Correspondence on ‘2023 ACR/EULAR antiphospholipid syndrome classification criteria’ by Barbhaiya et al

The following considerations are a response to the recently published 2023 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) antiphospholipid syndrome (APS) classification criteria by the steering committee on the APS from the ACR and EULAR.1,2 These updated criteria present an improvement from the Sapporo-modified classification criteria for APS, otherwise known as the Sydney’s classification criteria.3 Manifestly, the new criteria aim to classify APS patients with heightened specificity, up to 99%, to better investigate the underlying mechanisms of this autoimmune disease. This highlights the enduring challenge of defining these patients, which Dr Hugues identified and classified in the early 1980s.2,4 As per the Sydney’s classification criteria, and its echoed principles in these new criteria, patients must fulfill both clinical and laboratory criteria. One of the novelties in the new criteria is the scoring system for APS classification. Specifically, for the laboratory criteria, a patient must test positive for either anticardiolipin (aCL) or anti-β2-glycoprotein I (aβ2GPI) IgG/IgM on two separate occasions, with a 12-week gap between tests. Most commonly, the ELISA was the chosen method to measure levels of these antiphospholipid antibodies (aPL).5 However, contemporary CORE laboratories predominantly employ a cutting-edge chemiluminescence-based immunoassay (CLIA). Yet, certain challenges persist. Concretely, a patient’s aCL or aβ2GPI levels must surpass a specified threshold to be considered aPL-positive, standing at 40 GPL/MPL for aCL and 40 U/mL for aβ2GPI,1,2 and units expressed in reference to the Harris Standards.2,3 With the new criteria, the proposed APS score differs between moderate (40–79 units) and high (≥80 units) aPL positivity. However, researchers face the issue of arbitrary units used in standardised ELISA and CLIA tests, despite being labelled as GPL/MPL or U/mL by manufacturers, which claim they are running off values of 20 GPL/MPL or U/mL by manufactures, which they claim are running out of Harris Standards to calibrate their products. Distinctly, the aCL ELISA test from Orgentec (# ORG515; Mainz, Germany) indicates a positivity threshold of 10 GPL for aCL IgG and 7 MPL for aCL IgM. The positivity for aβ2GPI ELISA (#ORGS211) is set at 8 U/mL. The aCL (#3204) and aβ2GPI (#3206) ELISAs by AESKU (Wendelstein, Germany) have cut-off values of 18 GPL/MPL and 18 U/mL, respectively. Finally, Inova Diagnostics (San Diego, California, USA) has both ELISA and CLIA cut-off values of 20 GPL/MPL in aCL (#708625; #701233) and 20 U/mL in aβ2GPI (#708665; #701248). We assessed aCL levels of 21 individuals using all four methods. Pearson’s correlation coefficients (PCCs) were 0.889 and 0.936 (Orgentec vs AESKU), 0.868 and 0.943 (Orgentec vs Inova); and 0.909 and 0.923 (AESKU vs Inova) for ELISA aCL IgG and aβ2GPI IgG, respectively. The PCCs between ELISA and CLIA from Inova were 0.735 and 0.965 for aCL and aβ2GPI, respectively. Although they have optimal correlation, the maximum GPL readout was 168 (Orgentec), 62 (AESKU), 84 (Inova; ELISA) and 1700 (Inova; CLIA). A similar readout was observed for aβ2GPI assays. Discrepancies in the absolute values are a great inconvenience for APS scoring under the new criteria, as we are unaware of where to establish moderate (40–79 units) and high (≥80 units) positivity.1,2 The CLIA readout values for aCL and aβ2GPI are higher than the ELISA values, also observed by Vandevelde et al,4 making it possible for the same individual to score negative, moderate or high positivity depending on the method used, a notable concern for clinical and research settings. Although the authors advocate for the use of ELISA, side-lining the emerging CLIA method,1,2 there remains uncertainty in distinguishing between moderate and high positivity. Establishing the 99th percentile for positivity would be helpful, but the optimal percentile for moderate/high positivity remains unspecified, warranting further discussion.

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