Clinical and immunological characteristics of antiphospholipid syndrome in an Asian population: a retrospective study

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Abstract

Objectives: To describe the characteristics of patients with antiphospholipid syndrome (APS) in an Asian clinical practice setting.

Methods: We conducted a single-center, retrospective study of APS patients attending the rheumatology or hematology clinics, between January 2012 and December 2016.

Results: There were 450 patients suspected of having APS referred to our clinics. Seventy-four (16.4%) were diagnosed of APS, 51% of which were definite. Fifty-two (70%) patients were classified as primary APS, 50% of which were definite APS. The most common clinical manifestation was stroke (33%), followed by deep vein thrombosis of the lower extremities (30%) and pulmonary embolism (19%). Hypertension and the presence of at least one established cardiovascular risk factor were independently associated with stroke. Seven (9%) patients had multiorgan thrombosis as their first presentation of APS, 71% of which ultimately suffered from permanent organ damage or died of severe thrombosis, despite not fulfilling the criteria for 'definite' catastrophic APS (CAPS). Late fetal loss was the most prevalent obstetric complication. The majority of patients (79%) tested positive for lupus anticoagulant (LAC), while only 32% tested positive for anti-cardiolipin antibodies. Triple positive profile was documented in 14% of the cohort. Overall, recurrent thrombosis and bleeding complications were recorded in 9% and 28%, respectively.

Conclusion: APS patients in central Thailand demonstrated high prevalence of stroke, late fetal loss, LAC positivity, and multiorgan thrombosis at first presentation, leading to poor outcomes.

Key words: antiphospholipid syndrome, antiphospholipid antibodies, Hughes syndrome, thrombosis, stroke

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease, characterized by vascular thrombosis or obstetric complications, in conjunction with persistent antiphospholipid antibodies (APL).[1] According to the updated Sapporo classification criteria, a diagnosis of APS requires one clinical criteria, thrombosis or pregnancy morbidities, and at least one positive test for APL, on two occasions.[2] Approximately 1% of APS patients develop catastrophic APS (CAPS), defined as having thrombosis in three or more organs in less than a week, and histological confirmation of small vessel thrombosis in at least

one of the organs involved.[3] APS led to a mortality rate of 9% over a 10-year period in the Euro-phospholipid study,[4] but the rate could be as high as 37% in cases of CAPS.[5] In addition, 20% of APS patients also suffered from permanent organ damage, most prominently in the central nervous system.[6]

Since APS is an uncommon disease, the data on clinical features and outcomes of APS patients remains limited, especially in Asian populations. Furthermore, the existing studies of Asian APS demonstrate highly diverse clinical features between ethnic groups.[7-12] Stroke was the most common thrombotic event in

Singaporean and Japanese studies, while venous thrombosis of the lower limbs was the most common in Indian, Chinese and Malaysian studies. Late fetal loss was the most common pregnancy complication in Japanese and Indian populations, but early fetal loss was the most prevalent in other ethnic groups. As a result, we aim to determine the clinical characteristics of Thai patients with APS in a real-world clinical care setting.

Methods

Between January 2012 and December 2016, 450 patients with either thrombosis or obstetric complications, and at least one APL testing were referred to rheumatology and hematology clinic at Thammasat University Hospital. Patients were identified from diagnosis coding of D68.5 through D68.9 according to the 10th version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and electronic laboratory database for APL testing.

Medical records were reviewed manually to identify patients diagnosed with APS. We included patients who fulfilled the 2006 updated Sapporo classification criteria for APS[2] (definite APS), as well as patients who fulfilled the clinical criteria, tested positive for APL in at least one occasion, and were treated as APS by a rheumatologist or a hematologist (probable APS). Patients whose thrombotic events or obstetric complications could be explained by other causes were excluded.

The following data were collected: patient demographics, clinical manifestations, obstetric complications, duration between disease onset and diagnosis, comorbidities, coexisting autoimmune disease, risk factors for thrombosis, established cardiovascular risk (CV) factors, triggering factors, immunological profiles, treatment, duration of follow-up, recurrent thrombosis, bleeding complication and death.

