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2023 ACR/EULAR classification criteria in existing research cohorts: an international study

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Abstract

Objectives: To assess the impact of the updated ACR/EULAR APS classification criteria on two large research cohorts.

Methods: Consecutive patients who tested persistently positive for at least one aPL in the last three years were enrolled. The first APS Sydney index event was considered and computed for the comparison between Sydney and 2023 APS criteria. When computing the 2023 APS criteria, additional manifestations were also considered.

Results: The cohort comprised 249 patients (185 with APS and 64 aPL carriers according to Sydney criteria). The 185 patients had as first index event venous thrombosis in 55 cases (29.8%), arterial thrombosis in 63 (34%) and pregnancy morbidity in 67 (36.2%). When applying the updated criteria, 90 subjects (48.7%) failed to reach the composite score of the new criteria. The percentage of thrombotic APS per Sydney criteria decreased from 47.3% to 34.9% because of high cardiovascular risk in 23 cases, IgM aPL profile in six cases and in two patients for both reasons. Patients with pregnancy morbidity decreased from 26.9% to 3.2% (39 cases of recurrent early pregnancy loss and 20 of fetal losses). Consequently, the percentage of aPL carriers increased from 26% to 61%. When looking at the disease evolution at follow-up, 32 additional patients out of 90 (35.6%) fulfilled the new APS criteria, after developing additional clinical manifestation following index event.

Conclusion: When applying the new APS criteria to our research cohorts, not-negligible differences exist in patients' classification. A multidisciplinary approach will be mandatory to assess the impact of the new criteria on research and, ultimately, patients' care.

Keywords: 2023 ACR/EULAR APS criteria, antiphospholipid syndrome, classification

Introduction

Antiphospholipid syndrome (APS) was outlined as a distinct clinical entity in systemic lupus erythematosus (SLE) patients who presented with diverse clinical features linked to the presence of lupus anticoagulant (LA) and anti-cardiolipin antibodies (aCL) [1] over 40 years ago. This condition rapidly gained attention and its first description was quickly followed by numerous advances, both from clinical and laboratory perspectives, and with the creation of the updated Sydney criteria in 2006 [2].

Recently, the updated version of the APS classification criteria, which represents the results of an international joint effort supported by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), has been published [3]. This novel set of criteria has been developed through the employment of a rigorous evidence- and expert-based approach, with the explicit aim of improving specificity when classifying patients as having or not having APS. This is of crucial importance especially in the research setting, in order to create homogeneous and well-selected cohorts, thus constituting a solid ground for producing reliable scientific data [4]. Moreover, several aspects of the APS spectrum [5], such as haematological manifestations (thrombocytopenia), microvascular and cardiac involvement, as well as risk stratification based on antiphospholipid antibody (aPL) profile, which were not included in the updated Sydney criteria [2], are now considered for patients' classification, reducing the gap between past and current knowledge.

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.

Our main goal was to investigate the impact of the 2023 ACR/EULAR criteria in classifying patients included in a research cohort as having APS and to describe both qualitative and quantitative differences in patients' categorization.

Methods

For the purpose of this study, patients included in the research cohorts of two referral centres for APS were evaluated. All participants gave written informed consent for the study. The ethic committee Interaziendale AOU Città della Salute e della Scienza di Torino approved this study (file number 00323/2020).

