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Risk factors for progression of carotid intima-media thickness in patients with systemic lupus erythematosus: protocol for an observational cohort study in China

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ABSTRACT

Introduction Accelerated atherosclerosis is a major complication of systemic lupus erythematosus (SLE), and it leads to increased cardiovascular morbidity and mortality in patients with SLE. This study aimed to investigate the natural progression of carotid intima-media thickness (CIMT), and to examine the risk factors for progression of CIMT and atherosclerotic plaques based on a Chinese SLE cohort.

Methods and analysis Participants were continuously enrolled as outpatients of the Department of Rheumatology in Peking Union Medical College Hospital (PUMCH) from October 2013 to December 2016. Inclusion criteria were as follows: (1) age ≥18 years, (2) fulfilment of clinical classification criteria of SLE and (3) provision of signed written informed consent. Patients with clinically overt coronary artery disease, a history of cardiovascular disease (previous stroke, heart failure, myocardial infarction, angina or symptomatic peripheral artery disease) and malignancy, and pregnant/lactating women were excluded. The primary outcome is progression of CIMT from baseline. A total of 440 patients with SLE will be enrolled. Participants will receive follow-up surveys ~5 years after their baseline visit. A standard structural survey form, including demographic data, medical history, clinical and laboratory assessments and CIMT measurement, is planned for data collection at baseline and follow-up. The risk prediction model for progression of CIMT will be created by using a mixed effect model.

Ethics and dissemination The study protocol was approved by the institutional review board of PUMCH (S-599). Informed consent was obtained from all participants according to the Declaration of Helsinki on Biomedical Research Involving Human Studies. All data will be managed confidentially according to guidelines and legislation. Dissemination will include publication of scientific papers and/or presentations of the study findings at international conferences.

Strengths and limitations of this study

► This is the first prospective cohort to monitor carotid intima-media thickness (CIMT) among patients with systemic lupus erythematosus (SLE) in China.

► The risk prediction model for progression of CIMT in SLE will be created by using a mixed effect model.

► The sample size is relatively large, and we compensated for individual factors that may affect progression of atherosclerosis.

► This was not an inception cohort, and ~40% of patients were in their first year since SLE was diagnosed at baseline.

► Most participants are from the north of China because of the geographical position of the Peking Union Medical College Hospital, and our results might only be representative for patients with SLE in North China.

morbidity and mortality in patients with SLE.[1–4] Prevention and intervention of premature atherosclerosis is beneficial for prognosis and survival of patients with SLE.

Although the exact pathogenesis of accelerated atherosclerosis in SLE remains poorly defined, endothelial dysfunction and dysregulation of immune responses are the areas of greatest concern by researchers.[5] SLE may affect the integrity and repair mechanisms of endothelial cells through direct binding of antibodies to endothelial cells or deposition of circulating immune complexes. This then results in endothelial damage that promotes atherogenesis.[6] Accelerated atherosclerosis in SLE may also be related to the presence of antiphospholipid antibodies, which increase the risk of thrombosis in SLE.[7–9]

Traditional Framingham risk factors, including age, sex, hyperlipidemia, smoking, hypertension and C reactive protein, partly

INTRODUCTION

Accelerated atherosclerosis is a major complication of systemic lupus erythematosus (SLE), and it leads to increased cardiovascular

explain, but do not account entirely, for the increased incidence of premature atherosclerosis in patients with SLE.[10–13] Recent studies have shown that factors related to SLE, medication, psychological stress and novel non-traditional factors, such as inflammation, are likely to contribute to development of premature atherosclerosis.[14–21] Most studies have established an association between risk factors and accelerated atherosclerosis on the basis of frequency of myocardial infarction, stroke or cardiovascular deaths among patients with SLE.[22 23] However, evidence based on the process of quantitative monitoring of atherosclerosis is still lacking.

Several studies have demonstrated the usefulness of carotid intima-media thickness (CIMT) in predicting future vascular events.[24 25] Therefore, CIMT could be used as a quantitative clinical surrogate endpoint for the risk of accelerated atherosclerosis in patients with SLE. However, most results using CIMT as a surrogate endpoint have come from retrospective studies or cross-sectional studies. Little evidence has been reported longitudinally

on the pace and risk factors for progression of CIMT in SLE.

