



Identifying Additional Risk Factors for Thrombosis and Pregnancy Morbidities Among Antiphospholipid Antibodies Carriers

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Abstract

The evaluation of thrombotic and pregnancy risks associated with antiphospholipid antibodies (aPL) in individual patients without antiphospholipid syndrome (APS) clinical manifestation is challenging. Our aim is to identify additional risk factors or potential candidate “second hits” for APS clinical events in a large cohort of ethnically diverse aPL-positive patients. We included 219 consecutive aPL-positive patients who attended clinic at our institution. All patients had at least 1 persistent high titer (≥ 99 percentiles) aPL. Independent risk factors for thrombosis and pregnancy morbidities among patients with positive aPL were evaluated. When assessing risk factors associated with pregnancy morbidities, only female controls of reproductive age (age ≤ 45) were used. Pearson χ^2 analysis and multivariable logistic regression were used to evaluate correlation between different risk factors and clinical manifestations. Of the 219 aPL-positive patients, 120 (54.8%) patients had criteria APS clinical manifestations and 99 patients did not. A total of 46.1% were Caucasian, 26.4% of African descent, 16.9% Hispanic, 1.8% Asian, and 8.7% were unspecified. Among traditional risk factors and signs of endothelial injury, only hypertension demonstrated an independent association with arterial thrombosis (odds ratio [OR] = 3.826, 95% confidence interval [CI]: 1.597-9.167, $P = .0026$), and lupus anticoagulant (LA) demonstrated an independent association with venous thrombosis (OR = 3.308, 95% CI: 1.544-7.085, $P = .0021$). None of the evaluated risk factors demonstrated a significant association with pregnancy morbidity. Hypertension is a potential predictor of arterial thrombosis and the presence of LA is a potential predictor of venous thrombosis in aPL-positive patients.

Keywords

antiphospholipid syndrome, antiphospholipid antibodies, thrombosis risk, pregnancy risk, additional risk factors

Introduction

Antiphospholipid syndrome (APS) is an autoimmune prothrombotic condition with significant morbidity and mortality. Unlike most other causes of thrombophilia, it can involve both the venous and arterial circulations. The deep veins of the lower limbs and the cerebral arterial circulation are the most common sites of venous and arterial thrombosis, respectively. However, any tissue or organ vascular bed can be affected.¹ The other major category of clinical manifestations of APS is obstetrical. This includes unexplained death of 1 or more morphologically normal fetuses at or beyond the 10th week of gestation, premature birth of 1 or more morphologically normal neonates before the 34th week of gestation because of either eclampsia or severe preeclampsia, or 3 or more unexplained, consecutive spontaneous abortions before the 10th week of gestation.^{1,2}

Antiphospholipid antibodies (aPL) consist of a heterogeneous group of immunoglobulins detected by enzyme-linked

immunosorbent assay or lupus anticoagulant (LA) assay. There are criteria aPL which include IgG, IgM of anticardiolipin (aCL), IgG, IgM of anti- $\beta 2$ glycoprotein-I (anti- $\beta 2$ GPI), and LA. They are part of the current APS classification criteria and the most widely used tests in detecting aPL.³ There are also noncriteria aPL which include IgA to aCL and anti- $\beta 2$ GPI, antiprothrombin (aPT) antibodies, antiphosphatidylserine (anti-PhoS), anti-PhoS-prothrombin complex, and anti-domain I antibodies. They are not part of the current

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classification criteria, but their persistent presence is also linked to various APS clinical phenomena such as thrombosis and pregnancy complications.⁴

