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# Nailfold capillaroscopy by smartphone-dermatoscope for connective tissue disease diagnosis in interstitial lung disease: a prospective observational study

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**Take home message**

Nailfold capillaroscopy by smartphone-dermatoscope is a safe, feasible tool that may improve the identification of connective tissue disease in interstitial lung disease further to routine clinical assessment.

## Introduction

Interstitial lung disease (ILD) can be associated with all connective tissue diseases (CTDs), and when present is a major cause of morbidity and mortality. Accordingly, international guidelines recommend routine assessment for CTD in all ILD patients [1]. CTD-ILD most often manifests in the context of an established CTD, but the ILD may be the first or only presentation of CTD and can be difficult to distinguish from idiopathic interstitial pneumonia (IIP) [2].

Nailfold capillaroscopy (NFC) is a non-invasive tool validated for the diagnosis of systemic sclerosis (SSc) and distinguishing primary from secondary Raynaud's phenomenon, with potential utility in a broader array of CTDs [3, 4]. Quantitative and qualitative nailfold features have been associated with pulmonary involvement in CTD [5-7]. Thus, NFC has been proposed as a screening tool for CTD in ILD patients. However, a paucity of studies in non-rheumatological cohorts leaves the role and interpretation of NFC in ILD patients undefined. Furthermore, gold-standard capillaroscopic techniques, widefield stereomicroscopy and videocapillaroscopy, are expensive with limited access in many clinical settings. Thus, there is increasing interest in lower-cost, portable devices that can be easily applied in clinical practice, including the "smartphone-dermatoscope" [8].

Our primary objective was to describe quantitative and qualitative nailfold characteristics by smartphone-dermatoscope in well-defined cohorts of CTD-ILD and non-CTD ILD, (comprised of IIP and interstitial pneumonia with autoimmune features [IPAF]), at a tertiary ILD referral centre. Secondary objectives included evaluation of the association of nailfold characteristics with CTD-diagnosis and clinical variables in ILD. Empirical thresholds of nailfold characteristics to identify CTD in ILD were calculated. The association of nailfold characteristics with CTD in ILD together with clinical, serological and radiological variables were explored.

## Methods

### *Study design and participants*

Consecutive patients attending a specialist ILD clinic were prospectively screened for inclusion (18 August 2016 to 24 January 2018). Eligible patients were aged ≥18 years, with a consensus diagnosis of CTD-ILD or IIP by ILD multidisciplinary-meeting (ILD-MDM), and able to give informed consent. CTD diagnoses were defined by international criteria for systemic sclerosis (SSc) [3], rheumatoid arthritis (RA) [9], Sjögren's syndrome [10], mixed connective tissue disease [11], idiopathic inflammatory myositis (IIM) [12], and systemic lupus erythematosus [13]. IIPs were defined by American Thoracic Society/European Respiratory Society classification criteria [1, 14]. Of eligible participants, patients meeting IPAF criteria were separately identified [15]. CTD-ILD and IPAF classifications were confirmed by specialist Rheumatologist assessment. Patients unable to provide consent or without CTD-ILD or IIP by ILD-MDM consensus were excluded. Diagnosis at follow-up was censored on 15 June 2020. Ethical approval was granted by the Sydney Local Health District human ethics committee (protocol number X16-0111 HREC/16/RPAH/137).

### *Definitions*

To delineate a well-defined CTD-ILD cohort for analysis, "CTD-ILD" included only participants fulfilling CTD classification criteria as specified. "Non-CTD ILD" included IIP and IPAF participants. Disease duration was defined as time from onset of symptoms to first clinic presentation.

Considering IPAF criteria, participants with positive anti-tRNA synthetase autoantibodies, amyopathic disease, and no other features diagnostic of anti-synthetase syndrome were classified as IPAF. Anti-Ro52, anti-Mi2 and anti-SRP were considered as meeting serological IPAF criteria. "Unexplained vasculopathy" was defined as pulmonary hypertension (PH) on echocardiogram (systolic pulmonary arterial pressure [PAP] >35mmHg above right atrial pressure)[16] or right heart catheterisation (RHC;

mean PAP ≥25 mmHg) with FVC >70% predicted. "Unexplained airway disease" was defined as FEV1/FVC ratio <70% with no history of asthma, chronic obstructive airways disease or smoking.

***Data collection***

Standardised clinical assessment, extended autoantibody testing (ANA, ENAs [Ro-60/SS-A, Ro-52, La/SS-B, RNP, Scl-70, Smith, centromere, PCNA, ribosomal-P], myositis antigens [Mi-2, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ; Euroimmun Myositis Profile 3], dsDNA, RF, CCP, ANCA, MPO and PR-3; non-abbreviated labels provided in Supplementary Table S1), lung function testing and NFC were performed at baseline. ANA titre ≥1:320 or any titre if a nucleolar or centromere pattern were considered positive [15].

Pulmonary physiological indices included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), peripheral oxyhaemoglobin saturation ($SpO_2$), six-minute walk test (6MWT) distance and $SpO_2$ nadir. Composite physiologic index (CPI) and ILD gender-age-physiology (ILD-GAP) stage were calculated [17, 18].

Radiological pattern on high-resolution computed tomography (HRCT) and histopathology results reported by specialist radiologist and pathologist at ILD-MDM were obtained from medical records. The presence of PH was determined from echocardiogram and/or RHC results as available. Treatment remained as per the attending physician.

***Nailfold capillaroscopy***

A single clinician (AJ) performed NFC with a smartphone-dermatoscope (3M Dermlite DL4$^{TM}$ attached to iPhone 6plus$^{TM}$, Figure 1) on eight digits, excluding thumbs, at 20-times optical magnification after a period of acclimatisation at room temperature (20-24$^{O}$C). A photograph of a

measurement ruler taken at the same magnification was included with the images for assessment. The centre 3mm of each image was scored by two independent, blinded specialist rheumatologists (NM, MP) and recorded on a prespecified digital form (Supplementary Figure S2). Discordant results were discussed by the two scorers to reach consensus. Nailfold characteristics recorded for each image included: (1) capillary density (number of capillary loops in the most distal capillary row per millimetre); total number of (2) microhaemorrhages (haemosiderin deposits in the cuticle, not related to trauma); (3) giant capillaries (capillaries more than four times normal capillary size); (4) avascular areas (distinct areas >0.5mm in the distal capillary row with no capillaries visible); (5) abnormal capillary shapes (enlarged [<4 times normal], tortuous [capillary width >2 times apex width without capillary limb enlargement] or abrogated/"bushy" capillary loops). Figure 1 depicts capillaroscopic images and techniques. Abnormal capillary shapes (ACS) were recorded by semiquantitative score reflecting percentage of capillaries affected: 0 = <10% of capillaries demonstrating ACS; 1 = 10-50%; 2 = >50%. Qualitative scoring was performed using pre-specified Ingegnoli, Cutolo and Maricq criteria [19-21]. Patients meeting 2020 EULAR Study Group on Microcirculation in Rheumatic Disease (SG-MC) consensus for "scleroderma", published after initial qualitative data scoring, were identified post-hoc using quantitative data [22].

Study data were collected and managed using REDCap hosted at The University of Sydney [23].

***Statistical analysis***

Comparison between ILD groups were performed using two-tailed student's t-test or Fisher's exact test as appropriate. Continuous quantitative nailfold characteristics (mean capillary density, number of giant capillaries, avascular areas, microhaemorrhages, ACS), were evaluated for an empirical threshold using receiver operating characteristic (ROC) curve analysis and Youden index to maximise the sum of sensitivity and specificity. Threshold values were rounded to the closest whole number for

pragmatic assessment. Univariable and multivariable logistic regression (adjusted for age, gender, smoking, FVC% predicted [FVC%], PH and treatment), were used to evaluate associations between nailfold thresholds and clinical variables for the identification of CTD in ILD.

