SUPPLEMENTARY MATERIAL

2022 AMERICAN COLLEGE OF RHEUMATOLOGY AND EULAR CLASSIFICATION CRITERIA FOR LARGE-VESSEL VASCULITIS [GIANT CELL ARTERITIS AND TAKAYASU ARTERITIS]

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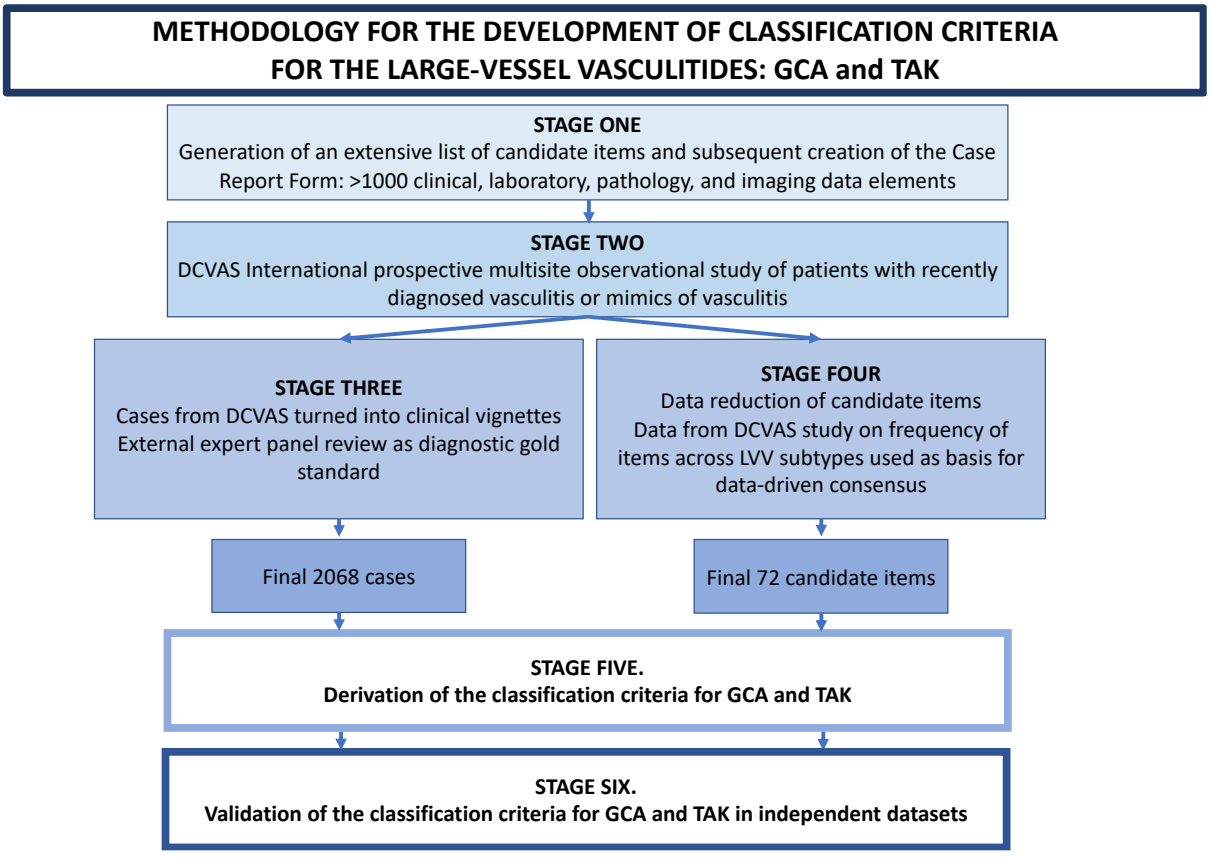
Supplementary Materials 1. Detailed description of the research methods for the development of classification criteria for giant cell arteritis and Takayasu arteritis

An international Steering Committee comprised of clinician investigators with expertise in vasculitis, statisticians, and data managers was established to oversee the overall Diagnostic and Classification Criteria in Vasculitis (DCVAS) project. The Steering Committee established a six-stage plan using data-driven and consensus methodology to develop the criteria for six systemic vasculitides: three small-vessel vasculitides (granulomatosis with polyangiitis [GPA], microscopic polyangiitis [MPA], and eosinophilic granulomatosis with polyangiitis [EGPA]), a medium-vessel vasculitis (PAN), and two large-vessel vasculitides (giant cell arteritis [GCA] and Takayasu arteritis [TAK]). A flow chart depicting an overview of each stage of the methodology used to develop classification criteria for GCA and TAK is listed below.



DCVAS: Diagnostic and Classification Criteria in Vasculitis; GCA: giant cell arteritis; LVV: large-vessel vasculitis; TAK: Takayasu arteritis

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 vasculitis [1–7]. 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 [8].

The University of Oxford sponsored the study and overall ethical approval was given by the UK Berkshire Research Ethics Committee (reference 10/H0505/19) on 7 May 2010.The study was performed in accordance with the 1964 Declaration of Helsinki. Additional 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:

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 ANCA-associated vasculitis, GCA, anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, Behçet's disease, primary central nervous system vasculitis, IgA vasculitis, isolated aortitis, other large-vessel vasculitis (LVV), or a diagnosis within the previous five years of PAN or TAK; 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).

Exclusion criteria:

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

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. 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 from all study participants was reviewed at a central location for completeness. Local investigators were contacted to resolve and data discrepancies.

Stage Three: Expert panel methodology to derive a gold standard-defined set of cases of large-vessel vasculitis

An online independent Expert Review Process was used to minimize investigator bias and to avoid the circularity of applying a previously derived gold standard such as the 1990 ACR Criteria [2]. Experts in vasculitis from a wide range of geographical locations and specialties were invited to review cases submitted to DCVAS (see **Supplementary Materials 6 & 7** for the expert reviewer characteristics). External experts reviewed approximately 50 cases each, blinded to the submitting physician's diagnosis. The review process took place over two time periods. In 2016, primarily cases of AAV, with a smaller fraction of LVV cases (233 cases, 8.1% of total number of cases), were reviewed. In 2018, 1596 cases of LVV (74.9% of total number of cases) were reviewed.

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 format (**Supplementary Materials 8**). All cases labeled GCA, TAK, or a different form of LVV by the submitting physician were reviewed. To ensure a rigorous process, in the 2018 review 25.1% of cases with a submitting physician diagnosis of other vasculitides (6.1%), or a condition mimicking vasculitis (19.0%) 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 no predominant size)

(iii) if a category was chosen in (ii) then which subtype of vasculitis was present (for example, if LVV was selected, then a choice of GCA, TAK, isolated aortitis, 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. A flow diagram depicting the results from the expert review process is provided in **Supplementary Materials 9**.

Stage Four: Refinement of candidate items specifically for large-vessel vasculitis

The DCVAS CRF included > 1000 data elements. The final statistical analysis to create classification criteria for LVV required approximately 100 predictors to avoid over-fitting of the final models during regression analysis [9]. Using a series of data-driven and consensus approaches, the number of candidate items was reduced, and specific items were further defined as necessary.

Age as a Classifier

Since age is a key differentiator between forms of LVV, distribution of age at symptom and diagnosis was plotted for GCA and TAK to determine whether specific age thresholds should be regarded as absolute requirements for disease classification (**Supplementary Materials 10).**

Vascular Physical Examination Findings

The elements of the vascular physical examination considered as candidate items were diminished or absent pulse, bruits, blood pressure asymmetry and arterial tenderness. Given the clinical challenge of accurately localizing a bruit to a specific arterial territory, presence of "any bruit" was considered as a candidate item [10]. Given the increased prevalence of vascular pathology in arterial territories above the diaphragm in LVV, vascular pulse abnormalities were studied separately in the upper and lower extremities. Carotidynia is a specific feature for TAK [11], and temporal artery abnormalities are specific for GCA. Consequently, vascular examination findings related to the temporal arteries (diminished or absent pulse, tenderness, or hard 'cord-like') and to the carotid arteries (diminished or absent pulse, or tenderness / carotidynia) were considered independently. Blood pressure readings were only recorded for the upper extremities in the database. Difference in systolic blood pressure in the upper extremities was categorized at 10 mmHg intervals. A difference in systolic blood pressure of 20 mmHg maximized sensitivity and specificity between TAK and GCA and was selected for further analysis.

Vascular Imaging Findings

Investigators recorded vascular imaging findings (luminal and wall abnormalities) detected by vascular ultrasound, angiography (computed tomography [CT], magnetic resonance [MR], or catheter-based), or positron emission tomography (PET). Temporal artery abnormalities documented by vascular ultrasound were stenosis, occlusion, wall thickening, and halo sign. However, halo sign was the only temporal artery ultrasound finding included for subsequent analyses, given its high specificity to diagnose GCA in comparison to other ultrasonographic abnormalities [12,13]. Increased fluorodeoxyglucose (FDG) uptake in specific arterial territories, as determined by the submitting physician, was recorded for the PET studies. Eleven territories related to the large arteries were evaluated: bilateral carotid, subclavian, axillary, renal, and mesenteric arteries; and thoracic and abdominal aorta. Given the lack of clear definitions to define vascular wall abnormalities (e.g. wall thickness) and the lack of specificity of these findings in comparison to other conditions such as

atherosclerosis [14], only findings of luminal damage (i.e. stenosis, occlusion, aneurysm) detected by angiography (i.e. computed tomography, magnetic resonance, or catheter-based angiography) or ultrasound were considered in the large arteries. Frequency of luminal damage was compared in each vascular territory between TAK and GCA (**Supplementary Materials 11**).

Prevalence of symmetric involvement of paired branch arteries (e.g., right and left subclavian artery) was evaluated. K-means cluster analysis of vascular imaging was performed to identify distinctive patterns of large vessel involvement in GCA and TAK, as previously reported [15] . (**Supplementary Materials 12**).

Vascular Biopsy Findings

Biopsy findings of the temporal artery and other arterial sites were recorded. Data from 784 temporal artery biopsies was collected. Other than the temporal arteries, there were too few biopsies of other arterial territories to consider in subsequent analysis (aorta = 6; other artery = 19).

Temporal artery biopsy findings were not subject to central review. Instead, the submitting physician provided information about histopathologic interpretation of biopsy findings which were reported as normal, non-diagnostic, consistent with vasculitis but not definite, or definite vasculitis. Specific histopathologic findings (e.g., giant cells, granuloma, etc.) were recorded at the discretion of the submitting physician. Histopathologic interpretation without details of accompanying histopathologic features were reported for 151 patients (19%). Consequently, a positive temporal artery biopsy for all subsequent analyses was defined as histopathologic interpretation of definite vasculitis by the local submitting physician. Specific histopathologic criteria do not exist to define “definite vasculitis” by a temporal artery biopsy. Presence of giant cells, mononuclear leukocyte infiltration, and fragmentation of the internal elastic lamina were independently associated with histopathologic interpretation of definite vasculitis in the DCVAS cohort [16]. These features can be used as a guide to inform the definition of a positive temporal artery biopsy when the criteria are applied in clinical practice.

