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Recommendations

Development and validation of a EULAR disease activity score in antiphospholipid syndrome

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ABSTRACT

Objectives: To develop and validate a European Alliance of Associations for Rheumatology (EULAR) disease activity score in antiphospholipid syndrome (EAPSDAS).
Methods: Twenty-four Task Force members and an international group of 53 antiphospholipid syndrome (APS) experts/collaborators, 65 patients with primary APS, and 21 healthcare professionals participated. EAPSDAS development proceeded in 4 phases: (i) item generation using a systematic literature review and 2 surveys; (ii) item reduction by rating items on their importance to be included in EAPSDAS and using Delphi methodology; (iii) item scoring based on real-world clinical vignettes and using as criterion standard the physician global assessment (PhysGA); and (iv) validation.
Results: One hundred seventy items representing APS activity were generated, and 140 deduplicated candidate items were rated by participants. Using a ≥75% vote threshold and Delphi consensus among Task Force members, 24 items were included in the EAPSDAS thrombotic/microvascular/nonthrombotic (TMN) scale and 6 in the obstetric scale. Item scoring was based on ratings of 3 versions of 60 vignettes with new/worsening manifestations (30 single TMN or obstetric manifestations, 26 combinations of 2 TMN manifestations, 2 inactive cases, 2 testing cases) by physicians. Item scores were calculated as the adjusted mean PhysGA in linear regression analysis. A 1-month time frame was defined for the TMN scale and the entire pregnancy for the obstetric scale. Scores for stable or improved TMN manifestations were also included. High face and content validity, construct validity (internal/external standard), and reliability were demonstrated using real-world clinical vignettes.
Conclusions: Using data-driven and consensus methodology, EAPSDAS was developed and initial validation was performed. Further validation in prospective studies is warranted.

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by the presence of antiphospholipid antibodies (aPL) and a broad spectrum of obstetric and thrombotic, microvascular, and non-thrombotic (TMN) clinical features, ranging from mild (eg, livedo reticularis) to major organ (eg, stroke, kidney failure) manifestations, and from single sites to multiple sites of involvement [1–5]. The clinical criteria of APS have been categorised into 5 main domains in the 2023 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria: macrovascular (venous and arterial thrombotic events), microvascular, obstetric, cardiac valve, and haematological [6]. Although not completely understood, the clinical heterogeneity of APS may be driven by a complex interplay between thrombotic and inflammatory mechanisms [7–12].

Newly occurring APS manifestations may be followed by long periods of inactivity, but some manifestations can be refractory or frequently recurring despite the standard anticoagulation and/or antiplatelet treatment [13–16]. Treatments that could decrease the development of new thromboses or pregnancy complications and treatments for microvascular and nonthrombotic manifestations are urgently needed [17–20]. However, testing of new treatments in APS has been hindered by a paucity of suitable outcome measures.

A disease activity score for APS that assesses multiple clinical manifestations would be useful in evaluating response to treatment in clinical trials and monitoring disease activity status in observational studies and clinical practice [21–23]. Disease activity refers to new-onset events (eg, new venous thromboembolism [VTE] rather than postphlebitic syndrome) or reversibility (eg, improvement of thrombocytopenia after treatment), as distinct from damage, which refers to irreversible manifestations of the disease or consequences of its treatment, including permanent organ or tissue injury [24,25]. In contrast, disease severity reflects aspects of both current activity and accumulated damage as well as their impact on an individual's health, functional ability, quality of life, and prognosis.

Our objective was to develop and validate a EULAR disease activity score for APS (EAPSDAS), with the contribution of an international group of APS experts, patients, and healthcare professionals.

METHODS

According to the EULAR standardised operating procedure, a Task Force was assembled after the submission of the project proposal by the convenor (MGT) and its approval by the EULAR Quality of Care Committee (QoC) and the EULAR Council. The Task Force consisted of 24 members from 13 countries: a 5-member Steering Committee (3 adult rheumatologists/APS experts: convenor [MGT], RC, and AT, and 2 fellows [GJP-E,

SS]), 3 methodologists (RBML, TS, MMW), 5 adult rheumatologists, 1 paediatric rheumatologist, 2 vascular medicine physicians, 2 physicians leading large obstetric APS cohorts, 1 immunologist, 2 members of the EMEUNET (Emerging EUlar-NETwork), 1 nonphysician health professional in rheumatology (HPR), and 2 patient research partners from People with Arthritis/Rheumatism (PARE). Five members were included through an open call to EULAR countries via a competitive application process. Task Force members were selected according to their experience in the field, participation in prior task forces, and balance in the geographical distribution. In addition, a multidisciplinary group of 53 experts in APS from 5 continents (Europe, North America, South America, Asia, and Australia/Oceania), designated as 'Collaborators' (listed in the Collaborators section), agreed to participate in the project phases. Ninety patients with primary APS and 21 HPRs agreed to participate anonymously in the phase I and II surveys.

Our approach to developing the activity measure was guided by several overarching considerations. First, we defined 2 broad main domains, the TMN domain and the obstetric domain, that would have separate stand-alone scores. This was done because nonpregnant women and men would not be eligible to register scores for obstetric manifestations, and combining scores from obstetric and TMN domains would thereby bias scores against anyone who was not pregnant. Second, because APS manifestations are often episodic events (eg, venous thrombosis, stroke) while only some are more continuous (eg, thrombocytopenia, proteinuria), we planned to create a scale rather than an index. A scale measures intensity based on a hierarchy of items or variables, whereas an index includes ratings of multiple items and adds them together in a single score [26]. For example, the ACR Functional Class [27] and the British Isles Lupus Activity Group-2004 [28] are scales, while the Disease Activity Score 28 [29] and Systemic Lupus Erythematosus (SLE) Disease Activity Index (SLEDAI) [30] are indices. Third, we focused primarily on rating new or worsening manifestations, as these provide the clearest evidence of activity, and secondarily addressed stable or improved manifestations. Fourth, in alignment with other outcome measures, we did not include treatment intensity as an indicator of activity, as doing so could create circularities of reasoning in treatment studies.

