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Original Article

QRISK3-based analysis of cardiovascular risk factors in patients with long-term but well-controlled systemic lupus erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is a multisystem inflammatory disease of unknown etiology. Corticosteroids and immunosuppressive agents are the principal forms of treatment for this condition. While cardiovascular disease (CVD) is known to be a major cause of death in patients with SLE, there has been no improvement over the last few decades with regard to diagnosis, treatment, or prognosis. The QRISK3 algorithm is a new algorithm that includes SLE-related risk factors; this tool can predict the risk of CVD over a ten-year period. In this study, involving 180 patients, we compared the performance of the Framingham risk score, the recalibrated risk prediction SCORE, and QRISK3 for the assessment of CVD in patients with a long course of disease and low disease activity. Then, we used a more efficient algorithm, QRISK3 to identify the risk factors for CVD. This was a prospective and cross-sectional study involving 116 patients. All patients fulfilled the ACR criteria. The systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) is widely used to assess disease activity in SLE patients; patients with a SLEDAI-2K less than or equal to 4 are considered to be stable. Thus, we defined well-controlled patients as those with a SLEDAI-2K score less than or equal to 4. The dose of glucocorticoid (GC) that patients received was less or equal to 10 mg per day. We recorded and assessed a range of traditional risk factors, current treatments, comorbidities, data at the time of onset, and SLE-related evaluations. The QRISK3 score, and the relative risk (RR) that this score defined, were used to estimate the risk of CVD in patients with SLE. According to these relative risks, the patients were divided into low- (n=28), intermediate- (n=46), and high-relative risk (n=31) groups for subgroup analysis. Of the 116 patients enrolled, 105 were eligible to be assessed for the risk of CVD. By univariate analyses, the RR was significantly related with age at the time of enrolment (p<0.001), age at onset (p<0.001), resting heart rate (RHR) (p<0.001), present dose of GCs (p<0.001), present SLEDAI-2K (p=0.015), aerobic exercise (p<0.001), initial SLEDAI-2K (p<0.001), and initial dose of GCs (p=0.048). In the multiple linear regression model, the RR of CVD was significantly correlated with the initial SLEDAI-2K score (β=2.112, p<0.001), initial dose of GCs (β=-0.009, p=0.041), resting heart rate (β=0.241, p=0.003) and age at onset (β=-0.208, p=0.004). Pearson's correlation showed that RHR was significantly associated with aerobic exercise (r=-0.322, p=0.001). Subgroup analysis further identified a positive correlation between the history of nephritis, metabolic syndrome (MetS), aerobic exercise, present dose of GCs, and the RR of CVD. Patients with long-term but well-controlled SLE had a high relative risk of CVD and that this was associated with resting heart rate (P=0.003), history of lupus nephritis (P<0.001), initial SLEDAI-2K score (P<0.001), and metabolic syndrome (P=0.017). However, age at onset (P<0.001), use of hydroxychloroquine (P=0.30) and Mycophenolate mofetil (P=0.01), and the initial dose of glucocorticoid (P=0.049), were protective factors. Younger SLE patients had a significantly higher relative risk of CVD than older patients (p<0.001). QRISK3 detected more SLE patients at high risk of CVD when compared to the Framingham and recalibrate SCORE. To reduce the risk of CVD in SLE patients, measures should be taken both during the initial stages of disease and for long-term management.

Keywords: Systemic lupus erythematosus, cardiovascular disease, glucocorticoids, mycophenolate mofetil, hydroxychloroquine, resting heart rate

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease with heterogeneous clinical manifestations. However, the etiology behind this disease has yet to be elucidated. Most patients initially present with cutaneous lesions, hair loss, fatigue, and joint

pain [1]. The systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) is widely used to assess disease activity in SLE patients; patients with a SLEDAI-2K less than or equal to 4 are considered to be stable [2]. Cumulative damage in patients with SLE is often assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), which has been proven to be effective and accurate by most clinicians and researchers in long-term practice [3].

Cardiovascular disease (CVD) is one of the leading factors that contributes to high mortality in SLE patients [4]. Furthermore, the mortality rate of SLE patients with CVD has remained persistently high over the last few decades [5]. Although the etiology of CVD is not understood, it is believed that premature cardiac involvement involves a combination of traditional cardiovascular risks, immune disorders, and the adverse effects of glucocorticoid (GC) treatment [6-8]. However, a reduction in the dose of prednisone after stabilization of the disease does not appear to reduce the risk of CVD, and patients receiving a lower dose of prednisone have a higher risk of CVD (10.4 mg/day *versus* 18.1 mg/day) which may be related to the initial dose of prednisone [4]. Furthermore, those who have a longer mean duration of SLE are more likely to suffer from CVD than those with a shorter duration of SLE (9.0 years *versus* 4.4 years); it is possible that this may be related to the accumulation of GC and the sustained dysfunction of the endothelium. However, there may be other factors involved, including the adverse effects of the GC treatment and the disease itself, excessive focus on disease activity in SLE patients during the process of remission induction and long-term treatment maintenance, inadequate assessment of CVD risk, and the lack of further interventions. However, the risk factors that are associated with CVD in long-term patients who are well-controlled and receiving very low doses of prednisolone or no prednisone, are uncertain.

