Antiphospholipid Antibody Profiles and Their Clinical Associations in Chinese Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Different prevalences of antiphospholipid antibodies (aPL) have been reported in different populations of patients with systemic lupus erythematosus (SLE). Chinese are generally believed to have lower risk of vascular thrombosis. We examined the prevalence of aPL including lupus anticoagulant (LAC), anticardiolipin (aCL) and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI) antibodies, the level of thrombotic risk, and the association of aPL with thrombotic and pregnancy outcomes in a Chinese cohort with SLE at the university lupus clinic during the period 1986-2003.

Methods. aPL were measured in 272 SLE patients, and medical records were reviewed for vascular thrombosis and pregnancy outcomes.

Results. The prevalence of LAC, IgG aCL, and IgG anti-ß$_2$-GPI antibodies was 22.4%, 29.0%, and 7.7%, respectively. There were 38 episodes of thrombosis after a mean duration of followup of 11.0 ± 6.8 SD years, giving a thrombotic rate of 1.26/100 patient-years. All aPL were shown to be associated with vascular thrombosis. IgG anti-ß$_2$-GPI antibodies were found to be associated with recurrent thrombosis [8.0/100 patient-years or 25.0% (7/28)]. Patients taking hydroxychloroquine were found to have fewer thrombotic complications than those who were not (OR 0.17, 95% CI 0.07–0.44; $p < 0.0001$). LAC was the strongest factor associated with recurrent miscarriages [relative risk 12.3, 95% CI 1.22–123.31; $p = 0.03$). The diagnosis of secondary antiphospholipid syndrome was satisfied in 8.9% of patients.

Conclusion. The lifetime and recurrent thrombotic rates in our patients with aPL were not particularly different from those in the literature. However, the lower prevalence of aPL in our cohort may suggest a role of other prothrombotic factors in predisposition to thrombosis. (J Rheumatol 2005; 32:622–8)

Key Indexing Terms:
ANTI-ß$_2$-GLYCOPROTEIN I ANTIBODIES ANTICARDIOLIPIN ANTIBODIES
ANTIPHOSPHOLIPID SYNDROME PREGNANCY OUTCOME THROMBOSIS

Ethnic differences in the prevalence of secondary antiphospholipid syndrome (APS) and the clinical association of antiphospholipid antibodies (aPL) and APS have been reported in patients with systemic lupus erythematosus (SLE)[1-6]. We examined the prevalence of aPL including lupus anticoagulant (LAC) and anticardiolipin (aCL) and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI) antibodies and their clinical associations in a cohort of Chinese patients with SLE. Chinese patients are generally considered to have lower risk of thrombosis than Caucasians. The annual incidence of venous thromboembolism in Hong Kong Chinese was estimated at 16.6 events per 100,000 population[7], which is lower than the incidence rates of 124 to 293/100,000 population reported in Caucasians[8,9]. We also examined if aPL confer a different level of thrombotic risk in Chinese patients with SLE.

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MATERIALS AND METHODS

A longitudinal cohort of consecutive patients who satisfied the 1982 revised American College of Rheumatology (ACR) classification criteria for SLE[10] and who were regularly followed at the university affiliated lupus clinic of Queen Mary Hospital, Hong Kong, during the period 1986–2003 were recruited. Demographic data including sex, age at onset of SLE, duration of disease, cumulative clinical manifestations, immune profiles including antinuclear antibodies (ANA), anti-doublestranded (ds) DNA antibodies and anti-extractable nuclear antigen (ENA) antibodies, and the use of corticosteroid, immunosuppressive agents and anticoagulation were recorded.

Records of patients were reviewed for thrombosis and pregnancy outcome that satisfied the preliminary criteria for APS[11]. These included the number of clinical thrombosis and other clinical conditions that were known to be associated with APS, the number of pregnancy losses, intrauterine growth retardation (IUGR), prematurity, and preeclampsia. Therapeutic termination of pregnancy was excluded in this study.

