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ORIGINAL ARTICLE

Capillaroscopic Skin Ulcer Risk Index: A New Prognostic Tool for Digital Skin Ulcer Development in Systemic Sclerosis Patients

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Objective. **Digital ulcerations are one of the most frequent manifestations of microangiopathy in patients with systemic sclerosis (SSc; scleroderma). The early detection of SSc patients who are at high risk to develop digital ulcers could allow a preventive treatment of these complications with reduction of morbidity and social costs. The aim of our study was to develop a capillaroscopic skin ulcer risk index (CSURI) that can predict the onset of new digital ulcers by using nailfold videocapillaroscopy (NVC) in patients with SSc.**

Methods. **We performed NVC in 120 consecutive unselected patients with SSc (13 men, 107 women, mean ± SD age 56.1 ± 13.4 years, mean ± SD SSc duration 44.7 ± 60.7 months) to assess the total number of capillaries in the distal row (N), maximum loop diameter (D), number of megacapillaries (M), and the M:N ratio.**

Results. **Within 3 months since NVC examination, 35 of 120 patients experienced digital ulcers. A significant association between ischemic lesions and the M:N ratio, N, and D was observed; the combination of these parameters allowed us to develop the CSURI, which is characterized by the formula $D \times M:N^2$. A receiver operating characteristic curve analysis showed an area under the curve of 0.926 for ulcer appearance, with specificity and sensitivity of 85.9% and 94.3%, respectively, at the cutoff value of 2.94. Interestingly, 33 of 35 patients with new skin ulcers had a CSURI >2.94, but only 2 of 35 had a CSURI ≤2.94.**

Conclusion. **The proposed CSURI may represent a novel tool with the ability to predict the development of digital ulcers in patients with scleroderma.**

INTRODUCTION

Systemic sclerosis (SSc; scleroderma) is a chronic connective tissue disease characterized by endothelial dysfunction and fibrosis of the skin and internal organs (1). Microangiopathy is one of the main histopathologic features that is detectable early in the course of the disease (2,3).

Nailfold videocapillaroscopy (NVC) is an imaging technique for microcirculation study and it represents one of the most reliable tools for the classification and diagnosis of SSc and related conditions (4–7). Although the diagnostic value of NVC in the differentiation between primary and secondary Raynaud's phenomenon is sufficiently defined (4–7), the usefulness of NVC in the followup of patients with SSc remains uncertain, namely in its correlation with disease activity/severity and its predictive role in SSc complications (8–15). Digital ulcerations represent one of the most frequent manifestations of SSc microangiopathy, often requiring hospital-based treatments (16–18). The early detection of patients with a high risk of developing digital ulcers could allow a preventive treatment of these complications, with a reduction of morbidity and social costs. The aim of this study was to develop a quantitative capillaroscopic prognostic index that can predict the onset of new digital skin ulcers.

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PATIENTS AND METHODS

A total of 120 unselected, consecutive patients with SSc were included in this NVC study. All patients met the preliminary American College of Rheumatology (formerly the American Rheumatism Association) classification criteria for SSc (19). NVC was performed on all patients after they had been in a comfortable ambient temperature of 22–25°C for 20 minutes. A drop of immersion oil was applied to the nailfold to maximize the translucency of the keratin layer, and the second through the fifth fingers of both hands were examined. NVC was performed with a

