



# A high-risk laboratory profile of antiphospholipid antibodies and thrombosis is associated with a large number of extra-criteria manifestations in obstetric antiphospholipid syndrome

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## Abstract

Extra-criteria manifestations such as thrombocytopenia and livedo are described associated with antiphospholipid syndrome (APS) but are not included in the current classification criteria. Their clinical expression might be important, as they may be associated with a high-risk profile of antiphospholipid antibodies (aPL) and thrombosis. We evaluated the association between the presence of extra-criteria manifestations in primary obstetric-APS (POAPS) and aPL profiles. We also evaluated whether the presence of extra-criteria manifestations in POAPS patients increases the risk of developing thrombosis during the follow-up period (median follow-up 5 years; range 3–9 years). We selected 79 women who were included in our study only if they were first diagnosed with POAPS (with no history of previous thrombosis) and reevaluated for the presence of thrombosis after the follow-up period. We evaluated the association between the aPL profile and extra-criteria manifestations. We also evaluated the relationship of thrombosis during the follow-up period with extra-criteria manifestations and other risk factors. Patients with three or more extra-criteria manifestations presented high rates of triple positivity for the aPL profile (75%) ( $p < 0.001$ ). We also found a relationship between the presence of extra-criteria manifestations and the presence of high titers of aPL: 91.7% of patients with three or more extra-criteria manifestations had high titers of aPL ( $p < 0.01$ ). We further evaluated the group of POAPS patients according to thrombotic events during the follow-up. Among these patients, 6 (7.6%) presented thrombosis. Notably, 100% of patients with a thrombotic event during the follow-up had more than three extra-criteria manifestations. POAPS patients with extra-criteria manifestations might have a high-risk aPL profile and a major risk of developing thrombosis.

**Keywords** Livedo reticularis · Thrombosis · Thrombocytopenia · Pregnancy morbidity · Risk factor

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## Introduction

Antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia defined by the presence of thrombosis and/or pregnancy morbidity and is associated with antiphospholipid antibodies (aPL) [1]. Despite this definition, patients with APS may also have other clinical manifestations (referred to as extra-criteria manifestations) that are not included in the Sydney criteria, such as livedo reticularis and other cutaneous manifestations, neurological manifestations, heart valve disease, thrombocytopenia, and renal microangiopathy [2].

Although these extra-criteria manifestations are not specifically observed in APS patients, some studies suggest that their clinical expression could be associated with high-risk antibody profiles, such as high titers of aPL and/or the presence of more than one positive aPL [3–5], which defines the

subjects as “increased risk” of developing clinical manifestations of APS. It is not completely clear whether a higher number of extra-criteria manifestations are associated with a defined laboratory profile. In fact, extra-criteria manifestations may not have any relevance at diagnosis. However, according to research and clinical studies on APS, some of these manifestations might be highly relevant regarding correlations with morbidities and mortality since they might be important for the risk of thrombosis [6–9].

The latest publications highlight the idea that thrombotic APS and obstetric APS might be two different clinical entities and should be separately studied in terms of risks and stratifications. Although these stratifications have been studied more extensively for thrombotic APS, there are no relevant studies on extra-criteria manifestations in obstetric APS [2, 3, 9, 10]. The first aim of our study was to evaluate the association between the presence of extra-criteria manifestations in primary obstetric-APS (POAPS) and aPL profiles. The second aim of our work was to conduct a thorough study on extra-criteria manifestation in a well-characterized POAPS population to determine a better method for the stratification of risks.

## Materials and methods

### Population study

We carefully selected 79 women with complete data who attended our center (Acute Hospital “Dr. Carlos G. Durand,” Buenos Aires, Argentina) between April 2010 and July 2016 and who were diagnosed with POAPS based on international consensus classification criteria [1]. These women were included in our study only if they were first diagnosed with POAPS (with no history of previous thrombosis) and prospectively reevaluated for the presence of thrombosis after the follow-up period.

The presence of extra-criteria manifestations and the baseline clinical and laboratory features were evaluated at the time of diagnosis. We also evaluated the association between the aPL profile and extra-criteria manifestations.

The second part of the study consisted of the identification of patients who developed thrombosis during the follow-up period between 2010 and 2019 (median follow-up 5 years; range 3–9 years). The follow-up time was calculated from delivery. We evaluated the relationship of thrombosis during the follow-up period with extra-criteria manifestations and other risk factors. During the follow-up period, no patient received any treatment.

