Characteristics and risk factors of pulmonary embolism in patients with systemic lupus erythematosus: a case control study

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Abstract

Objective

Pulmonary embolism (PE) is life threatening but evidence assessing risk factors of PE in systemic lupus erythematosus (SLE) is scarce. This study was conducted to explore the characteristics and risk factors of PE in SLE patients.

Methods

Using the Hospital Information System of Peking Union Medical College Hospital, we conducted a case-control study in SLE patients complicated with PE from January 2012 to December 2018 as the case group, and age-, sex-, and entry-time-matched SLE patients without PE at the ratio of 1:3 as the control group. We explored the risk factors of PE in SLE patients using multivariate logistic regression analyses.

Results

A total of 90 cases confirmed with PE from 6994 hospitalised SLE patients were identified and 257 matched controls were selected (in 13 cases only two controls could be found). The average annual incidence of PE from 2012 to 2018 among hospitalised SLE patients was 1.29% (95% CI: 1.15% to 1.42%), higher than that among all the hospitalised patients (0.347% and 95% CI: 0.34% to 0.354%). In the case group, the majority were female (74/90; 82.2%), with a mean duration of SLE before PE 3.04±2.16 years, and a high mortality rate of 8.9%. Multivariate analysis revealed that BMI >25 kg/m² [OR 8.221 (3.125–21.622), p<0.001], duration of SLE course <1.5 years [OR 3.815 (1.824–7.97), p<0.001], hypoalbuminaemia [OR 2.8 (1.226–6.397), p=0.015], hsCRP>3 mg/L [OR 3.744 (1.693–8.276), p=0.001], aPL positive [OR 10.57 (4.389–25.46), p<0.001] and the highest dose of glucocorticoids >0.5 mg/kg/day [OR 15.752 (4.753–52.198), p<0.001] were significant independent risk factors of PE in SLE patients. The use of hydroxychloroquine [OR 0.262 (0.117–0.589), p=0.001] was a protective factor of PE in SLE patients.

Conclusion

This study provides general population-based evidence that SLE patients have an increased risk of PE. Increased vigilance in preventing this serious, but preventable complication, especially within months after SLE diagnosis is recommended.

Key words

systemic lupus erythematosus, pulmonary embolism, antiphospholipid antibodies, prognosis

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Received on July 22, 2019; accepted in revised form on October 21, 2019.

Funding: this work was supported by the Chinese National Key Research R&D Program (grant no. 2017YFC0907601, 2017YFC0907602, 2017YFC0907603) and the Peking Union Medical College Hospital Fund for Distinguished Young Scholars (grant no. JQ201707).

Competing interests: none declared.

Introduction

Systemic lupus erythematosus (SLE) is an autoantibody-mediated, diffuse connective tissue disease with extremely variable and heterogeneous clinical presentation (1). It has been shown that the risk of venous thromboembolism (VTE) events, including pulmonary embolism (PE) and deep vein thrombosis (DVT), increased significantly in SLE patients (2), constituting the third most common cardiovascular event after myocardial infarction and stroke (3, 4). In the general population, the incidence rate of VTE is about 1/1000 (5), and PE 0.38 per 1000 person years (6). However, the incidence rate of VTE is 5–10% in SLE patients (7-10), with a significantly increased rate of PE as high as 1.6% (11, 12), especially during the first year after the diagnosis of SLE. Causative factors for VTE in SLE patients have been investigated, including antiphospholipid antibodies, age, smoking, higher doses of glucocorticoids and so on (13, 14).

PE is a potential fatal complication of VTE with a high mortality rate up to 15% in the first 3 months after diagnosis, making it potentially as deadly as acute myocardial infarction (15, 16). Since PE manifests as a common and fatal vascular event, an in-depth and accurate understanding of its risk among SLE patients is crucial. However, most studies mainly focused on potential cause of arterial diseases including premature atherosclerosis, acute myocardial infarction and ischaemic stroke (17, 18). As VTE is uncommon in Chinese SLE patients, with a lower incidence of VTE than African-American, and Caucasian patients with SLE (19), relatively few studies have reported data of PE in SLE, especially in Asians. In this case-control study, we aimed to estimate the characteristics and risk factors for PE in Chinese SLE patients. These findings will contribute to our knowledge about this condition and increase our ability to diagnose PE early, thereby improving the prognosis of affected patients.

