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FORUM

2023 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for antiphospholipid syndrome: good for patients or good for papers?

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Abstract

The American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for antiphospholipid syndrome (APS) is a new set of robust criteria, including clinical and laboratory criteria, to enhance the identification of patients in clinical studies and laboratory research. Based on a scoring system, patients accruing at least 3 points in the clinical and laboratory domains fulfill the classification criteria for APS. They are meant to define homogeneous patient groups for research. They are not to be used in a clinical setting for diagnosis to identify every patient with APS, where it is essential to include those with an atypical clinical presentation and/or antiphospholipid antibodies laboratory test result. These criteria have provoked a debate among workers in the field. Without nuance, the classification criteria cannot be used for diagnosing APS and may be a potential pitfall for clinicians when no difference is made between "classification" and "diagnostic" criteria. Complementing the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria with the recently available International Society on Thrombosis and Haemostasis guidance on laboratory detection and interpretation of antiphospholipid antibodies for diagnosis of APS has added value. It ensures rigorous research that leads to improvement of patient management and optimal clinical care in routine practice.

KEYWORDS
antiphospholipid syndrome, classification, clinical, diagnosis, laboratory, patient care, research

In late 2023, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) jointly proposed a new set of classification criteria for antiphospholipid syndrome (APS) to enhance the identification of patients in clinical trials and research [1]. These criteria have sparked significant debate among health care professionals in the field of APS, highlighting their strengths and limitations. The International Society on Thrombosis and Haemostasis (ISTH) has been a key player in these discussions, reflecting their mission to advance the understanding, diagnosis, and treatment of thrombotic diseases such as APS. This perspective

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explores how these new criteria align with real-world diagnostic and therapeutic challenges.

Key issues in the debate are (i) the diagnosis and management of APS that are intricate and multifaceted. The clinical presentation of APS spans a broad spectrum of symptoms in the vascular, hematological, and obstetric domains. Equally, antiphospholipid antibodies (aPL) exhibit a diverse character, and the combination of subgroups referred to as the antibody profile determines the probability of APS and the risk for symptoms. Moreover, aPL, believed to be pathogenic, do not always lead to clinical events, and a trigger is needed to advance the clinical symptoms. APS may be part of another autoimmune disease, mainly systemic lupus erythematosus, resulting in an even more complex clinical picture. This complexity underscores the challenge of under and overdiagnosis of APS [2]. (ii) The revised Sapporo classification criteria of 2006 [3] (also known as the "Sydney" classification criteria, referring to the workshop's location where experts addressed new clinical, laboratory, and experimental insights to update the criteria established in 1999 [4]) are relatively simple. They include 1 clinical criterion (thrombotic or obstetric) and 1 laboratory criterion (persistent lupus anticoagulant [LA], moderate to high levels of anticardiolipin antibodies [aCL], or anti–β2–glycoprotein I (aβ2GPI) immunoglobulin [Ig] G/IgM) [3]. These classification criteria resulted from relevant literature (not a systematic review), a grading by 3 experts, and an open discussion, resulting in a final consensus. Despite wide acceptance of the Sydney criteria, which were initially meant as a classification tool but generally used as a diagnostic tool for APS, after almost 20 years, the field found that more stringent criteria were needed. Developing these new classification criteria using a rigorous methodology and including many experts and 4 phases (Delphi exercise) took years [5,6]. The goal of these stringent definitions is clearly stated: to reach high specificity to ensure homogeneous cohorts fit for comparability in clinical studies and trials [1].

The ACR/EULAR classification criteria for APS reflect the diagnostic thinking of APS, combining clinical and laboratory criteria strictly [1]. This strictness is a positive aspect for the organization of research and clinical trials to further unravel the pathogenesis and the search for better treatment. In this context, it is crucial that patient entry criteria are comparable between studies. Consistent criteria could streamline enrolment in trials, allowing researchers to focus on cohorts with robust APS diagnoses and improving the reliability of research findings. The ACR/EULAR classification criteria emphasize the identification of high-risk patients with clear-cut APS manifestations. By integrating thrombotic events and validated laboratory markers, the requirements are seen as improving sensitivity and specificity for clinical trials. The structured approach of the scoring system, which considers both clinical and laboratory findings, allows for a more nuanced assessment of APS features compared with previous criteria like the Sydney classification, highlighting the need for a comprehensive approach.

