity Analyses:
Since the expert review could have resulted in the exclusion of cases which were less clear-cut to classify, the final classification criteria were applied to an unselected population of cases and comparators from the DCVAS dataset based on the submitting physician diagnosis. The *a priori* hypothesis of these analyses was that if the final criteria were fit for purpose, specificity should be unchanged but sensitivity should be reduced within the unselected population. Comparators used for the unselected population analysis were as follows:

- *Comparators for GPA analysis*: MPA (404, 19.9%), EGPA (315, 15.5%), AAV that could not be subtyped (59, 2.9%), non-AAV small-vessel vasculitis that could not be subtyped (171, 8.4%), anti-glomerular basement membrane disease (14, 0.6%), cryoglobulinemic vasculitis (46, 2.3%), IgA vasculitis (240, 11.8%), Behçet's disease (151, 7.4%), primary central nervous system vasculitis (39, 1.9%), other forms of vasculitis that could not be subtyped (23, 1.1%), polyarteritis nodosa (130, 6.4%), giant cell arteritis (92, 4.5%), Takayasu's arteritis (91,4.5%), idiopathic aortitis (22, 1.1%), large-vessel vasculitis that could not be subtyped (52, 2.6%), and vasculitis mimics (179, 8.8%).
- *Comparators for EGPA analysis*: MPA (404, 15.8%), GPA (843, 33.0%), AAV that could not be subtyped (59, 2.3%), non-AAV small-vessel vasculitis that could not be subtyped (171, 6.7%), anti-glomerular basement membrane disease (14, 0.6%), CV (46, 1.8%), IgA vasculitis (240, 9.4%), Behçet's disease (151, 5.9%), primary central nervous system vasculitis (39, 1.5%), other form of vasculitis that could not be subtyped (23, 0.9%), polyarteritis nodosa (130, 5.1%), giant cell arteritis (92, 3.6%) Takayasu's arteritis (91, 3.6%), isolated aortitis (22, 0.9%), large-vessel vasculitis that could not be subtyped (52, 2.0%), and vasculitis mimics (179, 7.0%).
- *Comparators for MPA analysis*: EGPA (315, 12.7%), GPA (843, 34.2%), AAV that could not be subtyped (59, 2.40%), non-AAV small-vessel vasculitis that could not be subtyped (171, 6.9%), anti-glomerular basement membrane disease (14, 0.6%), cryoglobulinemic vasculitis (46, 1.9%), IgA vasculitis (240, 9.7%), Behçet's disease (151, 6.1%), primary central nervous system vasculitis (39, 1.6%), other form of vasculitis that could not be subtyped (23, 0.9%), polyarteritis nodosa (130, 5.3%), giant cell arteritis (92, 3.7%) Takayasu's arteritis (91, 3.7%), isolated aortitis (22, 0.9%), large-vessel vasculitis that could not be subtyped (52, 2.1%), and vasculitis mimics (179, 7.3%).

Comparisons were also made between the measurement properties of the new classification criteria for GPA and EGPA and the respective 1990 ACR Classification Criteria for GPA and EGPA using pooled data from the development and validation sets. These comparisons were not performed for MPA as there are no pre-existing classification criteria for this disease.

Additional Acknowledgements:

The DCVAS study recognizes the contributions of Joe Barrett, David T Gray, Marian Montgomery, Ann-Marie Morgan, and Joe Rosa from the Oxford study team for efforts to design and implement the DCVAS database and clinical vignettes/expert panel review, perform quality control of submitted data elements, and communicate with participating sites.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

REFERENCES

1. Fries JF, Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum 1990;33:1135-6.
2. Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33:1068-73.
3. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
4. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990;33(8):1094-100.
5. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.
6. Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). Clin Exp Nephrol 2013;17:619-21.
7. Pavlou M, Ambler G, Seaman SR, Guttmann O, Elliott P, King M, et al. How to develop a more accurate risk prediction model when there are few events. BMJ 2015;351:h3868.
8. Bloch DA, Michel BA, Hunder GG, McShane DJ, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods. Arthritis Rheum 1990;33:1068-73.
9. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964-74.
10. Janssen KJ, Donders AR, Harrell FE, Jr., Vergouwe Y, Chen Q, Grobbee DE, et al. Missing covariate data in medical research: to impute is better than to ignore. J Clin Epidemiol 2010;63:721-7.
11. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Ann Intern Med 2015;162:735-6.
12. Musoro JZ, Zwinderman AH, Puhan MA, ter Riet G, Geskus RB. Validation of prediction models based on lasso regression with multiply imputed data. BMC Med Res Methodol 2014;14:116.
13. Judge A, Javaid MK, Arden NK, Cushnaghan J, Reading I, Croft P, et al. Clinical tool to identify patients who are most likely to achieve long-term improvement in physical function after total hip arthroplasty. Arthritis Care Res (Hoboken) 2012;64:881-9.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 2. DCVAS Case Report Form

See separate PDF file titled "DCVAS Case Report Form"

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 3: Diagnosis and Classification of Vasculitis Study (DCVAS) Sites and Investigators

Country	Investigator	Participating Center
Australia	Paul Gatenby	ANU Medical Centre, Canberra
Australia	Catherine Hill	Central Adelaide Local Health Network: The Queen Elizabeth Hospital
Australia	Dwarakanathan Ranganathan	Royal Brisbane and Women's Hospital
Austria	Andreas Kronbichler	Medical University Innsbruck
Belgium	Daniel Blockmans	University Hospitals Leuven
Canada	Lillian Barra	Lawson Health Research Institute, London, Ontario
Canada	Simon Carette/ Christian Pagnoux	Mount Sinai Hospital, Toronto
Canada	Navjot Dhindsa	University of Manitoba, Winnipeg
Canada	Aurore Fifi-Mah	University of Calgary, Alberta
Canada	Nader Khalidi	St Joseph's Healthcare Hamilton, Ontario
Canada	Patrick Liang	Sherbrooke University Hospital Centre
Canada	Nataliya Milman	University of Ottawa
Canada	Christian Pineau	McGill University
China	Xinping Tian	Peking Union Medical College Hospital, Beijing
China	Guochun Wang	China-Japan Friendship Hospital, Beijing
China	Tian Wang	Anzhen Hospital, Capital Medical University
China	Ming-hui Zhao	Peking University First Hospital
Czech Republic	Vladimir Tesar	General University Hospital, Prague
Denmark	Bo Baslund	University Hospital, Copenhagen (Rigshospitalet)
Egypt	Nevin Hammam	Assiut University
Egypt	Amira Shahin	Cairo University
Finland	Laura Pirila	Turku University Hospital, Finland
Finland	Jukka Putaala	Helsinki University Central Hospital
Germany	Bernhard Hellmich	Kreiskliniken Esslingen
Germany	Jörg Henes	Universitätsklinikum Tübingen
Germany	Julia Holle/ Frank Moosig	Klinikum Bad Bramstedt
Germany	Peter Lamprecht	University of Lübeck
Germany	Thomas Neumann	Universitätsklinikum Jena
Germany	Wolfgang Schmidt	Immanuel Krankenhaus Berlin
Germany	Cord Sunderkoetter	Universitätsklinikum Müenster
Hungary	Zoltan Szekanecz	University of Debrecen Medical and Health Science Center
India	Debashish Danda	Christian Medical College & Hospital, Vellore
India	Siddharth Das	Chatrapathi Shahuji Maharaj Medical Center, Lucknow (IP)
India	Rajiva Gupta	Medanta, Delhi
India	Liza Rajasekhar	NIMS, Hyderabad

