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Clinical science

Damage measured by Damage Index for Antiphospholipid Syndrome (DIAPS) in antiphospholipid antibody-positive patients included in the APS ACTION registry

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Abstract

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

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

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Results: Of the 826 aPL-positive patients included in the registry as of April 2020, 586 with no other systemic autoimmune diseases were included in the analysis (412 thrombotic and 174 non-thrombotic). In the thrombotic group, hyperlipidaemia (odds ratio [OR] 1.82; 95% CI 1.05, 3.15; adjusted $P=0.032$), obesity (OR 2.14; 95% CI 1.23, 3.71; adjusted $P=0.007$), aβ_2GPI high titres (OR 2.33; 95% CI 1.36, 4.02; adjusted $P=0.002$) and corticosteroid use (ever) (OR 3.73; 95% CI 1.80, 7.75; adjusted $P<0.001$) 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 hyperlipidaemia (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 indicates substantial damage in aPL-positive patients in the APS ACTION cohort. Selected traditional cardiovascular risk factors, steroids use and specific aPL profiles may help to identify patients more prone to present with a higher damage burden.

Keywords: antiphospholipid syndrome, antiphospholipid antibodies, lupus anticoagulant, anticardiolipin, anti-beta-2 glycoprotein I antibodies, damage, cardiovascular disease, risk factors

Rheumatology key messages

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

Introduction

APS is the most common acquired thrombophilia, characterized by thrombotic events and/or pregnancy morbidity in the presence of persistent aPL, namely lupus anticoagulant (LA), IgG and/or IgM anticardiolipin antibodies (aCL), and IgG and/or IgM anti-β-2 glycoprotein I antibodies (aβ2GPI). APS may develop in association with other autoimmune diseases, especially 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). Each item may receive up to 2 points (range 0–74 points) [3]. All domains and items included in DIAPS are presented in Supplementary Table S1 (available at *Rheumatology* online). 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 multicentre 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 centres 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 burden in populations other than those initially reported.

Our primary objective was to quantify damage burden 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.

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 1 year prior to enrolment.

The only exclusion criterion was autoimmune rheumatic diseases other than APS, given these diseases and their treatment, e.g. glucocorticosteroids (almost universally used) 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. However, we did not exclude patients that were using glucocorticoids to non-criteria manifestations related to APS or aPL-positivity (e.g. cytopenias).

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], was obtained at the baseline visit of APS ACTION. The aPL profile was obtained from local labs; high titres 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 aPL criteria, irrespective of isotype. Corticosteroid use was analysed binarily, as previous use (ever) or not (never). 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 (vascular venous insufficiency, abnormal movements, aPL-associated heart valve disease with or without valve replacement, renal thrombotic microangiopat, chronic cutaneous ulcers), or were collected as part of the general medical history (researchers are formally instructed to fulfil an open ended-form with all relevant medical conditions that developed between the current and the last visit, which occur every 12 ± 3 months). Since all information collected in DIAPS is critical and should be entered in the APS ACTION database, clinical information was considered absent if not properly recorded. Information not readily available, namely optic neuropathy, multi-infarct dementia and chronic thromboembolic pulmonary hypertension, was treated using regression imputation to conservatively predict the actual data, based on the presence, respectively, of multiple sclerosis-like symptoms and blindness; cognitive dysfunction and stroke; and pulmonary hypertension and pulmonary embolism. Calculation of DIAPS was performed as previously published by Amigo *et al.* [3]. Due to the nature of the registry and since there was no specification whether DIAPS items should be scored only after aPL identification/APS diagnosis in the original paper, we analysed all the damage burden present at the baseline assessment of APS ACTION, as long as it was attributed to aPL/APS by the researcher.

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 burden for each scenario: (i) a thrombotic group, and (ii) a 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 $\geq$3) *vs* low damage (DIAPS $<$3). The definition of high damage was based on the median values of DIAPS found in our cohort (high damage DIAPS $\geq$p50 *vs* low damage DIAPS $<$p50); those values were supported by a recent paper published by Medina *et al.*, who also defined DIAPS $\geq$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 analysis of multicentre APS ACTION registry patients. All patients included in the APS ACTION registry signed a written informed consent form following local ethical approvals at each institution. All procedures followed the principles embodied in the Declaration of Helsinki and were in accordance with local statutory requirements of each centre 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 the 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 the χ^2 test and Fisher's exact test for categorical variables, and the Mann–Whitney *U*-test and Student's *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 Statistics 22.0 (IBM Corp., Armonk, NY, USA).

