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ANTIPHOSPHOLIPID SYNDROME IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IMPLIES A MORE SEVERE DISEASE WITH MORE DAMAGE ACCRUAL AND HIGHER MORTALITY

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Abstract:	Introduction: Antiphospholipid antibodies (aPL) have been associated with organ damage and certain features in systemic lupus erythematosus(SLE) patients. Our aim was to investigate the differences between SLE patients according to the presence of aPL and/or clinical antiphospholipid syndrome (APS). Materials and methods: Patients from the RELESSER-T registry were included. RELESSER-T is a Spanish multicenter, hospital-based, retrospective, SLE registry. Results: We included 2398 SLE patients, 1372 of whom were positive for aPL. Overall 1026 patients were classified as SLE, 555 as SLE-APS and817 as SLE-aPL. Regarding cardiovascular risk factors, SLE-APS patients had higher rates of hypertension, dyslipidemia and diabetes than those with SLE-aPL and SLE ($p<0.001$). SLE-APS patients showed higher rates of neuropsychiatric, cardiac, pulmonary, renal and ophthalmological manifestations than the other groups ($p<0.001$). SLE-APS patients presented greater damage accrual with higher SLICC values (1.9±2.2 in SLE-APS, 0.9±1.4 in SLE-aPL and 1.1±1.6 in SLE, $p<0.001$) and more severe disease as defined by the Katz index (3±1.8 in SLE-APS, 2.7±1.7 in SLE-aPL and 2.6±1.6 in SLE, $p <0.001$). SLE-APS patients showed higher mortality rates ($p<0.001$). Conclusions: SLE-APS patients exhibited more severe clinical profiles with higher frequencies of major organ involvement, greater damage accrual and higher mortality than SLE-aPL and SLE patients.

ANTIPHOSPHOLIPID SYNDROME (APS) IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) IMPLIES A MORE SEVERE DISEASE WITH MORE DAMAGE ACCRUAL AND HIGHER MORTALITY

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ABSTRACT

Introduction: Antiphospholipid antibodies (aPL) have been associated with organ damage and certain features in systemic lupus erythematosus(SLE) patients. Our aim was to investigate the differences between SLE patients according to the presence of aPL and/or clinical antiphospholipid syndrome (APS).

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Conclusions: SLE-APS patients exhibited more severe clinical profiles with higher frequencies of major organ involvement, greater damage accrual and higher mortality than SLE-aPL and SLE patients.

Keywords: antiphospholipid antibody, lupus anticoagulant, antiphospholipid syndrome, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic rheumatic disease characterized by immune-mediated inflammation. Patients with SLE are characterized by the production of a wide variety of autoantibodies, including antiphospholipid antibodies (aPL). aPL are a heterogenous group of autoantibodies, including lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and/or anti-β2-glycoprotein-I antibodies (aβ2GPI). Around 20 to 40% of lupus patients are positive for aPL, and between 50 to 70% of patients with SLE and aPL develop clinical features of antiphospholipid syndrome (APS) after 20 years of follow-up (1). aPL have been extensively linked to thrombosis and pregnancy morbidities in patients with primary APS, as well as in APS associated with other autoimmune disorders (2;3). Moreover, in SLE, aPL have been associated with organ damage (4;5) and with certain clinical features such as thrombocytopenia (6), valvular heart disease (7) and/or neuropsychiatric manifestations (8). However, some of these associations with SLE clinical features, such as pleural or renal involvement among others, remain controversial, with conflicting results among previous studies (9;10). Furthermore, most studies make no difference between patients with positive aPL serology and those with clinically defined APS.

The aims of this study were to investigate the association between aPL and clinical and immunological manifestations of SLE in a large and well-defined cohort of lupus

patients and to identify potential differences in SLE expression in patients with positive aPL with no clinical criteria for APS versus those with associated APS.

PATIENTS AND METHODS

Patients

Patients from the Registry of SLE patients of the Spanish Society of Rheumatology (RELESSER) registry who met at least 4 American College of Rheumatology (ACR)-97 SLE criteria (11) were included. The methodology used, the definitions of the disease-related variables, and general characteristics of this cohort have been previously described in detail (12;13). Briefly, RELESSER is a multicenter, hospital-based registry, consisting of a large representative sample of adult non-selected patients with SLE attending Spanish rheumatology services from the national healthcare system. It involves a total of forty-five hospital centers. RELESSER is a retrospective cross-sectional collection of SLE patient data during a 12-month period from October 2011 to September 2012. All of the participating researchers had specific training on the study procedures and on the use of SLE assessment tools. The study was approved by the local ethics committees of all participating centers. The Research Unit of the Spanish Society of Rheumatology (SER) managed all data and data processing. This unit was the coordinating center, providing expert methodological support throughout all stages of the project, carrying out study monitoring and identifying potential inconsistencies

and solutions. The Research Unit of the SER has given expert methodological support to recognized registries of patients with different rheumatic diseases (14-18).