LAC and aCL were measured on blood samples taken at clinic visits and repeated at least 6 weeks apart when found to be positive. Measurement of anti-ß$_2$-GPI antibodies was from stored patient serum samples collected in previous clinic visits. Where sampling was positive, repeat testing was performed on another serum sample taken at a subsequent clinic visit at least 6 weeks later.

aCL antibodies. Serum IgG and IgM aCL antibodies were identified by a solid-phase immunoenzymatic ELISA using cardiolipin (Sigma Chemical Co., St Louis, MO, USA) as substrate according to standard aCL ELISA[12]. Levels of IgG aCL were graded as negative (0–15 GPL), low positive (> 15–25 GPL), medium positive (> 25–80 GPL), and high positive (> 80 GPL). Similarly, the level of IgM aCL were graded negative (0–13 MPL), low positive (> 13–23 MPL), medium positive (> 23–50 MPL), and high positive (> 50 MPL).

Anti-ß$_2$-GPI antibodies. Serum IgG and IgM anti-ß$_2$-GPI antibodies were measured with a commercial kit (ImmuLisa, Immco, Buffalo, NY, USA) as described[13]. The level of anti-ß$_2$-GPI antibody was graded as negative (< 20 EU/ml), borderline positive (20–25 EU/ml), and positive (> 25 EU/ml) for both classes.

LAC assay. The presence of LAC was screened by a dilute Russell viper venom time (DRVVT) assay as described[14]. Confirmatory tests by platelet neutralization[15] were performed where an underlying inhibitor was suspected following failure to normalize the coagulation time by the 1:1 patient:normal plasma mixing assay.

Statistical analysis. The Statistical Analysis System (SAS), version 8, was used for data analysis. Correlation between aCL and anti-ß$_2$-GPI antibodies was performed by Spearman's rank correlation test. Chi-square test and Fisher's exact test were performed to examine differences in various clinical features in patients with and without aPL. The relationship of LAC, aCL, and anti-ß$_2$-GPI antibodies and thrombosis and pregnancy outcome was explored using a Cox regression model with forward stepwise variable selection. Crude odds ratios (OR) and 95% confidence intervals (95% CI) were estimated. The effect of aPL on the timing of development of thrombosis in SLE patients was analyzed by Kaplan-Meier survival analysis. The accuracy of using aPL to predict thrombosis was examined using the area under the receiver operating characteristics (ROC) curve. P values less than 0.05 were considered to be significant.

RESULTS

Demographics of patients and prevalence of aPL. Altogether, 272 consecutive patients who satisfied the ACR criteria for classification of SLE were recruited. Table 1 shows patients' demographic characteristics. All were ethnic southern Chinese. There were 249 women and 23 men. The mean duration of SLE was 10.0 ± 6.8 SD years. The prevalence of aPL including LAC, IgG aCL, and IgG anti-ß$_2$-GPI antibodies is shown in Table 2. Eighty-three (30.5%) patients had one or more of these antibodies. LAC was found in 22.4% (61/272) of patients. The prevalence of IgG aCL and IgG anti-ß$_2$-GPI antibodies was 73/272 (29.0%) and 21/272 (7.7%), respectively. There were patients who had positive aCL but no anti-ß$_2$-GPI antibodies (30/272, 11.0%) and vice versa (9/272, 3.3%) for IgG isotypes, and 2.9% (8/272) and 11.4% (31/272), respectively, for IgM isotypes of these antibodies. Only moderate and high titers of aCL and anti-ß$_2$-GPI antibodies were regarded as significant in clinical associations and were analyzed further.

Patients with LAC were more likely to have concomitant IgG isotypes of aCL ($p < 0.001$) or anti-ß$_2$-GPI antibodies ($p < 0.001$), but not the IgM isotypes of these antibodies ($p =$

Table 1. Demographic characteristics of patients in this Chinese SLE cohort (n = 272).

