

Reappraisal of the 1990 American College of Rheumatology classification criteria for systemic vasculitis – Analysis of data from the Diagnostic & Classification Criteria in Vasculitis Study (DCVAS)

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ABSTRACT

Objectives. Advances in diagnostic techniques have led to better distinction between types of vasculitis, potentially affecting the utility of the 1990 American College of Rheumatology (ACR) classification criteria for vasculitis. This study tested the performance of these criteria in a contemporary vasculitis cohort.

Methods. The Diagnosis and Classification in Vasculitis Study provided detailed clinical, serological, pathological, and radiological data from patients with primary systemic vasculitis (PSV) and clinical context-specific comparator conditions. Fulfilment of six ACR criteria sets and their diagnostic performance was evaluated in patients with a given type of vasculitis and its comparator condition.

Results. Data from 1095 patients with PSV and 415 with comparator conditions were available. For classification, sensitivities and specificities for ACR classification criteria were 81.1% and 94.9% for giant cell arteritis; 73.6% and 98.3% for Takayasu's arteritis; 65.6% and 88.7% for granulomatosis with polyangiitis; 57.0% and 99.8% for eosinophilic granulomatosis with polyangiitis; 40.6% and 87.8% for polyarteritis nodosa; 28.9% and 88.5% for microscopic polyangiitis; and 72.7% and 96.3% for IgA-vasculitis. Overall sensitivity was 67.1%. 16.9% of cases identified by their respective criteria also met criteria for other vasculitides. Diagnostic specificity ranged from 64.2 to 98.9%; overall, 113/415 comparators (27.2%) fulfilled at least one of the ACR classification criteria sets.

Conclusions. Since publication of the ACR criteria for vasculitis, the sensitivity for each type of vasculitis, except giant cell arteritis, has diminished, although the specificities have remained high, highlighting the need for updated classification criteria.

INTRODUCTION

In 1990, the American College of Rheumatology (ACR) published criteria for the classification of seven types of systemic vasculitis: giant cell arteritis (GCA), Takayasu's arteritis (TAK), eosinophilic granulomatosis with polyangiitis (Churg-Strauss, EGPA), granulomatosis with polyangiitis (Wegener's, GPA), polyarteritis nodosa (PAN), IgA vasculitis (Henoch-Schönlein, IgAV) and hypersensitivity vasculitis [1].

Although the 1990 ACR Classification Criteria have been widely applied in clinical studies and facilitated research in vasculitis, they also have important limitations [2]. Firstly, microscopic polyangiitis (MPA) was not one of the named conditions because it was not a widely recognised condition in the 1980s. Secondly, the criteria were developed before the widespread use of testing for anti-neutrophil cytoplasm antibodies (ANCA) which has since become a fundamental aspect in the diagnosis and classification of ANCA-associated vasculitis (AAV) [3]. Thirdly, introduction and widespread use of new diagnostic techniques (e.g. computerised tomography and magnetic resonance imaging) have contributed to a better distinction between different types of vasculitis [4, 5]. Although their suboptimal performance in classification of vasculitides has been previously documented in several studies [6–9], they are still used in clinical research. Furthermore, many clinicians apply the ACR criteria in clinical practice for diagnosis, although these criteria were not designed for this purpose and are inadequate as diagnostic tools [10]. We aimed to test whether the 1990 ACR classification criteria would perform similarly in a large international and more heterogeneous cohort of vasculitis patients recruited to the "Diagnosis and Classification of Vasculitis Study" (DCVAS), a major international research initiative to develop a revised single classification system and a validated set of diagnostic criteria for the vasculitides.

This analysis tested the performance of six of the 1990 ACR classification criteria for vasculitis for use in both classification (original intent) and diagnosis of patients with vasculitis and comparator conditions enrolled in the DCVAS.

METHODS

Patients and inclusion criteria

The data source was the DCVAS project, a prospective multi-centre study to develop diagnostic and classification criteria in vasculitis [10], and included all patients recruited between September 2010 and June 2014. The dataset has detailed clinical, serological, pathological, and radiological data from patients with primary systemic vasculitis (PSV) and patients with clinical context-specific comparator conditions. The detailed methodology of the DCVAS study has been described elsewhere [11]. The physicians submitting cases were asked to confirm their opinion on the diagnosis and their level of diagnostic certainty (very certain, $\geq 75\%$; moderately certain, 50-74%; uncertain, 25-49%; very uncertain, $< 25\%$) for each patient. Included in this analysis was data from patients with a baseline diagnosis of any PSV with a recorded confidence in diagnosis of $\geq 75\%$ by the submitting clinician, as well as patients with conditions considered to be comparators for GCA, TAK, AAV, PAN and IgAV (definitions shown in supplementary Table S1, available at *Rheumatology* online). Patients who had a change of diagnosis at the six months follow-up, and patients with GPA or MPA without either a positive ANCA test or a biopsy were excluded from the analysis, because certainty of the initial diagnosis was deemed insufficient.

Analysis

The presence of each individual ACR criterion was evaluated in each case of PSV. The 1990 ACR classification criteria were considered fulfilled if the specified number of features for each criteria set was met (e.g. 3 out of 5 for GCA). The definitions for each criterion are shown in supplementary Table S2, available at *Rheumatology* online. Criteria involving imaging data were considered present based on either the originally described methods (e.g. conventional angiography) or by using current comparable methods (magnetic resonance angiography or computerized tomography angiography). Missing information was considered absent.

Each of the six sets of the 1990 ACR criteria was tested against all patients with PSV in the DCVAS cohort (including patients with other types of vasculitis not covered by the ACR criteria) to assess the sensitivity and specificity of the criteria for classification of GCA, TAK, GPA, EGPA, PAN, and IgAV. The ACR criteria for hypersensitivity vasculitis were not assessed due to low patient numbers (n=9); these patients were included as patients with other forms of PSV. Diagnostic specificity was evaluated by applying the respective criteria sets to patients with each given type of vasculitis and their comparators. (e.g. all patients with GCA plus GCA-comparators). Physician-submitted diagnosis was considered to be the gold standard. Because there was no distinction between PAN and MPA in the original ACR criteria, the ACR PAN criteria were used for both PAN and MPA in the DCVAS cohort, although we fully appreciate that this is a somewhat academic exercise.

RESULTS

Patients and diagnostic workup

Data from 2116 patients (1570 with PSV; 564 with comparator conditions) from 85 centres worldwide were available (Figure 1). Six-hundred-six patients (475 with PSV; 131 with comparator conditions) were excluded. In total, 1095 patients with a physician-submitted diagnosis of PSV were included in the analysis; 944 of these patients had one of the diagnoses for which ACR classification criteria are available, 151 had other types of PSV (supplementary Table S5, available at *Rheumatology* online). These 1095 patients were used to assess the criteria performance for *classification*. Four hundred and fifteen patients who did not have vasculitis were included in the analysis as comparators to assess diagnostic performance of the criteria; 38.3% of the comparator cases were included in more than one comparator group. An overview of clinical conditions in the comparator patients is shown in supplementary Table S3 available at *Rheumatology* online. .

