Venous and Arterial Thrombotic Events in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** The incidence of thrombosis in patients with systemic lupus erythematosus (SLE) is 25 to 50-fold higher than in the general population; we aimed to define the characteristics of venous thrombotic events (VTE) and arterial thrombotic events (ATE) to identify the patients at highest risk.

Methods. The study included 219 patients with recent-onset SLE. At baseline, standardized medical history and laboratory tests were done. Followup visits occurred quarterly, and information about damage accrual, comorbidities, and cardiovascular risk factors was updated annually. Main outcome was development of TE after SLE diagnosis.

Results. Thirty-five patients (16%) developed TE (27 VTE, 8 ATE) during 5.21 years of followup; incidence rate 31/1000 patient-years. Most events (57%) developed within the first year of diagnosis, and 69% were not associated with lupus anticoagulant (LAC), determined with 1 method. VTE developed earlier than ATE (2.0 vs 57.5 mos, $p = 0.02$). In the multivariate analysis, variables preceding VTE included cutaneous vasculitis, nephrotic syndrome, dose of prednisone, and LAC in combination with anti-RNP/Sm antibodies ($p < 0.03$). Patients with ATE were older (median age 44 vs 29 yrs, $p = 0.04$), smokers, and had hypertension, diabetes mellitus, dyslipidemia, at least 2 traditional risk factors, nephrotic syndrome, chronic damage, and a higher cumulative dose of prednisone ($p < 0.05$). LAC in combination with anti-RNP/Sm antibodies was associated with VTE and improved the accuracy for predicting it.

Conclusion. Our study suggests that in SLE, VTE and ATE have different risk factors. Understanding these differences is helpful for identifying patients at highest risk. The use of LAC plus anti-RNP/Sm for predicting VTE deserves further study. (First Release January 15 2016; J Rheumatol 2016;43:576–86; doi:10.3899/jrheum.150506)

Key Indexing Terms:
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Survival in patients with systemic lupus erythematosus (SLE) has improved meaningfully over recent decades. Nevertheless, mortality still remains higher than in the general population[1]. In a 10-year cohort study, the most frequent causes of death were disease activity, thrombotic events (TE), and infection, with TE representing 27% of mortality and dominating the second 5-year period[2]. From 1970 to 2001 there was a dramatic decrease in total standardized mortality ratio (SMR) estimates across calendar-year periods, which was demonstrable for specific causes including disease activity and infections; nevertheless, the SMR attributable to circulatory diseases tended to increase[1]. Prevention of TE is an unmet need to keep improving survival in SLE.

In the general population, the incidence rate of TE is 0.7–1.13 per 1000 person-years; in SLE, it is 10.5–29 per 1000 patient-years (PY)[3,4,5,6]. Thrombosis has been reported in 13.3–22.0% of patients with SLE, occurring mostly within the early years of disease with variations observed between ethnic groups and type of thrombosis[4,5,6,7].

TE cause considerable morbidity and mortality in SLE; however, few studies have assessed the risk factors in the years subsequent to diagnosis[4,6,7]. In 1 study including

mostly white patients, 66% of TE were arterial and associated with older age at SLE diagnosis, shorter disease duration, disease activity, smoking, and damage[4]. In another study including Chinese, African Americans, and white patients, arterial thrombosis (ATE) was more frequent and associated with Chinese ethnicity, low levels of high-density lipoprotein (HDL) cholesterol, oral ulcers, and serositis; meanwhile, venous thrombosis (VTE) was associated with male sex, low levels of HDL, antiphospholipid antibodies (aPL), non-Chinese ethnicity, renal disease, and hemolytic anemia[5]. Most information available about TE derives from retrospective studies, including prevalent cases with long disease duration at analysis, or descriptions missing the early months of disease[7,8,9,10,11]. The literature has placed emphasis on associations with aPL, even though other causative factors are more frequent.

Because the hazard of TE is highest within the early months of diagnosis, we aimed to define the characteristics of VTE and ATE in patients with recent-onset SLE to identify the subpopulation at highest risk to delineate preventive strategies.

MATERIALS AND METHODS

We studied 219 Mexican patients participating in a prospective cohort with recent-onset SLE at enrollment, defined as ≤ 1 year since the accrual of ≥ 4 American College of Rheumatology (ACR) revised and updated classification criteria[12,13]. The hospital institutional review board approved the study and all subjects provided written informed consent.

SLE cohort. In 1999, an inception cohort of patients aged ≥ 13 years was assembled at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care center in México City[14]. The objective of this cohort was the longitudinal evaluation of SLE outcomes and their risk factors.

At baseline, patients' medical histories were recorded, including demographic data, lifestyle habits, cardiovascular risk factors, clinical characteristics of SLE, and laboratory test results. Blood samples were taken and stored at –70°C. Followup visits were conducted every 3–4 months, when clinical and treatment information were obtained and disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[15].

Every year, information was updated, including damage accrual using the Systemic Lupus International Collaborative Clinics (SLICC)/ACR Damage Index (SDI)[16], comorbidities, cardiovascular risk factors, and a drawn blood sample. Clinical information was stored in a database.

Thrombosis incidence study. The main outcome of our analysis was the development of a TE after SLE onset. Thrombosis was defined as clinical signs and symptoms of vascular occlusion, confirmed by studies. Pulmonary thromboembolism was documented with computed tomography (CT), ventilation/perfusion scan, or lung biopsy. Deep vein thrombosis, ATE of the extremities, and visceral thrombosis were evaluated with Doppler ultrasound, CT, or angiography. Cerebrovascular events were documented with CT and/or magnetic resonance imaging, and myocardial infarction (MI) with electrocardiogram, cardiac enzymes, and coronarography. VTE included deep vein thrombosis of the extremities, pulmonary thromboembolism, cerebral, retinal, or visceral. ATE included stroke, MI, internal organ, retinal, or peripheral. All patients were followed during the whole period as part of their participation in the cohort and all TE were documented prospectively.