	N (%)
Female:male	249:23
Age at study, yrs*	37.9 ± 10.4 (17–75)
Age at onset of condition, yrs*	29.1 ± 10.3 (10–71)
Duration of disease, yrs*	11.0 ± 6.8 (2–33)
Clinical features of SLE	
Lymphopenia	193/272 (71.0)
Polyarthralgia	182/272 (66.9)
Malar rash	180/272 (66.2)
Renal involvement	112/272 (41.2)
Cutaneous vasculitis	94/272 (34.6)
Oral ulceration	88/272 (32.4)
Discoid	75/272 (27.6)
Neutropenia	74/272 (27.2)
Thrombocytopenia (< 100×10^9/l)	71/272 (26.1)
Thrombocytopenia (< 50×10^9/l)	41/272 (15.1)
Serositis	51/272 (18.8)
Autoimmune hemolytic anemia	32/272 (11.8)
Nervous system involvement	23/272 (8.5)
Serological features of SLE	
ANA positive	261/272 (96.0)
Anti-dsDNA	142/272 (52.8)
Anti-Ro	163/272 (59.9)
Anti-RNP	58/272 (21.3)
Anti-La	34/272 (12.5)
Anti-Sm	29/272 (10.7)
Medications	
Prednisolone	203/272 (74.6)
Hydroxychloroquine	152/272 (55.9)
Azathioprine	112/272 (41.2)
Cyclosporin A	11/272 (4.0)
Cyclophosphamide	8/272 (2.9)
Aspirin	38/272 (14.0)
Warfarin	17/272 (6.3)

* Mean ± SD (range).

Table 2. Prevalence (%) of different aPL and their combination in these patients.

Pattern	SLE (n = 272)	
Any aPL antibodies	83 (30.5)	
LAC positive	61 (22.4)	
aCL positive	IgG	IgM
High positive only	6 (2.2)	4 (1.5)
Moderate positive only	33 (12.1)	9 (3.3)
Low positive only	40 (14.7)	23 (8.5)
Anti-ß$_2$ positive		
High positive only	18 (6.6)	36 (13.2)
Low positive only	3 (1.1)	25 (9.2)
Profiles of aPL	IgG	IgM
LAC+/aCL+/anti-ß$_2$-GPI+	7 (2.6)	3 (1.1)
LAC+/aCL+/anti-ß$_2$-GPI–	14 (5.1)	1 (0.4)
LAC+/aCL–/anti-ß$_2$-GPI+	5 (1.8)	2 (0.7)
LAC+/aCL–/anti-ß$_2$-GPI–	35 (12.9)	55 (20.2)
LAC–/aCL+/anti-ß$_2$-GPI+	2 (0.7)	2 (0.7)
LAC–/aCL+/anti-ß$_2$-GPI–	16 (5.9)	7 (2.6)
LAC–/aCL–/anti-ß$_2$-GPI+	4 (1.5)	29 (10.7)
LAC–/aCL–/anti-ß$_2$-GPI–	189 (69.5)	173 (63.6)

0.28 and p = 0.49, respectively). The levels of the IgG isotypes of these antibodies in patients with LAC (23.6 ± 28.0 GPL for aCL antibodies and 18.7 ± 32.8 IU/ml for anti-ß$_2$-GPI antibodies) were also found to be higher than those without LAC (11.7 ± 14.1 GPL for aCL antibodies and 7.5 ± 14.7 IU/ml for anti-ß$_2$-GPI antibodies; p = 0.009 and p = 0.04, respectively). The levels of the IgM isotypes of these antibodies were not particularly different in patients with and those without LAC. The level of IgM aCL was found to correlate with the level of IgM anti-ß$_2$-GPI antibodies (r = 0.23, p < 0.0001). On the other hand, IgG aCL antibodies were not found to correlate with the level of IgG anti-ß$_2$-GPI antibodies (r = 0.11, p = 0.06).

Clinical thrombosis

Clinical thrombosis and APS associated conditions. Thirty-eight episodes of thrombosis from 28 (10.3%) patients were recorded in this cohort after a mean duration of followup of 11.0 ± 6.8 SD years, resulting in a thrombotic incidence of 1.26/100 patient-years. There were 28 thrombotic episodes from 18 patients among those with one or more aPL (n = 82) after a followup period of 12.2 ± 7.3 years (thrombotic incidence 2.80/100 patient-years). The incidence of thrombosis in patients without aPL (n = 190) was 0.55/100 patient-years, which was derived from 10 thrombotic episodes in 10 patients after 10.5 ± 6.6 years of followup. Table 3 shows the pattern of thrombosis and other APS associated conditions in these patients. There were 22 episodes of arterial and 16 episodes of venous thrombosis. Stroke was the most common arterial thrombotic event (17/22, 77.3%), whereas deep vein thrombosis (DVT) was the most common venous event (15/16, 93.8%).

