Do all antiphospholipid antibodies confer the same risk for major organ involvement in systemic lupus erythematosus patients?

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Abstract

Objective

We aimed to investigate the association between the different antiphospholipid antibodies (aPL) and both systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) manifestations.

Methods

Patients from the RELESSER registry, a Spanish retrospective, cross-sectional, forty-five hospital registry of adult SLE patients, were included.

Results

Out of a total of 3,658 SLE patients, 1372 were aPL positive (555 of them fulfilled criteria for APS). All aPL types showed a negative association with cutaneous SLE manifestations. Lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) were both associated with haematological, ophthalmological and neuropsychiatric manifestations. IgG isotypes were associated with a higher risk of lupus manifestations compared with IgM. We found that the risk of neuropsychiatric and ophthalmological manifestations significantly increased with a higher number of positive aPL whereas the risk of cutaneous symptoms showed a negative correlation. All types of aPL, and more strongly LA, were associated with non-criteria antiphospholipid syndrome (APS) manifestations such as thrombocytopenia and haemolytic anaemia. Moreover, LA and aCL (particularly IgG isotype) were also associated with Libman-Sacks endocarditis and cognitive impairment. This association was stronger with more than one positive aPL. All types of aPL were also associated with classic APS manifestations, although LA, IgG isotypes, and patients with more than one aPL displayed a higher risk.

Conclusion

There is a hierarchy for aPL and the risk of APS and SLE manifestations. aCL, and especially LA, confer a higher risk for major organ involvement in SLE. IgG isotypes seem to have a more important role. The load of aPL confer a higher risk for APS and certain SLE manifestations.

Key words

antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant, systemic lupus erythematosus

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Received on March 26, 2020; accepted in revised form on June 1, 2020.

Funding: this work was supported by the FIS grant PI11/02857 (Instituto Carlos III, FEDER funding). The RELESSER Registry was funded by grants from GSK, Roche, UCB, Lilly and Novartis.

Competing interests:
L. Riancho-Zarrabeitia has received travel grants/speaker honoraria from Abbvie, MSD, Novartis and Pfizer. A. Olivé-Marqués has received honoraria for consultations from GSK, Sanofi, Pfizer and Sobi. The other co-authors have declared no competing interests.

Introduction

Systemic lupus erythematosus (SLE) patients produce a wide variety of autoantibodies, some of which are simply markers of the disease or disease activity, while others, such as antiphospholipid antibodies (aPL), are definitely pathogenic (1). aPL include a heterogenous group of autoantibodies, including anticardiolipin antibodies (aCL), anti-β2-glycoprotein-I antibodies (aB2GPI) and lupus anticoagulant (LA). About 30 to 40% of SLE patients are positive for aPL(2), aCL seems to be the most frequently positive, followed by LA(3). Fewer data are available about the prevalence of aB2GPI (4).

aPL have been extensively associated with an increased risk of thrombosis and poor pregnancy outcomes in primary antiphospholipid syndrome (APS). Moreover, LA and particularly triple positivity have been associated with the highest risk for thrombosis and also for obstetric complications (5-7). However, less information addressing the association of aPL and thrombotic or obstetric manifestations in SLE is available (8, 9). Regarding SLE manifestations, aPL positivity has been related with higher damage accrual in SLE patients (10), valvular heart disease (11), pulmonary hypertension (12) or neuropsychiatric manifestations (13). However, most data rely on studies focused that do not take into account neither the influence of the different types of aPL nor their isotypes or the number of positive antibodies.

The aim of the present study was to investigate the association between the different aPL as well as their isotypes with both clinical criteria for APS and other APS-related manifestations and SLE-related clinical manifestations. Furthermore, we also attempt to elucidate the influence of the load of antibodies in the clinical profile of APS and SLE patients.

Material and methods

Patients

Patients from the Registry of SLE patients of the Spanish Society of Rheumatology (RELESSER) who met at least 4 ACR-97 SLE criteria (14) were included. The methodology used, the definitions of the disease related variables, and general characteristics of this cohort have been previously described in detail (15, 16). Briefly, RELESSER is a forty-five hospital registry, from a large representative sample of adult non-selected patients with SLE attending Spanish rheumatology services from the public national health system. It includes 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 carried a 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 centres. The Research Unit of the Spanish Society of Rheumatology (SER) managed all data and data processing. The Research Unit of the SER has given expert methodological support to recognised registries of patients with different rheumatic diseases (16-18).

