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Clinical characteristics of patients with systemic lupus erythematosus showing a false-positive result of syphilis screening

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Abstract

A false-positive result of syphilis screening test (FPST) is a characteristic finding in patients with systemic lupus erythematosus (SLE). We evaluated the clinical characteristics of SLE patients with FPST at SLE diagnosis. We reviewed the medical records of patients with SLE who underwent the Venereal Disease Research Laboratory or Rapid Plasma Reagin tests at SLE diagnosis at Severance Hospital between 2006 and 2016. The baseline characteristics and clinical outcomes were compared between patients with FPST and those with a negative result of syphilis screening test. Of 145 patients with SLE, 20 patients showed FPST and 125 patients showed a negative syphilis screening result. At SLE diagnosis, patients with a negative result had higher SLE disease activity index (5.0 vs. 8.0, $P<0.001$) and were more commonly complicated with nephritis (15.0% vs. 41.6%, $P=0.026$). High level of serum total protein (> 8 g/dL) and the presence of anti-cardiolipin antibodies were independently associated with FPST ($P=0.010$ and 0.037, respectively). During the follow-up (median 61 months), 5 patients with FPST (20.0%) and 12 patients without FPST (9.6%) were finally diagnosed with APS. The long-term risk of de novo thrombosis was higher in the FPST group ($n=4/20$, 20% vs $n=6/125$, 4.8%, $P=0.041$). However, all-cause mortality showed no difference between the FPST group and the negative group. Patients with SLE showing FPST showed lower disease activity at SLE diagnosis but higher thrombotic risk and similar overall survival compared to those without FPST.

Keywords Systemic lupus erythematosus · False-positive syphilis test · Anti-phospholipid syndrome · Disease activity · Clinical outcome

Introduction

Systemic lupus erythematosus (SLE) is a prototype of systemic autoimmune disease and is characterized by the production of pathogenic antibodies against self-antigens [1, 2]. The diversity of autoantibodies enables patients with SLE to show a wide spectrum of serological abnormalities and clinical manifestations. Owing to the highly heterogeneous and complex clinical features of the disease, various clinical and immunological criteria have been employed for the classification of SLE. Among the laboratory tests, a false-positive syphilis test (FPST) has been first proposed as one of the immunological domains by the American Rheumatology Association in 1971 [3]. This domain was maintained in the 1982 American College of Rheumatology (ACR) classification criteria [4], the 1997 revised ACR criteria [5], and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [6].

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Currently, the most commonly used tests for syphilis screening are nontreponemal tests, including the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) tests [7]. These tests identify the antibodies that react with cardiolipin, a mitochondrial phospholipid extracted from bovine hearts [8]. Despite the convenience of nontreponemal screening tests, their diagnostic accuracy is limited owing to biological false-positive results. FPST is associated with various acute or chronic medical conditions, including pregnancy, acute febrile illness, chronic infection, and autoimmune diseases [9, 10]. The prevalence of FPST was reported to be 1–5% in the general population in the United States [11, 12]. SLE shows a high prevalence of FPST, approximately to be 20% of SLE patients [13].

False-positive result of syphilis screening test in patients with SLE is due to the reaction between cardiolipin and antiphospholipid (aPL) antibodies directed to phospholipid or phospholipid-binding proteins [14]. Advances in diagnostic technique led to detection of aPL antibodies, including lupus anticoagulant, anti-cardiolipin (aCL) antibodies, and anti-beta-2 glycoprotein 1 (anti-β2GP1) antibodies [15]. The presence of aPL antibodies was reported to be associated with an increased risk of thrombosis in patients with SLE, a condition named as anti-phospholipid syndrome (APS). Thus, FPST is also expected to be closely related to APS. However, FPST is only included in the classification criteria for SLE, not in the classification criteria for APS [16].

In patients with SLE, especially with new-onset disease, the clinical significance of FPST is largely unknown. This study aimed to investigate the clinical and serological features of patients with FPST at the initial presentation of SLE and to evaluate the long-term clinical outcomes in these patients.