Therefore, the primary aim of this study was to investigate the natural progress of CIMT in 5 years, and examine the risk factors for progression of CIMT and atherosclerotic plaques based on a Chinese SLE cohort. The secondary aims of the study were to investigate progression of brachial-ankle pulse wave velocity (baPWV), and to examine the risk factors for increasing baPWV in patients with SLE. Our findings may provide a reference for prevention and intervention strategies for premature atherosclerosis in patients with SLE.

METHODS AND ANALYSIS
Main hypotheses
From a population point of view, all patients with SLE have a risk of developing atherosclerosis. Therefore, as a whole, patients with SLE are a population at risk for atherosclerosis. Each individual in this high-risk
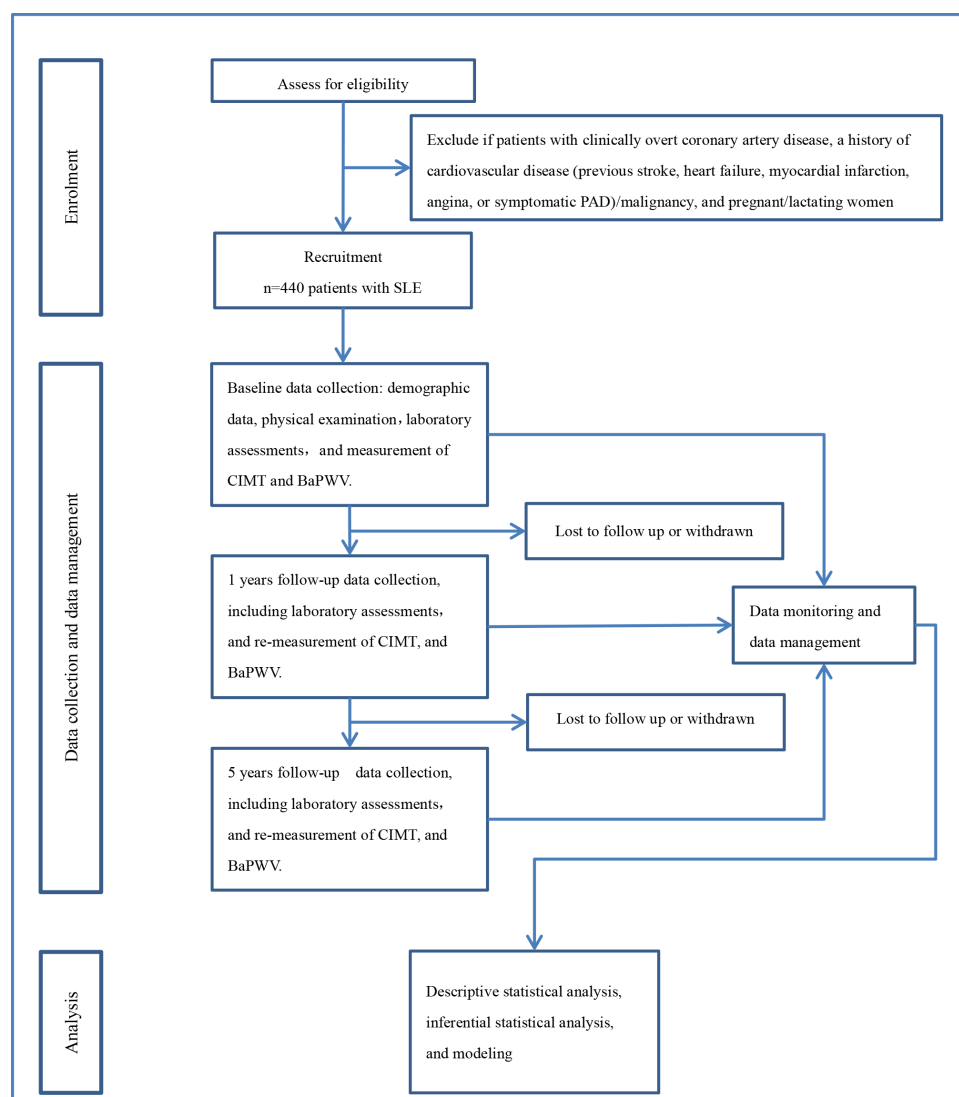
Figure 1 Study procedure and time points of data collection. baPWV, brachial-ankle pulse wave velocity; CIMT, carotid intima-media thickness; SLE, systemiclupus erythematosus.

population has different personal risk factors (eg, age, sex, disease duration). This means that their corresponding levels of risk for developing atherosclerosis are not the same. Under such an assumption, we conducted a cohort study to investigate the change in CIMT, examine the risk factors for progression of CIMT and create a risk prediction model on the basis of a Chinese SLE cohort.