Thrombosis was confirmed by appropriate imaging or histological studies. Multiorgan thrombosis was defined as involving at least two organ systems at disease onset. Patients with pulmonary embolism (PE) and deep vein thrombosis (DVT) of lower extremities, however, were not counted as having multiorgan thrombosis due to the high prevalence of their coexistence in general population.[13] Classification of 'definite CAPS' and 'probable CAPS' was made based on the 2003 preliminary criteria for CAPS[14] and the 2010 updated diagnostic algorithms.[15] Systemic lupus erythematous (SLE) was diagnosed based on the 1997 updated American College of Rheumatology revised criteria.[16] Stroke patients included those who had cerebral infarction or transient ischemic attack (TIA) as a result of intracranial or precerebral artery thrombosis. Obstetric complications were divided into early fetal loss (before the 10th week of gestation), late fetal loss (at or beyond the 10th week of gestation), and premature birth (before the 34th weeks of gestation). Established CV risk factors were defined as having hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or receiving treatment), dyslipidemia (low-density lipoprotein cholesterol > 140 mg/dl or receiving treatment), diabetes mellitus (hemoglobin A1C > 6.5% or receiving treatment), active cigarette smoking, body mass index $\geq$ 30 kg/m^2, or estimated glomerular filtration rate < 60 ml/min.

According to the recommendations by the International Society on Thrombosis and Hemostasis (ISTH),[17] diluted Russell's viper venom time and silica clotting time assays were performed, using Automated Coagulation Laboratory-7000 (Bedford, MA, USA). Three steps of LAC tests included screening, mixing and confirmatory tests. Anti-cardiolipin (ACL) and anti-β2 glycoprotein I (aβ2GPI) were measured using a commercially available ELISA kit (Euroimmun, Germany), with a cutoff value of > 40 GPL or MPL for ACL and a cutoff value at the 99th percentile of healthy individuals for aβ2GPI.

Categorical variables were expressed as frequency and percentage, while continuous variables were expressed as mean and standard deviation. The comparison was calculated using chi-square, Fisher's exact test or student's t test, as appropriate. Factors associated with stroke were identified using univariate logistic regression analysis. The variables with a p-value < 0.2 were then entered into a multivariate logistic regression model. Statistical analysis was done using SPSS software package version 16.0.

Compliance with ethical standards: This study was approved by the Human Research Ethics Committee of Thammasat University No.1 (Faculty of Medicine) in accordance with the Declaration of Helsinki. Certificate of approval No.196/2558, study ID: MTU-EC-IM-1-171/58. For this type of study, informed consent is not required.

Results

Of the 450 patients suspected to have APS, 74 (16.4%) met our inclusion criteria and were subsequently included into analyses. Among the 74 patients included, 38 (51.4%) patients were classified as definite APS and 36 (48.6%) as probable APS. There was no statistical difference between the two groups (**Table 1**). Fifty-two (70.3%) patients were categorized as having primary APS. Among the 22 patients diagnosed with APS associated with autoimmune rheumatic disease (ARD), 21 patients had SLE and one patient had polymyositis. The mean duration between the disease onset and the diagnosis was 5.9 months. Hypertension, dyslipidemia and cigarette smoking were the most common established CV risk factors, with 41 (55.4%) patients having at least one risk factor.

Vascular thrombosis was documented in 69 (93.2%) patients, with 33 (47.9%) having venous thrombosis, 28 (40.6%) having arterial thrombosis, 5 (7.2%) having thrombosis of the small vessels, and 3 (4.3%) having mixed venous and arterial thrombosis. Nevertheless, the most common clinical manifestation in our cohort was arterial stroke, followed by DVT of the lower extremities, and PE. A cumulative distribution of specific thrombosis locations is shown in **Table 1** and **Figure 1a**.