Patients and methods

Patients

We retrospectively reviewed the medical records of patients with SLE who underwent a syphilis screening test upon the diagnosis of SLE at Severance Hospital between January 2006 and December 2016. During the study period, 1734 patients visited the clinic with a diagnosis of SLE, and 673 (38.8%) patients were tested for syphilis screening test. We recruited patients who met the following inclusion criteria: (i) with a diagnosis of SLE according to the 1997 revised ACR or the 2012 SLICC classification criteria; (ii) with nontreponemal tests (VDRL and/or RPR) at SLE diagnosis; and (iii) with tests for other aPL antibodies, including lupus anticoagulant, IgM/IgG aCL antibodies, and IgM/IgG anti-β2GP1 antibodies at the diagnosis of SLE. Patients with a positive result in the syphilis confirmatory test were excluded because the possibility of syphilis cannot be ruled out. This study was approved by the institutional review board of Severance Hospital (4-2018-0980) and conducted in accordance with the principles set forth in the Declaration of Helsinki.

Clinical and laboratory data

Demographic data such as age and sex were collected at SLE diagnosis. The clinical and laboratory profiles including SLE disease activity index-2000 (SLEDAI-2K) [17] were also obtained for all included patients with SLE. The clinical manifestation of SLE was defined according to the 1997 revised ACR classification criteria. Laboratory data at SLE diagnosis included complete blood count with platelets, levels of inflammatory markers, and other blood chemistry values. Antibodies against extractable nuclear antigen (ENA), such as anti-dsDNA, anti-ribonucleoprotein, anti-Smith, anti-SSA/Ro and anti-SSB/La, IgG/IgM anti-β2GP1 antibodies, and IgG/IgM aCL antibodies were measured with an automated fluorescence enzyme immunoassay analyzer (Elia, Phadia, Sweden). Lupus anticoagulant tests were performed using HemosIL dRVVT reagent and the ACL TOP700 device (Instrument Laboratory, MA, USA). Anti-β2GP1 and aCL antibodies were examined for both positivity and absolute serum levels.

Definition of a false-positive result in syphilis screening

Nontreponemal test for syphilis screening was performed using the VDRL test or the RPR test. The VDRL test was performed using BD VDRL Antigen kits (Becton–Dickinson, Sparks, MD, USA) according to the manufacturer's instruction. For the RPR test, a latex turbidimetric immunoassay with latex particles coated with lecithin and cardiolipin was used. The latex particles react with the reagin in the serum. For automated analysis, CA 400 (Furuno Electric, Hyogo, Japan) and Toshiba TBA-c8000 (Canon Medical Systems Co., Tokyo, Japan) were used before 2016 and after 2016, respectively.

In patients with a positive test result in syphilis screening, the confirmatory test was performed using the fluorescent treponemal antibody absorption (FTA-ABS) assay and/or the *Treponema pallidum* particle agglutination (TPPA) assay [7]. The FTA-ABS assay uses the nonviable Nichols strain of *T. pallidum* to detect *T. pallidum*-specific total antibodies and was performed after heating samples at 56 °C for 30 min according to the manufacturer's instructions (Zeus Scientific, Raritan, NJ, USA). The result of the Serodia TPPA assay (Fujirebio, Tokyo, Japan) is interpreted according to the agglutination of colored gelatin particles that have been coated with *T. pallidum* (Nichols strain) antigens. FPST was

defined as a positive result in the screening test and a negative result in the confirmatory test.

Statistical analysis

The normal distribution of continuous variables was tested using the Shapiro–Wilk test. The normally distributed data were presented as mean with standard deviation and were compared using the Student's *t* test. Otherwise, the continuous variables were presented as median with interquartile ranges and were compared using the Mann–Whitney *U* test. Categorical variables were presented as frequencies. When the cells with expected frequency less than 5 are over 25% in the contingency table, the difference in categorical variables was assessed by the Fisher's exact test. Otherwise, the categorical variables were analyzed using the Chi-square test. The agreement between FPST and aPL antibodies was assessed with Cohen's kappa coefficients. To elucidate the association between FPST and clinical features, logistic regression analysis was performed. Variables with a P value of < 0.05 were included in the multivariate analysis. Kaplan–Meier curve analysis and the log-rank test were used to compare the overall survival and risk of thrombosis between patients with and those without FPST. All statistical analyses were performed using MedCalc statistical software version 18.11 (MedCalc Software, Ostend, Belgium). A two-tailed P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Among 673 patients with SLE, 54 showed a positive result in the syphilis screening test and 13 patients were excluded because of the positive result in the syphilis confirmatory test. According to the inclusion criteria, 20 patients with SLE showing FPST and 125 patients with SLE showing a negative syphilis test result were included in the analysis (Fig. 1). Among 145 patients, VDRL and RPR tests were performed in 121 and 29 patients, respectively. The remaining 5 patients were tested for syphilis screening, but the type of test was not clearly indicated. In patients with FPST, 18 patients were determined by VDRL test, and 2 patients were determined by RPR tests. The baseline characteristics of the included patients are presented in Table 1. The median age was 31 years, and 125 (86.2%) patients were women. The median SLEDAI-2K was 8 points, suggesting that the study population had active SLE at diagnosis. Patients with a negative result showed higher SLEDAI-2K scores and lower hemoglobin, total protein, albumin, and C3 levels than those with FPST. Among the clinical manifestations, hematological disorder (95.9%) was the most common, followed by immunological disorder and nephritis. Lupus nephritis was more common in the negative group than in the FPST group (41.6% vs. 15.0%, $P = 0.026$). The presence of thrombosis was not significantly different between both groups at the initial presentation of SLE.

