The trends in the incidence and thrombosis-related comorbidities of antiphospholipid syndrome: a 14-year nationwide population-based study

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Abstract

Background: This study aims to provide 14-year nationwide epidemiology data to evaluate the incidence ratio of APS in Taiwan and the condition of comorbidities by analyzing the National Health Insurance Research Database.

Methods: Nineteen thousand one hundred sixty-three patients newly diagnosed as having APS during the 2000–2013 period and 76,652 controls (with similar distributions of age and sex) were analyzed.

Results: The incidence of APS increased from 4.87 to 6.49 per 10,000 person-years in the Taiwan population during 2000–2013. The incidence of APS increased with age after 20 years old, especially in the female population, and it rose rapidly after age over 60 years old. In addition, APS cohorts presented a higher proportion of diabetes mellitus, hypertension, hyperlipidemia, stroke, heart failure, atrial fibrillation, myocardial infarction, PAOD, chronic kidney disease, COPD, deep vein thrombosis, pulmonary embolism, SLE, rheumatoid arthritis, Sjogren's syndrome, and polymyositis.

Conclusions: Our study indicated an increasing trend in APS incidence among the Taiwanese population and a relationship between APS and potential comorbidities. This large national study found that the APS risk is heavily influenced by sex and age. Thus, the distinctive sex and age patterns might be constructive given exploring potential causal mechanisms. Furthermore, our findings indicate that clinicians should have a heightened awareness of the probability of APS, especially in women in certain age groups presenting with symptoms of APS.

Keywords: Antiphospholipid syndrome, Epidemiology, Incidence, National health programs, Nationwide population-based study

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease associated with the presence of antiphospholipid antibodies(aPLs), such as anticardiolipin antibodies, antiβ2-glycoprotein 1 antibodies, and lupus anticoagulant. APS diagnosis is based on the combination of clinical features, including thrombosis in the arteries, veins, or small-vessels and/or obstetrical complications such as recurrent miscarriage and the detection of circulating aPLs [1]. However, the pathophysiology of APS remains...
largely unknown. Several mechanisms have been proposed, including the binding of aPLs to β2-glycoprotein 1 receptors, endothelial cell dysfunction, low activity of the epithelial nitric oxide system (eNOS), and complement activation and disposition. APS eventually leads to obstetric or thrombotic complications [2].

Because APS is a rare disease, high-quality epidemiological data from various ethnicities or groups with different comorbidities are required. Recently, a population-based study of 144,248 participants reported that during a 16-year study period, 33 incident cases were recorded, and the annual incidence and estimated prevalence of APS were approximately two people per 10^5 person-years and 50 per 10^5 people, respectively [3]. Another study based on the Korean Health Insurance and Review Agency database, which contains data on more than 52 million Koreans, revealed a total of 3088 newly diagnosed incident cases (1215 men and 1873 women) during 2009–2016. The incidence rate was 0.75 per 10^5 person-years, and the prevalence rate in 2016 was 6.19 per 10^5 individuals [4].

This study aims to provide ten-year nationwide epidemiology data to evaluate the incidence ratio of APS and the condition of comorbidities, which also affect the risk of thrombosis.

Method

Data sources

Taiwan’s National Health Insurance (NHI) program began in 1995 and covered approximately 99% of the 23 million people living in Taiwan [5–8]. This study used the hospitalization dataset from the National Health Insurance Research Database, which contains all inpatient insurance claims filed in Taiwan from 1996 to 2013. The database includes comprehensive information on inpatient care and provides researchers with encrypted personal data associated with relevant claims information, including demographic data, disease diagnosis, and treatments. The disease diagnosis is based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [9].

Definition of APS and non-APS cohorts

This study identified all patients with APS who received their diagnosis between January 1, 2000, to December 31, 2013, to calculate the incidence rates in Taiwan. All patients diagnosed as having APS as defined based on 2006 Revised classification criteria for antiphospholipid syndrome [1]. ICD-9-CM codes 286.53, 289.8, 287.3, 795.7, and 649.3 were classified as the case group. The date of the initial diagnosis of APS was set as the index date. For each APS patient, four cohorts without APS were randomly selected from the same database and frequency-matched according to age, sex, and index year at a 1:4 ratio. The index year for the (control) participants without APS was randomly assigned.

