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ORIGINAL ARTICLE

Clinical characteristics and laboratory findings of 252 Chinese patients with anti-phospholipid syndrome: comparison with Euro-Phospholipid cohort

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Abstract This study aims to characterize the Chinese Han patients with anti-phospholipid syndrome (APS) and compare the data with those of the Euro-Phospholipid cohort. We conducted a single center study consisting of 252 patients with definite APS from 2000 to 2015. We analyzed the clinical and laboratory characteristics of our cohort and compared the data with those of the Euro-Phospholipid cohort. Our cohort consisted of 216 females and 36 males, with a mean age at entry into this study of 41 years (range 11–74 years). Of these patients, 69 (27.4%) patients had primary APS, and 183 (72.6%) had secondary APS (SAPS), including 163 (64.7%) patients had systemic lupus erythematosus (SLE). Thrombotic events occurred in 190 (75.4%) patients, and the most common ones were deep vein thrombosis (40.1%) and stroke (23.8%), which were similar to the reports of the Euro-Phospholipid cohort. In contrast, our cohort had less pulmonary embolism (6.7%). Among 93 females with 299 pregnancy episodes, the rates of early (<10 weeks) and late fetal loss (≥10 weeks) were, respectively, 37.8% and 24.4%. The latter was significantly higher than that of the Euro-Phospholipid cohort. Moreover, 7 APS nephropathy patients (characterized histopathologically by thrombotic microangiopathy) and 8 catastrophic APS patients were found in our cohort. Anti-cardiolipin antibodies (aCL) were detected in 169 (67.1%) patients, lupus anti-coagulant (LA) was detected in 83 (32.9%), and anti-β2 glycoprotein I antibodies (anti-β2GPI) in 148 (58.7%) patients. These results show that some clinical manifestations of APS may vary among different racial groups.

Keywords Anti-phospholipid syndrome · Clinical · Cohort · Laboratory

Introduction

Anti-phospholipid syndrome (APS) is a multi-systemic autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity associated with the concomitant detection of anti-phospholipid antibodies (aPL), including lupus anti-coagulant (LA), anti-cardiolipin antibodies (aCL), and anti-β2 glycoprotein I antibodies (anti-β2GPI) [1]. APS occurs either as a primary condition (primary APS, PAPS) or in association with other autoimmune diseases, especially systemic lupus erythematosus (SLE). In the catastrophic variant of APS (CAPS), the acute failure of at least three tissues, organs, or systems caused predominantly by small vessel thrombosis can develop and lead to death rapidly [2].

Several researches had reported the clinical and laboratory characteristics of the patients with APS in different areas [3, 4]. Among them, the Euro-Phospholipid project group reported in 2002 the detailed information of 1000 APS patients from Europe [4]. Subsequently, Koike and his colleagues performed a retrospective cohort study of 141 Japanese APS patients in 2012 and noted a high prevalence of arterial thrombosis in Japanese APS patients [3]. However, the systemic analysis of the clinical and immunologic features from Chinese APS patients was still limited. Of note, the Chinese population is over 1.38 billion, including 91.5% Han Chinese.

Hui Shi and Jia-lin Teng contributed equally to this work.

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The aim of this study is to characterize the clinical and laboratory manifestations of Chinese Han APS patients at the times of disease onset and of entry into our database. Furthermore, we also compared the features of our cohort with the Euro-Phospholipid cohort in an effort to identify the different features of APS between the Chinese and Europeans.

Patients and methods

APS-SH database

The APS-SH database was established in 2000 by a group of qualified rheumatologists and statisticians in Shanghai Jiaotong University School of Medicine (Shanghai, China). The database included infobank and biobank of APS patients.

Patient selection

Our APS cohort included 252 consecutive patients from 2000 to 2015, and all patients met the criteria for the classification of APS [5, 6]. Patients enrolled before 2006 were rechecked by the revised Sydney criteria [5]. All patients had their medical histories, laboratory tests, imaging studies, and treatments documented and underwent a medical follow-up by a qualified rheumatologist. The study was performed in accordance with the Declaration of Helsinki and the Principles of Good Clinical Practice and was approved by the Institutional Review Board of Ruijin Hospital, Shanghai Jiaotong University School of Medicine (NO.2012-27).

