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Retrospective cohort study of thromboembolic events in systemic lupus erythematosus with or without secondary antiphospholipid syndrome and their correlation to lupus activity and dyslipidemia

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Abstract

Background Antiphospholipid syndrome (APS) is one of the most frequent forms of acquired thrombophilia and is associated with an increased risk of stroke, heart attack, pulmonary embolism, and miscarriage in young women. Thirty to 40% of systemic lupus erythematosus (SLE) patients have associated APS. Patients with SLE often have abnormal plasma lipid concentrations. The study aimed to assess the prevalence of thromboembolic insults in SLE patients, with or without APS, and its correlation with disease activity and dyslipidemia. This study included one hundred three patients, seventy-five of whom had SLE without associated APS and twenty-eight had SLE associated with APS.

Results Vascular affection, neurological affection, and abortion were significantly higher in SLE patients associated with APS than SLE patients without APS (39.3% vs 6.7%, 46.4% vs 14.7%, 28.6% vs 5.3%, respectively; $P < 0.001$). Thromboembolic insults were present in 20% of SLE patients without APS, and those patients with thromboembolism demonstrated significantly higher SLEDAI (median = 15 vs 10, $P < 0.001$) and TG (median = 27.5 vs 18.2, $P = 0.007$), respectively, than other patients of the same group. The SLEDAI score was significantly higher in SLE patients associated with APS than in SLE patients without APS ($P < 0.001$). Serum cholesterol and low-density lipoprotein (LDL) were significantly higher in SLE patients associated with APS (93.8 ± 25.3 mg/dl) than in SLE patients without APS (82.3 ± 19.6 mg/dl, $P = 0.018$; 50 ± 15.9 mg/dl, $P = 0.048$, respectively).

Conclusions SLE patients are at significantly high risk for accelerated atherosclerosis, thromboembolism, and pregnancy loss which is multifactorial. Active disease should be well controlled. Lupus patients should be screened for aPL antibodies, and positive cases must be treated according to international guidelines. All patients with SLE should undergo lipid profile screening, and any abnormalities should be managed promptly.

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Background

Systemic lupus erythematosus (SLE) which is an autoimmune disease affecting the connective tissues, leads to chronic inflammatory illness of the skin, joints, kidneys, lymph nodes, and the lining layers of the blood vessels with increased risk of thromboembolism [1]. Thrombosis (both venous and arterial) and miscarriage are symptoms of antiphospholipid antibody syndrome (APS) which is an autoimmune disorder associated with positive antiphospholipid antibodies (aPLs) including the lupus anticoagulant (LA), anticardiolipin antibodies (aCLs) IgG or IgM, and/or anti-ß2-glycoprotein I (anti-B2G1) IgG or IgM. According to the "two-hit theory," asymptomatic carrier patients with positive aPLs may need another trigger to have thrombotic problems and pregnancy loss [2].

In one study, the incidence of thromboembolic events was 16% of SLE patients without associated APS, while another study found thromboembolism in 13.3–22.0% of SLE patients, occurring in the early years of the disease with some variations recorded according to ethnic groups and type of thrombosis [3]. The incidence of thromboembolism may exceed 50% of SLE patients who have positive LA antibodies [4]. While thromboembolism occurs at a rate of 0.71 to 1.13 per 1000 person-years in the general population [5].

APS is one of the most frequent forms of acquired thrombophilia and it is associated with an increased risk of stroke, heart attack, pulmonary embolism, and miscarriage in young women. Dyslipidemia, atherosclerosis, and cardiovascular problems are other concerns for those patients [6]. Thirty to forty percent of SLE patients have associated secondary APS while primary APS occurs when there is no underlying autoimmune illness [7]. The 2006 modified Sapporo criteria are recommended for the diagnosis of APS [8].

Thromboembolic events caused by antiphospholipid syndrome may be generally categorized as being either venous, arterial, or obstetric APS; however, these subcategories are not mutually exclusive from one another. In a retrospective analysis of 160 patients with APS, venous thromboembolism (VTE) was found to be the commonest manifestation (47.5%) followed by arterial thromboembolism (43.1%) then materno fetal problems which were found only in 9.7% of patients, and finally, catastrophic antiphospholipid syndrome (CAPS) represented in only 2.5 percent of the cases [9].

Patients with SLE often have abnormal plasma lipid concentrations. A high total cholesterol (TC), high triglyceride (TG), low-density lipoprotein (LDL), and low high-density lipoprotein (HDL) levels are considered dyslipidemia [10].