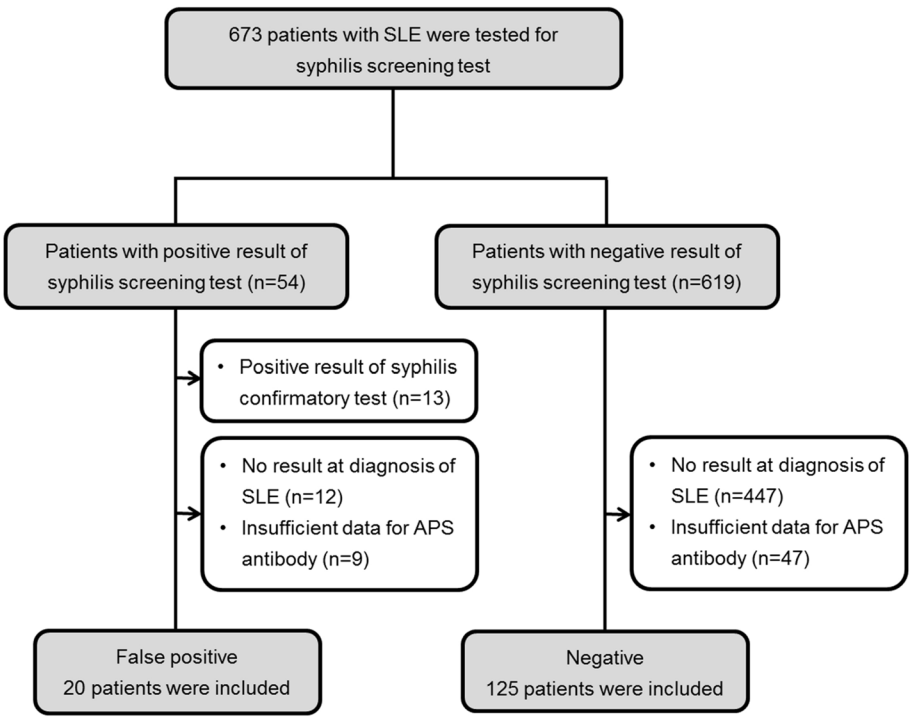

Fig. 1 Flowchart of patient inclusion. This study included patients with SLE who were tested for syphilis at the initial presentation of SLE. Of the total 673 patients who underwent a syphilis screening test, those with a positive result in the syphilis confirmatory test and insufficient data on aPL antibodies, and those without screening test results at SLE diagnosis were excluded. *SLE* systemic lupus erythematosus, *aPL* anti-phospholipid

Table 1 Baseline characteristics of SLE patients with false-positive and negative test result in syphilis screening

