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ORIGINAL ARTICLE

Association of nailfold capillaroscopic findings with clinical features in patients with systemic sclerosis

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ABSTRACT

Background: Microvascular damage is one of the most important etiopathogenetic and clinical characteristics of systemic sclerosis (SSc). Nailfold capillaroscopy (NFC) is a simple, non-invasive, and inexpensive imaging technique to assess the skin microcirculation. The aim of this study was to determine the association between NFC findings and clinical features in patients with SSc.

Methods: This study was done in the Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from July 2019 to August 2020. Twenty-nine adult patients with SSc were selected according to ACR/EULAR (American College of Rheumatology/European Alliance of Associations for Rheumatology) criteria 2013. NFC variables (capillary loss, avascular area, giant capillary, microhemorrhage and neoangiogenesis) and their NFC patterns (nonspecific, early, active, and late scleroderma) were analyzed using a dynamic nailfold capillaroscope. Their associations with disease duration, skin thickness score, interstitial lung disease (ILD), pulmonary hypertension (PH) and peripheral vascular involvement (pitting scar, and others) were examined.

Results: Among 29 patients, scleroderma patterns were present in 27 (93.1%) patients. Thirteen (44.8%) patients had late scleroderma pattern. Early scleroderma pattern and active scleroderma patterns were observed in 7 (24.1%) patients. Disease duration was significantly associated with avascular area (P=0.04) and NFC pattern (P=0.001). Microhemorrhage was significantly associated (P=0.04) with PH, but NFC pattern was associated with ILD (P=0.03).

Conclusion: NFC pattern found to be significantly associated with disease duration and ILD. Among the individual NFC findings, avascular area shows association with disease duration and microhaemorrhage showed association with pulmonary hypertension in SSc patients.

Keywords: *systemic sclerosis, nailfold capillaroscopy, disease duration, interstitial lung disease, pulmonary hypertension*

INTRODUCTION

Systemic sclerosis (SSc) is a complex disorder that involves small vessels and connective tissue, with deposition of fibrotic tissue and microvascular obliteration in the skin and internal organs. The vascular involvement primarily affecting small arteries and capillaries causes ischemia that may be linked with the typical clinical manifestations of this unique autoimmune disorder.[1] Nailfold capillaroscopy (NFC) is currently the best and validated imaging technique for the detection of peripheral microvascular morphology.[2] It is quick to perform and a non-invasive, reproducible, simple, safe, and inexpensive imaging technique.[3-5]

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HIGHLIGHTS

1. Nailfold capillaroscopy is a non-invasive technique to directly visualize the microangiopathy in patients with systemic sclerosis.
2. Utilization of nailfold capillaroscopy to identify the patients at a higher risk for the specific clinical features of systemic sclerosis patients is yet to be established.
3. Nailfold capillaroscopy findings may provide clue to the duration of the disease.
4. Nailfold capillaroscopy findings may be used to suspect the presence or absence of pulmonary hypertension, and interstitial lung disease in systemic sclerosis patients.

The scleroderma microangiopathy has been investigated by many authors during the last three decades.[4] The potential link between vascular abnormalities detected by NFC and visceral organ impairment increased interest in this field.[6] EULAR (European Alliance of Associations for Rheumatology) Study Group on Microcirculation in Rheumatic Diseases mentioned several reports of associations between NFC and clinical features of SSc from previous small pilot as well as in cohort studies in their article.[7]

Several studies linked SSc microangiopathy with disease duration and the peripheral vascular, skin, and lung involvement.[1,8] The association between disease duration and NFC findings were not found in similar direction in different studies.[9-13] So, further investigations are needed. Associations of NFC findings with digital ulcer and skin progression have been demonstrated in several European multicenter studies.[14-18] The association of structural and morphological capillary abnormalities revealed by NFC with the pulmonary involvement was explored in several studies and links have been reported.[9,19,20] Some researchers did not find any association between capillaroscopy variables and interstitial lung disease (ILD)[10,21] and pulmonary hypertension (PH).[1,8,9,21,22] It remains an unsolved issue and, therefore, demands further research to examine these associations.[20,22] Given the silent presentation of pulmonary involvement, early identification is highly desirable and remains an unmet need.[20]