Study groups

Patients were classified into three different groups: those with SLE and negative aPL serology (SLE), those with SLE and a positive serology for aPL, but not meeting clinical criteria for APS (SLE-aPL), and those with SLE and associated APS according to Sydney criteria (SLE-APS) (19). Patients with no aPL test data were excluded.

Data collection

The information collected consisted of a total of ≈ 400 variables per patient including the following domains: a) Demographics: age, gender, and ethnicity. b) Clinical variables: comorbidities, delay in SLE diagnosis, disease duration, ACR criteria (11), disease activity at the time of the last visit (or at death, if applicable) retrospectively measured by the Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity (SELENA-SLEDAI) (20)·(21), Sydney criteria for antiphospholipid syndrome (19), Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC) (22), Katz severity index (23), any history of drug use during the disease course, and death (all cause, due to infection, due to cancer, due to vascular causes including isquemic and hemorrhagic events, and related to SLE). The main SLE-related clinical manifestations analyzed in the present study are shown in

Supplementary Table 1. SLE manifestations related to thrombotic aetiology were excluded from analysis. c) Immunological domain: complement (C3, C4) levels, presence of autoantibodies (ANA, anti-ds-DNA, anti-Sm, anti-Ro, anti-La, anti-RNP, and aPL included in the Sydney criteria. LA was determined according to the standard guidelines issued by the Subcommittee on Lupus Anticoagulant/antiphospholipid antibody (scientific and standardization Committee of the International Society of Thrombosis and Haemostasis) (24). We considered positive aCL if medium or high titers (>40 GPL or MPL, or >the 99th percentile) were recorded using a standardized ELISA. aB2GPI were considered positive if titer >the 99th percentile, as also measured by standardized ELISA. aPL serology was considered positive when two different samples were positive, at least 12 weeks apart according to the Sidney Criteria (19).

Statistical analysis

Means and standard deviations for numeric variables based on normal distribution, and absolute and relative frequencies for qualitative variables were calculated for the global study population and for the different study groups. Student's T-test, ANOVA and Mann Whitney tests were used for numerical variables and Chi-square when categorical variables among groups were compared. To assess the differences in mortality, we constructed an exploratory model, adjusting it by potential confounders. A logistic multivariate model was run, using mortality as a dependent variable and adjusting for age, sex, traditional cardiovascular risk factors (hypertension, diabetes and

hyperlipidemia) as well as disease damage accrual. These variables were chosen due to their clinical significance and because there were differences in the study groups when performing the bivariate analysis. Regarding disease damage accrual, we proposed an exploratory model to estimate the differences in SLICC values among groups. We considered the same variables as potential confounders and ran a multivariate regression model to estimate the differences in SLICC scores. Statistical significance was assumed as $p \leq 0.001$ in order to minimize type I errors due to multiple test comparisons. All analyses were performed using Stata 13.1 for Windows (Copyright 1985-2013 StataCorp LP StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA).

RESULTS

Characteristics of the cohort

A total of 2398 SLE patients (90.4% female; 93.4% Caucasian) were included. **Table 1** presents the main demographic data and traditional cardiovascular risk factors among the study groups. Mean age at the time of the study visit was 46.1±14.2 years, and the mean follow-up duration was 142.8 ±102.3 months.

Detailed data on the main clinical SLE manifestations are shown in **Table 2**. Briefly, the most common clinical manifestations in this lupus cohort were haematological (79.4%), followed by musculoskeletal (77.3%) and cutaneous (72.1%).

APS-related manifestations not included in the Sydney criteria are shown in **Table 3.** Overall, Raynaud´s phenomenon was found in 34.1% of patients, followed by thrombocytopenia (25.9%), haemolytic anemia (9%) and headache (6.1%).

A total of 1372 patients (57.3%) were positive for aPL antibodies. The most frequently found aPL antibody was IgG aCL, with a prevalence of 34.7%, followed by LA with 26.6% and IgM aCL with 28.3%. aB2GPI, IgG and IgM were positive, respectively, in 12.2% and 12.5% of SLE patients. In **Supplementary Table 2** data on the positivity of the types and isotypes of antibodies are detailed. Among the 2398 patients included, 1026 (42.8%) were classified into the SLE group, 555 (23.1 %) into the SLE-APS and 817 (34.1%) into the SLE-aPL group. Clinical manifestations included in APS criteria are shown in **Supplementary Table 3**. Patients in the SLE-APS group not only had the more commonly found IgG isotypes of both aCL and aB2GPI, but also had a higher frequency of LA compared with SLE-aPL patients. Moreover, the number of positive antibodies was significantly higher in SLE-APS patients (**Supplementary Table 2)**.