Variables	Total ($N=145$)	False-positive ($n=20$)	Negative ($n=125$)	P value
Demographic data				
Age (years)[¶]	31.0 (22.0–44.3)	28.5 (22.5–42.0)	31.0 (22.0–45.3)	0.694
Female sex[†]	125 (86.2)	18 (90.0)	106 (84.8)	0.739
Disease activity				
SLEDAI-2 K[¶]	8.0 (4.0–11.0)	5.0 (4.0–6.0)	8.0 (5.0–11.3)	< 0.001
Clinical manifestations, *n* (%)*				
Skin rash[‡]	51 (35.2)	5 (25.0)	46 (36.8)	0.305
Photosensitivity[†]	15 (10.3)	1 (5.0)	14 (11.2)	0.694
Oral ulcers[†]	26 (17.9)	1 (5.0)	25 (20.0)	0.127
Arthritis[†]	24 (16.6)	4 (20.0)	20 (16.0)	0.745
Serositis[†]	31 (21.4)	3 (15.0)	28 (22.4)	0.568
Nephritis[†]	55 (37.9)	3 (15.0)	52 (41.6)	0.026
Neurological disorder[†]	4 (2.8)	0 (0.0)	4 (3.2)	0.999
Hematological disorder[†]	139 (95.9)	19 (95.0)	120 (96.0)	0.999
Immunological disorder[†]	136 (93.8)	20 (100.0)	116 (92.8)	0.612
Presence of thrombosis[†]	11 (6.2)	2 (10.0)	9 (5.6)	0.649
Laboratory data				
Leukocytes (/μL)[¶]	4120 (3193–6095)	4155 (3235–6900)	4120 (3193–6010)	0.904
Hemoglobin (g/dL)[§]	11.1 ± 2.1	12.0 ± 2.0	10.9 ± 2.1	0.040
Platelets (× 1000/μL)[¶]	199 (118–244)	206 (184–243)	193 (113–247)	0.213
Lymphocytes (/μL)[¶]	950 (550–1333)	1095 (750–1405)	930 (548–1283)	0.220
ESR (mm/h)[¶]	49 (25–76)	45.0 (32–79)	50 (24–76)	0.424
CRP (mg/L)[¶]	2.6 (1.0–9.2)	1.6 (1.0–4.3)	2.9 (1.0–9.7)	0.160
Creatinine (mg/dL)[¶]	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.705
Total protein (g/dL)[¶]	7.0 (5.7–7.7)	7.8 (7.3–8.5)	6.8 (5.6–7.5)	< 0.001
Albumin (g/dL)[¶]	3.5 (2.8–4.2)	4.3 (4.1–4.6)	3.4 (2.7–4.1)	< 0.001
AST (IU/L)[¶]	25.0 (18.0–43.0)	21.0 (17.5–26.0)	26.0 (18.0–51.0)	0.070
ALT (IU/L)[¶]	17.0 (12.0–34.3)	14.5 (11.0–23.5)	19.0 (12.0–36.0)	0.141
Complement 3 (mg/dL)[¶]	60.7 (36.5–91.6)	88.0 (72.1–103.4)	58.2 (32.8–86.4)	0.001
Complement 4 (mg/dL)[¶]	9.7 (4.3–16.8)	13.3 (7.8–17.9)	8.7 (4.0–16.4)	0.136

SLEDAI-2K systemic lupus erythematosus disease activity index-2000, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

*Clinical manifestations were evaluated based on the 1997 revised classification criteria

The normality test revealed that only hemoglobin value was normally distributed ($P=0.299$). [§]The value of hemoglobin was presented as mean ± standard deviation and was compared between groups using the Student's t test. [¶]All of the continuous variables except hemoglobin were presented as median (interquartile range), and were compared using the Mann–Whitney U test

The differences in categorical variables with expected frequency < 5 in each group[†] and those with expected frequencies ≥ 5 in each group[‡] were assessed by the Fisher's exact test and the Chi-square test, respectively

Differences in autoantibody profiles

Anti-ENA antibodies and aPL antibodies were evaluated in all patients (Table 2). No differences were found in the anti-ENA antibody profiles between the FPST group and the negative group. The serum level of anti-dsDNA was lower in the FPST group than in the negative group, although there was no statistically significant difference (21.5 vs. 114 IU/mL, $P=0.285$). As expected, patients with FPST showed a higher prevalence of aPL antibodies. Among the aPL antibodies, aCL antibodies (42.1%) were most commonly found, followed by lupus anticoagulant (37.2%) and anti-β2GP1 antibodies (26.2%). The agreement between syphilis screening test and other aPL antibodies was not so high, with Cohen's kappa coefficient of around 0.20 (Table 3).

