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Original Article

Non-corticosteroid-related risk factors for osteonecrosis in patients with systemic lupus erythematosus: a meta-analysis

Tao Wang[1,2], Zhijun Li[2], Xingfu Li[1]

[1]Department of Rheumatology, Qilu Hospital of Shandong University, Jinan 250012, PR China; [2]Department of Rheumatology, The First Affiliated Hospital of Bengbu Medical College, Bengbu 233004, PR China

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Abstract: Background: Systemic lupus erythematosus (SLE) is a heterogeneous disease, and differences in the clinical features may be risk factors for osteonecrosis (ON) in addition to treatment with glucocorticoids. Objective: To assess the major risk factors for ON in SLE, and provide evidence for decision-making on prevention. Methods: The Cochrane library, PubMed, Ovid, and Science Direct were searched for published case-control studies on the risk factors of ON in SLE. A meta-analysis of 23 case-control studies (1,071 cases and 23,065 controls) that met the inclusion criteria was conducted using Revman 5.3 software. After analysis of homogeneity, the pooled odds ratios (OR) and 95% confidence intervals (CI) of each risk factor were calculated. Results: The pooled OR and 95% CI of each risk factor of ON in the patients with SLE were as follows: arthritis 1.69 [1.32, 2.17], central nervous system (CNS) involvement 1.34 [1.06, 1.71], diabetes mellitus 1.59 [1.03, 2.46], hypertension 1.69 [1.42, 2.02], oral ulcer 1.48 [1.06, 2.08], renal involvement 1.53 [1.27, 1.83], vasculitis 2.45 [1.54, 3.89], smoking history 1.64 [1.01, 2.65], leucopenia 1.54 [1.11, 2.13], thrombocytopenia 1.63 [1.14, 2.32], cytotoxic drugs 1.79 [1.25, 2.57], cyclophosphamide 3.13 [1.58, 6.21] and anti-Sm antibodies 0.48 [0.27, 0.85]. Conclusion: In addition to glucocorticosteroids, other factors, including arthritis, CNS involvement, diabetes mellitus, hypertension, oral ulcer, renal involvement, vasculitis, smoking history, leucopenia, thrombocytopenia, cytotoxic drugs and cyclophosphamide are major risk factors of ON in patients with SLE. Anti-Sm antibodies represent a protective factor against ON in patients with SLE, while antimalarial drugs are not.

Keywords: Risk factor, osteonecrosis, systemic lupus erythematosus, meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with heterogeneous performance [1]. It can produce a variety of autoantibodies, with complement activation and immune complex deposition, resulting in damage to multiple tissues and organs. SLE occurs mainly in young female patients (female to male ratio of 9:1), with a peak age of onset of 20-40 years old, and often combined with arteriosclerosis, osteoporosis and even cancer. Consequently, the patient's quality of life and ability to work are severely affected [1].

Osteonecrosis (ON) is the death of cellular elements of the bone, which leads to collapse of the bony structure, culminating in joint pain and loss of function [2]. It is a common manifestation in patients with SLE and can cause significant disability [3].

Several factors have been associated with the development of ON in SLE, although corticosteroid (CS) therapy has been the most consistent association [4-9]. However, a considerable proportion of SLE patients with ON complications have no history of corticosteroid treatment [4, 10, 11], while most SLE patients who receive corticosteroid do not develop ON during the course of the disease [12].

Many other risk factors such as vasculitis, antiphospholipid antibodies, Raynaud's phenomenon and hyperlipidemia have been reported for ON in patients with SLE; however, no proven association factor has yet been found. In this study, we explored the major non-corticosteroid

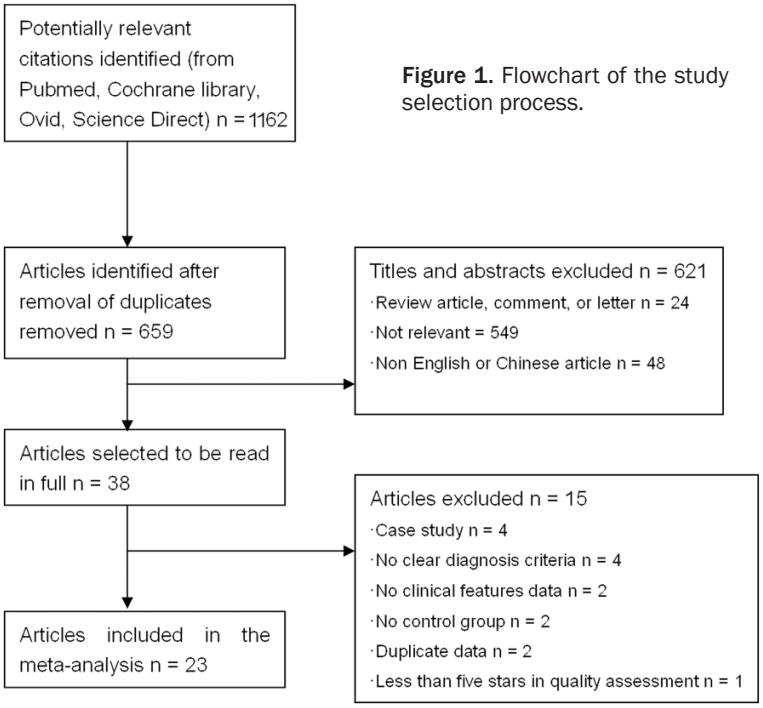


Figure 1. Flowchart of the study selection process.

risk factors of ON in patients with SLE using a meta-analysis approach.