There are several variables that have been hypothesized to enhance the likelihood of dyslipidemia and increased risk of cardiovascular diseases (CVD) in SLE patients. The constant immune reaction, chronic inflammation, and high disease activity have a role in the pathogenesis of atherosclerosis, CVD, and vascular damage, inducing thrombosis in SLE [11, 12]. In recent decades, there has been a significant rise in the life expectancy of persons diagnosed with SLE. However, both the morbidity and mortality rates for SLE patients remain greater than those seen in the general population. Infection, lupus nephritis (LN), CVD, and malignancy continue to be the leading causes of mortality worldwide [2, 13]. Smoking, lower illness duration, more disease activity, glucocorticoid dosage, and lupus anticoagulant antibodies were all baseline predictors of venous thromboembolism (VTE) in the Lupus in Minorities: Nature vs Nurture (LUMINA) study [14]. In autoimmune rheumatic illnesses, both conventional (advancing age, male gender, hypertension, smoking, hypercholesterolemia, diabetes) and so-called non-traditional risk factors contribute to CVD. When compared to the general population, those with SLE have a much higher risk of cardiovascular disease and stroke, and these increases cannot be accounted for by the Framingham risk factors [13].

Aim of the work

The purpose of this research was to record the prevalence of thromboembolic insults in SLE with or without antiphospholipid syndrome and to study its correlation with disease activity and dyslipidemia.

Methods

The retrospective cohort study included 103 patients who visited the Rheumatology Clinic at King Salman Armed Forces Hospital Tabuk (KSAFHT) from the duration of January 2020 to January 2022, 75 of whom had SLE without associated APS and 28 of whom had SLE associated with APS syndrome. Background, clinical signs, and laboratory results, including lipid profiles, were gathered from paper and computerized files.

Those who have SLE met the diagnostic criteria established by the Systemic Lupus International Classification Committee (SLICC) [15].

Disease activity was assessed according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) with scores 1–5 considered as mild disease activity, 6–11 as moderate, and 12 and more as severe [16].

APS was diagnosed according to the 2006 modified Sapporo criteria [8].

Exclusion criteria

All patients who have other causes of thrombophilia either congenital, such as protein C and protein S

deficiency, etc.,. or acquired causes, such as blood diseases, malignancy, etc., were excluded from our study.

The following procedures were collected for every patient:

All the parameters and the investigations were collected from the patient records.

- Comprehensive background checks.
- Standard laboratory procedures; complete blood count (CBC).
- The quantity of protein in one's urine throughout the course of a day is quantified in grams per 24 h.
- Serum complement (C3, C4); nephelometric analysis (C3 normal range: 84–160 mg/dl; C4 normal range: 12–36 mg/dl).
- Enzyme-linked immunosorbent assay for total cholesterol, expressed as mg/dl.
- Enzymatic colorimetric assay for total triglyceride, expressed as mg/dl.
- Quantification of LDL and HDL in milligrams per deciliter by enzyme colometry.
- Antinuclear antibody (ANA), anti-2-glycoprotein I (anti-B2GPI) and IgG and IgM, and anticardiolipin (aCL) antibodies were detected by enzyme-linked immunosorbent assay (ELISA). The anti-double-stranded deoxyribonucleic acid (anti-dsDNA) was processed by ELISA as recorded in the patient's electronic files [17, 18].

Ethical considerations

The study protocol was approved by the local ethics committee in KSAFHT. Written informed consent was obtained from all participants before participating in the study.

Results

Demographic characteristics

The study included 103 patients, all diagnosed as SLE and classified into 2 groups; a group of SLE patients without APS (75 cases); and another group of SLE patients with APS (28 cases). As shown in Table 1, the mean age of the studied patients was 39 ± 12 years, and females predominated in this study (81.6%). A significant association was reported between gender and the studied groups ($P = 0.029$); the female gender was significantly higher in the SLE group (86.7%) than in the SLE+APS group (67.9%). No significant difference was reported regarding age ($P = 0.491$).

Clinical findings

Table 2 shows the clinical findings of the studied patients. The most frequent clinical finding was musculoskeletal manifestations (68.9%), followed by mucocutaneous manifestations (64.1%), renal affection (60.2%), hematological affection (55.3%), neurological affection (23.3%), vascular affection (15.5%), pulmonary manifestation (13.6%), abortion (11.7%), cardiac manifestation (9.7%), psychiatric manifestation (9.7%), and serositis (4.9%).