The strict exclusion criteria consisted of the following: other rheumatic disease, the presence of other thrombophilias (Factor V Leiden and/or prothrombin G20210A, hyperhomocysteinemia, and a deficit of protein C, protein S, and/or anti-thrombin), the administration of any additional treatment for

POAPS and/or other rheumatic diseases, and a history of previous thrombosis at the time of diagnosis.

### Laboratory tests

All patients were diagnosed with APS when their laboratory criteria were positive on two or more occasions at least 12 weeks after their first positive result. The following aPL tests were used: lupus anticoagulant (LA), anti- $\beta_2$  glycoprotein I ( $\alpha\beta_2$ GPI) antibodies IgG and/or IgM, and anticardiolipin antibodies (aCLs) IgG and/or IgM [1].

### Blood samples

Blood was obtained by clean venipuncture (after an 8 h fast) and was collected into plastic tubes containing sodium citrate (ratio 9:1). After two centrifugation steps at  $2500\times g$  for 15 min, the platelet-poor plasma was immediately assayed for LA and then stored at  $-40\text{ }^\circ\text{C}$ . The blood was collected into tubes, allowed to clot at  $37\text{ }^\circ\text{C}$ , and then centrifuged at  $1500\times g$  for serum preparation. The serum was stored at  $-40\text{ }^\circ\text{C}$  until ready for use.

### Serum

The aCL was measured using standardized enzyme immunoassays of IgG and IgM isotypes that were developed in-house as previously reported [11].  $\alpha\beta_2$ GPI was measured by a commercial enzyme immunoassay kit for IgG and IgM isotypes (BioSystems S.A., Barcelona, Spain). Serum levels of aCL or  $\alpha\beta_2$ GPI at medium or high titers were considered a positive result. A medium titer was defined as  $>99$ th percentile (greater than 40 GPL or MPL or greater than 40 UG or UM according to the international criteria). A high titer was arbitrarily defined as 80 GPL or MPL or as 80 UG or UM (according to previous publications) [12, 13].

### Plasma citrate

The plasma samples were evaluated for the presence of LA activity using two tests: the dilute Russell viper venom time (TriniCLOT Lupus Screen and/or Confirm, Tcoag, Co. Wicklow, Ireland) and silica clotting time (Hemosil, Instrumentation Laboratory, Bedford, MA, USA). To identify the inhibitor, these clotting tests were conducted with a 1:1 mixture of the corresponding patient and normal plasma samples. As confirmatory tests, we used a phospholipid neutralization procedure. LA was diagnosed when at least one of the screening and one of the confirmatory procedures were positive according to the international criteria.

## aPL profile

We classified the patients according to aPL positivity in the laboratory tests: triple-positive for aPL (LA+, aCL+, and a $\beta$ 2GPI+), double-positive for aPL (LA+ and aCL+, LA and a $\beta$ 2GPI+, or aCL+, and a $\beta$ 2GPI+) and single-positive for aPL (LA+, aCL+, or a $\beta$ 2GPI+).

We classified the patients according to serum levels of aCL IgG, and IgM or a $\beta$ 2GPI IgG and IgM into low-, medium- or high-titer groups. A low titer was defined as a titer less than 39 GPL or MPL or less than 39 UG or UM. A medium titer was defined as 40 to 79 GPL or MPL or as 40 to 79 UG or UM. A high titer was arbitrarily defined as greater than or equal to 80 GPL or MPL or greater than or equal to 80 UG or UM (according to previous publications) [12, 13].

A high-risk laboratory profile was defined as patients having triple positivity for aPL and/or patients with high titers of aCL and/or a $\beta$ 2GPI.

A low-risk laboratory profile was defined as having double or single positivity for aPL and/or low or medium serum levels of aCL and/or a $\beta$ 2GPI.

## Ethics

This study was approved by the ethics committee of the respective medical center and was performed according to the principles of the Declaration of Helsinki and the current national law. Informed consent was obtained from all the participants.

## Extra-criteria manifestations of APS

Livedo reticularis, skin ulcerations, and other dermatological manifestations were diagnosed by a rheumatologist at the medical center. These conditions were also confirmed by skin biopsy when necessary.

