



Antiphospholipid Antibody Positivity and the Clinical Outcomes of Patients with Systemic Lupus Erythematosus

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Objective. To identify the prevalence of antiphospholipid antibodies (aPL) in systemic lupus erythematosus (SLE) patients and determine the relationship between aPL and the clinical outcomes. **Methods.** SLE patients with aPL test results within 2 years of enrollment were selected from Korean lupus network study. They were classified into two groups: aPL (+) group, patients positive for at least one aPL, and aPL (–) group, patients without an aPL. The clinical characteristics of the two groups were compared and the role of aPL in the risk of chronic kidney disease (CKD) in SLE patients was examined. **Results.** Among the 469 SLE patients, 69 (14.7%) had at least one aPL. The prevalence of cerebrovascular disease and CKD was higher in the aPL (+) group than in the aPL (–) group (10.1% vs. 1.8% and 13.8% vs. 5.1%, $p < 0.05$). Multivariable regression analysis showed that the aPL positivity (odds ratio = 3.93, 95% confidence interval = 1.48 ~ 10.47) was associated with the risk of CKD after adjusting for age, disease duration, and lupus nephritis history. **Conclusion.** The prevalence of aPL in Korean SLE patients is 14.7%, and it is associated with a higher prevalence of cerebrovascular disease and CKD in SLE patients. The aPL positivity is independently associated with the risk of CKD in SLE patients. (*J Rheum Dis* 2018;25:239-247)

Key Words. Antiphospholipid antibody, Systemic lupus erythematosus, Chronic kidney disease

INTRODUCTION

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by recurrent thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) [1,2]. Although APS is often associated with other autoimmune diseases, mainly systemic lupus erythematosus (SLE), it can also be seen in patients without a definable rheumatologic condition (primary APS), or it can accompany other conditions such as infection, drug use, or malignancy [1]. According to the Euro-Phospholipid project which included 1,000 patients who met the classification criteria for APS, 53.1% had primary APS, 36.2% had APS associated with SLE, and 10.7% were described to have APS associated with other diseases (5.0% with lupus-like syndrome and 5.7% with other diseases) [3].

aPL are present in 1% ~ 5% of the general population [2]. On the contrary, up to 40% of patients with SLE have aPL, but fewer than 40% of them will eventually experience thrombotic events [4]. It has been estimated that APS could develop in 50% ~ 70% of patients with both SLE and aPL after 20 years of follow up. Although SLE patients frequently harbor aPL, which significantly affects their clinical manifestations and prognosis, information about the characteristics of aPL positivity in SLE patients is insufficient. Previous studies of aPL in SLE might not have reflected the true prevalence of aPL, and their results were inconsistent [2]. Many SLE patients produce aPL intermittently, and their levels vary depending on SLE disease activity, hindering accurate estimation of the prevalence of aPL. Also, the methods used to measure serum aPL levels and the cut off values for positivity could have varied among studies, and one study result suggested that

Received : April 2, 2018, Revised : May 24, 2018, Accepted : June 9, 2018

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ethnic differences could influence the prevalence of aPL [4]. One of the main causes of mortality in SLE patients with aPL is related to thrombosis, and the prognosis of SLE appears to be significantly influenced by the presence of aPL [5-7]. Most previous studies on aPL in SLE patients focused on the relationship with thrombotic or obstetric complications [8-11]. In the renal aspect, previous studies demonstrated associations of aPL with aPL-associated nephropathy (APS nephropathy), which is characterized by acute or chronic renal vascular lesions [12-15]. In addition, studies of aPL on renal outcomes in SLE patients were mostly confined to patients with lupus nephritis (LN) [16-19]. APS nephropathy was associated with increased risk of end-stage renal disease in SLE patients [14]. Although LN is a well-known risk factor for adverse renal outcome [20], studies of the impact of aPL on renal outcomes in patients with LN showed inconsistent results [16-19]. Currently, we do not have enough data to determine the association of aPL with either LN or adverse renal outcomes in SLE patients.

In the current study, we identified the prevalence of patients with positive aPL in SLE patients with stricter cut off values in order to reflect revised classification criteria for APS published in 2006 [21], and we determined the relationships between the presence of aPL and clinical outcomes including renal outcomes, in Korean SLE patients.

