Multimodal imaging evaluation of pre-systemic sclerosis patients presenting with Raynaud's Phenomenon from a reference microcirculatory clinic versus healthy controls: a cross-sectional study

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PII: S0049-0172(26)00098-3
DOI: https://doi.org/10.1016/j.semarthrit.2026.153008
Reference: YSARH 153008

To appear in: *Seminars in Arthritis & Rheumatism*

Please cite this article as: Ramona Govender , Elvis Hysa , Rosanna Campitiello , Steven Wallaert , Matthias Vandycke , Emanuele Gotelli , Tessa Du Four , Yves Piette , Maurizio Cutolo , Vanessa Smith , Multimodal imaging evaluation of pre-systemic sclerosis patients presenting with Raynaud's Phenomenon from a reference microcirculatory clinic versus healthy controls: a cross-sectional study, *Seminars in Arthritis & Rheumatism* (2026), doi: https://doi.org/10.1016/j.semarthrit.2026.153008

Highlights

- First HFUS, LASCA, NVC study in LeRoy pre-SSc from an RP microcirculation clinic.
- HFUS detects early dermal thickening in pre-SSc before clinical skin involvement.
- LASCA and NVC detect early functional and structural microvascular changes.
- Multimodal imaging shows early biological activity in an organ-sparse pre-SSc cohort.

Title Page

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Multimodal imaging evaluation of pre-systemic sclerosis patients presenting with Raynaud's Phenomenon from a reference microcirculatory clinic versus healthy controls: a cross-sectional study

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Abstract

Objective:

To determine whether multimodal imaging tools can detect dermal and microvascular abnormalities in pre-systemic sclerosis (pre-SSc) patients compared with matched healthy controls (HC).

Methods:

Non-selected pre-SSc patients (n=20, fulfilling LeRoy's criteria) from the Ghent University (hospital) Raynaud's clinic and age-, sex-, and BMI-matched HC (n=20) were evaluated. Dermal thickness (DT) was measured using high-frequency ultrasound (HFUS, 18MHz) at 17 sites. Nailfold videocapillaroscopy (NVC, 200x magnification) was assessed using standardized consensus. Peripheral blood perfusion (PBP) was quantified using laser speckle contrast analysis (LASCA). Group differences were analysed using generalised linear mixed models with group, location and their interaction as fixed effects, accounting for matching and within-subject clustering.

Results:

HFUS showed an effect of group on mean DT ($p = 0.011$). Significant locations included the right and left fingers (0.80 ± 0.04 vs 0.68 ± 0.04 mm, $p = 0.012$; 0.81 ± 0.04 vs 0.67 ± 0.04 mm, $p = 0.015$) and left forearm (1.02 ± 0.05 vs 0.88 ± 0.05 mm, $p = 0.035$). LASCA demonstrated reduced (volar) fingertip PBP in pre-SSc (139 ± 12 vs 200 ± 12 perfusion units; mean difference = 61, 95% CI: 38-85; $p < 0.001$). NVC revealed lower capillary density (7.8 vs 9.8/mm, $p<0.001$), increased microhaemorrhages (18% vs 7.4%, $p = 0.032$), and exclusivity of giant capillaries and scleroderma pattern.

Conclusion:

Dermal, functional and structural microvascular abnormalities are detectable in pre-SSc in the absence of clinical skin thickening or overt organ involvement. Future multicentric longitudinal studies are required to confirm multimodal differentiative value.

Abstract word count: 249 words

Keywords:

systemic sclerosis, pre-systemic sclerosis, skin ultrasound, nailfold videocapillaroscopy (NVC), EULAR/ SCTC consensus, laser speckle contrast analysis (LASCA)

1. Introduction

Systemic sclerosis (SSc) is a complex connective tissue disease characterised by autoimmunity, vasculopathy and progressive fibrosis, leading to significant morbidity and mortality (1, 2). Early recognition is critical, as organ damage largely becomes irreversible once established (3). Microcirculatory dysfunction is a key pathogenic feature, with Raynaud's phenomenon (RP) often representing the first clinical symptom (1), and serves as a clinical entry point into efforts to define an early ("pre-SSc") stage before overt skin and organ involvement. Identifying a biologically active period preceding established SSc may provide a crucial window of opportunity to predict individuals at risk of severe and/or progressive disease, enabling earlier intervention strategies and improved outcomes.

Two frameworks have shaped current approaches to predict individuals at risk of progressing to definite SSc. LeRoy and Medsger (2001) classified patients with RP and either SSc-specific autoantibodies or scleroderma-type nailfold capillaroscopy changes as "limited or early SSc" (4), and a decade later, the very early diagnosis of systemic sclerosis (VEDOSS) initiative (2011) incorporated puffy fingers and antinuclear antibody (ANA) positivity (5). Both frameworks have been validated longitudinally, stratifying 5- and 10-year progression risks of 65.9% and 72.7%

respectively in LeRoy cohorts (6), and a 5-year risk of 94.1% in VEDOSS cohorts presenting with RP, SSc-specific antibodies and puffy fingers (5).

However, observational cohorts using these criteria demonstrate that they capture heterogenous populations with variable baseline SSc-related organ involvement. LeRoy-defined cohorts generally show less baseline organ involvement (7-10), whereas VEDOSS-defined cohorts often demonstrate patients with a higher burden of organ involvement or even early clinical disease (11-13). This heterogeneity complicates efforts to isolate a clinically silent but biologically active window, underscoring the need for additional and novel biomarkers beyond clinical features, to better define and study this pre-SSc stage.

Microvascular assessment is central to SSc diagnosis. Nailfold videocapillaroscopy (NVC) is a non-invasive method with excellent reliability (14) allowing for direct visualisation of the microcirculation to identify peripheral microangiopathy in SSc (15). Laser speckle contrast analysis (LASCA) is a validated technique with good-excellent intra- (ICC 0.74-0.95) and inter-rater (ICC 0.87-0.97) reliability that quantifies functional and dynamic peripheral blood perfusion (PBP) over large skin areas with high spatial and temporal resolution (16-18), and prior studies have demonstrated associations between reduced perfusion and more severe NVC microangiopathy patterns in SSc (13, 19, 20).

High frequency ultrasound (HFUS) provides a complementary structural assessment of dermal thickness (DT), potentially offering greater sensitivity than the modified Rodnan skin score (mRSS), which may be limited by intra- and inter-observer variability (21-23). DT measurement shows high reliability (inter-rater ICC~0.84, intra-rater ICC~0.92), discriminates between thickened skin in SSc and healthy controls (22, 24-26), correlates with mRSS and skin histology, and may detect subclinical skin involvement when mRSS is zero (27). Together, these three

modalities capture distinct functional and structural microvascular domains central to early SSc pathophysiology.

Although individual modalities have been evaluated in SSc and, to a lesser extent, in pre-SSc, no study has applied HFUS, LASCA and NVC in parallel within the same cohort or compared them directly with matched healthy controls (HC). Here, we apply multimodal imaging in a LeRoy-defined pre-SSc population, recruited in a microcirculatory reference unit, to determine whether vascular and dermal changes are detectable before overt organ involvement.

