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ORIGINAL RESEARCH

Frailty is independently associated with subclinical cardiovascular disease in patients with systemic lupus erythematosus

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ABSTRACT

Objectives Cardiovascular disease is a leading cause of mortality in systemic lupus erythematosus (SLE). Frailty has been associated with an increased cardiovascular disease risk (CVR) in the general population. We aimed to examine the association between frailty and subclinical cardiovascular disease in patients with SLE.

Methods In this cross-sectional study, we included all patients with SLE who underwent carotid/femoral artery ultrasound in our unit between 2016 and 2018. Clinical and laboratory data were collected at the time of ultrasound testing. Frailty was measured using the Systemic Lupus International Collaborating Clinics-Frailty Index (SLICC-FI). CVR (low, moderate, high, very high) was evaluated by the Systematic COronary Risk Evaluation (SCORE) model. Determinants of atherosclerotic plaque presence were assessed by logistic regression analyses, adjusting for potential confounders.

Results 202 patients were included in the study. Atherosclerotic plaques (20.8% carotid, 17.3% femoral) were observed in 52/202 (25.7%) patients (89.1% women, mean (±SD) age 46.7±12.6). Median (IQR) SLICC-FI was 0.08 (0.04–0.10). 39 (19.3%) patients were classified as robust, 91 (45%) as relatively less fit, 59 (29.2%) as least fit and 13 (6.4%) as frail. In univariate analysis, plaque presence was significantly associated with age, disease duration, smoking, hypertension, systolic blood pressure, dyslipidaemia, SCORE, CVR class and SLICC-FI. CVR class (OR 5.16, p=0.000) and SLICC-FI (OR 1.34, p=0.03 per 0.05 point increase) remained significant in multivariate analysis after adjustment for traditional and disease-related CVR factors.

Conclusions SLICC-FI is independently associated with plaque presence. Further studies are warranted to determine whether frailty-specific interventions can reduce CVR in patients with SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systemic lupus erythematosus (SLE) is associated with an increased risk of cardiovascular disease compared with the general population.
⇒ New evidence links frailty to cardiovascular morbidity and mortality, but no data exist on the association between frailty and cardiovascular disease in patients with rheumatic disorders, including SLE.

WHAT THIS STUDY ADDS

⇒ This is the first study to examine the relationship between frailty and subclinical cardiovascular disease in a rheumatic disorder.
⇒ Using the validated Systemic Lupus International Collaborating Clinics (SLICC)-Frailty Index, we found that frailty in patients with SLE is independently associated with carotid and femoral artery atherosclerotic plaques.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The SLICC-Frailty Index may help to assess cardiovascular risk in patients with SLE, and modify earlier disease-related and traditional cardiovascular risk factors. Further research is required to ascertain if interventions targeting pre-frailty and frailty in SLE can reduce cardiovascular disease burden.

INTRODUCTION

Systemic lupus erythematosus (SLE) is associated with an increased risk of cardiovascular disease (CVD)-related morbidity and mortality.[1] Subclinical atherosclerosis risk in SLE is 2.5-fold to 4-fold higher compared with the general population and has been shown to cause substantial cardiovascular morbidity and mortality.[1] Both traditional cardiovascular risk (CVR) factors and disease-related parameters (eg, disease duration and activity, disease damage, glucocorticoid exposure, comorbidities and antiphospholipid antibodies) have been associated with CVD and the presence and progression of subclinical atherosclerosis in SLE.[2–4]

Frailty is a relatively new concept in rheumatic and musculoskeletal disorders (RMDs) that represents a state of increased vulnerability resulting in reduced physiological

function in response to biological stressors.[5] Although frailty is typically associated with advanced age, augmenting evidence suggests that it comprises a distinct biological entity, beyond ageing.[6] Recent studies focus on the identification of frail young and middle-aged individuals at increased risk for adverse health outcomes.[6] In people living with RMDs, immune-mediated inflammageing has been associated with multimorbidity and frailty, which in turn, have been correlated with poor physical function and increased morbidity and mortality.[7 8] Various health deficits have been validated to classify frailty in the general population, while pre-frailty, a status before the onset of frailty, has been recognised as an important target for early intervention. Thus, having a useful clinical tool to measure pre-frailty and frailty in RMDs can help predict adverse outcomes.

The Systemic Lupus International Collaborating Clinics (SLICC)-Frailty Index (SLICC-FI) is a validated clinical tool developed to assess frailty in SLE by considering disease activity, organ damage, comorbidities and health-related quality of life measures.[9] It has been shown to predict hospitalisations, damage accrual and mortality in large SLE cohorts.[10–12] Recently, it has also been associated with impaired physical function, activities of daily living and quality of life measures.[7] Accumulating evidence suggests that frailty can also predict CVD events and CVD-related mortality in the general population.[13] However, no data are available on the association between frailty and clinical or subclinical CVD in patients with RMDs, including SLE.

This study aimed to examine the association between frailty, as assessed by SLICC-FI and subclinical atherosclerotic plaques in patients with SLE.

