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Original article

The clinical and laboratory manifestations profile of antiphospholipid syndrome among Saudi Arabia population: Examining the applicability of Sapporo criteria

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ABSTRACT

Antiphospholipid syndrome is a organized autoimmune disease presented with vascular thrombosis and pregnancy morbidity. The Sapporo classification criteria of APS were revised in 2006 and are used as the main diagnosis guideline, which validity as standard measurements is still in debate. This study observe the clinical and laboratory indices of APS among Saudi patients. This is a retrospective study hospital-based population. The clinical and Laboratory manifestations of diagnosed APS patients from electronical medical records identifies by ICD-9 code 795.79 in the King Saud University Medical City, Riyadh, Saudi Arabia, between 1990 and 2012. We selected patients with ICD-9 code 795.79 as. Sapporo criteria applied to all patients, then divided into cases fulfilled criteria and cases failed the criteria. To notice the difference in clinical and laboratory indices and comorbidities between the two groups, the T-test was performed and Logistic regression for the fulfilled criteria and clinical indices of vascular thrombosis, DVT/PE, recurrent, and pregnancy morbidity. A total of 72 (90%) females and 8 (10%) males, with the female-to-male ratio 9:1. The mean (±SD) age at diagnosis was 28.1 (±8.7) years (range 11–63 years). There were 22 patients (27.5%) attained the revised criteria (APS confirmed) and no significant difference between the two groups was observed ($p > 0.2$). However, we found Sapporo confirmed APS cases had significantly higher percentage of serological manifestation presence than clinically diagnosed APS cases. Though there is no statistically significance, Sapporo confirmed APS cases had advanced odds of undergoing vascular thrombosis (OR = 1.61, 95%CI) and DVT/PE (OR = 1.53, 95%CI) and lesser odds of undergoing recurrent DVT/PE (OR = 0.67, 95%CI) and pregnancy morbidity (OR = 0.63, 95%CI) than the clinically diagnosed APS cases. Over 70% of the study population with diagnosed APS did not accomplish the revised Sapporo criteria due to negative laboratory manifestations, which reflects heterogeneous but not degreed disease severity profiles.

1. Introduction

Antiphospholipid syndrome or antiphospholipid antibody syndrome (APS or APLS) is life threatening systematic autoimmune disease with significant mortality and morbidity. APS is characterized with the presence of antiphospholipid antibodies (aPL) in plasma that followed by adverse obstetrical outcome and vascular thrombotic events [1,2]. The prevalence of APS is 1–5% among asymptomatic subjects, however it goes up to 16–44% among people with thrombosis or pregnancy morbidities [3,4]. For most APS cases, early diagnosis is critical in controlling disease progression

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and managing clinical complications. In Sydney, Australia, 2006, a revision on the Sapporo criteria for APS diagnosis was made by the International Congress on antiphospholipid antibodies, which proposed the APS classification criteria include serological studies of lupus anticoagulant (LA), anticardiolipin (aCL) antibody IgG and/or IgM present in medium or high titer (i.e. > 40), or Anti-b2 glycoprotein-I antibody (anti B2GPI) IgG and/or IgM isotype in serum or plasma that present on two or more occasions, at least 12 weeks apart [2]. This criterion replaced the Sapporo preliminary classification criteria for antiphospholipid syndrome that had been used mainly in the clinical researches since 1998 [5]. Repeating the serology studies after 12 weeks rather than 6 weeks was one of the most significant changes in the current revised Sapporo criteria.

All over the world, the disease manifestations were studied in some countries like Singapore and Europe where the included patients were fulfilling the Sapporo criteria [6,7]. To our best knowledge, in Saudi Arabia, no study has been done to assess the APS clinical presentation on a large number of patients particularly those whom had fulfilled the 2006 updated international classification criteria. The only two studies conducted in Saudi Arabia about the clinical presentations of APS disease included patients with positive lupus and/or anticardiolipin antibodies regardless of fulfilling the diagnostic criteria [8,9]. The objective of our study is to examine the clinical and serological manifestations profile of APS among Saudi Arabia population, and assess the applicability of the revised Sapporo criteria in different population.

2. Methods

2.1. Study population

A retrospective study conducted and samples collected from the electronic medical records of King Saud University Medical City, Riyadh, Saudi Arabia, between 1990 and 2012. We identified total of 87 APS records, among them four patients were excluded due to missing the clinical or serological information and another three patients were excluded due to incomplete medical record data. Our study is IRB approved by the ethics committee at King Saud University Medical City. Patient's identity and their clinical data was secured, and not declared in any publication.

