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Future atherosclerotic cardiovascular disease in systemic lupus erythematosus based on CSTAR (XXVIII): the effect of different antiphospholipid antibodies isotypes

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Abstract

Background Patients with systemic lupus erythematosus (SLE) suffered from an increasing risk of cardiovascular diseases. In this multi-center prospective study, we aimed to determine the association between antiphospholipid antibodies (aPLs) and future atherosclerotic cardiovascular disease (ASCVD) in SLE.

Methods In total, 1573 SLE patients were recruited based on the Chinese SLE Treatment and Research group (CSTAR) registry. aPLs profile, including anticardiolipin antibodies (aCL) IgG/IgM, anti-β2 glycoprotein I antibodies (aβ2GPI) IgG/IgM, and lupus anticoagulant (LA), were measured in each center. Future ASCVD events were defined as new-onset myocardial infarction, stroke, artery revascularization, or cardiovascular death.

Results Among the 1573 SLE patients, 525 (33.4%) had positive aPLs. LA had the highest prevalence (324 [20.6%]), followed by aCL IgG (249 [15.8%]), aβ2GPI IgG (199 [12.7%]). 116 (7.37%) patients developed ASCVD during the mean follow-up of 4.51 ± 2.32 years and 92 patients were aPLs positive. In univariate Cox regression analysis, both aPLs (HR = 7.81, 95% CI 5.00–12.24, $p < 0.001$) and traditional risk factors of cardiovascular disease were associated with future ASCVD events. In multiple Cox regression analysis, aCL IgG (HR = 1.95, 95% CI 1.25–3.00, $p = 0.003$), aCL IgM (HR = 1.83, 95% CI 1.03–3.20, $p = 0.039$), and LA (HR = 5.13, 95% CI 3.23–8.20, $p < 0.001$) positivity remained associated with ASCVD; traditional risk factors for ASCVD, including smoking, gender, age and hypertension, also play an independent role in SLE patients. More importantly, Aspirin can reduce ASCVD risk in SLE patients with positive aPLs (HR = 0.57 95% CI, 0.25–0.93, $P = 0.026$).

Conclusions SLE patients with positive aPLs, especially positive aCL IgG/IgM and LA, warrant more care and surveillance of future ASCVD events during follow-up. Aspirin may have a protective effect on future ASCVD.

Keywords Systemic lupus erythematosus (SLE), Antiphospholipid syndrome (APS), Antiphospholipid antibodies (aPLs), Atherosclerotic cardiovascular disease (ASCVD), Aspirin

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Key messages

What is already known on this topic: The assessment of future atherosclerotic cardiovascular disease (ASCVD) risk in SLE patients, especially the impact of antiphospholipid antibodies (aPLs), remains a big challenge.

What this study adds: aCL IgG/M and LA are associated with a higher risk of ASCVD, after adjusting for traditional CVD risk factors. Furthermore, aspirin may reduce ASCVD risk in SLE patients with positive aPLs.

How this study might affect research: SLE patients with positive aCL or LA warrant more surveillance of future ASCVD events and may benefit from aspirin.

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem involvement, can compromise various organ systems, including the central nervous system, kidneys, cardiovascular system, and hematopoietic system [1]. Despite significant improvements in patient survival, the progression of irreversible organ damage contributes to morbidity [2]. Notably, despite stringent disease management, 30 to 50% of patients accrue organ damage within 5 years [3]. Atherosclerotic cardiovascular disease (ASCVD) constitutes a significant form of cardiovascular morbidity and portends a dismal prognosis [4]. Prior research has demonstrated a heightened risk of cardiovascular diseases in SLE, with an incidence rate of approximately 23.3 events per 1000 patient-years [5].

Accurate prediction of ASCVD risk in SLE patients is essential for guiding preventive strategies and early intervention. Antiphospholipid antibodies (aPLs), a serological feature of antiphospholipid syndrome (APS), are also detected in 30–40% of SLE patients [6]. aPLs is a heterogeneous group of autoantibodies comprising anticardiolipin (aCL) antibodies, anti-β2 glycoprotein I (anti-β2GPI) antibodies, and lupus anticoagulant (LA). Studies suggest that aPLs contribute to vasculopathy and thrombosis through several mechanisms in APS, such as impairing endothelial cell function and fostering coagulation [7], potentially expediting atherogenesis in SLE. In patients with SLE-APS, the incidence of asymptomatic coronary artery atherosclerosis is between 30 and 35%, and the rate of acute myocardial infarction is 3.8% [8]. The role of aspirin in the protection of thrombotic events was also explored in SLE-APS patients and asymptomatic aPLs-positive individuals. Nevertheless, data on the impact of aPLs on ASCVD risk in SLE, particularly different aPLs isotypes and their conjunction with traditional cardiovascular risk factors, remains sparse. The role of aspirin in preventing future ASCVD in aPLs-positive SLE patients also need further validation. Through this multicenter, prospective study, we aim to delineate the relationship between aPLs and the risk of future ASCVD in patients with SLE, thereby improve the clinical management of high-risk population.

Methods

Study participants, follow-up, and data collection

In this prospective cohort study, SLE patients from seven national centers through the Chinese SLE treatment and research (CSTAR) online registry [9, 10] were recruited between January 2009 and June 2022. Only centers that had completed the follow-up quality control process at the time of analysis were included, which is necessary for the integrity of our study's data. All patients fulfilled the 1997 American College of Rheumatology (ACR) criteria [11], the 2012 Systemic Lupus International Collaborating Clinics (SLICC)/ACR criteria [12], or the 2019 European League Against Rheumatism (EULAR)/ACR criteria [13]. The point of baseline was defined as the time of recruitment (the first visit to the medical center). After enrollment, all patients were followed every 3 to 6 months. Patients with only two or fewer follow-up records and patients with missing core clinical assessments or aPLs profile results were excluded.

Demographic data (gender, age, family history), past history (smoking history, diabetes mellitus, hypertension, and hyperlipidemia), body mass index (BMI), and disease duration were collected upon recruitment. The cardiovascular risk factors included smoking, diabetes, hypertension, and hyperlipidemia history were assessed following NICE guidelines as following: diabetes was defined as high fast glucose level on two occasions, hypertension was defined as high blood pressure (> 140/90 mmHg) on two occasions, and hyperlipidemia was defined as high cholesterol level. Clinical and laboratory data were collected at registration and during routine clinical assessments using electronic data-collection forms through the CSTAR registry [9, 10]. Organ or system involvement was documented at registration, including malar rash, discoid lesions, arthritis, serositis, hematological involvement, lupus nephritis, and neuropsychiatric lupus. Lupus nephritis was clinically defined as persistent proteinuria (≥ 0.5 g/24 h) or cellular casts [12], or histologically as renal biopsies aligned with lupus nephritis histopathology classes [14], while excluding renal disease attributable to non-SLE origins. Neurological involvement was identified by seizures, psychosis, mononeuritis multiplex, vasculitis myelitis, peripheral or cranial neuropathy, cerebrovascular accidents, or cognitive impairment in the absence of offending drugs or known metabolic derangements [12].