MATERIALS AND METHODS

Study population

This study was performed as part of KORean lupus NETwork (KORNET), a nationwide prospective lupus cohort study in South Korea. KORNET is a multicenter, hospital-based registry in 12 University Hospitals in South Korea [22]. KORNET allows studies of the clinical characteristics, treatment, and prognosis of Korean SLE patients. The ultimate goal of KORNET is to develop treatment guidelines for South Korean SLE patients and to investigate the characteristics of Korean SLE at the national level. We registered Korean SLE patients who met the 1997 update of the 1982 American College of Rheumatology (ACR) revised criteria for the classification of SLE beginning in September 2014 [23]. All subjects who agreed to enroll in this registry provided written informed consent. The KORNET registry contains demographics; socioeconomics; obstetrical history; comorbidities; symptoms and signs since diagnosis; medications; laboratory, imaging, and pathological findings;

disease activity; physiological damage; and health-related quality of life. Annual follow up of subjects using a common case report form is compulsory at each study site. As of November 2016, 640 Korean SLE patients had been enrolled and followed up in this registry. This study was approved by the Institutional Review Board/Ethics Committee (IRB no. CNUH-2015-250).

Among the 505 SLE patients registered in KORNET between September 2014 and December 2015, we selected 469 patients who underwent aPL tests within 2 years of enrollment. Using the laboratory values in the revised classification criteria for APS [21], these patients were classified into two groups: 1) the aPL (+) group contained patients positive for at least one aPL, immunoglobulin G (IgG) or IgM anticardiolipin antibody (aCL > 40 GPLU/ml), IgG or IgM anti- β_2 glycoprotein I (a β_2 GPI > 40 SGU/ml), and lupus anticoagulant (LAC, detected according to the guidelines of the International Society on Thrombosis and Haemostasis); 2) the aPL (-) group contained patients without any aPL (Figure 1).

Definition of clinical features

Data collected from the registry were epidemiologic and clinical characteristics, including comorbidities associated with thrombosis and obstetric complications. The thrombotic comorbidities collected were those characterized by the occurrence of thrombosis (arterial or venous): ischemic heart disease, peripheral vascular disorder, and cerebrovascular disease. The obstetric complications associated with APS were also collected that include history of spontaneous abortion, number of spontaneous abortions, and history of stillbirths. Information on the history of LN and its histological classification by the International Society of Nephrology and the Renal

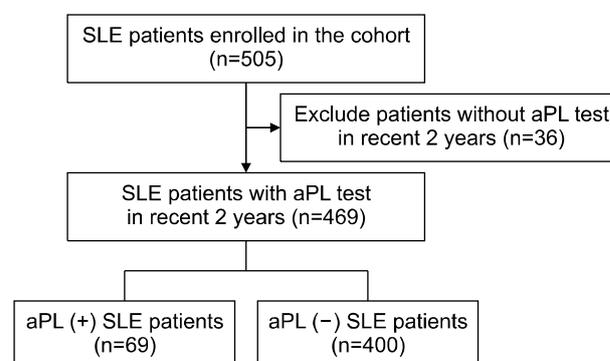


Figure 1. Patient selection flow. SLE: systemic lupus erythematosus, aPL: antiphospholipid antibody.

Pathology Society (ISN/RPS) 2003 classification of LN were also gathered from the registry [24]. Among them, LN class III and above were categorized as severe LN [25].

Laboratory studies

The prevalence of chronic kidney disease (stage ≥ 3) is defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² calculated by the Modification of Diet in Renal Disease Study Equation, which estimates GFR based on serum creatinine level and patient characteristics including age, sex, and race [26-28]. It was a major outcome of this study that we compared between the two groups of Korean SLE patients defined by aPL positivity. We also investigated the factors associated with increased risk of CKD including aPL.

Statistical analysis

The prevalence of aPL was estimated, and a descriptive analysis of the distribution of different aPL patterns was performed. After dividing patients into aPL (+) and aPL (-) groups, we determined the significance of the differences in clinical characteristics, including thrombotic complications, using the chi-square test or Fisher's exact test, independent t-test or Mann-Whitney U-test as appropriate. Analysis of covariance (ANCOVA) was used to determine the significance of differences in the prevalence of vascular comorbidities, renal manifestations, and obstetric complications between two groups. However, ANCOVA was not performed to determine the significance of difference in serum creatinine levels between the two groups due to the presence of heteroscedasticity.

To examine the factors associated with increased risk of CKD, we performed univariable and multivariable logistic regression analyses using various independent clinical variables including aPL. For multivariable regression analysis, variables with p-value less than 0.1 in univariable analysis were selected. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 21.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

Prevalence of aPL in SLE patients

Among the 469 SLE patients enrolled in this study, 69 (14.7%) were positive for any aPL (Figure 1). The distribution of antiphospholipid antibody positivity patterns is shown in Table 1; only one patient (1.4%) was positive

for all three aPL. Only LAC positivity was the most common aPL positivity pattern (72.5%) in this study. In contrast, both aCL and a β_2 GPI more commonly accompanied other aPL rather than showing single positivity patterns. Among the mixed aPL positivity patterns, aCL positivity combined with a β_2 GPI positivity was the most common.

