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# Associations between glucocorticoids, antiphospholipid antibodies and femur head necrosis in patients with SLE: a directed acyclic graph-based multicentre study

**Shengbao Chen*, Qianying Cai*, Yanjun Xu*, Qiong Fu, Yong Feng, Xiaoxiang Chen, Shengming Dai, Dongbao Zhao, Ce Zhan, Weidong Xu, Jiwei Wang, Yang Wang, Jinming Yu, Chunde Bao and Changqing Zhang**

***Abstract***

**Background:** Osteonecrosis of the femoral head (ONFH) remains a major cause of disability in patients with systemic lupus erythematosus (SLE) and seriously impairs quality of life. This study aimed to investigate associations between glucocorticoids (GCs), antiphospholipid antibodies (aPLs), and ONFH in patients with SLE.

**Methods:** We conducted a multicentre cohort study on patients with SLE and used a directed acyclic graph-based analysis strategy. Details of GC therapy, aPLs status, other drug administration and other SLE-related characteristics were collected. ONFH occurrence during follow-up was determined by magnetic resonance imaging. Multivariable logistic regression and generalized estimating equation models were performed to assess their effects on ONFH, and a simplified scoring system comprising these factors for short- and medium-term SLE-ONFH prediction was developed by receiver operating characteristic curve analysis.

**Results:** Of 449 SLE patients with a median follow-up duration of 5.3 years, 41 (9.1%) developed ONFH. Independently risk factors of SLE-ONFH including: average daily GC dose with an adjusted odds ratio (aOR) of 1.1 and 95% confidence interval (CI) of 1.0–1.1; GC therapy duration (3–5 years: aOR 3.3, 95% CI 1.4–7.8; >5 years: aOR 8.0, 95% CI 3.3–19.4); initial intravenous GC (aOR 4.4, 95% CI 1.9–10.1); positive aPLs (aOR 2.8, 95% CI 1.4–5.8); and Arterial hypertension secondary to GC usage (aOR 5.2, 95% CI 1.4–19.1). And we successfully developed the simplified scoring system (SCORE model) with an area under the curve of 0.88 (95% CI 0.82–0.94).

**Conclusion:** Based on the risk factors involved in the development of SLE-ONFH, a novel SCORE model was developed, which might be helpful for risk stratification of SLE-ONFH in clinical practice.

***Keywords:*** antiphospholipid antibodies, arterial hypertension, glucocorticoids, osteonecrosis of the femoral head, prediction model, systemic lupus erythematosus

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Correspondence to:
**Changqing Zhang**
Department of Orthopedic Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, NO 600, Yishan Road, Xuhui district, Shanghai 200233, China

Institute of Microsurgery on Extremities, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai 200233, China
**zhangcq@sjtu.edu.cn**

**Chunde Bao**
Department of Rheumatology, Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai 200021, China
**baochunde_1678@126.com**

**Shengbao Chen**
Institute of Microsurgery on Extremities, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

Department of Orthopedic Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

**Qianying Cai**
**Yang Wang**
Institute of Microsurgery on Extremities, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

**Yanjun Xu**
**Yong Feng**
Department of Orthopedic Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

**Qiong Fu**
**Xiaoxiang Chen**
Department of Rheumatology, Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai, China

## Introduction

Osteonecrosis of the femoral head (ONFH) in patients receiving systemic glucocorticoids (GCs) therapy is a common and frequently occurring disease. As a serious complication, high prevalence of ONFH is prominent in patients with systemic lupus erythematosus (SLE), with a reported worldwide prevalence of 4.2–43.1%.[1–7] The development of ONFH can cause irreversible damage to the femoral head, leading to severe dysfunction of the hip joint, disability, and ultimately requiring surgical interventions such as total hip arthroplasty.[8–11]

**Shengming Dai**
Department of Rheumatology and Immunology, Shanghai Jiao Tong University Affiliated Shanghai Sixth People's Hospital, Shanghai, China

**Dongbao Zhao**
Department of Rheumatology, Changhai Hospital, Shanghai, China

**Ce Zhan**
**Weidong Xu**
Department of Joint Surgery and Sports Medicine, Changhai Hospital, Shanghai, China

**Jiwei Wang**
**Jinming Yu**
School of Public Health, Fudan University, Shanghai, China

*Shengbao Chen, Qianying Cai and Yanjun Xu contributed equally to this work.

The pathogenesis of GC-induced ONFH from the primary disease of SLE (so called SLE-ONFH) is complex and has remained unclear. GC therapy has been recognised as a major contributor to SLE-ONFH, as GCs are known to inhibit osteoblasts or lead to coagulation/lipid metabolism disorders.[12–15] This situation retards bone formation and decreases blood flow, eventually leading to ONFH. Although high-dose GC administration is reported to be associated with ONFH, the dose–effect relationship between GC and ONFH remains controversial.[16–18] It is still unclear which specific GC-related factors are most strongly associated with ONFH. For example, is the dose–effect relationship consistent over time or does it increase over time? Equivocal results from GC dose–effect studies on ONFH have posed challenges for the management of GC treatment in patients with SLE.[18–20]

In addition, GC therapy may not be the only cause of SLE-ONFH.[2,8,21] Due to the complex nature of SLE [diverse clinical manifestations, disease activity and antiphospholipid antibodies (aPLs)] and a complicated process for drug administration [such as GC, immunosuppressive agents (ISs), hydroxychloroquine (HCQ), anticoagulant], some variables such as GCs, aPLs, ISs and HCQ were reported to interact or have different roles for the occurrence of SLE-ONFH.[1,3,5,19,22–28] Being aware of this complexity, several studies have used underlying comorbidities or mediators as potential confounders, such as arterial hypertension secondary to GC usage,[29] leading to inappropriate adjustments[30] and biased results. Thus, it is important to adjust appropriately for potentially confounding factors when studying the relationships between factors and occurrence of ONFH. What is needed is a way to accurately identify and analyse these relationships in order to appropriately direct clinical treatments for SLE that reduce the probability of SLE- ONFH. Hence, we conducted a multicentre cohort study with the aid of directed acyclic graphs (DAGs) to analyse the associations between GC dose and aPLs on the occurrence of ONFH in patients with SLE in Shanghai, China.