Potential comorbidities

APS-related comorbidities in the study population that were considered included diabetes mellitus [10] (ICD-9-CM 250), hypertension [11–13] (ICD-9-CM 401–405), hyperlipidemia [14] (ICD-9-CM 272), stroke [10] (ICD-9-CM 430–438), heart failure [15] (ICD-9-CM 428), atrial fibrillation [16] (ICD-9-CM 427.32), myocardial infarction [17] (ICD-9-CM 410–410.9, 412), peripheral arterial occlusive disease [10] (PAOD; ICD-9-CM 440–444), chronic kidney disease [13] (ICD-9-CM 580–589), chronic obstructive pulmonary disease [18] (COPD; ICD-9-CM 490–496), deep vein thrombosis [10] (ICD-9-CM 451.1, 451.2, 451.8, and 453), pulmonary embolism [10] (ICD-9-CM 415.1), systemic lupus erythematosus [10] (SLE; ICD-9-CM 710), rheumatoid arthritis [19] (ICD-9-CM 714), systemic sclerosis [20] (ICD-9-CM 710.1), Sjogren’s syndrome [21] (ICD-9-CM 710.2), and polymyositis [22] (ICD-9-CM 710.4).

Statistical analysis

We calculated the annual incidence and age-specific incidence during the 2000–2013 period. The annual incidence was defined as the number of patients with APS divided by the total person-years (per 10,000 person-years) of people in the NHI program annually [23]. The age-specific incidence of APS was calculated by dividing the total person-years (per 10,000 person-years) in each age group (10-year intervals). The ages of the study population were defined as their age in the middle of the follow-up period. We further stratified incidence by sex subgroups. Poisson regression was used to analyze trends of incidence by index year and in each age group. The descriptive statistics of the participants with APS and those without APS were summarized as means and standard deviations for continuous variables; data were presented as cases and percentages for categorical variables. Differences in age group, sex, and comorbidities between participants with and without APS were examined using the chi-square test; age distributions were analyzed using the independent-samples t-test. All statistical analyses were conducted using the SAS package (version 9.4; SAS Institute Inc., Cary, NC, United States). The incidence curve was generated using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value less than 0.05 was considered statistically significant.
Statement
According to previously established study designs, we conducted this study using data from the LHID. The present study was an analysis of de-identified and encrypted secondary data; therefore, no informed consent was required. This study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115(CR-6)), Min-Sheng General Hospital (NO:2022001) and MacKay Memorial Hospital (16MMHIS074). We confirmed that all the methods in this research were performed in accordance with the relevant guidelines and regulations.

Result
Table 1 and Fig. 1 display the annual incidence rates of APS for male and female participants separately during the 2000–2013 period. The study population included 19,163 patients newly diagnosed as having APS, of whom 7926 (41.36%) were male patients, and 11,237 (58.64%) were female patients (Table 2). The incidence of APS increased from 4.87 to 6.49 per 10,000 person-years in the total population during 2000–2013. With respect to sex subgroups, the incidence increased from 4.44 to 5.36 per 10,000 person-years in the male population and from 5.27 to 7.62 per 10,000 person-years in the female population. Overall, women exhibited a higher annual APS incidence than men.

The age-specific incidences of APS are presented in Table 3 and Fig. 2. Compared with the 0–10 age group, cases in the 11–20 age group markedly decreased from 7.52 per 10,000 person-years in the 0–10 age group to 2.67 per 10,000 person-years in the 11–20 age group. After the age of 20, the incidence of APS increased with age and rose rapidly after age 60 years in both the male and female populations. The female population exhibited a higher incidence of APS in the 11–80 age group, whereas the male population recorded a higher incidence of APS in the 0–10 and > 80 age groups.

The results of the Poisson regression model revealed that age, sex, and index year were significantly associated with the incidence of APS (p < 0.0001). It suggests that the annual incidence of APS increased markedly with increasing age and predominantly in the female population.