Clinical characteristics of SLE patients with positive aPL

The baseline characteristics of each group at study enrollment and the ACR criteria met for the classification of SLE at the time of diagnosis are shown in Table 2. We found no significant differences between the groups in age, sex, or autoantibody profile such as ANA and anti-dsDNA. However, the aPL (+) group showed a significantly higher number of patients with smoking history (21.7% in aPL (+) group vs. 9.5% in aPL (-) group, $p < 0.01$). There were no significant differences in the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA SLEDAI) and the proportions of patients with SLE flares measured by SELENA SLEDAI flare index between the two groups. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, which reflects accumulated damage of SLE patients, was significantly higher in the aPL (+) group (0.5 ± 0.9 in aPL (+) group vs. 0.3 ± 0.7 in aPL (-) group, $p = 0.04$). Hydroxychloroquine and corticosteroid were the most commonly used medications, with a prevalence of more than 80% (91.7% and 82.1%, respectively). Aspirin was significantly more frequently used in the aPL

Table 1. Distribution of antiphospholipid antibody positivity patterns in antiphospholipid antibody positive patients

Positive antiphospholipid antibodies	Number (%)
aCL (+)*	7 (10.1)
a β_2 GPI (+) [†]	2 (2.9)
LAC (+) [‡]	50 (72.5)
aCL (+) & a β_2 GPI (+)	5 (7.2)
aCL (+) & LAC (+)	3 (4.3)
a β_2 GPI (+) & LAC (+)	1 (1.4)
aCL (+) & a β_2 GPI (+) & LAC (+)	1 (1.4)
Total	69 (100)

aCL: anticardiolipin antibody, a β_2 GPI: anti- β_2 -glycoprotein I antibody, LAC: lupus anticoagulant, Ig: immunoglobulin. *IgG or IgM aCL > 40 GPLU/ml. [†]IgG or IgM a β_2 GPI > 40 SGU/ml. [‡]LAC, detected according to the guidelines of the International Society on Thrombosis and Haemostasis.

Table 2. Demographic and clinical characteristics of patients with or without antiphospholipid antibody

Variable	Total (n = 469)	aPL (+) (n = 69)	aPL (-) (n = 400)	p-value
Age (yr)	40.4 ± 11.3	40.6 ± 11.0	40.4 ± 11.4	0.85
Sex, female	436 (93.0)	64 (92.8)	372 (93.0)	1.00
Disease duration (yr)	8.3 ± 6.3	7.3 ± 6.4	8.5 ± 6.3	0.14
Smoking, ever	53 (11.3)	15 (21.7)	38 (9.5)	< 0.01
ACR criteria at diagnosis				
Malar rash	224 (47.8)	28 (40.6)	196 (49)	0.25
Discoïd rash	24 (5.1)	5 (7.2)	19 (4.8)	0.57
Photosensitivity	140 (29.9)	22 (31.9)	118 (29.5)	0.80
Oral ulcer	126 (26.9)	13 (18.8)	113 (28.3)	0.14
Arthritis	242 (51.6)	33 (47.8)	209 (52.3)	0.58
Serositis	86 (18.3)	10 (14.5)	76 (19.0)	0.47
Renal disorder	173 (36.9)	21 (30.4)	152 (38.0)	0.29
Neurologic disorder	20 (4.3)	4 (5.8)	16 (4.0)	0.72
Hematologic disorder	305 (65.0)	51 (73.9)	254 (63.5)	0.12
Hemolytic anemia	40 (8.5)	7 (10.1)	33 (8.3)	0.77
Leukopenia	209 (44.6)	31 (44.9)	178 (44.5)	1.00
Lymphopenia	79 (16.8)	16 (23.2)	63 (15.8)	0.18
Thrombocytopenia	101 (21.5)	20 (29.0)	81 (20.3)	0.14
Immunologic disorder	425 (90.6)	69 (100.0)	356 (89.0)	< 0.01
Anti-dsDNA Ab	381 (81.2)	58 (84.1)	323 (80.8)	0.63
Anti-Sm Ab	136 (29.0)	18 (26.1)	118 (29.5)	0.67
Antiphospholipid antibody*	137 (29.2)	69 (100.0)	68 (17.0)	< 0.01
Positive ANA	459 (97.9)	68 (98.6)	391 (97.8)	1.00
Number of ACR criteria	4.7 ± 1.4	4.7 ± 1.3	4.8 ± 1.4	0.76
SELENA SLEDAI score	3.7 ± 3.6	4.0 ± 3.6	3.7 ± 3.6	0.45
SELENA SLEDAI flare index				
Flare, regardless of severity	19 (4.1)	3 (4.3)	16 (4.0)	0.75
SLICC/ACR damage index	0.3 ± 0.7	0.5 ± 0.9	0.3 ± 0.7	0.04
Medication				
Corticosteroid	385 (82.1)	57 (82.6)	328 (82.0)	1.00
Mean dose (mg/d)	7.9 ± 8.5	7.1 ± 5.8	8.1 ± 8.9	0.42
Hydroxychloroquine	430 (91.7)	59 (85.5)	371 (92.8)	0.08
Methotrexate	18 (3.8)	5 (7.2)	13 (3.3)	0.21
Tacrolimus	41 (8.7)	6 (8.7)	35 (8.8)	1.00
Azathioprine	77 (16.4)	10 (14.5)	67 (16.8)	0.77
Mycophenolate mofetil	72 (15.4)	8 (11.6)	64 (16.0)	0.45
Cyclosporine	13 (2.8)	3 (4.3)	10 (2.5)	0.64
IV cyclophosphamide	6 (1.3)	2 (2.9)	4 (1.0)	0.47
Aspirin	86 (18.3)	35 (50.7)	51 (12.8)	< 0.01
Warfarin	13 (2.8)	3 (4.3)	10 (2.5)	0.64

