Prevalence of the Antiphospholipid Syndrome and Its Effect on Survival in 679 Chinese Patients With Systemic Lupus Erythematosus
A Cohort Study

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Abstract: In this work we evaluate the prevalence of the antiphospholipid syndrome (APS) and its impact on survival in Chinese patients with systemic lupus erythematosus (SLE). We studied a prospective cohort of southern Chinese patients who fulfilled ≥4 American College of Rheumatology criteria for SLE. The cumulative rate of survival over time was calculated by the Kaplan-Meier method. APS was defined by the 2006 updated consensus criteria. We evaluated the prevalence and manifestations of APS, and compared the survival of patients with and without APS. We followed 679 patients with SLE (92% women; age of onset, 32.5 ± 14 yr) for 9.7 ± 7.3 years. Sixty-eight (10%) patients died and 33 (4.9%) patients were lost to follow-up. Forty-four (6.5%) patients met the criteria for APS, manifested by the following: ischemic stroke (55%), deep venous thrombosis (32%), obstetric morbidity (14%), cardiovascular events (9%), and peripheral vascular disease (9%). Nine (9/44 [20%]) APS patients died, which was more frequent than the non-APS patients (59/635 [9%]; p = 0.02). The cumulative mortality of patients with APS was 4.6% at 5 years, 7.8% at 10 years, and 22.2% at 15 years, which was not significantly higher than that of non-APS patients (5.4% at 5 years, 9.2% at 10 years, and 11.3% at 15 years; p = 0.14). However, if we considered only patients with APS caused by arterial thrombosis, the presence of APS was significantly associated with mortality (hazard ratio, 2.29; 95% confidence interval, 1.13–4.64; p = 0.02). We conclude that the presence of APS increases the mortality risk of Chinese patients with SLE, which is mainly contributed by arterial thrombotic events.

Clinical significance: 1) APS is infrequent in southern Chinese patients with SLE compared to white patients. 2) Arterial thrombosis is a more common manifestation of APS than venous thrombosis in Chinese SLE patients. 3) APS related to arterial thrombosis is associated with increased mortality in Chinese patients with SLE.

(Medicine 2013;92: 217–222)

Abbreviations: aCL = anticoaguloid, aPL = antiphospholipid, APS = antiphospholipid syndrome, CAT = computer axial tomography, CI = confidence interval, HR = hazard ratio, LA = lupus anticoagulant, SDI = systemic lupus erythematosus damage index, SLE = systemic lupus erythematosus.

INTRODUCTION

Patients with systemic lupus erythematosus (SLE) are prone to thrombotic complications. This is related to multiple factors that include an increased prevalence of traditional vascular risk factors and a number of nontraditional lupus-related risk factors. Of the latter, the antiphospholipid (aPL) antibodies are important contributors to the increased risk of both arterial and venous thrombosis in SLE. A systematic review of 29 studies reported that thrombosis occurred in 53% of 160 SLE patients who were positive for lupus anticoagulant (LA), compared to 12% of 338 patients negative for LA. Similarly, thrombosis occurred in 40% SLE patients who were positive for the anticardiolipin (aCL) antibodies, in contrast to only 18% in those negative for aCL antibodies.

The antiphospholipid syndrome (APS) is characterized by recurrent arterial thrombosis, venous thrombosis, or pregnancy morbidity, alone or in combination, that is associated with the presence of aPL antibodies such as LA, aCL, and the anti-β2-glycoprotein-I antibodies. Mortality is increased in patients with APS. A 2009 multicenter European study of 1000 patients with APS (primary or secondary) reported a mortality rate of 5.3% 5 years after initial presentation. Another systematic review of 5 studies described a mortality rate of 6.7% in patients with APS after disease onset for 3–8 years, although 2 studies included in this analysis had single positive determination of aPL antibodies.