Materials and methods

Study population

We utilised the Hospital Inpatient Information Retrieval System to identify the SLE and PE patients admitted to the Peking Union Medical College Hospital (PUMCH) from January 2012 to December 2018. A case-control study was conducted in SLE patients complicated with PE as the case group and age-, sex-, and entry-time-matched SLE patients without PE at the ratio of 1:3 as the control group. We retrospectively examined the medical record of all patients. The diagnostic codes of the International Classification of Disease versions 9-10 Clinical Modification (ICD-9,10-CM) for the following conditions were used: ICD-9-CM 710.0 and ICD-10 M32.1, M32.8, M32.9 for SLE, ICD-9-CM: 415.1, 673.2, 639.6 and ICD-10-CM: O88.2, I26 for PE. SLE diagnosis was rigorously confirmed by medical record review according to the revised American College of Rheumatology classification criteria for SLE (20). PE was diagnosed by the evidence of pulmonary artery obstruction or filling defect in pulmonary angiography, thrombus in CT pulmonary angiogram (CTPA) or a high probability ventilation perfusion scan. Those patients presenting with overlapping scleroderma, dermatomyositis, rheumatoid arthritis, nodular polyarteritis, or other diffuse connective tissue diseases (CTD) were excluded. Those SLE patients who got PE for other reasons, including tumour, surgery, trauma, chronic obstructive pulmonary disease and heart disease such as atrial fibrillation were excluded. Furthermore, patients with a previous ICD-9/10-CM code for PE before the hospitalisation were excluded as well. The protocol was approved by the Medical Ethics Committee of PUMCH, and all patients provided written informed consent.

Clinical and laboratory data collection

We obtained the following data from medical records by well-trained rheumatologists: gender, age at SLE diagnosis and enrolment, body mass index (BMI) and duration of SLE before enrollment. Enrolment date was defined as the diagnostic PE date for the case group and as the hospital admission date for the control group. Systemic manifestations (neuropsychiatric SLE, vasculitis,

arthritis, myositis, lupus nephritis, rash, oral ulceration, pleuritis, pericarditis, fever and serological indicators) were evaluated using the SLE Disease Activity Index Index-2000 (SLEDAI-2K), stratified to stable (<5), mild active (5-9), moderate active (10-14), and severe active (>14). The definition of all events were based on SLEDAI-2K index system. Personal smoking history was defined as smoking at least one cigarette (filter or non-filter) per day for at least three months. Medications of glucocorticoids and hydroxychloroquine (HCQ) were collected. Medications of aspirin, stains, hydroxychloroquine (HCQ) and the current and highest dose of glucocorticoids were recorded at each visit; the highest prednisone dose was computed for each patient based on the data available for all the intervals between visits. Laboratory data including routine blood examination, urinalysis sediment examination, hepatic and renal function examination, erythrocyte sedimentation rate (ESR), hypersensitive C-reactive protein (hsCRP), lipid profile, complement, anti-double-stranded DNA (anti-dsDNA) antibody, anti-extractable nuclear antigen (anti-ENA) antibodies (including anti-SSA, anti-SSB, anti-Sm, anti-RNP, and anti-rRNP antibody) were collected. Medical records were also reviewed for results of antiphospholipid antibodies (aPL) testing, including lupus anticoagulant (LAC), anticardiolipin (ACL) and anti-β2-glycoprotein I (antiβ2GPI), IgG or IgM autoantibodies. Subjects were considered aPL positive if at least one of these autoantibodies, at least 12 weeks apart were documented. Leukocytopenia was defined as white blood cell count $<4.0\times10^9$/l., thrombocytopenia as platelets $<100\times10^9$/l and hypoalbuminaemia as serum albumin level <3.5 g/dl. The data of SLE patients with PE were collected before the onset of PE but no longer than 3 months earlier, and the data of SLE patients without PE were collected at the first time of admission to the hospital. Patients were followed up every 3–6 months.

Antibody assay

Anti-nuclear antibody (ANA) was tested by indirect immunofluorescence (IIF) using HEp-2 cell substrates. Anti-dsDNA antibody was measured by IIF using flagellate protoctista substrates and enzyme linked immunosorbent assay (ELISA). Anti-ENA antibodies were determined by immunodiffusion assay. IgG/IgM antibody of ACL and anti-β2-glycoprotein I were tested by ELISA. LAC was measured using activated partial thromboplastin time (APTT) based assay.

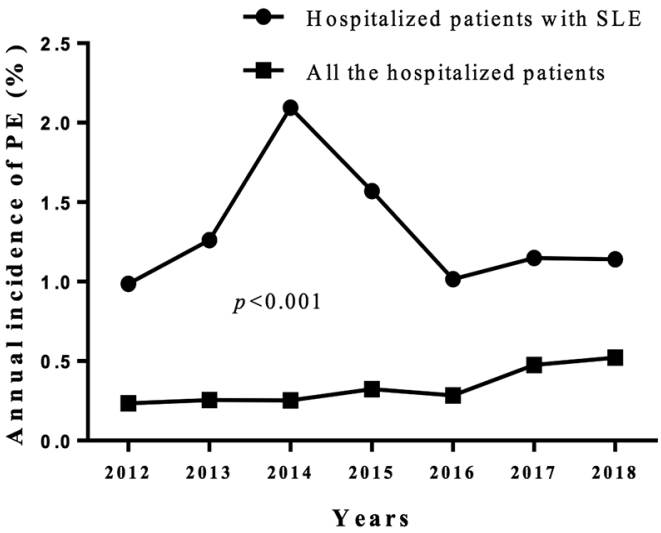


Fig. 1. The annual incidence rates of PE in hospitalised patients with SLE and all the hospitalised patients from 2012 to 2018.