Values are presented as mean ± standard deviation or number (%). aPL: antiphospholipid antibody, ACR: American College of Rheumatology, Anti-dsDNA Ab: anti-double stranded DNA antibody, Anti-Sm Ab: anti-Smith antibody, ANA: antinuclear antibody, SELENA SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index, SLICC: Systemic Lupus International Collaborating Clinics, IV: intravenous, Ig: immunoglobulin, LAC: lupus anticoagulant. *Positive finding of antiphospholipid antibodies based on 1) IgG aCL ≥ 10 GPLU/ml or IgM aCL ≥ 7 MPLU/ml, 2) LAC, detected according to the guidelines of the International Society on Thrombosis and Haemostasis, or 3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization of fluorescent treponemal antibody absorption test.

(+) group (50.7% in aPL (+) group vs. 12.8% in aPL (-) group, $p < 0.01$), but use of other medications did not differ between the groups.

Comorbidities and obstetric complications known to be associated with APS and renal manifestations were compared according to aPL positivity, as shown in Table 3.

Table 3. Prevalence of vascular comorbidities, renal manifestations, and obstetric complications associated with antiphospholipid antibody

Variable	aPL (+) (n=69)	aPL (-) (n=400)	p-value	p-value*
Vascular comorbidities (at enrollment)				
Ischemic heart disease	0 (0)	5 (1.3)	0.77	0.09
Peripheral vascular disorder	0 (0)	3 (0.8)	1.00	0.54
Cerebrovascular disease	7 (10.1)	7 (1.8)	<0.01	0.02
Renal manifestations				
Chronic kidney disease, stage $\geq 3^{\dagger}$ (n=440)	9/65 (13.8)	19/375 (5.1)	0.01	<0.01
Serum creatinine level (mg/dl)	0.87 \pm 0.63	0.72 \pm 0.24	<0.01	
eGFR (ml/min/1.73 m ²)	90.85 \pm 29.07	101.73 \pm 32.86	0.01	0.05
Lupus nephritis	20 (29.0)	115 (28.8)	0.97	0.87
Severe lupus nephritis (class \geq III) [‡]	8 (11.6)	77 (19.3)	0.13	0.19
Obstetric complication [§] (n=436)				
History of spontaneous abortion	n=64	n=372		
Number of spontaneous abortion			1.00	0.75
1	6 (9.4)	34 (9.1)	0.54	0.47
2	6 (9.4)	22 (5.9)		
3	0 (0)	8 (2.2)		
4	0 (0)	2 (0.5)		
History of stillbirth	0 (0)	2 (0.5)		
	2 (3.1)	7 (1.6)	0.87	0.81

Values are presented as number (%) or mean \pm standard deviation. aPL: antiphospholipid antibody, eGFR: estimated glomerular filtration rate. *p-value after adjustment for smoking and aspirin; [†]Defined as estimated glomerular filtration rate < 60 ml/min/1.73 m². [‡]Defined as lupus nephritis International society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, and V; [§]Obstetric complications were only evaluated in female patients (n=436).

Two independent variables (smoking and aspirin use history) with significant differences at baseline were selected as covariates for adjustment to remove the possible confounding effects. More patients in the aPL (+) group experienced cerebrovascular disease than in the aPL (-) group (10.1% vs. 1.8%, $p < 0.01$, p after adjustment = 0.02). However, no statistical difference was found in history of ischemic heart disease, peripheral vascular disorder, spontaneous abortion, or stillbirth.