Current classification criteria for APS require a positive test for at least one of the criteria aPL (LA, aCL IgG, or IgM or anti- β 2GPI IgG or IgM) in the presence of a thromboembolic event or pregnancy morbidity.^{3,5} However, aPL are often detected in the absence of thrombotic or obstetric manifestations. Typically, these are found incidentally during an evaluation for suspected autoimmune disease or the workup of thrombophilia. Management of these individuals is unclear. Anticoagulation is unwarranted in an individual without thrombosis, and antithrombotic agents such as aspirin have not been found to be effective.⁶ Ideally, one would like to identify individuals who are at high risk of developing thrombosis so they can be targeted for early preventive interventions. Many predictive models have been developed and successfully utilized for other disorders.⁷⁻⁹ However, when it comes to aPL-positive patients, there are no widely accepted prediction tools. Furthermore, recent studies suggest that the presence of aPL does not always lead to adverse clinical outcomes.^{1,10,11} This suggests a possible “two-second hit” pathogenesis of APS. In this scenario, autoantibodies trigger initial endothelial dysfunction and one or more additional risk factors that potentially damage vascular integrity are needed to potentiate thrombus formation.¹ The additional risk factors remain debatable and the assessment of such risk factors is challenging due to rarity of this disease and low event rates in asymptomatic patients.¹² Data from currently published studies are limited by study design, exclusion of noncriteria antibodies, omission of adverse pregnancy outcomes, and limited ethnic diversity.¹²⁻¹⁵ One such study is the Global Anti-Phospholipid Syndrome Score (GAPSS) which is the first risk stratification study that included cardiovascular risk factors; however, it is conducted in a cross-sectional cohort of European patients with systemic lupus erythematosus (SLE).¹⁶ Its result needs to be reexamined prospectively in ethnically diverse patient population. A recent study has shown that there is ethnic thrombotic risk disparity and ethnicity needs to be considered when risk stratifying patients with lupus.¹⁷ Our objective is to identify additional risk factors or potential candidate “second hits” for APS clinical events in a large cohort of aPL-positive patients.

Materials and Methods

We identified 997 consecutive patients who were referred for the evaluation of positive aPL or treatment of APS at the UT Southwestern Medical Center from 2000 to 2012. Charts were reviewed by 2 investigators (Y.Z. and J.F.). The aPL and LA testing was repeated in all patients in the university clinical laboratory. If one of the aPL or LA was positive, then it was considered true-positive aPL. The shortest documented period between 2 testing points was 11 weeks. Patients who did not have at least 1 positive test (either criteria or noncriteria aPL) at \geq 99th percentile cutoff values were excluded (Figure 1).

The aPL testing was performed using FDA-approved commercial kits. Lupus anticoagulant was tested by dilute Russell viper venom time, partial thromboplastin time-LA, and silica clotting time, with appropriate cutoffs established in the laboratory. The aCL was considered positive if values were \geq 40 GPL, MPL, or APL and the 99th percentile cutoff values were established for anti- β 2GPI (IgG, IgM, and IgA), Anti-PhoS (IgG, IgM, and IgA), and aPT (IgG and IgM) using healthy controls (N = 110). Table 1 shows the local 99th percentile cutoff values for all the criteria and noncriteria aPL.

Antiphospholipid syndrome clinical manifestations were defined by the revised Sydney criteria.³ We classified outcomes into 3 categories: (1) arterial thrombosis of cerebral, renal, retinal, gastrointestinal, coronary, or peripheral arteries; (2) venous thrombosis of deep veins in upper or lower extremities or pulmonary, renal, retinal, or gastrointestinal veins; and (3) pregnancy morbidity. Clinical patients with APS were defined as having at least 1 persistent positive criteria or noncriteria aPL in the setting of a documented Sydney criteria-defined APS clinical manifestations.

Medical records were reviewed to obtain demographic data including age, sex, and smoking status. Clinical data obtained were APS clinical manifestations and traditional risk factors for and signs of endothelial injury including hypertension (HTN), hyperlipidemia, diabetes, Raynaud phenomenon, and livedo reticularis. Hypertension was classified based on the 8th Joint National Committee guideline. Hyperlipidemia was defined as fasting total cholesterol \geq 200 mg/dL. Raynaud phenomenon and livedo reticularis were assessed based on medical record documentation. Triple positive aPL patients were defined as having positive aCL, a β 2GPI, and LA.

Baseline characteristics of patients with APS and control patients were summarized using means and standard deviations (SDs) for continuous variables and frequencies and proportions for categorical variables. Comparisons between groups were performed using 2-sample Student *t* test or Fisher exact test. The association between clinical risk factors and APS clinical manifestations was examined using univariate and multivariable logistic regression. When assessing risk factors associated with pregnancy morbidities, only patients with pure obstetric manifestation (n = 18) and female controls of reproductive age (age \leq 45) were used (n = 29). All analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, North Carolina). The study was approved by the UT Southwestern institutional review board.