Laboratory Values

The maximum value of erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were recorded in the DCVAS CRF as continuous variables. Fractional polynomial regression was used to check the assumption of a linear relationship of ESR and CRP with the panel-reviewed diagnosis as the outcome variable. Since there was evidence of non-linearity for both ESR and CRP, these variables were categorized into five groups with cut-points based on plots from fractional polynomial regression models [17]. Threshold values of ESR ≥ 50mm/hr and CRP ≥ 10mg/L were chosen by Steering Committee based on optimization of model fit and ease of clinical application. Other laboratory variables of interest were recorded in the DCVAS CRF only as categorical variables (e.g., anemia (hemoglobin < 10g/dL); thrombocythemia (platelets > 500 $x10^9$/L); and leukocytosis (white blood cell count > 15.0 $x10^9$/L).

Reduction of Candidate Items

A data-driven process was used to retain candidate items of relevance to cases and comparators for LVV. Seven members of the DCVAS steering committee (JR, RW, RS, RL, PM, PG, CP) were split into groups of two, and each group reviewed all variables within an assigned domain: clinical symptoms, vascular examination, laboratory, biopsy, and vascular imaging. Data on frequency of items was prepared for review from cases of GCA and TAK 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. Consensus on final items to include for the next phase of analysis was reached between the two independent steering committee members, and then within the wider steering committee. The final list of candidate predictors used in the next stage of data analysis is listed in **Supplementary Materials 13**.

Stage Five: Derivation of classification criteria for giant cell arteritis and Takayasu arteritis

The DCVAS dataset was split into development (70%) and validation (30%) datasets. A larger development dataset was chosen to maximize the potential to identify the best model. Comparisons were performed between cases defined in Stage Three as either having the diagnosis of GCA, or diagnosis of TAK, other vasculitis that mimic GCA and TAK (isolated aortitis, primary central nervous system vasculitis, PAN, Behçet's disease, and other LVV), or other diagnosis that mimic LVV (e.g., headache, atherosclerosis - **Supplementary Materials 14**). This process resulted in generation of a binary outcome variable (LVV sub-type or comparators). To ensure balance in the sample (50% cases vs. 50% controls) for outcome definition, the following splits were made, giving equal weighting to the three types of controls: GCA (50%) vs. TAK (16.6%), other vasculitis (16.6%), and other diagnosis that mimic LVV (16.6%); or TAK (50%) vs. GCA (16.6%), other vasculitis (16.6%), and other diagnosis that mimic LVV (16.6%).

The candidate predictors from Stage Four were included in a logistic regression model. Fractional polynomial regression modeling was used to assess evidence of linearity with outcome for continuous predictor variables [17]. Multiple imputation was used to overcome potential bias from missing data [18]. 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 [9,19,20]. 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 15 & 16**).

The reduced item model was tested for discrimination, area under the curve (AUC) sensitivity and specificity. This was an iterative process within the Steering Committee, with the clinician researchers and expert biostatisticians working collaboratively, to ensure face and content validity and acceptability of the resultant criteria.

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 [21] (**Supplementary Materials 17**). A threshold was identified for classification, which best balanced sensitivity

and specificity (**Supplementary Materials 18 & 19**). Absolute age requirements were imposed to cases and comparators as the final step of classification.

Stage Six: Validation of the final classification criteria for giant cell arteritis and Takayasu arteritis in an independent dataset

The performance characteristics of the final criteria were tested in an independent dataset of cases and comparators. These are the official final values that should be quoted when referring to the criteria.

Comparisons were made between the measurement properties of the new classification criteria for GCA and TAK and the respective 1990 ACR Classification Criteria for GCA and TAK using data from the validation datasets (**Supplementary Material 20**). Because an aim of the project was to develop criteria that were derived from an international dataset, the performance characteristics of the new criteria were tested in different regions of the world using pooled data from the development and validation datasets to maximize sample size for the subgroups. Since patients diagnosed with LVV between the ages of 50-60 years can be particularly difficult to classify, the performance characteristics of the GCA and TAK classification criteria were tested for all patients diagnosed with GCA or TAK in this age range (**Supplementary Material 21**).

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.

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Supplementary Materials 2. DCVAS case report form

See separate PDF file titled “DCVAS case report form”

Supplementary Materials 3: Diagnosis and Classification of Vasculitis Study (DCVAS) sites and investigators

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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

Supplementary Materials 4. Diagnosis and Classification of Vasculitis Study Sites/Investigators characteristics

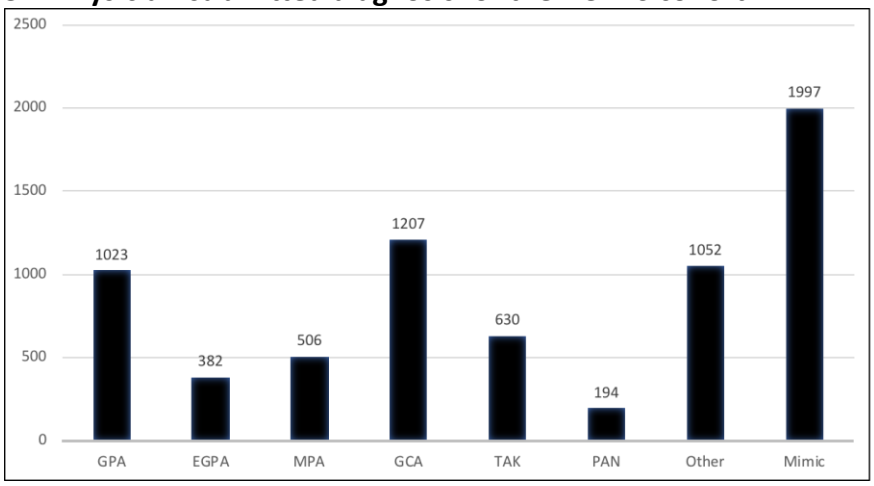
Characteristics	N=136 (%)	Characteristics	N=136 (%)	Characteristics	N=136 (%)
Country		**Country**		**Specialty**	
Australia	3 (2.2)	Norway	2 (1.5)	Rheumatology	99 (72.8)
Austria	1 (0.7)	Poland	1 (0.7)	Nephrology	21 (15.4)
Belgium	1 (0.7)	Portugal	4 (2.9)	Neurology	5 (3.7)
Canada	8 (5.9)	Republic of Korea	1 (0.7)	Internal Medicine	4 (2.9)
China	4 (2.9)	Russia	1 (0.7)	Immunology	4 (2.9)
Czech Republic	1 (0.7)	Slovenia	1 (0.7)	Dermatology	2 (1.5)
Denmark	1 (0.7)	Spain	2 (1.5)	Respiratory	1 (0.7)
Egypt	2 (1.5)	Sri Lanka	1 (0.7)		
Finland	2 (1.5)	Sweden	3 (2.2)	**Years within specialty**	
Germany	6 (4.4)	Switzerland	1 (0.7)	0-5	0 (0.0)
Hungary	1 (0.7)	Turkey	5 (3.7)	6-10	15 (11.0)
India	6 (4.4)	United Kingdom	31 (22.8)	11-15	22 (16.2)
Ireland	2 (1.5)	United States of America	12 (8.8)	16-20	21 (15.4)
Italy	4 (2.9)			>20	48 (35.3)
Japan	20 (14.7)	**Background**		Unknown	30 (22.1)
Malaysia	1 (0.7)	Academic hospital/ Medical school	89 (65.4)		
Mexico	2 (1.5)			**Sex of primary investigator**	
Netherlands	2 (1.5)	Non-academic hospital	17 (12.5)	Male	99 (72.8)
New Zealand	4 (2.9)	Unknown	30 (22.1)	Female	37 (27.2)

Supplementary Materials 5. Study participant details

5A. Patient recruitment by region

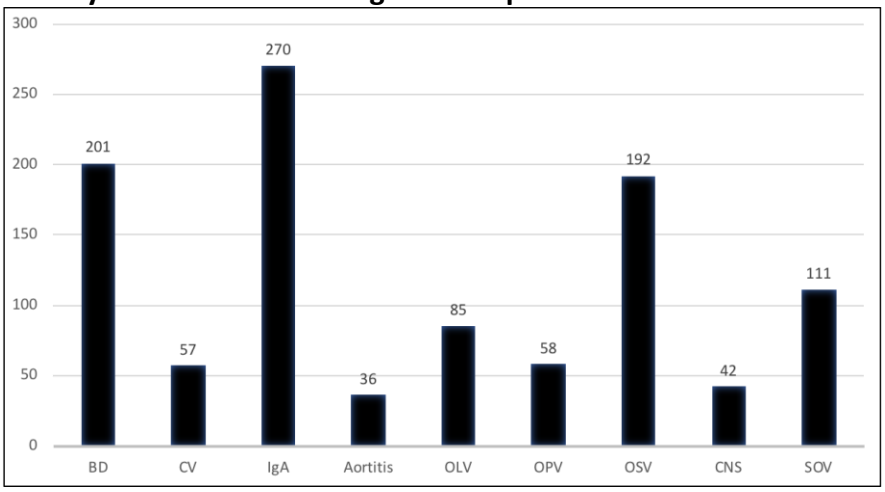
	Total Site	Total Patients Recruited	% Patients Recruited
Europe	71	4107	59%
North America	22	1497	21%
Asia	34	1152	17%
Oceania	7	142	2%
Africa	2	93	1%
TOTAL	**136**	**6991**	

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

Supplementary Materials 6. Expert reviewer characteristics

6A. Expert reviewer characteristics - 2016 review

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)	**Years in specialty**	
Italy	3 (5.5)	0-5	2 (3.6)
Japan	2 (3.6)	6-10	11 (20.0)
Mexico	2 (3.6)	11-15	13 (23.6)
Netherlands	2 (3.6)	16-20	9 (16.4)
New Zealand	1 (1.8)	>20	19 (34.5)
Portugal	2 (3.6)	Unknown	1 (1.8)
Russia	2 (3.6)		
Slovenia	1 (1.8)	**Sex**	
Spain	1 (1.8)	Male	38 (69.1)
Switzerland	2 (3.6)	Female	17 (30.9)
Turkey	2 (3.6)		
United Kingdom	6 (10.9)	**Background**	
United States of America	9 (16.4)	Clinician	11 (20.0)
		Clinician and researcher	44 (80.0)

6B. Expert reviewer characteristics - 2018 review

Characteristics	N=56 (%)	Characteristics	N=56 (%)
Country		**Specialty**	
Australia	1 (1.8)	Rheumatology	42 (75.0)
Austria	1 (1.8)	Internal Medicine	5 (8.9)
Belgium	1 (1.8)	Immunology	3 (5.4)
Canada	3 (5.4)	Nephrology	2 (3.6)
Czech Republic	1 (1.8)	Neurology	2 (3.6)
Denmark	4 (7.1)	Dermatology	1 (1.8)
Egypt	1 (1.8)	Pathology	1 (1.8)
France	2 (3.6)		
Germany	8 (14.3)	**Years in specialty**	
Iceland	1 (1.8)	0-5	1 (1.8)
India	2 (3.6)	6-10	16 (28.6)
Ireland	1 (1.8)	11-15	16 (28.6)
Italy	6 (10.7)	16-20	7 (12.5)
Japan	1 (1.8)	>20	16 (28.6)
Mexico	2 (3.6)		
Netherlands	1 (1.8)	**Sex**	
Norway	1 (1.8)	Male	40 (71.4)
Poland	1 (1.8)	Female	16 (28.6)
Portugal	2 (3.6)		
Russia	1 (1.8)	**Background**	
Slovenia	1 (1.8)	Clinician	9 (16.1)
Spain	2 (3.6)	Clinician and researcher	47 (83.9)
Switzerland	2 (3.6)		
Turkey	2 (3.6)		
United Kingdom	1 (1.8)		
United States of America	7 (12.5)		