Overall, corticosteroids were the most common drug used in 88.9% of patients, followed by antimalarials (85%) and NSAIDS (73.2%). Azathioprine (34.7%) was the most frequently used immunosuppressant, followed by cyclophosphamide (23.1%). Rituximab was the most frequently prescribed biologic (7.5%). Forty-five percent of patients were on low-dose aspirin (LDA) and 18.8% received oral anticoagulants.

Differences in the treatments regimens among the study groups are summarized in **Table 4**.

As shown in **Table 5**, the mortality in the global lupus cohort was 5.1%. The main causes of mortality in order of frequency were vascular events (31.5%) and infections (32.6%), followed by SLE (28.6%) and neoplasms (17.6%).

Impact of antiphospholipid antibody positivity (SLE-aPL *vs* SLE)

We found no differences in lupus clinical manifestations, although SLE tended to present more renal manifestations (p=0.03). However, SLE-aPL had more commonly encountered non-APS criteria manifestations such as thrombocytopenia (p<0.001), haemolytic anemia (p=0.006) and Raynaud's phenomenon (p=0.001). There were no differences in immunological parameters such as anti-ds-DNA antibodies and hypocomplementemia. As shown in **Figure 1**, no differences in disease activity between these two groups were found, although SLE-aPL patients tended to have lower values of damage accrual as measured by the SLICC index (0.9±1.4 *vs* 1.3±1.6, p=0.008). As expected, SLE-aPL patients were more frequently treated with LDA (*p*<0.001). SLE aPL patients tended to have higher mortality rates (p=0.04).

Impact of associated antiphospholipid syndrome (SLE-APS *vs* SLE)

SLE-APS patients were slightly older at the time of the study (48.7±14.4 *vs* 45.5 ± 14, p<0.001) and had higher rates of traditional CV risk factors such as hypertension (p=0.001), dyslipidemia (p<0.001) and diabetes (p=0.03). As shown in **Table 2**, a trend for differences in the frequencies of cutaneous manifestations did not reach statistical significance. The pairwise comparison of SLE-APS vs SLE showed fewer cutaneous manifestations in SLE-APS (p=0.012). SLE-APS patients suffered more severe lupus manifestations such as renal (p=0.014), respiratory, neuropsychiatric, cardiac and ophthalmological manifestations (p<0.001). As expected, thrombocytopenia, often considered a feature of APS, more frequently occurred in SLE-APS patients than in SLE patients (p<0.001). Moreover, SLE-APS more often suffered other common non-APS criteria manifestations such as haemolytic anemia, Evans syndrome, valvular dysfunction, Libman-Sacks en (LSE) (p<0.001), headache and cognitive dysfunction (p=0.001). Anti-ds-DNA antibodies tended to be more commonly observed in SLE-APS patients (p=0.013). As shown in **Figure 1**, SLE-APS patients had higher values in terms of damage accrual and severity indexes (p<0.001) as well as in the disease activity index (p=0.001). Regarding disease damage accrual, we adjusted the data for age, disease duration and traditional cardiovascular risk factors. We found that, after adjusting for those factors, the SLICC score was 0.6 points higher in SLE-APS patients than in those with SLE (CI 0.4-0.8, p <0.001).

(Supplementary Table 4).

As expected, SLE-APS patients required more LDA and oral anticoagulants (*p*<0.001). Moreover, in line with a more severe disease profile, these patients tended to require more azathioprine (p=0.033), IVIG (p=0.001), corticosteroids (p=0.011), and cyclophosphamide (p=0.019). SLE-APS showed a higher all-cause mortality (p<0.001), but no significant

differences were found when analyzing the different causes of death. Multivariate analysis encompassing age, disease duration, traditional cardiovascular risk factors (hypertension, diabetes and dyslipidemia), disease damage accrual and disease severity index demonstrated that the mortality differences remained significant. SLE-APS patients showed higher all-cause mortality with an OR of 2.94 (1.68-5.14) p< 0.001.**(Supplementary Table 5)**.