2. Methods

2.1 Study Population

Twenty non-selected pre-SSc patients (16 females, 4 males, mean age 46 ± 13 SD years), were recruited between 2022 and 2025 through the Raynaud's clinic of the Ghent University Microcirculatory Unit, a recognised European Alliance of Associations for Rheumatology (EULAR) Training and Research Centre and European Reference Network centre on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET). All patients had been referred for evaluation of RP and not for organ-related symptoms. Pre-SSc was defined according to criteria of LeRoy and Medsger (6) by the presence of RP together with a scleroderma capillaroscopic pattern and/or SSc-specific autoantibodies (anti-centromere, anti-topoisomerase I/Scl-70, anti-PM/Scl, anti-fibrillin, or anti-RNA polymerase I/III). Healthy controls (HC) were recruited from the Ghent University Hospital environment (hospital staff, staff relatives, and students) and had no history of RP or rheumatic diseases. Controls were matched 1:1 to pre-SSc patients for age, sex and body-mass index (BMI) (Table 1).

2.2 Data Collection

Clinicodemographic profiles were collected including age, sex, BMI, presence and duration of RP, autoantibody profile, inflammation markers, current vasoactive and immunosuppressive therapy and status of smoking (current/ previous/ never).

2.3 Assessment of SSc-related organ involvement

All pre-SSc patients underwent a standard SSc-specific baseline visit in our centre, as previously described (28, 29). This included structured recording of medical history and medication use, clinical examination with modified Rodnan skin score (mRSS) and standard blood tests. Cardiopulmonary screening tests included transthoracic echocardiography (TTE), pulmonary function tests (forced vital capacity and diffusing capacity for carbon monoxide, FVC and DLCO, expressed as % predicted), and electrocardiography. A high-resolution CT (HRCT) scan of the chest was performed on all patients at baseline.

Evaluated domains, in-line with SSc organ screening proposed by Medsger et al (30), included skin, peripheral vascular system, lungs, heart, gastrointestinal tract, kidneys, and musculoskeletal system. Skin involvement was defined as skin thickening (mRSS ≥1) or the presence of puffy fingers or hands or telangiectasia. Peripheral vascular involvement referred to the presence of RP or pitting scar or digital ulcer or gangrene (31, 32). Interstitial lung disease (ILD) was diagnosed on HRCT by the presence of interstitial abnormalities, including pulmonary fibrosis, ground-glass opacities, or honeycombing (33). To screen for pulmonary hypertension, all patients underwent TTE, and patients with a high probability of pulmonary arterial hypertension were referred for right heart catheterisation in accordance with the European Society of Cardiology (ESC)/ European Respiratory Society (ERS) guidelines (34, 35). Pulmonary arterial hypertension (PAH) was defined as a mean pulmonary artery pressure ≥ 20mmHg combined with a pulmonary capillary wedge pressure ≤ 15mmHg and pulmonary vascular resistance > 2WU on right heart catheterisation (35). Cardiac involvement included diastolic dysfunction or left ventricular systolic dysfunction (ejection fraction <50%) or pericardial effusion on TTE (31). Gastrointestinal symptom screening included oesophageal symptoms

(dysphagia and/or gastro-oesophageal reflux), stomach symptoms (early satiety and/or vomiting), and intestinal symptoms (diarrhoea, bloating and/or constipation) while overt gastrointestinal involvement was defined as the presence of intestinal obstruction or malabsorption syndrome (31). Renal involvement corresponded to the presence of scleroderma renal crisis (SRC) or abnormal elevated creatinine, and musculoskeletal involvement to elevated creatine kinase, arthritis, or muscle weakness (31, 33).

2.4 High frequency ultrasound (HFUS)

A Logiq S8 ultrasound system (GE Healthcare, Chalfont St Giles, UK), equipped with an 18 MHz linear probe in B-mode was used (Figure 1, panel A). All acquisitions were performed by trained operators (pre-SSc cohort: R.G., TD; healthy controls: R.G., E.H.) using a standardised protocol, with the probe placed perpendicular to the skin on a thick gel layer and minimal pressure applied. Images were obtained at 17 anatomical sites corresponding to the mRSS locations: dorsal aspect of the third finger (midway between metacarpophalangeal and proximal inter-phalangeal joints), dorsum of the hands between the first and second metacarpal bones bilaterally, mid-dorsum of the forearms bilaterally, lateral upper arms bilaterally, cheeks (1 cm inferior to the zygomatic arch), parasternal second intercostal space, right abdomen (5 cm to the right of the umbilicus), mid-dorsal thighs bilaterally, dorso-lateral lower legs bilaterally, and dorsum of the feet between the first and second metatarsal bones bilaterally (26, 36). DT measurements were extracted by two investigators (R.G., E.H.) and the mean value (in millimetres) of each region was taken from three measurements, as previously described (26).

2.5 Laser speckle contrast analysis (LASCA)

Peripheral blood perfusion (PBP) was analysed by LASCA (Pericam PSI, Perimed, Jarfalla, Sweden) using pre-defined protocols (17, 18) (Figure 1, panel B). For each participant, recordings were obtained over a 30-second period, covering a 12 x 12 cm field of view, with the device positioned 20 ± 0.5cm above the hand. In line with our standard RP microcirculation

clinic protocol, participants were instructed to avoid smoking, caffeinated beverages and strenuous exercise on the morning of the visit, and to maintain stable vasoactive therapy. Examinations were performed in a controlled environment, ensuring stable temperature and lighting, after a 20-minute acclimatisation phase. Circular regions of interest (ROIs, diameter 1cm) were placed on the volar aspect of the 2nd-5th fingertips of both hands. Mean PBP within the ROIs was derived and reported in perfusion units (PU) using the LASCA software (PIMSoft 15.1, Perimed AB) (16, 37).

2.6 Nailfold videocapillaroscopy (NVC)

NVC was performed using a videocapillaroscopic probe with a 200x magnification lens, and two images were obtained from the 2nd-5th fingers bilaterally in each participant (Figure 1, Panel C). The NVC images were analysed blindly by a trained assessor (R.C.) under the supervision of a microcirculation and capillaroscopy expert (V.S.). Assessments were performed in accordance with standardised definitions of the EULAR/ Scleroderma Clinical Trial Consortium (SCTC) Study Group on Microcirculation in Rheumatic Diseases consensus (15). Both quantitative (NVC parameters: capillary density, dimension, morphology and the presence of haemorrhages) and qualitative analysis (normal, non-specific, or scleroderma pattern) were evaluated at an image level (16 images per patient) and at a subject level over a 1-mm grid.

2.7 Ethical Approval

The study was approved by the Ethics Committee of the Ghent University Hospital (EC/2008/385 and EC/2019/1633), and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent for clinical data collection and for the acquisition of HFUS, LASCA, and NVC imaging as part of their evaluation.

