

# Risk factors of first thrombosis in obstetric antiphospholipid syndrome

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**To cite:** Luo L, Cai Q, Liu X, et al. Risk factors of first thrombosis in obstetric antiphospholipid syndrome. *Lupus Science & Medicine* 2024;**11**:e001044. doi:10.1136/lupus-2023-001044

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/lupus-2023-001044>).

LL and QC are joint first authors.

The results derived from this study were partially presented in the American College of Rheumatology Convergence 2023 conference.

Received 7 September 2023  
Accepted 9 December 2023



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## ABSTRACT

**Objective** There is limited evidence on long-term thrombosis risk in patients with obstetric antiphospholipid syndrome (OAPS). This study aimed to investigate the clinical features and risk factors associated with the first thrombosis in patients with isolated OAPS.

**Methods** Data from patients with isolated OAPS were collected. All patients were followed up until the first thrombotic event during or after delivery or until the end of the study. Logistic regression analysis identified independent risk factors associated with the first thrombosis in patients with isolated OAPS.

**Results** The study enrolled 186 patients with OAPS. During a mean 5.4-year follow-up, 11 (5.9%) patients experienced thrombotic events. Multivariate binary logistic regression analysis revealed that triple-positive antiphospholipid antibodies (aPLs, OR=11.662, 95% CI=2.117 to 64.243, p=0.005) and hypocomplementemia (OR=9.047, 95% CI=1.530 to 53.495, p=0.015) were identified as independent risk factors for the first thrombosis in OAPS, after adjustment for low-dose aspirin and hydroxychloroquine.

**Conclusions** Triple-positive aPLs and hypocomplementemia are risk factors for the first thrombosis in patients with OAPS.

## INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disease characterised by thrombotic and/or obstetric morbidity in the presence of persistent antiphospholipid antibodies (aPLs).<sup>1</sup> APS can be further classified into two subtypes, thrombotic APS (TAPS) and obstetric APS (OAPS), which share similar antibody profiles but differ in pathogenic mechanisms and clinical presentations.<sup>2,3</sup> At the time of diagnosis, only 13.5% of patients with APS experience both thrombosis and obstetric morbidity.<sup>4</sup> Unlike patients with TAPS, individuals with OAPS do not exhibit an elevated risk of subclinical atherosclerosis.<sup>5</sup> Previous studies investigating risk factors for thrombosis in OAPS have produced inconsistent and inconclusive findings (online supplemental table 1).<sup>2,4,6–16</sup> This variability can be attributed to disparities in sample sizes, geographical locations and duration of follow-up among these studies. Noteworthy

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited evidence exists regarding the long-term risk of thrombosis in patients with obstetric antiphospholipid syndrome (OAPS); previous studies investigating risk factors for thrombosis in OAPS have produced inconsistent and inconclusive findings.

## WHAT THIS STUDY ADDS

⇒ Triple-positive antiphospholipid antibodies and hypocomplementemia are risk factors for the first thrombosis in patients with OAPS.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identifying the risk factors for the first thrombosis in OAPS could facilitate more effective management of these patients.

risk factors identified include additional cardiovascular factors, lupus anticoagulant (LA) positivity, presence of multiple aPLs and a higher adjusted Global Antiphospholipid Syndrome Score (aGAPSS).<sup>4,7,14</sup>

Primary thromboprophylaxis following delivery remains a topic of debate due to varying annual prevalence rates of thrombosis in OAPS, ranging from less than 1% to 6.1%.<sup>2,4,6–16</sup> The divergent prevalence rates have led to conflicting opinions regarding the benefits of primary thromboprophylaxis. Currently, the strategies for primary prevention of thrombosis in OAPS are controversial. A meta-analysis suggests that primary prevention with low-dose aspirin (LDA) in patients with OAPS is associated with a reduced risk of thrombosis.<sup>17</sup> However, a recent systematic review concludes that there is insufficient evidence to determine the efficacy of LDA in preventing primary thrombotic events in patients with OAPS.<sup>18</sup>

Identifying the risk factors for the first thrombosis in OAPS could facilitate more effective management of these patients. Therefore, this study aims to investigate the clinical features and risk factors associated with the first thrombotic event in patients with isolated OAPS.

## MATERIALS AND METHODS

### Patients

This study included 424 consecutive patients diagnosed with APS who were admitted to Peking University People's Hospital between June 2008 and August 2022. All patients met the 2006 Sydney and 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for APS (including 17 patients whose aPLs transitioned from high titres to low titres upon admission).<sup>1,19,20</sup> Male patients and patients with a history of thrombosis prior to delivery were excluded. Clinical data from 186 patients with isolated OAPS were collected. Regular follow-up was conducted every 3–6 months for all participants. Patients were advised to promptly contact the research physicians if they experienced any symptoms of thrombosis, including deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, etc.