## Methods

### *Study patient inclusion and exclusion criteria*

This longitudinal prospective cohort study was conducted from January 2016 to December 2019 at three institutions (Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, and Changhai Hospital) in Shanghai, China. All patients fulfilled the following criteria were included: aged between 14 and 75 years old, classification of SLE fulfilling the 1997 modified American College of Rheumatology criteria,[31] having a history of consecutive GC treatment or planning to receive GC therapy longer than 6 months with expected total dosages above 1500 mg. The main exclusion criteria were as follows: history of hip fracture or traumatic brain surgery, diagnosed with ONFH before enrolment; a long-term history of GC therapy with usage/dosage not clearly identified; also diagnosed with rheumatoid arthritis, ankylosing spondylitis, or hip arthritis; unable to communicate normally, unable to undergo magnetic resonance imaging (MRI). Our study complies with the Declaration of Helsinki. This study was approved by the Medical Ethics Committee of Shanghai Sixth People's Hospital Institutional Review Board number: 2016-KY-001(K) and was registered online at the website of Chinese Clinical Trial Registry (registration number: ChiCTR-OOC-16009127). All participants signed informed consent before enrolment.

The study protocol was designed to investigate the medication records on inpatient admissions and outpatient that each participant received systematic GC therapy after being diagnosed with SLE. Since GC exposure, a minimum follow-up of 1 year was ensured, and follow-up ended at date of ONFH diagnosis, death, or 31 December 2019, whichever came first.

A custom-designed questionnaire was used, and data were recorded in the case report form. Data were collected in a prospective manner at diagnosis and during the subsequent prospective follow-up visits. For patients with SLE with previous GC usage but without ONFH, their information at baseline was collected retrospectively and continued at prospective follow-up (these data were also used in the following analyses and as part of the current study for patients with prevalent SLE). Data collected were mainly regarding the following five areas: baseline demographic data (age at diagnosis, sex, years of education, body mass index, cigarette and alcohol consumption after diagnosed); SLE clinical features [disease duration, clinical manifestations, disease activity at diagnosis and during the last follow-up visit based on the SLE Disease Activity Index 2000 (SLEDAI-2K)]; comorbidities or complications (arterial hypertension/arterial

hypertension secondary to GC usage, diabetes, osteoporosis observed at diagnosis and during follow-up visits); medication usage [details of GC treatment, hydroxychloroquine, statin, calcium, vitamin D, vitamin E, anti-platelet/anticoagulant drugs, diphosphonate, immunomodulatory agents (i.e. methotrexate, hydroxychloroquine)]; laboratory data (aPLs status at diagnosis). In this study, arterial hypertension was defined as blood pressure ⩾140/90 mmHg, or normotensive individuals treated with antihypertensive medications, or a self-reported history of arterial hypertension at diagnosis of SLE; arterial hypertension secondary to GC usage was defined as arterial hypertension first detected after a patient started using GCs, which referred to those normotensive individuals at diagnosis of SLE, and then newly met the criterion of 'hypertensive'.

### *Determination of GC exposure and aPLs status*

We were interested in two factors related to GC exposure: (1) whether or not the participant received initial intravenous infusion of GCs (methylprednisolone within the first 3 months of SLE diagnosis, regardless of the dose); and (2) average daily dose of GCs after SLE diagnosis. Other GC dose-related indicators were also measured, including maximum pulsed intravenous dose, cumulative intravenous dose in the first 3-month period, total cumulative dose, average dose during the first 2 years, average dose from year 3 to year 5, and average dose after 5 years. All indicators of GC doses were converted to the prednisone equivalent dose.[32]

APLs consisted of IgG/IgM anti-cardiolipin (aCL), IgG/IgM anti-β2 glycoprotein-1 (anti-β2GP1) antibodies, and lupus anticoagulant (LAC) in this study. IgG/IgM aCL and IgG/IgM anti-β2GP1 levels were determined by a Quantikine ELISA kit (anti-cardiolipin ELISA, anti-β2-glycoprotein 1 ELISA; Euroimmun, Luebeck, Germany). The detailed process and diagnosis criteria on aCL and anti-β2GP1 testing were performed according to the methods described in a previous paper from authors of this study.[33] LAC testing was performed according to guidelines for LAC detection established by the Subcommittee on Lupus Anticoagulant/Antiphospholipid Antibody of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[34] If a participant tested positive for any aPL (aCL or anti-β2GP1 antibodies or LAC), aPLs status for that participant was designated positive. Otherwise, they were designated as negative.

### *ONFH determination procedures and expert review*

Each participant included in the SLE cohort underwent MRI of both hips to check for ONFH; MRI has become the standard for initial diagnosis of ONFH (the sensitivity and specificity of the diagnosis are 100% and 94–99%, respectively), diagnosis criteria of ONFH (at stage I) were based on the low-intensity band on MRI T1-weighted coronal images (band-like pattern) and (or) the 'double-line sign' on T2-weighted images (consisting of a low-signal band with a high-signal inner border).[35,36] We used the Classification System of the Association Research Circulation Osseous.[37] Symptomatic ONFH was diagnosed when such MRI abnormalities plus continuous hip pain or hip mobility abnormalities appeared (such as subacute pain in one or both sides of the groin, the pain had come on spontaneously and appeared to be of mechanical origin, and with or without limited hip mobility). MRIs were performed at enrolment, during annual visits at follow-ups, or at any other time during follow-up if a participant who experienced lasted hip pain longer than 1 week. When participants complained they had a lasting symptomatic pain at incidental (not the time of routine follow-up), our research coordinator would arrange the cases to visit our designated orthopaedic surgeons (Z-CQ, X-WD), and an additional physical examination and reviewing the condition were done on site, and then it was decided whether to book an extra MRI examination for both hips. If participants from remote areas were not able to go to on site, we would suggest that they visit the local hospital and then evaluated whether to book the MRI examination, and then the detected compact disc of MRI images was sent or mailed to our centre for review independently (MRI detection of both hips was free for all patients in this cohort, regardless of extra or routinely MRI detection on the plan of follow-up; The fee of MRI detection was covered by the research project).