The number of imaging procedures, biopsies, and tests for ANCA, with the average number of investigations performed by contributing centres in the main vasculitis categories, are presented in Table 3. In 60 (5.5%) patients with PSV and 22 (5.3%) comparators, neither an imaging study, nor a biopsy had been performed; in 21 (1.1%) and 5 (1.2%) data was missing in these categories, respectively.

Performance of the criteria for classification

The performance of the individual 1990 ACR classification criteria for sensitivity and specificity within the DCVAS cohort is shown in Table 1. For classification, the sensitivity of the 1990 ACR criteria ranged from 81.1% for GCA to 28.9% for MPA and the specificity ranged from 99.8% for EGPA to 88.5% in MPA (using the PAN criteria).

The sensitivity of the criteria for GPA and EGPA improved when a positive ANCA was considered as a surrogate for a positive biopsy: GPA: 90.5 [CI: 86.5 – 93.7]; EGPA: 68.4 [CI: 56.9 – 78.4]. Specificity

remained high in EGPA (98.3 [CI: 97.3 – 99.0]), but was reduced in GPA (68.4 [CI: 56.9 – 78.4]). Applying solely positive PR3-ANCA as biopsy surrogate for GPA yielded a sensitivity of 89.1% [CI: 84.8 – 92.5] and a specificity of 85.1% [CI: 82.5 – 87.5].

There was substantial heterogeneity in sensitivity and specificity across centres for most of the diagnoses, however the number of cases with certain PSV was quite low in some centres (Supplementary Table S5, available at *Rheumatology* online).

Overall performance of the criteria

Overall, 633 of 944 patients with one of the forms of vasculitis covered by the ACR criteria were captured by the ACR classification criteria (sensitivity 67.1 %). 267 of all 1095 patients with PSV (24.4%) fulfilled criteria for at least one condition other than their physician-submitted diagnosis, including 107 of 633 patients (16.9%) who were correctly captured by ACR criteria. Overall accuracy and overlap of the application of the 1990 ACR criteria is illustrated by Figure 2.

Diagnostic performance of the criteria

When applied as diagnostic criteria, i.e. to patients with a given type of vasculitis and its disease context comparators, the specificity of the ACR criteria ranged from 64.2% in GCA to 98.9% in EGPA (Table 1); overall 113 of 415 (27.2%) patients with vasculitis comparator conditions fulfilled one of the ACR classification criteria sets.

Differences between patients captured and patients not captured by the criteria

Table 2 and supplementary Table S4, available at *Rheumatology* online, compare the demographic characteristics, disease manifestations, and fulfilment of individual ACR criteria in patients with physician-submitted diagnosis concordant with 1990 ACR criteria or not (“correctly” vs “not correctly” classified). Compared to patients “correctly” classified per ACR criteria (true positives), patients who were “not correctly” classified (false negatives) had fewer of each ACR criteria (online supplementary Table S4). However, in terms of non-criteria characteristics (table 2.), the percentage

of positive ANCA tests in both groups of patients with AAV were comparably high (87.4% vs 87.8%; $p=0.984$). Similarly, the groups did not differ in terms of positive biopsy results (70.5% vs 71.2%; $p=0.881$), when less stringent than ACR biopsy definitions were applied (“biopsy consistent with vasculitis but not definite” or “definite vasculitis”). In contrast, only 5.5% of patients with GPA or EGPA not captured by the criteria met the corresponding original ACR biopsy definitions. Patients with large vessel vasculitis (GCA or TAK) who were “not correctly” classified were more likely to have abnormal findings on angiography and positron emission tomography scans.

DISCUSSION

This analysis demonstrates that the sensitivity of the 1990 ACR classification criteria has declined substantially over the last two decades. Overall, one-third of patients who had a physician-submitted diagnosis consistent with one of the types of vasculitis covered by the ACR criteria were not correctly classified by using the criteria. This was most striking with GPA and EGPA and may reflect improved recognition of a wider spectrum of disease and greater reliance on novel diagnostic tests, especially due to routine testing for ANCA [12]. ANCA testing is especially helpful in the diagnosis of GPA and MPA, adds to the specificity for EGPA, and their presence helps rule out PAN [5].

Individual ACR criteria items were less frequently fulfilled in those cases with PSV who were not classified in agreement with the physician's diagnosis than in cases who were correctly classified. While this is an expected finding, it likely reflects the greater reliance on diagnostic tools not covered by the ACR criteria. Furthermore, that results of ANCA tests, modern imaging modalities, and biopsies, with less stringent definitions applied, were positive in majority of patients not captured by the ACR criteria. Thus, the stringency of the definitions for biopsy positivity and lack of inclusion of modern imaging tools and ANCA in the criteria may have had a large impact on the sensitivity of the ACR criteria. Indeed, sensitivity of the criteria for GPA improved when proteinase-3 ANCA was used as a surrogate for ACR biopsy criterion with almost no loss of specificity. Newer diagnostic tools may have enabled an expansion of the clinical phenotype described within disease subtypes and broadened the appreciation of overlap between diseases, including the spectrum of large vessel disease, and the overlap between classification of patients with small vessel vasculitis and PAN [10, 13, 14]. This expansion of the spectrum of disease can reduce sensitivity of classification criteria as shown in this study.

The sensitivity for PAN of 40.6% was particularly low compared to the originally reported 82.2%.

Since the 1990 ACR criteria for PAN were derived from combined cohort of patients with PAN and MPA, we wished to explore how these criteria performed in a cohort of patients with PAN compared

to patients with MPA. Results from these analyses highlight that the PAN criteria have poor sensitivity not only for MPA (28.9%), which is perhaps not surprising, but also for PAN (40.6%). The predominance of non-HBV related PAN in our cohort (84.4%) could be one of the reasons for the low sensitivity of the criteria for this entity. However, poor performance of the ACR PAN criteria was previously reported with a sensitivity of 50.8%, when compared with other vasculitides as controls [15]. It is also interesting that specificity of the 1990 PAN classification criteria is similar for PAN and MPA (87.8 vs 88.5%). These comparative analyses highlight that the 1990 criteria for PAN are not fit for purpose to classify either patients with MPA and PAN. Furthermore, the lack of MPA recognition by 1990 ACR criteria may have affected not only performance of the PAN criteria, but also the criteria for the other small vessel vasculitides.

