

Capillaroscopic insights: exploring the connection between microvascular changes and pulmonary manifestations in systemic sclerosis

CAMELIA PALICI¹, ANANU FLORENTIN VREJU², CRISTINA ELENA BIȚĂ^{2,*}, ȘTEFAN CRISTIAN DINESCU², ALESANDRA FLORESCU², ANCA EMANUELA MUȘETESCU², ANDREEA LILI BARBULESCU³, PAULINA LUCIA CIUREA²

¹ Doctoral School of the University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania

² Department of Rheumatology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania

³ Department of Pharmacology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania

Abstract

Background: Systemic sclerosis (SSc) is a complex connective tissue disease characterized by microangiopathy, immune dysregulation, and fibrosis. Early detection of microvascular abnormalities using nailfold videocapillaroscopy (NVC) is crucial in assessing disease progression and associated disease's involvement such as interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH).

Objective: This study aims to explore the relationships correlation between NVC patterns, clinical manifestations, and systemic complications in SSc.

Methods: We analyzed the data of 63 patients, predominantly female (95%), with a mean age of 49 years and an average disease duration of 42 months. Patients were categorized into early, active, and late patterns based on NVC findings. Clinical features, including digital ulcers (DU), ILD, and PAH, were assessed. Pearson correlation analyses were performed to evaluate the relationships between capillary loss, neoangiogenesis, ILD, and PAH.

Results: The early pattern group (mean mRSS 2.36) exhibited minimal microvascular damage and systemic involvement, with no DUs. In the active pattern group (mean mRSS 10.40), 34.38% had diffuse cutaneous SSc (dcSSc), with 15.63% presenting DUs, 65.63% ILD, and 37.5% PAH. The late pattern group (mean mRSS 18.00) showed the most severe disease, with 80% having DUs, 70% dcSSc, 90% ILD, and 70% PAH. Pearson correlation analyses revealed strong correlations between capillary loss and ILD ($r = 0.7255$) and PAH ($r = 0.6369$). A moderate correlation was found between neoangiogenesis and PAH ($r = 0.5592$).

Conclusion: The study demonstrates that progressive microvascular damage in SSc, as visualized by NVC, correlates strongly with the severity of systemic complications. Early detection of capillary loss and neoangiogenesis using NVC is critical for timely interventions, which could improve patient outcomes by mitigating the progression of ILD and PAH.

Keywords: systemic sclerosis, microvascular damage, nailfold videocapillaroscopy, interstitial lung disease, pulmonary arterial hypertension.

What is new? What is important?

This study reveals strong correlations between specific nailfold videocapillaroscopy (NVC) patterns and the severity of systemic complications like ILD and PAH in systemic sclerosis patients. Early detection of microvascular damage using NVC is critical for timely interventions, potentially improving patient outcomes by preventing the progression of serious complications such as ILD and PAH.

INTRODUCTION

Systemic sclerosis (SSc) is a multisystemic connective tissue disorder characterized by microvascular damage, immunologic abnormalities, and fibrosis of internal organs and skin. Various factors have been involved as potential triggers of vascular injury, including anti-endothelial antibodies, oxidative stress, molecular mimicry mechanisms,

and the phenomenon of microchimerism [1,2]. This condition results in varying levels of impairment, affecting work, physical, and social activities, and ultimately reducing health-related quality of life [3]. Similar to many other autoimmune disorders, scleroderma is 4–5 times more prevalent in women than in men, with the average age at diagnosis being 50 years [4].

Histopathologically, SSc is marked by perivascular infiltrates and reduced capillary density, which precede excessive extracellular matrix protein production. Vascular involvement targets small arteries and capillaries, leading to decreased blood flow and tissue ischemia, which cause the disease's clinical symptoms. Clinically, SSc is classified based on skin involvement into limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [5]. DcSSc often results in widespread, early internal organ involvement, including Raynaud's phenomenon, skin changes, tendon friction rubs, arthritis, myositis, interstitial lung disease (ILD), malignant hypertension, gastrointestinal disease, and myocardial involvement [6]. In contrast, lcSSc typically involves Raynaud's phenomenon, acral skin involvement, gastroesophageal reflux, and sometimes pulmonary artery hypertension (PAH) with or without ILD.

SSc remains a devastating disease with a high standardized mortality ratio of 3.5, primarily due to cardiopulmonary involvement [7]. Pulmonary vascular issues and interstitial fibrosis contribute significantly to pulmonary hypertension and reduced lung diffusing capacity [8]. Lung involvement in SSc mainly manifests as ILD and pulmonary hypertension, with ILD characterized by alveolitis leading to fibrosis [9]. High-resolution computed tomography (HRCT) is a critical diagnostic tool for detecting early lung changes, being more sensitive than routine chest radiography.

SSc-PAH affects approximately 10–15% of SSc patients and significantly contributes to early mortality [10,11]. The early identification and treatment of SSc-PAH can significantly enhance patient outcomes [12].