Study variables included demographic, anthropometric, and smoking. Comorbidities considered were diabetes mellitus (DM), hypertension (HTN; systolic blood pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg) on at least 2 occasions, and dyslipidemia (total serum cholesterol ≥ 200 mg/dl and/or total triglycerides ≥ 150 mg/dl); we had direct access to the medical records to confirm diagnoses and treatment of comorbidities. SLE clinical variables were defined according to the ACR criteria[12,13]; disease duration, followup time, cutaneous vasculitis, livedo reticularis, and nephrotic syndrome (urinary protein exceeding 3.5 g per 1.73 m^2 of body surface area per day) were considered. Disease duration was defined as the time elapsing from the date that the patient met ≥ 4 ACR criteria for SLE to TE/dummy date or last followup visit. Disease activity was assessed using the SLEDAI-2K, and adjusted mean of SLEDAI-2K[17]. Damage was evaluated using SDI modified to exclude those variables correlated with TE (i.e., cerebrovascular accident, pulmonary infarction, MI, VTE, and intestinal infarction). For patients with disease duration of < 6 months at baseline, SDI was considered as 0, except for items considered present ever.

Variables associated with TE were immobilization during at least 7 days, recent surgery, vascular insufficiency, menopause, use of hormone replacement therapy/oral contraceptives, and thrombocytosis (platelet count > 500,000/μl). We considered current and past use of medication, including cumulative doses of prednisone or equivalent, immunosuppressants, antimalarials, and aspirin.

Autoantibodies and prothrombotic markers. Laboratory variables were measured at baseline and included high-sensitivity C-reactive protein (hsCRP; turbidimetric assay), homocysteine (fluorescence polarization immunoassay; AXSYM, Abbott), free protein S levels (ELISA; Asserachrom Free Protein S)[18], protein S functional activity (coagulometric test Protein S Ac; Siemens)[19,20], protein C functional activity (chromogenic test Berichrom Protein C; Siemens)[21,22], antithrombin III activity (chromogenic test Berichrom AT III; Siemens)[23], and fibrinogen (coagulometric test assay Multifibren U; Siemens)[24,25]. Proteins C and S, antithrombin III, and fibrinogen were determined in 170 patients only. Patients were not receiving anticoagulants when the laboratory tests were performed.

Autoantibodies included anti-dsDNA, anti-Sm, anti-RNP/Sm, anti-SSA, anti-SSB, immunoglobulin G (IgG) and IgM anti-β2-glycoprotein I (anti-B2GPI), and IgG and IgM anticardiolipin (aCL) antibodies, all determined by ELISA. Anti-dsDNA, aCL, and anti-B2GPI were processed with INOVA Diagnostics and the other autoantibodies with Orgentec Diagnostika GmbH, according to the commercial manufacturer's instructions in a DSX system (DYNEX Technologies). Positivity was considered according to the 95th percentile in our healthy population for all autoantibodies except for aCL and anti-B2GPI, in which the 99th percentile was considered. Lupus anticoagulant (LAC) was processed with the coagulometric test (LA1 reagent screening/LA2 reagent confirmation; Siemens) based on the dilute Russell's viper venom time method[26,27]. Patients had repeated determinations for aPL antibodies during followup; time intervals were > 12 weeks and positivity for antibodies was corroborated during followup.

Statistical analysis. Only the first TE documented was considered for our study. Continuous variables were expressed as mean ± SD or median with minimum and maximum range, and categorical variables as counts and percentages. Differences between groups were evaluated with the Student t test or Mann-Whitney U test for continuous variables, and chi-square or Fisher's exact test for categorical variables. A value of $p < 0.05$ was set and 2-sided values are reported.

For time sensitive variables, i.e., disease activity, a dummy date (random date during followup) was calculated for patients without TE because large differences in followup time and disease duration were present between patients with and without TE. Followup time was defined as the period elapsed between the baseline visit and the occurrence of the first TE/dummy date, the last visit, or death. A composite variable, consisting of at least 2 traditional risk factors, was added, which included the concurrence of obesity, smoking, HTN, DM, dyslipidemia, use of oral contraceptives/hormone replacement therapy, vascular insufficiency, prolonged immobilization, menopause, or recent surgery.

Incidence density (ID) was calculated using the formula:

$$ID_{(t0–t)} = I \div PT$$

Where $ID_{(t0–t)}$ = incidence density for the period (t0–t), I = incident cases, and PT = person-time.

In multivariate analyses, adjusting for age and disease duration, logistic regression was used to analyze associations between significant variables ($p \leq 0.10$) identified from the bivariate analyses and risk for TE. Significant variables had to be present in at least 20% of patients with TE to be eligible to enter the model. OR and 95% CI were calculated. Kaplan-Meier survival graphs with log-rank test for VTE and ATE based on risk factors were plotted. We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio (LR+) for some autoantibodies to predict TE. All analyses were done using Stata, version 12.0 (Stata Corp.).

RESULTS

The cohort consisted of 223 patients with SLE. One patient receiving anticoagulants for severe pulmonary HTN without thrombosis, 1 who presented thrombosis 7 months prior to diagnosis of SLE, and 2 patients with malignancies were excluded. Therefore, we studied 219 patients with SLE. Ninety percent were women, with a mean ± SD age at diagnosis of 27.1 ± 9.1 years, a disease duration at enrollment of 5.3 ± 3.9 months (0–12), and a length of followup of 5.21 ± 3.7 years (0–11).

Incidence of thrombosis. Thirty-five patients (16%) developed TE during 1139 PY of followup; incidence rate 31/1000 PY (8 ATE, 23%, incidence rate 7.0/1000 PY, and 27 VTE, 77%, incidence rate 24.0/1000 PY). ATE occurred in the following areas: cerebral (n = 5), coronary (n = 1), upper limbs (n = 1), and retinal arteries (n = 1). VTE were localized as follows: pulmonary embolism (n = 13), deep venous thrombosis (n = 11), superior or inferior cava vein (n = 2), and cerebral (n = 1).

Twenty TE (57%) occurred during the first year of SLE diagnosis (median time to thrombosis: 11 mos, 0–101). Median time to ATE was longer than VTE (57.5 vs 2.0 mos, p = 0.02). In 10 patients, TE (all VTE) occurred simultaneously to diagnosis of SLE.

Variables associated with thrombosis. Patients with TE had shorter disease duration (0.9 vs 2 yrs, p = 0.003), obesity, DM, dyslipidemia, immobilization, at least 2 traditional risk factors, cutaneous vasculitis, nephrotic syndrome, higher disease activity at thrombosis, higher hsCRP, higher dose of prednisone, and higher cumulative dose of prednisone compared with patients without TE ($p < 0.05$; Table 1 and Table 2).