Hematologic involvement comprised hemolytic anemia with reticulocytosis, leukopenia (< 4000/mm^3 on ≥ 2 occasions), lymphopenia (< 1500/mm^3 on ≥ 2 occasions), or thrombocytopenia (< 100,000/mm^3) in the absence of culpable drugs. Laboratory parameters included routine blood tests, serum creatinine, serum albumin, complement level, autoantibodies profile, urinary sediment assessment results, and urine protein level. Autoantibodies profiles included antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), anti-Smith (anti-Sm) antibodies, anti-U1 ribonucleoprotein (anti-U1 RNP) antibodies, anti-ribosomal P (anti-RibP) antibodies, anti-nucleosome antibodies (ANuA), anti-histone antibodies (AHA), and aPLs. ANA at a titer of ≥ 1:80 on HEp-2 cells was considered as positive. Anti-dsDNA antibodies were assessed through IIF utilizing Crithidia luciliae immunofluorescence test (CLIFT) and enzyme-linked immunosorbent assay (ELISA) using ds-DNA Antibodies ELISA KT (EA 1571–9601 G, Euroimmun, Lübeck, Germany). As recommended by the manufacturer guidelines, the positive cut-off was set as ≥ 1:5 for CLIFT and ≥ 100 for ELISA. Either CLIFT or ELISA showed positive result was defined as positive anti-dsDNA antibodies. The ENA antibodies were tested with the immunoblotting assay using the EUROLINE ENA Profile 14 Ag (DL 1590-3G, Euroimmun, Lübeck, Germany) according to instructions. The central labs of each center were all assessed through the same quality control protocol. Treatment regimens, including prednisone dose (or equivalent glucocorticoids), types and dosages of immunosuppressive drugs (including cyclophosphamide, methotrexate, mycophenolate mofetil, azathioprine, tacrolimus, leflunomide, cyclosporin A, and hydroxychloroquine), cardiovascular prevention therapies (aspirin and statins), and anticoagulation therapy were also documented during visits. Disease activity based on Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) and organ damage according to the SLICC/ACR Damage Index (SDI) were obtained annually. Follow-up continued until the patient's death or their last recorded follow-up date. This study was approved by the Institute Review Board of Peking Union Medical College Hospital (Approval number, S-197) and the local Institute Review Board of each center. Written informed consents were obtained from all patients.

Antiphospholipid antibodies profile test

In our study, aPLs profile included 5 aPLs isotypes: IgG or IgM aCL antibodies, IgG or IgM anti-β2GPI antibodies, and LA. The aPLs profile was measured following the Scientific and Standardization Committee for lupus anticoagulant/aPLs of the International Society on Thrombosis and Haemostasis (ISTH) guideline [15] in each center. LA was tested using the activated partial thromboplastin time–based assay (aPTT) and the dilute Russell viper venom time (dRVVT) methods. Positivity was defined as an aPTT ratio of > 1.20 or a dRVVT ratio of > 1.20. The plasma samples were tried to be collected before anticoagulation. For patients on anticoagulation before tested, heparin neutralizer used in our test reagents was capable of quenching unfractionated heparin and low molecular-weight heparin to some level. aCL and anti-β2GPI antibodies were measured through ELISA (Euroimmun, Lübeck, Germany EA 1632–9601 G). This detection system was described in the previous study and showed good sensitivity and specificity [16]. The positivity of aCL or anti-β2GPI antibodies was defined as titers of either IgG or IgM exceeded 20 U/mL (the manufacturer's cut-off values). While the medium titers were defined as values between 40 and 79 units, and high titers were defined as values of ≥ 80 units.

According to Sydney criteria, positive aPLs were defined as positivity of at least one aPLs isotypes detected on two or more occasions at least 12 weeks apart. SLE patients who meet 2006 Sydney revised classification criteria [17] at baseline were defined as secondary APS. According to 2019 EULAR recommendations [18], high-risk aPLs profile was defined as the presence of LA, or of double (any combination of LA, aCL antibodies or anti-β2GPI antibodies) or triple (all three subtypes) aPLs positivity, or the presence of persistently high aPLs titres.

Outcome measures

The endpoint of this analysis was the occurrence of ASCVD events after SLE diagnosis. ASCVD events were defined as first myocardial infarction, first stroke, coronary or peripheral artery revascularization, or cardiovascular death, and were systematically ascertained and adjudicated as previously described [4]. Myocardial infarction was defined according to the Third Universal Definition of myocardial infarction. Arterial thrombosis was confirmed by imaging and clinical diagnosis, such as electrocardiogram, CT angiography, and coronary angiography. While the diagnosis of stroke was reviewed by a neurologist based on clinical symptoms and imaging evidence, including brain MRI/CT imaging and MR angiography. Patients were censored at the time of events, loss to follow-up, or the conclusion of the study period.

Potential confounding factors of ASCVD

When evaluating the association between aPLs and ASCVD, a total of 27 preselected clinical candidate variables were included as potential confounders based on clinical experience and current literature. Potential confounding factors included gender, age at recruitment, SLE disease duration, traditional cardiovascular disease risk

factors (hypertension, diabetes mellitus, smoking, BMI, and hyperlipidemia), clinical manifestations (malar rash, discoid lesions, arthritis, ulcerations, serositis, alopecia, nephropathy, hematological involvement, neurological involvement), autoantibody profiles (anti-dsDNA antibody, anti-Sm antibody, anti-U1 RNP antibody, anti-RibP antibody, anti-nucleosome antibody, anti-histone antibody), SLEDAI-2K at recruitment, SDI at recruitment, diagnosis of antiphospholipid syndrome at recruitment, and the adjust global APS score (aGAPSS). aGAPSS [19] was a risk prediction tool for thrombosis in SLE patients and was calculated based on LA, aCL antibodies, anti-β2GPI antibodies, hyperlipidemia, and arterial hypertension.

Statistical methods

Descriptive statistics are presented as frequency for categorical variables and mean ± standard deviations (SD) for continuous variables. To comprehensively characterize differences between patients with positive or negative aPLs profile, chi-square test and ANOVA were used. Continuous variables were compared using the *t*-test. Time-to-first-event outcomes were analyzed using Cox proportional hazards models and illustrated with Kaplan–Meier curves or cumulative incidence curve (estimated as 1- Kaplan–Meier curve). Outcomes were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were conducted using R (version 3.6.2), with two-tailed p values less than 0.05 considered statistically significant.