The primary outcome of this study was the incidence of thrombotic events. The diagnosis of thromboembolism was based on objective imaging techniques. All patients were followed up at the rheumatology outpatient clinic. DVT and arterial thrombosis of limb were confirmed by Doppler ultrasound examination.<sup>21</sup> PE was diagnosed by CT angiography.<sup>22</sup> Stroke was diagnosed by MRI. Myocardial infarction was diagnosed by raised cardiac enzymes and appropriate ECG changes.<sup>23</sup> The follow-up period was defined as the time from the first delivery until the occurrence of the first thrombotic event or the end of the study.

### LA testing

The test of LA was performed using the simplified Dilute Russell's Viper Venom Test (dRVVT) method on

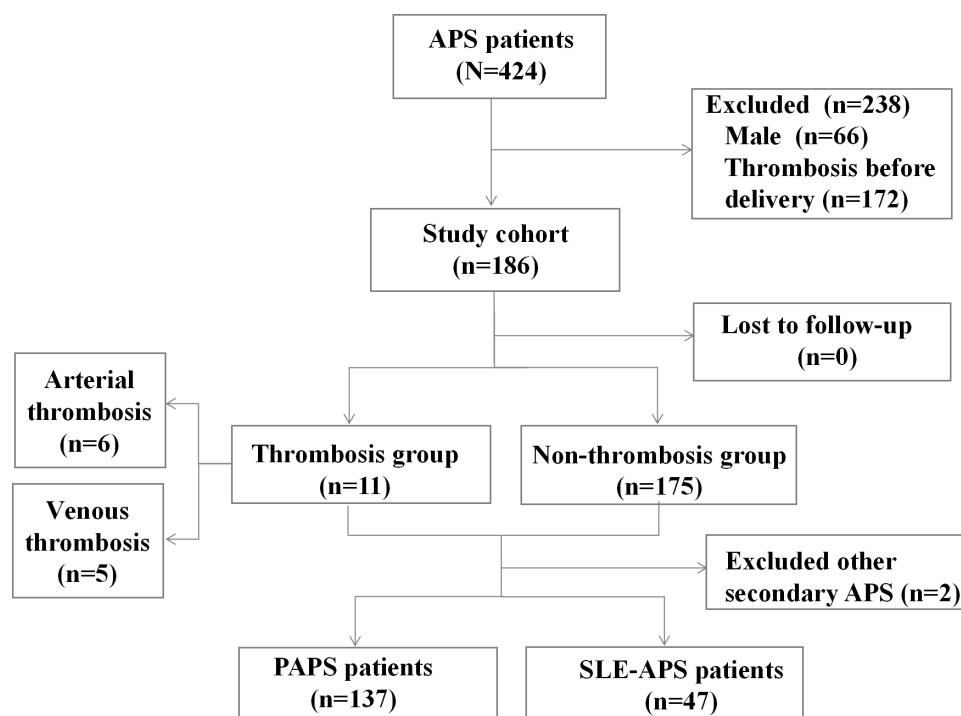
the Stago STA Compact Hemostasis System. STA (USA) provided the LA1 screening reagent and LA2 confirmatory reagent, and these were used in accordance with the manufacturer's guidelines. The presence of a positive LA activity was established based on dRVVT ratios (LA1 screen/LA2 confirmation) exceeding the threshold of 1.2. aPL positivity was confirmed 12 weeks apart.

### Data collection

This is a single-centre, observational cohort study with prospective clinical follow-up. We retrospectively collected information on hospitalised patients and prospectively enrolled new patients. Baseline data, including demographics, cardiovascular risk factors (hypertension, hyperlipidaemia, arteriosclerosis, diabetes), underlying autoimmune diseases, clinical manifestations, laboratory findings (aPLs) and post-delivery treatment, were collected. Serum levels of IgM/IgG anticardiolipin antibodies (aCL) and anti- $\beta$ 2-glycoprotein I antibodies (a $\beta$ 2GPI) were measured by an ELISA kit from EURO-IMMUN (Luebeck, Germany).<sup>24</sup> The aGAPSS was calculated for each patient.<sup>25</sup> During follow-up, the time from the first delivery to the first thrombotic event, types of thrombosis (venous or arterial) and site of thrombosis were recorded.