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 Fig. 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 (70.3%) had previous thrombotic events (the thrombotic group), while 174 (29.7%) did not (the non-thrombotic group). Clinical and laboratory characteristics of the included patients are summarized in Table 1.

DIAPS

The mean DIAPS value of thrombotic PAPS patients was 1.94 (1.46) and the median DIAPS was 2 (IQR 1–3, min 0, max 9). Of the 412 patients in this group, 348 (84.5%) presented with damage (DIAPS $>$0) and 110 (26.7%) with high damage (DIAPS $\geq$3) at the baseline evaluation. The peripheral vascular domain was the most commonly affected: 260 (63.1%) patients presented at least one item from this domain. This was followed by the neuropsychiatric ($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 (Table 2).

Patients from the non-thrombotic aPL-positive group had a mean DIAPS value of 0.28 (0.61) and median DIAPS value of 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 with patients without damage, the cardiovascular, neuropsychiatric, renal and cutaneous domains were significantly associated with the presence of damage (Table 2).

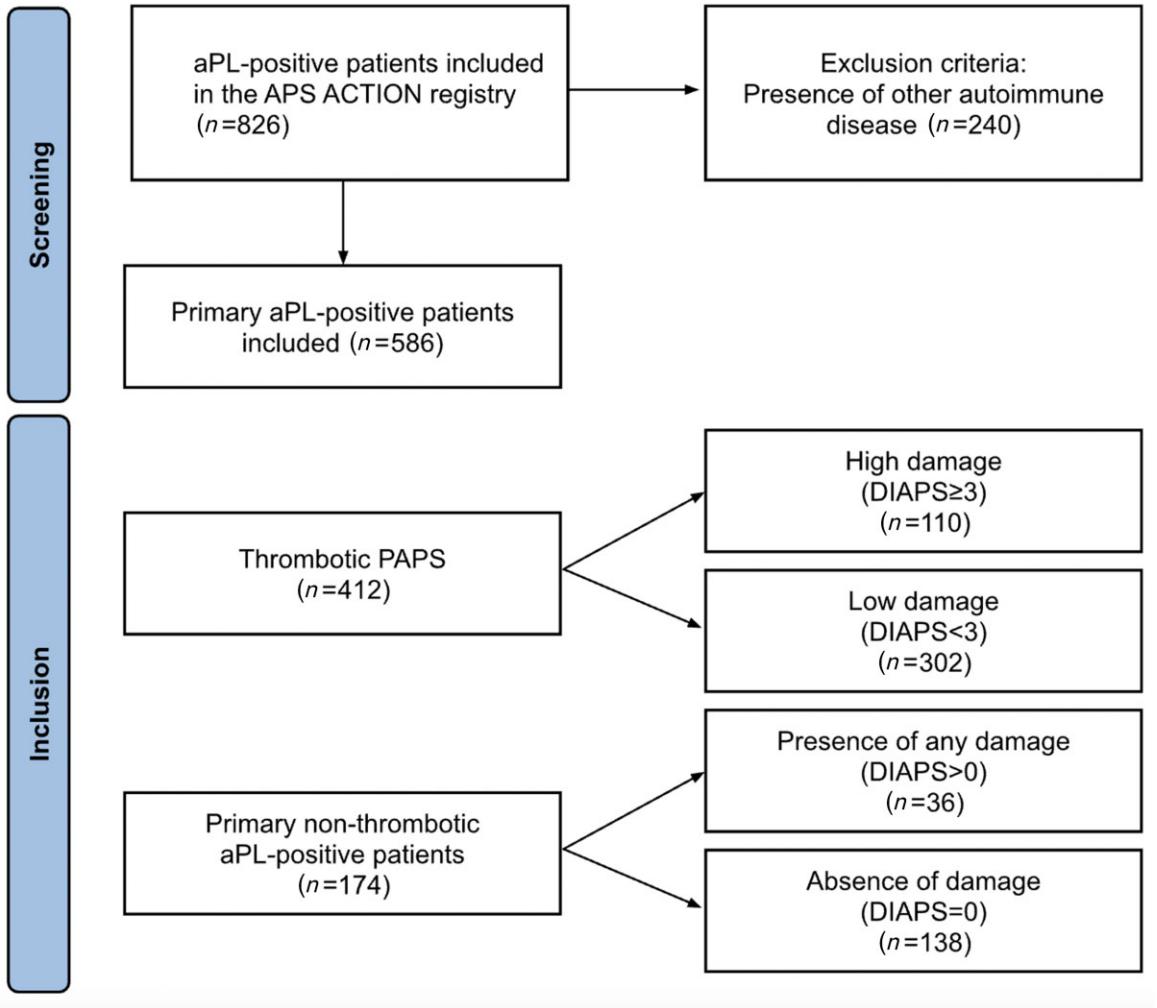

Figure 1. Flow diagram of patient selection. DIAPS: Damage Index for Antiphospholipid Syndrome; PAPS: primary APS

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%, $P = 0.002$), hyperlipidaemia (38.2% *vs* 26.2%, $P = 0.018$) and obesity (36.7% *vs* 21.9%, $P = 0.002$) (Table 1). High titres of aβ2GPI correlated with the presence of high damage (34.7% *vs* 22.3%, $P = 0.016$). Also, corticosteroid use was associated with high damage (21.8% *vs* 8.0%, $P < 0.001$).

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 hyperlipidaemia (30.6% *vs* 8.0%, $P = 0.001$). Patients without damage (DIAPS = 0) were more often single aPL positive, when compared with those with damage (DIAPS >0).

Multivariate analyses are presented in Table 3.

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 centres located in 14 different countries (USA, Brazil, Canada, Italy, Spain, UK, France, Greece, Japan, China, and others) and we found that this score was able to capture damage in aPL-positive patients both 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]. However, these high rates of organ damage measured by DIAPS contrast with previous studies assessing irreversible damage in APS patients using different definitions. Erkan *et al.* identified organ damage 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 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 varied widely across different studies. Data from the