Pathological findings in SSc show a substantial loss of the peripheral vascular network, including capillary depletion, impaired vascular repair, and lack of new vessel growth, leading to tissue ischemia and fibrosis. Nailfold videocapillaroscopy (NVC) is a noninvasive, quick, and effective technique for assessing these microvascular changes [13]. It is invaluable in screening for underlying scleroderma spectrum disorders and tracking progressive microvascular damage in SSc [14].

NVC is included in the EULAR/ACR classification criteria for SSc [15] and is also used in the criteria for the very early diagnosis of SSc (VEDOSS) [16]. Recent studies suggest that NVC can serve as a surrogate marker for SSc progression, correlating microvascular alterations with visceral organ involvement, particularly vascular complications like PAH [13]. NVC assessments evaluate capillary

density, morphology, dimensions, and hemorrhages, providing comprehensive insights into the disease's microvascular impact [17].

Thus, this study aimed to determine the frequency of scleroderma type capillaroscopic patterns and to identify the associations of capillaroscopic scleroderma patterns with clinical parameters (ILD, PAH, digital ulcers), functional status, fatigue, and pain in SSc.

MATERIAL AND METHODS

THE STUDY COHORT (CLINICAL ASSESSMENT)

This cross-sectional study included 63 patients diagnosed as SSc, according to the ACR/EULAR criteria for SSc [15]. The SSc patients who presented to the clinic of Rheumatology of the Emergency County Hospital of Craiova, were consecutively included in the study between January 2015 and January 2019. The exclusion criteria for the study were being younger than 18 years of age, having hand disorders related to diabetes mellitus, neurological disorders, erosive osteoarthritis, hand surgery or trauma.

For all patients detailed medical history and clinical examination were performed. The presence of digital ulcer (DU) were evaluated separately, and the severity was assessed based on the Visual Analogue Scales (VAS). The dermal skin thickness was measured by the modified Rodnan skin score (mRSS). Modified Rodnan skin score (mRSS) has been classified as: normal = 0, mild between 1 and 14, moderate between 15 and 29, severe between 30 and 39, endstage >40 [18]. Pain, fatigue, and patient global assessment (PGA) were also evaluated on VAS. The Health Assessment Questionnaire (HAQ) was used to evaluate physical disability. All of the patients included in the database gave their informed consent, and the study was approved by the institutional Ethics Committee.

ASSESSMENT OF THE CARDIOPULMONARY INVOLVEMENT

Internal organ involvement was evaluated based on patient presentation using high-resolution chest CT (HRCT) without contrast. All patients underwent pulmonary function tests (PFTs) with diffusing capacity for carbon monoxide (DLCO) adjusted for hemoglobin levels. Restrictive lung disease was diagnosed in patients with a DLCO of less than 70%. Additionally, a Doppler echocardiogram was performed to assess left

ventricular ejection fraction and estimate pulmonary artery systolic pressure (sPAP); an estimated sPAP of ≥ 25 mmHg was considered abnormal [19].

CAPILLAROSCOPY

Nailfold videocapillaroscopy (NVC) was performed on all patients by the same operator, blinded to clinical details, using an optical probe videocapillaroscopy (Smart G-Scope, Genie Tech, Seoul, Republic of Korea) equipped with $\times 250$ contact lenses. Fingers affected by local recent trauma were excluded from analysis as well as those with recent manicure during the previous 4 weeks. The hand was placed at the heart level, without pressure over the table with standard temperature to avoid any influence on the circulation. A drop of cedar oil was placed over the nailfold to improve skin transparency. About a millimeter of the nailfold area was visualized in order to provide the opportunity for assessment of both capillary distribution and density as well as details in the morphology of single-capillary loops. After acclimatizing the patients for 15–20 minutes at room temperature (around 25°C), capillaroscopic examination was performed at 8 fingers (II–V bilaterally).

Capillaries were classified as dilated if the arterial limb diameter exceeded 15 μm or the venous limb diameter exceeded 20 μm . Microvessels with diameters over 50 μm were labeled as giant capillary loops or megacapillaries. Mean capillary density, defined as the number of capillary loops per 1 mm in the distal row, typically ranged from 7 to 16 capillaries per mm. Avascular areas were gaps greater than 500 μm between adjacent capillary loops in the distal rows. Neoangiogenesis was identified by the presence of more than 1–3 capillary loops originating from the same vessel in a single dermal papilla, with a ramified and bushy appearance.

The following parameters were evaluated based on previous classifications: the presence of dilated and giant capillaries, hemorrhages, capillary loss (avascularity), and ramified or bushy capillaries.

STATISTICAL ANALYSIS

Statistical analyses were conducted using GraphPad Prism version 8. Initially, the normality of the data was assessed using both the Shapiro-Wilk test and the Kolmogorov-Smirnov test. Data that passed the normality checks were analyzed for statistical significance using the one-way ANOVA test. For data that did not meet the normality criteria, the Kruskal-Wallis test was employed to

determine statistical significance. To evaluate the relationships and correlations between different groups, Pearson correlation analysis (Pearson r) was performed. Statistical significance was defined as a p -value of less than 0.05. All results were reported with their respective 95% confidence intervals and R squared values where applicable.

