

Value of Nailfold Capillaroscopy as A Screening Method for Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) represents one of the main clinical pictures of microvascular damage in systemic sclerosis (SSc).

Objective: To assess the role of nailfold capillaroscopy (NFC) changes as a screening tool for the existence of PAH in patients with systemic sclerosis.

Patients and methods: Forty SSc patients were studied, included: 20 patients with PAH (diagnosed by transthoracic echocardiography and confirmed by right heart catheterization) and another 20 without PAH. History taking, clinical examination, and laboratory investigations including serological biomarkers (anti-centromere and anti-topoisomerase I antibodies) have been recorded. NFC was performed for all patients according to the standard method.

Results: Scleroderma patients with PAH had significantly a longer disease duration ($p=0.002$) and higher frequencies of positive anticentromere and anti-topoisomerase I antibodies ($p=0.011$ and $p=0.010$ respectively). As regard NFC picture, SSc patients without PAH had significantly higher frequencies of early scleroderma pattern changes in 73.7% ($p=0.003$), avascular area score 0 in 52.6% ($p=0.014$) and total NFC score 0 in 57.9% ($p=0.022$). In contrast, SSc patients with PAH showed higher frequencies of late scleroderma pattern changes in 50% ($p=0.005$) with lower capillary density ($p<0.001$), increased number of dilated mega-capillaries ($p=0.049$) together with more advanced avascular area of score 3 in 47.6% ($p=0.007$) and total NFC of score 3 in 45% ($p=0.003$). A significant negative correlation between mean pulmonary arterial pressure and capillary density ($r=-0.57$, $p<0.001$) was reported.

Conclusion: Low capillary density together with wide avascular areas and more severe NFC scores have a clear association with the presence of PAH.

Keywords: Systemic Sclerosis, Pulmonary Arterial Hypertension, Nailfold capillaroscopy.

INTRODUCTION

Systemic sclerosis (SSc) is a long term complex autoimmune illness that still poses a great challenge to clinicians⁽¹⁾. Autoimmunity, skin together with internal organs fibrosis, and vasculopathy are marked features⁽²⁾. Scleroderma is more common in women than men with male:female ratio equals 4-5:1. The average age of disease diagnosis is nearly 50 years⁽³⁾. The medical disease is classified according to the degree of skin affection into subclasses with diffuse cutaneous involvement (dcSSc) and limited cutaneous involvement (lcSSc)⁽⁴⁾. Systemic sclerosis is marked by early and progressive microvascular distortion which can lead to fatal organ disorders of SSc, such as pulmonary arterial hypertension (PAH), scleroderma renal crisis, and tissue ischemia linked to organ dysfunction and fibrosis⁽⁵⁾. Egyptian SSc patients are at an increased risk of subclinical atherosclerosis and peripheral arterial disease⁽⁶⁾ and interstitial lung disease (ILD) is a frequent consequence of PAH especially in dcSSc patients⁽⁷⁾. Therefore, improvement of vasculopathy in SSc patients is one of the key treatment targets⁽⁵⁾.

Pulmonary hypertension (PH) is considered one of the main causes of mortality in patients with scleroderma. Scleroderma patients with PH had poorer outcome compared to those with idiopathic pulmonary

hypertension⁽⁶⁾. The WHO has subtyped PH into 5 categories: (1) PAH, (2) PH with left-sided heart failure, (3) PH due to hypoxic lung illness, and (4) PH secondary to chronic thromboembolism⁽⁸⁾. Patients with scleroderma may develop type 1, 2, or 3⁽⁹⁾. PAH is a common late complication of scleroderma, mainly in those with limited cutaneous disease and anti-centromere antibodies⁽⁶⁾. PAH is a lethal and malignant manifestation of vasculopathy in SSc that causes a dramatic impact on prognosis; and thus, necessitates an early screening and management⁽⁴⁾. Circulating plasma levels of endothelin1 are elevated in patients with PAH and are raised in their pulmonary tissue; making this vasoconstrictor a potential target for therapeutic intervention⁽¹⁰⁾. Moreover, a high serum endothelin1 level was found in SSc with late nailfold videocapillaroscopy (NVC) pattern and visceral involvement⁽¹¹⁾.

