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ORIGINAL ARTICLE

The efficacy and safety of antithrombotic therapy in patients with positive antiphospholipid antibodies receiving invasive procedures: experience from a single tertiary center

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Abstract

Objectives To evaluate the efficacy and safety of antithrombotic prophylaxis and to explore potential risk factors for thrombotic/bleeding events in patients with positive antiphospholipid (aPL) antibodies receiving invasive procedures.

Method All aPL-positive patients who underwent invasive procedures in Peking Union Medical College Hospital, from January 2002 to April 2018, were retrospectively enrolled. Demographic features, clinical features, antiphospholipid antibody profiles, types of invasive procedures, and antithrombotic management, as well as complications and outcomes, were systematically reviewed and recorded.

Results A total of 111 aPL-positive patients with 130 invasive procedures were enrolled. One hundred nine (83.8%) cases were on regular antithrombotic therapy which started at least 1 month prior to the invasive procedures, with 58 (44.6%) receiving anticoagulation therapy, 27 (20.8%) receiving antiplatelet therapy, and 24 (18.5%) receiving both. During the periprocedural period, the median time free of antithrombotic therapy was 2.5 days (interquartile range 1.5–6.0 days). Two (1.5%) periprocedural thrombotic events and 18 (13.8%) bleeding events were identified. Large open/laparoscopic surgeries of the thorax and abdomen were associated with a higher risk of bleeding (OR 3.46, 95% CI 1.24–9.67, $p = 0.014$). All bleeding events were manageable and not life-threatening.

Conclusions Aggressive antithrombotic therapy was associated with fewer thrombotic events in aPL-positive patients receiving invasive procedures, but might contribute to an increased bleeding rate, especially in large open surgeries. This study justifies more caution in prophylactic antithrombotic therapy in periprocedural aPL-positive patients.

Keywords Antiphospholipid antibodies · Antithrombotic therapy · Bleeding · Invasive procedure

Introduction

Antiphospholipid syndrome (APS) is the most common cause of acquired thrombophilia, characterized by vascular thrombosis and/or obstetrical morbidity in patients with seropositive antiphospholipid antibodies (aPL), including lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and/or anti-β_2-glycoprotein-I antibodies (aβ_2-GPI). Erkan et al. reported that 6–18% of APS patients had undergone an invasive procedure at the time of their thrombotic events [1, 2]. An invasive procedure is also a trigger factor for new thrombosis, or even catastrophic APS (CAPS). Approximately 13% of CAPS episodes are preceded by trauma and invasive procedures [3]. Periprocedural management of aPL-positive patients is challenging, and no consensus or guideline is available so far. And perioperative antithrombotic therapy for aPL-positive patients

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relied mainly on physician's experience due to a lack of specific guidance. Both thrombosis and bleeding risks are of clinical concern and are carefully monitored by surgeons and rheumatologists throughout the treatment process, from preoperative preparation to postoperative recovery. Risks for thromboembolism and bleeding should be individually assessed, and antithrombotic treatment should be carefully titrated. Periprocedural thromboses can be attributed to withdrawal of antithrombotic agents, increased hypercoagulability (postoperative immobility, activation of the coagulation system upon procedure, and other concurrent thrombosis risk factors such as hyperlipidemia), and catastrophic exacerbation of APS upon stimulus from a "second hit" [4]. On the other hand, severe periprocedural bleeding can occur due to excessive and untimely anticoagulation, thrombocytopenia that presents in 20–40% of APS patients [3, 5], and associated coagulation factor deficiencies such as LA-hypoprothrombinemia syndrome (LA-HPS) and consumption of coagulation factors during/after procedures [6].

Here, we summarize a single-center experience in a retrospective cohort study of periprocedural antithrombotic therapy in aPL-positive patients, aiming to provide guidance for optimizing periprocedural antithrombosis scheme. To the best of our knowledge, this is the largest cohort of its kind in regard to this topic.