Data collection

Information was collected for 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, accumulated ACR criteria (14), Sydney criteria for APS (19). The main SLE-related clinical manifestations analysed in the present study are shown in Supplementary Table S1; 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 Sydney criteria (19). IgG and IgM aCL and aB-2GPI levels were measured by standardised ELISA. LA was determined according to the standard guidelines (20). aPL serology was considered positive when two different samples were positive, at least 12 weeks apart according to 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 popula-

tion and for the different study groups. Student's *t*-test and Krustal-Wallis were used for numerical variables and Chi-square when comparing categorical variables between groups. Finally, in order to assess association of the different aPL, their isotypes and the number of positive antibodies to clinical features an assessment calculating crude odds ratios (OR) through logistic regression was done. Statistically significance was assumed as $p<0.05$. All analyses were performed through Stata 13.1 for Windows (Copyright 1985-2013 StataCorp LP StataCorp 4905 Lakeway Drive College Station, Texas 77845 USA).

Results

Characteristics of the cohort

The study cohort included 3658 SLE patients. Among them, 2398 SLE patients had at least one aPL determination. As shown in Supplementary Table 2, the majority of patients had aCL and LA measurements, but about half of the patients were lacking aB2GP I determination (Suppl. Table S2). Among the 2398 SLE patients, 1372 (57.3%) tested positive for at least one aPL. 555 (23.1%) were diagnosed with associated APS and 817 (34.1%) had a positive aPL serology but did not meet clinical criteria for APS (19). The main demographic characteristics are summarised in Table I. Detailed information on clinical SLE manifestations, non-criteria APS manifestations and classic APS manifestations are included in Supplementary Tables S3-5. The frequencies of the different aPL are shown in Table II. Regarding the number of positive antibodies, 752 (31.4% of the cohort) patients had one positive aPL, 443 (18.5%) patients had two positive antibodies and 177 (7.4%) were triple positive.

Table I. Demographic data and traditional cardiovascular risk factors distribution in the study cohort.

	Patients with aPL determination (n=2398)	Whole study cohort (n=3658)
Female sex	2164 (90.4)	3298 (90.3)
Caucasic origin	2178 (93.4)	3309 (93.2)
Age, mean±SD (yr)	46.1 ± 14.2	46.8 ± 14.8
Age at SLE diagnosis, mean ± SD (yr)	34.3 ± 14.2	35.2 ± 14.7
Disease duration, mean ± SD (mo)	142.8 ± 102.3	142.6 ± 100.7
Tobacco use (n/%):		
Current	381 (17.4)	551 (16.7)
Former	531 (24.2)	802 (24.4)
High blood pressure (n/%)	697 (29.3)	1061 (29.3)
Dyslipidaemia (n/%):	731 (31.6)	1101 (31.3)
Diabetes (n/%):		
Without organ damage	95 (4)	151 (42)
With organ damage	18 (0.8)	28 (0.8)
Alcohol consumption (n/%):		
Current	18 (0.8)	25 (0.7)
Former	74 (3.3)	119 (3.6)

SLE: systemic lupus erythematosus; n: number; SD: standard deviation; yr: years; mo: months.

Table II. Distribution of the different antiphospholipid antibodies isotypes and the number of positive antibodies in the study cohort.

	Whole study cohort (n=3658)
IgM aCL (n / % of patients with this determination available / % of the whole cohort)	677 / 20.1/ 18.5
IgG aCL	833 / 24.7 / 22.8
IgM aB2GP I	300 / 13.8 / 8.2
IgG aB2GP I	293 / 13.5 / 8.0
LA	637 / 24.0/ 17.4
Number of positive aPL (n /% of patients with aPL determination / % of the whole cohort):	
1	752 / 31.4/ 20.6
2	443 / 18.5/ 12.1
3	177 / 7.4/ 4.8

aCL: anticardiolipin; aB2GPI: anti B2 glycoprotein I; LA: lupus anticoagulant.