Thrombocytopenia is defined as a platelet level < 100,000 mm<sup>3</sup> (confirmed by at least two determinations and evaluations of the peripheral blood smear). We excluded patients with low platelet levels during pregnancy or who were undergoing treatment with drugs such as heparin. Other hematologic manifestations were evaluated by blood samples and confirmed by at least two determinations.

Hemolytic anemia was defined as a decline in hemoglobin accompanied by increased reticulocyte count, high serum lactate dehydrogenase, and reduced haptoglobin levels in the presence of a positive Coombs test.

Valvulopathy was confirmed by evaluation by a cardiologist at the medical center (confirmed with echocardiography).

aPL-related nephropathy was assessed by considering the kidney laboratory alterations and through a nephrologist's evaluation (proteinuria and renal failure) [14]. The evaluation

of these extra-criteria manifestations was limited by the lack of kidney biopsies from all patients.

Central nervous system extra-criteria manifestations (migraines, seizures, and chorea) were diagnosed by a clinician or neurologist. We excluded other etiologies, such as metabolic abnormalities, drugs or medication, hypertension, endocrine disorders, and/or other related disorders. Another limitation of this study was that we did not use the International Headache Society Criteria. Furthermore, the study did not include brain imaging for all patients.

We subdivided the patients into 3 groups according to the number of extra-criteria manifestations: group 1, no extra-criteria manifestations; group 2, one or two extra-criteria manifestations; and group 3, three or more extra-criteria manifestations.

## Statistical analysis

The statistical analysis was performed using the SPSS statistical software package version 15.0 for Windows (SPSS, Chicago, IL, USA). Because the data were not normally distributed, they are presented as the median and percentile (25 and 75) or percentage. Nonparametric tests (Mann-Whitney *U* test) were used to compare the quantitative data, and the chi-squared test or Fisher's exact test was used to compare proportions. *p* < 0.05 indicated statistical significance.

## Results

This study included 79 nonconsecutive pregnant women diagnosed with POAPS (median age, 31 years; interquartile range, 28–36 years) who were treated at our clinical center between 2010 and 2016.

All patients had a history of pregnancy morbidity (Table 1): 30 (38.0%) experienced fetal loss, 57 (72.2%) experienced early miscarriage, 32 (40.5%) experienced late miscarriage, 20 (25.3%) experienced premature birth, 10 (12.7%) had a history of preeclampsia, and 12 (17.9%) had intrauterine growth restriction.

aCL was positive in 57 cases (72.1%) and presented with high titers in 15 cases (19.0%). a $\beta$ 2GPI was positive in 43 cases (54.4%) and presented with high titers in 15 cases (19.0%). LA was positive in 26 cases (32.9%). High aPL titers (aCL and/or a $\beta$ 2GPI) were present in 24 cases (30.4%).

A triple positivity profile for aPL was detected in 16 patients (20.3%), a double positivity profile for aPL was detected in 16 patients (20.3%), and a single positivity profile for aPL was detected in 47 patients (59.4%).

Extra-criteria manifestations of APS were present in 41 patients (51.8%): 20 (25.3%) had one extra-criteria manifestation, 9 (11.4%) had two extra-criteria manifestations, and 12 (15.2%) had three or more extra-criteria manifestations. A

**Table 1** Demographic, clinical, and laboratory characteristics of patients with POAPS

Number of patients	All ( <i>n</i> = 79)	%
Age	31 (28–36)	
Thrombosis (after at least 2 years of follow-up)	6	7.6
Pregnancy morbidity		
Preeclampsia	10	12.7
RCIU	12	17.9
Fetal loss	30	38.0
Premature	20	25.3
Early miscarriage		
0	22	27.8
1	15	19.0
2	19	24.1
3	11	13.9
$x > 4$	12	15.2
Late miscarriage		
0	47	59.5
1	25	31.6
2	3	3.8
3	2	2.5
$x > 4$	2	2.5
Lupus anticoagulant	26	32.9
aCL G titers (GPL)		
$x < 39$	33	41.8
40–79	32	40.5
$x > 80$	14	17.7
aCL M titers (MPL)		
$x < 39$	61	77.2
40–79	16	20.3
$x > 80$	2	2.5
M and/or G high titers	15	19.0
a $\beta$ 2GPI G titers (UG)		
$x < 39$	46	58.2
40–79	22	27.8
$x > 80$	11	14.0
a $\beta$ 2GPI M titers (UM)		
$x < 39$	63	79.7
40–79	12	15.2
$x > 80$	4	5.1
M and/or G high titers	15	19.0
a $\beta$ 2GPI and aCL high titers	24	30.4
aPL profile		
Single positivity	47	59.4
Double positivity	16	20.3
Triple positivity	16	20.3
Antinuclear antibodies	13	16.4
Anti-Ro	3	3.8
Extra-criteria manifestations		
Livedo reticularis	27	34.2
Total hematological	11	14.0