Variables with an area under the ROC curve (AUC) >0.6 and p-value<0.10 in univariable analyses were retained in exploratory multivariable analyses. Collinear variables were identified by pairwise correlation (r>0.5) and removed from further analysis. Independent predictors of CTD in ILD were identified using backward stepwise selection and the Akaike Information Criterion, further adjusted for age, sex, smoking, FVC%, PH and treatment. The association of nailfold characteristics with CTD-diagnosis in ILD in the absence of clinically overt CTD-manifestations was explored.

Inter-rater reliability of mean capillary density, total number of giant capillaries, microhaemorrhages, avascular areas and abnormal capillary shapes was assessed by intraclass correlation coefficients.

Continuous variables are reported as mean (standard deviation [SD]) and categorical variables as absolute number (relative frequency). Missing data were not estimated and removed from the denominator when calculating relative frequencies. P-values <0.05 were considered statistically significant. Statistical analysis was performed using Stata statistical software (v14.0, College station, TX) and GraphPad Prism (v8.3.0, San Diego, CA).

**Results**

Ninety-six patients met inclusion criteria, including 27 (28.1%) with definite CTD-ILD and 69 (71.9%) with non-CTD ILD (IIP n=42 [43.8%], IPAF n=27 [28.1%]). Specific diagnoses are shown in Figure 2.

***Baseline characteristics***

Baseline characteristics are shown in Table 1. Mean age was 66.4±10.3 years, 44.8% (n=43) female, 57.3% (n=55) ever-smokers, mean FVC 73.9% and DLCO 54.8% predicted. PH was present in 12 (14.5%) of 83 patients with available echocardiogram or RHC data, and did not differ between ILD subgroups.

CTD-ILD patients were younger, more female predominant and less likely to be smokers compared with non-CTD ILD patients. Disease duration was longer in CTD-ILD, with no difference in respiratory symptom duration. CTD-ILD patients overall had more favourable physiology (Table 1).

**Table 1.** Baseline characteristics and pulmonary physiology

| | **TOTAL** | **CTD-ILD** | **Non-CTD ILD** | | **CTD-ILD vs non-CTD ILD** |
|---|---|---|---|---|---|
| | **n=96** | **n=27** | **IPAF n=27** | **IIP n=42** | **p-value** |
| Age, years | 66.4 (10.3) | 61.5 (8.9) | 64.2 (11.1) | 71.0 (8.8) | 0.003 |
| Female, n(%) | 43 (44.8) | 20 (74.1) | 15 (55.6) | 8 (19.0) | <0.001 |
| Smoking ever, n(%) | 55 (57.3) | 10 (37.0) | 16 (59.3) | 29 (69.1) | 0.021 |
| Caucasian, n(%) | 79 (82.3) | 19 (70.4) | 23 (85.2) | 37 (88.1) | 0.075 |
| Disease duration, years | 7.4 (7.7) | 11.3 (10.6) | 4.3 (3.0) | 6.9 (6.5) | 0.002 |
| Respiratory symptoms, years | 5.7 (5.4) | 5.6 (4.8) | 4.3 (3.0) | 6.6 (6.7) | 0.292 |

| | | | | | |
|---|---|---|---|---|---|
| **Physiology** | | | | | |
| $SpO_2$, % | 96.6 (2.5) | 97.9 (2.4) | 96.7 (2.3) | 95.8 (2.4) | 0.003 |
| FVC% | 73.9 (17.8) | 77.0 (17.7) | 72.3 (18.8) | 72.8 (17.5) | 0.281 |
| DLCO% | 54.8 (16.6) | 60.7 (19.8) | 54.8 (16.2) | 50.9 (13.6) | 0.028 |
| 6MWT distance (m) | 446.5$^{\Delta}$ (126.1) | 463.0$^{\P}$ (88.6) | 421.5$^{\ddagger}$ (138.6) | 453.1$^{\lozenge}$ (137.3) | 0.479 |
| 6MWT $SpO_2$ nadir (%) | 90.0$^{\Delta}$ (7.1) | 94.3$^{\P}$ (3.6) | 90.0$^{\ddagger}$ (7.9) | 87.6$^{\lozenge}$ (7.2) | 0.001 |
| **Composite Indices** | | | | | |
| CPI | 43.1 (12.8) | 38.9 (14.2) | 46.2 (10.4) | 46.2 (10.4) | 0.044 |
| ILD-GAP score | 1.9 (2.2) | 0 (1.6) | 1.2 (1.5) | 2.5 (1.5) | <0.001 |

*Shown as mean (SD) unless stated.*

**p-value for CTD-ILD vs non-CTD-ILD.*

$^{\P}$*n=22;* $^{\Delta}$*n=82;* $^{\dagger}$*n=60;* $^{\ddagger}$*n=24;* $^{\lozenge}$*n=36*

*Abbreviations: $SpO_2$ peripheral oxygen saturation; FVC% percentage predicted forced vital capacity; DLCO% percentage predicted diffusing capacity for carbon monoxide; 6MWT six-minute walk test; CPI composite physiologic index; ILD-GAP ILD gender-age-physiology index.*

Clinical, serological and radiological characteristics are detailed in Supplementary Table S3 (ILD subgroup comparison see Supplementary Table S4). At baseline, treatment for ILD was more common in CTD-ILD compared with non-CTD ILD patients (p=0.017; Supplementary Table S5).

***Nailfold capillaroscopy characteristics at baseline***

Baseline NFC was available in 94 patients (total 687 images, median eight images per patient [interquartile range 7-8]; two patients excluded with insufficient image quality).

CTD-ILD patients demonstrated lower mean capillary density; higher prevalence of giant capillaries, avascular areas and microhaemorrhages; and a greater number of giant capillary and avascular areas compared with non-CTD ILD patients (Table 2). Nailfold characteristics did not differ between IIP and IPAF patients.

There were no correlations between nailfold characteristics and age, symptom duration, or physiology ($SpO_2$, FVC%, DLCO%, CPI).

Inter-rater reliability of low capillary density was excellent (intra-class correlation coefficient = 0.90), microhaemorrhages good (ICC=0.81) and remaining nailfold characteristics moderate (Supplementary Table S6) [24].

**Table 2.** Nailfold capillaroscopy characteristics by ILD group

| | **TOTAL** | **CTD-ILD** | **Non- CTD ILD** | | **CTD-ILD vs non-CTD ILD** |
|---|---|---|---|---|---|
| | **n=94** | **n=26** | **IPAF n=27** | **IIP n=41** | **p-value** |
| **Density** | | | | | |
| Number per mm | 6.7 (1.4) | 5.6 (1.6) | 6.8 (1.1) | 7.3 (0.9) | <0.001 |
| **Giant capillaries** | | | | | |
| Present, n(%) | 38 (40.4) | 16 (61.5) | 12 (44) | 10 (24.4) | 0.018 |
| Number per patient | 2.9 (6.3) | 7.0 (1.1) | 2.8 (6.1) | 0.5 (8.9) | <0.001 |
| **Avascular areas** | | | | | |
| Present, n(%) | 36 (38.3) | 15 (57.7) | 12 (44.4) | 9 (22.0) | 0.031 |
| Number per patient | 1.3 (2.2) | 2.7 (3.2) | 1.2 (1.6) | 0.5 (1.1) | <0.001 |
| **Microhaemorrhages** | | | | | |
| Present, n(%) | 72 (76.6) | 24 (92.3) | 18 (66.7) | 30 (73.2) | 0.030 |
| Number per patient | 5.8 (12.1) | 4.9 (6.7) | 8.2 (18.0) | 4.9 (9.9) | 0.640 |
| **Abnormal capillary shapes** | | | | | |
| Present, n(%) | 90 (95.7) | 26 (100) | 24 (88.9) | 40 (97.6) | 0.573 |

| | | | | | |
|---|---|---|---|---|---|
| Mode score | 0.7 (0.8) | 1.2 (0.8) | 0.7 (0.8) | 0.4 (0.6) | <0.001 |

