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ORIGINAL RESEARCH

Distribution of nailfold videocapillaroscopy parameters in systemic lupus erythematosus and their association with disease activity: an international blinded case–control analysis on behalf of the EULAR study group on microcirculation in rheumatic diseases

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ABSTRACT

Objectives To evaluate whether patients with systemic lupus erythematosus (SLE) have different nailfold videocapillaroscopy (NVC) findings compared with healthy controls (HCs) and whether there is an association between NVC abnormalities and disease activity, clinical and/or laboratory features in SLE.

Methods This is an observational, multicentre, international, matched case–control study. 381 subjects (203 patients with SLE and 178 HCs) were enrolled from 16 centres in 10 countries. Clinical and laboratory data were collected using ad hoc forms. 5861 NVC images were acquired, coded and uploaded for central blinded analysis.

Results A normal NVC pattern was observed in most patients with SLE (86.6%) and, a significantly higher frequency of NVC abnormalities such as enlarged and giant capillaries, microhaemorrhages and irregular nail bed architecture ($p<0.001$) were found in the remaining patients. Multiple correspondence analysis outlined two NVC patterns, one of which, the more severe (cluster 2), present in 12% of patients, was characterised by a higher prevalence of lower capillary density, abnormally shaped and enlarged capillaries and irregular nail bed architecture. NVC cluster 2 had significantly higher disease activity compared with cluster 1 for both Systemic Lupus Erythematosus Disease Activity Index cut-off points ≥3 and ≥4 ($p=0.016$ and $p=0.028$, respectively). SLE with 'more severe' NVC pattern (cluster 2) have a significantly higher frequency of arthritis, renal involvement and ongoing glucocorticoid therapy, whereas serositis was significantly associated with 'less severe' NVC pattern (cluster 1).

Conclusions This study has shown that changes in NVC patterns are associated with important aspects of SLE disease activity. Future prospective studies are needed to further support the use of NVC in SLE monitoring.

Trial registration number NCT02801812.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients with systemic lupus erythematosus (SLE), nailfold videocapillaroscopy (NVC) revealed a wide heterogeneity of capillary abnormalities ranging from normal to scleroderma patterns.

⇒ However, it is unclear whether NVC has a role in SLE diagnosis or monitoring because associations between NVC abnormalities and clinical or laboratory features are scattered and controversial.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with highly heterogeneous clinical manifestations ranging from mild to life-threatening

WHAT THIS STUDY ADDS

⇒ Patients with SLE have a different distribution of NVC abnormalities than healthy controls

⇒ A subgroup of patients with SLE has a higher frequency of enlarged and giant capillaries, microhaemorrhages and irregular nail bed architecture and this overall pattern does not fit into the validated NVC patterns.

⇒ Cluster analysis identified a peculiar NVC pattern with a high prevalence of low capillary density, irregular nail bed architecture, abnormally shaped and enlarged capillaries, associated with higher disease activity and arthritis, renal involvement and ongoing glucocorticoid therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data may support the rationale for using NVC in the clinical assessment of patients with SLE to capture patients with a high probability of active disease.

multiorgan involvement.[1–3] Macrovascular and microvascular dysfunction is often a common feature underlying various clinical manifestations, perpetuated by both traditional risk factors of atherosclerosis and early endothelial dysfunction due to systemic inflammation.[4] In SLE, vasculopathy must be assessed and quantified to properly manage the disease.[5–7]

Nailfold videocapillaroscopy (NVC) is a well-established, safe and non-invasive diagnostic test used in routine clinical practice to assess the microcirculation for the differential diagnosis of Raynaud's phenomenon in both adults and children. NVC is also used to monitor systemic autoimmune rheumatic diseases such as systemic sclerosis or dermatomyositis, as the severity of the patterns correlates with disease activity and prognosis.[8] Currently, the role of capillaroscopy in SLE remains to be elucidated, but it seems promising because vascular involvement in SLE is common and multisystem.

In SLE, reflecting the wide variability of clinical features, nail bed microcirculation assessed by NVC showed a variable prevalence of capillary abnormalities in 40–90% of cases, as well as non-specific abnormalities as observed in healthy subjects.[9] These changes vary over time and may be completely reversible in remission.[10–12] However, the diagnostic sensitivity of NVC is lower in patients with SLE than in patients with scleroderma spectrum disorders. Currently, studies of NVC in patients with SLE are mainly single-centre studies with small sample sizes and unblinded image interpretation focusing on various clinical or laboratory aspects.[11–17] Therefore, it is unclear how and which of these capillaroscopic abnormalities are related to clinical manifestations or disease activity and what is the role of NVC in the assessment and management of these patients.

Therefore, it seems reasonable to determine the role of NVC in the evaluation of patients with SLE. In order to do this, the European Alliance of Associations for Rheumatology (EULAR) Study Group on Microcirculation in Rheumatic Diseases (SG_MC/RD) planned the first international multicentre study to clarify whether patients with SLE have a peculiar capillaroscopic pattern and whether there is an association between nailfold capillary abnormalities and disease activity, clinical and/or laboratory features. We report the results of the first international matched case–control study to better define the potential role of NVC abnormalities in the evaluation of patients with SLE.

METHODS

Study design and population

This is an observational, multicentre, international, matched blinded case–control, non-profit study designed to evaluate NVC abnormalities in patients with SLE. The study protocol was registered on ClinicalTrials.gov (identifier: NCT02801812).

The study was conducted under the aegis of the EULAR SG_MC/RD (code SG_MC/RD4), and the list of participating centres is provided in online supplemental table S1.

As shown in figure 1A, each centre was asked to provide NVC images of patients with SLE attending the outpatient/inpatient clinic for NVC, as well as healthy controls (HCs) volunteers of a similar age and gender. The maximum allowed age difference between case and control was ±5 years for matching. Written informed consent was obtained from all the subjects.

For patients with SLE, the inclusion criteria were: (1) age 18 years or older, (2) SLE according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria,[18] (3) SLE onset after the age of 16 years, (4) SLE with or without secondary antiphospholipid syndrome.[19] Exclusion criteria were: (1) refusal to sign and/or inability to understand the informed consent, (2) subjects with periungual traumatic lesions that may produce artefacts, (3) SLE overlapping or transition forms with other rheumatic diseases such as systemic sclerosis, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, dermatomyositis, polymyositis. HCs were defined as shown in online supplemental table S2.

Clinical and laboratory evaluation

Clinical and laboratory data were collected using ad hoc forms provided to each centre (see online supplemental figure S1). The following parameters were collected for all subjects: date of birth, gender and ethnicity. All patients with SLE were screened for the presence of Raynaud's phenomenon, hypertension (ie, resting blood pressure at or above 140/90 mm Hg), smoking habits, diabetes mellitus, ongoing steroid treatment (if yes, mg per day equivalent of prednisone), cumulative dose of steroid treatment (mg equivalent of prednisone), ongoing immunomodulatory/suppressive treatment (if yes, drug had to be specified).