**Table 1** (continued)

Number of patients	All ( <i>n</i> = 79)	%
Thrombocytopenia	9	11.4
Hemolytic anemia	6	7.6
Valvulopathy	2	2.5
Nephropathy	1	1.3
Migraine	32	40.5
Chorea	2	2.5
Epilepsy	1	1.3
Superficial vein thrombosis	6	7.6
Neurological manifestation	32	40.5
Number of extra-criteria		
0	38	48.1
1	20	25.3
2	9	11.4
$x > 3$	12	15.2

aPL, antiphospholipid antibodies; aCL, anticardiolipin antibodies; a $\beta$ 2GPI, anti- $\beta$ 2 glycoprotein I; RCIU, intrauterine growth restriction

total of 27 patients (34.2%) had livedo reticularis, 9 patients (11.4%) had a history of confirmed thrombocytopenia, 6 patients (7.6%) had a history of confirmed hemolytic anemia, 2 patients (2.5%) had a history of valvulopathy, 1 patient (1.3%) had a history of nephropathy, 32 patients (40.5%) had a history of migraines (which was the most frequent extra-criteria manifestation), 2 patients had a history of chorea (2.5%), and 1 patient (1.3%) had a history of epilepsy. In addition, superficial vein thrombosis was present in 6 patients (7.6%) (Table 1).

Remarkably, patients with three or more extra-criteria manifestations presented high rates of triple positivity for the aPL profile (75%), whereas patients without extra-criteria manifestations presented high rates of single positivity for the aPL profile (81.6%). There was a close and statistically significant ( $p < 0.001$ ) relationship between the number of extra-criteria manifestations and the aPL profile (Table 2) (Fig. 1).

We also found a relationship between the presence of extra-criteria manifestations and the presence of high titers of aPL: 91.7% (11/12) of patients with 3 or more extra-criteria manifestations had high titers of aPL, whereas only 13.2% of patients without extra-criteria manifestations had high titers ( $p < 0.01$ ) (Table 3).

We further evaluated the group of POAPS patients according to thrombotic events during the follow-up period, and among these patients, 6 (7.6%) presented deep venous thrombosis of the lower limbs. All these events occurred away from the puerperium period. Notably, 100% of patients (6/6) with a thrombotic event during the follow-up period had more than 3 extra-criteria manifestations. Thrombocytopenia and livedo reticularis were present in 100% of the patients (6/6) with thrombotic manifestations + POAPS (Table 4). A triple

**Table 2** Distribution of extra-criteria manifestations according to the aPL profile

aPL profile	Extra-criteria manifestation			<i>p</i> < 0.01
	Group 1 no extra-criteria % ( <i>n</i> = 38)	Group 2 1–2% ( <i>n</i> = 29)	Group 3 <i>x</i> > 3% ( <i>n</i> = 12)	
Single positivity	81.6% (31/38)	48.3% (14/29)	16.7% (2/12)	
Double positivity	13.2% (5/38)	34.5% (10/29)	8.3% (1/12)	
Triple positivity	5.3% (2/38)	17.2% (5/29)	75.0% (9/12)	

