Damage Accrual Measured by DIAPS in Antiphospholipid Antibody (aPL)-positive Patients: Results from AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry")

Damage Measured by DIAPS in Antiphospholipid Antibody-positive Patients Included in APS ACTION Registry

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Key messages:

- DIAPS was able to discriminate damage in a large multicenter cohort of primary aPL-positive patients.
- Cardiovascular risk factors were associated with damage accrual in aPL-positive patients.
- Specific aPL profiles may help to identify patients more prone to accrue damage.

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The authors declare that they have no competing interests regarding this paper.

Authors' contributions

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Running title: DIAPS in primary aPL-positive patients.

Abstract

Objectives: Our primary objective was to quantify damage accrual measured by Damage Index for Antiphospholipid Syndrome (DIAPS) in(antiphospholipid antibody (aPL)-positive patients with or without a history of thrombosis in an international cohort. Secondly, we aimed to identify clinical and laboratory characteristics associated with damage in aPL-positive patients.

Methods: In this cross-sectional study, we analyzed the baseline damage in aPL-positive patients with or without APS classification. We excluded patients with other autoimmune diseases. We analyzed the demographic, clinical, and laboratory characteristics based on two subgroups: (1) thrombotic APS patients with high *versus* low damage; and (2) non-thrombotic aPL-positive patients with *versus* without damage.

Results: Of the 826 aPL-positive patients included in the registry as of April 2020, 576 with no other systemic autoimmune diseases were included in the analysis (412 thrombotic and 164 non-thrombotic). *In the thrombotic group*, hyperlipidemia (OR 1.75, 95%CI 1.02-2.98, adjusted p=0.041), obesity (OR 2.05, 95%CI 1.19-3.52, adjusted p=0.009), and aβ_2GPI high titers (OR 2.33, 95%CI 1.19-3.52, adjusted p=0.002) were independently associated with high damage at baseline. *In the non-thrombotic group*, hypertension (OR 4.55, 95%CI 1.82-11.35, adjusted p=0.001) and hyperlipidemia (OR 4.32, 95%CI 1.37-13.65, adjusted p=0.013) were independent predictors of damage at baseline; conversely, single aPL positivity was inversely correlated with damage (OR 0.24; 95%CI 0.075-0,77, adjusted p=0.016).

Conclusions: DIAPS was able to discriminate damage in a large multicenter cohort of aPL-positive patients. Selected traditional cardiovascular risk factors and specific aPL profiles may help to identify patients more prone to accumulate damage.

Introduction

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia, characterized by thrombotic events and/or pregnancy morbidity in the presence of persistent antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), IgG and/or IgM anticardiolipin antibodies (aCL), and IgG and/or IgM anti-beta-2 glycoprotein I antibodies (aβ2GPI). APS may develop in association with other autoimmune diseases, especially systemic lupus erythematosus (SLE), or without other autoimmune diseases (primary APS - PAPS) (1). Recurrent thrombotic events are frequent in APS patients and may lead to damage. In patients with SLE, Ruiz-Irastorza *et al*. demonstrated that APS is a major predictor of irreversible organ damage and death (2). Thus, quantifying damage associated with thrombosis and its treatment in APS patients is important for understanding disease severity and may help to predict outcomes.

Damage Index for APS (DIAPS) is an instrument developed for assessing damage accrual in thrombotic APS patients, which was initially validated in Latin American patients (3). It was derived from the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) (4) and encompasses 37 items (22 from SDI and 15 newly added after applying the Delphi methodology) (3). In the original study, DIAPS negatively correlated with quality of life measured by EuroQoL. (3,5). More recently, Medina *et al* found that DIAPS was able to capture damage accrual over a long-term follow-up in a similar population (6). However, only a few papers evaluated DIAPS in other APS populations, mostly with a limited number of subjects (7–9).