In the multivariate analysis, adjusting for age and disease duration, we found that cutaneous vasculitis (OR 3.41, 95% CI 1.21–9.65, p = 0.02), nephrotic syndrome (OR 3.36, 95% CI 1.21–9.32, p = 0.02), current dose of prednisone (OR 1.05, 95% CI 1.03–1.07, $p < 0.001$), at least 2 traditional risk factors (OR 3.41, 95% CI 1.24–9.37, p = 0.02), and LAC + anti-RNP/Sm (OR 6.53, 95% CI 1.71–24.98, p = 0.006) were independently associated with TE.

An additional analysis excluding 10 patients who developed thrombosis at SLE diagnosis did not show differences (data not shown).

Variables associated with venous and arterial thrombosis. Clinical and serological variables differed according to the type of TE.

Patients with VTE had shorter disease duration (median of 0.1 vs 2 yrs, $p < 0.0001$); were more frequently immobilized; had at least 2 traditional risk factors, vasculitis, nephrotic syndrome, higher disease activity at VTE, LAC, LAC + anti-RNP/Sm antibodies; and were taking a higher dose of prednisone, but the cumulative dose was lower ($p < 0.05$; Table 1 and Table 2).

A tendency for higher frequency of IgG anti-B2GPI antibodies (p = 0.06) and aPL triple marker (p = 0.07) was observed in patients with VTE, and the combination of IgG anti-B2GPI + LAC was significantly more frequent in these patients compared with patients without thrombosis (12% vs 2%, p = 0.04). This significance might be improved if there were not missing data.

In multivariate analysis, adjusting for age and disease duration, we found that cutaneous vasculitis (OR 4.21, 95% CI 1.28–13.86, p = 0.02), current dose of prednisone (OR 1.07, 95% CI 1.04–1.09, $p < 0.001$), nephrotic syndrome (OR 3.98, 95% CI 1.20–13.18, p = 0.02), and LAC + anti-RNP/Sm (OR 6.39, 95% CI 1.37–29.86, p = 0.02) were independent risk factors. Figure 1 shows Kaplan-Meier survival estimates based on risk factors for VTE.

Patients with ATE were older (median age 44 vs 29 yrs, p = 0.04), were smokers, and had HTN, DM, dyslipidemia, at least 2 traditional risk factors, nephrotic syndrome, a higher SDI score, and higher current and cumulative dose of prednisone. Disease duration did not differ from patients without TE (Table 1 and Table 2). The small number of patients precluded multivariate analysis.

When patients with ATE and VTE were compared, the former group was older (median age 44 vs 27 yrs, p = 0.02), had longer disease duration at TE, were smokers, had HTN, had at least 2 traditional risk factors, had higher damage indices (SDI score), and had a higher cumulative dose of prednisone ($p < 0.05$; Table 3).

Efficacy of LAC alone or in combination for predicting venous thrombosis. LAC was the single antibody strongly associated with VTE, and the combination with anti-RNP/Sm improved the accuracy for predicting VTE. This combination showed 25.9% sensitivity, 96.2% specificity, 50.0% PPV, 89.8% NPV, and LR+ 6.0 (95% CI 2.3–15.6; Table 4).

Thrombosis in patients with negative LAC. There were 185 patients who tested negative for LAC and 24 (13.0%) who developed TE (17 venous, 7 arterial); therefore, most TE (69%) occurred in this subpopulation. Patients with TE tended to have a shorter disease duration (median 0.9 vs 2.4 yrs, p = 0.06), were smokers, and had dyslipidemia,

Table 1. Demographic and serologic characteristics of patients with and without thrombosis. Number of patients tested with and without thrombosis: homocysteine 95% and 97%, hsCRP 100% and 92%, functional protein S and C 40% and 85%, free protein S 40% and 85%, antithrombin III 40% and 84%, and fibrinogen 37% and 85%. Values are n (%) or median (minimum–maximum) unless otherwise specified.

Variables	No Thrombosis, n = 184	Thrombosis, n = 35	p	Venous Thrombosis, n = 27	p	Arterial Thrombosis, n = 8	p
Demographic characteristics							
Female	165 (90)	31 (89)	0.76	24 (89)	0.55	7 (88)	0.59
Age, yrs	29 (13–60)	29 (15–57)	0.76	27 (18–45)	0.16	44 (15–57)	**0.04**
Length of followup, yrs*	6 (0–12)	0.8 (0–7)	**< 0.001**	0 (0–7)	**< 0.001**	4 (0–6)	0.09
Obesity	26 (14)	1 (3)	**0.04**	1 (4)	0.10	0	0.30
Smoking	15 (8)	6 (17)	0.11	2 (7)	0.62	4 (50)	**0.004**
Hypertension	29 (16)	9 (26)	0.22	4 (15)	0.58	5 (63)	**0.005**
Diabetes	5 (3)	4 (11)	**0.03**	2 (7)	0.22	2 (25)	**0.02**
Dyslipidemia	57 (31)	19 (54)	**0.01**	13 (48)	0.06	6 (75)	**0.01**
Vascular insufficiency	1 (1)	1 (3)	0.29	1 (4)	0.24	0	1.00
Immobilization	1 (1)	3 (9)	**0.01**	3 (11)	**0.007**	0	1.00
Surgery	1 (1)	2 (6)	0.06	2 (7)	**0.04**	0	1.00
Oral contraceptives	16 (9)	1 (3)	0.20	1 (4)	0.56	0	1.00
Menopause	2 (1)	1 (3)	0.40	1 (4)	0.33	0	1.00
At least 2 traditional risk factors	25 (14)	14 (40)	**0.001**	8 (30)	**0.04**	6 (75)	**< 0.001**
Serologic characteristics							
Homocysteine, mmol/l	10.5 (5.1–65)	11.4 (7–27.8)	0.31	12.9 (7–27.8)	0.08	9.2 (7.7–16.7)	0.27
hsCRP, mg/dl	1.26 (0.01–11.40)	2.39 (0.03–9.85)	**0.03**	1.98 (0.03–9.85)	0.05	3.58 (0.15–9.85)	0.32
Functional protein S, %	77.2 (20.7–130.3)	77.3 (35.5–130.3)	0.99	84.4 (35.5–130.3)	0.72	56 (55.2–127.3)	0.46
Functional protein S deficiency	31 (20)	5 (31)	0.33	3 (23)	0.72	2 (67)	0.10
Free protein S, %	46.4 (15.4–148)	37.2 (16.8–72.1)	0.05	35.2 (16.8–72.1)	0.13	38 (36.4–38.3)	0.16
Free protein S deficiency	149 (96)	14 (100)	1.00	11 (100)	1.00	3 (100)	1.00
Functional protein C, %	121.6 (52.8–150)	125.4 (23.8–150)	0.72	126.8 (23.8–150)	0.90	121.6 (102.6–124.4)	0.58
Functional protein C deficiency	2 (1)	1 (7)	0.22	1 (9)	0.18	0	1.00
Antithrombin III, %	113.7 (54–126.8)	106.3 (69.3–126.8)	0.61	105.3 (69.3–126.8)	0.44	112.1 (103.4–126.8)	0.69
Antithrombin III deficiency	5 (3)	1 (7)	0.41	1 (9)	0.34	0	1.00
Fibrinogen, mg/dl	234.1 (76.1–566.1)	232.2 (147.5–559.5)	0.32	304.8 (213.1–559.5)	0.10	180 (147.5–232.2)	0.34

