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		

Inggnoli 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)	–

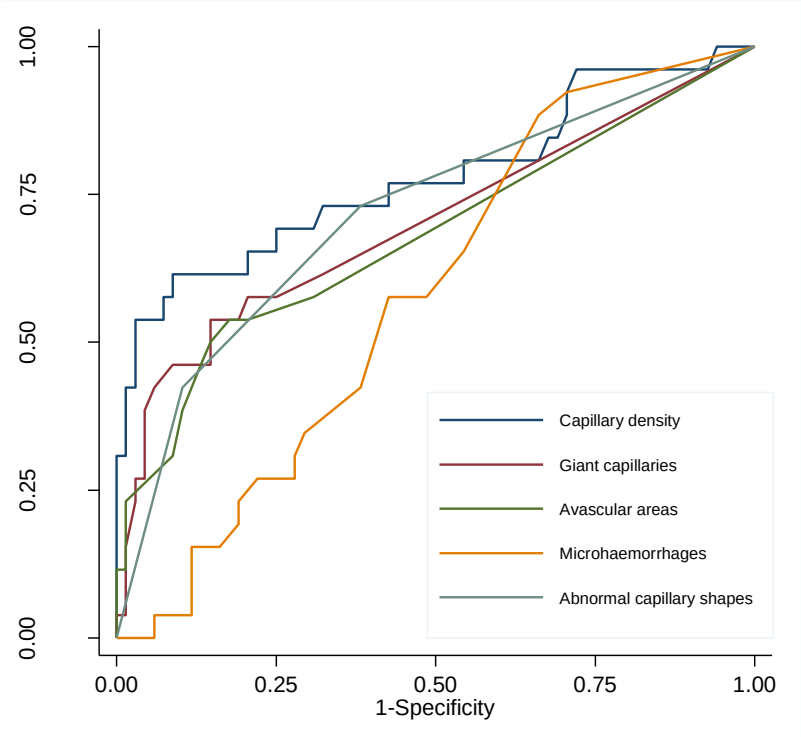
*where n/N(%) represents proportion out of patients on antifibrotic therapy.

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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