Table 3. Pattern of clinical thrombosis and APS associated conditions reported in this patient cohort.

Vascular thrombosis and APS associated conditions	All Patients (n = 272)	
	No. of Patients	No. of Episodes
Any thrombosis	28	38
Arterial alone	18	22
Venous alone	10	16
Recurrent arterial thrombosis		
Cerebral vascular disease	13	17
Retinal arterial occlusion	3	3
Left subclavian artery thrombosis	1	1
Acute myocardial infarction	1	1
Recurrent venous thrombosis		
Popliteal vein thrombosis with* or without pulmonary embolism	9 (3*)	15
Retinal venous thrombosis	1	1
Other APS associated conditions		
Transverse myelitis	7	8
Livedo reticularis	11	—
Cutaneous ulcer	7	—
Superficial thrombophlebitis	3	—
Digital gangrene	2	—
Valvular heart lesion	22/77	—
Coombs' positivity	55/146	—
Seizure	10	—
Transient ischemic attack	13	13

All aPL were found to predispose to thrombosis by univariate analysis. However, LAC was identified as the only predictive factor in multivariate analysis [relative risk (RR) 3.2, 95% CI 1.5–7.0; p = 0.004]. Both LAC and IgG anti-ß$_2$-GPI antibodies were found to be associated with venous thrombosis, with a relative risk of 4.4 and 5.3, respectively. DVT was found to be associated with IgG anti-ß$_2$-GPI antibodies in multivariate analysis (RR 6.2, 95% CI 1.4–28.1; p = 0.02). There were 13 patients with stroke at a mean age of 34.9 ± 12.3 years (range 16–49). Three patients had recurrent stroke. LAC was the single risk factor found to predispose to stroke (RR 3.2, 95% CI 1.0–9.8; p = 0.045). IgM isotypes of these aPL were not found to be associated with clinical thrombosis.

Recurrence of thrombosis. Recurrence of vascular thrombosis occurred in 25.0% (7/28) of patients after a further mean followup period of 12.6 ± 8.5 years (median 8.0), giving a recurrence risk of 8.0/100 patient-years. The second thrombotic episode followed the first episode by a mean duration of 5.3 ± 5.4 years (median 2.0). No recurrence was recorded for patients without aPL after a further mean followup period of 10.1 ± 9.1 years (median 6.0). The recurrent vascular event was found to occur in the same vascular system, i.e., arterial followed by arterial event and venous followed by venous event. IgG anti-ß$_2$-GPI antibodies were found to be the only independent risk factor for recurrence (RR 25.4, 95% CI 1.8–240.5; p = 0.01).

Medications and thrombosis. Thirty-eight and 17 patients with aPL were prescribed aspirin and warfarin, respectively, as primary or secondary prophylaxis. Patients with clinical thrombosis were more likely to be taking aspirin (p < 0.006) and warfarin (p < 0.0001). However, the risk of thrombosis was found to be lower in patients taking hydroxychloroquine (6/152, 3.9%) than in those who were not (23/120, 19.2%) (OR 0.17, 95% CI 0.07–0.44; p < 0.0001). This reduction in thrombotic risk was not particularly different in patients with (OR 0.21, 95% CI 0.06–0.81) and those without (OR 0.21, 95% CI 0.05–0.81) aPL antibodies (p = 0.13).

Time to thrombosis-survival curve. Using Kaplan-Meier survival analysis, more patients among those who had aPL were shown to develop clinical thrombosis and they had an earlier onset of thrombosis than patients without these antibodies (p = 0.0002; Figure 1).