Association of positive aPL and risk of CKD in SLE patients

Chronic kidney disease (stage ≥ 3) was more frequent in the aPL (+) group (13.8% vs. 5.1%, p before adjustment = 0.01, p after adjustment < 0.01), while the proportion of underlying LN and severe LN (ISN/RPS class III and above) was comparable between the two groups (Table 3). The serum creatinine level was higher (0.87 \pm 0.63 vs. 0.72 \pm 0.24, $p < 0.01$) and eGFR was lower (90.85 \pm 29.07 vs. 101.73 \pm 32.86, p before adjustment = 0.01, p after adjustment = 0.05) in the aPL (+) group compared to aPL (-) group. However, the difference in eGFR showed statistically borderline significance after adjusting for aspirin and smoking ($p = 0.05$) (Table 3).

Various clinical variables were evaluated for the association with increased risk of CKD, as shown in Table 4. Multivariable analysis showed that age, disease duration, LN history, and aPL positivity were significantly associated with increased CKD risk ($p = 0.03$ for disease duration and $p < 0.01$ for others). Especially, LN history and aPL positivity showed substantially high odds ratios (odds ratio [OR] = 5.36, 95% confidence interval [95% CI] = 2.02 ~ 14.21; OR = 3.93, 95% CI = 1.48 ~ 10.47, respectively).

DISCUSSION

In this study, we identified the prevalence of aPL in SLE patients and evaluated the relationships between the presence of aPL and clinical outcomes. According to our study results, 14.7% of Korean SLE patients showed aPL positivity (positivity for LAC, aCL, or a β_2 GPI). In patients with positive aPL, cerebrovascular disease and CKD were more common than they were in aPL (-) patients. Older age, longer disease duration, history of LN, and aPL positivity were factors associated with increased risk of CKD in our study. These key findings suggest that aPL positivity in SLE patients is associated with

Table 4. Univariable and multivariable logistic regression analyses of the variables associated with increased risk of chronic kidney disease (stage ≥ 3)

Variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (yr)	1.05 (1.01 ~ 1.09)	< 0.01	1.07 (1.03 ~ 1.12)	< 0.01
Sex, male	0.51 (0.07 ~ 3.88)	0.51		
Disease duration (yr)	1.08 (1.02 ~ 1.14)	< 0.01	1.07 (1.01 ~ 1.14)	0.03
Smoking history	0.60 (0.14 ~ 2.60)	0.49		
Lupus nephritis history	5.59 (2.46 ~ 12.71)	< 0.01	5.36 (2.02 ~ 14.21)	< 0.01
Antiphospholipid antibody	3.01 (1.30 ~ 6.99)	0.01	3.93 (1.48 ~ 10.47)	< 0.01
Anti-cardiolipin antibody*	2.19 (0.47 ~ 10.14)	0.32		
Anti- β_2 -glycoprotein I antibody [†]	2.51 (0.29 ~ 21.57)	0.40		
Lupus anticoagulant [‡]	3.26 (1.36 ~ 7.84)	< 0.01		
Anti-dsDNA Ab	2.04 (0.60 ~ 6.92)	0.25		
Anti-Sm Ab	0.51 (0.19 ~ 1.36)	0.18		
Medication				
Corticosteroid	6.01 (0.80 ~ 44.92)	0.08	7.48 (0.92 ~ 60.50)	0.06
Hydroxychloroquine	0.39 (0.14 ~ 1.09)	0.07	0.65 (0.19 ~ 2.21)	0.49
Methotrexate	2.19 (0.47 ~ 10.14)	0.32		
Tacrolimus	2.50 (0.89 ~ 7.00)	0.08	1.17 (0.35 ~ 3.89)	0.80
Azathioprine	1.48 (0.58 ~ 3.80)	0.41		
Mycophenolate mofetil	3.32 (1.46 ~ 7.55)	< 0.01	2.13 (0.77 ~ 5.89)	0.14
Cyclosporine	1.35 (0.17 ~ 10.85)	0.78		
IV cyclophosphamide	3.02 (0.34 ~ 26.73)	0.32		
NSAIDs	1.51 (0.55 ~ 4.13)	0.43		
Aspirin	1.57 (0.65 ~ 3.84)	0.32		

CI: confidence interval, Anti-dsDNA Ab: anti-double stranded DNA antibody, Anti-Sm Ab: anti-Smith antibody, IV: intravenous, NSAIDs: nonsteroidal anti-inflammatory drugs, Ig: immunoglobulin, aCL: anticardiolipin antibody, a β_2 GPI: anti- β_2 -glycoprotein I antibody. *IgG or IgM aCL > 40 GPLU/ml. [†]IgG or IgM a β_2 GPI > 40 SGU/ml. [‡]LAC, detected according to the guidelines of the International Society on Thrombosis and Haemostasis, LAC: lupus anticoagulant.

poor clinical outcomes, especially in the renal aspect.