Table 4 details the characteristics of age, sex, and comorbidities of the participants with and without APS. After frequency matching, 19,163 patients with APS and 76,652 controls (with similar distributions of age and sex) were analyzed. The mean ages of the participants with APS and those without APS were 43.02 ± 26.45 years and 42.71 ± 26.21 years, respectively (p = 0.49). Thus, more than 40% of cases were aged over 40 years. Compared with the participants without APS, more participants with APS also had cardiovascular risk factors (diabetes mellitus, hypertension, hyperlipidemia, stroke, heart failure, atrial fibrillation and myocardial infarction), autoimmune associations (SLE, rheumatoid arthritis, Sjogren's syndrome, and polymyositis), chronic kidney disease and COPD. The APS group most presented with the comorbidities of

| Index year | Total cases | Total person-year | Incidence rate (95% CI) | Male cases | Male person-year | Male incidence rate | Female cases | Female person-year | Female incidence rate |
|------------|-------------|-------------------|-------------------------|------------|------------------|---------------------|-------------|-------------------|----------------------|
| 2000       | 1111        | 22,823,451        | 4.87                    | 497        | 11,181,321       | 4.44                | 614         | 11,642,130        | 5.27                 |
| 2001       | 1060        | 23,170,145        | 4.57                    | 497        | 11,408,052       | 4.36                | 563         | 11,762,093        | 4.79                 |
| 2002       | 1102        | 23,365,986        | 4.72                    | 487        | 11,550,720       | 4.22                | 615         | 11,815,266        | 5.21                 |
| 2003       | 1014        | 23,490,871        | 4.32                    | 439        | 11,648,599       | 3.77                | 575         | 11,842,272        | 4.86                 |
| 2004       | 1316        | 23,642,983        | 5.57                    | 519        | 11,767,614       | 4.41                | 800         | 11,875,369        | 6.74                 |
| 2005       | 1328        | 23,785,305        | 5.58                    | 539        | 11,875,098       | 4.54                | 789         | 11,910,207        | 6.62                 |
| 2006       | 1378        | 23,892,455        | 5.77                    | 572        | 11,953,923       | 4.79                | 806         | 11,938,532        | 6.75                 |
| 2007       | 1353        | 23,999,660        | 5.64                    | 517        | 12,035,496       | 4.30                | 836         | 11,964,164        | 6.99                 |
| 2008       | 1435        | 24,099,774        | 5.95                    | 546        | 12,112,765       | 4.51                | 889         | 11,987,009        | 7.42                 |
| 2009       | 1466        | 24,140,628        | 6.07                    | 641        | 12,164,240       | 5.27                | 825         | 11,976,388        | 6.89                 |
| 2010       | 1608        | 24,193,125        | 6.65                    | 649        | 12,219,631       | 5.31                | 959         | 11,973,494        | 8.01                 |
| 2011       | 1725        | 24,289,377        | 7.10                    | 681        | 12,281,805       | 5.54                | 1044        | 12,007,572        | 8.69                 |
| 2012       | 1687        | 24,373,355        | 6.92                    | 680        | 12,348,656       | 5.51                | 1007        | 12,024,699        | 8.37                 |
| 2013       | 1580        | 24,354,771        | 6.49                    | 662        | 12,352,693       | 5.36                | 915         | 12,002,078        | 7.62                 |

P for trend <.0001 <.0001 <.0001

Incidence rate, per 10,000 person-years
PAOD, deep vein thrombosis, pulmonary embolism, \((p < 0.001)\).

**Discussion**

This is the most extensive study of APS incidence to date, including 19,163 participants with APS and using national population-based registry data. To our knowledge, this is also the first study to investigate the distributions of APS by sex and age in a population. Most epidemiological studies have not reported age distributions due to small study populations or have only declared the age distribution for women and men combined. Our study found that the female population had a higher annual incidence rate of APS than the male population. Female-to-male ratios ranging from 5:1 to 2:1 were reported in one study [24]. Furthermore, an increasing trend in APS incidence among the Taiwanese population was observed in our study. Environmental factors influence the onset of autoimmune diseases. However, an earlier study indicated that infection and drug exposure were correlated with APS [25]. The venereal disease research laboratory test, which involves using purified cardiolipin–lecithin–cholesterol antigen to detect anticardiolipin antibodies, is a screening test for syphilis; it can also positively identify autoimmune diseases such as APS and SLE [26]. Exposure to various bacteria and viruses, including *Mycoplasma pneumonia*, *Streptococcus pyogenes*, *Helicobacter pylori*, Epstein–Barr virus, and cytomegalovirus, is associated with an increased prevalence of aPLs [25]. Several drugs are involved in autoimmunity, including those that produce drug-induced lupus and drug-induced autoimmune hepatitis. Specifically, certain medications, such as procainamide, chlorothiazide, phenothiazines, quinine, and oral contraceptives, are associated with increased levels of aPLs [27]. Future studies are necessary to determine correlations between APS and environmental factors.