Development of the measure proceeded in 4 phases using consensus and data-driven methods: phase I: item generation; phase II: item reduction; phase III: item scoring; and phase IV: testing and validation (Box 1). This project was focused solely on patients with primary APS. A more detailed presentation of the methodology is provided in an accompanying article [31].

Box 1 Overall methodology for the development and validation of the European Alliance of Associations for Rheumatology (EULAR) antiphospholipid syndrome disease activity score

Phase I: item generation

a) Systematic literature review to identify potential features indicating disease activity.
b) Survey with open-ended questions to define the concept of disease activity in antiphospholipid syndrome (APS).
c) Survey with open-ended questions to describe all clinical, laboratory, radiological, and histological features that indicate disease activity in APS.

Phase II: item reduction

a) Elimination of highly related items among those retrieved in phase I.
b) Survey to rate items for importance to be included in a disease activity score for APS.
c) Delphi method consensus about the items to be included in the EULAR APS disease activity score.

Phase III: clinical vignettes—item scoring

a) Development of clinical vignettes based on real-world patient scenarios.
b) Survey to rate the degree of the patient's current disease activity in each clinical vignette, using a 0 to 10 rating scale.
c) Linear regression analysis to calculate each item's scoring.
d) Delphi methodology about the time interval for thrombotic manifestations, and the scoring of improved and stable manifestations.

Phase IV: validation

a) Face and content validity
b) Construct validity: external validity
c) Construct validity: internal validity
d) Reliability

Phase I: item generation

In phase I, we aimed to collect an inventory of all items potentially related to disease activity by using (i) a systematic literature review (SLR) to identify features indicating disease activity and their prevalence, and (ii) 2 surveys among experts in APS and patients with primary APS. The first survey asked respondents to describe, in an open-ended format, the 'concept' of disease activity in primary APS based on their experience, and the second asked to list all clinical, laboratory, radiological, and histological features that indicate disease activity in primary APS. The SLR and the second survey provided a list of candidate items.

Phase II: item reduction

In phase II, we reduced the number of items in the list of candidate items as follows: (i) the Steering Committee eliminated similar or closely related items among those reported in the second survey and those retrieved by the SLR, (ii) we created a new (third) survey asking participants (Task Force members/Collaborators, patients, and HPRs) to rate items of the deduplicated list on how important each was for inclusion in a disease activity score for APS, using a 0 to 10 rating scale (0 = not important at all; 10 = extremely important), and (iii) we followed a Delphi method to reach consensus in a 2-day video-conference meeting of the Task Force at which the results of the third survey were discussed and items were voted for inclusion. More than 75% of the Task Force members participated in both days.

The initial threshold for inclusion of an item was an endorsement by >50% of members. This threshold was subsequently changed to ≥75%, by approval of the Task Force members, to reduce the number of items included.

Phase III: item scoring

To develop scores for each item voted by the Task Force, we used clinical vignettes that described real-world patient histories in which a new or worsening disease manifestation occurred over a period of 1 month, a time frame decided after consensus with the Steering Committee and the Task Force group. Vignettes were based on real patient cases from the files of the Steering Committee members. Vignettes included patient demographics, APS history, and other medical history including comorbidities and related medications, current presentation including new/worsening manifestations, and laboratory, imaging, and histologic data. For each item, 3 different patient cases were abstracted for the same manifestation, and 3 vignette versions (A, B, C) were developed. Using 3 versions of clinical cases, patients with the same manifestation but different demographic characteristics and comorbidities were represented, to decrease the likelihood that item scores would be influenced by a given patient's background.

Since 2 different new/worsening manifestations may rarely occur concurrently (within a 1-month period) in APS (eg, arterial thrombosis and thrombocytopenia), a list of potential combinations of 2 items was also developed from those endorsed by the Task Force. We did not test vignettes with 3 or more different new manifestations occurring concurrently, because these were deemed clinically very unusual. Steering Committee members independently reviewed the list of candidate combinations of 2 items and suggested those with moderate-high probability to occur simultaneously; 26 combinations of manifestations that were most likely to co-occur in real life were selected to be included as 'double manifestation' scenarios. Real-world cases with these specific double manifestations were collected from the case files, as described above.

Physicians from the Task Force and the Collaborators were randomly assigned to rate 1 of the 3 vignette versions (A, B, C). Although the 3 sets of clinical vignettes included different single-item cases, the same 26 double-manifestation cases were included in all 3 versions due to their rarity. The criterion standard was the physician global assessment (PhysGA) of the patient's current disease activity using a 0 to 10 rating scale. Participants were asked to rate the level of activity, not severity.

Each item's score was calculated as the adjusted mean PhysGA, based on linear regression analysis that adjusted for physician characteristics: age (35-44/45-54/55-64/65+), gender, geographic region (Europe/North America/Rest of world), rheumatologist vs other specialty, years in practice (0-9/10-19/20+), average number of patients seen monthly (0-4/5-9/10-19/20+), and vignette version (A, B, C). We also examined the concordance of pairwise rankings of all items and the proportion of raters who ranked the items similarly.

We compared the scores of the vignettes with double new or worsening manifestations with the scores of each corresponding single manifestation to determine if summing the item scores was indicated. We also used paired t-tests and/or rank tests to determine if ratings for double manifestations were the approximate sum of the single manifestations, or if these ratings were dominated by the more highly rated single manifestation. Lastly, we tested if the lower-ranked item of the pair was significantly associated with the PhysGA after adjustment for the higher-ranked item in regression analyses. Significant items were retained, and scores for these items received a 'bump-up' when they co-occurred.

Following discussions during the second Task Force meeting on the 20 February 2024, we conducted an additional survey among the physicians from the Task Force and Collaborators to define the time interval between 2 thrombotic events to be considered as 'new' APS activity, and whether manifestations that were abnormal but stable, or manifestations that were improved but still present, should be scored (Box 1).