Hemorrhagic manifestations and other clotting defects. A number of patients with aPL developed hemorrhagic complications as their first manifestation of APS when they were not taking antiplatelet agent or anticoagulant. One patient had prolonged activated partial thromboplastin time and recurrent hematuria. One had adrenal hemorrhage. One

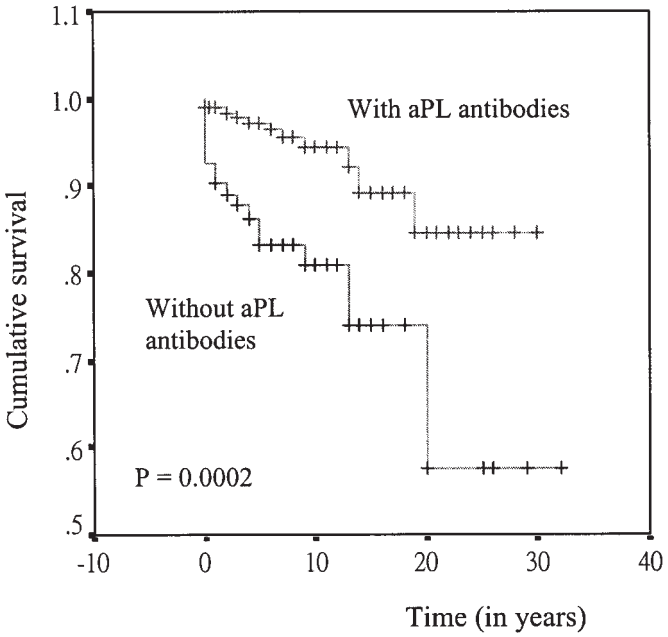

Figure 1. Kaplan-Meier survival curve for the development of clinical thrombosis of SLE patients with and without antiphospholipid antibodies.

patient died from cerebellar infarction with hemorrhagic transformation that progressed rapidly to brainstem coning despite urgent neurosurgical decompression.

One patient was found to have concomitant deficiencies in free protein C and protein S and increased activated protein C resistance, although clotting factor assay was not routinely performed in patients with aPL.

Other clinical features associated with aPL. LAC was found to be associated with transverse myelitis by multivariate analysis (RR 9.6, 95% CI 1.8–50.7, p = 0.008). IgG anti-$ß_2$-GPI antibody was found to be associated with livedo reticularis (RR 5.8, 95% CI 1.4–23.9; p = 0.02). Valvular heart lesions were detected in 22 of the 77 patients in whom echocardiograms were performed. Mitral valve was predominantly affected (15/22, 68.2%), followed by aortic valve (5/22, 22.7%). Valvular heart lesions were found to be associated with LAC (RR 3.4, 95% CI 1.2–9.9; p = 0.03). Patients with isolated pulmonary hypertension (n = 7) were not found to be related to aPL (p = 0.68). Other clinical features including transient ischemic attack (TIA; p = 0.22) and avascular necrosis (AVN; p = 1.0) were not found to be associated with aPL antibodies.

Thrombocytopenia was present in 26.1% (71/272) of patients, of whom 57.7% (41/71) had platelet count $< 50 \times 10^9$/l. LAC was found to be associated with thrombocytopenia (p = 0.045), but platelet count $< 50 \times 10^9$/l was found to be related to IgM aCL antibodies (p = 0.03) instead. The level of thrombocytopenia was not found to relate to thrombotic risk (p = 0.19). IgM aCL antibodies were also found to be associated with Coombs' test positivity (p = 0.003), but active hemolysis from autoimmune hemolytic anemia was found to be associated with IgG aCL antibodies (p = 0.01).

aPL and other SLE features. Oral ulceration was less commonly found in patients with LAC than those without LAC (p = 0.04). Patients who had IgG aCL were more likely to have anti-DNA antibodies (p = 0.04), while those who had IgM anti-$ß_2$-GPI antibodies were less likely to have anti-Ro antibodies (p = 0.02). Discoid rash was less likely to be associated with IgG (p = 0.03) or IgM (p = 0.02) anti-$ß_2$-GPI antibodies. However, none of these differences was statistically significant after Bonferroni corrections were applied.

Pregnancy morbidities. Among the 247 female patients, there were 238 pregnancies recorded from 121 patients, excluding therapeutic abortion. There were 48 episodes of pregnancy losses in 33 patients (48/238, 20.2%), 40 of which occurred in the first and second trimester in gestation. Seven patients had > 2 pregnancy losses and 4 patients had > 3 pregnancy losses. Four fetuses were found to have IUGR and 15 were born prematurely. Three patients developed preeclampsia at the time of delivery. None of these patients developed HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count). LAC was the only predictive factor for recurrent spontaneous abortion (RR 12.3, 95% CI 1.22–123.31) by multivariate analysis (p = 0.03). IgM anti-$ß_2$-GPI antibodies were found to predispose to the development of preeclampsia (RR 18.5, 95% CI 1.33–258.0; p = 0.03).