*Shown as mean(SD) unless stated*

***Nailfold capillaroscopy for CTD diagnosis in ILD***

Empirical thresholds of nailfold characteristics with the greatest sensitivity and specificity to identify CTD in ILD were <6 capillaries/mm, ≥3 giant capillaries, ≥2 avascular areas and ≥1 microhaemorrhage (ROC curve analysis shown in Supplementary Figure S7). ACS were present in all CTD-ILD patients and omitted from further analysis.

In univariable analysis, all nailfold characteristics at empirical thresholds identified CTD in ILD (unadjusted OR 5.00–7.47), maintained with multivariable adjustment (Table 3). The presence of clinical CTD-manifestations (any of inflammatory arthritis, Raynaud's phenomenon, digital oedema, palmar telangiectasia, digital tip ulceration, mechanic's hands, Gottron's papules/sign, sclerodactyly) had the highest discriminative performance for CTD-ILD diagnosis relative to non-CTD ILD (AUC 0.86).

**Table 3.** Univariable logistic regression for CTD-ILD diagnosis

| | **Unadjusted OR** | **95%CI** | **p-value** | **AUC** |
|---|---|---|---|---|
| **Nailfold characteristics** | | | | |
| Density <6/mm | 7.47 | 2.73–20.43 | <0.001* | 0.72 |
| Giant ≥3 total | 6.77 | 2.43–18.81 | <0.001* | 0.70 |
| Avascular ≥2 total | 5.44 | 2.02–14.68 | 0.001* | 0.68 |

| | | | | |
|---|---|---|---|---|
| Microhaemorrhages ≥1 total | 5.00 | 1.08–23.18 | 0.040* | 0.61 |
| **Baseline characteristics** | | | | |
| Age | 0.94 | 0.89–0.98 | 0.005* | 0.70 |
| Male | 0.18 | 0.06–0.47 | 0.001 | 0.70 |
| Smoking | 0.31 | 0.12–0.79 | 0.014 | 0.64 |
| FVC% predicted | 1.01 | 0.99–1.04 | 0.279 | 0.59 |
| DLCO% predicted | 1.03 | 1.00–1.06 | 0.032 | 0.64 |
| **Clinical CTD manifestations** | | | | |
| Any CTD manifestation† | 42.18 | 10.80–164.74 | <0.001* | 0.86 |
| **Serology and radiology** | | | | |
| ANA≥1:320 | 3.80 | 1.42–10.14 | 0.008 | 0.64 |
| Positive ENA | 5.38 | 2.04–14.20 | 0.001* | 0.68 |
| Any myositis autoantibody‡ | 0.33 | 0.10–1.05 | 0.061 | 0.60 |
| Radiological NSIP, OP or NSIP/OP | 7.48 | 2.33–23.93 | 0.001* | 0.71 |

*Odds ratios (OR) are shown for the bivariate relationship of each variable with CTD-ILD diagnosis.*

**Remains significant adjusted for age, sex, smoking, FVC%, treatment and pulmonary hypertension.*

†*Including any of inflammatory arthritis, Raynaud's phenomenon, digital oedema, palmar telangiectasia, digital tip ulceration, mechanic's hands, Gottron's papules/sign, sclerodactyly.*

‡*Patients with positive myositis autoantibody and no clinical features of myositis classified as IPAF (non-CTD ILD).*

Giant capillaries and avascular areas demonstrated collinearity with capillary density and were excluded from further analysis. Variables that remained for inclusion in exploratory multivariable analyses included capillary density, microhaemorrhages, age, gender, smoking, DLCO%, CTD manifestations, ANA, ENA and radiological NSIP, OP or NSIP/OP (multivariable regression of all retained variables shown in Supplementary Table S8). Respective to all included components, microhaemorrhages (aOR 13.45, 95%CI 2.14–84.32, p=0.006) and CTD-manifestations were identified as strong independent predictors of CTD-diagnosis in ILD, including after adjustment for age, sex, smoking, FVC%, PH and treatment (Table 4). In the absence of CTD manifestations, microhaemorrhages, low capillary density, and positive-ENA remained as independent predictors of CTD-ILD from non-CTD ILD (Table 4; included components see Supplementary Table S8).

**Table 4.** Independent predictors for CTD-diagnosis in ILD identified by exploratory multivariable regression

| | **Predictors*** | **aOR†** | **95% CI** | **p-value** |
|---|---|---|---|---|
| A) Including CTD-manifestations | Any CTD-manifestation | 62.84 | 13.93–283.40 | <0.001 |
| | Microhaemorrhages | 13.45 | 2.14–84.32 | 0.006 |
| B) Excluding CTD-manifestations | Positive-ENA | 11.59 | 1.80–74.55 | 0.010 |
| | Microhaemorrhages | 22.54 | 1.89–269.05 | 0.014 |
| | Low capillary density | 5.66 | 1.32–24.20 | 0.019 |

*A) Independent predictors for CTD-diagnosis in ILD respective to retained nailfold characteristics, clinical, serological and radiological variables. B) Independent predictors for CTD-diagnosis in ILD*

*excluding CTD-manifestations, respective to remaining nailfold characteristics, serological and radiological variables.*

**All retained variables in initial multivariable regression shown in Supplementary Table S8.*

*†Adjusted for age, gender, smoking, FVC%, treatment and pulmonary hypertension.*

*Abbreviations: aOR = adjusted odds ratio; NSIP non-specific interstitial pneumonia pattern on radiology; OP organising pneumonia pattern on radiology.*

***Qualitative nailfold capillaroscopy analysis***

A "scleroderma" or "active/late" pattern by all pre-specified qualitative classification criteria identified CTD-ILD (Table 5). Frequency of qualitative patterns by ILD group are shown in Supplementary Table S9. Four non-CTD ILD patients (IIP n=2, IPAF n=2) demonstrated a "scleroderma" or "active/late" pattern across all criteria (clinical details shown in Supplementary Table S10).

**Table 5.** Association of qualitative NFC pattern with CTD-ILD diagnosis

| Proposed criteria | Pattern | Unadjusted OR* | 95%CI | p-value |
|---|---|---|---|---|
| Ingegnoli [19] | Normal | 1 | | |
| | Minor | 2.15 | 0.58–7.98 | 0.254 |
| | Major | 3.02 | 0.67–13.63 | 0.015 |
| | Scleroderma | 15.30 | 3.37–68.99 | <0.001† |
| Maricq [21] | Normal | 1 | | |
| | Non-specific | 2.05 | 0.58–7.22 | 0.262 |
| | Scleroderma | 9.39 | 2.80–31.45 | <0.001† |

| | | | | |
|---|---|---|---|---|
| Cutolo [20] | Normal | 1 | | |
| | Early | 2.01 | 0.57–7.04 | 0.276 |
| | Active | 6.09 | 1.66–22.42 | 0.007† |
| | Late | 15.67 | 1.46–168.07 | 0.023† |
| EULAR SG-MC [22] | Scleroderma | 3.91 | 1.47–10.42 | 0.006† |

**Odds ratios (OR) relative to a normal pattern for each classification criteria.*

*†p-value remains <0.05 adjusted for age, sex, smoking, FVC%, treatment, pulmonary hypertension.*

*Abbreviations: EULAR SG-MC European League Against Rheumatism Study Group on Microcirculation*

***Follow-up***

Mean follow-up time was 2.5 years (range 72 days to 3.8 years). No non-CTD ILD patients with abnormal NFC at baseline developed a diagnostic CTD during the study period.