Materials and methods

Patients

We included 111 consecutive in-patients undergoing a total of 130 invasive procedures at Peking Union Medical College (PUMC) Hospital, the tertiary referral center in China, from January 2002 to April 2018. The study was approved by the institutional ethical review board (approval number: S-K482). As the study was based on review of existing medical records, patients' written informed consent was waived. We reviewed the medical records and collected relevant data. All patients had positive LA, aCL, and/or aβ_2-GPI. All patients had a history of vascular thrombosis and/or obstetrical morbidity. Patients with malignancies were excluded.

Classification of invasive procedures

Patients were regarded as having a very high risk for thromboembolism during the periprocedural period [7]. Invasive procedures were classified according to bleeding risk [8–10]. We classified procedures into six categories in this study: (1) large open/laparoscopic surgeries, including cardiac surgeries (coronary artery bypass, heart valve replacement), thoracic surgeries, abdominal surgeries, cesarean section, and large vascular surgeries; (2) otolaryngologic, oral, and maxillofacial surgeries; (3) large orthopedic surgeries such as hip replacement; (4) biopsies of hypervascular organs, such as kidney and liver; (5) surgeries of superficial tissues, including skin, lymph node, breast, thyroid, eye, hand, and foot; (6) other low-bleeding-risk procedures, including endoscopy with biopsy, dilatation and curettage, cervical conization, and vascular intervention. Categories 1 to 4 were regarded as high-bleeding-risk procedures, and categories 5 and 6 were regarded as low-bleeding-risk procedures [8–10].

Periprocedural management and outcomes

A multidisciplinary team discussion had been held before the invasive procedure in most cases, especially for high-risk surgeries. The multidisciplinary team typically included at least the operator who performed the procedure, a rheumatologist, a hematologist, and an anesthetist. We collected the details of the periprocedural antithrombotic therapy, including the type of agents used and the timing of their use. The periprocedural time frame was defined as from 1 week prior to the procedure to 1 week after the procedure. A thrombotic event was defined as clinical evidence corroborated by imaging proof (Doppler ultrasound or computed tomography). A bleeding event was defined as clinically overt bleeding, or insidious bleeding associated with a decrease of ≥ 2 g/dL in hemoglobin or requiring transfusion of ≥ 2 units red blood cells, or bleeding requiring cessation of antithrombotic treatment [11].

Antiphospholipid antibody detection

The method to detect LA was concurrent with published guidelines [12], namely, using the dilute Russell's viper venom time (dRVVT) test. The LA was considered positive if the ratio of dRVVT screening time/dRVVT confirming time > 1.20. The aCL and aβ_2-GPI were determined by enzyme-linked immunosorbent assay (ELISA) [5] using commercially available kits (Euroimmun, Luebeck, Germany). Cutoff points for medium titer of positivity of aCL and aβ_2-GPI were 40 PL-U/mL and 40 RU/mL, respectively. Positivity of LA, aCL, or aβ_2-GPI was confirmed on two or more occasions, at least 12 weeks apart. Because the ELISA kits used in our institute during the time period of this study did not give separate readout of IgG and IgM of aCL or aβ2-GPI, strictly speaking, some of these patients could not fulfill the 2006 APS classification criteria [5].

Statistics

Categorical variables were reported as the proportion and/or percentage. Continuous variables were stated as the mean (± standard deviation) or median (interquartile range, IQR) values. The chi-square test or Fisher's exact test for categorical variables and Student's *t* test or the Mann-Whitney *U* test for

continuous variables were applied, as appropriate. Significance was assigned for two-tailed p values ≤ 0.05, and when significant, the odds ratio (OR) with 95% confidence interval (CI) was indicated. All data were analyzed using SPSS 20.0 software (SPSS, Chicago, IL, USA).