Table 1 Demographic characteristics of the studied patients

	Total ($n = 103$)	SLE without APS ($n = 75$)	SLE with APS ($n = 28$)	*P*-value
Age (years)	39 ± 12	40 ± 11	38 ± 12	0.491
Gender				
Males	19 (18.4)	10 (13.3)	9 (32.1)	0.029*
Females	84 (81.6)	65 (86.7)	19 (67.9)	

Data were presented as mean ± SD or number (percentage)

*≤ 0.05 significant results

Vascular affection was significantly higher in those with SLE and 2ry APS (39.3%) than in those with SLE alone (6.7%) ($P < 0.001$). In addition, neurological affection was significantly higher in those with SLE with 2ry APS (46.4%) than in those with SLE (14.7%) ($P < 0.001$). Furthermore, abortion was significantly higher in those with SLE with 2ry APS (28.6%) than in those with SLE (5.3%) ($P = 0.001$) (Table 2, Fig. 1).

Laboratory findings and disease activity

The serology results of all patients showed positive ANA (99%). About two-thirds were positive anti-dsDNA (65%). Less than one-quarter were positive LA (19.4%), aCL-IgM (15.5%), anti-B2GPI–IgG (6.8%), aCL-IgG (5.8%), anti-B2GPI-IgM (4.9%), anti-RO (4.9%), anti-Smith (4.9%), anti-U1 ribonucleoprotein (Anti-U1RNP) (2.9%), and anti-LA (1.9%). C3 and C4 were low in two-thirds of the patients (64.1%).

The mean cholesterol level for all patients was 85.4 ± 21.7 mg/dl. The median TG level was 20.7, ranging from 7 to 65.7. The mean LDL and HDL levels were 52.1 ± 17.4 and 23.7 ± 8.1 mg/dl, respectively. The median SLEDAI score for all patients was 12, ranging from 4 to 29.

Positive anti-RO was significantly higher in those with SLE with 2ry APS (17.9%) than in SLE without APS (0.0%) ($P = 0.001$).

Thromboembolic insults were present in 20% of SLE patients without APS and those patients with thromboembolic complications demonstrated significantly higher SLEDAI (median = 15 vs 10, $P < 0.001$) and TG (median = 27.5 vs 18.2, $P = 0.007$), respectively, than other patients of the same group. No significant differences in the same group were detected regarding cholesterol ($P = 0.077$), LDL ($P = 0.129$), and HDL ($P =$

Table 2 Clinical manifestations of the studied patients

	Total ($n = 103$)	SLE without APS ($n = 75$)	SLE + APS ($n = 28$)	*P*-value
Musculoskeletal manifestations	71 (68.9)	51 (68.0)	20 (71.4)	0.738
Mucocutaneous manifestations	66 (64.1)	49 (65.3)	17 (60.7)	0.664
Serositis	5 (4.9)	3 (4.0)	2 (7.1)	0.611
Renal manifestations	62 (60.2)	45 (60.0)	17 (60.7)	0.947
Hematological manifestations	57 (55.3)	41 (54.7)	16 (57.1)	0.822
Cardiac manifestations	10 (9.7)	6 (8.0)	4 (14.3)	0.338
Vascular manifestations	16 (15.5)	5 (6.7)	11 (39.3)	< 0.001**
Neurological manifestations	24 (23.3)	11 (14.7)	13 (46.4)	< 0.001**
Psychiatric manifestations	10 (9.7)	7 (9.3)	3 (10.7)	0.833
Pulmonary manifestations	14 (13.6)	8 (10.7)	6 (21.4)	0.156
Abortion	12 (11.7)	4 (5.3)	8 (28.6)	< 0.001**

Data were presented as number (percentage)