Definition of clinical features

Secondary APS (SAPS) was considered when the patient met the specific criteria of autoimmune diseases, as follows: SLE, classified according to the American College of Rheumatology (ACR) revised criteria [7]; lupus-like syndrome, for those who fulfilled only 2–3 ACR criteria for SLE; rheumatoid arthritis, according to the ACR criteria [8]; primary Sjogren's syndrome, according to the European Study Group criteria [9]. PAPS was considered for those who did not fulfill classification criteria for any of the other conditions. Patients were considered to have CAPS if they presented with an acutely devastating APS with multiple organ involvement [10]. In addition, APS nephropathy (APSN) was characterized by small renal vascular occlusive lesions, including acute vascular disease like thrombotic microangiopathy (TMA), and chronic vascular lesions, such as fibrous intimal hyperplasia (FIH) of interlobular arteries and renal focal cortical atrophy (FCA) [11].

Thrombosis was confirmed according to the established criteria for each manifestation, using laboratory, imaging/Doppler, or histopathologic studies. Histopathologic confirmation of thrombosis required the absence of significant evidence of inflammation in the vessel wall.

Laboratory studies

IgG/IgM aCL and IgG/IgM/IgA anti-β2GPI antibodies were measured by commercially available ELISA kits (Euroimmun, Luebeck, Germany). The cutoff values for medium/high titers for aCL were 40 GPL (IgG phospholipid units) or MPL (IgM phospholipid units). The cutoff values for anti-β2GPI were calculated by the 99th percentile of healthy subjects.

All plasma samples were tested for the presence of LAC when enrolled in our database according to the recommended criteria from the ISTH Subcommittee on Lupus Anticoagulant-Phospholipid-dependent antibodies [12, 13], using the Automated Coagulation Laboratory (ACL) 300R (Instrumentation Laboratory, Milan, Italy). All samples were screened using the dilute Russell's viper venom time (dRVVT) testing and activated partial thromboplastin time (APTT Instrumentation Laboratory). Ratios higher than 1.10 and that could not be corrected by the 50:50 mixture with normal plasma were considered as suggestive of LA and subjected to dRVVT testing. Both screening and confirming steps were performed. The LAC was considered positive if the ratio of dRVVT screening time/dRVVT confirming time >1.20.

Anti-nuclear antibodies (ANA) were determined by indirect immunofluorescence on mouse liver and HEp-2 cell substrate. Anti-double stranded DNA (anti-dsDNA) antibodies were determined by Farr's ammonium sulfate precipitation technique and ELISA. Extractable nuclear antigen (ENA) antibodies were detected by ELISA kits (Euroimmun). All these tests were performed in the same laboratory that adhered to strict quality controls.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows (version 23.0; SPSS). Statistical analysis was performed by *t* test or chi-square test as appropriate. A P value of less than 0.05 was considered statistically significant.

Results

General characteristics

As shown in Table 1, our cohort consisted of 216 (85.7%) female patients and 36 (14.3%) male patients (female:male ratio 6:1). The mean (±standard deviation, SD) age at the time of entry into our cohort was 41 ± 12 (range 11–74 years, median 43). Eighteen percent of patients were diagnosed as

Table 1 General characteristics and underlying conditions in the APS Chinese cohort compared with the Euro-Phospholipid cohort

Variable	Chinese cohort	Euro-Phospholipid cohort	*P*
Number of patients	252	1000	–
Race (%)	Chinese Han (100)	White (98.5)	–
Gender (female/male)	216/36	820/180	0.163
Mean age at study entry (years)	41 ± 12	42 ± 14	0.131
Primary anti-phospholipid syndrome no. (%)	69 (27.4)	531 (53.1)	<0.001
Systemic lupus erythematosus no. (%)	163 (64.7)	362 (36.2)	<0.001
Lupus-like syndrome no. (%)	16 (6.3)	50 (5)	0.392
Primary Sjogren's syndrome no. (%)	12 (4.8)	22 (2.2)	0.025
Rheumatoid arthritis no. (%)	3 (1.2)	18 (1.8)	0.501

APS after age 50 years. The mean duration of disease was 83 ± 79 months (range 2–422 months, median 95). In our cohort, 27.4% of the patients had PAPS, 64.7% had APS associated with SLE (SLE-APS), 6.3% had APS associated with lupus-like syndrome, and 4.8% associated with primary Sjogren's syndrome. A catastrophic APS occurred in 8 (3.2%) patients. Of note, the ratio of the female to male was 2.18 in PAPS, while 12 in SAPS. Comparing with the Euro-Phospholipid cohort, our cohort had similar gender ($P = 0.163$) and age ($P = 0.131$). However, our cohort had higher incidence of SAPS (72.6 vs.46.9%, $P < 0.001$), whereas the European cohort had higher incidence of PAPS ($P < 0.001$).