Several groups have confirmed that the ACR/EULAR classification criteria show higher specificity, comparing the classification of APS patients according to the Sydney criteria with the ACR/EULAR criteria [7–11]. Besides the high specificity reached by the scoring system, the scoring might reflect the risk for clinical events. Only the highest weighted criterion toward the total score can be included within each domain. A score of 10 vs 22 (lowest vs highest score in each clinical domain) illustrates that the combination of events in the macrovascular, microvascular, obstetric, valvular cardiac, and hematology, together with persistent and elevated aPL levels, contributes to a higher risk of clinical complications [1].

Nonthrombotic features (eg, livedo racemosa, thrombocytopenia, or heart valve lesions) and new pregnancy morbidity definitions have been added [1]. On the other hand, the risk profile of thrombotic and cardiovascular disease is considered. When there is a more likely cause of a clinical criterion, it means that this criterion is not scored. Both ensure that manifestations that are clinically significant in APS patients are included but that overdiagnosis is avoided, taking into consideration comorbidities for thrombotic events and other reasons for pregnancy morbidity. However, downranking thrombosis with a high-risk thrombotic profile and arterial thrombosis with a high-risk cardiovascular disease profile may lead to "non-APS" classification when incorrectly applied in diagnosis with the discontinuation of anticoagulation as a consequence.

Including the nonvascular events (cardiac valve disease and thrombocytopenia) into the ACR/EULAR classification criteria ensures that for research, patients with, for instance, thrombocytopenia and aPL will also be studied [1]. On the other hand, the presence of thrombocytopenia does not contribute enough points to fulfill the clinical domain. Consequently, patients with aPL who only exhibit thrombocytopenia as a clinical manifestation do not meet the classification criteria. Indeed, the attribution of this feature should be done with caution, as thrombocytopenia is frequent in systemic lupus erythematosus. Also, the changes in the obstetric domain represent a notable difference from the Sydney criteria in which an unexplained fetal death of a morphologically normal fetus was a sufficient pregnancy morbidity clinical criterion [1,3]. In the ACR/EULAR criteria, this is insufficient for APS classification, requiring preeclampsia and/or placental insufficiency to meet the clinical criteria. Expanding the clinical domains toward microvascular thrombosis will likely have significant implications [1]. It may help facilitate APS identification in established microvascular pathology (has a score of 5). Catastrophic APS (CAPS) is a rare but life-threatening APS variant that deserves special note [12]. It is characterized by microvascular ischemia in multiple organs [12]. CAPS's rapid onset and complexity make classifying using weighted scoring systems difficult, potentially leaving this group underrepresented in research based on the ACR/EULAR classification criteria. The criteria should be used to classify APS and not interchangeably to diagnose CAPS. To prevent spuriously ruling CAPS in or out, it is essential to use the diagnostic criteria specific to CAPS and assess APS separately [12].

Since the publication of the ACR/EULAR APS criteria, several authors have pointed out that the classification criteria are not fit for diagnosis of APS and may be a potential pitfall for clinicians, especially with focus on laboratory criteria. One publication captured the issue perfectly in its title, highlighting the distinction between "classification" and "diagnostic" criteria [13]. While the ACR/EULAR criteria are

designed for research purposes, it is important to note that they could inadvertently influence clinical practice. Physicians may hesitate to diagnose or treat APS in patients who fall outside the strict classification, potentially leading to undertreatment. Misusing the classification criteria as a diagnostic tool instead of a classification tool may increase the incorrect labeling of APS cases. The criteria prioritizing specificity for homogenous research cohorts of true APS patients cannot be employed as strict clinical diagnostic criteria. Diagnosis aims to identify every patient with APS, including those with an atypical clinical presentation and/or aPL laboratory test result. However, being too tolerant regarding the diagnostic criteria can lead to overdiagnosis, implicating unnecessary anticoagulant therapy and exposing patients to a potential bleeding risk. This potential for overdiagnosis and undertreatment underscores the crucial need for a balanced approach in APS diagnosis and management, where patient safety and well-being are paramount. Therefore, we must translate the ACR/EULAR classification criteria into clinical practice.

There are 2 laboratory domains in the ACR/EULAR classification [1]. LA measured with coagulation assays according to ISTH guidelines [14], and IgG/IgM aCL and/or aβ2GPI measured by solid phase enzyme-linked immunosorbent assays (ELISAs). The varying weights assigned to aPL profiles are new and indicate a risk stratification. This approach, which was not included in the updated Sydney criteria [3], is now considered for patient classification, helping to bridge the gap between past and current knowledge.