Nailfold video capillaroscopy is considered a useful safe non-invasive tool used in evaluation and follow-up of systemic rheumatic illnesses and constitutes one of the best assessment tools of microvascular defects in SSc. The capillary changes in SSc usually incorporate dilated and giant capillaries, capillary hemorrhages, disarrayed capillary loops, ramified/bushy capillaries, and capillary



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loss⁽¹²⁾. Interestingly, the association between progressive capillaroscopic changes (detecting microvascular damage) and the presence of PAH were evaluated in the last few years⁽¹³⁾. It is now obvious that the severity of the microvascular damage as evaluated by NVC varies among SSc patients with and without PAH and associates with pulmonary hemodynamic parameters. Remarkably, in comparison with healthy controls, the same is correct for those with idiopathic PAH, a state not known to have a characterizing systemic microvascular involvement⁽¹⁴⁾.

The current study aimed to assess the role of nailfold capillaroscopic (NFC) changes as a screening tool for the existence of PAH in patients with systemic sclerosis.

PATIENTS AND METHODS

In our cross-sectional study, we included 40 patients with SSc diagnosed according to the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Systemic Sclerosis Classification Criteria⁽¹⁵⁾. Patients were classified as diffuse (dSSc) or limited (lSSc) cutaneous SSc following the classification by **Le Roy et al.**⁽¹⁶⁾. Patients were enrolled from the Outpatient Clinic and the Inpatient Department of Rheumatology at Ain Shams University Hospital. Twenty patients with PAH were included; diagnosed by transthoracic echocardiography (TTE) and confirmed by right heart catheterization and another 20 patients without PAH were also recruited. Patients with previous pulmonary or venous thromboembolism, diabetes mellitus, systemic arterial hypertension, interstitial lung disease, any chest disease-causing chronic hypoxia, cardiac disease, or other concomitant connective tissue diseases were excluded.

Ethical approval: The study was approved by the Local Research Ethical Committee of Ain Shams University and followed the provisions of the Declaration of Helsinki in 1995.

Every patients signed an informed consent.

All Patients were subjected to careful history taking and clinical examination. Laboratory investigations included a complete blood picture (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-nuclear antibody (ANA), and anti-centromere and anti-topoisomerase 1 (anti-Scl 70) by indirect immunofluorescence assay.

Transthoracic echocardiography was done using two-dimensional, M-mode, color flow mapping, and spectral Doppler techniques. Special attention was paid for detection of tricuspid regurgitation, its degree, estimation of right ventricular systolic pressure (RVSP) using Bernoulli equation ($PASP = 4xV^2$ (of peak TR velocity)+ right atrial pressure), right ventricle (RV) size, RV systolic function using fractional area change (

$RV FAC = 100 \times (RVED \text{ area} - RVES \text{ area}) / RVED \text{ area}$)⁽¹⁷⁾, and pulmonary regurgitation for estimation of mean pulmonary arterial pressure (PAP) using Bernoulli equation (mean PAP = $4xV^2$ (of peak PR velocity)+ right atrial pressure)⁽¹⁸⁾. Patients with estimated RVSP >35 mmHg or mean PAP more than 25 mmHg were taken to the catheterization laboratory for invasive measurement of PAP. Mean PAP > or equal 25 with pulmonary capillary wedge pressure (PCWP) < or equal 15 mmHg confirmed having PAH according to 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension⁽¹⁹⁾.