Anti-phospholipid syndrome was diagnosed in 8 patients (5.5%) of the whole study population at SLE diagnosis and in additional 9 patients (6.2%) during the follow-up. During the study period, 5 patients with FPST (20.0%) and 12 patients without FPST (9.6%) were diagnosed with

Table 2 Autoantibody profiles in SLE patients with false-positive and negative test result in syphilis screening

	Total ($N=145$)	False-positive ($n=20$)	Negative ($n=125$)	P value
Anti-extractable nuclear antigen antibodies				
Anti-dsDNA (IU/mL)[¶]	113.2 (0.0–310.8)	21.5 (0.0–226.1)	114.0 (0.0–334.5)	0.285
Anti-dsDNA positivity[‡]	95 (65.5)	11 (55.0)	84 (67.2)	0.287
Anti-RNP positivity[‡]	72 (49.7)	9 (45.0)	63 (50.4)	0.655
Anti-Sm positivity[‡]	61 (42.1)	6 (30.0)	55 (44.0)	0.241
Anti-Ro positivity[‡]	86 (59.3)	11 (55.0)	75 (60.0)	0.674
Anti-La positivity[‡]	38 (26.2)	6 (30.0)	32 (25.6)	0.679
Anti-phospholipid antibodies				
Lupus anticoagulant positivity[‡]	54 (37.2)	13 (65.0)	41 (32.8)	0.006
Anti-cardiolipin antibody positivity[‡]	61 (42.1)	15 (75.0)	46 (36.8)	0.001
Anti-cardiolipin IgM (U/mL)[¶]	0.0 (0.0–0.0)	23.3 (0.0–54.8)	0.0 (0.0–0.0)	< 0.001
Anti-cardiolipin IgG (U/mL)[¶]	0.0 (0.0–21.9)	17.0 (0.0–50.5)	0.0 (0.0–20.1)	0.009
Anti-β2GP1 antibody positivity[‡]	38 (26.2)	10 (50.0)	28 (22.4)	0.009
Anti-β2GP1 antibody IgM (U/mL)[¶]	0.0 (0.0–0.0)	0.0 (0.0–61.8)	0.0 (0.0–0.0)	0.024
Anti-β2GP1 antibody IgG (U/mL)[¶]	0.0 (0.0–0.0)	0.0 (0.0–12.5)	0.0 (0.0–0.0)	0.162

dsDNA double-stranded DNA, *RNP* ribonucleoprotein, *β2GP1* β2-glycoprotein 1

[¶]The normality test revealed that all continuous variables were not normally distributed. The continuous variables were presented as median (interquartile range), and were compared using the Mann–Whitney *U* test

[‡]The difference in categorical variables was assessed by the Chi-square test

Table 3 Agreement between syphilis screening test and antiphospholipid antibody

	Syphilis screening	
	False-positive	Negative
Lupus anticoagulant		
Positive	13	41
Negative	7	84
% Agreement	65.0	67.2
κ (95% CI)	0.19 (0.04–0.33)	
Anti-cardiolipin antibody		
Positive	15	46
Negative	5	79
% Agreement	75.0	63.2
κ (95% CI)	0.21 (0.07–0.34)	
Anti-β2GP1 antibody		
Positive	10	28
Negative	10	97
% Agreement	50.0	77.6
κ (95% CI)	0.20 (0.03–0.37)	

β2GP1 β2-glycoprotein 1, *CI* confidence interval

APS. Although FPST was not associated with APS diagnosis at the presentation of SLE ($P=0.304$), the long-term association between FPST and APS during follow-up was statistically significant ($P=0.047$).

Clinical and laboratory factors associated with a false-positive result in syphilis screening

To elucidate the clinical and serological factors associated with FPST, logistic regression analysis was performed (Table 4). The cutoff values of clinical and laboratory variables with a significant difference between both groups were determined using receiver operating characteristic curves. In univariate analysis, FPST was associated with low disease activity, presence of anemia, high protein level, presence of nephritis, and positivity to aPL antibodies. Among these variables, the higher level of total serum protein (total protein > 8 g/dL) (odds ratio 4.937, $P=0.010$) and the presence of aCL antibody (odds ratio 4.346, $P=0.037$) were independently related to FPST.

Clinical outcomes

The median follow-up duration was 61 months (interquartile range 28.0–94.9 months) in the whole study population. Of the total 145 patients, all-cause death and de novo thrombosis were detected in 7 and 10 patients, respectively. There were no differences in the overall survival rate between patients with FPST and those with a negative screening result (Fig. 2a, $P=0.945$). However, the occurrence of new thrombotic events was more common in the FPST group than in the negative group (Fig. 2b, $P=0.041$). New occurrence of thrombosis was observed in 4 (20.0%) patients with FPST and 6 (4.8%) patients with a negative screening result.