### Statistical analysis

Analyses were conducted on all eligible patients, as well as primary APS (PAPS) and SLE-related APS (SLE-APS) to identify the risk factors for thrombosis. Descriptive analyses were performed using SPSS V.26.0. The single-sample Kolmogorov-Smirnov test was used to assess the distribution of the data. The independent sample Student's t-test



**Figure 1** Flow chart of the study. APS, antiphospholipid syndrome; PAPS, primary APS.

**Table 1** Comparison of baseline characteristics, clinical features and treatment between patients with OAPS with or without thrombotic events

Variables	Thrombosis group (n=11)	Venous thrombosis group (n=5)	Arterial thrombosis group (n=6)	Non-thrombosis group (n=175)	P value*	P value†	P value‡
Age at onset (years), mean±SD	27.6±4.0	27.4±4.5	27.7±4.0	31.2±4.8	<b>0.013</b>	0.130	0.083
Disease duration (years), IQR	5.0 (1.0–25.0)	2.0 (0.8–20.5)	13.5 (0.8–27.0)	1.0 (0.3–3.0)	<b>0.049</b>	0.332	0.069
BMI (kg/m <sup>2</sup> ), mean±SD	24.3±4.8	22.1±4.4	26.1±4.7	24.4±3.9	0.924	0.305	0.429
Smoking, n (%)	0 (0)	0 (0)	0 (0)	3 (1.7)	1.000	1.000	1.000
Cardiovascular risk factors, n (%)							
Hypertension	3 (27.3)	1 (20.0)	2 (33.3)	16 (9.1)	0.158	0.966	0.110
Hyperlipidaemia	4 (36.4)	2 (40.0)	2 (33.3)	36 (20.6)	0.393	0.632	0.806
Arteriosclerosis	1 (9.1)	1 (20.0)	0 (0)	0 (0)	0.059	<b>0.028</b>	–
Diabetes	1 (9.1)	1 (20.0)	0 (0)	8 (4.6)	1.000	0.603	1.000
Underlying autoimmune diseases, n (%)							
SLE	6 (54.5)	2 (40)	4 (66.7)	41 (23.4)	0.052	0.475	0.054
RA	1 (9.1)	1 (20.0)	0 (0)	7 (4.0)	0.392	0.205	1.000
SS	1 (9.1)	1 (20.0)	0 (0)	3 (1.7)	0.218	0.107	1.000
Clinical manifestations							
Fetal loss, n (%)							
<10 weeks	9 (81.8)	4 (80.0)	5 (83.3)	104 (59.4)	0.247	0.643	0.452
≥10 weeks	4 (36.4)	1 (20.0)	3 (50.0)	74 (42.3)	0.943	0.943	1.000
Premature birth <34 weeks, n (%)	4 (36.4)	2 (40.0)	2 (33.3)	27 (15.4)	0.164	0.392	0.246
Pre-eclampsia, n (%)	4 (36.4)	1 (20.0)	3 (50.0)	30 (17.1)	0.231	1.000	0.131
FGR, n (%)	2 (18.2)	2 (40.0)	0 (0)	23 (13.1)	0.984	0.291	1.000
Stillbirth, n (%)	1 (9.1)	0 (0)	1 (16.7)	6 (3.4)	0.888	1.000	0.213
Thrombocytopenia, n (%)	6 (54.5)	2 (40.0)	4 (66.7)	28 (16.0)	<b>0.005</b>	0.417	<b>0.008</b>
Hypocomplementemia, n (%)	9 (81.8)	4 (80.0)	5 (83.3)	41 (23.4)	<b>&lt;0.001</b>	<b>0.018</b>	<b>0.005</b>
Laboratory tests, n (%)							
LA positive	9 (81.8)	3 (60.0)	6 (100.0)	74 (42.3)	<b>0.025</b>	0.741	<b>0.017</b>
aβ2GPI positive	8 (72.7)	3 (60.0)	5 (83.3)	106 (60.6)	0.629	1.000	0.484
aCL positive	8 (72.7)	3 (60.0)	5 (83.3)	55 (31.4)	<b>0.013</b>	0.388	<b>0.027</b>
Double-positive aPLs	0 (0)	0 (0)	0 (0)	24 (13.7)	0.364	1.000	1.000
Triple-positive aPLs	8 (72.7)	3 (60.0)	5 (83.3)	30 (17.1)	<b>&lt;0.001</b>	<b>0.044</b>	<b>&lt;0.001</b>
High-risk aPLs	9 (81.8)	3 (60.0)	6 (100.0)	93 (53.1)	0.123	1.000	0.064
Treatment after delivery, n (%)							
LDA	3 (27.3)	2 (40.0)	1 (16.7)	111 (63.4)	<b>0.043</b>	0.549	0.059
LMWH	5 (45.5)	4 (80.0)	1 (16.7)	123 (70.3)	0.165	1.000	<b>0.020</b>