There are several risk algorithms used to predict CVD over a 10-year period including the Framingham risk score, the QRISK3, and the recalibrated SCORE prediction model. The Framingham risk score [9] and the recalibrated SCORE prediction model [10] are two widely used tools that provide estimates of the risk of developing CVD over the next decade. The QRISK3 is another algorithm that uses specific items in addition to traditional factors to predict the risk of CVD. However, the efficiencies of these models differ significantly because each model is based on different data and algorithms. The QRISK model has been used in the UK to evaluate the 10-year CVD risk since 2007; following a 10-year update, the QRISK3 algorithms emerged in 2017 [11]. The QRISK3 score performs better for detecting the risk of CV over the next 10 years in patients with SLE than the QRISK2 because it considers eight different risk factors, including SLE, steroid use, and antihypertensive treatment [11-13]. These additional risk factors in the QRISK3 are all prevalent in the long-term management of SLE and may be key to the development of cardiovascular disease in SLE patients. However, almost none of the other predictive models take these risk factors into account. To some extent, the QRISK3 is more suitable for patients with SLE.

In this study, we compared the efficacy of the three different assessment methods in patients with SLE. Then, we selected the most effective model to assess the factors associated with cardiovascular risk in SLE patients with a long disease duration (more than 5 years), low levels of disease activity (SLEDAI-2K $\leq$ 4), and receiving a low dose of prednisone (less than 10 mg per day). We also introduced resting heart rate (RHR), prednisone dose, disease activity at onset, metabolic syndrome (MetS), and aerobic exercise, to investigate the relationship between features of the clinical disease and the risk of CVD.

Materials and methods

Study subjects

This was a cross-sectional study that recruited patients who fulfilled the criteria for SLE published by the American College of Rheumatology (1997) [14]. All patients were over 25 years old and had been diagnosed with SLE for at least five years. The present SLEDAI-2K needed to be no more than 4, as evaluated by an experienced rheumatologist. We evaluated all

patients with SDI at the time of enrollment. Patients were excluded for the following reasons: (1) they were taking medicine that affected the levels of glucose or lipid in the blood; (2) their medical records were missing information that was relevant to disease onset; (3) there was any evidence of other heart diseases and other autoimmune diseases; (4) they had already had a CV event; and (5) the patient was pregnant. Current treatments were recorded including GCs and immunosuppressants which should be used for at least a year.

We evaluated the enrolled patients by way of the Framingham risk score, the QRISK3, and the recalibrated SCORE, respectively. The data required for these assessments were obtained through physical examination, medical records, and questionnaires at enrollment. Based on different algorithms and data sources, the three models have different definitions of risk classification. The Framingham risk score (adapted according to the National Institute for Health and Care Excellence guidelines) [15] and the QRISK3 classify patients with scores of more than 10% as high risk. The QRISK3 also provides scores for healthy people with the same age, gender, and ethnicity. However, the recalibrated SCORE stratifies patients into a high-risk group if the score is >5%, with >10% being very high risk.

After comparison, we finally selected the QRISK3 score to assess the factors associated with cardiovascular risk in our patients. To eliminate confounding data related to gender and age, we used the relative risk (RR) parameter, as calculated by the QRISK3, to compare the cardiovascular risk factors. According to the RRs, patients were divided into three different groups: a low relative risk group (0-2.5; group 1), an intermediate relative risk group (2.5-10; group 2), and high relative risk group (>10, group 3) for subgroup analysis. Clinical manifestations and laboratory data were collected from medical records retained by the First Affiliated Hospital of Zhengzhou University.

Demographic data were analyzed along with the duration of disease; resting heart rate (RHR); cardiac symptoms, including angina and precordial discomfort; osteonecrosis of the femoral head (ONFH); Raynaud's phenomenon (RP); pulmonary arterial hypertension (PAH); lupus nephritis (LN), and medical history. We also recorded the current dose of GC, and the dose of GC administered at onset, the SLEDAI-2K and SDI score, the mean daily aerobic exercise duration, and information required by the QRISK3. The QRISK3 score and relative risk (RR) were determined by online resources available at https://qrisk.org/three/. Laboratory evaluations included routine blood tests, urinalysis, liver, and kidney function, fasting plasma glucose and lipid profiles, serum complement (C3 and C4), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). RHR measurement complied with international recommendations published previously [16]. Metabolic syndrome (MetS) was diagnosed in accordance with The National Cholesterol Education Program Adult Treatment Panel III (NCEP) [17]. All participants provided informed consent and the study was approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University (Ethical approval number: 2020-KY-447).

Statistical analysis

Categorical variables were described as numbers and percentages while continuous variables were expressed as mean ± standard deviation (SD) or median and 25^{th}-75^{th} percentiles depending on variable distribution. The T-test and the non-parametric Wilcoxon test were used to detect differences in patient risk assessment according to the three different models. The multiple linear regression model was used to evaluate associations between the relative risk calculated by QRISK3 and potential influencing factors. Comparisons between the three different groups were performed by the Kruskal-Wallis test. Pairwise comparisons were used to evaluate negative results arising from the linear regression model. We also adjusted *p* values for multiple comparisons by Bonferroni correction. For categorical variables, we applied the Chi-squared or Fisher's exact test, as appropriate. The continuous correction of the Chi-squared test was used when necessary. Pearson's test was performed to evaluate correlations between different variables. All data were analyzed with the SPSS statistical software package (version 26.0) and *p* values <0.05 were considered significant.