2.8 Statistical Analysis

After matching, balance was assessed numerically using standardised mean differences and graphically with density plots. Differences between pre-SSc patients and HCs were analysed with linear mixed models for continuous outcomes (e.g. skin thickness, peripheral blood perfusion) and generalized linear mixed models for categorical or count outcomes (e.g. giants, microhaemorrhages, scleroderma/non-specific/normal patterns, capillary density, abnormal shapes, dilatation). Models included group, location, and their interaction as fixed effects, with appropriate random effects structures (specified at two levels: within-subject correlation and within matched pair correlation) to account for clustering. For outcomes with complete separation (e.g. presence of giant capillaries or scleroderma pattern, which were absent in healthy controls), estimates were obtained using maximum a posteriori method with Gaussian priors to stabilise results. For LASCA analyses, sex and vasodilator use were additionally included as fixed effects, given their potential influence on microvascular perfusion. Model-based estimates for continuous outcomes are presented as mean ± SE; categorical outcomes are presented as proportions with 95% confidence intervals or risk differences, with SEs provided from the model to indicate estimate precision. Model selection was guided by the Akaike Information Criterion (AIC). Analyses were performed in R (version 4.4.2) (38) with the glmmTMB package (39).

3. Results

3.1 Study population

Mean age, sex and BMI distribution were comparable between groups. All pre-SSc patients presented with RP, while puffy fingers and telangiectasia were noted in 30% and 25% respectively. Oesophageal symptoms, predominantly gastro-oesophageal reflux, were observed in 30%, however there was no corresponding oesophageal dilation on chest HRCT. Mild diastolic dysfunction (Grade 1) was noted in 2 (10%) patients. Mean pulmonary function was within the normal range, with FVC 106.6% (SD 13.3) and DLCO 100.6% (SD 15.1) of predicted. No patients

had ILD on HRCT, and none met ESC/ERS criteria for referral to right heart catheterisation; consequently, no patient was diagnosed with PAH (Table 1, Supplementary table 1).

3.2 HFUS

HFUS showed an effect of group on mean DT (likelihood ratio test [LRT] p = 0.011). Significant locations (Figure 2, supplementary table 2) included the right and left middle fingers (0.80 ± 0.04 vs 0.68 ± 0.04 mm, p = 0.012; 0.81 ± 0.04 vs 0.67 ± 0.04 mm, p = 0.015), the left forearm (1.02 ± 0.05 vs 0.88 ± 0.05 mm, p = 0.035), and tendency in the right foot (0.80 ± 0.04 vs 0.72 ± 0.04 mm, p = 0.088).

3.3 LASCA

Peripheral blood perfusion at the volar aspect of the fingers was significantly reduced in pre-SSc compared with HC (139 ± 12 vs 200 ± 12 PU; mean difference −61 PU, 95% CI −85 to −38; p < 0.001), after adjusting for sex and vasodilator use. This reduction was consistent across all examined fingers (Figure 2, Supplementary Tables 3 and 4), with no significant finger-to-finger differences (group by finger interaction: p=0.544).

3.4 NVC

Quantitative analysis showed significantly lower capillary density in pre-SSc compared with healthy controls (7.84 ± 0.25 vs 9.75 ± 0.31 per linear mm; mean difference −1.90, 95% CI −2.68 to −1.12; p < 0.001). The prevalence of microhaemorrhages (18% vs 7.4%; RD −10.6%, 95% CI −20.4 to −0.9; p = 0.032) was also higher in pre-SSc. Abnormal capillary morphology trended higher (0.38 vs 0.23 per mm, p = 0.060), whereas mean dilations per linear mm showed no significant differences. Giant capillaries and scleroderma patterns were observed exclusively in pre-SSc (Figure 3, Supplementary Table 5). At the patient level, 12/20 pre-SSc patients (60%)

exhibited a scleroderma pattern, comprising 5 early and 7 active patterns, with no late patterns (Table 1).

4. Discussion

This is, to our knowledge, the first study to apply instrumental investigations (HFUS, LASCA and NVC) in a pre-SSc cohort defined by RP and characterized by either SSc-specific autoantibodies and/or a scleroderma capillaroscopic pattern, recruited through a reference microcirculatory clinic where patients were referred for RP evaluation rather than for organ-related symptoms, reflecting an early, pre-organ stage of disease.

Clinically, our patients showed minimal organ involvement, limited to puffy fingers (30%), oesophageal symptoms (30%), and mild diastolic dysfunction (10%). Prior LeRoy-defined cohorts reported similarly low frequencies: puffy fingers 9–15% (7, 8, 40), oesophageal involvement (symptoms or manometry) 21–30% (7, 9, 10), and diastolic dysfunction 6–9% (7, 8). Some also described occasional digital scars (2.9%) (8), ILD/PAH (2.5%) (40), or lung function decline (28%) (7), which were absent in our cohort. By contrast, VEDOSS-defined cohorts, where puffy fingers is an entry criterion, consistently report higher organ burden, including digital ulcers/scars (2–23%) (11-13, 41), sclerodactyly (15%) (11), tendon friction rubs (0.4-2%) (11, 13, 41), HRCT-defined ILD (up to 49%) (13) and SRC (0.4%) (13).

Against this background of minimal burden, we show that multimodal imaging can already detect dermal and microvascular abnormalities in pre-SSc, distinguishing patients from healthy controls before overt skin and organ disease develops. In parallel, biomarker studies demonstrate that even LeRoy-defined cohorts with minimal organ involvement show measurable biological activity. Cossu et al. (10) found elevated serum angiogenetic and endothelial dysfunction markers in a pre-SSc cohort with only oesophageal symptoms and no puffy fingers or SSc-related organ involvement. Angiopoietin-2 was already significantly

elevated compared to controls (2876 vs 1949 pg/ml, p<0.05), with stepwise increases through definite SSc subsets (p<0.0001 for trend). Other endothelial markers such as with CXCL16, E-selectin and soluble intercellular adhesion molecule-1 showed a graded rise, reaching significance in established SSc. Together with our results, this reinforces the concept that pre-SSc is not biologically silent and that both circulating biomarkers and imaging can capture subclinical disease processes before overt clinical involvement.

HFUS revealed a group-level signal of dermal thickening in pre-SSc compared with HC (LRT p=0.011), and the interaction of location with group (p=0.001) indicated that differences varied by anatomical site. In this cohort, significant differences were noted at the fingers and forearm, with a trend in the right foot, consistent with the clinical distribution of early skin changes in SSc. These results may suggest detectable subclinical skin involvement in pre-SSc patients even before overt clinical thickening.

To date, no study has evaluated dermal thickness in a pre-SSc cohort recruited through a reference microcirculatory clinic, where patients were included solely on the basis of RP fulfilling LeRoy's criteria. In this context, our study represents the largest HFUS investigation to assess dermal thickness across 17 anatomical sites in pre-SSc, demonstrating that differences are already detectable prior to fulfilment of the 2013 ACR/EULAR classification criteria. Notably, a small exploratory study using photoacoustic/HFUS in 5 VEDOSS patients (mRSS = 0) also reported thicker dermis at the finger level compared with 5 primary RP (finger 3 median DT 0.50 mm [IQR 0.45–0.52] in pre-SSc vs. 0.28 mm [0.26–0.27] in PRP; p = 0.0079) (42), supporting the concept that HFUS may detect early dermal changes when clinical skin thickening is absent. Future large-scale multicentre pre-SSc studies will be important to determine whether early increases in DT on HFUS are specifically driven by patients with concomitant puffy fingers.