Nailfold capillary microscopy was performed using a video capillaroscopy with a probe (magnification $\times 200$) according to the standard method⁽²⁰⁾. All images were collected and registered using a dedicated software system (Blu Vision). The following parameters were considered; Comment on the shape of the capillaries (normal hairpin, or abnormal shapes e.g. Branching capillaries or tortuous), the diameter of the capillaries (dilated loops if the diameter is $>20 \mu\text{m}$ and mega capillaries if $\geq 50 \mu\text{m}$), the capillary length (normal or elongated $\geq 300 \mu\text{m}$), the mean capillary density (low capillary density is defined as a reduction of the number $<7/\text{linear mm}$), and the avascular area (inter capillary distance $\geq 500 \mu\text{m}$). The presence of micro hemorrhage and of morphological abnormalities such as; tortuous, bizarre, enlarged, and irregular distribution of capillary array were considered. A rating scale was adopted to score the changes: score 0: no changes, score 1: few (≤ 4 alterations/linear mm), score 2: between 4 and 6 alterations, score 3: frequent (>6 alterations/mm)⁽²¹⁾. The score system for avascular areas (a vascularity of the capillary bed) was graded as: grade 0 = no obvious avascular area, grade 1 = mild (1 or 2 discrete areas of vascular deletion), grade 2 = moderate (>2 discrete areas of vascular deletion), and grade 3 = severe (large, confluent avascular areas)⁽²²⁾. The NFC findings were further classified into normal patterns or changes suggestive for SSc which include early pattern (few giant capillaries, few hemorrhages and no capillary loss), active pattern (numerous giant capillaries and micro hemorrhages, mild capillary architecture disturbance and moderate capillary loss), and late pattern (severe capillary loss with extensive avascular areas, disorganized capillaries and ramified capillaries)⁽²³⁾.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS 20) was used. Data were presented and a suitable analysis was performed. Unpaired Student T-test was used to compare two independent groups regarding quantitative data. The Chi-square was used to compare qualitative variables. Pearson's correlation coefficient (r) test was used to assess the degree of association between two sets of variables. P-value <0.05 was considered significant.

RESULTS

The demographic data of the patients are presented in table 1. SSc patients with PAH had significantly a longer disease duration, more limited subtype (lcSSc), more evident peripheral vascular

manifestations in the form of Raynaud’s phenomenon, telangiectasia, digital ulcers and pitting scars, and higher frequencies of positive anti centromere and anti-Sc170.

Table (1): Comparison between scleroderma patients with or without pulmonary artery hypertension (PAH) according to various demographic, clinical and laboratory data

Parameter Mean ±SD (range) or n (%)	SSc patients (n=40)			p
	All (n=40)	with PAH (n=20)	without PAH (n=20)	
Age (years)	39.1±8.24 (22-55)	41.1±6.3 (33-52)	37.2±10.2 (22-55)	0.26
Female :male	33:7 (82.5/17.5)	16:4 (80/20)	17:3 (85/15)	0.68
Age at onset (years)	27.2±6.9 (16.6-45.5)	25.2±6.2 (16.6-37.1)	29.2±7.5 (18.2-45.5)	0.16
Disease duration (years)	15.4±8.4 (2-43)	21.4±10.4 (5-43)	9.3±6.5 (2-22)	0.002
<i>Clinical manifestations</i>				
lcSSc	25 (62.5)	17 (85)	8 (40)	<0.004
dcSSc	15 (37.5)	3 (15)	12 (60)	<0.004
Raynaud’s	32 (80)	20 (100)	12 (60)	0.032
Pitting scar	21 (52.5)	15 (75)	6 (30)	0.043
Digital ulcer	15 (37.5)	11 (55)	4 (20)	0.022
Renal crisis	3 (7.5)	2 (10)	1 (5)	0.548
Telangiectasia	25 (62.5)	17 (85)	8 (40)	0.033
Esophageal dysmobility	34 (85)	19 (95)	15 (95)	0.765
Arthritis/arthralgia	25 (62.5)	15 (75)	10 (50)	0.102
<i>Laboratory investigations</i>				
Hemoglobin (g/dl)	10.6±1.2 (7.9-13.9)	10.1±0.7 (8.9-11)	11.1±1.8 (7.9-13.9)	<0.03
WBC (10 ⁹ /l)	7.1±2.5 (3.4-11.8)	7.6±2.8 (3.4-11.8)	6.5±2.1 (3.5-10.6)	0.26
Platelets (10 ⁹ /l)	252.1±56.1 (133-340)	263.4±45.7 (150-310)	240.8±66.4 (133-340)	0.33
ESR (mm/1st hr)	56.7±15.4 (23-102)	75.2±17.7 (47-102)	38.2±13.1 (23-65)	<0.001
Anti-centromere	21 (52.5)	15 (75)	6 (30)	0.043
anti- Scl70	17 (42.5)	13 (65)	4 (20)	0.004
ANA	16 (40)	9 (45)	7 (35)	0.518

SSc: systemic sclerosis, PAH: pulmonary artery hypertension, dcSSc: diffuse cutaneous involvement, lcSSc: limited cutaneous involvement, ESR: erythrocyte sedimentation rate, WBC: white blood cells, ANA: anti-nuclear antibody.