Table 1. Epidemiological and clinical characteristics of patients at time of enrollment

Patients at enrollment time	161 (100)
Female (%)	148 (91.9)
Age at enrolment (yrs)	37 (32-48)
Age at onset (yrs)	27 (21.5-37)
Disease duration (yrs)	10 (7-13)
Systolic pressure (mmHg)	120 (108-130)
RHR (bpm)	78 (72.5-87)
Aerobic exercise (min/day)	0 (0-15)
Smoker (%)	2 (1.2)
Metabolic syndrome (%)	38 (23.6)
Present SLEDAI-2K	0 (0-1)
Initial SLEDAI-2K	4 (2-7)
Initial GC (mg/day)	60 (42.5-80)
QRISK3 score	3.3 (1.4-6.2)
-Patients with high risk (%)	22 (16.7)
Framingham risk score	2.4 (3.9-1.4)
-Patients with high risk (%)	11 (6.8%)
Recalibrated SCORE	2.9 (3.5-1.2)
-Patients with high risk (%)	13 (8.1%)
Clinical manifestations	
Angina (%)	12 (7.5)
Precordial discomfort (%)	29 (18)
ONFH (%)	28 (17.4)
RP (%)	64 (39.8)
PAH (%)	12 (7.5)
LN (%)	60 (37.3)
Laboratory findings	
Total cholesterol (mmol/L)	3.9 (3.4-4.8)
Triglyceride (mmol/L)	1.19 (0.9-1.7)
HDL-C (mmol/L)	1.25 (0.39)
LDL-C (mmol/L)	2.2 (1.8-2.8)
WBC ($\times 10^9$/L)	4 (3.6-4.3)
RBC ($\times 10^{12}$/L)	4.8 (3.8-6.2)
PLT ($\times 10^9$/L)	199 (143.5-248.5)
CRP (g/L)	1.9 (1-3.1)
ESR (mm/h)	16 (9-34.9)
C3 (g/L)	0.9 (0.7)
C4 (g/L)	0.2 (0.1-0.2)
IgA (g/L)	2.8 (3.6-2.1)
IgM (g/L)	0.9 (0.5-1.3)
IgG (g/L)	12.9 (10.6-12.9)
UA (umol/L)	274 (219.3-325.8)
Immunosuppressants for Induction of remission	
-MMF (%)	65 (49.4)
-CTX (%)	83 (51.6)
-Other (%)	13 (8.1)
Ongoing therapy	
GC (%)	110 (68.3)

Results

Demographic information and clinical features

One hundred and eighty patients were enrolled in this study. Nineteen patients (10.6%) were excluded from the estimation of CVD risk because SLE-related information at the time of onset was unavailable. Of the remaining 161 patients, 148 (91.9%) were female and 13 (8.1%) were male. Overall, the mean duration of disease ranged from 5 to 27 years while patient age ranged from 25 to 72 years. The median RHR was 78 (72.5-87) bpm. At the time of onset, the media SLEDAI-2K was 0 (0-1) and all patients were treated with GC at a mean dose of 1.3 (0-5) mg per day. In total, 141 (87.6%) patients accepted hydroxychloroquine (HCQ) at the time of enrolment, all of whom had been treated for at least five years. Clinical characteristics, ongoing therapy, and laboratory findings are presented in **Table 1**.

The numbers of patients in group 1, group 2, and group 3, were 51 (31.7%), 56 (46.3%), and 54 (33.5%), respectively. The age at onset in group 1 was significantly higher than that in group 2 ($P< 0.001$) and group 3 ($P<0.001$). **Table 2** shows the distribution of the data by group.

Comparison of performance of the three different prediction models

The number of patients defined as having a high cardiovascular risk by the Framingham risk score, the recalibrated SCORE, and the QRISK3 was 6 (4.3%), 6 (5.6%), and 25 (17.6%), respectively (**Figure 1**). All patients identified as high CVD risk by the Framingham and recalibrated SCORE were also identified by the QRISK3 algorithm. The median risk score showed by the

-Daily intake (g)	1.3 (0-5)
HCQ (%)	141 (87.6)
-Daily intake (g)	0.3 (0.2-0.3)
Other immunosuppressants	
-MMF (%)	46 (28.6)
-AZA (%)	21 (13)
-MTX (%)	47 (29.2)
-Thalidomide (%)	3 (1.9)
-Tacrolimus (%)	11 (6.8)
-Leflunomide (%)	16 (9.9)
-CTX (%)	5 (3.1)
-Belimumab (%)	2 (1.2)

Data are presented as mean ± standard deviation (SD) or median and 25th-75th percentiles, N.S.: non-significant. RHR: rest heart rate; GC: glucocorticoid; ONFH: osteonecrosis of the femoral head; RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; LN: lupus nephritis; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; WBC: white blood cell; RBC: red blood cell; PLT: blood platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; C3: complement C3; C4: complement C4; UA: uric Acid; HCQ: hydroxychloroquine; CQ: chloroquine; MMF: Mycophenolate Mofetil; AZA: azathioprine; MTX: methotrexate; CTX: cyclophosphamide.

Framingham risk score, the recalibrated SCORE, and the QRISK3 was 2.4% (3.9-1.4), 2.9% (3.5-1.2), and 3.3% (6.2-1.4), respectively. The nonparametric Wilcoxon test detected statistically significant differences between the ten-year CVD risks derived from the three models for the same patients, and the score calculated by the QRISK3 was greater than the other two algorithms (P<0.001).