Statistical analysis

We compared the parameters between the case and control groups. Variables were examined in bivariate analysis using the Chi-squared test (for categorical variables) and Mann-Whitney U -test (for continuous variables). Variables with $p<0.10$ in these analyses were entered into the univariable (UV) logistic regression model. A multivariate (MV) logistic regression model was then constructed using a stepwise forward selection procedure among those candidate variables with the significance level $p<0.10$ in the UV logistic regression analysis. Continuous variables are converted to binary or ordered multiple variables when entered into UV or MV logistic regression models. Odds ratios and 95% confidence intervals were calculated. The *p*-value was two tailed and defined as significant if the value was <0.05. SPSS software, v. 23 (Chicago, IL, USA) used for all of the statistical descriptions, analyses and inferences.

Results

Demographics characteristics and clinical manifestations

Between January of 2012 and December of 2018, 2206 patients admitted to the inpatient ward were diagnosed as PE from 635696 patients admitted to the inpatient ward. We included 95 cases of SLE patients complicated with PE out of 6994 hospitalised SLE patients as the case group. Then 5 cases were excluded because of tumor or surgery. Finally, 90 patients were eligible for enrolment in this study. 257 contemporaneous SLE patients without PE hospitalised in our centre were randomly selected to create the control cohorts.

The average annual incidence of PE from 2012 to 2018 among hospitalised SLE patients was 1.29% (90/6994, 95% CI: 1.15% to 1.42%), higher than that among all the patients admitted to the hospital (2206/635696, 0.347% and 95% CI: 0.34% to 0.354%) (Fig. 1). The overall incidence of PE in male SLE patients (1.86% and 95% CI: 1.40% to 2.32%) was higher than that in female SLE patients (1.21% and 95% CI: 1.07% to 1.35%). The incidence of PE in hospitalised SLE patients by age and gender (%) during 7 years (from 2012 to 2018) is shown in Table I.

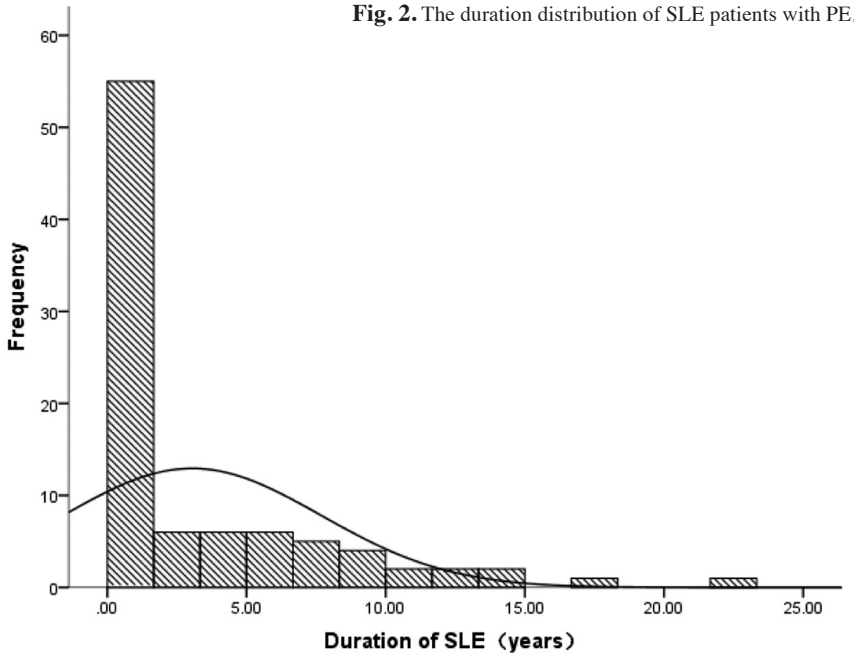
We analysed the characteristics of the case group. Among the 90 SLE patients with PE, 51 cases were acute and 39 cases were chronic. Short-term symptoms and complications include

Table I. The average annual incidence of PE in hospitalised SLE patients by age and gender (%) over 7 years (from 2012 to 2018).

