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

We appreciate the comments by Miro-Mur et al\(^1\) in response to the publication of 2023 American College of Rheumatology/European League Against Rheumatism (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) levels of 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 ‘sidelined’. 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 differences 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 defined ‘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,\(^2\) new automated systems require further investigation. As Miro-Mur et al\(^1\) comment, 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 Anti-coagulant/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 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.

**Correspondence response**

Doruk Erkan,\(^1\) Medha Barbhaiya,\(^1\) Stephane Zuily,\(^2\) Maria Laura Bertolaccini,\(^1\) Rohan Willis,\(^5\) Katrien DeVreese\(^3\)

\(^1\)Barbara Volcker Center for Women and Rheumatic Diseases, Division of Rheumatology, Hospital for Special Surgery; Weill Cornell Medicine, New York, NY, USA
\(^2\)Vascular Medicine Division and Regional Diseases, Université de Lorraine, Inserm, DCAC and CHRU-Nancy, F-54000, Nancy, France
\(^3\)Academic Department of Vascular Surgery, School of Cardiovascular and Metabolic Medicine & Sciences, King’s College, London, UK
\(^4\)Antiphospholipid Standardization Laboratory, University of Texas Medical Branch, Galveston, Texas, USA
\(^5\)Coagulation Laboratory, Department of Laboratory Medicine, Ghent University Hospital, Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

**Correspondence to** Doruk Erkan, Rheumatology, Hospital for Special Surgery, New York, New York, USA; erkan@dhs.edu

**Handling editor** Josel S Smolen

**Contributors** All authors contributed equally and approved the final version.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Commissioned; internally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and
is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ on behalf of EULAR.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2023-225054).

To cite Erkan D, Barbhaiya M, Zuily S, et al. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/ard-2023-225054

Received 9 October 2023
Accepted 10 October 2023

► http://dx.doi.org/10.1136/ard-2023-225042

Ann Rheum Dis 2023;0:1–2. doi:10.1136/ard-2023-225054

ORCID iDs
Doruk Erkan http://orcid.org/0000-0001-7216-677X
Medha Barbhaiya http://orcid.org/0000-0002-6670-7696
Stephane Zuily http://orcid.org/0000-0002-9326-6881

REFERENCES