METHODS

Study design and population

This is a cross-sectional study including all patients with SLE who were regularly followed-up in our department and underwent carotid and femoral ultrasound examinations in our cardiovascular research unit between September 2016 and January 2018 for research purposes. All patients fulfilled the 2012 SLICC classification criteria for SLE.[14] Patients with a history of atherosclerotic CVD, diabetes mellitus, advanced chronic kidney disease, active infection, malignancy and pregnancy were excluded.

Recorded parameters

We recorded patient demographics (age, sex, ethnicity), clinical characteristics and medication use, including glucocorticoids (both cumulative (estimated since SLE diagnosis) and current prednisone dose in mg), current hydroxychloroquine, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, leflunomide and ciclosporin) and biological agents (eg, rituximab and belimumab) use. Disease activity and damage measures were assessed at the time of ultrasound testing: the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K),[15] the SLICC/American College of Rheumatolog Damage Index (SDI)[16] and the lupus low disease activity state (LLDAS) which was defined as follows: SLEDAI-2K≤4 without major organ activity, no new disease activity, physician's global assessment (0–3) ≤1, prednisone dose ≤7.5 mg/day and standard maintenance doses of immunosuppressive medications, with antimalarials allowed.[17]

The laboratory parameters examined at the time of ultrasound testing included a complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum creatinine levels, antinuclear antibodies, anti-double strand DNA antibodies, C3 and C4 levels and antiphospholipid antibodies. We also recorded traditional CVR factors, such as: (1) systolic and diastolic blood pressure measured after at least 10 min of rest and recorded as the average of three sequential readings taken 1 min apart (Microlife Watch BP Office, Microlife AG, Windau, Switzerland); (2) lipid profile, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides; (3) smoking status (current smoking and pack-years smoking); (4) physical activity assessed via a specific question directed to patients 'In general, how many minutes per week did you regularly participate in sports and other vigorous physical activities, excluding occupational activity' and measured in minutes per week); (5) family history of coronary artery disease; (6) body mass index (weight/ height^2); (7) waist circumference; and (8) use of antihypertensives, lipid-lowering agents, antiplatelets or anticoagulants.

To stratify CVR, we used the Systemic COronary Risk Evaluation (SCORE) which is a validated instrument recommended by the European Society of Cardiology. SCORE estimates the 10-year risk of fatal CVD based on age, sex, smoking, measurements of systolic blood pressure and fasting total and HDL cholesterol levels.[18] Participants were classified into the following CVR categories based on SCORE: low (<1%), moderate (≥1% and <5%), high (≥5% and <10%) and very-high risk (≥10%). Individuals with extremely elevated blood pressure (systolic blood pressure (BP>180 or diastolic BP>110 mm Hg) or lipids (total cholesterol >310 mg/dL) were classified as high-risk individuals. Although modified versions of generic risk scores using multipliers, such as the modified SCORE that is multiplied by 1.5, have been suggested for patients with rheumatoid arthritis and other forms of inflammatory joint disorders,[19] recent studies have shown that they do not improve CVD risk assessment in patients with SLE compared with the original versions.[20] Therefore, we believe it is more appropriate to include the SCORE prediction tool in our analyses, as it has also been validated in the Greek population.[21]

We also conducted a vascular ultrasound examination to evaluate the presence of atherosclerotic plaques in patients with SLE.

Vascular ultrasound methodology

All vascular ultrasound assessments were performed in the Cardiovascular Risk Research Unit of our Department by the same blinded experienced sonographer, as part of approximately 2100 healthy controls and patients' recruitment since 2010, using a high-resolution B-mode ultrasound device (Vivid V.7 Pro, GE HealthCare, Chicago, Illinois, USA) with a 140 MHz multifrequency linear transducer, as previously described.[22] The assessments were performed in a specially configured quiet room and all participants were given the same instructions prior to the assessment: to avoid vasoactive medications, caffeine and smoking, and requested to fast for at least 3 hours prior to the ultrasound.[2] The presence of atherosclerotic plaques was evaluated in the near and far wall of eight arterial sites: left and right common carotid arteries, carotid bulbs and internal carotid arteries and left and right common femoral arteries. A local thickening of the intima-media thickness (IMT)>1.5 mm or an increase of either 0.5 mm or 50% compared with the adjacent arterial wall IMT was defined as atherosclerotic plaque, according to the Mannheim Carotid IMT and Plaque Consensus.[23] Imaging results were validated with intraobserver and interobserver reproducibility >0.8.

SLICC-FI assessment tool

The SLICC-FI was developed to assess 48 health deficits, including 14 items for active inflammation, 14 for organ damage, 6 for comorbidities and 14 related to functional impairment, mobility, health attitude and mental health, as described elsewhere.[7] The health deficits included in the SLICC-FI and the scoring system for each health deficit are available in table 1. Each health deficit is scored from 0 (complete absence) to 1 (fully present) and the total SLICC-FI score is calculated as the sum of a person's health deficit scores divided by the total number of health deficits. Patients are classified as robust (SLICC-FI<0.03), relatively less fit (0.03<SLICC FI <0.10), least fit (0.10<SLICC-FI<0.21) or frail (SLICC-FI>0.21). We did not make any modifications to the definitions of the SLICC-FI variables compared with the original instrument.