Results

Patient Demographic and Clinical Characteristics

Of 997 patients who were referred to our center for the evaluation of positive aPL or treatment of APS, 219 patients had at least 1 persistent positive criteria or noncriteria aPL at the 99th percentile cutoff. A total of 46.1% were Caucasian, 26.4% of African descent, 16.9% Hispanic, 1.8% Asian, and 8.7% were unspecified. Of the 219 patients with persistently positive aPL,

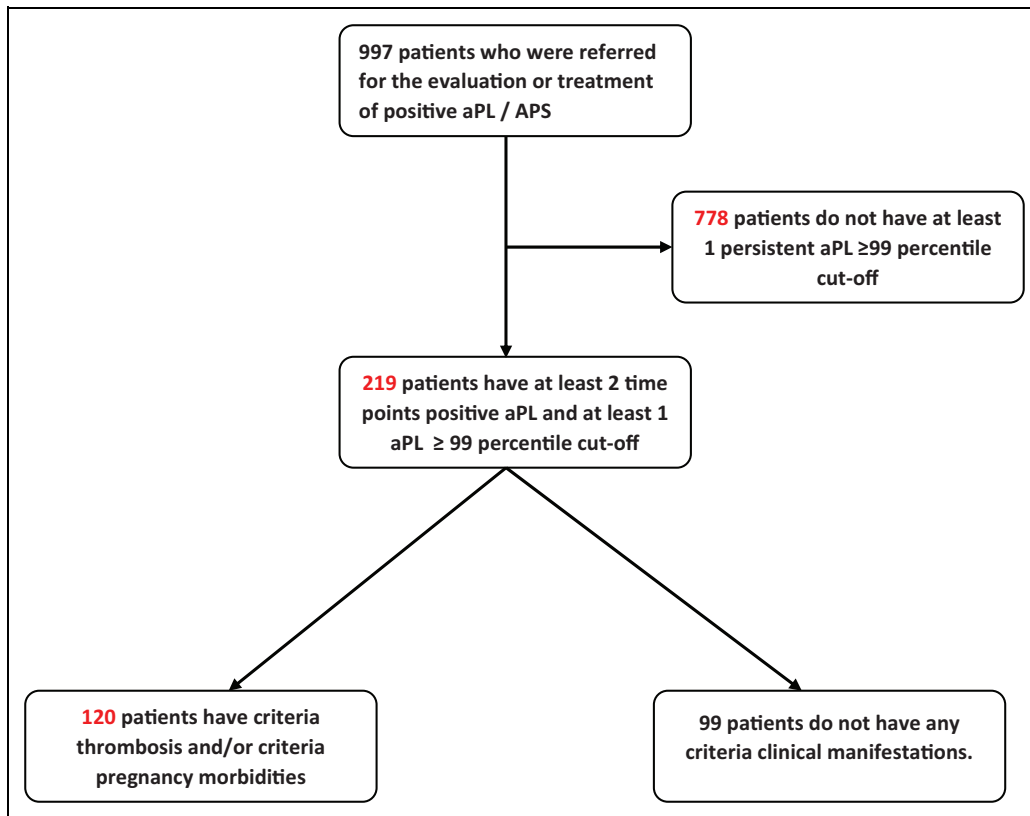


Figure 1. Flow diagram of study design.

Table 1. UT Southwestern Medical Center aPL 99th Percentile Cutoff Derived From 110 Healthy Control Samples.

Local 99th Percentile Antiphospholipid Antibodies Cutoff	
Anticardiolipin IgG	>40 GPL
Anticardiolipin IgM	>40 GPL
Anticardiolipin IgA	>40 GPL
Anti- β 2glycoprotein-I IgG	>16 GPS
Anti- β 2glycoprotein-I IgM	>14 GPS
Anti- β 2glycoprotein-I IgA	>17 GPS
Antiphosphatidylserine IgG	>9 GPS
Antiphosphatidylserine IgM	>13 MPS
Antiphosphatidylserine IgA	>8 APS
Antiprothrombin IgG	>7 GPS
Antiprothrombin IgM	>15 GPS

Abbreviation: APS, antiphospholipid syndrome.