The research cohorts included consecutive patients enrolled at the Giovanni Bosco Hospital of Turin (Italy) and at the Hospital Córdoba and Materno Neonatal Rare Diseases (Córdoba, Argentina) over the last 3 years (January 2021–January 2023). To be included in the research cohort, subjects needed to test persistently positive at medium–high titres (at least in two occasions, at least 12 weeks apart) for at least one aPL, including LA, aCL IgG and/or IgM and anti-β2glycoprotein I (aβ2GPI) IgG and/or IgM and a follow up time >6 months [2]. Patients with incomplete records were excluded from the recruitment. Patients were classified as having APS or referred as 'aPL carriers' based on the presence or absence of the clinical manifestations of the disease following Sydney criteria [2]. For each patient, clinical and laboratory charts were reviewed and patients were re-categorized by applying the 2023 ACR/EULAR criteria [3], considering both clinical and laboratory domains. When analysing patients with multiple APS clinical manifestations [2], the first APS Sydney index event was considered and computed for the comparison between Sydney and the 2023 ACR/EULAR APS

criteria. Additional manifestations (such as those previously known as 'extra criteria' [5] or those that occurred after the index event) were also considered when computing the 2023 APS criteria. Qualitative and quantitative differences in patient classification were analysed based on the two sets of classification criteria.

Patient selection was performed by two researchers (S.G.F.) and (C.G.A.). In case of discrepancy, a patient's selection was discussed. If an agreement was not achievable, a third researcher (S.S.) resolved the discrepancy.

Statistical analyses were performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables are presented as number (%) and continuous variables are presented as mean (s.d.).

Results

Cohort description

Among the 249 patients enrolled, 195 (78.3%) were women. Mean age at study inclusion was 46.9 years (s.d. 13.8). By applying Sydney criteria [2], 185 patients (74.3%) were classifiable as having APS, while 64 patients (25.7%) were considered aPL carriers. Out of the 185 APS patients, 146 (78.9%) were classified as primary APS (PAPS), while in 39 subjects (21.1%) APS was associated to another autoimmune disease (also known as secondary APS, SAPS). The main clinical and laboratory characteristics of the cohort are detailed in Table 1.

Impact of 2023 ACR/EULAR criteria for APS

When considering our 185 patients previously classified as having APS [2] [133 women, mean age 46.9 years (s.d. 13.8)], the first index event was a venous thrombosis in 55 cases (29.8%), in 63 patients (34%) an arterial thrombosis, and 67 patients (36.2%) suffered from pregnancy morbidity (PM).

Ninety-five subjects out of 185 (51.3%) fulfilled both sets of criteria, including 40 (42.1%) patients with previous venous thrombosis, 47 (49.5%) with previous arterial event and eight patients (8.4%) who experienced PM. Differences in patients classification according to the two sets of classification criteria are described in Fig. 1.

A total of 90 (48.7%) patients previously identified as having APS, failed to reach a sufficient composite score when applying the 2023 ACR/EULAR classification criteria. Reasons for exclusion are detailed and graphically illustrated in Fig. 2.

When considering patients with previous venous events, 14 (7.6% from the total patients defined as affected by APS per Sydney criteria) did not reach the threshold for classification using the composite index score for the clinical domain due to the concomitant presence of cardiovascular (CV) disease, and one patient (0.5%) did not meet the 2023 ACR/EULAR APS classification due to the aPL profile (aCL and aβ2GPI IgM isotype).

Among the patients with previous arterial events who did not fulfil the 2023 classification criteria for the disease, we observed that nine (4.9%) subjects had high CV risk, five (2.8%) tested positive for IgM isotype and two (1%) patients had both high CV risk and were positive solely for aPL with IgM isotype.

With regard to PM, none of the 39 (21.1%) women who experienced recurrent early miscarriages as defined in the Sydney criteria fulfilled the 2023 clinical criteria. In one of these

cases with previous history of recurrent early miscarriages, the re-classification as having APS was also not possible due to laboratory profile (aCL and aβ2GPI of IgM isotype).

All the 21 (11.3%) patients with previous fetal losses (unexplained death >10th week of gestation) did not fulfil the 2023 clinical criteria; one patient also failed to reach the laboratory criteria (aCL IgM isotype).

When comparing clinical domains of patients with PAPS and SAPS diagnosis, patients without a secondary autoimmune disorders had a higher rate of PM (45.2% vs 5.1%; $P < 0.0001$).