Results

Demographic and clinical data

One hundred eleven aPL-positive patients with 130 procedures were enrolled in this study; 80 of the patients were female (72.1%), and 35 (43.8%) of them had history of pregnancy morbidities. The mean age was 36.6 ± 13.0 years at the time of the procedure. Seventy-two secondary aPL-positive patients had a history of autoimmune or infectious diseases. Among them, 53 cases were associated with systemic lupus erythematosus (SLE). The median duration of disease was 12 (range 1–300, IQR 2–48) months. Fifty-four (48.6%) patients had a history of venous thrombosis, 26 (23.4%) had a history of pulmonary embolism, and 19 (17.1%) had a history of arterial thrombosis. Thirty-five (43.8%) females had at least one episode of obstetrical morbidity, among whom 20 females experienced no thrombotic events other than obstetrical morbidities. The median time duration from last thrombotic event or obstetrical morbidity was 8 months (IQR 2–40). Demographic and clinical characteristics are summarized in Table 1.

Periprocedural antithrombotic therapy

In 109 (83.8%) of the 130 invasive procedure events, patients received antithrombotic therapy before the procedures. Among them, 58 (44.6%) cases were treated with anticoagulants, 27 (20.8%) with antiplatelet agents, and 24 (18.5%) with both.

Of 82 cases in which patients received periprocedural anticoagulation, warfarin was used in 33 (40.2%) cases (in 23 of these cases, the transition from warfarin to low molecular weight heparin (LMWH) was used for bridging therapy 3–7 days before the procedure), LMWH in 49 (59.8%) cases, unfractionated heparin (UFH) in three (3.7%) cases, and rivaroxaban in one (1.2%) case. Among 49 cases in which patients received LMWH (including bridging therapy), 37 had a full anticoagulation dose (enoxaparin 1 mg/kg twice daily subcutaneously or equivalent) and 12 received prophylactic doses (enoxaparin 1 mg/kg once daily subcutaneously or equivalent). The median time of anticoagulation suspension before the procedure was 12 h (IQR 12–24 h), and the median time for resumption of anticoagulation therapy after the procedure was 24 h (IQR 12–48 h). Of 51 cases in which patients received periprocedural antiplatelet therapy, aspirin was used in 48 cases, and dual antiplatelet therapy (aspirin plus clopidogrel or ticagrelor for coronary angiography) was used in three cases. The median time that antiplatelet therapy was suspended before the procedure was 7 days (IQR 1–7 days), and the median time for resumption of antiplatelet therapy after the procedure was 5 days (IQR 1–7 days). During the periprocedural period, the median time free of antithrombotic therapy was 2.5 days (IQR 1.5–6.0 days).

Table 1 Patient demographic and clinical characteristics

Characteristics	Total ($N = 111$)
Female, *n* (%)	80 (72.1)
Age at procedure (years), mean ± SD	36.6 ± 13.0
Positive aPL without an identifiable cause, *n* (%)	39 (35.1)
Associated conditions, *n* (%)	
SLE	53 (47.7)
Rheumatoid arthritis	2 (1.8)
Sjögren's syndrome	3 (2.7)
ANCA-associated vasculitis	4 (3.6)
Undifferentiated connective tissue disease	9 (8.1)
Tuberculosis	1 (0.9)
CAPS, *n* (%)	2 (1.8)
Clinical manifestations	
Venous thrombosis, *n* (%)	54 (48.6)
Arterial thrombosis, *n* (%)	19 (17.1)
Obstetrical morbidity, *n*/*N* (%)	35/80 (43.8)
Thrombocytopenia (< 100,000 platelets/μL), *n* (%)	53 (47.7)
Antiphospholipid antibodies, *n* (%)	
Single positive	50 (45.0)
aCL	12 (10.8)
$a\beta_2$-GPI	5 (4.5)
LA	33 (29.7)
Double positive	28 (25.2)
Triple positive	33 (29.7)
aCL value (PL-U/mL), mean ± SD	98.6 ± 31.1
$a\beta_2$-GPI value (RU/mL), mean ± SD	152.2 ± 58.4
LA ratio, mean ± SD	2.06 ± 0.54
BMI > 28 kg/m^2, *n* (%)	6 (5.4)
Smoking history, *n* (%)	14 (12.6)
Hypertension, *n* (%)	21 (18.9)
Diabetes mellitus, *n* (%)	6 (5.4)
Hyperlipidemia, *n* (%)	25 (22.5)
Bleeding history, *n* (%)	12 (10.8)
Steroid use, *n* (%)	66 (59.5)
Hydroxychloroquine, *n* (%)	47 (42.3)
Anticoagulant, *n* (%)	71 (64.0)
Antiplatelet agent, *n* (%)	41 (36.9)