* Length of followup in patients without thrombosis was considered until last visit or death. Significant data are in bold face. hsCRP: high-sensitivity C-reactive protein.

prolonged immobilization, at least 2 traditional risk factors, serositis, cutaneous vasculitis, livedo reticularis, nephrotic syndrome, higher disease activity, lower levels of free S protein, and a higher dose of prednisone ($p < 0.05$; Table 5).

In multivariate analysis, these were independent risk factors for TE: age (OR 1.09, 95% CI 1.02–1.16, $p = 0.02$), cutaneous vasculitis (OR 7.04, 95% CI 1.91–25.99, $p = 0.003$), nephrotic syndrome (OR 4.22, 95% CI 1.23–14.46, $p = 0.02$), serositis (OR 4.32, 95% CI 1.26–14.83, $p = 0.02$), and current dose of prednisone (OR 1.07, 95% CI 1.04–1.10, $p < 0.001$); whereas smoking showed borderline significance (OR 4.61, 95% CI 0.97–21.86, $p = 0.05$).

DISCUSSION

In our analysis of 219 young patients, mostly women, with recent-onset SLE, 16% developed TE. Most events occurred within the first year of diagnosis, were not associated with LAC, and involved the venous territory; however, the incidence rate of ATE was also increased. Clinical variables preceding the onset of TE included short disease duration, traditional risk factors, disease activity, chronic damage, current and cumulative dose of prednisone, and LAC, particularly in combination with anti-RNP/Sm antibodies.

Patients were assessed by protocol since the diagnosis of SLE, all TE occurred during the followup, and were ascertained by the investigators. Independent variables were collected at enrollment and followup; blood tests and autoantibodies were measured in samples collected at baseline and confirmed during followup. The incidence rate of VTE and ATE fall within the range reported in SLE[4,6].

The incidence of thrombosis was 27 to 43–fold higher than in the general population[3]. Variables associated with TE showed a mixture of traditional risk factors and SLE-related factors; however, multivariate analysis retained primarily SLE-related variables because 77% were VTE. Although VTE and ATE shared some risk variables, there were peculiarities. VTE occurred early in the course of SLE, were associated with disease activity in general, and were particularly associated with vasculitis and nephrotic syndrome, current dose of prednisone, and the presence of LAC, mainly

Table 2. Systemic lupus erythematosus characteristics and treatment of patients with and without thrombosis. Number of patients tested with and without thrombosis: anti-dsDNA 100% and 97%, anti-Sm and anti-RNP/Sm 100% and 95%, anti-SSA and anti-SSB 100% and 96%, LAC 94% and 96%, IgG/IgM aCL and anti-B2GPI 100% and 92%, aPL triple marker in 94% and 90%, and anti-RNP/Sm + LAC 94% and 96%. Values are n (%) or median (minimum–maximum) unless otherwise specified.