APS is considered a rare disease, with an estimated prevalence of 50 cases per 100,000 population aged ≥18 years (10). Therefore, implementing international multicenter efforts to conduct studies to understand the disease and its mechanisms is crucial. APS ACTION is an international clinical database and repository (prospective ‘registry’) that includes a large number of aPL-positive patients from different centers worldwide (11). Studying DIAPS in this large international cohort may provide insights into risk factors

associated with damage accrual in aPL-positive patients and may also verify the capability of DIAPS to capture damage accrual in populations other than those initially reported.

Our primary objective was to quantify damage accrual measured by DIAPS in aPL-positive patients with or without a history of thrombosis in a large international cohort. Secondly, we aimed to identify clinical and laboratory characteristics associated with damage in aPL-positive patients.

Materials and Methods

Study design and patient selection

This is a cross-sectional analysis of baseline damage (measured by DIAPS) of the patients included in the APS ACTION Registry. We screened all patients (aged ≥18 years) registered in the APS ACTION Clinical Database as of April 2020. All patients were aPL positive according to the Updated Sapporo Classification Criteria (1) and tested within one year prior to enrollment.

The only exclusion criterion was autoimmune rheumatic diseases other than APS, given these diseases and their treatment, e.g., glucocorticosteroids and cyclophosphamide, may be associated with damage (12–15), which could interfere with the analysis of the contribution of aPL positivity itself for damage accrual, leading to biases.

All relevant information, such as demographic, thrombotic (including microvascular and catastrophic APS [CAPS] (16) events), non-thrombotic (including thrombocytopenia defined as <100,000 per microliter tested twice at least 12 weeks apart), and obstetrical APS manifestations, and traditional cardiovascular disease (CVD) risk factors (17–20) were obtained at the baseline visit of APS ACTION. The aPL profile was obtained from local labs; high titers of aCL and aβ2GPI were defined as ≥80 units (highest ever), and patients were further classified as single, double or triple aPL-positive according to the number of positive criteria aPL, irrespective of isotype. Study data were collected and managed using REDCap electronic capture tools hosted at Weill Cornell Medicine Clinical & Translational Science Center.

DIAPS calculation

All data needed to calculate DIAPS were retrospectively retrieved from the baseline assessment of the APS ACTION Registry. All 22 items derived from the SLICC/ACR-DI were routinely recorded by the APS ACTION registry since its inception. The 15 newly added items were either already collected in a structured fashion as part of the aPL/APS-related history, or were collected as part of the general medical history. Missing data were treated using regression imputation to conservatively predict the actual data. Calculation of DIAPS was performed as previously published by Amigo et al. (3).

Since DIAPS was initially validated only for thrombotic APS, we divided aPL-positive patients into two groups and performed different analyses to understand the contribution of different clinical and laboratory characteristics in damage accrual for each scenario: [1] *thrombotic group*, and [2] *non-thrombotic group* (including obstetric APS and aPL-positive patients without criteria manifestations).

Thrombotic group

To be included in the thrombotic group, a patient must have presented with at least one episode of thrombosis documented by imaging or histopathology, irrespective of its site (arterial, venous or microvascular) (1). We further divided thrombotic PAPS patients into two groups according to high damage (DIAPS ≥3) versus low damage (DIAPS <3). The definition of high damage was based on the median values of DIAPS found in our cohort (high damage DIAPS ≥p50 versus low damage DIAPS <p50); those values were supported by a recent paper published by Medina *et al*., which also defined DIAPS ≥3 as severe damage in their cohort. (6) Groups were then compared regarding demographics, clinical and laboratory characteristics (including aPL profile) to identify variables associated with the presence of high damage.

Non-thrombotic group

To be included in the non-thrombotic group, a patient must not have presented with any history of documented thrombosis. Since DIAPS was not initially validated for use in non-thrombotic patients, we further classified non-thrombotic patients according to the presence (DIAPS >0) or absence of damage (DIAPS=0), to understand if DIAPS was able to capture damage in this scenario. Groups were then compared regarding demographics, clinical and laboratory characteristics to identify variables associated with the presence of damage.