Correlations between QRISK3-defined relative risk and risk factors in SLE patients

Considering the entire cohort of patients, the RR ranged from 1 to 66 (median: 4.2). To explore impact factors, we carried out linear regression analysis. Regression analysis results are presented in **Table 3**. Univariate analyses showed that the RR was significantly associated with age at the time of enrollment (P<0.001), the age at onset (P<0.001), the RHR (P<0.001), the present dose of GCs (P=0.021), aerobic exercise (P<0.001), the initial SLEDAI-2K score (P<0.001), SDI score (P=0.001), and the initial dose of GCs (P<0.001). Multiple linear regression analysis was then performed with the stepwise method and adjusted by age at the time of enrolment and onset, the SDI score, the present dose of GCs, aerobic exercise, the initial SLEDAI-2K, the initial dose of GCs, the duration of disease, inflammatory biomarkers, and blood lipid profile. In summary, the R^2 for the multiple linear regression model to predict RR was 59.5% (57.9% for adjusted R^2). The initial SLEDAI-2K score and RHR were positively correlated with the RR, whereas the initial GC dose, dose of HCQ and Mycophenolate Mofetil (MMF), and the age at onset were negatively correlated with the RR. The initial SLEDAI-2K score (β=0.50, P< 0.001) was the strongest predictor; this was followed by age at onset (β=-0.22, P<0.001), RHR (β=0.17, P=0.003), present dose of MMF (β=-0.14, P=0.01) and HCQ (β=-0.11, P=0.03), and the initial dose of GC (β=-0.11, P= 0.049). Further Pearson correlation tests were also performed; these showed that RHR was significantly associated with aerobic exercise (r=-0.322, P= 0.001). Moreover, dyslipidemia was observed in 23 of the 60 LN patients (38.3%) and 49 of the 101 patients without LN (48.5%); there was no significant difference in this respect.

Comparison of variables between groups with low, intermediate, and high relative risk

Figure 2 shows comparisons between the three different groups. The Bonferroni post hoc test was used for post hoc analysis. Data showed that the present GC dose was significantly higher in group 3 than in group 1 (P= 0.002) and in group 2 (P=0.006). The mean time spent performing aerobic exercise per day in group 3 was significantly lower than that in group 1 (P<0.001) and group 2 (P<0.001). Continuous correction of the Chi-squared test showed that LN and MetS were significantly more common in group 3 than in group 1 (P<0.001; P=0.017) and group 2 (P<0.001; P=0.002), although there was no significant difference between group 1 and group 2. Finally, we failed to identify any form of statistical significance among the three groups with regards to laboratory data, metabolic syndrome, the history of precordial pain, precordial discomfort, ONFH, RP, or PAH.

Table 2. Comparison of clinical variables between SLE patients in different groups

	Group 1	Group 2	Group 3	p
Number of patients (%)	51 (31.7)	56 (46.3)	54 (33.5)	
Age at enrolment (yrs)	50 (34-57)	36 (32-47)	33.5 (30.8-39)	<0.001
Age at onset (yrs)	37 (26-44)	27 (22.3-35.8)	23 (18-27.3)	<0.001
Disease duration (yrs)	9 (7-13)	10 (7-12.8)	11 (8-15)	N.S.
Systolic pressure (mmHg)	110 (101-125)	119 (108.5-125.8)	128 (117.8-132.2)	<0.001
RHR (bpm)	76 (69-79)	76 (72-85)	85.5 (78-90.8)	<0.001
Aerobic exercise (min/day)	15 (0-20)	0 (0-10)	0 (0-0)	<0.001
Smoker (%)	1 (0.6)	1 (0.6)	0 (0)	N.S.
Metabolic syndrome (%)	9 (5.5)	7 (4.3)	22 (13.7)	0.001
Present SLEDAI-2K	0 (0-1)	0 (0-0.8)	0 (0-1)	N.S.
Initial SLEDAI-2K	2 (1-4)	3 (2-4)	7 (6-8)	<0.001
Initial GC (mg/day)	60 (50-500)	60 (50-75)	45 (30-60)	<0.001
QRISK3 score	2.3 (0.7-5.2)	1.8 (1-3.5)	5.4 (4.3-8.8)	<0.001
Relative risk	1.7 (1.4-2.2)	4 (2.7-6.5)	20 (16.1-24.3)	<0.001
Clinical manifestations				
Angina (%)	2 (1.2)	6 (3.7)	4 (2.5)	N.S.
Precordial discomfort (%)	10 (6.2)	9 (5.6)	10 (6.2)	N.S.
ONFH (%)	6 (3.7)	10 (6.2)	12 (7.5)	N.S.
RP (%)	20 (12.4)	22 (13.7)	22 (13.7)	N.S.
PAH (%)	2 (1.2)	4 (2.5)	6 (3.7)	N.S.
LN (%)	12 (7.5)	12 (7.5)	36 (22.4)	<0.001
Laboratory findings				
Total cholesterol (mmol/L)	3.8 (3.3-4.4)	4.0 (3.5-4.8)	4.2 (3.3-5.0)	N.S.
Triglyceride (mmol/L)	1.1 (0.9-1.5)	1.1 (0.9-1.6)	1.3 (0.9-2.0)	N.S.
HDL-C (mmol/L)	1.2 (0.4)	1.3 (0.3)	1.3 (0.4)	N.S.
LDL-C (mmol/L)	2.0 (1.8-2.6)	2.2 (1.8-2.7)	2.2 (1.8-3.0)	N.S.
WBC ($\times 10^9$/L)	4.2 (3.3-5.8)	4.7 (3.6-6.1)	5.4 (4.5-7.0)	0.007
RBC ($\times 10^{12}$/L)	3.9 (3.5-4)	4.0 (3.7-4.4)	4.0 (3.5-4.3)	N.S.
PLT ($\times 10^9$/L)	178 (125-232)	199 (162.5-254.5)	206.5 (149-255)	N.S.
CRP (g/L)	2.0 (1-6.4)	22.1 (1.3-3.1)	1.5 (1-3.1)	N.S.
ESR (mm/h)	16 (8.8-31.4)	14 (9-32)	19 (7-41.8)	N.S.
C3 (g/L)	0.8 (0.3)	0.9 (0.3)	0.9 (0.29)	N.S.
C4 (g/L)	0.2 (0.1-0.2)	0.2 (0.1-0.2)	0.2 (0.1-0.2)	N.S.
IgA (g/L)	3.1 (2.3-4.5)	2.9 (2.2-3.5)	2.6 (2-3.35)	N.S.
IgM (g/L)	0.8 (0.6-1.1)	0.9 (0.5-1.3)	1 (0.5-1.4)	N.S.
IgG (g/L)	13.3 (10.7-17.1)	14.5 (10.8-17.1)	11.8 (10.2-15.7)	N.S.
UA (umol/L)	269 (219-322)	281 (209-325)	284 (221.5-333)	N.S.
Immunosuppressants for Induction of remission				
-MMF (%)	22 (13.7)	20 (12.4)	23 (14.3)	N.S.
-CTX (%)	32 (19.9)	27 (18.6)	24 (14.9)	N.S.
-Other (%)	7 (4.3)	3 (1.9)	3 (1.9)	N.S.
Ongoing therapy				
Daily intake of GC (mg)	0.8 (0-2.5)	1.3 (0-2.5)	2.5 (1.3-5)	0.001
Daily intake of HCQ (g)	0.3 (0-0.4)	0.3 (0.2-0.4)	0.2 (0.2-0.3)	N.S.
Other immunosuppressants				
-MMF (%)	2 (1.2)	7 (4.3)	10 (6.2)	N.S.
-AZA (%)	6 (3.7)	5 (3.1)	10 (6.2)	N.S.
-MTX (%)	16 (9.9)	17 (10.6)	14 (8.7)	N.S.