Variables	No Thrombosis, n = 184	Thrombosis, n = 35	p	Venous Thrombosis, n = 27	p	Arterial Thrombosis, n = 8	p
Disease duration, yrs	2 (0–8)	0.9 (0–7)	**0.003**	0.1 (0–7)	**< 0.001**	5 (0–7)	0.18
Malar rash	86 (47)	11 (31)	0.06	7 (26)	0.06	4 (50)	1.00
Discoid lupus	17 (9)	2 (6)	0.74	2 (7)	1.00	0	1.00
Oral ulcers	82 (45)	16 (46)	1.00	11 (41)	0.83	5 (63)	0.47
Serositis	69 (38)	19 (54)	0.08	15 (56)	0.09	4 (50)	0.48
Arthritis	161 (88)	30 (86)	0.58	24 (89)	1.00	6 (75)	0.27
Photosensitivity	61 (33)	8 (23)	0.32	5 (19)	0.18	3 (38)	1.00
Renal disorder	102 (55)	25 (71)	0.09	19 (70)	0.21	6 (75)	0.46
Neurological disorder	10 (5)	3 (9)	0.44	1 (4)	1.00	2 (25)	0.08
Hematologic disorder	142 (77)	30 (86)	0.36	24 (89)	0.21	6 (75)	1.00
Immunologic disorder	156 (85)	29 (83)	0.80	22 (81)	0.58	7 (88)	1.00
ANA	163 (89)	32 (91)	0.77	25 (93)	0.74	7 (88)	1.00
Vasculitis	30 (16)	12 (34)	**0.01**	10 (37)	**0.01**	2 (25)	0.62
Livedo reticularis	24 (13)	9 (26)	0.07	6 (22)	0.23	3 (38)	0.08
Nephrotic syndrome	31 (17)	14 (40)	**0.005**	10 (37)	**0.01**	4 (50)	**0.03**
SLEDAI-2K score	4 (0–22)	8 (0–17)	**0.02**	8 (0–17)	**0.01**	6 (0–12)	0.65
SLEDAI, adjusted mean	4.2 (0–20.5)	4.5 (1.1–10.1)	0.81	3.8 (1.1–10.1)	0.86	5.4 (2.3–9.8)	0.53
SLICC/ACR Damage Index, modified	0 (0–5)	0 (0–3)	0.58	0 (0–2)	0.49	1 (0–3)	**0.01**
SLICC/ACR Damage Index > 0	1 (1–5)	1 (1–2)	0.09	1 (1–2)	0.15	1 (1–2)	0.30
Anti-dsDNA antibodies	84 (47)	18 (51)	0.71	13 (48)	1.0	5 (63)	0.48
Anti-Sm antibodies	102 (58)	25 (71)	0.17	19 (70)	0.29	6 (75)	0.47
Anti-RNP/Sm antibodies	81 (45)	22 (63)	0.06	17 (63)	0.09	5 (63)	0.47
Anti-SSA	99 (56)	22 (63)	0.57	15 (56)	1.00	7 (88)	0.14
Anti-SSB	52 (29)	12 (34)	0.54	8 (30)	1.00	4 (50)	0.24
LAC	15 (8)	9 (27)	**0.005**	8 (32)	**0.003**	1 (13)	0.52
Anti-RNP/Sm+ LAC	7 (4)	8 (24)	**< 0.001**	7 (28)	**< 0.001**	1 (13)	0.30
IgG aCL	38 (22)	12 (34)	0.19	9 (33)	0.23	3 (38)	0.38
IgM aCL	27 (16)	5 (14)	1.00	4 (15)	1.00	1 (13)	1.00
Any aCL	49 (29)	14 (40)	0.22	10 (37)	0.49	4 (50)	0.24
IgG anti-B2GPI antibodies	8 (5)	4 (11)	0.13	4 (15)	0.06	0	1.00
IgM anti-B2GPI antibodies	9 (5)	1 (3)	1.00	1 (4)	1.00	0	1.00
Any anti-B2GPI antibodies	14 (8)	4 (11)	0.52	4 (15)	0.28	0	1.00
aPL triple marker positivity	5 (3)	3 (9)	0.12	3 (12)	0.07	0	1.00
Prednisone	179 (97)	35 (100)	1.00	27 (100)	1.00	8 (100)	1.00
Current dose of prednisone, mg	5 (0–100)	30 (0–262)	**< 0.001**	45 (0–80)	**< 0.001**	18.7 (5–262)	**0.008**
Cumulative dose of prednisone, g	11.8 (0–62.1)	7.8 (0–58)	**0.04**	6 (0–58)	**< 0.001**	17.3 (10–39.5)	**0.04**
Methylprednisolone IV	27 (15)	4 (11)	0.79	3 (11)	0.77	1 (13)	1.00
Azathioprine	135 (73)	28 (80)	0.52	20 (74)	1.00	8 (100)	0.20
Cyclophosphamide	50 (27)	9 (25)	1.00	5 (19)	0.48	4 (50)	0.22
Methotrexate	22 (12)	5 (14)	0.77	4 (15)	0.75	1 (13)	1.00
Mycophenolate mofetil	18 (10)	2 (6)	0.74	2 (7)	1.00	0	1.00
Antimalarials	123 (67)	20 (57)	0.33	15 (56)	0.28	5 (63)	1.00
Aspirin	64 (34)	9 (26)	0.43	7 (26)	0.51	2 (25)	0.71

Significant data are in bold face. LAC: lupus anticoagulant; IgG: immunoglobulin G; IgM: immunoglobulin M; aCL: anticardiolipin antibodies; anti-B2GPI: anti-β2-glycoprotein I; aPL: antiphospholipid antibodies; ANA: antinuclear antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborative Clinics/American College of Rheumatology.

in combination with anti-RNP/Sm antibodies. ATE happened at an older age, had a longer disease duration, and occurred with traditional thrombotic risk factors, chronic damage, current/cumulative dose of prednisone, and nephrotic syndrome. Nevertheless, we are cautious about the robustness of the results considering the small number of ATE.

Most TE occurred in patients with a negative LAC. In this subgroup, the VTE:ATE ratio decreased to 2.4:1 from 4.4:1 in the full group; however, 70% were still VTE and the analyses did not differ significantly from the results of the full group. These findings show that although LAC is involved in the risk of TE, other elements (i.e., inflammation and traditional risk factors) impose the major burden in SLE. Although LAC is strongly linked with thrombosis, disap-