2.2. APS case definition

We identified the APS cases through the ICD-9 code 795.79, which were used in the King Saud University Medical City upon the time of our study. The source of selected cases ranged from rheumatology, hematology and anticoagulant clinics. We applied the 2006 revised Sapporo criteria to our study population, and further classified the APS cases into "Sapporo confirmed" cases and "clinical diagnosed" cases. We defined the Sapporo confirmed APS cases as APS patients who were identified through the ICD-9 code and fulfill the Sapporo criteria (i.e. patients with at least one of the vascular thrombosis or pregnancy morbidity conditions and fulfill at least one of the laboratory criteria). The rest of the patients who failed to meet thee Sapporo criteria are classified as the "clinical diagnosed" APS cases.

According to the Sapporo criteria, vascular thrombosis includes deep vein thrombosis DVT, pulmonary embolism, ischemic heart disease, myocardial infraction, stroke, cerebral vein thrombosis, venous sinus thrombosis, superior sagittal sinus thrombosis, gastric presentation of thrombosis, and ophthalmic presentation of thrombosis. DVT was diagnosed by Doppler ultrasound in many vascular distributions namely, popliteal, tibiofemoral, superior and inferior vena cava, axillary and brachial veins. Pregnancy morbidity included the gestational age and counts of spontaneous abortion, intrauterine fetal death (IUFD), and premature birth. Serology data included lupus anticoagulant (LA) and anticardiolipin (aCL) antibodies of IgM and/or IgG. However, we did not include the presence of Anti-β_2 glycoprotein-I (B2GPI) antibody due to no available measurement in the hospital.

2.3. Other medical information

We extracted the patients' demographic information of age at disease onset (defined as the initial manifestation attributable to APS), gender, nationality, and follow-up response. We classified the follow-up response into multiple visits without recurrent event, multiple visits with recurrent event, single visit, and death. We obtained patients diagnosis of systemic lupus erythematous (SLE, based on the American College of Rheumatology criteria), inherited hypercoagulable diseases (protein S deficiency, protein C deficiency, factor V Leiden, ABO incompatibility, and antithrombin III deficiency), and any underlying autoimmune diseases. We also gathered ASP patients' treatment information (use of aspirin, warfarin, Imuran, cyclosporine, CellCept, Enoxaparin, Rituximab, low-molecular-weight heparin, immune globulin, methotrexate, steroid, inferior vena caval filters, Danazol, Thalidomide, and Splenectomy) from the electronic medical records.

2.4. Statistical analysis

Age at APS diagnosis was summarized in mean (SD), and we used independent *t*-test to examine the age difference between Sapporo confirmed and clinically diagnosed APS cases. We summarized the clinical and laboratory manifestation profile, disease/comorbidity distribution, and treatments/drug prescription of APS in count (%) and stratified by case type (Sapporo confirmed APS cases versus clinical diagnosed APS cases). for descriptive analysis purpose, we generated a APS manifestation pattern map comparing the two case groups. Restricted to the clinical diagnosed APS cases, we cross-tabulated the serology results and clinical manifestations in count (%). We used Chi^2 test and compared the statistical difference in the clinical and laboratory manifestation profile, disease/comorbidity distribution, and treatments/drug prescription between Sapporo confirmed and clinical diagnosed APS cases. We used logistic regression to explore which major clinical manifestations (vascular thrombosis, DVT/PE, recurrent DVT/PE, and pregnancy comorbidity) driven the difference between the two case groups. We constructed three models for the logistic regression. The crude associations showed by model 1; the age, gender and nationality adjusted by model 2; the covariates in model 2 plus the follow-up response adjusted by model 3. We performed statistical analyses with Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). The statistical significance was set at two-tailed $p < 0.05$.