Supplementary Materials 7. Expert panel reviewers

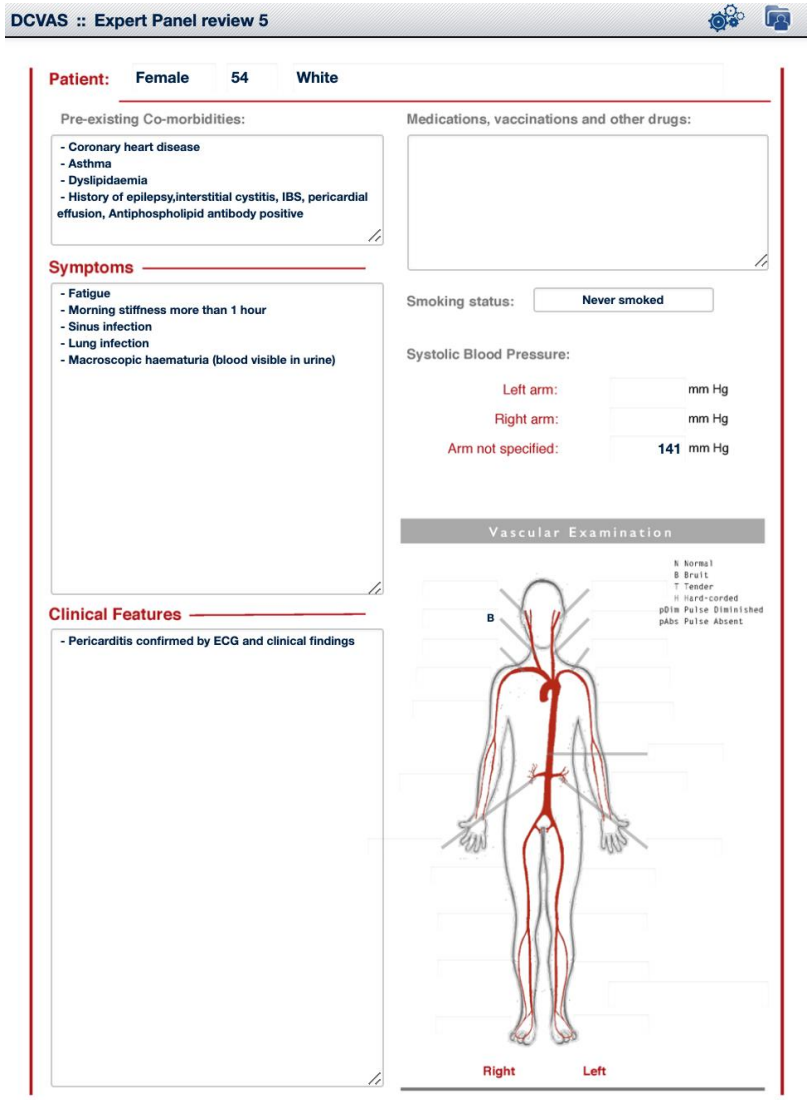
7A. List of expert panel reviewers - 2016 review

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

7B. List of expert panel reviewers - 2018 review

Alba, Marco
Barra, Lillian
Basu, Neil
Blockmans, Daniel
Brouwer, Elisabeth
Buttgereit, Frank
Camellino, Dario
Chrysidis, Stavros
Cid, Maria
Daikeler, Thomas
de Boysson, Hubert
de Miguel, Eugenio
Dejaco, Christian
Diamantopoulos, Andreas
Direskeneli, Haner
Duftner, Christina
Emmi, Giamoco
Faurschou, Mikkel
Flores-Suárez, Luis Felipe
Gatenby, Paul
Geraldes, Ruth
Gewurz-Singer, Ora
Guillevin, Loïc
Hammam, Nevin
Hauser, Thomas
Hellmich, Bernhard
Henes, Jörg
Hinojosa-Azaola, Andrea
Hočevar, Alojzija
Holle, Julia
Jennette, Charles
Juche, Aaron
Karadağ, Ömer
Kermani, Tanaz
Khalidi, Nader
Koster, Matthew
Macieira, Carla
Matsui, Kazuo
Milchert, Marcin
Molloy, Eamonn
Monti, Sara
Neumann, Thomas
Nielsen, Berit
Novikov, Pavel
Pagnoux, Christian
Salvarani, Carlo
Schmidt, Wolfgang
Sharma, Aman
Sivakumar, Rajappa
Springer, Jason
Sunderkötter, Cord
Terslev, Lene
Tesar, Vladimir
Tomasson, Gunnar
Vaglio, Augusto
Warrington, Kenneth

Supplementary Materials 8. Example of a clinical vignette extracted from the case report form



DCVAS :: Expert Panel review 5

Patient: Female 54 White

Pre-existing Co-morbidities:

- Coronary heart disease
- Asthma
- Dyslipidaemia
- History of epilepsy,interstitial cystitis, IBS, pericardial effusion, Antiphospholipid antibody positive

Medications, vaccinations and other drugs:

Smoking status: Never smoked

Systolic Blood Pressure:

Left arm: mm Hg

Right arm: mm Hg

Arm not specified: 141 mm Hg

Symptoms

- Fatigue
- Morning stiffness more than 1 hour
- Sinus infection
- Lung infection
- Macroscopic haematuria (blood visible in urine)

Clinical Features

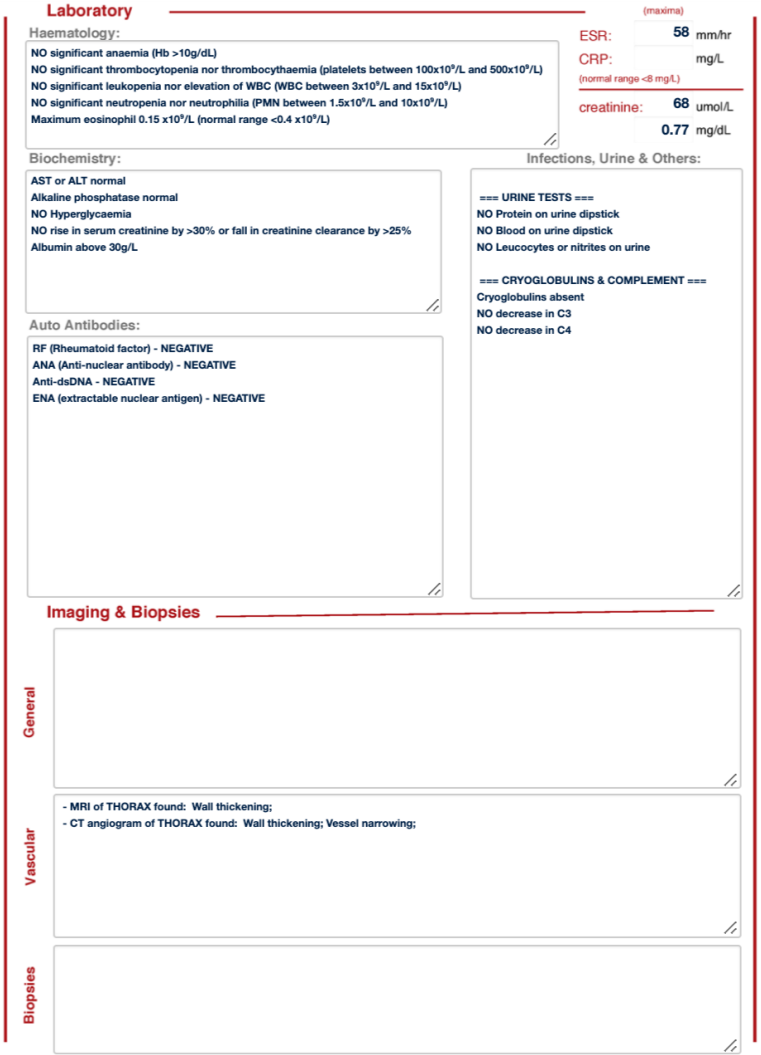
- Pericarditis confirmed by ECG and clinical findings

Vascular Examination

N Normal
B Bruit
T Tender
H Hard-corded
pDim Pulse Diminished
pAbs Pulse Absent

B

Right Left



Laboratory

Haematology:

NO significant anaemia (Hb >10g/dL)
NO significant thrombocytopenia nor thrombocythaemia (platelets between 100x10⁹/L and 500x10⁹/L)
NO significant leukopenia nor elevation of WBC (WBC between 3x10⁹/L and 15x10⁹/L)
NO significant neutropenia nor neutrophilia (PMN between 1.5x10⁹/L and 10x10⁹/L)
Maximum eosinophil 0.15 x10⁹/L (normal range <0.4 x10⁹/L)

(maxima)

ESR: 58 mm/hr

CRP: mg/L

(normal range <8 mg/L)

creatinine: 68 umol/L

0.77 mg/dL

Biochemistry:

AST or ALT normal
Alkaline phosphatase normal
NO Hyperglycaemia
NO rise in serum creatinine by >30% or fall in creatinine clearance by >25%
Albumin above 30g/L

Infections, Urine & Others:

=== URINE TESTS ===
NO Protein on urine dipstick
NO Blood on urine dipstick
NO Leucocytes or nitrites on urine

=== CRYOGLOBULINS & COMPLEMENT ===
Cryoglobulins absent
NO decrease in C3
NO decrease in C4

Auto Antibodies:

RF (Rheumatoid factor) - NEGATIVE
ANA (Anti-nuclear antibody) - NEGATIVE
Anti-dsDNA - NEGATIVE
ENA (extractable nuclear antigen) - NEGATIVE