**≤ 0.001 highly significant results

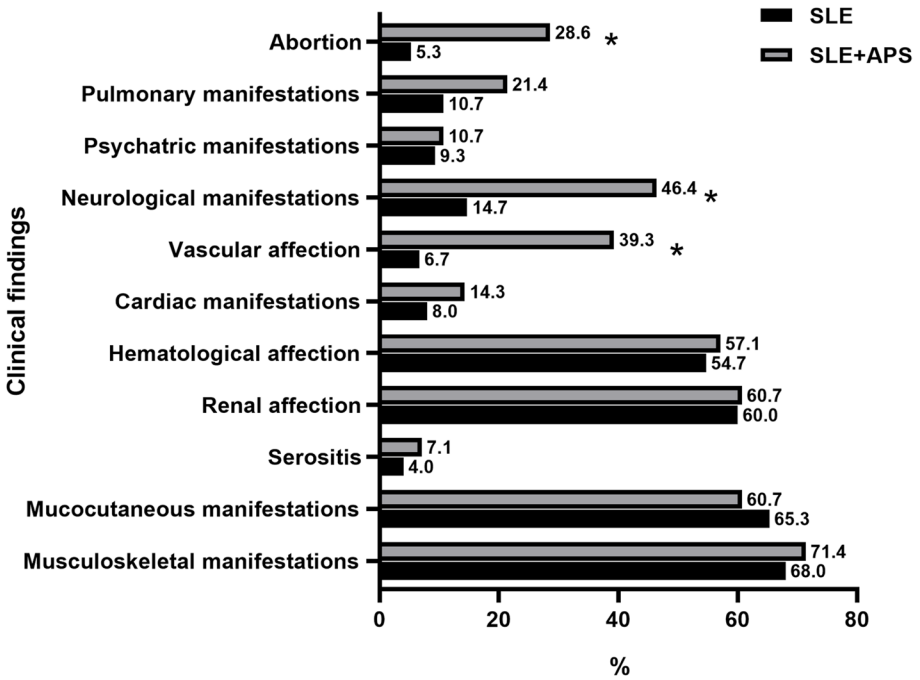

Fig. 1 Bar graph showing a comparison of the prevalence of clinical manifestations in the two studied groups

0.222) in relation to thromboembolic events (Table 3, Fig. 2).

SLEDAI score was significantly higher in those with SLE with 2ry APS (median = 17, range = 6–29) than in those with SLE (median = 11, range = 4–29) ($P = 0.001$). Serum total cholesterol (TC) was significantly higher in those with SLE with 2ry APS (93.8 ± 25.3 mg/dl) than in those with SLE (82.3 ± 19.6 mg/dl) ($P = 0.018$). LDL was significantly higher in those with SLE with 2ry APS (57.7 ± 20.3 mg/dl) than in those with SLE (50 ± 15.9 mg/dl) ($P = 0.048$) (Table 4, Fig. 3).

No significant differences were detected regarding ANA ($P = 1$), anti-dsDNA ($P = 0.196$), anti-LA ($P = 0.072$), anti-SMITH ($P = 0.611$), anti-U1RNP ($P = 0.179$), C3 (P = 0.979), C4 ($P = 0.979$), triglycerides ($P = 0.126$), and HDL ($P = 0.514$) (Table 4).

Table 3 SLEDAI and lipid profile according to thromboembolism in SLE without APS

	Yes ($n = 15$)	No ($n = 59$)	*P*-value
SLEDAI	15 (8–29)	10 (4–28)	< 0.001**
TC	90.3 ± 16.7	80.3 ± 19.9	0.077
TG	27.5 (13.5–65.7)	18.2 (7–64.8)	0.007*
LDL	55.6 ± 15.9	48.6 ± 15.7	0.129
HDL	21.2 ± 8.9	23.9 ± 7.5	0.222

Data were presented as mean ± SD

*≤ 0.05 significant results

**≤ 0.001 highly significant results

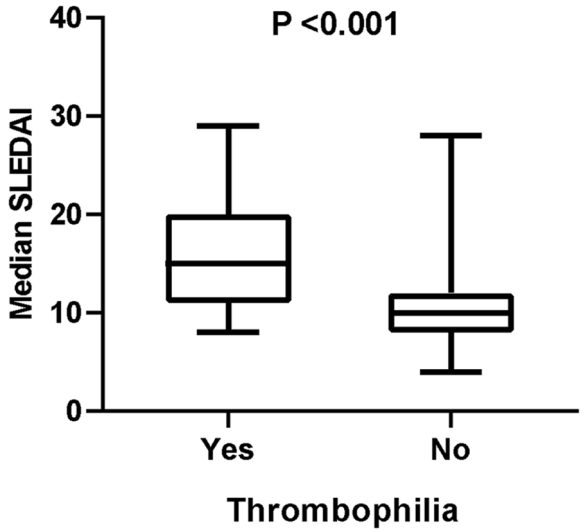

Fig. 2 Correlation of SLEDAI with thromboembolic events in SLE patients without APS

Statistical methods

SPSS version 28 was used for data administration and statistical analysis (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test, the Shapiro-Wilk test, and direct data visualization were used to check the normality of the quantitative data. Numbers were reported as means and standard deviations or medians and ranges in accordance with the assumption of normalcy. Quantitative and percentage summaries of categorical data were prepared. Independent *t*-tests or Mann-Whitney *U* tests were used to compare regularly distributed and non-normally distributed numerical variables between SLE and SLE with 2y APS. The chi-square test or Fisher's exact test was used to compare the categorical data. All statistical analysis was unidirectional. Significant results were determined at $P \leq 0.05$ and highly significant at $P \leq 0.001$.