Materials and methods

Data sources

We searched the Cochrane library, PubMed, Ovid and Science Direct databases for studies published up to 30 June in 2015. The following key words and subject terms were searched: "osteonecrosis", "necrosis of bone", "bone necrosis", "avascular necrosis", and "lupus", "systemic lupus erythematosus", "SLE", and "risk factors", and "predictive factors".

Inclusion/exclusion criteria

Inclusion and exclusion criteria were established before reviewing abstracts and articles. The inclusion criteria were as follows: inclusion of human subjects; cohort or case-control study design; comparison of the clinical features and/or laboratory parameters of SLE concomitant ON (case group) to SLE without ON (control group); clear diagnostic criteria for SLE and ON: SLE patients fulfilled the 1982 or 1997 revised American College of Rheumatology (ACR) criteria for the classification of SLE [13, 14]; identification of ON by one or more of the following imaging techniques: plain X-ray, radioisotope bone scan, and magnetic resonance imaging (MRI); sufficient data of the incidence of the clinical features and/or laboratory parameters to determine the odds ratios (ORs) with 95% confidence intervals (CIs). The exclusion criteria were as follows: non-primary literature; no clear diagnostic criteria; incomplete data or no raw data insufficient to determine the ORs and 95% CIs; violation of statistical analysis principles; case reports, case series, reviews, or purely descriptive reports, with no comparison groups.

Data extraction

Two investigators, (Wang and Li) screened the citations independently based on the inclusion and exclusion criteria. In instances of disagreement, consensus was achieved by discussion. Data were also extracted and registered from the eligible publications independently. The following data were extracted from each article: first author, year of publication, number of cases, number of controls, country, risk factors, clinical features, and laboratory features (expressed as either the number or percentage of cases and controls). All disagreements were resolved through group discussion.

Quality assessment

This meta-analysis included only case-control studies that reported data involving the clinical and/or laboratory features of ON in patients with SLE. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) [15] checklist for case-control studies. The NOS checklist consists of eight items within three domains: selection, comparability, and exposure. The NOS uses a "star" rating system to judge quality; a study receives one star for meeting each criterion. We interpreted the quality according to star values as follows: > 8, very good; 7-8, good; 5-6, moderate; 3-4, fair; and ≤ 2 poor. Reports allocated a star rating of less than 5 were excluded from this analysis.

Table 1. Characteristics of included studies

	First author	Year of publication	Number of cases	Number of controls	Study location	NOS score
1	Joo YB [35]	2015	319	20319	South Korea	7
2	Gontero RP [3]	2015	15	143	Argentina	6
3	Faezi ST [12]	2015	105	560	Iran	6
4	Lee J [21]	2014	64	64	South Korea	7
5	Kunyakham W [10]	2012	65	671	Thailand	6
6	Sayarlioglu M [19]	2012	49	154	Turkey	5
7	Uea-areewongsa P [29]	2009	20	20	Thailand	7
8	Wang DX [18]	2009	32	64	China	7
9	Hamijoyo L [27]	2008	43	93	Philippines	7
10	Fialho SC [28]	2007	10	36	Brazil	7
11	Prasad R [46]	2007	65	65	Canada	6
12	Calvo-Alen J [23]	2006	32	59	USA	6
13	Gladman DD [11]	2001	70	70	Canada	6
14	Mok CC [4]	1998	38	143	Hong Kong	6
15	Sheikh JS [55]	1998	15	11	USA	6
16	Watanabe T [24]	1997	7	106	Japan	6
17	Mont A [5]	1997	31	72	USA	6
18	Migliaresi S [6]	1994	7	62	Italy	6
19	Massardo L [25]	1992	17	173	Chile	6
20	Nagasawa K [7]	1989	24	87	Japan	5
21	Zizic TM [8]	1985	28	26	USA	6
22	Griffiths ID [22]	1979	8	60	England	5
23	Smith FE [26]	1976	7	7	USA	6

NOS score: Newcastle-Ottawa score.

Statistical analysis

The raw numerical data/rates were extracted from the studies, and the ORs were recalculated. Extracted data were used for combining the studies for clinical and laboratory features of interest using forest plots. The meta-analysis was processed using Review Manager 5.3. The actual statistical analysis method used in the study was Mantel-Haenszel test. We estimated the ORs and 95% CIs, and the statistical heterogeneity of the studies was assessed before combining the results.

The Q test and x^2-based I^2 test were used to examine the between-study variations and heterogeneity. The effect of heterogeneity was quantified using P and I^2 values. I^2 values of 25%, 50%, and 75% were nominally considered low, moderate, and high estimates, respectively [16]. Based on the results of the heterogeneity tests (using the x^2 test), a fixed effect model (where $P > 0.05$) or a random effect model (where $P \leq 0.05$) was used to estimate the pooled effect of risk factors of ON in patients with SLE.

A sensitivity analysis was performed by calculating the outcomes after each individual study was omitted in turn. Finally, publication bias was assessed by the construction of funnel plots [17].

