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EDITORIAL

Classification criteria for large vessel vasculitis

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Classification criteria play a crucial role in the management of many rheumatic diseases, particularly vasculitis[1]. Although they are not meant for diagnostic purposes and have been shown to perform poorly when applied to this effect[2], classification criteria are vital for identifying homogeneous groups of patients for recruitment into clinical trials and other research studies, ultimately leading to improved clinical care.

1. The 1990 American College of Rheumatology classification criteria and the Chapel Hill Consensus Conference nomenclature

The first systematic approach to classifying vasculitis was introduced by the American College of Rheumatology (ACR) in 1990. It used a cohort of patients with various forms of vasculitis to identify clinicopathologic features that most accurately distinguished them. This effort led to the establishment of classification criteria for seven types of vasculitis, including giant cell arteritis (GCA) and Takayasu arteritis (TAK), the two primary forms of large-vessel vasculitis (LVV)[3,4] (Figure 1). However, these criteria were developed before the widespread use of advanced vascular imaging modalities, namely temporal artery ultrasound, which have become crucial in diagnosing GCA. Moreover, the clinical phenotype of GCA has expanded since then. Imaging has proven that GCA is no longer a disease confined to the cranial arteries and can frequently involve the aorta and its primary branches[5]. In addition, the ACR criteria for both GCA and TAK had many methodological issues, namely: (i) lack of an independent validation set; (ii) low number of patients with TAK included within an overall cohort of 807 patients with vasculitis (n=63; 8.3%); (iii) inclusion of only patients from North America, without representation from Europe or Asia, where clinical patterns of disease are known to differ[6]; (iv) inclusion of many cases of small-vessel vasculitis as comparators, a form of vasculitis which generally does not pose a challenge in differentiating from either GCA or TAK; and (v) application of the "number of criteria" rule, where all items were weighted equally despite their differing clinical significance.

The limitations of the ACR 1990 classification criteria for LVV became increasingly apparent in the conduct of clinical trials and research studies, where they were often adapted to align with modern practice[7,8]. However, it is crucial to emphasise that trial-specific modifications to inclusion criteria can introduce bias, potentially favouring the intervention under evaluation.

Notably, in 1994, the Chapel Hill Consensus Conference (CHCC) introduced mutually exclusive clinicopathologic definitions for the major types of vasculitis, mainly categorized by vessel size. This nomenclature was later revised in 2012 to encompass a broader spectrum of vasculitides[9]. While the CHCC nomenclature was a thoughtfully constructed and comprehensive effort, it was not designed for classification purposes, including for LVV, and relied predominantly on expert opinion rather than data-driven analysis. As a result, it should not be applied as a substitute for formal classification criteria in clinical or research settings.

2. The new 2022 ACR/EULAR Classification Criteria For LVV

To address the numerous challenges associated with previous classification criteria for vasculitis, including LVV, a multinational observational study— the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study—was conducted between January 2011 and December 2017 to develop diagnostic criteria and revise classification criteria for systemic vasculitis[10]. It was the largest international study on vasculitis performed so far, enrolling 4,994 patients with systemic vasculitis and 1,997 comparators (clinical mimics of vasculitis) across 136 sites in 32 countries. The data collected encompassed different clinical, histologic, laboratory and imaging findings, reflecting the contemporary diagnostic work-up for patients with vasculitis.

When the classification criteria for LVV were developed using the DCVAS data, one of the initial key challenges in differentiating GCA from TAK, its main comparator, was the relatively recent recognition that patients with GCA often present with large-vessel involvement (LV-GCA) in a pattern resembling TAK. Additionally, while age had frequently been used as a distinguishing factor, specific age thresholds for classifying GCA and TAK were not well defined, making

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GIANT CELL ARTERITIS

1. Age at onset >50 years
2. New onset headache
3. Temporal artery abnormality (tenderness to palpation or decreased pulsation)
4. Increased ESR (>50 mm)
5. Abnormal artery biopsy (showing vasculitis characterised by a predominance of mononuclear infiltration or granulomatous inflammation)

The patient is classified as having giant-cell arteritis if at least three of these five criteria are present

TAKAYASU ARTERITIS

1. Age <40 years old
2. Claudication of extremities
3. Decreased brachial arterial pulse
4. BP difference >10 mm Hg in systolic blood pressure between arms
5. Bruit over subclavian arteries or aorta
6. Arteriogram abnormality (narrowing or occlusion of the aorta, its proximal branches, or large arteries in the proximal upper or lower extremities)

The patient is classified as having Takayasu arteritis if at least three of these six criteria are present

Adapted from [3]. ACR: American College of Rheumatology; BP: Blood pressure; ESR: erythrocyte sedimentation rate