Phase IV: testing and validation

Face and content validity

To evaluate the measure's face and content validity, we asked physician experts in APS or SLE and patients with primary APS, not previously involved in the project, to rate each of the 2 EAPSDAS scales (TMN and obstetric) as a whole for relevance and comprehensiveness. Relevance referred to whether the scales' items reflect disease activity in APS, and comprehensiveness referred to whether the scales included diverse manifestations and did not omit critical items.

Construct validity-external standard

We tested the construct validity of the item scores using real-world clinical vignettes, with the PhysGA (0-10 rating scale) as the external standard. Physicians (Task Force members and Collaborators) scored a different vignette version than the one they scored in Phase III. We computed the Spearman correlation between the PhysGA and the items' scores for each physician.

Construct validity-internal standard

This exercise directly compared item scores against each other with regard to the level of disease activity represented by each item. Physicians from the Task Force and Collaborators' group, blinded to item scores, were asked to rank the vignettes from most active to least active, with ties allowed. The item rankings were then correlated with the item scores. This differed from the prior exercise, where each item was rated against an external standard (the PhysGA).

Reliability

Inter-rater reliability of the scale was tested using clinical vignettes. Thirty physicians (half were not previously involved in the project) were asked to apply the EAPSDAS scales to each of 20 clinical vignettes on 16 TMN manifestations and 4 obstetric manifestations. Reliability was measured using intraclass correlations, based on a 2-factor random effects model for agreement.

RESULTS

Phase I: item generation

First survey: concept of disease activity in APS

Responses from 74 Task Force members and Collaborators to the open-ended question about the concept of disease activity in APS were consistent in that the concept was mainly defined by clinical manifestations (71 of 74 responses). The qualifiers of the disease activity concept were new/acute events (30/74), recurrence or worsening (22/74), modifiable with treatment (7/74), and relapse or risk of relapse (4/74). Among the 90 patients who responded to the survey, 25 had incomplete data. Six patients reported that they were unaware or could not explain the meaning of disease activity in APS, and 59 described clinical manifestations/symptoms. Nineteen patients reported on qualifiers of the disease activity concept, including new/acute events (n = 5), worsening events (n = 8), recurrent events (n = 1), and modifiable with treatment features (n = 7).

SLR results and second survey

The SLR yielded 77 items potentially related to disease activity in APS. A detailed presentation of the results of the SLRs is presented in the methodology manuscript published separately [31]. Task Force members/Collaborators (n = 73) nominated 132 items, and patients (n = 59) nominated 74 items.

Phase II: item reduction

Combining items from the SLR and the second survey, 170 items were generated. Similar or highly related items were eliminated to avoid redundancy, which reduced the number of items to 140.

In the third survey, participants' (74 Task Force members and Collaborators, 53 patients and 21 HPRs) ratings of the importance of the 140 items to be included in a disease activity score were calculated separately for each of the 3 groups of participants (physicians, HPRs, and patients). The items rated most highly by all participant groups were catastrophic APS (thrombosis in 3 or more territories in 1 week), pulmonary embolism, arterial thrombosis, deep vein thrombosis, and ischaemic stroke.

At the first Task Force meeting, 52 items were voted upon by 50% of participants (Table 1) and 24 items ultimately met the ≥75% vote threshold and were carried forward (Table 2). The Steering Committee subsequently modified some items to increase their specificity: venous thrombosis was divided into provoked and nonprovoked thrombosis, both venous and arterial thrombosis were classified as thrombosis in 1 or 2 or 3 territories, thrombocytopenia was divided into moderate and severe, and APS nephropathy was replaced by APS nephropathy-related acute kidney injury, nephrotic range proteinuria, and nonnephrotic proteinuria [32]. With these changes, 30 single items were included in the list of APS disease activity items.

Phase III: item scoring based on clinical vignettes

In total, 180 real-world patient scenarios (3 versions of 60 vignettes) were sent to 67 physicians, split into 3 groups (each received 1 of 3 vignette versions). Each rater was asked to rate 30 clinical vignettes with 1 new or worsening APS manifestation (24 TMN and 6 obstetric manifestations), 26 vignettes with 2 new APS manifestations, along with 1 vignette with no new thrombotic manifestations, and 1 vignette with a normal pregnancy. Two testing vignettes to orient raters to the task were also included. Two physicians did not score more than 10% of the vignettes, and their responses were omitted. We asked respondents to rate whether the patient described in each vignette was typical of one that they might see in their practice (very typical, somewhat typical, not typical). Seventy-five per cent of TMN manifestations and 91% of obstetric manifestations were rated as very typical or somewhat typical. High consistency of physician ratings of PhysGA was observed (intraclass correlation [95% CI] 0.98 [0.97, 0.99] and 0.99 [0.98, 1.00] for the TMN and obstetric manifestations, respectively).

We first compared scores of the vignettes with 2 new manifestations occurring in a 1-month period to the corresponding single-item vignettes. Ratings of these vignettes were not the sum of each single-item rating, but rather were dominated by the more highly rated manifestation in each case. This was universally true for combinations involving either arterial events or venous thrombotic events, which were the most highly rated manifestations, and were also present in many of the other vignettes. Scores of 6 vignettes describing 2 new manifestations concurrently (defined as within 1 month) were significantly higher than the single manifestation alone, indicating a 'bump up' in these scores was justified (Table 3).

Among the TMN manifestations, we used paired t-tests to determine if item scores were significantly different between VTE unprovoked or provoked; proteinuria nephrotic or nonnephrotic; and thrombocytopenia moderate or severe, to determine whether these distinctions should be retained or merged. Each pair had significantly different mean ratings, so these were retained as separate items. Item scores based on adjusted means are provided in Table 3.