Results

Participants and aPLs profile

A total of 2564 consecutive patients who registered between January 2009 and June 2022 were initially considered for inclusion in the study. Of these, 432 patients with two or fewer follow-up records and 559 patients lacking essential clinical assessments or results for aPLs were excluded. Consequently, 1573 patients with SLE were included in the analysis (Fig. 1). A total of 37 patients have history of ASCVD event before SLE diagnosis. One

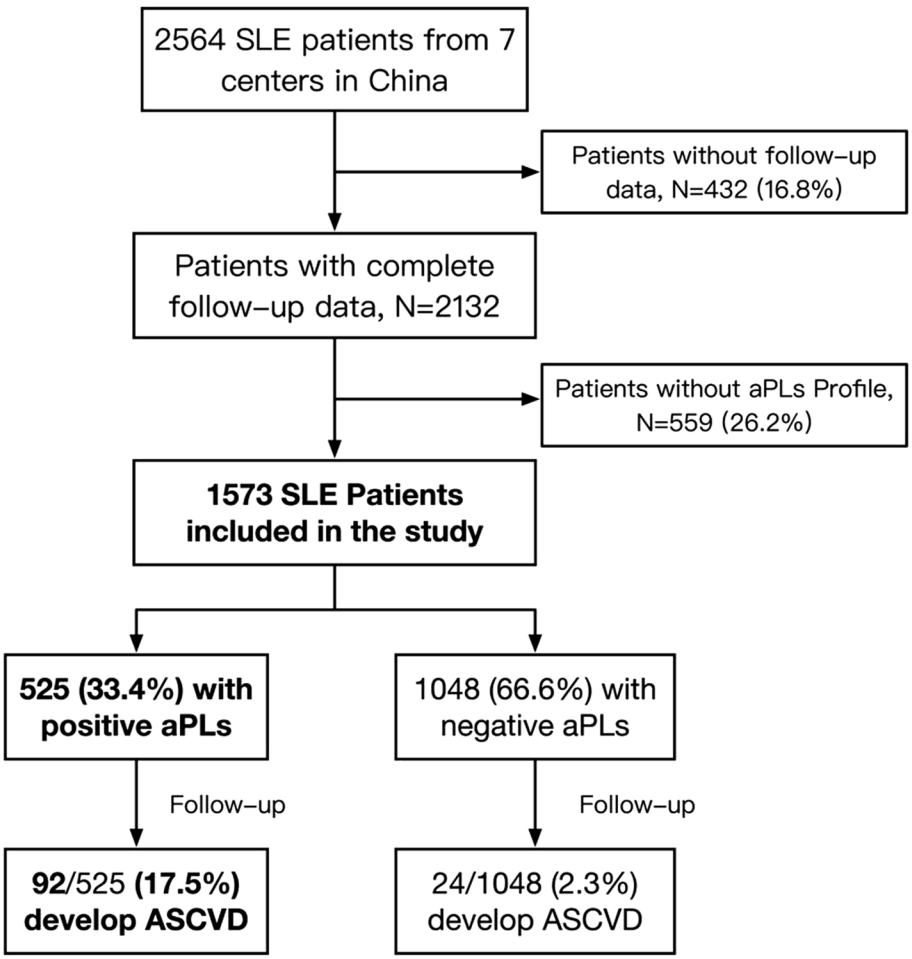


Fig. 1 Study flowchart

Table 1 The baseline characteristics, profile of autoantibodies, and profile of clinical manifestations of 1573 SLE patients, 525 patients with, and 1048 patients without positive anti-phospholipid antibodies profiles

	SLE Cohort (*n* = 1573)	aPLs (+) (*n* = 525)	aPLs (−) (*n* = 1048)	*p*
Demographic information				
Female, *n* (%)	1512(96.1)	504(96.0)	1008(96.2)	0.859
Age at recruitment (years), mean ± S.D	34.9 ± 11.0	33.5 ± 11.0	35.0 ± 11.0	0.360
Disease duration(years), median (IQR)	0.3(0.08-1.1)	0.4(0.07-1.2)	0.3(0.07-1.0)	0.550
Follow up duration (years), mean ± S.D	4.4 ± 2.7	4.3 ± 2.8	4.5 ± 2.6	0.283
Previous medical history				
Hypertension, *n* (%)	117(7.4)	44(8.4)	73(7.0)	0.313
Diabetes mellitus, *n* (%)	27(1.7)	15(2.9)	12(1.1)	**0.014**
Smoking, *n* (%)	41(2.6)	22(4.2)	19(1.8)	**0.005**
BMI, mean ± S.D	20.5 ± 12.1	20.5 ± 2.0	20.6 ± 2.4	0.089
Hyperlipidemia, *n* (%)	62 (3.9)	28(5.3)	34(3.2)	**0.045**
Clinical manifestations				
Malar rash, *n* (%)	586(37.3)	178(33.9)	408(38.9)	0.052
Discoid lesions, *n* (%)	169 (10.7)	50(9.5)	119(11.4)	0.269
Arthritis, *n* (%)	729(46.3)	245(46.7)	484(46.3)	0.856
Oral Ulcerations, *n* (%)	305(19.4)	107(20.4)	198(18.9)	0.482
Serositis, *n* (%)	207(13.2)	71(13.5)	136(13.0)	0.762
Alopecia, *n* (%)	546(34.7)	184(35.0)	362(34.7)	0.843
Nephropathy, *n* (%)	493(31.3)	206(39.2)	287(27.4)	**< 0.001**
Hematological involvement, *n* (%)	754(47.9)	273(52.0)	481(45.9)	**0.022**
Neurological involvement, *n* (%)	136(8.6)	65(12.4)	71(6.8)	**< 0.001**
SLEDAI-2K, mean ± S.D	7.98 ± 4.73	8.45 ± 4.93	7.75 ± 4.61	0.245
Baseline SDI > 0, *n* (%)	184(11.7)	80(15.2)	104(9.9)	**0.002**
Diagnosis APS, *n* (%)	131(8.3)	131(25.0)	0(0)	**< 0.001**
Arterial thrombosis	42 (2.7)	42 (8.0)	/	**/**
Venous thrombosis	56 (3.6)	56 (10.7)	/	**/**
Microvascular manifestations	25 (1.6)	25(4.8)	/	**/**
CAPS	3(0.2)	3(0.6)	/	**/**
Pregnancy morbidity	72 (4.6)	72(13.7)	/	**/**
Cardiac valve disease	2 (0.1)	2 (0.4)	/	**/**
aGAPSS, mean ± S.D	5.48 ± 3.14	9.18 ± 3.45	4.17 ± 0.67	**< 0.001**
Autoantibodies profile				
Anti-nuclear antibody (ANA), *n* (%)	1573(100)	525(100)	1048(100)	/
Anti-dsDNA antibody, *n* (%)	1050(66.8)	377(71.8)	673(64.2)	**0.003**
Anti-Sm antibody, *n* (%)	523(33.2)	154(29.3)	369(35.2)	**0.020**
Anti-U1 RNP antibody, *n* (%)	698(44.4)	198(37.7)	500(47.7)	**< 0.001**
Anti-RibP antibody, *n* (%)	389(24.7)	155(29.5)	234(22.3)	**0.002**
Anti-nucleosome antibody (ANuA), *n* (%)	406(25.8)	167(29.9)	249(23.8)	**0.009**
Anti-histone antibody (AHA), *n* (%)	309(19.7)	123(23.4)	186(17.7)	**0.007**
Anti-phospholipid (aPLs) antibodies, *n* (%)	525(33.4)	525(100.0)	0(0)	
Anticardiolipin antibodies, *n* (%)	299(19.0)	299 (56.95)	0(0)	/
IgG	249(15.8)	249 (47.4)	0(0)	/
IgM	48(3.1)	48 (9.1)	0(0)	/
Anti-β2 glycoprotein I IgG/M, *n* (%)	245(15.6)	245 (46.7)	0(0)	/
IgG	199(12.7)	199 (37.9)	0(0)	/
IgM	83(5.3)	83 (15.8)	0(0)	/
Lupus anticoagulant, *n* (%)	324(20.6)	324 (61.7)	0(0)	/