Differences between positive aPL serology and clinical APS in SLE patients (SLE-aPL *vs* SLE-APS)

We also explored the differences in SLE patients with positive aPL with and without APS clinical manifestations. SLE-APS patients tended to be older at the time of the study (48.6±14.4 *vs* 45.1±14.2, p=0.015). and, not surprisingly, had higher cardiovascular risk, presenting higher rates of diabetes (p<0.001), hypertension (p<0.001) and dyslipidemia (p<0.001). Additionally, SLE-APS patients more often suffered major lupus manifestations, to include renal, respiratory, neuropsychiatric and cardiac manifestations (p<0.001). Non-criteria APS manifestations such as valvular dysfunction, LSE and cognitive dysfunction were also more frequent in SLE-APS patients (p<0.001). Other APS-related symptoms such as thrombocytopenia, haemolytic anemia, Evans syndrome and headache also tended to be more common in SLE-APS patients (p=0.004, 0.003, 0.003 and 0.002, respectively). Furthermore, these subjects tended to show higher frequencies of anti-ds-DNA antibodies (p=0.014), greater organ

damage accrual and disease severity than SLE-aPL patients (p<0.001) (**Figure 1**). No differences in SLEDAI values were found. As expected, SLE-APS patients more often received oral anticoagulants (p<0.001). Moreover, they tended to require more often corticosteroids (p=0.001), plasmapheresis (p=0.001) and other immunosuppressive drugs such as mycophenolate (p=0.003) and cyclophosphamide (p=0.011). On the other hand, antimalarials tended to be more commonly used in SLE-aPL patients (p=0.002). SLE-APS patients showed higher all-cause mortality (p<0.001). In addition, although no differences were evident in the global analysis, SLE-related mortality tended to be higher in SLE-APS patients (p=0.014).

DISCUSSION

The present study describes the impact of aPL and APS in a large cohort of well-characterized lupus patients. In this cohort we found that 34.1% of the patients had positive aPL and 23.1% met the criteria for APS. Our results are slightly above the frequency of the previously published series regarding the percentage of aPL positivity (range 31-47%) and at the upper limit of the proportion of APS (range 9-23%) as shown in **Supplementary Table 6**. (It should be noted that all of the studies were carried out prior to 2017, and that they includes a small number of patients).

Overall, we found that patients with SLE-APS were slightly older and presented more severe clinical disease, with major lupus manifestations, to include respiratory, cardiac,

renal and neuropsychiatric manifestations. Moreover, SLE-APS patients also suffered more severe (measured by Katz index) disease and also more irreversible organ damage (as indicated by the SLICC index). In line with more aggressive disease, SLE-APS patients tended to more often require high-dose corticosteroids and immunosuppressants during the disease course. As a result of more severe disease, these patients suffered a higher rate of mortality. This severe clinical profile of SLE-APS was not found in those with positive aPL serology, probably due to the fact that those with SLE-aPL presented less immunogenic antibodies, such as IgM isotypes, and also lower numbers of positive antibodies. Probably, and although this aspect has not been addressed in this study, their positive aPL profile might have been transient in nature.

In agreement with previous studies (25;26) (**Supplementary Table 6**), we found that SLE-APS patients more commonly suffered cardiac manifestations than those with either SLE-aPL or SLE. Pulmonary manifestations such as pulmonary hypertension (27) and pleuritis (28) have also been reported to be more frequent in those with positive aPL (28) or, as was true in our case series, in patients with SLE-APS (25). Regarding neuropsychiatric manifestations, our results are consistent with those published previously. We found a higher proportion of seizures, psychosis and neurological manifestations in SLE-APS patients compared to those with SLE and SLE-aPL. This supports the hypothesis that aPL plays a causal role in the neuropsychiatric manifestations observed in SLE patients, either through microvascular thrombosis or as

a direct effect of aPL antibodies on brain tissue (29). On the other hand, no clear association has been established between aPL and lupus renal nephritis (10;25;26;28). Conversely, we found a higher frequency of lupus renal manifestations in those with SLE-APS, including proteinuria over 0.5 g and urinary cell casts (data not shown). Regarding cutaneous manifestations, recent studies have reported controversial results (25;26;28). However, in line with most of the previous literature, we found that aPL-positive SLE patients develop less commonly encountered cutaneous manifestations, particularly photosensitivity. The inverse association between acute cutaneous lupus and aPL probably reflects the fact that SLE-aPL patients have a different disease phenotype, possibly influenced by a diverse genetic background that also influences positivity for certain antibodies such as anti-Ro (as suggested by the increased frequency of anti-Ro antibodies in the SLE patients in our cohort). This is in line with previous studies suggesting that antibody clustering, such as occurs with anti-Ro and anti-La or aPL, could be predictive of a clinical phenotype in SLE patients (30-32). aPL are associated with thrombosis and pregnancy morbidities, both in primary APS and the APS associated with other autoimmune diseases, including SLE (33). There are other manifestations, not included in the Sidney classification criteria (19), that have also been associated with aPL. Consistent with previous studies (25;28;30;31;34-36), we found that SLE-aPL patients had higher rates of thrombocytopenia than those with SLE. Indeed, SLE-APS patients had higher frequencies of thrombocytopenia than the