The prevalence of aPL positivity in our study seems substantially low compared to results from previous studies on SLE patients, even though our results include a β_2 GPI positivity [2,29,30]. However, our results are not comparable to the results from previous studies because we used stricter cut off values (moderate or high titer of aPL), which can lower the apparent prevalence. Also, we classified the aPL (+) group using two-year data at study enrollment, which could include laboratory values from times with low disease activity. Previous studies have shown that the presence and titers of aPL related to disease activity in SLE and the titers of aPL decreased by treatment [31,32]. aPL positivity as reported in this study could reflect concrete positivity that persisted through the use of corticosteroids, immunosuppressants, or anticoagulants because all of our study population had been followed and treated properly by rheumatologists for years. According to the SELENA SLEDAI flare index that

was developed for reliable distinction of flares in SLE activity, most patients in our study (95.9% of the total study population) did not show a disease flare status [33]. In a prospective cohort of 625 SLE patients that compared risk factors of thromboembolism among three ethnic groups (Chinese, African Americans, Caucasians), presence of aPL was less frequent in Chinese patients (29% in Chinese vs. 42% in African Americans vs. 46% in Caucasians, $p < 0.001$) [4]. Those results suggest that interethnic differences exist in the prevalence of aPL positivity in SLE patients. Our results further support the idea that aPL positivity could be less frequent in Asian SLE patients than in other ethnic groups. Additional study of genetic factors will be necessary to account for this racial difference.

We found no significant differences in most of the baseline characteristics between the two groups. The most interesting result is the relationship between aPL positivity and smoking history. The aPL (+) group had a sig-

nificantly higher prevalence of smoking history, which is a well-known risk factor for increasing thrombotic vascular events [34]. However, our logistic regression analysis data showed that smoking history was not associated with increased risk of CKD in SLE patients. According to a study analyzing the association between smoking history and SLE-associated autoantibodies, smoking was positively associated only with aPL, not with other autoantibodies [35]. The underlying mechanism and temporality between smoking and aPL needs further investigation. aPL (+) patients used aspirin or warfarin more frequently than aPL (-) patients, though the difference in warfarin use was not statistically significant. Among patients without aPL, 10 (2.5%) used warfarin at study enrollment. The causes for using warfarin in those patients included cerebrovascular accidents, peripheral vascular disorders, and pulmonary thromboembolism. Four of them had aPL positivity of low titer or previous history of aPL positivity. However, as only 13 patients (2.8% of the total study population) used warfarin at study enrollment, further study with a larger sample is needed for proper comparison between the two groups.

Though the International APS Classification Criteria provide a uniform approach to APS research, aPL can correlate with a spectrum of clinical manifestations, some of which are not included in those criteria including renal microangiopathy [1,36]. aPL-associated nephropathy (APS nephropathy) is clinically characterized as a syndrome of vascular nephropathy associated with hypertension, renal insufficiency, proteinuria, and inconstant hematuria that can present differently depending on pathophysiology including thrombotic microangiopathy, arterial fibrous intimal hyperplasia, tubular thyroid-like appearance, arteriosclerosis, arteriolar occlusion, and focal cortical atrophy [37]. The prevalence of APS nephropathy in SLE patients was reported as 32% and 23.2%, respectively, in two prior studies [12,13]. A cross-sectional study conducted on 112 SLE patients with renal involvement and who underwent renal biopsies revealed the association between APS nephropathy pathology and presence of aPL. Their results indicated that APS nephropathy is a separate renal disease entity with different underlying pathogenic mechanisms compared to LN. Therefore, the importance of conducting renal biopsy to differentiate those two conditions was emphasized [14]. According to a recently reported study encompassing a prospective cohort of 64 biopsy-proven active LN patients without concomitant APS nephropathy and cross-sectional analysis

of 498 SLE patients with or without LN, both aPL positivity and level were similar in patients with active LN and non-renal SLE. However, IgG aCL or IgG β_2 GPI positive patients had higher creatinine levels compared with patients without those IgG aPL both at active LN and after induction therapy, but not in the long-term data analyses. The authors concluded that aPL are not associated with occurrence of LN, and IgG aPL might contribute to an impaired renal function during a LN flare in the absence of APS nephropathy, probably due to their own pathogenic roles. But, no association was found between IgG aPL and additional renal function deterioration in the long-term follow up [17]. Our results also showed no difference in the prevalence of LN between aPL (+) and aPL (-) groups further supporting the idea that aPL is not associated with LN. Previous studies revealed that patients with severe LN (WHO class III and above) more likely progress to end-stage kidney disease [25]. Even though the proportion of severe LN was higher in aPL (-) group (without statistical significance), CKD was more prevalent in aPL (+) patients in our study. In addition, both LN history and aPL positivity were independent factors associated with increased CKD risk in SLE patients. Taken together with previous reports, the aPL seems to increase the risk of CKD in SLE patients by a mechanism different from that of LN. However, we are unsure if the mechanism leading to deteriorating renal function is related with APS nephropathy or other pathogenic mechanism of aPL is concerned if not biopsy proven in this study. aPL is believed to have pathogenic roles not limited to thrombosis, mediating several clinical manifestations of APS [34].