The MRI results were all handed over to a designated group of orthopaedic experts (C-SB, FY, Z-CQ) for review independently. The same panel of experts discussed the results of disputed cases until consensus was reached.

### Covariates identified by DAGs

Recently, DAGs have proven to be a useful tool for identifying confounding variables and mediators in exposure–outcome relationships, decreasing the influence of confounding bias and avoiding over-adjustment.[38–40] The basic classification and structure of covariates in the putative exposure–outcome association are illustrated in Supplementary Table S1 and Figure S1. By reviewing possible causal mechanisms reported by previously published studies (Supplementary Table S2),[1–6,16–19,22,24,41] we constructed a DAG framework for evaluating the effects of GC therapy (initial intravenous GC infusion and average daily dose) and aPLs status on the occurrence of SLE-ONFH in temporal order. Then we identified potential confounders of each exposure (i.e. GC therapy and aPLs status at diagnosis; Supplementary Figures S2 and S3). When referring to the possible risk of introducing collider bias or risk of over-adjustments,[30,42,43] we did not condition the data based on the underlying mediators, such as arterial hypertension secondary to GC usage, the potential mediator for main exposures (GC therapy and aPLs) and the occurrence of SLE-ONFH (Supplementary Figures S2 and S3). These DAGs revealed the minimal sufficient adjustment sets (MSAS) to evaluate the effects of GC therapy, aPLs, and arterial hypertension secondary to GC usage on SLE-ONFH (Supplementary Figure S4). All DAGs were created according to standard procedures and analysed with DAGitty 3.0 software.[44]

### Statistical analysis

Clinical characteristics are presented as the median (interquartile range) for continuous variables and counts (percentages) for categorical variables. In univariate analyses for all included patients with SLE, we used the Mann–Whitney *U*-test and Pearson's Chi-squared test (or Fisher's exact test when appropriate) to compare the medians and proportions, respectively. Multivariable logistic regression models and generalized estimating equations (GEE) models were used to evaluate the subgroup of SLE participants who also had available aPL data. The effects of GC exposure and aPLs on ONFH are presented as adjusted odds ratio (aOR) with 95% confidence interval (CI) before or after adjusting for potential confounding factors. Receiver operating characteristic (ROC) curves were then conducted for predicting SLE-ONFH. The survival curve and the number of cumulative ONFH cases was presented using 'survival' and 'survminer' packages in R 4.0.0 software. $p$ values were two-sided and considered statistically significant at $<0.05$. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Cary, NC, USA).

## Results

### Baseline characteristics and general follow-up results

A total of 514 patients who received systemic GC therapy were recruited from January 2016 to June 2019, and 473 participants of them met the diagnostic criteria for SLE were subsequently enrolled in this study (Figure 1). Of the 473 SLE patients invited to participate in this study, 22 of them used GCs and were followed-up for less than 6 months and 2 died after therapy less than 1 year with uncertain ONFH and were thus excluded from further analyses. As a result, 449 patients with SLE (94.9%) were eligible for follow-up and included in the final analyses. All patients without ONFH received GC therapy longer than 1 year.

Of the 449 participants (median age at SLE diagnosis, 29.8 years), 418 (93.1%) were female, and median SLEDAI-2K score was 13.0. Median GC therapy duration was 5.3 (2.0, 10.5) years, a total of 41 (9.1%) patients with SLE developed ONFH (Figure 2), 27 of them (65.9%) experienced symptomatic ONFH, the other 14 (34.1%) were diagnosed as asymptomatic early ONFH, and bilateral involvement was observed in 28 (68.3%) patients. Short- to medium-term ($\leqslant$5 years) and long-term ($>$5 years) SLE-ONFH prevalence were 5.6% and 6.9%, respectively (Figure 1). Compared with patients who did not develop ONFH, those who developed ONFH had higher percentages of severe SLE disease activity, greater aPL positivity, more skin manifestations and renal involvement at SLE diagnosis (Table 1).

### Univariate analysis

In the whole course of treatment until the last follow-up, patients with ONFH received a higher average daily dose of GC than patients without ONFH (13.0 *versus* 10.7 mg/day, $p=0.004$; $\geqslant$30 mg/day: 17.1% *versus* 3.4%), regardless of whether they received an initial single dose of intravenous GC (73.2% *versus* 40.7%, $p<0.001$) or multiple doses after diagnosis (i.e. cumulative dose during the first 3 months) [4.0 g (3.1, 4.6) *versus* 2.7 g (1.8, 4.0), $p<0.001$]. In addition, patients with ONFH were followed-up for a shorter time