Discussion

In our research, the group of SLE patients without APS has developed thromboembolism (TE) in 20% of cases. In the study of Azaola et al., which included 219 young patients, 16% of cases developed TE and were not associated with LAC. Other research stated that the incidence of thromboembolism in SLE patients was 13.3–22.0% of patients, occurring in the early years of the disease with some variations between ethnic groups and type of thrombosis [3]. The incidence of thromboembolism may exceed 50% of SLE patients who have positive LA [4], while thromboembolism occurs at a rate of 0.71 to 1.13 per 1000 person-years in the general population [5].

SLE patients without APS who developed thromboembolic events demonstrated significantly higher SLEDAI (median = 15 vs 10, $P < 0.001$) and TG (median = 27.5 vs 18.2, $P = 0.007$) than SLE patients without thromboembolism, so our study is ongoing with Khalil F et al. (2018) and Zhou et al. who concluded that serum lipid profile was significantly dysregulated in young SLE patients. Dyslipidemia and continuous disease activity of lupus patients increase the risk of atherosclerosis and cardiovascular disease [19, 20].

In the group of SLE with APS, the vascular affection, neurological affection, and pregnancy loss were significantly higher than SLE without APS. In SLE patients associated with APS, the SLEDAI score was high (median = 17, range = 6–29), and this was significantly higher than that in SLE patients without APS (median = 11, range = 4–29) ($P = 0.001$). The immune reaction, continuous inflammation, and high disease activity have a role in the pathogenesis of atherosclerosis and vascular damage, inducing thrombosis in SLE with or without APS. These results agreed with the study of Borba and Bonfa [11].

This current study found that the lupus anticoagulant (LA) is the main serological factor associated with thrombosis in SLE with 2ry APS, and it was positive in 18 cases of 28 (64.3%). ACL-IgG was positive in 5 cases (17.9%), and aCL-IgM was positive in 12 cases (42.9%), while anti-B2GPI-IgG was positive in 5 cases (17.9%) and anti-B2GPI-IgM was also positive in another 5 cases (17.9%). These results suggested that LA is the main predictive factor of thrombosis in aPL-positive patients, and this agrees with the EULAR recommendations for the management of antiphospholipid syndrome in adults [21].

Adriana et al. in 2009 concluded that about half of SLE patients with positive LA may get venous thrombosis within 20 years. To develop thrombotic problems and pregnancy morbidity, an asymptomatic patient with positive aPL antibodies may need a second trigger, according to the "two-hit theory" [2]. Total serum cholesterol was

Table 4 Laboratory findings and disease activity of SLE patients with and without APS

	Total ($n = 103$)	SLE ($n = 75$)	SLE + APS ($n = 28$)	*P*-value
Positive aCL-IgM	16 (15.5)	4 (5.3)	12 (42.9)	< 0.001**
Positive aCL-IgG	6 (5.8)	1 (1.3)	5 (17.9)	0.005*
Positive anti-B2GP-IgM	5 (4.9)	0 (0.0)	5 (17.9)	0.001*
Positive anti-B2GP-IgG	7 (6.8)	2 (2.7)	5 (17.9)	0.006*
Positive LA	20 (19.4)	2 (2.7)	18 (64.3)	< 0.001**
Positive ANA	102 (99.0)	74 (98.7)	28 (100.0)	1.0
Positive anti-dsDNA	67 (65.0)	46 (61.3)	21 (75.0)	0.196
Positive anti-RO	5 (4.9)	0 (0.0)	5 (17.9)	< 0.001**
Positive anti-LA	2 (1.9)	0 (0.0)	2 (7.1)	0.072
Positive anti-SMITH	5 (4.9)	3 (4.0)	2 (7.1)	0.611
Positive anti-U1RNP	3 (2.9)	1 (1.3)	2 (7.1)	0.179
C3				
Normal	37 (35.9)	27 (36.0)	10 (35.7)	0.979
Low	66 (64.1)	48 (64.0)	18 (64.3)	
C4				
Normal	37 (35.9)	27 (36.0)	10 (35.7)	0.979
Low	66 (64.1)	48 (64.0)	18 (64.3)	
TC (mg/dl)	85.4 ± 21.7	82.3 ± 19.6	93.8 ± 25.3	0.018*
TG (mg/dl)	20.7 (7–65.7)	20 (7–65.7)	28.8 (8.1–47.2)	0.126
LDL (mg/dl)	52.1 ± 17.4	50 ± 15.9	57.7 ± 20.3	0.048*
HDL (mg/dl)	23.7 ± 8.1	23.4 ± 7.8	24.6 ± 8.9	0.514
SLEDAI	12 (4–29)	11 (4–29)	17 (6–29)	< 0.001*

