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ORIGINAL ARTICLE

Clinical applicability of quantitative nailfold capillaroscopy in differential diagnosis of connective tissue diseases with Raynaud's phenomenon

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Background/Purpose: Nailfold capillaroscopy is a useful tool to distinguish primary from secondary Raynaud's phenomenon (RP) by examining the morphology of nailfold capillaries but its role in disease diagnosis is not clearly established. The purpose of this study was to evaluate the roles of quantitative nailfold capillaroscopy in differential diagnosis of connective tissue diseases (CTDs) with RP.

Methods: The data between the year 2005 and 2009 were retrieved from the nailfold capillaroscopic database of National Taiwan University Hospital (NTUH). Only the data from the patients with RP were analyzed. The criteria for interpretation of capillaroscopic findings were predefined. The final diagnoses of the patients were based on the American College of Rheumatology classification criteria for individual diseases, independent of nailfold capillaroscopic findings. The sensitivity and the specificity of each capillaroscopic pattern to the diseases were determined.

Results: The data from a total of 67 patients were qualified for the current study. We found the sensitivity and specificity of scleroderma pattern for systemic sclerosis (SSc) were 89.47% and 80%, and the specificity of the early, active, and late scleroderma patterns for SSc reached 87.5%, 97.5%, and 95%, respectively. The sensitivity/specificity of systemic lupus

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erythematosus (SLE) pattern for SLE and polymyositis/dermatomyositis (PM/DM) pattern for PM/DM were 33.33%/95.45% and 60%/96.3%, respectively. The sensitivity/specificity of mixed connective tissue disease (MCTD) pattern for MCTD were 20%/100%.
Conclusion: The nailfold capillaroscopic (NC) patterns may be useful in the differential diagnosis of CTDs with RP. The NC patterns for SSc and PM/DM are both sensitive and specific to the diseases, while the SLE and MCTD patterns exhibit high specificity but relatively low sensitivity.
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Introduction

Raynaud's phenomenon (RP) is the earliest[1,2] and the most common clinical manifestation of diffuse connective tissue diseases (CTDs), which include systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), and dermatomyositis (DM)/polymyositis (PM).[3] Primary RP, as a functional vascular disorder,[4] is diagnosed for no identifiable underlying disease. Only a small percentage (12.6%) of the patients with primary RP develop a CTD thereafter.[2] Contrarily, the diagnosis of secondary RP would be favored for the patients if any disease associated with RP is evident or suspected.[4] However, given the usual obscure early signs of CTDs, it is often a challenge in clinical practice to confidently distinguish the primary RP from the secondary RP solely based on the identification of an associated CTD in the early stage of the disease. It has been reported that the presence of an abnormal nailfold capillary pattern is an excellent indicator to predict the development of CTD in patients with initial diagnosis of primary RP.[2] To visualize nailfold capillaries *in vivo*, nailfold capillaroscopy (NC) has been applied clinically to evaluate the morphological abnormalities of nailfold capillaries in patients with RP.[5] Several studies have confirmed the role of NC in discrimination between primary and secondary RP.[6,7]

Primary RP typically presents the normal NC pattern[8] characterized by parallel arrangement of hairpin-like capillaries in appropriate caliber and shape (Fig. 1).[9] However, secondary RP usually features with several characteristic abnormal morphologies of nailfold capillaries readily discernible in NC.[10–13] The sensitivity of the presence of mega capillaries, one of the most characterized NC abnormalities, for different CTDs has been estimated from 56% for MCTD to 100% for diffuse SSc.[14] Moreover, several disease-associated NC patterns have been identified in SSc,[10] PM/DM,[11] SLE,[12] and MCTD[13] (Fig. 1 and Table 1),[10–13] which may imply a potential role of NC in diagnosis of CTDs with RP.

To further advance the application of NC in diagnosis of CTDs with RP, however, more data are needed regarding the sensitivity and the specificity of each disease-associated NC pattern for the corresponding CTD. To address this issue, we established a NC database to continuously collect the clinical records from the examinees of NC since 2005 based on the pre-defined quantitative NC patterns developed from the previous studies[7,10–13,15] (Table 1). We compared the final clinical diagnosis based on American College of Rheumatology (ACR) criteria with the initial NC pattern in each patient and determined the sensitivity and the specificity of the NC patterns for the corresponding RP-associated CTDs.