Study design and timeline
This study was a prospective cohort in design and was initiated in October 2013. The study procedure is shown in figure 1. The plan for two stages of data collections is as follows.

Baseline
The overall design and pilot study were conducted from May 2013 to September 2013. We recruited participants and collected baseline data from October 2013 to December 2016. These data comprised demographic information, medical history, clinical and laboratory assessments, as well as baseline CIMT and baPWV, in patients with SLE.

Five-year follow-up
We will conduct clinical and laboratory assessments, and re-evaluate CIMT and baPWV from October 2018 to December 2021.

Planned substudies
The project includes two planned substudies. In substudy 1, we will evaluate differences in arterial stiffness in different age groups among patients with SLE. In substudy 2, we will examine the relationship between the interarm blood pressure difference and peripheral artery disease, which will be diagnosed with the ankle-brachial index in patients with SLE.

Organisational structure
The Central Project Group is at the top of the organisational structure, and is responsible for designing, supervising the entire process, checking data quality, statistical analysis, proposing interim seminars and project conferences and disseminating all project materials and protocols (figure 2). The following layers of the process comprise functional teams, which are further divided into two groups as follows: (1) clinical doctor team of cardiology, rheumatology and ultrasound; and (2) supporting teams that are responsible for constructing an information system, maintenance and updates.

Study population
The target population was patients with the clinical diagnosis of SLE. Study participants were recruited through a nationwide registry system created by the Chinese SLE Treatment and Research group.[26–31] All patients were continuously enrolled as outpatients of the Department of Rheumatology in Peking Union Medical College Hospital (PUMCH), which is a renowned hospital in China.

Inclusion criteria for the study were as follows: (1) age ≥18 years, (2) fulfilment of clinical classification criteria of SLE (four or more 1997 American College of Rheumatology classification criteria)[32] and (3) provision of signed written informed consent. Patients with clinically overt coronary artery disease, a history of cardiovascular disease (previous stroke, heart failure, myocardial infarction, angina, or symptomatic peripheral artery disease) and malignancy, and pregnant/lactating women were excluded.

Outcome measures and data collection
Major study outcomes
The primary outcome is the quantitative change in CIMT from baseline. The secondary outcome is the quantitative change in baPWV from baseline.

Clinical data collection
A standard structural survey form that included demographic data, medical history and clinical and laboratory assessments was used for data collection. All patients with SLE underwent a complete medical history survey and physical examination, according to the study protocol. Traditional risk factors of coronary artery disease (eg, age, family history, hypertension, diabetes mellitus and specific therapy, cholesterol, body mass index, current smoking
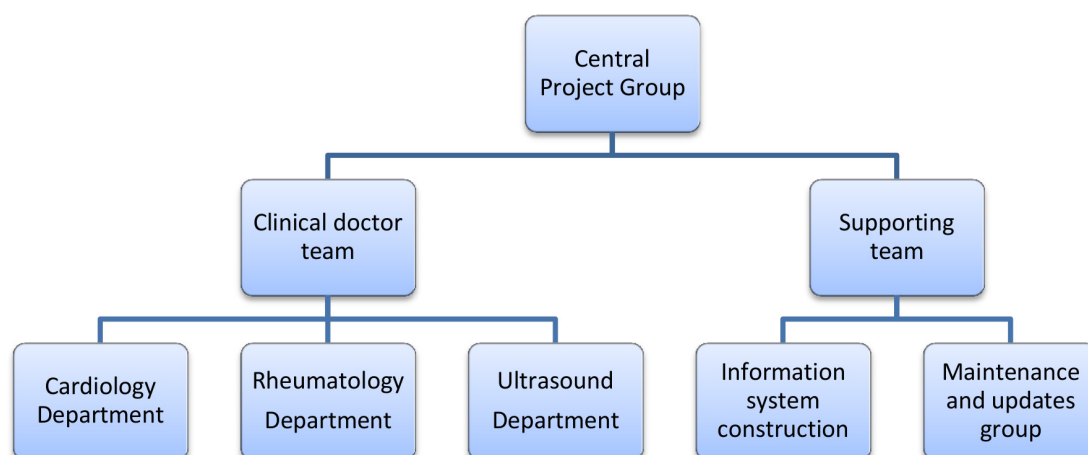
Figure 2 Organisational structure of the project.