$a\beta_2$-GPI anti-β_2-glycoprotein-I antibodies, *aCL* anticardiolipin antibodies, *ANCA* anti-neutrophil cytoplasmic antibodies, *BMI* body mass index, *CAPS* catastrophic antiphospholipid syndrome, *LA* lupus anticoagulant, *SD* standard deviation, *SLE* systemic lupus erythematosus

There were 19 pregnancy-associated invasive procedures (16 cases of cesarean section and 3 cases of curettage after intrauterine fetal death) in 17 females in this cohort. During 11 pregnancies (10 gave live birth), patients received both low-dose oral aspirin and subcutaneous LMWH to decrease the risk of adverse pregnancy outcomes. Aspirin was used alone in another two pregnancies (both gave live birth), and LMWH was used alone in another three pregnancies (none gave live birth). No antithrombotic agent had been given in the other three pregnancies (none gave live birth). The overall live birth rate in patients receiving antithrombotic therapy during pregnancies was 75% (12/16).

Among the other 21 cases that did not receive periprocedural antithrombotic agents, one patient was diagnosed with APS only after the procedure, and the other 20 cases did not have a history of thrombosis other than obstetrical morbidities. Ten of them used graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC) for thromboprophylaxis.

Categories of procedures and periprocedural adverse events

Of the 130 procedures (Table 2), 46 belonged to category 1, including 17 abdominal surgeries, 16 cesarean sections, 7 cardiac surgeries, 5 vascular surgeries, and 1 thoracic surgery; and 9 were emergency procedures, including 5 cases of emergency open partial enterectomy due to acute thrombotic mesenteric ischemia, 3 cases of emergency cesarean section, and 1 case of emergency vascular intervention due to acute arterial thrombosis of the lower extremity.

We identified two (1.5%) periprocedural thrombotic events in total. Both patients developed a pulmonary embolism after the procedure. In case 1, a 64-year-old female had been found to have thrombosis in the upper mesenteric vein. Warfarin was prescribed and was suspended 21 days before the open partial enterectomy because of gastrointestinal bleeding. Although the patient started LMWH 24 h after surgery, she still developed a pulmonary embolism on the third day after surgery. In case 2, a 40-year-old female had bronchoscopy with transbronchial lung biopsy because of interstitial lung disease. She had no history of thrombosis and received no antithrombotic therapy before the procedure. She had a pulmonary embolism 7 days after the procedure and was subsequently diagnosed with APS.

Bleeding events occurred in 18 (13.8%) cases and were treated with blood transfusion and/or cessation of antithrombotic agents. All bleeding events were controllable, and no patient died of hemorrhage. Most (16/19, 84.2%) of the bleeding events occurred during or right after the procedure. Two bleeding events presenting as hematoma were discovered on the day 3 after renal biopsy. Another bleeding event occurred on day 6 after the procedure when the patient had resumed the use of LMWH since day 5. All cases of bleeding occurred at the surgical site.

Risk factors for periprocedural bleeding events

Among different categories of procedures, category 1 (large open/laparoscopic surgeries) had the highest risk (OR 3.46, 95% CI 1.24–9.67, $p = 0.014$). Among the 71 cases with high-bleeding-risk procedures of categories 1, 2, 3, and 4, patients with smoking history were more likely to have bleeding complications (OR 8.83, 95% CI 1.45~53.94, $p = 0.028$).

