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The Impact of Systemic Lupus Erythematosus on the Clinical Phenotype of Antiphospholipid Antibody–Positive Patients: Results From the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Clinical Database and Repository

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Objective. Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with antiphospholipid antibodies (aPL), limited data exist regarding the impact of SLE on the clinical phenotype of aPL-positive patients. The primary objective of this study was to compare the clinical, laboratory, and treatment characteristics of aPL-positive patients with SLE with those of aPL-positive patients without SLE.

Methods. A secure web-based data capture system was used to store patient demographic characteristics and aPL-related clinical and laboratory characteristics. Inclusion criteria included positive aPL according to the updated Sapporo classification criteria. Antiphospholipid antibody–positive patients fulfilling the American College of Rheumatology criteria for the classification of SLE ("aPL with SLE") and those with no other autoimmune diseases ("aPL only") were included in the analysis.

Results. Six hundred seventy-two aPL-positive patients were recruited from 24 international centers; 426 of these patients did not have other autoimmune disease, and 197 had SLE. The frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti–β_2-glycoprotein I (anti-β_2GPI) antibodies was higher in the aPL-positive patients with SLE, whereas the frequency of cognitive dysfunction and IgG anti-β_2GPI antibodies was higher in the aPL-only group. The frequency of arterial and venous thromboses (including recurrent) as well as pregnancy morbidity was similar in the 2 groups. The prevalence of cardiovascular disease risk factors at the time of entry into the registry entry did not differ between the 2 groups, with the exception of current smoking, which was more frequent in aPL-positive patients with SLE.

Conclusion. Although the frequencies of thrombosis and pregnancy morbidity are similar in aPL-positive patients with and those without SLE, the diagnosis of SLE in patients with persistently positive aPL is associated with an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and positive IgA anti-β_2GPI antibodies.

INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by thromboses and/or pregnancy morbidity associated with persistently positive antiphospholipid antibodies (aPL), lupus anticoagulant (LAC), anticardiolipin antibodies (aCL), and/or anti–β_2-glycoprotein I (anti-β_2GPI) antibodies (1). Thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis/racemosa, aPL-associated nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers can also occur in aPL-positive patients (1,2), characterized as "non-criteria" APS manifestations.

APS can occur in individuals without an underlying systemic autoimmune disease (primary APS) or in the context of other systemic autoimmune diseases, with systemic lupus erythe-

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SIGNIFICANCE & INNOVATIONS

- Although systemic lupus erythematosus (SLE) is the most common autoimmune disease associated with antiphospholipid antibodies (aPL), limited data exist regarding the impact of SLE on the clinical phenotype of aPL-positive patients.
- Based on the analysis of a large-scale international registry, our study demonstrates that a concomitant SLE diagnosis in patients with persistently positive aPL does not increase the frequency of thrombosis (including recurrent) and pregnancy morbidity. However, aPL-positive patients with SLE have an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti–β_2-glycoprotein I antibody positivity compared with aPL-positive patients without other autoimmune diseases.
- Additionally, aPL-positive patients with SLE had a significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune diseases had an increased frequency of cognitive dysfunction.
- Although hydroxychloroquine (HCQ) use was more common in aPL-positive patients with SLE, 40% of aPL-positive patients with no other autoimmune diseases, especially those with lupus-related clinical and serologic manifestations, also received HCQ.

matosus (SLE) being the most common (30–50%) (3). Variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, and/or central nervous system manifestations can occur in patients with SLE. (4). Thirty percent to forty percent of SLE patients are positive for aPL (5); the prevalence of a "clinically significant" aPL profile (positive LAC test result based on the International Society of Thrombosis and Hemostasis [ISTH] guidelines [6]), IgG/IgM aCL levels ≥40 IgG phospholipid (GPL)/IgM phospholipid (MPL) units and/or IgG/IgM anti-β_2GPI levels ≥40 GPL/MPL units, tested twice at least 12 weeks apart is ~30% (7). Although persistently positive aPL has an impact on the clinical presentation and prognosis of patients with SLE (5), a limited number of studies have analyzed the impact of SLE on the clinical phenotype and prognosis of aPL-positive patients (8).

The AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) is an international network created to design and conduct large-scale, multicenter studies and clinical trials in patients with persistent aPL positivity (9). The APS ACTION clinical database and repository ("registry") was created to study the natural disease course in patients with persistently positive aPL with or without autoimmune disorders over at least 10 years; the registry allows us to perform cross-sectional and prospective analyses.

In this international multicenter study, our primary objective was to compare the clinical, laboratory, and treatment characteristics of aPL-positive patients with SLE and those without SLE. Second, we analyzed the frequencies of traditional cardiovascular disease (CVD) risk factors in aPL-positive patients with and those without SLE, and the pattern of use of hydroxychloroquine (HCQ), an immunoregulatory agent with antithrombotic effects, among aPL-positive patients with no other autoimmune diseases. We hypothesized that aPL-positive patients with SLE have increased rates of aPL-related clinical manifestations, traditional CVD risk factors, lupus-related antibodies, and immunosuppressive use (including HCQ), compared with those without SLE.

PATIENTS AND METHODS

APS ACTION registry and data collection. An international web-based application, Research electronic data capture (REDCap) (10), captures data on patient demographics, aPL-related clinical and laboratory characteristics, and medications. Data are collected once each year and at the time of a new aPL-related thrombosis or pregnancy morbidity. The inclusion criteria are age 18–60 years and persistent (at least 12 weeks apart) aPL positivity within 12 months prior to screening. Positivity is defined as the presence of IgG/IgM/IgA aCL at medium-to-high levels (≥40 GPL/MPL/IgG antiphospholipid [APL] units and/or greater than the 99th percentile) and/or the presence of IgG/IgM/IgA anti-β_2GPI antibodies at medium-to-high levels (≥40 GPL/MPL/APL units and/or greater than the 99th percentile), and/or positive LAC tests based on the ISTH guidelines (6). Patients are followed up every 12 ± 3 (mean ± SD) months with clinical data and blood collection; they also receive advice on CVD and thrombosis prevention at each visit.

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Table 1. Clinical and laboratory characteristics (historic and/or at registry entry) of patients with persistent aPL positivity, overall and stratified by SLE*

Variables	All aPL-positive patients (n = 623)	aPL-positive patients without SLE (n = 426)	aPL-positive patients with SLE (n = 197)	*P*
Demographics				
Age at entry into registry, mean ± SD years	44.2 ± 12.8	44.58 ± 12.9	43.24 ± 12.5	0.22
Female sex	459 (74)	307 (72)	152 (77)	0.18
Race†				
White	397 (71)	274 (71)	123 (71)	
Latin American Mestizos	81 (15)	66 (17)	15 (9)	
Asian	48 (9)	28 (7)	20 (12)	
Black	21(4)	10 (3)	11 (6)	
American Indian or Alaskan Native	1 (0.2)	0	1 (0.6)	
Reported as "other"	12 (2)	9 (2)	3 (2)	
Ethnicity‡				
US, Canada, Europe	261 (51)	183 (50)	78 (55)	
Non–Latin American	242 (48)	168 (46)	74 (48)	
Latin American	19 (4)	15 (4)	4 (3)	
South America	124 (24)	96 (26)	28 (20)	
Afro-descendant	16 (3)	8 (2)	8 (6)	
Mestizo	67 (13)	54 (15)	13 (9)	
Caucasian	41 (8)	34 (9)	7 (5)	
Australia	3 (0.6)	2 (0.5)	1 (0.7)	
Aboriginal	0	0	0	
Not Aboriginal	3 (0.6)	2 (0.5)	1 (0.7)	
Other	121 (24)	85 (23)	36 (24)	
Clinical manifestations				
Arterial thrombosis (AT)	193 (31)	139 (33)	54 (27)	0.26
Venous thrombosis (VT)	272 (44)	185 (43)	87 (44)	0.13
Microthrombosis (MT)	37 (6)	27 (6)	10 (5)	0.23
Any vascular event (AT/VT/MT)	422 (68)	297 (70)	125 (64)	0.12
Recurrent vascular event	198/422 (47)	163/297 (55)	61/125 (49)	0.25
Pregnancy (ever)	318 (51)	221(52)	97 (49)	0.06
Pregnancy morbidity	210 (34)	154 (36)	56 (28)	0.1
≥1 fetal death after 10th week of gestation	110 (18)	76 (18)	34 (17)	0.15
≥1 premature birth before 34th week of gestation	54 (9)	43 (10)	11 (6)	0.09
≥3 consecutive unexplained spontaneous abortions before 10th week of gestation	23 (4)	19 (5)	4 (2)	0.1
Catastrophic APS	6 (1)	4 (1)	2 (1)	0.24
Livedo reticularis/racemosa	80 (13)	52 (12)	28 (14)	0.48
Persistent thrombocytopenia	124 (20)	69 (16)	55 (28)	0.001
Autoimmune hemolytic anemia	32 (5)	9 (2)	23 (12)	<0.001
ECG-proven cardiac valve disease	50/518 (10)	30/349 (9)	20/169 (12)	0.31
Biopsy-proven aPL-associated nephropathy	19/577 (3)	11/397 (3)	8/180 (4)	0.30
Skin ulcers	32 (5)	21 (5)	11 (6)	0.12
Cognitive dysfunction	19/148 (13)	14/90 (16)	5/58 (9)	<0.001