Ethical statement

This is a retrospective non-interventional study in humans. The study protocol was submitted for approval by the APS ACTION Executive Committee. All patients included in this study signed written informed consent during recruitment to the APS ACTION Registry. All procedures followed the principles embodied in the Declaration of Helsinki and were in accordance with local statutory requirements of each center involved.

Statistical analysis

No sample size was calculated, as it was a convenience sample. We screened all 826 aPL-positive patients included in the APS ACTION Registry when data were locked.

Data are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The significance level was defined as 5%. Statistical analysis was performed using chi-square and Fisher's exact test for categorical variables, and Mann–Whitney U and t-test for continuous variables, as appropriate. Normality was tested using graphical analyses and the Shapiro-Wilk test. Multivariate analyses were performed using variables with $p<0.10$ in the univariate analyses. Statistical analyses were performed with SPSS 22.0 (Chicago, Illinois).

Results

Patients' characteristics

Of the 826 patients screened, 586 aPL-positive patients without other autoimmune rheumatic systemic diseases were included. The flowchart of patient inclusion and exclusion is presented in Figure 1. The majority of the patients were female (71.0%) and white (66.9%), with a mean age of 51.5 (13.3) years. Out of the 586 included patients, 412 (%) had previous thrombotic events (*thrombotic group*), while 174 (%) did not (*non-thrombotic group*).

Among thrombotic PAPS patients, the majority were also female and white, mean age 52.3 (13.5) years (Table 1). Venous events were the most common (60.0%), followed by arterial events (49.8%). Approximately 10% of patients had microvascular events documented by histopathology (35 small vessel events and 4 CAPS). Obstetric events occurred in 74 patients (28.1% of the 263 women included). The most frequently reported non-thrombotic manifestations were thrombocytopenia and livedo. Traditional CVD risk factors were common: hypertension, hyperlipidemia and obesity were found in approximately one-fourth to one-third of patients. Triple aPL-positivity was the most frequent aPL profile (48.0%). The non-thrombotic aPL-positive group presented a similar profile, except for a lower frequency of traditional cardiovascular risk factors and the absence of thrombotic events.

DIAPS

Mean DIAPS value of thrombotic PAPS patients was 1.94 (1.46) and median DIAPS was 2 (IQR 1-3, min 0, max 9) (Table 2). Of the 412 patients in this group, 348 (84.5%) presented with damage (DIAPS >0) and 110 (26.7%) with high damage (DIAPS ≥3) at the baseline evaluation. The peripheral vascular domain was the most commonly affected: 260 (63.1%) patients presented at least one item from this domain. This was followed by the neuropsychiatric (N=107, 30.0%) and the cardiovascular (N=57, 13.8%) domains. All domains were significantly more frequent in patients with high damage, except for gastrointestinal and endocrine.

Patients from the *non-thrombotic aPL-positive* group had a mean DIAPS value of 0.28 (0.61), median DIAPS value 0 (IQR 0-0, min 0, max 3). Thirty-six (20.7%) had some type of damage (DIAPS >0) at baseline. The neuropsychiatric (N=22, 12.6%) and the cardiovascular (N=13, 7.5%) domains were the most frequently affected in this group. When compared to patients without damage, the cardiovascular, neuropsychiatric, renal and cutaneous domains were significantly associated with the presence of damage.

Factors associated with increased damage

In the thrombotic group, patients with high damage were more likely to be older (54.9 (13.2) vs. 51.4 (13.6) years, p=0.022), male (46.4 vs. 32.5%, p=0.008) and to have hypertension (45.5 vs. 29.5%, p=0.002), hyperlipidemia (38.2 vs. 26.2%, p=0.018) and obesity (36.7 vs. 21.9%, p=0.002) (Table 1). High titers of aβ2GPI correlated with the presence of high damage (34.7% vs. 22.3%, p=0.016). In the multivariate analysis, hyperlipidemia (OR 1.75, 95%CI 1.02-2.98, adjusted p=0.041), obesity (OR 2.05, 95%CI 1.19-3.52, adjusted p=0.009) and aβ2GPI high titers (OR 2.33, 95%CI 1.19-3.52, adjusted p=0.002) were independently associated with the presence of high damage at baseline (Table 2).