The SLICC-FI was retrospectively calculated for each patient but all relevant information was collected and recorded in patient files at the time of vascular ultrasound. Specifically, items regarding active inflammation, organ damage or comorbidities were collected in detail at the patient visit for the ultrasound examination. Items related to functional impairment, mobility, health attitude and mental health were also obtained at the time of ultrasound evaluation in the context of another project we ran at the same time,[7] for which detailed information was collected for each of the above parameters involving also the completion of the Health Assessment Questionnaire (HAQ), Disabilities of the Arm, Shoulder, and Hand (DASH), Lupus Quality of Life (LupusQoL) and Pain Visual Analogue scale (VAS) questionnaires.

Statistical analysis

The distribution of variables was examined by the D'Agostino-Pearson and Shapiro-Wilk tests. Continuous variables were presented as mean±SD when normal distribution was applied, or as median, IQR when it was not. Mann-Whitney U test was applied for comparisons of continuous variables. We applied logistic regression models using the presence of atherosclerotic plaques in SLE as the outcome variable. We evaluated patient demographics, disease-related factors, SLICC-FI and traditional CVR factors as determinants of plaque presence in SLE, including disease manifestations, immunological tests, antiphospholipid syndrome, double or triple antiphospholipid antibody positivity, traditional CVR factors, medications (hydroxycloroquine, immunosuppressants, antihypertensives, antiplatelet agents, statins) and LLDAS as categorical variables and disease duration, cumulative prednisone dose (estimated since SLE diagnosis), SLEDAI-2K, SDI and SCORE as continuous variables. There were no missing data in the examined parameters. All variables that were found to be statistically significant in the univariate logistic regression analysis were included in the multivariate logistic regression models using a stepwise backward method.

We performed separate analyses for the associations with (1) carotid and/or femoral plaque presence, (2) carotid plaque presence and (3) femoral plaque presence. CVR classification in our univariate and multivariate models was based on SCORE estimates. Since hypertension is a common item between the SLICC-FI and SCORE models, we performed a sensitivity analysis by excluding hypertension from the SLICC-FI.

The quality of the models was assessed by AIC (Akaike information criteria) in terms of predictive value. The level of statistical significance was set at p<0.05. Statistical analysis was performed using Stata software (V.13.0, College Station, Texas, USA) and SPSS V.26 software (IBM, USA).

RESULTS

SLE cohort characteristics

From 295 consecutive patients with SLE who were regularly followed-up in our rheumatology unit between September 2016 and January 2018, 34 patients were excluded due to prior history of atherosclerotic CVD, 22 due to diabetes mellitus, advanced chronic kidney disease, active infection, malignancy or pregnancy and 37 denied to participate in the vascular ultrasound assessment (figure 1, flow chart). A total of 202 eligible patients (89.1% women, all white, mean age 46.7 years (SD 12.6)) were included in the study. Patient characteristics are shown in table 2, and the CVR factors are presented in table 3.

Carotid and/or femoral plaque presence was identified in 25.7% of patients (20.8% carotid, 17.3% femoral). The median SCORE was 1.7 (IQR 0.8–3.8). In total, 34.7% of patients were classified as having low CVR, 49%

Table 1 Systemic Lupus international Collaborating Clinics Frailty Index health deficits

Health deficit	Scoring system
Diabetes	No=0, yes=1
Malignancy	No=0, yes=1
Coronary artery disease	No=0, yes=1
Congestive heart failure	No=0, yes=1
Peripheral vascular disease	No=0, yes=1
Cerebrovascular disease	No=0, yes=1
Chronic kidney disease	None=0, stage 1=0.2, stage 2=0.4, stage 3=0.6, stage 4=0.8, stage 5=1
Deforming or erosive arthritis	No=0, yes=1
Venous thromboembolism	No=0, yes=1
Pulmonary disease	No=0, yes=1
Gastrointestinal disease	No=0, yes=1
Osteoporosis/avascular necrosis	No=0, yes=1
Ocular manifestations related to SLE	No=0, yes=1
SLE myocarditis/endocarditis	No=0, yes=1
Cognitive impairment	No=0, yes=1
Seizures/seizure disorders	No=0, yes=1
Altered mental status	No=0, yes=1
Neuropathy	No=0, yes=1
Other neuropsychiatric manifestations	No=0, yes=1
Active nephritis	No=0, yes=1
Active nephrotic syndrome	No=0, yes=1
Active serositis	No=0, yes=1
Active inflammatory arthritis	No=0, yes=1
Active inflammatory rash	No=0, yes=1
Active mucosal ulcers	No=0, yes=1
Alopecia	No=0, yes (acute)=0.5, yes (chronic)=1
Active vasculitis	No=0, yes=1
Haematological disorders	No=0, yes=1
Immunological disorders	No=0, yes=1
Complement levels	Normal/high=0, low and negative dsDNA=0.5, low and positive dsDNA=1
Sjogren's syndrome	No=0, yes=1
Hypothyroidism	No=0, yes=1
Hypertension	No=0, yes=1
Body mass index (BMI)	BMI 18.5–24.9 kg/m^2=0, BMI 25–29.9 kg/m^2=0.5, BMI>30 kg/m^2=1
Mood disorder	No=0, yes=1
Anxiety disorder	No=0, yes=1
Headache disorder	No=0, yes=1
Self-rated health	Excellent=0, very good=0.25, good=0.5, fail=0.75, Poor=1
Self-reported deterioration in health	Better or same=0, somewhat worse=0.5, much worse=1
Vigorous activities	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Moderate activities	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Lifting/carrying groceries	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Climbing stairs	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Bending, kneeling or stooping	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Walking 100 metres	Not limited at all=0, somewhat limited=0.5, limited a lot=1