(continued)

Table 1. (*Cont'd*)

Variables	All aPL-positive patients (n = 623)	aPL-positive patients without SLE (n = 426)	aPL-positive patients with SLE (n = 197)	*P*
Complement level				
Low complement 3 (C3) level	93/240 (39)	29/126 (23)	64/114 (56)	<0.001
Low complement 4 (C4) level	92/240 (38)	30/126 (24)	62/114 (54)	<0.001
Antiphospholipid antibodies				
Lupus anticoagulant (LAC)	417 (67)	288 (68)	129 (66)	0.6
Anticardiolipin antibody (aCL)				
IgG (positive defined as ≥20 GPL)	357 (57)	245 (58)	15/89 (17)	0.87
IgG (positive defined as ≥40 GPL)	280 (45)	202 (47)	112 (57)	0.07
IgM (positive defined as ≥20 MPL)	223 (36)	154 (36)	78 (40)	0.79
IgM (positive defined as ≥40 MPL)	139 (22)	96 (23)	43 (22)	0.84
IgA (positive defined as ≥20 APL)	41/149 (28)	24/89 (27)	17/60 (28)	0.85
IgA (positive defined as ≥40 APL)	26/149 (17)	15/89 (17)	11/60 (18)	0.81
Anti-β_2GPI§				
IgG (positive defined as ≥20 GPL)	265 (43)	194 (46)	71 (36)	0.03
IgG (positive defined as ≥40 GPL)	208 (33)	157 (37)	51 (26)	0.01
IgM (positive defined as ≥20 MPL)	173 (28)	124 (29)	49 (25)	0.27
IgM (positive defined as ≥40 MPL)	114 (18)	81 (19)	33 (17)	0.5
IgA (positive defined as ≥20 APL)	58/160 (36)	30/104 (29)	28/56 (50)	0.02
IgA (positive defined as ≥40 APL)	37/160 (23)	19/104 (18)	18/56 (32)	0.04
Double aPL positive (LAC + aCL, LAC + anti-β_2GPI, or aCL + anti-β_2GPI)	187 (30)	121 (28)	66 (34)	0.1
Triple aPL positive (LAC + aCL + anti-β_2GPI)	209 (34)	158 (37)	51 (26)	0.1
Medications at registry entry				
Low-dose aspirin	273 (44)	183 (43)	90 (44)	0.52
Warfarin	344 (55)	245 (58)	99 (50)	0.09
Direct oral anticoagulants	15 (2)	10 (2)	5 (3)	0.89
Glucocorticoids	111 (18)	39 (9)	72 (37)	<0.001
Hydroxychloroquine	276 (44)	133 (31)	143 (72)	<0.001
Immunosuppressive agents				
IV immunoglobulin	2 (0.3)	1 (0.2)	1 (1)	0.58
Rituximab	7 (1)	3 (1)	4 (2)	0.14
Azathioprine	46 (7)	11 (3)	35 (18)	<0.001
Cyclophosphamide	8 (1)	2 (1)	6 (3)	0.008
Cyclosporine	4 (1)	2 (1)	2 (1)	0.43
Methotrexate	17 (3)	4 (1)	13 (7)	<0.001
Mycophenolate mofetil	45 (7)	11 (3)	34 (17)	<0.001