Imaging & Biopsies

General

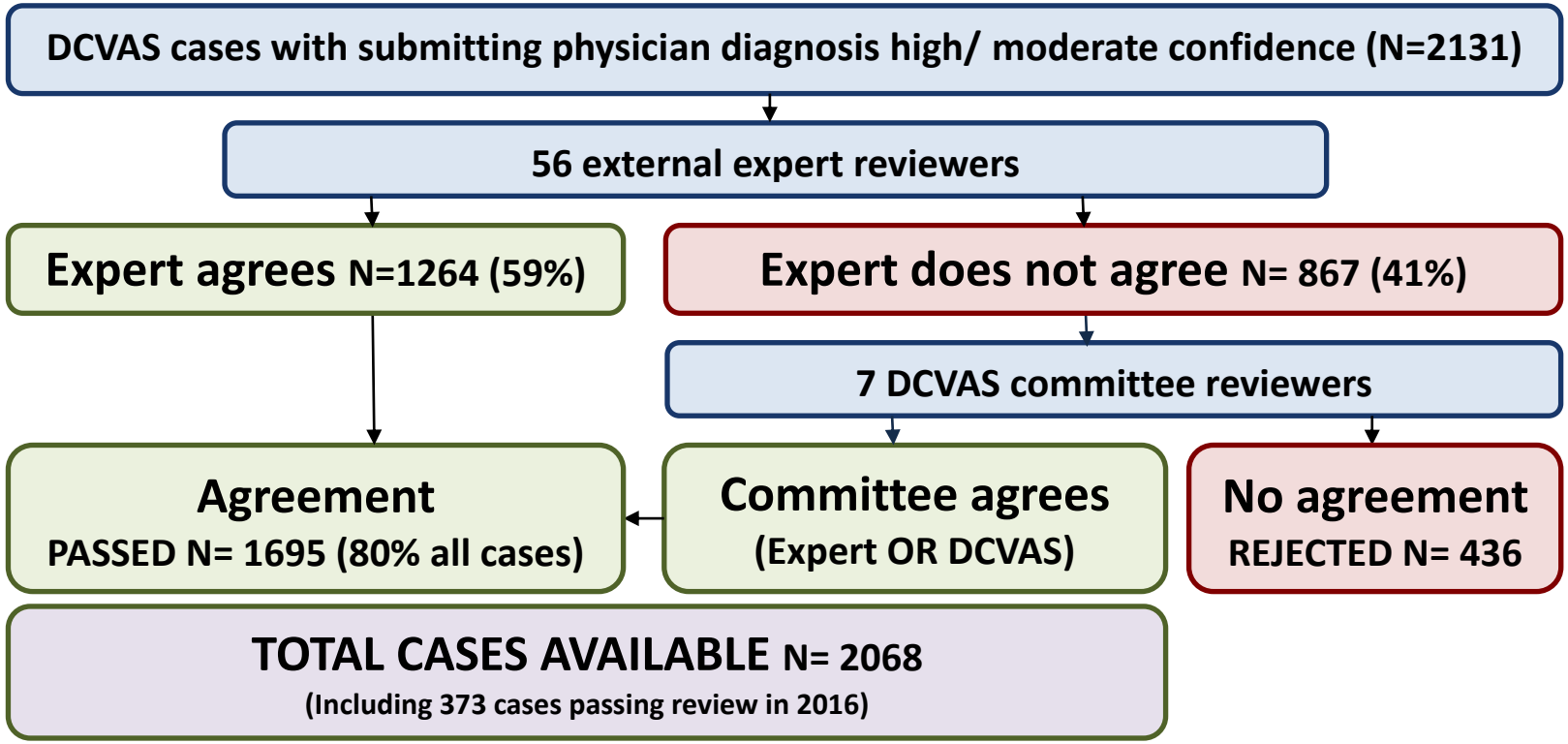
Vascular

- MRI of THORAX found: Wall thickening;
- CT angiogram of THORAX found: Wall thickening; Vessel narrowing;

Biopsies

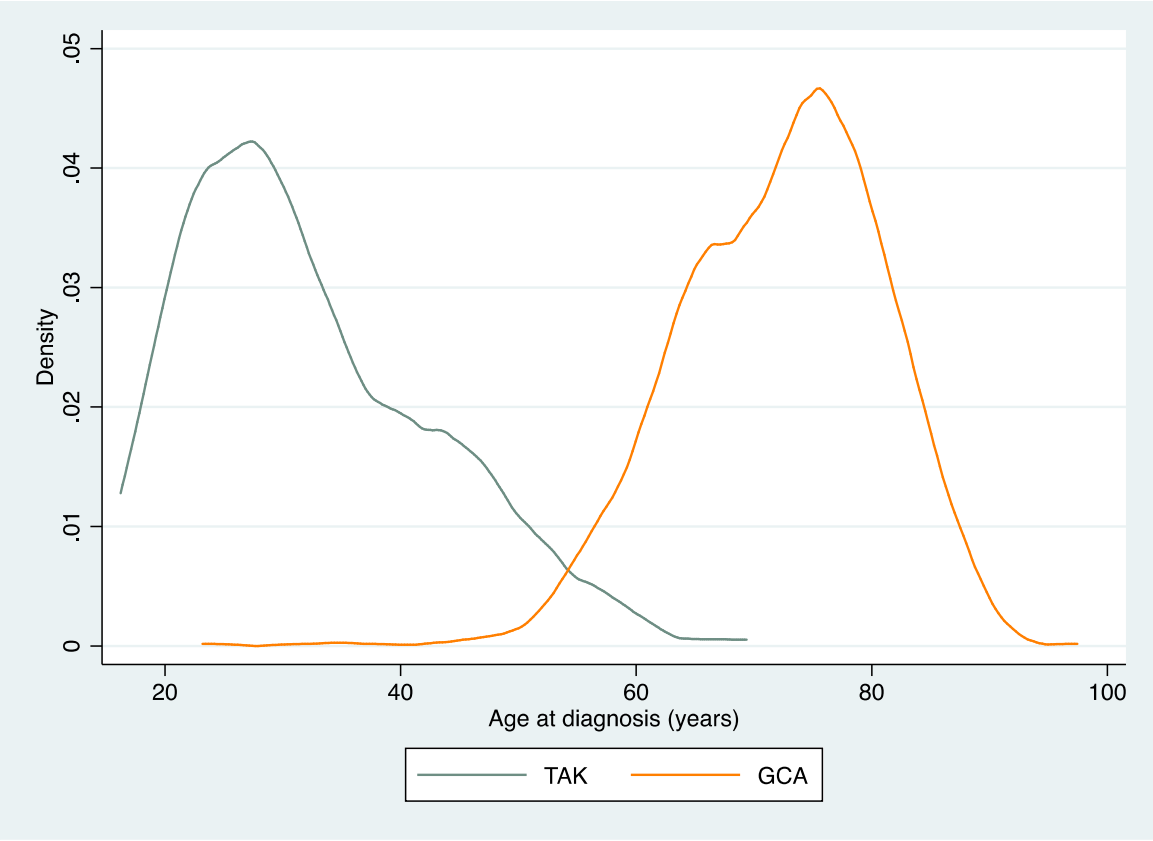
Supplementary Materials 9. Flow chart of expert review process to create the large-vessel vasculitis Diagnosis and Classification of Vasculitis Study dataset

Two expert panel reviews were conducted. In 2016, with the aim of deriving the classification criteria for ANCA-associated vasculitis, in which a total of 2871 cases were reviewed, and 2072 (72%) cases passed the process, including 174 (8.4%) cases of large-vessel vasculitis. In 2018, with the aim of deriving the classification criteria for large-vessel vasculitis, flow chart below:



Supplementary Materials 10. Age distribution in Takayasu arteritis and giant cell arteritis

10A. Graphic and table with distribution overlap in age at diagnosis for TAK and GCA

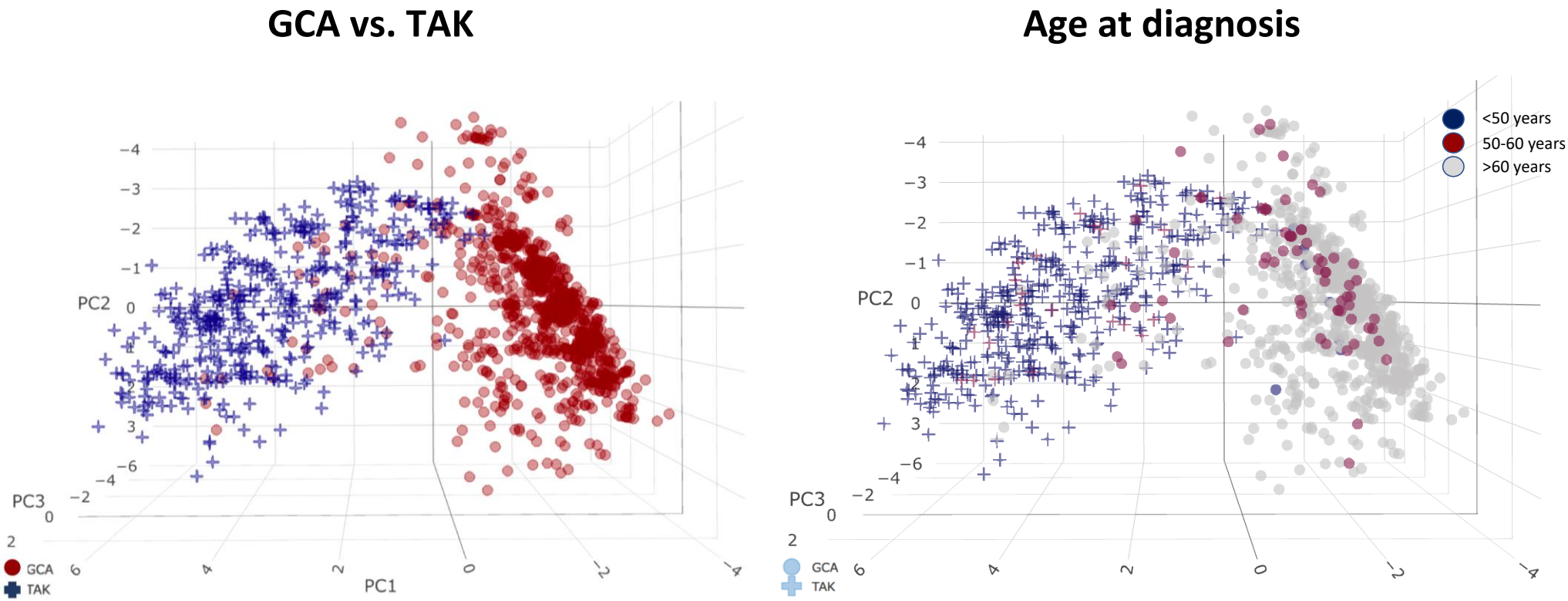


Age at diagnosis	TAK N=462	GCA* N=941	Total N=1404
< 40	355	3	358
40 to 49	78	4	82
50 to 59	26	70	96
≥ 60	3	864	867