Table 4 Clinical factors associated with a false-positive syphilis test result

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Low disease activity (SLEDAI-2K ≤ 6)	6.638	2.094–21.047	0.001			
Anemia (Hb < 12 g/dL)	0.337	0.128–0.889	0.028			
High level of serum total protein (> 8 g/dL)	4.960	1.775–13.859	0.002	4.937	1.464–16.647	0.010
Hypocomplementemia	0.788	0.262–2.368	0.671			
Presence of nephritis	0.428	0.069–0.889	0.032			
Lupus anticoagulant positivity	3.805	1.411–10.258	0.008			
aCL antibody positivity	5.152	1.758–15.103	0.003	4.346	1.099–21.133	0.037
Anti-β2GP1 antibody positivity	3.464	1.310–9.158	0.012			

CI confidence interval, *SLEDAI-2K* systemic lupus erythematosus disease activity index-2000, *Hb* hemoglobin, *aCL* anticardiolipin, *β2GP1* β2-glycoprotein 1

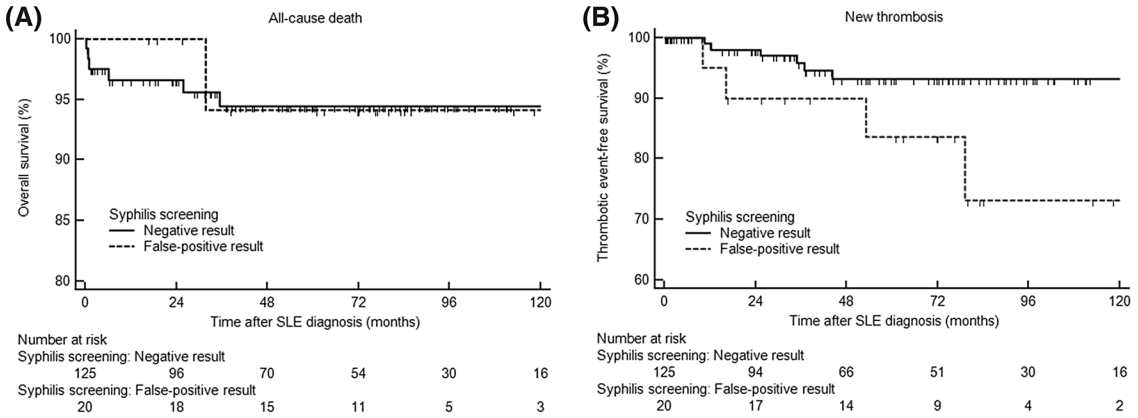

Fig. 2 Clinical outcomes of patients with SLE with a false-positive result and those with a negative result of syphilis screening test. The overall survival and thrombotic event-free survival were evaluated according to the test results of syphilis screening. The median follow-up period was 61 months (interquartile range 28.0–94.9 months) in patients with SLE. **a** All-cause mortality was not significantly different between the false-positive and negative groups ($P = 0.945$). **b** The risk of new thrombosis was significantly higher in patients with SLE with a false-positive test result of syphilis screening test than the other patients ($P = 0.041$)

The median time to the occurrence of a new thrombotic event was 30 months.

Discussion

In the present study, patients with SLE with FPST showed discriminating features compared to patients with a negative result. Patients with FPST showed lower disease activity and lower prevalence of lupus nephritis at the initial presentation. Although the disease activity at SLE diagnosis was lower in patients with FPST, the overall survival rate was comparable, regardless of the result of syphilis screening. New diagnosis of APS and the development of de novo thrombosis were more common in patients with FPST.

Although FPST is frequently observed in patients with SLE, the clinical characteristics of these patients are rarely elucidated. Previously, Al Attia suggested that clinical features such as malar rash, hemolytic anemia, and APS, and the laboratory feature of C3 hypocomplementemia were more common in patients with FPST [18]. In our study, the clinical features at the presentation of SLE were not significantly different between patients with FPST and those with a negative result of syphilis screening except lupus nephritis, which was more common in patients with a negative result. In addition, patients with a negative syphilis serology were more likely to have low C3 at diagnosis of SLE. This discrepancy may be due to several factors, including ethnic differences and patient inclusion criteria. There are differences in the prevalence of SLE and the rate of FPST in the general population according to ethnicity [2, 19], which lead to differences in study population. Furthermore, we included patients with available test results at the initial presentation of SLE, whereas Al Attia did not mention the timing of the syphilis screening test. FPST is one of the laboratory domains for

the classification of SLE. Thus, patients with FPST can be classified as having SLE, even though other characteristic findings of SLE are insufficient.