Seven (9.5%) patients had multiorgan thrombosis (**Table 2**). Based on the 2003 preliminary criteria for CAPS and the 2010 updated diagnostic algorithm, none was defined as definite CAPS, but two patients could be classified as probable CAPS (one with thrombosis of three organs but no microthrombosis, and another with thrombosis of two organs, one of which had microthrombosis). Multiorgan thrombosis occurred frequently in the young and the elderly, as 3 (42.9%) patients were 18 years old or younger, and 3 (42.9%) patients were 60 years or older.

Table 1. Patient characteristics

Patient characteristics	Overall (n = 74)	Definite APS (n = 38)	Probable APS (n = 36)	*p*-value†
Age (years), mean ± SD	41.6 ± 17.3	41.3 ± 16.6	41.9 ± 18.2	NS
Female (%)	50 (67.6)	24 (63.2)	26 (72.2)	NS
Comorbidities and cardiovascular risk factors				
Hypertension	26 (35.1)	14 (36.8)	12 (33.3)	NS
Dyslipidemia	23 (31.1)	11 (28.9)	12 (33.3)	NS
Diabetes mellitus	6 (8.1)	2 (5.3)	4 (11.1)	NS
BMI > 30	5 (6.8)	2 (5.3)	3 (8.3)	NS
GFR < 60 ml/min	3 (4.1)	0 (0.0)	3 (8.3)	NS
Active smoking	9 (12.2)	6 (15.8)	3 (8.3)	NS
Coronary artery disease	3 (4.1)	0 (0.0)	3 (8.3)	NS
Most common location of thrombosis (n = 69)‡				
Arterial Stroke	23 (33.3)	15 (42.9)	8 (23.5)	NS
Cerebral arteries	11 (15.9)	5 (14.3)	6 (17.6)	NS
Carotid artery	6 (8.7)	6 (17.1)	0 (0.0)	0.025
Lacunar infarction	4 (5.8)	2 (5.7)	2 (5.9)	NS
TIA	2 (2.9)	2 (5.7)	0 (0.0)	NS
Deep veins of the lower limbs	21 (30.4)	10 (28.6)	11 (32.4)	NS
Pulmonary arteries	13 (18.8)	5 (14.3)	8 (23.5)	NS
Cerebral venous sinus	8 (11.6)	2 (5.7)	6 (17.6)	NS
Arteries of the lower limbs	5 (7.2)	2 (5.7)	3 (8.8)	NS
Renal vein/TMA	5 (7.2)	3 (8.6)	2 (5.9)	NS
Jugular vein	3 (4.3)	0 (0.0)	3 (8.8)	NS
Deep veins of the upper limbs	2 (2.9)	1 (2.9)	1 (2.9)	NS
Arteries of the upper limbs	2 (2.9)	2 (5.7)	0 (0.0)	NS
Pregnancy complications (total pregnancy = 54)				
Late pregnancy loss	11 (20.3)	6 (15.4)	5 (33.3)	NS
Early pregnancy loss	7 (13.0)	3 (7.7)	4 (26.7)	NS
Preterm birth	2 (3.7)	2 (5.1)	0 (0.0)	NS
Non-criteria manifestations				
Thrombocytopenia	16 (21.6)	11 (28.9)	5 (13.9)	NS
Arthritis	9 (12.2)	5 (13.2)	4 (11.1)	NS
Autoimmune hemolysis	8 (10.8)	7 (18.4)	1 (2.8)	NS
Leukopenia	6 (8.1)	3 (7.9)	3 (8.3)	NS
Livedo reticularis	4 (5.4)	3 (7.9)	1 (2.8)	NS
Cutaneous vaculitis	2 (2.7)	0 (0.0)	2 (5.6)	NS
Endocarditis	2 (2.7)	1 (2.6)	1 (2.8)	NS

Data presented using frequency and percentage unless otherwise specified
†comparison between patients with definite and probable APS
‡12 patients had thrombosis in more than one locations
ACL, anti-cardiolipin; Anti-β2GPI, anti-β2-glycoprotein-I; BMI, body mass index; GFR, glomerular filtration rate; NS, not significant; TIA, transient ischemic attack; TMA, thrombotic microangiopathy