**Discussion**

We describe NFC by smartphone-dermatoscope in 94 patients with well-defined ILD and demonstrate its potential to identify CTD in ILD patients further to multidisciplinary assessment at empirical thresholds. NFC has been proposed as a non-invasive tool to screen for CTD in ILD patients, but a paucity of studies in dedicated ILD cohorts has limited its use and interpretation in clinical practice. We have demonstrated the feasibility and utility of NFC by smartphone-dermatoscope in the ILD clinical setting, and its potential to improve the identification of CTD further to standard clinical assessment.

To our knowledge, our study is the first to evaluate quantitative NFC in well-characterised ILD populations, and its combination with clinical variables including empirical thresholds. Low capillary density, increased giant capillaries, avascular areas and microhaemorrhages all strongly enhanced the discrimination of CTD-ILD from non-CTD ILD, independent of baseline age, gender, smoking-history, FVC%, prevalent PH and treatment. CTD-manifestations were unequivocally the strongest predictor of CTD, underlining that careful clinical assessment remains at the core of accurate diagnosis. Nevertheless, confirming a diagnosis of CTD in ILD patients can remain elusive despite comprehensive multidisciplinary assessment, owing to disease heterogeneity, and in particular, occult or clinically-amyopathic CTD. Surprisingly, microhaemorrhages remained a strong predictor for CTD in our ILD cohort after accounting for all other clinical, serological and radiological findings, including CTD-manifestations, despite a weaker association in univariable analysis. Encouragingly, in the absence of CTD-manifestations, low capillary density and microhaemorrhages were independent predictors of CTD-ILD relative to non-CTD ILD, signalling the potential utility of NFC to identify occult CTD in ILD populations. Lower capillary density by videocapillaroscopy, but not microhaemorrhages, has been associated with SSc-ILD in prior studies, acknowledging different study populations and capillaroscopy techniques [5-7]. Whilst the optimal combination of nailfold characteristics and clinical variables requires validation, taken together, our data demonstrate the potential of NFC as an additional tool to aid CTD identification together with ILD assessment following international guidelines.

Qualitative assessment further supported the utility of NFC to identify CTD in ILD, regardless of putative classification criteria (OR range 3.27–8.47). However, derived thresholds of nailfold characteristics that optimally identified CTD in our ILD cohort differed from those recommended for SSc-spectrum diseases [22]. We also observed a high prevalence of major capillaroscopic abnormalities (giant capillaries, avascular areas), in patients without a definable CTD-ILD. These data

raise the important question of how to define “abnormal” NFC in ILD populations. Capillaroscopy studies in non-CTD ILD populations are limited, but prior IIP cohorts have reported major nailfold abnormalities in 5.7% to 46.7% [25-27]. No non-CTD ILD patients with nailfold abnormalities developed a definable CTD during our study, recognising that diagnostic CTD features can develop many years after ILD onset [2]. Long-term studies of heterogeneous ILD cohorts are required to characterise the pathogenic mechanisms, clinical implications, and outcomes of microvascular changes in non-CTD ILD patients. We suggest caution extrapolating pre-specified nailfold criteria established in rheumatology populations to broader ILD cohorts until further validation.

We have clearly demonstrated the feasibility of NFC by smartphone-dermatoscope in a real-world clinical setting, which may serve as an accessible, lower-cost, screening test for CTD in ILD patients. This may guide the need for formal NFC or rheumatologist referral, particularly when there is concern for occult or non-diagnostic CTD features despite standard assessment. Nailfold characteristics retained in our multivariable models, particularly capillary density, have demonstrated ease of measurement, good reproducibility, and reliability in our, and prior studies [28-30]. The smartphone-dermatoscope is unlikely to replace gold-standard techniques, but may strike a pragmatic balance between applicability and performance, with comparable inter- and intra-rater reliability to videocapillaroscopy [8, 31-33]. Its portability and ease-of-use across broad experience-levels also improves access to this valuable tool in remote and community settings where specialised services may be limited. Smartphone technology allows the assessment of images by remote experts, amplified magnification, comparison of serial imaging, and blinding in the research setting. To define the clinical role of NFC in ILD patients, it will be important to understand its impact on diagnostic reasoning, outcomes, and comparison or combination with established and emerging modalities, including USB microscopy and computer-automated scoring systems [34].

Our data support the hypothesis that microvascular dysfunction is a key pathogenic mechanism in pulmonary fibrosis [25, 35]. The lack of correlation between NFC and $SaO_2$ or DLCO% complements the study by Corrado et al. demonstrating normal capillaroscopy in COPD patients, suggestive that microvascular changes are not a simple sequelae of hypoxia [25]. Integrating these findings with ILD-associated serum biomarkers of vascular remodelling (e.g., vascular endothelial growth factor, endothelin-1, interleukin-8), may provide pathogenic insights on the role of systemic vascular dysfunction in CTD-related and non-CTD ILDs. The theragnostic potential of NFC remains unknown. At present, a lack of standardised treatment guidelines for CTD-ILD and small study numbers limit conclusions on treatment associations. Nintedanib, an antifibrotic able to slow disease progression in SSc-ILD and progressive-fibrosing ILD, has demonstrated vascular remodelling in animal models [36-38]. However, how this relates to its antifibrotic activity in ILD, the impact on microvascular changes represented in NFC, and whether this can be used to guide therapy remains to be determined.

Our study has several limitations. The single-centre design and small numbers necessitate validation in larger, heterogeneous ILD cohorts. Our IIP cohort was predominantly IPF, reflecting referral patterns to the centre, and further study of non-IPF IIP cohorts is needed. Comparison with formal capillaroscopy was not possible and individual capillary dimensions were only measurable to the nearest 0.2mm. To minimise misclassification, images were scored by two independent, blinded experts in capillaroscopy. Nevertheless, our results reflect applicability in daily practice, with prior studies demonstrating good comparability between the dermatoscope and videocapillaroscopy, and the potential for operators of varying experience to reliably interpret NFC with brief training [8, 32, 33, 39]. Qualitative assessment by EULAR SG-MC consensus, included to aid comparison with future studies, was calculated post-hoc with possible misclassification. Nevertheless, to date, our study remains one of the largest prospective, quantitative NFC studies with ILD diagnosed by ILD-MDM,

the gold-standard for ILD diagnosis. All CTD-ILD and IPAF participants were assessed by an expert rheumatologist, allowing delineation of a well-defined CTD-ILD cohort.

In conclusion, NFC is a safe, feasible tool that improves discrimination of CTD further to routine clinical assessment of the ILD patient. The smartphone-dermatoscope holds potential as a pragmatic, reliable capillaroscopic device with increased feasibility across broad experience-levels. Longitudinal study in heterogeneous populations will aid more uniform application and interpretation of NFC for CTD diagnosis in ILD patients.