Continued

Table 1 Continued

Variables	Thrombosis group (n=11)	Venous thrombosis group (n=5)	Arterial thrombosis group (n=6)	Non-thrombosis group (n=175)	P value*	P value†	P value‡
LDA+LMWH	3 (27.3)	3 (60.0)	0 (0)	85 (48.6)	0.170	0.960	0.054
HCQ	5 (45.5)	3 (60.0)	2 (33.3)	135 (77.1)	<b>0.045</b>	0.721	<b>0.048</b>
Azathioprine	1 (9.1)	0 (0)	1 (16.7)	2 (1.1)	0.168	1.000	0.097
Mycophenolate mofetil	0 (0)	0 (0)	0 (0)	9 (5.1)	1.000	1.000	1.000
Cyclosporin A	2 (18.2)	0 (0)	2 (33.3)	11 (6.3)	0.173	1.000	0.061
Tacrolimus	0 (0)	0 (0)	0 (0)	2 (1.1)	1.000	1.000	1.000
Cyclophosphamide	1 (9.1)	0 (0)	1 (16.7)	5 (2.9)	0.310	1.000	0.185
Statins	0 (0)	0 (0)	0 (0)	7 (4.0)	1.000	1.000	1.000

Bold entries indicate statistically significant differences between the two groups.  
 \*Baseline comparison between thrombosis and non-thrombosis groups.  
 †Baseline comparison between venous thrombosis and non-thrombosis groups.  
 ‡Baseline comparison between arterial thrombosis and non-thrombosis groups.  
 aCL, anticardiolipin antibodies; aPLs, antiphospholipid antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies; BMI, body mass index; FGR, fetal growth restriction; HCQ, hydroxychloroquine; LA, lupus anticoagulant; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; OAPS, obstetric antiphospholipid syndrome; RA, rheumatoid arthritis; SS, Sjögren's syndrome.

was employed to compare differences in variables with a normal distribution, while the Wilcoxon-Mann-Whitney test was used for variables that did not follow a normal distribution. Categorical variables were analysed using the  $\chi^2$  test or Fisher's exact test, as appropriate. All significant variables associated with thrombosis in OAPS identified through univariate analysis were included in a multivariable binary logistic regression model, except for aPLs, which were included in the aGAPSS. Both unadjusted and adjusted regression models (adjusted for LDA and hydroxychloroquine (HCQ)) were presented. Kaplan-Meier survival analysis was conducted to assess the cumulative incidence of thrombosis in patients with OAPS and in the two subsets of OAPS (with/without LA). A  $p < 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of thrombotic events

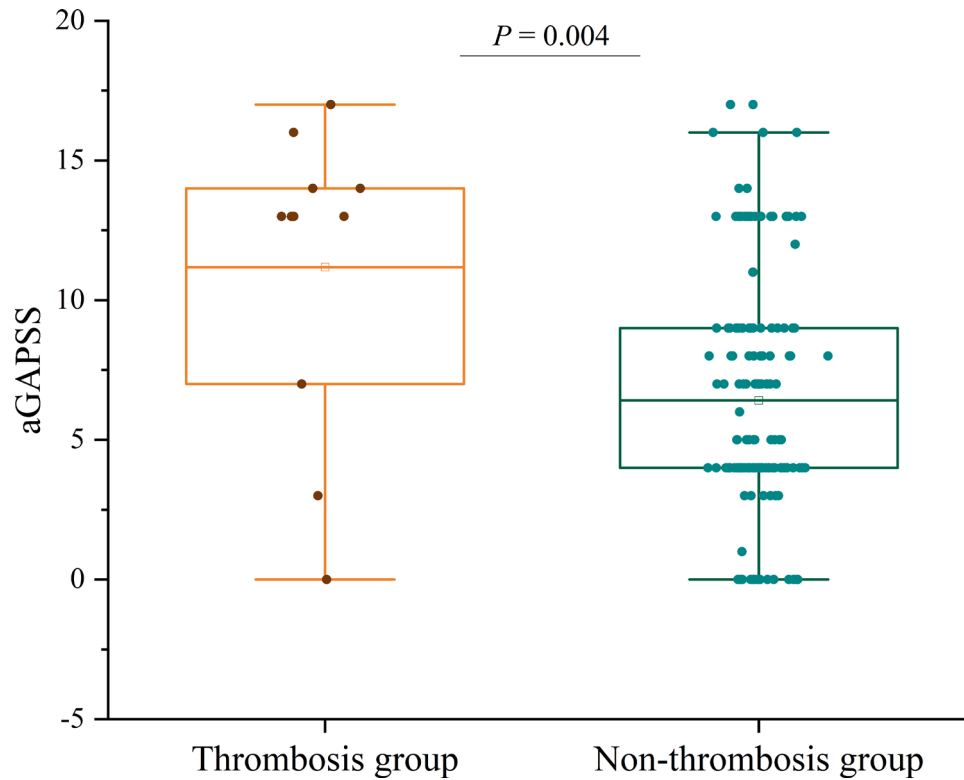
A total of 186 out of 424 patients with APS were included in this study (figure 1). Over a mean follow-up period of 5.4 years, thrombotic events occurred in 11 (5.9%) patients. Among them, six experienced arterial thromboses, including five strokes and one myocardial infarction, while five had venous thromboses, including three DVTs and two PEs. The median time from the first delivery to the first thrombosis was 4.8 (0.9–24.2) years.