Continued

Table 1 Continued

Health deficit	Scoring system
Bathing or dressing	Not limited at all=0, somewhat limited=0.5, limited a lot=1
Self-rated fatigue	None=0, a little=0.2, some=0.4, moderate=0.6, most=0.8, always=1
Self-rated pain	None=0, very mild=0.2, mild=0.4, moderate=0.6, severe=0.8, very severe=1

dsDNA, double strand DNA; SLE, systemic lupus erythematosus.

as moderate, 15.3% as high and 1% as having very high CVR based on SCORE.[18] The median SLICC-FI score was 0.08 (IQR 0.04–0.10); 19.3% of patients were classified as robust, 45% as less fit, 29.2% as least fit and 6.4% as frail. The median SLICC-FI was significantly higher in patients with SLE at high/very-high risk versus those at low/moderate risk (p=0.002). In addition, least fit or frail patients exhibited a higher prevalence of atherosclerotic plaques compared with robust or less fit patients (27/72 (37.5%) vs 25/130 (19.2%), p=0.007).

Predictors of atherosclerotic plaques in patients with SLE

In univariate regression analysis, factors significantly associated with plaque presence (carotid and/or femoral) were older age, disease duration, higher systolic blood pressure, current smoking and smoking pack-years, hypertension, dyslipidaemia, higher CVR class, as assessed by the SCORE prediction tool and higher SLICC-FI score (table 4). Among disease-related parameters, only disease duration was significantly associated with atherosclerotic plaques. No statistically significant association between plaque presence and cumulative prednisone dose (OR 1.00, 95% CI 0.99 to 1.00, p=0.053), or current hydroxychloroquine use was observed (OR 0.81, 95% CI 0.34 to 1.90, p=0.637). In contrast, almost all traditional CVR factors were significantly associated with carotid and/or femoral plaques (table 4). A separate analysis for carotid or femoral plaques is shown in tables 5 and 6, respectively.

In multivariate analysis, instead of each of the classic CVR factors found statistically significant in univariate analysis, we included the SCORE CVR prediction model, which incorporates these factors, in order to reduce the number of covariates. After controlling for disease duration and the risk attributed to traditional CVR factors incorporated in the SCORE model, CVR class (OR 5.16, 95% CI 2.75 to 9.70, p<0.001) and SLICC-FI (OR 1.34, 95% CI 1.00 to 1.76, p=0.003 per 0.05 point increase) were

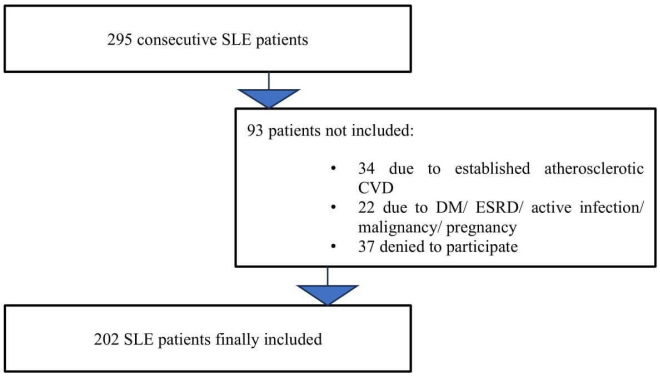

Figure 1 Flow chart. CVD, cardiovascular disease; DM, diabetes mellitus; ESRD, end-stage renal disease; SLE, systemic lupus erythematosus.