As regard NFC picture, SSc patients without PAH had a significantly higher frequency of early scleroderma pattern changes, avascular area score 0, and total NFC score 0. In contrast, SSc patients with PAH showed a higher frequency of late scleroderma pattern changes with a lower capillary density, increased capillary width, increased number of dilated mega-capillaries together with increased areas of capillary hemorrhages, and areas of sub-capillary venous plexuses (Figure 1 and 2). Furthermore, those with PAH had more advanced avascular areas of score 3 and total NFC of score 3 (Table 2). There were no significant differences in the NFC findings according to the gender or between the lcSSc and dcSSc subtypes.



Figure (1): Nail fold capillaroscopy picture of systemic sclerosis patient with pulmonary arterial hypertension showing dilated capillary loops, giant capillaries, capillary hemorrhage and wide avascular area. **a:**giant capillary **b:**avascular area **c:**capillary hemorrhage



Figure (2): Nail fold capillaroscopy picture of systemic sclerosis patient with pulmonary arterial hypertension showing giant capillaries, wide avascular areas and telangiectasia (neoangiogenesis). **a:** giant loop **b:** avascular area **c:**neoangiogenesis.

Table (2): Comparison between scleroderma patients with or without pulmonary artery hypertension (PAH) according to various nailfold capillaroscopy findings.

Parameter mean±SD (range) or n (%)	SSc patients (n=40)			P
	All (n=40)	with PAH (n=20)	without (n=20)	
Capillary density	7.6±1.4 (5-10)	6.6±1.3 (5-8)	8.6±1.6 (7-10)	<0.001
Capillary length	186.9±35.5 (120-250)	181.8±34.5 (120-240)	189.9±36.5 (130-250)	0.475
Capillary width	40.4±7.7 (20-60)	50.5±9.6 (40-60)	35.4±6.7 (20-50)	<0.001
Capillary hemorrhage	13 (32.5)	11 (55)	2 (10)	0.002
Capillary shape				
- Normal shape	7 (17.5)	0 (0)	7 (35)	0.008
- Dilated- mega-capillaries	28 (70)	18 (90)	10 (50)	0.006
- Tortuous capillaries	5 (12.5)	3 (15)	2 (10)	0.633
Sub- capillary venous plexus	26 (65)	18 (90)	8 (10)	0.001
NFC pattern				
Early	16 (40)	2 (10)	14 (70)	0.001
Active	13 (32.5)	8 (40)	5 (25)	0.311
Late	11 (27.5)	10 (50)	1 (5)	0.002
Avascular area score				
Score 0	10 (25)	0 (0)	10 (50)	0.001
Score 1	14 (35)	5 (25)	9 (45)	0.185
Score 2	7 (17.5)	6 (30)	1 (5)	0.037
Score 3	11 (27.5)	10 (50)	1 (5)	0.002
Telangiectasia score				
0	13 (32.5)	2 (9.5)	11 (57.9)	0.002
1	19 (47.5)	10 (50)	9 (45)	0.752
2	8 (20)	8 (40)	0 (0)	0.004
NFC score				
Score 0	13 (32.5)	2 (10)	11 (55)	0.002
Score 1	11 (27.5)	3 (15)	8 (40)	0.077
Score 2	7 (17.5)	6 (30)	1 (5)	0.037
Score 3	9 (22.5)	9 (45)	0 (0)	0.002

SSc: systemic sclerosis, PAH: pulmonary artery hypertension, NFC: nail fold capillaroscopy.

Correlating the mean PAP with various demographic, clinical data and NFC changes documented a significant correlation between PAP with the disease duration (r=0.52), and telangiectasia (r=0.49) together with significant negative correlation regarding capillary density (r= - 0.57) (Figures 3).