Follow-up after first index event

When considering the evolution during the follow-up (at least 6 months from the inclusion in the research cohort), 32 subjects (35.5%) after the first index event developed additional clinical manifestations among those listed in the 2023 APS criteria, as follows (subdivided by domain):

- domain 1–2 (macrovascular): 4 venous thrombotic events, 7 arterial events;
- domain 3 (microvascular): 11 suspected livedo racemosa, 5 livedoid vasculopathy, 1 myocardial infarction;
- domain 4 (obstetric): 3 fetal deaths, 13 severe preeclampsia and placental insufficiency, 5 early recurrent miscarriages;
- domain 5: 2 valvular thickening, 1 valvular vegetation;
- domain 6: 6 thrombocytopenia.

When considering their aPL profile, 12 subjects were double aPL positive (37.5%), 7 (21.9%) triple positive and the remaining 13 were single positive (40.6%). Further detailed follow-up data for each of the 32 subjects who evolved through time are reported in Table 2.

Considering both index event and subsequent event developed/identified during the follow-up, a total of 122 APS patients fulfilled both Sydney and 2023 classification criteria.

It is worth noticing that additional obstetric clinical manifestations (n = 21) occurred despite standard of care treatment; new thrombotic events (n = 11) occurred while patients were treated with vitamin K antagonist (VKA).

Further, all subjects who developed further clinical manifestations presented an aPL profile to meet the new ACR/EULAR classification criteria satisfaction (namely, single LA positivity, high titre of aCL IgG and or aβ2GPI IgG, regardless of concurrent presence of positivity for IgM isotypes). None of the 64 aPL carriers according to the Sydney definition fulfilled the 2023 criteria for APS. However, eight aPL carriers presented thrombocytopenia (without other clinical manifestations).

Discussion

APS poses unique challenges due to its low prevalence and the often-heterogeneous clinical manifestations [6]. Establishing accurate and effective classification criteria is crucial for enabling better research collaboration, facilitating the development of targeted therapies and, ultimately, improving patients' outcomes [7–9]. The new criteria undoubtedly present some advantages: first, the differential weighting of criteria better represents their relative contribution to an individual's classification of APS; second, the inclusion of non-thrombotic

manifestations (previously referred to as 'extra criteria', such as thrombocytopenia) and a better characterization of microvascular involvement; and third, the numerical goal of improving the specificity when compared with the previous set of criteria. Altogether these aspects have the potential to directly benefit clinical research in APS and facilitate the design of clinical trials. Indeed, well-defined classification criteria can streamline the process of recruiting eligible patients with homogeneous characteristics, potentially leading to an increase in the chances of meeting trial outcomes.

At the same time, the release of the new criteria will pose the need to redefine available research cohorts. Our analysis underlines that not-negligible discrepancies exist. In fact, up to 36% of patients included in our research cohort over the last 3 years will need to be re-classified when applying the new classification criteria. In details, the prevalence of patients previously classified as having thrombotic APS will decrease from 47.3% to 34.9%. Similarly, the percentage of patients included based on a PM history as classified according to Sydney will move from 26.9% to 3.2% when using the new criteria. Conversely, the percentage of patients with aPL but not definite APS will increase from 26% (when applying Sydney criteria) to 61% (with the new classification criteria). When referring to the laboratory profile, 10 patients previously classified as having APS according to Sydney criteria (eight thrombotic index event and two PM) did not meet the new criteria.

With much interest in early or latent autoimmune diseases, the additive point system will allow for systematic study of individuals who fall below the classification threshold who might evolve into an overt form of APS over time. This will facilitate studies of disease evolution and early intervention. Furthermore, the use of an additive scoring system will allow for investigating the potential implications of having very high scores and subsequent prognosis. One challenge for the future will be to reconsider the relative contribution of individual criteria (weights) and analyse the impact of additional criteria acquired during the follow-up that potentially contribute to classification over time. On the other side, the higher specificity might impact the way we could classify a significant percentage of patients in our research cohorts who might experience new clinical manifestation over time. Importantly, patients might develop new clinical manifestations of the disease, potentially changing their classification status. In our cohort, a significant proportion of patients (32 patients, 17.2% of the total cohort who met the Sydney criteria at index event) would be captured by the new criteria only after the occurrence of new event(s) observed during the follow-up. Research specifically targeting these subgroups of patients is warranted in order to identify target approach and management.