120 patients had APS-related clinical manifestations and were classified as having clinical APS. The mean age for clinical patients with APS was 52 (SD: ± 14.1). Ninety-one (75.8%) patients did not have an underlying autoimmune disease. Twenty-nine (24.2%) patients had an underlying systemic autoimmune disease. Among those patients, the associated underlying autoimmune diseases included SLE, rheumatoid arthritis, systemic sclerosis, undifferentiated connective tissue disease, systemic vasculitis, ankylosing spondylitis, and Sjögren syndrome. Thirty-eight (31.7%) patients had experienced arterial thrombosis and 72 (60%) patients had venous thrombosis.

Thirty-six (30%) of those had recurrent thrombosis. Twenty-two patients had classifiable criteria pregnancy morbidities. Eighteen (15%) had pure obstetric manifestations without any thrombosis. Among those patients, 2 had fetal loss as a result of preeclampsia, 2 had intrauterine growth retardations, 1 had a placenta rupture secondary to placental insufficiency resulting in fetal loss, and the rest had consecutive spontaneous abortions. Sixty (50%) patients had a clinical diagnosis of HTN and 23 (19.2%) patients had a clinical diagnosis of hyperlipidemia. Twenty-seven (22.5%) patients had a history of smoking.

Ninety-nine patients with persistently positive aPL but without any APS-related clinical manifestations were considered controls. Seventy (70.7%) were females and 29 (29.3%) were males. Twenty-six (26.3%) of those patients had underlying autoimmune connective tissue diseases which included SLE, rheumatoid arthritis, systemic sclerosis, mixed connective tissue disease, sarcoidosis, Sjögren syndrome, Behçet disease, systemic vasculitis, and adult onset of Still disease. Forty-nine (49.5%) had a clinical diagnosis of HTN and 25 (25.2%) had a clinical diagnosis of hyperlipidemia. Sixteen (16.2%) patients were current or former smokers (Table 2).

Clinical Risk Factors for Thrombosis and Pregnancy Morbidities

Among traditional risk factors and signs of endothelial injury, only HTN demonstrated an independent association with

Table 2. Demographic and Clinical Characteristics of aPL-Positive Patients.

Characteristics	aPL-Positive Patients With APS Clinical Manifestations (n = 120)		aPL-Positive Control (n = 99)	Percent	P
		Percent			
Female	73	60.8%	70	70.7%	.1265
Age, mean (SD)	52.0 (14.1)		54.6 (15.4)		.1941
Primary APS	91	75.8%			
Secondary APS	29	24.2%			
Thrombosis	102	85.0%			
Arterial thrombosis	38	31.7%			
Venous thrombosis	72	60.0%			
Recurrent thrombosis	36	30.0%			
Pregnancy morbidities only	18	15.0%			
Thrombosis + pregnancy morbidities	4	3.3%			
HTN	60	50.0%	49	49.5%	.9414
HLD	23	19.2%	25	25.2%	.2865
Smoking	27	22.5%	16	16.2%	.2440
Raynaud	14	11.7%	10	10.1%	.7068
Livedoid reticularis	6	5.0%	3	3.0%	.4584
aCL IgG/IgM/IgA	11	9.2%	3	3.0%	.0626
aβ2GPI IgG/IgM/IgA	66	55.0%	55	55.6%	.9293
LA	31	25.8%	13	13.1%	.0198
Triple positive	3	2.5%	1	1.0%	.4098

Abbreviations: aCL, anticardiolipin; aβ2GPI, anti-beta 2 glycoprotein I; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; HLD, hyperlipidemia; HTN, hypertension; LA, lupus anticoagulant; SD, standard deviation; triple positive: positive aCL, aβ2GPI, and LA.

arterial thrombosis (odds ratio [OR] = 3.826, 95% confidence interval [CI]: 1.597-9.167, $P = .0026$) and LA demonstrated an independent association with venous thrombosis (OR = 3.308, 95% CI: 1.544-7.085, $P = .0021$). Fisher exact test showed a marginally significant association between Caucasian race and thrombosis ($P = .045$); however, multivariable analysis did not confirm an independent association. Age, diabetes, hyperlipidemia, smoking, Raynaud phenomenon, livedo reticularis, and triple positive aPLs were not significantly associated with either arterial or venous thrombosis. None of the evaluated risk factors demonstrated a significant association with pregnancy morbidity (Figure 2).