GCA: giant cell arteritis; TAK: Takayasu arteritis

* Age at diagnosis missing for one patient with GCA

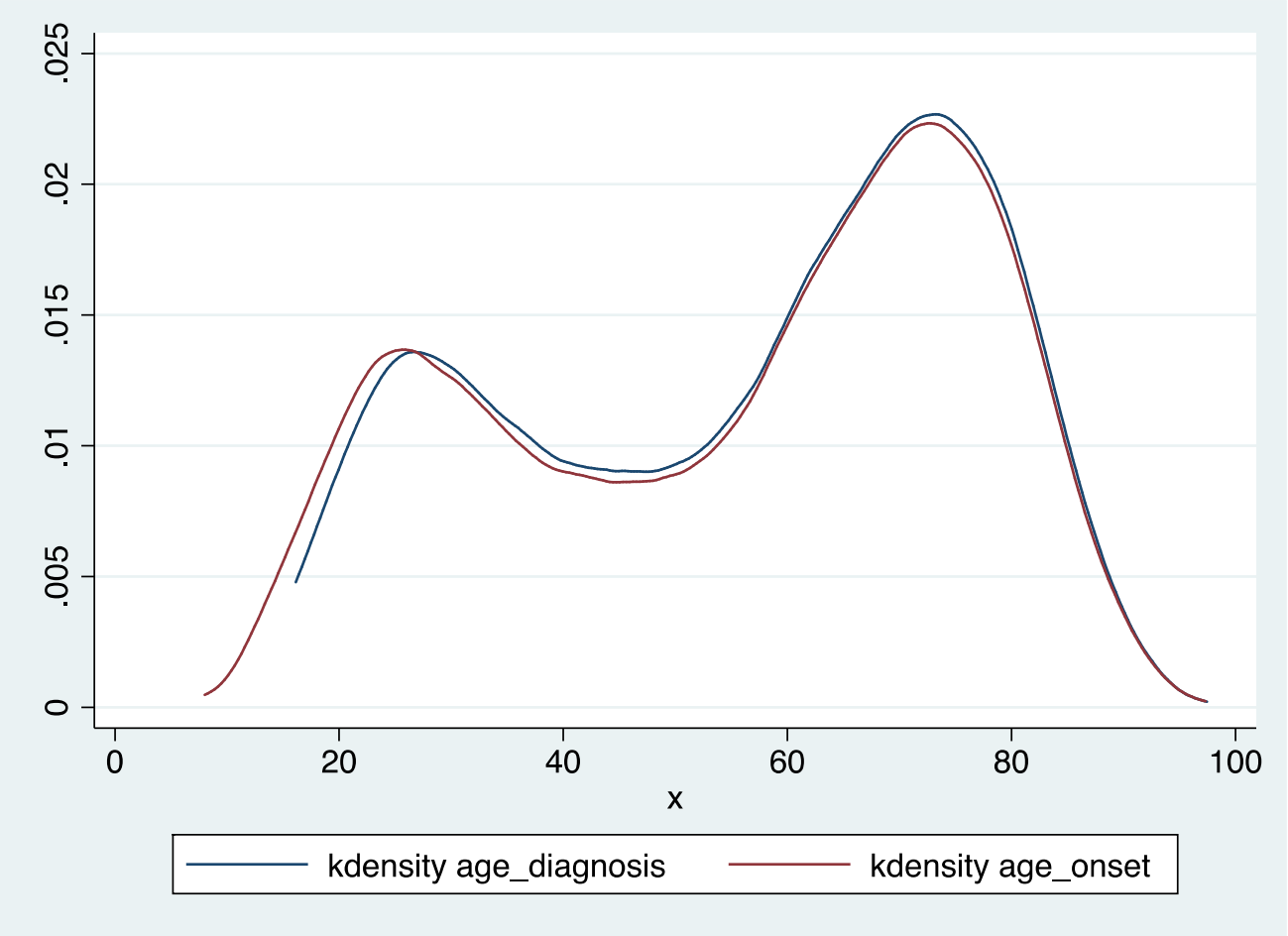
10B. Cluster distribution of giant cell arteritis vs. Takayasu arteritis and different categories of age at diagnosis



GCA: giant cell arteritis; TAK: Takayasu arteritis

An overlap between both graphics can be seen (≥ 60 years almost exclusive of GCA, and ≤ 50 years almost exclusive of TAK)

10C. Kernel density distribution plots for age at diagnosis and age at disease onset in patients with giant cell arteritis and Takayasu arteritis



The distribution plots show almost a perfect overlap between age at diagnosis and age at disease onset

Supplementary Materials 11. Frequency of damage (stenosis, occlusion, or aneurysm) in key arterial territories in TAK and LV-GCA

	TAK n = 462	LV-GCA n = 225	P value
Thoracic aorta	107 (23.2)	13 (5.8)	<0.0001
Abdominal aorta	116 (25.1)	7 (3.1)	<0.0001
Left carotid	198 (42.9)	22 (9.8)	<0.0001
Right carotid	163 (35.3)	23 (10.2)	<0.0001
Left subclavian	248 (53.7)	31 (13.8)	<0.0001
Right subclavian	173 (37.5)	26 (11.6)	<0.0001
Left renal	108 (23.4)	2 (0.9)	<0.0001
Right renal	102 (22.1)	2 (0.9)	<0.0001
Mesenteric	132 (28.6)	3 (1.33)	<0.0001
Left axillary	22 (4.8)	43 (19.1)	<0.0001
Right axillary	21 (4.6)	47 (20.9)	<0.0001

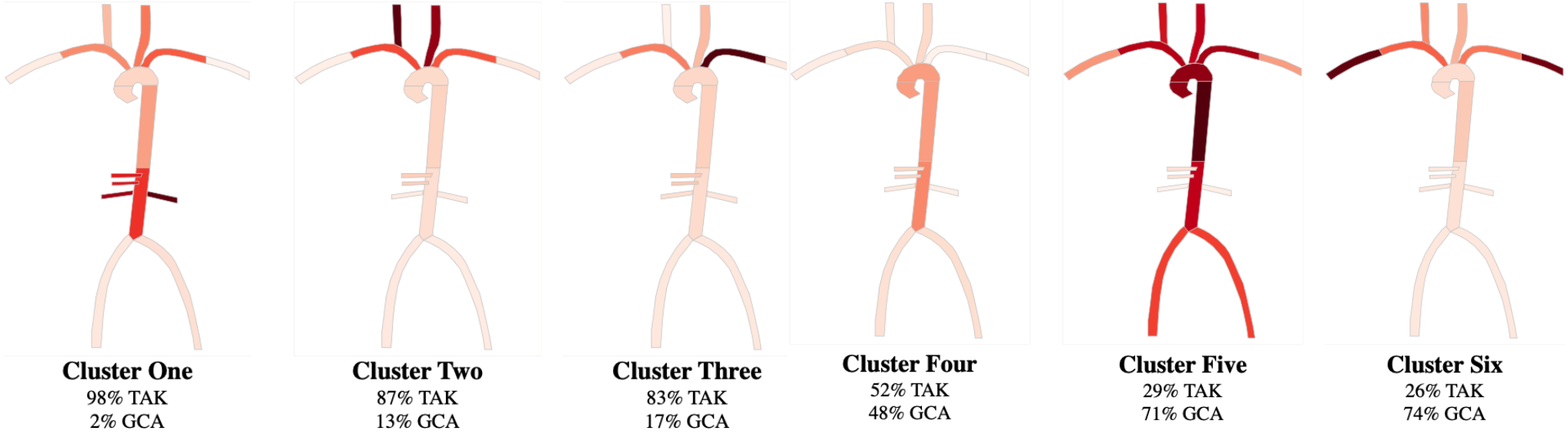
Mesenteric: celiac, superior, and inferior mesenteric arteries

LV-GCA: large-vessel giant cell arteritis defined as any vasculitic involvement of the large arteries assessed by ultrasonography, angiography, or positron emission tomography. Note that 225 patients with LV-GCA had damage in 219 arterial territories.

TAK: Takayasu arteritis

Supplementary Materials 12. Incorporation of unique imaging patterns

Unique imaging patterns of disease in Takayasu arteritis (TAK) and large-vessel giant cell arteritis (GCA) identified by K-means clustering



Cluster One - renal and mesenteric arteries, and abdominal aorta
Cluster Two - carotid and subclavian arteries
Cluster Three - left subclavian artery
Cluster Four - low burden of disease rather than a specific pattern of arterial involvement
Cluster Five - descending and abdominal aorta and subclavian and carotid arteries
Cluster Six - axillary and subclavian arteries.

Patients with TAK were more likely to have vasculitic manifestations on the abdominal aorta and renal or mesenteric arteries, bilateral disease involvement in paired branch arteries, and more damage by angiography (computed tomography, magnetic resonance, or catheter-based angiography) or ultrasonography, Patients with GCA were more likely to have diffuse FDG-PET activity throughout the aorta or bilateral axillary

Gribbons KB, et al. Patterns of Arterial Disease in Takayasu Arteritis and Giant Cell Arteritis. Arthritis Care Res (Hoboken). 2020 Nov;72(11):1615-1624.

Supplementary Materials 13. Final candidate items used within each regression analysis to derive classification criteria for giant cell arteritis and Takayasu arteritis

N refers to number of patients and % refers to percentage relative to the comparator group (i.e. frequencies of items higher than 50% indicate that they are more prevalent in patients with giant cell arteritis or Takayasu arteritis than in the comparator group) Significant differences between giant cell arteritis or Takayasu arteritis and the comparator group are noted as *p<0.05, **p<0.01.

Item	Description	Composite Items	GCA N= 756	TAK N=462
DEMOGRAPHIC				
Sex	Female		511 (53.3) **	391 (61.4) **
CLINICAL				
GenSym1	Light-headedness		57 (26.5) **	139 (70.9) **
GenSym2	Syncope / Fainting		14 (18.4) **	76 (80.9) **
GenSym4	Night sweats		208 (66.2) **	41 (33.9) **
GenSym5	Rigors		26 (49.1)	8 (36.4)
GenCF6	Fever ≥ 38ºC (≥ 100.4F)		137 (43.8) *	97 (49.7)
MskSym1	Arthralgia (Joint pain)		151 (39.6) **	98 (43.6) *
MskSym2	Morning stiffness ≥ 1 hour		124 (75.6) **	12 (22.6) **
MskSym6	Myalgia (muscle pain) or muscle cramps		214 (66.1) **	43 (35.5) **
MskCF2	Muscle tenderness		62 (64.6) **	8 (22.2) **
MskCF3	Muscle weakness		45 (55.6)	14 (40.0)
MskSym3	Morning stiffness neck/torso		88 (85.4) **	7 (21.9) **
MskSym4	Morning stiffness shoulders/ arms		174 (88.3) **	12 (22.6) **
MskSym5	Morning stiffness hips/ thighs		122 (89.1) **	3 (9.1) **
EyeSym1	Amaurosis fugax (transient / temp loss)		75 (78.1) **	21 (60.0)
EyeSym2	Sudden visual loss - ongoing		102 (77.9) **	4 (8.3) **
EyeSym3	Blurred vision in either eye		148 (57.1) *	30 (24.4) **
EyeSym6	Diplopia (double vision)		74 (80.4) **	5 (17.2) **
ENTSym1	Jaw claudication		356 (94.9) **	14 (15.4) **
ENTSym2	Tongue claudication		21 (95.5) **	1 (14.3)
CPSym1	Dyspnea / Shortness of Breath		46 (24.3) **	114 (67.9) **
CPSym2	Non-productive cough		57 (47.9)	24 (40.0)
CVSym1	Angina / ischemic cardiac pain		9 (22.0) **	56 (88.9) **
CVSym2	Arm claudication		29 (17.1) **	233 (95.5) **
CVSym3	Leg claudication		33 (34.4) **	88 (83.8) **
CVCF1	Any cardiac murmur		20 (33.9) *	42 (75.0) **
GISym2	Postprandial abdominal pain / ischemic abdominal pain		3 (12.0) **	14 (48.3)
NeurSym6	New persistent headache - frontal		169 (70.4) **	25 (26.6) **
NeurSym7	New persistent headache - occipital or cervical		161 (74.2) **	26 (32.5) **