* Except where indicated otherwise, values are the number (%). aPL = antiphospholipid antibody; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome; ECG = electrocardiography; GPL = IgG phospholipid; MPL = IgM phospholipid; anti-β_2GPI = anti–β_2-glycoprotein I; LAC = lupus anticoagulant; IV = intravenous.
† Information was collected for 560 patients (387 in the aPL only group and 173 in the aPL with SLE group).
‡ Information was collected for 509 patients (366 in aPL only group and 143 in the aPL with SLE group).

Study cohort. Although the APS ACTION registry captures data for patients with a variety of autoimmune diseases, for the purpose of this analysis, patients with autoimmune diseases other than SLE were excluded. Thus, 2 mutually exclusive groups were included: aPL-positive patients with no other systemic autoimmune diseases ("aPL only") and aPL-positive patients who also met the American College of Rheumatology (ACR) SLE classification criteria ("aPL with SLE") (11).

Covariates. We evaluated demographic characteristics at the time of cohort entry, including mean age, race (white, Latin American Mestizos, Asian, black, American Indian or Alaskan, Native American, "other"), ethnicity (non–Latin American or Latin American [for US, Canada, Europe], Afro-descendent, Mestizo, or Caucasian [for South America], Aboriginal or non-Aboriginal [for Australia], or "other"). Clinical data retrieved were history of arterial and venous thrombosis, biopsy-proven microthrombosis (pulmonary, skin, kidney, and "other"), pregnancy morbidity based on the updated Sapporo classification criteria, catastrophic APS based on the preliminary classification criteria (12), livedo reticularis/racemosa, persistent thrombocytopenia (defined as a platelet count <100,000/μl [2 tests performed at least 12 weeks apart]), autoimmune hemolytic anemia, echocardiography-proven cardiac valve disease, biopsy-proven aPL nephropathy, skin ulcers, and neuropsychiatric test–proven cognitive dysfunction. Laboratory data retrieved at baseline were aPL-related (LAC, IgG/IgM/IgA aCL, and IgG/IgM/IgA anti-β_2GPI antibodies) and lupus-related antibodies (antinuclear antibody, anti–double-stranded DNA antibodies), anti-Sm, and complement components C3 and C4). Cardiovascular risk factors assessed at the time of entry into the registry were hypertension, diabetes mellitus, and hyperlipidemia requiring treatment; current and past smoking; estrogen use; obesity; family history of CVD; and sedentary lifestyle. Medications (low-dose aspirin, warfarin, direct oral anticoagulants, glucocorticoids, HCQ, intravenous immunoglobulin, rituximab, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil) were included in the analysis as "ever used" or "never used."

Statistical analysis. Data from the APS ACTION registry were locked in on February 2017. We compared the prevalence of covariates (historical or baseline) in the aPL only and aPL with SLE groups using the chi-square test for categorical variables. One-way analysis of variance was used to test the differences in means between multiple independent groups, and Student's *t*-test was used for 2-group comparisons. We calculated 2-sided *P* values to determine the significance of all findings, with the significance level set at $P < 0.05$. Analyses were conducted using SPSS version 24.0.