### Comparison of baseline characteristic in patients with OAPS with or without thrombosis

Compared with patients without thrombosis, those with thrombosis had a lower age of onset (the age at which aPL-associated obstetric complications first occurred,  $27.6 \pm 4.0$  years vs  $31.2 \pm 4.8$  years,  $p = 0.013$ ) and longer disease duration ( $5.0$  (1.0–25.0) years vs  $1.0$  (0.3–3.0) years,  $p = 0.049$ ) (table 1). Thrombocytopenia was more frequent in patients with OAPS with thrombotic events (54.5% vs 16.0%,  $p = 0.005$ ). Furthermore, patients who experienced thrombotic events showed a higher frequency of hypocomplementemia (81.8% vs 23.4%,  $p < 0.001$ ) (table 1). The aGAPSS was significantly higher in patients with thrombosis compared with those without thrombosis (13.0 (7.0–14.0) vs 5.0 (4.0–9.0),  $p = 0.004$ ) (figure 2). The positive rate of LA was significantly higher in patients with thrombosis (81.8% vs 42.3%,  $p = 0.025$ ), as was the frequency of aCL positivity (72.7% vs 31.4%,  $p = 0.013$ ). Triple-positive aPLs were more common in patients with thrombosis (72.7% vs 17.7%,  $p < 0.001$ ) (table 1). In comparison with patients without thrombosis, the utilisation of LDA (27.3% vs 63.4%,  $p = 0.043$ ) and HCQ (45.5% vs 77.1%,  $p = 0.045$ ) was lower among patients with OAPS with thrombosis (table 1).

### Risk factors of first thrombosis in patients with OAPS

Multivariate binary logistic regression analysis revealed that triple-positive aPLs (OR=11.662, 95% CI=2.117 to 64.243,  $p = 0.005$ ) and hypocomplementemia (OR=9.047, 95% CI=1.530 to 53.495,  $p = 0.015$ ) were risk factors for the



**Figure 2** Comparison of aGAPSS between patients with or without thrombosis. aGAPSS, adjusted Global Antiphospholipid Syndrome Score.

first thrombosis in patients with OAPS, after adjustment for LDA and HCQ (table 2).

### Subgroup analysis

The comparison between patients with APS with arterial or venous thrombosis and patients without thrombosis was shown in table 1. In the unadjusted analysis, multivariable analysis revealed that the presence of triple-positive aPLs (OR=24.167, 95% CI=2.724 to 214.369,  $p=0.004$ ) was identified as an independent risk factor for arterial

thrombosis, while hypocomplementemia (OR=13.073, 95% CI=1.421 to 120.255,  $p=0.023$ ) was an independent risk factor for venous thrombosis (table 2). The comparison of thrombotic and non-thrombotic data among patients with PAPS and those with SLE-APS was presented in table 3. In the unadjusted model without considering medication, preterm birth <34 weeks (OR=21.599, 95% CI=1.247 to 374.179,  $p=0.035$ ), triple-positive aPLs (OR=36.195, 95% CI=2.037 to 643.120,  $p=0.015$ ) and

**Table 2** Multivariate logistic regression of first thrombosis in patients with OAPS

	OR	95% CI	P value	aOR*	95% CI	P value
All patients						
Disease duration, years	1.072	0.999 to 1.149	0.052			
Triple-positive aPLs	4.758	1.016 to 22.276	0.048	11.662	2.117 to 64.243	0.005
Hypocomplementemia	7.682	1.444 to 40.875	0.017	9.047	1.530 to 53.495	0.015
Arterial thrombosis subgroup						
Triple-positive aPLs	24.167	2.724 to 214.369	0.004	NA		
Venous thrombosis subgroup						
Hypocomplementemia	13.073	1.421 to 120.255	0.023	7.966	0.788 to 80.552	0.079
PAPS subgroup						
Premature birth <34 weeks	21.599	1.247 to 374.179	0.035	NA		
Triple-positive aPLs	36.195	2.037 to 643.120	0.015	NA		
Hypocomplementemia	25.738	1.725 to 383.955	0.018	NA		

Data on IQR or n (%).

\*aOR (adjustment for low-dose aspirin and hydroxychloroquine).