In the non-thrombotic group, patients who presented with damage at baseline also presented more frequently with hypertension (44.4% vs 15.2%, p<0.001) and hyperlipidemia (30.6% vs. 8.0%, p=0.001). Patients without damage (DIAPS=0) were more often single aPL positive, when compared to those with damage (DIAPS >0). In the multivariate analysis, hypertension (OR 4.55, 95%CI 1.82-11.35, adjusted p=0.001) and hyperlipidemia (OR 4.32, 95%CI 1.37-13.65, adjusted p=0.013) were independent predictors of the presence of damage at baseline; on the contrary, single positivity was inversely correlated with the presence of damage (OR 0.24; 95%CI 0.075-0,77, adjusted p=0.016).

Discussion

This is the first study to evaluate damage measured by DIAPS in a multiethnic international cohort of primary aPL-positive patients. We independently assessed the use of

DIAPS in a cohort including patients from 27 centers located in 14 different countries (USA, Brazil, Canada, Italy, Spain, England, France, Greece, Japan, China, and others) and we found that this score was able to capture damage in both aPL-positive patients with and without a history of thrombosis (7–9,21).

The majority (85%) of our thrombotic PAPS patients presented with some type of damage, and approximately one fourth presented with high damage. In a recently published study, Medina *et al*. found rates of severe organ damage higher than ours, affecting 59.7% of thrombotic PAPS patients, with a median DIAPS value of 3 (IQR 2-5) (6). Since the rates of traditional CVD risk factors were similar between cohorts, we hypothesize that this difference may be attributable to a longer follow-up, longer disease duration, genetic background or other factors not specifically evaluated, such as non-traditional CVD risk factors, socioeconomic status, access to medical care and time in therapeutic range.

However, these high rates of organ damage measured by DIAPS contrast with previous studies assessing irreversible damage in APS patients. Erkan *et al*. identified organ damage (defined as hemiparesis, dementia, quadriplegia, ischemic dilated cardiomyopathy, vascular insufficiency, massive pulmonary infarction and/or end-stage renal disease) in 38% of patients after 10 years of follow-up (21). Grika *et al*. reported that 29% of 135 patients experienced damage assessed by SDI, after 7.5 year of follow-up (22). Finally, Dall'Ara *et al*. described damage (defined as irreversible failure at any organ or amputation due to vascular event) in 20% of 35 PAPS patients (23). Therefore, our findings reinforce that DIAPS may be a more sensitive tool, capturing a broad spectrum of damage-related clinical complications in APS patients.

In thrombotic PAPS patients, the most affected domains of DIAPS vary widely across different studies. In our population, the most important domains accounting for damage were peripheral vascular, neuropsychiatric, and cardiovascular. Data from the other four studies that provided information on this matter are compared to our data in Figure 2 (6–9). Even though this heterogeneity may arise from differences between populations, it may also reflect

the consequence of different screening strategies adopted in different clinical facilities. Prospective studies with structured screening protocols are crucial to clarify this issue.