Clinical manifestations

At disease onset, 158 (62.7%) patients presented with only thrombotic events, 62 (24.6%) with only pregnancy morbidity, and 32 (12.7%) showed both thrombosis and pregnancy morbidity. As shown in Table 2, the most common clinical manifestations were deep vein thrombosis (35.7%), thrombocytopenia (19.8%), fetal loss (18.7%), stroke (16.7%), and livedo reticularis (8.3%). Of note, while thrombocytopenia and livedo reticularis were clearly prevalent in our cohort, they are not included in classification criteria for APS [5]. In addition, the patients with APS occurred after age 50 had a higher incidence of stroke (48.5%), as compared to 22.7% in the patients with APS onset before age 50. Furthermore, 7 patients had APS nephropathy as indicated by glomerular microthrombosis in their renal biopsy. In comparison, the European cohort had significantly lower incidence rate of fetal loss but higher incidence rate of livedo reticularis ($P < 0.001$, Table 2).

By the time of entry into the study, many clinical manifestations were recorded in vessels of almost all organ systems (Table 3). Briefly, there were 326 thrombotic events, including

Table 2 Clinical features at disease onset in the APS Chinese cohort compared with the Euro-Phospholipid cohort

Manifestations	Chinese cohort no. (%) Total 252 patients	Euro-Phospholipid cohort no. (%) Total 1000 patients	*P*
Deep vein thrombosis	90 (35.7)	317 (31.7)	0.224
Thrombocytopenia (<100,000 platelets/μl)	50 (19.8)	219 (21.9)	0.477
Fetal loss	47 (18.7)	83 (8.3)	<0.001
Stroke	42 (16.7)	131 (13.1)	0.143
Livedo reticularis	21 (8.3)	204 (20.4)	<0.001
Pulmonary embolism	12 (4.8)	90 (9.0)	0.028
Skin ulcers	12 (4.8)	39 (3.9)	0.536
Transient ischemic attack	11 (4.4)	70 (7.0)	0.129
Digital gangrene	11 (4.4)	19 (1.9)	0.022
Hemolytic anemia	8 (3.2)	66 (6.6)	0.039
Epilepsy	5 (2.0)	34 (3.4)	0.248
Superficial thrombophlebitis	4 (1.6)	91 (9.1)	<0.001
Myocardial infarction	3 (1.2)	28 (2.8)	0.142
Amaurosis fugax	2 (0.8)	28 (2.8)	0.063
Pseudovasculitic skin lesions	0 (0)	26 (2.6)	0.010

Table 3 Cumulative clinical features during the evolution of disease at entry in Chinese cohort compared with the Euro-Phospholipid cohort