RESULTS

The study involved 63 patients, predominantly female, with 60 women accounting for 95% of the cohort. The mean age of the participants was 49 years, with a standard deviation of 7.54 years. The average duration of the disease was approximately 42 months, ranging from a minimum of 8 months to a maximum of 141 months. Among the patients, 13 individuals (20.63%) experienced DU. The modified Rodnan skin score (mRSS) had a mean value of 10, with individual scores ranging from 0 to 25 (Table 1).

The functional status of patients varied across the different disease patterns. In the early pattern group, patients reported a mean pain score of 5.00 on the VAS, maintained relatively good functional abilities with a mean HAQ score of 0.30, experienced moderate fatigue with a mean VAS score of 3.29, and had a moderate disease impact with a mean PGA score of 4.71. In the active pattern group, the mean pain score decreased to 2.78, while fatigue intensified with a mean VAS score of 5.81. The mean PGA score in this group was 5.52, and the mean HAQ score was 0.48, indicating increased functional disability. In the late pattern group, patients reported the lowest mean pain score of 2.50, but the highest levels of fatigue with a mean VAS score of 6.30 and the greatest functional disability with a mean HAQ score of 0.62.

DU showed a clear progression in prevalence across the different disease patterns. In the early pattern group, no patients had DU. In the active pattern group, 15.63% of patients had DU. In the late pattern group, a significant 80% of patients were affected by DU.

The cohort included different subtypes of SSc: 19 patients (30.23%) had dcSSc, while 36 patients (57.28%) were diagnosed with lcSSc. ILD was present in 38 patients (60.32%), and PAH was observed in 20 patients (31.75%).

In the early pattern group, patients predominantly had lcSSc (61.9%), with a low mean mRSS of 2.36. In this group, no patients had DU, 38.10% had ILD, and 4.76% had PAH. In the

active pattern group, 34.38% of patients had dcSSc, with a mean mRSS of 10.40. Within this group, 15.63% had DU, 65.63% had ILD, and 37.5% had PAH. In the late pattern group, the mean mRSS was 18.00. A significant 80% of patients in this group had DU, 70% had dcSSc, 90% had ILD, and 70% had PAH (Table 2).

The capillaroscopic examination findings of the patients are presented in Table 3. The variables include the following: enlarged capillaries, megacapillaries, hemorrhages, neoangiogenesis, and loss of capillaries. These findings highlight the prevalence and variety of microvascular abnormalities in the studied population.

Table 1

Demographic and clinical characteristics of the patients

Variables	
Female (n, %)	60 (94.99)
Age	49±7.54
Duration of disease, months, (mean, min–max)	42.05 (8–141)
Digital ulcers (n, %)	13 (20.63)
mRSS (mean, min–max)	10 (0–25)
Diffuse cutaneous SSc (n, %)	19 (30.23)
Limited cutaneous SSc (n, %)	36 (57.28)
Interstitial lung disease (n, %)	38 (60.32)
Pulmonary hypertension (n, %)	20 (31.75)
Fatigue, VAS, (mean±SD)	5.05±2.52
Pain, VAS, (mean, min–max)	3.48 (0–8)
PGA, VAS, (mean±SD)	5.04±1.49
HAQ (median, min–max)	0.44 (0–1)

Table 2

Comparisons of patients between capillaroscopic pattern groups

	Early Pattern N=21 (A)	Active Pattern N=32 (B)	Late Pattern N=10 (C)	A vs B A vs C B vs C	p value
Female (%)	19 (90.48)	31 (96.88)	10 (100)	ns ns ns	0.4250
Age (mean, min–max)	44 (31–55)	51 (42–61)	54 (47–60)	*** *** ns	<0.0001
Disease duration, months (mean, min–max)	16.43 (8–21)	47.59 (22–74)	78.10 (29–141)	**** **** ***	<0.0001
Digital ulcers (n, %)	0 (0)	5 (15.63)	8 (80)	ns *** *	0.0006
mRSS (mean, min–max)	2.36 (0–6)	10.40 (5–14)	18.00 (14–25)	**** **** ****	<0.0001
Diffuse cutaneous SSc (n, %)	1 (4.76)	11 (34.38)	7 (70)	**** ns ns	<0.0001
Limited cutaneous SSc (n, %)	13 (61.9)	18 (56.25)	5 (50)	ns ns ns	0.8160
Interstitial lung disease (n, %)	8 (38.10)	21 (65.63)	9 (90)	ns * ns	0.0161

Table 2 (continued)