Few studies have reported the effect of concomitant (secondary) APS on mortality in patients with SLE. Although the prevalence of aPL antibodies and venous thrombosis has been reported to be lower in Chinese than in white or African American patients with SLE, little is known about the prevalence and mortality rate of APS in Chinese patients. We undertook this study to evaluate the prevalence of secondary APS and its effect on survival in a cohort of Chinese patients with SLE.

PATIENTS AND METHODS

Study Population

Tuen Mun Hospital is a large government-subsidized regional public hospital in Hong Kong providing medical services to a population of one million residing in the region of Tuen Mun. Between 1995 and 2011, patients who were newly diagnosed as having SLE in the outpatient clinics of our hospital or during hospitalization, or referred to our unit within 12 months of diagnosis of SLE, were recruited into our prospective cohort database. Patients under the care of all specialists such as rheumatologists, nephrologists, pediatricians, geriatricians, and hematologists were included. All patients were ethnic Chinese and fulfilled ≥4 American College of Rheumatology criteria for the classification of SLE. These patients were longitudinally followed by the
same group of physicians with an interval of 12 weeks. More frequent clinic visits were arranged for those with active or unstable disease or complications.

**Cumulative Survival Rate and APS**

The latest status (alive or death) of our SLE patients was retrieved. The causes of death of those patients who died were documented and coded by their attending specialists according to the clinical picture and investigation results. Autopsy would be arranged when the cause of death was uncertain, or when there were medicolegal implications or academic interest. The patients’ cumulative survival rate over time was studied and compared between those with and without concomitant APS.

**Definition of APS**

Antiphospholipid syndrome was classified according to the consensus criteria updated in 2006. A definite diagnosis of APS can be made when ≥1 clinical plus 1 laboratory criterion are met. Clinical criteria include vascular thrombosis and obstetric morbidity. Vascular thrombosis refers to ≥1 clinical episode of arterial, venous, or small vessel thrombosis in any tissue or organ. Obstetric morbidity refers to 1 of the following: 1) ≥1 unexplained death of a morphologically normal fetus at or beyond the 10th week of gestation; 2) ≥1 premature birth of a morphologically normal neonate before the 34th week of gestation because of eclampsia or severe pre-eclampsia, or recognized features of placental insufficiency; and 3) ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation, after exclusion of maternal anatomic or hormonal abnormalities and paternal/maternal chromosomal causes. Laboratory criteria include any 1 of the following: 1) the presence of LA; 2) anticardiolipin antibodies (IgG and/or IgM isotype) present in medium or high titer; and 3) anti-β2-glycoprotein-I antibody (IgG and/or IgM isotype) present in titer >99th percentile. All these tests have to be performed by standard techniques and must be present for at least 2 occasions at least 12 weeks apart (but <5 yr). For patients with manifestations of APS presented before 2006, classification of APS was made retrospectively with repeat testing of the aPL antibodies if necessary, so that every APS patient was at least twice positive for the aPL antibodies.

**Ascertainment of Thrombotic Events and Obstetric Morbidities**

Thrombotic episodes of our patients were diagnosed when there were compatible signs and symptoms, confirmed by imaging studies. Cerebrovascular events were documented to be acute infarction of the brain and brain stem by computer axial tomography (CAT) or magnetic resonance imaging (MRI), with and without additional angiographic studies. Acute coronary and peripheral vascular thrombotic events were documented by angiographic studies. Venous thrombosis was confirmed by the use of Doppler ultrasound, spiral CAT scan, or angiography.

Patients who presented with recurrent abortion in the first trimester were examined for any structural abnormalities of the genital tract, and karyotyping of the couples was performed to exclude genetic causes. Definite fetal losses, if available, would also be sent for chromosomal analysis. For intrauterine death beyond the 10th week of gestation, fetal and placental tissues were routinely sent for histopathologic examination to exclude congenital anomalies that would suggest chromosomal abnormalities.