Table 1 (continued)

	SLE Cohort ($n=1573$)	aPLs (+) ($n=525$)	aPLs (−) ($n=1048$)	*p*
High risk aPLs antibodies profile, *n* (%)	377(24.0)	377 (71.8)	0(0)	/
Double aPLs positivity, *n* (%)	174(11.1)	174 (33.1)	0(0)	/
Triple aPLs positivity, *n* (%)	84(5.3)	84 (16.0)	0(0)	/
Low risk aPLs antibodies profile, *n* (%)	148(9.4)	148 (28.2)	0(0)	/
Therapeutic regime				
Glucocorticoids, *n* (%)	1454(92.4)	488(93.0)	966(92.2)	0.583
Pulse therapy, *n* (%)	92(9.0)	45(13.0)	47(7.0)	**0.001**
Immunosuppressant, *n* (%)	1548(98.4)	514(97.9)	1034(98.7)	0.256
Hydroxychloroquine, *n* (%)	1429(90.8)	480(91.4)	949(90.6)	0.570
Antithrombotic therapy, *n* (%)	391(24.9)	358(68.2)	33(3.1)	**<0.001**
Low dose aspirin, *n* (%)	335(21.3)	302(57.5)	33(3.1)	**<0.001**
Anticoagulant therapy, *n* (%)	101(6.4)	101(19.2)	0(0)	**/**

Data are presented as mean ± S.D. or n (%), unless otherwise stated. $P<0.05$ were shown in bold

BMI Body mass index, *APS* Antiphospholipid syndrome, *aGAPSS* the adjust global APS score, *anti-dsDNA antibodies* anti-double-stranded DNA antibodies, *anti-Sm antibodies* anti-Smith antibodies, *anti-U1 RNP antibodies* anti-U1 ribonucleoprotein antibodies, *anti-RibP antibodies* anti-ribosomal P antibodies, *aPLs* antiphospholipid antibodies, *aCL antibodies* anticardiolipin antibodies, *anti-β2GPI antibodies* anti-β2 glycoprotein I antibodies, *LA* lupus anticoagulant

hundred sixteen further ASCVD events occurred during a mean follow-up period of 3.8 ± 2.1 years. Among them, 82 (5.2%) developed myocardial infarction, 56 (3.6%) developed stroke, 105 (6.7%) underwent coronary or peripheral artery revascularization, and 4 (0.3%) cardiovascular death occurred. Of these, 525 (33.4%) tested positive for aPLs; within this subgroup, 131 were diagnosed with APS, and 92 developed ASCVD during the follow-up period. Among the 1048 (66.6%) aPLs-negative patients, 24 developed ASCVD. For the 37 patients showed ASCVD events before SLE diagnosis, 9 developed ASCVD again during follow-up.

Table 1 presents the baseline characteristics, clinical manifestations, autoantibody profiles, and therapeutic regimens of the SLE cohort, stratified by aPLs status. SLE patients with positive aPLs exhibited a significantly higher prevalence of traditional cardiovascular risk factors, including smoking (4.2% vs 1.8%, $p=0.005$), diabetes (2.9% vs 1.1%, $p=0.014$), and hyperlipidemia (5.3% vs 3.2%, $p=0.045$). Hematological (52.0% vs 45.9%, $p=0.022$), nephrological (39.2% vs 27.4%, $p<0.001$), and neurological (12.4% vs 6.8%, $p<0.001$) manifestations were more frequent among aPLs-positive SLE patients. With the exception of anti-Sm (29.3% vs 35.2%, $p=0.020$) and anti-U1 RNP antibodies (37.7% vs 47.7%, $p<0.001$), the positivity rates for anti-dsDNA (71.8% vs 64.2%, $p=0.003$), anti-RibP (29.5% vs 22.3%, $p=0.002$), ANuA (29.9% vs 23.8%, $p=0.009$), and AHA (23.4% vs 17.7%, $p=0.007$) were all elevated in SLE patients who tested positive for aPLs.

Association between aPLs isotypes and ASCVD

In our SLE cohort, the overall prevalence of aPLs was 33.4%, as detailed in Table 1. aCL antibody represented 57% of aPLs, with 47.4% accounting for aCL-IgG and 9.1% for aCL-IgM; anti-β2GPI antibody comprised 46.7%, of which 37.9% were anti-β2GPI-IgG, and 15.8% anti-β2GPI-IgM. LA was found in 61.7% of aPL-positive SLE patients. High-risk aPLs profiles were observed in 71.8% of cases, while 28.2% exhibited a low-risk profile.

We performed a comprehensive analysis of the impact of different aPLs isotypes on the development of ASCVD, as presented in Table 2. Among the 525 SLE patients with positive aPLs, 92 developed ASCVD during the follow-up period. The HR for ASCVD in the presence of positive aPLs was 7.81 (95%CI, 5.00–12.24, $p<0.001$). LA was associated with the highest risk for ASCVD, followed by aCL and anti-β2GPI, with HRs of 7.87 (95%CI, 5.31–11.67, $p<0.001$), 6.07 (95%CI, 4.19–8.77, $p<0.001$), and 2.38 (95%CI, 1.59–3.56, $p<0.001$), respectively. The risk associated with the IgG isotype was greater than that with the IgM isotype for both aCL (HR = 4.76 vs 4.01) and anti-β2GPI antibodies (HR = 2.72 vs 2.30). Figure 2 illustrates the cumulative probability of ASCVD across different aPLs isotypes, providing a visual representation of their effects on ASCVD risk.