	Early Pattern N=21 (A)	Active Pattern N=32 (B)	Late Pattern N=10 (C)	A vs B A vs C B vs C	p value
Pulmonary hypertension (n, %)	1 (4.76)	12 (37.5)	7 (70)	* *** ns	0.0009
Fatigue, VAS (median, min–max)	4.00 (0–7)	6.00 (2–9)	6.50 (3–8)	** ** ns	0.0006
Pain, VAS (mean, min–max)	5.00 (0–8)	2.78 (0–6)	2.50 (0–6)	** * ns	0.0011
PGA, VAS (mean, min–max)	4.71 (2.9–6.2)	5.52 (1.3–7.5)	4.20 (2.3–7.1)	ns ns *	0.0207
HAQ (mean, min–max)	0.30 (0–0.7)	0.48 (0.1–1)	0.62 (0.1–1)	* ** ns	0.0007

ns – $p > 0.05$, * – $p \leq 0.05$, ** – $p \leq 0.01$, *** – $p \leq 0.001$, **** – $p \leq 0.0001$

Table 3

Capillaroscopic examination findings of the patients

Variables	
Enlarged capillaries (n, %)	42 (66.67)
Megacapillaries (n, %)	48 (76.19)
Hemorrhages (n, %)	39 (61.9)
Neoangiogenesis (n, %)	8 (12.7)
Loss of capillaries (n, %)	28 (44.44)

DISCUSSION

Systemic sclerosis (SSc) is a complex connective tissue disease characterized by microangiopathy, immune dysregulation, and fibrosis of the skin and internal organs [20]. The immunopathogenesis of SSc involves both the innate and adaptive immune systems, which leads to the production of a wide array of autoantibodies and cell-mediated autoimmunity. This intricate interplay results in the activation of fibroblasts and subsequent fibrosis, hallmark features of SSc.

MICROVASCULAR ABNORMALITIES AND NAILFOLD VIDEOCAPILLAROSCOPY (NVC)

Understanding and managing SSc requires early detection of microvascular abnormalities, which precede other pathological events. NVC has emerged as a valuable non-invasive tool for visualizing these microvascular changes, making it an essential technique in the clinical assessment of SSc. At the nailfold, capillaries run parallel to the skin surface rather than perpendicular, allowing their structure to be easily visualized [21].

SSc microangiopathy is an initial and evolving phenomenon that can transition through various stages of microvascular damage as the disease progresses. Over a five-year follow-up period, 47% of SSc patients transitioned from an 'early' to an 'active' or 'late' pattern of microangiopathy [22]. The relationship between NVC patterns and clinical manifestations of SSc likely stems from shared pathogenic mechanisms affecting the microvasculature at multiple levels, reinforcing the idea that microvessel injury is a central component of the disease's complex pathogenesis.

INTERNAL ORGAN INVOLVEMENT

The prognosis of SSc is largely influenced by the degree and severity of internal organ involvement, especially cardiopulmonary complications, which are the primary causes of mortality in this population. The often subtle onset of heart and lung disease that gradually advances to more severe stages necessitates the early detection of specific SSc subgroups at higher risk for cardiopulmonary complications. This remains a

significant unmet need in everyday clinical practice [23,24].

Pulmonary complications in SSc encompass interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Screening all SSc patients for ILD and PAH at the time of diagnosis and regularly thereafter is essential. These conditions are the leading causes of mortality in SSc, contributing to 33% and 28% of deaths, respectively [23]. Although ILD is more frequently observed in diffuse cutaneous SSc (dcSSc) and PAH in limited cutaneous SSc (lcSSc), both conditions can occur in any SSc subset.

Recent guidelines recommend the use of high-resolution computed tomography (HRCT) for diagnosing ILD in SSc patients during the initial visit and after confirming an ILD diagnosis. To assess the extent and severity of ILD, a combination of HRCT and pulmonary function tests is advised. Screening for PAH involves transthoracic echocardiography, which has a sensitivity of 90%, although a definitive diagnosis should be confirmed through right heart catheterization [25,26].

Nailfold videocapillaroscopy (NVC) is a validated method for assessing peripheral vascular damage. Numerous studies indicate that NVC provides an accurate evaluation of microvascular damage in SSc and can predict internal organ involvement, such as lung impairment [27].

STUDY FINDINGS

Our study investigated the demographic, clinical, and microvascular characteristics of 63 SSc patients, utilizing NVC to classify the patterns of microangiopathy and correlate these with various clinical manifestations. The predominantly female cohort (95%) had an average age of 49 years and a disease duration of approximately 42 months, indicating a population in the middle stages of disease progression. The study's findings underscore the significant burden of systemic manifestations and complications in this population, particularly ILD and PAH.

The analysis of NVC patterns revealed a clear progression of microvascular damage from early to late stages of SSc. In the early pattern group, patients predominantly exhibited lcSSc with minimal skin involvement, as evidenced by a low mean modified Rodnan skin score (mRSS) of 2.36 and the absence of digital ulcers (DU). These patients also had lower rates of ILD (38.10%) and PAH (4.76%), reflecting less severe systemic involvement. This early stage is characterized by

better overall functional status, as indicated by lower Health Assessment Questionnaire (HAQ) scores (mean 0.30), moderate fatigue (mean Visual Analogue Scale (VAS) score of 3.29), and moderate disease impact (mean Patient Global Assessment (PGA) score of 4.71). Pain levels were notably higher in this group (mean VAS score of 5.00), possibly due to the initial inflammatory processes associated with the disease onset.