Materials and methods

Patients and data collection

The database of the NC examinees in the National Taiwan University Hospital has been established based on the continuous collection of the medical records from the patients receiving quantitative NC examination since 2005. We reviewed the records in the NC database during the period between 2005 and 2009 and identified the records from the patients indicated for NC examination because of RP. The medical records kept in the database for analysis include several relevant clinical and laboratory parameters (Table 2), final diagnosis, and initial NC patterns. The final diagnosis was solely based on the ACR classification criteria for the RP-associated CTDs, including SSc, SLE, MCTD, and PM/DM.

Quantitative nailfold capillaroscopy

The nailfold skin was made transparent by adding a drop of immersion oil and was illuminated by laser light source. Real-time images were generated by a microscope with total magnification of 200× and a charged-coupled device (CCD) camera giving high-resolution images of 752 × 582 pixels. The capillaries in the distal row were observed. A 1 mm graticule was imaged along with each finger to allow quantification of capillary density, length, width, and diameters (CapiScope; KK Research Technology LTD, Devon, UK). At least four finger nailfolds on each hand were examined. A minimum of four photomicrographs were taken for each patient.

Loops longer than 300 μm were classified as elongated capillaries.[15] The capillary was determined by measuring the projection of the visible part of the capillary. Vascular loops were estimated to be of normal width (<25 μm),[15] widened (>50 μm),[7] or giant (> 125 μm). The most common morphologic pattern of the capillaries was an open pattern that the capillary limbs did not cross each other. There were some variations such as tortuous (the limbs curled but did not cross), crossed (the limbs crossed at least once), and cuticular (only the end point of the capillary loop was visible) morphology of the capillaries. The dominant morphological pattern was documented for each participant as described. In the absence of a single dominant pattern, the term "mixed pattern" was applied.[15]