**Assay of aPL Antibodies**

Two aPL antibodies were assayed in the current study: LA and aCL antibody. LA was screened for and confirmed by a panel of phospholipid-dependent clotting assays in accordance with the ‘International Society on Thrombosis and Haemostasis.’ These assays included activated partial thromboplastin time (Actin FSL, Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), dilute Russell viper venom time (LA-screen and LA-confirm, Siemens, Marburg, Germany), kaolin clotting time (Kaoclot, Life Diagnostics, Clarkston, GA) and platelet neutralization. Double spin platelet-poor plasma (platelet count <10 × 10^9/L) was used in all clotting assays and analyzed using Sysmex CA-7000 coagulometer. The aCL antibody (IgG) was measured by an enzyme-linked immunooassay (EIA) kit (Relisa Cardiolipin EIA, Sacramento, CA). A moderately elevated aCL titer was defined as values between 40 and 80 GPL, and a high aCL titer referred to values of >80 GPL.

**Assessment of Organ Damage in SLE**

Damage of SLE was measured by the Systemic Lupus International Collaborating Clinics Damage Index (SDI), a validated instrument consisting of 41 items that measure irreversible organ damage unrelated to active inflammation in 12 organ systems. Each item should be present for at least 6 consecutive months in order to be scored. As thrombotic complications of SLE scored points in the SDI, only those points contributed by nonthrombotic complications were compared between patients with and without APS.

**Statistical Analyses**

Unless otherwise stated, values in the current study are expressed as mean ± standard deviation. Continuous variables were compared between 2 groups using the Student t test, with adjustment for confounding covariates by analysis of covariance (ANCOVA). Categorical variables were compared by the chi-square test. When the frequency was <5, the Fisher exact test was used.

The cumulative probability of survival of the patients over time was studied by the Kaplan-Meier method. For those who died or were lost to follow-up, data were censored at the time of their deaths and last clinic visits or hospitalization, respectively. We compared the cumulative survival rate of patients with and without APS by the log-rank test. We used the Cox proportional hazard model to compute the hazard ratio (HR) and 95% confidence interval (CI) for mortality in patients with APS or arterial thrombosis related to APS compared to those patients without these features.

Statistical significance was defined as a 2-tailed p value of <0.05. All statistical analyses were performed using the SPSS program, v. 11.5 for Windows Vista.

**RESULTS**

**Characteristics of the Study Population**

We prospectively followed 679 patients with SLE (628 women, 92%). The mean age at onset of SLE was 32.5 ± 14 years, and the mean follow-up time of the entire cohort of patients was 9.7 ± 7.3 years. Table 1 shows the cumulative clinical features of the patients. Sixty-eight (10%) patients died during the course of illness, and 33 (4.9%) patients were lost to follow-up. The main contributing causes of death of these 68 patients were sepsis/infection (53%), cerebrovascular events (15%), cancer (9%), and cardiovascular events (6%) (Table 2).

**Prevalence and Manifestations of APS**

Forty-four (6.5%) patients met the criteria for APS: 23 (52%) patients developed APS after the diagnosis of SLE, 16 (36%) patients had concomitant APS diagnosed at the same time as SLE, and 5 (11%) patients had APS preceding SLE diagnosis. All the thrombotic episodes were diagnosed and confirmed by imaging studies. Anticardiolipin antibodies (medium or high
titers) were present in 31 (70%) patients, and LA was present in 32 (73%) patients. Nineteen (43%) patients had both aCL antibodies and LA. All patients had at least 1 of these aPL antibodies positive 2 times, 3–12 months apart. None of our patients had catastrophic APS.

The nonthrombotic manifestations of SLE patients with and without APS are compared in Table 1. Patients with APS had a significantly lower prevalence of malar rash and photosensitivity, but were more likely to have seizure disorder. The anti-La antibody was also significantly less common in patients with APS.