3. Results

After excluding 7 subjects with missing data, we included 80 patients as our analytical population. The Sapporo confirmed APS cases is n = 22 (27.5%). The rest n = 58 (72.5%) not fulfilled the Sapporo criteria but were clinically diagnosed as APS cases based on their clinical presentations and/or serology studies of medium–high titer of aCL or positive LA. Regardless of the fulfillment of the Sapporo criteria, 5 (8.6%) clinical diagnosed APS patients had subsequent high risk profile of recurrent DVT, PE, and fetal loss. Fig. 1 shows the heat map of the clinical and laboratory manifestation profiles of the two case groups. Four clinical diagnosed cases failed to meet the Sapporo criteria due to missing both clinical

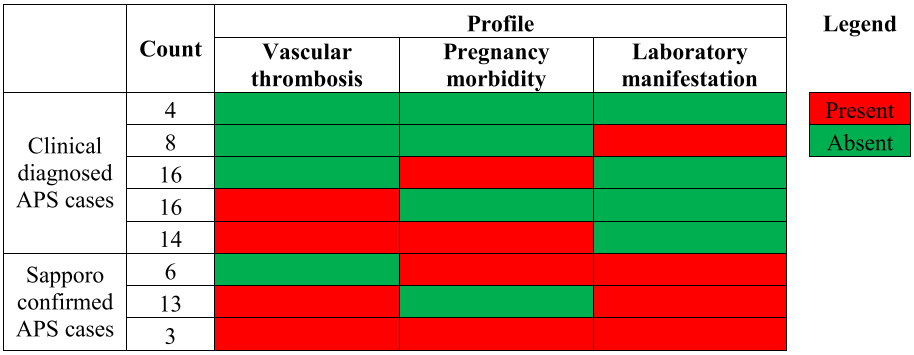

Fig. 1. The heat map1 of fulfillment of revised classification criteria for the APS between clinical diagnosed and Sapporo confirmed APS cases. Abbreviation: APS: Antiphospholipid syndrome. [1] Color legend: red: manifestation present; green: manifestation absent.

and laboratory manifestations, eight due to missing clinical manifestations, and 36 due to missing laboratory manifestations.

Table 1 shows the population characteristics stratified by Sapporo confirmed versus clinically diagnosed APS cases. In total, 72 (90%) patients were females and 8 were (10%) males (the female-to-male ratio = 9:1). The overall population mean (±SD) age at diagnosis of was 28.5 (±8.8) years (range 11–63 years). There was no significant difference in age at diagnosis between Sapporo confirmed APS cases (29.7 ± 9.3, range 14–49) versus clinical diagnosed APS cases (28.1 ± 8.7, age 11–63), p = 0.46. Fig. 1 shows the overlapping age distribution of the two case groups. The nationality distribution was 71 (88.7%) Saudi patients, three Egyptians, two Yemenis, two Sudanese, one Palestine and one Syrian. Clinical diagnosed APS cases had a higher female percentage than Sapporo confirmed APS cases (93.1% versus 81.8%). Sapporo confirmed APS cases had a higher percentage of having complications than the clinical diagnosed APS cases (27.3% versus 6.9%, p = 0.014). Upon 12-year follow up, 30 (37.5%) patients had remission without recurrent event, 14 (17.5%) patients had recurrent events, 1 (2.5%) died, and the rest 35 (43.8%) patients had single visit. The follow-up response was the similar between the two APS case groups (see Fig. 2).

Table 2 shows the application of the revised APS criteria between Sapporo confirmed and clinical diagnosed APS cases. The percentage of DVT, recurrent DVT and PE were higher among Sapporo confirmed APS cases compared to clinical diagnosed APS cases. However, the percentage of spontaneous abortion during 1st trimester (≤10 weeks of gestational age), IUFD, and preterm birth before 3rd trimester were higher among clinical diagnosed APS cases versus Sapporo confirmed APS cases. No preterm birth was reported in the Sapporo confirmed APS patients. The above differences were not statistically significant (p > 0.05). We observed the presence of fetal loss like recurrent abortions (≥2 times) happened in 6 Sapporo confirmed and 26 clinical diagnosed APS cases.

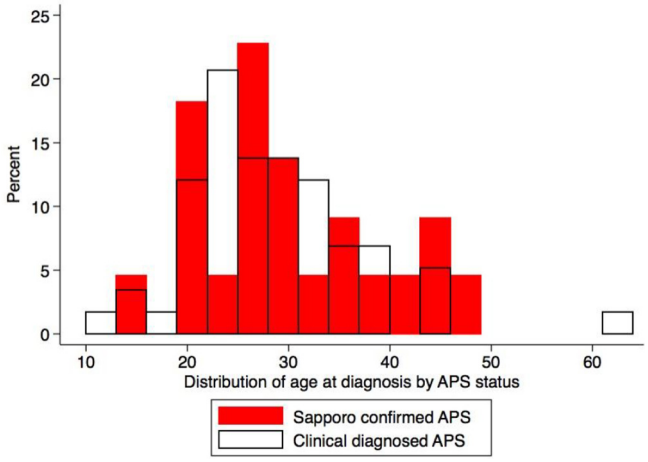

Fig. 2. The age distribution of Sapporo confirmed and clinical diagnosed APS cases. Abbreviation: APS: Antiphospholipid syndrome.