The specificity of the ACR criteria for classification of most of the vasculitides within the DCVAS cohort was comparable with the original reports on the performance of the criteria. However, application of the criteria to the whole vasculitis cohort resulted in considerable overlap between types of AAV and PAN (Figure 2), which may have a negative impact on the criteria's accuracy in classifying patients enrolled into clinical studies and trials [13]. It is important that the high specificity for classification is also derived from the analogous approach to the original ACR criteria development: Each criteria set was applied to all patients with PSV. With a total of 1095 patients in this study, among many had large-vessel disease, the overall specificity for EPGA is likely to be high. Their unsuitability to distinguish between the more similar forms of PSV is demonstrated by their considerable overlap amongst these diagnoses (Figure 2).

When the ACR criteria were applied to comparator patients (i.e. those without vasculitis), over a quarter of patients met at least one ACR criteria set, highlighting that the 1990 ACR classification criteria are not well suited for diagnostic use, as demonstrated previously [10]. The individual diagnostic specificity was however high for each individual criteria set. Since many of the patients

included in the comparator groups did not have multisystem disease and hypereosinophilic disorders were rare, this may account for the particular high specificity e.g. for EGPA.

This study has some limitations to consider. Firstly, DCVAS was collecting data only up to the time of diagnosis. Some potentially relevant data for the criteria like biopsy results could have been available only after the date of diagnosis. However, we formally asked investigators to report any change in diagnosis which might have occurred as a result of new information becoming available during the six months after the initial diagnosis. In contrast, for some patients in the original 1990 ACR cohort, autopsy data was included in the analysis [16]. The lower sensitivity found in the present analysis might thus be anticipated, however, over 70% of patients with AAV had a biopsy performed with the result available at the time of study enrolment. Furthermore, patients who were captured by the criteria did not differ in terms of available biopsy results from patients who were not. This makes a significant impact on sensitivity less likely, although in some cases diagnosis could be made based on clinical presentation and ANCA alone without biopsy results, hence highlighting the need for future incorporation of these tests. Secondly, the use of the clinical diagnosis submitted by the recruiting physician as the gold standard could lead to circularity in attempts to classify patients.

Thirdly, centres may differ in their diagnostic approach, potentially leading to considerable heterogeneity in the criteria's performance between centres. The validity of these findings, however, is augmented by the testing of the criteria in the largest and most heterogeneous cohort of patients with vasculitis recruited and the large number of specialised vasculitis centres worldwide participating in the study, the setting for which the 1990 ACR classification criteria were designed to be used.

In conclusion, the results of this study emphasise the need for updated classification and diagnostic criteria for the systemic vasculitides that incorporate newer diagnostic modalities and potentially redefine the boundaries between the individual diseases.

Key Messages:

- **At diagnosis, the sensitivity of the 1990 ACR Criteria for the vasculitides was low (67.1%).**
- **There is a need for diagnostic criteria - as none exist, and the ACR criteria perform poorly if they are used as such. There is a need for updated classification and diagnostic criteria for vasculitis that include MPA and incorporate some widely available tests.**

Conflict of interest statement:

BS, JS, JCR, AC, PCG, RS, RAW: None

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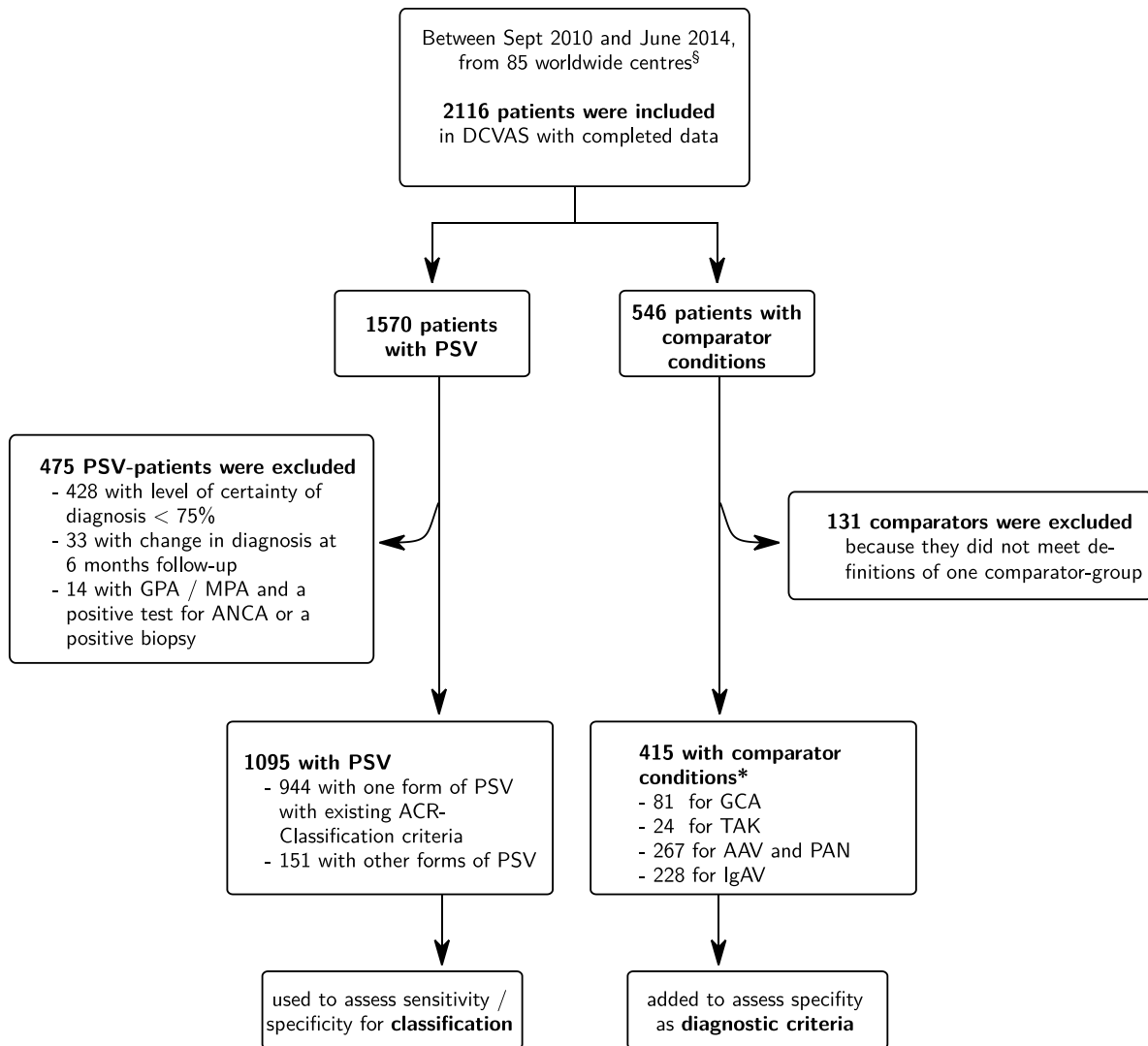


Figure 1: Study population.