APS is characterized by vascular thromboses and pregnancy-related morbidity associated with persistently elevated aPLs [1], which are autoantibodies that recognize a variety of phospholipid-binding plasma proteins beta2-glycoprotein I, prothrombin, and annexin A5. The main pathogenetic mechanisms of aPL-induced thrombosis involve stimulation of the extrinsic coagulation pathway, platelet aggregation, and complement activation and inhibition of tPA, protein C, and protein S [28]. Oxidative stress was reported to affect the structure and function of beta2-glycoprotein I, a complement control protein constructed of five domains [29]. There are two forms of beta2-glycoprotein I – free thiol form (contains broken disulfide bridge at cysteine (Cys) 32 and Cys 60 in domain I and Cys 288 and Cys 326 in domain V) and oxidized form (contains disulfide bonds at these sites) [30]. The level of oxidized form was significantly higher in patients with APS. Lower levels of free thiol form cause a lack of buffer against oxidative stress [31]. Oxidative stress from exogenous sources followed by vascular endothelial injury can stimulate platelet aggregation.
Table 2 Characteristics among patients with Antiphospholipid Syndrome

| Characteristics                        | Antiphospholipid Syndrome (n = 19,163) |
|----------------------------------------|----------------------------------------|
|                                        | n   | %      |
| **Age, years**                         |     |        |
| 0–10                                   | 3242| 16.92  |
| 11–20                                  | 1112| 5.80   |
| 21–30                                  | 1964| 10.25  |
| 31–40                                  | 2709| 14.14  |
| 41–50                                  | 2021| 10.55  |
| 51–60                                  | 2150| 11.22  |
| 61–70                                  | 2031| 10.60  |
| 71–80                                  | 2368| 12.36  |
| > 80                                   | 1566| 8.16   |
| mean± SD                               | 43.02± 26.45 |
| **Gender**                             |     |        |
| Female                                 | 11,237| 58.64 |
| Male                                   | 7926 | 41.36  |
| **Comorbidity**                        |     |        |
| Diabetes mellitus                      | 3548| 18.51  |
| Hypertension                           | 3632| 18.95  |
| Hyperlipidemia                         | 2729| 14.24  |
| Stroke                                 | 4006| 20.90  |
| Heart failure                          | 2646| 13.81  |
| Atrial fibrillation                    | 411 | 2.15   |
| Myocardial infarction                  | 2197| 11.46  |
| PAOD                                   | 1879| 9.81   |
| Chronic kidney disease                 | 3072| 16.03  |
| COPD                                   | 3672| 19.16  |
| Deep vein thrombosis                   | 1167| 6.09   |
| Pulmonary embolism                     | 410 | 2.14   |
| Systemic lupus erythematosus           | 419 | 2.19   |
| Rheumatoid arthritis                   | 816 | 4.26   |
| Systemic sclerosis                     | 53  | 0.28   |
| Sjogren’s syndrome                     | 498 | 2.6    |
| Polymyositis & dermatomyositis         | 34  | 0.18   |

Data shown as n(%) or mean ± SD

and von Willebrand factor expression [32]. Antibodies binding to a particular epitope in domain I of beta2-glycoprotein I have been indicated to increase the risk of thrombosis [33]. Furthermore, beta2-glycoprotein I immune complexes can induce up-regulated activation of toll-like receptor 7 (TLR7) in plasmacytoid dendritic cells and monocytes to release pro-inflammatory cytokine and create a positive-feedback loop for further autoantibody generation [34]. Understanding these pathophysiology provide insight into APS management. Rituximab, a chimeric monoclonal antibody that targets CD20, inhibits B cells involved in aPL-induced clinical manifestations of APS [35]. Hydroxychloroquine has been reported to decrease the overexpression of GPIIb/IIIa on the membrane of aPL-activated platelets and inhibit platelet aggregation [36]. In pregnancy-related morbidity, 20% of female patients with APS experience recurrent pregnancy losses, including miscarriage, fetal loss, and stillbirth at any stage of pregnancy [37]. aPL binding to monocytes, endothelial cells, platelets, and plasma components of the coagulation cascade in the induction of thrombosis causes fetal death in APS. Direct effects of anti-β2GPI autoantibodies on the placenta include an inflammatory response resulting in trophoblast damage, binding to cultured cytotoxic platelets that causes trophoblast membrane perturbation, and a reduction in the secretion of human chorionic gonadotropin [38, 39].