There were 93 pregnancies in 39 patients with aPL antibodies. Aspirin with or without subcutaneous heparin was given during 6 pregnancies in 4 patients among those who had aPL with variable and inconclusive pregnancy outcomes. Among those untreated pregnancies (n = 87), 21 (24.1%) pregnancy losses from 10 patients were recorded. There were 16 (76.2%), 2 (9.5%), and 3 (14.3%) pregnancy losses in the first, second, and third trimester, respectively. Nine (23.1%) patients fulfilled one or more diagnostic criteria on pregnancy morbidity for APS: 3 patients had > 1 unexplained fetal loss at or beyond the 10th gestational week, 5 patients had ≥ 1 premature birth at or before the 34th gestational week because of preeclampsia (n = 1) or placental insufficiency (n = 4), and 3 patients had ≥ 3 unexplained spontaneous abortions before the 10th gestational week. There was one fetus with IUGR in this subset.

Secondary APS in SLE patients. Twenty-four (8.8%) patients in this SLE cohort satisfied the preliminary criteria for secondary APS. These included 21 female and 3 male patients who had been followed for 14.1 ± 7.6 years. Their age at onset of SLE was 28.4 ± 8.1 years. Eighteen patients (75%) presented with clinical vascular thrombosis and 9 (37.5%) patients satisfied one (or more) criterion for pregnancy morbidity. Three patients had both clinical thrombosis and pregnancy morbidities. No patient had catastrophic APS.

Usefulness of measurement of aPL antibody panel and asso-

ciations of clinical thrombosis. The prevalence of LAC, aCL, and anti-ß$_2$-GPI antibodies in patients with APS was 75.0%, 58.3%, and 45.8%, respectively. When only high titer aCL and anti-ß$_2$-GPI antibodies were taken into account, the prevalence of aCL and anti-ß$_2$-GPI antibodies in these patients was 45.8% and 29.2%, respectively. Table 4 shows the sensitivity and specificity of various aPL antibodies in high titers and their combinations in the diagnosis of APS. LAC was most sensitive (75.0%) among all aPL antibodies in the diagnosis of APS. IgG anti-ß$_2$-GPI antibodies gave the lowest sensitivity (29.2%) but the highest specificity (95.2%). IgG aCL had an intermediate sensitivity (45.8%) and specificity (88.8%) compared to the LAC and anti-ß$_2$-GPI. Combining LAC and IgG anti-ß$_2$-GPI antibodies gave a higher specificity (97.2%) than each measured alone. Measurement of IgG aCL in addition to IgG anti-ß$_2$-GPI antibodies gave no additional value for prediction of APS (p = 0.22). The same was observed when LAC was also measured in the panel (p = 0.07).

DISCUSSION

The prevalence of aPL antibodies was 30.8% and that of LAC, IgG aCL, and IgG anti-ß$_2$-GPI antibodies was 22.4%, 29.0%, and 7.7%, respectively, in our cohort of Chinese patients with SLE. The prevalence of aPL reported in other populations was around 34%–44%[16] and those of aCL and anti-ß$_2$-GPI antibodies were 17%–61% and 16%–73%, respectively[6]. This variation may be due to the different sensitivity of the assays, the cutoff point for positivity, or lack of standardization in particular, concerning the assay for anti-ß$_2$-GPI antibodies and ethnic differences.

The lifetime thrombotic rate in our population of unselected patients with SLE was comparable to that reported in a multicenter study involving 7 European countries (9.2%)[17]. As well, the thrombotic risk in our patients with aPL was similar to that previously reported (2.5/100 patient-years)[18] and was 5 times higher than for those patients without aPL antibodies. The prevalence of secondary APS in our cohort was 8.9% compared to 10% reported in another population[19]. However, it is interesting that African American patients with SLE were found to have fewer thrombotic manifestations than in Caucasians, which may be due to a low incidence of IgG antibodies[20]. IgA aCL antibodies were reported to be the most common aCL antibodies in the African American population[2].