Manifestation	Chinese cohort no. (%) Total 252 patients	Euro-Phospholipid cohort no. (%) Total 1000 patients	*P*
Peripheral thrombosis			
Deep vein thrombosis	101 (40.1)	389 (38.9)	0.732
Superficial thrombophlebitis in the legs	12 (4.8)	117 (11.7)	0.001
Arterial thrombosis in the legs	6 (2.4)	43 (4.3)	0.160
Jugular vein thrombosis	3 (1.2)	9 (0.9)	0.672
Arterial thrombosis in the arms	2 (0.8)	27 (2.7)	0.072
Venous thrombosis in the arms	2 (0.8)	34 (3.4)	0.027
Subclavian vein thrombosis	1 (0.4)	18 (1.8)	0.103
Neurologic manifestations			
Stroke	60 (23.8)	198 (19.8)	0.160
Migraine	18 (7.1)	202 (20.2)	<0.001
Multi-infarct dementia	12 (4.8)	25 (2.5)	0.058
Transient ischemic attack	11 (4.4)	111 (11.1)	0.001
Epilepsy	9 (3.6)	70 (7.0)	0.624
Acute encephalopathy	3 (1.2)	11 (1.1)	1.0
Transient amnesia	2 (0.8)	7 (0.7)	1.0
Cerebral venous thrombosis	2 (0.8)	7 (0.7)	1.0
Cerebellar ataxia	2 (0.8)	7 (0.7)	1.0
Transverse myelopathy	0 (0)	4 (0.4)	0.589
Hemiballismus	0 (0)	3 (0.3)	1.0
Chorea	0 (0)	13 (1.3)	0.083
Pulmonary manifestations			
Pulmonary embolism	17 (6.7)	141 (14.1)	0.002
Pulmonary hypertension	12 (4.8)	22 (2.2)	0.025
Other (adult respiratory distress syndrome, pulmonary hemorrhage, pulmonary artery thrombosis)	12 (4.8)	7 (0.7)	<0.001
Pulmonary microthrombosis	0 (0)	15 (1.5)	0.052
Fibrosing alveolitis	0 (0)	12 (1.2)	0.140
Cardiac manifestations			
Valve thickening/dysfunction	10 (4.0)	116 (11.6)	<0.001
Angina	7 (2.8)	27 (2.7)	0.946
Myocardial infarction	5 (2.0)	55 (5.5)	0.020
Myocardiopathy	1 (0.4)	29 (2.9)	0.020
Coronary bypass rethrombosis	1 (0.4)	11 (1.1)	0.478
Vegetations	0 (0)	27 (2.7)	0.003
Intra-cardiac thrombus	0 (0)	4 (0.4)	0.589
Intra-abdominal manifestations			
Renal manifestations (glomerular thrombosis, renal infarction, renal artery thrombosis, renal vein thrombosis)	10 (4.0)	27 (2.7)	0.288
Gastrointestinal manifestations (esophageal or mesenteric ischemia)	2 (0.8)	15 (1.5)	0.548
Splenic infarction	3 (1.2)	11 (1.1)	1.0
Pancreatic infarction	0 (0)	5 (0.5)	0.59
Addison's syndrome	0 (0)	4 (0.4)	0.589
Hepatic manifestations (Budd-Chiari syndrome, small hepatic vein thrombosis)	1 (0.4)	7 (0.7)	1.0
Cutaneous manifestations			
Livedo reticularis	21 (8.3)	241 (24.1)	<0.001

Table 3 (continued)

Manifestation	Chinese cohort no. (%) Total 252 patients	Euro-Phospholipid cohort no. (%) Total 1000 patients	*P*
Digital gangrene	14 (5.6)	33 (3.3)	0.092
Cutaneous necrosis	3 (1.2)	21 (2.1)	0.448
Leg ulcers	11 (4.4)	55 (5.5)	0.471
Pseudovasculitic lesions	0 (0)	39 (3.9)	<0.001
Splinter hemorrhages	0 (0)	7 (0.7)	0.356
Osteoarticular manifestations			
Arthralgia	42 (16.7)	387 (38.7)	<0.001
Arthritis	32 (12.7)	271 (27.1)	<0.001
Avascular necrosis of bone	4 (1.6)	24 (2.4)	0.436
Ophthalmologic manifestations			
Retinal vein thrombosis	5 (2.0)	9 (0.9)	0.174
Retinal artery thrombosis	4 (1.6)	15 (1.5)	1.0
Amaurosis fugax	3 (1.2)	54 (5.4)	0.004
Optic neuropathy	1 (0.4)	10 (1.0)	0.704
Ear, nose, and throat manifestations			
Nasal septum perforation	0 (0)	8 (0.8)	0.370
Hematologic manifestations			
Thrombocytopenia	79 (31.3)	296 (29.6)	0.588
Hemolytic anemia	9 (3.6)	97 (9.7)	0.002

184 (56.4%) venous thrombotic events and 142 (43.6%) arterial ones. The most common thrombotic events were deep vein thrombosis (40.1%), stroke (23.8%), and pulmonary embolism (6.7%). The figures of deep vein thrombosis and stroke were similar to the data of the European cohort at entry, but the prevalence of pulmonary embolism was significantly lower than 14.1% of the European cohort ($P = 0.002$). Moreover, the European cohort exhibited significantly more livedo reticularis (24.1 vs. 8.3%, $P < 0.001$), transient ischemic attack (11.1 vs. 4.4%, $P = 0.001$), superficial thrombophlebitis in the legs (11.7 vs. 4.8%, $P = 0.001$), myocardial infarction (5.5 vs. 2%, $P = 0.02$), and venous thrombosis in the arms (3.4 vs. 0.8%, $P = 0.027$) (Table 3).