Moreover, emergency surgery had a higher rate of bleeding events than nonemergency procedures (33.3% vs. 12.4%), although the difference was not statistically significant ($p = 0.210$). This high risk was mainly due to the type of procedure, as 8 of the 9 emergency procedures belonged to category 1,

Table 2 Categories and periprocedural events of procedures

	Categories	*N* (%)	Antithrombotic agent[a] use, *n*/*N* (%)	Thrombotic events, *n*/*N* (%)	Bleeding events, *n*/*N* (%)	Bleeding risk OR (95% CI, *p* value)
1	Large open/laparoscopic surgeries	46 (35.4)	40/46 (87.0)	1/46 (2.2)	11/46 (23.9)	3.46 (1.24–9.67, 0.014)
2	Otolaryngologic, oral, and maxillofacial surgeries	4 (3.1)	4/4 (100)	0/4 (0.0)	0/4 (0.0)	0.65 (0.03–12.61, 1.000)
3	Large orthopedic surgeries	5 (3.8)	5/5 (100)	0/5 (0.0)	2/5 (40.0)	4.54 (0.70–29.31, 0.141)
4	Biopsies of hypervascular organs[b]	16 (12.3)	9/16 (56.3)	0/16 (0.0)	3/16 (18.8)	1.52 (0.39–5.98, 0.826)
5	Surgeries of superficial tissues[c]	24 (18.5)	19/24 (79.2)	0/24 (0.0)	1/24 (4.2)	0.23 (0.03–1.80, 0.233)
6	Other low-bleeding-risk procedures[d]	35 (26.9)	32/35 (91.4)	1/35 (2.9)	1/35 (2.9)	0.14 (0.02–1.06, 0.055)
	Total	130 (100.0)	109/130 (83.8)	2/130 (1.5)	18/130 (13.8)	

CI confidence interval, *OR* odds ratio

[a] Including use of anticoagulant, antiplatelet agent, or both

[b] Including kidney and liver

[c] Including skin, lymph node, breast, thyroid, eye, hand, and foot

[d] Including endoscopy with biopsy, dilatation and curettage, cervical conization, and vascular intervention

i.e., had a high bleeding risk. In addition, more patients were complicated with severe thrombocytopenia ($\leq 50 \times 10^9$/L) in the emergency than in the nonemergency group (3/11 vs. 6/119, $p = 0.029$). There was no significant difference in the rate or timing of antithrombotic agent administration.

Two bleeding events occurred after low-risk procedures. One was due to continuation of LMWH in the perioperative period of skin grafting, and bleeding stopped after the cessation of LMWH. The other was a LA-HPS case, in which the patient was prone to bleeding even though she did not receive any antithrombotic therapy.

There were no significant differences in sex, age, aPL profile (single, double, or triple positive), types or timing of antithrombotic therapy, or preprocedural platelet (PLT) counts between patients with and without bleeding events (Table 3). However, patients with bleeding events did have lower platelet counts after the procedure than patients without bleeding events (107×10^9/L vs. 132×10^9/L, $p = 0.023$). No differences in the levels of international normalized ratio (INR), activated partial thromboplastin time (APTT), or fibrinogen were found.

Primary versus secondary aPL-positive cases

There were 39 primary and 72 secondary aPL-positive patients in this cohort. We did not observe significant differences in sex, age, aPL positivity, rate of hydroxychloroquine use, or categories of procedures between the two groups. The rate of steroid use was higher in the secondary aPL-positive group (30.8% vs. 75.0%, $p < 0.001$), which was justified in treating primary diseases. For 12 primary aPL-positive patients, oral steroid (equivalent to prednisone 5–30 mg daily) was used to treat concurrent thrombocytopenia, glomerular nephritis, interstitial lung disease, CAPS, or to prevent spontaneous abortion during pregnancy. There was no significant difference in the rate of antithrombotic agents use (anticoagulant or antiplatelet agents). And there were no significant differences in the timing of antithrombotic therapy or preprocedural platelet counts.