Finally, a further question might arise. How should we translate our observations into clinical practice? As discussed elsewhere [10], redefining the weight of some clinical manifestations (e.g. PM) may result in some patients not fulfilling the new criteria, leading to concerns about managing these patients (e.g. in terms of affecting primary or secondary prophylaxis). From this perspective, it is worth noting that classification criteria should not be used to guide treatment decisions but should help guide clinical trials and studies in relevant aPL-positive subgroups. To date, one could only speculate on the outcome of future clinical investigations applying the new set of criteria when compared with previous versions. Classification criteria should never be used to exclude patients who do not fully meet these criteria from receiving appropriate therapies according to their clinical presentation and in line with international treatment recommendations. This is also pertinent to specific subgroups of patients with aPL (e.g. the patients with PM discussed above) [11]. Diagnosis of APS remains the purview of an appropriately trained physician evaluating an individual patient. It is anticipated that other groups will independently test these criteria, which will constitute important external

validation. This will be particularly important for paediatric APS and those with organ dominant manifestations, e.g. haematological or skin involvement, since it was a limitation of previous criteria that the APS patient cohorts might not have adequately represented these subgroups. Similar limitations also pertain to several ethnic groups.

Managing the transition from previous classification criteria to a new set of criteria for rare diseases is a complex process that requires careful planning, communication and collaboration among healthcare professionals, patients and other stakeholders. These criteria have strong operating characteristics and were built using rigorous methodology that was both data-driven and expert-based.

While challenges might arise in the process of applying the new system in available and upcoming cohorts, the potential benefits of improved accuracy in diagnosis and treatment undoubtedly justify the effort.

Limitations

We acknowledge that our study presents some limitations. First, our cohorts are selected from consecutive patients attending our referral centres. We cannot exclude that an intrinsic risk of bias in terms of patients category representation might exist (e.g. the cohort might appear to be enriched for obstetric manifestations). Further, despite some of the manifestations included in new classification criteria not being inserted in the previous Sydney criteria, our data collection system was developed in 2016 to capture both criteria and previously called extra-manifestation criteria [10]. We are therefore confident that manifestations such as livedo reticularis or livedoid vasculopathy were correctly recorded if present. It was outside of the scope of this study to provide a prospective validation in terms of accuracy of the new criteria set or to perform a comparison among all previously suggested APS classification criteria.

Finally, the development process of the 2023 EULAR/ACR criteria included a validation exercise. In brief, main findings are summarized as follow: two cohorts, each of 284 patients, during phase IV of establishing the ACR/EULAR classification set were formed by requesting that phase IV collaborators (none of whom participated in phase III) contribute with 30 cases each. We hope our study might further strengthen the robustness of the validation process of the proposed criteria and might pave the way for future studies.

Data availability

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Author contributions

Silvia G. Foddai (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Massimo Radin (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Irene Cecchi (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Elena Rubini (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft),

Alice Barinotti (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Paula Alba (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Supervision, Writing—original draft, Writing—review & editing), Carla Gimen Alonso (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Daniela Rossi (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft), Dario Roccatello (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft) and Savino Sciascia (Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Visualization, Writing—original draft. Supervision, Writing—review & editing). S.S. takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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TABLE 1. Main clinical and laboratory characteristics of the cohort