* Some comparator patients were used for more than one comparator group.

§ The study was promoted at international conferences; all centres willing to participate were invited to take part in the study. At the time of this analysis data had been collected in rheumatology, renal, internal medicine, immunology and neurology centres in a total of 31 countries in Asia, Australasia, Europe, North America, and South America.

DCVAS: Diagnostic & Classification in Vasculitis Study; PSV: primary systemic vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ACR: American College of Rheumatology; GCA: giant cell arteritis; TAK: Takayasu's arteritis; AAV: ANCA-associated vasculitis, IgAV: IgA-vasculitis.

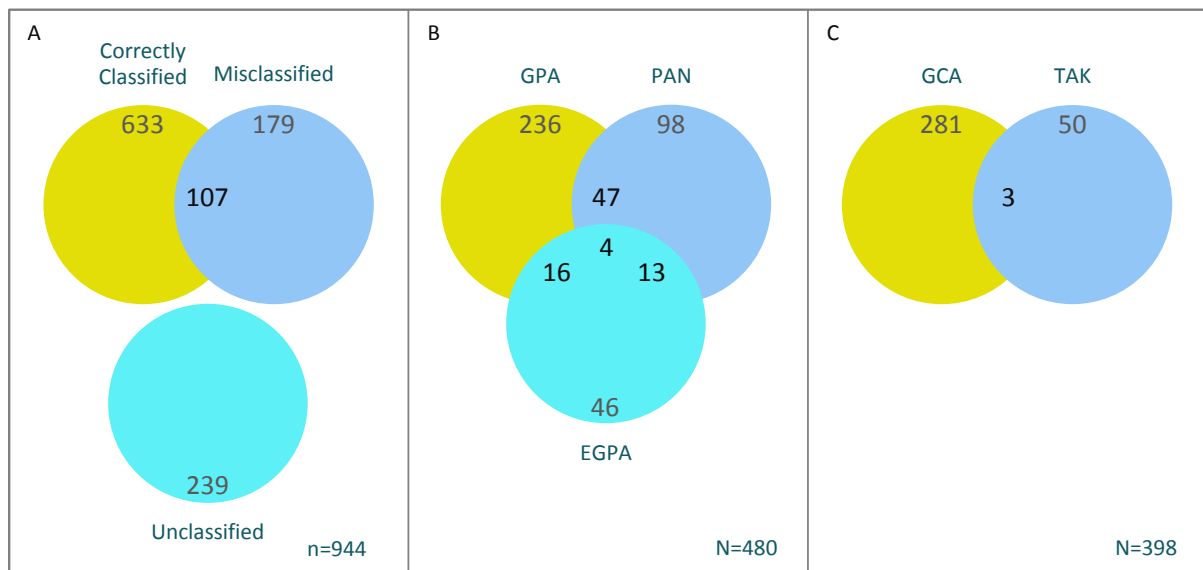


Figure 2. Accuracy and overlap of the application of the 1990 ACR classification criteria to patients with various forms of vasculitis

(A) Patients in DCVAS with one of the forms of primary systemic vasculitis with existing 1990 ACR Criteria (**n=944**) that were: classified in accordance with physician’s submitted diagnosis (“Correctly Classified”), not classified in accordance with physician’s submitted diagnosis (“Misclassified”), or not classified by any of the ACR criteria sets (“Unclassified”); overlap between “Correctly Classified” and “Misclassified” includes patients who were classified by ACR criteria as having more than one diagnosis (one concordant and another non-concordant with physician’s submitted diagnosis.

(B) The number of overlapping diagnoses when ACR 1990 criteria were applied to patients determined by the submitting physician as having a form of “small-vessel vasculitis”

(C) The number of overlapping diagnoses when ACR 1990 criteria were applied to patients determined by the submitting physician as having a form of “large-vessel vasculitis”.

DCVAS: Diagnostic & Classification Criteria in Vasculitis Study; ACR: American College of Rheumatology; GPA: granulomatosis with polyangiitis; PAN: polyarteritis nodosa; EGPA: eosinophilic granulomatosis with polyangiitis; TAK: Takayasu’s arteritis; GCA: giant cell arteritis.

Table 1: Sensitivity and specificity of the ACR 1990 classification criteria to classify and diagnose patients with and without vasculitis in DCVAS cohort

Vasculitis	N	<u>1990 ACR Criteria tested in the DCVAS population</u>			<u>1990 ACR Criteria performance characteristics in original cohort</u>	
		Sensitivity ^a % (95% CI)	Specificity % (95% CI)		Sensitivity %	Specificity %
			Classification ^b	Diagnostic ^c	Classification	
GCA	345	81.1 (76.6 – 85.1)	94.9 (93.1 – 96.3)	64.2 (52.8 – 74.6)	93.5	91.2
TAK	53	73.6 (59.7 – 84.7)	98.3 (97.3 – 99.0)	87.5 (67.6 – 97.3)	90.5	97.8
GPA	275	65.6 (59.9 – 71.4)	88.7 (86.3 – 90.7)	88.0 (83.5 – 91.7)	88.2	92.0
EGPA	79	57.0 (45.3 – 68.1)	99.8 (99.3 – 100)	98.9 (96.8 – 99.8)	85.0	99.7
PAN	32	40.6 (23.7 – 59.4)	87.8 (85.7 – 89.7)	92.5 (88.7 – 95.7)	82.2	86.6
MPA	94	28.9 (20.1 – 39.0)	88.5 (86.4 – 90.4)	92.5 (88.7 – 95.3)	NS	NS
IgAV	66	72.7 (60.4 – 83.0)	96.3 (94.9 – 97.3)	90.4 (87.6 – 93.9)	87.1	87.7

ACR: American College of Rheumatology; DCVAS: Diagnostic & Classification Criteria in Vasculitis Study; 95% CI: 95% confidence interval; GCA: giant cell arteritis; TAK: Takayasu's arteritis; PAN: polyarteritis nodosa; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; IgAV: IgA-Vasculitis

^aSensitivity is the same for diagnosis and classification because the same vasculitis patients were used for both analyses.

^bIndividual ACR criteria were applied to all patients with PSV (N=1095) including 151 patients with other forms of vasculitis without existing ACR criteria (aortitis (n=7), other large vessel vasculitis (n=15), single organ vasculitis (n=25), undefined small vessel vasculitis (n=51), Behçet's disease (n=30), other undefined primary vasculitis with no specific vessel size (n=2), cryoglobulinaemic vasculitis (n=12), and central nervous system vasculitis (n=9)).