NeurSym8	New persistent headache - temporal		475 (84.1) **	28 (17.4) **
NeurSym9	New persistent headache - other (please specify)		57 (54.3)	15 (27.8) **
NeurSym4	Scalp tenderness		260 (91.2) **	5 (6.4) **
LABORATORY				
TstHaem1	Significant anemia (hemoglobin < 10g/dL or 100g/L)		109 (47.6)	101 (60.5) **
TstHaem3	Significant thrombocythemia (platelets > 500 x 10^9/L)		141 (74.6) **	32 (38.6) *
TstHaem5	Significant elevation of WBC (total WBC > 15 x 10^9/L)		78 (50.7)	37 (43.5)
TstChem8	Albumin below 30g/L		102 (62.6) **	16 (25.0) **
TstChem1Dn	Maximum CRP:		**	**
	- ≤10 mg/L		73 (19.4)	185 (56.2)
	- 10 to 49 mg/L		234 (47.9)	179 (55.9)
	- 50 to 99 mg/L		207 (70.7)	63 (45.3)
	- 100 to 149 mg/L		119 (73.9)	23 (36.5)
	- ≥150 mg/L		123 (66.5)	12 (19.7)
TstHaem9Dn	Maximum ESR:		**	*
	- ≤10 mm/hr		19 (12.9)	45 (38.5)
	- 10 to 49 mm/hr		179 (35.2)	199 (55.6)
	- 50 to 74 mm/hr		198 (56.9)	115 (53.5)
	- 75 to 99 mm/hr		196 (70.8)	61 (47.3)
	- ≥100 mm/hr		164 (73.2)	42 (45.2)
VASCULAR EXAM				
	Any Bruit (carotid, subclavian, axillary, brachial, radial, renal, abdominal aorta, or iliofemoral)	Y	65 (28.9) **	263 (89.2) **
	Diminished or absent pulse of the lower limbs (femoral, popliteal, posterior tibial, or dorsalis pedis)	Y	61 (38.1) **	134 (80.7) **
	Diminished or absent pulse of upper limbs (axillary, brachial, or radial arteries)	Y	35 (16.0) **	309 (95.1) **
	Carotid abnormality (absent/diminished pulse, or tenderness/carotidynia)	Y	41 (29.9) **	171 (91.4) **
	Temporal artery abnormality (absent/diminished pulse, tenderness, or hard 'cord-like')	Y	354 (91.0) **	4 (5.1) **
	Absent upper extremity blood pressure:		**	**
	- No abnormality		753 (52.6)	351 (44.0)
	- Absent in one arm		3 (5.8)	80 (98.8)
	- Absent in both arms		0 (0.0)	31 (93.9)
	Difference in upper extremity blood pressure:		**	**
	- <10 mmHg		654 (53.4)	224 (36.1)
	- 10 to 20 mmHg		73 (58.9)	48 (56.5)
	- ≥20 mmHg		29 (18.5)	190 (92.2)
IMAGING				
	Abdominal aorta and renal/mesenteric (damage on angiography or US only)	Y	0 (0.0) **	83 (94.3) **
	Paired artery involvement of the carotid, subclavian, or renal arteries (damage on angiography or US only)	Y	13 (13.3) **	140 (92.1) **

	Number territories with damage on angiography or US (from nine possible territories: thoracic aorta, abdominal aorta, mesenteric, carotid, subclavian, or renal arteries):	Y	**	**
	- 0 territories	Y	698 (61.1)	22 (5.4)
	- 1 territory	Y	26 (24.1)	76 (67.9)
	- 2 territories	Y	24 (22.6)	114 (90.5)
	- 3 territories	Y	6 (10.9)	89 (94.7)
	- 4 territories	Y	2 (4.2)	80 (95.2)
	- 5 territories	Y	0 (0.0)	47 (95.9)
	- 6 territories	Y	0 (0.0)	20 (95.2)
	- 7 territories	Y	0 (0.0)	12 (92.3)
	- 8 territories	Y	0 (0.0)	1 (100.0)
	Temporal artery – US halo sign		211 (99.5) **	0 (0.0) **
	Bilateral axillary involvement (damage on angiography /damage or halo sign on US/ FDG uptake on PET)	Y	57 (82.6) **	12 (40.0)
	FDG-PET activity throughout the descending thoracic and abdominal aorta	Y	52 (85.3) **	6 (26.1) *
BIOPSY				
	Definitive vasculitis on temporal artery biopsy		335 (99.7) **	0 (0.0) **

CRP: C-reactive protein; ESR - erythrocyte sedimentation rate; FDG - fluorodeoxyglucose; GCA - giant cell arteritis; PET - positron emission tomography; US - ultrasound; TAK - Takayasu arteritis; WBC - white blood count

Damage on image: presence of stenosis, occlusion, or aneurysm

Angiography: computed tomography, magnetic resonance, or catheter-based angiography

Supplementary Materials 14: Mimics used to develop the giant cell arteritis and Takayasu arteritis criteria

Mimics used to develop the GCA criteria	N
Cardiovascular	**60**
Arterial dissection	4
Atheroembolic disease	5
Atherosclerosis	26
Fibromuscular dysplasia	2
IgG4-related arterial disease	1
Other vasculopathies	13
Relapsing polychondritis	3
Temporal artery aneurysm	2
Thromboangiitis obliterans (Buerger's disease)	2
Venous disease	2
Hematologic	**2**
Systemic amyloidosis	2
Infectious Disease	**35**
Bacterial endocarditis / bacteremia	13
Bacterial or viral pneumonia	9
Tuberculosis	13
Malignancy	**29**
Hematologic	15
Solid Malignancy	14
Neurologic	**62**
Central nervous system vasculopathy associated to hepatitis C	1
Cranial nerve lesion	7
Migraine or other headache syndromes	29
Multiple sclerosis	5
Myelopathy	1
Myopathy	1
Neurofibromatosis	1
Neuropathy not due to vasculitis	9
Reversible cerebral vasoconstriction syndrome	2
Stroke / transient ischemic attack	6
Non-primary vasculitis after panel review	**35**
Initially diagnosed as Behçet's disease	5
Initially diagnosed as GCA	18
Initially diagnosed as other LVV	1
Initially diagnosed as PAN	4
Initially diagnosed as primary vasculitis with no specific vessel size	3
Initially diagnosed as TAK	4
Ophthalmologic	**27**
Birdshot retinochoroidopathy	1
Central retinal / ophthalmic artery occlusion	2
Central retinal vein occlusion	2
Glaucoma	3
Non-arteritic anterior ischemic optic neuropathy	5
Optic neuritis	2
Other non-vasculitic vision loss	10
Uveitis	2
TOTAL	**250**

Mimics used to develop the TAK criteria	N
Cardiovascular	**39**
Arterial dissection	1
Atheroembolic disease	4
Atherosclerosis	19
Idiopathic retroperitoneal fibrosis (M. Ormond)	1
IgG4-related arterial disease	1
Other vasculopathies	9
Relapsing polychondritis	2
Temporal artery aneurysm	1
Venous disease	1
Hematologic	**1**
Systemic amyloidosis	1
Infectious Disease	**16**
Bacterial endocarditis / bacteremia	6
Bacterial or viral pneumonia	5
Tuberculosis	5
Malignancy	**23**
Hematologic	16
Solid Malignancy	7
Neurologic	**34**
Cranial nerve lesion	5
Migraine or other headache syndromes	14
Multiple sclerosis	2
Myopathy	2
Neurofibromatosis	1
Neuropathy not due to vasculitis	6
Reversible cerebral vasoconstriction syndrome	1
Sneddon's syndrome	1
Stroke / transient ischemic attack	2
Non-primary vasculitis after panel review	**22**
Initially diagnosed as Behçet's disease	4
Initially diagnosed as GCA	12
Initially diagnosed as other LVV	1
Initially diagnosed as PAN	2
Initially diagnosed as primary vasculitis with no specific vessel size	1
Initially diagnosed as TAK	2
Ophthalmologic	**15**
Birdshot retinochoroidopathy	1
Central retinal / ophthalmic artery occlusion	1
Glaucoma	2
Non-arteritic anterior ischemic optic neuropathy	2
Optic neuritis	2
Other non-vasculitic vision loss	5
Uveitis	2
TOTAL	**150**

GCA: giant cell arteritis, TAK: Takayasu arteritis; PAN: polyarteritis nodosa; LVV: large-vessel vasculitis

Supplementary Materials 15A. Results of regression analysis for giant cell arteritis

Predictor variables	Odds Ratio (95%CI)	P-value
CLINICAL		
Light-headedness	0.42 (0.19 - 0.92)	0.030
Syncope / Fainting	0.62 (0.20 - 1.90)	0.401
Night sweats	1.38 (0.78 - 2.46)	0.268
Fever ≥ 38ºC (≥ 100.4F)	0.58 (0.33 - 1.04)	0.068
Arthralgia	0.39 (0.22 - 0.68)	0.001
Myalgia or muscle cramps	2.27 (1.30 - 3.97)	0.004
Morning stiffness shoulders/ neck	8.96 (3.83 - 20.92)	<0.001
Sudden visual loss - ongoing	14.31 (5.67 - 36.11)	<0.001
Jaw or tongue claudication	13.83 (6.54 - 29.22)	<0.001
Dyspnea	0.60 (0.29 - 1.25)	0.173
Arm claudication	0.91 (0.34 - 2.44)	0.845
New persistent headache - occipital or cervical	2.63 (1.37 - 5.05)	0.004
New persistent headache - temporal	6.33 (3.80 - 10.55)	<0.001
New persistent headache - other	1.73 (0.76 - 3.95)	0.192
Scalp tenderness	5.33 (2.56 - 11.08)	<0.001
LABORATORY		
Significant thrombocythemia	3.01 (1.60 - 5.67)	0.001
Maximum ESR (>50 mm/hr) or maximum CRP (>10 mg/L)	13.46 (6.46 - 28.07)	<0.001
VASCULAR EXAM		
Diminished or absent pulse of upper limbs	0.57 (0.24 - 1.38)	0.213
Carotid absent/reduced pulse or tenderness	0.46 (0.16 - 1.31)	0.147
Temporal artery abnormality on vascular exam	3.71 (2.01 – 6.84)	<0.001
Difference in upper extremity blood pressure “10 – 20mgHg”	2.16 (0.97 – 4.80)	0.059
Difference in upper extremity blood pressure “≥20mmHg”	0.88 (0.35 – 2.23)	0.788
IMAGING		
Bilateral disease of the large vessels (angiography /US, without PET)	0.40 (0.13 – 1.23)	0.112
Bilateral axillary involvement (angiography /US/PET)	9.04 (3.08 – 26.52)	<0.001
Aorta Involvement on PET	8.84 (2.69 – 29.07)	<0.001

