Response to: Correspondence on 'ACR/EULAR antiphospholipid syndrome classification criteria' by Damoiseaux and van Beers

We appreciate the comments by Damoiseaux and van Beers[1] in response to the publication of the 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) Antiphospholipid Syndrome (APS) classification criteria.[2 3] Here, we address a few of the authors points, including: (1) choosing ELISA for antiphospholipid antibodies (aPL) as compared with automated methods, is 'disputable'; (2) anticardiolipin antibody (aCL) and anti-β_2-glycoprotein-I antibody (aβ_2GPI) IgM alone, or single one-time lupus-anticoagulant (LA) positivity alone is 'not of any value for classification'; (3) although 'high' aCL/aβ_2GPI level receives more points, 'this has no effect on the dichotomous outcome of the classification criteria'; and (4) differentially scoring aCL/aβ_2GPI levels 'is not really effectuated'.

Regarding the first point, we refer the authors to our response[4] to the correspondence by Miro-Mur *et al*[5] on the 2023 ACR/EULAR APS classification criteria. Additionally, we want to address the author's point about using likelihood ratios (LR) for harmonisation by using 'test-result intervals defined by levels of specificity'. This method has been described in the field of autoantibodies,[6] and also for aPL.[7–9] LRs and interval-specific LR (IS-LR) should be calculated in large patient cohorts, and even then, they will be influenced by the characteristics of the diseased and non-diseased cohorts studied. In APS, regarding LR, a differentiation should be made between thrombotic and obstetric APS, and the choice of the control population (eg, non-APS systemic autoimmune disease patients, non-APS thrombosis patients, healthy controls) will define the specificity of the assays in the cohort. The literature that Damoiseaux and van Beers refers to by Van Hoovels *et al*,[6] has arbitrarily chosen specificities of 90.0%, 92.5%, 95.0%, 97.5%, 99.0% and 99.5%. Alternatively, LR can also be calculated based on sensitivity as illustrated for aCL and aβ_2GPI,[7] or at certain predefined intervals.[8] So even with the LR method, there can be variation in the outcome of reporting. Further studies are ongoing applying the method of IS-LR with the aim of achieving harmonisation in reporting in APS. With test result specific LRs, relevant differences in clinical significance between low antibody levels versus higher antibody levels can be illustrated. The higher the antibody titre, the higher the LR and the higher the likelihood for disease.[7] However, at the end, titres will have to be translated to an IS-LR with corresponding titre interval that can be applied interlaboratory, but that will stay specific for the type of assay.

Second, one of the novel features of the 2023 ACR/EULAR APS classification criteria is the separation of aCL/aβ_2GPI IgG and IgM isotypes. Based on literature reviews, derivation cohort analyses, as well as steering committee consensus, the current understanding is that IgM isotypes for aCL/aβ_2GPI confer lower APS likelihood and specificity than IgG isotypes. Thus, Damoiseaux and van Beers are correct in noting that the low weight attributed to isolated IgM positivity renders it insufficient for APS classification, even when clinical criteria are met. Additionally, this effectively precludes the possibility that aPL-positive patients with isolated aCL/aβ_2GPI IgM isotypes (ie, no other aPL-positivity) are included in the same research studies as those with aCL/aβ_2GPI IgG isotypes. Furthermore, as extensively discussed in our manuscript, cases with isolated IgM positivity were 'controversial' for APS classification during multiple phases of the new classification criteria development. Thus, we would argue that the main 'value' in its inclusion (or the inclusion of single LA positivity) in the classification criteria is the ability to consider its role in cases where clinical criteria are met, which we report as a 'high priority' research agenda item (table 6 of the original manuscript).[2 3] In fact, efforts to better understand the clinical significance of isolated aCL/aβ_2GPI IgM isotypes are ongoing.[10] Similarly, in the clinical domains, certain items have been included, for example, otherwise unexplained recurrent prefetal and/or early fetal deaths, that alone are insufficient for APS classification but for which further research is needed.

Third, the 2023 ACR/EULAR APS classification criteria are point-based with hierarchical levels in each laboratory and clinical domain organised by their relative weights. The 'dichotomous outcome', that is, APS classification or not, inherently implies that certain patients will not fulfil the criteria despite presenting with some item(s) included in the criteria, whereas others will be classified as APS with relatively high scores. The research implications for this classification system are important. As already discussed in table 6 of the original article,[2 3] high priority research agenda to guide future updates of the new classification criteria include patients: (1) with clinical and laboratory criteria but not fulfilling the classification criteria; (2) fulfilling the clinical criteria but not the laboratory criteria and (3) fulfilling the laboratory criteria but not the clinical criteria. To address the authors' point, we agree that although accumulating points above the threshold for classification would not affect classification itself, our hope is that that the classification criteria system will stimulate research attempting to correlate criteria scores with patient outcomes.

Finally, related to the authors point that the 'recognition that aPL levels are to be differentially scored is not really effectuated', we point out that novel features of the new criteria include the ability to score aCL/aβ_2GPI results by 'moderate' and 'high' levels, and to quantify single-aPL, double-aPL and triple-aPL positivity based on different domains and weights. The classification criteria system includes and extends beyond a simple dichotomous 'fulfils criteria versus not' approach, since the impact of increasing levels of aPL and multiplicity of aPL tests on clinical outcomes has been illustrated in many studies.[11–13]

While international harmonisation efforts and studies to improve laboratory standardisation are underway,[4] the 2023 ACR/EULAR APS criteria reflect real-world thinking about APS and provides high specificity for the identification of homogeneous APS patients for research purposes. We want to conclude with a reminder that all ACR/EULAR-approved criteria sets are expected to undergo future updates; the classification system allows for individual domain modification, with the possibility of incorporating additional data if shown to be highly specific for APS.

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