Recurrent thrombotic risk as reported varies from 29% to 53%[19,21,22] and the risk in our cohort was 8.0/100 patient-years. The greater variability in recurrent risk may be due to the number of patients taking longterm aspirin and/or warfarin after the last thrombotic episode. IgG anti-ß$_2$-GPI antibodies were identified in our study as the only independent predictor of recurrent vascular complications. Further, thrombotic risk may also be governed by the proportion of patients taking hydroxychloroquine, which was shown to be protective against thrombosis in this study. Hydroxychloroquine has been found to reverse thrombogenic properties of human IgG aPL antibodies[23,24], and has been suggested to be useful in the prevention of thrombosis in asymptomatic subjects with aPL[25]. Indeed, a recently formed consensus committee recommended hydroxychloroquine use in APS patients for cardiac protection[26].

Patients who had aPL antibodies were found in this study to have earlier onset of thrombosis than patients without these antibodies. The time to first thrombosis event was taken from the diagnosis of SLE in these patients. As the assays for aPL were only introduced in our hospital in the late 1980s, some of the patients with long disease duration (i.e., disease onset before the 1980s) only had their aPL checked late in the disease course. However, there were only a few of these patients in the cohort (mean duration of followup was 11 years). For these patients, an assumption of the presence of aPL at the onset of SLE was made in the analysis of their clinical manifestations including thrombosis and pregnancy morbidities.

In accord with data reported from other ethnic groups, aPL in this Chinese cohort were found to be associated with thrombosis and pregnancy morbidities. However, as isolated aPL, but not the full panel, were measured in some case-control studies, there were some differences in the association between specific aPL antibodies and certain clinical conditions. For instance, we found that LAC was associated with stroke at young age, but another study where only aCL antibodies were measured revealed that subjects under 50 years of age with these antibodies had 8.3 times increased risk for stroke than those without[27]. Thrombocytopenia was found in previous studies to be associated with aCL anti-

Table 4. Sensitivity and specificity of various aPL and their combination in the diagnosis of APS.

aPL Antibodies	LAC	IgG aCL	IgG Anti-ß$_2$-GPI	IgG aCL + IgG Anti-ß$_2$-GPI	LAC + IgG aCL + IgG anti-ß$_2$-GPI	LAC + IgG anti-ß$_2$-GPI
Sensitivity	18/25 (72.0%)	11/25 (44.0%)	7/25 (28.0%)	4/25 (16.0%)	2/25 (8.3%)	5/25 (20.8%)
Specificity	204/247 (82.6%)	219/247 (88.7%)	236/247 (95.5%)	242/247 (98.0%)	243/247 (98.4%)	240/247 (97.2%)
Area under the curve	79.1%	67.3%	63.2%	67.9%	85.4%	83.0%
(95% CI)	(68.6%, 89.5%)	(54.4%, 80.1%)	(48.2%, 78.2%)	(54.5%, 81.3%)	(78.1%, 92.6%)	(73.8%, 92.2%)
p (1-sided)			0.22		0.07	

bodies[16] and LAC[28]. We found an association with the latter, but not the former. Unlike another cohort[29], we had a higher proportion of patients with significant thrombocytopenia < 50×10^9/l. In particular, these were patients who had IgM aCL antibodies. These antibodies were also found to be associated with Coombs' test positivity in our study, an association that had been described previously[30]. As in one other study[31], IgG aCL antibodies were shown to relate to the development of autoimmune hemolytic anemia. Controversial conditions like TIA and AVN were not found to be more frequent in patients with aPL antibodies than those without.

Presence of LAC was found to be the strongest risk factor for recurrent pregnancy losses, in accord with some other studies[32-36]. Other studies identified higher risk of pregnancy losses in patients with aCL antibodies[37-40] and anti-ß$_2$-GPI antibodies[41]. IgM anti-ß$_2$-GPI antibodies were found to be related to preeclampsia in our study, as in one other study[42].

Finally, given the stronger association of IgG anti-ß$_2$-GPI antibodies with thrombosis than IgG aCL antibodies, and a higher specificity when combined with LAC in the diagnosis of APS, further standardization of the assay for anti-ß$_2$-GPI antibodies is needed, and subsequent substitution of IgG aCL antibodies should more commonly be brought into clinical practice.

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