There are reports of relatively poor performance of pulmonary function tests as a method for ILD screening and early diagnosis.[23] NFC represents a favorable method to determine a subgroup of SSc patients at higher risk of developing PH which can supplement the physician's clinical assessment, echocardiography, and pulmonary function tests.[20] The availability of such type of non-invasive markers to predict disease progression might provide a window of opportunity for initiation and/or escalation of treatment in specific subgroups of SSc.[20] This study was aimed at determining the potential associations of NFC findings with several clinical features of patients with SSc.

METHODS

It was a cross-sectional study carried out in the Department of Rheumatology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from July 2019 to August 2020. Inclusion criteria were age >18 years, fulfilling the 2013 ACR/ EULAR (American College of Rheumatology/ European Alliance of Associations for Rheumatology) criteria for the classification of SSc and the patients who had at least six evaluable nailfolds. Exclusion criteria were, overlap with other connective tissue diseases, local trauma in tip of the fingers within last 8 weeks and digital ulcers involving all nailfolds. All the patients were enrolled after taking the written informed consent. The patients from scleroderma clinic of rheumatology outdoor and admitted SSc patients were collected or referred to the investigator by respective residents of the department. The patients were evaluated by two investigators.

The age of disease onset was considered as the age at which the patient first noticed skin changes including Raynaud's phenomenon. The skin thickness was scored by the modified Rodnan Skin Score (mRSS).[24] After the history taking and clinical examination, pulmonary involvements were assessed by the relevant investigations like chest X-ray, multi-slice thin segment computed tomography scan of chest, electrocardiogram, doppler echocardiography and spirometry with diffusing capacity of lung for carbon mono-oxide (DLCO). Hematology, renal function, and urinalysis were performed at the central laboratory of BSMMU using standard validated methods. HRCT (High-resolution computed tomography) of chest was done in the radiology department of BSMMU in patients with a suggestive history and/or clinical examination findings

or chest X-ray (posteroanterior view) showing features of ILD. ECG (Electrocardiogram) and doppler echocardiography with pulmonary artery systolic pressure were done for all patients in BSMMU.

Nailfold capillaroscopy

NFC was done using a dynamic capillaroscope (Dino lite 2) consisting of a light source, green filter, dimming control, charge coupled device camera connected to a frame grabber and a desktop, with a software dedicated to calibrating and measuring linear dimensions and areas. All subjects were examined in the sitting position with the hand at the level of the heart. The patients were asked to wash their hands gently with plain water and soap. Each patient was acclimatized for 15 minutes at a room temperature of 20 – 24^{0}C prior to the procedure. All the fingers of both hands except the thumbs were examined. The finger chosen for investigation was placed under microscope. A drop of olive oil was applied to the nailfold before recording to improve resolution. Two consecutive fields extending over 1 mm, in the middle of the nailfold and corresponding to the distal row of capillaries, were studied per finger. Individual capillaroscopic variables recorded as 'present' or 'absent' in the distal row of the nailfold were following: loss of capillaries, avascular area, microhemorrhages (dark mass due to hemosiderin deposit linked to a disappearing capillary), giant capillaries (hairpin-shaped or horseshoe-shaped homogeneously large capillary with diameter ≥50μM), neoangiogenesis (meandering, ramified, branching, bushy, bizarre capillaries, and capillaries with more than two crossings), abnormal shaped capillaries, elongated capillaries, and irregularly enlarged capillaries.