LA and aCL are associated with an increased burden of disease in SLE patients

Both LA and aCL were associated with major SLE organ manifestations (Fig. 1A and Suppl. Table S3). LA and aCL were also associated with ophthalmological and haematological manifestations. Besides, LA was also related to renal disease (OR: 1.21 (1.01–1.44], $p=0.042$). In contrast, aB2GPI were only associated with ophthalmological and gastrointestinal manifestations (OR: 1.57 [1.02–2.41], $p=0.039$ and OR: 1.64 [1.08–2.48], $p=0.019$, respectively). As shown in Figure 1A, all three aPL were inversely associated with SLE cutaneous manifestations (OR: 0.81 [0.70–0.95], $p=0.011$ for aCL, OR: 0.78 [0.63–0.97], $p=0.027$ for aB2GPI and OR: 0.79 [0.65–0.97], $p=0.021$ for LA). LA was also inversely associated with musculoskeletal manifestations (OR: 0.72 [0.58–0.88], $p=0.001$).

As shown in Figure 1B and Supplementary Table S3, all types of aPL were associated with non-criteria haematological APS manifestations such as thrombocytopenia and haemolytic anaemia. LA and also aCL were associated with Evans syndrome. The association was stronger for LA in all cases, with an OR: 2.29 [1.88–2.79], $p<0.001$ for thrombocytopenia, OR: 2.08 [1.58–2.74], $p<0.001$ for haemolytic anaemia and OR: 2.65 [1.80–3.88], $p<0.001$ for Evans syndrome. Moreover, aCL and LA were also associated with Libman-Sacks endocarditis and cognitive impairment, and, whereas LA showed also an association with valvular dysfunction, aCL correlated with headache. aB2GPI only showed an association with cognitive impairment (OR: 1.67 [1.01–2.78], $p=0.047$).

As expected, all types of aPL were associated with classic APS manifestations (Fig. 1C and Suppl. Table S3).

A

	ACL	AB2GPI	LA
Constitutional			
Cutaneous			
Musculoskeletal			
Respiratory			
Cardiac			
Renal			
Neuropsychiatric			
Opthalmological			
Hematological			
Gastrointestinal			

B

	ACL	AB2GPI	LA
Thrombocytopenia			
Hemolytic anemia			
Evans syndrome			
Raynaud phenomenom			
Skin ulcers			
LS endocarditis			
Valvular dysfunction			
Headache			
Cognitive impairment			
Thrombotic microangyopathy			

C

	ACL	AB2GPI	LA
Arterial thrombosis			
Venous thrombosis			
Small vessel thrombosis			
Fetal death			
Preterm birth			
≥ 3 early pregnancy losses			

OR <1 OR >1 y <2 OR ≥2 y <3 OR ≥3

Fig. 1. Antiphospholipid antibody type and their association with clinical manifestations in SLE patients.
A: includes SLE organ manifestations.
B: includes non criteria APS manifestations.
C: includes classic APS manifestations.
All the associations represented in the figure were statistically significant (p<0.05).

The association was stronger with thrombotic events and recurrent pregnancy losses with more than a threefold increased risk for the three aPL. aCL showed the highest risk for arterial thrombosis (OR: 5.74 [4.13–7.97], p<0.001) whereas LA showed the highest risk for venous thrombosis (OR: 4.86 [3.77–6.26], p<0.001). Both aCL and aB2GPI confer analogous risk for recurrent pregnancy losses (OR: 4.47 [2.58–7.74] and OR: 4.48 [2.59–7.75], p<0.001, respectively)

IgG isotypes increase the risk for major SLE manifestations and clinical APS

When evaluating the influence of aPL isotypes, we found that particularly IgG aCL were associated with respiratory, cardiac, neuropsychiatric, ophthalmological and gastrointestinal manifestations (Fig. 2A and Suppl. Table S4). Conversely, IgM aCL were only associated with neuropsychiatric manifestations. In line, IgG aB2GPI antibodies showed a positive association with cardiac, ophthalmological and gastrointestinal manifestations, whereas IgM aB2GPI were only associated with gastrointestinal manifestations. Interestingly, both IgG aCL, IgM aCL and IgM aB2GPI were inversely associated with SLE cutaneous manifestations (OR: 0.80 [0.68–0.96], p=0.013, OR: 0.68 [0.57–0.82], p<0.001 and OR: 0.74 [0.–0.96], p=0.022, respectively).