Age	Total	Male	Female
<=20	0.62 (0.43-0.82)	1.05 (0.45-1.66)	0.53 (0.33-0.73)
21-30	1.63 (1.32-1.94)	4.02 (2.53-5.52)	1.35 (1.05-1.65)
31-40	0.94 (0.67-1.22)	0.70 (0.00-1.41)	0.98 (0.68-1.27)
41-50	2.03 (1.59-2.47)	0.00 (0.00-0.00)	2.21 (1.73-2.69)
51-60	1.61 (1.15-2.07)	4.05 (1.75-6.36)	1.34 (0.90-1.78)
61-70	1.72 (1.08-2.37)	3.45 (1.03-5.87)	1.44 (0.80-2.08)
71+	0.36 (0.00-0.72)	0.00 (0.00-0.00)	0.43 (0.00-0.86)
Total	1.29 (1.15-1.42)	1.86 (1.40-2.32)	1.21 (1.07-1.35v

SLE: systemic lupus erythematosus; PE: pulmonary embolism.

Fig. 2. The duration distribution of SLE patients with PE.



haemoptysis (8, 8.9%), chest pain (22, 24.4%), right heart failure (29, 32.2%), cardiac shock (3, 3.3%) and death (8, 8.9%). Survival rate declined sharply after the first month after PE event. Long-term complications in this article mainly incorporated chronic thromboembolic pulmonary hypertension (27, 30%). We also found that most PE patients (54, 60%) have a disease duration of less than 1 year (Fig. 2).

Comparison of demographic characteristics, clinical manifestations and treatment between the case and control groups are shown in Table II. The majority inthe case group were female (74/90; 82.2%). The mean (±SE) age of the case group at the time of SLE diagnosis was 34.62±3.85 years (range 10–71 years). There were no significant differences in gender, age at study entry between the case and control groups. The mean BMI of the case group is higher than that of the control group (23.44±2.15 kg/m^2 *vs*. 22.13±1.98 kg/m^2). The duration of SLE of the case group was 3.04±2.16 years, significantly lower than the control group (6.16±2.54 years). The mean (±SE) SLEDAI-2K score of the case group was 10.17±2.65, significantly higher than the control group (6.06±2.54), indicating that SLE patients with PE had higher disease activity. Pleuritis, lupus nephritis, highest dose of glucocorticoids and the use of HCQ were significantly correlated with PE (p<0.05); There were no significant differences in the presence of other systemic manifestations and the use of asprin and statins between the groups.

Laboratory characteristics

Rates of thrombocytopenia, autoimmune haemolytic anaemia, leukocytopenia, haematuria, albuminuria, hypocomplementaemia, ESR, hsCRP, lipid profile and autoantibodies were compared between the case and control group. As shown in Table III, the ratios of autoimmune haemolytic anaemia, thrombocytopenia, microscopic haematuria, albuminuria, hypoalbuminaemia, ESR >20 mm/h, hsCRP >3 mg/L, hypocomplementaemia and aPL positive were significantly higher in SLE patients with PE.

UV and MV logistic regression analyses

UV logistic regression analysis: The variables entered the UV logistic regression model included: BMI >25 kg/m^2, SLE course <1.5 years, SLEDAI-2K (stratified as 0-4, 5-10, 10-14 and >14), pleuritis, lupus nephritis, autoimmune haemolytic anaemia, thrombocytopenia, haematuresis >5 urine RBC per hpf, proteinuria >0.5g/24h, hypoalbuminaemia, ESR >20 mm/h, hsCRP>3 mg/L, hypocomplementaemia, aPL positive (ACL and/or LAC and/or anti β2GPI), the highest dose of glucocorticoids >0.5 mg/kg/day and hydroxychloroquine. All the above variables had significant differences between the case and the control groups in the UV logistic regression analysis.

MV logistic regression analysis: All the variables above were then entered into the MV logistic regression analysis model. After the stepwise forward selection procedure, the only variables retained in the MV logistic regression model were: BMI >25 kg/m^2, SLE course <1.5 years, hypoalbuminaemia, hsCRP>3 mg/L, aPL positive, glucocorticoids-highest dose >0.5 mg/kg/day, and hydroxychloroquine. Multivariate analysis revealed that BMI >25 kg/m^2 [OR 8.221 (3.125–21.622), p<0.001], duration of SLE course <1.5 years [OR 3.815 (1.824–7.977), p<0.001], hypoalbuminaemia [OR 2.8 (1.226–6.397), p=0.015], hsCRP>3 mg/L [OR 3.744 (1.693–8.276), p=0.001], aPL positive [OR 10.57 (4.389–25.46), p <0.001] and the highest dose of glucocorticoids >0.5 mg/kg/day [OR 15.752 (4.753–52.198), p<0.001] were significant independent risk factors of PE in SLE pa-

Table II. Comparison of demographic characteristics, clinical manifestations and treatment between PE and non-PE groups in SLE patients.