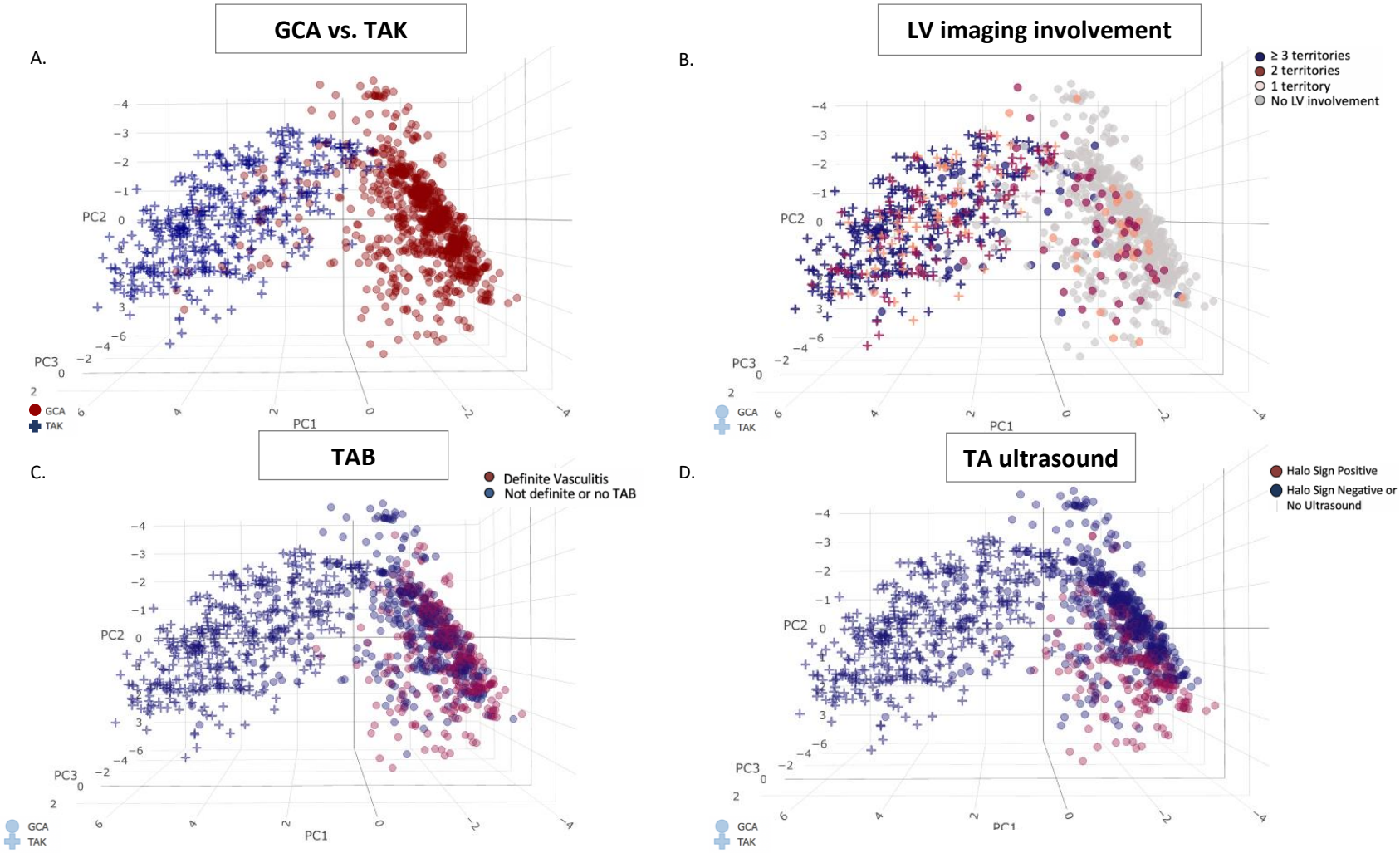
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PET: positron emission tomography; US: ultrasound
Angiography: computed tomography, magnetic resonance, or catheter-based angiography

Supplementary Materials 15B. Results of regression analysis for Takayasu arteritis

Predictor variables	Odds Ratio (95%CI)	P-value
CLINICAL		
Female sex	2.57 (1.31 – 5.05)	0.006
Arthralgia	0.67 (0.33 – 1.36)	0.267
Myalgia or muscle cramps	0.53 (0.21 – 1.36)	0.189
Vision (sudden vision loss, blurred vision, or diplopia)	0.20 (0.07 – 0.56)	0.002
Jaw or tongue claudication	0.15 (0.03 – 0.71)	0.017
Dyspnea	2.05 (0.90 – 4.67)	0.090
Angina / ischemic cardiac pain	6.22 (1.09 – 35.60)	0.040
Arm or leg claudication	6.53 (2.89 – 14.76)	<0.001
New persistent headache – temporal	1.23 (0.49 – 3.08)	0.655
Scalp tenderness	0.10 (0.01 – 0.72)	0.022
LABORATORY		
Albumin below 30g/L	0.27 (0.07 – 1.00)	0.050
Maximum ESR (>50 mm/hr) or maximum CRP (>10 mg/L)	2.26 (1.1 – 4.65)	0.027
VASCULAR EXAM		
Any Bruit (thorax or abdomen or limbs)	5.73 (2.66 – 12.32)	<0.001
Diminished or absent pulse of lower limbs	1.61 (0.66 – 3.90)	0.295
Diminished or absent pulse of upper limbs	5.32 (2.22 – 12.73)	<0.001
Carotid absent/reduced pulse or tenderness	7.02 (2.33 – 21.17)	0.001
Temporal artery abnormality on vascular exam	0.20 (0.03 – 1.23)	0.082
Difference in upper extremity blood pressure “10 – 20mgHg”	1.57 (0.60 – 4.06)	0.356
Difference in upper extremity blood pressure “≥20mmHg”	4.39 (1.47 – 13.08)	0.008
IMAGING		
Abdominal aorta and renal/mesenteric arteries (angiography /US, without PET)	14.29 (4.08 – 50.05)	<0.001
Bilateral disease of the large vessels (angiography /US, without PET)	2.02 (0.73 – 5.59)	0.175

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PET: positron emission tomography; US: ultrasound
Angiography: computed tomography, magnetic resonance, or catheter-based angiography

Supplementary Materials 16. Cluster distribution plots of giant cell arteritis vs. Takayasu arteritis, large-vessel involvement on imaging, temporal artery biopsy results and presence of halo sign on temporal artery ultrasound



There is an overlap between the diagnosis of TAK and the presence of higher number of LV territories involved in imaging (B). By contrast, there is an overlap between the diagnosis of GCA and the presence of definitive vasculitis on TA biopsy (C), and positive halo sign on TA ultrasound (D).

GCA: giant cell arteritis; LV: large vessel; TA: temporal artery; TAB: temporal artery biopsy; TAK: Takayasu arteritis.

Supplementary Table 17A. Data-driven and clinically-selected models for giant cell arteritis with associated risk scored based off beta coefficient weighting

Description	OR (95% CI)	Risk Score	P-value
*Vasculitis on TAB or TA halo on ultrasound **		5	
ESR ≥50 mm or CRP ≥10 mg/L	16.25 (7.96 – 33.17)	3	<0.001
Sudden visual loss	13.52 (5.72 – 31.96)	3	<0.001
Jaw or tongue claudication	11.24 (5.66 – 22.33)	2	<0.001
FDG-PET activity throughout aorta	8.97 (2.96 – 27.17)	2	<0.001
Bilateral axillary disease on imaging (angiography /US/PET)	8.75 (3.57 – 21.47)	2	<0.001
Morning stiffness in shoulders/neck	7.78 (3.61 – 16.76)	2	<0.001
New temporal headache	7.21 (4.54 – 11.46)	2	<0.001
Scalp tenderness	6.76 (3.35 – 13.64)	2	<0.001
TA abnormality on vascular exam[§]	5.33 (2.99 – 9.51)	2	<0.001

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FDG: fluorodeoxyglucose; OR: odds ratio; PET: positron emission tomography; TA: temporal artery; TAB: temporal artery biopsy; US: ultrasound

* Added after cluster analysis (Supplementary Materials 16)
§ Tenderness, hard 'cord-like', diminished or absent pulse

Supplementary Table 17B. Data-driven and clinically-selected models for Takayasu arteritis with associated risk scored based off beta coefficient weighting

Description	OR (95% CI)	Risk Score	P-value
Abdominal aorta and renal/mesenteric involvement (angiography /US)	23.06 (7.35 - 72.39)	3	<0.001
*Three or more affected arteries on imaging (angiography /US, without PET) **		3	
Diminished or absent pulse in upper extremity	7.89 (3.54 - 17.56)	2	<0.001
Arm or leg claudication	7.45 (3.74 - 14.81)	2	<0.001
Angina or ischemic cardiac pain	7.39 (1.80 - 30.31)	2	<0.001
Arterial bruit	5.09 (2.66 - 9.75)	2	<0.001
Carotid absent/reduced pulse or tenderness	4.65 (1.9 - 10.89)	2	<0.001
*Two affected arteries on imaging (angiography /US, without PET) **		2	
SBP difference in arms ≥ 20mmHg	3.56 (1.40 - 9.07)	1	0.008
Female sex	2.45 (1.34 - 4.49)	1	0.004
Imaging involvement of paired branch arteries (angiography /US, without PET)	2.36 (0.92 - 6.05)	1	0.074
*One affected artery on imaging (angiography /US, without PET) **		1	

SBP: systolic blood pressure; US: ultrasound

* Added after cluster analysis (Supplementary Materials 16)

Supplementary Materials 18A: Performance characteristics of a points-based risk score for giant cell arteritis with different thresholds (development dataset)

Threshold Score	Sensitivity (%)	Specificity (%)	AUC (95%CI)
3	98.84	72.76	0.86 (0.84-0.88)
4	95.37	88.99	0.92 (0.91-0.94)
5	95.17	90.49	0.93 (0.91-0.94)
6	84.75	94.96	0.90 (0.88-0.92)
7	83.59	96.83	0.90 (0.88-0.92)
8	75.48	99.07	0.87 (0.85-0.89)

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 losing too much 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 giant cell arteritis.

AUC: area under the curve; CI: confidence interval

Supplementary Materials 18B: Performance characteristics of a points-based risk score for Takayasu arteritis with different thresholds (development dataset)

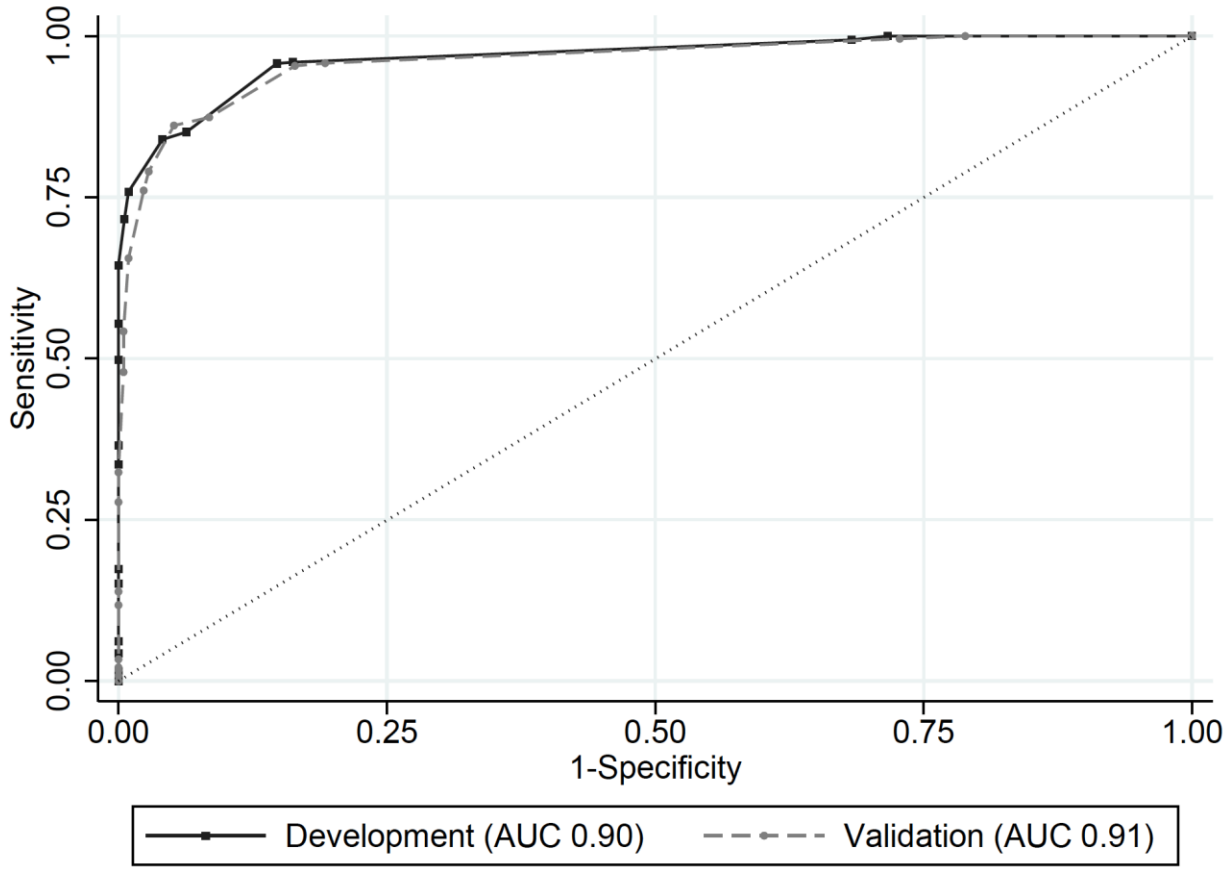
Threshold	Sensitivity (%)	Specificity (%)	AUC (95%CI)
2	97.47	93.19	0.95 (0.94-0.97)
3	96.20	94.74	0.95 (0.94-0.97)
4	93.35	96.28	0.95 (0.93-0.97)
5	89.87	96.59	0.93 (0.91-0.95)
6	85.44	98.45	0.92 (0.90-0.94)

