Correspondence on 'The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease' by Wallace *et al*

IgG4-related disease (IgG4-RD) was initially discovered as a clearly different entity in patients with sclerosing cholangitis with elevated levels of serum IgG4.[1] Subsequently, the term 'IgG4-related disease' was proposed, and many other organ system manifestations were then linked to the IgG4-related disease. The first widely accepted and used diagnostic criteria for IgG4-RD was established in 2011. The comprehensive diagnostic criteria for IgG4-RD consisted of three major domains: organ involvement showing characteristic diffused or localised swelling or masses; elevated serum IgG4 concentrations (>135 mg/dL); histopathological examination showing marked lymphoplasmacytic infiltration and fibrosis or >40% of IgG+ plasma cells being IgG4+ and >10 IgG4+ cells per high power field.[2] These criteria were essentially derived from patients with IgG4-related kidney disease, Mikulicz's disease and IgG4-related autoimmune pancreatitis, and the sensitivities were comparatively good in the former two subgroups. The diversity in organ involvements and manifestations in IgG4-RD necessitated formulating new criteria. Recently, to maximise the specificity with acceptable sensitivity, the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) published a set of classification criteria (AECC) for IgG4-RD and validated two large cohorts.[3] The 2019 AECC for IgG4-RD uses clinical, radiological or pathological evidence of involvement of a specific organ as an entry criterion. A typical organ should include pancreas, salivary glands, bile ducts, kidneys, orbits, aorta, retroperitoneum, pachymeninges or thyroid glands. The 2019 AECC for IgG4-RD is quite unique for having exclusion criteria in rheumatology, and patients must not meet any of them. All inclusion criteria items have individual weights on histopathological, immunostaining, serum IgG4 level and five organ site domains. Twenty points are necessary for being classified as having IgG4-RD.

Additionally, four distinctive phenotypes of IgG4-RD have been described with typical patterns of IgG4-related organ involvement.[4] A latent class analysis showed pancreatobiliary disease (PHB), retroperitoneal and/or aortitis (RPF-Aortitis), head and neck limited disease and Mikulicz's syndrome (MS) phenotypes. Each clinical phenotype has disparate epidemiological, clinical and serological aspects, and results in different outcomes.[5]

From January 2014 to December 2021, 96 patients with IgG4-RD (54.2% male) who met the 2011 comprehensive diagnostic criteria were recorded to the Hacettepe University Vasculitis Research Centre (HUVAC) prospective database. Aiming to describe the clinical phenotypes and fulfilment of 2019 AECC, we reviewed the patients' medical records and determined the following clinical factors: age, gender, serum IgG4 levels, serology, histopathologies with immunostaining and distributions of organ involvements. In total, 64.6% of the patients had multiple organ involvements, median (IQR) organ involvement was 2 (1–3), and median (IQR) serum IgG4 level 179 (85–349) mg/dL. The majority of the patients had retroperitoneal fibrosis (RPF)/periaortitis (table 1). RPF-periaortitis accounted for 39.6% of the phenotypes, followed by head and neck limited (26.0%), MS (14.6%) and PHB (10.4%). In total, 9.4% had an undefined phenotype. RPF-periaortitis phenotype had a male predominance, whereas females predominated the head and neck group. MS phenotype had the highest IgG4 levels.

We also evaluated the usefulness of AECC for IgG4-RD for different phenotypes in our cohort. Overall, 55 (57.3%) patients were classified as having IgG4-RD, with a median score of 27 points. As IgG4-RD new manifestations may develop over time, 3.1% of the patients met the criteria in the follow-up. All patients (except for one who had peritoneal limited disease) fulfilled the entry criteria. Of the 41 false-negative cases, only one did not meet the entry criteria, 8 had at least one exclusion criteria and 38 did not get sufficient inclusion criteria scores. MS, PHB and RPF-aortitis phenotype met the 2019 AECC at a higher rate. However, the differences were not statistically significant.

Classification criteria can affect the understanding of the disease, and they are essential tools for providing consistent case definitions and, in particular, enrolling patients in clinical trials. Since no set of classification criteria can encompass all patients across the disease spectrum, the 2019 AECC for IgG4-RD achieved their goal reaching a high specificity (99.2%) with a good sensitivity (85.5%).

In our IgG4-RD cohort, approximately two-thirds of the patients met the 2019 AECC criteria. This rate was 66% in a large Latin American group, 59.9% in an Italian cohort, and a Spanish cohort had the highest rate of 77%.[6–8] Remarkably one-third of the our patients did not meet the AECC criteria and had statistically significant more single organ involvement, fewer histopathological evaluation.

Table 1 Clinical phenotypes, general characteristics and 2019 ACR/EULAR Classification Criteria (AECC) for IgG4-RD

	Group 1. Pancreato-hepatobiliary (n=10)	Group 2. Retroperitoneum and aorta (n=38)	Group 3. Head and neck limited (n=26)	Group 4. Mikulicz and systemic (n=14)	Undefined phenotype (n=8)	P value
Sex, male (%)	50.0	68.4	38.5	50.0	50.0	0.279
Age, median (IQR), years	49 (42–71)	61 (51–67)	55 (30–66)	61 (40–68)	45 (36–56)	0.101
Age at diagnosis, median (IQR), years	44 (36–66)	51(44-59)	50 (29–61)	48 (34–60)	40 (32–47)	0.358
IgG4 level, median (IQR), mg/dL	210 (86–25)	204 (138–361)	127 (56–300)	336 (65–683)	135 (77–160)	0.200
ESR/CRP ↑ (%)	70.0	76.3	**38.5**	71.4	75.0	0.028
Available biopsy at IgG4 involvement site (%)	80.0	71.1	84.6	100.0	87.5	0.066
2019 AECC points, median	24.50 (8.00–29.25)	23.00 (12.00–32.50)	20.00 (15.00–27.00)	25.50 (20.00–36.75)	15.00 (4.00–19.75)	0.026
Fulfillment of 2019 AECC, n (%)	60.0	57.9	53.8	78.6	25.0	0.769

ACR, American Collefe of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; IgG4-RD, immunoglobulin G4-related disease.

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Phenotype distributions in our cohort were similar to the previous reports, except with a more prevalent RPF-aortitis phenotype and slightly less head and neck limited group. Group 3 (head and neck limited phenotype) met the 2019 AECC for IgG4-RD at the lowest rate among the previously determined groups.

Classification criteria were developed for the purpose of clinical research study inclusion and these criteria establish the patients for clinical studies with high specificity. To be more precise, classification is not identical to the diagnosis, although they frequently concur. The usefulness of the 2019 AECC for IgG4-RD differs both between clinical phenotypes and between limited and multiorgan disease. Thus, it would be appropriate to consider this heterogeneity in clinical and drug studies as it may have an impact on our clinical practice.

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