-Thalidomide (%)	1 (0.6)	2 (1.2)	0 (0)	N.S.
-Tacrolimus (%)	2 (1.2)	2 (1.2)	7 (4.3)	N.S.
-Leflunomide (%)	2 (1.2)	4 (2.5)	10 (6.2)	N.S.
-CTX (%)	1 (0.6)	1 (0.6)	3 (1.9)	N.S.
-Belimumab (%)	1 (0.6)	1 (0.6)	0 (0)	N.S.

Data are presented as mean ± standard deviation (SD) or median and 25th-75th percentiles, N.S.: non-significant. RHR: rest heart rate; GC: glucocorticoid; ONFH: osteonecrosis of the femoral head; RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; LN: lupus nephritis; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; WBC: white blood cell; RBC: red blood cell; PLT: blood platelet; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; C3: complement C3; C4: complement C4; UA: uric Acid; HCQ: hydroxychloroquine; CQ: chloroquine; MMF: Mycophenolate Mofetil; AZA: azathioprine; MTX: methotrexate; CTX: cyclophosphamide.

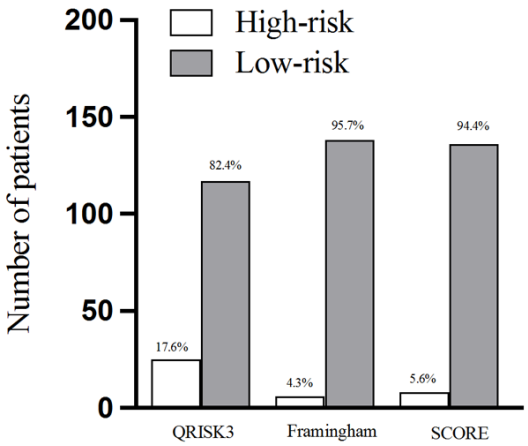

Figure 1. Numbers and percentages of 142 patients in the high-risk and low-risk groups identified by the three different models.

Discussion

Although there is an increasing number of drugs available to treat SLE, the primary form of treatment is still GC. However, this form of treatment could lead to several complications, including CVD. The prevalence of ischemic heart disease in SLE patients is approximately 3.8-16%; this is 10 times higher than in the general population [18]. It has been known for some time now that mortality of SLE patients is bimodal in that mortality in the early stages tends to be associated with SLE complications while in the late stages of disease, cardiovascular factors are more prevalent [4]. However, despite this bimodal mortality association, the all-cause mortality rate for SLE has shown a steady trend for reduction over recent years, and there has been no significant change in the rate of cardiovascular mortality [5, 19].

In this study, we showed that the relative risk of CVD in well-controlled patients with a long disease duration is higher if they have a higher initial SLEDAI-2K score. It appears that disease activity can influence the development of cardiovascular disease. This might be explained by a recent study that found that the SLEDAI-2K score was associated with antibodies to oxidized low density lipoprotein (anti-oxLDL) which is known to be able to stimulate LDL to enter the endothelial wall and cause further damage to the endothelial cells, thus accelerating atherosclerosis [20]. Similarly, high levels of disease activity could also lead to reduced levels of lipoprotein lipase (LPL) activity, thus causing increased levels of apolipoprotein E (ApoE) and an increased risk of CVD [20]. In addition, high SLEDAI-2K scores have also been correlated with calcification of the aorta, abnormal left heart function, PAH, arrhythmia, and other cardiovascular diseases, thus providing evidence of cardiovascular damage caused by disease activation [21-23]. Interestingly, we found that there was no significant correlation between present SLEDAI-2K scores, disease duration, and the relative risk of CVD in SLE patients who had remained stable over the long-term. However, damage to other organs caused by SLE may also increase the risk of cardiovascular disease. SDI is a widely used clinical tool to assess organ damage in patients with SLE. Higher SDI scores indicate more severe systemic damage. As shown in our study, patients with high SDI are at high risk of cardiovascular disease. In this way, disease duration does not increase the risk of cardiovascular disease, and long-term effective management can reduce the incidence of cardiovascular events. Cardiovascular lesions might exist at the beginning of the disease; this damage is irreversible, even if the disease stabilizes after long-term treatment. Our current data appear to support this because we identified significant differenc-