Table 1
Items voted by >50% of Task Force members (ordered by the physician's mean importance in the third survey)

New or worsening manifestations
Catastrophic APS
Pulmonary embolism
Arterial thrombosis
Deep vein thrombosis
Ischaemic stroke
Splanchnic venous thrombosis
Splanchnic arterial thrombosis
Microangiopathy, microvascular thrombosis
Cerebral venous sinus thrombosis
Radiologic signs of thrombosis
Severe pre-eclampsia/eclampsia
Histologic signs of microthrombi or thrombotic microangiopathy (eg, renal, skin)
Venous thrombosis
APS nephropathy
Myocardial infarction
Thrombocytopenia
Triple antiphospholipid antibody positivity
Intracardiac thrombi
Ophthalmic arterial or venous thrombosis
Foetal death unexplained
Extensive villous ischaemia, villitis, and utero-placental vasculitis, multifocal utero-placental thromboses
Haemolytic anaemia
Persistently high/increase in anti-β2GPI antibody titres
Brain ischaemic lesions on magnetic resonance imaging
Cardiac valve vegetations
Digital ischaemia/gangrene
Skin ulcers
Transient ischaemic attack
HELLP syndrome
Cardiac microvascular disease on magnetic resonance
Intrauterine growth restriction (IUGR)
New recurrent first-trimester miscarriage
Diffuse alveolar haemorrhage
Adrenal haemorrhage
Transverse myelitis
Livedoid vasculopathy
Livedo racemosa
Livedo reticularis
Amaurosis fugax
Noninfectious endocarditis (Libman-Sacks)
Angina
Pulmonary hypertension
Epilepsy/new seizures
Proteinuria
Cognitive/memory impairment
APS nephropathy-related acute kidney injury
Premature birth due to placental insufficiency
Superficial venous thrombosis
Avascular necrosis/osteonecrosis
Cardiac valve thickening
Longitudinal myelitis
Migraine

APS, antiphospholipid syndrome; HELLP, haemolysis, elevated liver enzyme levels, and low platelet levels.

Table 2
Items voted by ≥75% of Task Force members (ordered by the physician's mean importance in the third survey)

New or worsening manifestations
Catastrophic APS
Venous thromboembolism[a]
Arterial thrombosis[b]
Severe pre-eclampsia/eclampsia
APS nephropathy
Thrombocytopenia
Foetal death unexplained
Haemolytic anaemia
Cardiac valve vegetations including noninfectious endocarditis
Digital ischaemia/gangrene
Skin ulcers
HELLP syndrome
Itrauterine growth restriction (IUGR)
New recurrent first-trimester miscarriage
Diffuse alveolar haemorrhage
Adrenal haemorrhage
Transverse myelitis
Livedoid vasculopathy
Livedo reticularis/livedo racemosa
Pulmonary hypertension
Epilepsy, new seizures
Premature birth due to placental insufficiency
Avascular necrosis/osteonecrosis
Cardiac valve thickening

APS, antiphospholipid syndrome; HELLP, haemolysis, elevated liver enzyme levels, and low platelet levels.
[a] Venous thromboembolism (confirmed by imaging) includes pulmonary embolism, deep vein thrombosis, thrombosis/occlusion in splanchnic, renal, cerebral, retinal, and upper extremity veins deep vein thrombosis, pulmonary embolism, and thrombosis/occlusion in splanchnic, renal, cerebral, retinal, and upper extremity veins.
[b] Arterial thrombosis (confirmed by imaging) includes thromboses in coronary arteries, cerebral arteries, or peripheral, splanchnic, retinal arteries, and organ infarcts (eg, kidney, liver, or spleen).

Pairwise ranking comparisons

We compared the ratings between pairs of manifestations to examine whether the item scores were consistent with the predominant opinion among physicians. This analysis supported the mean vignette rankings. Of 276 comparisons between all possible pairs of items, 259 comparisons of individual physician rankings were consistent with the ranking of PhysGA means (eg, the item score for unprovoked VTE was higher than the item score for non-nephrotic proteinuria, and 74% of physicians rated unprovoked VTE as higher than non-nephrotic proteinuria, while 18% rated these items the same, and 8% rated proteinuria higher). Seventeen comparisons (6.1%) were inconsistent (eg, mean vignette rating was higher in A vs B, while a higher proportion of physicians rated B higher than A). In 14 of these 17 cases, the inconsistency was the result of rounding of item scores to integers (0 to 10), which made some manifestations 'equal' when the mean rating and the pairwise ranking were consistent. Therefore, we omitted rounding and used a scale of 0 to 100. In 3 cases (digital ischaemia/transverse myelitis; avascular necrosis/VTE provoked; avascular necrosis/severe thrombocytopenia), there were slight true` discrepancies between the mean ratings and the pairwise comparison.

Time interval for scoring of thrombotic events

Sixty-six physicians (Task Force members and international Collaborators) completed the survey about the time interval between 2 thrombotic events for scoring the second event as 'new' APS activity and the scoring of stable or improved manifestations. Concerning the time interval for scoring an arterial or venous thrombosis as 'new', 50% voted for 1 month and 50% voted for greater than 1 month. Voting among the Task Force members was then conducted to decide between 1 month and 3 months; 14 of 18 physicians voted in favour of the 1-month interval for arterial thrombosis and 13 of 18 in favour of the 1-month interval for venous thrombosis.

Scoring of stable or improved manifestations

The majority of physicians who participated in the survey (67%-75%) favoured scoring either stable or improved severe thrombocytopenia and stable or improved haemolytic anaemia. If unchanged, both severe thrombocytopenia and haemolytic anaemia were voted to be scored with the original score. If improved, haemolytic anaemia will be scored with 50% of the original score. If severe thrombocytopenia improves to moderate thrombocytopenia, the score for moderate thrombocytopenia would be used. Moderate thrombocytopenia would be considered 'improved' only if normalised, in which case the item will not be scored. If unchanged, moderate thrombocytopenia would be scored with the original score. For skin ulcers and proteinuria, more than 60% voted in favour of scoring when either stable or improved. If unchanged, these items will be scored with the original score (100%). Skin ulcers will be scored with 50% of the original score if improved as judged by the physician. Nephrotic-range proteinuria will be considered improved only if it decreases to the non-nephrotic range, while non-nephrotic proteinuria will be considered improved if it decreases to <500 mg/24 h. Fewer than 60% of respondents voted to retain scores for digital ischaemia/gangrene, seizures, livedoid vasculopathy, and livedo reticularis/livedo racemosa when these items were unchanged (50%-59%) or improved (44%-53%). It was, therefore, decided that these manifestations would only be scored if new or worsened. Scoring of stable or improved aseptic necrosis, pulmonary hypertension, APS nephropathy-related acute kidney injury, valve vegetations, and valve thickening was endorsed by less than 50%, and so these would also only be scored if new or worsened.