A total number of 93 females experienced 299 pregnancy episodes; of these, 202 had obstetric complications, including 37.8% (113/299) of early fetal loss (<10 weeks), 24.4% (73/299) of late fetal loss (≥10 weeks), and 14.2% (16/113) of premature birth in all live birth (Table 4). When compared with the corresponding data of the European cohort, our cohort had an increased incidence of late fetal loss but a decreased incidence of live birth (both $P = 0.002$).

Immunologic features

As shown in Table 5, aCL were detected in 169 patients (67.1%), including IgG alone (42.1%), IgM alone (10.7%), and both positive (14.3%) in our cohort. LA was detected in 83 patients (32.9%). When compared with the European cohort, the presence of both aCL and LA in our cohort was significantly lower ($P < 0.001$) (Table 5). Anti-β2GPI

Table 4 Fetal manifestations in Chinese cohort compared with Euro-Phospholipid cohort

Fetal manifestations	Chinese cohort no. (%) Total 299 pregnancies	Euro-Phospholipid cohort no. (%) Total 1580 pregnancies	*P*
Early fetal loss (<10 weeks)	113 (37.8)	560 (35.4)	0.437
Late fetal loss (≥10 weeks)	73 (24.4)	267 (16.9)	0.002
Live birth	113 (37.8)	753 (47.7)	0.002
Premature birth, no. premature/no. live births	16/113 (14.2)	80/753 (10.6)	0.264

Table 5 Immunologic findings in Chinese cohort compared with Euro-Phospholipid cohort

Parameter	Chinese cohort no. (%) Total 252 patients	Euro-Phospholipid cohort no. (%) Total 1000 patients	*P*
Anti-cardiolipin antibodies	169 (67.1)	879 (87.9)	<0.001
IgG alone	106 (42.1)	436 (43.6)	0.660
IgM alone	27 (10.7)	122 (12.2)	0.515
IgG and IgM	36 (14.3)	321 (32.1)	<0.001
Lupus anti-coagulant	83 (32.9)	536 (53.6)	<0.001
Alone	12 (4.8)	121 (12.1)	<0.001
With aCL	26 (10.3)	415 (41.5)	<0.001
With anti-β2GPI	10 (4.0)	–	–
With aCL and anti-β2GPI	35 (13.9)	–	–
Anti-β2GPI antibodies	148 (58.7)	–	–
IgG alone	45 (17.9)	–	–
IgM alone	21 (8.3)	–	–
IgA alone	20 (7.9)	–	–
Dual positive	49 (19.4)	–	–
Triple positive	13 (5.2)	–	–
Anti-nuclear antibodies	206 (81.7)	597 (59.7)	<0.001
Anti-double stranded DNA	102 (40.4)	292 (29.2)	<0.001
Anti-Ro/SSA	52 (2.6)	140 (14)	0.009
Anti-La/SSB	46 (18.3)	57 (5.7)	<0.001
Anti-Sm	31 (12.3)	55 (5.5)	<0.001

antibodies were detected in 148 patients (58.7%); of which, 17.9% was IgG alone, 8.3% was IgM alone, and 7.9% was IgA alone. Of note, the frequency of LA single positivity (4.8%) was the lowest among the anti-phospholipid antibodies (aPL) examined in this cohort. One hundred thirty-seven (54.4%) patients in our cohort had more than one laboratory criteria of aPL present (any combination of aCL, anti-β2GPI, and LA). In addition to aPL, some patients had other autoantibodies. These included ANA in 206 (81.7%) patients, of which 34 (13.5%) were PAPS patients and 172 (68.3%) were SAPS patients. Our cohort had higher positive rate of ANA, anti-dsDNA antibody, and anti-Sm antibody than the European cohort.

