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Journal of Onychology and Nail Surgery

Review Article

Nail-fold capillaroscopy: A review of literature

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ABSTRACT

Nail-fold capillaroscopy (NFC) has emerged as a pivotal non-invasive imaging technique crucial for diagnosing and monitoring collagen vascular diseases and various related conditions. This review provides a comprehensive overview of NFC, encapsulating its historical evolution, principles, techniques, parameters for analysis, indications and clinical applications. In addition, NFC's role in non-rheumatic conditions such as psoriasis, rosacea, alopecia areata and leprosy is discussed, highlighting its versatility in dermatological and non-dermatological disorders.

Keywords: Nail-fold capillaroscopy, Non-scleroderma, Pattern, Review, Scleroderma pattern, Techniques

INTRODUCTION

Nail-fold capillaroscopy (NFC) is an easy, simple, quick and non-invasive tool used to evaluate microcirculation and classify connective tissue diseases. As the direction of capillaries is parallel to the surface of skin near nailfold, it is fairly simple to assess their size, shape and morphology across the entire length.[1-3] NFC is useful in identifying and tracking early microvascular alterations that could occur before the emergence of clinically relevant consequences such as nephropathy, neuropathy and retinopathy.[4] By directing incident light at an acute angle, capillary architecture can be highlighted and vascular systems in the superficial papillary dermis can be seen '*in vivo*'.[4]

PRINCIPLES OF CAPILLAROSCOPY

Both deep and superficial horizontally oriented plexuses make up the cutaneous microcirculation. The superficial plexus is composed of 1–3 capillary loops per dermal papilla which appear as dots or commas. However, in the nailfold region, capillary loops are uniquely positioned as they are aligned parallel to the skin surface. This arrangement allows for the appreciation of the morphological characteristics of the capillaries along its entire length.[4]

NORMAL CAPILLAROSCOPY PATTERN–HEALTHY SUBJECTS

Qualitatively, a normal capillaroscopy pattern is characterised by a homogeneous regular distribution of hairpin-shaped capillaries seen as a 'comb-like structure'. A density between 9 and 14 cap/mm (average 10/mm), capillary length <300 µm, and capillary diameter <20 µm for each loop (afferent, apical, efferent) is considered normal [Figure 1]. Subpapillary venous plexus is visualised in up to 30% of normal subjects. Age has a direct correlation with capillary density, and pigmented skin can impede capillary visualization even with the best of equipment. In certain situations, even skilled observers may be unable to detect changes in NFC.

PREREQUISITES

Before doing NFC, it is advisable to ask the patient to avoid caffeine and smoking 4–6 h before the test. At least 2–3 weeks before the NFC, the patient's nail paint should be carefully removed because the nailfolds can display staining from previous nail paint application upto 10 days, resembling microhaemorrhages. Patient should be asked to refrain from activities such as manicure, onychophagy or any cosmetic procedure involving the nailfold area within the preceding 3 weeks.[4,5]

During the procedure, an excess of immersion fluid may obscure the field of vision. A minimum of four images should

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Received: 20 September 2024 **Accepted:** 17 April 2025 **Published:** 11 June 2025 **DOI**: 10.25259/JONS_23_2024

Figure 1: Nailfold capillaroscopy of healthy individual showing regular and parallel arrangement of proximal nail-fold capillaries (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×160 magnification in polarised mode).

be captured from a single finger. It is advisable to avoid capturing images from fingers that have undergone physical injury. A video lasting 10–20 s can be recorded from the nailfold midline to record and assess blood flow. To reduce reflection of light, it may be necessary to adjust the contact angle and the orientation of the instrument.[4,5]

A schematic representation of NFC procedure is depicted in Figure 2. The equipment which have been used for NFC include a hand-held magnifying glass, light stereomicroscope, dermatoscope and videodermatoscope, digital Universal Serial Bus devices (up to ×300), and smartphone devices. Magnification attained with hand-held dermatoscopes is less (×10 mostly), but the area examined is wider. The gold standard for examination of nailfold capillaries is Nailfold video capillaroscopy (NVC) with 200× magnification.[6]

INDICATION FOR NFC

These are wide and varied. NFC is primarily used in patients with a history of Raynaud phenomenon (RP) (to differentiate primary and secondary Raynaud's), patients with connective tissue diseases (CTDs) (for severity/staging, follow-up/and treatment response), and for diagnostic approach in patients with idiopathic interstitial lung disease (ILD).[7]