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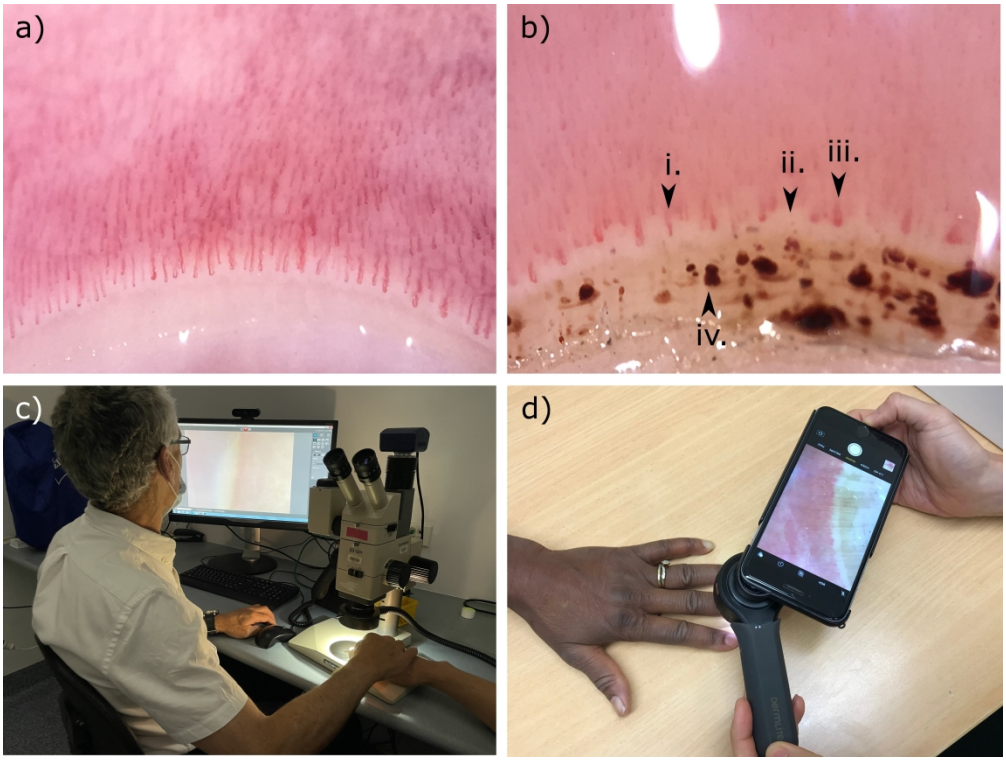



Figure 1. Nailfold patterns, characteristics and technique. a) Normal nailfold capillaroscopy pattern b) "Scleroderma" pattern with i) abnormal capillary shape ii) avascular area iii) giant capillary iv) microhaemorrhages c) capillaroscopy by widefield stereomicroscopy d) nailfold capillaroscopy by 'smartphone-dermatoscope'

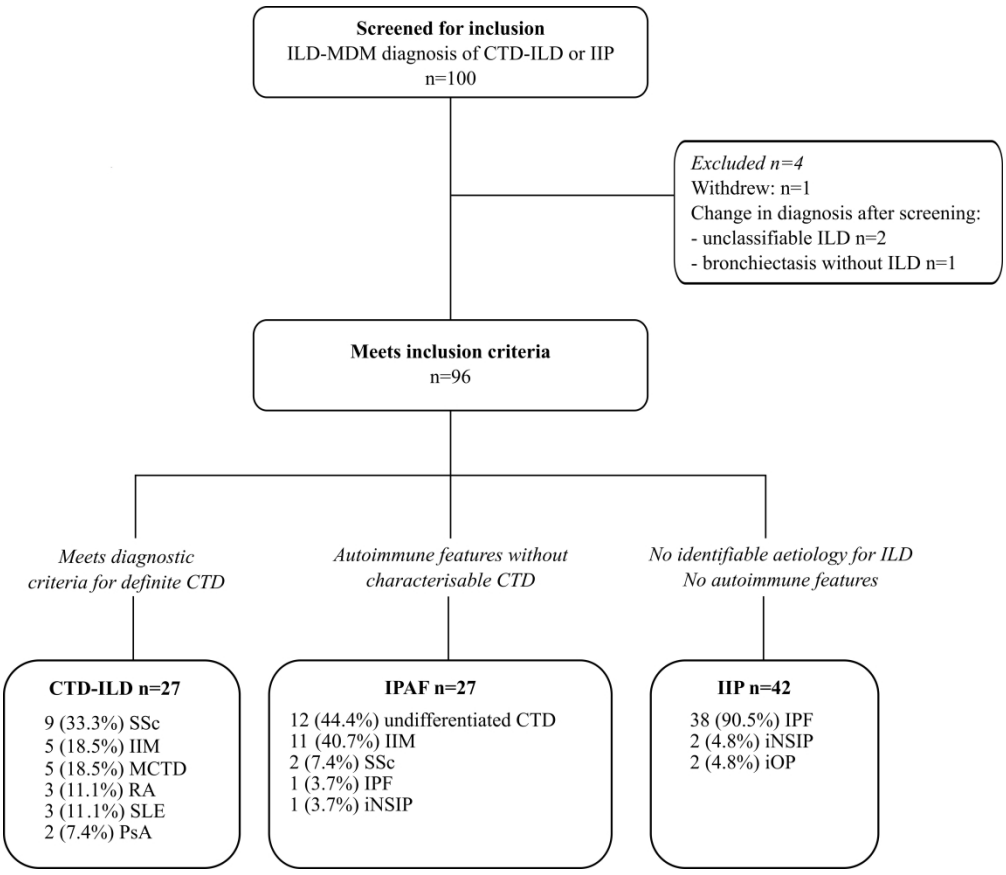



Figure 2. Study flowchart and ILD diagnoses. †IPAF – "working diagnosis" based on clinical, serological and radiological features as per ILD-MDM discussion. *Undifferentiated CTD = features of autoimmune disease without an identifiable provisional phenotype. Abbreviations ILD-MDM interstitial lung disease multidisciplinary meeting; CTD-ILD connective tissue disease associated ILD; IIP idiopathic interstitial pneumonia; SSc systemic sclerosis; IIM idiopathic inflammatory myositis; MCTD mixed connective tissue disease; RA rheumatoid arthritis; SLE systemic lupus erythematosus; PsA psoriatic arthritis; IPF idiopathic pulmonary fibrosis; iNSIP idiopathic non-specific interstitial pneumonia; iOP idiopathic organising pneumonia.

## Supplementary data

**Supplementary Table S1.** Complete autoantibody antigen labels

| Autoantibody | Complete antigen label |
|---|---|
| ANA | Anti-nuclear antigen |
| ENA | Extractable nuclear antigens |
| Ro-60/SS-A | Ro-60/Sjogren syndrome-type A |
| La/SS-B | La/Sjogren syndrome-type B |
| RNP | Ribonuclear protein |
| PCNA | Proliferating cell nuclear antigen |
| SRP | Signal recognition particle |
| PM-Scl | Polymyositis-systemic sclerosis |
| dsDNA | Double stranded deoxyribonucleic acid |
| RF | Rheumatoid factor |
| CCP | Cyclic citrullinated peptide |
| ANCA | Autoantibody to neutrophilic cytoplasmic antigens |
| MPO | Myeloperoxidase |
| PR3 | Proteinase 3 |