However, Sapporo confirmed APS cases had significantly higher percentage of laboratory manifestation presence than the clinical diagnosed APS cases (100% versus 6.9%, P < 0.001), which was driven by the presence of aCL antibodies of IgG and/or IgM (P < 0.001).

Table 3 shows the disease distribution among Sapporo confirmed and clinical diagnosed APS cases. We found the majority of the APS cases from both groups were in concurrent with SLE. There was significant difference in the distribution of protein S and protein C deficiency across the two groups. Sapporo confirmed APS cases had significantly higher percentage of protein S (22.7% vs 6.9%, P = 0.045) and protein C (22.7% vs 5.2%, P = 0.019) deficiency. One patients had underlying rheumatic heart disease, one had factor V Leiden disease, one had ABO incompatibility, one had both

Table 1
The population characteristics stratified by Sapporo confirmed versus clinically diagnosed APS cases.

	Sapporo confirmed APS[1] (%, N = 22)	Clinical diagnosed APS[1] (%, N = 58)	P value
Age at diagnosis, yr	29.7 (9.3)	28.1 (8.7)	0.46
Year at diagnosis	2001 (4)	2002 (4)	0.6
Female	18 (81.8)	54 (93.1)	0.13
Nationality (Saudi)	18 (81.8)	53 (91.4)	0.23
Complications (Y/N)	6 (27.3)	4 (6.9)	0.014
Follow-up response			
Remission without recurrent event	8 (36.4)	22 (37.9)	0.94
Recurrent event	4 (18.2)	10 (17.2)	
Single visit	10 (45.5)	25 (43.1)	
Died	0 (0)	1 (1.72)	

[1] Abbreviations: APS: Antiphospholipid syndrome.

Table 2
The fulfillment of the revised antiphospholipid syndrome classification criteria between Sapporo confirmed and clinical diagnosed APS cases.

	Sapporo confirmed APS[1] (%, N = 22)	Clinical diagnosed APS[1] (%, N = 58)	P value
Vascular thrombosis	15 (68.2)	31 (53.5)	0.23
Deep vein thrombosis	12 (54.6)	20 (34.5)	0.1
Recurrent deep vein thrombosis	4 (18.2)	9 (15.5)	0.77
Pulmonary embolism	5 (22.7)	6 (10.3)	0.15
Pregnancy morbidity	8 (36.4)	30 (51.7)	0.22
Spontaneous abortion in 1st trimester	4 (18.2)	18 (31.0)	0.25
IUFD[1]	2 (9.1)	8 (13.8)	0.57
Preterm birth before 3rd trimester	0 (0)	1 (1.7)	0.54
Laboratory Manifestation	22 (1 0 0)	4 (6.9)	<0.001
Repeat LA[1] positive	1 (4.6)	0 (0)	0.1
Repeat aCL[1] positive	21 (95.5)	4 (6.9)	<0.001

[1] Abbreviations: APS: Antiphospholipid syndrome; IUFD: intrauterine fetal death; LA: lupus anticoagulant; aCL: anticardiolipin.

Table 3
Disease distribution among Sapporo confirmed and clinical diagnosed APS[1] cases.

Disease	Sapporo confirmed APS (N = 22)	Clinical diagnosed APS (N = 58)	P value
SLE	16 (72.7)	49 (84.5)	0.23
Protein S deficiency	5 (22.7)	4 (6.9)	0.045
Protein C deficiency	5 (22.7)	3 (5.2)	0.019
Sjogren's syndrome	1 (4.55)	4 (6.9)	0.7
Antithrombin III deficiency	1 (4.6)	1 (1.7)	0.47
Behcet's syndrome	0 (0)	1 (1.7)	0.55
Rheumatic heart disease	1 (4.6)	0 (0)	0.1
Celiac disease	1 (4.6)	0 (0)	0.1
Factor V Leiden	0 (0)	1 (1.7)	0.55
ABO incompatibility	0 (0)	1 (1.7)	0.55
Hematology manifestation	4 (18.2)	10 (17.2)	0.92
Pulmonary manifestation	6 (27.3)	9 (15.5)	0.23
Cardiac manifestation	5 (22.7)	5 (8.6)	0.09
Neurological manifestation	2 (9.1)	14 (24.1)	0.13
Gastric manifestation	3 (13.6)	4 (6.9)	0.34
Cutaneous manifestation	1 (4.6)	5 (8.6)	0.54
Ophthalmic manifestation	1 (4.6)	3 (5.2)	0.91