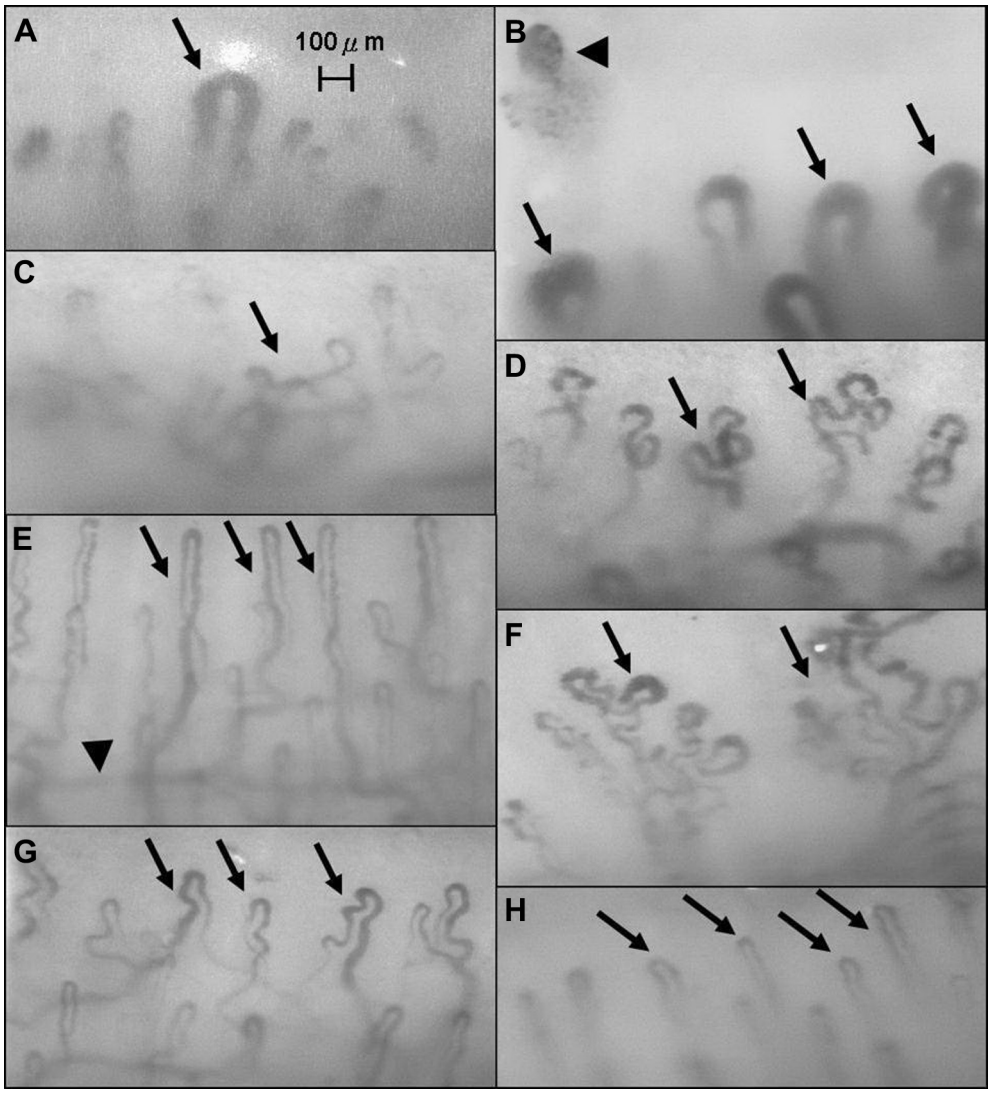

Figure 1 The defined nailfold capillaroscopic patterns. (A) Early scleroderma pattern: few giant capillaries (arrow) and no evident loss of capillaries; (B) active scleroderma pattern-frequent giant capillaries (arrows) with capillary hemorrhage (arrow head); (C) late scleroderma pattern-absent giant capillaries and hemorrhages, severe loss of capillaries with neoangiogenesis (arrow); (D) PM/DM pattern-"bushy" capillaries (arrows), twisted enlarged capillaries; (E) SLE pattern-long capillary loops (arrows) with venular visibility (arrow head); (F) MCTD pattern-dystrophic, extremely convoluted, branched capillary with pseudoglomeruli capillary formation (arrows); (G) nonspecific capillary abnormalities-abnormal NC findings (arrows) with no patterns suggestive of scleroderma, PM/DM, SLE, or MCTD; (H) normal pattern-hairpin capillaries, arranged in a parallel fashion to each other (arrows). MCTD = mixed connective tissue disease; NC = nailfold capillaroscopy; PM/DM = polymyositis/dermatomyositis; SLE = systemic lupus erythematosus.

Distinctive morphologic alterations such as bushy and bizarre were also recorded along with their average count, which were classified as few (<4 mm), moderate (4—6 mm), or frequent (>6 mm). The severity of nailfold capillary hemorrhage in each finger was classified as grade 1 (punctate hemorrhages ≤2/finger), grade 2 (punctate hemorrhages >2), or grade 3 (confluent areas of hemorrhage).[15] Avascularity of the capillary bed was classified as grade 1 (≤2 discrete areas of vascular deletion), grade 2 (more than discrete areas of vascular deletion), or grade 3 (large avascular areas).[15] Visibility of the subpapillary venous plexus (PVS) was classified as faint or prominent. Capillary disarrangement was graded as 1 (slight irregularity), 2 (obvious disarray of vasculature), or 3 (extremely disarranged pattern).[16]

Interpretation of quantitative nailfold capillaroscopic findings

The quantitative NC examination was performed by experienced clinicians unaware of the clinical information about the examinees. NC findings were defined, according to previous studies,[10—13] into eight distinct patterns: normal, early scleroderma pattern (Scl-early), active scleroderma pattern (Scl-active), late scleroderma pattern (Scl-late),

Table 1 Definition of nailfold capillaroscopic patterns based on quantitative nailfold capillaroscopic observation.

NC pattern	Definition
Normal	Hairpin capillaries, arranged in a parallel fashion to each other
Scl-early	Few giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution, and no evident loss of capillaries[10]
Scl-active	Frequent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries, mild disorganization of the capillary architecture, and absent or mild ramified capillaries[10]
Scl-late	Irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, severe loss of capillaries with extensive avascular areas, disorganization of the normal capillary array, and ramified capillaries[10]
PM/DM pattern	Two or more of the following findings in at least two nailfolds: enlargement of capillary loops, loss of capillaries, disorganization of the normal distribution of capillaries, "bushy" capillaries, twisted enlarged capillaries, and capillary haemorrhages[11]
SLE pattern	Morphologic changes in capillary loops, venular visibility, and sludging of blood with variability of capillary loop length[12]
MCTD pattern	Presence of dystrophic, extremely convoluted, branched capillary, sometimes termed a pseudoglomerulus or bushy capillary formation[13]
Nonspecific capillary abnormalities	Abnormal NC findings with no patterns suggestive of scleroderma, PM/DM, SLE, or MCTD[13]