NFC findings in patients with SSc were classified as several patterns: "normal", "nonspecific", "early", "active", or "late" scleroderma patterns. Normal pattern was considered as 6 – 8 capillaries/mm, capillary length between 200 – 500 μm, hair pin shaped loops arranged in parallel rows, absence of hemorrhages. Non-specific changes were defined by minor and major changes without a specific scleroderma pattern. Minor abnormalities are 6 – 8 capillaries/mm, less than 50% tortuous loops, arranged in parallel rows, with no hemorrhages. Major abnormalities are normal or decreased capillary density, more than 50% tortuous, enlarged loops, disarranged, with hemorrhages. Early scleroderma pattern was a few (<4) altered capillaries per millimeter) enlarged/giant capillaries, a few capillary hemorrhages, relatively well-preserved capillary distribution, no evident loss of capillaries. Active scleroderma pattern was defined by frequent (>6 altered capillaries per millimeter), giant capillaries, frequent capillary hemorrhages, moderate (20 - 30%) loss of capillaries, mild (4 - 6 altered capillaries per millimeter) disorganization of the capillary architecture and absent or mildly ramified capillaries. Late scleroderma pattern was characterized by irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, severe (50 - 70%) loss of capillaries with extensive avascular areas, disorganization of the normal capillary array, and ramified/bushy capillaries.[8,11]

Statistical analysis

The analyses were performed using Statistical Package of Social Science (SPSS) version-25 software. Quantitative variables (skin thickness score and disease duration) were expressed as mean (standard deviation) or median (interquartile range) depending on their distribution. Categorical data (ILD, PH and peripheral vascular involvement) were expressed as number and percent. Associations of individual NFC findings with normally distributed skin thickness score (mRSS) and non-normally distributed disease duration were assessed by using Student's *t* test or Mann-Whitney *U* test, respectively. Associations of NFC patterns were seen with mRSS and disease duration by performing one-way ANOVA and Kruskal Wallis test, respectively. Fisher's exact test was done to assess the associations between NFC patterns and other organ involvement. *P* less than 0.05 were considered statistically significant.

RESULTS

A total of 29 patients of SSc were included in this study. Twenty (69%) patients had diffuse cutaneous systemic sclerosis. The mean (standard deviation) age was 38.6 (13.4) years with a median (interquartile range) disease duration of 36 (8-96) months. The mean (standard deviation) mRSS was 19.9 (11.8). The frequency of clinical features is summarized in **TABLE 1**.

The most frequent NFC variable was capillary loss in 27 patients, followed by abnormal shaped capillary in 26 patients, irregularly enlarged capillaries in 24 patients, giant capillary in 22 patients, avascular area in 21 patients, microhemorrhages in 19 patients and neoangiogenesis in 19 patients.

TABLE 1 Clinical features of the study patients (n=29)

Clinical features	Number	Percent
Peripheral vascular involvement		
Raynaud's phenomenon	29	100.0
Digital pitting scar	21	72.4
Active ulcer	7	24.1
Necrosis/amputation	2	6.9
Telangiectasia	2	6.9
Pulmonary involvement		
Interstitial lung disease	13	44.8
Pulmonary hypertension	5	17.2

Of the 29 patients, 27 (93.1%) had specific scleroderma pattern and only 2 had nonspecific pattern. Thirteen patients had late scleroderma pattern, 7 had early and 7 had active scleroderma patterns.

Avascular area and NFC pattern showed significant associations with disease duration (P=0.04 and 0.001 respectively) **(TABLE 2)**. There was no significant association between individual NFC variables or patterns with skin thickening and the individual components of the peripheral vascular involvement.

TABLE 2 Median (interquartile range) of disease duration according to nailfold capillaroscopic findings (n=29)

Capillaroscopic findings	Present	Absent	*P*
Variables			
Capillary loss	48.0 (8.0 – 96.0)	7.0 (4.0 – 10.0)	0.21
Avascular areas	50.0 (12.5 – 108.0)	9.0 (4.5 – 47.5)	0.04[a]
Giant capillary	49.0 (9.5 – 96.0)	10.0 (4.0 – 96.0)	0.18
Microhaemorrhages	48.0 (8.0 – 96.0)	30.5 (8.5 – 85.5)	0.81
Neoangiogenesis	50.0 (15.0 – 96.0)	9.0 (3.8 – 75.0)	0.08
Pattern			
Early[b]	6.0 (3.5 – 9.0)		0.001[c]
Active	15.0 (10.0 – 60.0)		
Late	84.0 (49.0 – 108.0)		