**TABLE 1.** Nonthrombotic Clinical Manifestations of SLE Patients, by APS Status

| Manifestation                  | APS Total | No (n = 679) No. (%) | P*  |
|-------------------------------|-----------|----------------------|-----|
| Age at SLE onset, yr†         | 34.2 ± 15 | 32.3 ± 13            | 0.43|
| Follow-up duration, yr†       | 11.7 ± 8.0| 9.5 ± 7.2            | 0.08|
| Women                         | 40 (91)   | 588 (93)             | 0.78|
| Arthritis                     | 30 (68)   | 450 (71)             | 0.73|
| Myositis                      | 2 (5)     | 18 (28)              | 0.38|
| Malar rash                    | 13 (30)   | 304 (48)             | 0.02|
| Raynaud phenomenon            | 10 (23)   | 132 (21)             | 0.76|
| Discoid lupus                 | 3 (7)     | 65 (10)              | 0.61|
| Mucosal ulceration            | 3 (7)     | 97 (15)              | 0.18|
| Photosensitivity              | 6 (14)    | 179 (28)             | 0.04|
| Hemolytic anemia              | 12 (27)   | 123 (19)             | 0.20|
| Leukopenia (<4 × 10^9/L)      | 12 (27)   | 238 (37)             | 0.18|
| Lymphocytopenia (<100 × 10^9/L) | 16 (36)   | 153 (24)             | 0.07|
| Lymphopenia (<1.5 × 10^9/L)   | 31 (70)   | 454 (71)             | 0.88|
| Seizure                       | 7 (16)    | 41 (6)               | 0.02|
| Psychosis                     | 2 (5)     | 28 (4)               | >0.99|
| Myelopathy                    | 1 (2)     | 6 (0.9)              | 0.38|
| Acute confusional state       | 0 (0)     | 10 (1.6)             | >0.99|
| Neuropathy (peripheral or cranial) | 0 (0)     | 7 (1.1)              | >0.99|
| Optic neuritis                | 0 (0)     | 4 (0.9)              | >0.99|
| Renal                         | 26 (59)   | 335 (53)             | 0.42|
| Serositis                     | 7 (16)    | 124 (20)             | 0.56|
| Anti-dsDNA                    | 32 (73)   | 439 (69)             | 0.62|
| Anti-Sm                       | 5 (11)    | 95 (15)              | 0.66|
| Anti-Ro                       | 23 (52)   | 359 (57)             | 0.58|
| Anti-La                       | 3 (7)     | 120 (19)             | 0.04|
| Anti-nRNP                     | 10 (23)   | 170 (27)             | 0.56|

*Comparison between patients with and without APS.
†Mean ± SD.

**TABLE 2.** Causes of Death in SLE Patients, by APS Status

| Cause of Death                                      | APS Total | No (n = 68) No. (%) | P*  |
|-----------------------------------------------------|-----------|---------------------|-----|
| Myocardial infarction/acute coronary syndrome       | 3 (33)    | 4 (6)               | 0.006|
| Cerebrovascular accident                            | 3 (33)    | 10 (15)             | 0.12|
| Cancer                                              | 1 (11)    | 6 (9)               | >0.99|
| Septicemia/infection                               | 2 (22)    | 36 (53)             | 0.07|
| Renal failure                                       | 0 (0)     | 1 (1.5)             | >0.99|
| Suicide                                             | 0 (0)     | 2 (3)               | >0.99|
| Sudden death with unknown cause                     | 0 (0)     | 4 (6)               | >0.99|
| Status epilepticus                                 | 0 (0)     | 2 (3)               | >0.99|
| Pulmonary hypertension                              | 0 (0)     | 3 (4)               | >0.99|

*Comparison between patients with and without APS.
The Table 3 shows the clinical presentation of the 44 SLE patients with APS. The most common manifestations were cerebrovascular accident (n = 24, 55%), followed by deep venous thrombosis (n = 14, 32%), obstetric morbidity (n = 6, 14%), cardiovascular thrombotic events (n = 5, 11%), peripheral vascular thrombotic events (n = 4, 9%) and retinal artery thrombosis (n = 1, 2%). Four (9%) patients had both arterial and venous thrombosis. Among the 6 patients with pregnancy morbidity, 4 (67%) patients had intrauterine fetal death at the second trimester and 2 (33%) patients had recurrent first trimester abortion. All 14 cases of deep vein thrombosis involved the popliteal veins. One patient had concomitant pulmonary embolism, and another patient had dural sinus thrombosis.