MCTD = mixed connective tissue disease; NC = nailfold capillaroscopy; PM/DM = polymyositis/dermatomyositis; Scl-active = active scleroderma pattern; Scl-early = early scleroderma pattern; Scl-late = late scleroderma pattern; SLE = systemic lupus erythematosus.

PM/DM pattern, SLE pattern, MCTD pattern, and nonspecific capillary abnormalities (NS). The quantitative NC-based definition and the representative picture of each NC pattern were shown in Table 1 and Fig. 1, respectively.

Statistical analysis

Results are expressed as means ± standard deviation (SD). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each disease-associated NC pattern for the corresponding CTD were calculated after exclusion of the eight cases with SSc-SLE overlap syndrome that may confound the statistical interpretation.

Results

Demographic data and clinical characteristics

A total of 67 patients were identified in the database with presentation of RP. The number of the patients for each final diagnosis was 19 with SSc, 15 with SLE, eight with SSc-SLE overlap syndrome, five with PM/DM, five with MCTD and

Table 2 Patient demographics and clinical characteristics.

	SSc (n = 19)	SLE (n = 15)	SSc-SLE (n = 8)	PM/DM (n = 5)	MCTD (n = 5)	Other disease[a] (n = 15)
Age (y)	48.26 ± 14.25	38.87 ± 14.07	35.63 ± 14.48	49 ± 17.45	45.2 ± 17.53	46.13 ± 17.87
Sex (Men:Women)	4:15	1:14	0:8	0:5	0:5	5:10
Smoking	2	0	0	0	0	2
Alcohol	0	0	0	0	0	0
Diabetes	0	0	0	0	0	2
Duration of RP (mo)	45.95 ± 55.12	25.43 ± 17.23	42.25 ± 23.21	22.55 ± 16.39	21.75 ± 19.51	34.42 ± 37.56
Pulmonary, HTN	1	0	0	0	1	1
ILD	2	1	3	3	2	1
ANA titer (≥ 1:320)	18/19	10/15	8/8	0/5	5/5	3/15
C3 (mg/dl)	109 ± 18.49	92.61 ± 36.60	99.89 ± 36.97	103.33 ± 31.46	92.58 ± 20.74	111.22 ± 18.39
C4 (mg/dl)	19.01 ± 6.15	15.11 ± 6.42	17.09 ± 6.32	19.93 ± 9.03	15.04 ± 3.05	19.64±10.68
CRP (mg/dl)	0.17 ± 0.19	0.40 ± 0.46	1.31 ± 2.31	0.18 ± 0.22	1.23 ± 1.12	0.51 ± 1.18
D-dimer (ug/ml)	1.14 ± 1.01	1.59 ± 0.73	2.96 ± 1.29	NA	4.49 ± 4.80	2.15 ± 2.47

ANA = antinuclear antibody test; CRP = C-reactive protein; HTN = hypertension; ILD = interstitial lung disease; MCTD = mixed connective tissue disease; NC = nailfold capillaroscopy; PM/DM = polymyositis/dermatomyositis; SSc = systemic sclerosis; SLE = systemic lupus erythematosus; RP = Raynaud's phenomenon.

[a] See Table 3.

15 patients with other non-DCTD diagnoses (Tables 2 and 3). The duration of RP was longer (mean, 45.95 months) in the patients with SSc than that in the patients with non-SSc diagnosis (Table 2). The demographic and clinical parameters were generally compatible with the features of each different DCTD (Table 2). There were 15 patients with non-DCTD diagnosis and most of them were diagnosed with other forms of autoimmune diseases including four patient with primary Sjögren syndrome and two patient with primary vasculitis, while two of these patients were diagnosed with primary RP and chronic hepatitis C, respectively (Table 3).