Discussion

This is a single-center cross-sectional cohort study of an ethnically diverse aPL-positive patients in a real-world clinical setting. Our data suggest that clinical diagnosis of APS remains challenging. Only 22% (219/997) of patients referred for a positive aPL or APS could be confirmed to have an aPL persistently positive ≥ 99 th percentile for healthy controls. This challenge has long been recognized but remains an obstacle in the diagnosis and management of patients with APS.¹⁸

We assessed multiple potential additional risk factors for arterial thrombosis, venous thrombosis, and pregnancy morbidities. Similar to other studies, we found that among traditional risk factors, only HTN is independently associated with arterial thrombosis.^{14,19} A cross-sectional study of 122 lupus patients showed that HTN was associated with a 2.4-fold increase in the risk of arterial thrombosis among patients with aPL-positive lupus.¹⁵ However, only aCL and LA were assessed among those

patients and the study was designed to risk stratify patients with lupus, not patients without a known autoimmune disease. A cross-sectional study of 163 Polish patients with APS demonstrated that patients with HTN were more likely to experience arterial thrombosis.²⁰ This group was not able to determine the additional risk among aPL-positive patients as all control patients also had APS. Ruffatti et al had shown in a prospective multicenter follow-up study of 258 aPL carriers that HTN is significantly associated with first thrombotic event.¹³ On the contrary, a study of 104 aPL-positive patients showed that when combining the arterial risks of HTN, diabetes, hyperlipidemia, obesity, smoking, and family history as one independent variable, its presence was not associated with thrombosis.²¹ However, due to the low event rate and generalization of arterial risks, it is difficult to infer the true effect of individual risk factors. A recent prospective study of thrombotic risk among 150 LA-positive patients did not show an association between HTN and thrombosis.²² Our study demonstrates that HTN is an independent risk factor for arterial thrombosis among ethnically diverse aPL carriers.

There is a paucity of data for additional risk factors for venous thrombosis among aPL-positive patients. In a study of patients with aPL-positive lupus, hypertriglyceridemia and known hereditary thrombophilia were associated with venous thromboembolic events.¹⁵ An observational study of 177 patients with APS showed that diabetes and hereditary thrombophilia were associated with recurrent thrombosis and the majority of recurrences were venous thrombosis.²³ A systematic review of 25 studies conducted prior to the revised APS classification criteria suggested that LA is a strong risk factor for both arterial and venous thrombosis.²⁴ A prospective follow-up observation of 258 aPL carriers showed that the