Previous studies about the impact of aPL on renal outcome were mostly confined to patients with LN and have shown conflicting results [16-19]. Ünlü et al. [38] suggested aPL as a marker to predict renal prognosis in SLE patients by referring to an abstract report on meta-analysis of 1,820 patients. But, we still did not have sufficient evidence to clarify the role of aPL as a distinct factor associated with poor renal outcome in SLE patients excluding the impact of other influential factors such as old age, longer disease duration, or presence of LN. History of LN and aPL positivity were the most influential clinical factors associated with increased risk of CKD even after adjusting for other confounding factors in multivariable logistic regression analysis (OR=5.36 and 3.93, respectively). The most important findings of this study were the poor renal outcome in aPL (+) SLE patients and the clarified role of aPL as an independent factor associated with increased

risk of CKD.

We note three limitations of this study. First, though we used the revised classification criteria for APS to generate our aPL (+) group, we defined positivity as those confirmed to be positive for aPL at one point in the past two years instead of confirming aPL positivity twice with an at least six-week interval between tests. This approach might increase the possibility of false positives for aPL. On the other hand, because we used stricter laboratory cut off values and did not include data from more than 2 years before enrollment, the possibility of false positives for aPL seems low. In addition, as all patients in the aPL (+) group met the criteria for aPL positivity in the ACR revised criteria for the classification of SLE at study enrollment, the possibility of clinically significant firm aPL positivity in this group is high. However, we had limited information on which specific criterion for aPL positivity was satisfied at the time of diagnosis. Second, the presence of APS nephropathy must have been noteworthy when discussing adverse renal outcomes regarding aPL positivity in SLE patients. However, because our clinical data were insufficient to define the presence of APS nephropathy without renal histology results, we could not discuss correlations with the presence of APS nephropathy or other renal pathologic features. Succeeding researches need to overcome this limitation to more clearly explain how aPL positivity influences renal outcomes in SLE patients. Last, even though we collected data from a prospective cohort study, our results were produced using cross-sectional data collected at enrollment. Therefore, this study has limitations in explaining long term prognosis including renal prognosis in the study population. We expect to explain the long-term relationship more clearly using accumulated clinical data as we proceed further through this cohort study.

CONCLUSION

The prevalence of aPL is 14.7% in Korean SLE patients. The aPL is associated with higher prevalence of cerebrovascular disease and CKD in SLE patients. And, aPL positivity is independently associated with the risk of CKD in SLE patients.

ACKNOWLEDGMENTS

We thank the patients and their families for their participation in this study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. George D, Erkan D. Antiphospholipid syndrome. *Prog Cardiovasc Dis* 2009;52:115-25.
2. Petri M. Epidemiology of the antiphospholipid antibody syndrome. *J Autoimmun* 2000;15:145-51.
3. Cervera R, Serrano R, Pons-Estel GJ, Cervera R, Hualde L, Shoenfeld Y, de Ramón 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.
4. Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemic lupus erythematosus: a comparison of three ethnic groups. *Arthritis Rheum* 2005; 52:2774-82.
5. Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A. The antiphospholipid syndrome in patients with systemic lupus erythematosus. *J Autoimmun* 2017;76:10-20.
6. Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. *Arch Intern Med* 2004;164:77-82.
7. Broder A, Mowrey WB, Kim M, Murakhovskaya I, Billett H, Neugarten J, et al. Association between antiphospholipid antibodies and all-cause mortality among end-stage renal disease patients with and without SLE: a retrospective cohort study. *Rheumatology (Oxford)* 2016;55:817-25.
8. Yelnik CM, Urbanski G, Drumez E, Sobanski V, Maillard H, Lanteri A, et al. Persistent triple antiphospholipid antibody positivity as a strong risk factor of first thrombosis, in a long-term follow-up study of patients without history of thrombosis or obstetrical morbidity. *Lupus* 2017;26:163-9.
9. Horbach DA, van Oort E, Donders RC, Derksen RH, de Groot PG. Lupus anticoagulant is the strongest risk factor for both venous and arterial thrombosis in patients with systemic lupus erythematosus. Comparison between different assays for the detection of antiphospholipid antibodies. *Thromb Haemost* 1996;76:916-24.
10. Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus--a meta-analysis. *Lupus* 1997;6:467-73.
11. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005;(2):CD002859.
12. Daugas E, Nochy D, Huong DL, Duhaut P, Beaufile H, Caudwell V, et al. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. *J Am Soc Nephrol* 2002;13:42-52.
13. Tektonidou MG, Sotsiou F, Nakopoulou L, Vlachoyiannopoulos PG, Moutsopoulos HM. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: prevalence, clinical associa-