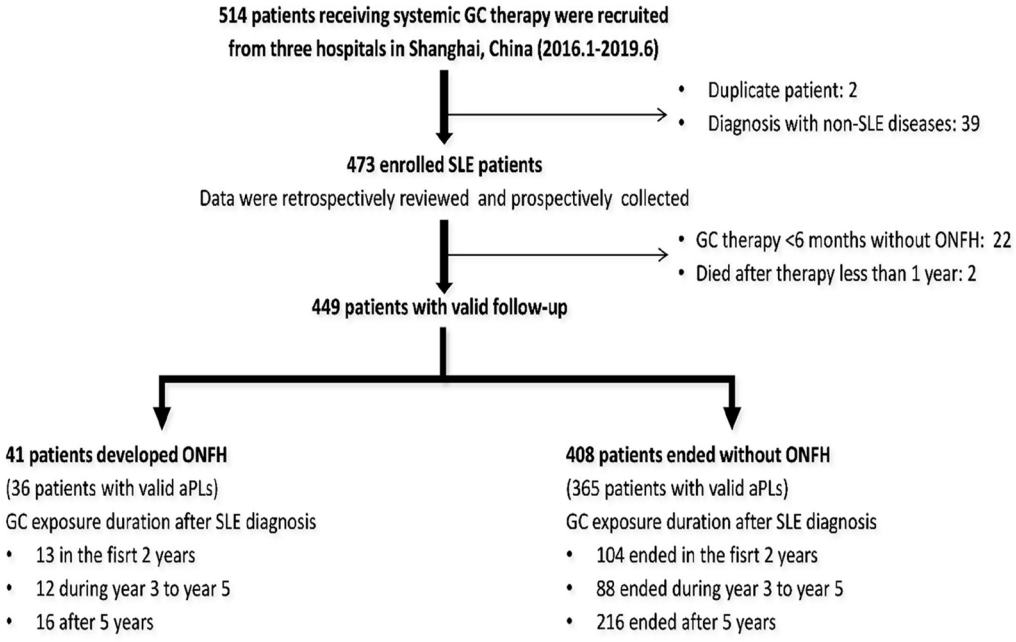


**Figure 1.** Flow chart for SLE-ONFH cohort study.
ONFH, osteonecrosis of the femoral head; SLE, systemic lupus erythematosus.

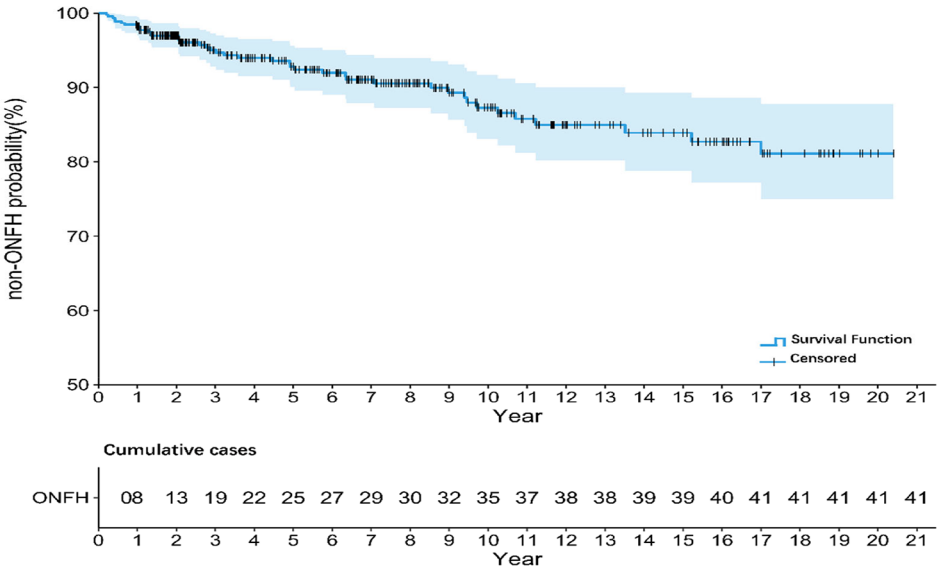


**Figure 2.** The survival curve and cumulative cases of ONFH in our cohort.
ONFH, osteonecrosis of the femoral head.

(3.2 *versus* 5.5 years); and had higher prevalence of arterial hypertension secondary to GC usage (26.8 *versus* 14.7%) than patients without ONFH (Table 2). Also, a greater proportion of patients with ONFH took anti-platelet drugs during follow-up (43.9% *versus* 27.7%).

### *Multivariable and GEE analysis guided by DAGs*

Associations between SLE-ONFH and the GC therapy, and aPLs status were analysed with multivariable logistic models; data from 401 SLE participants who had accompanying valid aPLs measurements were evaluated in the multivariable

**Table 1.** Baseline characteristics of the included participants at the time of SLE diagnosis.

| Baseline characteristic | Total ($n=449$) | ONFH ($n=41$) | Non-ONFH ($n=408$) | $p$-value |
|---|---|---|---|---|
| Age (years) | 29.8 (23.2, 40.9) | 26.5 (23.2, 34.6) | 30.0 (23.3, 41.7) | 0.11 |
| BMI (kg/m$^2$) | 21.5 (19.8, 23.8) | 20.6 (19.1, 23.6) | 21.5 (19.8, 23.8) | 0.43 |
| Male (%) | 31 (6.9) | 4 (9.8) | 27 (6.6) | 0.51 |
| More than 12 years of education (%) | 205 (49.2) | 24 (61.5) | 181 (48.0) | 0.11 |
| Drinking (%) | 6 (1.3) | 0 (0.0) | 6 (1.5) | 1.00 |
| Smoking (%) | 2 (0.5) | 0 (0.0) | 2 (0.5) | 1.00 |
| Clinical manifestations | | | | |
| Skin manifestation[a] (%) | 231 (51.5) | 29 (70.7) | 202 (49.5) | 0.01 |
| Lupus nephritis (%) | 230 (51.5) | 27 (65.9) | 203 (49.8) | 0.05 |
| Arthrosis (%) | 212 (47.2) | 16 (39.0) | 196 (48.0) | 0.27 |
| Serositis (%) | 36 (8.0) | 6 (14.6) | 30 (7.4) | 0.12 |
| Haematological disorder (%) | 215 (47.9) | 21 (51.2) | 194 (47.6) | 0.65 |
| Neurological disorder (%) | 15 (3.3) | 3 (7.3) | 12 (2.9) | 0.15 |
| SLEDAI-2K score | 13.0 (10.0, 17.0) | 15.0 (10.0, 18.0) | 13 (10.0, 16.5) | 0.08 |
| Severe (SLEDAI-2K $\geqslant$ 15, %) | 182 (40.5) | 23 (56.1) | 159 (39.0) | 0.03 |
| Comorbidities | | | | |
| Arterial hypertension (%) | 72 (16.1) | 6 (15.0) | 66 (16.2) | 0.85 |
| Diabetes (%) | 7 (1.6) | 0 (0.0) | 7 (1.7) | 1.00 |
| Renal diseases (%) | 20 (4.5) | 4 (9.8) | 16 (3.9) | 0.10 |
| Liver diseases (%) | 12 (2.7) | 3 (7.3) | 9 (2.2) | 0.09 |
| Osteoporosis (%) | 22 (4.9) | 4 (10.0) | 18 (4.4) | 0.12 |
| Any aPLs (%) | 89 (22.2) | 15 (41.7) | 74 (20.3) | 0.003 |
| aCLs (%) | 64 (16.0) | 12 (33.3) | 52 (14.3) | 0.003 |
| aβ2GP1 (%) | 53 (21.3) | 8 (33.3) | 45 (20.0) | 0.13 |
| LAC (%) | 42 (21.2) | 6 (25.0) | 36 (20.7) | 0.63 |