Variable	SLE patients with PE (n=90)	SLE patients without PE (n=257)	*p*-value
Female sex	74 (82.2)	216 (84)	0.688
Age at study entry (years)	38.14 ± 3.91(10-72)	38.07 ± 3.75(11-74)	0.965
Age at SLE diagnosis (years)	34.62 ± 3.85 (10-71)	32.49 ± 3.77(7-74)	0.227
BMI (kg/m^2)	23.44 ± 2.15	22.13 ± 1.98	**<0.01**
Ever smoker, cigarette	8 (8.9)	11 (4.3)	0.110
Duration of SLE (years)	3.04 ± 2.16(0-22)	6.16 ± 2.54(0-33)	**<0.001**
SLEDAI-2K	10.17 ± 2.65	6.06 ± 2.54	**<0.001**
NPSLE	11 (12.2)	27 (10.5)	0.654
Vasculitis	1 (1.1)	8 (3.1)	0.520
Arthritis	11 (12.2)	27 (10.5)	0.654
Pleuritis	13 (14.6)	15 (5.8)	**0.010**
Pericarditis	11 (12.2)	23 (8.9)	0.369
Myositis	1 (1.1)	3 (1.2)	0.966
Lupus nephritis	56 (62.2)	87 (33.9)	**<0.001**
Rash	13 (14.6)	47 (18.3)	0.429
Oral ulceration	9 (10.1)	16 (6.2)	0.222
Alopecia	15 (16.7)	35 (13.6)	0.479
Fever	14 (15.6)	25 (9.7)	0.132
Aspirin	3 (3.3)	8 (3.1)	1
Statins[a]	7/71 (9.9)	6/114 (5.3)	0.234
Glucocorticoids, current dose (mg/kg/day)	0.46 ± 0.05	0.41 ± 0.03	0.319
Glucocorticoids, highest dose (mg/kg/day)	4.66 ± 0.70	1.48 ± 0.26	**<0.001**
Hydroxychloroquine	15 (16.7)	141 (54.9)	**<0.001**

Data on glucocorticoids, current dose were missing from 12 patients in non-PE SLE patients.
SLE: systemic lupus erythematosus; PE: pulmonary embolism; BMI: body mass index; SLEDAI-2K: SLE Disease Activity Index Index-2000; NPSLE: neuropsychiatric systemic lupus erythematosus.
Values are mean ± standard error or n (%) unless otherwise specified.
Values in bold are statistically significant at $p<0.05$.
p-values are estimated by either Chi-squared test (for categorical variables) or Mann-Whitney U-test (for continuous variables).
[a]Data on Statins were missing from 19 patients in SLE patients with PE and 143 patients in SLE patients without PE.

tients. The use of hydroxychloroquine [OR 0.262 (0.117-0.589), p=0.001] was a protective factor of PE in SLE patients (Table IV).

Discussion

SLE patients have an increased risk of PE. In our cohort, the average annual incidence rate of PE in SLE patients was 1.30%, higher than the average annual incidence 0.347% among all the hospitalised patients. A multicentre registration study in China has reported that the annual incidence of PE of hospitalised patients was 0.1% (95% CI: 0.1% to 0.2%) during the 1997-2008 (21), lower than that in USA hospitals (0.4%) (22). Our cohort reported a higher incidence rate of PE in hospitalised patients than the previous study in China (21). Such results may be related to the improvement of diagnostic technology of PE over the years. Relatively few studies have reported incidence data of PE in SLE. A study cohort in Canada reported the incidence rate of PE was 2.58 per 1000 person-years among SLE patients(11). Another retrospective study in Taiwan found that there was a 1.6 % incidence of PE in patients with SLE(12). In our cohort, the mortality rate in SLE patients with PE is 8.9%. It has been reported that PE has a high mortality rate up to 15% in the first 3 months after diagnosis(15,16). Mortality rate of diagnosed and treated PE ranges from 3 to 8%, but increases to about 30% in untreated PE (23). According to a multicentre registration study in China, the case fatality rate of PE was apparently decreasing: 25.1% (95% CI: 16.2% to 36.9%) in 1997 to 8.7% (95% CI: 3.5% to 15.8%) in 2008 (21).

The pathogenesis of PE in SLE is multifactorial. It is well known that thrombus is mainly due to a higher incidence of traditional Framingham risk factors (24). Besides traditional cardiovascular risk factors, such as obesity, hyperglycaemia and hyperlipidaemia, there are other additional mechanisms of thrombosis in SLE patients, such as inflammation damage to the vascular wall due to vasculitis and the hypercoagulable state led by antiphospholipid antibodies (13, 14). In this study, we researched the risk factors of PE from the perspective of clinical rheumatologists. We found that certain status in SLE patients was related to considerably increased risks of PE when compared to the age-sex-matched controls.