RESULTS

As of February 2017, 672 aPL-positive patients were recruited from 24 centers; 43 patients (6%) were excluded due to underlying autoimmune diseases other than SLE, and 6 (1%) were excluded due to missing data. Of the remaining 623 patients, 426 did not have other autoimmune diseases (aPL only) and 197 had SLE (aPL with SLE). Fifty-nine patients in the aPL only group had SLE-like diseases (3 of 11 ACR SLE classification criteria were met) (11).

Table 1 shows the clinical, laboratory, and treatment characteristics collected at the time of entry into the registry. The mean ± SD age of the participants was 44.2 ± 12.8 years, and the majority of patients (74%) were categorized as white. Three hundred thirty-eight (79%) of 426 patients in the aPL only group and 137 (70%) of 426 patients in the aPL with SLE group were classified as having APS according to the updated Sapporo classification criteria (1). Overall, 422 (68%) of 623 patients had a history of thrombotic APS, and 57 (9%) had obstetric APS only. The mean ± SD disease duration (time from the first available positive aPL test result to the enrollment date) was similar in the 2 groups (5.6 ± 4.9 years in the aPL only group and 6.3 ± 5.1 years in the aPL with SLE group ($P = 0.1$).

Antiphospholipid antibody–positive patients with SLE had higher rates of persistent thrombocytopenia, autoimmune hemolytic anemia, low C3 and C4 levels, and IgA anti-β_2GPI antibody positivity, whereas the aPL only group had significantly higher rates of cognitive dysfunction and IgG anti-β_2GPI antibody positivity. Glucocorticoids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil were more frequently used in the aPL with SLE group.

The prevalence of traditional CVD risk factors at the time of entry into the registry did not differ between the 2 groups, with the exception of current smoking, which was more frequent in aPL-positive SLE patients (15% versus 9% in the aPL only group; $P = 0.03$) (Table 2). In the aPL only group, 262 patients (62%) were never treated with HCQ, 133 (31%) were current users (200–400 mg daily), and 31 (7%) were past users; 99 (74%) of the 133 current users and 26 (84%) of the 31 past users were classified as having APS. Patients with lupus-related clinical manifestations, low C4 levels, and lupus-related autoantibodies were more likely to be treated with HCQ (Table 3). After patients with SLE-like diseases (i.e., 3 of 11 ACR classification criteria for SLE were met) (n = 59) were excluded, when we analyzed 367 patients in the aPL only group, we observed a higher frequency of HCQ treatment in patients with low C4 levels and lupus-related autoantibodies.

DISCUSSION

Based on the analysis of a large-scale international registry of patients with persistently positive aPL, our study demonstrated that the frequencies of thrombosis (including recurrent) and pregnancy morbidity were similar between aPL-positive patients with SLE and aPL-positive patients without SLE. However, a concomitant SLE diagnosis in patients with persistent aPL positivity was associated with an increased frequency of

Table 2. Prevalence of CVD and thrombosis risk factors at the time of registry entry among patients with persistent aPL positivity, stratified by the presence of SLE*

Variable	aPL only (n = 426)	aPL with SLE (n = 197)	*P*
Hypertension	118 (28)	66 (34)	0.14
Diabetes	22 (5)	8 (4)	0.55
Hyperlipidemia	103 (24)	36 (18)	0.1
Smoking ever	116 (27)	49 (25)	0.65
Current smoking	40 (9)	30 (15)	0.03
Estrogen use	3 (1)	3 (2)	0.54
Obesity	107 (25)	59 (30)	0.37
Family history of CVD	67 (16)	21 (11)	0.18
Sedentary lifestyle	197 (46)	94 (48)	0.73

* Values are the number (%). CVD = cardiovascular disease; aPL = antiphospholipid antibody; SLE = systemic lupus erythematosus.

thrombocytopenia, hemolytic anemia, low C3 and C4 levels, and IgA anti-β_2GPI antibody positivity compared with the frequency in aPL-positive patients without other autoimmune diseases. Additionally, aPL-positive patients with SLE had a significantly higher frequency of current smoking, while aPL-positive patients without other autoimmune diseases had an increased prevalence of cognitive dysfunction. Although HCQ use was more common in the aPL with SLE group, 40% of the aPL only group also received HCQ, especially those with lupus-related clinical and serologic manifestations.

