Response to: Correspondence on ‘2023 ACR/EULAR antiphospholipid syndrome classification criteria’ by Miro-Mur et al

We appreciate the comments by Miro-Mur et al1 in response to the publication of 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) Antiphospholipid Syndrome (APS) classification criteria.2 3 The authors discuss the challenge of establishing thresholds to define ‘moderate’ (40–79 U) and ‘high’ (≥80 U) level anticardiolipin antibody (aCL) and anti-β2-glycoprotein-I antibody (aβ2GPI), which are required laboratory parameters of the new classification system. We also note their concern that ELISA tests are ‘advocated’, while other non-ELISA methods are ‘sidedlined’. Here, we would like to reply to some of the authors’ queries and discuss our future plans.

First, maximising the specificity of the classification criteria was a major goal at the outset of the project, as overly inclusive criteria with a heterogeneous group of patients (including those with aPL-positivity detected based on different aPL cut-offs and methods) would decrease the ability of investigators to understand disease pathophysiology and treatment effects in clinical trials and research. Thus, the 2023 ACR/EULAR APS classification criteria intentionally include stringent definitions for both laboratory and clinical domain items.2 3 In contrast, diagnosis in a clinical setting requires careful consideration of a broader range of laboratory and clinical features.

Second, aCL/aβ2GPI ‘positivity’ (a titre higher than the cut-off value) should not be mixed up with grouping results into ‘moderate’ or ‘high’ aCL/aβ2GPI levels. Because non-ELISA automated platform readout values for aCL/aβ2GPI are generally higher than the ELISA values, a ‘moderate’ or ‘high’ level definition should be method-specific, as further discussed below. Given that misclassification into ‘negative’ or ‘positive’ results is more common with low aCL/aβ2GPI levels due to issues in assay sensitivity and specificity, the APS classification criteria steering committee agreed that at least moderate levels are required for APS classification.2 3

Third, we define ‘moderate’ and ‘high’ level aCL/aβ2GPI positivity based on literature reviews, steering committee consensus, as well as our derivation cohort analysis, the latter of which demonstrated: (a) no significant association for aCL/aβ2GPI levels of <40 U with highly likely APS cases; (b) pronounced sequential relative risk increase above aCL/aβ2GPI IgG≥40 (supported by our literature review demonstrating increased association with aCL/aβ2GPI levels of ≥40 U and aPL-related events); (c) the upper limit of aCL/aβ2GPI normal range varying between 5 U and 40 U (ELISA) based on the aCL/aβ2GPI reference ranges of the derivation cohort and (d) median titres of aCL/aβ2GPI IgG in the ‘highly likely’ case as 96/90 U, compared with 35/46 U in the ‘equivocal or unlikely’ cases. In addition, there was a strong consensus among steering committee members that: (a) aCL/aβ2GPI levels above the laboratory cut-off but <40 U do not provide enough confidence for APS classification for research purposes, even in the setting of an acceptable clinical event and (b) above >80 U provide unquestionable confidence for APS classification in the setting of an acceptable clinical event.2 3

Fourth, while the threshold of >40 U has excellent ability to discriminate between low and moderate–high aCL and aβ2GPI IgG titres using ELISA,4 as also illustrated based on risk ratios of our derivation cohort,2 3 new automated systems require further investigation. As Miro-Mur et al comment,1 although titres show good statistical correlation,5 numerical values between ‘moderate’ and ‘high’ threshold levels of ELISA compared with automated platforms vary substantially. This was extensively discussed in our manuscript; for example, based on a communication of the International Society on Thrombosis and Hemostasis Scientific Standardization Committee on Lupus Anticoagulant/Antiphospholipid Antibodies (ISTH-SSC LA/aPL), an IgG aCL ELISA value of 40–79 units corresponds to a chemiluminescent immunoassay (CLIA) value of 200–400 units and MFI of 700–2000 (please refer to table 1 of the original manuscript for further information).2 3 Given their increased use in various countries, establishing ‘moderate’ and ‘high’ thresholds of non-ELISA aCL/aβ2GPI ELISA testing platforms, for example, automated laboratory systems, with corresponding ELISA thresholds, was included as one of our high priority research agenda items to guide the future update of the 2023 ACR/EULAR APS classification criteria. For laboratories without options besides the use of automated platforms for APS research, the new classification criteria request that investigators attempt to identify and validate moderate/high thresholds of their platform, correlating it with aCL/aβ2GPI ELISA moderate/high thresholds, and to be transparent about their methodology and results.2 3

Finally, we acknowledge the need for harmonisation of ‘moderate’ and ‘high’ levels of ELISA and non-ELISA tests and are pleased to report that a new international initiative, launched by the Laboratory Subcommittee of the 2023 ACR/EULAR APS Classification Criteria Steering Committee in collaboration with the ISTH-SSC LA/aPL Subcommittee and Antiphospholipid Syndrome Alliance for Clinical Trials and International Working,6 is being developed.

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