Table 1. (Continued)

Patient characteristics	Overall (n = 74)	Definite APS (n = 38)	Probable APS (n = 36)	*p*-value†
Cardiomyopathy	2 (2.7)	1 (2.6)	1 (2.8)	NS
Seizure	2 (2.7)	2 (5.3)	0 (0.0)	NS
Immunological profiles				
Lupus anticoagulant (n = 65)	51 (78.5)	24 (70.6)	27 (87.1)	NS
ACL IgG (n = 73)	19 (26.0)	11 (29.7)	8 (22.2)	NS
ACL IgM (n = 71)	12 (16.9)	5 (13.5)	7 (20.6)	NS
Anti-β2GPI IgG (n = 61)	22 (36.1)	12 (41.4)	10 (31.2)	NS
Anti-β2GPI IgM (n = 59)	40 (67.8)	23 (79.3)	17 (56.7)	NS
Triple positive profile	10 (13.5)	6 (15.8)	4 (11.1)	NS
Treatment				
Warfarin	52 (70.3)	28 (73.7)	24 (66.7)	NS
Statins	27 (36.5)	14 (36.8)	13 (36.1)	NS
Corticosteroids	22 (29.7)	13 (34.2)	9 (25.0)	NS
Antimalarials	21 (28.4)	11 (28.9)	10 (27.8)	NS
Antipletelets	19 (25.7)	9 (23.7)	10 (27.8)	NS
Immunosuppressants	12 (16.2)	9 (23.7)	3 (8.3)	NS
Outcomes				
INR ≥ 2.0 at latest visit (n = 46)	34 (73.9)	19 (70.4)	15 (78.9)	NS
Recurrent thrombosis (n = 69)	6 (8.7)	1 (2.9)	5 (14.7)	NS
Bleeding complications (n = 57)	16 (28.1)	9 (30.0)	7 (25.9)	NS
Irreversible organ damage	15 (20.3)	10 (26.3)	5 (13.9)	NS
Death	5 (6.8)	1 (2.6)	4 (11.1)	NS

Data presented using frequency and percentage unless otherwise specified
†comparison between patients with definite and probable APS
‡12 patients had thrombosis in more than one locations
ACL, anti-cardiolipin; Anti-β2GPI, anti-β2-glycoprotein-I; BMI, body mass index; GFR, glomerular filtration rate; NS, not significant; TIA, transient ischemic attack; TMA, thrombotic microangiopathy

(a) Types of thrombosis

Multiorgan · DVT+PE · Stroke · DVT · PE · Other

(b) Obstetric outcomes

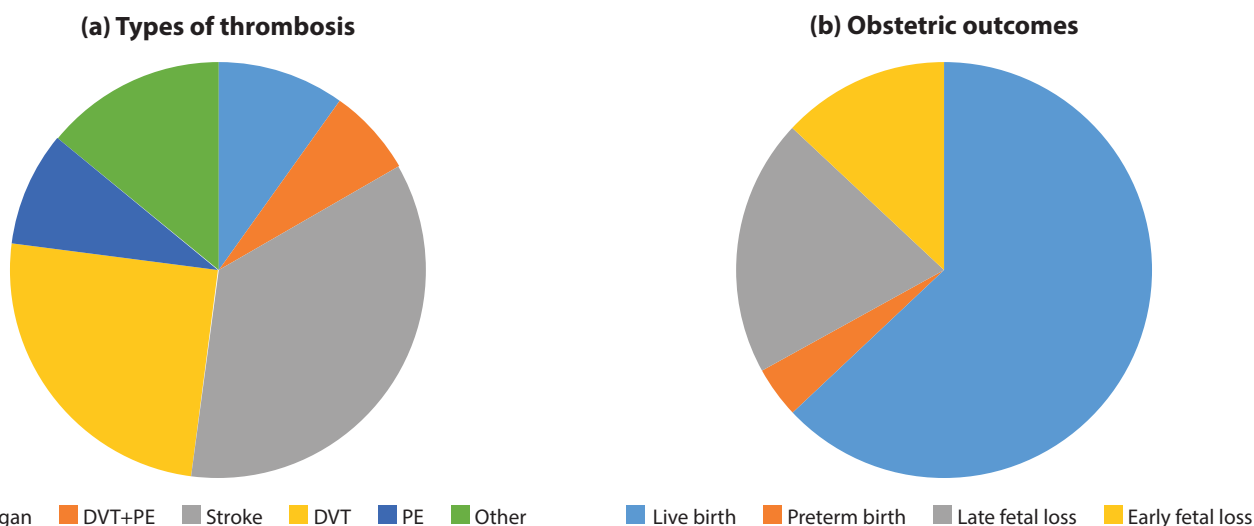Live birth · Preterm birth · Late fetal loss · Early fetal loss