In conclusion, the EAPSDAS scales are presented in Table 3. EAPSDAS is composed of 2 separate scales: a scale for TMN manifestations to be used in evaluating all patients with APS, and an obstetric scale to be used in evaluating pregnant patients with a history of APS. Manifestations are scored if they are new (first or relapsing) or worsening, and should be attributed to APS. Other causes should be ruled out. The time frame for the TMN scale is the past 1 month. The time frame for the obstetric scale is any time during the pregnancy. The scoring for bump-up items and the stable or improved manifestations are shown in the corresponding columns.

Phase IV: validation

Face and content validity

Twenty-one experts in APS or SLE and 45 patients with primary APS from 4 continents (Europe, North America, South America, and Asia) not involved in any previous phase of the project, rated the TMN and obstetric scales of the APS disease activity score for face and content validity. For both scales, the majority of raters assessed the relevance and comprehensiveness as very good or adequate (Table 4).

Table 3
Scores for thrombotic, microvascular, and nonthrombotic (TMN) manifestations, and obstetric manifestations attributed to APS (other causes are ruled out)

A. Scores for TMN manifestations. Interval = 1 mo					
New or worsening manifestations	Score for new or worsening manifestations	Score for 'bump-up' manifestations (both new or worsening manifestations occurring in a 1-mo period)	Score for 'abnormal but stable' single manifestations	Score for 'improved but still present' single manifestations	TMN-1/TMN-2 items
Thrombosis (arterial or venous) in 3 territories	95				TMN-1
Pulmonary haemorrhage	93				TMN-1
Arterial thrombosis[a] in 2 territories	91				TMN-1
Venous thromboembolism[b] in 2 territories	88				TMN-1
Arterial thrombosis in 1 territory	87				TMN-1
Venous thromboembolism in 1 territory, unprovoked	85				TMN-1
Adrenal haemorrhage	84				TMN-1
Digital ischaemia/gangrene	82				TMN-1
Transverse myelitis	80				TMN-1
Haemolytic anaemia	75		75	37 if haemoglobin levels improved by 50%	TMN-2
Pulmonary hypertension	72				TMN-1
Livedoid vasculopathy	71				TMN-1
APS nephropathy-related nephrotic range proteinuria	71	Nephrotic-range proteinuria and livedo reticularis or livedo racemosa: 81	71	59 if improved to non-nephrotic range; 0 if improved to <500 mg/24 h proteinuria	TMN-2
APS nephropathy-related acute kidney injury	67	APS nephropathy-related acute kidney injury and severe thrombocytopenia: 82			TMN-1
Thrombocytopenia, severe (platelet count: ≤50,000/μL)	66	Severe thrombocytopenia and skin ulcers: 77	66	47 if platelet count improved to 51,000-100,000/μL; 0 if improved to >100,000/μL	TMN-2
Venous thromboembolism in 1 territory, provoked	66				TMN-1
Avascular necrosis (osteonecrosis)	66				TMN-1
Cardiac valve vegetation	65				TMN-1
Skin ulcers	64	Skin ulcers and livedo reticularis or livedo racemosa: 70 Skin ulcers and nephrotic range or non-nephrotic proteinuria: 76	64	32 if improved 50% by physician judgement	TMN-2
Seizures/epilepsy	61				TMN-1
APS nephropathy-related non-nephrotic proteinuria (>500 mg/24 h)	59	APS nephropathy-related non-nephrotic proteinuria and moderate or severe thrombocytopenia: 76	59	0 if <500 mg/24 h proteinuria	TMN-2
Cardiac valve thickening	50				TMN-1
Thrombocytopenia, moderate (platelet count: 51-100,000/μL)	47		47	0 if platelet count >100,000/μL	TMN-2
Livedo reticularis or livedo racemosa	39				TMN-1
No new or worsening manifestations	0				TMN-1
B. Scores for obstetric manifestations					
Interval = pregnancy; score = highest rated manifestation that occurred during the pregnancy					
New manifestation					Score
HELLP syndrome					85
Eclampsia or severe pre-eclampsia					82
Foetal death					72
Premature birth due to placental insufficiency (with or without severe features):					72
Intrauterine growth restriction					67
New recurrent first-trimester miscarriage					46
No pregnancy complications					0

APS, antiphospholipid syndrome; HELLP, haemolysis, elevated liver enzyme levels, and low platelet levels.
Grey colour, 'not scored' items; TMN-1, items not scored if they are stable or improved; TMN-2, items scored if they are stable or improved.
Provoked venous thromboembolism is a venous thromboembolism that occurs in the setting of a transient risk factor (major or minor) or a persistent risk factor.
[a] Arterial thrombosis (confirmed by imaging) includes thromboses in coronary arteries, cerebral arteries, or peripheral, splanchnic, retinal arteries, and organ infarcts (eg, kidney, liver, or spleen).
[b] Venous thromboembolism (confirmed by imaging) includes pulmonary embolism, deep vein thrombosis (legs or arms), thrombosis/occlusion in splanchnic, renal, cerebral, or retinal veins.

Table 4
Face and content validity appraisals by physicians and patients

Rater	Scale	Feature	Judgement			
			Very good (%)	Adequate (%)	Doubtful (%)	Inadequate
Physicians N = 21	TMN scale	Relevance	62	33	5	0
	TMN scale	Comprehensiveness	81	14	5	0
	Obstetric scale	Relevance	90	5	5	0
	Obstetric scale	Comprehensiveness	76	24	0	0
Patients N = 45	TMN scale	Relevance	84	16	0	0
	TMN scale	Comprehensiveness	74.5	25.5	0	0
	Obstetric scale	Relevance	87.5	12.5	0	0
	Obstetric scale	Comprehensiveness	85	15	0	0

TMN, thrombotic, microvascular, nonthrombotic manifestations.