Our study discovered that patients with APS suffered more comorbidities such as hypertension, hyperlipidemia, heart failure, atrial fibrillation, and chronic kidney disease. To the best of our knowledge, one study indicated that the patients with hypertension have higher IgG levels of antibodies to endothelial cells and β2GPI (Beta-2-Glycoprotein I) than control groups. Furthermore, elevated insulin levels, insulin-like growth factor binding protein-1, and greater insulin resistance were associated with Anti-β2GP1 levels. These findings were correlated to our result and provided evidence of linkage between APS and metabolic variables [40]. Adipocytokine, a product produced by adipose tissues, was believed to contribute to low-grade inflammation and several diseases such as metabolic syndrome, atherosclerosis, and type 2 diabetes mellitus [41]. The patients with primary APS and coexistence of metabolic syndrome were reported to have more risks of arterial events by the deterioration of existing endothelial cell dysfunction [42].

Since the initial descriptions of APS were developed, hypertension has been considered one of the frequent signs related to the disease. Hughes identified that an association between livedo reticularis and elevated blood pressure contributed to renovascular etiology; the study population included patients with APS with varying degrees of hypertension ranging from mildly elevated to malignant [11, 12]. Renal involvement was an etiology of the elevated blood pressure in APS [13]. One research demonstrated an extensive series of renal biopsies in APS patients with renal manifestation. Vascular nephropathies such as small vessel vaso-occlusive lesions, recanalizing thrombi in arteries and arterioles, and focal cortical atrophy were found. In addition, 93% of those participants had systemic hypertension; given the high prevalence of hypertension in APS nephropathy (APSN), elevated blood pressure is considered a key marker of renal status [43]. One study indicated that anti-prothrombin antibodies are related to hypertension through a comparison of a patient
group with severe essential hypertension with a matched group of healthy controls; it revealed that 8% of the participants in a patient group had anti-prothrombin antibodies compared with none of the healthy controls [44]. Shajit Sadanand et al. mentioned the association between lipid profile and aPLs. The most general dyslipidemia case in the study population is TG level > 150 mg/dL (51.9%), while LDL > 150 mg/dL (40.2%) takes second place. Statistics show a significant correlation among anti-β2G IgG levels, HDL and LDL level, and aCL IgM level and LDL [14]. Antibodies to oxidized LDLs and cardiolipins were associated with thrombosis and atherosclerotic complications in patients with SLE as early as 1993 [45]. These antibodies interfere with the regulation between platelets, endothelial cells, and coagulation factors and disturb the balance of coagulation and fibrinolysis [46, 47]. One study suggested the assay of anti-β2GP1 with lupus anticoagulant can be used for early detection to those with APS and e thromboembolic events [48].

Our study population was mainly composed of East Asians living in Taiwan. We confirmed that APS was strongly associated with other autoimmune diseases, a finding that is consistent with research undertaken in Western countries. In one such cohort study, up to 36% of

| Age   | Total cases person-year incidence rate | Male cases person-year incidence rate | Female cases person-year incidence rate |
|-------|----------------------------------------|----------------------------------------|------------------------------------------|
|       |                                        |                                        |                                          |
| 0–10  | 3242 43,104,064 7.52                   | 1879 20,597,858 9.12                  | 1363 22,506,206 6.06                    |
| 11–20 | 1112 41,682,562 2.67                   | 411 19,988,749 2.06                   | 701 21,693,813 3.23                    |
| 21–30 | 1964 53,879,919 3.65                   | 516 27,818,813 1.85                   | 1448 26,061,106 5.56                   |
| 31–40 | 2709 53,481,640 5.07                   | 589 27,105,783 2.17                   | 2120 26,375,857 8.04                   |
| 41–50 | 2021 48,388,269 4.18                   | 674 23,992,840 2.81                   | 1347 24,395,429 5.52                   |
| 51–60  | 2150 31,268,709 6.88                    | 848 15,630,505 5.43                    | 1302 15,638,204 8.33                    |
| 61–70  | 2031 20,243,970 10.03                   | 887 10,329,812 8.59                    | 1144 9,914,158 11.54                   |
| 71–80  | 2368 14,267,786 16.60                   | 1241 6,668,043 18.61                   | 1127 7,599,743 14.83                   |
| >80   | 1566 4,481,516 34.94                    | 881 2,382,772 36.97                    | 685 2,098,744 32.64                    |