SLE-aPL and SLE groups. Moreover, we found that SLE-APS more frequently suffered haemolytic anemia and Evans syndrome, as previously suggested by other authors (25). We also found that valvular dysfunction and LSE were more frequent in SLE-APS patients. Previous studies (7;25;26) suggested that SLE-aPL have a 3-fold greater risk of heart valve disease and LSE. It has been suggested that thrombosis at the valvular surface could be a possible mechanism of heart valve disease in aPL-positive patients. Consistent with previous reports (8;25;26;28;37-39), we found that SLE-APS patients more often suffered cognitive impairment than those with SLE-aPL or SLE. Moreover, there were differences in the frequency of headaches, with higher rates in the SLE-APS group, confirming the results published by Sahin (40), suggesting that aPL play a role in the pathogenesis of headaches. aPL have also been associated with certain vascular lesions such as skin ulcers, livedo reticularis and fingertip erythema (41).

The present study is the first to address the potential relationship between aPL positivity and disease severity, according to the Katz index. We confirmed that SLE-APS patients present more severe disease than those SLE-aPL or SLE. APS has been previously linked to lupus organ damage (4;31). Moreover aPL positivity (independently of APS) increases the risk of damage in SLE patients during follow-up (5;42). Our results support the idea of aPL playing a role in disease damage. Indeed, it should be regarded as an adverse prognostic factor in SLE patients, as confirmed after multivariate adjustment.

As a consequence of more active and severe disease, SLE-APS patients required more complex treatment, including high-dose corticosteroids and immunosuppressants. As shown in **Supplementary Table 6**, very few studies have addressed this issue. Our results support those from Deak (25) et al., who found that APS patients required *iv* corticosteroids, cyclophosphamide and azathioprine more often than those with SLE. In keeping with more severe disease, requiring more intense treatments**,** SLE-APS patients showed a higher rate of all-cause mortality ($p<0.001$). Previous studies reported lower survival rates in SLE-APS patients (4;43). Interestingly, although there were no differences in deaths of vascular origin, we found that lupus disease-related mortality tended to be higher in SLE-APS patients compared to those with SLE-aPL. This is consistent with previous studies (4;44) concluding that thrombosis only partially explained the deaths of SLE-APS patients. APS itself, probably due to the increase in damage accrual leading to organ dysfunction, and due to the potential complications arising from treatment requirements, could be considered a predictor of death in SLE patients.

This study has several limitations. First, and most importantly, the present study is a cross-sectional in nature. Therefore, baseline variables were retrospectively collected several years into the disease course rather than at the onset of SLE. Disease manifestations, and the treatments required, were investigated at any time during the course of the disease. We cannot exclude random associations due to the large number

of variables analysed. However, *p* values <0.001 were considered statistically significant in order to minimize type I errors. Second, aPL and LA assays were not homogeneous, as they were performed in different laboratories. Nevertheless, Sydney classification criteria (19) were strictly followed for the classification of patients. We do not have data on the serological evolution of aPL (i.e., whether the serology remained persistently/transiently positive or became persistently negative). Nonetheless, when considering aPL positivity two determinations should have been performed at least 12 weeks apart. Third, the study includes only lupus patients attending Spanish hospitals. Nevertheless, as the vast majority of centres participating in the study were not referral centres for complex SLE patients, this makes a selection bias towards more severe patients unlikely. Finally, another limitation is the fact that all thrombotic events recorded in patients with positive serology were attributed to APS, not taking into account other aspects of their disease, atherosclerosis or the treatments used. Despite this, we believe this condition more closely reflect what occurs in daily practice, since APS classification criteria (19) do not take into account any other prothrombotic risk factors. This limitation could potentially explain why up to 38% of our patients with SLE-APS did not receive therapy with oral anticoagulants during their disease course. Nevertheless, 25% of APS-related manifestations were obstetric in nature, which are usually treated with prophylactic dosages of low molecular weight heparin and are not included as part of anticoagulant treatments.

We also believe that our study has several strengths. First of all, it is the largest cohort reported thus far that analyzes the association of aPL with SLE (**Supplementary Table 6**). The RELESSER project was designed and developed according to a rigorous protocol. Indeed, all co-investigators completed mandatory clinical training. Moreover, the large number of variables included and the use of highly standardized definitions based on the most widely used validated index to assess SLE patients make the results of our study reliable. Ours is a well-characterized cohort of Spanish SLE patients and this study constitutes a substantial contribution to the knowledge of the disease in southern Europe (13-15;18;45-48).