Difference between primary APS and SLE-APS in the Chinese cohort

As noted above, our cohort has significantly higher percentage of SLE-APS than that in the European cohort (64.7 vs. 36.2%). It is possible that this difference may account for the differences in clinical and laboratory profiles between the two cohorts. To assess this possibility, we compared the critical clinical and laboratory profiles of PAPS with those of SLE-APS in our cohort. As can be seen in Table 6, there are five significant differences between these two groups. Clinically, patients with SLE-APS exhibited more thrombocytopenia (40.4 vs. 10.1% for PAPS, $P < 0.001$) and arthritis (16.6 vs. 4.3% for PAPS, $P = 0.011$) but less pulmonary embolism (4.5 vs. 14.5% for PAPS, $P = 0.006$). There were no differences in deep vein thrombosis ($P = 0.38$), early fetal loss ($P = 0.137$), late fetal loss ($P = 0.760$), and stroke ($P = 0.870$) between the two groups. For laboratory profiles, there was no significant difference in aCL, anti-β2GPI antibodies, and LA between the two groups. On the other hand, as would be expected, SLE-APS group displayed higher incidence of ANA (100 vs. 62.3% for PAPS, $P < 0.001$), anti-Sm (19 vs. 0% for PAPS, $P < 0.001$), anti-double stranded DNA (49.1 vs. 30.4% for PAPS, $P = 0.009$), anti-SSA (21.5 vs. 10.1% for PAPS, $P = 0.041$), and anti-SSB (19.6 vs. 5.8% for PAPS, $P = 0.008$).

Discussion

To obtain a systemic picture of the Chinese APS patients, we performed a cross-sectional study to analyze clinical and immunological characteristics of a large cohort of 252 patients with APS from a single medical center in Shanghai. Moreover, to identify unique features of the Chinese APS patients, we compared our data with the Euro-Phospholipid project which was a prospective study comprised 1000 patients from 20 university centers in 2002.

A notable difference of our cohort was that 64.7% of patients had SLE, compared with only 36.2% in the

Table 6 Comparison of clinical and immunological profiles of the primary APS (PAPS group) and the APS associated with SLE (SLE-APS group) at entry in Chinese cohort

	PAPS group (%) Total 69 patients	SLE-APS group (%) Total 163 patients	*P*
Clinical profiles			
Deep vein thrombosis	31(44.9)	62 (38.0)	0.38
Stroke	17 (24.6)	43 (26.4)	0.870
Thrombocytopenia	7 (10.1)	66 (40.4)	< 0.001
Pulmonary embolism	10 (14.5)	7 (4.5)	0.006
Pulmonary hypertension	3 (4.3)	9 (5.5)	0.712
Arthritis	3 (4.3)	27 (16.6)	0.011
Arthralgia	11 (15.9)	18 (11.0)	0.302
Superficial thrombophlebitis	4 (5.8)	7 (4.3)	0.736
Venous thrombosis in the arms	1 (1.4)	1 (0.6)	0.507
Migraine	5 (7.2)	12 (7.4)	0.975
Transient ischemic attack	4 (5.8)	6 (3.7)	0.489
Valve thickening/dysfunction	2 (2.9)	8 (4.9)	0.727
Myocardial infarction	1 (1.4)	4 (2.5)	1.0
Livedo reticularis	4 (5.8)	16 (9.8)	0.319
Hemolytic anemia	3 (4.3)	6 (3.7)	0.728
Fetal manifestations[a]	*n* = 83 pregnancies	*n* = 195 pregnancies	
Early fetal loss (<10 weeks)	27 (32.5)	82 (42.1)	0.137
Late fetal loss (≥10 weeks)	21 (25.3)	46 (23.6)	0.760
Live birth	35 (42.2)	67 (34.4)	0.216
Immunological profiles			
Anti-cardiolipin antibodies	46 (66.7)	112 (68.7)	0.760
IgG alone	29 (42.0)	75 (46.0)	0.577
IgM alone	7 (10.1)	16 (9.8)	0.934
IgG and IgM	10 (14.5)	21 (12.9)	0.742
Anti-β2GPI antibodies	38 (55.1)	97 (59.5)	0.531
IgG alone	9 (13.0)	29 (17.8)	0.372
IgM alone	7 (10.1)	12 (7.4)	0.480
IgA alone	1 (1.4)	17 (10.4)	0.019
Dual positive	18 (26.1)	29 (17.8)	0.151
Triple positive	3 (4.3)	10 (6.1)	0.760
Lupus anti-coagulant	30 (43.5)	41 (25.2)	0.072
Anti-nuclear antibodies	43 (62.3)	163 (100.0)	<0.001
Anti-double stranded DNA	21 (30.4)	80 (49.1)	0.009
Anti-Ro/SSA	7 (10.1)	35 (21.5)	0.041
Anti-La/SSB	4 (5.8)	32 (19.6)	0.008
Anti-Sm	0 (0.0)	31 (19.0)	<0.001

[a] Pregnancies

Euro-Phospholipid cohort. Of note, the incidence of SLE was reported to be relatively higher in the non-Caucasian racial groups than in the Caucasian populations [14] and might represent one of the plausible explanations of why the Chinese patients with APS have more SAPS than the European patients with APS. The high prevalence of SLE in our cohort led to a low 27.4% PAPS (vs. 53.1% for the Euro-Phospholipid cohort) [4].