Characteristic	**Value**
Whole cohort (n = 249, 100%)	
Age at inclusion, mean (s.d.), years	47 (14)
Follow-up, mean (s.d.), years	12 (7)
Sex, n (%)	
Male	54 (22)
Female	195 (78)
APS cohort according to Sydney criteria (n = 185, 74%)	
PAPS, n (%)	146 (59)
SAPS, n (%)	39 (16)
Systemic lupus erythematosus, n (%)	35 (14)
Psoriatic arthritis, n (%)	2 (1)
Undifferentiated connective tissue disease, n (%)	2 (1)
aPL profile	
Single, n (%)	72 (29)
Double, n (%)	57 (23)
Triple, n (%)	56 (23)
First clinical manifestation (index event)[a] (n = 185)	
Venous thrombosis, n (%)	55 (29.8)
Arterial thrombosis, n (%)	63 (34)
Pregnancy complications, n (%)	67 (36.2)
>3 early miscarriages, n (%)	39 (21.1)
>1 fetal loss after 10th WOG, n (%)	21 (11.3)
Premature birth <34th WOG for preeclampsia/placental insufficiency, n (%)	7 (3.8)
aPL carriers, n (%)	64 (26)
Single, n (%)	33 (13)
Double, n (%)	21 (9)
Triple, n (%)	10 (4)

Percentage are rounded to the first decimal.

a Refers only to patients classified as APS per Sydney criteria (n = 185), and subsequent clinical presentation percentage are calculated based on this assumption. aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; PAPS: primary APS; SAPS: secondary APS; WOG: weeks of gestation.

FIGURE 1. Characterization of the cohort based on first index event according to the Sydney criteria and 2023 criteria on antiphospholipid syndrome. aPL: means antiphospholipid antibodies; APS: antiphospholipid syndrome; PM: pregnancy morbidity

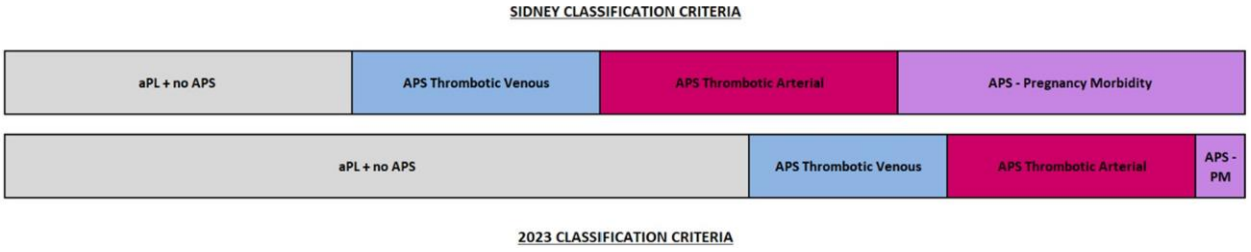

FIGURE 2. Percentages of patients fulfilling 2023 criteria and reason of exclusion, based on first index event according to the Sydney criteria. aPL means: antiphospholipid antibodies; APS: antiphospholipid syndrome; CVD: cardiovascular disease