Figure 1. 1990 ACR Classification Criteria for Large Vessel Vasculitis

it particularly challenging to differentiate between the two diseases in patients aged between 40 and 60 years. Indeed, several authors have even questioned whether GCA and TAK represented a spectrum of the same clinical entity rather than two distinct diseases, particularly for cases of LV-GCA[11,12]. To address these issues, DCVAS data on vascular imaging (ultrasound, CT, MRI, conventional angiography and FDG-PET) was used to identify distinct patterns of arterial involvement that could differentiate LV-GCA from TAK. These findings were then validated using a North American cohort[13] and included in the analyses to develop the classification criteria for LVV. In summary, patients with LV-GCA were more likely to exhibit diffuse vascular disease, with vascular involvement throughout the aorta and the aortic arch branch vessels, minimal disease of the large arteries not defined by a specific pattern of involvement, involvement of bilateral axillary/subclavian arteries, and more arterial FDG-uptake by PET than patients with TAK. On the other hand, patients with TAK more often had involvement of the abdominal vasculature, bilateral subclavian/carotid artery involvement, focal disease in the left subclavian artery, and greater vascular damage (i.e., stenosis, occlusion, or aneurysm) as detected by angiography than those with GCA. As for the age issue, age distribution at diagnosis was plotted for GCA and TAK to determine whether specific age thresholds could be regarded as absolute requirements for disease classification. Only 7 out of 942 patients with GCA (<1%) were diagnosed at the age < 50 years, and only 3 out of 464 patients with TAK (<1%) were diagnosed at age >60 years, hence age at diagnosis ≥ 50 years was considered an absolute requirement to classify GCA and ≤60 years to classify a patient as having TAK.

The remaining overall methodology to develop the classification criteria for LVV closely followed the process employed in DCVAS for ANCA-associated vasculitis[14–16]. There was initially a case selection, where clinical vignettes were created based on submitted DCVAS data and presented to vasculitis experts, who reached a consensus diagnosis, thereby establishing a gold-standard set of LVV cases. Next, candidate items from the DCVAS case report form (CRF) were selected through a combination of data-driven analysis and expert consensus, reducing the original pool of over 8,000 items to 72 key variables suitable for regression analysis. The dataset was then divided into development (70%) and validation (30%) sets, and comparisons were made between LVV cases and randomly selected comparators. To ensure balance in the sample (50% cases vs. 50% comparators), the following splits were applied: GCA (50%) vs. TAK (16.6%), other vasculitides (16.6%), and other diagnoses that mimic LVV (16.6%); or TAK (50%) vs. GCA (16.6%), other vasculitides (16.6%), and other diagnoses that mimic LVV (16.6%). LASSO (Least Absolute Shrinkage and Selection Operator) logistic regression was used to identify predictors from the dataset and develop a parsimonious model containing only the most relevant predictors. The model's performance was rigorously tested and refined for face validity and discriminatory power. The final predictors were incorporated into a clinical risk-scoring tool, with each factor assigned a weight based on its regression coefficient. A threshold was established that optimized the balance between sensitivity and specificity. The performance of these new classification criteria was then validated in an independent set of cases and comparators.

Figure 2 shows the new 2022 ACR/EULAR classification criteria developed and validated for both GCA and TAK [17,18]. The new 2022 ACR/EULAR classification criteria for GCA showed a sensitivity of 87.0% (95%CI: 82.0-91.0%) and a specificity of 94.8% (95%CI: 91.0-97.4%). Although the previous 1990 ACR classification criteria for GCA criteria had a sensitivity of 93.5% and a specificity of 91.2%[3], when these criteria were applied to the DCVAS dataset, their sensitivity dropped to 80.3% (95%CI: 74.6-85.1%) but retained a good specificity of 92.5% (95%CI: 88.1-95.7%). This was par-

Giant Cell Arteritis

Considerations when applying these criteria:

- These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has already been made.
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria.