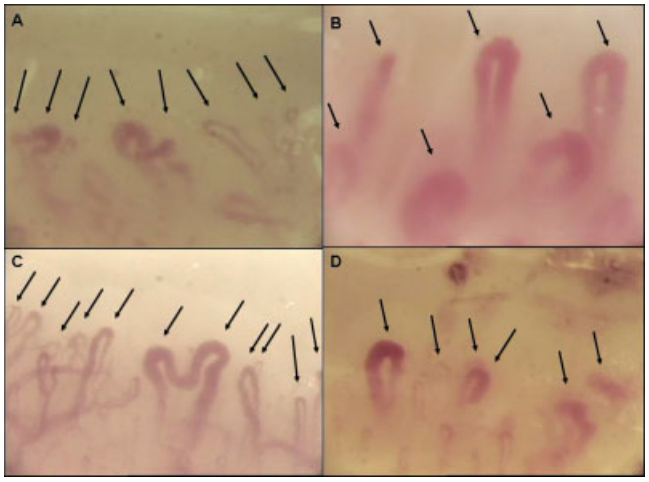

Figure 1. Examples of measurements of capillaroscopic findings (**arrows**). **A**, 8 capillaries, 2 giant capillaries (2 ramified giant capillaries occupying both dermal papillae), **B**, 6 capillaries, 4 giant capillaries (every capillary was counted in the distal row even if it was not on the same level), **C**, 11 capillaries, 1 giant capillary (1 ramified giant capillary computed as 2 in the total number count), **D**, 6 capillaries, 4 giant capillaries.

videocapillaroscope (Videocap software, version 9.07; DS Medica, Milan, Italy) equipped with a 200× optical probe.

During NVC examination, the most representative images of capillaroscopic pattern (at least 1 image per finger) were saved for each finger. All images were captured, coded, stored, and analyzed during the next week by 2 blinded observers (MS and MC) without knowledge of clinical history of the patients. To further minimize interobserver bias, all parameters were strictly defined on the basis of previous classifications (20–24), as follows (Figure 1): 1) megacapillary (a capillary with a homogeneously enlarged loop with a diameter >50 μm, as opposed to a microaneurysm, which is an irregular enlarged loop with circumscribed dilatation); 2) maximum diameter of megacapillary (the largest giant capillary diameter present in a capillaroscopic image, except at the level of microaneurysm); 3) microhemorrhage (presence of a dark red mass characterized by hemosiderin deposit derived from capillary injury); 4) tortuosity (a variation of the typical hairpin capillary shape, sometimes with ramified aspect); and 5) number of capillaries (usually, capillaries are placed on parallel rows; however, in our study we evaluated all of the capillaries in the distal row corresponding to the entire distal front line, which may include capillaries placed at different levels [Figure 1B]. In the case of a ramified capillary, which occupies >1 dermal papilla, it corresponds to the number of papillae in the total capillary count, whereas a ramified giant capillary is considered as 1 in the megacapillary count and as ≥2 in the total capillary count, according to the number of occupied papillae).

In agreement with other authors (4,6,8–10,12–15,20–24), in each NVC image we analyzed the total number of capillaries in the distal row (N), the number of megacapillaries (M), the M:N ratio, the maximum diameter of megacapillaries (D), and the presence or absence of tortuosities and microhemorrhages. Among all images, we then chose only the one with the lowest N and, secondarily, with the highest M.

At the time of NVC, 42 patients were receiving prostanoid therapy, 4 were receiving endothelin receptor antagonists, and 4 were receiving immunosuppressive agents (e.g., cyclophosphamide or mycophenolate mofetil). After NVC evaluation, the patients were examined for the appearance of new digital skin ulcers after 3 months of followup without any changes in previous treatments.

A logistic regression analysis was performed to assess the association between the above capillaroscopic findings and new ulcers. A receiver operating characteristic (ROC) curve analysis was performed to analyze the prognostic accuracy of each parameter in regard to ulcer development (25). Group comparisons were made by Student's unpaired 2-tailed *t*-test. *P* values less than 0.05 were considered significant. Finally, to evaluate the interobserver agreement, all parameters were transformed into semiquantitative variables and examined by means of weighted kappa