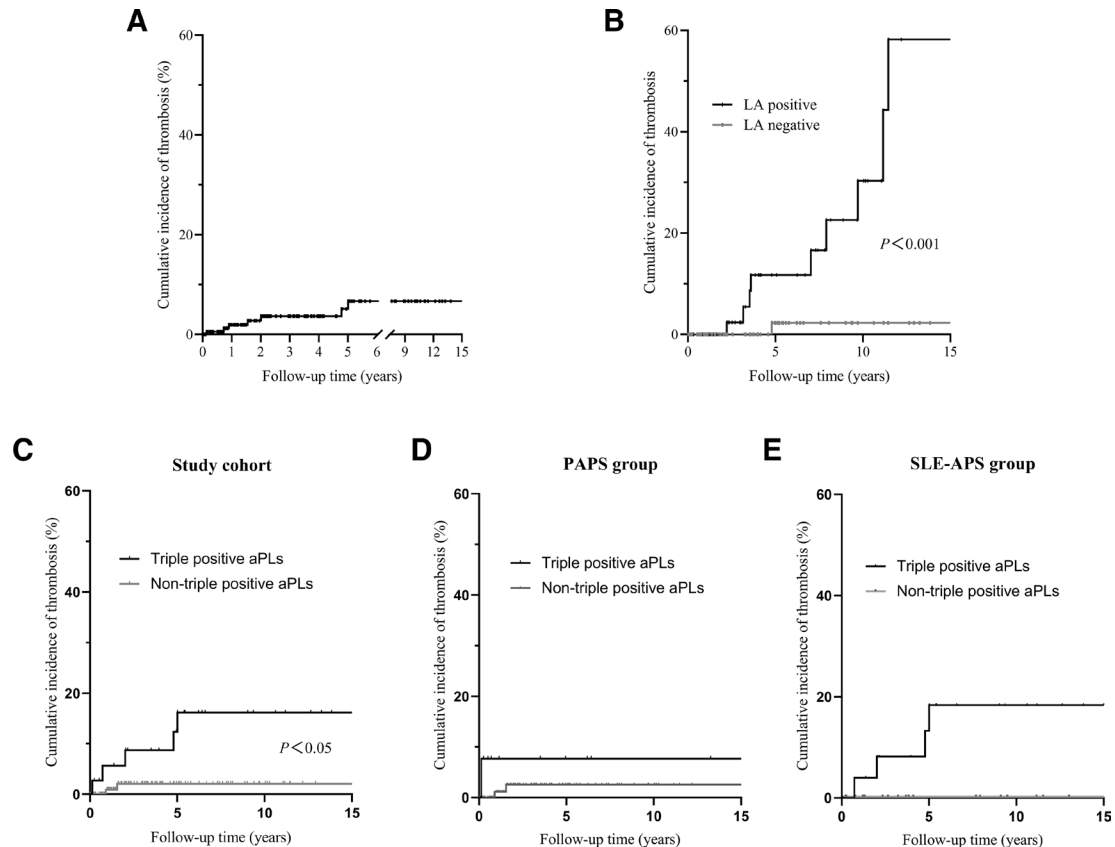
aOR, adjusted OR; aPLs, antiphospholipid antibodies; NA, not applicable; OAPS, obstetric antiphospholipid syndrome; PAPS, primary antiphospholipid syndrome.

**Table 3** Comparison of baseline characteristics, clinical features and treatment among patients with PAPS and those with SLE-APS