Table 2 Demographics and disease-related characteristics of patients with SLE

Characteristics	SLE (n=202)
Age (mean±SD)	46.7±12.6
Female, n (%)	180 (89.1)
Disease duration (years, median, IQR)	9 (4–15)
History of lupus nephritis, n (%)	39 (19.3)
History of central nervous system involvement, n (%)	20 (9.9)
History of pericarditis, n (%)	26 (12.8)
History of pleuritis, n (%)	20 (9.9)
Low C3, n (%)	54 (26.7)
Low C4, n (%)	22 (10.9)
Anti-dsDNA antibodies, n (%)	31 (15.3)
Antiphospholipid syndrome, n (%)	36 (17.8)
Double or triple aPL positivity, n (%)	57 (28.2)
Prednisone, current use, n (%)	110 (54)
Cumulative prednisone dose, ever use, (grams) (median, IQR)	5.8 (0.3–16.4)
Prednisone daily dose, (mg) (median, IQR)	4 (0.1–7.6)
Hydroxychloroquine, current use, n (%)	169 (83.7)
Immunosuppressives, current use, n (%)	89 (44.1)
Biologic agents, current use, n (%)	12 (5.9)
SLEDAI-2K, median (IQR)	2 (0–4)
SDI, median (IQR)	0 (0–1)
SDI>0, n (%)	58 (28.7)
LLDAS, n (%)	134 (66.3)
SLICC-FI score, median (IQR)	0.08 (0.04–0.1)

anti-dsDNA antibodies, anti-double strand DNA antibodies; aPL, antiphospholipid antibodies; LLDAS, lupus low disease activity state; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLE, systemic lupus erythematosus; SLICC-FI, Systemic Lupus International Collaborating Clinics-Frailty Index.

Table 3 Traditional cardiovascular risk factors and atherosclerotic plaque presence in patients with SLE

Characteristics	SLE (n=202)
Systolic blood pressure, mm Hg (median, range)	117 (109–126)
Smoking, pack-years (mean±SD)	10.3±14.6
Smoking current, n (%)	71 (35.1)
Family history of premature CAD, n (%)	20 (9.9)
Total Cholesterol, mg/dL (mean±SD)	183±40.9
HDL, mg/dL (mean±SD)	60.6±20.6
LDL, mg/dL (mean±SD)	103.6±32.9
Triglycerides, mg/dL (mean±SD)	101.1±61.3
BMI, kg/m^2 (median, IQR)	24.6 (7.9)
Exercise, min/week (mean, range)	103 (0–720)
Hypertension, n (%)	73 (36.1)
Dyslipidaemia, n (%)	99 (49)
Antihypertensives, n (%)	63 (32)
Statins, n (%)	24 (11.9)
Antiplatelet agents, n (%)	57 (28.2)
SCORE, median (IQR)	1.7 (3)
Plaque presence (carotid and/or femoral), n (%)	52 (25.7)
Carotid plaque presence, n (%)	42 (20.8)
Femoral plaque presence, n (%)	35 (17.3)

BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLDAS, lupus low disease activity state; SCORE, Systematic COronary Risk Evaluation prediction of 10-year fatal cardiovascular disease.

Table 4 Univariate analysis for the association between carotid and/or femoral plaque presence and several disease-related and traditional cardiovascular risk factors in patients with systemic lupus erythematosus (n=202)

Variables	OR	95% CI	P value
Age	1.13	1.08 to 1.17	**0.000**
Gender	0.57	0.22 to 1.44	0.238
Disease duration	1.06	1.02 to 1.10	**0.002**
SLEDAI-2K	0.96	0.88 to 1.06	0.472
SDI	1.35	0.91 to 1.99	0.126
LLDAS	0.93	0.47 to 1.82	0.840
Antiphospholipid syndrome	0.99	0.43 to 2.27	0.981
Double or triple aPL positivity	0.88	0.43 to 1.79	0.728
Cumulative prednisone dose	1.00	0.99 to 1.00	0.053
Hydroxychloroquine use	0.81	0.34 to 1.90	0.637
Immunosuppressives use	0.97	0.51 to 1.86	0.942
Systolic blood pressure	1.02	1.00 to 1.04	**0.018**
Smoking, pack-years	1.05	1.03 to 1.08	**0.000**
Smoking, current	1.87	1.23 to 2.83	**0.003**
Family history of premature CAD	0.70	0.22 to 2.20	0.544
Total cholesterol	1.00	9.99 to 1.01	0.087
HDL	0.99	0.98 to 1.01	0.849
LDL	1.00	0.99 to 1.01	0.075
Triglycerides	1.00	1.00 to 1.00	**0.047**
BMI	0.99	0.97 to 1.02	0.935
Hypertension	2.64	1.38 to 5.05	**0.003**
Dyslipidaemia	2.35	1.21 to 4.54	**0.011**
Antihypertensives	1.00	0.97 to 1.03	0.718
Statins	1.88	0.76 to 4.62	0.165
Antiplatelets	1.18	0.59 to 2.36	0.636
SCORE	1.77	1.48 to 2.10	**0.000**
Cardiovascular risk class	6.04	3.31 to 11.02	**0.000**
SLICC-FI score*	1.47	1.16 to 5.57	**0.001**