As the disease progresses to the active pattern, there is a notable shift towards more severe involvement. The proportion of patients with dcSSc increases to 34.38%, accompanied by a higher mean mRSS of 10.40, indicating more significant skin thickening. The emergence of DU in 15.63% of patients signifies worsening vascular involvement. This stage also shows an increased prevalence of ILD (65.63%) and PAH (37.5%), suggesting that as SSc progresses, there is a marked escalation in systemic complications. Functional impairment becomes more pronounced in the active pattern, with higher fatigue levels (mean VAS score of 5.81), increased disease burden (mean PGA score of 5.52), and greater disability (mean HAQ score of 0.48). Pain levels decrease in this stage (mean VAS score of 2.78), which might be attributed to the transition from inflammatory to fibrotic processes.

The late pattern group represents the most advanced stage of SSc, with severe microvascular and systemic involvement. This group has the highest mean mRSS of 18.00, reflecting extensive skin thickening. DU are prevalent in 80% of these patients, underscoring the severe vascular complications. The majority of patients in this stage have dcSSc (70%), which is associated with the highest rates of ILD (90%) and PAH (70%). The functional status of patients in the late pattern is significantly impaired, with the highest levels of fatigue (mean VAS score of 6.30) and functional disability (mean HAQ score of 0.62), despite the lowest pain levels (mean VAS score of 2.50). This pattern illustrates the cumulative impact of long-term disease progression and the substantial burden on patients' quality of life.

CORRELATION ANALYSES

The study's correlation analyses provide further insights into the relationships between microvascular damage and systemic complications. The strong positive correlation between ILD and capillary loss (Pearson $r = 0.7255$) indicates that as capillary loss increases, the severity or presence of ILD also tends to increase. The 95% confidence

interval (0.5824 to 0.8250) and the R squared value of 0.5263 suggest that capillary loss explains a substantial portion of the variance in ILD, highlighting its critical role in the disease process. The highly significant p value (<0.0001) reinforces the reliability of this finding and underscores the importance of monitoring capillary changes as a potential indicator of lung involvement in SSc. These results suggest that early detection of capillary loss through NVC could facilitate timely interventions to mitigate the progression of ILD.

Similarly, the correlation between PAH and capillary loss (Pearson $r = 0.6369$) reveals a substantial relationship, with capillary loss explaining approximately 40.57% of the variance in PAH. The 95% confidence interval (0.4621 to 0.7641) and the significant p value (<0.0001) confirm the robustness of this association. This finding suggests that capillary loss is a significant factor in the development or severity of PAH in SSc patients. Additionally, the moderate positive correlation between PAH and neoangiogenesis (Pearson $r = 0.5592$) indicates that increased neoangiogenesis is associated with higher instances or severity of PAH, though to a lesser extent than capillary loss. The R squared value of 0.3127 and the significant p value (<0.0001) support the validity of this relationship, highlighting the complex interplay between vascular remodeling processes and pulmonary hypertension in SSc.

Moreover, the study's findings have important clinical implications. Early detection of microvascular abnormalities through NVC can help identify patients at higher risk for severe complications such as ILD and PAH. This early identification is crucial for timely and targeted therapeutic interventions aimed at preserving vascular integrity and managing systemic involvement. The progression from limited to diffuse cutaneous involvement, increasing functional disability, and worsening internal organ complications emphasize the need for comprehensive management strategies in SSc. Interventions that can slow or reverse microvascular damage may improve outcomes and quality of life for patients [28].

The significant correlations between NVC patterns and clinical manifestations of SSc underscore the relevance of NVC as a diagnostic and prognostic tool. NVC abnormalities correlate with disease activity and severity and may be predictive of disease progression. Successful treatments have been shown to reduce NVC abnormalities in SSc cases, supporting the importance of NVC in monitoring SSc patients and suggesting its potential

role as an outcome measure for microangiopathy in clinical trials [29].

Furthermore, this study highlights the dynamic progression of microvascular damage in SSc and its correlation with functional impairment and internal organ involvement. The findings reinforce the need for integrated care approaches that address both the vascular and systemic aspects of SSc, aiming to improve patient outcomes through early detection and targeted treatment strategies. Monitoring and managing microvascular health is crucial in mitigating the development and progression of severe complications such as ILD and PAH in SSc patients.

Our study's findings align closely with those from the reviews and meta-analyses by Erdem Gürsoy *et al.* (2022) and Umashankar *et al.* (2021), highlighting the critical role of NVC in the assessment and management of SSc.

Also, the study by Erdem Gürsoy *et al.* investigated the relationship between NVC patterns and clinical features, functional status, pain, and fatigue in SSc patients. Their findings underscore the importance of NVC in identifying severe disease manifestations, echoing our results.

Both studies observed that capillary loss is a significant marker of disease severity. In our study, capillary loss was strongly correlated with increased severity of ILD and PAH. Similarly, Erdem Gürsoy *et al.* found that capillary loss was associated with digital ulcers, pulmonary hypertension, and gastrointestinal involvement. This consistency across studies reinforces the role of capillary loss as a critical indicator of systemic complications in SSc.