Table 1. Interobserver agreement concerning capillary measurements*

	Observer 1, %	Observer 2, %	Weighted κ
Total no. of capillaries			0.702
1–3	6.7	5.8	
4–6	18.3	24.2	
7–9	42.5	41.7	
≥10	32.5	28.3	
Maximum loop diameter, μm			0.655
<60	17.5	12.5	
60–69	22.5	18.3	
70–79	15.8	14.2	
80–89	13.3	14.2	
90–99	8.3	10.8	
100–109	7.5	6.7	
≥110	15.0	23.3	
No. of giant capillaries			0.666
1	40.8	35	
2	28.3	34.1	
3	20.0	20.0	
4	8.3	5.8	
5	1.7	1.7	
6	0.8	2.5	
7	0	0.8	
Ratio of giant:total no. of capillaries			0.660
≤0.20	10.8	10.8	
0.21–0.30	25	31.7	
0.31–0.40	32.5	23.3	
0.41–0.50	13.3	18.3	
0.51–0.60	7.5	4.2	
0.61–0.70	0.8	2.5	
0.71–0.80	1.7	1.7	
0.81–0.90	0	1.7	
0.91–1	8.3	5.8	
Capillaroscopic skin ulcer risk index			0.964
<2.94	62.5	61.7	
≥2.94	37.5	38.3	

Table 2. Clinical and serologic features of 120 SSc patients who underwent nailfold videocapillaroscopy*

	Value
Men/women, no.	13/107
Age, years	56.1 ± 13.4
Raynaud's phenomenon duration, months	112 ± 117.8
SSc duration, months	44.7 ± 60.7
Cutaneous subset, no. dcSSc/icSSc/lcSSc	11/8/101
Anti–Scl-70/ACAs/ANoAs, no.	38/52/21
New digital skin ulcers, no.	35
Previous digital skin ulcers, no.	59
Maximum loop diameter, μm	84.27 ± 29.93
No. of giant capillaries	2.14 ± 1.25
Ratio of giant:total no. of capillaries	0.32 ± 0.24
Total no. of capillaries	8.11 ± 2.85

* Values are the mean ± SD unless otherwise indicated. SSc = systemic sclerosis; dcSSc = diffuse cutaneous SSc; icSSc = intermediate cutaneous SSc; lcSSc = limited cutaneous SSc; ACAs = anticentromere antibodies; ANoAs = antinucleolar antibodies.

statistics. Good interobserver agreement was observed for all parameter evaluations (Table 1).

RESULTS

Clinical and capillaroscopic features of patients with SSc are shown in Table 2. Within 3 months of NVC examination, 35 (29.2%) of 120 patients developed digital ulcers.

Comparing patients with and without ulcers, we observed significant differences in many capillaroscopic parameters (Table 3). In particular, a significantly lower N and a significantly higher M, D, and M:N ratio were observed in patients with development of new digital ulcers. In this respect, the ROC curves showed a progressively better performance for the M, D, M:N ratio, and N (areas under the ROC curve 0.57, 0.67, 0.85, and 0.89, respectively) (Figure 2).

A logistic regression analysis showed a significant association between both the M:N ratio (odds ratio [OR] 424.97, 95% confidence interval [95% CI] 24.31–7,428.566; $P < 0.0001$) and the N (OR 0.47, 95% CI 0.35–0.62; $P < 0.0001$) and ulcers at univariate analysis, whereas a less close association was observed between the D (OR 1.02, 95% CI 1.01–1.04; $P = 0.002$) or the M (OR 1.38, 95% CI 1.01–1.89; $P = 0.04$) and new ulcers.

The appearance of new ulcers did not correlate with microhemorrhages, capillary tortuosities, autoantibodies, cutaneous SSc subsets, and SSc and Raynaud's phenomenon durations (Table 3). On the basis of these statistical correlations, we expanded on a prognostic index including the significant parameters D, M:N ratio (direct correlation with ulcer development), and N (inverse correlation), using the equation (M:N × D): N simplified to D × M:N^2, which we named the capillaroscopic skin ulcer risk index (CSURI). At ROC curve analysis, the CSURI showed an area under the ROC curve of 0.926 (95% CI 0.863–0.965). Sensitivity and specificity were 94.3 (95% CI 80.8–99.1) and 85.9 (95% CI 76.6–92.5), respectively, at the cutoff value of 2.94, whereas the positive and negative likelihood ratios were 6.68 and 0.07, respectively (Figure 2). Patients with new digital ulcers showed a mean ± SD CSURI of 13.286 ± 16.132 versus 3.185 ± 9.386 in patients without new ischemic lesions ($P < 0.0001$).