Figure 1. illustrates the characteristics of the current cohort according to (a) types of thrombosis, (b) obstetric outcomes and (c) pattern of antiphospholipid antibody positivity.
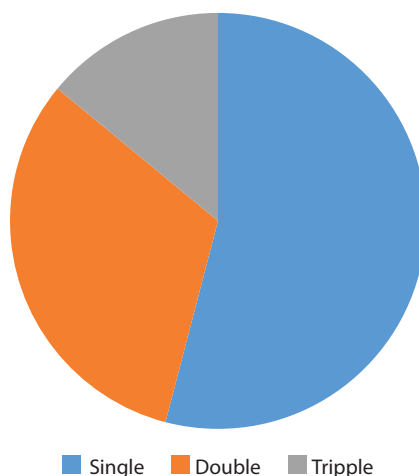
(c) Pattern of antiphospholipid antibody positivity

■ Single ■ Double ■ Tripple

Figure 1. (Continued)

Table 2. Characteristics and outcomes of APS patients presenting with multiorgan thrombosis

Patient no.	Age, gender	No. of organ	Details of thrombosis	ARD	Triggers	Treatment	Outcomes	Long-term organ damage
1	14, M	2	Renal TMA and DVT (lower limb)	SLE	Lupus flare	AC, CS, CYC	Survived	None
2	58, F	2	MCA (bilateral) and arteries of the lower limb	-	-	AC	Died of cerebral infarction	-
3	60, F	2	Jugular vein, inferior vena cava	-	-	AC	Survived	None
4	75, F	3	Cerebral venous sinus, PE and DVT (lower limb)	-	-	AC	Survived	Hemiplegia
5	89, F	3	Cerebral venous sinus, PE and jugular vein	-	Infection	AC	Died of respiratory failure	-
6	11, M	4	PE, cardiac chamber (right atrium), renal vein and arteries of both lower limbs	-	-	AC, CS, thrombectomy	Survived	Amputation of both legs
7	18, F	5	MCA, jugular vein, DVT (upper limb), cardiac chamber (both ventricles) and renal vein	SLE	-	AC, CS, plasma exchange	Survived	Cardiomyopathy

AC, anticoagulant; ARD, autoimmune rheumatic disease; CS, corticosteroids; CYC, cyclophosphamide; DVT, deep vein thrombosis; MCA, middle cerebral artery; PE, pulmonary embolism; TMA, thrombotic microangiopathy

Triggering factors for the occurrence of thrombosis were identified in two patients: preceding infection in one patient and lupus flare in another.

Since arterial stroke was the predominant clinical manifestation in our cohort, the factors associated with the development of stroke was determined using a logistic regression analysis. The presence of hypertension, dyslipidemia, triple APL positivity, and the presence of at least one CV risk factor were identified by the univariate regression analysis. These variables were entered into multivariate model and only hypertension and the presence of at least one CV risk factor were identified as independent risk factors for stroke. The odds ratio and 95% confidence interval was 4.2 (1.2-15.1) for hypertension and 7.9 (2.0-30.9) for the presence of at least one CV risk factor. Using similar model, no factor was found to be associated with the development of arterial thrombosis.