Construct validity-external standard

Sixty physicians from the Task Force group and Collaborators, all blinded to the EAPSDAS scale scores, were invited to participate in the construct validity exercise, which involved rating 30 clinical vignettes for overall APS activity. Fifty-four physicians replied (90%); 2 had incomplete data. Correlations of the physicians' ratings (PhysGA) with the APS disease activity item scores were high for both the TMN scale (median Spearman $r = 0.74$) and the obstetric scale (median Spearman $r = 0.88$) (Table 5). Differences among raters were not attributable to differences in scoring any particular item.

Construct validity-internal standard

Fifty-five physicians, blinded to item scores, completed a survey in which they placed each vignette in rank order of APS activity (highest to lowest), separately for TMN vignettes and obstetric vignettes. These rankings were highly correlated with item scores of each scale (median Spearman $r = 0.79$ for the TMN scale; median Spearman $r = 0.91$ for the obstetric scale) (Table 5).

Reliability

When tested by applying the EAPSDAS to 20 clinical vignettes, inter-rater reliability (by intraclass correlations) was 0.82 (95% CI 0.72, 0.92) for the TMN scale and 0.97 (95% CI 0.92, 1.00) for the obstetric scale.

Implementation of EAPSDAS

In the implementation of EAPSDAS, the observation time for the TMN scale would be divided into monthly intervals. The score for each month is the score of the highest-rated item that is new/worsened in that month. For example, if a patient developed in a 1-month period unprovoked VTE (rated as 85) and non-nephrotic proteinuria (rated as 59), the score for this month would be 85 (the VTE would count (highest rated), but the proteinuria would not contribute). The only exception is the 6 double manifestation combinations (bump-up items), which have their own scores, which are not the sum of each of the 2 single manifestations (Table 3).

In the context of a clinical trial or observational study having a defined time frame, the maximum rating achieved for each patient in any monthly interval over the entire observation time would be their 'maximum' TMN score, while their average TMN score would be the average of each monthly score over the observation time. The maximum score provides an indication of the highest or peak level of activity over the observation interval. The average score gives an indication of the persistence of activity, analogous to an area under the curve.

No average score exists for the obstetric scale since only a single event may occur during the pregnancy (eg, foetal loss). For the TMN scale, some items are scored only once (eg, thrombosis), while others are scored multiple times (eg, proteinuria), which may distort the average score. Therefore, the Task Force members voted (unanimously) that average scores be calculated separately for the items scored if they were stable/improved (TMN-2 items) and items scored only when new/worsening (TMN-1 items) (Table 3). The scores of TMN-1 and TMN-2 items are not added or combined; they are independent outcomes. In total, there are 3 maximum scores (TMN-1, TMN-2, Obstetric) and 2 average scores (TMN-1, TMN-2). Some hypothetical cases that demonstrate the average and maximum scoring are shown in Table 6. Although we acknowledge that multiple different manifestations over a short time are not necessarily common in APS, more than 1 manifestation per patient was included for purposes of illustration.

The definitions for the items of the EAPSDAS scales are presented in Supplementary Text S1 (Glossary). Most are based on

Table 5
Construct validity

	Scale	Number of physician raters	Median (25th, 75th)
External standard	TMN scale	52	0.74 (0.64, 0.81)
	Obstetric scale	52	0.88 (0.77, 0.96)
Internal standard	TMN scale	55	0.79 (0.70, 0.83)
	Obstetric scale	55	0.91 (0.81, 0.98)

TMN, thrombotic, microvascular, nonthrombotic manifestations.
Spearman correlations between item scores and physician global assessment (external standard) and between item scores and rank order of vignettes by activity (internal standard).

Table 6
Hypothetical cases for scoring the EAPSDAS

Age/sex	Scale	Clinical and laboratory manifestations												Maximum score	Average score
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12		
51 yo man		–	Unprovoked VTE (one territory)	–	–	–	–	–	–		Moderate				thrombocytopenia
Moderate															thrombocytopenia
Moderate															thrombocytopenia
	TMN-1	0	85	0	0	0	0	0	0	0	0	0	0	85	85/12 = 7.08
	TMN-2	0	0	0	0	0	0	0	0	0	47	47	47	47	47 × 3 = 141 141/12 = 11.75
	Obstetric	–	–	–	–	–	–	–	–	–	–	–	–	–	N/A
32 yo woman		–	Pregnancy	Pregnancy	Pregnancy	Pregnancy	Foetal death	Provoked VTE	–	–	–	–	–		
	TMN-1	0	0	0	0	0	0	66	0	0	0	0	0	66	66/12 = 5.5
	TMN-2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Obstetric	0	0	0	0	0	72	0	0	0	0	0	0	72	N/A
19 yo woman		–	LR (new)	LR	LR; digital ischaemia	LR; digital ischaemia	LR; digital ischaemia	LR; digital ischaemia	LR; digital ischaemia	LR	LR; pregnancy	LR; first-trimester miscarriage	LR		
	TMN-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	TMN-2		39	0	82	0	0	0	0	0	0	0	0	82	39 + 82 = 121 121/12 = 10
	Obstetric	0	0	0	0	0	0	0	0	0	0	46	0	46	N/A
36 yo man		–	Nephrotic range proteinuria*	Nephrotic range proteinuria	Nephrotic range proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	Non-nephrotic proteinuria	–		
	TMN-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	TMN-2	0	71	71	71	59	59	59	59	59	59	59	0	71	71 × 3 + 59 × 7 = 626 626/12 = 52.1
	Obstetric	–	–	–	–	–	–	–	–	–	–	–	–	–	N/A
47 yo woman		–	–	Stroke	–	–	–	Stroke	Haemolytic anaemia	Haemolytic anaemia	Haemolytic anaemia	–	–	–	
	TMN-1	0	0	87	0	0	0	87	0	0	0	0	0	87	87 × 2 = 174 174/12 = 14.5
	TMN-2	0	0	0	0	0	0	0	75	75	75	0	0	75	75 × 3 = 225 225/12 = 18.75
	Obstetric	–	–	–	–	–	–	–	–	–	–	–	–	–	N/A
39 yo man	Clinical	–	–	Arterial thrombosis in 2 territories	–	–	–	–	Skin ulcer (one)	Skin ulcer	Skin ulcer improved 50% by physician judgement	Skin ulcer improved 50% by physician judgement	Skin ulcer improved 50% by physician judgement	–	
	TMN-1	0	0	91	0	0	0	0	0	0	0	0	0	91	91/12 = 7.58
	TMN-2	0	0		0	0	0	0	64	64	32	32	32	64	64 × 2 + 32 × 3 = 229 229/12 = 18.66
	Obstetric	–	–	–	–	–	–	–	–	–	–	–	–	–	N/A
46 yo man			–	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening,	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening	Cardiac valve thickening		
	TMN-1		0	0	0	0	0	0	0	0	0	0	0	0	0
	TMN-2	0	0	50	0	0	0	0	0	0	0	0	0	50	50/12 = 4.1
	Obstetric	–	–	–	–	–	–	–	–	–	–	–	–	–	N/A