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Country	Investigator	Participating Center
India	Aman Sharma	Postgraduate Institute of Medical Education and Research, Chandigarh
India	Shrikant Wagh	Jehangir Clinical Development Centre, Pune (IP)
Ireland	Michael Clarkson	Cork University Hospital
Ireland	Eamonn Molloy	St. Vincent's University Hospital, Dublin
Italy	Carlo Salvarani	Santa Maria Nuova Hospital, Reggio Emilia
Italy	Franco Schiavon	L'Azienda Ospedaliera of University of Padua
Italy	Enrico Tombetti	Università Vita-Salute San Raffaele Milano
Italy	Augusto Vaglio	University of Parma
Japan	Koichi Amano	Saitama Medical University
Japan	Yoshihiro Arimura	Kyorin University Hospital
Japan	Hiroaki Dobashi	Kagawa University Hospital
Japan	Shouichi Fujimoto	Miyazaki University Hospital (HUB)
Japan	Masayoshi Harigai/Fumio Hirano	Tokyo Medical and Dental University Hospital
Japan	Junichi Hirahashi	University Tokyo Hospital
Japan	Sakae Honma	Toho University Hospital
Japan	Tamihiro Kawakami	St. Marianna University Hospital Dermatology
Japan	Shigeto Kobayashi	Juntendo University Koshigaya Hospital
Japan	Hajime Kono	Teikyo University
Japan	Hirofumi Makino	Okayama University Hospital
Japan	Kazuo Matsui	Kameda Medical Centre, Kamogawa
Japan	Eri Muso	Kitano Hospital
Japan	Kazuo Suzuki/Kei Ikeda	Chiba University Hospital
Japan	Tsutomu Takeuchi	Keio University Hospital
Japan	Tatsuo Tsukamoto	Kyoto University Hospital
Japan	Shunya Uchida	Teikyo University Hospital
Japan	Takashi Wada	Kanazawa University Hospital
Japan	Hidehiro Yamada	St. Marianna University Hospital Internal Medicine
Japan	Kunihiro Yamagata	Tsukuba University Hospital
Japan	Wako Yumura	IUHW Hospital (Jichi Medical University Hospital)
Malaysia	Kan Sow Lai	Penang General Hospital
Mexico	Luis Felipe Flores-Suarez	Instituto Nacional de Enfermedades Respiratorias, Mexico City
Mexico	Andrea Hinojosa-Azaola	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City
Netherlands	Bram Rutgers	University Hospital Groningen
Netherlands	Paul-Peter Tak	Academic Medical Centre, University of Amsterdam
New Zealand	Rebecca Grainger	Wellington, Otago
New Zealand	Vicki Quincey	Waikato District Health Board
New Zealand	Lisa Stamp	University of Otago, Christchurch
New Zealand	Ravi Suppiah	Auckland District Health Board

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Country	Investigator	Participating Center
Norway	Emilio Besada	Tromsø, Northern Norway
Norway	Andreas Diamantopoulos	Hospital of Southern Norway, Kristiansand
Poland	Jan Sznajd	University of Jagiellonian
Portugal	Elsa Azevedo	Centro Hospitalar de São João, Porto
Portugal	Ruth Geraldes	Hospital de Santa Maria, Lisbon
Portugal	Miguel Rodrigues	Hospital Garcia de Orta, Almada
Portugal	Ernestina Santos	Hospital Santo Antonio, Porto
Republic of Korea	Yeong-Wook Song	Seoul National University Hospital
Russia	Sergey Moiseev	First Moscow State Medical University
Slovenia	Alojzija Hočevar	University Medical Centre Ljubljana
Spain	Maria Cinta Cid	Hospital Clinic de Barcelona
Spain	Xavier Solanich Moreno	Hospital de Bellvitge-Idibell
Sri Lanka	Inoshi Atukorala	University of Colombo
Sweden	Ewa Berglin	Umeå University Hospital
Sweden	Aladdin Mohammed	Lund-Malmo University
Sweden	Mårten Segelmark	Linköping University
Switzerland	Thomas Daikeler	University Hospital Basel
Turkey	Haner Direskeneli	Marmara University Medical School
Turkey	Gulen Hatemi	Istanbul University, Cerrahpasa Medical School
Turkey	Sevil Kamali	Istanbul University, Istanbul Medical School
Turkey	Ömer Karadağ	Hacettepe University
Turkey	Seval Pehlevan	Fatih University Medical Faculty
United Kingdom	Matthew Adler	Frimley Health NHS Foundation Trust, Wexham Park Hospital,
United Kingdom	Neil Basu	NHS Grampian, Aberdeen Royal Infirmary
United Kingdom	Iain Bruce	Manchester University Hospitals NHS Foundation Trust
United Kingdom	Kuntal Chakravarty	Barking, Havering and Redbridge University Hospitals NHS Trust
United Kingdom	Bhaskar Dasgupta	Southend University Hospital NHS Foundation Trust
United Kingdom	Oliver Flossmann	Royal Berkshire NHS Foundation Trust
United Kingdom	Nagui Gendi	Basildon and Thurrock University Hospitals NHS Foundation Trust
United Kingdom	Alaa Hassan	North Cumbria University Hospitals
United Kingdom	Rachel Hoyles	Oxford University Hospitals NHS Foundation Trust
United Kingdom	David Jayne	Cambridge University Hospitals NHS Foundation Trust
United Kingdom	Colin Jones	York Teaching Hospitals NHS Foundation Trust
United Kingdom	Rainer Klocke	The Dudley Group NHS Foundation Trust
United Kingdom	Peter Lanyon	Nottingham University Hospitals NHS Trust
United Kingdom	Cathy Laversuch	Taunton & Somerset NHS Foundation Trust, Musgrove Park Hospital