CAPILLAROSCOPIC PARAMETERS

- Quantitative parameters analysed are mean capillary density (capillary number/mm length of the proximal nailfold), capillary length, mean capillary width, arterial and venous limb diameter, apical width, internal diameter and intercapillary distance [Figure 3] which require more advanced calibration instruments.[4]
- Qualitative parameters (overall pattern recognition) include detection of capillary dilatation, micro-haemorrhages, capillary dropouts, avascular areas, tortuous capillaries, criss-cross forms, neoangiogenesis, dilated/prominent subpapillary plexus, and dystrophic capillary loops.[4]

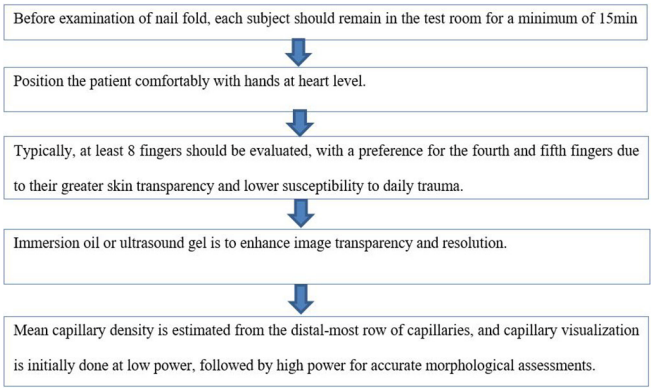

Figure 2: Schematic representation of Nailfold capillaroscopy procedure.

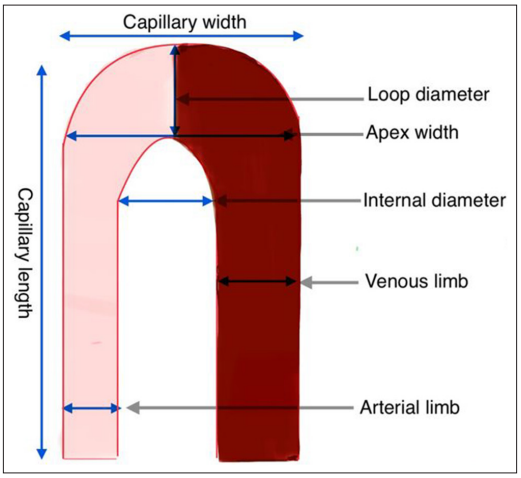

Figure 3: Schematic representation nail-fold capillary loop.

DEFINITION OF CAPILLAROSCOPIC PARAMETERS

Mean capillary density

It is described as the number of capillary loops visualised in each finger per millimetre. Having abnormal range of capillary density (<7/mm) is one of the most important factors for an early identification of those at high risk for the development of autoimmune disease, especially those with RP [Figure 4].

Capillary dilatation

It is considered as the first microvascular change in reaction to tissue hypoxia. Dilated capillaries are more than 2 times wider than surrounding normal capillaries [Figure 5].

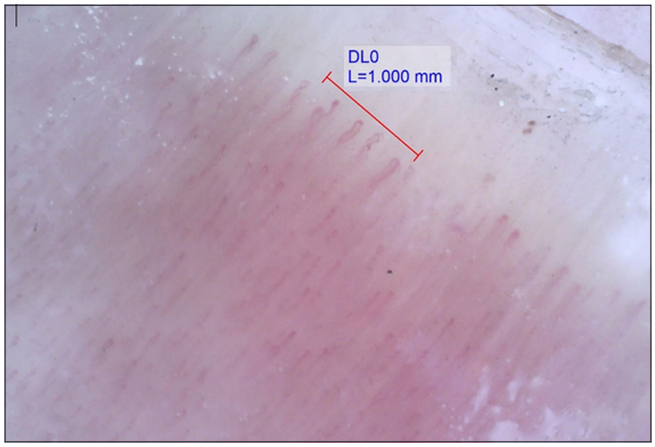

Figure 4: Nailfold capillaroscopy of patient with Raynaud's phenomenon showing reduced capillary density of 5/mm (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×60 magnification in polarised mode).