SLE patients with PE had a significant higher BMI than SLE patients without PE. BMI >25 kg/m^2 is an independent risk factor of PE among lupus patients. These findings are consistent with prior researches. It has been reported that excess body weight is a risk factor of venous thromboembolism (25, 26) and PE (27-29). Studies using crosssectional or case-control designs demonstrate that individuals with VTE have higher BMI than those without (26, 28). Kabrhel *et al*. reported a strong, independent, positive linear association between BMI and the risk of idiopathic and non-idiopathic PE in a large cohort of female nurses. The risk of PE increased even with modest increases in BMI (27). Those subjects with higher BMI also have a greater risk of PE in patients with DVT (28). There are several explanations for how adiposity might increase PE risk. Leptin may mediate the relationship between obesity and PE by inducing tissue factor expression (30). Another possibility is that the relationship is mediated by oestrogen and progesterone, which are linked to obesity and the risk of PE in women (31-33).

Intriguingly, our results showed that short duration of SLE less than 1.5 years was a high risk factor PE, consistent with another research in Canada (11). This result suggests clinicians to pay more attention to potential PE events, especially in the period immediately after SLE diagnosis. It may be explained by the high inflammatory status in the early onset and might reduce over time because of medical intervention. The decrease in risk of PE over time implies that the thrombotic

Table III. Comparison of laboratory data between SLE patients with PE and SLE patients without PE.

Laboratory test outcome	SLE patients with PE (n=90)	SLE patients without PE (n=257)	*p*-value
Leukocytopenia	11 (12.2)	24 (9.3)	0.434
Autoimmune haemolytic anaemia	47 (52.2)	81 (31.5)	**<0.001**
Thrombocytopenia	32 (35.6)	35 (13.6)	**<0.001**
Haematuresis > 5 urine RBC per hpf	28 (31.1)	38 (14.8)	**0.001**
Proteinuria > 0.5g/24h	51 (56.7)	79 (30.7)	**<0.001**
Hypoalbuminaemia	63 (70)	83 (32.3)	**<0.001**
ESR >20 mm/h	75 (83.3)	128 (49.8)	**<0.001**
hsCRP>3 mg/L	72 (80)	109 (42.4)	**<0.001**
total cholesterol >5.7 mmol/L[b]	23/71 (32.4)	29/111 (26.1)	0.361
total triglycerides>1.7 mmol/L[c]	41/71 (57.7)	53/113 (46.9)	0.152
Hypocomplementaemia	63 (70)	135 (52.5)	**0.004**
Autoantibodies			
ANA positive	88 (97.8)	242 (94.2)	0.172
Anti-dsDNA	45 (50)	126 (49)	0.874
Anti-Sm	32 (35.6)	76 (29.6)	0.291
Anti-RNP	34 (37.8)	96 (37.4)	0.943
Anti-SSA	50 (55.6)	124 (48.2)	0.233
Anti-SSB	12 (13.3)	24 (9.3)	0.285
Anti-rRNP	16 (17.8)	36 (14)	0.388
aPL positive (ACL and/or LAC and/or anti β2GPI)	45 (50)	26 (10.1)	**<0.001**

Values in bold are statistically significant at $p<0.05$.
SLE: systemic lupus erythematosus; PE: pulmonary embolism; ESR: erythrocyte sedimentation rate; hsCRP: hypersensitive C-reactive protein; ANA: anti-nuclear antibodies; anti-dsDNA: anti-double-stranded DNA; anti-RNP: anti-ribonucleoprotein; anti-rRNP: anti-ribosomal RNP; anti-Sm: anti-Smith; anti-SSA: anti-SSA/Ro; anti-SSB: anti-SSB/La; LAC: lupus anticoagulant; ACL: anticardiolipin; antiβ2GPI: anti-β2-glycoprotein I.
thrombocytopenia: platelets $<100\times10^9$/l, leukocytopenia: white blood cell count $<4.0\times10^9$/l; hypoalbuminaemia: serum albumin level <3.5 g/dl.
[b]Data on total cholesterol >5.7 mmol/L were missing from 19 patients in SLE patients with PE and 146 patients in SLE patients without PE.
[c]Data on total triglycerides>1.7 mmol/L were missing from 19 patients in SLE patients with PE and 144 patients in SLE patients without PE.

risk is related to the inflammatory conditions of the disease.