Interestingly, a very recent report from another APS study in China showed that PAPS was about 40.5% among 84 APS patients [15]; the difference between two APS studies in China may be attributed to the variation resulted from recruitment of patients. Besides, it was reported that Shanghai had a higher prevalence of SLE (70/100,000) than other cities in Asia [16]. In the future, it will be important to study the prevalence of SLE in various parts of China, as well as, the prevalence of APS among the Chinese APS patients.

It is conceivable that the high prevalence of SLE-APS in our cohort may account for some observed clinical and immunological differences between our cohort and the European cohort. Table 6 shows that PAPS and SLE-PAPS have similar prevalence of late fetal loss and aCL but significant difference in pulmonary embolism (14.5% for PAPS vs. 4.5% for SLE-APS, $P = 0.006$), as well as a lower trend for LA in SLE-APS (25.2 vs. 43.5% for PAPS). The data suggest that lower prevalence of pulmonary embolism in our Chinese cohort may, in part, be due to the high prevalence of SLE-APS in our cohort. On the other hand, the higher prevalence of late fetal loss and lower prevalence of some minor clinical APS features (such as superficial thrombophlebitis in the legs, transient ischemic attack, myocardial infarction, and venous thrombosis in the arms) in our Chinese cohort may be due to ethnical and/or environmental difference(s). These findings imply that more attentions are needed to study APS in China.

In addition to comparing the clinical characteristics and immunological profiles of the PAPS with those of SLE-APS in our cohort, we also perform similar comparison between PAPS and SAPS. The results were similar to the above comparison between PAPS and SLE-APS, except that the presence of LA in the SAPS patients was significantly lower than that in the PAPS patients (29 vs. 43.5%, $P = 0.029$; data not shown due to the limitation of 6 Tables). Thus, lower LA positivity in our cohort (as compared with the European cohort) may, in part, be due to the high prevalence of SAPS in our cohort.

Regarding the lower prevalence of aCL in our Chinse cohort, it should be noted that we followed the revised Sydney criteria in 2006 and used 40 GPL or MPL as the cutoff values, while the 2002 Euro-Phospholipid cohort followed the Sapporo criteria in 1999 and used 20 GPL or MPL as the cutoff values. Therefore, the lower rate of aCL in our cohort may be explained, at least in part, due to the higher cutoff values in our present study.

The prevalence and genetic risk factors of venous thrombosis vary significantly among different ethnic/racial groups [17–19]. For examples, the incidences per 100,000 of venous thrombosis were, respectively, 104 in the Caucasians and 21 in Asian-Pacific Islanders ($P < 0.001$) [20]. Moreover, the annual incidences per 100,000 Chinese of DVT and PE were, respectively, 17.1 and 3.9 [21].

At the genetic level, a genome-wide association study (GWAS) showed that only 7 of 2.5 million studied single nucleotide polymorphisms (SNPs) were associated with venous thrombosis in the European-Ancestry populations at a genome-wide significant level ($P < 5 \times 10^{-8}$) [22]. Subsequent analyses showed that rs6025 (factor V Leiden mutation), rs8176719 (ABO blood type O allele), rs2519093 (ABO blood type, intron 1), and rs1799963 (prothrombin G20210A) were the major high-thrombosis risk SNP in the European-Ancestry populations. However, these genetic variants do not confer susceptibility to venous thrombosis in the Chinese population. Instead, two variants of protein C gene (Arg-189 to Trp substitution, R189W, and Lys-192 deletion, K150del, leading to impaired anti-coagulant activity of protein C) and one variant of thrombomodulin gene (c.-151G > T, detected with the rs16984852 SNP, in the 5′ UTR, resulting in reduced thrombomodulin expression) increased risks toward venous thrombosis in the Chinese population [18, 23, 24].