[a]Mann-Whitney *U* test
[b]Included 2 nonspecific capillaroscopic patterns
[c]Kruskal-Wallis test

But, if the pitting scar is analyzed exclusively, association with avascular area was found **(TABLE 3)**. The patients who had microhemorrhages in their NFC mostly (94.7%) had no PH. Microhemorrhage showed a significant negative association with PH (P=0.04). On the other hand, NFC patterns i.e., nonspecific, early, active, and late scleroderma patterns showed significant association with ILD (P=0.03), but not with PH **(TABLE 4)**.

TABLE 3 Association of Nailfold capillaroscopic findings with peripheral vascular involvement (n=29)

Capillaroscopic findings	Number	Peripheral vascular involvement		
		Pitting scar only	Others	*P*[a]
Variables				
Capillary loss	27	13 (48.1)	14 (51.9)	0.49
Avascular areas	21	12 (57.1)	9 (42.9)	0.04
Giant capillary	22	10 (45.5)	12 (54.5)	0.99
Microhaemorrhages	19	8 (42.1)	11 (57.9)	0.71
Neoangiogenesis	19	9 (47.4)	10 (52.6)	0.99
Pattern				
Early[b]	9	3 (33.3)	6 (66.7)	0.40
Active	7	3 (42.9)	4 (57.1)	0.99
Late	13	7 (53.8)	6 (46.2)	0.38

[a]All are Fisher's exact test or chi-square as appropriate
[b]Included 2 nonspecific capillaroscopic patterns

DISCUSSION

This was the first study in Bangladesh where we had seen if there was any association of NFC findings with clinical features in SSc. Microvascular damage is a distinguishing feature of SSc.[6] NFC is currently viewed as the standard non-invasive method for evaluating microcirculation and might be beneficial to detect which patients are prone to develop complications.[25,26] In this study we found significant associations between NFC variables like, "avascular area" with the disease duration and "micro-hemorrhage" in PH patients. We found an association of NFC pattern (e.g., early, active, and late) with disease duration and ILD in patients with SSc.

We found a significant association between the disease duration with avascular area. It may indicate that if NFC reveals the avascular area, the patient has been suffering from for a prolonged period. A similar association was also observed in another one study.[10] In this study we also observed an association between disease duration and NFC patterns. Shorter disease duration was associated with early NFC changes, whereas prolonged disease duration was associated with active and late NFC changes. Therefore, early intervention with appropriate drugs may be beneficial to halt the progression of the disease. Similar findings were also reported in some other studies.[11,12] However, some studies did not find any association of disease duration with early, active, and late NFC patterns.[9,13] and they did not explain in favor of their observation.

Although skin thickening is one of the most common manifestations of the disease, we did not find any

TABLE 4 Nailfold capillaroscopic findings in interstitial lung diseases and pulmonary hypertension (n=29)

Capillaroscopic findings	Number	Interstitial lung disease			Pulmonary hypertension		
		Present (n=13)	Absent (n=16)	P[a]	Present (n=5)	Absent (n=24)	P[a]
Variables							
Capillary loss	27	13 (100.0)	14 (87.5)	0.49	5 (100.0)	22 (91.7)	0.99
Avascular areas	21	10 (76.9)	11 (68.8)	0.70	5 (100.0)	16 (66.7)	0.28
Giant capillary	22	11 (84.6)	11 (68.8)	0.41	4 (80.0)	18 (75.0)	0.99
Microhaemorrhages	19	9 (69.2)	10 (62.5)	0.99	1 (20.0)	18 (75.0)	0.04
Neoangiogenesis	19	10 (76.9)	9 (56.3)	0.43	4 (80.0)	15 (62.5)	0.63
Pattern							
Early[b]	9	1 (7.7)	8 (50)	0.03	1 (0.1)	8 (33.3)	0.10
Active	7	5 (38.5)	2 (12.5)		0 (-)	7 (29.2)	
Late	13	7 (53.8)	6 (38.3)		4 (80.0)	9 (37.5)	

All are number (percent)
[a]Fisher's exact test
[b]Included 2 nonspecific capillaroscopic patterns

association between either NFC variables or NFC patterns with skin thickness score. One study in Iran also did not find any association between any NFC variables with skin involvement (22). Although, in Italy one study showed association between NFC patterns with skin involvement.[1] Disparities of findings among the researchers are not well explained and further study with large sample size is required.