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Country	Investigator	Participating Center
United Kingdom	Raashid Luqmani/ Joanna Robson	Nuffield Orthopaedic Centre, Oxford
United Kingdom	Malgorzata Magliano	Buckinghamshire Healthcare NHS Trust
United Kingdom	Justin Mason	Imperial College Healthcare NHS Trust
United Kingdom	Win Win Maw	Mid Essex Hospital Services NHS Trust
United Kingdom	Iain McInnes	NHS Greater Glasgow & Clyde, Gartnavel Hospital & GRI
United Kingdom	John Mclaren	NHS Fife, Whyteman's Brae Hospital
United Kingdom	Matthew Morgan	University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital
United Kingdom	Ann Morgan	Leeds Teaching Hospitals NHS Trust
United Kingdom	Chetan Mukhtyar	Norfolk and Norwich University Hospitals NHS Foundation Trust
United Kingdom	Edmond O'Riordan	Salford Royal NHS Foundation Trust
United Kingdom	Sanjeev Patel	Epsom and St Helier University Hospitals NHS Trust
United Kingdom	Adrian Peall	Wye Valley NHS Trust, Hereford County Hospital
United Kingdom	Joanna Robson	University Hospitals Bristol NHS Foundation Trust
United Kingdom	Srinivasan Venkatachalam	The Royal Wolverhampton NHS Trust
United Kingdom	Erin Vermaak / Ajit Menon	Staffordshire & Stoke on Trent Partnership NHS Trust, Haywood Hospital
United Kingdom	Richard Watts	East Suffolk and North Essex NHS Foundation Trust
United Kingdom	Chee-Seng Yee	Doncaster and Bassetlaw Hospitals NHS Foundation Trust
United States	Daniel Albert	Dartmouth-Hichcock Medical Center
United States	Leonard Calabrese	Cleveland Clinic Foundation
United States	Sharon Chung	University of California, San Francisco
United States	Lindsy Forbess	Cedars-Sinai Medical Center
United States	Angelo Gaffo	University of Alabama at Birmingham
United States	Ora Gewurz-Singer	University of Michigan
United States	Peter Grayson	Boston University School of Medicine
United States	Kimberly Liang	University of Pittsburgh
United States	Eric Matteson	Mayo Clinic
United States	Peter A. Merkel Rennie Rhee Antoine Sreih	University of Pennsylvania
United States	Jason Springer	University of Kansas Medical Center Research Institute
United States	Antoine Sreih	Rush University Medical Center

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 4. Diagnosis and Classification of Vasculitis Study Sites and Investigators' Characteristics

Characteristics	**N=136**	**Characteristics**	**N=136**	**Characteristics**	**N=136 (%)**
Country		**Country**		**Specialty**	
Australia	3	Mexico	2	Rheumatology	99 (72.8)
Austria	1	Netherlands	2	Nephrology	21 (15.4)
Belgium	1	New Zealand	4	Neurology	5 (3.7)
Canada	8	Norway	2	Internal Medicine	4 (2.9)
China	4	Poland	1	Immunology	4 (2.9)
Czech Republic	1	Portugal	4	Dermatology	2 (1.5)
Denmark	1	Republic of Korea	1	Respiratory	1 (0.7)
Egypt	2	Russia	1		
Finland	2	Slovenia	1	**Number of patients with ANCA-associated vasculitis seen annually**	
Germany	6	Spain	2		
Hungary	1	Sri Lanka	1	0-10	1 (0.7)
India	6	Sweden	3	11-20	3 (2.2)
Ireland	2	Switzerland	1	21-50	20 (14.7)
Italy	4	Turkey	5	51-100	22 (16.2)
Japan	20	United Kingdom	31	>100	60 (44.1)
Malaysia	1	United States of America	12	Unknown	30 (22.1)
Background	**N (%)**	**Sex of primary investigator**	**N (%)**	**Years within specialty**	**N (%)**
Academic hospital/ Medical school	89 (65.4)	Male	99 (72.8)	0-5	0
		Female	37 (27.2)	6-10	15 (11.0)
Non-academic hospital	17 (12.5)			11-15	22 (16.2)
Unknown	30 (22.1)			16-20	21 (15.4)
				>20	48 (35.3)
				Unknown	30 (22.1)

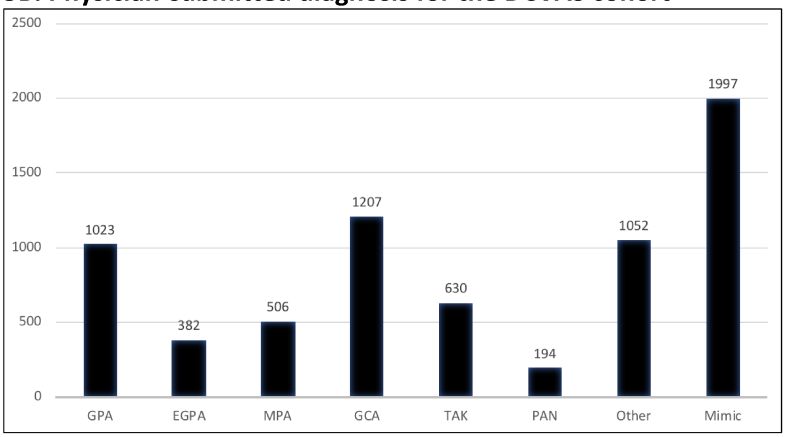
ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 5. Study Participant Details

5a. Patient recruitment by region

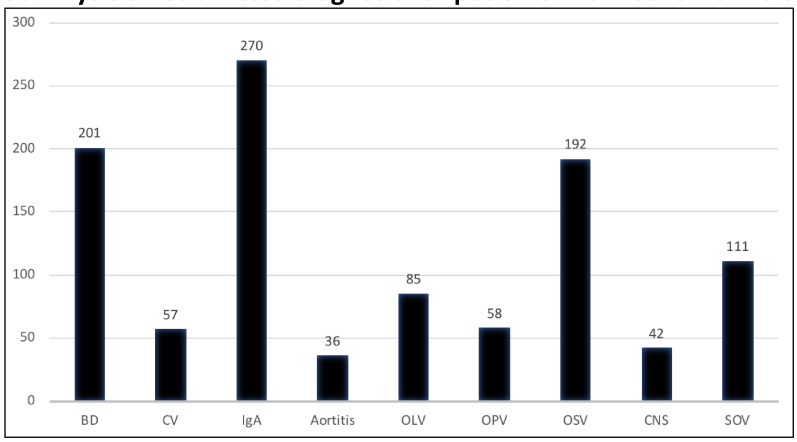
	Total Sites	Total Patients Recruited	% Patients Recruited
Europe	71	4107	59%
North America	22	1497	21%
Other Regions	43	1387	20%
TOTAL	136	6991	

5B. Physician-submitted diagnosis for the DCVAS cohort



GPA = granulomatosis with polyangiitis
EGPA = eosinophilic granulomatosis with polyangiitis
MPA = microscopic polyangiitis
GCA = giant cell arteritis
TAK = Takayasu's arteritis
PAN = polyarteritis nodosa
Other = other form of vasculitis
Mimic = other condition that mimics vasculitis