aPL, antiphospholipid antibodies

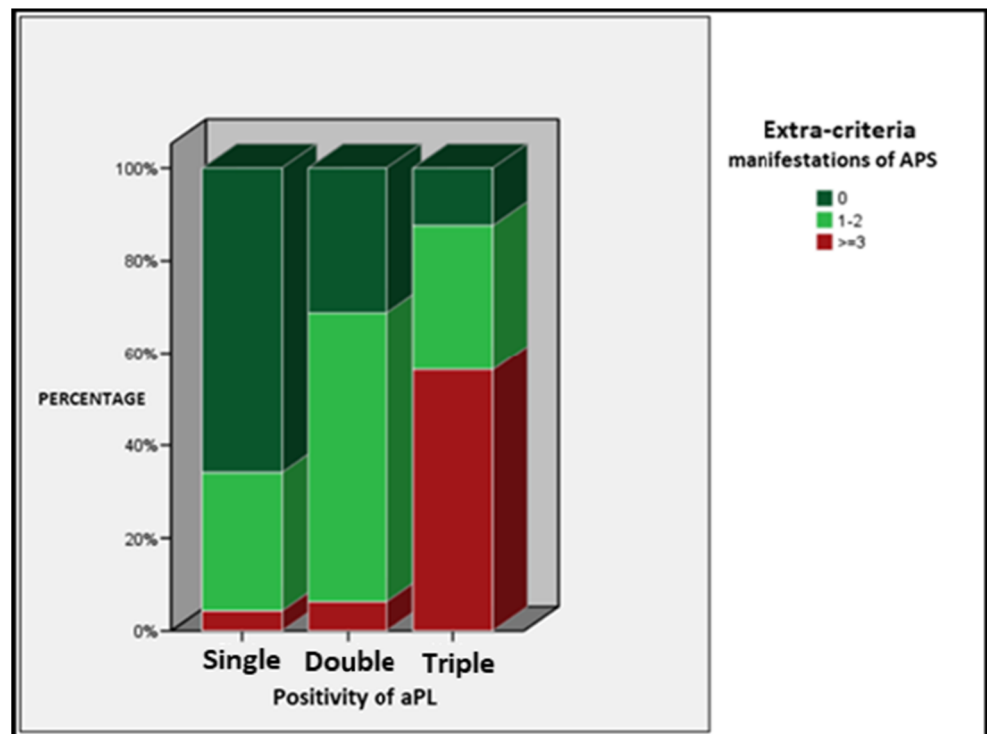
positivity profile of aPL was present in 50.0% (3/6) of those patients. From another point of view, for those patients who presented 3 or more extra-criteria manifestations, 50% (6/12) developed thrombosis during the follow-up period.

### Discussion

Extra-criteria manifestations are frequently observed in APS patients [6]. Although they are not included in the Sydney criteria for the definition of APS, recent studies have highlighted the importance of extra-criteria manifestations in the prognosis or morbidity of APS patients [2, 3, 10, 15–17]; however, there are few studies that focus on extra-criteria manifestations in POAPS patients. Therefore, we considered that the association between extra-criteria manifestations in POAPS and its association with aPL profile and thrombotic risk should be explored.

To increase the specificity of the extra-criteria manifestations of POAPS (considering that they are not exclusively observed in APS patients), we subdivided groups of patients according to the number of extra-criteria manifestations observed in each patient. Despite the distribution of aPL profiles which was heterogeneous among our group of POAPS patients, we found that it was directly associated with extra-criteria manifestations of APS. Specifically, patients with three or more extra-criteria manifestations more frequently presented a high-risk laboratory aPL profile. Furthermore, patients without extra-criteria manifestations more frequently presented a low-risk laboratory aPL profile. These findings are in agreement with the previous results from different groups worldwide who reported that extra-criteria manifestations of APS would be associated with high titers of antibodies [4, 5] and/or with positive results for more than one type of aPL antibody [3], even though most of these studies were conducted in patients with thrombotic APS. Hence, we hypothesized that extra-criteria manifestations might not occur

**Fig. 1** Relationship between the distribution of extra-criteria manifestations according to the aPL profile. aPL, antiphospholipid antibodies; APS: antiphospholipid syndrome



**Table 3** Extra-criteria manifestations according to aPL titers

aPL titers	Group 1 extra-criteria = 0% (n = 38)	Group 2 extra-criteria = 1–2% (n = 29)	Group 3 extra-criteria = x > 3% (n = 12)	
aCL high titers (GPL/MPL)	5.3% (2/38)	24.1% (7/29)	50.0% (6/12)	<i>p</i> < 0.01
aβ2GPI high titers (UG/UM)	13.2% (5/38)	10.3% (3/29)	58.3% (7/12)	
aβ2GPI and aCL High titers	13.2% (5/38)	27.6% (8/29)	91.7% (11/12)	

aPL, antiphospholipid antibodies; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2 glycoprotein I antibodies

incidentally in POAPS patients, since their onset might be linked to complex mechanisms directly related to the presence of aPL. Therefore, extra-criteria manifestations could be interpreted as markers of autoimmunity associated with POAPS [6, 18, 19]. Thus, those patients with high-risk laboratory profiles could more frequently develop extra-criteria manifestations.