Bold values denote statistical significance at the p < 0.05 level.
*Per 0.05 increase.
aPL, antiphospholipid antibodies; BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLDAS, lupus low disease activity state; SCORE, Systematic COronary Risk Evaluation prediction of 10-year fatal cardiovascular disease; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLICC-FI, Systemic Lupus International Collaborating Clinics-Frailty Index.

the only parameters independently associated with atherosclerotic plaques (table 7A). The addition of SLICC-FI improved the predictive value of the proposed multivariate model (AIC=1.01 vs AIC=1.06, if SLICC-FI was not incorporated). When cumulative prednisone dose was added to the model, the association between plaque presence and both CVR class and SLICC-FI remained significant (OR 3.95, 95% CI 2.15 to 7.25, p<0.001 and OR=1.06, 95% CI 1.00 to 1.13, p=0.048, respectively). Since hypertension is a common item between the SLICC-FI and the SCORE (including age, sex, smoking, systolic blood pressure and total and HDL cholesterol levels), we performed a sensitivity analysis by excluding hypertension from the SLICC-FI. The association between the modified SLICC-FI (after excluding hypertension) and the presence of atherosclerotic plaques remained significant in the multivariate model (OR 1.06, 95% CI 1.01 to 1.12, p=0.013 per 0.01 point increase).

Further analysis of plaque presence in carotid or femoral vascular beds separately, revealed that the SLICC-FI was an independent predictor of femoral artery plaques (OR 1.40, 95% CI 1.00 to 1.1.93, p=0.045) but not of carotid artery plaques (OR 1.28, 95% CI 0.95 to 1.69, p=0.081) (table 7B,C).

DISCUSSION

In this study, we examined, for the first time, the association between frailty, as assessed by the SLICC-FI score and subclinical CVD in a well-characterised SLE cohort. Higher SLICC-FI values (per 0.01 increase) were independently associated with the presence of

Table 5 Univariate analysis of the association between carotid plaque presence and several disease-related and traditional cardiovascular risk factors in patients with systemic lupus erythematosus (n=202)

Variables	OR	95% CI	P value
Age	1.12	1.08 to 1.17	**0.000**
Gender	0.88	0.30 to 2.55	0.823
Disease duration	1.06	11.02 to 1.11	**0.002**
SLEDAI-2K	0.98	0.89 to 1.08	0.780
SDI	1.02	0.65 to 1.59	0.918
LLDAS	1.11	0.54 to 2.26	0.772
Antiphospholipid syndrome	1.15	0.47 to 2.75	0.754
Double or triple aPL positivity	0.79	0.36 to 1.70	0.549
Cumulative prednisone dose	1.00	1.00 to 1.00	0.035
Hydroxychloroquine use	0.57	0.24 to 1.36	0.211
Immunosuppressives use	0.97	0.48 to 1.94	0.937
Systolic blood pressure	1.01	0.99 to 1.03	0.077
Smoking, pack-years	1.05	1.02 to 1.07	**0.000**
Smoking current	2.02	1.29 to 3.16	**0.002**
Family history of premature CAD	0.63	0.17 to 2.28	0.488
Total cholesterol	1.00	0.99 to 1.01	0.051
HDL	0.99	0.98 to 1.01	0.969
LDL	1.01	1.00 to 1.02	**0.038**
Triglycerides	1.00	0.99 to 1.00	0.218
BMI	0.99	0.97 to 1.02	0.952
Hypertension	2.59	1.29 to 5.18	**0.007**
Dyslipidaemia	2.74	1.32 to 5.66	**0.007**
Antihypertensives	0.97	0.89 to 1.05	0.522
Statins	1.69	0.65 to 4.41	0.279
Antiplatelets	1.50	0.73 to 3.10	0.266
SCORE	1.63	1.38 to 1.92	**0.000**
Cardiovascular risk class	5.45	2.96 to 10.02	**0.000**
SLICC-FI score*	1.40	1.10 to 1.84	**0.005**

Bold values denote statistical significance at the p < 0.05 level.
*Per 0.05 increase.
aPL, antiphospholipid antibodies; BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLDAS, lupus low disease activity state; SCORE, Systematic COronary Risk Evaluation prediction of 10-year fatal cardiovascular disease; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLICC-FI, Systemic Lupus International Collaborating Clinics-Frailty Index.

Table 6 Univariate analysis of the association between femoral plaque presence and several disease-related and traditional cardiovascular risk factors in patients with systemic lupus erythematosus (n=202)