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

Characteristic	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 (S.D.), years	54.9 (13.2)	51.4 (13.6)	**0.022**	52.5 (12.6)	48.8 (12.7)	0.260
Female, *n* (%)	59 (53.6)	204 (67.5)	**0.008**	31 (86.1)	122 (88.4)	0.774
White, *n* (%)	72 (65.5)	198 (65.6)	0.522	27 (75.0)	95 (68.8)	0.533
Cardiovascular disease risk factors, *n* (%)						
Hypertension	50 (45.5)	89 (29.5)	**0.002**	16 (44.4)	21 (15.2)	**<0.001**
Diabetes	8 (7.3)	18 (6.0)	0.628	2 (5.6)	5 (3.6)	0.635
Hyperlipidaemia	42 (38.2)	79 (26.2)	**0.018**	11 (30.6)	11 (8.0)	**0.001**
Obesity	40 (36.7)	66 (21.9)	**0.002**	8 (22.2)	27 (19.6)	0.723
Criteria manifestations, *n* (%)						
Arterial event	60 (54.5)	145 (48.0)	0.266	NA	NA	NA
Venous event	82 (74.5)	165 (54.6)	**<0.001**	NA	NA	NA
Microvascular event or CAPS	14 (12.7)	24 (7.9)	0.138	NA	NA	NA
Obstetric event	19/59 (32.2)	55/204 (27)	0.826	8 (22.2)	51 (37.0)	0.096
Non-criteria manifestations, *n* (%)						
Livedo	20 (18.2)	36 (11.9)	0.101	3 (8.3)	12 (8.7)	>0.999
Thrombocytopenia	24 (21.8)	45 (14.9)	0.096	7 (19.4)	23 (16.6)	0.694
Autoimmune haemolytic anaemia	3 (2.7)	8 (2.6)	0.965	0	4 (2.9)	0.582
aPL profile, *n* (%)						
LA	92/104 (88.5)	261/291 (89.7)	0.727	31/35 (88.6)	100/136 (73.6)	0.061
aCL	76/109 (69.7)	198/289 (68.5)	0.816	26/35 (74.3)	90/135 (66.7)	0.388
High titres (≥80)	60/109 (55.0)	147/289 (50.9)	0.457	17/35 (48.6)	58/135 (43.0)	0.552
aβ2GPI	66/101 (65.3)	147/264 (55.7)	0.094	24/34 (70.6)	78/129 (60.5)	0.278
High titres (≥80)	35/101 (34.7)	59/264 (22.3)	**0.016**	15/34 (44.1)	56/129 (43.4)	0.941
Single positive	24/94 (25.5)	75/248 (30.2)	0.439	5/32 (15.7)	43/123 (35.0)	**0.042**
LA only	19/94 (20.2)	64/248 (25.8)	0.315	4/32(12.5)	26/123 (21.1)	0.301
Double positive	23/94 (24.5)	56/248 (22.6)	0.658	8/32 (25.0)	31/123 (25.2)	0.963
Triple positive	47/94 (50.0)	117/248 (47.2)	0.554	18/32 (56.3)	49/123 (39.8)	0.076
Treatment						
Corticosteroid use (ever), *n* (%)	24 (21.8)	24 (8.0)	**<0.001**	5 (13.9)	11 (8.0)	0.329