[1] APS: Antiphospholipid syndrome; SLE: lupus erythematous.

Sjogren's and celiac diseases, and one had Behcer's syndrome. We observed anti-thrombin III deficiency presented in one Sapporo confirmed APS patient and one clinical diagnosed APS patient. Hepatic presentations of Buddchiary syndrome were seen in 2 (9%) Sapporo confirmed APS cases, who were complicated by liver infarction and portal vein thrombosis respectively. We did not observe significant difference between the two APS case groups in total hematology, pulmonary, cardiac, neurological, gastric, cutaneous, or ophthalmic manifestations ($P \geq 0.09$).

Table 4 presents the associations of fulfilling Sapporo criteria with major clinical manifestations. After adjusting for age at diagnosis, gender, nationality and follow-up response (model 3), The criteria fulfilled APS patients had advanced odds of undergoing vascular thrombosis (OR = 1.61, 95%CI 0.55, 4.71; P = 0.39) and DVT/PE (OR = 1.53, 95%CI 0.55, 4.31; P = 0.42) than the clinical diagnosed APS cases. However, the Sapporo confirmed APS cases had a lesser odds of undergoing recurrent DVT/PE (OR = 0.67, 95%CI 0.12, 3.81; P = 0.65) and pregnancy morbidity (OR = 0.63, 95%CI 0.21, 1.92; P = 0.42). Due to small sample size and limited power, the above associations were not statistically significant.

Table 5 displayed the treatment used for Sapporo confirmed and clinical diagnosed APS patients. Aspirin, Warfarin and Imuran were the top three most commonly prescribed drugs for APS cases. We did not find significant difference in their prescription between the two APS case groups. No significant difference was observed in the use of cyclosporine, enoxaparin, low-molecular-weight heparin, immune globulin, methotrexate, steroid, inferior vena caval filters, danazol, thalidomide, or splenectomy. However, we found significant difference in the prescription of CellCept, which was only prescribed to 10 clinical diagnosed APS patients (P = 0.04), and in the prescription of rituximab, which was more like to be used among Sapporo confirmed APS patients (18.2% vs 3.5%, P = 0.03) (see Table 6).

4. Discussion

Antiphospholipid syndrome is a common autoimmune disease in the Saudi Arabia community. APS is featured with recurrent vein thrombosis events, and/or recurrent pregnancy morbidity, and abnormal antiphospholipid antibodies levels. In this hospital-based, single-center retrospective study, we found that only less than 30% of the APS patients (Sapporo confirmed cases) with eligible ICD-9 code actually fulfilled the revised Sapporo criteria. The clinical diagnosed APS patients who had classification disagreement were included as a comparison group to assess the diagnose validity of the revised Sapporo criteria as a clinical diagnostic tool [10–13]. The clinical and serological presentations of APS varied depending on the patients' ethnic background. We found that there is no significant difference in the clinical manifestations between cases that fulfill the new classification criteria (Sapporo confirmed APS cases) versus not (clinical diagnosed APS cases). However, Sapporo confirmed APS cases had significantly higher serological manifestations (antiphospholipid antibodies presence) than their counterpart. Comorbidity/other disease distributions are similar between the two groups, except for the higher presence of protein S and protein C deficiency observed among the Sapporo confirmed

Table 4
The association of Sapporo criteria fulfillment with major clinical manifestations.