Our study extends this evidence by demonstrating HFUS-detectable dermal changes in a well-characterised, organ-sparse RP-defined pre-SSc cohort. Meanwhile in established SSc (LcSSc and DcSSc), our group has proposed a simple HFUS cut-off at the finger level (1.5 mm at the left index finger) with high specificity but low sensitivity (AUC 0.83, 95% CI: 0.75 - 0.90) (26). Whether analogous thresholds can be defined in pre-SSc remains to be determined and would require larger, longitudinal reference datasets, which were beyond the scope of the present study. Collectively, these results position HFUS as a promising tool to capture early structural change in pre-SSc.

LASCA provided complementary evidence of functional microvascular impairment. In our matched cohort, mean finger PBP was consistently lower in pre-SSc compared to HC (mean difference ~61 PU, 95% CI 38 to 85, $p < 0.001$), after controlling for sex and vasodilator use. These findings align with Ruaro et al. (20) who similarly reported reduced fingertip PBP in 31 RP patients fulfilling LeRoy's criteria compared with 70 age-matched HC (90 ± 28 vs 187 ± 72 PU, $p < 0.0001$). Notably, they and Willems et al. (37) observed no significant difference between pre-SSc and established SSc, reinforcing the concept that perfusion impairment emerges at the pre-SSc stage. Together, this supports LASCA as a sensitive marker of early functional vascular change, detectable in the absence of overt organ involvement.

Nailfold videocapillaroscopy corroborated both quantitative and qualitative abnormalities in our LeRoy-defined pre-SSc cohort. Qualitatively, early and active scleroderma patterns (and thus giant capillaries) were observed exclusively in the pre-SSc group, with absence of a late pattern, consistent with prior work (43). Quantitatively, patients showed significantly reduced mean capillary density and a higher prevalence of microhaemorrhages compared with matched healthy controls. Comparative quantitative NVC data in LeRoy-defined pre-SSc cohorts recruited solely through microcirculatory reference units for Raynaud’s phenomenon as the presenting

symptom remain scarce as most prior studies (8, 10) have focused on longitudinal predictors of progression, without paired cross-sectional analyses with HCs.

Camargo et al. (43) reported cross-sectional NVC differences between early SSc (n=46,defined by LeRoy criteria) and HCs (n=45). Consistent with our findings, they observed a significantly reduced mean capillary density per linear millimetre (9.36±100 vs 10.12 ± 0.58, p<0.001) and increased microhaemorrhages (0.07 ± 0.16 vs 0, p<0.001) in their cohort. However, they also noted significantly increased dilations (0.43 ± 0.37 vs 0.01 ± 0.02; p < 0.001), not seen in our cohort. While these results support the presence of microvascular alterations in pre-SSc, the authors note the limitation of partial organ evaluation and use of the 1980 ACR classification criteria to determine definite SSc. This potentially introduces misclassification within their early group, thus limiting direct comparability. Our study refined these observations by assessing a well-characterised, minimally burdened, pre-SSc population through a reference microcirculation clinic, with all NVC parameters assessed according to recent EULAR/SCTC consensus definitions (15), ensuring methodological harmonisation and future cross-study comparability.

5. Conclusion

We observed dermal thickening and both functional and structural microvascular abnormalities across multimodal imaging techniques in pre-SSc patients, recruited for Raynaud's phenomenon in an expert microcirculatory unit, compared with matched HC. This is the first application of HFUS, LASCA, and NVC in a LeRoy-defined pre-SSc cohort, extending prior work that has largely focused on clinical features and progression outcomes. Importantly, these changes were detectable in a population with minimal baseline organ involvement, highlighting their potential to capture subclinical disease. Limitations include the single-center design, modest sample size, and homogenous Caucasian ethnicity, which may restrict generalisability. Future studies should prioritise larger, multi-center, longitudinal cohorts to determine prognostic thresholds and

clarify whether multimodal imaging can refine pre-SSc definitions, discriminate indolent disease from progressive phenotypes, and ultimately inform early intervention strategies.

6. Acknowledgements

Prof. V. Smith and Prof. M. Cutolo are founding and steering committee members of the European Reference Network on Rare Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET). Prof. V. Smith is chair of the EULAR study group on microcirculation in Rheumatic diseases. Prof. V. Smith is a Senior Clinical Investigator of the Research Foundation - Flanders (Belgium) (FWO) [1802925N]. The authors thank Melissa De Decker and Lieze Van Eetvelde for their valuable assistance with healthy control recruitment and data acquisition.

7. Author Contributions: CRediT

Ramona Govender: Investigation, Formal analysis, Validation, Data curation, Writing (original draft), Writing (Review and editing), Visualization, Final approval of manuscript. **Elvis Hysa**: Investigation, Writing (Review and editing), Final approval of manuscript. **Rosanna Campitiello**: Investigation, Writing (Review and editing), Final approval of manuscript. **Steven Wallaert**: Investigation, Formal analysis, Validation, Data curation, Writing (original draft), Writing (Review and editing), Visualization, Final approval of manuscript. **Matthias Vandyke**: Investigation, Final approval of manuscript. **Emanuele Gotelli**: Investigation, Writing (Review and editing), Final approval of manuscript. **Tessa Du Four**: Investigation, Final approval of manuscript. **Yves Piette**: Investigation, Writing (Review and editing), Final approval of manuscript. **Maurizio Cutolo**: Investigation, Validation, Supervision, Final approval of manuscript. **Vanessa Smith**: Conceptualization, Methodology, Investigation, Formal analysis, Validation, Resources, Data curation, Writing (original draft), Writing (Review and editing),

Visualization, Supervision, Project administration, Funding acquisition, Final approval of manuscript.

8. Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

9. Data availability statement

The datasets generated and/or analysed contains sensitive clinical patient data and cannot be made be made publicly available due to confidentiality. De-identified data may be made available from the corresponding author on reasonable request, subject to institutional and ethical regulations.

10. Reference

1. Cutolo M, Soldano S, Smith V. Pathophysiology of systemic sclerosis: current understanding and new insights. Expert Rev Clin Immunol. 2019;15(7):753-64.

2. Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. Lancet. 2023;401(10373):304-18.

3. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-47.

4. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573-6.

5. Bellando-Randone S, Del Galdo F, Lepri G, Minier T, Huscher D, Furst DE, et al. Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study

for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). Lancet Rheumatol. 2021;3(12):e834-e43.

6. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum. 2008;58(12):3902-12.

7. Valentini G, Vettori S, Cuomo G, Iudici M, D'Abrosca V, Capocotta D, et al. Early systemic sclerosis: short-term disease evolution and factors predicting the development of new manifestations of organ involvement. Arthritis Res Ther. 2012;14(4):R188.