Correlation between the final diagnoses and the disease-associated NC patterns

The correlation between the final diagnoses and the NC patterns in the patients were shown in Table 4. For the eight patients with SSc-SLE overlap syndrome, two exhibited an early scleroderma pattern, three showed an active scleroderma pattern, and three presented late a scleroderma pattern. Among the 19 patients with SSc alone, 17 (89.47%) showed a scleroderma pattern, one presented a PM/DM pattern and 1 exhibited a nonspecific pattern. For the 15 patients with SLE alone, five of them (33.33%) presented an SLE pattern, four showed a scleroderma pattern, and six exhibited nonspecific pattern. Three of the five patients with PM/DM (60%) exhibited a PM/DM pattern, and two showed a nonspecific pattern. One out of the five MCTD patients (20%) showed an MCTD pattern, three presented a scleroderma pattern, and one exhibited a nonspecific pattern. Among the 15 patients with other diagnoses, 11 showed a nonspecific pattern (Table 3). The patient with chronic hepatitis C—related liver cirrhosis exhibited an early scleroderma pattern and the two patients with SLE pattern were diagnosed with autoimmune thyroiditis and undifferentiated CTD, respectively (Table 3).

Sensitivity and the specificity of the disease-associated NC patterns in diagnosis of the CTDs with RP

The sensitivity and the specificity of each specific NC pattern in the diagnosis of the associated CTD were shown in Table 5. The sensitivity and specificity of scleroderma patterns for SSc were 89.47% and 80%, respectively. The PPV and NPV of scleroderma patterns for SSc were 68% and 94.12%, respectively. The sensitivity and specificity of SLE patterns for SLE were 33.33% and 95.45%, respectively. The PPV and NPV of SLE patterns for SLE were 71.43% and 80.77%, respectively. The sensitivity and specificity of PM/DM patterns for PM/DM were 60% and 96.30%, respectively. The PPV and NPV of PM/DM patterns for PM/DM were 60% and 96.30%, respectively. The sensitivity and specificity of MCTD patterns for MCTD were 20% and 100%, respectively. The PPV and NPV of MCTD patterns for MCTD were 100% and 93.1%, respectively. Further analysis of the specificity for the diagnosis of SSc in each scleroderma "subpattern," namely early, active, and late scleroderma patterns, revealed 87.5%, 97.5%, and 95%, respectively (Table 5).

Discussion

Our study clearly demonstrated the correlation between nailfold capillary patterns and a wide spectrum of connective tissue diseases. The disease-associated NC patterns are highly specific to the corresponding diseases with decent sensitivity in SSc (89.47%) and PM/DM (60%) but suboptimal sensitivity in SLE (33.33%) and MCTD (20%). Our data indicate the descriptive criteria and the quantitative parameters exploited in the previous studies[7,10–18] for each distinct NC pattern can be useful in differential diagnosis for a significant proportion of the patients with both RP and DCTD.

Table 3 NC Patterns of 15 patients with non-DCTD diagnoses.

Patient no.	Age (y)	Sex	Diagnosis	Duration of RP	NC pattern
1	54	M	Primary Raynaud's phenomenon	1 mo	NS
2	73	M	Chronic hepatitis C with liver cirrhosis	10 mo	Scl-early
3	26	W	Autoimmune thyroiditis	10 y	SLE
4	28	W	UCTD	10 y	SLE
5	25	W	Kikuchi disease	1 wk	NS
6	68	W	Primary Sjögren syndrome	2 mo	NS
7	59	W	Systemic vasculitic syndrome	11 mo	NS
8	33	W	Chronic oral ulcer	1 y	NS
9	19	M	ITP	2 y	NS
10	35	W	Suspect APS with secondary PAH	3 y	NS
11	64	M	Familial amyloid neuropathy	3 y	NS
12	61	W	Primary Sjögren syndrome	3 y	PM/DM
13	61	W	Primary Sjögren syndrome	3 y	NS
14	38	M	Takayasu's arteritis with APS	3 y	NS
15	48	W	Primary Sjögren syndrome	3 y	NS

APS = antiphospholipid syndrome; ITP = idiopathic thrombocytopenic purpura; M = men; NC = nailfold capillaroscopy; NS = nonspecific capillary abnormalities; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon; Scl-early = early scleroderma pattern; SLE = systemic lupus erythematosus; UCTD = undifferentiated connective tissue disease; W = women.

Table 4 Correlation between specific NC patterns and final diagnoses.