	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Vascular thrombosis	1.87 (0.66, 5.25)	0.24	1.59 (0.55, 4.65)	0.39	1.61 (0.55, 4.71)	0.39
DVT or PE[1]	1.83 (0.68, 4.92)	0.23	1.54 (0.55, 4.32)	0.41	1.53 (0.55, 4.31)	0.42
Recurrent[2] DVT or PE	0.65 (0.15, 2.79)	0.56	0.77 (0.14, 4.21)	0.77	0.67 (0.12, 3.81)	0.65
Pregnancy morbidity	0.53 (0.19, 1.46)	0.22	0.61 (0.21, 1.84)	0.39	0.63 (0.21, 1.92)	0.42

Model 1: crude associations.
Model 2: adjusted for age at diagnosis, gender, nationality.
Model 3: adjusted for covariates in model 2 and follow-up response.
[1] DVT: deep vein thrombosis; PE: pulmonary embolism.
[2] Analysis for recurrent DVT or PE was restricted to 35 patients with previous DVT or PE event.

Table 5
Treatment for Sapporo confirmed and clinical diagnosed APS[1] patients.

Treatments	Sapporo confirmed APS (N = 22)	Clinical diagnosed APS (N = 58)	P value
Aspirin	10 (45.5)	31 (53.5)	0.52
Warfarin	11 (50)	20 (34.5)	0.2
Imuran	8 (36.4)	16 (27.6)	0.44
Cyclosporine	5 (22.7)	13 (22.4)	0.98
CellCept	0 (0)	10 (17.2)	0.04
Enoxaparin	4 (18.2)	7 (12.1)	0.34
Rituximab	4 (18.2)	2 (3.5)	0.03
LMWH	2 (9.1)	3 (5.2)	0.52
Immune globulin	1 (4.6)	2 (3.5)	0.82
Methotrexate	0 (0)	2 (3.5)	0.38
Steroid	0 (0)	2 (3.5)	0.38
Inferior vena caval filters	1 (4.6)	1 (1.72)	0.47
Danazol	1 (4.6)	0 (0)	0.1
Thalidomide	1 (4.6)	0 (0)	0.1
Splenectomy	0 (0)	1 (1.72)	0.54

[1] Abbreviation: APS: Antiphospholipid syndrome; LMWH: low-molecular-weight heparin.

cases. On the contrary to the serological difference between the two groups, we found that Sapporo confirmed APS cases and clinical diagnosed APS cases were treated indifferently for common drug prescription, except that the usage of CellCept was in favor among the clinical diagnosed APS cases.

The biological rationale behind the identified key comorbidities and APS incidence and progression [1,24] indicates that the presence of protein C and/or S deficiency is likely to increase the risk of internal organ thrombosis and its recurrence. In SLE patients, the cardiac, neurological and thrombocytopenia were more common than among the APS patients without concurrent SLE. However, it is still controversial that the presence of SLE would increase the risk of or being the cause of arterial thrombosis [2].

Our study had several limitations. First, the dependence on the medical records may result in information bias when physicians in training, who usually handled the medical records, missed the documentation of clinical features or details. Second, the APS patients' selection was based on the digitalized medical records in the hospital system, which we think restricted the size of our source population. Third, we did not have enough power due to sample population size, either could we examine temporary relationship between clinical and serological manifestations due to our retrospective study design.

Our study filled the evidence gap of clinical and serological manifestation of APS in the Saudi Arabia population. So far, few studies had been done to properly assess the profiles of APS. These studies included a small number of patients that did not fulfill the international classification criteria. The two available studies were conducted only among patients with positive lupus and/or anticardiolipin antibodies presence [8,9]. Many studies in the Gulf region were case reports, case series or included non-definitive APS patients [14–22]. Although one hospital-based population study from Middle East was conducted in Kuwait on 1996 among APS patients[23], it came before the Sapporo preliminary classification was published in 1999 [2], and thus did not overlap with the evidence provided by our study.

The comparison of our study and studies conducted in other countries (Kuwait [23], Singapore [6] and 13 European countries [7]) on APS manifestation profiles is showed in Table 5. 32 patients

Table 6
Comparative manifestations of APS[1] among different countries.