Discussion

Stasis, vascular intimal injury, and hypercoagulability are the three major factors that contribute to the development of thromboembolic events, and aPL-positive patients receiving invasive procedures present all of these factors. aPL-positive patients are predisposed to both thromboembolism and bleeding, and they are at additional risk during the periprocedural period, which causes dilemma in clinical practice when invasive procedures in these patients are imperative. Serious complications (including recurrent thrombosis, catastrophic exacerbation of APS, and bleeding) can occur despite prophylaxis. Though there are published recommendations on perioperative management of aPL-positive patients [13], there is yet insufficient evidence to support it. Here, we describe our experience of this clinical scenario. It should be noted that, although the patients included in our study could not be classified to APS based on the relevant criteria because of the limitation of laboratory technique, they were diagnosed and managed as APS by the clinicians in our institute. Apart from being aPL-positive, all patients had a history of vascular thrombosis and/or obstetrical morbidity. Consistent with previous reports, most of the patients in our study were female of reproductive age. To the best of our knowledge, this report was the largest cohort in which this topic has been investigated. Thus, these data may help physicians in their periprocedural evaluation and management of aPL-positive patients.

As aPL-positive patients with a history of thrombosis were at a high risk of developing new thrombosis at discontinuation of anticoagulation, a careful bridging therapy should be considered before the invasive procedure, and the time interval of antithrombotic cessation should be reduced to a minimum. Patients diagnosed as APS because of pregnancy morbidities and without previous history of vascular thrombosis usually were not prescribed regular pharmacological antithrombotic therapy and most of this kind of patients in our cohort underwent only mechanical prophylaxis, including GCS and IPC. These physical methods prevent venous stasis, increase venous return, and increase tissue factor pathway inhibitor [13], and they are also recommended for patients at a high risk of bleeding as a safe non-pharmaceutical strategy to prevent thrombosis [14].

With all the abovementioned measures, only two periprocedural thrombotic events (1.5%) occurred in this cohort, a rate that was lower than that reported in literature (6.0~8.9%) [15, 16]. Neither of the two patients received adequate antithrombotic therapy at the periprocedural period. One was due to gastrointestinal bleeding, and the other had not been diagnosed with APS before the procedure. During the periprocedural period, the median time without antithrombotic therapy in our cohort was 2.5 days (IQR 1.5–6.0 days). Intriguingly, 47 patients (42.3%) received hydroxychloroquine, including some primary aPL-positive patients. Hydroxychloroquine is a regimen widely used for primary thrombosis prophylaxis in SLE patients complicated with APS [17]. In addition to its anti-inflammatory effects, hydroxychloroquine exerts an antithrombotic effect by inhibiting platelet aggregation and arachidonic acid release from stimulated platelets [18]. Due to the limited number of thrombotic events, we were unable to evaluate the association of aCL positivity (single, double, or triple positive) or the use of hydroxychloroquine with the risk of thrombosis.

Very few thrombotic events occurred in our cohort, probably due to the aggressive antithrombotic therapy in our medical center, which justifies the necessity of antithrombotic treatment in aPL-positive patients undergoing invasive procedures, but a relatively high rate of bleeding events in this

Table 3 Comparison of cases with bleeding events and cases without bleeding events