5c. Physician-submitted diagnosis for patients with "other forms of vasculitis"



BD = Behcet's disease
CV = cryoglobulinemic vasculitis
IgA = IgA vasculitis
Aortitis = isolated aortitis
OLV = other form of large-vessel vasculitis
OPV = other form of primary vasculitis
OSV = other form of small-vessel vasculitisi
CNS = primary central nervous system vasculitis
SOV = single organ vasculitis

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 6. Final candidate items used within each regression analysis to derive classification criteria for granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis

Significant differences in frequencies of item between the specific types of ANCA-associated vasculitis [granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis] and comparators: *p<0.05, **p<0.01

Item	Description	Composite Items	GPA N= 724	MPA N=291	EGPA N=226
Sex	Sex (female)		340 (47.0)*	164 (56.4)*	113 (50.0)
Age	Age (years)		56.6 (16.2)*	65.5 (13.2)**	52.9 (14.4)*
Smoke1	Smoking status (current)		77 (10.6)	29 (10.0)	4 (1.8)**
CLINICAL					
Bron3	Bronchitic changes or mucosal injury		52 (7.2)	6 (2.1)	16 (7.1)*
Bron6	Blood stained bronchoalveolar lavage		32 (4.4)*	13 (4.5)	3 (1.3)
CPCF2	Crackles / râles on auscultation		109 (15.1)	87 (29.9)**	36 (15.9)
CPCF4	Respiratory compromise requiring oxygen		58 (8.0)	39 (13.4)*	23 (10.2)
CPSym1	Dyspnea / Shortness of Breath		317 (43.8)*	124 (42.6)	155 (68.6)**
CPSym2	Non-productive cough		169 (23.3)*	64 (22.0)	75 (33.2)**
CPSym3	Productive cough with purulent sputum		83 (11.5)	39 (13.4)	43 (19.0)**
CPSym4	Minor hemoptysis		135 (18.6)**	39 (13.4)	18 (8.0)
CVCF5	Arrhythmia		10 (1.4)	5 (1.7)	14 (6.2)**
CVSym1	Angina / ischemic cardiac pain		7 (1.0)*	4 (1.4)	16 (7.1)**
entcf3entcf4	Conductive hearing loss/sensorineural hearing loss	Y	172 (23.8)	12 (4.1)**	21 (9.3)
ENTCF5	Nasal polyps		35 (4.8)**	4 (1.4)**	84 (37.2)**
ENTSym5	Non-blood stained nasal discharge		139 (19.2)**	17 (5.8)*	45 (19.9)**
ENTSym7	Loss of smell (anosmia)		74 (10.2)**	1 (0.3)	32 (14.2)**
EyeCF3	Conjunctivitis		47 (6.5)**	4 (1.4)	2 (0.9)
GenSym3	Fatigue		411 (56.8)	208 (71.5)**	139 (61.5)*
GeUrSym1	Macroscopic hematuria (blood visible in urine)		25 (3.5)*	31 (10.7)**	2 (0.9)*
GISym1	Abdominal pain (any)		64 (8.8)**	27 (9.3)*	42 (18.6)

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Item	Description	Composite Items	GPA N= 724	MPA N=291	EGPA N=226
Lung4	Reduced DLCO or KCO		40 (5.5)	33 (11.3)**	15 (6.6)
MskCF2	Muscle tenderness		36 (5.0)	20 (6.9)	23 (10.2)*
MskCF3	Muscle weakness		36 (5.0)*	32 (11.0)*	30 (13.3)*
MskSym6	Myalgia (muscle pain) or muscle cramps		177 (24.4)	65 (22.3)	72 (31.9)*
SknCF3	Maculopapular or papular rash		48 (6.6)*	18 (6.2)	30 (13.3)*
SknCF10	Ulcer		32 (4.4)*	4 (1.4)**	8 (3.5)
SknSym2	Painful skin lesions of any type		63 (8.7)*	11 (3.8)**	23 (10.2)
VMDMeds6	Leukotriene antagonist		2 (0.3)**	0 (0)*	29 (12.8)**
Bron5CPSym5Lung5	Evidence of alveolar hemorrhage/major hemoptysis/increased KCO	Y	88 (12.2)**	35 (12.0)*	4 (1.8)**
bron8entcf1entcf8entcf2	Endobronchial involvement/inflamed ear or nose cartilage/hoarse voice stridor/saddle nose deformity	Y	157 (21.7)**	6 (2.1)**	13 (5.8)
CVCF2CVCF3	Congestive cardiac failure/cardiomyopathy	Y	7 (1.0)**	13 (4.5)	38 (16.8)**
entcf6entsym6entsym4entCF7	Bloody nasal discharge/nasal ulcers, mucosal abnormalities, crusting/sino nasal congestion or blockage/nasal septal defect, perforation	Y	527 (72.8)**	32 (11.0)**	124 (54.9)**
eyecf5eyecf6eyecf7	Keratitis (inflammation of the cornea)/scleritis or episcleritis/uveitis	Y	103 (14.2)**	6 (2.1)**	2 (0.9)**
gencf6gensym4gensym5	Fever ≥ 38^{o}C (≥ 100.4F)/night sweats/rigors	Y	355 (49.0)**	116 (39.9)	85 (36.3)
GenCFWt2or3	Weight loss 2 -5kg/weight loss ≥5 Kg	Y	271 (37.4)*	114 (39.2)*	82 (36.3)
lung3cpcf3	Obstructive airways disease/wheeze	Y	67 (9.3)**	18 (6.2)**	148 (65.5)**
mskcf1msksym1	Swollen or inflamed joint(s)/arthralgia	Y	406 (56.1)**	82 (28.2)**	82 (36.3)
msksym2msksym3msksym4msksym5	Morning stiffness ≥ 1 hour in any of neck/torso/shoulders/arms/hips/thighs	Y	127 (17.5)**	25 (8.60)	15 (6.6)
NeurCF10	Sensory neuropathy (not due to radiculopathy)		96 (13.3)**	50 (17.2)	84 (37.2)**
neurcf6neurcf8	Mononeuritis multiplex/motor neuropathy (not due to radiculopathy)	Y	79 (10.9)**	44 (15.1)*	108 (47.8)**
SknCF1SknCF2SknCF9	Cutaneous infarct/petechiae or purpura/splinter hemorrhage	Y	130 (18.0)*	26 (8.9)**	53 (23.5)
gisym3gisym6	Diarrhea/bloody diarrhea	Y	33 (4.6)**	26 (8.9)**	26 (11.5)