Criteria absolute requirement

Age ≥ 50 years at time of diagnosis

Criteria Items

CLINICAL FEATURES	
Morning stiffness in shoulders/neck	**+2**
Sudden visual loss	**+3**
Jaw or tongue claudication	**+2**
New temporal headache	**+2**
Scalp tenderness	**+2**
Abnormal examination of the temporal artery[1]	**+2**
INVESTIGATIONS	
Laboratory	
Maximum ESR ≥ 50mm/hour or maximum CRP ≥ 10mg/L[2]	**+3**
Biopsy / Imaging Findings	
Positive temporal artery biopsy or halo sign on temporal artery ultrasound[3]	**+5**
Bilateral axillary involvement[4]	**+2**
FDG-PET activity throughout aorta[5]	**+2**

Sum the scores for all 10 items, if present. A score of ≥ 6 points is needed for the classification of giant cell arteritis

1. Examination of the temporal artery showing absent or diminished pulse, tenderness, or hard 'cord-like'.
2. Maximum erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) values prior to initiation of treatment for vasculitis.
3. Presence of either definitive vasculitis on temporal artery biopsy or halo sign on temporal artery ultrasound. There are no specific histopathologic criteria to define definitive vasculitis on 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 [24]. Halo sign is defined by the presence of a homogenous, hypoechoic wall thickening on ultrasound [25].
4. Bilateral axillary involvement is defined as luminal damage (stenosis, occlusion, or aneurysm) on angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasound, halo sign on ultrasound, or fluorodeoxyglucose uptake on positron emission tomography.
5. Abnormal fluorodeoxyglucose (FDG) uptake in the arterial wall (e.g., greater than liver uptake by visual inspection) throughout the descending thoracic and abdominal aorta on positron emission tomography (PET).

Takayasu arteritis

Considerations when applying these criteria:

- These classification criteria should be applied to classify the patient as having giant cell arteritis when a diagnosis of medium-vessel or large-vessel vasculitis has already been made.
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria.

Criteria absolute requirement

Age ≤ 60 years at time of diagnosis
Evidence of vasculitis on imaging[1]

Criteria Items

CLINICAL FEATURES	
Female sex	**+1**
Angina or ischemic cardiac pain	**+2**
Arm or leg claudication	**+2**
Vascular bruit[2]	**+2**
Reduced pulse in upper extremity[3]	**+2**
Carotid artery abnormality[4]	**+2**
Systolic blood pressure difference in arms ≥ 20 mm Hg	**+1**
IMAGING FINDINGS	
Number of affected arterial territories (select one)[5]	
One territory	**+1**
Two territories	**+2**
Three or more territories	**+3**
Symmetric involvement of paired arteries[6]	**+1**
Abdominal aorta involvement with renal or mesenteric involvement[7]	**+3**

Sum the scores for all 10 items, if present. A score of ≥ 5 points is needed for the classification of Takayasu arteritis

1. Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (e.g., computed tomographic/catheter-based/magnetic resonance angiography, ultrasound, positron emission tomography).
2. Bruit detected by auscultation of a large artery, including the aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries.
3. Reduction or absence of pulse by physical examination of the axillary, brachial, or radial arteries.
4. Reduction or absence of pulse of the carotid artery or tenderness of the carotid artery.
5. Number of arterial territories with luminal damage (e.g., stenosis, occlusion, or aneurysm) detected by angiography or ultrasonography from the following nine territories: thoracic aorta, abdominal aorta, mesenteric, left or right carotid, left or right subclavian, left or right renal arteries.
6. Bilateral luminal damage (stenosis, occlusion, or aneurysm) detected by angiography (computed tomography, magnetic resonance, or catheter-based) or ultrasonography in any of the following paired vascular territories: carotid, subclavian, or renal arteries.
7. Luminal damage (stenosis, occlusion, aneurysm) detected by angiography or ultrasonography involving the abdominal aorta *and* either the renal or mesenteric arteries.

Adapted from[17, 18].

Figure 2. 2022 ACR/EULAR Classification Criteria for Large Vessel Vasculitis

ticularly evident for patients with a LV-GCA subtype, in whom both criteria showed low sensitivity, but the new 2022 ACR/EULAR criteria outperformed the 1990 ACR criteria (55.7% [95%CI: 46.5-64.6%] vs 37.1% [95%CI: 28.6-46.2%]). The new 2022 ACR/EULAR classification criteria for TAK showed a sensitivity of 93.8% (95%CI: 88.6-97.1%) and a specificity of 99.2% (95%CI: 95.7-100.0%). Although the previous 1990 ACR TAK criteria had a sensitivity of 90.5% and a specificity of 97.8%[4], when these criteria were applied to the DCVAS dataset, their sensitivity dropped to 84.3% (95% CI:77.3-89.7%), but retained an excellent specificity of 99.2% (95%CI: 95.7-100.0%).

In conclusion, the updated 2022 ACR/EULAR classification criteria for LVV represent a major advancement over the outdated 1990 ACR criteria. Developed through a rigorous methodological process and informed by a comprehensive international dataset, these criteria reflect the collaborative efforts of experts worldwide. By addressing previous limitations, they offer improved sensitivity and specificity, making them essential for accurately identifying patients in clinical trials and research. Ultimately, these advancements will help raise the standard of care in LVV management.

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