Another notable finding of our study is that the presence of traditional CVD risk factors was associated with higher damage in both thrombotic and non-thrombotic aPL-positive patients. In the pathogenesis of APS, the 'two hit hypothesis' is used to explain the clinical observation that the sole presence of aPL ('first hit'), even if persistent, is not sufficient for inducing thrombotic events. A 'second hit' capable of triggering damage to the vessel wall and activation of the endothelial cells and the coagulation cascade is, therefore, needed to create a prothrombotic environment that leads to clot formation (24–26). In our patients with higher damage, the presence of CVD risk factors, namely male gender, older age, hypertension, hyperlipidemia and obesity, may have acted as the 'second hit' and facilitated thrombotic recurrence, which results in increased damage accrual over time and may explain the higher DIAPS values in this group, when compared to patients without those risk factors. In their cluster analysis study, Uludag *et al*. identified a cluster (n=74) that consisted of older patients with CVD risk factors and predominance of arterial events; this cluster showed a mean DIAPS of 2.24 (1.44), which ranked second among the four identified clusters, in terms of damage (9). This may provide further evidence that CVD risk factors could play an important role in damage accrual. However, in contrast to our study, this paper included both PAPS and SLE-associated APS patients, which may introduce confounding factors (renal manifestations are more frequent in SLE patients and therapies with corticosteroids and cyclophosphamide may lead to irreversible damage themselves, such as avascular necrosis and infertility, respectively) (12–15), which negatively impacts interpretation and precludes us from drawing definite conclusions about the importance of CVD risk factors in damage progression in their cohort. A recent study published by Torricelli *et al.*, have shown that high risk PAPS and APS with lupus show differences in damage kinetics during disease evolution. (7) Thus, prospective studies analyzing the kinetics of damage accrual in PAPS patients with CVD risk factors are required.

A further finding was that high titers of aβ2GPI correlated with high damage in thrombotic PAPS patients and that single aPL positivity negatively correlated with damage in the non-thrombotic group. This reinforces the importance of aβ2GPI and high risk profiles in APS pathogenesis (27).

Our study has limitations. First, this is a cross-sectional study with retrospective analysis of records from a database; future studies using prospective data from APS ACTION may provide more conclusive data on the impact of CVD risk factors on damage accrual in PAPS patients. Second, referral bias should be considered, since APS ACTION centers are mostly tertiary referral academic centers, which may have led to selection bias and reduced external validity. However, our study also has strengths. APS ACTION has the largest active APS cohort in the world. Among the studies that analyzed damage in aPL-positive patients, this is the largest one to date, with almost 600 participants. Furthermore, we are able to include patients from all continents, except from Africa.

In conclusion, DIAPS was able to discriminate damage in a large multicenter cohort of aPL-positive patients. A significant proportion of patients with thrombotic PAPS presented with severe organ damage, and the most frequently affected domains were peripheral vascular, neuropsychiatric and cardiovascular. Neuropsychiatric and cardiovascular domains were also relevant to non-thrombotic patients. Selected traditional CVD risk factors and the presence of high titers of aβ2GPI correlated with higher damage in thrombotic primary APS patients. Also, hypertension and obesity positively correlated and single positivity negatively correlated with damage in the non-thrombotic group. Prospective studies are needed to understand the kinetics of damage accrual in PAPS patients with CVD risk factors.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figure 1. Flow diagram of patient selection.