Regarding non-criteria APS manifestations, both IgG and IgM isotypes were similarly associated with thrombocytopenia and haemolytic anaemia (Fig. 2B and Suppl. Table S4). However, IgG isotypes were more strongly associated with other non-criteria manifestations such as Libman Sacks endocarditis (OR: 3.94 [1.99–7.79], p<0.001 for IgG aCL and OR: 3.56 [1.31–9.71], p=0.013 for IgG aB2GPI) and cognitive impairment (OR: 1.81 [1.19–2.74], p=0.005 for IgG aCL and OR: 1.90 [1.05–3.42], p=0.033 for IgG aB2GPI).

When analysing the IgG and IgM isotypes of aCL and aB2 GPI antibodies, we found that all of them were associated with thrombotic manifestations, fetal death and recurrent pregnancy losses. However, as showed in Figure 2C and Supplementary Table S4, the association was again stronger for IgG isotypes. Moreover, only IgG aCL was significantly related with preterm birth, OR: 1.7 [1.03–2.82], p=0.038.

The load of aPL antibodies is associated with the risk for certain clinical SLE manifestations and APS clinical features

We found that the number of positive aPL antibodies influences the presence of certain SLE manifestations (Fig. 3A and Suppl. Table S5). The inverse association between aPL and cutaneous manifestations was stronger with double and triple positivity (OR: 0.90 [0.75–1.09], p=0.273 for single positivity, OR 0.77 [0.62–0.96], p=0.021 for double positivity and OR: 0.71 [0.51–0.98], p=0.038 for triple positivity). Indeed,