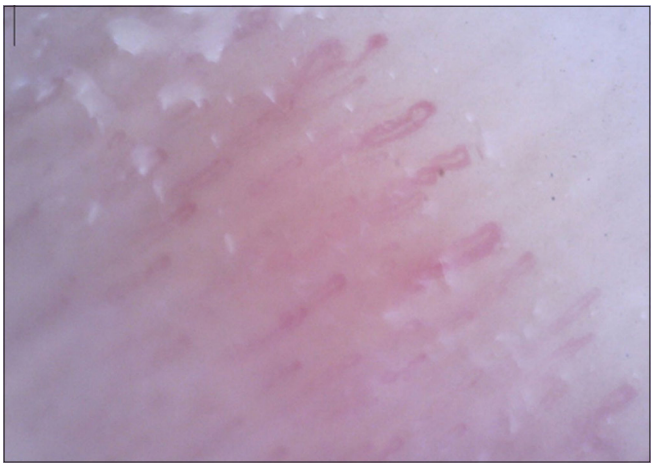

Figure 5: Nailfold capillaroscopy of patient with SLE showing dilated capillaries (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×175 magnification in polarised mode).

Enlarged capillaries with diameter >20µm [Figure 6] are found almost exclusively in systemic sclerosis (SSc). Giant capillaries are the ones having a width more than 10 times that of normal capillaries (arterial, venous or apical diameters over 50 µm). Even if one giant capillary is present, it indicates a microangiopathy [Figure 6].

Micro-haemorrhages

These represent extra-capillary brown aggregates of clotted blood in variable forms and sizes. They appear secondary to the rupture of dilated capillary walls. Focal microhaemorrhages are discrete, single micro-petechiae. They can be present in normal healthy individuals due to microtrauma. Diffuse microhaemorrhages are multiple, grouped micro-petechiae [Figure 7]. Microhaemorrhages are more commonly seen in early and active SSc patients.

Capillary dropouts

It represents the loss of a capillary loop [Figure 8]. It is considered as the first marker of the development of avascular areas.

Avascular areas

It is another parameter for capillary density, defined as an absence of ≥2 adjacent capillaries from the distal row, or a distance ≥500 µm between adjacent capillaries. To compensate for the progressive capillary loss, the surrounding capillaries display alterations in distribution and orientation (tend to orient towards capillary loss). It is indicative of severe peripheral ischaemia and increased probability of developing digital ulcers. Extensive avascular areas are seen in late scleroderma patterns. Cutolo *et al*.[8] quantify the extension of devascularisation by means of a semiquantitative scale ranging from 0 to 3 [Table 1].

Table 1: Semiquantitative scale for extension of devascularisation.

0	Absence of avascular areas
1	Discrete devascularisation (1 or 2 avascular areas)
2	Moderate devascularisation (>2 avascular areas)
3	Extensive and confluent devascularisation areas

Tortuous capillaries

These are serpentine branches of capillary limbs, without crossing over themselves. It is the most common abnormal finding in healthy subject [Figure 9]. Less than 5% tortuous capillaries are considered normal.

Criss-cross forms (Figure of eight forms)

Capillary branches that cross over more than once are criss-cross capillaries. It could be a normal variant, visualised depending on the angle of observation [Figure 10].

Neoangiogenesis

A diminished capillary density determines local hypoxia with subsequent local increase in growth factors, further stimulating new vessel organisation. Branched capillaries with a highly heterogeneous shape can also be seen owing to capillary neoformation (angiogenesis) [Figure 10]. various morphologies representative of neoangiogenesis include

a. Bushy capillaries: Loops whose limbs originate from small and multiple buds [Figure 11].
b. Meandering capillaries: Crossing of limbs upon themselves or on other capillaries, numerous times over, unlike criss-cross capillaries where branches cross in a limited way.
c. Bizzare capillaries: Atypical morphology, not fitting into hairpin, tortuous, bushy or crossed categories.

Dystrophic capillary loops

These are ill-formed or malformed capillary loops, of abnormal size and calibre.

Capillary disarray

Capillaries not oriented perpendicular to a horizontal line drawn through the proximal nailfold are referred to as disarray.[9]

UTILITY OF NFC IN VARIOUS CONDITIONS

Raynaud's Phenomenon

It is a vascular disorder characterised by recurrent episodic attacks of digital ischaemia, provoked by exposure to cold or emotional stress and is the most frequent indication for NFC. RP can be primary or secondary [Table 2].[10] NFC examination is recommended for all patients with RP, given that up to 15% of individuals with initial diagnosis of idiopathic RP may develop features of scleroderma within 3 years. However, there is currently no consensus on the optimal frequency of conducting this examination.[11]

Table 2: Differences between primary and secondary RP.