For patients with SLE the following parameters were requested: age at disease onset, disease activity (Systemic

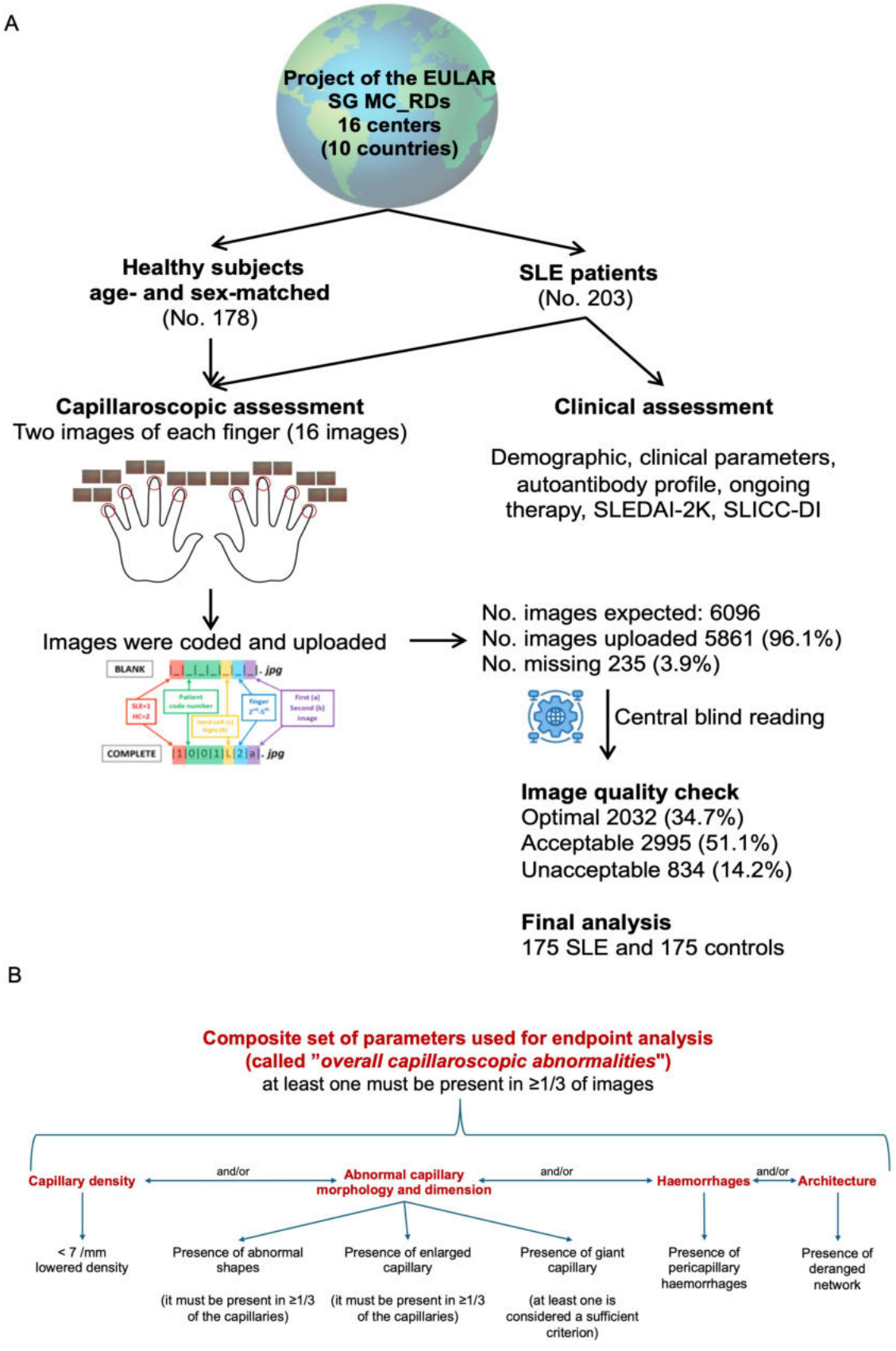

Figure 1 Study design flow, from image acquisition to blinded analysis (A), and the definition of the composite set of capillaroscopic variables ('overall capillaroscopic abnormalities') used as primary endpoint (B). EULAR, European Alliance of Associations for Rheumatology; SG MC_RDs, Study Group on Microcirculation in Rheumatic Diseases; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI, Systemic Lupus International Collaborating Clinics-Damage Index.

Lupus Erythematosus Disease Activity Index 2000, SLEDAI-2000)[20]; Damage Index[21] to measure irreversible damage resulting from SLE disease activity. Moreover, antinuclear antibodies, anti-dsDNA, anti-extractable nuclear antigen (if present, specify if Sm, RNP, SSA/Ro, SSB/La), LAC (lupus anticoagulant), anticardiolipin and anti-β2 glycoprotein I (β2GPI) antibodies (IgG and/or IgM) positivity (present, absent, absent but present in the past). If present, the titre to be reported (low, medium, high). The SLEDAI-2000 score was used to classify patients with active SLE if the score was 3 or 4 or higher, otherwise they were classified as non-active.[22]

Capillaroscopic image acquisition and analysis

Each centre was required to collect digital capillaroscopic images with a magnification of ×100 or higher and marked with a ruler or grid of 1 mm per image. For each subject, eight fingers, excluding the thumb, were examined. If one or more fingers were not suitable for evaluation, reason (eg, amputation) was required and the corresponding images were considered unavailable. For each finger, two NVC images were required for analysis. Images had to be selected based on the investigator's judgement of appropriateness (ie, image quality, representativeness of the entire nailfold, presence of relevant abnormalities). The NVC images were then coded and uploaded for central blinded analysis (figure 1A).

All NVC images underwent a central blinded analysis by four raters who were pre-tested for their agreement in grading NVC abnormalities. After blinding, NVC images were randomly assigned to four raters (FI, VR, NU and KS).[23] In the central analysis, capillaroscopic data were collected using ad hoc forms (see online supplemental figure S2). After grading, the images were unblinded and statistical analysis was performed.

This study protocol was designed and approved in 2016. In 2020, an updated EULAR nomenclature for improved standardisation of capillaroscopy was published.[24] Therefore, for the current analysis, we decided to adapt the nomenclature according to the updated version, as explained in online supplemental table S3. The capillaroscopic pattern was classified in the original 2016 protocol as 'normal', 'perfect normal' and 'unusual normal' according to a previous study,[25] but was subsequently adapted to the EULAR nomenclature[24] as normal (previously called 'perfect normal') and non-specific abnormalities (previously called 'normal' and 'unusual normal'), while the scleroderma patterns ('early', 'active' and 'late') were defined according to the same current classification.[26]

Moreover, due to the lack of a specific SLE capillaroscopic pattern, the frequency of a composite set of NVC parameters outside of the 'normal pattern' was studied as primary endpoint. For simplicity, we referred to this composite set as 'overall capillaroscopic abnormalities', which included lowered density (<7 capillaries/mm) and/or presence of abnormal morphology (shape) and/or presence of enlarged dimensions of capillaries and/or presence of giant capillaries and/or presence of microhaemorrhages and/or presence of deranged capillary network (figure 1B). The detection of at least one NVC parameter in each image was considered to define its presence. To define the presence of overall capillaroscopic abnormality pattern in a subject, at least one NVC parameter had to be present in both ≥1/3 of the capillaries and ≥1/3 of the images, whereas for giant capillaries the detection of at least one parameter was considered a sufficient criterion.

Endpoints

The primary endpoint was to compare the frequency of the 'overall capillaroscopic abnormalities' (as described above and in figure 1B) between patients with SLE and HCs.