Variables	OR	95% CI	P value
Age	1.14	1.09 to 1.20	**0.000**
Gender	0.51	0.18 to 1.42	0.203
Disease duration	1.06	1.01 to 1.11	**0.007**
SLEDAI-2K	0.97	0.87 to 1.08	0.663
SDI	1.33	0.86 to 2.05	0.191
LLDAS	0.87	0.40 to 1.91	0.741
Antiphospholipid syndrome	1.23	0.48 to 3.09	0.657
Double or triple aPL positivity	1.02	0.45 to 2.30	0.961
Cumulative prednisone dose	1.00	0.99 to 1.00	0.186
Hydroxychloroquine use	0.86	0.32 to 2.30	0.779
Immunosuppressives use	1.13	0.54 to 2.38	0.736
Systolic blood pressure	1.01	0.99 to 1.03	0.121
Smoking, pack-years	1.06	1.03 to 1.09	**0.000**
Smoking current	1.70	1.06 to 2.72	**0.026**
Family history of premature CAD	0.22	0.02 to 1.75	0.155
Total cholesterol	1.00	0.99 to 1.01	0.454
HDL	0.97	0.95 to 0.99	**0.023**
LDL	1.00	0.99 to 1.01	0.128
Triglycerides	1.00	1.00 to 1.01	**0.024**
BMI	1.00	0.98 to 1.02	0.704
Hypertension	2.79	1.32 to 5.88	**0.007**
Dyslipidaemia	3.00	1.35 to 6.66	**0.007**
Antihypertensives	0.97	0.89 to 1.06	0.563
Statins	2.14	0.81 to 5.65	0.122
Antiplatelets	1.44	0.65 to 3.15	0.359
SCORE	1.99	1.61 to 2.45	**0.000**
Cardiovascular risk class	10.82	4.88 to 23.96	**0.000**
SLICC-FI score*	1.54	1.16 to 2.01	**0.002**

Bold values denote statistical significance at the p < 0.05 level.
*Per 0.05 increase.
aPL, antiphospholipid antibodies; BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LLDAS, lupus low disease activity state; SCORE, Systematic COronary Risk Evaluation prediction of 10-year fatal cardiovascular disease; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SLICC-FI, Systemic Lupus International Collaborating Clinics-Frailty Index.

atherosclerotic plaques, after adjusting for several traditional and disease-related CVR factors.

Current evidence on CVD pathogenesis in SLE supports the role of both traditional CVR factors (eg, hypertension, smoking, dyslipidaemia) and disease-related parameters, such as immune dysregulation, disease activity, disease duration and treatment effects, such as prolonged use of glucocorticoids. Immune dysregulation involves the role of both B cells and T cells, endothelial cell activation and proliferation, type I interferon expression, monocyte and neutrophil activation, antiphospholipid antibody-mediated oxidative stress and macrophage differentiation to foam cells.[24–27] This complex interplay leads to atherosclerotic plaque formation and eventually to CVD

Table 7 Multivariate regression analysis of the associations with (A) carotid and/or femoral plaque presence; (B) carotid plaque presence; (C) femoral plaque presence in patients with systemic lupus erythematosus

	OR	95% CI	P value
(A)			
Disease duration	1.01	0.96 to 1.06	0.527
CVR class*	5.16	2.75 to 9.70	0
SLICC-FI score (per 0.05 increase)	1.34	1.00 to 1.76	0.033
(B)			
Disease duration	1.02	0.97 to 1.07	0.366
CVR class*	4.6	2.43 to 8.72	0
SLICC-FI score (per 0.05 increase)	1.28	0.95 to 1.69	0.081
(C)			
Disease duration	0.99	0.94 to 1.05	0.919
CVR class*	10.18	4.43 to 23.40	0
SLICC-FI score (per 0.05 increase)	1.4	1.00 to 1.93	0.045

*CVR stratification is based on Systemic COronary Risk Evaluation estimates.
CVR, cardiovascular risk; SLICC-FI, Lupus International Collaborating Clinics-Frailty Index.

events, which represent the leading cause of morbidity and mortality in SLE, along with infections.[28 29]

Emerging evidence from large, prospective studies in the general population suggests that frailty is an independent predictor risk factor for CVD-related morbidity and mortality. This is considered to be mediated by traditional CVR factors, comorbidities, immune cell dysregulation, oxidative stress and inflammageing.[30 31] Ekram *et al* investigated the association between frailty and CVD, major adverse cardiovascular events (MACE) and CVD mortality in a mixed Australian-American cohort of nearly 20 000 older adults with no previous CVD events. They found that frail and pre-frail groups were more likely to develop CVD, including MACE, compared with non-frail adults after adjustments for traditional CVR factors.[32] In addition, many studies have highlighted the association between low physical performance (a frailty domain represented by slow gait speed and weakness) and CVD. A large meta-analysis including over 100 000 participants (mean age 72 years old) showed that each reduction of 0.1 m/s in gait speed was associated with a 12% increased risk of earlier mortality and an 8% increased risk of CVD.[33] A population-based study from the UK including 502 293 middle-aged participants (54% women), reported an association between muscle weakness defined as low handgrip strength and increased cardiovascular mortality.[34]

Regarding frailty in RMDs, several cross-sectional studies have shown a higher prevalence of frailty in these disorders compared with the general population, potentially correlated to chronic inflammation and immunosenescence.[8] Rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis often present features of frailty such as sarcopenia, fatigue and low physical activity, which appear to be related to higher disease activity.[8 35] Frailty has also been studied in systemic sclerosis. A frailty index was developed by the Canadian Scleroderma Research Group and has been associated with several disease characteristics and increased risk of mortality.[36] SLE studies have shown that about 20–27% of these patients were classified as 'frail' using Fried's frailty criteria[37] or the newest SLICC-FI, which includes domains related to active inflammation (ie, arthritis or serositis), organ damage (ie, heart failure or CKD), comorbidities (ie, hypertension or obesity) and physical function, mobility, health attitude and mental health. Consequently, the SLICC-FI score reflects the whole spectrum of vulnerability attributable to both disease-related characteristics and several comorbidities, irrespective of their inter-relationship.