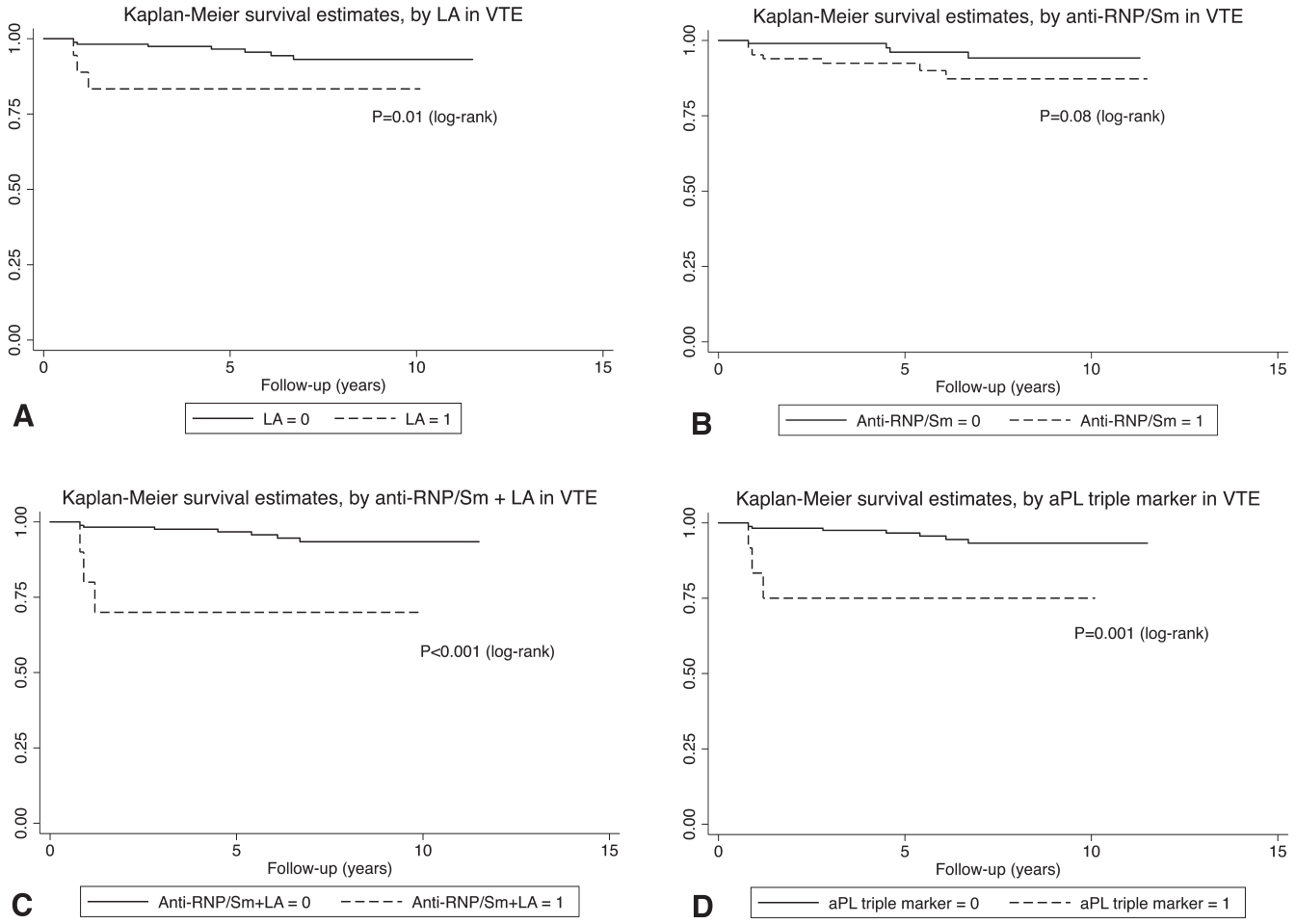

Figure 1. Kaplan-Meier survival curves showing the percentage of patients who presented VTE during followup according to (A) LA, (B) anti-RNP/Sm, (C) anti-RNP/Sm + LA, and (D) aPL triple marker. "0" implies negativity for the antibody and "1" implies positivity for the antibody. LA: lupus anticoagulant; VTE: venous thrombotic events; aPL: antiphospholipid antibodies.

pearance of the antibody during TE has been reported, most likely explained as an aPL being masked by the interaction of inflammatory, thrombotic, and fibrinolytic processes[28,29].

The differential incidence of VTE and ATE during the evolution of SLE was also reported in a study of 144 patients. Although the frequency of events was similar, half of the VTE occurred within 2.5 years and half of the ATE during 8.5 years since diagnosis[30]. In a study of 544 patients with SLE, half of the VTE happened during 2 years, and half of ATE within 6 years after diagnosis[4]. Besides SLE, other autoimmune diseases confer the risk of VTE during the first year of diagnosis[31].

Our results are consistent with those reported in the LUMINA (Lupus in Minority: NAture vs Nurture) cohort, where baseline predictors for VTE included smoking, shorter disease duration, higher disease activity, dose of glucocorticoids, and LAC[10]. In the same cohort, predictors for ATE included older age, longer disease duration, smoking, aPL antibodies, concurrence of traditional risk factors, and higher SDI scores[9]. In a multiethnic study, VTE were associated with Chinese ethnicity, aPL antibodies, hemolytic anemia, and nephrotic syndrome; however, traditional risk factors were not associated with ATE[5]. The association of vasculitis and thrombosis was identified previously in patients with SLE[11]. It is unclear how the prothrombotic environment is generated in vasculitis, but episodes of thrombosis cluster around periods of increased disease activity or shortly after diagnosis, especially in primary vasculitides[32].

An unexpected finding of our study was the association of LAC with anti-RNP/Sm antibodies as a predictor of VTE, which has not been described. This finding resulted from the systematic measurement of several antibodies. Although this association might be fortuitous or resulting from multiple comparisons, the strength of the association was higher than with LAC alone and aPL triple marker, and retained in the multivariate analysis. Also, the specificity, PPV, and LR+ were enhanced. A report of 201 patients with mixed connective tissue disease, characterized by the presence of anti-RNP/Sm

Table 3. Comparison of risk factors for arterial and venous thrombosis. Number of patients tested with arterial or venous thrombosis: homocysteine 100% and 96%, hsCRP 100% and 100%, functional protein S and C 38% and 41%, free protein S 38% and 41%, antithrombin III 38% and 41%, fibrinogen 38% and 37%, anti-Sm 100% and 100%, anti-RNP/Sm 100% and 100%, anti-RNP/Sm + LAC 100% and 93%, anti-SSA and anti-SSB 100% and 100%, LAC 100% and 93%, IgG and IgM aCL and anti-B2GPI 100% and 100%, and aPL triple marker 100% and 93%. Values are n (%) or median (minimum–maximum) unless otherwise specified.

Variables	Arterial Thrombosis, n = 8	Venous Thrombosis, n = 27	p
Demographic characteristics			
Female	7 (88)	24 (89)	1.00
Age, yrs	44 (15–57)	27 (18–45)	**0.02**
Length of followup, yrs	4 (0–6)	0 (0–7)	**0.01**
Obesity	0	1 (4)	1.00
Smoking	4 (50)	2 (7)	**0.01**
Hypertension	5 (63)	4 (15)	**0.01**
Diabetes	2 (25)	2 (7)	0.21
Dyslipidemia	6 (75)	13 (48)	0.17
Vascular insufficiency	0	1 (4)	0.77
Immobilization	0	3 (11)	0.44
Surgery	0	2 (7)	0.59
Oral contraceptives	0	1 (4)	0.77
Menopause	0	1 (4)	0.77
At least 2 traditional risk factors	6 (75)	8 (30)	**0.03**
Serologic characteristics			
Homocysteine, mmol/l	9.2 (7.7–16.7)	12.9 (7–27.8)	0.07
hsCRP, mg/dl	3.58 (0.15–9.85)	1.98 (0.03–9.85)	0.82
Functional protein S, %	56 (55.2–127.3)	84.4 (35.5–130.3)	0.48
Functional protein S deficiency	2 (67)	3 (23)	0.21
Free protein S, %	38 (36.4–38.3)	35.2 (16.8–72.1)	0.81
Free protein S deficiency	3 (100)	11 (100)	—
Functional protein C, %	121.6 (102.6–124.4)	126.8 (23.8–150)	0.39
Functional protein C deficiency	0	1 (9)	1.00
Antithrombin III, %	112.1 (103.4–126.8)	105.3 (69.3–126.8)	0.38
Antithrombin III deficiency	0	1 (9)	1.00
Fibrinogen, mg/dl	180 (147.5–232.2)	304.8 (213.1–559.5)	0.06
SLE characteristics and treatment			
Time to first event, mos	57.5 (1–84)	2 (0–101)	**0.02**
Disease duration, yrs	5 (0–7)	0 (0–7)	**0.01**
Malar rash	4 (50)	7 (26)	0.19
Discoid lupus	0	2 (7)	0.59
Oral ulcers	5 (63)	11 (41)	0.24
Serositis	4 (50)	15 (56)	0.54
Arthritis	6 (75)	25 (89)	0.31
Photosensitivity	3 (38)	5 (19)	0.25
Renal disorder	6 (75)	19 (70)	0.58
Neurological disorder	2 (25)	1 (4)	0.12
Hematologic disorder	6 (75)	24 (89)	0.31
Immunologic disorder	7 (88)	22 (82)	0.58
ANA	7 (88)	25 (93)	0.55
Vasculitis	2 (25)	10 (37)	0.42
Livedo reticularis	3 (38)	6 (22)	0.33
Nephrotic syndrome	4 (50)	10 (37)	0.39
SLEDAI-2K score	6 (0–12)	8 (0–17)	0.39
SLEDAI, adjusted mean	5.4 (2.3–9.8)	3.8 (1.1–10.1)	0.55
SLICC/ACR Damage Index, modified	1 (0–3)	0 (0–2)	**0.008**
SLICC/ACR Damage Index > 0	1 (1–2)	1 (1–2)	0.80
Anti-dsDNA antibodies	5 (63)	13 (48)	0.38
Anti-Sm antibodies	6 (75)	19 (70)	0.58
Anti-RNP/Sm antibodies	5 (63)	17 (63)	1.00
Anti-SSA	7 (88)	15 (56)	0.10
Anti-SSB	4 (50)	8 (30)	0.25
LAC	1 (13)	8 (32)	0.27
Anti-RNP/Sm + LAC	1 (13)	7 (28)	0.35
IgG aCL	3 (38)	9 (33)	0.57
IgM aCL	1 (13)	4 (15)	1.00