Results

Study selection and characteristics

Figure 1 shows a schematic representation of the selection process and the reasons for excluding studies. Among the total of 1,162 potentially relevant citations identified, 503 duplicates were removed, leaving 659 article titles for initial checking. After screening titles and scanning abstracts, 38 articles were selected to be read in full. Fifteen studies failed to meet the inclusion criteria for the following reasons: case study, no clear diagnosis criteria, no clinical features data, no control group, and duplicate data. Twenty-three independent studies met all of the inclusion criteria. The characteristics of the included studies are summarized in **Table 1**.

Pooled analysis of risk factors

A comparison of clinical manifestations (**Table 2**), laboratory parameters (**Table 3**) and immunosuppressive drug use (**Table 4**) in patients with SLE and SLE-ON was conducted. The pooled ORs and 95%CIs for each risk factor for ON in the patients with SLE were as follows: arthritis 1.69 [1.32, 2.17], central nervous system (CNS) involvement 1.34 [1.06, 1.71], diabetes mellitus 1.59 [1.03, 2.46], hypertension 1.69 [1.42, 2.02], oral ulcer 1.48 [1.06, 2.08], renal involvement 1.53 [1.27, 1.83], vasculitis 2.45 [1.54, 3.89], smoking history 1.64 [1.01, 2.65], leucopenia 1.54 [1.11, 2.13], thrombo-

Table 2. Comparison of clinical manifestations in patients with SLE and SLE-ON

Risk factor	No. of studies [references]	OR [95% CI]	*P*-value	I^2 (%)
Alopecia	7 [3, 4, 8, 19, 21, 22, 26]	1.05 [0.73, 1.50]	0.81	30
Arthritis	15 [3, 4, 8, 10-12, 19, 21-26, 46, 55]	1.69 [1.32, 2.17]	< 0.0001	12
CNS involvement	15 [3, 4, 7, 8, 10-12, 19, 21, 22, 24-26, 29, 55]	1.34 [1.06, 1.71]	0.02	37
Diabetes mellitus	9 [3, 4, 10, 18, 19, 21, 23, 29, 35]	1.15 [0.88, 1.50]	0.31	0
Diabetes mellitus▲	8 [3, 4, 10, 18, 19, 21, 23, 29]	1.59 [1.03, 2.45]	0.03	0
Hypertension	12 [3, 4, 7, 8, 10, 18, 19, 21, 23, 26, 29, 35]	1.69 [1.42, 2.02]	< 0.0001	0
Malar rash	10 [3, 4, 8, 12, 18, 19, 21, 22, 24, 26]	1.09 [0.64, 1.84]	0.76	66*
Discoid rash	8 [4, 8, 12, 19, 21, 22, 24, 26]	1.41 [0.97, 2.05]	0.07	47
Oral ulcer	9 [3, 4, 8, 12, 18, 19, 21, 22, 26]	1.11 [0.62, 2.01]	0.72	73*
Oral ulcer▲	8 [3, 4, 8, 18, 19, 21, 22, 26]	1.48 [1.06, 2.08]	0.02	15
Photosensitivity	7 [3, 4, 8, 19, 21, 22, 26]	1.08 [0.75, 1.55]	0.69	48
Raynaud's phenomenon	18 [3, 4, 7, 8, 11, 12, 18, 19, 21-28, 46, 55]	1.13 [0.92, 1.39]	0.26	25
Renal involvement	17 [3, 4, 7, 10, 12, 18, 19, 21, 22, 24-26, 29, 35, 46, 55]	1.53 [1.27, 1.83]	< 0.0001	0
Serocitis	6 [4, 8, 10, 19, 21, 22]	1.37 [0.94, 2.01]	0.10	35
Vasculitis	12 [3-5, 10, 11, 18, 19, 21, 25, 27, 28, 55]	2.45 [1.54, 3.89]	0.0002	60*
Smoking history	8 [3-5, 21, 23, 27, 29, 46]	1.46 [0.93, 2.30]	0.10	3
Smoking history▲	7 [4, 5, 21, 23, 27, 29, 46]	1.64 [1.01, 2.65]	0.05	0
Alcohol use	6 [3, 4, 21, 23, 27, 29]	1.66 [0.74, 3.72]	0.22	0
Osteoporosis	6 [5, 12, 18, 21, 35, 46]	1.54 [0.89, 2.66]	0.12	68*

OR: Odds ratio. 95% CI: confidential intervals. I^2 describes heterogeneity across studies. *Using random effect model; ▲Sensitivity analysis by excluding a study.