Primary RP	Secondary RP
Increased physiological reaction to cold or stress	Secondary to underlying disease
Attacks are symmetric	Painful asymmetric attacks
Normal NFC	Abnormal NFC
Median age of onset is 14 years	Age at onset is >30 years
Clinical features of CTD are not present	Clinical features of CTD such as fever, weight loss arthritis and cardiopulmonary abnormality are present myalgia, sclerodactyly, fever, sicca symptoms and rash
ANA and other autoantibodies are absent	ANA and other autoantibodies can be present

NFC: Nailfold capillaroscopy, RP: Raynaud phenomenon, CTD: Connective tissue diseases, ANA: Antinuclear antibody

Systemic Sclerosis (SSc)

The American College of Rheumatology/European League against Rheumatism (ACR/EULAR) classification criteria for SSc, include NFC as an evaluation parameter. It is a crucial component for scoring and evaluation of patients with SSc. NFC changes emerge and progress in a predefined sequence referred to as the scleroderma pattern, seen in 90–95% SSc patients. A scleroderma pattern on NFC, along with RP, puffy fingers, antinuclear antibody positivity, and SSc-specific antibodies are part of a 'very early' diagnosis of SSc.[8] Capillaroscopic patterns for scleroderma microangiopathy are detailed in Table 3.[8,12]

Table 3: Capillaroscopic patterns for scleroderma microangiopathy.

Characteristics	Early	Active	Late
Density	Preserved	Moderate loss	Severe loss
Giant capillaries	Present	Present	Absent
Abnormal morphology	–	+	++
Haemorrhages	+/–	+/–	Absent

Capillary density appears to be the most dependable parameter for monitoring SSc. In the initial stages, a decrease in density is not characteristic. Giant capillaries [Figure 6] are distinctive features of the early pattern, whereas avascularity characterises the late pattern. Neoangiogenesis is a hallmark of advanced microvascular involvement found in late SSc stages [Figure 10]. The existence of giant capillaries enables differentiation between scleroderma and non-scleroderma patterns with a specificity exceeding 95.6%.[13] Diffuse cutaneous SSc is commonly associated with higher incidence of capillary loss whereas limited cutaneous SSc is more frequently associated with dilated capillaries without significant capillary loss.

The presence of Anti-topoisomerase antibody (anti-Scl-70) is linked to both 'active' and 'late' capillaroscopic changes, likely accelerating their manifestation. Conversely, a positive anti-centromere antibody is more frequently linked to an 'early' phase capillaroscopic pattern and is believed to potentially postpone the beginning of 'late' capillaroscopic changes.[14] A relation between capillary density and severity of pulmonary arterial hypertension (PAH) in both SSc-related and idiopathic PAH has also been suggested. It has been suggested that avascular regions on NFC represent a significant risk factor for the emergence of skin ulcers in SSc patients.

There are several NFC indices predicting outcomes in SSc. The "capillaroscopic skin ulcer risk index" is designed to predict onset of digital ulcerations in SSc patients over a 3-month follow-up period. It incorporates factors such as total capillary count, maximum loop diameter size and the number of mega capillaries.[15] The Number of Elementary Micro Obstruction (NEMO) score, specifically, assesses the cumulative count of microhaemorrhages and microthromboses, serving as an indicator of disease activity in SSc patients and monitoring changes over time.[16] In addition, a composite score named clinical data, imaging and patient history for digital ulcers incorporates a combination of clinical data, disease history, NFC, colour Doppler ultrasonography and imaging, to predict digital ulcer occurrence over a 12-month follow-up period.[17]

SCLERODERMA SPECTRUM DISORDERS

Dermatomyositis (DM)

Apart from SSc, the most consistent NFC findings are associated with DM. The scleroderma pattern is observed in

20–60% of DM patients with more frequent and pronounced findings in DM.[18] Presence of two or more of the following: capillary dilation, bushy capillaries [Figure 11], loss of capillaries disorganisation of capillary architecture, twisted enlarged capillaries and microhaemorrhages in two or more nailfolds, characterises DM. In DM, phasic changes are less obvious. In addition, a correlation between capillary abnormalities, interstitial lung disease (ILD), Raynaud's phenomenon, and malignancy has been reported.[19]

Mixed connective tissue disease (MCTD)