P for trend <.0001 <.0001 <.0001

Incidence rate, per 10,000 person-years
patients with APS were observed to have a history of SLE [10]. Compared with patients diagnosed as having primary APS, patients with APS as well as an SLE history presented increased incidences of arthralgias and arthritis, leukopenia, autoimmune hemolytic anemia, livedo reticularis, epilepsy, and myocardial infarction [17]. Furthermore, those patients exhibited higher rates of hypertension, dyslipidemia, diabetes, and severe lupus profiles with major organ involvement and higher rates of mortality [10, 49]. Their conditions required long-term anticoagulant treatment and immunosuppressive therapy, including high-dose corticosteroids, cyclophosphamide, and azathioprine [50].

The strength of this study was its employment of a database containing nationwide population-based data of approximately 99% of the 23 million people living in Taiwan. The database's reliability and validity for epidemiological investigations have been reported previously [51].

The use of the ICD-10 definition of APS is uncommon rather than the more standard ICD-9-CM one. However, we suggest that future studies seek access to the medical records and laboratory data to investigate the diagnostic criteria applied to individual medical examinations. The limitation of this study was the anonymity of the NHIRD. The patients' personal information, family histories and laboratory data were not available.

Our current findings indicate a relationship between APS and nonautoimmune comorbidities, such as hypertension, hyperlipidemia, heart failure, atrial fibrillation, and chronic kidney disease.

### Conclusion

In summary, in addition to the known pathophysiology of the disease, various thrombosis-related diseases may influence the risk for APS. Knowing how APS is distributed by sex and age in a population aid in understanding the relationship between APS and complications. Further
research is warranted to investigate the relationship between nonautoimmune comorbidities and APS. Additionally, this study underscores how clinicians should pay close attention to APS-related complications, especially in patient groups prone to high incidences of such complications.

Abbreviations
APS: Antiphospholipid syndrome; aPLs: Antiphospholipid antibodies; NHI: National Health Insurance; PAOD: Peripheral arterial occlusive disease; COPD: Chronic obstructive pulmonary disease; SLE: Systemic lupus erythematosus; IgG: Immunoglobulin G; IgM: Immunoglobulin M; APSN: APS nephropathy; β2GPI: Beta-2-Glycoprotein I.

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Authors’ contributions
Conceptualization: Shin-Yi Tsai; Methodology: Wei-Cheng Yao, Lu-Ting Chiu, Li-Chih Wu, Shin-Yi Tsai; Software: Lu-Ting Chiu; Validation: Lu-Ting Chiu and Shin-Yi Tsai; Formal analysis, Lu-Ting Chiu and Shin-Yi Tsai; Investigation: Wei-Cheng Yao, Kam-Hang Leong, Lu-Ting Chiu, Chien-Feng Kuo and Shin-Yi Tsai; Resources: Lu-Ting Chiu and Shin-Yi Tsai; Data curation: Lu-Ting Chiu; Writing—original draft preparation: all authors; Writing—review and editing: Wei-Cheng Yao, Kam-Hang Leong, Chien-Feng Kuo and Shin-Yi Tsai; Visualization: Lu-Ting Chiu and Shin-Yi Tsai; Supervision: Shin-Yi Tsai; Project administration: Shin-Yi Tsai; Funding acquisition: Wei-Cheng Yao, Lu-Ting Chiu and Shin-Yi Tsai; Submission: Kam-Hang Leong and Shin-Yi Tsai. The authors read and approved the final manuscript.

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Availability of data and materials
The data underlying this study is from the National Health Insurance Research Database (NHIRD). Interested researchers can obtain the data through formal application to the Ministry of Health and Welfare, Taiwan.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee at China Medical University Hospital (CMUH104-REC2-115(CR-6)), the Institutional Review Board of Min-Sheng General Hospital (NO.20200101) and the Institutional Review Board of Mackay Memorial Hospital (16MMHIS074).

Consent for publication
The authors agree with the publication of this paper.