Table 3. Variables associated with the relative risk of CVD as determined by linear regression analysis

Independent Variable	Relative risk of CVD			
	Univariable analysis		Multivariable analysis	
	β coefficient (IC 95%)	P	β coefficient (IC 95%)	P
Initial SLEDAI-2K	0.68 (1.91 to 2.67)	<0.001	0.50 (1.276 to 2.05)	<0.001
Initial GCs (mg/day)	-0.24 (-0.017 to -0.004)	0.002	-0.11 (-0.009 to -0.0)	0.049
Resting heart rate (bpm)	0.49 (0.36 to 0.63)	<0.001	0.17 (0.06 to 0.29)	0.003
Age at onset (yrs)	-0.42 (-0.56 to -0.28)	<0.001	-0.22 (-0.33 to -0.11)	<0.001
HCQ (g/day)	-0.19 (-29.21 to -2.96)	0.017	-0.11 (-18.4 to -0.92)	0.3
MMF (maintenance) (g/day)	-0.23 (-8.81 to -1.70)	0.004	-0.14 (-5.62 to -0.78)	0.01
Age at enrolment (yrs)	-0.35 (-0.47 to -0.20)	<0.001	Not significant to the mode	
Aerobic exercise (min/day)	-0.35 (-0.43 to -0.17)	<0.001	Not significant to the mode	
SDI	-0.27 (1.14 to 4.16)	0.001	Not significant to the mode	
Present GCs (mg/day)	0.18 (0.13 to 1.53)	0.021	Not significant to the mode	

Dependent variable: Relative risk of CVD. Multiple regression analysis was performed using a stepwise method. Model was adjusted by SDI score, age at time of enrollment and onset, aerobic exercise, initial SLEDAI-2K, disease duration, inflammatory biomarkers and blood lipid profile, initial and present glucocorticoid doses expressed as equivalent of prednisone doses (GCs), and initial and present SLEDAI-2K and inflammatory biomarkers. R^2 for multivariable model was 0.595. Adjusted R^2 for multivariable model was 0.579. Covariates included in this analysis were those variables with statistical significance in the univariate analysis or were considered with biological plausibility to CVD risks in SLE patients.