The secondary endpoints were to compare the frequency of the 'overall capillaroscopic abnormalities' in (1) patients with SLE with active and non-active disease (2) in patients with SLE with active disease and HCs (3) in patients with SLE with non-active disease and HCs.

Exploratory endpoints were to analyse (1) whether SLE and HCs differed for each capillaroscopic parameter; (2) capillaroscopic variables were clustered in a specific NVC pattern; and (3) capillaroscopic parameters or patterns associated with disease activity, disease damage, demographic, clinical (data extrapolated from SLICC), laboratory and therapy data.

Statistical analysis

All data were analysed by the coordinating centres. Descriptive statistics were reported as proportions or averages (mean and SD or median and range) where the variables were categorical or continuous, respectively.

The sample size was determined during the design phase, and it was based on the frequency of the detection of overall capillaroscopic abnormalities in the study subjects. Since it is difficult to predict the frequency of concordant and discordant pairs needed to calculate the sample size by McNemar's test, an approximate sample size was obtained by ignoring the correlation induced by matching and considering Fisher's exact test. An association of OR=2 was considered clinically relevant. Based on previous studies,[12 25] the prevalence of the capillaroscopic parameters included in the composite core set in HCs was assumed to be 21.1%. To detect an OR=2, the percentage of abnormal cases should be 34.8%. For a two-sided test with a significance level of 5% and a power of 80%, 182 cases and 182 HCs were required.

For the analysis of the primary endpoint (ie, frequency of the NVC pattern at subject level), a McNemar's test and a conditional logistic regression model for matched case–control data were used to account for the matching design on the basis of age and gender. A conditional OR and a risk difference with a 95% CI were reported to estimate the strength of the association. A sensitivity analysis was performed by using a logistic regression model without matching and a logistic model with penalisation

(Firth regression) to take into account the low frequencies of the outcomes.

In the secondary endpoint analysis, Fisher's exact test was used to compare the frequency of capillaroscopic parameters included in the composite core set at subject level between patients with SLE with active and non-active disease. An OR with 95% CI was reported to estimate the strength of the association. Then, a logistic regression model was used to assess the association between capillaroscopic parameters and subject disease status (SLE and HCs, active SLE and non-active SLE, active SLE and HCs and non-active SLE and HCs). Model results were reported as OR and 95% CI.

Based on the observation of increased NVC abnormalities and considering the heterogeneity of the disease, we convened to use multiple correspondence analysis to test whether there are associations between NVC parameters and underlying patterns in SLE that do not fit the already validated patterns. To explore the associations between the NVC parameters in subjects with SLE and controls, a multiple correspondence analysis was performed by analysing each capillaroscopic variable per image and the distribution was shown in a plot. Finally, a complete-linkage hierarchical cluster analysis was performed in SLE subjects to explore if groups could be identified on the basis of the distribution of capillaroscopic parameters. When the generation of more than two clusters was detected, the further subgrouping was decided to be limited by the size of each group (n<10) and the number of clusters was chosen for the following analyses: description of the distribution of capillaroscopic parameters in the clusters, and comparison of demographic, biometric, clinical and laboratory features between the clusters.

Statistical analysis was performed using StataCorp 2017 Stata Statistical Software: Release 15.1. College Station, Texas, USA: StataCorp.

RESULTS

Study population

A total of 381 subjects (203 patients with SLE and 178 HCs) were enrolled from 16 centres in 10 different countries: Italy, Spain, France, Poland, Finland, Belgium, UK, Mexico, USA and Japan (figure 1A). Subjects of the two groups were of similar age and sex (43.8 vs 45.3 years/194 vs 173 females). The mean disease duration was 11.3 years. Raynaud's phenomenon was present in 88 (43.3%) cases. SLE was associated with secondary antiphospholipid syndrome in 32 (15.8%) cases. 108 patients (53.2%) had ongoing glucocorticoid therapy with an average daily prednisone equivalent of 2.5 mg. Further details are shown in table 1.

Capillaroscopic image analysis

Of the 6096 expected NVC images (16 images per subject, 2 per finger of 4 fingers both hands) from 381 enrolled subjects, 235 (3.9%) were missing and

Table 1 The main characteristics of the 203 patients with SLE. Demographics, clinical, laboratory and therapeutic data are reported

	SLE **N=203**
Demographics	
Age, years, mean (SD)	43.8 (14.6)
Gender, female, n (%)	194 (95.6)
Ethnicity, n (%)	
Caucasian	131 (64.5)
African	2 (1.0)
Asian	13 (6.4)
Hispanic	4 (2.0)
Other or mixed	24 (11.8)
Unknown	22 (10.8)
Active smoker, yes, n (%)	27 (13.3)
Clinical parameters	
Age at disease onset, years, mean (SD)	32.6 (12.7)
Disease duration, years, mean (SD) (range)	11.3 (10.0) (0–45)
Diabetes mellitus, n (%)	8 (3.9)
High blood pressure, n (%)	36 (17.7)
Raynaud's phenomenon, yes, n (%)	88 (43.3)
Secondary anti-phospholipid syndrome, yes, n (%)	32 (15.8)
SLEDAI-2000 score, median (IQR)	3 (0–8)*
SLICC-DI score, median (IQR)	0.5 (0–2)*
Antibody profile	
ANA presence ever, yes, n (%)	190 (93.6)
Anti-dsDNA presence ever, yes, n (%)	155 (76.3)
High titre†, yes, n (%)	48/108 (44.4)
Anti-ENA presence ever, yes, n (%)	115 (56.7)
Anti-Sm, yes, n (%)	45 (26.5)
Anti-RNP, yes, n (%)	55 (32.3)
Anti-SSA/Ro, yes, n (%)	70 (42.4)
Anti-SSB/La, yes, n (%)	26 (16.2)
Other‡, yes, n (%)	15 (8.8)
LAC presence ever, n (%)	36/150 (24.0)
antiCardiolipin IgM and/or IgG presence ever, n (%)	73/166 (44.0)
Medium or high titre†, yes, n (%)	33/56 (58.9)
Anti-β_2GPI IgM and/or IgG presence ever, n (%)	44/149 (29.5)
Medium or high titre†, yes, n (%)	25/36 (69.4)
Therapy	
Ongoing glucocorticoids, yes, n (%)	108 (53.2)
Daily prednisone equivalent mg, median (IQR) (range)	2.5 (0–5) (0–60)
Cumulative prednisone equivalent mg, median (IQR) (range)	8863 (2000–28115) (0–82 400)

Continued

Table 1 Continued

	SLE N=203
Ongoing immunomodulation, yes, n (%)	165 (81.3)
Hydroxychloroquine	116 (59.8)
Azathioprine	40 (20.7)
Mycophenolate	43 (22.3)
Belimumab	9 (4.7)
Methotrexate	17 (8.8)
Tacrolimus	5 (2.6)
Ciclosporin A	2 (1.0)
Other†	5 (2.6)

*SLEDAI-2000 n=193, SLICC-DI, n=192.
†One intravenous immunoglobulin, two cyclophosphamide, one rituximab, one leflunomide.
‡Unspecified. IQR.
§According to local laboratory reference.
ANA, antinuclear antibodies; anti-dsDNA, anti-double strand DNA; IQR, interquartile range; LAC, lupus anticoagulant; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI-2000, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC-DI, The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus; β2GPI, anti-β2 glycoprotein I.

the 5861 (96.1%) images were recoded with a random number for blinding. After blinding, the NVC images were randomly assigned to four raters. Of the 5861 images graded, 2032 (34.7%), 2995 (51.1%) and 834 (14.2%) were considered optimal, acceptable and unacceptable for grading, respectively (figure 1A). Only in two subjects (0.5%) was the quality of all images provided too low to perform a grading. Image magnification was 200× in 324 (85%) subjects, 100× in 46 (12.1%) subjects and missing in 11 (2.9%) subjects.