Table 3. Comparison of laboratory parameters in patients with SLE and SLE-ON

Risk factor	No. of studies [references]	OR [95% CI]	*P*-value	I^2 (%)
Anti-CL	8 [3, 11, 18, 23, 24, 26, 46, 55]	0.93 [0.59, 1.46]	0.75	2
Anti-CL (IgG)	6 [4, 19, 21, 28, 29, 55]	0.71 [0.43, 1.17]	0.18	1
Anti-CL (IgM)	4 [4, 19, 28, 55]	1.01 [0.48, 2.12]	0.98	24
Lupus anticoagulant	6 [3, 4, 19, 21, 23, 28]	1.08 [0.60, 1.94]	0.81	51
Anemia	8 [3, 4, 8, 18, 19, 21, 25, 26]	1.07 [0.73, 1.55]	0.73	19
Anti-dsDNA	8 [4, 7, 8, 19, 21, 25, 26, 55]	1.28 [0.81, 2.02]	0.29	9
Anti-Sm	5 [3, 4, 21, 24, 29]	0.48 [0.27, 0.85]	0.01	0
Anti-Ro	4 [3, 4, 21, 24]	0.75 [0.30, 1.90]	0.55	68*
Anti-La	4 [3, 4, 21, 24]	0.75 [0.42, 1.34]	0.33	49
Anti-RNP	5 [3, 4, 21, 24, 29]	0.70 [0.43, 1.13]	0.14	40
Leucopenia	8 [3, 4, 8, 19, 21, 24-26]	1.54 [1.11, 2.13]	0.01	27
Thrombocytopenia	8 [3, 4, 7, 8, 19, 21, 25, 26]	1.63 [1.14, 2.32]	0.007	0
Increased CHO	5 [7, 8, 11, 18, 46]	1.37 [0.89, 2.11]	0.15	0
Increased TG	5 [7, 8, 11, 18, 46]	0.94 [0.64, 1.38]	0.76	0

OR: Odds ratio. 95% CI: confidential intervals. I^2 describes heterogeneity across studies. *Using random effect model.

cytopenia 1.63 [1.14, 2.32], cytotoxic drugs 1.79 [1.25, 2.57], cyclophosphamide 3.13 [1.58, 6.21] and anti-Sm antibodies 0.48 [0.27, 0.85]. Representative Forest plots are shown in **Figure 2**.

Bias evaluation

Funnel plots are a visual tool for investigating publication and other biases in meta-analyses. Funnel plots were used in this study to identify publication bias by constructing a scatter plot of ORs of the enrolled studies on the x-axis against the standard error of log OR of each study on the y-axis. In the absence of publication bias, ORs of small-scale studies scatter widely at the bottom of the graph, with the spread narrowing among large-scale studies and the funnel plot resembles a symmetrical inverted funnel; publication bias yields asym-

Table 4. Comparison of immunosuppressive drug use in patients with SLE and SLE-ON

Risk factor	No. of studies [references]	OR [95% CI]	*P*-value	I^2 (%)
Cytotoxic drug	4 [11, 19, 23, 27]	1.79 [1.25, 2.57]	0.002	54
Immunosuppressive drug	7 [7, 10, 18, 25, 28, 35, 46]	1.32 [0.69, 2.52]	0.40	84*
Antimalarials	9 [4, 10-12, 23, 28, 29, 35, 46]	0.72 [0.41, 1.28]	0.27	85*
Cyclophosphamide	3 [4, 12, 29]	1.61 [0.43, 5.96]	0.48	87*
Cyclophosphamide▲	2 [4, 29]	3.13 [1.58, 6.21]	0.001	1
Azathioprine	3 [4, 12, 29]	0.90 [0.63, 1.29]	0.57	21

OR: Odds ratio. 95% CI: confidential intervals. I^2 describes heterogeneity across studies. *Using random effect model; ▲Sensitivity analysis by excluding a study.

metry in the funnel plot. We found no significant evidence for publication bias in this study. Representative funnel plots are shown in **Figure 3**.

Discussion

With the improvement of modern treatments, the prognosis of patients with SLE has improved significantly and the prevention of related complications has become a more urgent requirement. ON occurs as a serious complication in 4.6% to 8.2% of patients with SLE and has a significant impact on their quality of life [9, 18]. ON can result from inflammation and narrowing of the arteries, and from increased pressure outside the blood vessels. Sayarlioglu et al. [19] highlighted Raynaud's phenomenon, pleurisy, lymphadenopathy, vasculitis, peripheral neuropathy, Sjögren's syndrome, and other factors associated with ON in SLE. The main purposes of the present study were to identify the risk factors for ON in patients with SLE based on the existing information and to provide a basis for further research. A single study may be too underpowered to detect a risk factor, especially when the sample size is relatively small. Therefore, we carried out the present meta-analysis of all the eligible studies of risk factors for ON in patients with SLE to derive a better estimation.

Zhu et al. [20] identified alopecia as a unique protective factor for SLE; however, the current meta-analysis, which included three studies [3, 21, 22] did not reveal any significant relevance of alopecia in SLE patients with ON.

Kunyakham et al. [10] and Gladman et al. [11] both found that arthritis was significantly associated with the development of ON; However, this association was not identified in a number of other studies [8, 19, 23-26]. Hamijoyo et al. [27] reported higher prevalence of arthritis in the ON group compared with that in the control (92 vs. 82 %), although the association was not statistically significant ($P > 0.05$). In our meta-analysis, arthritis was significantly associated with the development of ON. Arthritis remained an important factor in the multivariate analysis [11].

Kunyakham et al. [10] also reported that hematological involvement was related to the development of ON in SLE patients, particularly, among patients with hemolytic anemia. This result might be explained by the low capacity of red blood cells to carry oxygen to the target tissue. The hip joint, which is sensitive to ischemia, might be affected by tissue hypoxia, which ultimately leads to ON. We found significant relevance of leucopenia and thrombocytopenia, but not anemia, appearing in those patients who had developed ON.

The presence of Raynaud's phenomenon was found to be associated with ON in an early [8] and a more recent [19] study, but was not confirmed by others [4, 8, 11, 18, 25, 27, 28]. The presence of Raynaud's phenomenon was not found to be a risk for the development of ON in our meta-analysis.