Disease pattern	SSc	SLE	SSc-SLE	PM/DM	MCTD	Other diseases[a]	Total numbers
Scleroderma	17	4	8	0	3	1	33
Early	3	4	2	0	0	1	10
Active	11	0	3	0	1	0	15
Late	3	0	3	0	2	0	8
SLE	0	5	0	0	0	2	7
PM/DM	1	0	0	3	0	1	5
MCTD	0	0	0	0	1	0	1
NS	1	6	0	2	1	11	21
Normal	0	0	0	0	0	0	0
Total numbers	19	15	8	5	5	15	67

MCTD = mixed connective tissue disease; NS = nonspecific capillary abnormalities; PM/DM = polymyositis/dermatomyositis; SSc = systemic sclerosis; SLE = systemic lupus erythematosus.
[a] See Table 3.

The cohort of the patients analyzed in the current study—though small in size—presented a typical clinical picture of each individual disease (Table 2). The patients with SSc had the longest duration of RP and at least one of the patients in each individual disease has interstitial lung disease. Fifteen patients in our cohort were diagnosed with the diseases other than diffuse CTD (Table 3). Eleven of them nicely exhibited nonspecific NC pattern but one patient with chronic hepatitis C-associated liver cirrhosis had Scl-early pattern, and the other two with either autoimmune thyroiditis or undifferentiated CTD showed SLE pattern. While the patient with chronic hepatitis C—associated liver cirrhosis had relatively short history of RP (10 months), the other two patients with SLE pattern had been noted with RP for 10 years. It may be worth being further explored whether UCTD or organ-specific autoimmune disease would evolve to a distinct diffuse CTD suggested by its initial NC patterns. It may also be worth being further explored if chronic viral infection would lead to diffuse CTD-associated NC patterns or long-term nonspecific NC pattern would tend to evolve into an SLE pattern.

In the current study, we have demonstrated both the sensitivity and specificity of each diffuse CTD-associated NC pattern to their corresponding diseases. A previous study[19] showed the sensitivity of a "scleroderma pattern," for SSc was 82%. The "scleroderma pattern" was defined in a relatively general way by the presence of enlarged and deformed capillary loops surrounded by relatively avascular areas.[19] In addition, it has been shown that the sensitivity of the presence of mega capillaries to different DCTD ranged from 56% in MCTD to 100% in diffuse SSc but with a low positive predictive value for the diseases because of the vaguely defined NC pattern.[14] The criteria we adopted in this study were modified from integration of several independent studies with a stringent definition,[7,10–18] but the overall sensitivity of NC patterns to the diseases within the diffuse CTD spectrum was not greatly hampered and the specificity was much improved because of the well-defined interpretation if the examinees had the history of RP (Table 5).

Eight cases with SSc-SLE overlap syndrome presented with clinical SSc phenotype and active SLE serology and were identified in this study, all of these patients exhibit different stages of "scleroderma pattern" at NC examination. These patients were noticed to have a higher prevalence of ILD (37.5%) than that of patient with SLE alone (6.7%). For the patients with RP, we also found that the early scleroderma pattern was the least specific NC pattern to SSc (Table 5) since 4 patients in our cohort with this NC pattern were actually diagnosed with the diseases other than SSc, such as SLE and chronic hepatitis C (Table 3 & 4).

In conclusion, our study demonstrated the potential value of the quantitative parameters of nailfold capillaroscopy in differential diagnosis of CTD with RP based on the integrated criteria for several distinct disease-associated NC patterns. Larger-scale studies may be warranted to further consolidate the current findings.

Table 5 Sensitivity and specificity of disease-associated NC patterns for diagnosis of the CTDs with RP.[a]

Nailfold capillaroscopic pattern	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Scleroderma	89.47	80	68	94.12
Early scleroderma	15.79	87.5	37.5	68.63
Active scleroderma	57.89	97.5	91.67	82.98
Late scleroderma	15.79	95	60	70.37
SLE	33.33	95.45	71.43	80.77
PM/DM	60	96.30	60	96.30
MCTD	20	100	100	93.10

MCTD = mixed connective tissue disease; PM/DM = polymyositis/dermatomyositis; SLE = systemic lupus erythematosus.
[a] The eight cases with systemic sclerosis-SLE overlap syndrome were excluded from the data for this analysis.

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