Univariate Cox regression analysis identified traditional cardiovascular risk factors as predictors of future ASCVD events, including age, gender, obesity, diabetes, hypertension, hyperlipidemia, and smoking. Additional SLE-related factors associated with ASCVD included the SLEDAI-2K at recruitment, neurological involvement, baseline APS diagnosis, and the aGAPSS, a risk prediction tool for thrombosis in SLE patients. The HRs, CIs, and *p* value are shown in details in Table 2.

In multivariable analyses, after adjusting for traditional cardiovascular risk factors, such as smoking, male gender, age, hypertension, diabetes, and hyperlipidemia, we

Table 2 Proportion of ASCVD in patients with different isotypes of anti-phospholipid antibodies profiles and risk factors of ASCVD

	ASCVD, *n* (%)	HR	95% CI	*p*
Anti-phospholipid antibodies (*n* = 525)	92 (17.5)	7.81	5.00–12.24	**< 0.001**
Anticardiolipin antibodies (*n* = 299)	66(22.1)	6.07	4.19–8.77	**< 0.001**
IgG (*n* = 249)	51(20.5)	4.76	3.29–6.88	**< 0.001**
IgM (*n* = 48)	15(31.3)	4.01	2.32–6.91	**< 0.001**
Anti-β2 glycoprotein I antibodies (*n* = 245)	47 (19.2)	2.38	1.59–3.56	**< 0.001**
IgG (*n* = 199)	29(14.6)	2.72	1.78–4.15	**< 0.001**
IgM (*n* = 83)	15(18.1)	2.30	1.34–3.97	**0.002**
Lupus anticoagulant (*n* = 324)	80(24.7)	7.87	5.31–11.67	**< 0.001**
High risk aPLs antibodies profile, (*n* = 377)	83(21.9)	7.45	2.97–11.16	**< 0.001**
Double aPLs positivity, (*n* = 174)	37(21.3)	2.97	1.99–4.45	**< 0.001**
Triple aPLs positivity, (*1* = 84)	38(45.2)	6.07	3.91–9.41	**< 0.001**
Low-risk aPLs antibodies profile, (*n* = 148)	9 (6.1)	1.02	0.52–2.02	0.947
Risk factors of cardiovascular disease				
Age > 50 years old (*n* = 169)	29(17.2)	2.50	1.63–3.83	**< 0.001**
Gender (male) (*n* = 61)	17(27.9)	3.99	2.38–6.69	**< 0.001**
BMI	/	1.12	1.08–1.17	**< 0.001**
Diabetes mellitus (*n* = 27)	12(44.4)	7.16	3.93–13.50	**< 0.001**
Hypertension (*n* = 117)	34(29.1)	3.11	3.42–7.64	**< 0.001**
Smoking (*n* = 41)	12(29.3)	7.80	4.24–14.35	**< 0.001**
Hyperlipidemia (*n* = 62)	27(43.5)	1.30	1.25–1.46	**< 0.001**
SLE manifestations				
SLE duration, years	/	0.99	0.93–1.05	0.633
Malar rash (*n* = 586)	40(6.8)	0.65	0.44–0.95	**0.023**
Discoid lesions (*n* = 169)	15(8.9)	1.37	0.79–2.36	0.258
Arthritis (*n* = 729)	59(8.1)	1.11	0.77–1.60	0.579
Oral Ulcerations (*n* = 305)	23(7.5)	0.92	0.59–1.47	0.761
Serositis (*n* = 207)	15(7.2)	0.94	0.55–1.63	0.837
Alopecia (*n* = 546)	37(6.8)	0.85	0.58–1.26	0.424
Nephropathy (*n* = 493)	40(8.1)	0.97	0.66–1.42	0.858
Hematological involvement (*n* = 754)	57(7.6)	0.87	0.60–1.26	0.458
Neurological involvement (*n* = 136)	36(26.5)	3.52	2.36–5.25	**< 0.001**
Baseline SDI > 0 (*n* = 184)	20(10.9)	2.26	1.49–3.42	**< 0.001**
SLEDAI-2K	/	1.10	1.05–1.13	**< 0.001**
Diagnose APS at baseline (*n* = 131)	41(31.1)	5.06	3.45–7.42	**0.001**
aGAPSS	/	1.30	1.25–1.36	**< 0.001**

HR hazard ratio, *P* < 0.05 were shown in bold

ASCVD Arteriosclerotic cardiovascular disease, *BMI* Body mass index, *APS* Antiphospholipid syndrome, *aGAPSS* the adjust global APS score

found that anti-β2GPI-IgG, aCL-IgG, aCL-IgM, and LA positivity were independently associated with ASCVD. Furthermore, the aGAPSS score, smoking status, hypertension, hyperlipidemia, age over 50 years old, diagnosis APS at baseline, and SLEDAI-2K score at recruitment remained significant predictors of ASCVD (Fig. 3).

The influence of aspirin on ASCVD risk

Treatment regimens administered to patients with SLE are outlined in the Table 1. An analysis of the use of glucocorticoids, immunosuppressants, and hydroxychloroquine revealed no significant differences between SLE patients with aPLs positivity and those with aPLs negativity.

The potential impact of aspirin and anticoagulant therapy on the risk of ASCVD is illustrated in Fig. 4. Of the 525 SLE patients who tested positive for aPLs, 358 (68.2%) were administered antithrombotic therapy (including aspirin and anticoagulant therapy), 302 (57.5%) used low-dose aspirin (75 to 100 mg daily), and 101(19.2%) adopted anticoagulant therapy (e.g., warfarin, heparin). The incidence of ASCVD was 7.3% among