**Supplementary Figure S2.** Nailfold capillaroscopy scoring sheet

| Study ID: | Investigator ID: | Date of scoring: |
|---|---|---|
| | | |

**Nailfold Scoring Sheet**

- Characteristics of nailfolds from central 3mm of image
- Record "U" for unclassifiable and state reason (eg. Image quality)

| Characteristics: | Capillary density (loops/3mm) | Micro-haemorrhages (number/3mm) | Abnormal capillary shapes (0=none <10%, 1=few 10-50%; 2=many >50%) | Giant capillaries (number/3mm) | Avascular areas (number/3mm) |
|---|---|---|---|---|---|
| **Left index** | | | | | |
| **Left middle** | | | | | |
| **Left ring** | | | | | |
| **Left little** | | | | | |
| **Right index** | | | | | |
| **Right middle** | | | | | |
| **Right ring** | | | | | |
| **Right little** | | | | | |
| **MEAN:** | | | N/A | | |

| Ingegnoli Criteria | | Tick |
|---|---|---|
| **Normal** | Normal density, no abnormal capillaries, no avascular areas, <10% tortuous vessels present | |
| **Minor** | Normal density, no haemorrhages, 10-50% tortuous | |
| **Major** | Reduced density (<6mm), widespread capillary abnormalities (>50%), haemorrhages | |
| **SD pattern** | Reduced density, widespread capillary abnormalities, giant capillaries, avascular areas, haemorrhages | |
| **Unclassifiable** | Not classifiable by above criteria | |

| Cutolo Criteria | | Tick |
|---|---|---|
| **Normal** | | |
| **Early** | Few giant capillaries, few haemorrhages and no capillary loss | |
| **Active** | Numerous giant capillaries and microhaemorrhages, mild capillary architecture disturbance and moderate capillary loss | |
| **Late** | Severe capillary loss with extensive avascular areas, disorganised capillaries and ramified capillaries. | |
| **Unclassifiable** | Not classifiable by above criteria | |

| Maricq Criteria | Tick |
|---|---|
| **Normal** | |
| **Non-specific** | |
| **SD-Pattern** | |
| **Unclassifiable** | |

*Definitions:*

- *Microhaemorrhages = not related to trauma*
- *Abnormal capillary shapes = enlarged (≤ 4x normal); tortuous (capillary width >2x apex width without capillary limb enlargement; arbogated)*
- *Giant Capillaries = >4x normal size*
- *Avascular areas = Distinct areas in the nailfold where there are 2 or more missing capillaries and a distance between capillaries of >0.5mm*

**Supplementary Table S3.** Baseline clinical, serological, morphological features by ILD group

| | TOTAL | CTD-ILD | Non-CTD ILD | | CTD-ILD vs non-CTD-ILD |
|---|---|---|---|---|---|
| | n=96 | n=27 | IPAF n=27 | IIP n=42 | p-value |
| **Clinical CTD manifestations** | | | | | |
| Any manifestation | 50 (52.1) | 26 (96.3) | 20 (74.1) | 4 (9.5) | <0.001 |
| Inflammatory arthritis* | 22 (22.9) | 20 (74.1) | 2 (7.4) | 0 | <0.001 |
| Raynaud's phenomenon | 21 (21.8) | 15 (55.6) | 5 (18.5) | 1 (2.4) | <0.001 |
| Digital oedema | 11 (11.5) | 8 (29.6) | 3 (11.1) | 0 | <0.001 |
| Palmar telangiectasia | 7 (7.3) | 7 (25.9) | 0 | 0 | <0.001 |
| Digital tip ulceration | 6 (6.3) | 6 (22.2) | 0 | 0 | 0.001 |
| Mechanic's hands | 5 (5.2) | 2 (7.4) | 3 (11.1) | 0 | 0.618 |
| Gottron's papules/sign | 4 (4.2) | 3 (11.1) | 1 (3.7) | 0 | 0.066 |
| Reflux | 28 (29.2) | 16 (59.3) | 12 (44.4) | 0 | <0.001 |
| Sclerodactyly | 13 (13.5) | 12 (44.4) | 1 (3.7) | 0 | <0.001 |
| Proximal weakness or myalgia | 12 (12.5) | 9 (33.3) | 3 (11) | 0 | <0.001 |
| Sicca | 17 (17.7) | 7 (25.9) | 8 (29.6) | 2 (4.8) | 0.236 |
| Unexplained rash | 11 (11.5) | 6 (22.2) | 5 (18.5) | 0 | 0.069 |
| Pleurisy | 5 (5.2) | 3 (11.1) | 1 (3.7) | 1 (2.4) | 0.133 |
| **Serology** | | | | | |
| ANA >1:320 | 24 (25) | 12 (44.4) | 10 (37.0) | 2 (4.8) | 0.009 |
| Any ENA† | 28 (29.2) | 15 (55.6) | 11 (40.7) | 2 (4.8) | 0.001 |
| Ro60 (SS-A) | 3 (3.1) | 3 (11.1) | 0 | 0 | 0.020 |
| Ro52 | 16 (16.7) | 6 (22.2) | 9 (33.3) | 1 (2.4) | 0.373 |
| RNP | 5 (5.2) | 5 (18.5) | 0 | 0 | 0.001 |
| Scl-70 | 6 (6.3) | 4 (14.8) | 2 (7.4) | 0 | 0.051 |
| Centromere | 2 (2.1) | 2 (7.4) | 0 | 0 | 0.077 |
| Ribosomal P | 1 (1.0) | 0 | 0 | 1 (2.3) | 1.000 |
| Any myositis autoantibody | 28 (29.2) | 4 (14.8) | 13 (48.1) | 11 (26.2) | 0.079 |
| Any t-RNA synthetase‡ | 13 (13.5) | 2 (7.4) | 8 (29.6) | 3 (7.1) | 0.340 |
| ANCA | 18 (18.8) | 4 (14.8) | 2 (7.4) | 12 (28.6) | 0.772 |
| MPO/PR3 | 0 | 0 | 0 | 0 | - |
| RF and/or CCP | 8 (8.3) | 5 (18.5) | 3 (11.1) | 0 | 0.038 |
| Anti-dsDNA | 4 (4.2) | 2 (7.4) | 1 (3.7) | 1 (2.4) | 0.314 |
| **Radiology** | | | | | |
| UIP | 47 (49.0) | 4 (14.8) | 7 (25.9) | 36 (85.7) | <0.001 |
| NSIP | 37 (38.5) | 18 (66.7) | 17 (63.0) | 2 (4.8) | 0.001 |
| OP | 7 (7.3) | 3 (11.1) | 3 (11.1) | 1 (2.4) | 0.397 |
| NSIP/OP overlap | 9 (9.4) | 2 (7.4) | 5 (18.5) | 2 (4.8) | 1.000 |
| Honeycombing | 42 (43.8) | 4 (14.8) | 8 (29.6) | 30 (71.4) | <0.001 |
| CTD features** | 8 (10.4) | 5 (23.8) | 3 (11.1) | 0 | 0.031 |
| **Histopathology** | | | | | |
| Available | 25 (26.0) | 5 (18.5) | 10 (37.0) | 10 (23.8) | 0.438 |
| NSIP, OP or NSIP/OP overlap | 8 (32) | 3 (60) | 5 (50) | 0 | 0.283 |
| UIP | 13 (52) | 2 (40) | 2 (20) | 9 (90) | 0.645 |

*Defined as inflammatory arthritis and/or early morning stiffness lasting ≥60 minutes.

†No autoantibodies to La/SS-B, Smith or PCNA antigens were detected and are not shown

‡Including anti-EJ, OJ, Jo-1, PL-7, PL-12 autoantibodies

**Including oesophageal dilatation, pleural-pericardial involvement, rheumatoid nodules.

Abbreviations: ANA anti-nuclear antigen; ENA extractable nuclear antigen; RNP ribonuclear protein; ANCA neutrophilic cytoplasmic antigens; MPO myeloperoxidase; PR3 proteinase 3; RF rheumatoid factor; CCP cyclic citrullinated peptide; dsDNA double stranded deoxyribonucleic acid; UIP usual interstitial pneumonia; NSIP non-specific interstitial pneumonia; OP organising pneumonia.