Characteristics	With bleeding events ($N = 18$)	Without bleeding events ($N = 112$)	p value
Women, *n* (%)	12 (66.7)	85 (75.9)	0.587
Age at procedure (years), mean ± SD	40.1 ± 12.7	35.5 ± 12.5	0.155
Disease duration, median (IQR)	22 (2–54)	24 (2–53)	0.723
SLE, *n* (%)	7 (38.9)	58 (51.8)	0.310
Catastrophic APS, *n* (%)	0 (0.0)	2 (1.8)	1.000
Smoking history, *n* (%)	4 (22.2)	12 (10.7)	0.321
Bleeding history, *n* (%)	3 (16.7)	9 (8.0)	0.462
History of thrombocytopenia, *n* (%)	6 (33.3)	57 (50.9)	0.166
Steroid use, *n* (%)	11 (61.1)	67 (59.8)	0.917
Hydroxychloroquine use, *n* (%)	6 (33.3)	53 (47.3)	0.267
Antithrombotic agent use, *n* (%)	13 (72.2)	96 (85.7)	0.272
Anticoagulant use, *n* (%)	9 (50.0)	49 (43.8)	0.621
Antiplatelet agent use, *n* (%)	2 (11.1)	25 (22.4)	0.438
Anticoagulant and antiplatelet agent use, *n* (%)	2 (11.1)	22 (19.6)	0.590
Multidisciplinary team discussion, *n* (%)	3 (16.7)	24 (21.4)	0.881
Time of suspension of anticoagulation before procedure (days), median (IQR)	0.5 (0.5–1.0)	0.5 (0.5–1.0)	0.134
Time for resumption of anticoagulation after procedure (days), median (IQR)	1.0 (0.6–2.8)	1.0 (0.5–1.8)	0.506
Time of suspension of antiplatelet before procedure (days), median (IQR)	4.0 (0.5–7.0)	7.0 (1.0–7.0)	0.511
Time for resumption of antiplatelet after procedure (days), median (IQR)	5.5 (0.8–14.0)	5.0 (1.0–7.0)	0.521
Time without antithrombotic therapy (days), median (IQR)	2.0 (1.4–4.8)	2.5 (1.5–6.0)	0.745
PLT before procedure ($\times 10^9$/L), median (IQR)	138 (72–203)	158 (106–230)	0.211
PLT after procedure ($\times 10^9$/L), median (IQR)	107 (69–120)	132 (95–227)	*0.023**
INR before procedure, mean ± SD	1.24 ± 0.52	1.07 ± 0.23	0.233
INR after procedure, mean ± SD	1.16 ± 0.24	1.07 ± 0.12	0.214
APTT before procedure (s), mean ± SD	37.2 ± 14.6	37.1 ± 16.6	0.981
APTT after procedure (s), mean ± SD	31.8 ± 7.4	37.4 ± 13.4	0.131
Fibrinogen before procedure (g/L), mean ± SD	2.73 ± 0.73	3.35 ± 1.34	0.131
Fibrinogen after procedure (g/L), mean ± SD	2.85 ± 1.17	3.57 ± 2.71	0.392

Reference ranges: PLT, 100–350 × 10^9 /L; INR, 0.86–1.14; APTT, 22.7–31.8 s; fibrinogen, 1.80–3.50 g/L

APS antiphospholipid syndrome, *APTT* activated partial thromboplastin time, *INR* international normalized ratio, *IQR* interquartile range, *SD* standard deviation, *SLE* systemic lupus erythematosus, * $p < 0.05$

group of patients also implicated to explore the potential predictors for bleeding and fine-tune the periprocedural management. The rate of bleeding events was 13.8% in our cohort, similar to the 12% reported in a previous study [15]. Not surprisingly, large open or laparoscopic surgeries were more likely to have bleeding complications. Major orthopedic surgeries and biopsies of hypervascular organs such as the kidney and liver also were subjected to a high risk of bleeding. Moreover, emergent procedures carried a higher risk of complications than elective well-prepared procedures, although the difference was not statistically significant in our cohort. Elective procedures may benefit from well-controlled disease status, sufficient discussion on periprocedural antithrombotic therapy regimen, and enough time for bridging therapy from warfarin to heparin, thus have a lower risk of thromboembolism or hemorrhage, especially for patients with thrombocytopenia and/or autoimmune diseases like SLE. When severe thrombocytopenia is present in the setting of emergency surgery, the first-line therapeutic options include high-dose corticosteroids and/or intravenous immunoglobulin [13]. These strategies were used in some patients in our cohort and proved to be effective. Elective procedures allowed sufficient time for bridging therapy from warfarin to heparin. In the general population, low-dose vitamin K is often administered for patients who are taking warfarin and require emergency surgery [10]. Fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), or activated recombinant factor VII can be used as well. However, in aPL-positive patients receiving warfarin,