Although the impact of aPL on SLE is well studied (5,7), limited data exist regarding the impact of SLE on the clinical phenotype of patients with persistently positive aPL. In a European multicenter cohort of 1,000 mainly Caucasian patients with APS, patients with concomitant SLE had a higher prevalence of livedo reticularis, thrombocytopenia, arthritis, and leukopenia (13). Our multiethnic study also showed an increased frequency of thrombocytopenia and autoimmune hemolytic anemia in aPL-positive patients with SLE compared with the frequency in those without SLE; however, with the exception of cognitive dysfunction, similar frequencies of the classification criteria or other non-criteria aPL manifestations, namely livedo reticularis, cardiac valve disease, and aPL-associated nephropathy, were observed in the 2 groups. Given that our SLE patients were classified based on the ACR classification criteria (11), which incorporate thrombocytopenia and autoimmune hemolytic anemia, the increased frequency of these hematologic abnormalities in aPL-positive patients with SLE was not unexpected.

Cognitive dysfunction is common in APS and SLE and is frequently associated with livedo reticularis and white matter lesions on brain magnetic resonance imaging in patients with APS. Tektonidou et al previously showed no difference in cognitive performance as assessed by a 3-hour battery of neurocognitive tests among patients with primary APS and those with SLE and APS (14). Kozora et al demonstrated that 12 (60%) of

Table 3. Analysis of 426 aPL-positive patients without other systemic autoimmune diseases, stratified by HCQ use*

Variable	HCQ use (n = 164)	No HCQ use (n = 262)	*P*
Clinical profile			
Thrombotic APS	89 (54)	148 (57)	0.65
Arterial thrombosis	52 (32)	87 (33)	0.84
Venous thrombosis	75 (46)	110 (42)	0.3
Microthrombosis	11 (7)	16 (6)	0.74
Obstetric APS	16 (10)	28 (11)	0.76
Thrombotic and obstetric APS	21 (13)	37 (14)	0.70
3 of 11 ACR SLE criteria met	42 (26)	17 (7)	<0.001
Laboratory profile			
Persistent triple aPL positive	60 (37)	98 (37)	0.87
Persistent double aPL positive	50 (30)	97 (27)	0.1
Persistent single aPL positive	102 (62)	67 (26)	0.16
ANA positive	30 (18)	86 (33)	<0.001
Anti-dsDNA positive	5 (3)	10 (4)	<0.001
Anti-Sm positive	17/66 (26)	0 (0)	0.008
Low complement 3 (C3) level	54 (33)	12/60 (20)	0.44
Low complement 4 (C4) level	20/66 (30)	10/60 (17)	0.02

* Patients were considered to be positive for antinuclear antibodies (ANAs), anti–double-stranded DNA (anti-dsDNA), or anti-Sm if they ever had a positive test result for these antibodies. A low C3 or C4 level was based on a level below normal and the most recent C3/4 tests before registry entry. Values are the number/number assessed (%). aPL = antiphospholipid antibody; HCQ = hydroxychloroquine; APS = aPL syndrome; ACR = American College of Rheumatology; SLE = systemic lupus erythematosus.

20 aPL-positive SLE patients and 8 (40%) of 20 aPL-positive patients without SLE had global cognitive impairment on a ACR-SLE cognitive impairment index, which is a validated neuropsychologic instrument; there were no group differences on the cognitive impairment index or on individual measures (15). Our study included SLE patients with persistently positive aPL and aPL-positive patients who did not meet the APS classification criteria (1) and still showed that neuropsychiatric test–proven cognitive dysfunction was more common in aPL-positive patients without SLE. These findings further support the importance of research for cognitive dysfunction and clinical assessment in aPL-positive patients without other systemic autoimmune diseases.