**Supplementary Table S4.** Comparison of frequency of clinical, serological and radiological features at baseline

| | p-value IIP v CTD | p-value IPAF v CTD | p-value IPAF v IIP |
|---|---|---|---|
| **Clinical** | | | |
| Any CTD manifestation | <0.001 | 0.05 | <0.001 |
| IPAF criteria | <0.001 | 0.001 | <0.001 |
| Mechanic's hands | 0.15 | 1.00 | 0.06 |
| Digital tip ulceration | 0.002 | 0.02 | - |
| Inflammatory arthritis | <0.001 | <0.001 | 0.15 |
| Palmar telangiectasia | 0.001 | 0.01 | - |
| Raynaud's phenomenon | <0.001 | 0.01 | 0.03 |
| Digital oedema | <0.001 | 0.18 | 0.06 |
| Gottron's papules/sign | 0.06 | 0.61 | 0.39 |
| NON-CRITERIA | | | |
| Reflux | <0.001 | 0.41 | <0.001 |
| Sclerodactyly | <0.001 | 0.001 | 0.39 |
| Proximal weakness/myalgia | <0.001 | 0.10 | 0.06 |
| Sicca | 0.02 | 1.00 | 0.01 |
| Unexplained rash | 0.002 | 1.00 | 0.007 |
| Pleurisy | 0.29 | 0.61 | 1.00 |
| **Serological** | | | |
| ANA | <0.001 | 0.78 | 0.001 |
| RF and/or CCP | 0.007 | 0.70 | 0.06 |
| Anti-dsDNA | 0.56 | 1.00 | 1.00 |
| Any ENA | <0.001 | 0.41 | <0.001 |
| Ro60 (SS-A) | 0.06 | 0.24 | - |
| Ro52 | 0.01 | 0.54 | 0.001 |
| RNP | 0.007 | 0.05 | - |
| Scl-70 | 0.02 | 0.67 | 0.15 |
| Centromere | 0.15 | 0.49 | - |
| Ribosomal P | 1.00 | - | 1.00 |
| Any myositis antibody | 0.37 | 0.02 | 0.08 |
| MSA | 0.70 | 0.04* | 0.06 |
| Any tRNA synthetase[†] | 1.00 | 0.08 | 0.02 |
| MAA | 0.47 | 0.25 | 0.75 |
| ANCA | 0.25 | 0.67 | 0.04 |
| **Radiology** | | | |
| NSIP | <0.001 | 1 | <0.001 |
| OP | 0.29 | 1.00 | 0.29 |
| NSIP/OP overlap | 0.64 | 0.42 | 0.10 |
| UIP | <0.001 | 0.50 | <0.001 |
| Honeycombing | <0.001 | 0.33 | 0.001 |
| Emphysema | 0.11 | 0.67 | 0.38 |
| CTD features** | 0.005 | 0.70 | 0.048 |
| **Histology** | | | |
| NSIP | 0.10 | 0.56 | 0.47 |
| OP | 0.33 | 1.00 | 0.47 |
| NSIP/OP overlap | - | 1 | 1 |
| UIP | 0.08 | 0.56 | 0.005 |

*Patients with positive MSA and no myopathic features classified as IPAF for purposes of the study.

[†]Including anti-EJ, OJ, Jo-1, PL-7, PL-12 autoantibodies.

[‡]No autoantibodies to La/SS-B, Smith or PCNA antigens were detected and are not shown.

**Including oesophageal dilatation, pleural-pericardial involvement, rheumatoid nodules.

Abbreviations: ANA anti-nuclear antigen; RF rheumatoid factor; CCP cyclic citrullinated peptide; dsDNA double stranded deoxyribonucleic acid; ENA extractable nuclear antigen; RNP ribonuclear protein; MSA myositis specific autoantibody; tRNA synthetase aminoacyl tRNA synthetase; MAA myositis associated autoantibody; ANCA neutrophilic cytoplasmic antigens; NSIP non-specific interstitial pneumonia; OP organising pneumonia; UIP usual interstitial pneumonia.

**Supplementary Table S5.** Treatment at baseline by ILD group

| | **TOTAL** | **CTD-ILD** | **Non-CTD ILD** | | **CTD-ILD vs non-CTD-ILD** |
|---|---|---|---|---|---|
| | **n=96** | **n=27** | **IPAF n=27** | **IIP n=42** | **p-value** |
| Any ILD treatment | 72 (75.0) | 25 (92.6) | 15 (55.6) | 32 (76.2) | 0.017 |
| Immunosuppression | 45 (46.9) | 25 (92.6) | 15 (55.6) | 5 (11.9) | <0.001 |
| Anti-fibrotic therapy | 27 (28.1) | 0 | 0 | 27 (64.3) | <0.001 |
| Nintedanib n/N(%)* | 13/27 (48.1) | – | – | 13/27 (48.1) | – |
| Pirfenidone n/N(%)* | 14/27 (51.9) | – | – | 14/27 (51.9) | – |

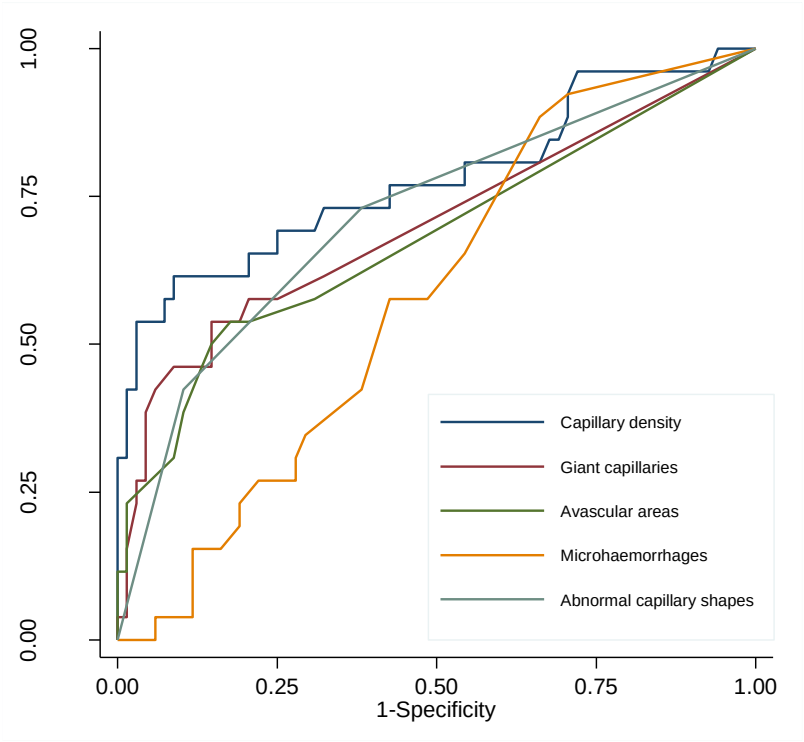
*where n/N(%) represents proportion out of patients on antifibrotic therapy.