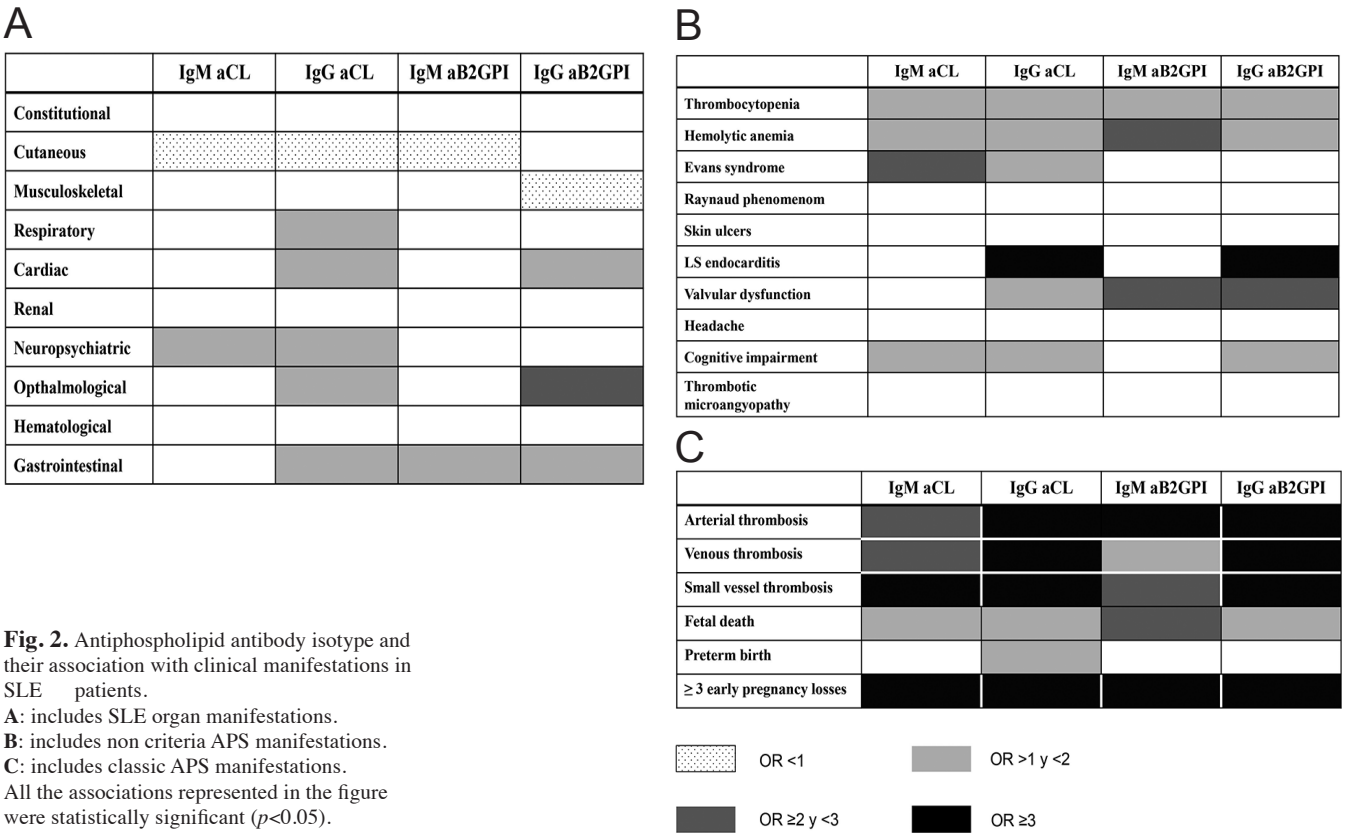

Fig. 2. Antiphospholipid antibody isotype and their association with clinical manifestations in SLE patients.
A: includes SLE organ manifestations.
B: includes non criteria APS manifestations.
C: includes classic APS manifestations.
All the associations represented in the figure were statistically significant ($p<0.05$).

particularly the higher load of positive antibodies, the less likely to suffer photosensitivity (Fig. 3A). Moreover, the association between aPL and neuropsychiatric manifestations was more consistent with more than one positive aPL (OR: 1.19 [0.95–1.48], $p=0.129$ for single positivity, OR: 1.71 [1.33–2.19], $p<0.001$ for double positivity and OR: 1.68 [1.16–2.42], $p=0.006$ for triple positivity). This was particularly true for psychosis, where positivity for one, two and three antibodies conferred an OR: 1.67 [0.96–2.81] $p=0.071$, OR: 2.17 [1.20–3.91] $p=0.010$ and OR: 2.36 [1.04–5.35] $p=0.040$, respectively. The risk for ophthalmological manifestations also increased with the higher number of positive aPL (OR:1.44 [0.96–2.16], $p=0.076$ for single positivity, OR: 1.79 [1.13–2.82], $p=0.013$ for double positivity and OR: 3.05 [1.76–5.28], $p<0.001$) for triple positivity).
There was a linear association between the number of positive antibodies and the risk of thrombocytopenia, haemolytic anaemia, Libman Sacks endocarditis and cognitive impairment (Fig. 3B and Suppl. Table S5). The risk was particularly high for Libman Sacks endocarditis where positivity for three antibodies conferred more than a six-fold increased risk, OR: 6.66 [2.25–19.71], $p=0.001$.
We also found a direct association between the number of positive antibodies and APS thrombotic manifestations and recurrent pregnancy losses. The higher the number of positive antibodies, the higher the risk for developing thrombotic manifestations and recurrent pregnancy losses. Regarding fetal death, double and triple positivity increased the risk for fetal death comparing with single positivity, but no differences were found between positivity for two or three antibodies. This association was not found for preterm birth (Fig. 3C and Suppl. Table S5).

Discussion

The present study describes a large multicentric cohort of well characterised SLE patients and the impact of aPL in the disease phenotype, not only in APS manifestations, but also in non-criteria APS and SLE-specific clinical features. aCL was the most common antibody, and the majority of patients carried only one positive aPL. When evaluating the influence of each type of antibody, we found that LA and aCL were associated with SLE major manifestations and also with certain non-criteria APS manifestations. Regarding the relevance of the aPL isotypes, IgG isotypes were responsible for most of the SLE related manifestations, and they were also responsible for the highest risk of classic APS manifestations. We also found that the higher the number of positive aPL the higher the risk for neuropsychiatric and ophthalmological SLE manifestations and the lower the risk for cutaneous manifestations. Moreover, we found that the higher load of antibodies also increased the risk for non-criteria and classic APS manifestations.
aPL have been associated with certain SLE manifestations such as valvular heart disease(11) or neuropsychiatric manifestations (13,21), and also with organ damage (10, 22) and hypocomplementaemia (23-25). We found that LA, IgM aB2GPI and both IgG and IgM aCL were inversely associated with SLE cutaneous manifestations. The strength of this association was reinforced by the negative linear effect of the autoantibody burden on cutane-