In our cohort, the high level of hsCRP was an independent risk factor of PE in SLE patients, which indicated a status of inflammation. Immune and coagulation systems are linked and have a shared evolutionary origin (34, 35), with many molecular components being important for both systems (36). Inflammation leads to several procoagulant disorders in the coagulation and anti-coagulation systems. In our cohort, high SLE disease activity was closely linked to high risk of thrombosis. This may be a result of high inflammation and coagulation system imbalance. The inflammatory status in active SLE could affect vascular homeostasis, or elevate blood coagulability through vascular endothelial dysfunction (37), decreased blood flow speed and inflammation associated pathogenesis (38).

Low albumin concentration has been well described in correlating with venous thromboembolism (39, 40). The reasons for this might be protein loss from kidney in patients with lupus nephritis (41) or from digestive tract in lupus patients with protein-losing bowel disease. Previous studies have found that patients with lupus nephritis are more susceptible to venous thrombosis, especially those with heavy proteinuria (42). Chronic inflammation or generalised malnutrition that alters liver synthetic function can also lead to hypoproteinaemia. Hypothetically, natural protein anticoagulants such as antithrombin may be produced in less than homeostatic quantities and tip the balance towards a procoagulant state. Insufficient blood volume resulting from hypoproteinaemia and the use of diuretic may also involve in the process of thrombosis (42).

In our cohort, aPL positive was associated with high risk of PE with the highest OR (10.262). This has also been reported in previous studies (43, 44). The pathogenesis of aPL induced thrombosis is complex and involves the activation of platelet and neutrophil and injury of endothelium, finally resulting in abnormal coagulation cascade (45). The prevalence of positive aPL varies from 10% to 40% in SLE patients (46) and it was estimated that up to 50% of SLE patients with positive aPL will develop antiphospholipid syndrome (APS) (47). Indeed, 44% of "triple-positive" APS patients will develop recurrent thrombosis over a 10-year follow-up period, even with the majority being prescribed anticoagulants (48). Among Chinese patients, the proportion of APS patients secondary to SLE accounts for two thirds of all APS patients, higher than one third in the other countries (49). Therefore, we speculate that anti-phospholipid antibodies may contribute more to thrombosis in Chinese SLE patients.

In addition to the above risk factors finally included in the MV model, SLE patients combined with PE may present with thrombocytopenia. In our cohort, the case group had a significantly higher rate of thrombocytopenia than the control group. But this does not suggest a state of hypocoagulability. Conversely, thrombocytopenia is more likely to represent a state of hypercoagulability. The pathophysiology of thrombocytopenia in SLE patients with PE is complicated. Thrombocytopenia is a manifestation of disease activity in patients with SLE and those patients with PE usually have high disease activity. Besides, the direct binding of antiphospholipid antibodies could also lead to platelet activation and aggregation, which eventually leads to thrombocytopenia (50). The thrombosis process also consumes a large amount of platelets. Hypersplenism, bone marrow haematopoietic inhibition, and drugs (such as heparin) may also be involved in the process of thrombocytopenia. In patients with antiphospholipid syndrome, thrombocytopenia is also a risk factor for death (51). Therefore, thrombocytopenia has no protective

Table IV. Univariate and multivariate logistic regression analyses for variables predictive of a PE event in SLE patients.

Variables	UV		MV	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
BMI >25 kg/m^2	3.941 (2.211-7.025)	**<0.001**	8.221 (3.125-21.622)	**<0.001**
SLE course <1.5 years	3.64 (2.207-6.002)	**<0.001**	3.815 (1.824-7.977)	**<0.001**
SLEDAI-2K				
0-4	Reference			
5-10	3.525 (1.787-6.955)	**<0.001**		
10-14	1.505 (0.751-3.017)	0.249		
>14	1.333 (0.622-2.858)	0.46		
Pleuritis	2.724 (1.241-5.976)	**0.012**		
Lupus nephritis	3.218 (1.955-5.297)	**<0.001**		
Autoimmune haemolytic anaemia	2.375 (1.455-3.878)	**0.001**		
Thrombocytopenia	3.5 (1.999-6.125)	**<0.001**		
Haematuresis >5 urine RBC per hpf	2.603 (1.481-4.574)	**0.001**		
Proteinuria >0.5g/24h	2.946 (1.798-4.829)	**<0.001**		
Hypoalbuminaemia	4.892 (2.905-8.237)	**<0.001**	2.8 (1.226-6.397)	**0.015**
ESR >20 mm/h	5.039 (2.749-9.236)	**<0.001**		
hsCRP>3 mg/L	5.431 (3.063-9.63)	**<0.001**	3.744 (1.693-8.276)	**0.001**
Hypocomplementaemia	2.109 (1.262-3.522)	**0.004**		
aPL positive (ACL and/or LAC and/or anti β2GPI)	8.885 (4.98-15.851)	**<0.001**	10.57 (4.389-25.46)	**<0.001**
Glucocorticoids, highest dose >0.5 mg/kg/day	22.36 (8.778-56.962)	**<0.001**	15.752 (4.753-52.198)	**<0.001**
Hydroxychloroquine	0.165 (0.09-0.302)	**<0.001**	0.262 (0.117-0.589)	**0.001**