Of 381 enrolled subjects, 25 (6.6%, all SLE cases, 4 males) could not be matched due to lack of age/sex matched HCs. Of the 356 matched subjects (178 SLE, 178 HCs), 6 subjects (3 SLE, 3 HCs) were excluded from the primary analysis due to lack of images with optimal or acceptable quality. Thus, 350 (91.9%) subjects, 175 SLE and 175 controls, were included in the matched analysis of the primary endpoint. Unmatched subjects were also considered for sensitivity and secondary analyses.

Patients with SLE have a significantly higher frequency of the overall NVC abnormalities than HCs

Regarding the primary endpoint of the study, the frequency of the composite set of capillaroscopic parameters called 'overall capillaroscopic abnormalities' was significantly higher in patients with SLE compared with HCs (p<0.001). In detail (table 2A), 21 of the 175 patients with SLE (12% of cases) compared with 3 HCs (1.7%) with OR (95% CI), 10.0 (2.43 to 88.24) and a risk difference (95% CI), +10.3% (+4.7% to +15.9%).

These results were confirmed in the unmatched analysis on 377 subjects (202 patients with SLE and 175 HCs) and 27 SLE cases (13.4%) showed overall capillaroscopic abnormalities (OR (95% CI), 8.83 (2.63 to 29.68), p<0.001; penalised model OR (95% CI), 7.68 (2.48 to 23.83)), both adjusted for age, while gender was not included due to problems with perfect prediction.

Higher frequency of NVC abnormalities and different distribution of patterns distinguishes patients with SLE from HCs

Looking at individual NVC parameters in detail, SLE is statistically different from HCs for hairpin capillaries (p=0.010), enlarged capillaries (p<0.001), haemorrhages (p<0.001), irregular architecture (p=0.011) and giant capillaries (p<0.001) as shown in table 2B, online supplemental table S4 and figure 2A.

In addition, a normal NVC pattern was observed in the majority of patients with SLE 175 (86.6%) and in 172 (98.3%) of the HCs, while a pattern with non-specific capillary abnormalities was reported in 8 (3.9%) of the patients with SLE and in 3 (1.7%) of the HCs. Finally, scleroderma patterns were observed in 19 (9.5%) patients with SLE, of whom 12 (63%) had an 'early' pattern, 2 (10.5%) an 'active' pattern and 5 (26.3%) a 'late' pattern, while no scleroderma patterns were detected in HCs (figure 2B and online supplemental table S4).

Cluster analysis identified two NVC patterns in patients with SLE: cluster 1 (less severe) and cluster 2 (more severe)

Based on previous results that highlighted differences in the distribution of individual capillaroscopy parameters without fitting a specific validated pattern, we used multiple correspondence analysis to determine whether patients with SLE have a unique NVC pattern that distinguishes them from HCs (online supplemental figure S3). There were no relevant associations between NVC parameters and disease status. Giant capillaries were rare (79/5311 images, 1.5% images) and detected only in SLE. All other parameters were detected both in SLE and controls, and an association of mixed capillary parameters was mostly detected per image (online supplemental figure S3).

Furthermore, a cluster analysis was performed in SLE subjects (n=202) to investigate whether specific NVC patterns could be identified based on the distribution of NVC parameters (table 3). Finally, two clusters were selected for the analyses since the further subgrouping was limited by the size of each group (n<10). Of the two SLE clusters generated, cluster 1 ('less severe pattern') included the majority of patients with SLE (88%, n=178), while the minority (12%, n=24) was included

Table 2 Results of the comparison between patients with SLE and healthy controls

	SLE		HCs	P value
A. Overall capillaroscopic abnormalities				
Matched analysis, n=350	N=175		N=175	
Presence, n (%)	21 (12.0)		3 (1.7)	<0.001
OR (95% CI)	10.0 (2.43 to 88.24)			
Risk difference (95% CI)	+10.3% (+4.7% to +15.9%)			
Unmatched analysis, n=377	N=202		N=175	
Presence, n (%)	27 (13.4)		3 (1.7)	<0.001
OR (95% CI)				
Logistic model*	8.83 (2.63 to 29.68)			
Penalised logistic model*	7.68 (2.48 to 23.83)			
	OR (95% CI)	**P value**	**OR* (95% CI)**	**P value**
B. Mixed model analysis of capillaroscopy parameters (SLE vs HCs)				
N of subjects=377				
Density, <7 capillary/mm	2.10 (0.77 to 5.74)	0.147	2.08 (0.76 to 5.67)	0.152
Hairpin	2.85 (1.35 to 6.01)	0.006	2.66 (1.26 to 5.60)	0.01
Non-specific variations†	0.84 (0.40 to 1.80)	0.659	0.87 (0.41 to 1.88)	0.734
Crossed	1.59 (0.83 to 3.08)	0.162	1.66 (0.86 to 3.20)	0.129
Tortuous	0.94 (0.45 to 1.96)	0.876	0.96 (0.46 to 1.99)	0.903
Abnormal shapes‡	1.54 (0.76 to 3.14)	0.23	1.57 (0.77 to 3.19)	0.217
Bushy	2.34 (0.87 to 6.36)	0.093	2.41 (0.90 to 6.48)	0.081
Ramified	1.47 (0.63 to 3.43)	0.371	1.48 (0.64 to 3.43)	0.361
Enlarged	5.33 (2.67 to 10.62)	<0.001	5.51 (2.75 to 11.01)	<0.001
Giant§	–	–	–	–
Microhaemorrhages	3.39 (2.06 to 5.57)	<0.001	3.44 (2.09 to 5.66)	<0.001
Venous plexus	0.92 (0.56 to 1.50)	0.734	0.93 (0.57 to 1.52)	0.776
Irregular architecture¶	1060.22 (15.12 to 74 323.48)	0.001	467.66 (4.11 to 50 981.99)	0.011

There was a significantly higher frequency of the overall capillaroscopic abnormalities in SLE compared with HCs (A., primary endpoint) and a different distribution of capillaroscopic abnormalities (B).
*Adjusted for age and gender.
†Crossed and/or tortuous.
‡Bushy and/or ramified. Two-level mixed logistic model with random intercept (subject). Observations varied from a minimum of 5227 to a maximum of 5444.
§Not calculable due to absence of events in controls.
¶OR estimation inflated due to low number of events in controls.
CI, confidence interval; HCs, healthy controls; OR, Odd Ratio; SLE, systemic lupus erythematosus.

in cluster 2 ('more severe pattern'), figure 3A,B. Both clusters had giant capillaries and microhaemorrhages, but they were more common in cluster 2 than in cluster 1 (figure 3C). In addition, cluster 2 had a significantly higher prevalence of low capillary density, abnormal morphology of capillaries (ie, ramified) and enlarged capillaries and irregular architecture than cluster 1. The pattern of overall abnormalities and the scleroderma pattern were also less common in cluster 1 than in cluster 2. On the other hand, as shown in table 3, when SLE clusters were compared with HCs, fewer differences were found in cluster 1 (microhaemorrhages, hairpin, abnormally shaped and giant capillaries) than in cluster 2 (microhaemorrhages, capillary density, non-specific variations of morphology, abnormally shaped, enlarged and giant capillaries, irregular architecture).