Competing interests
The authors declare that there is no conflict of interest regarding the publication of this paper.

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References
1. Miyakis S, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295–306.
2. Oliveira DC, Correa A, Oliveira C. The issue of the antiphospholipid antibody syndrome. J Clin Med Res. 2020;12(5):286–92.
3. Duarte-Garcia A, et al. The epidemiology of antiphospholipid syndrome: a population-based study. Arthritis Rheumatol. 2019;71(9):1545–52.
4. Hwang JJ, et al. Epidemiology of antiphospholipid syndrome in Korea: a nationwide population-based study. J Korean Med Sci. 2020;35(Di65).
5. Tsai SY, et al. Increased risk of chronic fatigue syndrome following burn injuries. J Transl Med. 2018;16(1):342.
6. Tsai SY, et al. Increased risk of chronic fatigue syndrome in patients with inflammatory bowel disease: a population-based retrospective cohort study. J Transl Med. 2019;17(1):55.
7. Kuo CP, et al. How peptic ulcer disease could potentially lead to the lifelong, debilitating effects of chronic fatigue syndrome: an insight. Sci Rep. 2021;11(1):7520.
8. Shi L, et al. The risk of developing osteoporosis in hemolytic anemia—what aggravates the bone loss? J Clin Med. 2021;10(15):3364.
9. Yao WC, et al. The risk of fibromyalgia in patients with iron deficiency anemia: a nationwide population-based cohort study. Sci Rep. 2021;11(1):10496.
10. Cervera R, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheumatol. 2002;46(4):1019–27.
11. Hughes GR. The Prosser-white oration 1983. Connective tissue disease and the skin. Clin Exp Dermatol. 1984;9(5):335–44.
12. Hughes GR, Harris NN, Gharavi AE. The antiphospholipid syndrome. J Rheumatol. 1986;13(3):486–9.
13. Turrent-Carriles A, Herrera-Felix JP, Amigo MC. Renal involvement in antiphospholipid antibodies. Front Immunol. 2018;9:1008.
14. Badanan S, et al. Dyslipidemia and its relationship with antiphospholipid antibodies in APS patients in North Kerala. Eur J Rheumatol. 2016;3(4):161–4.
15. Pastorri D, et al. Antiphospholipid antibodies and heart failure with preserved ejection fraction. The multicenter ATHERO-APS study. J Clin Med. 2021;10(14):3180.
16. Booth S, et al. Antiphospholipid syndrome and challenges with direct oral anticoagulants. Br J Hosp Med (Lond). 2020;81(S):1–11.
17. Pons-Estel GJ, et al. The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun. 2017;76:10–20.
18. Tanaseanu C, et al. Vascular endothelial growth factor, lipoprotein-associated phospholipase A2, sP-selectin and antiphospholipid antibodies, biological markers with prognostic value in pulmonary hypertension associated with chronic obstructive pulmonary disease and systemic lupus erythematosus. Eur J Med Res. 2007;12(4):45–51.
19. Olech E, Merrill JT. The prevalence and clinical significance of antiphospholipid antibodies in rheumatoid arthritis. Curr Rheumatol Rep. 2006;8(2):100–8.
20. Chatterjee S, Pauling JD. Anti-phospholipid syndrome leading to digital ischaemia and rare organ complications in systemic sclerosis and related disorders. Clin Rheumatol. 2021;40(8):2457–65.
21. Fauvelais AL, et al. Antiphospholipid antibodies in primary Sjogren’s syndrome: prevalence and clinical significance in a series of 74 patients. Lupus. 2004;13(4):245–8.
22. Shere Y, et al. Dermatomyositis and polymyositis associated with the antiphospholipid syndrome—a novel overlap syndrome. Lupus. 2000;9(1):42–6.
23. Tsai SY, et al. Increased risk of chronic fatigue syndrome following prioria: a nationwide population-based cohort study. J Transl Med. 2019;17(1):154.
24. Vianna JL, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European multicenter study of 114 patients. Am J Med. 1994;96(1):3–9.
25. Levy Y, et al. The environment and antiphospholipid syndrome. Lupus. 2006;15(11):784–90.
26. Harris EN, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet. 1983;2(8361):1211–4.