The comparison of functional status and disease severity revealed similar trends. While Erdem Gürsoy *et al.* did not find significant differences in HAQ scores between different NVC patterns, likely due to their smaller sample size, our study demonstrated a clear increase in HAQ scores from early to late NVC patterns. This indicates worsening functional status as the disease progresses. Furthermore, both studies noted variations in fatigue and pain levels. Erdem Gürsoy *et al.* reported similar levels across NVC patterns, whereas our study found higher pain levels in the early pattern group and increased fatigue in the late pattern group. This suggests that pain may be more prominent during the initial inflammatory stages, while fatigue increases with progressive fibrosis and systemic involvement.

The meta-analysis by Umashankar *et al.* focused on the role of NVC in classifying and diagnosing ILD in connective tissue diseases,

including SSc. Their findings support our observations about the diagnostic utility of NVC. Umashankar *et al.* reported that the prevalence of NVC abnormalities is highest in connective tissue disease-related ILD (CTD-ILD), with a prevalence ratio of 80.4%. This aligns with our findings that NVC is a crucial diagnostic tool for identifying ILD in SSc patients, as capillary abnormalities are strongly associated with the presence and severity of ILD. Within the CTD-ILD cohort, the late scleroderma pattern was most prevalent, consistent with our observation that advanced NVC patterns correlate with more severe disease manifestations, including ILD.

The meta-analysis also highlighted the importance of a multidisciplinary approach in utilizing NVC for diagnosing ILD, which aligns with our recommendation to integrate NVC findings with other clinical assessments such as HRCT and pulmonary function tests. This comprehensive approach ensures a thorough evaluation of SSc patients, improving diagnostic accuracy and patient management.

Moreover, Umashankar *et al.* emphasized the potential prognostic value of NVC in predicting disease progression and severity. Our correlation analyses between capillary loss and systemic complications, such as ILD and PAH, reinforce the utility of NVC as a prognostic tool in SSc. Early detection of capillary loss through NVC enables timely interventions, potentially mitigating the progression of severe complications.

Both our study and the reviewed literature underscore the critical role of early detection of microvascular abnormalities through NVC. Identifying these changes early allows for prompt therapeutic interventions aimed at preserving vascular integrity and managing systemic involvement, ultimately improving patient outcomes. Successful treatments have been shown to reduce NVC abnormalities, further supporting the importance of NVC in monitoring SSc patients and suggesting its potential role as an outcome measure for microangiopathy in clinical trials.

The significant correlations between NVC patterns and clinical manifestations of SSc underscore the relevance of NVC as both a diagnostic and prognostic tool. Monitoring and managing microvascular health is crucial in mitigating the development and progression of severe complications such as ILD and PAH in SSc patients. The integrated care approach, which addresses both the vascular and systemic aspects of SSc, is essential for improving patient outcomes through early detection and targeted treatment strategies.

NOVELTY OF FINDINGS COMPARED TO PREVIOUS LITERATURE

Our study introduces several novel insights into the management of SSc using NVC. We provide robust statistical correlations between NVC patterns and the severity of ILD and PAH, demonstrating that capillary loss is a significant predictor of these complications. Additionally, we offer a dynamic view of disease progression by categorizing patients into early, active, and late NVC patterns, enhancing our understanding of SSc pathogenesis. Our emphasis on early detection through NVC highlights its role in identifying systemic involvement early, allowing for timely interventions, which is more pronounced in our study compared to previous literature.

We also correlate NVC patterns with measures of functional status and quality of life, such as HAQ and VAS scores, illustrating how these factors deteriorate as NVC patterns progress. Advocating for a multidisciplinary approach, we recommend integrating NVC findings with other clinical assessments for enhanced diagnostic accuracy and patient management. Our findings support the inclusion of NVC in clinical guidelines for SSc management, emphasizing its potential for monitoring treatment efficacy and guiding therapeutic strategies. These contributions advance the understanding and management of SSc, highlighting NVC's critical role in improving patient outcomes.

A limitation of our study is the absence of post-hoc tests when comparing three or more subgroups. This omission may impact the robustness of our subgroup comparisons and the accuracy of our conclusions regarding subgroup differences. Additionally, the relatively small sample size may limit the generalizability of our findings and reduce statistical power, making it more challenging to detect subtle effects or differences among groups. The lack of a multivariate analysis is another limitation, as it restricts our ability to control for potential confounding variables and evaluate the independent effects of each factor on the outcomes studied.

CONCLUSIONS

The study highlights the critical role of microvascular abnormalities in the progression of SSc. Using NVC, it was observed that microvascular damage progresses from minimal in the early stages to severe in the late stages, correlating with increased disease severity and functional

impairment. DU, ILD, and PAH showed significant increases in prevalence as the disease advanced, with the late pattern group exhibiting the highest levels of these complications. Pearson correlation analyses revealed strong positive correlations between capillary loss and both ILD and PAH, while a moderate correlation was found between neoangiogenesis and PAH.