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Item	Description	Composite Items	GPA N= 724	MPA N=291	EGPA N=226
LABORATORY					
TstHaem8_cat	Maximum eosinophil count (x10^9/L) category >=1		0.08 (0.27)**	15 (5.2)**	206 (91.2)**
TstChem1dn	Maximum CRP (mg/L) (range)		97.6 (103.5)**	94.6 (151.6)*	67.0 (69.3)*
TstChem6dn	Maximum creatinine - µmol/L (range)		168.3 (185.2)	336.7 (302.7)**	85.3 (53.6)**
Tsthaem9dn	Maximum ESR (mm/hr) (range)		66.3 (35.0)**	74.4 (36.5)**	47.1 (30.2)**
TstHaem1	Significant anemia (Hb <10g/dL)		250 (34.5)	187 (64.3)**	27 (11.9)**
TstHaem3	Significant thrombocythemia (platelets > 500 x 10^9/L)		170 (23.5)**	42 (14.4)	34 (15.0)
TstHaem5	Significant elevation of WBC (total WBC > 15 x 10^9/L)		180 (24.9)	65 (22.3)	115 (50.9)**
TstHaem7	Significant neutrophilia (PMN > 10 x 10^9/L)		200 (27.6)*	80 (27.5)*	52 (23.0)
TstChem3	AST(SGOT) or ALT(SGPT)>2 upper limit normal		48 (6.6)	8 (2.7)*	21 (9.3)*
TstChem4	Alkaline phosphatase >2x upper limit of normal		44 (6.1)	14 (4.8)	17 (7.5)
TstChem8	Albumin below 30g/L		168 (23.2)	125 (43.0)**	35 (15.5)*
tstur1tstur5	Protein on urine dipstick* or 24 hour protein		418 (57.7)*	240 (82.5)**	60 (26.5)**
TstUr2	Blood on urine dipstick*		436 (60.2)**	252 (86.6)**	54 (23.9)**
TstUr3	Leucocytes or nitrites on urine dipstick*		161 (85.1)	103 (35.4)**	26 (11.5)**
TstUr4	Red cell casts in urine		136 (18.8)	99 (34.0)**	10 (4.4)**
TstCC1	Serum cryoglobulins present		3 (0.4)**	7 (2.4)*	8 (3.5)
TstAA1=1	cANCA on immunofluorescence present		531 (73.3)**	11 (3.8)**	17 (7.5) **
TstAA3=1	PR3 ANCA (ELISA) present		595 (82.2)**	6 (2.1)**	7 (3.1)**
TstAA2=1	pANCA on immunofluorescence present		71 (9.8)**	236 (81.1)**	83 (36.7)
TstAA4=1	MPO ANCA (ELISA) present		59 (8.1)**	279 (95.9)**	98 (43.3)
TstAA5	Other ANCA by immunofluorescence		13 (1.8)	3 (1.0)	6 (2.7)
TstAA7	Rheumatoid factor present		161 (22.2)	60 (20.6)	62 (27.4)*
ancagrp6	cANCA or PR3 (composite to replace individual items TstAA1 and TstAA3)	Y	616 (85.1)**	12 (4.1)**	21 (9.3)**
ancagrp7	pANCA or MPO (composite item to replace individual items TstAA2 and TstAA4)	Y	84 (11.6)**	284 (97.6)**	107 (47.2)*

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Item	Description	Composite Items	GPA N= 724	MPA N=291	EGPA N=226
IMAGING					
imag1	Imaging of the chest/lungs with nodules OR mass/tumor OR cavitation	Y	263 (36.3)**	31 (10.7)*	31 (13.7)
imag2p1	Imaging of the chest/lungs with hemorrhage OR infiltrates OR consolidation OR ground glass changes	Y	203 (28.0)**	67 (23.0)	73 (32.3)**
imag2p3	Imaging of the chest/lungs with hemorrhage	Y	59 (8.1)**	22 (7.6)*	1 (0.4)*
imag3	Imaging of the pleura/chest with effusion	Y	68 (9.4)	38 (13.1)	27 (11.9)
imag4	Imaging of the chest/lungs with fibrosis OR ILD	Y	15 (2.1)**	67 (23.0)**	16 (7.1)
imag5	Imaging of the trachea/epiglottis with stenosis OR inflammation OR ulceration	Y	9 (1.2)	0 (0)	0 (0)
imag6	Imaging of the nasal/paranasal sinuses with inflammation OR effusion OR consolidation OR wall thickness OR mastoiditis	Y	212 (29.3)**	5 (1.7)**	64 (28.3)**
imag7	Imaging of the nasal/paranasal sinuses with (deviated septum OR bony destruction OR septal perforation)	Y	41 (5.7)**	0 (0)*	2 (0.9)
imag8	Imaging of the nasal/paranasal sinuses with polyps	Y	17 (2.3)	0 (0.0)*	14 (6.2)**
imag9	Imaging of the orbital wall with mass/tumor OR inflammation	Y	13 (1.8)*	1 (0.3)	2 (0.9)
imag10	Imaging of the heart/cardiac muscle with EF<50% OR myocarditis OR myocardiopathy OR cardiomyopathy OR hypokinesis OR akinesis OR MRI of the heart/cardiac muscle with inflammation	Y	7 (1.0)**	6 (2.10	38 (16.8)**

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Item	Description	Composite Items	GPA N= 724	MPA N=291	EGPA N=226
BIOPSY					
biop1	Pauci-immune glomerulonephritis		201 (27.8)*	141 (48.5)**	11 (4.9)**
biop2	Necrotizing arteritis +/- fibrinoid necrosis	Y	82 (11.3)	40 (13.7)	15 (6.6)*
biop3	Perivascular infiltrates or perivascular inflammation (combined item)	Y	17 (2.3)	6 (2.1)	10 (4.4)
biop4	Prominent neutrophils in vasculitis		26 (3.6)	3 (1.0)***	3 (1.3)*
biop5	Absence or paucity of immune complex deposition vessels other than glomeruli		16 (2.2)	16 (5.5)***	5 (2.2)
biop7	Prominent eosinophils in vasculitis		5 (0.7)**	1 (0.3)**	42 (18.6)**
biop8	Predominant mononuclear leucocytes in vasculitis		11 (1.5)	10 (3.4)	2 (0.9)
biop9	Anti-GBM staining on immunofluorescence		0 (0)	0 (0)	0 (0)
biop10	Immune complex glomerulonephritis		3 (0.4)	4 (1.4)	0 (0)
biop12	Immune complex deposition in vessels other than glomeruli with prominent IgA/IgA dominant immune complex glomerulonephritis	Y	6 (0.8)**	1 (0.3)**	0 (0)
biop13	Necrotizing or leucocytoclastic arteriolitis/venulitis/leucocytoclastic vasculitis	Y	48 (6.6)*	11 (3.8)**	17 (7.5)
biop14	Extravascular eosinophil predominant inflammation/increased eosinophils in bone marrow	Y	9 (1.2)**	1 (0.3)**	47 (20.8)**
biop6biop15	Granuloma/extravascular granulomatous inflammation/giant cells	Y	160 (22.1)**	7 (2.4)**	13 (5.8)
biop16	Unspecified tissue inflammation/extravascular non-granulomatous inflammation	Y	147 (20.3)**	20 (6.9)*	34 (15.0)