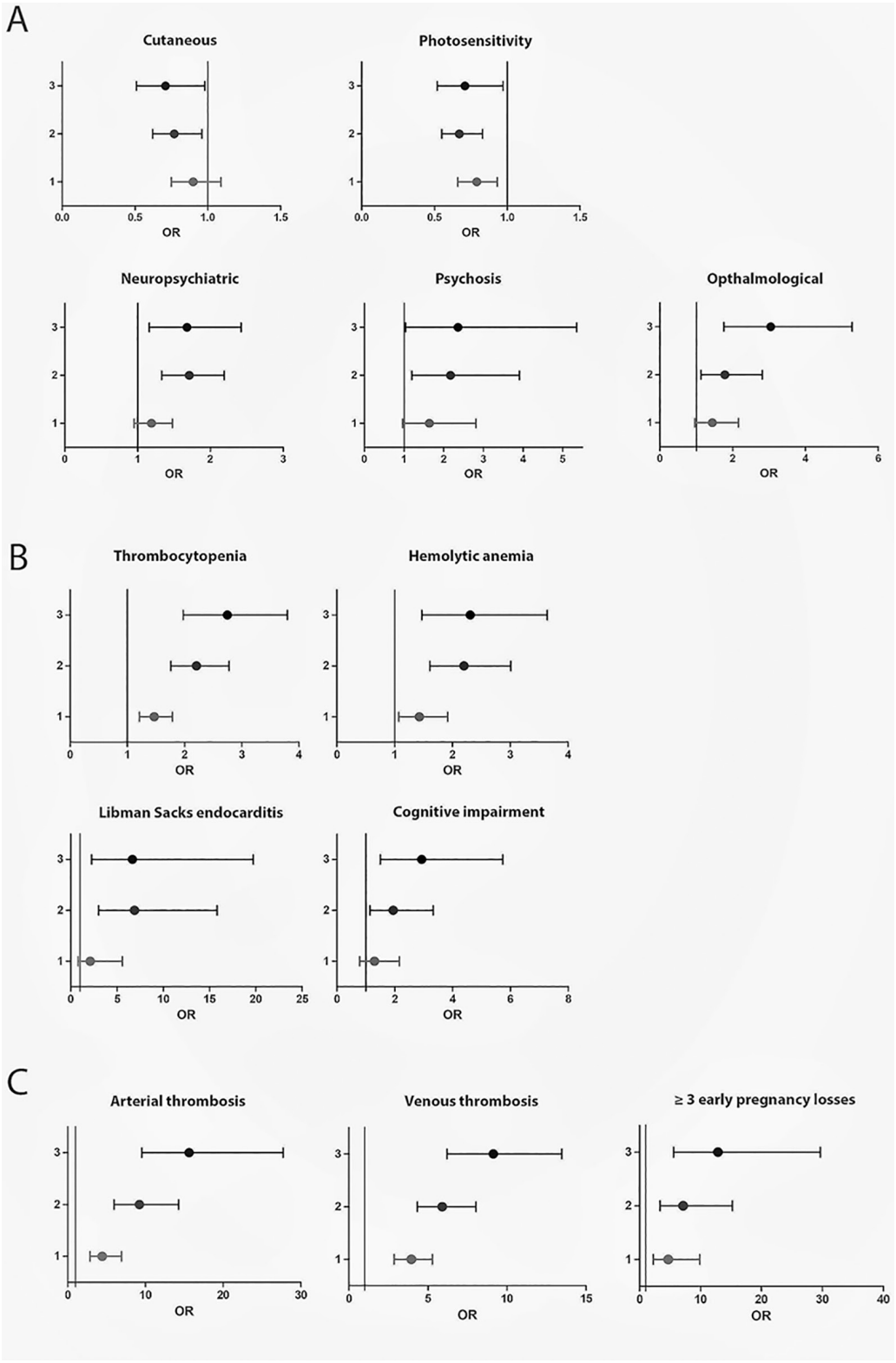

Fig. 3. Number of antiphospholipid antibodies and their association with clinical manifestations in SLE patients.
A: includes SLE organ manifestations.
B: includes non criteria APS manifestations.
C: includes classic APS manifestations.
The number of positive antibodies is represented in the Y-axis.