^cIndividual ACR criteria were applied to vasculitis-specific comparators (GCA comparators: 81; AAV / PAN comparators: 267; IgAV comparators: 228; TAK comparators: 24); some of the comparators served for more than one form of vasculitis

Table 2: Demographic data and non-criteria clinical characteristics of patients in DCVAS (n=944) who had primary systemic vasculitis of a type for which ACR criteria are available, sorted by whether patients were correctly or incorrectly classified by the 1990 ACR classification criteria

Characteristic	Correctly classified by the 1990 ACR criteria				p-value ^a
	YES		NO ^b		
ALL PATIENTS (n=944)	633	(67.1)	311	(32.9)	
Age, years (±SD)	60.9	(±17.6)	58.1	(±17.5)	0.022
Sex (female)	360	(56.9)	178	(56.6)	0.944
LARGE-VESSEL VASCULITIS (n=398)	319	(80.2)	79	(19.8)	
Age, years (±SD)	68.5	(±15.4)	63.3	(±15.7)	0.010
LV-GCA ^c	5	(1.6)	26	(32.9)	<0.001
Vascular ultrasound performed	107	(33.5)	28	(35.4)	0.749
Positive vascular ultrasound	84	(26.3)	22	(27.8)	0.785
PET-scan performed	37	(11.6)	37	(46.8)	<0.001
Positive PET-scan	21	(6.6)	31	(39.2)	<0.001
MRA / CTA performed	63	(19.8)	26	(32.9)	0.012
Positive MRA / CTA	49	(77.8)	23	(88.5)	0.005
ANCA-ASSOCIATED VASCULITIS (n=448)	253	(56.5)	195	(43.5)	
Age, years (±SD)	54.3	(±15.2)	58.2	(±16.5)	0.009
ANCA positive	221	(87.4)	171	(87.8)	0.914
PR3 / MPO positive	218	(86.2)	161	(82.6)	0.295
Limited disease ^d (only GPA and EGPA)	43	(19.0)	33	(25.8)	0.137
Biopsy performed	193	(76.3)	139	(71.3)	0.231
Consistent with vasculitis ^e	136	(70.5)	99	(71.2)	0.881

Figures refer to number of patients with characteristic and percentage of group, unless depicted otherwise.

^aDemographics and characteristics between patients with regards to classification by the ACR criteria were analysed using Pearson- χ^2 -test or t-test for equality of means, as appropriate. All p-values are two-tailed and were considered significant if < 0.05.

^bNot correctly classified by 1990 ACR criteria means that either they did not meet the criteria or were classified with a vasculitis not concordant with the one submitted by the investigator.

^cDefined as GCA with clinical or radiologic evidence of large-vessel involvement but without clinical evidence of cranial involvement.

^dDefined as GPA / EGPA with upper / lower respiratory tract disease without any other systemic involvement or constitutional symptoms.

^ebased on DCVAS items: “biopsy consistent with vasculitis but not definite” or “definite vasculitis” (not necessarily reflecting the ACR-biopsy definitions).

DCVAS: Diagnostic & Classification Criteria in Vasculitis Study; ACR: American College of Rheumatology; ANCA: anti-neutrophil cytoplasm antibodies; PR3: proteinase 3, MPO: myeloperoxidase; CT: computed tomography; CTA: CT-angiography; MRA: MR-angiography; PET: Positron emission tomography; GCA: giant cell arteritis; TAK: Takayasu’s arteritis; PAN: polyarteritis nodosa; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; IgAV: IgA-Vasculitis.

Table 3: Diagnostic workup by contributing centres

Diagnostic tests	No. of patients (%)	Median by centre (IQR)
GCA	n=345 (45 centres)	3 (1-8)
TA Biopsy, n (%)	289 (83.8)	100 (80-100)
Ultrasound, n (%)	120 (34.8)	0 (0-68.8)*
CTA/MRA, n (%)	50 (14.5)	0 (0-38)
PET, n (%)	61 (17.8)	0 (0-10)**
TAKAYASU'S ARTERITIS	n=53 (23 centres)	2 (1-3)
Biopsy, n (%)	12 (22.6)	0 (0-50)
CTA/MRA/Ultrasound, n (%)	43 (81.1)	100 (71-100)
PET, n (%)	13 (24.5)	0 (0-45)
AAV/PAN	n=546 (70 centres)	4 (2-10)
ANCA, n (%)	545 (99.8)	100 (100-100)
Biopsy, n (%)	416 (76.2)	88.2 (62.5-100)

* Majority of ultrasound scans were performed by the major GCA-recruiting centres: 1 Slovenian, 1 Swiss, 1 German (all with performance rate > 70%) and 4 UK centres (performance rate 9-33%). The centres that recruited less than 10 GCA patients infrequently performed ultrasound as a part of regular diagnostic workup.

** PET-scans were performed in 12 centres in 9-100% of GCA patients/centre

GCA: Giant Cell Arteritis; TA: Temporal artery; CTA: Computerized tomography angiogram; MRA: Magnetic resonance imaging – angiography; PET: Positron emission tomography; AAV: ANCA-associated vasculitis; PAN: polyarteritis nodosa; ANCA: Antineutrophil cytoplasm antibodies

ONLINE SUPPLEMENTARY TABLES:

Table S1: Definitions for comparator groups

Comparator Group	Applied definition in DCVAS database
Giant Cell Arteritis Comparator Group	<ul style="list-style-type: none">• Presenting clinical scenario of New-onset headache, sudden visual loss, ischaemic jaw or tongue pain AND• Age > 40 years at onset of symptoms
Takayasu's Arteritis Comparator Group	<ul style="list-style-type: none">• Presenting clinical scenario of Aortic aneurysm, new-onset hypertension associated with other systemic features, Stroke, Limb claudication, chronic headache AND• Age ≤ 50 years at onset of symptoms
ANCA-Associated Vasculitis + PAN Comparator Group	<ul style="list-style-type: none">• Presenting clinical scenario of acute and progressive renal impairment and/or failure, Haemoptysis/pulmonary haemorrhage, Acute respiratory distress, exacerbation of asthma or unexplained pulmonary fibrosis, new-onset hypertension associated with other systemic features, Peripheral blood eosinophilia, peripheral neuropathy, inflammatory polyarthritis, acute or chronic abdominal pain
IgA Vasculitis Comparator Group	<ul style="list-style-type: none">• Presenting clinical scenario of acute or progressive renal impairment and/or failure, Rash/skin abnormalities (including nodules and ulcers), Acute or chronic abdominal pain