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 7A. Expert Reviewer Characteristics

Characteristics	N=55 (%)	Characteristics	N=55 (%)
Country		**Specialty**	
Australia	1 (1.8)	Rheumatology	33 (60.0)
Canada	3 (5.5)	Nephrology	11 (20.0)
Czech Republic	2 (3.6)	Internal Medicine	4 (7.3)
Denmark	1 (1.8)	Immunology	3 (5.5)
Egypt	1 (1.8)	Dermatology	2 (3.6)
France	1 (1.8)	Neurology	1 (1.8)
Germany	7 (12.7)	Pathology	1(1.8)
India	2 (3.6)		
Ireland	2 (3.6)	**Number of patients with AAV seen at site per year**	
Italy	3 (5.5)		
Japan	2 (3.6)	>50	32 (58.2)
Mexico	2 (3.6)	21-50	11 (20.0)
Netherlands	2 (3.6)	6-20	11 (20.0)
New Zealand	1 (1.8)	Unknown	1
Portugal	2 (3.6)		
Russia	2 (3.6)	**Years in specialty**	
Slovenia	1 (1.8)	0-5	2 (3.6)
Spain	1 (1.8)	6-10	11 (20.0)
Switzerland	2 (3.6)	11-15	13 (23.6)
Turkey	2 (3.6)	16-20	9 (16.4)
United Kingdom	6 (10.9)	>20	19 (34.5)
United States of America	9 (16.4)	Unknown	1
Background		**Sex**	
Clinician	11 (20.0)	Male	38 (69.1)
Clinician and researcher	44 (80.0)	Female	17 (30.9)

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

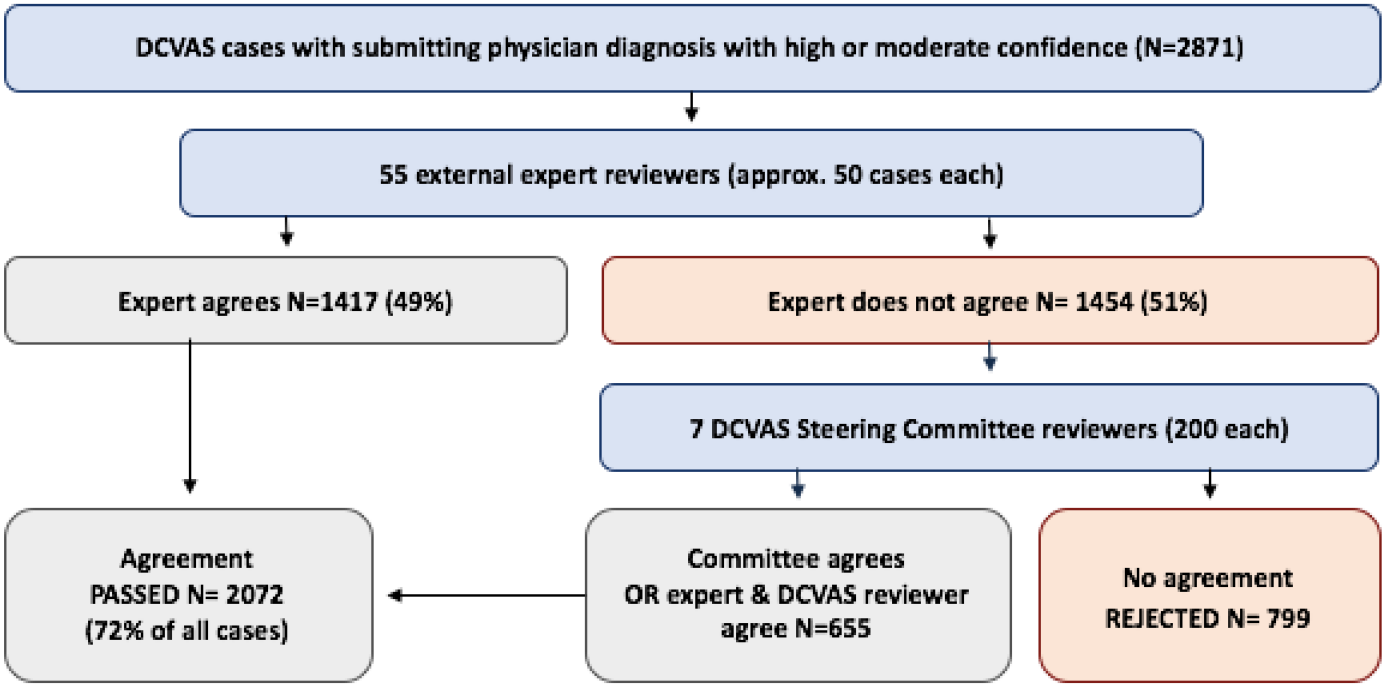
Supplementary Materials 7B. Names of the Expert Reviewers

Alba, Marco
Barra, Lillian
Baslund, Bo
Basu, Neil
Brown, Nina
Cid, Maria
Daikeler, Thomas
Direskeneli, Haner
Emmi, Giamoco
Flores-Suárez, Luis Felipe
Fujimoto, Shouichi
Gatenby, Paul
Geetha, Duvuru
Geraldes, Ruth
Gewurz-Singer, Ora
Guillevin, Loïc
Hammam, Nevin
Hauser, Thomas
Hellmich, Bernhard
Henes, Jörg
Hinojosa-Azaola, Andrea
Hočevar, Alojzija
Holle, Julia
Hruskova, Zdenka
Jayne, David
Jennette, Charles
Kallenberg, Cees
Karadağ, Ömer
Khalidi, Nader
Lamprecht, Peter
Langford, Carol
Little, Mark
Macieira, Carla
Matsui, Kazuo
Matteson, Eric
Micheletti, Robert
Milman, Nataliya
Moiseev, Sergey
Molloy, Eamonn
Monach, Paul
Neumann, Thomas
Novikov, Pavel
Quincey, Vicki
Rajasekhar, Liza
Salama, Alan
Salvarani, Carlo
Schmidt, Wolfgang
Sharma, Aman
Smith, Rona
Springer, Jason
Sunderkötter, Cord
Sznajd, Jan
Teng, Yko
Tesar, Vladimir
Vaglio, Augusto

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 8. Flow chart of expert review process to create the Diagnosis and Classification of Vasculitis Study dataset for ANCA-associated vasculitis.

Cases passed by the expert review process were used to derive classification criteria for granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.



ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 9A. Results of regression analysis (n=91 candidate items) for eosinophilic granulomatosis with polyangiitis. Top ten strongest independent variables

Predictor Variables	Odds Ratio (95% CI)	P-value
Serum eosinophil count >1x10^9/L	122.88 (34, 596)	<0.001
Nasal polyps	21.56 (3.84, 156.37)	<0.001
Evidence of obstructive airway disease	17.3 (4.15, 83.65)	<0.001
cANCA or anti-PR3-ANCA	0.03 (0, 0.15)	<0.001
Pauci-immune glomerulonephritis	0.02 (0, 0.27)	0.01
Extravascular eosinophil inflammation	15.72 (1.71, 172.54)	0.02
Non-productive cough	6.07 (1.46, 28.97)	0.02
Mononeuritis multiplex or motor neuropathy	3.75 (1.05, 13.73)	0.04
Hematuria	0.26 (0.06, 0.94)	0.05
Dyspnea	2.98 (10.77, 12.48)	0.12
Maximum value of serum creatinine	1.00 (1.00, 1.00)	0.97

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 9B. Results of regression analysis (n=91 candidate items) for granulomatosis with polyangiitis. Top ten strongest independent variables

Predictor Variables	Odds Ratio (95% CI)	P-value
cANCA or anti-PR3 ANCA positive	142.3 (65.9, 335.0)	<0.001
Nasal bloody discharge, ulcers, crusting, or sinonasal congestion/blockage	28.1 (14.1, 59.4)	<0.001
Eosinophil count (x10^9/L) (≥1 vs. <1)	0.03 (0.01, 0.09)	<0.001
Granuloma or giant cells on biopsy	13.3 (4.29, 44.8)	<0.001
Pulmonary nodules, mass, or cavitation on chest imaging	7.65 (3.59, 17.0)	<0.001
Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	9.48 (3.51, 27.9)	<0.001
pANCA or anti-MPO ANCA positive	0.30 (0.15, 0.60)	<0.001
Nasal polyps	0.16 (0.04, 0.53)	<0.001
Abdominal pain	0.21 (0.08, 0.51)	<0.001
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses on imaging	3.13 (1.38, 7.37)	<0.001

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 9C. Results of regression analysis (n=91 candidate items) for microscopic polyangiitis. Top ten strongest independent variables

Predictor Variables	Odds Ratio (95% CI)	P-value
pANCA or anti-MPO ANCA positive	251.22 (64.78, 1587.65)	<0.01
Maximum serum eosinophil count ≥1 x10^9/L	0.02 (0.004, 0.10)	<0.01
Nasal bloody discharge, ulcers, crusting, or sinonasal congestion or blockage, or nasal septal defect /perforation	0.09 (0.03, 0.26)	<0.01
Pauci-immune glomerulonephritis on biopsy	10.73 (3.73, 36.09)	<0.01
Fibrosis or interstitial lung disease on chest imaging	16.23 (4.00, 85.26)	<0.01
Significant anemia (Hb <10g/dL)	3.61 (1.30, 10.71)	0.02
Microscopic hematuria	1.83 (0.69, 4.87)	0.22
cANCA or anti-PR3 ANCA positive	0.25 (0.07, 0.89)	0.03
Maximum value of serum creatinine	1.06 (0.87, 1.35)	0.61

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Table 10A. Data-driven and clinically-selected seven-item model for classification of eosinophilic granulomatosis with polyangiitis with associated risk score based off beta coefficient weighting.

Predictor Variables	Odds Ratio (95% CI)	Beta Coefficient	Risk Score
Eosinophil count >1x10^9/L	109.57 (36.05, 410.43)	4.70	+5
Nasal polyps	14.44 (3.64, 66.45)	2.89	+3
Evidence of obstructive airway disease	19.75 (5.91, 60.31)	-3.27	+3
cANCA or anti-PR3-ANCA	0.04 (0.01, 0.15)	2.67	-3
Extravascular eosinophil inflammation	10.68 (1.59, 97.24)	2.37	+2
Mononeuritis multiplex or motor neuropathy	3.19 (1.07, 9.62)	1.16	+1
Hematuria	0.23 (0.07, 0.67)	-1.48	-1

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 10B: Data-driven and clinically-selected ten-item model for classification of granulomatosis with polyangiitis with associated risk scored based off beta coefficient weighting

Predictor Variables	Odds Ratio (95% CI)	Beta Coefficient	Risk Score
cANCA or anti-PR3 ANCA positive	100.0 (53.8, 196.2)	4.61	+5
Nasal bloody discharge, ulcers, crusting, or sinonasal congestion	16.9 (9.38, 31.6)	2.83	+3
Granuloma, or giant cells, extravascular granulomatous inflammation on biopsy	8.94 (3.59, 22.7)	2.19	+2
Pulmonary nodules, mass, or cavitation on chest imaging	6.40 (3.31, 12.66)	1.86	+2
Cartilaginous involvement (cartilage inflammation of the ear or nose, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	6.84 (2.92, 16.7)	1.92	+2
Hearing loss (conductive or sensorineural)	3.22 (1.35, 7.91)	1.17	+1
Pauci-immune glomerulonephritis	2.17 (1.19, 4.01)	0.75	+1
Inflammation, consolidation, or effusion of the nasal/ paranasal sinuses or mastoiditis on imaging	2.11 (1.07, 4.23)	0.75	+1
pANCA- or anti-MPO ANCA-positive	0.30 (0.16, 0.53)	-1.21	-1
Maximum serum eosinophil count ($x10^9$/L) (≥1 vs. <1)	0.03 (0.01, 0.06)	-3.58	-4

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Table 10C. Data-driven and clinically-selected six-item model for classification of microscopic polyangiitis with associated risk scored based off beta coefficient weighting

Predictor Variables	Odds Ratio (95% CI)	Beta Coefficient	Risk Score
pANCA- or anti-MPO ANCA-positive	284.7 (83.7, 1481.2)	5.65	+6
Pauci-immune glomerulonephritis	15.5 (5.71, 49.2)	2.74	+3
Fibrosis or interstitial lung disease on chest imaging	13.2 (3.7, 57.2)	2.58	+3
Serum eosinophil count ≥ 1 $x10^9$/L	0.03 (0.01, 0.09)	-3.68	-4
Nasal bloody discharge, ulcers, crusting or sinonasal congestion	0.07 (0.02, 0.19)	-2.71	-3
cANCA- or anti-PR3 ANCA-positive	0.25 (0.06, 0.88)	-1.39	-1

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

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 11A: Performance characteristics of a points-based risk score for eosinophilic granulomatosis with polyangiitis with different thresholds in the development set

Threshold Score	Sensitivity (%)	Specificity (%)
1	99.2	55.1
2	95.8	83.5
3	95.8	89.0
4	92.4	95.2
5	89.1	97.5
6	84.9	99.1
7	76.5	99.3
8	68.1	100.0