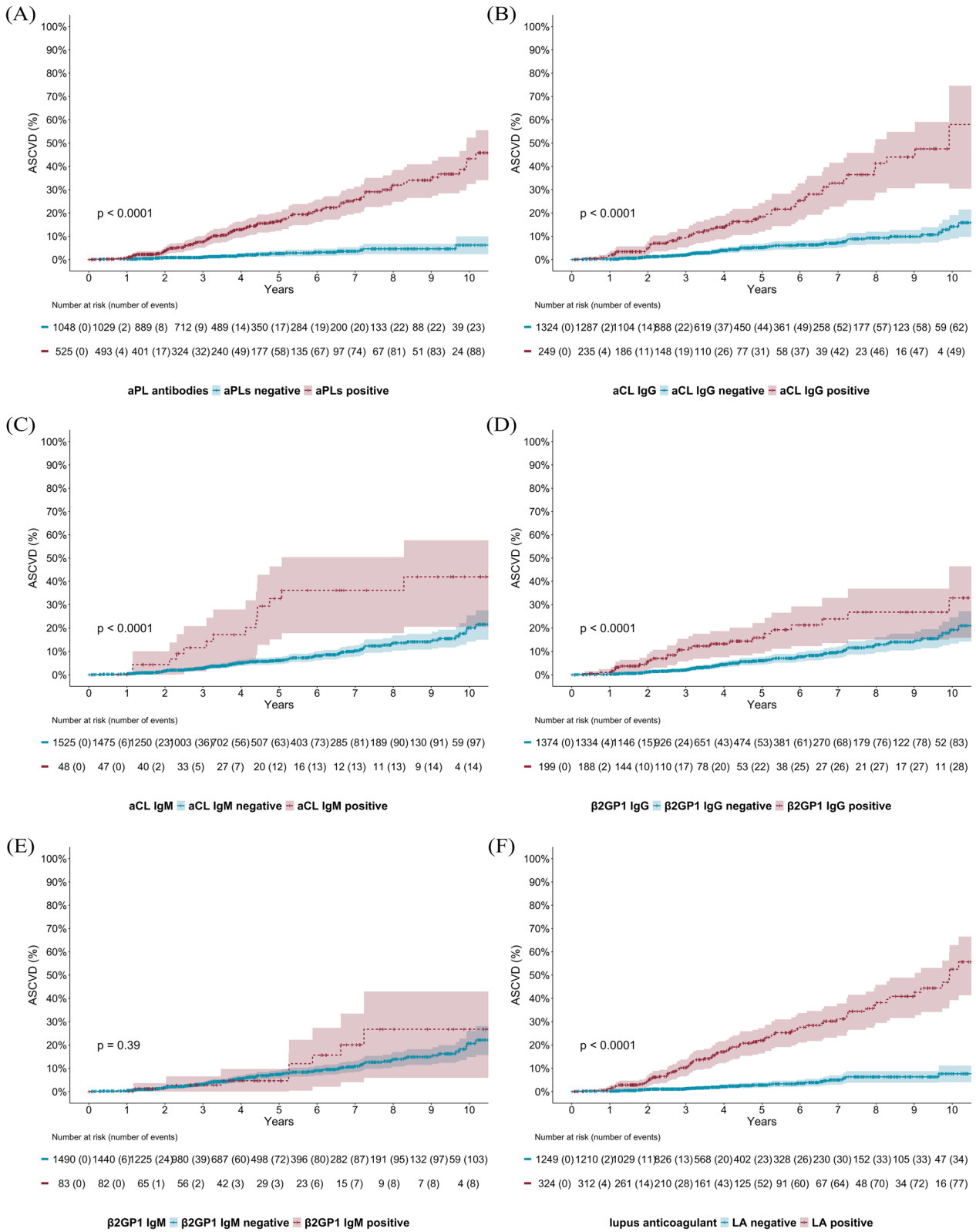


Fig. 2 Cumulative probability of ASCVD in patients with or without **A** aPLs profile, **B** aCL IgG antibody, **C** aCL IgM antibody, **D** β2-GPI IgG antibody, **E** β2-GPI IgM antibody, and **F** LA. The *y*-axis represents the cumulative rate of ASCVD event and the *x*-axis represents the follow-up time (years). aPLs: antiphospholipid antibodies; aCL antibodies: anticardiolipin antibodies; anti-β2GPI antibodies: anti-β2 glycoprotein I antibodies; LA: lupus anticoagulant

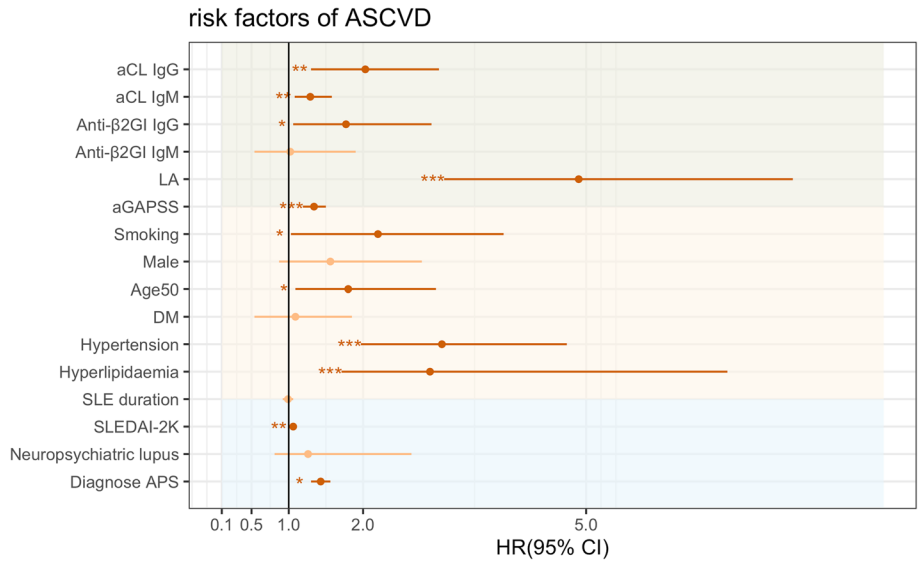


Fig. 3 The effect of aPLs profile, traditional cardiovascular disease risk factors, and SLE features on ASCVD. The forest plot illustrated the hazard ratios (HRs) and 95% confidence intervals in Multivariable Cox regression analysis. aCL antibodies: anticardiolipin antibodies; anti-β2GPI antibodies: anti-β2 glycoprotein I antibodies; LA: lupus anticoagulant; aGAPSS: adjust global APS score; DM: diabetes mellitus; SLEDAI-2 K: Systemic Lupus Erythematosus Disease Activity Index 2000; APS: antiphospholipid syndrome