[a]Skin manifestation is defined as malar rash, discoid rash or oral ulcers; median (interquartile range) and Mann–Whitney *U*-tests were used for continuous variables; percentage and Pearson's Chi-squared test or Fisher's exact test were used for categorical variables.
Ab2GP1, anti-β2 glycoprotein-1 antibodies; aCL, anti-cardiolipins antibody; aPL, antiphospholipid antibody; BMI, body mass index; LAC, lupus anticoagulant; ONFH, osteonecrosis of the femoral head; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

analysis guided by DAGs. After adjusting the MSAS for each exposure, the following variables were all independently positively associated with ONFH: initial intravenous GCs (aOR 4.4, 95% CI 1.9–10.1, $p<0.001$); average daily dose (aOR 1.1, 95% CI 1.0–1.1, $p=0.007$); positive aPL state at diagnosis (aOR 2.8, 95% CI 1.4–5.8, $p=0.004$); and arterial hypertension secondary to GC usage (aOR 3.4, 95% CI 1.2–9.1; $p=0.02$) (Table 3).

**Table 2.** Drugs therapy and SLE-related features of the included participants after diagnosis.

| Characteristics | Total ($n=449$) | ONFH ($n=41$) | Non-ONFH ($n=408$) | $p$-value |
|---|---|---|---|---|
| GC used duration (years) | 5.3 (2.0, 10.5) | 3.2 (1.3, 8.5) | 5.5 (2.0, 11.2) | 0.03 |
| GC exposures (all converted to prednisone) | | | | |
| Maximal intravenous dose (mg/day) | 100 (50, 100) | 100 (100, 125) | 100 (50, 100) | 0.08 |
| Initial intravenous GC (%) | 196 (43.7) | 30 (73.2) | 166 (40.7) | <0.001 |
| Total intravenous dose (g) | 0.9 (0.5, 1.4) | 1.1 (0.6, 2.0) | 0.8 (0.5, 1.4) | 0.047 |
| Cumulative dose in 3 months (g) | 3.0 (1.8, 4.1) | 4.0 (3.1, 4.6) | 2.7 (1.8, 4.0) | <0.001 |
| >30 mg/day | 235 (52.3) | 33 (80.5) | 202 (49.5) | 0.0001 |
| Total cumulative dose (g) | 18.0 (9.6, 35.2) | 14.1 (8.7, 24.6) | 18.2 (9.6, 37.2) | 0.15 |
| Average daily dose (mg/day) | 10.9 (7.2, 16.2) | 13.0 (10.6, 21.3) | 10.7 (6.9, 15.8) | 0.004 |
| ⩽7.5 mg/day | 122 (21.2) | 6 (14.6) | 116 (28.4) | <0.001 |
| >7.5 and ⩽15.0 mg/day | 193 (43.0) | 18 (43.9) | 175 (42.9) | |
| >15.0 and ⩽30.0 mg/day | 113 (25.2) | 10 (24.4) | 103 (25.3) | |
| >30.0 mg/day | 21 (4.7) | 7 (17.1) | 14 (3.4) | |
| Average daily dose stratified by GC exposure time (mg/day) | | | | |
| First 1 year | 11.3 (7.6, 17.2) | 13.0 (10.9, 21.6) | 11.0 (7.5, 16.8) | 0.005 |
| First 2 years | 11.3 (7.6, 16.7) | 13.0 (10.9, 21.3) | 10.9 (7.4, 16.4) | 0.005 |
| 3–5 years | 7.3 (4.0, 10.9) | 8.3 (4.7, 11.1) | 7.1 (4.0, 10.8) | 0.63 |
| More than 5 years | 8.2 (5.6, 11.2) | 10.6 (6.3, 11.3) | 8.1 (5.6, 11.2) | 0.39 |
| Complications | | | | |
| Arterial hypertension secondary to GC usage (%) | 71 (15.8) | 11 (26.8) | 60 (14.7) | 0.04 |
| Osteoporosis (%) | 22 (4.9) | 1 (2.4) | 21 (5.2) | 0.71 |
| Diabetes (%) | 6 (2.9) | 0 (0.0) | 6 (1.5) | 0.62 |
| Cutaneous vasculitis (%) | 6 (1.3) | 1 (2.4) | 5 (1.2) | 0.44 |
| Oral ulcers (%) | 39 (8.7) | 6 (14.6) | 33 (8.1) | 0.15 |
| SLEDAI-2K at last visit | 7.0 (4.0, 9.0) | 8.0 (4.0, 10.0) | 6.0 (4.0, 9.0) | 0.23 |
| Other drugs use | | | | |
| Anti-platelet (%) | 131 (29.2) | 18 (43.9) | 113 (27.7) | 0.03 |
| Anticoagulants (%) | 11 (2.5) | 1 (2.4) | 10 (2.5) | 1.00 |
| Statin (%) | 37 (8.2) | 7 (17.1) | 30 (7.4) | 0.07 |
| Hydroxychloroquine (%) | 312 (69.5) | 31 (75.6) | 281 (68.9) | 0.37 |
| Immunomodulatory/immunosuppressive (%) | 277 (61.7) | 27 (65.9) | 250 (61.3) | 0.57 |
| Calcium (%) | 426 (94.9) | 38 (92.7) | 388 (95.1) | 0.46 |
| Vitamin D (%) | 424 (94.4) | 39 (95.1) | 385 (94.4) | 1.00 |
| Vitamin E (%) | 11 (2.5) | 0 (0.0) | 11 (2.7) | 0.61 |
| Diphosphonate (%) | 44 (9.8) | 4 (9.8) | 40 (9.8) | 1.00 |