APS, nephropathy-related nephrotic range proteinuria; EAPSDAS, EULAR antiphospholipid syndrome disease activity score; LR, livedo reticularis; N/A: not applicable; TMN, thrombotic, microvascular, nonthrombotic manifestations; VTE, venous thromboembolism; yo, year old.
Assume each patient is observed for 12 months. No average score exists for the obstetric scale. Average TMN score is the average of each monthly score over the observation time.

the glossary developed for the 2023 ACR/EULAR APS classification criteria. Instructions about the scoring of items and the implementation of EAPSDAS are presented in Supplementary Text S1 (instructions for the EPSDAS implementation).

DISCUSSION

Primary APS is a complex disorder with a wide variety of clinical manifestations and heterogeneity in response to standard treatments. Developing outcome measures in primary APS is crucial for assessing disease status, treatment response, and outcomes in clinical practice, observational studies, and clinical trials. Using consensus and data-driven methods, a EULAR disease activity score was developed, and initial validation was performed.

We followed the main methodology phases used in other disease activity scores in rheumatic diseases, including item generation, item reduction, item scoring based on clinical vignettes, and validation [33–35]. A primary goal and a strength of the project was using a combination of evidence-based data from an SLR, a Delphi consensus methodology, and multiple surveys. A major strength is the participation of an international multidisciplinary group of APS experts, patients with primary APS, as well as nonphysicians HPRs familiar with APS. Another strength is the contribution of the above international participants in defining the concept of disease activity in APS in the first open-ended question, as well as the consistent reporting of 'new or worsened events' and the 'ability to change', which differentiate disease activity from disease damage.

Since the first descriptions of APS clinical characteristics, including mainly macrovascular thrombosis and adverse events in pregnancy, various microvascular, cardiac, and haematological manifestations of APS have been recognised and recently incorporated in the new ACR/EULAR APS classification criteria [6]. Although development of the EAPSDAS began before the new APS classification criteria were published, all the above manifestations and others, previously classified as noncriteria APS manifestations [36], as well as transverse myelitis [37], seizures [38], aseptic necrosis [39], pulmonary hypertension [40], and haemolytic anaemia [41], have been retrieved by the SLR and the second open-ended survey aimed to generate all potential manifestations related to disease activity. This is also reflected by the high percentage of physicians and patients who graded the comprehensiveness and relevance of the EAPSDAS items as very good/adequate in the face and content validity exercise.

Another strength of the project is the use of real-world patient cases for the item scoring and the validation of EAPSDAS. Since the derivation of the EAPSDAS was mainly based on the PhysGA, estimates on one set of case profiles might differ if different sets of case profiles were used. To minimise bias, we included 3 versions of clinical vignettes for each item, randomly assigned to each of the 3 groups of participants. The 3 versions differed in patient demographics: APS history, general medical history, and current presentation.

The upward skew of the item scores is likely the result of 2 processes. First, these items were those that survived a multistep selection process that focused on identifying manifestations that were highly specific for APS activity. Less specific manifestations, which might have scored in the range of 0 to 30, would have been removed at earlier stages. Second, we interpret the distribution as reflecting ratings of activity rather than severity. If severity was the dominating factor, we would expect thrombosis in 3 territories (ie, catastrophic APS) to be rated much higher than any other item, and yet scores of all acute thrombotic manifestations are clustered together. Similarly, if severity was the determining factor, we might expect livedo reticularis/livedo racemosa to be rated much lower. This scoring indicates that new events, including less serious manifestations such as new or worsening livedo reticularis/livedo racemosa, were accorded somewhat high scores by the raters, likely because these were interpreted to represent new activity.

EAPSDAS differs from other outcome measures, eg, SLEDAI, in that an interval between 2 events was defined to confirm that the second event should be counted as a new APS activity rather than a continuation of the previous activity. For the obstetric items, the interval is the entire pregnancy period, and the score is the highest-rated manifestation during pregnancy. The interval for TMN manifestations is 1 month. Thus, scores of items in different organ systems are not added together to arrive at the final score if the manifestations occur over 1 month; rather, the highest-rated item, which reflects the highest degree of APS activity attained in that interval, is used. The only exception is the 6 'bump-up' manifestations, which are scored differently. During a predefined observation time (eg, 12 or 24 months in a clinical trial), the 'maximum' score for the TMN manifestations will be the highest score in any monthly interval, while the average of each monthly score during this period will be the average score. Another difference from other scores is the lack of a dichotomous (all-or-none) approach to score variables. In EAPSDAS, new/worsening events, abnormal but stable (eg, persistent moderate thrombocytopenia or non-nephrotic proteinuria) manifestations, or manifestations that are improved but still present are scored differently. In addition, a separate average score is calculated for the items in the TMN scale scored when stable/improved, from those not scored if stable/improved.

The choice between a numerical score and an ordinal measure reflects the competing priorities of reliability and sensitivity to change of the measure. Ordinal measures are typically highly reliable but often less sensitive to smaller changes because patients need to switch to different categories for the score to register a change, which requires a more substantial shift in their condition. This is in contrast to numerical scores that can detect smaller changes. Given the motivation to develop a score for use as an endpoint in clinical trials, where sensitivity to change is important, we decided that a numerical score would be more useful.