Using this cutoff value of 2.94, the positive predictive value of CSURI was 73.33%. A CSURI >2.94 was present in 33 of 45 patients with new digital skin ulcers, and the negative predictive value was 97.33% (2 of 75 patients with a CSURI ≤2.94 experienced new digital ulcers) (Table 4). At the time of NVC examination, 8 of 12 patients with a CSURI >2.94 who did not develop digital skin ulcers were receiving prostanoid therapy, which could partially explain the absence of ischemic lesions. Interestingly, a patient with a very high CSURI of 85 without digital ulcers and without other relevant comorbidities presented with a large wound to the right leg at the time of NVC.

The area under the ROC curve obtained for the CSURI was significantly higher compared with that of the single parameters ($P = 0.0001$, 0.0001, and 0.004 for the D, M, and M:N ratio, respectively) (Figure 2), with the exception

Table 3. Capillaroscopic features in patients with or without digital ulcers*

	Ulcers (n = 35)	No ulcers (n = 85)	*P*
Maximum loop diameter, μm	98.23 ± 36.96	78.53 ± 24.53	0.0009
No. of giant capillaries	2.52 ± 1.70	1.99 ± 0.98	0.0335
Ratio of giant:total no. of capillaries	0.52 ± 0.30	0.23 ± 0.15	< 0.0001
Total no. of capillaries	5.37 ± 2.28	9.23 ± 2.24	< 0.0001
Tortuosities, %	72	76	NS
Microhemorrhages, %	36	33	NS
Raynaud's phenomenon duration, months	132.7 ± 126.7	103.5 ± 113.6	NS
SSc duration, months	52.1 ± 62.0	41.7 ± 60.3	NS
Skin cutaneous subsets, no. dcSSc/icSSc/lcSSc	3/3/29	8/5/72	NS
Autoantibodies, no. anti–Scl-70/ACAs/ANoAs	12/17/5	26/35/16	NS
Previous digital ulcers, no. (%)	31 (89)	28 (33)	< 0.0001

* Values are the mean ± SD unless otherwise indicated. NS = not significant; see Table 2 for additional definitions.

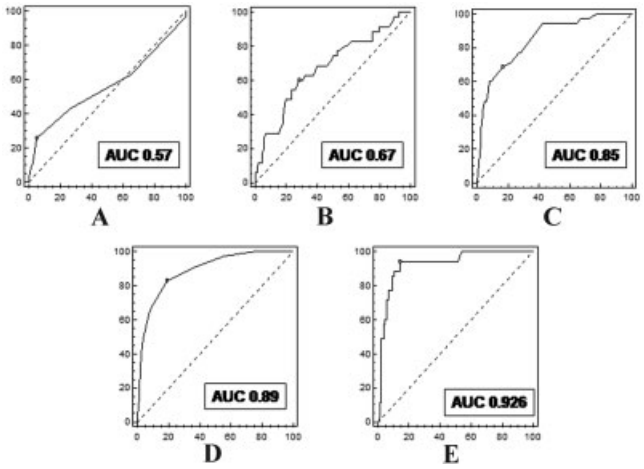

Figure 2. Receiver operating characteristic curves of **A**, number of giant capillaries, **B**, maximum diameter, **C**, ratio of number of giant capillaries to number of total capillaries, **D**, number of total capillaries, **E**, capillaroscopic skin ulcer risk index. AUC = area under the curve.

of the N ($P = 0.248$). The N represents an important predictive parameter: all patients with >11 capillaries did not experience digital ulcers during followup, whereas patients with <4 capillaries developed skin ulcers in all cases except for one. However, focusing on the intermediate group of patients with 5–10 capillaries per field, a more predictive value of the CSURI was observed if compared with the single parameters, including the N. In particular, the comparison of the areas under the ROC curve for the N and CSURI again showed a statistically significant difference (0.895 and 0.795, respectively; $P = 0.047$).