Data were presented as mean ± SD

*≤ 0.05 significant results

**≤ 0.001 highly significant results

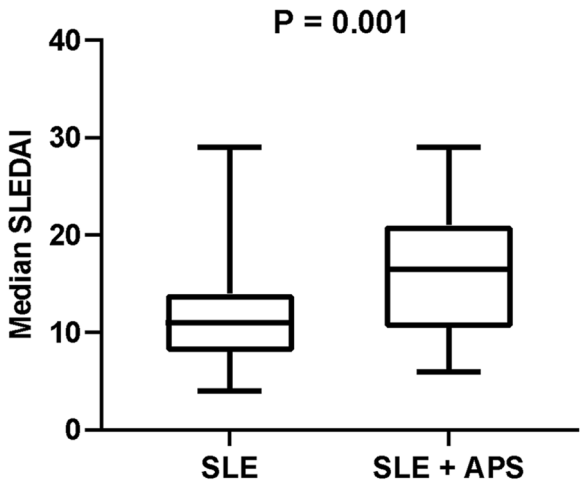

Fig. 3 SLEDAI score in SLE patients with and without APS

observed to be substantially higher among individuals with SLE with 2y APS (93.8 25.3 mg/dl) compared to SLE patients without APS (82.3 19% mg/dl) ($P = 0.018$). These results disagreed with Zhou et al. (2020) who found that young SLE patients have lower total cholesterol levels than control subjects meaning that the disease activity itself can cause dyslipidemia [20]. LDL was significantly higher in those with SLE with 2ry APS (57.7 ± 20.3 mg/dl) than in SLE without APS (50 ± 15.9 mg/dl) ($P = 0.048$), and these results correlate with the study of Sadanand et al. [6] and Khalil et al. [19].

The findings in this current study are ongoing with the previous studies noting that serum lipid profile abnormalities are more common in SLE and APS patients than in the general population with more risk of atherosclerosis and CVD [22, 23].

Conclusions

SLE patients are at significantly high risk for accelerated atherosclerosis, thromboembolism, and pregnancy loss which is multifactorial. Active disease should be well controlled. Lupus patients should be screened for aPL antibodies, and positive cases must be treated according to international guidelines. All patients with SLE should undergo lipid profile screening, and any abnormalities should be managed promptly.

Abbreviations

ACL	Anticardiolipin
ANA	Antinuclear antibody
Anti-ß2G	Anti-B2 glycoprotein
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
Anti-U1RNP	Anti-U1 ribonucleoprotein
APS	Antiphospholipid syndrome
C3, C4	Complement c3, complement4
CAPS	Catastrophic antiphospholipid syndrome
CBC	Complete blood count
CT	Computerized tomography
CVD	Cardiovascular diseases
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
HDL	High-density lipoproteins
KSA FT	King Salman Armed Forces Hospital Tabuk
LA	Lupus anticoagulant
LDL	Low-density lipoproteins
LN	Lupus nephritis
LUMINA	Lupus in Minorities: Nature vs Nurture
MI	Myocardial infarction
MRI	Magnetic resonant image
PE	Pulmonary embolism
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Classification Committee
TC	Total cholesterol
TE	Thromboembolism
TG	Triglycerides
US	Ultrasound
VTE	Venous thromboembolism

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Authors' contributions
Study concept and design: HWES and AAYE. Collection of the data from patient files and analysis and interpretation of the data: AAGI. Preparation of the mother sheet and statistical analysis and drafting of the manuscript: HED. The authors read and approved the final manuscript.

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Availability of data and materials
All data and materials are available when requested.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the local ethics committee in KSAFHT. Written informed consent was obtained from all participants before participating in the study.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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