Patients with SLE with the more severe NVC pattern (cluster 2) had significantly higher disease activity

Data on SLE disease activity as measured by SLEDAI-2000 are shown in online supplemental table S5. The frequencies of the composite set of capillaroscopic parameters called 'overall capillaroscopic abnormalities' were not significantly different in active and non-active SLE, as shown in table 4A. A significantly higher frequency of capillaroscopic

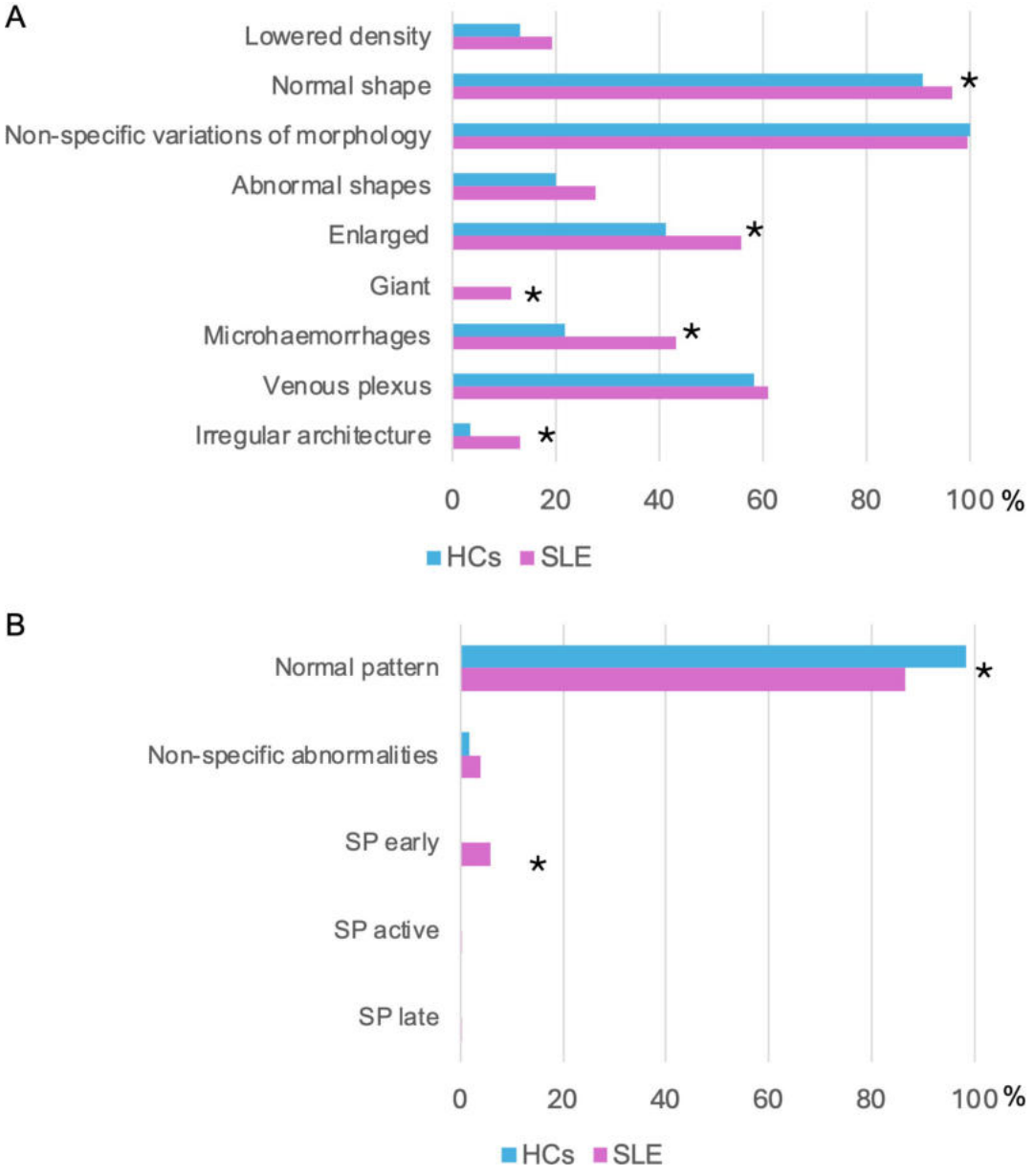

Figure 2 Frequency of capillaroscopic parameters (A) and patterns (B) in patients with SLE (n=202) and HCs (n=175). Figure A, B and D: *p<0.05. HCs, healthy controls; SLE, systemic lupus erythematosus; SP, scleroderma pattern.

parameters was observed in both active or non-active SLE than in HCs (online supplemental tables S6 and S7). When SLE subjects were grouped into clusters, SLE cluster 2 had significantly higher disease activity compared with SLE cluster 1 for both cut-off points ≥3 and ≥4 (p=0.016 and p=0.028, respectively) as shown in table 4B. When disease activity was considered as a continuous predictor instead of classification by cut-off points ≥3 and ≥4, univariable logistic regression showed an OR of 1.08 (95% CI, 1.01 to 1.15, p value=0.027) per 1 point increase in SLEDAI-2000. Single parameter analysis did not reveal a significant difference with respect to disease activity as shown in table 4C.

Different clinical and laboratory associations were observed with overall NVC abnormalities and clusters

The presence of Raynaud's phenomenon, anti-U1RNP antibodies and mucosal manifestations were significantly associated with the presence of overall NVC abnormalities (p<0.001, p=0.046 and p=0.012, respectively), data shown in the online supplemental tables S8–S11.

As shown in online supplemental tables S12 and S13, further analyses considering capillaroscopic clusters 1 and 2 revealed a significantly higher frequency of arthritis, renal involvement and ongoing glucocorticoid therapy in cluster 2 (p=0.011, p=0.041 p=0.011, respectively), whereas serositis was significantly associated with cluster 1 (p=0.044). No significant associations were observed between NVC parameters and the presence of secondary antiphospholipid syndrome or isolated antibody positivity (ie, LAC, anticardiolipin or anti-β2GPI).