Bold text represents statistically significant differences. aβ2GPI: anti-β-2 glycoprotein I; aCL: anticardiolipin; CAPS: catastrophic APS; DIAPS: Damage Index for Antiphospholipid Syndrome; LA: lupus anticoagulant; NA: not applicable; PAPS: primary APS.

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, *n* (%)	83 (75.5)	177 (58.6)	**0.002**	1 (2.8)	0 (0.0)	0.207
Pulmonary, *n* (%)	19 (17.3)	4 (1.3)	**<0.001**	0 (0.0)	0 (0.0)	NA
Cardiovascular, *n* (%)	36 (32.7)	21 (7.0)	**<0.001**	13 (36.1)	0 (0.0)	**<0.001**
Neuropsychiatric, *n* (%)	65 (59.1)	42 (13.9)	**<0.001**	22 (61.1)	0 (0.0)	**<0.001**
Ophthalmologic, *n* (%)	4 (3.6)	0 (0.0)	**0.005**	0 (0.0)	0 (0.0)	NA
Renal, *n* (%)	19 (17.3)	5 (1.7)	**<0.001**	4 (11.1)	0 (0.0)	**0.002**
Musculoskeletal, *n* (%)	2 (1.8)	0 (0.0)	**0.019**	1 (2.8)	0 (0.0)	0.207
Cutaneous, *n* (%)	20 (18.2)	4 (1.3)	**<0.001**	3 (8.3)	0 (0.0)	**0.008**
Gastrointestinal, *n* (%)	3 (2.7)	2 (0.7)	0.121	0 (0.0)	0 (0.0)	NA
Endocrine, *n* (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

Bold text represents statistically significant differences. DIAPS: Damage Index for Antiphospholipid Syndrome; NA: not available; PAPS: primary antiphospholipid syndrome.

Table 3. Risk factors associated with damage in aPL-positive patients, in the multivariate analysis

	Thrombotic PAPS ($n = 412$)		Non-thrombotic patients ($n = 174$)	
	High damage (DIAPS ≥ 3)		Presence of damage (DIAPS >0)	
Variable	OR (95% CI)	Adjusted *P*-value	OR (95% CI)	Adjusted *P*-value
Hyperlipidaemia	1.82 (1.05, 3.15)	**0.032**	4.32 (1.37, 13.65)	**0.001**
Obesity	2.14 (1.23, 3.71)	**0.007**	—	—
aβ2GPI high titres (≥ 80)	2.33 (1.36, 4.02)	**0.002**	—	—
Corticosteroids use	3.73 (1.80, 7.75)	**<0.001**	—	—
Hypertension	2.75 (0.92, 2.69)	0.097	4.55 (1.82, 11.35)	**0.001**
Single positivity	—	—	0.24 (0.08, 0.77)	**0.016**

Bold text represents statistically significant differences. aβ2GPI: anti-β-2 glycoprotein I; DIAPS: Damage Index for Antiphospholipid Syndrome; OR: odds ratio; PAPS: primary antiphospholipid syndrome.