Variables	PAPS			SLE-APS		
	Thrombosis group (n=5)	Non-thrombosis group (n=132)	P value	Thrombosis group (n=6)	Non-thrombosis group (n=41)	P value
Age at onset (years), mean±SD	29.6±3.5	31.5±4.1	0.287	25.8±3.9	30.7±6.4	<b>0.028</b>
Disease duration (years), IQR	6.0 (0.8–30.0)	1.0 (0.4–3.0)	0.111	3.5 (0.8–24.8)	2.0 (0.1–5.0)	0.369
BMI (kg/m <sup>2</sup> ), mean±SD	23.0±5.2	24.3±3.8	0.603	25.4±4.5	24.8±3.9	0.772
Smoking, n (%)	0 (0)	0 (0)	–	0 (0)	2 (4.9)	1.000
Cardiovascular risk factors, n (%)						
Hypertension	2 (40.0)	10 (7.6)	0.087	1 (16.7)	6 (14.6)	1.000
Hyperlipidaemia	3 (60.0)	28 (21.5)	0.143	1 (16.7)	7 (17.1)	1.000
Arteriosclerosis	1 (20.0)	0 (0)	<b>0.036</b>	0 (0)	0 (0)	–
Diabetes	1 (20.0)	4 (3.0)	0.440	0 (0)	4 (9.8)	1.000
Clinical manifestations						
Fetal loss, n (%)						
<10 weeks	4 (80.0)	84 (63.6)	0.784	5 (83.3)	20 (48.8)	0.252
≥10 weeks	2 (40.0)	44 (33.3)	1.000	2 (33.3)	28 (68.3)	0.226
Premature birth <34 weeks, n (%)	3 (60.0)	16 (12.1)	<b>0.017</b>	1 (16.7)	11 (26.8)	0.974
Pre-eclampsia, n (%)	1 (20.0)	22 (16.7)	1.000	3 (50.0)	8 (19.5)	0.258
FGR, n (%)	2 (18.2)	23 (13.1)	0.984	1 (16.7)	5 (12.2)	1.000
Stillbirth, n (%)	1 (20.0)	18 (13.6)	1.000	0 (0)	2 (4.9)	1.000
Thrombocytopenia, n (%)	3 (60.0)	15 (11.4)	<b>0.013</b>	3 (50.0)	13 (31.7)	0.673
Hypocomplementemia, n (%)	4 (80.0)	16 (12.1)	<b>&lt;0.001</b>	5 (83.3)	23 (56.1)	0.410
Laboratory tests, n (%)						
LA positive	3 (60.0)	47 (35.6)	0.523	6 (100.0)	26 (63.4)	0.185
aβ2GPI positive	3 (60.0)	71 (53.8)	1.000	5 (83.3)	35 (85.4)	1.000
aCL positive	3 (60.0)	27 (20.5)	0.122	5 (83.3)	28 (68.3)	0.784
Double-positive aPLs	0 (0)	16 (12.1)	1.000	0 (0)	9 (22.0)	0.579
Triple-positive aPLs	3 (60.0)	9 (6.8)	<b>0.001</b>	5 (83.3)	21 (51.2)	0.299
High-risk aPLs	3 (60.0)	61 (46.2)	0.881	6 (100.0)	32 (78.0)	0.471
Treatment after delivery, n (%)						
LDA	1 (20.0)	89 (67.4)	0.087	2 (33.3)	33 (80.5)	<b>0.049</b>
LMWH	4 (20.0)	104 (78.8)	0.136	3 (50.0)	19 (46.3)	1.000
LDA+LMWH	1 (20.0)	74 (56.1)	0.257	2 (33.3)	12 (29.3)	1.000
HCQ	3 (60.0)	104 (78.8)	0.655	2 (33.3)	34 (82.9)	<b>0.030</b>
Azathioprine	0 (0)	0 (0)	–	1 (16.7)	0 (0)	0.128
Mycophenolate mofetil	0 (0)	1 (0.8)	1.000	0 (0)	8 (19.5)	0.544
Cyclosporin A	1 (20)	2 (1.5)	0.106	2 (33.3)	9 (22.0)	0.921
Tacrolimus	0 (0)	1 (0.8)	1.000	0 (0)	1 (2.4)	1.000
Cyclophosphamide	0 (0)	1 (0.8)	1.000	0 (0)	2 (4.9)	1.000
Statins	0 (0)	5 (3.8)	1.000	0 (0)	0 (0)	–
Follow-up						
Arterial thrombosis, n (%)	2 (20.0)	–	–	4 (66.7)	–	–
Venous thrombosis, n (%)	3 (60.0)	–	–	2 (33.3)	–	–

Bold entries indicate statistically significant differences between the two groups.

aCL, anticardiolipin antibodies; aPLs, antiphospholipid antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies; BMI, body mass index; FGR, fetal growth restriction; HCQ, hydroxychloroquine; LA, lupus anticoagulant; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; PAPS, primary antiphospholipid syndrome; SLE-APS, SLE-related antiphospholipid syndrome.



**Figure 3** Kaplan-Meier survival analysis. Cumulative incidence of thrombosis in patients with OAPS (A). Cumulative incidence of thrombosis in the LA-negative and LA-positive groups (B). Cumulative incidence of thrombosis in the triple-positive aPL and non-triple-positive aPL patients in the entire cohort (C), PAPS group (D) and SLE-APS group (E). aPLs, antiphospholipid antibodies; LA, lupus anticoagulant; OAPS, obstetric antiphospholipid syndrome; PAPS, primary antiphospholipid syndrome; SLE-APS, SLE-related antiphospholipid syndrome.

hypocomplementemia (OR=25.738, 95% CI=1.725 to 383.955,  $p=0.018$ ) were defined as independent risk factors for the first thrombosis in PAPS. However, this association was not observed in patients with SLE-APS (table 2). No significant thrombotic risk factors were identified in subgroups after adjustment for LDA and HCQ (table 2).

### Survival analysis

Kaplan-Meier survival analysis demonstrated a 15-year cumulative thrombosis rate of 6.7% in patients with OAPS, with a significantly higher cumulative incidence of first thrombosis in patients positive for LA compared with those negative for LA (58.2% vs 2.3%,  $p<0.001$ ) (figure 3A,B). In the study cohort, the 15-year cumulative thrombosis rate was significantly higher in triple-positive aPLs patients with OAPS compared with non-triple-positive individuals (16.2% vs 2.1%,  $p=0.014$ ) (figure 3C). However, this trend was no longer significant in patients with PAPS (7.7% vs 2.6%,  $p=0.065$ ) and those with SLE-APS (18.4% vs 0%,  $p=0.139$ ) (figure 3D,E).