MCTD is an autoimmune disorder marked by elevated anti-U1-RNP titres. In MCTD, the term 'scleroderma-like' is often used to describe NFC abnormalities, even though a distinct capillaroscopic pattern for MCTD has not been established. Pulmonary involvement in MCTD can be associated with NFC findings. A scleroderma-like pattern should prompt consideration of pulmonary involvement in MCTD. Giant capillaries on NFC are a marker of early lung involvement in otherwise asymptomatic patient.[7]

NON-SCLERODERMA SPECTRUM DISORDERS

Systemic lupus erythematosus (SLE)

NFC abnormalities are seen in around 30% of SLE cases. A systematic review aimed to characterise a distinct pattern for SLE through NFC explored features such as heightened capillary loop length, increased tortuosity and meandering, well-visualised subpapillary plexus and dilated capillaries [Figure 5] without avascular areas. Changes in NFC have been linked to systemic symptoms and disease activity in SLE.[3] Amongst the SLE-related antibodies, only the anti-Ro/SS-A antibodies were found to correlate with NFC changes.[20] SLE patients with anti-U1-RNP more frequently exhibit a scleroderma pattern characterised by enlarged loops and avascular areas. In contrast, SLE patients displaying microhaemorrhages are found to be more commonly associated with antiphospholipid syndrome antibodies.[21]

Sjogren's syndrome (SS)

Approximately 30% of individuals with primary SS experience RP. In terms of NFC findings in primary SS, studies consistently indicate a predominant occurrence of a normal pattern, followed by non-specific abnormalities, and less commonly, a scleroderma-like pattern. In a study, NFC tests were performed on all primary SS patients who tested positive for anticentromere antibodies, 80% of whom displayed a scleroderma pattern. Capillary density was inversely correlated with the presence of RP. Giant or bushy capillaries were generally not present.[22]

Rheumatoid arthritis

Patients with rheumatoid arthritis often exhibit primary NFC abnormalities such as tiny and elongated capillaries, tortuosity and a prominent sub-papillary venous plexus. This is especially noticeable in people whose anti-nuclear antibody status is positive.[23]

NFC IN HEALTHY CHILDREN

The capillary density per millimetre was significantly lower in children under ten. In addition, as compared to white patients (7.3 cap/mm), non-white patients tended to have lower capillary densities (6.8 cap/mm). Differences in capillary density in different skin colours were confirmed by Bergkamp with a significantly lower capillary density (down to 5.9 cap/mm) in children with darker skin. Healthy children are more likely to experience more trauma, so haemorrhages and aberrant morphology are more common in them.[24]

Juvenile rheumatic disease

Giant capillaries and avascular areas, the distinctive features of the 'scleroderma pattern', have been consistently identified as pathological and primarily characteristic of Juvenile systemic sclerosis (JSS) and Juvenile dermatomyositis (JDM). NFC morphology in patients with JDM is often indistinguishable from children with scleroderma, but the presence of 'bushy loops' is specific for JDM.[25] The primary reason for doing NFC in children and adolescents is to assess RP, as the existence of a 'scleroderma pattern' may offer diagnostic and prognostic insights into the emergence of connective tissue diseases such as JSS and JDM. However, there is lack of literature regarding normal age-related capillary pattern and association between capillaroscopy findings and disease course.[26]

NFC IN NON-RHEUMATIC CONDITIONS

NFC has been found useful in many non-rheumatologic diseases as well.

Psoriasis

In comparison to controls, psoriasis patients show increased avascular areas, decreased capillary density and

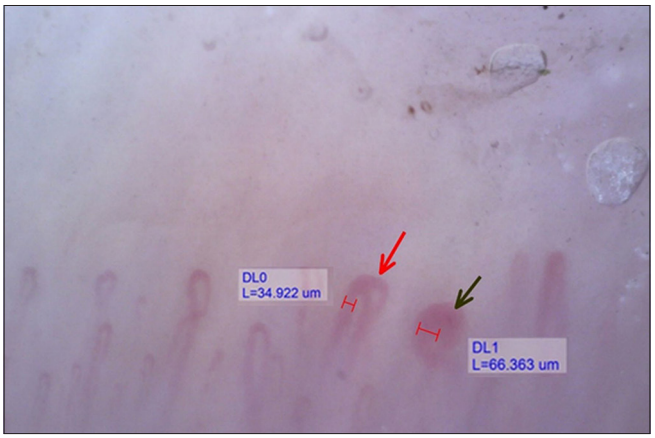

Figure 6: Nailfold capillaroscopy of patient with systemic sclerosis showing enlarged (red arrow) and giant (black arrow) capillaries (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×168 magnification in polarised mode).