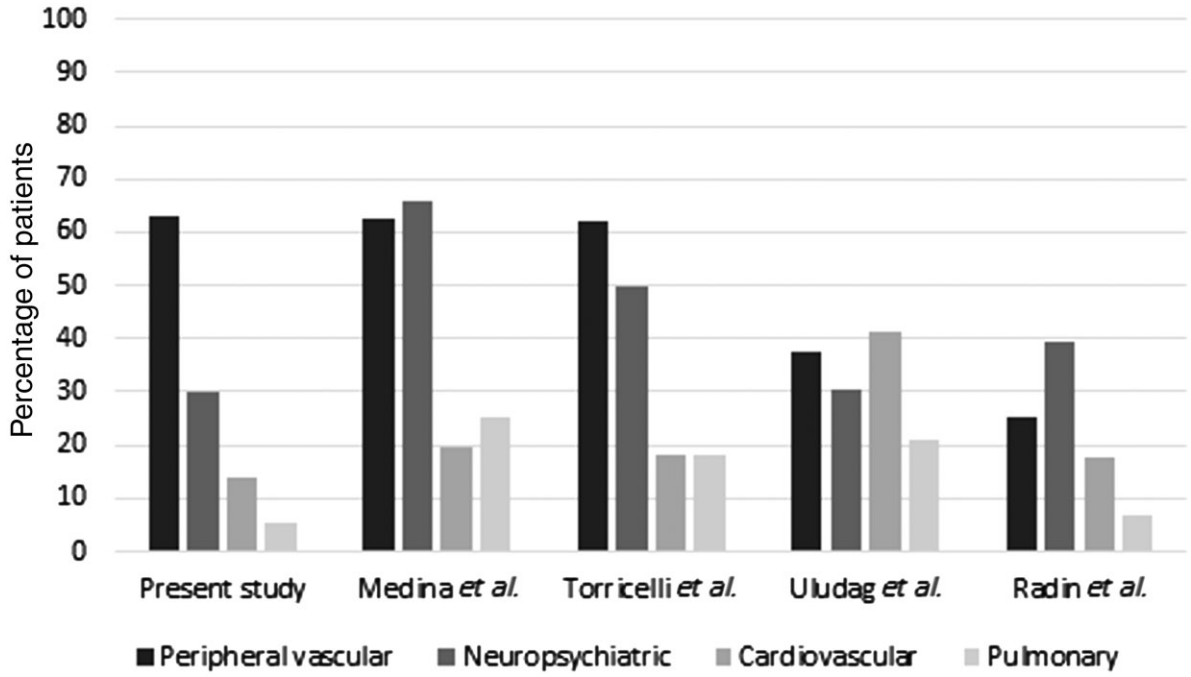

Figure 2. Comparative analysis of the most affected domains of DIAPS in PAPS patients according to different published studies. DIAPS: Damage Index for Antiphospholipid Syndrome; PAPS: primary APS

other four studies that provided information on this matter are compared with our data in Fig. 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.

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 [24–28]. In our patients with higher damage, the presence of CVD risk factors, namely male gender, older age, hypertension, hyperlipidaemia 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 with patients without those risk factors. In their cluster analysis study, Uludağ *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 treatment with either corticosteroids or cyclophosphamide may itself lead to irreversible damage, namely avascular necrosis or infertility, respectively [12–15]. Thus, the inclusion of SLE patients 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.* showed that high risk PAPS and APS with lupus show differences in damage kinetics during disease

evolution [7]. Thus, prospective studies analysing the kinetics of damage accrual in PAPS patients with CVD risk factors are required.

A further finding was that high titres 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 [29]. Curiously, lupus anticoagulant and triple positivity, important risk factors for thrombotic recurrence in patients with APS, were not associated with increased damage in our cohort, which raises concern about DIAPS content validity. An updated version of the damage index for APS may be needed to address this issue. Also, previous corticosteroid use was an independent risk factor for high damage in patients with PAPS, similar to what was previously demonstrated for SLE patients [13, 30, 31].

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 centres are mostly tertiary referral academic centres, which may have led to selection bias and reduced external validity. Also, the exclusion of SLE and other autoimmune diseases associated with APS may limit its external validity. However, our study also has strengths. APS ACTION has the largest active APS cohort in the world. Among the studies that analysed 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 Africa.

In conclusion, DIAPS indicates substantial damage in aPL-positive patients in the APS ACTION cohort. 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, corticosteroid use, and the presence of high titres 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.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Contribution statement

All authors provided critical review, relevant edits and feedback to direct content during multiple rounds of review. In addition, all authors have read and approved the final version of this manuscript.

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