DISCUSSION

To our knowledge, this study is the first to compare patients with SLE with matched HCs for NVC parameters

Table 3 Cluster analysis of the capillaroscopic parameters among SLE subjects (n=202) in comparison with controls (n=175) showed two main clusters (1 pattern less severe and 2 pattern more severe)

	SLE cluster 1	SLE cluster 2	P value	HCs	P value	P value
	N=178 (88.1%)	N=24 (11.9%)	Cluster 1 vs cluster 2	N=175	Cluster 1 vs HCs	Cluster 2 vs HCs
Density <7 capillary/mm, n (%)	27 (15.2)	12 (50.0)	<0.001	23 (13.1)	0.571	<0.001
Hairpin, n (%)	171 (96.1)	24 (100)	1.000	159 (90.9)	0.047	0.123
Non-specific variations						
Tortuous, n (%)	172 (96.6)	21 (87.5)	0.077	170 (97.1)	0.788	0.025
Crossed, n (%)	177 (99.4)	23 (95.8)	0.224	173 (98.9)	0.608	0.237
Abnormal shapes						
Ramified, n (%)	28 (15.7)	9 (37.5)	0.020	21 (12.0)	0.314	0.001
Bushy, n (%)	34 (19.1)	3 (12.5)	0.579	19 (10.9)	0.031	0.815
Enlarged, n (%)	91 (51.1)	22 (91.7)	<0.001	72 (41.1)	0.060	<0.001
Giant, n (%)	12 (6.7)	11 (45.8)	<0.001	0 (0.0)	<0.001	<0.001
Microhaemorrhages, n (%)	70 (39.3)	17 (70.8)	0.004	38 (21.7)	<0.001	<0.001
Plex venous, n (%)	106 (59.6)	17 (70.8)	0.374	102 (58.3)	0.804	0.245
Irregular architecture, n (%)	3 (1.7)	23 (95.8)	<0.001	6 (3.4)	0.310	<0.001
Overall abnormalities, n (%)	16 (9.0)	11 (45.8)	<0.001	0 (0.0)	<0.001	<0.001
Scleroderma pattern, n (%)	12 (6.8)	7 (30.4)	<0.002	0 (0.0)	<0.001	<0.001

HCs, healthy controls; SLE, systemic lupus erythematosus.

and disease status in a cross-sectional, international, multicentre cohort using blinded image reading. The first part of the study analysed the differences in NVC between patients with SLE and HCs, as conflicting results have been reported in the literature.[9] We observed a normal NVC pattern in most of the patients with SLE (86.6%) and, less frequently but worth mentioning, a higher frequency of NVC abnormalities such as enlarged dimension and giant capillaries, microhaemorrhages and irregular nail bed architecture in the remaining patients. Some of these data have been reported in the literature, but they are scattered and very heterogeneous.[9] Then, we outlined two capillaroscopic patterns one of which the more severe (cluster 2), found in 12% of patients, was characterised by a higher prevalence of low capillary density, abnormally shaped capillaries, enlarged capillaries and irregular nail bed architecture. Only five studies have previously reported a specific SLE NVC pattern.[27–31] These were single-centre studies with small numbers of patients (21, 30, 15, 9 and 85, respectively), and none of them compared the SLE pattern with HCs.[27–31] The definition of the previously described SLE pattern varies among authors and has been characterised by tortuous (ie, the afferent and efferent capillary limbs are curled), abnormal shapes (ie, meandering), prominent subpapillary venular plexus, haemorrhages or increased loop length.[27–31]

Second, we addressed a very controversial issue, namely the associations of NVC with clinical and laboratory features of SLE. Our results indicate that patients with SLE and a 'more severe' NVC pattern (cluster 2) have a significantly higher disease activity and frequency of arthritis, renal involvement and ongoing glucocorticoid therapy, whereas serositis was significantly associated with the 'less severe' NVC pattern (cluster 1). Regarding the presence of joint involvement, a recent study showed that NVC could not discriminate patients with SLE with or without Jaccoud's arthropathy,[14] but we cannot confirm these results as these data were not collected in our database. Evidence from the literature supports the association between the presence of anti-U1RNP antibodies and Raynaud's phenomenon with capillary abnormalities, and in some studies the presence of these antibodies has been proposed as a 'red flag' for potential progression to an overlap syndrome.[12 13 32–37] Our study design allowed us to confirm these significant associations of these antibodies and Raynaud's phenomenon with the presence of overall NVC abnormalities.

Third, we are consistent with data from the literature reporting significant associations between disease activity and individual NVC parameters in SLE.[9 11 12 15 16] In addition, by grouping NVC parameters into patterns, we showed a significant association between disease activity and the more severe pattern (cluster 2).

The strengths of our study are the robust case–control design and the blinded reading of images to address important limitations often encountered in NVC research, such as the unblinded reading, the small number of patients analysed in previous single-centre studies, and the lack of comparison with HCs. However, some caveats may be listed. First, NVC is still an operator-dependent technique, which sometimes could raise concerns about