Table 3. Continued.

Variables	Arterial Thrombosis, n = 8	Venous Thrombosis, n = 27	p
Any aCL	4 (50)	10 (37)	0.68
IgG anti-B2GPI antibodies	0	4 (15)	0.55
IgM anti-B2GPI antibodies	0	1 (4)	1.00
Any anti-B2GPI antibodies	0	4 (15)	0.55
aPL triple marker positivity	0	3 (12)	0.56
Prednisone	8 (100)	27 (100)	—
Current dose of prednisone, mg	19 (5–262)	45 (0–80)	0.18
Cumulative dose of prednisone, g	17.3 (10–39.5)	6 (0–58)	**0.003**
Methylprednisolone IV	1 (13)	3 (11)	0.66
Azathioprine	8 (100)	20 (74)	0.13
Cyclophosphamide	4 (50)	5 (19)	0.09
Methotrexate	1 (13)	4 (15)	0.68
Mycophenolate mofetil	0	2 (7)	0.59
Antimalarials	5 (63)	15 (56)	0.52
Aspirin	2 (25)	7 (26)	1.00

Significant data are in bold face. hsCRP: high-sensitivity C-reactive protein; LAC: lupus anticoagulant; IgG: immunoglobulin G; IgM: immunoglobulin M; aCL: anticardiolipin antibodies; anti-B2GPI: anti-β2-glycoprotein I; aPL: antiphospholipid antibodies; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies; SLEDAI: SLE Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborative Clinics/American College of Rheumatology.

Table 4. Accuracy of antibodies for predicting venous thrombosis. Values are % unless otherwise specified.

Tests	SN	SP	PPV	NPV	Likelihood Ratio (95% CI)
LAC	29.6	91.8	34.8	89.9	3.2 (1.5–6.6)
aPL triple marker	11.1	97.3	37.5	88.2	3.9 (1.0–15.6)
LAC + anti-RNP/Sm	25.9	96.2	50.0	89.8	6.0 (2.3–15.6)

SN: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; aPL: antiphospholipid antibodies; LAC: lupus anticoagulant.

antibodies, supports this finding: 45% of patients tested positive for aCL antibodies, and 26% developed VTE/ATE. Further, patients with vascular damage and aCL antibodies frequently developed ATE and VTE compared with other clusters of the disease[33]. Although that study did not report LAC, we might assume that some patients did have it, resembling the coexistence of antibodies that we describe. The synergic effect of LAC with anti-RNP/Sm antibodies deserves further investigation because, if confirmed, it will aid in identifying patients at highest risk of VTE.

We also evaluated the contribution of thrombophilic defects to the risk of thrombosis, but the results were negative. These findings agree with those reported previously, where only factor V Leiden and the prothrombin G20210A mutation contributed to the risk of VTE in SLE[30]. Nevertheless, we are cautious about the results because these tests were not performed in all our patients. Patients tested and not tested for the thrombophilic markers were compared and no differences were found regarding sex, age, disease duration, antinuclear antibody, and anti-dsDNA antibody positivity, or disease activity at baseline.

We found low levels of free protein S in almost all our patients, independently of thrombosis. The contribution of this defect to thrombotic risk deserves certain considerations because protein S assays are associated with high interassay variability; also, lower levels of protein S are present during premenopause, nephrotic syndrome, and inflammation[19,34,35].

Our study has some limitations. All patients were referred to a specialized center, so they might be at higher risk of TE because of more severe disease. Our study was conducted in a single center with limited ethnic variation; one must be cautious about extrapolating the results because the risk of TE varies among ethnic groups[5]. The small number of ATE limits the conclusions for this type of TE. LAC was detected using a single assay, and because no single test is 100% sensitive for LAC, it is advised to use 2 or more tests with different assay principles before the presence of LAC is excluded[27,36]. A second assay would increase the detection of LAC and its prevalence in our population. If the number of patients who were false-negative for LAC were high, the relevance of LAC as a risk factor for thrombosis would be underestimated and our conclusion that most TE were not associated with LAC would be invalid. Finally, IgA aPL isotypes were not determined. The isotype appears to identify patient subgroups rather than adding diagnostic power, while IgA anti-B2GP1 seems to have no association with clinical manifestations of aPL syndrome[36].

The strengths of our study include the general approach of thrombosis in SLE, the ability of following a group of young patients since diagnosis, the development of TE during the followup, and the ascertainment of TE by the investigators.