Twenty-nine (66%) patients received long-term warfarin (standard intensity anticoagulation with INR target between 2.0 and 3.0) for treatment, whereas 17 (39%) received aspirin. Three (7%) patients received both warfarin and aspirin, but 1 patient with obstetric APS did not receive any treatment because she had decided not to for further pregnancy attempts. The reasons for not using warfarin in 15 patients were the following: minor lacunar infarction on imaging (n = 6), risk of fall and fracture (n = 2), patient’s refusal (n = 3), bleeding tendency (n = 2), and obstetric APS (n = 2). Anticoagulation was stopped in 2 patients because of the development of bleeding complications (intracerebral hemorrhage). Recurrence of arterial thrombosis occurred in 6 (19%) patients (4 ischemic stroke, 1 myocardial infarction, and 1 peripheral vascular disease), whereas only 1 patient (7%) had recurrence of venous thrombosis.

**Effect of APS on SLE Damage and Mortality**

Organ damage, defined as a SDI score of ≥1, was present in 295 (43%) patients. The SDI scores (after deduction of points contributed by thrombosis) of patients with APS were higher than those of patients without APS, but the difference was not statistically significant (1.16 ± 1.36 vs. 0.87 ± 1.41; p = 0.50 adjusted for SLE duration). The damage scores of individual systems after exclusion of thrombotic complications were not significantly different between patients with and without APS (data not shown).

Nine of 44 (20%) patients with APS died, which was significantly more frequent than in non-APS patients (59 deaths/635 patients, 9%; p = 0.02). Patients with APS died at an older age than those without APS, but the difference was not statistically significant (54.0 ± 11.4 vs. 45.1 ± 18.2 yr; p = 0.07). The duration of SLE at the time of death was also not significantly longer in patients with APS than in those without (13.9 ± 10.4 vs. 7.47 ± 7.4 yr; p = 0.11). Regarding the causes of death, patients with APS were more likely to die of the direct effect of thrombosis, particularly myocardial infarction, than were patients without APS (see Table 2). Conversely, infective complications as the main cause of death was less common in SLE patients with APS.

The cumulative mortality of patients with APS was 4.6% at 5 years, 7.8% at 10 years, and 22.2% at 15 years, whereas the cumulative mortality of patients without APS was 5.4% at 5 years, 9.2% at 10 years, and 11.3% at 15 years. Although the survival of patients with APS was poorer than that of patients without APS, the difference did not reach statistical significance (p = 0.14). However, if patients with only APS-related arterial thrombosis were considered, the presence of APS was significantly associated with mortality (HR, 2.29; 95% CI, 1.13–4.64; p = 0.02) (Figure 1). None of the APS patients with venous thrombosis died during the study. APS-related venous thrombosis was not associated with higher mortality in SLE (log-rank test: p = 0.28). Patients with APS who were positive for LA did not have a significantly higher mortality than those without APS (HR, 1.36; 95% CI, 0.58–3.17; p = 0.48). Similarly, the mortality of APS patients who were positive for aCL was not significantly higher than those without (HR, 2.08; 95% CI, 0.95–4.57; p = 0.07).