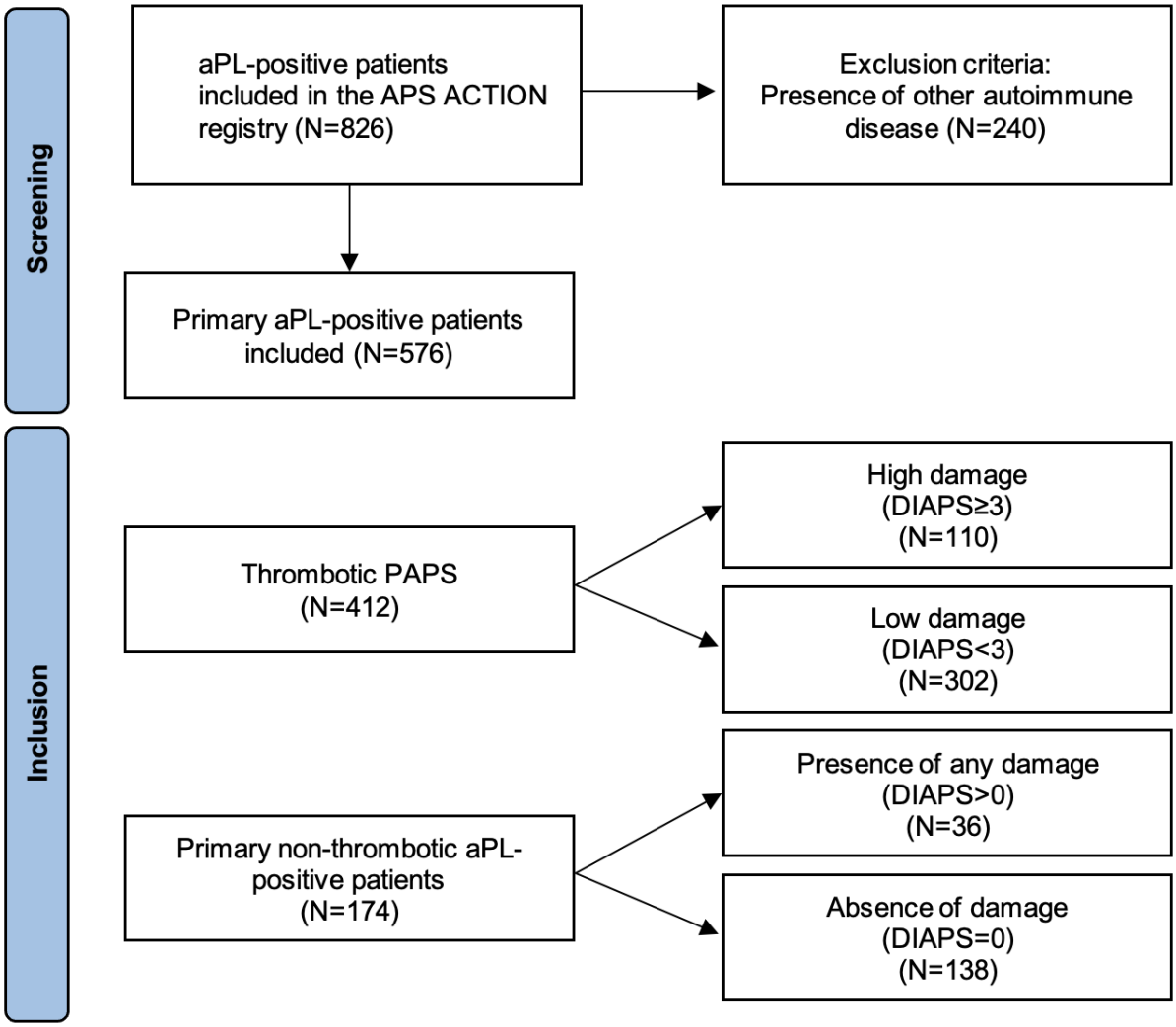

Figure 2. Comparative analysis of the most affected domains of DIAPS in PAPS patients according to different published studies.