The incidence of thrombosis in our study was 27 to 43-fold higher than reported in the general population. Time of onset and the underlying variables associated with VTE and ATE were different; understanding this dual mechanism

Table 5. Risk factors for thrombosis in patients with negative lupus anticoagulant (n = 185). Number of patients tested with and without thrombosis: homocysteine 96% and 99%, hsCRP 100% and 94%, functional protein S and C 42% and 88%, free protein S 42% and 89%, antithrombin III 42% and 88%, fibrinogen 42% and 89%, anti-dsDNA 100% and 99%, anti-Sm 100% and 97%, anti-RNP/Sm 100% and 100%, anti-SSA and anti-SSB 100% and 97%, IgG and IgM aCL and anti-B2GPI 100% and 94%, and aPL double marker 100% and 94%. Values are n (%) or median (minimum–maximum) unless otherwise specified.

Variables	Thrombosis, n = 24	No Thrombosis, n = 161	p
Demographic characteristics			
Female	21 (88)	144 (90)	0.72
Age, yrs	33 (15–57)	29 (16–56)	0.53
Length of followup, yrs*	0.8 (0–7)	6 (0–12)	**< 0.001**
Obesity	1 (4)	22 (14)	0.31
Smoking	6 (25)	13 (8)	**0.02**
Hypertension	7 (29)	26 (16)	0.15
Diabetes	2 (8)	3 (2)	0.12
Dyslipidemia	14 (58)	51 (32)	**0.02**
Vascular insufficiency	1 (4)	1 (1)	0.24
Immobilization	2 (8)	1 (1)	**0.04**
Surgery	2 (8)	1 (1)	**0.04**
Oral contraceptives	1 (4)	12 (7)	1.00
Menopause	0	2 (1)	0.34
At least 2 traditional risk factors	12 (50)	21 (13)	**< 0.001**
Serologic characteristics			
Homocysteine, mmol/l	11 (7–27.8)	10.5 (5.1–65)	0.42
hsCRP, mg/dl	2.81 (0.03–9.85)	1.11 (0.01–11.40)	0.05
Functional protein S, %	67.4 (35.5–130.3)	77.2 (20.7–130.3)	0.24
Functional protein S deficiency	5 (42)	27 (19)	0.07
Free protein S, %	37.2 (16.8–55.8)	46.4 (15.4–148)	**0.01**
Free protein S deficiency	10 (100)	136 (96)	1.00
Functional protein C, %	123 (23.8–146.2)	120.3 (52.8–150)	0.24
Functional protein C deficiency	1 (10)	2 (1)	0.18
Antithrombin III, %	107.7 (95.8–126.8)	114.0 (54–126.8)	0.92
Antithrombin III deficiency	0	5 (4)	1.00
Fibrinogen, mg/dl	231.7 (147.5–396.4)	234.1 (76.1–566.1)	0.58
SLE characteristics and treatment			
Disease duration, yrs	0.9 (0–7)	2 (0–8)	0.06
Malar rash	6 (25)	76 (47)	**0.04**
Discoid lupus	1 (4)	14 (9)	0.69
Oral ulcers	9 (38)	74 (46)	0.51
Serositis	15 (63)	59 (37)	**0.02**
Arthritis	21 (88)	149 (91)	0.70
Photosensitivity	5 (21)	56 (35)	0.24
Renal disorder	16 (67)	90 (56)	0.38
Neurological disorder	2 (8)	8 (5)	0.62
Hematologic disorder	22 (91)	122 (76)	0.11
Immunologic disorder	21 (88)	139 (86)	1.00
ANA	23 (96)	144 (89)	0.47
Vasculitis	10 (42)	28 (17)	**0.01**
Livedo reticularis	9 (38)	23 (14)	**0.009**
Nephrotic syndrome	10 (42)	27 (17)	**0.01**
SLEDAI-2K score	8 (0–17)	4 (0–22)	**0.04**
SLEDAI, adjusted mean	4.9 (1.1–10.1)	4.2 (0–20)	0.52
SLICC/ACR Damage Index, modified	0 (0–3)	0 (0–4)	0.61
SLICC/ACR Damage Index > 0	1 (1–2)	1 (1–4)	0.12
Anti-dsDNA antibodies	13 (54)	75 (47)	0.52
Anti-Sm antibodies	16 (67)	90 (58)	0.50
Anti-RNP/Sm antibodies	13 (54)	70 (43)	0.38
Anti-SSA	14 (58)	85 (54)	0.82
Anti-SSB	7 (29)	43 (28)	1.00
IgG aCL	7 (29)	31 (20)	0.42
IgM aCL	2 (8)	20 (13)	0.74
Any aCL	8 (33)	40 (26)	0.46
IgG anti-B2GPI antibodies	1 (4)	4 (3)	0.52
IgM anti-B2GPI antibodies	0	4 (3)	1.00

Table 5. Continued.

Variables	Thrombosis, n = 24	No Thrombosis, n = 161	p
Any anti-B2GPI antibodies	1 (4)	8 (5)	1.00
aPL double marker positivity aCL + Anti-B2GPI	0	5 (3)	1.00
Prednisone	24 (100)	157 (98)	1.00
Current dose of prednisone, mg	40 (5–262)	5 (0–100)	**< 0.001**
Cumulative dose of prednisone, g	10.6 (0–58)	11.9 (0–62.1)	0.51
Methylprednisolone IV	3 (13)	23 (14)	1.00
Azathioprine	19 (79)	121 (75)	0.80
Cyclophosphamide	7 (29)	45 (28)	1.00
Methotrexate	4 (17)	21 (13)	0.74
Mycophenolate mofetil	1 (4)	16 (10)	0.70
Antimalarials	16 (67)	108 (67)	1.00
Aspirin	6 (25)	57 (35)	0.36

* Length of followup in patients without thrombosis was considered until last visit or death. Significant data are in bold face. hsCRP: high-sensitivity C-reactive protein; IgG: immunoglobulin G; IgM: immunoglobulin M; aCL: anticardiolipin antibodies; anti-B2GPI: anti-β2-glycoprotein I; aPL: antiphospholipid antibodies; SLE: systemic lupus erythematosus; ANA: antinuclear antibodies; SLEDAI: SLE Disease Activity Index; SLICC: Systemic Lupus International Collaborative Clinics; ACR: American College of Rheumatology.

is helpful for the implementation of strategies to cope with TE in SLE. An association of thrombosis with positive LAC and presence of anti-RNP/Sm antibodies was identified, which if confirmed may help to identify patients at highest risk. The use of the combination of LAC and anti-RNP/Sm antibodies as a predictor of VTE deserves to be studied, and further analyses should include other races/ethnicities.

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