A threshold score of ≥ 4 or ≥ 5 was considered equivalent to maximize specificity while retaining good sensitivity in the development dataset. In the validation dataset, the specificity for a cut-point of ≥ 5 remained greater than for a cut-point of ≥ 4 (99.2 vs 98.4%). Therefore, a cut-point of ≥ 5 was chosen to maximize specificity for the purpose of enrolling patients into clinical trials. 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 Takayasu arteritis.

AUC: area under the curve; CI: confidence interval

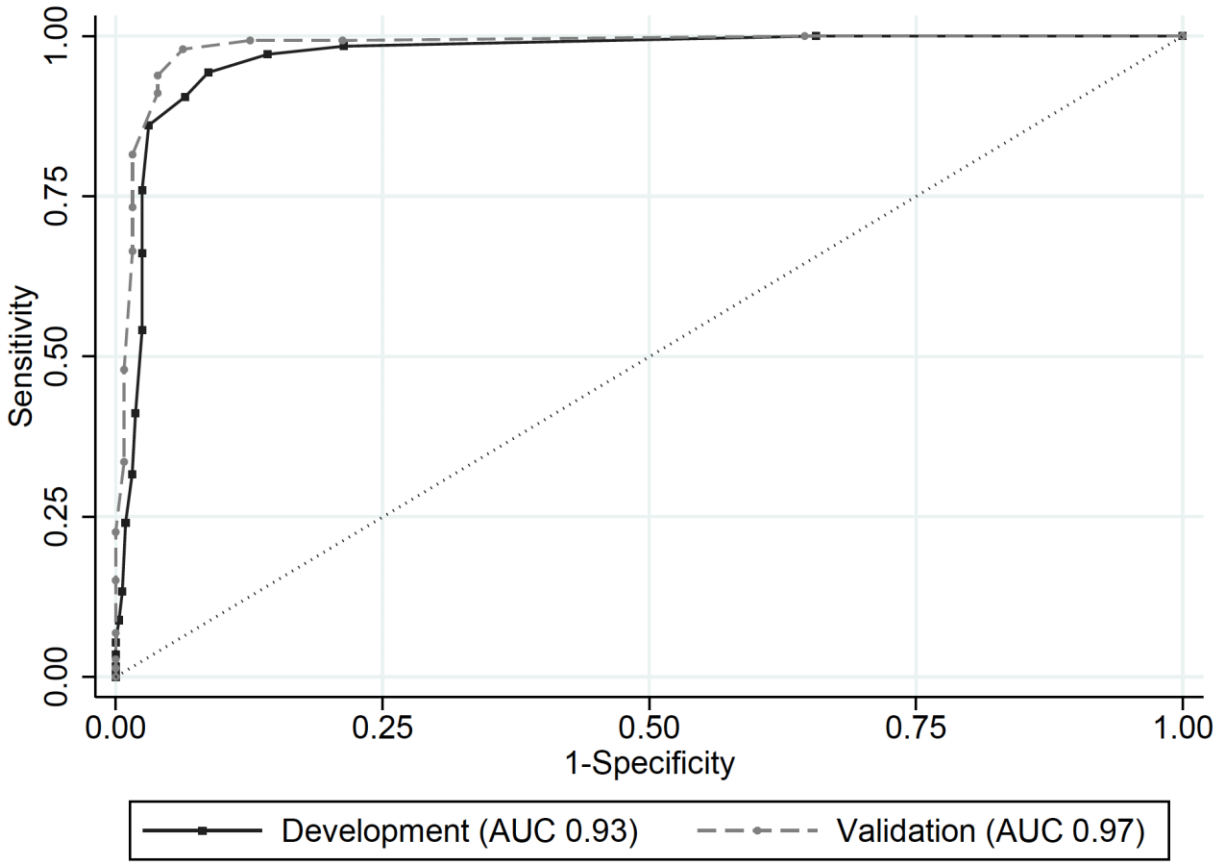
Supplementary Materials 19A. Discrimination curves for the classification criteria for giant cell arteritis

Classification criteria applied to 1,505 cases confirmed by Expert Review, 756 (50.2%) with giant cell arteritis and 749 (49.8%) comparators divided into a development dataset (70%) and validation dataset (30%). The Area Under Curve (AUC) for the development dataset is shown (solid line) and the AUC for the validation dataset is shown (dotted line).



Supplementary Materials 19B. Discrimination curves for the classification criteria for Takayasu arteritis

Classification criteria applied to 912 cases confirmed by Expert Review, 462 with Takayasu arteritis (50.7%) and 450 (49.3%) comparators divided into a development dataset (70%) and a validation dataset (30%). The Area Under Curve (AUC) for the development dataset is shown (solid line) and the AUC for the validation dataset is shown (dotted line).



Supplementary Materials 20A. Performance characteristics of the 2022 ACR-EULAR and the 1990 ACR classification criteria for giant cell arteritis in the complete DCVAS database (development and validation datasets)

		2022 ACR-EULAR classification criteria for GCA			1990 ACR classification criteria for GCA		
Subset of patients	**N total (N GCA)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**AUC (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**AUC (95% CI)**
GCA subtypes							
Biopsy-proven GCA	1104 (355)	100.0% (99.0-100.0%)	94.9% (93.1-96.4%)	0.97 (0.97-0.98)	93.0% (89.8-95.4%)	92.8% (90.7-94.5%)	0.93 (0.91-0.94)
Large-vessel GCA	873 (124)	55.7% (46.5-64.6%)	94.9% (93.1-96.4%)	0.75 (0.71-0.80)	37.1% (28.6-46.2%)	92.8% (90.7-94.5%)	0.65 (0.61-0.69)
World regions							
North America	226 (90)	77.8% (67.8-85.9%)	95.6% (90.6-98.4%)	0.87 (0.82-0.91)	70.0% (59.4-79.2%)	91.9% (86.0-95.9%)	0.81 (0.76-0.86)
Europe	973 (642)	87.2% (84.4-89.7%)	88.8% (84.9-92.0%)	0.88 (0.86-0.90)	81.0% (77.7-84.0%)	88.2% (84.3-91.5%)	0.85 (0.82-0.87)

ACR: American College of Rheumatology; AUC: Area under the curve; CI: Confidence interval; EULAR: European Alliance of Associations for Rheumatology; GCA: giant cell arteritis.

GCA subtypes: biopsy-proven GCA (definite vasculitis on TAB) and large-vessel GCA (involvement of the aorta or its branch arteries on either angiography [computed tomography, magnetic resonance, or catheter-based angiography], ultrasound or PET, without vasculitis on TAB)

N total (N GCA): N of total cases used in the model (number of GCA cases); for the world region analysis all the available cases and comparators were selected for each region.

Supplementary Materials 20B. Performance Characteristics of the 2022 ACR-EULAR and the 1990 ACR Criteria for Takayasu arteritis in the complete DCVAS database (development and validation datasets)

		2022 ACR-EULAR classification criteria for TAK			1990 ACR classification criteria for TAK		
Subset of patients	**N total (N TAK)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**AUC (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**AUC (95% CI)**
Age intervals							
Age 18–39 years	437 (351)	94.0% (91.0-96.3%)	97.7% (91.9-99.7%)	0.96 (0.94-0.98)	89.2% (85.4-92.2%)	97.7% (91.9-99.7%)	0.93 (0.91-0.96)
Age 40–60 years	226 (104)	83.7% (75.1-90.2%)	91.8% (85.4-96.0%)	0.88 (0.83-0.92)	62.5% (52.5-71.8%)	96.7% (91.8-99.1%)	0.80 (0.75-0.93)
World regions							
North America	127 (28)	85.7% (67.3-96.0%)	92.9% (86.0-97.1%)	0.89 (0.82-0.96)	85.7% (67.3-96.0%)	93.94% (87.3-97.7%)	0.90 (0.83-0.97)
Europe	422 (130)	91.5% (85.4-95.7%)	94.9% (91.7-97.1%)	0.93 (0.90-0.96)	80.8% (72.9-87.2%)	98.63% (96.5-99.6%)	0.90 (0.86-0.93)
North America/Europe	549 (158)	90.5% (84.8-94.6%)	94.4% (91.6-96.4%)	0.92 (0.90-0.95)	81.7% (67.3-96.0%)	97.44% (95.4-98.8%)	0.90 (0.86-0.97)
Asia	357 (298)	92.0% (88.3-94.8%)	93.2% (83.5-98.1%)	0.94 (0.89-0.96)	83.9% (79.3-87.4%)	96.61% (88.3-99.6%)	0.90 (0.87-0.93)

ACR: American College of Rheumatology; AUC: Area under the curve; CI: Confidence interval; EULAR: European Alliance of Associations for Rheumatology; TAK: Takayasu arteritis

N total (N TAK): N of total cases used in the model (number of TAK cases); for the world region analysis all the available cases and comparators were selected for each region.

Supplementary Materials 21. Age in the new classification criteria – the 50-60 years interval

In all the DCVAS dataset there were 1451 patients diagnosed with large vessel vasculitis (942 GCA and 509 TAK) after expert panel review. A total of 96/1451 patients (6.6%) were aged between 50 and 60 years, 26/96 (27.1%) with the diagnosis of TAK and 70/96 (72.9%) with the diagnosis of GCA.

Patients with Large-Vessel Vasculitis Diagnosed Between 50-60 Years of Age			
Takayasu arteritis (n=26)		**Giant cell arteritis (n=70)**	
Patients who meet the TAK criteria	23 (88.5%)	Patients who meet the GCA criteria	44 (62.9%)
Patients who meet the GCA criteria	1 (3.9%)	Patients who meet the TAK criteria	9 (12.9%)
Patients who meet both TAK and GCA criteria	1 (3.9%)	Patients who meet both GCA and TAK criteria	2 (2.9%)

GCA: giant cell arteritis; TAK: Takayasu arteritis

In this age interval only 3/96 (3.1%) patients fulfilled both TAK and GCA 2022 ACR-EULAR classification criteria.