8. Zumstein Camargo C, Kayser C. Capillaroscopy changes are associated with disease progression in patients with early systemic sclerosis: A prospective study. Int J Rheum Dis. 2019;22(7):1319-26.

9. Bellocchi C, Beretta L, Wang X, Lyons MA, Marchini M, Lorini M, et al. Longitudinal global transcriptomic profiling of preclinical systemic sclerosis reveals molecular changes associated with disease progression. Rheumatology (Oxford). 2023;62(4):1662-8.

10. Cossu M, Andracco R, Santaniello A, Marchini M, Severino A, Caronni M, et al. Serum levels of vascular dysfunction markers reflect disease severity and stage in systemic sclerosis patients. Rheumatology (Oxford). 2016;55(6):1112-6.

11. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirják L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73(12):2087-93.

12. Lepri G, Guiducci S, Bellando-Randone S, Giani I, Bruni C, Blagojevic J, et al. Evidence for oesophageal and anorectal involvement in very early systemic sclerosis (VEDOSS): report from a single VEDOSS/EUSTAR centre. Ann Rheum Dis. 2015;74(1):124-8.

13. Ferri C, Giuggioli D, Guiducci S, Lumetti F, Bajocchi G, Magnani L, et al. Systemic sclerosis Progression INvestiGation (SPRING) Italian registry: demographic and clinico-serological features of the scleroderma spectrum. Clin Exp Rheumatol. 2020;38 Suppl 125(3):40-7.

14. Smith V, Vanhaecke A, Herrick AL, Distler O, Guerra MG, Denton CP, et al. Fast track algorithm: How to differentiate a "scleroderma pattern" from a "non-scleroderma pattern". Autoimmun Rev. 2019;18(11):102394.

15. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev. 2020;19(3):102458.

16. Ruaro B, Sulli A, Alessandri E, Pizzorni C, Ferrari G, Cutolo M. Laser speckle contrast analysis: a new method to evaluate peripheral blood perfusion in systemic sclerosis patients. Ann Rheum Dis. 2014;73(6):1181-5.

17. Cutolo M, Vanhaecke A, Ruaro B, Deschepper E, Ickinger C, Melsens K, et al. Is laser speckle contrast analysis (LASCA) the new kid on the block in systemic sclerosis? A systematic literature review and pilot study to evaluate reliability of LASCA to measure peripheral blood perfusion in scleroderma patients. Autoimmun Rev. 2018;17(8):775-80.

18. Lambrecht V, Cutolo M, De Keyser F, Decuman S, Ruaro B, Sulli A, et al. Reliability of the quantitative assessment of peripheral blood perfusion by laser speckle contrast analysis in a systemic sclerosis cohort. Ann Rheum Dis. 75. United States2016. p. 1263-4.

19. Ruaro B, Sulli A, Pizzorni C, Paolino S, Smith V, Cutolo M. Correlations between skin blood perfusion values and nailfold capillaroscopy scores in systemic sclerosis patients. Microvasc Res. 2016;105:119-24.

20. Ruaro B, Smith V, Sulli A, Pizzorni C, Tardito S, Patané M, et al. Innovations in the Assessment of Primary and Secondary Raynaud's Phenomenon. Front Pharmacol. 2019;10:360.

21. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Relat Disord. 2017;2(1):11-8.

22. Santiago T, Santiago M, Ruaro B, Salvador MJ, Cutolo M, da Silva JAP. Ultrasonography for the Assessment of Skin in Systemic Sclerosis: A Systematic Review. Arthritis Care Res (Hoboken). 2019;71(4):563-74.

23. Santiago T, Santos E, Ruaro B, Lepri G, Green L, Wildt M, et al. Ultrasound and elastography in the assessment of skin involvement in systemic sclerosis: A systematic literature review focusing on validation and standardization - WSF Skin Ultrasound Group. Semin Arthritis Rheum. 2022;52:151954.

24. Vanhaecke A, Cutolo M, Heeman L, Vilela V, Deschepper E, Melsens K, et al. High frequency ultrasonography: reliable tool to measure skin fibrosis in SSC? A systematic literature review and additional pilot study. Rheumatology (Oxford). 2021;61(1):42-52.

25. Palici C, Ciurea PL, Bita CE, Barbulescu AL, Florescu A, Musetescu AE, et al. Skin Ultrasound Assessment of Patients with Systemic Scleroderma-An Observational Study. J Pers Med. 2024;14(7).

26. Smith V, Berghen N, Hysa E, Vanhaecke A, Wallaert S, Gotelli E, et al. Ultrasound for day-to-day clinical use: construction of a simple discriminator between healthy skin and thickened systemic sclerosis skin. Clin Exp Rheumatol. 2025;43(8):1386-90.

27. Sulli A, Ruaro B, Smith V, Paolino S, Pizzorni C, Pesce G, et al. Subclinical dermal involvement is detectable by high frequency ultrasound even in patients with limited cutaneous systemic sclerosis. Arthritis Res Ther. 2017;19(1):61.

28. Vandecasteele E, Drieghe B, Melsens K, Thevissen K, De Pauw M, Deschepper E, et al. Screening for pulmonary arterial hypertension in an unselected prospective systemic sclerosis cohort. Eur Respir J. 2017;49(5).

29. Vandecasteele E, Melsens K, Vanhaecke A, Blockmans D, Bonroy C, Carton C, et al. Incidence, prevalence and long-term progression of Goh algorithm rated interstitial lung disease in systemic sclerosis in two independent cohorts in flanders: A retrospective cohort study. Semin Arthritis Rheum. 2021;51(5):969-76.

30. Medsger TA, Jr., Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol. 1999;26(10):2159-67.

31. Avouac J, Lepri G, Smith V, Toniolo E, Hurabielle C, Vallet A, et al. Sequential nailfold videocapillaroscopy examinations have responsiveness to detect organ progression in systemic sclerosis. Semin Arthritis Rheum. 2017;47(1):86-94.

32. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, Carpentier P, et al. Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. Arthritis Rheumatol. 2016;68(10):2527-39.

33. Vanhaecke A, Cutolo M, Distler O, Riccieri V, Allanore Y, Denton CP, et al. Nailfold capillaroscopy in SSc: innocent bystander or promising biomarker for novel severe organ involvement/progression? Rheumatology (Oxford). 2022;61(11):4384-96.

34. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67-119.

35. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-731.

36. Cutolo M, Hysa E, Berghen N, du Four T, Cere A, Wyckstandt K, et al. Mapping in healthy subjects different body areas for dermal thickness and skin hardness by high frequency ultrasound and durometry. Clin Exp Rheumatol. 2025;43(1):70-8.

37. Willems S, Smith V, Wallaert S, Gotelli E, Du Four T, Wyckstandt K, et al. Description of Peripheral Blood Perfusion by Laser Speckle Contrast Analysis (LASCA) in 'Early' versus 'Clinically Overt' Systemic Sclerosis in Routine Clinics. Diagnostics (Basel). 2023;13(9).

38. Team RC. R: A language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2024.

39. McGillycuddy M, DI W, G P, Bolker B. Parsimoniously Fitting Large Multivariate Random Effects in glmmTMB. *Journal of Statistical Software*. 2025;112(1):1-19.