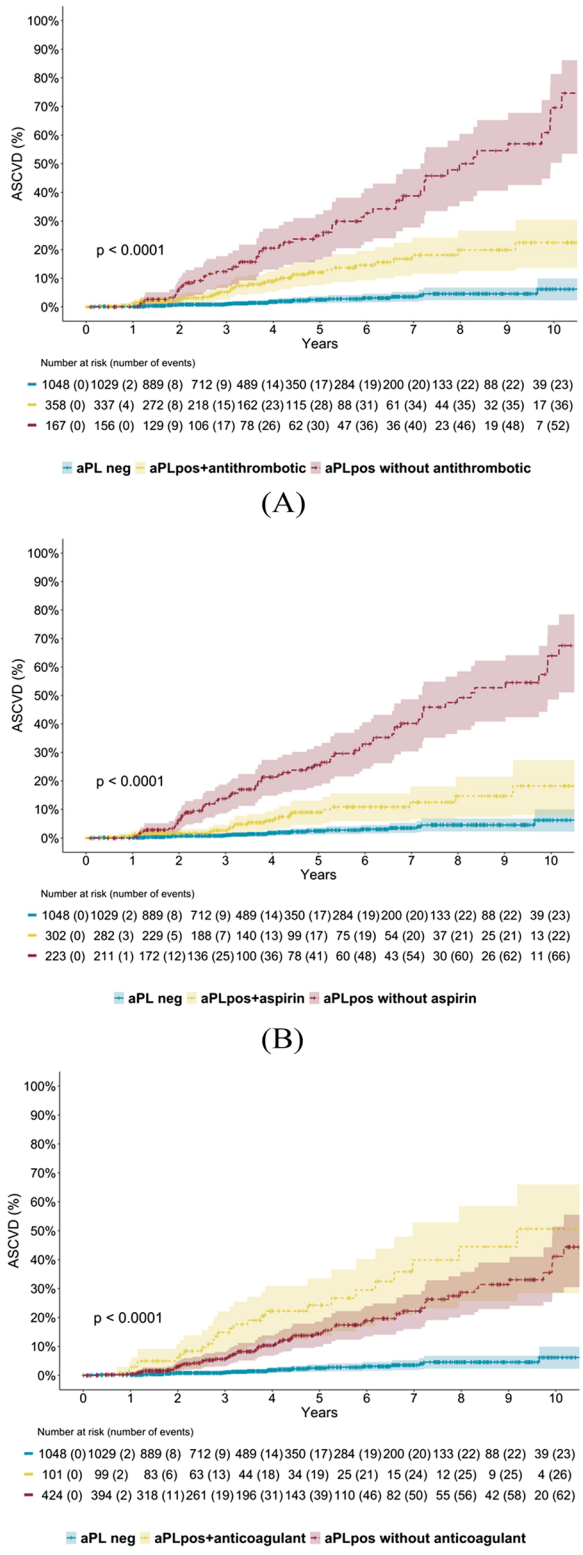
aPLs-positive patients receiving aspirin therapy, compared to 31.4% in those who did not receive aspirin. As depicted in Fig. 4, aPLs-positive patients on aspirin treatment exhibited a reduced risk of ASCVD during the follow-up period when contrasted with those not taking aspirin, as well as patients who were aPLs-negative. As contrasted, compared with patients without anticoagulant therapy, aPLs-positive patients with anticoagulant therapy showed a higher risk of ASCVD.

Discussion

SLE is a chronic inflammatory disease characterized by multisystem involvement and antinuclear antibodies positivity. In the long-term management of SLE patients, accumulated organ damage contributed to mortality and morbidity of SLE [20]. aPLs were predicting factors for damage accrual [6, 21, 22], they may contribute via thrombosis, especially in cardiovascular system [23] and neurological system [24], which might lead to death in SLE.

Studies have shown that the risk of CVD in SLE patients is three times higher than that in healthy people [5, 25]. Specifically, Lu et al. reported that SLE was associated with a significantly higher risk of atherosclerosis (relative risk (RR) = 2.31), myocardial infarction (RR = 2.66), stroke (RR = 2.30), and peripheral vascular disease (RR = 2.56) compared with healthy controls [26]. The first 10 years of lupus are a high-risk period for CVD [27], and approximately 10% of SLE patients develop atherosclerosis each year without CVD manifestations [28]. Therefore, early attention should be paid to the screening and prevention of high-risk patients, which is helpful to improve the prognosis of patients.

aPLs may play a pivotal role in ASCVD development. Recently, a cohort study of 2427 participants reported the prevalence of positive aPLs test was 14.5% [29]. This study suggested that aCL IgA (HR = 4.92, 95% CI, 1.52–15.98) and anti-β2GPI IgA (HR = 2.91, 95% CI, 1.32–6.41) were independently associated with future ASCVD events in participants without autoimmune disease. Besides, previous studies have found aPLs may play a role in the development of CVD in patients with SLE [30]. The prevalence of aPLs positivity in SLE patients ranges from 30% to 40% [31, 32]. Studies have shown that the incidence of asymptomatic coronary artery atherosclerosis in patients with SLE-APS is between 30% and 35%, and the rate of acute myocardial infarction is 3.8% [8]. Antiphospholipid antibodies are a heterogeneous group of autoantibodies that activate endothelial cells, platelets, and neutrophils. They can promote the uptake of oxidized low-density lipoprotein by macrophages, leading to foam cell formation and the development of atherosclerosis; additionally, aPLs induce endothelial cell proliferation, resulting in vascular thickening and luminal narrowing; furthermore, aPLs activate platelets, triggering downstream coagulation pathways and complement pathway activation; together, these mechanisms can cause arterial damage, affecting the coronary arteries and manifesting as coronary heart disease [33]. These studies provide theoretical evidence for the roles of aPLs in ASCVD development in SLE.



◀ **Fig. 4** Cumulative probability of ASCVD in patients with negative aPLs profile, positive aPLs profile and antithrombotic therapy (**A**), aspirin (**B**), or anticoagulant therapy (**C**), and positive aPLs profile without those therapies. The *y*-axis represents the cumulative rate of ASCVD event and the *x*-axis represents the follow-up time (years)

Different subtypes of aPLs have varying impacts on ASCVD events. The IgG or IgM isotypes of aCL or anti-β2GPI antibodies were usually used for the definition of aPLs positivity. Compared with IgM, the clinical significance of IgG isotypes was more through described. Previous research has found that in women with anti-β2GPI antibodies, the risk of ischemic stroke was increased 2.3-fold, though the risk of myocardial infarction was not elevated; in contrast, aCL and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies did not affect the risk of myocardial infarction or ischemic stroke [34]; however, the study was conducted in young women, not in SLE patients. In myocardial infarction patients, aPLs IgG subtype is significantly enriched in both myocardial infarction with non-obstructive coronary arteries (MINOCA) and myocardial infarction with coronary artery disease (MICAD), while the IgM subtype is not [35]. In primary APS patients, LA is considered significantly associated with AMI, and aCL-IgG is more closely related to valvular heart disease [36]. For aCL-IgM, the association between pregnancy morbidity and aCL IgM was reported in obstetric APS [37]. No increase in either venous or arterial thrombosis in patients with IgM anticardiolipin positivity was found in Danowski et al.'s study [38]. Nevertheless, there is limited research on the impact of different aPLs subtypes on ASCVD in SLE patients. Based on our study, LA remains the strongest independent risk factor for ASCVD in SLE patients, with IgG subtype aPLs presenting a higher risk of ASCVD compared to the IgM subtype. As mentioned above, most of the previous studies on the risk of aPLs were based on general population, myocardial infarction cohort or primary APS cohort. This study investigated the risk of different subtypes of aPLs on ASCVD in a long-term follow-up, large sample and multi-center SLE cohort, which has important implications for the risk management of ASCVD in lupus patients.