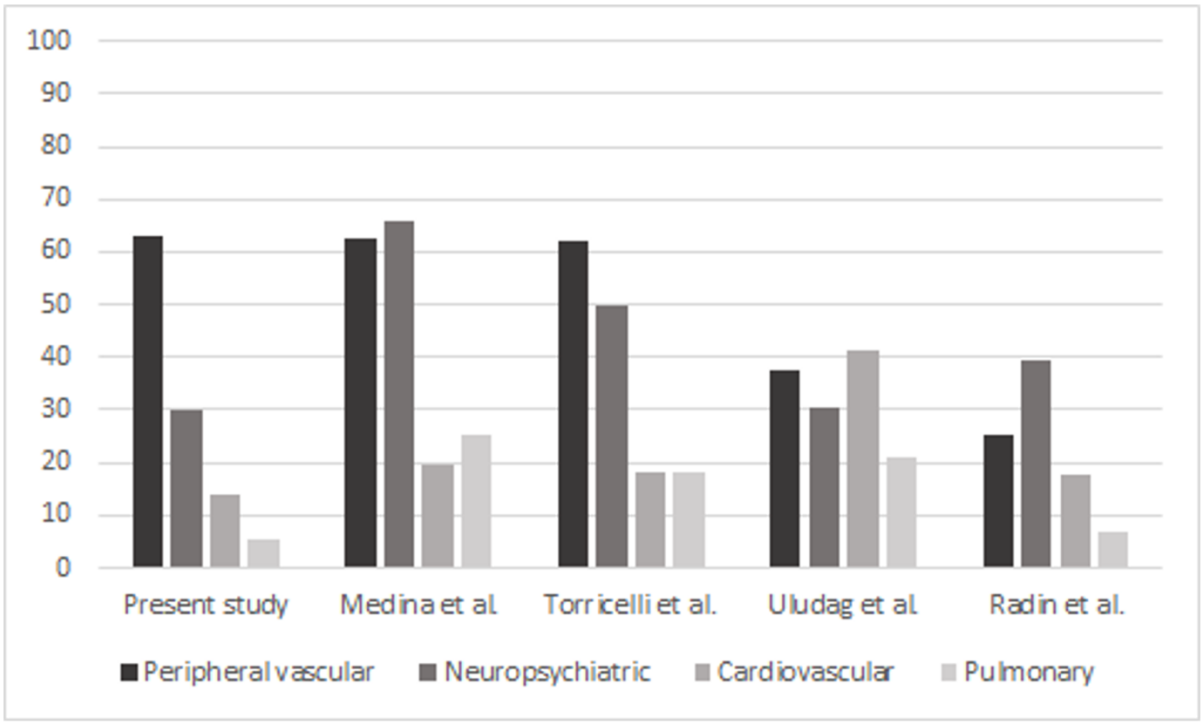

Table 1. Demographic, clinical and laboratory characteristics of aPL-positive patients.

	Thrombotic PAPS (N=412)			Non-Thrombotic patients (N=174)		
	Patients with high damage (DIAPS ≥3) (N=110)	**Patients with low damage (DIAPS <3) (N=302)**	**p-value**	**Patients with damage (DIAPS >0) (N=36)**	**Patients without damage (DIAPS=0) (N=138)**	**p-value**
Demographics						
Age (mean±SD)	54.9±13.2	51.4±13.6	**.022**	52.5±12.6	48.8±12.7	.260
Female	59 (53.6%)	204 (67.5%)	**.008**	31 (86.1%)	122 (88.4%)	.774
White	72 (65.5%)	198 (65.6%)	.522	27 (75.0%)	95 (68.8%)	.533
Cardiovascular Disease Risk Factors						
Hypertension	50 (45.5%)	89 (29.5%)	**.002**	16 (44.4%)	21 (15.2%)	**<.001**
Diabetes	8 (7.3%)	18 (6.0%)	.628	2 (5.6%)	5 (3.6%)	.635
Hyperlipidemia	42 (38.2%)	79 (26.2%)	**.018**	11 (30.6%)	11 (8.0%)	**.001**
Obesity	40 (36.7%)	66 (21.9%)	**.002**	8 (22.2%)	27 (19.6%)	.723
Criteria Manifestations						
Arterial event	60 (54.5%)	145 (48.0%)	.266	NA	NA	NA
Venous event	82 (74.5%)	165 (54.6%)	**<.001**	NA	NA	NA