reversal of anticoagulation should be performed with caution, as overcorrection may increase the risk of thrombosis and make it difficult to rapidly achieve the therapeutic range for anticoagulation after surgery [13]. In our cohort, there were nine cases of emergent procedures, of which three received no antithrombotic therapy before the procedure, four received LMWH, one received UFH, and one received aspirin. Thus, we need to accumulate data of the reversal treatment with the vitamin K antagonist in cases of emergent procedures.

Thrombocytopenia can also increase the risk of bleeding. There was no significant difference in the platelet count before the procedure between patients with and without bleeding ($p = 0.211$). However, the median platelet count after the procedure for patients with bleeding was lower than in patients without bleeding ($p = 0.023$). The platelet count should be carefully monitored during the periprocedural period. If the platelet count is low, antithrombotic therapy should be cautiously resumed after the procedure. However, it should be noted that thrombocytopenia does not protect against thrombosis. Furthermore, platelet transfusion is not usually helpful in patients with aPL-positive, as the mechanism of thrombocytopenia is thought to be destructive and may even increase the risk of thrombosis [13].

We did not find significant differences in the time of suspension or resumption of antithrombotic agents between patients with and without bleeding. However, the median time of suspension of antiplatelet agents was shorter in the bleeding group (4.0 days vs. 7.0 days, $p = 0.511$). The recommended interval between the last dose of aspirin and the procedure is 7 to 10 days [8], unless aspirin is indispensable, such as in cases of coronary artery intervention. Our result supports this recommendation in aPL-positive patients.

In subgroup analysis of cases with high-bleeding-risk procedures, patients with smoking history were found to be more likely to have bleeding complications. Although this association was not found in the whole cohort, clinicians should be more cautious when managing this group of patients.

In women diagnosed with APS and with a history of recurrent spontaneous abortion, combination treatment with low-dose aspirin and LMWH is recommended to decrease the risk of adverse pregnancy outcomes [19]. Our cohort included 16 cases of cesarean section and 3 cases of curettage after intrauterine fetal death. Vaginal deliveries were not included in this study. When patients received both low-dose aspirin with or without LMWH, the live birth rate was 92.3% (12/13). When patients received LMWH alone or none of the antithrombotic agents, all six pregnancies ended up as still birth, justifying the necessity of antiplatelet therapy in such condition. There were no major bleeding complications.

There were some limitations in our study. The relatively small study population from a single medical center and the retrospective design compromised the level of evidence in our study. There may have been insidious minor thrombotic events in the periprocedural period that were not clinically overt and thus not recorded. However, the median follow-up period of patients in our cohort was 10 months (range 1 to 160 months). Thus, clinically significant periprocedural events were unlikely to be missed. Further prospective studies with a larger study population are needed to support our findings that may help physicians to identify patients with the highest risks of thrombosis and/or bleeding and thereby initiate an appropriate periprocedural management.

Conclusions

Aggressive antithrombotic therapy was associated with a lower rate of thrombosis in this cohort of aPL-positive patients undergoing invasive procedures, though it might also contribute to relatively high bleeding rate. Open or laparoscopic surgeries in the thoracic and abdominal areas and thrombocytopenia after procedure are associated with a higher risk of bleeding, suggesting a delicate modification of dosage and timing of resumed antithrombotic therapy in these patients. Bleeding risk stratification according to the types of procedures may help to make subtle adjustment.

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Compliance with ethical standards

The study was approved by the institutional ethical review board (approval number: S-K482). As the study was based on review of existing medical records, patients' written informed consent was waived.

Disclosures None.

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