Table S2: Definitions for each individual criterion in the ACR classification criteria sets

ACR-Criterion	Applied definition in DCVAS database (any of the definitions per criteria, unless specified otherwise)
GIANT CELL ARTERITIS	
1. Age ≥ 50 years	<ul style="list-style-type: none"> • Age ≥ 50 years at time of diagnosis
2. New onset headache	<ul style="list-style-type: none"> • Presenting clinical scenario of new onset headache • Clinical feature of headache regardless of specific location
3. Temporal artery abnormalities	<ul style="list-style-type: none"> • Diminished pulse, tenderness over the temporal artery or cord-like-sign over left or right temporal artery
4. ESR ≥ 50 mm/h	<ul style="list-style-type: none"> • Erythrocyte sedimentation rate ≥ 50 mm/h
5. Abnormal biopsy	<ul style="list-style-type: none"> • Biopsy of the temporal artery, aorta or other artery with • Findings consistent or diagnostic of vasculitis
TAKAYASU'S ARTERITIS	
1. Age ≤ 40	<ul style="list-style-type: none"> • Age ≤ 40 years at time of diagnosis
2. Claudication	<ul style="list-style-type: none"> • Presenting clinical scenario of limb claudication OR • Leg or Arm claudication
3. Decreased brachial artery pulse	<ul style="list-style-type: none"> • Either diminished or absent pulse of brachial artery on vascular examination
4. Brachial artery blood pressure difference > 10mmHg	<ul style="list-style-type: none"> • Brachial artery blood pressure difference > 10mmHg
5. Bruit over subclavian artery or aorta	<ul style="list-style-type: none"> • Bruit over subclavian artery or aorta on vascular examination
6. Arteriogram abnormalities	<ul style="list-style-type: none"> • Vessel narrowing or vessel occlusion in any large artery detected on catheter-based angiogram, CT(-angiogram), MR(-angiogram), fluorescein-angiogram or ultrasound • In the absence of calcification of the vessel involved
GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)	
1. Nasal / oral inflammation	<ul style="list-style-type: none"> • Bloody nasal discharge • Non-blood stained nasal discharge • Mouth ulcers
2. Abnormal chest x-ray	<ul style="list-style-type: none"> • Nodules or consolidation, cavities, infiltration, inflammation or pleural thickening on CT, MRI or x-ray of the chest
3. Urinary sediment	<ul style="list-style-type: none"> • Blood on urine dipstick or • Red cell casts in urine on urine-microscopy
4. Granulomatous inflammation on biopsy	<ul style="list-style-type: none"> • Biopsy regardless of site showing granuloma or extravascular granulomatous inflammation
EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS)	
1. Asthma	<ul style="list-style-type: none"> • Positive history of asthma
2. Blood eosinophilia > 10%	<ul style="list-style-type: none"> • Blood eosinophilia > 1.5x10⁹/l
3. Neuropathy	<ul style="list-style-type: none"> • Presenting clinical scenario of peripheral neuropathy (either sensory or motor) or • Mononeuritis multiplex or • Motor neuropathy (not due to radiculopathy) or • Sensory neuropathy (not due to radiculopathy) • Confirmation by EMG/NCS was not required
4. Non-fixed pulmonary infiltrates	<ul style="list-style-type: none"> • Infiltration, consolidation or inflammation on CT, MRI or x-ray of the chest
5. Paranasal sinus abnormalities	<ul style="list-style-type: none"> • Non-blood stained nasal discharge or • Sino nasal congestion or blockage or • Inflammation, effusion or polyps in the paranasal sinuses on CT, MRI or x-ray.
6. Extravascular eosinophilic infiltration	<ul style="list-style-type: none"> • Biopsy regardless of site showing extravascular eosinophil-predominant inflammation
POLYARTERITIS NODOSA	
1. Weight loss ≥ 4kg	<ul style="list-style-type: none"> • Weight loss ≥ 5kg
2. Livedo reticularis	<ul style="list-style-type: none"> • Livedo reticularis on examination

ACR-Criterion	Applied definition in DCVAS database (any of the definitions per criteria, unless specified otherwise)
3. Testicular pain or tenderness	<ul style="list-style-type: none"> • Testicular pain or • Testicular tenderness on examination
4. Myalgia, weakness or leg tenderness	<ul style="list-style-type: none"> • Myalgia (muscle pain) or muscle cramps or • Muscle weakness on examination or • Muscle tenderness on examination • In the absence of a presenting clinical scenario of inflammatory shoulder and/or hip girdle symptoms (polymyalgia-like symptoms)
5. Mono- or polyneuropathy	<ul style="list-style-type: none"> • Presenting clinical scenario of peripheral neuropathy (either sensory or motor) or • Mononeuritis multiplex or • Motor neuropathy (not due to radiculopathy) or • Sensory neuropathy (not due to radiculopathy) • Confirmation by EMG/NCS was not required
6. Diastolic blood pressure > 90 mmHg	<ul style="list-style-type: none"> • Systolic Blood Pressure > 140 mmHg
7. Elevated blood urea nitrogen or creatinine (>1.5 mg/dl)	<ul style="list-style-type: none"> • Creatinine > 130 µmol/l
8. Presence of HBV-surface antigen or antibody in serum	<ul style="list-style-type: none"> • Hepatitis B (evidence of acute or ongoing chronic infection)
9. Arteriographic abnormality	<ul style="list-style-type: none"> • Vessel occlusion, aneurysm, beading or micro aneurysms of the mesenteric arteries demonstrated by catheter-based dye angiogram, CT(-angiogram) or MR(-angiogram)
10. Biopsy of small or medium-sized artery containing PMN	<ul style="list-style-type: none"> • Biopsy of a small or medium sized artery with predominantly neutrophilic vasculitis or predominantly mononuclear leukocytes in vasculitis
<i>IGA VASCULITIS (HENOCH-SCHÖNLEIN)</i>	
1. Palpable purpura not related to thrombocytopenia	<ul style="list-style-type: none"> • Palpable purpura on examination without presence of thrombocytopenia (<100x10⁹/l)
2. Age ≤ 20 years at disease onset	<ul style="list-style-type: none"> • Age ≤ 20 years at onset of symptoms
3. Bowel angina	<ul style="list-style-type: none"> • Abdominal pain (any) • Postprandial abdominal pain / ischaemic abdominal pain • Peritonism on examination • Mesenteric ischaemia
4. Wall granulocytes on biopsy	<ul style="list-style-type: none"> • Biopsy presenting • Predominantly mononuclear leukocytes in vasculitis or • Necrotizing or leukocytoclastic arteriolitis or • Necrotizing or leukocytoclastic venulitis