Microvascular event or CAPS	14 (12.7%)	24 (7.9%)	.138	NA	NA	NA
Obstetric event	19/59 (32.2%)	55/204 (27%)	.826	8 (22.2%)	51 (37.0%)	.096
Non-criteria Manifestations						
Livedo	20 (18.2%)	36 (11.9%)	.101	3 (8.3%)	12 (8.7%)	>.999
Thrombocytopenia	24 (21.8%)	45 (14.9%)	.096	7 (19.4%)	23 (16.6%)	.694
Autoimmune hemolytic anemia	3 (2.7%)	8 (2.6%)	.965	0	4 (2.9%)	.582
aPL profile						
LA	92/104 (88.5%)	261/291 (89.7%)	.727	31/35 (88.6%)	100/136 (73.6%)	.061
aCL	76/109 (69.7%)	198/289 (68.5%)	.816	26/35 (74.3%)	90/135 (66.7%)	.388
High titers (≥80)	60/109 (55.0%)	147/289 (50.9%)	.457	17/35 (48.6%)	58/135 (43.0%)	.552
aβ2GPI	66/101 (65.3%)	147/264 (55.7%)	.094	24/34 (70.6%)	78/129 (60.5%)	.278
High titers (≥80)	35/101 (34.7%)	59/264 (22.3%)	**.016**	15/34 (44.1%)	56/129 (43.4%)	.941
Single positive	24/94 (25.5%)	75/248 (30.2%)	.439	5/32 (15.7%)	43/123 (35.0%)	**.042**
LA only	19/94 (20.2%)	64/248 (25.8%)	.315	4/32(12.5%)	26/123 (21.1%)	.301

Double positive	23/94 (24.5%)	56/248 (22.6%)	.658	8/32 (25.0%)	31/123 (25.2%)	.963
Triple positive	47/94 (50.0%)	117/248 (47.2%)	.554	18/32 (56.3%)	49/123 (39.8%)	.076

Legend: Abbreviations: aCL – anticardiolipin, aβ2GPI – anti-beta-2 glycoprotein I, CAPS - catastrophic APS, DIAPS – Damage Index for Antiphospholipid Syndrome, LA – lupus anticoagulant, PAPS – primary antiphospholipid syndrome, SD – standard deviation. Bold text represents statistically significant differences.

Table 2. Frequency of DIAPS domains affected in thrombotic PAPS and non-thrombotic aPL-positive patients.

	Thrombotic PAPS (N=412)			Non-Thrombotic patients (N=174)		
	Patients with high damage (DIAPS ≥3) (N=110)	**Patients with low damage (DIAPS <3) (N=302)**	**p-value**	**Patients with damage (DIAPS >0) (N=36)**	**Patients without damage (DIAPS=0) (N=138)**	**p-value**
Peripheral vascular	83 (75.5%)	177 (58.6%)	**.002**	1 (2.8%)	0 (0.0%)	.207
Pulmonary	19 (17.3%)	4 (1.3%)	**<.001**	0 (0.0%)	0 (0.0%)	NA
Cardiovascular	36 (32.7%)	21 (7.0%)	**<.001**	13 (36.1%)	0 (0.0%)	**<.001**
Neuropsychiatric	65 (59.1%)	42 (13.9%)	**<.001**	22 (61.1%)	0 (0.0%)	**<.001**
Ophthalmologic	4 (3.6%)	0 (0.0%)	**.005**	0 (0.0%)	0 (0.0%)	NA
Renal	19 (17.3%)	5 (1.7%)	**<.001**	4 (11.1%)	0 (0.0%)	**.002**
Musculoskeletal	2 (1.8%)	0 (0.0%)	**.019**	1 (2.8%)	0 (0.0%)	.207
Cutaneous	20 (18.2%)	4 (1.3%)	**<.001**	3 (8.3%)	0 (0.0%)	**.008**
Gastrointestinal	3 (2.7%)	2 (0.7%)	.121	0 (0.0%)	0 (0.0%)	NA
Endocrine	0 (0.0%)	0 (0.0%)	NA	0 (0.0%)	0 (0.0%)	NA

Legend: DIAPS – Damage Index for Antiphospholipid Syndrome, PAPS – primary antiphospholipid syndrome. Bold text represents statistically significant differences.