Median (interquartile range) and Mann–Whitney *U*-tests were used for continuous variables; percentage and Pearson's Chi-squared test or Fisher's exact test were used for categorical variables.
GC, glucocorticoid; ONFH, osteonecrosis of the femoral head; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

**Table 3.** Associations of GC exposure, aPLs with SLE-ONFH adjusting for MSAS.

| Independent variables | Multivariable logistic models | | GEE models | |
|---|---|---|---|---|
| | Adjusted OR (95% CI) | *p*-value | Adjusted OR (95% CI) | *p*-value |
| GC therapy | | | | |
| Initial intravenous GC | 4.4 (1.9, 10.1) | <0.001 | — | — |
| [a]Average daily dose (mg/day) | 1.1 (1.0, 1.1) | 0.007 | 1.1 (1.0, 1.1) | <0.001 |
| ⩾15 mg/day | 1.4 (0.6, 3.1) | 0.44 | 2.6 (1.3, 5.1) | 0.005 |
| [a]GC exposure time (years) | | | | |
| First 2 years | — | — | 1.00 | — |
| 3–5 years | — | — | 3.3 (1.4, 7.8) | 0.008 |
| More than 5 years | — | — | 8.0 (3.3, 19.4) | <0.001 |
| Positive aPLs state at diagnosis | 2.8 (1.4, 5.8) | 0.004 | — | — |
| [b]Arterial hypertension secondary to GC usage | 3.4 (1.2, 9.1) | 0.02 | 5.2 (1.4, 19.1) | 0.01 |

[a]analysis in the same GEE model with following confounders in MSAS: age at diagnosis, sex, arterial hypertension at diagnosis, lupus nephritis, skin manifestation, haematological disorder, neurological disorder, SLEDAI-2K score, aPL status at diagnosis and initial intravenous GC.
[b]MSAS for arterial hypertension secondary to GC usage in the multivariable logistic model and GEE model is consistent: arterial hypertension at diagnosis, lupus nephritis, SLEDAI-2K, aPL status at diagnosis, initial intravenous GC and GC dose.
Exposure time was not included in multivariable logistic models as considering the tightly associated relationship of time and average daily dose. As the associations of initial intravenous GC, positive aPL state before therapy and arterial hypertension secondary to GC usage with ONFH would not be biased by time; GEE models were not performed in their analysis.
aPL, antiphospholipid antibody; CI, confidence interval; GC, glucocorticoid; GEE, generalized estimating equation; MSAS, minimal sufficient adjustment sets; ONFH, osteonecrosis of the femoral head; OR, odds ratio; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000.

Because the duration and dose of GC treatment were strongly associated, we used a GEE model to clarify and valid their individual effects on ONFH development. The GEE model revealed that both higher average daily GC dose (⩾15 mg/day: aOR 2.6, 95% CI 1.3–5.1, $p=0.005$) and longer GC exposure time (3–5 years: aOR 3.3, 95% CI 1.4–7.8, $p=0.008$; >5 years: aOR 8.0, 95% CI 3.3–19.4, $p<0.001$) were linked to an increased likelihood of ONFH development. And then arterial hypertension secondary to GC usage was also positively associated with ONFH according to the GEE model (aOR 5.2, 95% CI 1.4–19.1; $p=0.01$) (Table 3).

### *Short- and medium-term SCORE model for predicting SLE-ONFH*

According to the results of multivariable analyses and a method of model construction in literature,[45] we developed a simplified scoring system (hereinafter referred to as the SCORE model) for predicting ONFH in patients who received short- and medium-term GC therapy (⩽5 years). SCORE model consisted of four predictors as follow: (a) GC dose (average daily dose ⩾15 mg or GC treatment >2 years); (b) initial intravenous GC; (c) positive aPL state; and (d) arterial hypertension secondary to GC usage. Each predictor is given a binary score of 0 (not present) or 1 (present); the total possible score can range from 0 to 4. The detail SCORE model was shown in Table 4. The score of 2 was the most sensitive cut-off value (sensitivity: 90.9%), while the score of 4 was the most specific value (specificity: 90.5%). By applying the SCORE model in this cohort, we found that the successful prediction rate (PPV) for SLE-ONFH increased with higher scores. PPV changed from 7.9% to 66.7% as the cut-off score increased from 1 to 4.