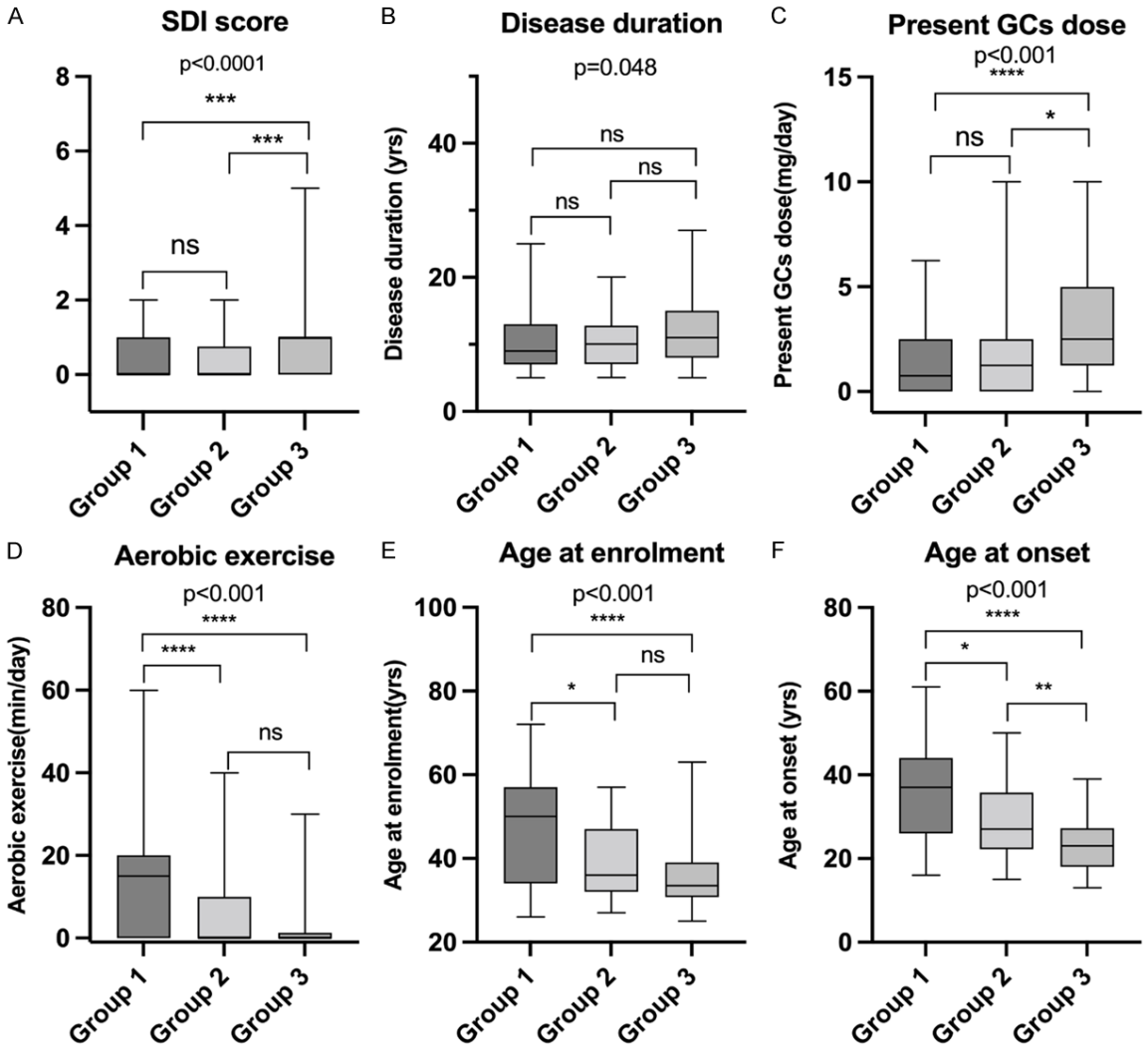

Figure 2. Comparison of SDI score, disease duration, present GC dose, aerobic exercise, age at enrollment and age at onset in low-, intermediate-, and high-relative risk groups (group 1, group 2, and group 3, respectively). Comparisons between quantitative variables were performed with the Kruskal-Wallis test. *P* values for multiple comparisons were adjusted by Bonferroni correction. ns: $P \geq 0.05$. *: $P<0.05$, **: $P \leq 0.01$, ***: $P \leq 0.001$; ****: $P \leq 0.0001$.

es in the initial SLEDAI-2K scores between the three subgroups. Therefore, in order to reduce the risk of CVD caused by SLE, it is important that disease activity should be reduced rapidly and timely at the beginning of the disease. It is then important to maintain disease stability and avoid vital organ damage over the long-term.

GC still plays an important role in the treatment of SLE. However, the relationship between GC and CVD has been controversial for some time. On the one hand, the administration of GC may directly lead to atherosclerosis. On the other hand, however, GC can indirectly prevent a range of complications, including CVD, by rapidly and effectively controlling the systemic inflammatory state [24]. Petri et al. reported that a high dose of GC represented an independent risk factor for CVD and was related to hyperlipidemia, hyperglycemia, hypertension, and obesity [25]. Another study indicated that a cumulative dosage and/or a longer duration of corticosteroid therapy may contribute to atherosclerosis in patients with SLE [26]. Moreover, the use of corticosteroids could promote carotid intima-media thickness (cIMT) progression [27] and also increase the occurrence of myocardial infarction (MI), angina, and sudden cardiac death [28, 29]. However, the increased incidence of coronary heart disease (CHD) and MI in SLE patients cannot be fully explained by traditional risk factors such as smoking, blood pressure, and cholesterol; furthermore, lupus itself may cause atherosclerosis due to the persistence of chronic inflammation [30, 31]. In a previous case-control study, SLE patients with plaques were given lower doses of GC; on the basis of their results, the authors proposed that aggressive therapy involving corticosteroids could act as a protective factor against atherosclerosis [31]. Therefore, it is possible that the anti-inflammatory effects of GC may indirectly reduce the risk of CVD [24]. Similarly, the present study found that a high dose of GC was efficacious; this finding suggests that a high dose given at disease onset could rapidly control abnormal activation of the immune system and therefore reduce the relative risk of CVD, regardless of the severity of the disease. Nevertheless, the dose of GC should be reduced as much as possible to minimize the accumulation and duration of GC administration during the maintenance period, especially in patients with a relative risk that is more than 10-fold higher than normal.

In addition to GC, we found that MMF and HCQ can also reduce the risk of cardiovascular disease. In a recent 12-month intention-to-treat analysis, MMF did not perform better than cyclophosphamide (CYC) and azathioprine (AZA) in reducing the risk of CVD [32]. However, we found that although the cardiovascular protective effect of MMF during the induction of remission was modest, long-term use during the maintenance phase may convey benefit. In fact, many studies have shown the benefits of MMF in preventing atherosclerosis in both human subjects and lupus-susceptible murine models [32]. The administration of HCQ showed a favorable effect on the serum concentrations of cholesterol, lipoproteins, and triglycerides [33], which may lead to a decreased incidence of CVD events. As with previous studies, we found that there was significant correlation between HCQ dose and a reduced relative risk of CVD. Our study also suggested that patients treated with HCQ showed lower lipid profiles than others, although there was no significant difference with this respect.

RHR is a reliable indicator for autonomic function and has been proven to be relevant to arterial stiffness and inflammatory biomarkers in the general population, including high-sensitivity C-reactive protein and interleukin-6 [34, 35]. A recent study implied that a high RHR may reflect systemic low grade-inflammation and increased pulse wave velocity in female patients with SLE [36]. Although our study did not show a relationship between inflammation and RHR because of the fact that the disease status in our patients was well-controlled, our results did concur with previous research in that RHR could be reduced by exercise and was a protective factor for CVD [37]. Consequently, regular and long-term aerobic exercise can

reduce the risk of CVD to some extent, especially for patients with a 10-fold relative risk, as shown by our intergroup analysis.

Lupus nephritis (LN) is one of the organ and life-threatening complications of SLE and is characterized by immune damage to the kidney that is caused by a number of different pathological types. The pathogenesis of LN is related to immune complex formation, immune cells, cytokines, and other immune abnormalities. The main clinical manifestations of LN are hematuria, proteinuria, and renal dysfunction. However, the specific effects of LN on cardiovascular risk have yet to be determined. The current consensus of opinion is that LN affects lipid metabolism and thus increases the risk of early CVD and that proteinuria is also associated with this increased risk [27, 38, 39]. Nevertheless, in a previous study, Manzi et al. found no correlation between renal disease and CVD [40]. In contrast to many other studies, although we found that LN was associated with an increased risk of CVD in the present study, there was no significant difference in lipid profile between patients with and without nephritis. This might be because all of our patients were negative for proteinuria at baseline or that there are additional pathways involved that have yet to be identified with regards to lipids and urinary proteins.