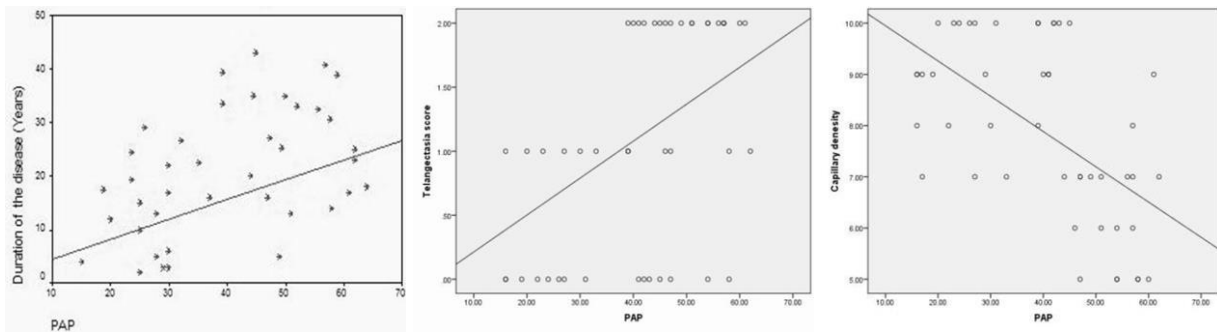


Figure 3: Significant correlation between the mean pulmonary arterial pressure (PAP) with disease duration (left), telangiectasia score (middle) and inversely with the capillary density score (right) in systemic sclerosis.

DISCUSSION

Pulmonary arterial hypertension is a lethal complication with bad prognostic value that affects 10-15% of patients with SSc and even with advances in treatment still accounts for significant morbidity and mortality⁽²³⁾. PAH is marked by increased resistance of pulmonary vessels because of remodeling and obstruction of pulmonary arterioles with subsequent increase of the mean pulmonary artery pressure (PAP) >25 mmHg at rest or >30 mmHg during exercise, without raised pulmonary capillary wedge pressure (measured by right heart catheterization (RHC))⁽²⁴⁾. The majority of patients are usually presented with serious manifestations, marked functional distortion, severe hemodynamic impairment, resulting in poor outcome. So, early screening through systematic evaluation of asymptomatic individuals can diagnose PAH at an early stage for better physical outcomes⁽²⁵⁾.

Isolated PH occurs as a late-stage complication after about 20 years from the onset of SSc⁽²⁶⁾. Similarly, our study reported that SSc patients with PAH have significantly a longer disease *duration* than those without, which was in agreement with previous studies^(9,26). According to the extent of skin fibrosis, patients with PAH were more of the limited *subtype* (lcSSc). This was similar to **Chang et al.**⁽²⁶⁾ and **Walker et al.**⁽²⁷⁾ who found that the PAH happened more in lcSSc than in dcSSc. Patients with PAH had significantly more evident peripheral vascular manifestations in the form of Raynaud's phenomenon, telangiectasia, digital ulcers, and pitting scars. This comes according to previous studies^(9, 26, 27) who documented Raynaud's phenomenon, multiple telangiectasia's, and digital ulceration as important clinical manifestations linked to higher risk of developing PAH in the setting of SSc.

Serological biomarkers have been suggested to have a better predictive value for the occurrence of PAH than conventional clinical risk factors⁽⁹⁾. The current study revealed that patients with PAH had more positivity of both anti-centromere and anti-Scl70 antibodies together with a significantly higher ESR level. In agreement, **Elshereef et al.**⁽⁹⁾ found significant differences in the level of ESR, complement, and anti-centromere antibodies in patients with PAH versus those without. Furthermore, **Walker et al.**⁽²⁷⁾ documented that PH without pulmonary fibrosis was more common in those with anti-centromere versus anti-Scl-70 antibodies (13 vs. 5%).

Nailfold capillaroscopy (NFC) is a highly sensitive, inexpensive, simple, safe, and non-invasive imaging technique used to analyze the morphology of nourishing capillaries in the nailfold area⁽²⁸⁾. Marked by its presence in the most recent ACR/EULAR consensus classification criteria, NFC has shown to predict disease activity, many organ-target

complications like digital ulcers, pulmonary hypertension, interstitial lung disease, and even death⁽²⁹⁾. Because of the relatively lower occurrence of PAH than other organ-specific manifestations, it is harder to investigate the role of NFC in predicting its existence or severity. In a Dutch group of over 200 patients, NFC changes were separately predictive of cardio-respiratory complications and interestingly, all patients with pulmonary hypertension had abnormal NFC picture⁽²⁴⁾.