Table S3: Overview of clinical conditions in the comparator patients

Comparator conditions	GIANT CELL ARTERITIS n=81	TAKAYASU'S ARTERITIS n=24	ANCA-ASSOCIATED VASCULITIDES +PAN n=267	IgA-VASCULITIS n=228
Dermatologic	0	1	5	13
Non-ischaemic skin-lesions				3
Other dermatologic condition*		1	5	10
Endocrinologic/metabolic	1	0	1	2
Thyroid disease	1			
Pituitary macroadenoma			1	1
Other endocrinologic conditions			0	1
Gastrointestinal	0	0	9	10
Cholecystitis			1	1
Eosinophilic esophagitis			2	
Other gastroenterologic conditions			4	10
Genitourinary	0	0	7	4
Nephrotic / nephretic syndrome			5	4
Interstitial tubular nephritis			1	1
Acute kidney injury			1	1
Focal progressive IgA-Nephritis			1	1
Haematologic	2	1	8	10
Systemic amyloidosis	1		1	1
Coagulopathy / Thrombosis		1		1
Hypereosinophilic syndrome			3	2
Myeloma / Paraproteinaemia			3	3
Monoclonal cryoglobulinaemia			1	
Other hematologic	1			3
Infectious diseases	3	1	23	26
Bacterial endocarditis	1		8	7
Pneumonia (bacterial / viral)		1	2	1
Upper respiratory infection				1
Urinary tract infection			3	3
Eosinophilic pneumonia			1	
Streptococcal Group A infection			2	
Other infections	2		7	14
Malignancy	2	0	4	5
Solid malignancy	2			1
Haematologic malignancy			4	4
Neurologic	26	5	7	3
Migraine / headache syndrome	21	1	2	1
Neuropathy not due to vasculitis	1		2	
Stroke not due to vasculitis	1	1		1
Multiple sclerosis		1	1	1
Other neurologic conditions**	5	2	2	
Ophthalmologic	10	0	1	0
Vision loss not due to vasculitis	8			
Other ophthalmologic conditions	2		1	1
Other	4	0	7	12
Respiratory	1	0	20	9
Asthma			6	4
Allergic eosinophilic pneumonia			2	
COPD			1	
Interstitial lung disease			7	3
Other respiratory conditions***	1		4	2
Rheumatologic	25	10	158	105
SLE	3	6	40	34
Rheumatoid arthritis	1	0	27	10
Sarcoidosis	0	0	14	8
Dermatomyositis / Polymyositis	2	0	11	13
Sjogren's syndrome	4	0	5	2
Periodic fever syndrome	0	1	3	5
Antiphospholipid-syndrome	0	1	1	1
Adult onset Still syndrome	1		4	4
Anti-synthetase syndrome			3	2
Polymyalgia rheumatic	2		5	1
IgG4-related disease		1	6	2
Other rheumatologic ****	7		12	10
Other CTD*****	0	0	16	11

Table S3: Overview of clinical conditions in the comparator patients [continued]

Comparator conditions	GIANT CELL ARTERITIS n=81	TAKAYASU'S ARTERITIS n=24	ANCA-ASSOCIATED VASCULITIDES n=267	IgA-VASCULITIS n=228
Other inflammatory arthritis	5	1	14	3
Vascular	5	6	9	13
Artherosclerosis	3	3	3	1
Thrombangiitis obliterans				1
Other vascular conditions	2	3	6	11
Toxic	0	0	5	11
Propylthiouracil induced vasculitis			3	
Other drug-induced			2	
* including bullous pemphigoid and unspecified dermatitis				
** including Bell's palsy, Moyamoya and subarachnoidal haemorrhage, lumbosacral radiculopathy				
*** including cryptogenic organizing pneumonia, granulomatous disease				
**** including relapsing polychondritis, eosinophilic fasciitis, fibromyalgia				
***** including overlaps of systemic sclerosis with SLE and poly-/dermatomyositis				

Table S4: Differences between patients who were classified by the 1990 ACR criteria in accordance with physician's submitted diagnosis or not with respect to fulfilment of individual ACR criteria

ACR-Criterion	Correctly classified by the ACR criteria		p-value
	YES	NO [#]	
GIANT CELL ARTERITIS (n=345)	280 (67.1)	65 (32.9)	
1 - Age > 50 years	278 (99.3)	60 (92.3)	<0.001
2 - Headache	249 (88.9)	17 (26.2)	<0.001
3 - Temporal artery abnormalities	130 (46.4)	2 (3.1)	<0.001
4 - ESR ≥ 50	217 (77.5)	37 (56.9)	0.001
5 - Positive temporal artery biopsy	204 (72.9)	5 (7.7)	<0.001
TAKAYASU'S ARTERITIS (n=53)	39 (73.6)	14 (26.4)	
1 - Age ≤ 40 years	28 (71.8)	8 (57.1)	0.314
2 - Claudication	26 (56.6)	4 (28.6)	0.014
3 - Reduced brachial pulse	17 (43.6)	1 (7.1)	0.014
4 - Difference in brachial artery blood pressure	16 (41.0)	0	0.004
5 - Bruits (aorta or subclavian artery)	27 (69.2)	2 (14.3)	<0.001
6 - Arteriogram abnormalities	34 (87.2)	8 (50.0)	0.004
GRANULOMATOSIS WITH POLYANGIITIS (n=275)	181 (65.8)	94 (34.2)	
1 - Oral / nasal Inflammation	138 (76.2)	27 (28.7)	<0.001
2 - Abnormal chest imaging	117 (64.6)	17 (18.1)	<0.001
3 - Urinary sediment	133 (73.5)	28 (30.8)	<0.001
4 - Positive biopsy	51 (28.2)	6 (6.4)	<0.001
EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (n=97)	45 (57.0)	34 (43.0)	
1 - Asthma	34 (75.6)	18 (52.9)	0.036
2 - Eosinophilia	40 (89)	25 (73.53)	0.077
3 - Neuropathy	39 (86.7)	20 (58.8)	0.005
4 - Abnormal chest imaging	28 (62.2)	4 (11.7)	<0.001
5 - Paranasal sinus abnormalities	37 (82.2)	18 (50)	0.002
6 - Positive biopsy	14 (31.1)	1 (2.9)	0.002
POLYARTERITIS NODOSA (n=32)	13 (40.6)	19 (59.4)	
1 - Weight loss > 4 kilograms	7 (53.9)	4 (21.1)	0.055
2 - Livedo reticularis	3 (23.1)	1 (5.3)	0.135
3 - Testicular tenderness / pain	4 (30.8)	0	0.01
4 - Myalgia, weakness, leg tenderness	10 (76.9)	5 (26.3)	0.005
5 - Mono- / polyneuropathy	8 (61.5)	4 (21.1)	0.02
6 - Diastolic blood pressure > 90mmHg	4 (30.8)	3 (15.8)	0.314
7 - Elevated BUN or Creatinine	3 (23.1)	1 (5.3)	0.135
8 - Presence of HBV-infection	4 (30.8)	1 (5.3)	0.051
9 - Arteriographic abnormalities	1 (7.7)	1 (5.7)	0.78
10 - Biopsy of vasculitis with PMN	1 (7.7)	2 (10.5)	0.787