For this reason, patients with FPST may have lower disease activity than patients with a negative syphilis serology at initial presentation of SLE. In the present study, the SLEDAI-2 K score was significantly higher and lupus nephritis was more frequently diagnosed in the negative group. However, the inverse relationship between FPST and high lupus activity is difficult to explain. There is little known about the association between aPL antibodies and lupus activity. Although aPL antibodies were associated with other lupus manifestations, such as neuropathy and thrombocytopenia [20–22], the evaluation has been limited to patients with aPL antibodies other than FPST. The impact of aPL antibodies on lupus nephritis is also uncertain. Because the main pathophysiology of aPL antibody-associated renal lesions is thrombosis or ischemia [23], the association between aPL antibodies and inflammation in lupus nephritis still remains to be determined. Thus, further studies are warranted to better understand the mechanisms of low lupus activity and low prevalence of lupus nephritis in patients with FPST.

Despite the lower disease activity at initial presentation of SLE, patients with FPST showed a similar mortality rate compared with patients with a negative syphilis serology. In general, high disease activity at SLE diagnosis is associated with unfavorable long-term outcomes [24, 25], and high disease activity may be sustained during follow-up in patients with SLE [26]. However, this study suggests that even in low disease activity at SLE diagnosis, special caution may be required in patients with FPST. In addition, the development of de novo thrombosis was more frequent in the FPST group than the negative group. At the initial presentation of SLE, the detection of thrombosis and the diagnosis of APS were not significantly different between patients with FPST and those with a negative result. However, patients with FPST were more likely to develop new thrombotic events and to be classified as APS during follow-up. Although the current classification criteria for APS do not include FPST in the laboratory domain [16], FPST still had a significant impact on the risk of de novo thrombosis in patients with SLE.

Interestingly, the agreement between the syphilis screening test and aPL antibodies was not fair. In the multivariate analysis, FPST was only correlated with aCL antibodies, but not with lupus anticoagulants and anti-β2GP1 antibodies. Because false-positive results in the VDRL or RPR test indicate the presence of reactive components to cardiolipin in the patient's serum, FPST can be independently correlated with the positivity of aCL antibodies [27]. However, the other aPL antibodies failed to show an independent correlation with FPST. This finding suggests that patients with different aPL antibodies may have different characteristics in several aspects.

This study has several limitations. First, a selection bias exists because patients with new-onset SLE are not necessarily tested for syphilis. However, the prevalence of FPST was 14.4% in this study (29 patients among 201 patients who were tested for syphilis at SLE diagnosis in Fig. 1), which was not much different from the reported prevalence of 20% in previous studies [13]. The prevalence of other aPL antibodies was also similar to that in previous report [21]. Second, we evaluated only the clinical features of patients with SLE with FPST, but not the underlying mechanisms for the association between FPST and disease activity. Further studies would be required to elucidate the molecular mechanism of how the presence of reactive components to cardiolipin is associated with low disease activity in SLE. Third, the syphilis screening test was performed only at the initial presentation of SLE and was not repeated after the treatment of SLE. Thus, changes in the results of the syphilis screening test after SLE treatment were not evaluated.

Nevertheless, this study evaluated the correlation between FPST and other aPL antibodies and investigated the baseline characteristics and long-term clinical outcomes according to the test result for syphilis screening. To our knowledge, this is the first study to show the long-term risk of thrombosis and the mortality rate in patients with FPST compared to patients with a negative syphilis result.

Taken together, patients with new-onset SLE showing FPST had low disease activity and low rates of lupus nephritis. At the diagnosis of SLE, FPST was not correlated with an increase in thrombosis. However, the long-term follow-up data revealed that patients with FPST had higher risk of de novo thrombosis and similar mortality rate compared to patients with a negative syphilis test result. On the basis of the current findings, special attention would be required in patients with new-onset SLE showing FPST, although they have low disease activity at the initial presentation.

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Author contributions SSA and SMJ conceived and designed the work; SSA, JY, S-WL, and SMJ acquired and analyzed the data; SSA, S-WL, JJS, Y-BP, and SMJ interpreted the data; all authors contributed to drafting and revising the work, and approved the final version of the manuscript; all authors agreed on all aspect of the work.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by the institutional review board of Severance Hospital (approval no. 4-2018-0980; approval date 2018-12-06) and all procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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