Two other prediction models (GC model, aPL model) were also developed (Figure 3). Analyses of

**Table 4.** Sensitivities, specificities, PPVs, NPVs and Youden index of SCORE model for occurrence of ONFH.

| Score cut-offs | Predictors | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Youden index |
|---|---|---|---|---|---|---|
| 0 and ⩾1 | a/b/c/d | 22/22 (100) | 124/379 (32.7) | 22/277 (7.9) | 124/124 (100) | 0.327 |
| ⩽1 and ⩾2 | ab/ac/ad/bc/bd/cd | 20/22 (90.9) | 259/379 (68.3) | 20/140 (14.3) | 259/261 (99.2) | 0.592 |
| ⩽2 and ⩾3 | abc/abd/acd/bcd | 13/22 (59.1) | 354/379 (93.4) | 13/38 (34.2) | 354/363 (97.5) | 0.525 |
| ⩽3 and 4 | abcd | 4/22 (18.2) | 377/379 (99.5) | 4/6 (66.7) | 377/395 (95.4) | 0.177 |

SCORE model consisted of four predictors: (a) GC dose (average daily dose ⩾15 mg or GC treatment >2 years); (b) initial intravenous GC; (c) positive aPLs state; and (d) Arterial hypertension secondary to GC usage. Each predictor is given a binary score of 0 (not present) or 1 (present); the total possible score can range from 0 to 4.
GC, glucocorticoid; NPV, negative prediction value; ONFH, osteonecrosis of the femoral head; PPV, positive prediction value.

ROC curves indicated that the SCORE model [area under the curve (AUC) 0.88, 95% CI 0.82–0.94] was more accurate in predicting ONFH than either the GC model (AUC 0.70, 95% CI 0.60–0.81) or the aPL model (AUC 0.67, 95% CI 0.56–0.78).

## Discussion

In this multicentre cohort study, we investigated the prevalence of ONFH, potential dose–effect relationship between glucocorticoids used and ONFH, and other independent risk factors for SLE-ONFH. All patients with SLE received GC therapy for a median of 5.3 years and at an average GC dose of 10.9 mg/day, which was similar to several previous studies.[1,23,46] In our study, the prevalence of ONFH was 9.1% (41 of 449) in patients with SLE detected with MRI and it was higher than that in others reports.[1,9,23] It may be due to more asymptomatic ONFH are detected early by MRI than other methods.

Our results showed that patients with SLE who received a higher average daily GC dose, had a longer GC exposure over time, and had initial intravenous GC treatment at diagnosis, had a higher independent risk of developing ONFH. These associations remained after adjusting appropriately for confounders identified by DAGs. We overcame some limitations of previous similar studies, which were focussed solely on the effect of GC dose (either highest daily dose or the total cumulative dose), ignoring the inseparable temporal relationship between GC therapy (i.e. when and how long) and the effect of dose on ONFH during GC therapy.[3–5,7,17] Therefore, our results provided more convincing evidence for the dose–effect association with GC and SLE-ONFH.

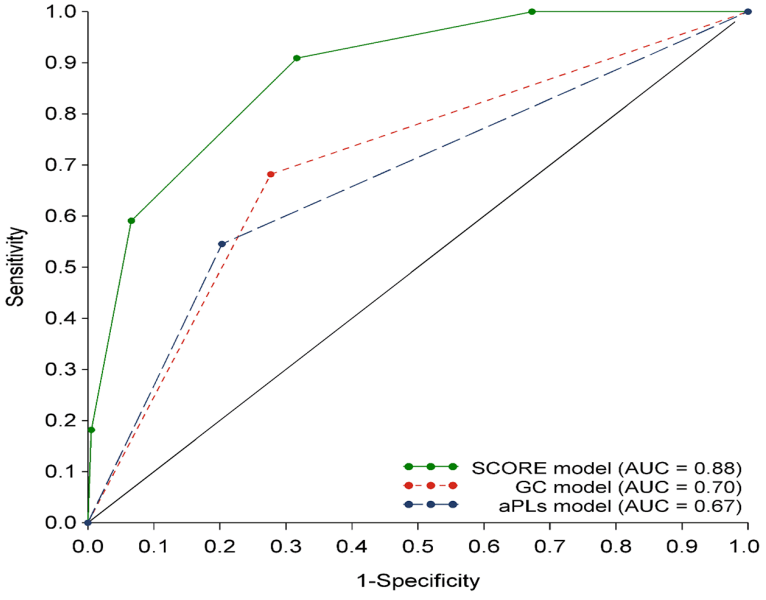


**Figure 3.** ROC curves of three models for short- and medium-term prediction of SLE-ONFH.
GC model consisted of average daily GC dose with a cut-off point of 15 mg/day. aPL model was used for the status of aPLs at diagnosis (positive or negative). AUC for the SCORE model (scoring from 1 to 4) is statistically significant when compared to the GC model ($p = 0.004$) and aPL model ($p < 0.001$).
aPL, antiphospholipid antibody; AUC, area under the curve; GCs, glucocorticoid; ONFH, osteonecrosis of the femoral head; ROC, receiver operating characteristic; SLE, systemic lupus erythematosus.

Our results confirmed that positive aPL status at diagnosis was associated with a higher risk of developing ONFH in for patients with SLE after adjusting for potential confounders. Potential pathophysiological mechanisms of aPL involvement in ONFH have been proposed. One theory is that aPLs may induce a hypercoagulable state, subsequently increasing the risk of small-vessel thrombosis in terminal-end arteries of bone.[19,47] Previous studies have produced conflicting results

on what role aPL status plays in the development of SLE-ONFH.[23–25,46] This inconsistency may, in part, be due to sensitivity differences of aPL detection methods used, which class of antibody is being targeted (IgG or IgM), and what kind of aPL (aCL or aβ2GP1) is being measured.[22] In our study, we used a more sensitive quantitative ELISA method to detect and measure levels of aCL or aβ2GP1.[33] In the present study, the percentage of patients with and without ONFH who tested positive for aPLs at SLE diagnosis was lower than that reported in a single-centre retrospective study (ONFH: 57.9%, non-ONFH: 32%), which included anti-phosphatidylserine/prothrombin antibodies (aPS-PT) as aPL indicators, in addition to aCL, aβ2GP1 and lupus anticoagulants.[48] Since aPLs status in our study was obtained before the patients received GC therapy, the effect of aPLs on ONFH would not be biased by GC-associated factors, as guided by DAGs. Our results suggest that aPLs play an important and independent role in the development of ONFH in patients with SLE.