40. Araújo FC, Camargo CZ, Kayser C. Validation of the ACR/EULAR classification criteria for systemic sclerosis in patients with early scleroderma. Rheumatology International. 2017;37(11):1825-33.

41. Blaja E, Jordan S, Mihai CM, Dobrota R, Becker MO, Maurer B, et al. The Challenge of Very Early Systemic Sclerosis: A Combination of Mild and Early Disease? J Rheumatol. 2021;48(1):82-6.

42. Daoudi K, Kersten BE, van den Ende CHM, van den Hoogen FHJ, Vonk MC, de Korte CL. Photoacoustic and high-frequency ultrasound imaging of systemic sclerosis patients. Arthritis Res Ther. 2021;23(1):22.

43. Camargo CZ, Sekiyama JY, Arismendi MI, Kayser C. Microvascular abnormalities in patients with early systemic sclerosis: less severe morphological changes than in patients with definite disease. Scandinavian Journal of Rheumatology. 2015;44(1):48-55.

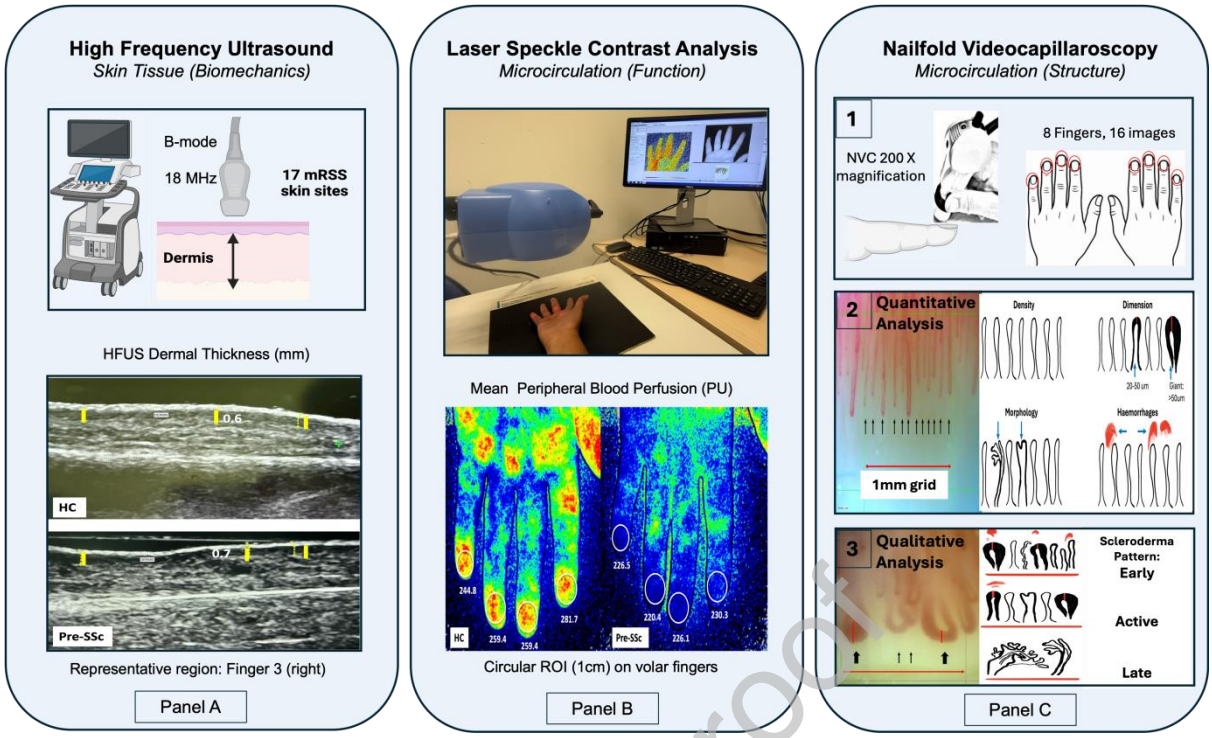


Figure1: Multimodal assessment of skin and microcirculation in pre-systemic sclerosis (pre-SSc).

Three complementary imaging modalities were used to evaluate structural and functional microcirculation and skin biomechanical changes in pre-SSc patients and HCs.

Panel (A) – High frequency ultrasound (HFUS): Dermal thickness was measured at 17 modified Rodnan Skin Score (mRSS) sites using an 18-MHz linear transducer in B-mode. Representative ultrasound images from a healthy control (HC) and a pre-SSc patient of the right third finger are shown, with measurements taken between the epidermis–dermis and dermis–subdermis interfaces.

Panel (B) – Laser Speckle Contrast Analysis (LASCA): Finger perfusion was recorded by the Pericam PSI (Perimed, Jarfalla, Sweden), using pre-defined protocols (*above*). Mean PBP (measured in PU) was obtained from a 1-cm ROI on the volar aspect of digits 2–5. Images from an HC and a pre-SSc patient illustrate perfusion differences (*below*).

Panel (C) – Nailfold Videocapillaroscopy (NVC): Capillaroscopy was performed at 200× magnification on eight fingers (excluding thumbs), yielding 16 images per person (*box 1*). Both quantitative and qualitative analysis was performed using the SCTC/EULAR Study Group

consensus reporting framework. In the quantitative assessment (*box 2*), four parameters are assessed (density, dimension, abnormal morphology and haemorrhages) over 16 fields on a 1-mm grid. On the left side, a NVC image shows a normal pattern with density of 12 capillaries (*black arrows*)(normal ≥ 7) and no dilations, abnormal shapes or haemorrhages. On the right side, each parameter is drawn with examples. In the qualitative assessment (box 3), the overall evaluation is done after going through 16 images to classify into scleroderma or non-scleroderma pattern. On the left side, a NVC image showing a scleroderma pattern characterised by the presence of giant capillaries (diameter ≥ 50um). On the right side, the different patterns of early (presence of giant capillaries with haemorrhages and a normal density) , active (presence of giant capillaries with haemorrhages and a reduced density) and late (markedly reduced density ≤ 3 and abnormal shapes) scleroderma patterns are shown.

Abbreviations: Pre-SSc: pre-systemic sclerosis, HC: healthy control, MHz: megahertz, mm: millimetres, PU: perfusion units, ROI: region of interest.