Metabolic syndrome involves a range of cardiovascular risk factors, including obesity, hyperlipidemia, and hyperglycemia. However, MetS is also an independent risk factor for cardiovascular disease [41]. A previous meta-analysis found that subjects with MetS were nearly twice as likely to develop cardiovascular disease as healthy people [42]. In addition, some studies have found that subjects with MetS have a higher all-cause mortality rate and a much higher likelihood of dying from CVD [43, 44]. Currently, the global incidence of metabolic syndrome is between 10% and 84% [45]. However, MetS is known to be more prevalent in patients with SLE [46, 47]. It is possible that this may be due to chronic inflammation and long-term glucocorticoid therapy [47]. Similar to previous studies, patients with MetS in our study had higher levels of CRP; however, there were no differences in the dose of glucocorticoids being administered. This may have been because the dose of glucocorticoids was strictly controlled when patients were first enrolled [46, 48, 49]. Furthermore, MetS, as a strong predictor for SLE, is associated with an increased risk of cardiovascular events in patients [50]. In the present study, we also found that MetS was more common in patients with a relative risk of CVD that was greater than 10. A number of diagnostic factors are known to be related to SLE, including obesity, dyslipidemia, and abnormal blood glucose levels. Previous research has suggested that the cause of MetS may be related to the levels of leptin [51]. This adipokine plays an important role in the pathogenesis of SLE by activating immune cells, but is also known to inhibit appetite, generate energy, and regulate lipid metabolism, by activating the Janus kinase (JAK) pathway/signal transducer and the activator of transcription (STAT) pathway [52]. It is possible that the reduction of leptin production might represent a novel treatment for SLE and metabolic syndrome; further research is required to confirm this possibility. For now, however, the main approaches to treat MetS and further reduce the risk of CVD include weight control, dietary modification, lipid regulation with statins, and the control of inflammation [46, 53].

In spite of the fact that 72 of our current patients developed dyslipidemia, only five of our patients received statins. These findings were in line with another recent study that demonstrated that the use of statins was rare in patients with SLE who were eligible for statin therapy [18]. The effect of statin intervention on hyperlipidemia in SLE is often underestimated. In fact, statins not only improve blood lipid levels and cardiovascular prognosis in SLE patients but can also exert pleiotropic immunomodulatory effects. Statins exert several effects with regards to modulation of the immune system; for example, by inhibiting the Rho-associated coiled-coil-containing protein kinase (ROCK) pathway [54], reversing lipid raft-associated signaling abnormalities [55], reducing the plasma levels of interferon-regulated chemokine CXCL9 [56] and the production of IL-6 and IL-10 [57]. Therefore, the immunemodulatory effects of statins have largely been underestimated in the past. However, a recent randomized controlled trial (RCT) showed that SLE patients with dyslipidemia and other risk factors for traditional CVD are recommended to use statins routinely while SLE patients that do

not have these additional complications should use statins with caution [58]. The use of statins in SLE patients has largely been neglected. It is likely that this is due to excessive focus on disease activity and the lack of effective assessment tools [18]. Currently, there is no clinically available tool to evaluate the risks of CVD in patients with SLE, even though SLE has been shown to be an independent risk factor for CVD. However, significant progress has now been made in this respect because SLE and regular use of steroid have now been included as an evaluation criterion in the QRISK3 [11]; indeed, this ats than other algorithms [12, 13]. Our study also found tlgorithm has been shown to detect more high-risk patienhat the QRISK3 could detect more patients at high risk of CVD than the Framingham risk score and the recalibrated SCORE. However, more data are needed to fully verify the validity of the QRISK3 with this respect.

The abnormal activation of the immune system and the excessive release of inflammatory cytokines in patients with high disease activity are the most important factors underlying an increased relative risk of CVD [59]. Interestingly, we found that patients under 36 years of age in our study had higher relative risks, although patients older than 49 years had the highest absolute risk for cardiovascular disease. These findings were similar to those described in a previous study [60]. We hypothesized that these findings might be associated with the age of onset, as the onset of disease occurred later in the older patients; previous research has shown that late-onset SLE has a lower disease activity and a more favorable prognosis [61]. Similarly, the younger patients in our study had higher SLEDAI-2K scores than the older patients, although this difference was not statistically significant. The prevention of CVD in young patients is particularly important and should therefore be emphasized in future research.

Our study has several limitations. First, due to the long duration of disease, it was difficult to accurately acquire data relating to the accumulation of GC use; consequently, it was not possible to investigate the effect of GC administration on the risk of CVD. Second, our study used a cross-sectional design relying on a predictive algorithm rather than actual cardiovascular events or early lesions to evaluate CVD risks. Due to these limitations, the findings described in this study should be interpreted with caution and verified in future validation studies.

Conclusion

The QRISK3 performed better than the Framingham and ACC/AHA with regards to the detection of patients with long-term but well-controlled SLE at high-risk of developing CVD over the next 10 years. To reduce the risk of CVD in these patients, it is particularly important to administer GCs at the time of onset to reduce disease activity and carry out effective long-term management, especially in patients under 36 years of age with nephritis and MetS. Long-term treatment with HCQ, the use of MMF during the maintenance period, and regular aerobic exercise, may reduce the risk of CVD in this population.

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Disclosure of conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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