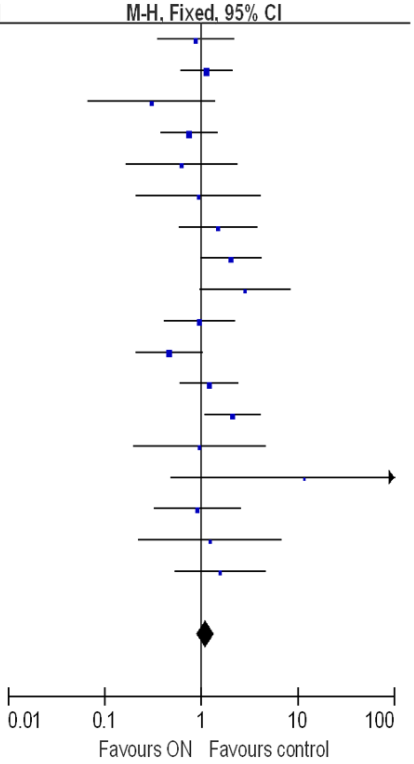
Uea-areewongsa et al. [29] demonstrated that renal involvement was associated with the development of ON of the femoral head in SLE. They proposed several mechanisms for this finding. First, patients with renal involvement had dyslipidemia and premature atherosclerosis leading to the occurrence of arterial thrombosis [30, 31]. Subgroup analysis revealed that patients with renal involvement had hypercholesterolemia more frequently than those without. Second, nephritic syndrome was associated with changes in the turnover and concentration of most plasma proteins, including those involved in the coagulation pathways, again, leading to the occurrence of arterial thrombosis [30-33]. Arterial thrombosis may have caused

A

Study or Subgroup	ON Events	ON Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Calvo 2006	11	32	22	59	6.3%	0.88 [0.36, 2.17]
Faezi ST 2015	15	105	72	560	12.0%	1.13 [0.62, 2.06]
Fialhol 2007	3	10	21	36	3.9%	0.31 [0.07, 1.38]
Glad 2001	38	70	43	70	12.1%	0.75 [0.38, 1.46]
Gontero RP 2015	3	15	41	143	3.8%	0.62 [0.17, 2.32]
Grifiths 1979	4	8	31	60	2.2%	0.94 [0.21, 4.09]
Hamijoyo 2008	9	43	14	93	4.3%	1.49 [0.59, 3.78]
Lee 2014	33	64	22	64	6.6%	2.03 [1.00, 4.14]
Massardo 1992	6	17	28	173	2.0%	2.82 [0.97, 8.27]
Mok 1998	9	38	35	143	6.9%	0.96 [0.41, 2.22]
Nagasawa 1989	12	44	39	87	11.7%	0.46 [0.21, 1.01]
prasad 2007	37	65	34	65	9.0%	1.20 [0.60, 2.41]
Sayarlioglu 2012	25	49	51	154	7.4%	2.10 [1.10, 4.04]
sheikh 1998	8	15	6	11	2.0%	0.95 [0.20, 4.54]
Smith 1976	3	7	0	7	0.2%	11.67 [0.48, 282.04]
Wang 2009	7	32	15	64	4.8%	0.91 [0.33, 2.53]
watanabe 1997	2	7	26	106	1.4%	1.23 [0.23, 6.73]
Zizic 1985	15	28	11	26	3.3%	1.57 [0.54, 4.61]
Total (95% CI)		**649**		**1921**	**100.0%**	**1.13 [0.92, 1.39]**
Total events	240		511			

Heterogeneity: Chi² = 22.55, df = 17 (P = 0.16); I² = 25%

Test for overall effect: Z = 1.13 (P = 0.26)

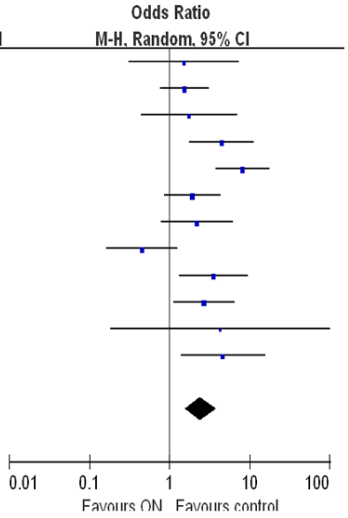


B

Study or Subgroup	ON Events	ON Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Fialhol 2007	3	10	8	36	5.5%	1.50 [0.31, 7.17]
Glad 2001	47	70	40	70	11.3%	1.53 [0.77, 3.05]
Gontero RP 2015	3	15	18	143	6.6%	1.74 [0.45, 6.75]
Hamijoyo 2008	15	43	10	93	9.5%	4.45 [1.79, 11.02]
Kunyakham 2012	13	65	20	671	10.8%	8.14 [3.83, 17.28]
Lee 2014	21	64	13	64	10.4%	1.92 [0.86, 4.27]
Massardo 1992	7	17	42	173	8.7%	2.18 [0.78, 6.09]
Mok 1998	5	38	36	143	8.8%	0.45 [0.16, 1.24]
Mont 1997	12	31	11	72	9.1%	3.50 [1.33, 9.21]
Sayarlioglu 2012	11	49	15	154	9.9%	2.68 [1.14, 6.32]
sheikh 1998	2	15	0	11	1.9%	4.26 [0.18, 98.07]
Wang 2009	9	32	5	64	7.5%	4.62 [1.40, 15.25]
Total (95% CI)		**449**		**1694**	**100.0%**	**2.45 [1.54, 3.89]**
Total events	148		218			