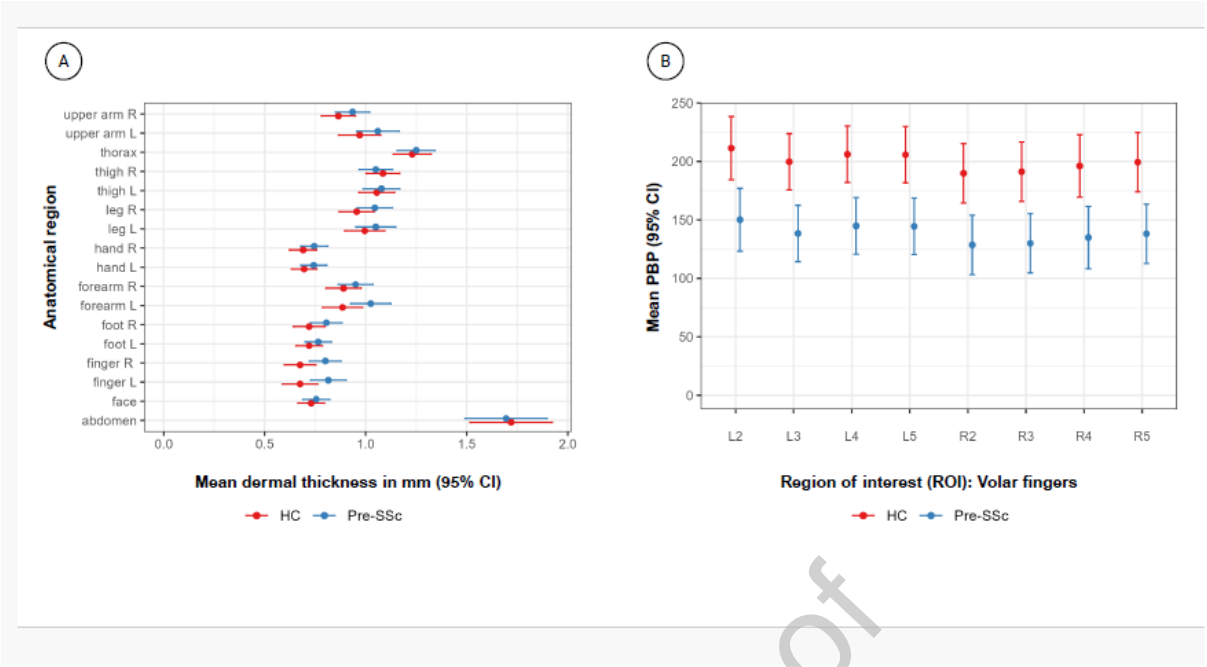


Figure 2: **Dermal thickness (HFUS) and perfusion (LASCA) findings in pre-SSc compared with healthy controls.**

Panel (A): **HFUS**: Group means of DT (mm) across 17 anatomical sites in pre-SSc (*blue*) and HC (*red*). Dots represent means, horizontal whiskers represent 95% CI (forest plot style)

Panel (B): **LASCA**: Mean PBP, as measured in PU, on volar aspect of fingers pre-SSc (*blue*) and HC (*red*).

Abbreviations: HFUS: high frequency skin ultrasound; LASCA: laser speckle contrast analysis; pre-SSc: pre-systemic sclerosis; HC: healthy controls; CI: confidence interval; L: left, R: right; PBP: peripheral blood perfusion; PU: perfusion units; DT: dermal thickness

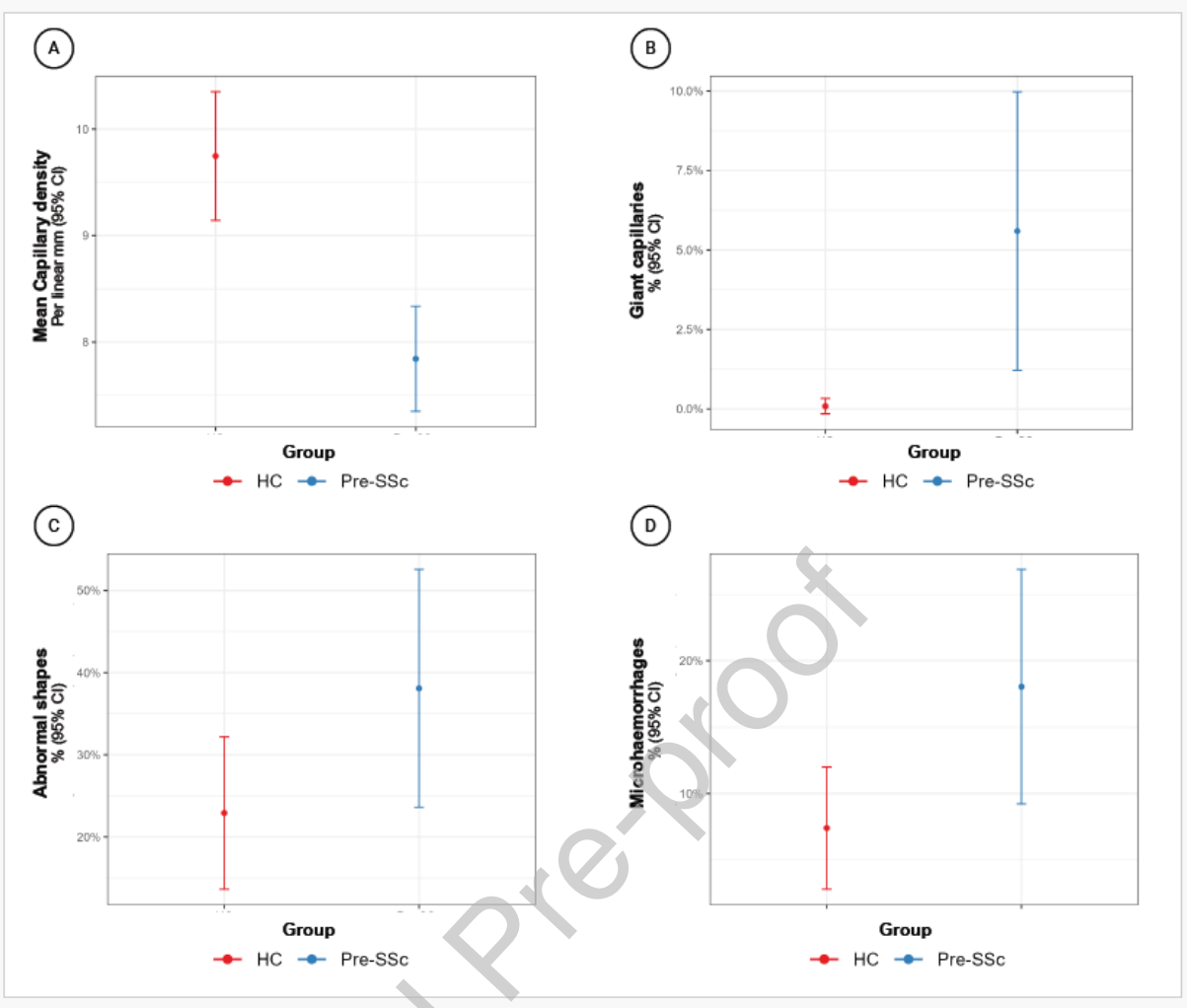


Figure 3: Nailfold videocapillaroscopy (NVC) findings in pre-SSc compared with healthy controls.

Panels (A-D): NVC parameters in pre-SSc (*blue*) and HC (*red*) as measured per linear mm. **(A)** mean capillary density, **(B)** percentage of measurements with giant capillaries, **(C)** percentage of abnormal shapes, **(D)** percentage of microhaemorrhages.

Error bars represent 95% confidence intervals (CI)

Abbreviations: pre-SSc: pre-systemic sclerosis; HC: healthy controls; CI: confidence interval; mm: millimetres.