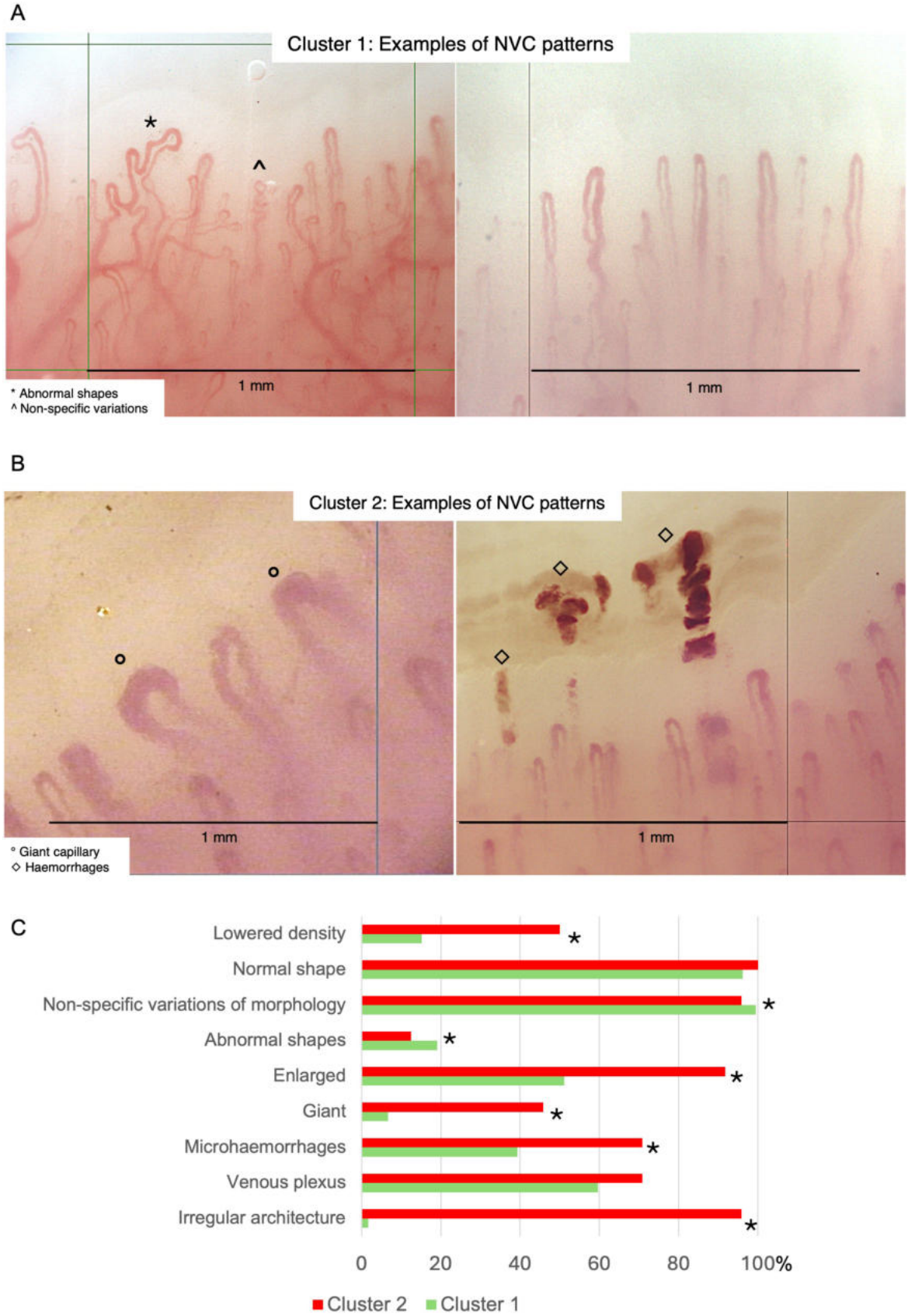

Figure 3 Capillaroscopic cluster patterns. Examples of capillaroscopic patterns classified as (A) the less severe cluster 1 characterised by normal capillary density, regular microvascular architecture, non-specific capillary morphology and abnormally shaped capillaries and (B) the more severe cluster 2, characterised by decreased capillary density, irregular microvascular architecture, giant capillaries and microhaemorrhages. The main capillaroscopic features of the two main clusters (1 pattern less severe, n=178, and 2 pattern more severe, n=24) are shown in the histogram (C). NVC, nailfold videocapillaroscopy.

Table 4 Results of the comparison between patients with SLE with active and non-active disease

	Active SLE	Non-active SLE	P value
A. Overall capillary abnormalities			
SLEDAI-2000 cutpoint ≥3	Patients=96	Patients=97	
Presence, n (%)	14 (14.4)	12 (12.5)	0.694
OR (95% CI)	1.18 (0.51 to 2.70)		
SLEDAI-2000 cutpoint ≥4	N=92	N=101	
presence, n (%)	14 (15.2)	12 (11.9)	0.498
OR (95% CI)	1.1 (0.58 to 3.05)		
B. Capillaroscopic clusters			
SLEDAI-2000 cutpoint ≥3	Patients=96	Patients=97	
SLE cluster 1, n (%)	80 (82.5)	90 (93.7)	
SLE cluster 2, n (%)	17 (17.5)	6 (6.3)	0.016
OR (95% CI)	3.18 (1.19 to 8.48)		
SLEDAI-2000 cutpoint ≥4	Patients=92	Patients=101	
SLE cluster 1, n (%)	76 (82.6)	94 (93.1)	
SLE cluster 2, n (%)	16 (17.4)	7 (6.9)	0.028
OR (95% CI)	1.1 (1.11 to 7.22)		
C. Capillaroscopic parameters			
SLEDAI-2000 cutpoint ≥3	Patients=96	Patients=97	
Density, <7capillary/mm, n (%)	17 (17.7)	21 (21.6)	0.588
Hairpin, n (%)	93 (96.9)	93 (95.9)	1.000
Non-specific variations			
Crossed, n (%)	96 (100)	96 (99.0)	1.000
Tortuous, n (%)	90 (93.7)	94 (96.9)	0.331
Abnormal shapes			
Bushy, n (%)	19 (19.8)	17 (17.5)	0.715
Ramified, n (%)	20 (20.8)	15 (15.5)	0.356
Enlarged, n (%)	48 (50.0)	59 (60.8)	0.149
Giant, n (%)	10 (10.4)	12 (12.4)	0.821
Microhaemorrhages, n (%)	38 (39.6)	43 (44.3)	0.560
Venous plexus, n (%)	66 (69.7)	54 (55.7)	0.075
Irregular architecture, n (%)	7 (7.3)	17 (17.5)	0.048
SLEDAI-2000 cutpoint ≥4	N=92	N=101	
Density, <7 capillary/mm, n (%)	20 (21.7)	18 (17.8)	0.587
Hairpin, n (%)	88 (95.6)	98 (97.0)	0.711
Non-specific variations			
Crossed, n (%)	91 (98.9)	101 (100)	0.477
Tortuous, n (%)	89 (96.7)	95 (94.1)	0.502
Abnormal shapes			
Bushy, n (%)	16 (17.4)	20 (19.8)	0.714
Ramified, n (%)	15 (16.3)	20 (19.8)	0.578
Enlarged, n (%)	56 (60.9)	51 (50.5)	0.192
Giant, n (%)	12 (13.0)	10 (9.9)	0.507
Microhaemorrhages, n (%)	41 (44.6)	40 (39.6)	0.560
Venous plexus, n (%)	51 (55.4)	69 (68.3)	0.075
Irregular architecture, n (%)	16 (17.4)	8 (7.9)	0.052

There was no significant association when analysing total capillary abnormalities and individual capillaroscopic parameters (A and C), while SLE cluster 2 had significantly higher disease activity compared with SLE cluster 1 (B).
HCs, healthy controls; SLE, systemic lupus erythematosus; SLEDAI-2000, Systemic Lupus Erythematosus Disease Activity Index 2000.

the reliability of the image reading. Nevertheless, our results were robust to this variability, which is known and reported for several NVC parameters other than giant capillaries and scleroderma pattern. In the published literature, the reliability of different NVC parameters varies, being the number of capillaries is the most reliable parameter.[23 38–43] Second, the optimal sample size for 80% power (n=182 per group) was not achieved due to the lack of HCs enrolment, but according to the study design, enrolment of 175 subjects per group was expected to provide 79% power, which could be considered reasonably close to the original target.

In conclusion, our study in patients with SLE has highlighted the potential role of NVC in capturing important aspects of disease activity. Future prospective studies are needed to further support the use of NVC in monitoring patients with SLE over time and to validate the presence of the 'more severe' cluster 2 NVC pattern as a proxy measure of disease activity in clinical and research settings.