In conclusion, our study shows that SLE APS patients are not only at higher risk of thrombotic manifestations and pregnancy complications, but also tend to present more clinically severe lupus profiles, with major organ involvement, damage accrual and higher rates of mortality. Our study suggests that SLE-APS patients should be carefully monitored in order to properly treat their disease and prevent damage accrual.

Conflicts of interest: LRZ has been paid as a speaker for Abbvie, MSD, Lilly and Pfizer. IC has been a consultant for Kern and Actelion, and an instructor for Boehringer -Ingelheim, Novartis and Gebro. The rest of authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Mean and standard deviation values for SLICC, KATZ and SLEDAI scores in the study groups.

Table 1. Demographic data and traditional cardiovascular risk factors among the studied groups.

	SLE	SLE-APS	SLE-aPL	*p*
Female sex, n (%)	941 (91.8)	486 (88)	737 (90.3%)	0.053
Age, mean±SD (yr)	45.5 ±14.	48.6±14.4	45.1±14.2	<0.001
Disease duration, mean±SD (mo)	140.8± 104.2	157.5±110.5	135.3±92.7	<0.001
Caucasian origin, n (%)	925 (93)	501 (92.4)	752 (94.6)	0.205
Tobacco use, n (%):				
• Current	165 (17.4)	97 (18.9)	119 (16.4)	
• Former	223 (23.4)	124 (24.1)	184 (25.3)	0.774
High blood pressure, n (%)	283 (27.8)	224 (40.8)	190 (23.5)	<0.001
Dyslipidemia, n (%)	294 (29.7)	226 (42.0)	211 (26.8)	<0.001
Diabetes, n (%):	48 (4.7)	43 (7.9)	22 (2.8)	0.001

N: number; SD: standard deviation; yr: years; mo: months

Table 2. Distribution of the main clinical manifestations in the different SLE groups.

	SLE **n (%)**	**SLE-APS** **n (%)**	**SLE-aPL** **n (%)**	***p***
Constitutional symptoms	169 (16.5)	119 (21.4)	154 (18.8)	0.048
Cutaneous	760 (74.1)	378 (68.1)	591 (72.3)	0.041
Musculoskeletal	807 (78.6)	421 (75.9)	626 (76.6)	0.378
Respiratory	246 (24.0)	185 (33.3)	189 (23.1)	<0.001
Cardiac	223 (21.7)	147 (26.5)	122 (14.9)	<0.001
Renal	411 (40.1)	258 (46.5)	287 (35.1)	<0.001
Neuropsychiatric	156 (15.2)	153 (27.6)	124 (15.2)	<0.001
Ophthalmological	34 (3.8)	40 (7.2)	39 (4.8)	0.002
Hematological	802 (78.2)	444 (80)	659 (80.7)	0.393
Gastrointestinal	47 (4.6)	29 (5.2)	40 (4.9)	0.846

Table 3. Distribution of clinical manifestations related to APS, but not included in the classification criteria.

	SLE n (%)	SLE-APS n (%)	SLE-aPL n (%)	*p*
Raynaud's phenomenon	345 (34.6)	201 (37.9)	246 (30.9)	0.03
Skin ulcers	29 (2.9)	26 (4.7)	22 (2.7)	0.08
Thrombocytopenia	197 (20.1)	185 (34.7)	214 (27.3)	<0.001
Haemolytic anemia	66 (6.6)	74 (13.6)	85 (10.7)	<0.001
Evan's syndrome	28 (2.9)	44 (8.3)	34 (4.4)	<0.001
Valvular dysfunction	28 (2.8)	38 (7.3)	16 (2.1)	<0.001
Libman-Sacks endocarditis (LSE)	5 (0.5)	21 (3.9)	4 (0.5)	<0.001
Headache	51 (5.1)	53 (9.9)	39 (4.9)	0.001
Cognitive impairment	29 (2.9)	34 (6.3)	18 (2.2)	<0.001
Renal thrombotic microangiopathy	6 (0.6)	6 (1.2)	1 (0.1)	0.05