Among the 54 pregnancies recorded in our cohort, 34 (63.0%) pregnancies resulted in live birth, and 2 (3.7%) pregnancies resulted in premature birth due to severe preeclampsia. The most common obstetric complication was late pregnancy loss (11, 20.3%), followed by early pregnancy loss (7, 13.0%) (**Figure 1b**). Non-criteria manifestations were documented in 30 (40.5%) patients. The most prevalent manifestations were thrombocytopenia, arthritis and autoimmune hemolysis (**Table 1**). Fifty-one (78.5%) patients tested positive for LAC, making it the predominant type of APL detected in our cohort. Thirty-four (45.9%) patients tested positive for at least two types of APL, and triple APL positivity was found in 10 (13.5%) patients (**Figure 1c**).

A total of 57 (77.0%) patients received anticoagulants, 99.2% of which were warfarin. Antiplatelets, statins, and antimalarials were prescribed in 19 (25.7%), 27 (36.5) and 21 (28.4%),

respectively. The mean duration of follow-up was 16.3 months. Among those who received anticoagulants, 73.9% achieved the target INR of 2-3 at their latest visits. Recurrent thrombosis was observed in 6 (8.7%) patients, and no recurrent obstetric complication after treatment initiation was recorded. Among the 16 (28.1%) patients who experienced bleeding complications, 11 patients had major bleeding from warfarin overdose, requiring transfusion or hospitalization. We documented five deaths (6.8%), two of which had multiorgan thrombosis at presentation. The causes of death were as followed: respiratory failure (2 patients), hospital-acquired infections (2 patients) and massive cerebral infarction (1 patient). Overall, irreversible organ damage was observed in 15 (20.3%) patients. Finally, the outcomes among those who had multiorgan thrombosis

was poor, as 5/7 (71.4%) patients either died or suffered from permanent organ damages (**Table 2**).

Discussion

In this real-world retrospective study, we have illustrated the clinical characteristics of APS in the ethnic Thai population in central Thailand. The high prevalence of stroke was in agreement with previous Asian studies (**Table 3**).[7,10,12] We identified hypertension and the presence of at least one CV risk factor as independent risk factors for arterial stroke in our patients. Hypertension has been reported as a risk factor for arterial thrombosis in APS by other investigators.[7,18] As stroke patients made up the majority with arterial thrombosis in our cohort, our study provided supporting evidence for the

Table 3. Characteristics of APS patients from the current study, compared to the Euro-phospholipid study and other Asian cohorts