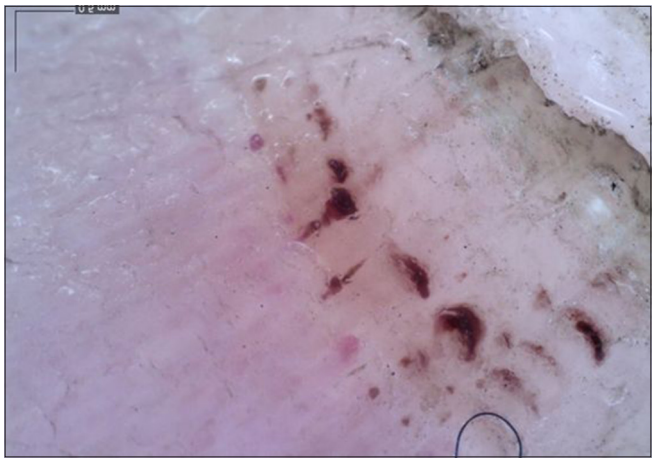

Figure 7: Nailfold capillaroscopy of patient with diffuse systemic sclerosis showing multiple micro-petechiae (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×70 magnification in polarised mode).

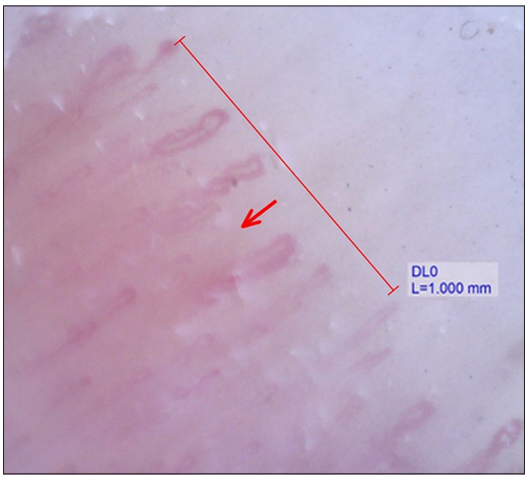

Figure 8: Nailfold capillaroscopy of a patient with systemic lupus erythematosus showing capillary dropout (red arrow) (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×175 magnification in polarised mode).

morphologically abnormal capillaries [Figure 12]. However, no correlation has been found with the extent of skin involvement, disease or duration.[27]

Rosacea

Kaminiska-Winciorek *et al.* conducted a study on 16 female patients with rosacea, examining microcirculation through NVC. The research revealed NVC abnormalities in all patients, specifically noting meandering capillaries, elongations and an increased number of capillaries.[28,29]

Alopecia areata (AA)

In AA, two types of NVC images were identified. The first type showed no abnormalities, while the second type exhibited

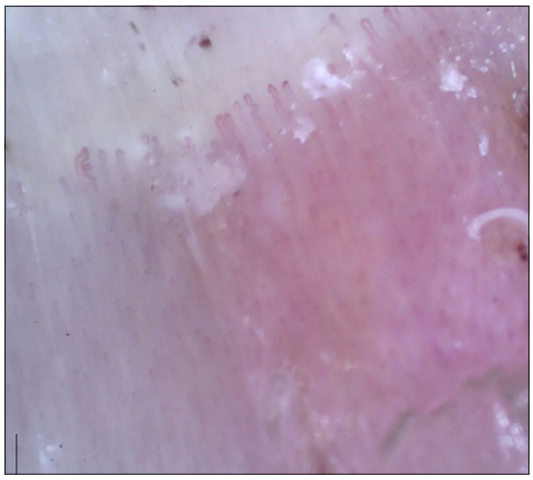

Figure 9: Nailfold capillaroscopy of patient with systemic lupus erythematosus showing tortuous capillary (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×65 magnification in polarised mode).