A clinical history of previous digital ulcers correlated significantly with the development of new ulcers (Table 3). However, among 59 patients with a positive clinical history of digital ulcers during the last year before NVC examination, only 31 developed new ulcers during the followup period. This clinical observation was mirrored by the lower sensitivity and specificity (88.6% and 67.0%, respectively) of the anamnestic predictive model compared with the CSURI (94.3% and 85.9%, respectively).

DISCUSSION

Since initial observations by Maricq and colleagues, a relationship between capillaroscopic findings and scleroderma visceral organ involvement has been hypothesized (7–10), although the main attempts to quantify the capillaroscopic damage were directed toward discriminating primary from secondary Raynaud's phenomenon (9–13).

Lovy et al observed a correlation between capillary loss and disease duration in 42 patients with SSc by means of semiquantitative graduation, although no association with visceral involvement was detected (26). Similarly, Statham et al concluded that capillaroscopy could not provide prognostic information in SSc (27). In the following years, some studies suggested an association between the grade of capillary dilation or capillary loss and SSc-related organ involvement (20,28–32), whereas others did not confirm these observations (3,10,26,27). These discordant results could possibly be related to differences in patient selection, the quantification methods of clinical and capillaroscopic alterations, and/or technical limitations.

In 1995, Scheja et al first evaluated the feasibility of objective calculation of SSc microangiopathy using a computer-based technology. This method showed a low interoperator variability and the authors observed a correlation between capillaroscopic alterations and von Willebrand factor plasmatic concentration (33).

Interestingly, several studies showed a correlation between capillaroscopic damage and lung involvement (29–31). In particular, Silver et al reported that patients with alveolitis on bronchoalveolar lavage have a greater, but not significant, prevalence of the capillaroscopic slow damage pattern than patients without alveolitis (20,34). In 2004, an association between active lung involvement and the mean avascular score, a semiquantitative method to quantify the capillary loss, was described in patients who had a disease duration less than 5 years (35,36).

Recently, the introduction of NVC, an evolution of wide-field nailfold microscopy, permitted the measurement of any loop abnormality and the recording of images for later analysis or reanalysis (4,7). In 2004, Cutolo et al confirmed an association between capillaroscopic alterations and disease duration, also showing a correlation between different capillaroscopic scleroderma patterns (early, active, late) and the presence of autoantibodies (anticentromere, anti–topoisomerase I), as well as cutaneous subsets, namely limited, intermediate, and diffuse (14,15).

The possibility of using NVC to evaluate SSc activity or the response to treatment has been investigated in some studies. In a recent longitudinal study, Sulli et al reported a worsening of microvascular features in 59% of patients and an improvement in 24% using a semiquantitative score. However, the real value of these data is uncertain, because no correlations with skin score or organ involvement were observed (37). At the same time, other studies reported a change in the capillary features together with the improvement of SSc visceral involvement after immunosuppressive therapy (38,39).

Many attempts to quantify or classify microcirculation abnormalities are weakened by wide operator dependence and interoperator variability. Ingegnoli et al analyzed the reliability of the major NVC measurements concerning the number, organization, shape, and size of capillaries. The

Table 4. Predictive value of the capillaroscopic skin ulcer risk index (CSURI) in patients with or without digital ulcers

	CSURI, no. (%)		
	≤2.94	>2.94	Total, no. (%)
Ulcers	2 (2.67)	33 (73.33)	35 (29.17)
No ulcers	73 (97.33)	12 (26.67)	85 (70.83)
Total	75 (100)	45 (100)	120 (100)

authors observed generally good interoperator and intraoperator agreement, although it was better for some parameters such as capillary density and other minor alterations. On the contrary, the measurement of capillary width had poor reproducibility (40).