Characteristics	Euro-APS	Yoon KH	Tan BE	Fujieda Y	Singh NK	Teh CL	Shi H	Current study
Year of publication	2002	2003	2009	2012	2013	2015	2017	2018
Dominant ethnic group	European	Chinese	Chinese	Japanese	Indian	Chinese	Chinese	Thai
Total patient	1,000	146	134	141	231	59	252	74
Age, mean ± SD	34 ± 13	44	46 ± 10	41	27 ± 4*	42 ± 12	41 ± 12	42 ± 17
Female	82%	69%	84%	84%	93%*	90%	86%	68%
Primary APS	53%	61%	16%	50%	77%	27%	27%	70%
Venous thrombosis	37%	25%	58%	33%	22%	39%	56%	48%
Arterial thrombosis	27%	56%	42%	66%	14%	39%	44%	41%
Most common thromboses	DVT (32%) Stroke/TIA (20%) PE (9%)	Stroke/TIA (40%) DVT (20%) MI (12%)	Stroke/TIA (34%) DVT (29%) PE (22%)	Stroke (61%) DVT (23%) PE (10%)	DVT (11%) CVT (7%) Stroke (6%)	DVT (31%) Stroke (31%) PE (3%)	DVT (40%) Stroke/TIA (28%) PE (7%)	Stroke/TIA (33%) DVT (30%) PE (19%)
Multiorgan thrombosis	NR	CAPS (1%)	None	NR	NR	NR	CAPS (3%)	10%
Obstetric complications	26%	12%	13%	64%†	71%	44%	68%†	37%†
Fetal loss†	Early (35%) Late (17%)	Early (58%) Late (17%)	NR	Late (46%) Early (14%)	Late (48%) Early (16%)	Early (32%) Late (14%)	Early (38%) Late (24%)	Late (20%) Early (13%)
Livedo reticularis	24%	3%	16%	NR	3%	2%	8%	5%
Most common APL	ACL (88%) LAC (54%)	ACL IgG (69%) Anti-β2GPI (67%) LAC (53%)	ACL IgG (66%) LAC (43%) ACL IgM (18%)	LAC (82%) ACL (59%) Anti-β2GPI (52%)	ACL-IgG (79%) LAC (55%)	ACL (71%) LAC (32%)	ACL (67%) Anti-β2GPI (59%) LAC (33%)	LAC (79%) Anti-β2GPI IgM (68%) ACL IgG (26%)
Triple positivity	NR‡	NR	NR	4%	NR‡	NR‡	14%	14%
Most common CVD risk factors	NR	HTN (49%) DM (16%) DLP (12%)	HTN (58%) DLP (54%) DM (13%)	HTN (35%) DLP (33%) DM (13%)	NR	HTN (44%) DLP (10%) DM (7%)	NR	HTN (35%) DLP (31%) DM (8%)
Smoking	NR	NR	12%	33%	NR	NR	NR	12%
Mortality	NR	10%	NR	NR	NR	5%	NR	7%

*Based on primary APS group (n = 179)
†Percentage of total pregnancy
‡Anti-β2GPI not tested
ACL, anti-cardiolipin; AIHA, autoimmune hemolytic anemia; APS, antiphospholipid syndrome; CAPS, catastrophic APS; CVD, cardiovascular disease; CVT, cerebral venous thrombosis; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; LAC, lupus anticoagulant; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism

role of this traditional risk factor in Thai patients with APS.

In contrast to studies in Chinese and European populations, late fetal loss was the most common obstetric complication in our population. Our results are similar to the obstetric complications reported in Japanese and Indian populations.[7,9] Although ACL was the most prevalent type of APL in almost all previous studies, we found that ACL was the least common type of APL in our cohort. Instead, nearly 80% of our patients tested positive for LAC, followed by aβ2GPI. This finding is similar to one other Asian study by Fujieda et al.[7] Thrombocytopenia occurred in approximately one-fifth of our patients, a prevalence similar to those reported by the Euro-phospholipid project. However, compared to the European population, we found livedo relicularis in much lower frequency. A similar pattern was also observed in other Asian countries (**Table 3**).

Multiorgan thrombosis as the first presentation was found in over 9% of our patients. Although none of these patients could be classified as definite CAPS, the severity and adverse outcomes were similar to those reported in CAPS cases. Also similar to CAPS, 29% of our patients had a history of preceding infection or lupus flare as the triggering factors (**Table 2**). Of note, none of our patients presenting with multiorgan thrombosis had any prior history of APS diagnosis. This observation is different from the report of a large European CAPS registry, which found that 50% of CAPS events occurred in patients previously diagnosed with APS.[5] The age at disease onset in our patients was also different from those reported in the CAPS patients, as only 29% of our patients were between 18-65 years of age, compared to 80% in CAPS registry.[5] Currently, it is not clear what percentage of patients from the previously published APS cohort had multiorgan thrombosis as the first presentation, and how many of them met the CAPS criteria. Our study demonstrated that, despite not meeting CAPS criteria, a clinically significant number of our patients had multiple thrombosis as first presentation, which lead to negative outcome similar to CAPS.