	Saudi Arabia, % (N = 22; 2002)	Kuwait, % (N = 32; 1996)	Asia, % (N = 146; 2003)	Europe, % (N = 1000; 2002)
Study year	2012	1996	2003	2002
Total patient number	22	32	146	1000
Primary deep vein thrombosis	12 (54.5)	8 (25)	29 (19.9)	389 (38.9)
Fetal loss	8 (36.3)	8 (25)	16 (11)	907 (90.7)
Pulmonary embolism	5 (22.7)	5 (25)	16 (11)	141 (14.1)
Pulmonary hypertension	1 (4.5)	–	–	22 (2.2)
Thrombocytopenia	3 (13.6)	5 (25)	40 (28)	296 (29.6)
Autoimmune hemolytic anemia	2 (9.0)	4 (12.5)	–	97 (9.7)
Myocardial infarction	3 (13.6)	2 (6.0)	17 (11.6)	55 (5.5)
Pericarditis	2 (9.0)	–	10 (6.8)	29 (2.9)
Stroke	1 (4.5)	2 (6.0)	59 (40.4)	198 (19.8)
Migraine	1 (4.5)	–	1 (0.7)	202 (20.2)
Seizure	2 (9.0)	–	8 (5.5)	70 (7.0)
Buddchiary syndrome/liver infarction	2 (9.0)	2 (6.0)	1 (0.7)	7 (0.7)
Portal vein thrombosis	1 (4.5)	–	–	–
Hepatosplenomegaly	1 (4.5)	–	–	–
Retinal infarction	1 (4.5)	1 (5.0)	4 (2.7)	15 (1.5)
Papilledema	1 (4.5)	–	–	–

[1] Abbreviation: APS: Antiphospholipid syndrome.

were included in the Kuwait study, 37.5% of them had primary APS (PAPS) and 62.5% had secondary APS (SAPS) [23]. Compared to the Kuwait study, our study represented smaller median population age and greater female-to-male ratio. The percentage of vascular thrombosis and pregnancy morbidity were higher in our study as compare to the Kuwait patient populations. In Singapore, Yoon et al 2002 published the first cohort of APS in Asia which included 146 patients [6] and reported the most common manifestation of arterial thrombosis and venous thrombosis, which was similar to our study. In Europe, the Euro-Phospholipid Project Group (EPPG), so far, reported the largest APS cohort, which included 1000 patients from 13 European countries, with 82% female and population median age at diagnosis of 31 years of age. This population was predominantly APS cases without SLE (53%), which was larger than the percentage (13.6%) in our study population. As illustrated in Table 5, the key features and comorbidities of APS across our study population to the patients from other countries. DVT was the most common manifestation among our patients, while the thrombocytopenia and stroke were less common compare to Asia and Europe studies. Fetal loss was as high as 90.7% in European patients, which exceeded the percentage of DVT events.

We observed significant difference in the serological features between Sapporo confirmed APS cases and clinical diagnosed APS cases. All of our patients, except for one, had medium–high aCL titer with predominating IgG than IgM. Upon 5 to10 years of follow-up, the aCL titers remained elevated (>40), even among patients receiving anticoagulant treatment (86.3%), and the aCL was continuously over 100 for 59% of patients during follow-up. This phenomenon could reflect the potential risk of recurrent thrombosis and fetal loss while the patient on treatments. This piece of evidence suggests that regular serology testing should be incorporated as a monitoring parameter for treatment response, especially for patients with repeated high tire of aCL-IgG. In contrast, 40 patients (50%) that had negative serology results were diagnosed based on their clinical presentation of thrombosis and/or fetal loss events. However, we cannot confirm that these APS patients were sero-negative since the measurement of anti B2GPI titer was not available in our hospital. Indeed, the value of the serology studies are still debatable as reliable biomarkers in APS diagnosis, including anti B2GPI titer which was added to the criteria to reduce the number of sero-negative APS patients [2,12].

Given our study population, if the Sapporo classification criteria were to be used as a gold standard for diagnosing APS patients, the positive predictive value of this diagnostic tool will be less than 30%, which would raise concerns in clinical practice. Many factors contribute to the higher percentage of APS patients that fail to meet the revised Sapporo criteria. The most important one is that the classification criteria itself, as a diagnostic tool, had been tackled in may studies over the last ten years [10–13]. Second, physicians' awareness and understanding of this criterion plays a vital role on the accurate diagnosis of APS in the real clinical practice. Regardless of the availability, some physicians didn't request the LA test in negative aCL IgM and/or IgG patients or ordered repeated serological tests for patients only received single test.

5. Conclusion

This study presented the APS patients, and identified the gap in applying the international Sapporo classification criteria in this population. Over 70% of the clinical diagnosed APS patients were misdiagnosed by the Sapporo criteria, mainly due to negative laboratory manifestations. Further studies are needed, along with a clinical protocol for interpreting and following up the test results. In the meanwhile, physicians should raise their awareness of the patient subgroups of the sero-negative and the asymptomatic APS cases.

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