Antiphospholipid antibodies (aPL), including newly positive aPL, lupus anticoagulant, high anti-β2GP1 antibodies, high anticardiolipin antibodies, aPL triple positivity, and antiprothrombin antibodies, were among the items nominated in the item generation phase but excluded in subsequent surveys and rounds of voting by Task Force members on the most important items to include in the activity measure. Similarly, C-reactive protein, erythrocyte sedimentation rate, D-dimers, prothrombin fragments, complement split products, and other laboratory measures were excluded during the voting process. The stage at which each item was omitted is presented in the accompanying methodology paper [31].

Other potential equally likely or more likely causes should be excluded, and only items attributed to APS should be scored. EAPSDAS manifestations are differentiated from disease damage, even those that are persistent (eg, thrombocytopenia or proteinuria), considering that they represent activity and are potentially reversible. In addition to face and content validity, we examined construct validity using 2 separate comparisons: with the PhysGA as an external standard and with item ranks as an internal standard. Both results supported the validity of the

item scores. In all validation exercises, physicians and patients with APS from different centres and countries across 5 continents participated. We also found high inter-rater reliability when scores were tested using real-world clinical vignettes.

We used the PhysGA as the reference standard for item scores, which may be viewed as a limitation. However, PhysGA has been validated in disease activity scores for other systemic autoimmune disorders [33,34], and we found a high consistency of physician ratings of PhysGA on the initial vignette survey. Another potential limitation is that although different surveys were designed for patients and the introduction and questionnaire were presented in patient-friendly language, a glossary for each manifestation was not provided. This is because we considered that APS manifestations would be known as a standard medical term rather than as a descriptive presentation of the terms. In the surveys asking for item ratings, the following statement was included 'If you do not know a specific item, please do not rate it''. Concerning language barriers, the first 2 open-ended questions were answered in English but also in different languages. The face and content validity exercises were translated into multiple languages.

EAPSDAS use as a primary outcome in future clinical trials on new treatments for the classical (thrombotic and obstetric) and nonclassical (microvascular, nonthrombotic) APS manifestations may help to better assess the response to therapy. The latter manifestations usually do not respond to the standard anticoagulation therapy. In addition, recurrences of classical thrombotic or obstetric manifestations often occur despite adequate anticoagulant/antiplatelet treatment. The lack of response or recurrence to standard anticoagulation treatment may relate to the involvement of inflammation, in addition to or independently of thrombotic mechanisms in APS [7–12]. With the contribution of high-throughput 'omic' technologies, new pathways involving adaptive and innate immunity and the corresponding therapeutic targets are being explored [42–50]. Given that new treatment targets and drugs are emerging, using EAPSDAS as an endpoint in future clinical trials in primary APS constitutes a major implementation plan.

We anticipate that the EAPSDAS can be used to evaluate APS activity in trials of new treatments in one of 2 ways. In the case of trials that enrol patients with diverse active manifestations (eg, APS-nephropathy-related nephrotic-range proteinuria, severe thrombocytopenia, etc.), we would expect an efficacious treatment to result in lower average EAPSDAS scores over the trial period compared to placebo. In APS, preventive trials may be particularly important. In these cases, patients with currently inactive disease but with a history of recurrent events would be enrolled and treated with either a new treatment or placebo, and followed for new activity based on EAPSDAS.

In conclusion, an APS disease activity scale that quantifies the level of disease activity was developed. We used a rigorous evidence-based and consensus-based approach with special attention to face, content, internal and external construct validity, and reliability. Future plans include prospective validation of the score in multicentre and multiethnic APS cohorts, with PhysGA, and patient-reported quality of life as the reference standards.

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Contributors

MGT was convenor, and was responsible for study conception and design, supervision of the project, preparation of surveys, acquisition of data, analysis and interpretation of data, and manuscript writing. RC and AT (Steering Committee members) were responsible for study conception, acquisition of data, and interpretation of data. GJP-E and SS (Steering Committee members/Fellows) were responsible for systematic literature review, acquisition of data, analysis of some data, and interpretation of data. TS was responsible for study design and supervision of methodology. RBML was responsible for study design, supervision of methodology, and interpretation of data. MMW was responsible for study design, supervision of methodology, analysis of data, and interpretation of data.

The Task force members participated in project surveys (data acquisition), discussions during the Task force meetings, and the Delphi methodology. MR, LVDH (EMEUNET members), and KS also contributed to the systematic literature review. The Collaborators participated in project surveys (data acquisition). All Task Force members and Collaborators reviewed critically the manuscript for important intellectual content and approved the submitted version.

MGT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests

MGT reports grants to the institution were provided by AbbVie, Boehringer Ingelheim, DEMO, Faran, GSK, and UCB, and MGT has participated in advisory boards from GSK, Lilly, and UCB. AT has participated in advisory boards from UCB and Galapagos. VP has received lecture fees from Werfen group, Milan, Italy. TS has received grant support from Roche and personal fees from AbbVie, Roche, Sanofi, Takeda, and Novartis, outside the submitted work. RBML has received consulting fees from AbbVie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, GlaxoSmith-Kline, Janssen, Merck, Novartis, Pfizer, Roche, and UCB and is Director of Rheumatology Consultancy BV. MMW worked as consultant to Advanced Clinical LLC. RC, GJP-E, SS, JA-R, TA, MLB, TJ, FM, AM, P-LM, MR, AR, GR-I, KS, SS, LVDH, RVV, and DW report no conflict of interest.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by the Laiko General Hospital Institutional Review Board (protocol number 148, 14-03-22); the Ethics Committee of Centro Regional de Enfermedades Autoinmunes y Reumáticas, Rosario, Argentina; and the Ethics Committee AOU Città della Salute e della Scienza di Torino (approval number 0126695, 31/10/2023, file number 386/2023) for a shared project with the University of Brescia.

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Data availability statement

All data relevant to the study are included in this article, and the accompanying methodology article is published simultaneously.

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Appendix

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.10.006.

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