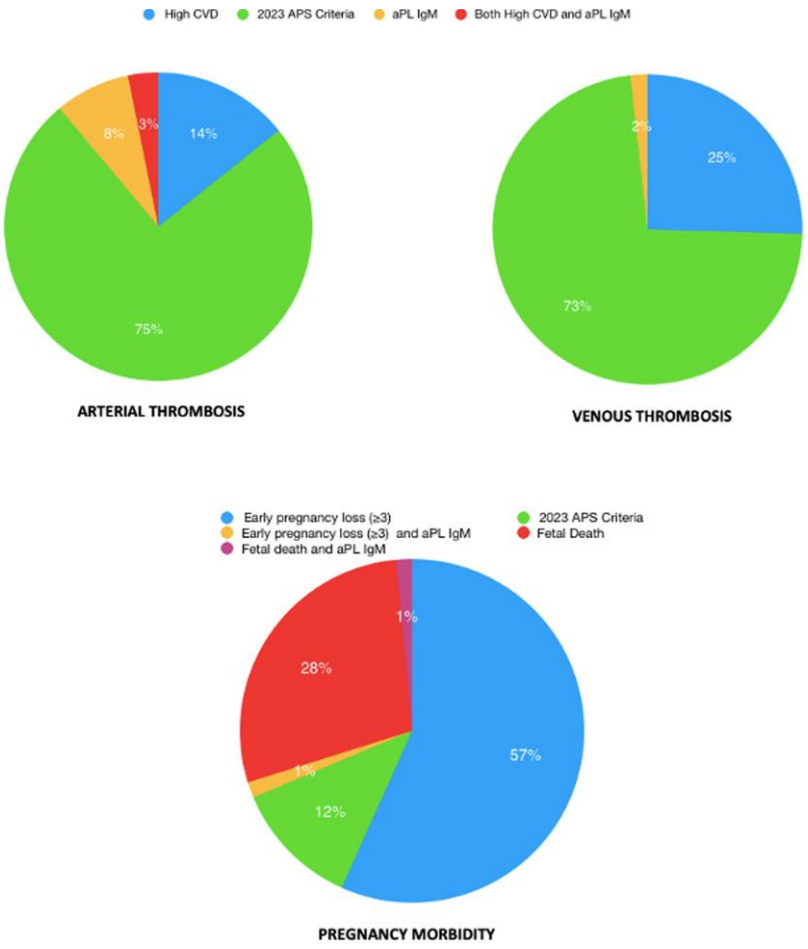

TABLE 2. Follow-up data of the 32 patients who reached 2023 criteria through time

First index event per Sydney criteria (n)	**Manifestations during follow-up**
Venous thrombotic event with high CVD risk (3)	Arterial thrombotic event
	Arterial thrombotic event
	Cardiac valve thickening
Arterial thrombotic event with high CVD risk (3)	Suspected livedo racemosa
	Thrombocytopenia
	Venous thrombotic event
≥3 Consecutive pre-embrional losses (<10w) and/or fetal death (10w 0d–15w 6d) (12)	Arterial thrombotic event with no high CVD risk and thrombocytopenia
	Arterial thrombotic event with no high CVD risk and fetal death
	Suspected livedo racemosa and livedoid vasculopathy
	Suspected livedo racemosa and livedoid vasculopathy
	Arterial thrombotic event with no high CVD risk, fetal death
	Arterial thrombotic event with high CVD risk, suspected livedo racemosa, fetal death
	Venous thrombotic event with no high CVD risk
	Suspected livedo racemosa, thrombocytopenia
	Suspected livedo racemosa, severe PEC and PI
	Suspected livedo racemosa, suspected livedoid vasculopathy, fetal death
	Suspected livedo racemosa, thrombocytopenia
	Heart valve thickening and vegetation
Fetal death (10w 0d–33w 6d), no PE with severe PI (14)	Thrombocytopenia, severe PE and PI, >3 early miscarriages, suspected livedo racemosa
	Venous thrombotic event with no high CVD risk
	Venous thrombotic event with no high CVD risk
	Severe PE and PI
	Severe PE and PI
	Severe PE and PI
	Severe PE and PI
	Severe PE and PI
	Severe PE and PI
	Arterial thrombotic event with no high CVD risk, myocardial disease, severe PE and PI
	Suspected livedo racemosa, suspected livedoid vasculopathy, severe PE and PI, >3 consecutive early miscarriages
	Suspected livedo racemosa, livedoid vasculopathy, >3 consecutive early miscarriages, severe PE and PI
	Severe PE and PI, >3 early consecutive miscarriages
	Thrombocytopenia, >3 early consecutive miscarriages, severe PE and PI

CVD means: cardiovascular disease; d: days; PE: preeclampsia; PI: placental insufficiency; w: weeks.