These findings underscore the importance of early detection and continuous monitoring of

microvascular changes using NVC in managing SSc. Early identification of capillary loss and neoangiogenesis can guide timely interventions aimed at preserving vascular health and mitigating the progression of severe complications such as ILD and PAH. By integrating NVC into routine clinical practice, healthcare providers can improve patient outcomes and quality of life through targeted treatment strategies that address both vascular and systemic aspects of SSc.

Introducere: Sclerodermia sistemică (SSc) este o boală complexă a țesutului conjunctiv, caracterizată prin microangiopatie, disfuncție imună și fibroză. Detectarea precoce a anomaliilor microvasculare prin videocapilaroscopie la nivelul patului unghial (NVC) este esențială pentru evaluarea progresiei bolii și a complicațiilor asociate, cum ar fi pneumopatia interstițială difuză (PID) și hipertensiunea arterială pulmonară (HTP).

Obiectiv: Acest studiu își propune să exploreze relațiile dintre pattern-urile NVC, manifestările clinice și complicațiile sistemice în SSc.

Metode: Am analizat 63 de pacienți, predominant femei (95%), cu o vârstă medie de 49 de ani și o durată medie a bolii de 42 de luni. Pacienții au fost distribuiți în pattern capilaroscopic precoce, activ și tardiv, pe baza modificărilor NVC. Caracteristicile clinice, inclusiv ulcerele digitale (DU), PID și HTP, au fost evaluate. S-au efectuat analize de corelație Pearson pentru a evalua relațiile dintre pierderea capilară, neoangiogeneza, PID și HTP.

Rezultate: Grupul cu pattern precoce (mRSS mediu 2,36) a prezentat leziuni microvasculare minime și implicare sistemică redusă, fără DU. În grupul cu pattern activ (mRSS mediu 10,40), 34,38% au avut SSc cutanată difuză (dcSSc), 15,63% prezentând DU, 65,63% PID și 37,5% HTP. Grupul cu pattern tardiv (mRSS mediu 18,00) a prezentat cea mai severă formă de boală, cu 80% având DU, 70% dcSSc, 90% PID și 70% HTP. Analizele de corelație Pearson au relevat corelații puternice între pierderea capilară și PID ($r = 0.7255$) și HTP ($r = 0.6369$). S-a constatat o corelație moderată între neoangiogeneza și HTP ($r = 0.5592$).

Concluzie: Studiul demonstrează că alterarea progresivă a microvascularizației în SSc, evidențiată prin NVC, se corelează cu severitatea complicațiilor sistemice. Detectarea precoce a pierderii de anse capilare și a neoangiogenezei folosind NVC este esențială pentru intervenții terapeutice precoce, care ar putea îmbunătăți rezultatele pacienților prin atenuarea progresiei PID și HTP.

Correspondence to: Cristina Elena Biță, M.D. Department of Rheumatology, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareș Street, 200349 Craiova, Romania, E-mail: cristina.gofita@umfcv.ro

REFERENCES

- DERK C.T., JIMENEZ S.A. Systemic sclerosis: current views of its pathogenesis. *Autoimmun. Rev.* 2003; **2**:181–191
- HERRICK A.L., MATUCCI CERINIC M. The emerging problem of oxidative stress and the role of antioxidants in systemic sclerosis. *Clin. Exp. Rheumatol.* 2001; **19**:4–8
- ASSASSI S., MAYES M.D., ARNETT F.C., GOURH P., AGARWAL S.K., MCNEARNEY T.A., et al. Systemic sclerosis and lupus: Points in an interferon-mediated continuum. *Arthritis Rheum.* 2010; **62**:589–598
- DOMSIC R.T. Scleroderma. *Curr. Opin. Rheumatol.* 2014; **26**:646–652
- SMITH V., DECUMAN S., SULLI A., BONROY C., PIETTTE Y., DESCHEPPER E., et al. Do worsening scleroderma capillaroscopic patterns predict future severe organ involvement? a pilot study. *Ann. Rheum. Dis.* 2012; **71**:1636–1639
- ELSAIED A.M., ELHEFNY A.M., ABOGABAL M.M., MOBASHER S.A., ABDELZAHER A., ALHASSANEIN K.F., et al. Progressive systemic sclerosis in Egyptian patients: Clinical characteristics and nail fold capillaroscopy. *Egypt. Rheumatol.* 2019; **41**:47–51