### DISCUSSION

The 15-year cumulative thrombosis rate among patients with OAPS in this study was 6.7%. We found that

triple-positive aPLs and hypocomplementemia were risk factors for the first thrombosis in OAPS.

Consistent with previous studies,<sup>11 26-28</sup> our findings revealed higher rates of LA positivity and triple-positive aPLs in patients with OAPS with thrombosis. Furthermore, the cumulative thrombosis rates were higher in LA-positive patients over time. The RATIO Study also demonstrated a significant association between LA positivity and an elevated risk of thrombosis.<sup>29</sup>

The utility of GAPSS in predicting thrombosis in patients with APS has been demonstrated in prior studies and validated in the APS ACTION Study.<sup>4 30 31</sup> Although aGAPSS is a simplified version of GAPSS, it does not include anti-phosphatidylserine/prothrombin complex. This makes testing more convenient, and in recent years, aGAPSS has also been reported for its role in thrombosis prediction.<sup>32 33</sup> Similarly, our study observed a relatively higher aGAPSS in patients with OAPS with thrombosis compared with those without. However, this effect was attenuated when adjusted for relevant confounding factors.

Our results suggest that hypocomplementemia might be a biomarker of thrombotic risk in APS. Complement activation-induced thromboinflammation plays an important role in thrombosis.<sup>34</sup> Recent research has

shown an association between complement activation induced by aPLs and thrombotic events.<sup>35</sup> Nevertheless, further investigation is needed to elucidate the role of the complement system in thrombosis among patients with OAPS.

Maternal hypercoagulability can persist until approximately 12 weeks after delivery. To mitigate the risk of postpartum thrombotic events in patients with OAPS, it is recommended continuing prophylactic doses of heparin for 6 weeks.<sup>36–37</sup> However, strategies for primary thromboprophylaxis against long-term thrombosis in patients with isolated OAPS remain uncertain. A previous study demonstrated that the combination of LDA and low-molecular-weight heparin reduces the risk of maternal thrombosis in OAPS.<sup>38</sup> A meta-analysis indicated that LDA is associated with a lower risk of thrombosis.<sup>17</sup> The benefits of LDA in thrombosis prevention in patients with OAPS have not been fully confirmed, yet, it is essential to take into account traditional cardiovascular risk factors and other clinical factors for individualised interventions in patients.

The beneficial effects of HCQ in OAPS have been primarily reported in relation to the prevention of obstetric complications,<sup>39–40</sup> with limited evidence regarding its role in postpartum thromboprophylaxis in OAPS. HCQ can disrupt aPL IgG- $\beta$ 2GPI complexes, diminishing the affinity of both individual proteins and complexes to phospholipid bilayers.<sup>41</sup> Additionally, HCQ has the capacity to safeguard the anticoagulant shield of annexin A5 against disruption by aPLs on phospholipid bilayers, on the apical membranes of cultured human umbilical vein endothelial cells and syncytialised trophoblast cells, or in samples of plasma of patients with APS.<sup>42</sup> This action effectively reverses the thrombogenic properties of aPLs. Our study revealed a lower thrombosis rate among patients with OAPS using HCQ, likely due to its inhibition of inflammatory cytokines, platelet aggregation and adhesion.<sup>42–43</sup>

Our study has certain limitations. It is important to note that this was not a multicentre study, which may limit the generalisability of our findings to diverse populations. However, the utilisation of the same medical centre and a single laboratory ensured a controlled quality of research.

## CONCLUSION

In conclusion, our study highlights that triple-positive aPLs and hypocomplementemia are risk factors for the first thrombosis in OAPS.

**Acknowledgements** We are thankful to all the participants for their generous contributions to this study.

**Contributors** LL and QC performed the data collection and wrote the manuscript. CL conceived the study and made substantial contributions to the interpretation of data for the work, revising it critically for important intellectual content. XL and YH contributed to statistical analysis. All authors read and approved the final manuscript. CL is responsible for the overall content as the guarantor.

**Funding** This work was supported by the Natural Science Foundation of China (32141004), Peking University Clinical Scientist Training Program

(BMU2023PYJH010), Beijing Natural Science Foundation (no. 7192211) and the People's Hospital of Yubei District of Chongqing City Clinical Research Project (ybyk2023-06).

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study involves human participants and was approved by the Ethics Committee of Peking University People's Hospital (2019PHB252). Informed consent was obtained from all participants.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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