Heterogeneity: Tau² = 0.37; Chi² = 27.28, df = 11 (P = 0.004); I² = 60%

Test for overall effect: Z = 3.79 (P = 0.0002)

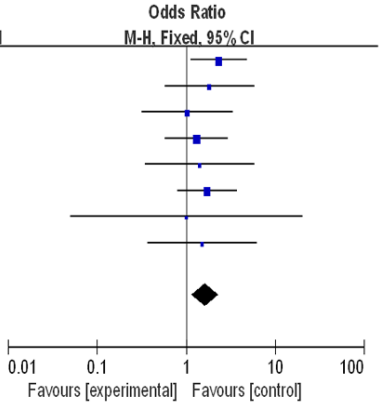


C

Study or Subgroup	ON Events	ON Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Calvo 2006	34	64	21	64	21.4%	2.32 [1.13, 4.75]
Gontero RP 2015	5	15	31	143	8.5%	1.81 [0.57, 5.68]
Massardo 1992	4	17	40	173	11.9%	1.02 [0.32, 3.31]
Mok 1998	11	38	34	143	22.0%	1.31 [0.59, 2.91]
Nagasawa 1989	3	24	8	87	6.6%	1.41 [0.34, 5.79]
Sayarlioglu 2012	13	49	27	154	20.8%	1.70 [0.80, 3.63]
Smith 1976	1	7	1	7	1.9%	1.00 [0.05, 19.96]
Zizic 1985	6	28	4	26	7.1%	1.50 [0.37, 6.06]
Total (95% CI)		**242**		**797**	**100.0%**	**1.63 [1.14, 2.32]**
Total events	77		166			

Heterogeneity: Chi² = 2.03, df = 7 (P = 0.96); I² = 0%

Test for overall effect: Z = 2.71 (P = 0.007)



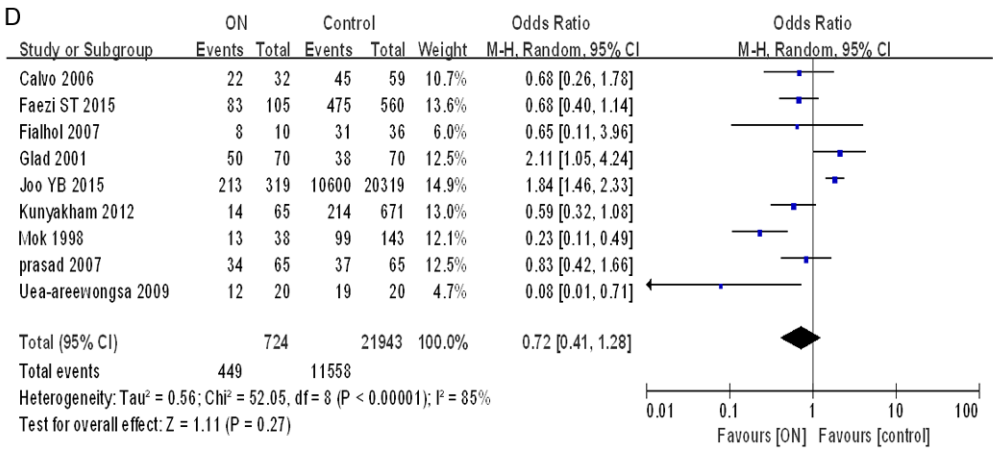


Figure 2. Forest plot of studies of Reynaud's phenomenon/Vasculitis/Thrombocytopenia/Antimalarials associated with ON in SLE patients included in the meta-analysis. A. Reynaud's phenomenon; B. Vasculitis; C. Thrombocytopenia; D. Antimalarials treatment. A. Forest plot of studies in meta-analysis results of Reynaud's phenomenon associated with ON in SLE patients. B. Forest plot of studies in meta-analysis results of vasculitis associated with ON in SLE patients. C. Forest plot of studies in meta-analysis results of thrombocytopenia associated with ON in SLE patients. D. Forest plot of studies in meta-analysis results of antimalarials treatment associated with ON in SLE patients.