status and smoking history) and lupus-specific factors (eg, disease activity, duration of the disease, organ involvement, cumulative dose of steroids, current and initial dose of prednisone and use of antimalarial and immunosuppressive medications) that may affect development of coronary artery disease were determined by interviewing patients. Disease activity and damage were assessed using the SLE disease activity index and the Systemic Lupus International Collaborating Clinics Damage Index, respectively.[18]

CIMT measurement

An ultrasound scan of CIMT was performed in all participants using a standard protocol at baseline and at the follow-up visit. Ultrasound was performed by using a Philips IU22 ultrasound system with a 9–3 and 12–5 MHz linear array transducer. The patient was placed in the supine position for ultrasonographic examination of the carotid artery. The far wall CIMT was measured on the far wall of the common carotid arteries (1 cm), bifurcation (1 cm) and distal internal carotid artery (1 cm) at the bifurcation, with a total length of 3 cm of the proximal carotid artery (anterior wall) and distal carotid artery (posterior wall). The ultrasound scan was performed by an experienced sonographer and interpreted by a single highly experienced cardiologist who was blinded to the clinical characteristics of the participants.

According to sonographic criteria, a normal CIMT is <0.9 mm, an increased CIMT (>0.9 mm) is considered indicative of a thickened intima and a CIMT >1.3 mm indicates an atherosclerotic plaque.[33 34]

Pulse wave velocity measurement

Blood pressure and baPWV were measured using a noninvasive vascular screening device (BP-203RPEIII VP-1000; Omron Corp, Kyoto, Japan). This device simultaneously records an ECG, phonocardiogram and pulse volume, and calculates the time delay of the pulse to obtain pulse wave transmission time.

Laboratory assessments

Blood tests included fasting plasma glucose levels, glycated haemoglobin levels, the erythrocyte sedimentation rate, complement 3 (C3) levels, C4 levels and routine biochemical parameters, including urea, creatinine, albumin, triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels. Biochemical parameters were measured by routine laboratory methods. Data on antinuclear antibody, anti-double-stranded DNA and anticardiolipin antibodies to IgM and IgG, as determined by an ELISA method within 3 months before enrolment, were extracted from the patients' medical records.

Follow-up

All participants will be followed longitudinally for 1 and 5 years after enrolment at the Department of Rheumatology, PUMCH. Clinical assessments, laboratory assessments, and CIMT and baPWV measurements will be repeated at the follow-up visit. For a change in treatment (especially steroids), we will obtain the change in medication type and dosage by the patient's medical record, as well as by visiting the patient.

Quality assurance

All data collectors were trained according to unified standards of data extraction and form completion. Survey forms were completed by doctoral candidates of internal medicine and rechecked by clinicians to ensure data accuracy and logicality.

All data were uploaded to the registry system data centre by the study data manager. The central project group will perform random checks of data against logic and the original paper forms. An item error rate of ≥5.0% will result in rejection and repeated entry. Individual questions and errors can be resolved by discussing them with the clinical team. In terms of data security, authority for raw data scanning will be restricted to the central project group level and only specified project personnel have authority to access the entire database.

Data analysis plan

Data processing and statistical analyses were performed using SAS V.9.3. Analysis of baseline data was conducted by age group to describe the disease status and basic socioeconomic characteristics of the patients with SLE. Normally distributed continuous data are expressed as mean±SD and non-normally distributed continuous data are expressed as the median (25th percentile, 75th percentile). A test for normality was performed by the Shapiro-Wilk test. Categorical variables are expressed as a constituent ratio or rate. The χ^2 or Fisher's exact test was performed to test comparability between patients in different subgroups. Baseline data were analysed cross-sectionally to determine the relationship between risk factors and CIMT/baPWV by using appropriate statistical methods (eg, linear regression analysis, analysis of covariance, logistic regression analysis), with adjustment for potential covariates, such as age and disease duration.

Follow-up data will be analysed longitudinally to calculate the change in CIMT/baPWV. The linear mixed effect model will be used to identify risk factors (traditional risk factors and lupus-specific factors) for progression of CTMT/baPWV.[19] We first performed univariate analysis to select statistically significant risk factors. We then combined these risk factors with clinical considerations to conduct multivariate analysis, with adjustment for potential covariates, such as age and disease duration. Statistical significance for each variable in the model will be analysed by the Wald test.