Table 1. Baseline characteristics of the study population (n=20)

Baseline characteristics	**Pre- SSc** (n=20)	**HC** (n=20)
Demographics		
Age (years), mean (SD)	46 (13)	46 (14)
Female, n (%)	16 (80)	16 (80)
Caucasian, n (%)	20 (100)	20 (100)
BMI (kg/m2), median (IQR)	24.9 (19.8, 26.4)	23.6 (21.6, 27.3)
Smoker, current, n (%)	2 (10)	0
Pre-SSc subsets*, n(%)*		
RP + scleroderma pattern** only	9 (45)	
RP + SSc-specific antibody only	8 (40)	
RP + scleroderma pattern + SSc-specific antibody only	3 (15)	
Antibody status*, n (%)*		
ANA	18 (90)	
SSc-specific antibody	11 (55)	
Anti-centromere antibody	5 (25)	
Anti-topoisomerase-I antibody	3 (15)	
Anti-RNA-polymerase III antibody	2 (10)	
Anti-PM/Scl antibody	1 (5)	
Inflammatory markers		
CRP (mg/L), mean (SD), (normal: 0-5)	1.99 (1.91)	
ESR (mm.hr), mean (SD) (normal 0-20)	8.1 (5.5)	
SSc-related organ involvement		
Peripheral vascular involvement, n (%)		

RP	20 (100)
Digital ulcers	0
Gangrene	0
Pitting scars	0
NVC pattern, n (%)	
Non-specific pattern	8 (40)
Early scleroderma pattern	5 (25)
Active scleroderma pattern	7 (35)
Late scleroderma pattern	0
Pulmonary Involvement	
ILD, n (%)	0
FVC % predicted, mean (SD)	106.6 (13.3)
DLCO %predicted, mean (SD)	100.6 (15.1)
PAH, n (%)	0
Skin	
mRSS, mean	0
Puffy fingers, n (%)	6 (30)
Telangiectasia, n (%)	5 (25)
Heart	
Diastolic dysfunction (grade 1), n (%)	2 (10)
LVEF < 50%, n (%)	0
Pericardial effusion, n (%)	0
Gastrointestinal tract	
Esophageal symptoms, n (%)	6 (30)
Stomach symptoms, n (%)	0
Intestinal symptoms, n (%)	0
Intestinal obstruction, n (%)	0

Malabsorption, n (%)	0
Renal	
Creatinine level (mg/dl), mean (SD)	0.76 (0.11)
(normal: 0.6 - 1.1)	
SRC, n (%)	0
Musculoskeletal involvement	
Arthritis, n (%)	0
Muscle weakness, n (%)	0
CK elevation, n (%)	0
Medication	
Vasodilator therapy, n (%)	4 (20)
Prostacyclin, n (%)	0
Calcium antagonists, n (%)	4 (20)
Endothelin receptor antagonists, n (%)	0
Phosphodiesterase type 5 inhibitor, n (%)	0
Immunosuppressive therapy	
HCQ, n (%)	2 (10)[#]
MTX, n (%)	0
MMF, n (%)	0
CYC, n (%)	0
AZA, n (%)	0
Rituximab, n (%)	0
Autologous stem cell transplantation, n (%)	0

HC: healthy controls, n= number; SD= standard deviation; BMI= body mass index; IQR= inter-quartile range; RMDs= rheumatic musculoskeletal diseases; SSc= systemic sclerosis;

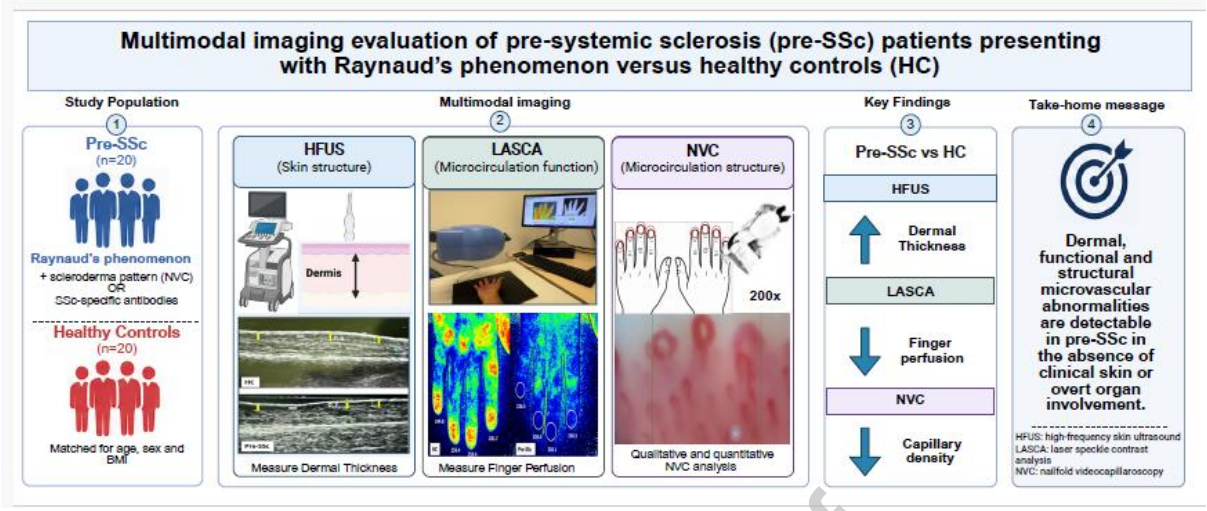
RP=Raynaud's phenomenon; SDP= scleroderma pattern; Ab= antibodies; ANA= antinuclear antibody; NVC= Nailfold videocapillaroscopy; ILD= interstitial lung disease; FVC= forced vital capacity; DLCO= diffusing capacity of the lungs for carbon monoxide; PAH= pulmonary arterial hypertension; mRSS= modified Rodnan skin score; LVEF= left ventricular ejection fraction; SRC= scleroderma renal crisis; CK= creatinine kinase; HCQ= hydroxychloroquine; MTX= methotrexate; MMF= mycophenolate mofetil; CYC= cyclophosphamide; AZA= azathioprine

* Pre-SSc subsets were defined as RP patients fulfilling LeRoy's criteria (RP plus SSc-specific antibodies, RP plus scleroderma pattern, or RP plus both)

** Scleroderma pattern as seen on 200x magnification nailfold videocapillaroscopy, defined as per EULAR Study Group on Microcirculation in Rheumatic Diseases (EULAR SG MC/RD).

Both patients were on HCQ for inflammatory arthralgia.

Graphical abstract



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Vanessa Smith reports a relationship with Janssen-Cilag Ltd that includes: consulting or advisory and speaking and lecture fees. Vanessa Smith reports a relationship with Boehringer Ingelheim Ltd that includes: consulting or advisory and speaking and lecture fees. Vanessa Smith reports a relationship with argenx BV that includes: consulting or advisory. Vanessa Smith reports a relationship with GSK that includes: consulting or advisory. Vanessa Smith reports a relationship with AstraZeneca that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.