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REFERENCES

1 Kaul A, Gordon C, Crow MK, *et al*. Systemic lupus erythematosus. *Nat Rev Dis Primers* 2016;2:16039.

2 Tamirou F, Arnaud L, Talarico R, *et al*. Systemic lupus erythematosus: state of the art on clinical practice guidelines. *RMD Open* 2018;4:e000793.
3 Crow MK. Pathogenesis of systemic lupus erythematosus: risks, mechanisms and therapeutic targets. *Ann Rheum Dis* 2023;82:999–1014.
4 Soltész P, Kerekes G, Dér H, *et al*. Comparative assessment of vascular function in autoimmune rheumatic diseases: considerations of prevention and treatment. *Autoimmun Rev* 2011;10:416–25.
5 Svensson C, Eriksson P, Bjarnegård N, *et al*. Impaired Microcirculation and Vascular Hemodynamics in Relation to Macrocirculation in Patients With Systemic Lupus Erythematosus. *Front Med (Lausanne)* 2021;8:722758.
6 Forte F, Buonaiuto A, Calcaterra I, *et al*. Association of systemic lupus erythematosus with peripheral arterial disease: a meta-analysis of literature studies. *Rheumatology (Oxford)* 2020;59:3181–92.
7 Kostopoulou M, Mukhtyar CB, Bertsias G, *et al*. Management of systemic lupus erythematosus: a systematic literature review informing the 2023 update of the EULAR recommendations. *Ann Rheum Dis* 2024;83:e225319:1489–501:.
8 Cutolo M, Smith V. Detection of microvascular changes in systemic sclerosis and other rheumatic diseases. *Nat Rev Rheumatol* 2021;17:665–77.
9 Cutolo M, Melsens K, Wijnant S, *et al*. Nailfold capillaroscopy in systemic lupus erythematosus: A systematic review and critical appraisal. *Autoimmun Rev* 2018;17:344–52.
10 Saygin D, Highland KB, Tonelli AR. Microvascular involvement in systemic sclerosis and systemic lupus erythematosus. *Microcirculation* 2019;26:e12440.
11 Riccieri V, Spadaro A, Ceccarelli F, *et al*. Nailfold capillaroscopy changes in systemic lupus erythematosus: correlations with disease activity and autoantibody profile. *Lupus (Los Angel)* 2005;14:521–5.
12 Ingegnoli F, Zeni S, Meani L, *et al*. Evaluation of Nailfold Videocapillaroscopic Abnormalities in Patients With Systemic Lupus Erythematosus. *JCR: Journal of Clinical Rheumatology* 2005;11:295–8.
13 Chebbi PP, Goel R, Ramya J, *et al*. Nailfold capillaroscopy changes associated with anti-RNP antibodies in systemic lupus erythematosus. *Rheumatol Int* 2022;42:1355–61.
14 Pimenta da Fonseca E, Lins CF, de Sá Ribeiro DL, *et al*. Videocapillaroscopic Findings in Patients With Systemic Lupus Erythematosus With or Without Jaccoud Arthropathy. *J Clin Rheumatol* 2021;27:S198–203.
15 Fatemi A, Erlandsson B-E, Emrani Z, *et al*. Nailfold microvascular changes in patients with systemic lupus erythematosus and their associative factors. *Microvasc Res* 2019;126:103910.
16 Shenavandeh S, Habibi S. Nailfold capillaroscopic changes in patients with systemic lupus erythematosus: correlations with disease activity, skin manifestation and nephritis. *Lupus (Los Angel)* 2017;26:959–66.
17 Munguía-Realpozo P, García-Carrasco M, Mendoza-Pinto C, *et al*. Absence of association between nailfold capillary findings and mild cognitive dysfunction in systemic lupus erythematosus. *Clin Rheumatol* 2022;41:2737–43.
18 Petri M, Orbai A, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis & Rheumatism* 2012;64:2677–86.
19 Solano C, Lamuño M, Vargas A, *et al*. Comparison of the 1999 Sapporo and 2006 revised criteria for the classification of the antiphospholipid syndrome. *Clin Exp Rheumatol* 2009;27:914–9.
20 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
21 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–9.
22 Yee C-S, Farewell VT, Isenberg DA, *et al*. The use of Systemic Lupus Erythematosus Disease Activity Index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients. *Rheumatology (Oxford)* 2011;50:982–8.
23 Ingegnoli F, Gualtierotti R, Lubatti C, *et al*. Feasibility of Different Capillaroscopic Measures for Identifying Nailfold Microvascular Alterations. *Semin Arthritis Rheum* 2009;38:289–95.
24 Smith V, Herrick AL, Ingegnoli F, *et al*. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev* 2020;19:102458.
25 Ingegnoli F, Gualtierotti R, Lubatti C, *et al*. Nailfold capillary patterns in healthy subjects: a real issue in capillaroscopy. *Microvasc Res* 2013;90:90–5.
26 Cutolo M, Pizzorni C, Sulli A. Nailfold video-capillaroscopy in systemic sclerosis. *Z Rheumatol* 2004;63:457–62.
27 Granier F, Vayssairat M, Priollet P, *et al*. Nailfold capillary microscopy in mixed connective tissue disease. Comparison with systemic sclerosis and systemic lupus erythematosus. *Arthritis Rheum* 1986;29:189–95.
28 Lambova SN, Müller-Ladner U. Capillaroscopic pattern in systemic lupus erythematosus and undifferentiated connective tissue disease: what we still have to learn? *Rheumatol Int* 2013;33:689–95.
29 Wu P-C, Huang M-N, Kuo Y-M, *et al*. Clinical applicability of quantitative nailfold capillaroscopy in differential diagnosis of connective tissue diseases with Raynaud's phenomenon. *J Formos Med Assoc* 2013;112:482–8.
30 McGill NW, Gow PJ. Nailfold capillaroscopy: a blinded study of its discriminatory value in scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. *Aust N Z J Med* 1986;16:457–60.
31 Zhao T, Lin FA, Chen HP. Pattern of Nailfold Capillaroscopy in Patients With Systemic Lupus Erythematosus. *Arch Rheumatol* 2020;35:568–74.
32 Furtado RN, Pucinelli ML, Cristo VV, *et al*. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud's phenomenon in SLE patients. *Lupus (Los Angel)* 2002;11:35–41.
33 Pavlov-Dolijanovic S, Damjanov NS, Vujasinovic Stupar NZ, *et al*. Is there a difference in systemic lupus erythematosus with and without Raynaud's phenomenon? *Rheumatol Int* 2013;33:859–65.
34 Choi MY, Chen I, Clarke AE, *et al*. Machine learning identifies clusters of longitudinal autoantibody profiles predictive of systemic lupus erythematosus disease outcomes. *Ann Rheum Dis* 2023;82:927–36.
35 Le Tallec E, Bourg C, Bouzillé G, *et al*. Prognostic insights from symptom clustering analysis in systemic lupus erythematosus. *RMD Open* 2025;11:e005330.
36 Ahmad A, Brylid A, Dahle C, *et al*. Doubtful Clinical Value of Subtyping Anti-U1-RNP Antibodies Regarding the RNP-70 kDa Antigen in Sera of Patients with Systemic Lupus Erythematosus. *Int J Mol Sci* 2023;24:10398.
37 Makarem YS, Selim ZI, Ismail S, *et al*. Nailfold capillaroscopy changes in systemic lupus erythematosus patients: Correlation with disease activity and anti-uridin1-ribonucleoprotein antibodies. *Reumatol Clin (Engl Ed)* 2025;21:501840.
38 Smith V, Pizzorni C, De Keyser F, *et al*. Reliability of the qualitative and semiquantitative nailfold videocapillaroscopy assessment in a systemic sclerosis cohort: a two-centre study. *Ann Rheum Dis* 2010;69:1092–6.
39 Hofstee HMA, Serné EH, Roberts C, *et al*. A multicentre study on the reliability of qualitative and quantitative nail-fold videocapillaroscopy assessment. *Rheumatology (Oxford)* 2012;51:749–55.
40 Dinsdale G, Moore T, O'Leary N, *et al*. Intra-and inter-observer reliability of nailfold videocapillaroscopy - A possible outcome measure for systemic sclerosis-related microangiopathy. *Microvasc Res* 2017;112:1–6.
41 Dinsdale G, Moore T, O'Leary N, *et al*. Quantitative outcome measures for systemic sclerosis-related Microangiopathy - Reliability of image acquisition in Nailfold Capillaroscopy. *Microvasc Res* 2017;113:56–9.
42 Boulon C, Devos S, Mangin M, *et al*. Reproducibility of capillaroscopic classifications of systemic sclerosis: results from the SCLEROCAP study. *Rheumatology (Oxford)* 2017;56:1713–20.
43 Karbalaie A, Etehadtavakol M, Abtahi F, *et al*. Image enhancement effect on inter and intra-observer reliability of nailfold capillary assessment. *Microvasc Res* 2018;120:100–10.