Of all thrombotic events in our cohort, venous thrombosis was more prevalent (56.4%) than that of arterial thrombosis (43.6%), similar to the European cohort. However, a Japanese cohort study observed a higher incidence of arterial thrombotic events than venous ones (66 and 32.6%, respectively) [3]. The authors of the study suggested that the genetic and/or environmental background may affect the prevalence of thrombotic events, as the Japanese had been known to have higher blood pressure values than populations in other developed countries. In addition, it was reported that cerebral infarction/TIA was more prevalent in female than male PAPS patients, and mesenteric thrombosis and Budd-Chiari syndrome were more prevalent in male than female PAPS patients in Mexico cohort [25]. But, we did not find such a difference in our cohort. Meanwhile, we did not observe certain reported manifestations of APS such as transverse myelopathy, hemiballismus, chorea, pulmonary microthrombosis, and fibrosing alveolitis. This may be due to the smaller patient number of our cohort than that of the European cohort and/or the regular long-term prophylactic use of anti-coagulants in our cohort.

For fetal loss in general population, there were also some variations among different ethnic/racial groups. For examples, in 2015, the estimated stillbirth rates (deaths per 1000 live births) were 2.65 (2.39 to 2.95) for the Western Europeans and 6.87 (4.84 to 9.56) for the Chinese, resulting in total stillbirths (in thousands) of 11.72 (10.53 to 13.05) and 12.32 (8.60 to 17.18), respectively [26]. For APS patients, Koike and his colleagues reported that the pregnant Japanese APS patients experienced high incidence of late fetal loss (29.6 vs. 16.9% for the Euro-Phospholipid cohort) [3].

At the genetic level, results from two GWAS had been published [27, 28]. The Li study was a pilot study in 44 Han Chinese patients with idiopathic recurrent miscarriage (IRM) and 44 matched healthy controls and identified three regions (6q27, 9q33.1, and Xp22.1) that were significantly associated with IRM. On the other hand, the Kolte study used ~60,000 SNPs to analyze 30 affected Danish sibling pairs with IRM and identified 4 potential areas: rs10514716 (3p14.2), rs10511668 (9p22.1), rs341048 (11q13.4), and rs10485275 (6q16.3). Significantly, there was no overlap in the areas associated with IRM from these two studies, suggesting that there may be racial difference in genetic risk factors associated with IRM.

Our study showed that APS is prone to female patients (female:male ratio 6:1), implying the effect of estrogen in the pathogenesis of APS. In our study, the female:male ratio was decreased to 2.18 in patients with PAPS but increased to 12 in APS patients associated with SLE. The lower female:male ratio in PAPS was consistent with the reported ratio from 1.2:1 to 5:1 in different cohorts [25, 29, 30]. Regarding the effect of the patient's age at disease onset on APS expression, our study revealed that the APS patients aged more than 50 years old had a higher incidence of stroke compared to the patients less than 50 years old. This finding is consistent with the previous finding from the Euro-Phospholipid project. Of note, it was shown that the risk of stroke increases with age after the age of 45 [31].

APS nephropathy (APSN) had been reported in patients with PAPS, SAPS, and SLE (aPL positive) [32]. In our cohort, 7 patients with APSN were all histologically diagnosed by the detection of thrombotic microangiopathy (TMA) and small blood vessels fibrous intimal hyperplasia (FIH) in partial renal pathology. TMA is the most common manifestation of acute APSN in PAPS, and the chronic diseases such as FIH and renal FCA are preceded by acute TMA lesion [11]. The main manifestations of all 7 patients with APSN in our study were hypertension (medium to severe), proteinuria, and renal insufficiency, which were the important factors that affect prognosis.

There is growing evidence that patients with combined aPL positivity are associated with increasing thrombotic risk [33, 34]. Therefore, the combined detection of aPL profiles are more important in guiding clinical diagnosis and prognosis. Our cohort showed that more than 50% patients had more than one laboratory criteria of aPL present (any combination of aCL, anti-β2GPI, and LA); it will be critically important to follow these patients carefully to reduce their thrombotic risks.

In summary, this is the first large cohort study of the Chinese patients with APS on their clinical and immunological features; the results represent the profile of the general Chinese APS population. Compared with the data from Euro-Phospholipid cohort, higher rates of SAPS and abnormal pregnancies were found. Incidence of common thrombotic events was similar to Euro-Phospholipid cohort. Lower positive rates of aCL and LA in our cohort were noted. Differences between the two compared populations show that some clinical manifestations of APS may vary among different racial groups. Our intention is to follow up these APS patients from our database in order to describe the APS prospectively in the Chinese Han population. More data from our database will follow.

Compliance with ethical standards

Disclosures None.

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