- tions, and long-term outcome. *Arthritis Rheum* 2004;50:2569-79.
14. Gerhardsson J, Sundelin B, Zickert A, Padyukov L, Svenungsson E, Gunnarsson I. Histological antiphospholipid-associated nephropathy versus lupus nephritis in patients with systemic lupus erythematosus: an observational cross-sectional study with longitudinal follow-up. *Arthritis Res Ther* 2015;17:109.
 15. Zheng H, Chen Y, Ao W, Shen Y, Chen XW, Dai M, et al. Antiphospholipid antibody profiles in lupus nephritis with glomerular microthrombosis: a prospective study of 124 cases. *Arthritis Res Ther* 2009;11:R93.
 16. Moroni G, Ventura D, Riva P, Panzeri P, Quaglini S, Banfi G, et al. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. *Am J Kidney Dis* 2004;43:28-36.
 17. Parodis I, Arnaud L, Gerhardsson J, Zickert A, Sundelin B, Malmström V, et al. Antiphospholipid antibodies in lupus nephritis. *PLoS One* 2016;11:e0158076.
 18. Mehrani T, Petri M. IgM anti- β 2 glycoprotein I is protective against lupus nephritis and renal damage in systemic lupus erythematosus. *J Rheumatol* 2011;38:450-3.
 19. Frampton G, Hicks J, Cameron JS. Significance of anti-phospholipid antibodies in patients with lupus nephritis. *Kidney Int* 1991;39:1225-31.
 20. Costenbader KH, Desai A, Alarcón GS, Hiraki LT, Shaykovich T, Brookhart MA, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. *Arthritis Rheum* 2011;63:1681-8.
 21. 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.
 22. Lee JW, Park DJ, Kang JH, Choi SE, Yim YR, Kim JE, et al. The rate of and risk factors for frequent hospitalization in systemic lupus erythematosus: results from the Korean lupus network registry. *Lupus* 2016;25:1412-9.
 23. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
 24. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 2004;65:521-30.
 25. Maroz N, Segal MS. Lupus nephritis and end-stage kidney disease. *Am J Med Sci* 2013;346:319-23.
 26. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-70.
 27. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003;139:137-47.
 28. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013;158:825-30.
 29. Skare T, Borba EA, Utiyama SR, Nisihara R. Lymphocytopenia is associated with anti-Beta-2 glycoprotein-1 in patients with 220 systemic lupus erythematosus. *Acta Reumatol Port* 2016;41:220-5.
 30. Taraborelli M, Leuenberger L, Lazzaroni MG, Martinazzi N, Zhang W, Franceschini F, et al. The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. *Lupus* 2016;25:1365-8.
 31. Sarabi ZS, Sahebari M, Rezaie AE, Norouzi MT, Hashemzadeh K, Mirfeizi Z. The relationship between systemic lupus erythematosus activity and persistent positive antiphospholipid antibodies. *Curr Rheumatol Rev* 2018;14:145-52.
 32. Alarcón-Segovia D, Delezé M, Oria CV, Sánchez-Guerrero J, Gómez-Pacheco L, Cabiedes J, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. *Medicine (Baltimore)* 1989;68:353-65.
 33. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. *Ann Intern Med* 2005;142:953-62.
 34. Meroni PL, Borghi MO, Raschi E, Tedesco F. Pathogenesis of antiphospholipid syndrome: understanding the antibodies. *Nat Rev Rheumatol* 2011;7:330-9.
 35. Gustafsson JT, Gunnarsson I, Källberg H, Pettersson S, Zickert A, Vikerfors A, et al. Cigarette smoking, antiphospholipid antibodies and vascular events in Systemic Lupus Erythematosus. *Ann Rheum Dis* 2015;74:1537-43.
 36. Abreu MM, Danowski A, Wahl DG, Amigo MC, Tektonidou M, Pacheco MS, et al. The relevance of "non-criteria" clinical manifestations of antiphospholipid syndrome: 14th International Congress on Antiphospholipid Antibodies Technical Task Force Report on Antiphospholipid Syndrome Clinical Features. *Autoimmun Rev* 2015;14:401-14.
 37. Sciascia S, Cuadrado MJ, Khamashta M, Roccatello D. Renal involvement in antiphospholipid syndrome. *Nat Rev Nephrol* 2014;10:279-89.
 38. Ünlü O, Zuily S, Erkan D. The clinical significance of antiphospholipid antibodies in systemic lupus erythematosus. *Eur J Rheumatol* 2016;3:75-84.