SLE: systemic lupus erythematosus; PE: pulmonary embolism; UV: Univariate; MV: multivariate; OR: odds ratio; CI: confidence interval; BMI: body mass index; SLEDAI-2K: SLE Disease Activity Index Index-2000; ESR: erythrocyte sedimentation rate; hsCRP: hypersensitive C-reactive protein; LAC: lupus anticoagulant; ACL: anticardiolipin; antiβ2GPI: anti-β2-glycoprotein I.
hypoalbuminaemia: serum albumin level <3.5 g/dl.
Values in bold are statistically significant at $p<0.05$.

effect on thrombosis. It means that haemorrhage and hypercoagulability exist at the same time, which is a high risk factor for recurrence of thrombus and requires more attention in clinical practice.

Glucocorticoids are commonly used in SLE patients. We found an association between glucocorticoid use (the highest dose) and the development of PE. Previous cohort studies of SLE have also reported an association between VTE and dose of glucocorticoids (10, 14). Higher dosages as well as cumulative dosages have been widely believed to cause higher risk of thrombosis probably mediated by endothelial damage, accelerated atherosclerosis and abnormalities in the coagulation cascade (52). Moreover, Cushing's syndrome is often regarded as a prothrombotic condition (53) because of clotting abnormalities and decreased fibrinolysis associated with the high levels of adrenal steroids (53). Furthermore, higher dosages of glucocorticoids are associated with disease activity. Besides, long-term application of glucocorticoids could lead to other traditional risk factors such as elevated blood pressure, abnormal glucose and lipid metabolism disorder, all contributint to the thrombotic events in SLE patients (37). Regarding the protective effect of HCQ against thromboembolism, inconsistent opinions have been expressed in the literature. A database prospective cohort study in Taiwan reported that long-term HCQ appears to have no vascular protective effect in patients with SLE (54). However, another prospective research in Spain showed that taking antimalarials was protective against thrombosis (55). HCQ have also shown to ameliorate lipid profiles, decreasing total and low density lipoprotein cholesterol, increasing high density lipoprotein levels and, interestingly, being able to reverse the negative effect of corticosteroids on serum lipid levels (56, 57). We have analysed the lipid profile and treatment of stains in our cohort and there was no significant difference between the case and control groups. Since this was a retrospective study and the data of lipid profile of some patients were missing, further research about lipid metabolism should be conducted in the future. The percentage of patients treated with asprin in SLE patients with PE was also very low as only 3.3% despite of the high aPL positive rate of 50%. It is recommended to use antiplatelet agents for thrombosis prevention in aPL positive patients with high risk of cardiovascular diseases (49). The relatively high rate of thrombocytopenia in the case group partly explains why the rate of our use of aspirin is so low. However, some high-risk patients still do not receive antiplatelet therapy. This suggests that we should pay more attention to these aPL-positive high-risk patients, and antiplatelet and statins therapy should be added if necessary.

Our research had several limitations. The major limitation of the study is the retrospective design. Although we analysed all known and reported risk factors of PE available in our data, our study did not cover other potential confounding traditional risk factors like oral contraceptive, diet habits, tumor, surgery and trauma. Background therapy of different immunosuppressant could also potentially confound the results. This is a recurring issue in trials for systemic lupus erythematosus (60). We were unable to obtain outpatient data, thus we included only the most serious cases from hospital admissions. However, most cases of PE in SLE patients were admitted in hospital. Because of the limited sample size, we did not study the risk factors for poor prognosis. More detailed study including outpatients with a larger sample size can be conducted in the future. Our study had several advantages. The database of our research population included all the hospitalised SLE patients with PE in PUMCH during the whole study period. In addition, we chose SLE patients without PE as the control group instead of health population. This provides a basis for the study of thrombosis risk factors in SLE patients, and may be helpful for the establishment of the thrombosis risk prediction model of PE in SLE patients in the future.

Conclusion

In conclusion, the risk is higher during the first year and a half immediately after the diagnosis of SLE. High BMI, hypoalbuminaemia, positivity of antiphospholipid antibodies, high level of hsCRP, and the highest dose of glucocorticoids >0.5 mg/kg/day are independent risk factors of PE in SLE. Use of HCQ could be a protective factor of PE but deserve more research. Increased vigilance in preventing this serious, but preventable complication, especially in the first year and a half after SLE diagnosis is recommended. Further studies are needed to deepen the understanding of the risk of thrombosis in SLE patients, achieve early identification, timely intervention and ultimately improve the prognosis of SLE patients.

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