Table 4. Differences in treatments used across the study groups

	SLE **n (%)**	**SLE-APS** **n (%)**	**SLE-aPL** **n (%)**	***p***
NSAIDs	740 (78)	337 (66.1)	554 (72.1)	<0.001
Corticosteroids	858 (88.5)	483 (92.7)	680 (86.8)	0.004
• Low dose	127 (16.1)	43 (9.6)	101 (15.2)	
• High dose		143 (32.1)	191 (28.7)	0.007
Antimalarial drugs	837 (86.2)	413 (80.4)	678 (86.7)	0.003
Methotrexate	197 (20.4)	76 (14.8)	128 (16.5)	0.015
Azathioprine	323 (33.3)	197 (38.9)	263 (33.8)	0.081
Mycophenolate M.	175 (18.2)	100 (19.6)	3 (13.4)	0.005
Cyclophosphamide	213 (22.1)	142 (27.6)	167 (21.4)	0.023
Iv IG	38 (4)	40 (8.3)	42 (5.3)	0.002
Rituximab	76 (7.8)	41 (8.3)	53 (6.7)	0.35
Low-dose aspirin	191 (23.2)	276 (64.2)	413 (58.9)	<0.001
Oral anticoagulants	72 (7.6)	305 (62.1)	44 (5.5)	<0.001
Plasmapheresis	15 (1.5)	14 (2.8)	4 (0.5)	0.005
Dialysis	33(3.4)	16 (3.3)	12 (1.5)	0.047

NSAIDs: non-steroidal anti-inflammatory drugs; IvIG: intravenous immunoglobulins

Table 5. All-cause mortality and by-cause mortality distribution in the study groups.

	SLE **n (%)**	**SLE-APS** **n (%)**	**SLE-aPL** **n (%)**	***p***
Death (all cause)	24(2.5)	58 (11.4)	32 (4.2)	<0.001
Causes:				
• Infection	5 (26.3)	13 (27.7)	13 (44.8)	0.242
• Cancer	4 (22.2)	6 (13)	6 (22.2)	0.516
• Vascular	5 (29.4)	18 (38.3)	5 (20)	0.276
• SLE	6 (33.3)	19 (36.5)	3 (10.7)	0.045

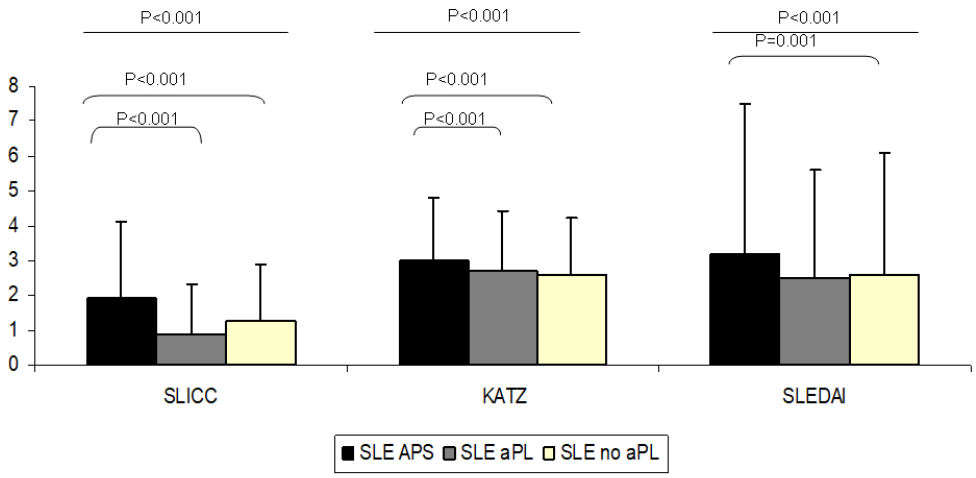

Figure 1. Mean and standard deviation values of SLICC, KATZ and SLEDAI scores in the study groups.

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Supplementary Table 1. Clinical manifestations of SLE included in the present study.

Clinical manifestation	Items included
Constitutional symptoms	Fever (according to SLEDAI), and weight loss, lymphadenopathy and splenomegaly (according to BILAG)
Cutaneous	Inflammatory skin eruption and alopecia (according to SLEDAI),
Musculoskeletal	Arthritis and myositis (according to SLEDAI)
Respiratory	Pleurisy, pulmonary haemorrhage/vasculitis, interstitial alveolitis/pneumonitis, shrinking lung syndrome (according to SLEDAI and BILAG),
Cardiac	Pericarditis, myocarditis, endocarditis, valvular dysfunction (according to SLEDAI and BILAG)
Renal	Nephritis and thrombotic mycroangiopathy
Neuropsychiatric	Psychosis, seizure disorder, organic brain syndrome, myelopathy, neuropathies, cognitive dysfunction, lupus headache (according to SLEDAI and BILAG)
Ophtalmological	Ophtalmic manifestatios (according to SLEDAI and BILAG)
Hematological	Leukopenia, lymphopenia, thrombocytopenia and hemolitic anemia (according to SLEDAI and BILAG)
Gastrointestinal	Abdominal serositis, enteropathy and lupus hepatitis (according to BILAG)

Supplementary Table 2. Distribution of the different antiphospholipid antibodies isotypes and the number of positive antibodies.