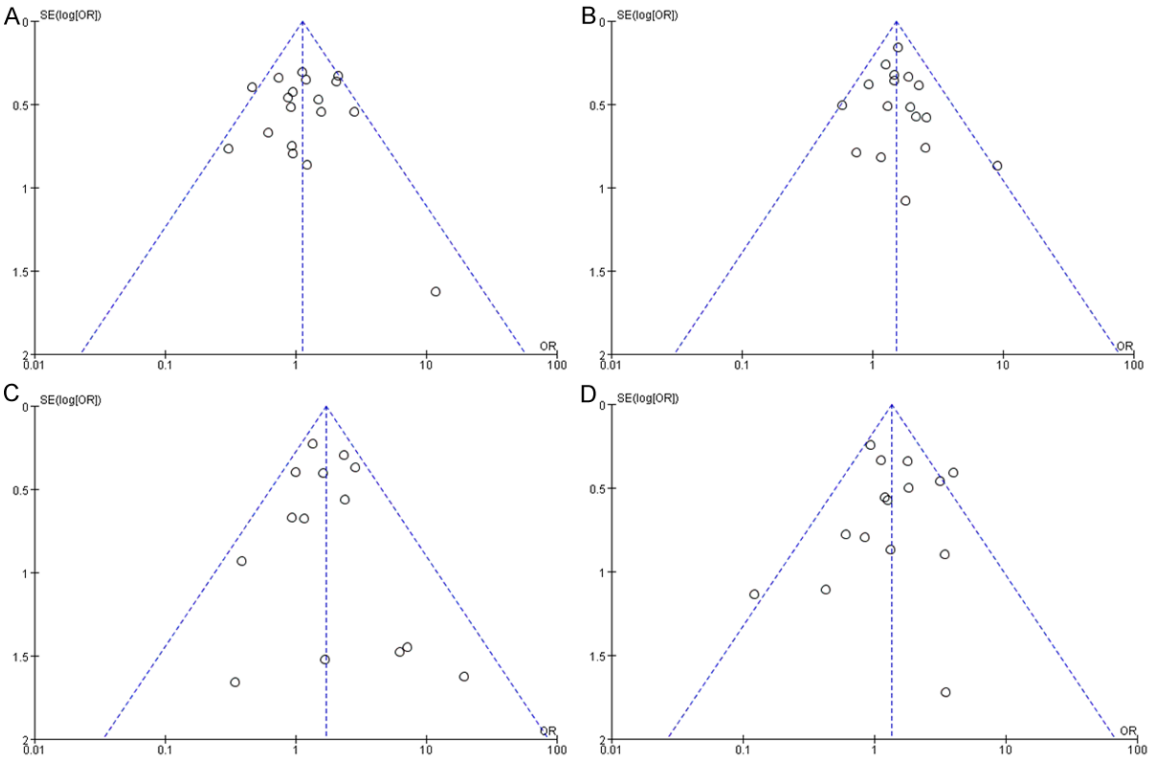


Figure 3. Funnel plot of studies of Reynaud's phenomenon/renal involvement/arthritis/CNS involvement associated with ON in SLE patients included in the meta-analysis. A. Reynaud's phenomenon, B. Renal involvement, C. arthritis, D. CNS involvement.

ischemia of the affected bone, leading to the occurrence of ON. Third, when patients have active renal involvement, concurrent active vasculitis is possible in other small vessels, which, if located in the femoral heads, might compromise the blood supply leading to the occur-

rence of ON. Cozen et al. [34] also reported that the presence of renal involvement was associated with the occurrence of ON. Massardo et al. [25] found that proteinuria and hematuria were risk factors associated with this complication. The results of these studies were confirmed in our meta-analysis.

With regard to clinical manifestations, neuropsychiatric SLE (NPSLE) remained an independent predictor of ON in multivariate analysis [21]. Some of the manifestations of NPSLE are life-threatening conditions that require treatment with large amounts of corticosteroids in a relatively short time. Therefore, NPSLE could be expected to reflect steroid use. However, NPSLE remained a significant predictor even after adjustment for steroid usage. We found a significant association between NPSLE and patients with SLE who developed ON.

Co-morbidities included smoking history, alcohol use, diabetes mellitus and hypertension. Our meta-analysis revealed an association between hypertension and ON development in patients with SLE. However, corticosteroid treatment has been associated with acute side-effects, such as hypertension in some cases.

Alcohol use, smoking history, and diabetes mellitus were not identified as significant risk factors for ON in patients with SLE in our meta-analysis. However, sensitivity analysis performed by excluding a study revealed different results regarding diabetes mellitus [35] and smoking history [12]. It can be speculated that these differences may be due to the effects of these factors on the blood vessels, especially the arteries.

Although controversial, anti-phospholipid antibodies have been proposed as a risk factor for the occurrence of ON because of their prothrombotic properties. There are conflicting data on the role of anti-phospholipid antibodies in SLE; some data support [5, 36] an association, while others do not [5, 11, 19, 23, 29, 37]. The retrospective study by Asherson et al. [36] showed that the prevalence of anti-phospholipid antibodies (anti-cardiolipin antibodies [αCL]) or lupus anticoagulant [LAC]) was higher in SLE patients with ON than in those without. Tektonidou et al. [38] reported that 20% of patients with primary anti-phospholipid syndrome had evidence of asymptomatic ON (in the absence of corticosteroid use) in magnetic resonance imaging. The presence of microthrombi at the intravascular level or a thrombotic vasculopathy related to the anti-phospholipid antibodies is thought to be the underlying etiological mechanism. In the study reported by Mok et al., [4] a significantly higher prevalence of lupus anticoagulant (LAC) was found in patents with ON. x^2 analysis showed that LAC was associated with ON. Logistic regression also confirmed that LAC was an independent risk factor for ON. However, Sayarlioglu et al. reported that similar prevalence of IgG and IgM anticardiolipin antibodies and LAC in both the patients with ON and control patients. Our meta-analysis did not reveal any significant association between all these factors (anti-phospholipid antibodies, IgM, IgG, LAC) and ON.