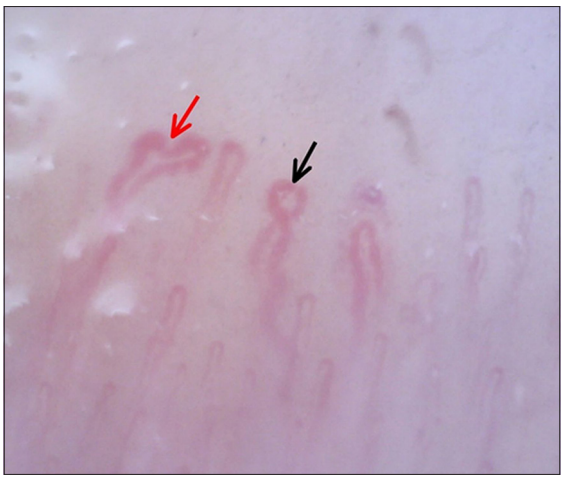

Figure 10: Nailfold capillaroscopy of patient with late systemic sclerosis showing budding (red arrow) suggestive of neoangiogenesis and criss-cross capillary (black arrow) (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×170 magnification in polarised mode).

anomalies such as branching capillaries, dilated loops and tortuosity. Notably, patients with various forms of AA did not show any discernible changes. In addition, there was no association between nail changes and NVC findings.[29]

Leprosy

A study examining NFC alterations in leprosy revealed that 60% of patients exhibited NFC abnormalities, like micro-haemorrhages, dilated, bushy and corkscrew capillaries. Despite the lack of specificity, numerous pieces of evidence pointed to the involvement of Hansen's bacilli

interacting with the endothelium in the pathogenesis of the disease.[30]

Diabetes

One of the non-invasive diagnostic techniques for assessing microvascular alterations in type 2 diabetes mellitus is NFC. One study found that in diabetic retinopathy (DR), there is higher frequency of tortuous, dilated, bushy, meandering, angulated capillaries, avascular areas and micro-haemorrhages as compared to healthy controls. In comparison to non-proliferative DR, proliferative DR had a lower capillary density and a statistically higher incidence of tortuous, bushy capillaries and avascular regions. The prevalence of twisted capillaries, avascular regions, meandering, angulated and dilated capillaries was considerably higher in DR patients with prolonged duration of illness (>20 years). Patients with poor glycaemic control (HbA1c>11) had significantly greater rates of tortuosity, avascular regions and bushy areas.[31]

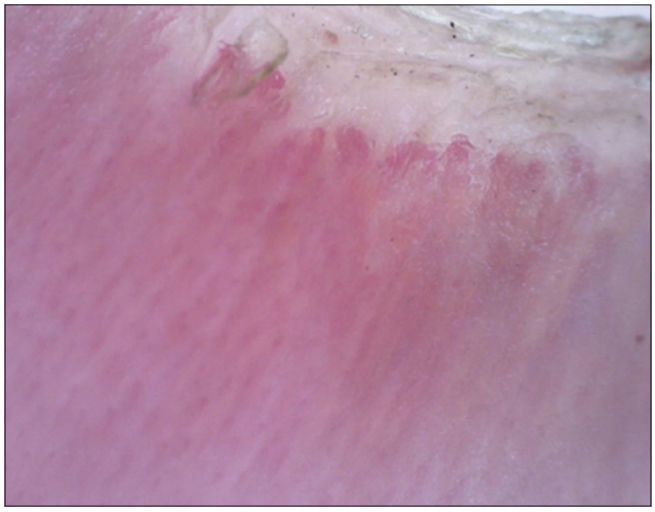

Figure 11: Nailfold capillaroscopy of patient with dermatomyositis having bushy capillaries (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×70 magnification in polarised mode).

Hypertension

Meandering capillaries, capillary disarray, capillary dilation, avascular areas, bushy capillaries and microhaemorrhages are noted more commonly in hypertensive patients. Capillary dilation and avascular areas were significantly more commonly seen in hypertensive patients with retinopathy. Morphological features like avascular areas were found to be were more frequent in patients with microalbuminuria.[9] Arteriovenous sludge, dilated, twisted capillaries and 'flea bite' juxtacapillary microhaemorrhages were more common in patients with isolated systolic hypertension, which is linked to the atherosclerotic nature of the illness.[32]

ARTIFICIAL INTELLIGENCE IN NFC

Raster-scanning optoacoustic mesoscopy offers promising visualisation and quantification of nailfold capillaries in three dimensions. Res-Unet is effective for capillary segmentation in NFC images. NFC with Convolutional Neural Networks analysis holds promise for diabetes screening and cardiovascular risk assessment. Vision Transformer algorithm demonstrates robust performance in identifying microangiopathy in NFC images.[33] The various indications for NFC with corresponding important findings are outlined in Table 4.[34-37]

Table 4: Indications of NFC with salient findings in rheumatologic disease.