	Total **N=2398**	**SLE-APS** **n (%)**	**SLE-aPL** **n (%)**	***p***
IgM aCL	677 (28.2)	281 (51.7)	396 (49.3)	0.399
IgG aCL	833 (34.7)	379 (69.3)	454 (56.5)	<0.001
IgM aB2GPI	300 (12.5)	132 (36.3)	168 (31.2)	0.111
IgG aB2GPI	293 (12.2)	147 (40.6)	146 (27.2)	<0.001
LA	637 (26.6)	323 (68.1)	314 (48)	<0.001
Nº of antibodies • 1 • 2 • 3	 752 (31.4) 443 (18.5) 177 (7.4)	 248 (42.9) 216 (38.9) 101 (18.2)	 514 (62.9) 227 (27.8) 76 (9.3)	<0.001

SLE: systemic lupus erythematosus, APS: antiphospholipid syndrome, aPL: antiphospholipid antibodies, aCL: anticardiolipin, ab2GP I: antiß2glycoprotein I, LA: lupus anticoagulant

Supplementary Table 3. Clinical manifestations included in APS criteria.

	SLE **n (%)**	**SLE-APS** **n (%)**	***p***
Arterial thrombosis	19 (1.9)	140 (25.4)	<0.001
Venous thrombosis	47 (4.6)	250 (45.4)	<0.001
Small vessel thrombosis	20 (2)	103 (19.6)	<0.001
Fetal death	42 (4.3)	84 (16.7)	<0.001
Premature birth	17 (1.8)	33 (6.7)	<0.001
> 3 early pregnancy losses	5 (0.5)	45 (1)	<0.001

SLE: systemic lupus erythematosus, APS: antiphospholipid syndrome

Supplementary Table 4. Multivariate analysis assessing the differences in SLICC in the study groups

SLICC	Coefficient	CI 95%	P-value
SLE APS	**0.62**	**(0.46 - 0.78)**	**<0.001**
SLE aPL	-0.11	(-0.26 - 0.03)	0.114
Age	0.01	(0.00 - 0.01)	<0.001
Disease duration	0.00	(0.00 - 0.00)	<0.001
Hypertension	0.68	(0.53 - 0.83)	<0.001
Diabetes	0.95	(0.64-1.27)	<0.001
Dyslipidemia	0.36	(0.22 - 0.51)	<0.001

Supplementary Table 5. Multivariate analysis assessing the differences in mortality in the study groups

Death	OR	CI 95%	P-value
SLE APS	**2.94**	**(1.68 - 5.14)**	**<0.001**
SLE aPL	**2.32**	**(1.27 - 4.25)**	**0.006**
Age	1.03	(1.02 - 1.05)	<0.001
Disease duration	1.00	(0.99 - 1.00)	<0.001
Hypertension	1.15	(0.71 - 1.86)	0.570
Diabetes	1.47	(0.71-3.03)	0.301
Dyslipidemia	1.56	(0.99 - 2.48)	0.057
SLICC index	1.44	(1.30 - 1.61)	<0.001
KATZ index	1.28	(1.13 - 1.45)	<0.001

Supplementary Table 6. Main studies addressing the impact of aPL in patients with SLE

Author, year	Nº SLE patients	aPL subgroups	Results
Deak, 2014	224	aPL positive (total): 105 (47%) • APS: 52 (23%)	aPL positive (vs aPL negative): higher venous thromboembolism, endocarditis, haemolytic anemia and thrombocytopenia. APS (vs aPL): higher major SLE manifestations, higher total number of organ involvements. Higher frequency of myocarditis, pleuritis, nephritis, interstitial pulmonary involvement, organic brain syndrome and thrombocytopenia.
Franco, 2014	376	aPL positive: 116 (31%) APS: 35 (9%)	APS: associated with CVD, pulmonary involvement and positivity for RF. Inversely associated with alopecia.
Taraborelli, 2016	317	aPL positive (total): 117 (37%) • APS: 51 (16%)	aPL positive: increased prevalence cardiac valvular disease and APS. Reduced prevalence of acute cutaneous lupus, ENA antibodies. Positive association between triple aPL positivity and APS, and negative association with acute cutaneous lupus
Ilgen, 2017	295 150 (had aPL measurements)	aPL positive: 25 (16.7%) APS: 26 (17.3%)	SLE-APS and SLE-aPL (vs SLE): higher frequency of livedo reticularis, pleuritis, neurologic involvement, thrombocytopenia, endocarditis and cytoplasmic ANA and lower rate of malar rash and lower C4

SLE: systemic lupus erythematosus, aPL: antiphospholipid antibodies, APS: antiphospholipid syndrome, CVD: cardiovascular disease, ENA: extractable nuclear antigens, ANA: antinuclear antibodies