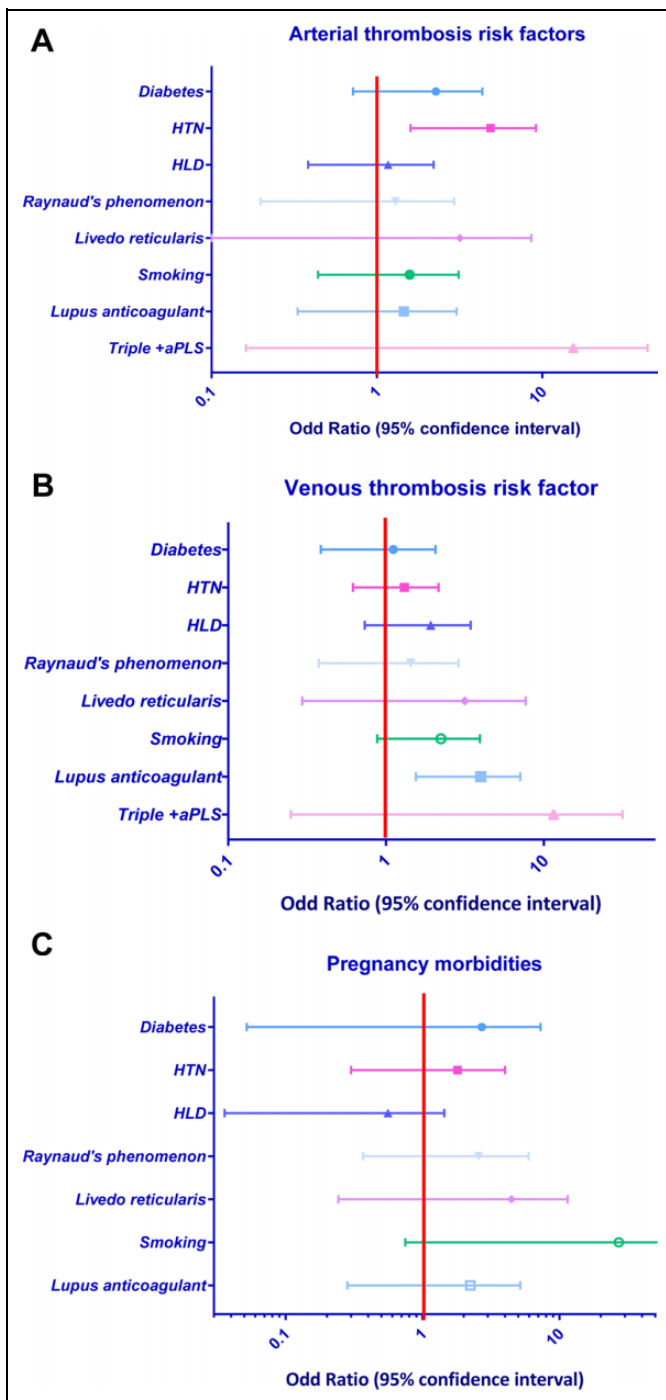


Figure 2. Logistic regression analyses for arterial thrombosis, venous thrombosis, and pregnancy morbidity risk. Forest plots showing the results of multivariate analysis for “second hit” arterial thrombosis risk (A) and venous thrombosis risk (B). The covariates selected in the final model are shown. Univariate analysis of “second hit” risk of pregnancy morbidities is shown in (C).

presence of LA is significantly associated with first thromboembolic event and the majority of first thrombosis was venous thrombosis.¹³ In contrast, a Dutch study comparing 473 patients with deep venous thrombosis (DVT) and 472 healthy controls showed that the presence of LA alone did not

affect DVT risk.²⁵ Our study demonstrates that the presence of LA is an independent risk for venous thrombosis.

The pregnancy risk assessment among aPL carriers remains challenging.² Current available studies are limited by high variability of positive aPL definition and inconsistent clinical definition of pregnancy morbidities.^{26,27} A multicenter, prospective, observational study of patients with SLE lupus and/or positive aPLs concluded that the presence of LA is a strong risk factor for adverse pregnancy outcomes.²⁸⁻³⁰ Kim et al recently reported that imbalance of angiogenic factor levels such as high fms-like tyrosine kinase level, high-soluble endoglin level, and low placental growth factors level during pregnancy may serve as predictors of adverse pregnancy outcome among patients with SLE and/or aPL-positive patients.³¹ In our study, none of the tested traditional APS risk factors showed significant association with pregnancy morbidities. This suggests that the pathogenesis of obstetric APS is unique. Nontraditional APS risk factors, new biomarkers, and noncriteria aPL need further evaluation as additional risk factors for adverse pregnancy outcomes.

The strengths of this study include sample size, the ethnic heterogeneity of the cohort, real-life clinical setting, inclusion of aPL-positive controls, rigorous clinical and laboratory definitions, inclusion of noncriteria aPL, and consideration of multiple clinical, demographic, and laboratory variables. The cross-sectional design is a major limitation of our study. We were not able to account for all potential confounding variables, including medication use.

In summary, we identified possible additional risk factors for arterial and venous thrombosis among ethnically diverse aPL carriers. It highlights the need for additional research in aPL-related pregnancy morbidity risk. Longitudinal assessment to evaluate chronology between additional risk factors and APS clinical manifestations is needed to confirm our findings. Hypertension is a modifiable risk among aPL-positive patients, and aggressive management strategies may be warranted in LA-positive aPL carriers in high venous thrombosis risk scenarios such as major surgery, long distance travel, or pregnancy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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