27. Cervera R, Asherson RA. Clinical and epidemiological aspects in the antiphospholipid syndrome. Immunology. 2003;207(1):5–11.
28. Mehi AA, Uthman I, Khamashta M. Antiphospholipid syndrome: pathogenesis and a window of treatment opportunities in the future. Eur J Clin Invest. 2010;40(5):451–64.
29. Schwarzenbacher R, et al. Crystal structure of human beta2-glycoprotein I: implications for phospholipid binding and the antiphospholipid syndrome. EMBO J. 1999;18(22):6228–39.
30. Ioannou Y, et al. Novel assays of thrombogenic pathogenicity in the antiphospholipid syndrome based on the detection of molecular oxidative modification of the major autoantigen beta2-glycoprotein I. Arthritis Rheum. 2011;63(9):2774–82.
31. Ioannou Y, et al. Naturally occurring free thiols within beta 2-glycoprotein I in vivo: nitrosylation, redox modification by endothelial cells, and regulation of oxidative stress-induced cell injury. Blood. 2010;116(1):1961–70.
32. Giannakopoulos B, Krilis SA. The pathogenesis of the antiphospholipid syndrome. N Engl J Med. 2013;368(11):1033–44.
33. de laat B, et al. IgG antibodies that recognize epitope Gly40-Arg43 in domain I of beta 2-glycoprotein I cause LAC, and their presence correlates strongly with thrombosis. Blood. 2005;105(4):1540–5.
34. Lau CM, et al. RNA-associated autoantigens activate B cells by combined B cell antigen receptor/toll-like receptor 7 engagement. J Exp Med. 2003;202(9):1171–2.
35. Youinou P, Renaudineau Y. The antiphospholipid syndrome as a model for B cell-induced autoimmune diseases. Thromb Res. 2004;114(S-6):363–9.
36. Espinola RG, et al. Hydroxychloroquine reverses platelet activation induced by human IgG antiphospholipid antibodies. Thromb Haemost. 2002;87(3):518–22.
37. De Carolis S, et al. Antiphospholipid syndrome: an update on risk factors for pregnancy outcome. Autoimmun Rev. 2018;17(10):956–66.
38. Meroni PL, et al. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. Nat Rev Rheumatol. 2011;7(6):330–9.
39. Ruiz-Irastorza G, et al. Antiphospholipid syndrome. Lancet. 2010;376(9751):1498–509.
40. Frostegard J, et al. Antibodies to endothelial cells in borderline hypertension. Circulation. 1998;98(11):1092–8.
41. Rodrigues CE, et al. Adipocytokines in primary antiphospholipid syndrome: potential markers of low-grade inflammation, insulin resistance and metabolic syndrome. Clin Exp Rheumatol. 2012;30(6):871–8.
42. Rodrigues CE, et al. Association of arterial events with the coexistence of metabolic syndrome and primary antiphospholipid syndrome. Arthritis Care Res (Hoboken). 2012;64(10):1576–83.
43. Nochy D, et al. The intrarenal vascular lesions associated with primary antiphospholipid syndrome. J Am Soc Nephrol. 1999;10(3):507–18.
44. Rollino C, et al. Antiphospholipid antibodies and hypertension. Lupus. 2004;13(10):769–72.
45. Vaatala O, et al. Crossreaction between antibodies to oxidised low-density lipoprotein and to cardioliopin in systemic lupus erythematosus. Lancet. 1993;341(8850):923–5.
46. Mackworth-Young CG. Antiphospholipid syndrome: multiple mechanisms. Clin Exp Immunol. 2004;136(3):393–401.
47. Espinosa G, et al. Antiphospholipid syndrome: pathogenic mechanisms. Autoimmun Rev. 2003;2(2):86–93.
48. de laat HB, et al. beta2-glycoprotein I-dependent lupus anticoagulant highly correlates with thrombosis in the antiphospholipid syndrome. Blood. 2004;104(12):3598–602.
49. Riancho-Zarrabeitia L, et al. Antiphospholipid syndrome (APS) in patients with systemic lupus erythematosus (SLE) implies a more severe disease with more damage accrual and higher mortality. Lupus. 2020;29(12):1556–65.
50. Deak M, et al. Non-thromboembolic risk in systemic lupus erythematosus associated with antiphospholipid syndrome. Lupus. 2014;23(9):913–8.
51. Hsieh CY, et al. Taiwan’s National Health Insurance Research Database: past and future. Clin Epidemiol. 2019;11:349–58.

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