The updated Sapporo criteria for the classification of APS do not include IgA aCL and IgA anti-β_2GPI antibodies. Although the IgA isotype is common in black patients with SLE (16) and now is included in the revised Systemic Lupus International Collaborating Clinics criteria for the classification of SLE (17), the prevalence and clinical significance of this isotype have been controversial (18). We observed that although aPL types and isotypes as well as double or triple aPL positivity were generally comparable between the 2 groups, aPL-positive patients with SLE more frequently had IgA anti-β_2GPI antibodies, while IgG anti-β_2GPI antibodies were more frequent in those without SLE. Although it remains unknown why patients develop different isotypes of aPL, our findings support those of previous studies (19), thus demonstrating the potential diagnostic and clinical significance of the IgA isotype in lupus patients compared with those without lupus.

Traditional CVD risk factors, including diabetes mellitus and smoking, increase the risk of thrombosis in aPL-positive patients (20). SLE itself is an independent risk factor for CVD, which remains the major cause of mortality in patients with SLE (21). It is not well-studied whether CVD risk factors differ between aPL-positive patients with SLE and those without SLE; our study demonstrated that the prevalence of CVD risk factors was similar between aPL-positive patients with and those without SLE, with the exception of current smoking. In addition, although the role of smoking in the development of aPL, APS, and/or SLE is not well-established (22), smoking is associated with worse outcomes and venous thrombosis in patients with SLE as well as the development of SLE subtypes, as defined by autoantibody status (23). All of these findings support the importance of similar diligence in CVD risk assessment and management measures in both aPL-positive patients with SLE and aPL-positive patients without SLE.

In our study, use of glucocorticoids, HCQ, azathioprine, cyclophosphamide, methotrexate, and mycophenolate mofetil was more frequent in aPL-positive patients with SLE compared with aPL-positive patients without SLE at the time of entry into the cohort. Use of HCQ in patients with SLE is well-established; however, no strong clinical data exist to recommend HCQ treatment for aPL-positive patients without other systemic autoimmune diseases. Given animal and in vitro studies showing that HCQ has a potential antithrombotic role in addition to its immunoregulatory and metabolic effects (24–29), HCQ has been used in some centers to prevent thrombosis in aPL-positive patients without other systemic autoimmune diseases (30–32). An international study aimed at determining the effectiveness of HCQ for thrombosis prevention in asymptomatic aPL-positive patients was terminated early for reasons related to logistics (33). In the current study, ~40% of aPL-positive patients without other systemic autoimmune diseases reported HCQ use, and the frequency of serologic features of SLE was higher in aPL-positive patients using HCQ. Our study was not designed to determine the prophylactic role of HCQ; however, we believe that prospective follow-up of patients in our registry will provide further valuable data on outcomes in HCQ-treated aPL-positive patients.

Although our study was limited due to its retrospective, cross-sectional study design, we used a large, multicenter, international patient cohort. Our data set is enriched by inclusion of granular sociodemographic, clinical, laboratory, and medication data. However, data for CVD risk factors were collected at the time of the patient's enrollment and not at the time of the thrombotic event, which may have resulted in inaccurate CVD prevalence estimates in different groups of aPL-positive patients.

In conclusion, our analysis of a large, multicenter, international cohort of patients who are persistently aPL-positive demonstrates an increased frequency of thrombocytopenia, hemolytic anemia, low complement levels, and IgA anti-β_2GPI antibody positivity but not the risk of thrombotic, obstetric, and non-criteria APS manifestations (except cognitive dysfunction) among aPL-positive patients with a concomitant SLE diagnosis compared with those without SLE. Our exploratory study provides pilot data for future risk-stratified prospective analyses using the APS ACTION registry, which will better determine the clinical impact of SLE on the presentation of aPL-positive patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Unlu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Unlu, Erkan, Barbhaiya, Andrade, Nascimento, Rosa, Banzato, Pengo, Ugarte, Gerosa, Ji, Efthymiou, Branch, Ramires de Jesus, Tincani, Belmont, Fortin, Petri, Rodriguez, Pons-Estel, Knight, Atsumi, Willis, Zuily, Tektonidou.

Analysis and interpretation of data. Unlu, Erkan, Barbhaiya, Tektonidou.

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