On studying the frequency of NVC scleroderma pattern (early, active, and late), patients without PAH showed an earlier pattern of capillary abnormalities in comparison with those with. While, those with PAH had an increased number of late scleroderma pattern. This was in agreement with the findings of **Ricciari et al.**⁽³⁰⁾ and **Reyes-Rueda et al.**⁽³¹⁾, in which late and active patterns were more frequent among patients with PAH. On the other hand, a study by **Greidinger et al.**⁽³²⁾ found no variations in capillary patterns between SSc with and without PAH. Moreover, the present study revealed that patients with PAH had a lower capillary density, increased capillary width, increased number of dilated mega-capillaries together with increased areas of capillary hemorrhages and areas of sub-capillary venous plexuses in comparison to those without. Similarly, **Ong et al.**⁽³³⁾ found a significant reduction of capillary density in SSc patients with PAH in contrast to those without. Also, **Corrado et al.**⁽¹³⁾ reported that patients with PAH had a significantly lower capillary density and higher capillary width compared to SSc patients without. Furthermore, **Hofstee et al.**⁽¹⁴⁾ stated a lower capillary density in those with PAH, however, loop dimensions were comparable.

A report enrolling patients with idiopathic PAH showed no differences in capillary densities or patterns compared to healthy controls. However, a reduction of capillary density in both SSc associated and idiopathic PAH was found, albeit to a milder extent in the latter⁽¹⁴⁾. A suggested explanation for the more profound capillary reduction in SSc patients with PAH may be due to the PAH itself which amplifies the reduction of capillary density already existing in SSc. Another explanation is the decrease in the density of capillaries may differ among the two diseases. In SSc, changes in the structure of the systemic microcirculation are generally assumed to occur before the pulmonary circulation changes, since systemic microvascular changes can occur several years before SSc develops⁽³⁴⁾.

Also, the current study reported that nearly 75% of patients with PAH had an avascular area score ≥ 2 in contrast to 10% in those without. Also, about 73% of SSc with associated PAH had a total NFC score ≥ 2 compared to 5% in those without. In accordance, **Ricciari et al.**⁽³⁰⁾ reported NVC abnormalities among

SSc patients with PAH scoring >1 and avascular area score ≥ 1 were present in 83% compared to 11% in patients without. Moreover, **Reyes-Reuda *et al.*** ⁽³¹⁾ found on NFC examination higher score of abnormalities among patients with PAH in contrast to those without and avascular area of score 3 was more frequently present among patients with PAH. Therefore, NVC changes might reveal what is going on in the pulmonary circulation supporting the hypothesis that structural changes in the microcirculation may be related to those vascular abnormalities presenting in the pulmonary circulation. The common loss of capillaries at nailfold and pulmonary bed may be in a similar pathway ⁽³⁵⁾. This may not be true for all capillary abnormalities, because most patients with SSc show NFC abnormalities whereas only a minority develops PAH. Although the great loss of capillaries may be due to PAH itself, a condition able to augment the reduction of vascularity. Thus NVC findings seem to reflect what occurred in the pulmonary circulation, with reduced capillary density and broad avascular areas signifying disease severity and organ involvements in SSc ⁽³⁶⁾.

Correlating the mean PAP with various demographic, clinical data and NFC changes documented a significant correlation with disease duration, telangiectasia score and inversely with the capillary density score. In accordance, **Elshereef *et al.*** ⁽⁹⁾ found a significant correlation between PAP and disease duration. Also, **Hofstee *et al.*** ⁽¹⁴⁾ revealed that capillary density correlated with mean PAP at rest in SSc patients with PAH. Moreover, **Ricciari *et al.*** ⁽³⁰⁾ reported significant correlations between pulmonary pressure values with NVC and with the avascular areas score. Conversely, **Reyes-Rueda *et al.*** ⁽³¹⁾ found no correlation between abnormal capillaroscopy with pulmonary hypertension.

Limitations of the current study is that not all received medications were investigated. Also, the study included a relatively small number of patients. Larger cohorts with longitudinal study design are recommended in future studies.

In conclusion, low capillary density together with wide avascular areas and more severe scores were associated with the presence of PAH indicating that either systemic microvascular changes play a role in the development of PAH, or that PAH itself amplifies the systemic microvascular impairment constantly detectable in SSc. So, a complete NVC study seems to be a helpful simple screening tool required for all SSc patients to identify those at risk for PAH in a very early phase of the disease for a proper diagnosis and intervention. Special consideration should be given to those with long disease duration, evident peripheral microvascular manifestations, and positive auto-antibodies. Therapeutic clinical trials with NVC monitoring to

measure the treatment outcome for SSc with PAH should be considered in future studies.

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