

Correspondence on “ACR/EULAR antiphospholipid syndrome classification criteria”

The new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) antiphospholipid syndrome (APS) classification criteria were generated by a well-structured stepwise approach.¹ Contrary to the revised Sapporo criteria,² the new criteria are characterised by high specificity. Obviously, this is at the cost of sensitivity, but for clinical intervention studies and understanding pathogenic mechanisms more homogeneous patient populations, as achieved by more stringent disease criteria, are a prerequisite. With respect to the definition and implementation of the laboratory parameters, an essential pillar in the classification, some considerations are missing.

First, choosing for ELISA for antiphospholipid antibody (aPL) detection because of better alignment of units as compared with novel, automated methods, is disputable.³ In contrast to the revised Sapporo criteria, the aPL definitions in the current criteria do not refer to any reference materials, often erroneously called standards (Harris standards, HCAL/EY2C9 standards, and recently released reference material for IgG β 2-GPI antibodies). Although reference material can be used for calibration of immunoassays and this may result in similar test results for the respective reference material, this will not hold for individual patient samples.⁴ This is due to the variable nature of polyclonal autoantibodies in terms of epitope recognition, affinity, isotype/subclass distribution and glycosylation. Choosing for a single method, that is, ELISA, will reveal somewhat better alignment of patient results, but external quality assessments for aPL show wide variation, even between ELISA users. Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and rheumatoid arthritis, however, have shown that harmonisation of autoantibody results can be achieved by expressing likelihood ratio's for test-result intervals defined by levels of specificity.^{5,6} This successful approach has been underscored by experts in the field of autoimmune diagnostics, by representatives of societies involved in harmonisation/standardisation and of diagnostic companies.⁷ Although such data are not yet available for aPL, acquisition of such data likely also allows harmonisation of test results obtained in distinct immunoassays.

Second, the IgM aPL test appears to be not of any value for classification. The presence of these antibodies is awarded one point (the simplified weight of 0.4 was even rounded up to 1 to enable a score for these antibodies), while the presence of IgG aPL reveals four to seven points depending on the level and combination of antigen specificity. Since three points from the laboratory domain are required, simultaneous detection of IgG aPL and/or positive lupus anticoagulant (LAC; five points) is needed, which on their own are already sufficient if present. The same holds for a single—one time positive LAC. Since the added value for IgM aPL is considered very low, it is also questionable if these antibodies should be included in the entry criteria and, perhaps, even in the diagnostic workup of patients with APS.

Third, it is important that the level of aPL is incorporated in the scoring. Indeed, higher antibody levels in general have a stronger association with disease.⁸ However, although more points are given to higher antibody levels, this has no effect on the dichotomous outcome of the classification criteria, that is, it is sufficient if three points for aPL are scored in the laboratory domain.

Altogether, while the 2023 ACR/EULAR APS criteria are definitely an improvement due to the high specificity, the positioning of ELISA as the method of choice is disputable and the inclusion of IgM aPL and one time positive LAC is of no added value in the application of the criteria. Moreover, the recognition that aPL levels are to be differentially scored is not really effectuated. A scoring system based on likelihood ratio's for test-result intervals may in future criteria fill in this gap and additionally compensate for the lack of standardisation of distinct aPL assays.

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