However, no evidence exists about the relationship between frailty and clinical or subclinical CVD in RMDs, including SLE. To the best of our knowledge, this is the first study to evaluate the association between frailty and subclinical atherosclerosis in a systemic autoimmune disorder. Although SLICC-FI is a multidimensional, yet validated, frailty index, its application in clinical practice could improve our perspective of the heterogeneous health outcomes in SLE. Early identification of pre-frail and frail individuals could enable the implementation of comprehensive lifestyle strategies and interventions that target mobility, strength, balance, physical activity, exercise and diet.[38 39] This approach may include (1) aerobic and resistance training programmes adapted for each individual, (2) adherence to a healthy diet and (3) a combination of various non-pharmacological interventions such as the incorporation of physical activity components with nutrition or other factors like smoking cessation, as recently recommended by the European Alliance of Associations for Rheumatology (EULAR) recommendations for the non-pharmacological management of SLE.[40] Targeting also disease-related features that are part of the SLICC-FI may help reduce both frailty and CVD risk. For example, minimisation of disease activity can prevent frailty related to pain and low physical activity, and CVD risk associated with inflammation-mediated endothelial dysfunction. Similarly, minimisation and eventually discontinuation of glucocorticoids can help prevent muscle atrophy, obesity, hypertension and diabetes, which are associated with both frailty and CVD risk.

No association was observed between the cumulative prednisone dose and plaque presence in our study. This may be explained by a mild disease course in the majority of patients; 77% of patients with SLE had mean SLEDAI<4, 66% achieved LLDAS and most importantly, the median (IQR) cumulative prednisone dose was 5.8 grams (0.3–16.4) over a 9-year median disease duration (IQR 4–15). In addition, no association between

hydroxychloroquine and plaque presence was detected. A possible explanation is that the majority (84%) of patients with SLE were receiving hydroxychloroquine, in line with the EULAR recommendations for SLE management, unless contraindicated.

The main strengths of our study are the inclusion of a large cohort of well-characterised patients with SLE and the extensive vascular ultrasound screening for subclinical atherosclerosis at eight different arterial sites, both in the carotid and femoral arteries and by the same operator. Additionally, all reported associations were based on multivariate analyses after adjustments for a wide range of disease-related and traditional CVR factors, and the CVR class of each patient based on the SCORE, a prediction tool of 10-year fatal CVR that has also been validated for the Greek population. Nevertheless, our study has some limitations. This is a cross-sectional study that examines an association between frailty and subclinical atherosclerosis, rather than incident CVD events. However, it is well-established that subclinical atherosclerosis is the strongest predictor of future CVD events[41] and therefore, the identification of a clinical tool that may predict its presence is of high importance. Since all participants in this study are white Europeans, our results could not be generalised to different ethnic/racial groups. Furthermore, given that the majority of patients with SLE had low disease activity (mean SLEDAI-2K: 2), our data do not allow safe conclusions for patients with high disease activity. We also acknowledge that SLICC-FI includes multiple domains, thus, its completion might be less convenient than the shorter SCORE algorithm. However, in addition to traditional CVR factors included in the SCORE algorithm, CVD risk in SLE has been associated with several disease-related characteristics such as disease activity, disease damage and comorbidities.[24] The importance of a thorough assessment and management of disease-related risk factors for the prevention of CVD in SLE has also been highlighted by the 2022 EULAR recommendations for CVR management in RMDs, including SLE and antiphospholipid syndrome.[42] Thus, evaluating frailty through SLICC-FI could provide a more global perspective of CVD risk in this multisystem and complex disorder.

In conclusion, considering the trade-off of simplicity with the SCORE alone versus the size of predictive gain by adding the burden of scoring the SLICC-FI, the SLICC-FI can provide a more holistic approach to CVR in patients with SLE as a multidimensional index incorporating a wide range of disease-related risk factors, in addition to traditional CVR factors. It can facilitate their early identification and modification, helping to address unmet needs related to the high prevalence of CVR factors and their inadequate control of SLE.[43 44] Rheumatologists, in collaboration with other healthcare providers, should be responsible for CVR assessment, regular screening of modifiable CVR factors and lifestyle modifications such as regular exercise, healthy diet and smoking cessation in patients with RMDs, including SLE. Prospective studies examining the association between frailty and incident cardiovascular events are warranted in SLE as well as in other autoimmune disorders.

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