In our study, avascular area was associated with pitting scar, when patient with only pitting scar without other peripheral vascular involvement was being analyzed. Otherwise, association was not found between NFC variables or NFC patterns with peripheral vascular involvement (e.g., pitting scar, active ulcer, necrosis/ amputation, and telangiectasia). Although some studies found associations between some variables and patterns.[12-15,26] One study in Iran found association of NFC pattern with telangiectasia and pitting scar.[22] These studies had larger sample size and could be the reason for the positive findings, which reflect the real scenario.

ILD is a common pulmonary manifestation in SSc that constitutes one of the main causes of mortality.[20] In our study, NFC pattern was found to be associated with ILD. Several studies also reported similar findings and suggested appropriate intervention and periodic follow-up.[1,9,13,27] One study showed late pattern of NFC was associated with severe ILD[28], while a Spanish study did not find any association between any pattern with ILD, and the reason of the negative association was not explained.[6] Association of individual NFC variables with ILD was not observed in some other studies[21,29], and reason for the negative association was not explained.

PH is one of the severe complications of SSc that causes significant morbidity and mortality.[20] In our study NFC pattern showed no association with PH [5 (17.2%) of all]. Similar findings were observed in two other studies.[9,22] Both the studies had a few patients with PH, so there is a need for more patients to be evaluated. However, some studies found significant associations of PH with NFC pattern.[13,30,31] The first study analyzed the early, active, and late scleroderma pattern, while the rest two studies compared the scleroderma pattern and normal/non-specific NFC pattern. Due to wider variability among the studies, drawing proper explanation behind the different study outcome is difficult.

Of the NFC variable findings, in our study we found in patients those had positive NFC variable e.g., microhemorrhage had less PH. Although we had only 5 patients with PH, it is difficult to draw any conclusion from this finding. In several other studies, decreased capillary density and neoangiogenesis were associated with PH which reflects the pathogenic mechanisms run parallelly.[6,19,28,32] In contrary, a study in Brazil did not find any association of NFC variable with PH.[21]

In this study, a quantitative assessment of NFC findings was not included. The sample size was small. The NFC procedure was not blinded to the clinical features of the patients. Inter-observer variability was not assessed. Right heart catheterization could not be arranged for PH. However, all our patients were selected from a public hospital that provides services to people of all socioeconomic backgrounds. Therefore, our subjects had a high potential of being representative of SSc patients in general.

Conclusion

In conclusion, our study suggested that positive NFC findings may be useful to suspect the involvement of the lung, especially ILD and PH. Because of disparities of the findings among studies demand further studies with large sample size along with qualitative and quantitative NFC findings.

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Author contributions

Conception and design: TH, MRC, MAS, MAI, SAH. *Acquisition, analysis and interpretation of data:* TH, MAS, MAI, IHB, MMZ. *Manuscript drafting and revising it critically:* TH, MAS, MAI, MRC, SAH, IHB, MMZ. *Approval of the final version of the manuscript:* TH, MRC, MAS, MAI, IHB, MMZ, SAH. *Guarantor accuracy and integrity of the work:* TH and MAS.

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Conflict of interest

We declare no conflict of interest.

Ethical approval

Ethical clearance was obtained from the Institutional Review Board of BSMMU, Dhaka to undertake the present study. According to Helsinki Declaration for Medical Research involving Human Subjects 1964 (as revised in 2013), the study was conducted.

Data sharing

The authors confirm that the data supporting the findings of this study will be shared upon request.

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