A total score of ≥6 was considered the best cut-point to provide high enough specificity for purposes of enrolling patients into clinical trials without compromising sensitivity. If a higher total score is chosen, specificity increases but there is a corresponding disproportionate drop in sensitivity. When scoring an individual patient, the higher the score, the higher the specificity for eosinophilic granulomatosis with polyangiitis.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 11B: Performance characteristics of a points-based risk score for granulomatosis with polyangiitis with different thresholds in the development set

Threshold Score	Sensitivity (%)	Specificity (%)
3	97.3	90.7
4	94.5	92.5
5	92.5	93.8
6	84.2	98.1

A total score of ≥ 5 was considered the best cut-point to provide high enough specificity for purposes of enrolling patients into clinical trials without compromising sensitivity. If a higher total score is chosen, specificity increases but there is a corresponding disproportionate drop in sensitivity. When scoring an individual patient, the higher the score, the higher the specificity for granulomatosis with polyangiitis.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 11C: Performance characteristics of a points-based risk score for microscopic polyangiitis with different thresholds in the development set

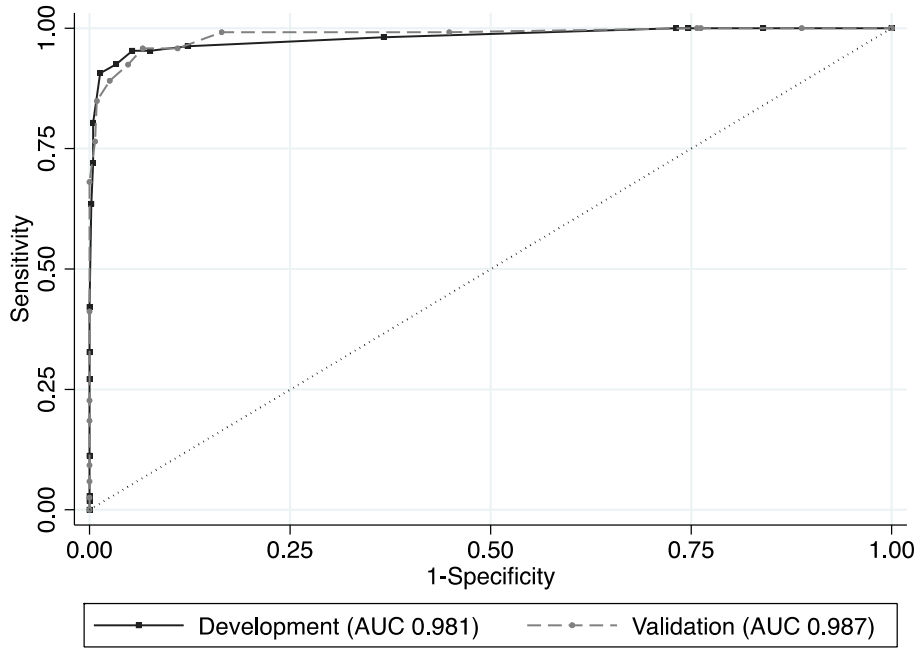
Threshold Score	Sensitivity (%)	Specificity (%)
1	98.6	82.1
2	98.6	82.6
3	94.3	90.6
4	90.8	94.0
5	90.8	94.2
6	86.6	95.7
7	50.7	98.1

A total score of ≥ 5 was considered the best cut-point to provide high enough specificity for purposes of enrolling patients into clinical trials without compromising sensitivity. If a higher total score is chosen, specificity increases but there is a corresponding disproportionate drop in sensitivity. When scoring an individual patient, the higher the score, the higher the specificity for microscopic polyangiitis.

ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 12A. Discrimination curves for the classification criteria for eosinophilic granulomatosis with polyangiitis.

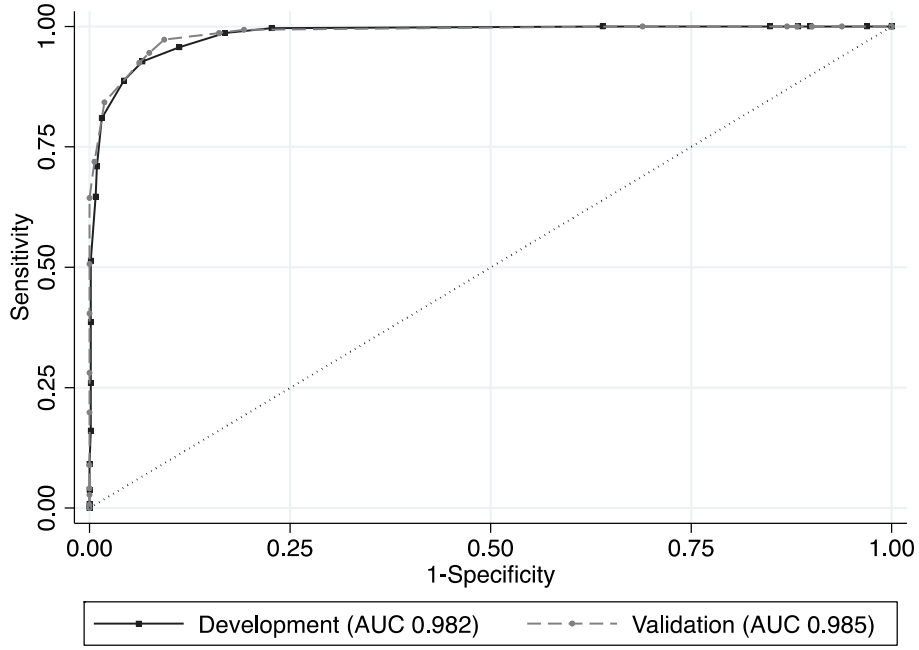
Classification criteria applied to 1,113 cases confirmed by Expert Review, 226 with EGPA and 887 comparators divided into a development set (50%) and validation set (50%). The Area Under Curve (AUC) for the development set is shown (solid line) and the AUV for the validation set is shown (dotted line).



ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 12B. Discrimination curves for the classification criteria for granulomatosis with polyangiitis.

Classification criteria applied to 1537 cases confirmed by Expert Review (N= 1537), 724 with GPA (47.1%) and 813 (52.9%) comparators divided into a development set (80%) and validation set (20%). The Area Under Curve (AUC) for the development set is shown (solid line) and the AUC for the validation set is shown (dotted line).



ACR-EULAR Classification Criteria for ANCA-Associated Vasculitis

Supplementary Materials 12C. Discrimination curves for the classification criteria for microscopic polyangiitis.

Classification criteria applied to 1,113 cases confirmed by Expert Review, 291 with MPA and 822 comparators divided into a development set (50%) and validation set (50%). The Area Under Curve (AUC) for the development set is shown (solid line) and the AUV for the validation set is shown (dotted line).