Other potential risk factors associated with the onset of ASCVD in patients with SLE include traditional CVD risk factors as well as factors related to the disease characteristics of SLE, such as disease activity, neuropsychiatric lupus, or organ damage [39]. In the Hopkins Lupus Cohort, hypertension has been identified as being associated with the occurrence of coronary heart disease in SLE [40]. In the Toronto Lupus Cohort, it was suggested that the cumulative exposure instead of hypertension at

the first visit can better predict CVD occurrence [41]. In a meta-analysis, hypertension was a risk factor for CVD in SLE, with a RR of 2.31 [26]. Numerous cohort studies have found dyslipidemia to be associated with CVD events in SLE patients [40–43]; while some studies indicated that the association between dyslipidemia and CVD in SLE remains controversial [26]. Diabetes, smoking, and obesity have all been identified as being associated with the occurrence of ASCVD [44]. The risk for CVD in male SLE patients has also been found to be higher than in females [45, 46]. These traditional risk factors, in conjunction with different aPLs, may lead to thrombotic events. The aGAPSS score, which predicts thrombosis formation in antiphospholipid syndrome, includes hypertension, dyslipidemia, and the three main antiphospholipid antibodies [47]. The aGAPSS-CVD score further incorporates diabetes, smoking, and obesity, improving its predictive power for CVD [48].

Following the 2022 EULAR recommendations for the management of cardiovascular disease risk in patients with rheumatic diseases, the use of low-dose aspirin (75–100 mg) is advised as primary prevention for SLE patients with high-risk aPLs. A meta-analysis including 1208 asymptomatic aPLs individuals showed low-dose aspirin can reduce the risk of a first thrombotic event (OR = 0.50, 95% CI, 0.27 to 0.93, $p < 0.0001$) [49]. In SLE patients with positive aPLs, previous research has indicated that long-term use of low-dose aspirin has a protective effect against thrombosis, especially arterial thrombosis, which may be explained by their anti-thrombosis and anti-inflammatory effects. As contrast, anticoagulation therapy was more effective in deep venous thromboses, pulmonary emboli, and ischemic strokes. However, there is less research on the protective effect of aspirin against CVD [50]. In this study, long-term cohort follow-up and data analysis have demonstrated the role of aspirin in primary prevention for SLE patients positive for aPLs. Despite the addition of aspirin, the risk of ASCVD in patients positive for aPLs remains higher than in those with SLE who are aPLs negative. Furthermore, previous studies have focused on the cardioprotective effects of hydroxychloroquine [51], but as the usage rates of hydroxychloroquine exceeded 90% in both aPLs-positive and -negative patients in this study, no preventive effect against ASCVD was observed. Besides, colchicine may also reduce future ASCVD risk in SLE patients with positive aPLs. Previous studies have found that colchicine can reduce the risk of cardiovascular events in adult patients with atherosclerotic disease through a decrease in the adhesion of neutrophils and leukocytes to inflamed endothelium, and suppress the production of interleukin (IL)-1β and IL-18 [52–55]. Their promising role in aPLs-positive SLE patients needs further validation.

The innovation of this study lies in the exploration of the impact of different subtypes of aPLs on the occurrence of ASCVD in SLE patients within a large-scale follow-up cohort, finding that LA and IgG-type aPLs are associated with a higher risk of ASCVD in SLE patients. aPLs profile test is recommended at SLE diagnosis and physician should pay close attention to ASCVD events in patients with positive LA or IgG type-aPLs. Secondly, the study analyzed different traditional CVD risk factors and combined these with aPLs. Thirdly, the study validated the primary preventive role of aspirin against future ASCVD events in aPLs-positive patients within a long-term SLE follow-up cohort, providing more robust support for guidelines. However, the study has several limitations. Firstly, aPLs testing did not fully cover this SLE cohort, resulting in missing data that could not be included for all patients in the study. Secondly, the rate of cardiovascular disease might be influenced by the follow-up duration, and a longer period of observation would allow for a thorough evaluation of the effects of aPLs on ASCVD.

Conclusions

In conclusion, SLE patients with positive aPLs, especially positive aCL IgG/IgM and LA, warrant more care and surveillance of future ASCVD events during follow-up. Aspirin may have a protective effect on future ASCVD.

Abbreviations

SLE	Systemic lupus erythematosus
ASCVD	Atherosclerotic cardiovascular disease
aPLs	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
aCL antibodies	Anticardiolipin antibodies
anti-β2GPI antibodies	Anti-β2 glycoprotein I antibodies
LA	Lupus anticoagulant
CSTAR	Chinese SLE treatment and research
ACR	American College of Rheumatology
SLICC	Systemic Lupus International Collaborating Clinics
EULAR	European League Against Rheumatism
ANA	Antinuclear antibodies
Anti-dsDNA antibodies	Anti-double-stranded DNA antibodies
Anti-Sm antibodies	Anti-Smith antibodies
Anti-U1 RNP antibodies	Anti-U1 ribonucleoprotein antibodies
Anti-RibP antibodies	Anti-ribosomal P antibodies
ANuA	Anti-nucleosome antibodies
AHA	Anti-histone antibodies
CLIFT	Crithidia luciliae immunofluorescence test
ELISA	Enzyme-linked immunosorbent assay
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SDI	SLICC/ACR Damage Index
ISTH	International Society on Thrombosis and Haemostasis
aPTT	Activated partial thromboplastin time–based assay
dRVVT	The dilute Russell viper venom time
aGAPSS	Adjust global APS score
SD	Standard deviations
HRs	Hazard ratios
CIs	95% Confidence intervals
RR	Relative risk
aPS/PT	Anti-phosphatidylserine/prothrombin

MINOCA	Myocardial infarction with non-obstructive coronary arteries
MICAD	Myocardial infarction with coronary artery disease
IL	Interleukin

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Authors' contributions
HC, DYF, ZC, JLZ, and MTL contributed to the conception and design of the study. DYF and HC performed the data analysis and drafted the manuscript. DYF, HC, ZC, JLZ, and MTL critically revised the manuscript. All authors contributed to the cases collection and interpretation of the data. JLZ and MTL are the guarantor and take responsibilities for the integrity of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (Approval number, S-197). Each participating institution obtained informed patient consent and ethics approval from the local Institute Review Board.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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