All p values are two-sided, with the significance level set at 0.1 for univariate analysis and 0.05 for other statistical tests. To improve translation and dissemination of the findings in this project into real clinical practice, the final study findings will be analysed and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology standards proposed by von Elm et al.[35]

Sample size estimation

This study was primarily designed to test the change in CIMT in 5 years of follow-up compared with baseline in patients with SLE. The sample size was calculated using PASS software V.11.0. The parameter assumption was based on results from previous studies that an increase in CIMT in patients with SLE is ~0.05–0.10 mm during 5 years.[14 15] We conservatively assumed that the mean progression in CIMT was 0.05 mm. We calculated that, with a SD of 0.20 mm, a type I error probability of 5% and a power of 90%, 171 participants will be required. Additionally, in considering the sample size to perform a linear mixed effect model, we calculated that, with a power of >90% to detect a 10% difference in CIMT between subgroups of independent variables, 400 participants will be required. Allowing for a 10% dropout rate, we estimated that the final sample size will be ~440 patients.

Patient and public involvement

Although participants were not directly involved in the design of the study, we consulted patients and their families about the feasibility of the investigation. Results will be disseminated to the participants through newsletters in the outpatient department or patient meeting.

Study status

The baseline stages of the study have been completed. Follow-up started on October 2018 and is anticipated to be completed by December 2021. A paper reporting the main results of the whole project will then be submitted for publication.

Ethics and dissemination

Informed consent was obtained from all participants according to the Declaration of Helsinki on Biomedical Research Involving Human Studies.

The results from the main study regarding the primary objectives and findings will be submitted to peer-reviewed journals, as well as presented at national and international conferences. All data will be managed confidentially according to guidelines and legislation. We will apply for a patent for the technical details of construction of the database.

DISCUSSION

The current study has some unique features, which are different from previous studies[13–15 17 18 24] First, to the best of our knowledge, most related previous studies were from Europe or North America, they comprised mostly Caucasian people, and some of the previous evidence was secondary analysis of data from placebo-controlled clinical trials with a short follow-up time. This study is the first prospective cohort to monitor CIMT in Chinese patients with SLE. Second, the sample size of this study is relatively large. This study will construct a Chinese population risk factor model and provide a robust parameter estimation about the progress of arteriosclerosis in patients with SLE in China. Furthermore, the data analysis attempts to compensate for individual factors that may affect progression of atherosclerosis. Our results may also help future development of guidelines and strategies for preventing arteriosclerosis in patients with SLE in China.

Subclinical atherosclerosis is an early finding and an important predictor of premature atherosclerosis and cardiovascular events in SLE.[12 36] To assess subclinical atherosclerosis, we used non-invasive imaging surrogate indices, such as CIMT as the primary outcome, which is the most widely used sensitive marker for the early stages of atherosclerosis, stroke and myocardial infarction.[37–39] With regard to consensus definitions, the criteria used to measure CIMT are based on the published consensus statement recommendations regarding sonographic criteria.

Establishing long-term preoperative trajectories is the most challenging aspect of any SLE cohort study. Most patients with SLE in PUMCH should return for an outpatient review every 3–6 months. Regular periodic review of patients will ensure follow-up data collection in the current hospital-based prospective study.

This study has the following challenges. First, this is not an inception cohort. A pilot study showed that the median disease duration was 1.91 years at baseline, and ~40% of patients were in their first year since SLE was diagnosed. A stratified disease duration will be considered in future sensitivity analysis. Second, all participants in this cohort study were recruited from a single centre of PUMCH. In this centre, ultrasound and laboratory testing are carried out in accordance with unified standards, and patients have good outpatient compliance of follow-up. Third, we did not enrol a control group. Progression of arteriosclerosis should be compared with baseline individually. Finally, most participants are from the north of China because of the geographical position of the hospital, and our results might only be representative of North China.

Despite these limitations, this protocol describes an approach to enable further testing of evidence concerning progression of arteriosclerosis in patients with SLE. We aim to identify clinically significant risk factors that can potentially guide management of patients with SLE. These results are expected to add further potential risk factors of SLE besides already known risk factors.

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