In addition to the above risk factors, the most novel of our findings was that arterial hypertension secondary to GC usage is an independent risk factor for ONFH. A previous report in Korea that shown an association between hypertension (as a comorbidity) and avascular necrosis (OR 1.39) in an SLE population, but no distinction that hypertension was come from initial comorbidity or second complication after GC.[29] However, a series of case–control studies failed to find a significant relationship between hypertension and ONFH.[24,27,28] This outcome could possibly be due to their small sample sizes and uncontrolled influence of confounding variables related to the presence of hypertension before GC therapy began.[24,27,28] In our study, we evaluated a possible causal relationship between arterial hypertension secondary to GC usage and SLE-ONFH by adjusting for SLE participants' baseline arterial hypertension. Controlling for this variable produced a strong positive association (aOR 5.2, 95% CI 1.4–19.1), which was confirmed using a GEE model that took into account the association of arterial hypertension secondary to GC usage with GC dose and time. What biological mechanism might account for the association between arterial hypertension secondary to GC usage and ONFH in patients with SLE? The result in this study indicated an obviously distinction between the biological effects of initial and arterial hypertension secondary to GC usage on ONFH, this may be attributable to different pathogenesis in development of both hypertensions. The pathogenesis of arterial hypertension secondary to GC usage may be more complex. Previous studies showed that the combined action of multiple factors (such as circulating autoantibodies, soluble inflammatory mediators, increased levels of circulating endothelial cells and endothelial cell progenitors, blood-enhanced apoptosis by GCs) could cause vascular endothelial cell dysfunction,[49–51] and endothelial cell dysfunction may contribute to arterial hypertension development and vascular injury in SLE.[52] The underlying pathophysiological mechanisms between arterial hypertension and ONFH are still undetermined. Meanwhile, the arterial hypertension secondary to GC usage was confirmed an independent risk factor for myocardial perfusion defects in the SLE population,[53] which indicated that arterial hypertension secondary to GC usage has an important role in progress of local insufficient blood supply of coronary artery diseases. ONFH and coronary artery diseases are both serious comorbidities of SLE, with a common mechanism resulting in local insufficient blood supply. Therefore, proper management of arterial hypertension secondary to GC usage is of paramount importance in SLE.[54] This result of the present study is notable, rational blood pressure monitoring and controlling could be targeted as a strategy to prevent part of the development of ONFH during GC treatment in patients with SLE.

In our study, the very low proportion of smokers (after diagnosis of SLE) was a concern. In the distribution of demographic characteristics, most patients with SLE were female (93.1%), and the rate of smoking was extremely low in Chinese women;[55] in addition, some participants had stopped smoking after the diagnosis of SLE. Another point in our study showed that other therapy factors (such as HCQ, immunosuppressant agents) were not found to be associated with ONFH. This is inconsistent with the findings of other studies;[23,24,27] however, this may be partially due to differences in criteria for ONFH, source population or study types. In fact, HCQ has become a basic treatment for SLE when there are no contraindications.

While various predictors have been found to be associated with the development of ONFH, few practical models exist that can accurately predict

risk for ONFH within a specific period.[46] In the present study, we developed a practical model for predicting ONFH within 5 years. By including GC-related factors (i.e. dose, duration of therapy), positive aPLs status, and arterial hypertension secondary to GC usage into our SCORE model (AUC 0.88, 95% CI 0.82–0.94), we were able to predict short-and medium-term (⩽5 years) ONFH in patients with SLE. To our knowledge, the SCORE model is the first simplified scoring system for predicting risk for SLE-ONFH that could help physicians identify patients with SLE at higher risk for ONFH in clinical practice.

The present study has several strengths. First, the cohort study comprising 449 patients with SLE was conducted at three tertiary-level hospitals in Shanghai, China. Since most previous cohort studies were retrospective, with symptomatic ONFH as an outcome event and were carried out in a single centre, the results of our prospective study may more accurately represent the characteristics of SLE in a patient population receiving GC therapy, for that 34.1% asymptomatic early ONFH were detected by MRI in this cohort.[1,3,11,26] Second, by leveraging the power of DAGs to identify confounding variables and mediators in exposure–outcome relationships,[38–40] we were able to appropriately identify underlying confounders in evaluating the effects of GC-related factors and aPL status on ONFH. As arterial hypertension secondary to GC usage was also identified as a potential mediator in the development of ONFH, we avoided over-adjusting for it unnecessarily. Finally, we further developed a simplified scoring system to predict ONFH in the short-term in patients with SLE. This model can help physicians to assess their patients' risk for SLE-ONFH in clinical practice.

Our study also has a few limitations. First, laboratory indicators such as blood lipids and coagulation indexes were not included in the analyses in this study, and the effects of GC are not fully explained. Second, selection bias was unavoidable in this clinical cohort study. Not all participants were new cases at their enrolment, which means that patients died before the recruitment were not included. In addition, ONFH cases diagnosed before enrolment were excluded as the onset were unable to enter for analysing. These biases may have an impact on the accuracy of ONFH prevalence and association estimating, which needs to be further explored in future. Third, the derived SCORE prediction model was not validated in an external SLE population. Therefore, in the future, the accuracy and clinical value of the SCORE model needs to be confirmed in an external SLE cohort with qualified data.

## Conclusion

Our study provides new evidence that average daily GC dose, initial intravenous GC, and GC treatment duration are all involved in the development of ONFH in patients with SLE. In addition, careful surveillance of aPL status at SLE diagnosis and arterial hypertension secondary to GC usage is also essential for the risk assessment of ONFH. We established a short- and medium-term simplified scoring system that might have implications for strategies on prediction and prevention of the SLE-ONFH.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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## ORCID iDs

Shengbao Chen https://orcid.org/0000-0001-6236-5134

Qianying Cai https://orcid.org/0000-0002-9187-8315

Changqing Zhang https://orcid.org/0000-0002-7408-4126

## Supplemental material

Supplemental material for this article is available online.

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