**DISCUSSION**

There is considerable inter-ethnic difference in the incidence of thrombosis in the general population. It is well recognized that Asian patients are less prone to venous thrombosis than are white patients.23 While the explanation for this remains obscure, many hypotheses, such as the variation in the prevalence of genetic polymorphisms, have been suggested. A meta-analysis involving 126,525 cases and 184,068 controls derived from 173 case-control studies showed that genetic mutations related to venous thromboembolism like factor V Leiden, prothrombin, PAI-1, alpha-fibrinogen, MTHFR, and ACE varied in frequency and statistical significance in different ethnic groups.5 In particular, certain mutations commonly reported in white patients, such as the factor V Leiden and prothrombin gene, were uncommon in Chinese patients, and they were not significantly associated with venous thrombosis.7,10

In a cohort of 667 Mexican patients with SLE, the prevalence of APS according to the authors’ own definition was 15%.1 Another prospective study showed that 28 of 202 (14%) Spanish SLE patients had coexisting APS.20 Among 300 British SLE patients who participated in a renal outcome study, 25 (8.3%) had coexisting APS.18 The incidence of venous thromboembolism in Chinese patients with SLE was at least 50% lower than that of the African American and white patients.16 Moreover, the prevalence of the aPL antibodies (aCL or LA) was also significantly lower in Chinese patients (29% vs. 42% in African American and 46% in white patients). These contribute to a lower prevalence of APS in Chinese patients with SLE, which is confirmed by the current study (6.5% prevalence). In the prospective Euro-Phospholipid cohort that involved 1000 patients (36% SLE), venous thrombosis was more common than arterial thrombosis, but no significant difference was reported between SLE and non-SLE patients.2 This is in contrast with the current study, in which the contribution of venous thrombosis to APS was much lower in our Chinese SLE patients (<30%).

A bimodal pattern of SLE mortality is well recognized.22 Early SLE death is often due to infective complications, whereas late SLE death is more likely caused by atherosclerotic vascular disease.14 An increased standardized incidence ratio of stroke and myocardial infarction has been well reported in SLE patients compared to the general population,11,22 and an association between arterial/venous thrombosis and the aPL antibodies in SLE has also been well documented.12,17 As severe arterial and venous thrombosis is a main cause of mortality in the general population,
the presence of concomitant APS may adversely affect the prognosis of SLE. Drenkard et al.3 studied the mortality rate of a large cohort of Mexican patients with SLE and demonstrated that the presence of aPL-associated manifestations, namely arterial thrombosis and thrombocytopenia, was associated with reduced survival. Ruiz-Irastorza et al.20 also demonstrated a significant reduction in the 15-year cumulative survival rate of their Spanish SLE patients with APS compared to those without (65% vs. 90%, p = 0.03). The observation from our Chinese cohort is in keeping with these studies in that patients with APS-related arterial thrombosis had a higher mortality than those without (HR, 2.3).

In the study by Ruiz-Irastorza et al.20, 50% of the deaths in SLE patients with APS were due to the direct effect of arterial thrombosis, while the other contributing causes were cancer (25%), infection (12.5%) and suicide (12.5%). Among the 1000 patients with APS recruited in the Euro-Phospholipid project,2 the main causes of death were bacterial infection (21%), myocardial infarction (19%), stroke (13%), cancer (11%), catastrophic APS (9.4%), and pulmonary embolism (9.4%). No significant difference in the causes of death was observed between SLE and non-SLE patients. In the current study, arterial thrombosis was the main contributing cause of death in two-thirds of the SLE patients with APS, whereas infection (22%) and cancer (11%) as the direct cause of mortality was less common than in SLE patients without APS. This is consistent with the European studies in which thrombosis was a relatively more important cause of death than infection and cancer in patients with APS and without underlying SLE.2,20

Although the current study involved a relatively big cohort of patients, the outcome of interest was mortality instead of vascular thrombosis. The sample size and the number of events may not be large enough to allow for adjustment of confounding variables and vascular risk factors on the contribution of APS to mortality.

In summary, to our knowledge this is the first cohort study on the prevalence and presentation of APS in Chinese patients with SLE. Although the prevalence of APS in the current SLE cohort could have been slightly underestimated because the anti-β2-glycoprotein-I antibody was not routinely tested, it is infrequent compared to the white patients. Venous thrombosis, in particular, is a less important contributor to APS in Chinese patients. APS-related arterial thrombosis, which occurs in patients with longer disease duration, is significantly associated with increased mortality in our SLE patients.

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