Dyslipidaemia has been associated with idiopathic ON [39-41]; however, this association had not been reported in SLE. An independent negative association between serum levels of triglycerides (TG) and ON was found in a study [42] which included 62 SLE patients who were being treated with high doses of glucocorticoids, nine of whom developed ON, suggesting a protective effect of this lipid. Higher rather than lower levels of TG have been associated with ON in other studies [43, 44]. A linear relationship between TG levels and disease activity in SLE has been demonstrated; [45] therefore, it is conceivable that the more aggressive management of the disease observed among patients with symptomatic ON (higher doses of glucocorticoids and more frequent use of cytotoxic drugs) could have resulted in decreased serum TG levels. In our study, the prevalence of increased TG or cholesterol (CHO) in both the ON and control groups of patients were similar, possibly because the data extracted from the studies in our meta-analysis are qualitative (classified as elevated or not). A more objective conclusion may be reached by including sufficient quantitative data as new studies are published.

Recently, Lee et al. [21] found that the proportion of patients who received immunosuppressants was significantly higher among those with ON, even after adjustment for lupus nephritis and NPSLE. This suggests that immu-

nosuppressant use may be an independent risk factor, irrespective of SLE disease activity. Their results are supported by previous findings [11, 23] and are consistent with the results of our meta-analysis, indicating a role for immunosuppressants in developing ON in SLE patients; however, the mechanism underlying this association remains unknown.

The association between cytotoxic drug treatment and ON has been described previously [11, 19, 23]. Calvo-Alen et al. [23] found that these drugs are a risk factor for the development of symptomatic ON. It can be speculated that cytotoxic drug use acts only as a proxy for more aggressive disease. However, no differences were observed between cases and controls in terms of disease activity, yet cytotoxic drug use remained significant in the multivariable analyses after adjusting for the use of glucocorticoids, other treatments, and other potential confounding variables. Sayarlioglu et al. [19] also showed that use of these drugs may be a risk factor for the development of ON, although the mechanism underlying the association remains to be elucidated. However, our analysis did not reveal an association between cytotoxic drugs and the occurrence of ON. The reasons for these discrepancies are complex and diverse although different definitions of cytotoxic drugs may account, at least in part, for the different conclusions.

In our meta-analysis, the effects of antimalarials, cyclophosphamide, and azathioprine were investigated separately. We found that cyclophosphamide was a risk factor for the development of ON, while there were no differences between patients with ON and control groups in terms of azathioprine use.

Antimalarials have been recognized as beneficial for the lipid profile and protective against thromboembolism [46]. We were unable to find any protective effect of antimalarials in the development of ON. However, Uea-areewongsa et al. [29] reported that antimalarial agents significantly decreased the risk for the occurrence of ON in lupus patients. Four previous studies examined the association between the use of antimalarials and the occurrence of ON in SLE patients [4, 23, 29, 46]. All reported no significant association between the use of antimalarials and the occurrence of ON; however, the studies by Mok et al. and Calvo-Alen et al. [23] revealed that antimalarial drugs were prescribed less frequently in SLE patients who had ON, although the difference did not reach the level of statistical significance in the multivariate analyses. A protective effect of antimalarials against the occurrence of ON could be explained by several mechanisms [29]. First, use of antimalarial agents had been reported to improve lipid profiles in SLE patients by decreasing LDL, while raising HDL [47-49]. Second, it has been suggested that antimalarial agents have anti-platelet [50] and anti-thrombogenic [51, 52] effects. Hydroxychloroquine may reverse the platelet activation induced by human IgG anti-phospholipid antibodies [50] and protect the annexin A5 anticoagulant shield from disruption by anti-phospholipid antibodies [53]. Third, antimalarial agents have been reported to prevent disease flares and improve SLE disease activity [54] All of these mechanisms may have beneficial effects in the prevention of ON.

Despite including most factors that were previously reported to be associated with the occurrence of ON in either SLE or non-SLE patients, our analysis failed to identify other risk factors for the occurrence of symptomatic ON, such as osteoporosis, serositis, malar rash, discoid rash and anti-dsDNA antibodies. This might be due to the limited number of studies included in this meta-analysis.

The limitations of our study should be noted. First, our analysis may have been influence by compounding factors and heterogeneity. Furthermore, publication bias also may have distorted the analysis, since studies that have produced negative results may have been missed or may not have been published. Second, we only included patients with symptomatic ON; thus, we could have missed the early cases or included asymptomatic ON patients in the control group. Third, the number of studies included in our analysis was not sufficient to yield high statistical power; therefore, our results should be interpreted with caution.

Conclusion

The results of our meta-analysis demonstrate that arthritis, CNS involvement, diabetes mellitus, hypertension, oral ulcer, renal involvement,

vasculitis, smoking history, leucopenia, thrombocytopenia, cytotoxic drugs and cyclophosphamide are major risk factors for ON in patients with SLE, while alcohol use, Raynaud's phenomenon, lupus anticoagulant, αCL, increased CHO, and increased TG are not. Anti-Sm antibodies were identified as a protective factor against ON in patients with SLE, while antimalarial drug use was not. These findings require confirmation in further investigations in a large prospective cohort.

Disclosure of conflict of interest

None.

Address correspondence to: Xingfu Li, Department of Rheumatology, Qilu Hospital of Shandong University, 44#, Wenhua Xi Road, Jinan 250012, PR China. E-mail: xingfu_lee888@126.com

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