Table S4: Differences between patients who were classified by the 1990 ACR criteria in accordance with physician's submitted diagnosis or not with respect to fulfilment of individual ACR criteria [continued]

MICROSCOPIC POLYANGIITIS (n=94)	27 (28.7)	67 (71.3)	
1 – Weight loss > 4 kilograms	15 (55.6)	10 (14.9)	<0.001
2 - Livedo reticularis	4 (14.8)	2 (3.0)	0.034
3 - Testicular tenderness / pain	0	0	-
4 - Myalgia, weakness, leg tenderness	15 (55.7)	10 (14.9)	<0.001
5 - Mono- / Polyneuropathy	15 (55.7)	12 (17.9)	0.001
6 - Diastolic Blood Pressure > 90 mmHg	19 (70.4)	24 (35.8)	0.002
7 - Elevated BUN or Creatinine	19 (70.4)	41 (61.2)	0.402
8 - Presence of HBV-infection	0	0	-
9 - Arteriographic abnormalities	0	0	-
10 - Biopsy showing vasculitis with PMN	2 (7.4)	1 (1.5)	0.14
IGA-VASCULITIS (HENOCH-SCHÖNLEIN) (n=66)	48 (72.7)	18 (27.3)	
1 - Palpable purpura	47 (97.9)	15 (83.3)	0.027
2 - Age ≤ 20 years at onset	2 (4.2)	0	0.379
3 - Bowel angina	27 (56.3)	3 (16.7)	0.004
4 - Wall granulocytes on biopsy	31 (64.6)	0	<0.001
Definitions applied for each of the criteria are shown in Supplementary Table S2 . Differences between criteria fulfilment were analysed using Pearson- χ^2 -test. All p-values are two-tailed and were considered significant if < 0.05.			
#not correctly classified by 1990 ACR criteria means that either they did not meet the criteria or were classified with a diagnosis not concordant with the one submitted by the investigator.			
ACR: American College of Rheumatology, BUN: blood urea nitrogen, ESR: erythrocyte sedimentation rate, HBV: hepatitis B virus, PMN: polymorphonuclear leukocytes			

Table S5: Number of patients recruited per centre and centre-specific sensitivity and specificity of the 1990 ACR classification criteria for each form of PSV. 24 of 85 centres with at least 15 PSV patients with primary systemic vasculitis are displayed

Centre	Country	Speciality	PSV patients																				Other PSV	Comparators				
			All			GCA			TAK			GPA			MPA*			EGPA			PAN				IgAV			
			n	n	Sens	Spec	n	Sens	Spec	n	Sens	Spec	n	Sens	Spec	n	Sens	Spec	n	Sens	Spec	n			Sens	Spec	n	n
1	SL	Rhe	89	44	91	97			97	9	78	90	1	100	95	4	100	100	2	0	96	29	76	93	13	21		
2	ENG	Rhe/Nephr	61	35	91	93	2	50	100	18	50	100	2	50	97	1	100	100			94	3	100	100	1	27		
3	ENG	Rhe	49	31	81	96	2	0	100	11	73	94			78	3	67	98	1	100	79	1	100	98	10	59		
4	GER	Rhe	41	22	50	87	4	50	95	13	62	97			96			100	2	100	100			100	4	35		
5	USA	Rhe	37	10	90	85	4	50	100	10	40	93	4	25	85	7	0	100	1	0	78	1	0	97		7		
6	RU	Nephr	34	2	100	100	2	50	100	16	56	100	1	0	100	10	40	100			97	3	0	100		35		
7	GER	Rhe	33	2	50	100	2	50	100	24	79	100	3	0	91	1	0	100			83	1	0	97	2	1		
8	ENG	Rhe	32	26	85	75			100	4	50	93	1	100	97			100			94	1	0	97	2			
9	ENG	Rhe/Opth	31	22	100	100			100	5	40	90	4	25	90			100			79			100	3	11		
10	DK	Rhe	31	8	63	100	5	80	96	17	29	100			100			100			100	1	100	94	1	3		
11	CH	Rhe	26	22	59	100			97	2	50	100	2	0	93			100			87			97	5	24		
12	CAN	Rhe	26	8	88	95			100	8	63	74			89	7	57	100			89	3	100	92	1	20		
13	CAN	Rhe	26	3	100	100			100	11	55	65	6	33	86	1	100	100	4	25	79	1	0	96	2	4		
14	ENG	Rhe	25	15	87	79			100	5	80	96	2	50	96	2	0	100			90	1	100	100	4	16		
15	CAN	Rhe	25	5	100	81	2	100	90	1	100	80	4	50	78	12	75	100	1	100	70			90	6	9		
16	PL	Int Med	18	1	100	86			100	8	88	60	3	33	75	5	100	100			65	1	100	91	5	6		
17	TK	Rhe	18	3	100	93	7	100	100	1	0	94	2	50	100			100	1	0	94	4	100	100		2		
18	BEL	Int Med	17	10	80	100			100	5	100	92	1	0	94			100	1	0	94			100		1		
19	JP	Nephr	16	1	100	93			100	2	50	71	12	50	100			100	1	0	27			100		8		
20	IT	Rhe	16	4	50	93	1	100	100	4	50	100	1	0	89	3s	100	100	3	33	100			95	3			
21	CN	Rhe	15	1	0	100	5	40	88	4	100	88	2	0	84	1	0	100	2	50	84			95	6	14		
22	SCO	Rhe	15	2	0	94			100	8	88	82	1	100	83	3	33	100	1	0	83			100	4	13		
23	CN	Nephr	15			94			100	5	100	69	10	60	50			100			22			94	3	1		
24	PT	Neuro	15	10	100	100	2	100	100	1	100	100	1	0	93			100	1	100	93			100				

PSV: primary systemic vasculitis; Sens: Sensitivity; Spec: Specificity; Rhe: Rheumatology; Nephr: Nephrology; Opth: Ophthalmology; Int Med: Internal medicine; Neuro: Neurology; GCA: giant cell arteritis; TAK: Takayasu's arteritis; PAN: polyarteritis nodosa; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; IgAV: IgA-vasculitis. *Sensitivities and specificities are shown for PAN criteria applied to MPA patients (details given in the Methods)