The second aim of our study was to evaluate the impact of extra-criteria manifestations of APS on the risk of developing thrombosis during a follow-up period. We found an association between the presence of extra-criteria manifestations and the risk of developing thrombosis and that this risk might increase according to the number of extra-criteria manifestations of APS. Remarkably, extra-criteria manifestations of APS seemed to better predict thrombotic events than triple positivity profiles in our cohort POAPS patients [16].

Kato et al. proposed in an elegant and well written review to include thrombocytopenia in the thrombotic risk assessment of APS patients based on the idea that thrombocytopenia in the presence of aPL may unexpectedly increase the risk of thrombosis in patients with APS [10, 20]. This was based on a publication by Hisada et al. [21], who demonstrated that a low platelet count in patients with aPL is associated with a high risk of developing thrombosis. In our study, 100% of patients who developed thrombosis during the follow-up period presented thrombocytopenia, and strikingly, 66% of the patients who manifested thrombocytopenia developed thrombosis.

This finding is also reinforced by the observations of Potara et al. [9], who showed that low platelet counts occurred early in patients with a risk of developing catastrophic APS, and this was considered a warning signal for disease activity.

Kato et al. also proposed that other extra-criteria manifestations, such as livedo reticularis, heart valve disease, superficial vein thrombosis, and renal microangiopathy, should be included in the thrombotic risk assessment of APS patients since different studies suggested their association with thrombosis [8, 10, 22–25]. We consider that this proposal could be reinforced by our findings that all patients who presented thrombosis had several extra-criteria manifestations in their clinical features.

The latest publications highlight the idea that there are two main distinct clinical variants of APS: obstetric and vascular [26]. According to recent data from the EUROAPS project, POAPS is associated with a low frequency of thrombotic events and requires less aggressive treatment for vascular events than thrombotic APS [26, 27]. The identification of risk factors associated with thrombosis in POAPS patients, such as triple positivity of antibodies and the presence of a high number of extra-criteria manifestations, could be a tool to predict thrombotic events in POAPS patients and consequently to identify patients who should receive a thromboprophylactic treatment beyond pregnancy [6–8, 21, 22, 28–30]. Indeed, in our study, those patients who did not present extra-criteria manifestations and had “low-risk” laboratory aPL profiles did not seem to display an elevated risk of developing thrombosis.

**Table 4** Distribution of extra-criteria manifestations of obstetric APS according to a thrombotic event

Extra-criteria manifestations	Obstetric + thrombotic APS (%) (n = 6)	Obstetric APS (%) (n = 73)	<i>p</i> value
Heart valve disease	33.3% (2/6)	0% (0/73)	0.005
Thrombocytopenia	100% (6/6)	4.1% (3/73)	< 0.001
Hemolytic anemia	50% (3/6)	4.1% (3/73)	0.005
Superficial vein Thrombosis	16.7% (1/6)	6.8% (5/73)	0.388
Migraine (neurological)	100% (6/6)	35.6% (26/73)	0.003
Livedo	100% (6/6)	28.8% (21/73)	0.001
Skin ulcer	0% (0/6)	4.1% (3/73)	1.0
x > 3 extra-criteria Manifestations	100% (6/6)	8.2% (6/73)	< 0.001

APS, antiphospholipid syndrome

In our opinion, one of the main strengths of our study arises from the selection of our group of POAPS patients. In previous studies, there were included series of patients with all kinds of APS without discriminating between them as obstetric or thrombotic APS patients. Besides, we consider that another robust point of our study is that we performed a comprehensive analysis of the global distribution of extra-criteria manifestations according to aPL and the associated risk of developing thrombosis. However, we must acknowledge that one of the limitations of our study is its small sample size but, unfortunately, the limited number of patients with extra-criteria manifestations is a crucial problem suffered from of all studies performed on this subject.

In conclusion, our findings suggest that POAPS patients with extra-criteria manifestations typically display a high-risk aPL profile and a high risk of developing thrombosis, especially when they have a large number of clinical manifestations.

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## Compliance with ethical standards

This study was approved by the ethics committee of the respective medical center and was performed according to the principles of the Declaration of Helsinki and the current national law. Informed consent was obtained from all the participants.

**Conflict of interest** The authors declare that they have no conflicts of interest.

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