ous manifestations, especially in photosensitivity. In keeping with our results, Taraborelli *et al*. (26) and Ilgen *et al*. (23) found an inverse association between aPL positivity and acute cutaneous lupus. It probably reflects that SLE aPL positive patients have a different disease phenotype possible influenced by a certain genetic background or different molecular signatures (26). It is also possible, that certain clusters based on the autoantibody profile might also identify subgroups of patients with a different clinical phenotype (27).

A striking finding of this work was the association of major SLE manifestations with aCL and especially with LA. However, aB2GPI was only associated with less frequent SLE manifestations such as gastrointestinal and ophthalmologic ones. LA and aCL (both IgG and

IgM) were also associated with neuropsychiatric lupus in our cohort. Some studies have linked aPL with cognitive impairment in SLE patients (13, 28, 29) but did not analyse the influence of the different antibodies. Other studies found no associations (30, 31) except for a link between LA and thrombosis (21). Some reasons explaining the frequency of nervous system affection in APS, included the fact that the endothelial surface and anti-clotting biology of cerebral blood vessels differ from vessels elsewhere. Moreover, some experts (32) have suggested that some aPL have direct anti-neuronal specificity. Indeed, brain-blood 'sludging' can explain why anticoagulation improves mini-strokes, seizures and memory loss (32). We also found that SLE renal manifestations were associated with LA. Some authors (23, 26, 33) reported no association either between aPL positivity or with the levels of antibodies and SLE nephritis.

The aPL isotype and titre are also important for severity assessment in SLE patients (35). The results of our study suggest that the IgG isotype is associated, more frequently than IgM, to the development not only of characteristic manifestations of APS, but also of specific manifestations of SLE. We found that IgG aCL were related with respiratory symptoms in SLE patients. In line with this, a previous meta-analysis (12) reported an association between LA and IgG aCL and pulmonary hypertension in SLE patients. This association was not shown for IgM aCL and aB2GPI. Regarding cardiac manifestations, we found that IgG aCL and IgG aB2GPI were both associated with SLE cardiac affection. This keeps in line with a meta-analysis by Zuily *et al*. (11) who found that SLE patients with LA or IgG aCL had six times higher risk of valve disease that those without aPL (the studies included in the meta-analysis did not have data on aB2GPI). The prevailing theory behind SLE-related valvular disease is that aPL contribute to damage via inflammatory and thrombotic mediated pathways (36).

Previous studies have suggested that certain aPL types might be related with non-criteria APS manifestations (37). Libman Sacks endocarditis can be found in 10% of patients with SLE, and is associated with disease duration, disease activity, presence of aPL and clinical APS (38). In the present study, LA conferred a seven-fold increased risk of Libman Sacks endocarditis, whereas aCL conferred a two-fold increased risk. When analysing the isotypes, IgG aCL and IgG aB2GPI significantly increased the risk of this manifestation. Zuily *et al*. (11) found an OR of 3.5 for Libman Sacks endocarditis in aPL positive patients. In line with valvular dysfunction, Perez-Villa *et al*. (39) found that IgG aCL were associated with severe valvular regurgitation in SLE patients.

Thrombocytopenia has been associated with aPL positivity in several studies (23, 27, 34, 40-43). We confirmed these results as we found an association between thrombocytopenia and all three aPL, including IgG and IgM isotypes, being LA responsible for the strongest association. We found that haemolytic anemia was associated with the three types of antibodies, with the highest risk for LA and aCL, confirming previous unpublished findings by Unlu (44). Cognitive deficit has also been reported (13) to be two times more frequent in SLE patients with aPL. We found also that all aPL except aB2GPI were associated with cognitive impairment.