**Supplementary Table S6.** Inter-rater reliability of nailfold characteristics

| | ICC* | 95%CI | p-value |
|---|---|---|---|
| Mean capillary density | 0.90 | 0.84–0.94 | <0.001 |
| Microhaemorrhages | 0.81 | 0.43–0.91 | <0.001 |
| Abnormal capillary shapes | 0.72 | 0.18–0.82 | <0.001 |
| Giant capillaries | 0.66 | 0.41–0.79 | <0.001 |
| Avascular areas | 0.54 | 0.13–0.74 | <0.001 |

*ICC = intraclass correlation coefficient; where values <0.5=poor, 0.5-0.75 = moderate; 0.75-0.9=good, >0.90 = excellent reliability[1]

**Supplementary Figure S7.** ROC curve analysis of NFC measures and empirical thresholds for CTD-ILD




| Nailfold characteristic | AUC* | 95%CI | Threshold† | AUC‡ | Sensitivity | Specificity |
|---|---|---|---|---|---|---|
| Density, per mm | 0.76 | 0.66–0.90 | 6 | 0.72 | 82.35 | 76.60 |
| Giant capillaries, n | 0.70 | 0.58–0.82 | 3 | 0.70 | 53.85 | 85.29 |
| Avascular areas, n | 0.68 | 0.56–0.80 | 2 | 0.68 | 53.85 | 82.35 |
| Microhaemorrhages, n | 0.61 | 0.46–0.70 | 1 | 0.61 | 92.31 | 29.41 |
| Abnormal capillary shapes, mode | 0.67 | 0.60–0.83 | 1 | 0.53 | 100 | 5.88 |

*Nailfold characteristics as a continuous measure.
†Rounded to the nearest whole number for pragmatic assessment.
‡Nailfold characteristics as a bivariate measure defined as above or below the specified threshold.

**Supplementary Table S8.** Full Exploratory multivariable models for CTD diagnosis in ILD

| | OR* | 95%CI | p-value |
|---|---|---|---|
| **Including CTD-features** | | | |
| Low density | 2.52 | 0.50–12.66 | 0.261 |
| Microhaemorrhages | 23.08 | 2.36–226.08 | 0.007 |
| CTD-features | 44.45 | 6.25–316.24 | <0.001 |
| Positive-ENA | 1.56 | 0.27–9.10 | 0.623 |
| Positive-ANA | 0.83 | 0.14–4.96 | 0.842 |
| Radiology* | 3.63 | 0.33–39.72 | 0.291 |
| Age | 1.03 | 0.94–1.14 | 0.522 |
| Sex | 0.35 | 0.06–1.99 | 0.236 |
| DLCO% | 1.01 | 0.96–1.07 | 0.610 |
| Smoking | 0.41 | 0.08–2.18 | 0.293 |
| **Excluding CTD-features** | | | |
| Low density | 4.65 | 1.31–16.44 | 0.017 |
| Microhaemorrhages | 14.77 | 1.79–121.60 | 0.012 |
| Positive-ENA | 2.68 | 0.62–11.57 | 0.187 |
| Positive-ANA | 0.86 | 0.20–3.67 | 0.839 |
| Radiology | 1.79 | 0.33–9.61 | 0.497 |
| Age | 0.95 | 0.89–1.02 | 0.192 |
| Sex | 0.46 | 0.11–1.91 | 0.288 |
| DLCO% | 1.03 | 0.99–1.07 | 0.092 |
| Smoking | 0.45 | 0.11–1.87 | 0.272 |

*OR = Odds ratio for the identification of CTD-ILD relative to non-CTD ILD; †Radiology = presence of an NSIP, OP or NSIP/OP pattern on HRCT

**Supplementary Table S9.** Frequency of qualitative NFC patterns by ILD group

| | TOTAL n=94 | CTD-ILD n=26 | IPAF n=27 | IIP n=41 | p-value CTD vs non-CTD ILD |
|---|---|---|---|---|---|
| **Ingegnoli** | | | | | |
| Normal | 39 (41.5) | 5 (19.2) | 12 (44.4) | 22 (53.7) | 0.009 |
| Minor | 25 (26.6) | 6 (23.1) | 7 (25.9) | 12 (29.3) | 0.795 |
| Major | 13 (13.8) | 4 (15.4) | 4 (14.8) | 5 (12.2) | 0.749 |
| Scleroderma | 13 (13.8) | 9 (34.6) | 2 (7.4) | 2 (4.9) | 0.001 |
| Unclassifiable* | 4 (4.3) | 2 (7.7) | 2 (7.4) | 0 | 0.306 |
| **Cutolo** | | | | | |
| Normal | 24 (45.3) | 9 (34.6) | 15 (55.6) | 32 (78.1) | 0.004 |
| Early | 12 (22.6) | 5 (19.2) | 7 (25.9) | 6 (14.6) | 1.000 |
| Active | 11 (20.8) | 7 (26.9) | 4 (14.8) | 2 (4.9) | 0.041 |
| Late | 3 (5.7) | 3 (11.5) | 0 | 1 (2.4) | 0.063 |
| Unclassifiable* | 3 (5.7) | 2 (7.7) | 1 (3.7) | 0 | 0.184 |
| **Maricq** | | | | | |
| Normal | 45 (47.9) | 6 (23.1) | 13 (48.2) | 26 (63.4) | 0.005 |
| Non-specific | 25 (26.6) | 6 (23.1) | 8 (29.6) | 11 (26.8) | 0.795 |
| Scleroderma | 22 (23.4) | 13 (50) | 5 (18.5) | 4 (9.8) | 0.001 |
| Unclassifiable* | 2 (2.1) | 1 (3.9) | 1 (3.7) | 0 | 0.479 |
| **EULAR SG-MC consensus** | | | | | |
| Non-scleroderma | 24 (45.3) | 9 (34.6) | 15 (55.6) | 32 (78.1) | 0.004 |
| Scleroderma | 38 (40.4) | 17 (65.4) | 12 (44.4) | 9 (22.0) | 0.004 |

*Unclassifiable by specified criteria

Abbreviations: CTD-ILD connective tissue disease associated ILD; IPAF interstitial pneumonia with autoimmune features; IIP idiopathic interstitial pneumonia; EULAR SG-MC European League Against Rheumatism Study Group on Microcirculation in Rheumatic Disease

**Supplementary Table S10.** Clinical details of non-CTD ILD patients with a scleroderma or active/late NFC pattern across pre-specified qualitative criteria

| Patient | ILD group | ILD-MDM working diagnosis | Serology positive* | HRCT pattern | Atypical HRCT? | Clinical CTD manifestations† |
|---|---|---|---|---|---|---|
| 1 | IIP | NSIP | No | NSIP | Yes | No |
| 2 | IIP | IPF | Yes | UIP | No | No |
| 3 | IPAF | SSc-ILD | Yes | NSIP | Yes | Yes |
| 4 | IPAF | Anti-synthetase ILD | Yes | UIP | Yes | Yes |

Above patients classified as a "scleroderma pattern" by Ingegnoli , Maricq and EULAR SC-MG consensus, and an "active/late pattern" by Cutolo criteria on qualitative assessment [2-5].

*Serology positive as per IPAF criteria.

†Any of inflammatory arthritis, early morning stiffness, Raynaud's phenomenon, digital oedema, palmar telangiectasia, digital tip ulceration, mechanic's hands, Gottron's papules/sign, sclerodactyly.

‡ANCA positive on historical result, repeat baseline test negative

◊Histopathological UIP confirmed on lung biopsy

Abbreviations: EULAR SG-MC European League Against Rheumatism Study Group on Microcirculation in Rheumatic Disease; ILD-MDM ILD multidisciplinary meeting; IIP idiopathic interstitial pneumonia; IPAF interstitial pneumonia with autoimmune features; IIM-ILD idiopathic inflammatory myositis associated ILD; UIP usual interstitial pneumonia; NSIP non-specific interstitial pneumonia; OP organising pneumonia

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