Our precise definition of every parameter probably reduced the interobserver variability, and the combination of these parameters in the CSURI permitted acquisition of a very good interobserver agreement (weighted $\kappa = 0.964$). The image selection can be another source of miscalculation. In this regard, some studies have analyzed the entire nailfold microcirculation using a low magnification probe or saving several images to piece together in a unique image (9,31). Other studies instead performed the calculation in a 1-mm section of a capillaroscopic image (24,37). To minimize interobserver variability, we decided to calculate the score using one entire image.

The prevention and the treatment of sclerodermic skin ulcers are currently the subjects of much debate and research (17), and considerable attention is being paid to new clinical trials (41–45). Currently, prostanoids represent the gold standard of management for acute digital ischemia (17,41). They may be effective in SSc-related peripheral vascular disease through several mechanisms such as strong vasodilatation, inhibition of platelet aggregation, and promotion of neoangiogenesis (46).

Recently, considerable interest has been shown in endothelin 1 receptor antagonists as a treatment for digital ischemia in patients with SSc. A recent large, multicenter, double-blind, controlled clinical trial showed that bosentan reduced the number of new digital ulcers, but had no effect on healing existing lesions (42).

The cost/effectiveness ratio for the therapy of sclerodermic skin ulcers is very unfavorable and the strategy for their treatment or prevention is under debate (17). Some studies proposed a long-term therapy with prostanoids for the supposed benefit on disease mechanism and endothelial dysfunction (46–48). Because only 50–60% of patients with SSc experience a digital skin ulcer in their clinical history (1,18), the advantage of this approach is questionable. On the other hand, a wait-and-see strategy exposes the patients to potential severe complications that require hospitalization and long-term treatments (49,50). In the Randomized Placebo-Controlled Study on the Prevention of Ischemic Digital Ulcers Secondary to Systemic Sclerosis 1 (42), the patient's clinical history of multiple digital ulcers represents the most helpful predictor and indicator of preventive therapy. However, the clinical observations in our patients' series suggest a lower sensitivity and specificity of the patient's clinical history compared with CSURI.

Therefore, the development and validation of new outcome measures may facilitate the recognition of patients at high risk to develop digital ulcers and may improve the monitoring of vascular complications and treatments (17). Finally, careful selection of SSc patients who are candidates for preventive treatment with prostanoids or endothelin receptor antagonists could optimize the cost/effectiveness ratio and resource management.

CSURI represents one of the first attempts to quantify microangiopathy and to predict the development of digital ulcers, which is a direct consequence of SSc-related vasculopathy. This method could constitute an easy and rapid tool that can be usefully employed in the clinical followup and therapeutic strategy of patients with SSc.

Capillary loss is the most relevant parameter to evaluate the severity of SSc microangiopathy (35,36); concordantly, the N or M:N ratio alone have a prominent role in predicting the development of new digital ulcers. In particular, the value of the CSURI should be stressed when the number of capillaries per field was greater than 4 or less than 11. In fact, in this intermediate group of patients, the predictive value of CSURI is greater than other clinical and/or capillaroscopic parameters.

Even if videocapillaroscopy is expensive and not available in most rheumatologic centers, its use is progressively increasing. Furthermore, CSURI is hypothetically applicable by means of any stereomicroscope that is able to save and measure images.

Only long-term studies can exactly define the usefulness of CSURI in the management and prevention of digital ulcers in patients with SSc. A validation process in larger patient populations and multicenter longitudinal studies are necessary to evaluate the feasibility and reproducibility of CSURI. It may also be of interest to investigate the possible relationship between CSURI variations, disease progression, and treatment response.

AUTHOR CONTRIBUTIONS

Dr. Sebastiani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Sebastiani, Manfredi, Colaci.
Acquisition of data. Malagoli, Giuggioli.
Analysis and interpretation of data. Sebastiani, Manfredi, Colaci, D'Amico.
Manuscript preparation. Sebastiani, Manfredi, Colaci, D'Amico, Ferri.
Statistical analysis. D'Amico.

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