The ISTH Scientific and Standardization Committee on Lupus anticoagulant/antiphospholipid antibodies (ISTH-SSC LA/aPL) supports not including aPL other than LA, aCL, and aβ2GPI IgG/IgM, such as IgA aPL, anti–β2GPI domain I antibodies, and anti-phosphatidylserine/prothrombin antibodies, as evidence so far is not strong enough to use these aPL in first-line diagnosis [15]. Especially, antiphosphatidylserine/prothrombin are emerging, and strong evidence supports their clinical relevance, particularly in improving risk assessment for both thrombotic and obstetric APS. While they are not included in the classification criteria, their role in APS diagnosis and prognosis is becoming increasingly clear and are useful in specific situations [15]. The main challenge is their limited availability in routine clinical practice. Both the ISTH-SSC and ACR/EULAR have put this on their research agendas [1,15]. Further research and wider implementation of these tests could help refine APS diagnosis and ensure that patients who do not meet classification criteria but are still at risk receive appropriate management.

Also, the ISTH-SSC LA/aPL is critical for the so-called "seronegative APS," where patients exhibit clinical features of APS without detectable aPL [15]. In the laboratory diagnosis of APS, at least 1 aPL must be persistently positive [15]. Equally, in the ACR/EULAR classification criteria, one of the entry criteria is to have at least 1 positive aPL test [1]. Granting that clinical challenges in these patients are big, but classifying them as APS patients includes overtreatment risks.

Although the type of laboratory parameters remain essentially unchanged compared with the Sydney criteria [1,3], from a laboratory perspective, there were 2 primary concerns about the new classification criteria: (i) the use of standardized ELISA only for aCL and aβ2GPI and (ii) the use of fixed cutoff values for both aCL and aβ2GPI defined as moderate (40-79 Units) and high positive (≥ 80 Units) [1]. These 2 points provoked many reactions despite the restriction of ELISA being explained and not closing the door to other solid-phase test systems. The classification criteria recommend delaying the use of the automated platforms for APS classification, but if no other options exist, researchers should direct efforts to correlate aPL results obtained with non–ELISA techniques with the moderate/high thresholds set in the classification criteria for ELISA [1]. Also, in the Sydney criteria, this restriction toward ELISA was included [3], and in clinical trials and routine practice, non–ELISA systems were used. Indeed, traditionally, aCL and aβ2GPI were detected by ELISA; however, over the last years, automated platforms with variations in the solid phase and various detection systems have been introduced into the market. At the time of publication of the classification criteria, we have to recognize that most of the diagnostic laboratories have moved toward automated systems. The fixed cutoff of 40/80 and the cutoffs calculated by the 99th percentile abandoned are even more challenging to accept. Regardless of the test system, ELISA or non–ELISA, a significant problem is high variability between the commercially available aCL and aβ2GPI assays. There is variation in classifying samples as positive or negative, and in antibody levels, the latter, especially when we compare ELISA and non–ELISA systems [16–18]. Currently, collaborative efforts from APS-ACTION and the ISTH-SSC to harmonize ELSIA and non–ELISA aPL results are ongoing as an ISTH-SSC project [19] following 2 communications from the ISTH-SSC LA/aPL on the topic [17,20]. Also, other laboratory-related issues, such as the role of isolated positivity of IgM aCL/aβ2GPI, are added to the research agenda to guide the future update of the 2023 ACR/EULAR classification criteria [1].

To meet the concerns on the laboratory diagnosis of APS, some months after the publication of the classification criteria [1], a position paper by the ACR/EULAR and ISTH-SSC was published, stressing that both requirements (fixed cutoff and restriction to ELISA) should not impact the routine practice of diagnostic laboratories that efficiently employ different platforms other than ELISA and that clinicians should be aware of the various ranges of ELISA and non–ELISA solid phase–based aCL/aβ2GPI assays [21]. In addition, updated guidance on laboratory detection and interpretation of aPL for diagnosis of APS has been published recently [15].

In conclusion, the ACR/EULAR classification criteria for APS are a step forward in standardizing research cohorts and addressing high-risk patients. The newly released APS classification criteria have the potential to represent a step forward in understanding this complex disease, with important implications for patients' management and treatment. Therefore, classification criteria serve both patients and the publication of high-quality studies. Concerns about its potential impact on clinical practice are justified. Still, we may not forget that clinicians must consider additional factors and follow their clinical judgment in diagnostic practice. I suggest complementing the ACR/EULAR classification criteria with the recently available diagnostic

criteria for clinical use [1,15]. This dual approach would ensure that research remains rigorous without compromising clinical care.

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There are no competing interests to disclose.

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