7. MEIJS J., SCHOUFFOER A.A., AJMONE MARSAN N., KROFT L.J.M., STIJNEN T., NINABER M.K., et al. *Therapeutic and diagnostic outcomes of a standardised, comprehensive care pathway for patients with systemic sclerosis*. RMD Open 2016; **2**:e000159
8. PRESTON I.R., HILL N.S. *Evaluation and management of pulmonary hypertension in systemic sclerosis*. Curr. Opin. Rheumatol. 2003; **15**:761–765
9. BEHR J., VOGELMEIER C., BEINERT T., MEURER M., KROMBACH F., KÖNIG G., et al. *Bronchoalveolar lavage for evaluation and management of scleroderma disease of the lung*. Am. J. Respir. Crit. Care Med. 1996; **154**:400–406
10. TYNDALL A.J., BANNERT B., VONK M., AIRO P., COZZI F., CARREIRA P.E., et al. *Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database*. Ann. Rheum. Dis. 2010; **69**:1809–1815
11. MUKERJEE D. *Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach*. Ann. Rheum. Dis. 2003; **62**:1088–1093
12. DEMEROUTI E., TSANGARIS I., DIMITROULAS T., GIANNAKOULAS G., KATSIMPRI P., MITROUSKA I., et al. *Pulmonary Arterial Hypertension in Connective Tissue Disorders: The emerging role of screening and early diagnosis. A position paper for Greek Rheumatologists*. Mediterr. J. Rheumatol. 2019; **30**:90–93
13. INGEGNOLI F., ARDOINO I., BORACCHI P., CUTOLO M., AIRÒ P., ANANIEVA L.P., et al. *Nailfold capillaroscopy in systemic sclerosis: Data from the EULAR scleroderma trials and research (EUSTAR) database*. Microvasc. Res. 2013; **89**:122–128
14. HERRICK A.L., CUTOLO M. *Clinical implications from capillaroscopic analysis in patients with Raynaud's phenomenon and systemic sclerosis*. Arthritis Rheum. 2010; **62**:2595–2604
15. VAN DEN HOOGEN F., KHANNA D., FRANSEN J., JOHNSON S.R., BARON M., TYNDALL A., et al. *2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative*. Ann. Rheum. Dis. 2013; **72**:1747–1755
16. VASILE M., AVOUAC J., SCIARRA I., STEFANANTONI K., IANNACE N., CRAVOTTO E., et al. *From VEDOSS to established systemic sclerosis diagnosis according to ACR/EULAR 2013 classification criteria: a French-Italian capillaroscopic survey*. Clin. Exp. Rheumatol. 2018; **36 Suppl 1**:82–87
17. CUTOLO M., MELSENS K., WIJNANT S., INGEGNOLI F., THEVISSSEN K., DE KEYSER F., et al. *Nailfold capillaroscopy in systemic lupus erythematosus: A systematic review and critical appraisal*. Autoimmun. Rev. 2018; **17**:344–352
18. MEDSGER T.A., BOMBARDIERI S., CZIRJAK L., SCORZA R., DELLA ROSSA A., BENCIVELLI W. *Assessment of disease severity and prognosis*. Clin. Exp. Rheumatol. 2003; **21**:S42–6
19. INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMIES. *Cardiovascular Disability: Updating the Social Security Listings*, The National Academies Press, Washington, DC, 2010
20. PATTANAIK D., BROWN M., POSTLETHWAITE B.C., POSTLETHWAITE A.E. *Pathogenesis of Systemic Sclerosis*. Front. Immunol. 2015; **6**:272
21. CUTOLO M., SULLI A., SMITH V. *How to perform and interpret capillaroscopy*. Best Pract. Res. Clin. Rheumatol. 2013; **27**:237–248
22. SULLI A., PIZZORNI C., SMITH V., ZAMPOGNA G., RAVERA F., CUTOLO M. *Timing of transition between capillaroscopic patterns in systemic sclerosis*. Arthritis Rheum. 2012; **64**:821–825
23. MOORE D.F., STEEN V.D. *Overall mortality*. J. Scleroderma Relat. Disord. 2021; **6**:3–10
24. WALKER U.A., TYNDALL A., CZIRJAK L., DENTON C., FARGE-BANCEL D., KOWAL-BIELECKA O., et al. *Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database*. Ann. Rheum. Dis. 2007; **66**:754–763
25. RAHAGHI F.F., HSU V.M., KANER R.J., MAYES M.D., ROSAS I.O., SAGGAR R., et al. *Expert consensus on the management of systemic sclerosis-associated interstitial lung disease*. Respir. Res. 2023; **24**:6
26. COGHLAN J.G., DENTON C.P., GRÜNIG E., BONDERMAN D., DISTLER O., KHANNA D., et al. *Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study*. Ann. Rheum. Dis. 2014; **73**:1340–1349
27. VOLKMANN E.R., FISCHER A. *Update on morbidity and mortality in systemic sclerosis-related interstitial lung disease*. J. Scleroderma Relat. Disord. 2021; **6**:11–20
28. GUALTIEROTTI R., INGEGNOLI F., GRIFFINI S., GROVETTI E., BORGHI M.O., BUCCIARELLI P., et al. *Detection of early endothelial damage in patients with Raynaud's phenomenon*. Microvasc. Res. 2017; **113**:22–28
29. CESTELLI V., MANFREDI A., SEBASTIANI M., PRAINO E., CANNARILE F., GIUGGIOLI D., et al. *Effect of treatment with iloprost with or without bosentan on nailfold videocapillaroscopic alterations in patients with systemic sclerosis*. Mod. Rheumatol. 2017; **27**:110–114