There are few studies addressing the global influence of aPL and classic APS manifestations in SLE patients. Wahl *et al*. back in 1997 (8) reported a higher risk for thrombotic events in lupus patients with LA than in those with aCL. We also found that all antibodies were associated with APS manifestations, with the strongest association between LA with venous thrombosis and aCL with arterial thrombosis. Previous studies suggested that aCL seemed more often associated with arterial events, and aB2GPI antibodies with venous thrombosis in APS patients (45). Moreover, we confirmed that IgG isotypes were more strongly associated with APS symptoms than IgM isotypes. IgM isotypes and their relation with thrombosis has been debated, although included in the classification criteria for APS, many authors question their single positivity as a risk factor for thrombosis (46, 47). A recent review confirmed more significant correlations with thrombotic complications for the IgG isotype than for the IgM isotype (48).

In patients with isolated APS a clear relationship has been established between the number of autoantibodies present and the development of clinical manifestations (5-7). In the present study, we found that the risk for certain SLE manifestations such as neuropsychiatric (particularly psychosis) and ophthalmological manifestations increased with a higher number of positive antibodies. Moreover, and as stated above, the aPL protective effect for cutaneous manifestations increased with more than one positive antibody. Regarding non-criteria APS manifestations, we also found that there was an increased risk for these symptoms in SLE patients with higher load of antibodies. In line with classic APS manifestations, we confirmed the data reported in primary APS, that the higher the number of positive aPL, the higher the risk for thrombotic and obstetric manifestations. Thus, our study confirms that those SLE patients with triple positivity are prone to have a more severe disease, with higher thrombotic risk and also with a higher risk for development other APS related manifestations.

This study has several limitations. First, aPL and LA assays have not been 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, however, for considering aPL positivity there should have two determinations performed at least 12 weeks apart. Furthermore, not all patients had measurements of the three aPL and data mainly on aB2GPI were missing in some of them. Although other aPL (IgA isotypes or antiphosphatidylserine/prothrombin antibodies) have been related with clinical manifestations in SLE (49), we were focused only in those aPL included in the classification criteria. Second, due to the retrospective nature of the study, not all the relevant clinical data, such as livedo reticularis, were recorded. Third, the study includes only lupus patients

attending Spanish hospitals. Nevertheless, as the vast majority of centres participating in the study were not referral units for complex SLE patients, this makes a selection bias towards more severe patients unlikely. Forth, and very important, the present study has a cross sectional design. Therefore, baseline variables were retrospectively collected several years into the disease course rather than at the beginning of SLE. Finally, another limitation is the fact that all thrombotic events when in patients with positive serology were attributed to APS, not taking into account other aspects of their disease or treatments used. However, we think that this situation reflects what happens in daily practice as APS classification criteria do not take into account any other prothrombotic risk factors.

We also consider that our study has several strengths. First of all, it is the widest cohort reported so far that analysed the influence of aPL in SLE. In fact, the analysis not only included the type of aPL, but also the influence of the isotype and the number of autoantibodies in the disease phenotype. Furthermore, the influence of aPL were not only analysed in APS manifestations, but also in non-criteria APS manifestations and classic SLE clinical features. Thus, the present study provides a global approach to the role of aPL in SLE patients. The RELESSER project has been design and developed according to a rigorous protocol. Indeed, all coinvestigators who included patients in the cohort performed mandatory clinical trainings. This cohort is a well characterised cohort of Spanish SLE patients with a substantial contribution to the knowledge of the disease in southern Europe.

In conclusion, the present study in a large SLE cohort confirms than there is a hierarchy for aPL and their association with SLE and APS manifestations. Although all types of antibodies confer risk for APS classic manifestations and other manifestations such as thrombocytopenia and haemolytic anaemia, only aCL, and especially LA, confer a higher risk for major organ involvement in SLE patients and non-criteria APS manifestations such as Libman Sacks endocarditis or cognitive impairment. IgG isotypes are mostly responsible for these associations. The load of aPL antibodies significantly increases the risk for clinical and non-criteria APS and also for certain neuropsychiatric and ophthalmological lupus manifestations whereas it decreases the risk for cutaneous lupus manifestations.

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