One of the reasons preventing our patients with multiorgan thrombosis from fully complying with the CAPS criteria was the lack of small vessels thrombosis. Only one of our patients with multiorgan thrombosis had renal thrombotic microangiopathy, and no other manifestations compatible with microvascular occlusion were recorded. Given the paucity of data of APS patients, it is not known if the similar pattern of small vessel involvement is shared by other Asian populations.

Regarding our study's limitation, we recognize the risk of misclassification among those labelled as probable APS. The retrospective design inevitably leads to possible missing data. Furthermore, APL tests are not fully covered by certain types of our present national healthcare coverage schemes, leading to incomplete laboratory testing. However, we have demonstrated that there was no difference between definite and probable APS in our cohort. We also ensured that all recruited patients were evaluated by a specialist and that all other alternative diagnoses had been excluded. This limitation reflects our current situation as a healthcare provider in a resource-limited setting. A number of previously published Asian studies also shared similar limitations.[10,11]

In conclusion, we observed several characteristics of Thai APS patients: high prevalence of primary APS, stroke, late fetal loss, and LAC positivity. A significant portion of our patients had multiorgan thrombosis as the first presentation, leading to high rate of adverse outcomes.

Acknowledgements

Conflict of interest

The authors declare that they have no conflicts of interest.

References

1. Gomez-Puerta JA, Cervera R. Diagnosis and classification of the antiphospholipid syndrome. J Autoimmun. 2014;48-49:20-5.
2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.
3. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002;46:1019-27.
4. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramon E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis. 2015;74:1011-8.
5. Rodriguez-Pinto I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15:1120-4.
6. Dall'Ara F, Reggia R, Taraborelli M, Andreoli L, Taglietti M, Frassi M, et al. Patients with longstanding primary antiphospholipid syndrome: retrospective analysis of organ damage and mortality. Lupus. 2014;23:1255-8.
7. Fujieda Y, Atsumi T, Amengual O, Odani T, Otomo K, Kato M, et al. Predominant prevalence of arterial thrombosis in Japanese patients with antiphospholipid syndrome. Lupus. 2012;21:1506-14.
8. Shi H, Teng JL, Sun Y, Wu XY, Hu QY, Liu HL, et al. Clinical characteristics and laboratory findings of 252 Chinese patients with anti-phospholipid syndrome: comparison with Euro-Phospholipid cohort. Clin Rheumatol. 2017;36:599-608.
9. Singh NK, Behera DR, Agrawal A, Singh MN, Kumar V, Godhra M, et al. Hospital based prospective longitudinal clinical and immunologic study of 179 patients of primary anti-phospholipid syndrome. Int J Rheum Dis. 2013;16:547-55.
10. Tan BE, Thong BY, Shivananda S, Han WW, Chng HH. Clinical manifestations and outcomes of antithrombotic treatment of the Tan Tock Seng Hospital Singapore antiphospholipid syndrome cohort. Lupus. 2009;18:752-8.
11. Teh CL, Leong TS. Antiphospholipid syndrome in Sarawak: real world experience in a developing country. Clin Rheumatol. 2015;34:175-8.
12. Yoon KH, Fong KY, Sivalingam P, Koh DR, Ng SC, Lim TC, et al. Antiphospholipid syndrome in Asians: clinical manifestations, serological markers and outcome of the National University of Singapore/National University Hospital antiphospholipid cohort. APLAR J Rheumatol. 2003;6:128-36.
13. Di Nisio M, van Es N, Buller HR. Deep vein thrombosis and pulmonary embolism. Lancet. 2016;388:3060-73.
14. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12:530-4.

15. Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. Autoimmun Rev. 2010;10:74-9.

16. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725.

17. Pengo V, Tripodi A, Reber G, Rand JH, Ortel TL, Galli M, et al. Update of the guidelines for lupus anticoagulant detection. Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2009;7:1737-40.

18. de Souza AW, Silva NP, de Carvalho JF, D'Almeida V, Noguti MA, Sato EI. Impact of hypertension and hyperhomocysteinemia on arterial thrombosis in primary antiphospholipid syndrome. Lupus. 2007;16:782-7.