Systemic sclerosis	Cutolo *et al*.[8] 2000	Early pattern: Appearance of few dilated and/or giant capillaries and a few haemorrhages. Distribution is relatively preserved without loss of capillaries Active pattern: Large number of giant capillaries and haemorrhages. Moderate loss of capillaries, slight derangement, and diffuse pericapillary oedema can be found Late pattern: Severe loss of capillaries with extensive avascular areas
Raynaud's phenomenon	Ture *et al*.[36] 2024	NFC helps differentiate between primary and secondary Raynaud's. In primary Raynauds, NFC is usually normal while secondary Raynaud's show scleroderma spectrum
Systemic lupus erythematosus	Shenavandeh and Habibi[37] 2017	While SLE does not have a specific capillaroscopic pattern like scleroderma but abnormalities are quite common and also related to active skin disease and renal involvement in few studies. Microhaemorrhages, increased elongation, crossing and crossover pattern, increased tortuosity, disturbed distribution of capillaries, dilated capillaries avascular areas and giant loops are seen in SLE patients
DM, PM, Overlap syndrome	Ibrahim *et al*.[38] 2020	Capillary enlargement is seen in all subtypes (DM, PM and overlap). Giant capillaries, capillary haemorrhage and avascular areas significantly higher in DM patients in comparison to PM and overlap patients Scleroderma like pattern significantly higher in dermatomyositis patients than in polymyositis and overlap
MCTD	Ornowska *et al*.[39] 2024	Early scleroderma-like pattern is seen in MCTD. Common findings include giant, branched, dilated and reduced capillary density

MCTD: Mixed connective tissue disease, SLE: Systemic lupus erythematosus, DM: Dermatomyositis, PM: Polymyositis, NCF: Nail fold capillaroscopy

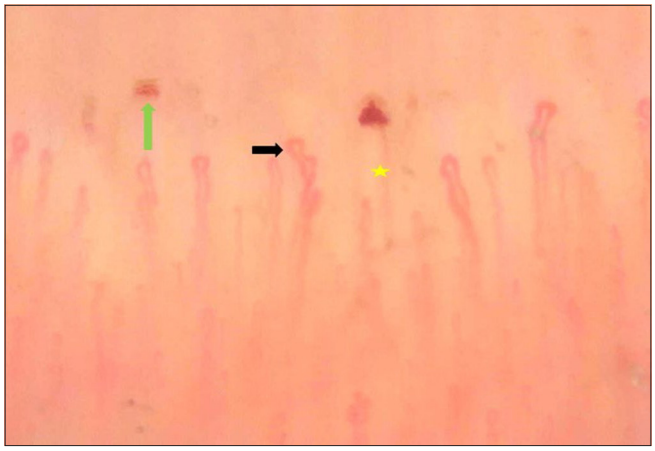

Figure 12: Nailfold capillaroscopy of psoriasis patient showing reduce capillary density, Capillary drop-out (yellow-star) Microhaemorrhage (green arrow) Dilated capillary (black arrow) (Dino-Lite AF4115ZT 5MP, AnMo Electronics Corporation, Taiwan ×170 magnification in polarised mode).

CONCLUSION

NFC stands as a pivotal tool in the diagnosis and monitoring of collagen vascular diseases. From its historical roots to contemporary applications, NFC has evolved into a non-invasive method offering crucial insights into microcirculatory abnormalities. Its utility extends beyond rheumatic diseases, encompassing various dermatological and non-dermatological conditions. The technique's ability to detect vascular alterations before clinical symptoms manifest underscores its significance in early disease identification. NFC's role in SSc classification criteria and its predictive value in juvenile rheumatic diseases highlight its clinical importance. As a safe and accessible imaging technique, NFC provides a unique window into capillary morphology, aiding clinicians in differentiating normal and pathological patterns. To enhance the diagnostic sensitivity and specificity of this valuable non-invasive investigative tool, a greater number of studies are required.

Authors' contributions: PC and AD take responsibility for the integrity and accuracy of the data. Study concept and design: PC, VR, VP. Acquisition, analysis, and interpretation of data: AD,PC,VR. Drafting of the manuscript: AD, PC,VR, VP. Critical revision of the manuscript for important intellectual content: VR , PC.

Ethical approval: Institutional Review Board approval is not required.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
Financial support and sponsorship: Nil.
Conflicts of interest: Dr. Vineet Relhan is on the editorial board of the journal.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Dhiman A, Relhan V, Pal V, Chauhan P. Nail-fold capillaroscopy: A review of literature. J Onychol Nail Surg. 2025;2:10-8. doi: 10.25259/JONS_23_2024