Supplementary Appendix

Pulmonary Function Protocol

Pulmonary function tests (PFT) were analysed if performed within 3 months of the corresponding CT scan according to established protocols (25). Spirometry (Jaeger Master screen PFT, Carefusion Ltd., Warwick, UK and Houten, NL, Alpha Spirometer; Vitalograph, Buckingham, UK), plethysmographic lung volumes (Jaeger Master screen Body, Carefusion Ltd., Warwick, UK and Houten, NL), and diffusion capacity for carbon monoxide (Jaeger Master screen PFT, Carefusion Ltd., Warwick. UK and Houten, NL). Parameters assessed: forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and single breath carbon monoxide diffusing capacity corrected for hemoglobin concentration (DLco). The composite physiologic index (CPI) was calculated using the formula: 91·0 - (0·65 x % predicted DLco) - (0·53 x % predicted FVC) + (0·34 x % predicted FEV1). (26)

CT Protocol

CT scans at the Royal Brompton Hospital were obtained using a 64-slice multiple detector CT scanner (Somatom Sensation 64; Siemens, Erlangen, Germany) or a 4-slice multiple-detector CT scanner (Siemens Volume Zoom; Siemens, Erlangen, Germany). All images were reconstructed using a high spatial frequency, B70 kernel (Siemens, Munich, Germany). CT scans at the St. Antonius Hospital, Nieuwegein, were obtained using a 64-slice multiple detector CT scanner (Phillips Brilliance 64; Cleveland, Ohio, USA) or a 256-slice multiple-detector iCT scanner (Phillips, Cleveland, Ohio, USA). All images were reconstructed using C, EC, L or YC kernels (Phillips, Cleveland, Ohio, USA). CT images at Edinburgh Royal Infirmary were acquired using a high-resolution CT (HRCT) scanner (Aquilion One [Toshiba Medical Systems, Toshiba Corp] or Somatom Volume Zoom [Siemens AG]). The following kernals

were used for the CT imaging reconstructions: Siemens (B20f, B60f, B60s or I70f\3), General Electric (Bone, Lung) and Toshiba (FC03, FC07, FC12 and FC51). The Siemens B80 algorithm was markedly edge-enhancing and resulted in misclassification of parenchymal features such as honeycombing by CALIPER. As a result, CT imaging reconstructed with the Siemens B80 algorithm (St Antonius n=6, Edinburgh Royal Infirmary n=3) were excluded from the study.

All patients were scanned from lung apices to bases, at full inspiration, using a peak voltage of 120 kVp with tube current modulation (range, 30 to 140 mA). Images of 0.5-2mm thickness were viewed at window settings optimized for the assessment of the lung parenchyma (width 1500 HU; level -500 HU).

Variable	Royal Brompton Cohort (n=90)	Edinburgh Royal Infirmary Cohort (n=67)	Cohort differences
Median Age (range)	64 (38-85)	67 (30-85)	0.03^
Male/female	43/47	28/39	0.46*
Survival (alive/dead)	48/42	55/12	0.0002*
Never smokers/ever-smokers (n=230)	27/57	18/48	0.52*
Honeycombing presence (N/Y)	48/42	50/17	0.006*
FEV1 % predicted	70.2 ± 19.5 (87)	91.5 ± 18.5 (67)	<0.0001
FVC % predicted	74.8 ± 22.9 (87)	97.0 ± 19.4 (67)	<0.0001
FEV1/FVC % predicted	96.3 ± 16.2 (83)	94.7 ± 9.8 (67)	0.50
DLco % predicted	40.9 ± 15.8 (84)	58.7 ± 15.1 (47)	<0.0001
CPI	48.6 ± 15.8 (81)	31.9 ± 12.1 (47)	<0.0001
Visual CT scores (%)			
Total ILD extent	31.3 ± 19.0	16.7 ± 8.5	<0.0001
Emphysema extent	7.9 ± 13.4	7.5 ± 10.2	0.86
Honeycombing extent	5.2 ± 9.3	0.4 ± 1.0	0.00004
TxBx severity (max score 18)	8.7 ± 4.0	6.4 ± 2.5	0.0001
CALIPER CT scores (%)			
Total ILD extent	18.0 ± 16.9	12.5 ± 14.1	0.03
Emphysema extent	2.2 ± 7.8	3.0 ± 5.3	0.45
Honeycombing extent	1.2 ± 2.7	0.4 ± 0.7	0.02
Vessel-related structures	4.5 ± 1.8	3.4 ± 1.5	0.0001

Supplementary Table S1. Patient age, gender and mean and standard deviations of pulmonary function indices and visually scored CT parameters in patients with rheumatoid arthritis-related interstitial lung disease subdivided according to study centre. Data represent mean values with standard deviations. Comparisons were made with the Students t-test, unless indicated: ^=Mann Whitey U test, *=Chi-squared test. FEV1=forced expiratory volume in one second, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, CPI=composite physiological index, ILD=interstitial lung disease, TxBx=traction bronchiectasis.

Visual CT Variable	Single determination standard deviation
CT Interstitial lung disease extent	3.95
CT Ground glass opacity	3.49
CT Reticular pattern	4.01
CT Honeycombing	2.08
CT Total emphysema	3.47
CT Traction bronchiectasis	1.74

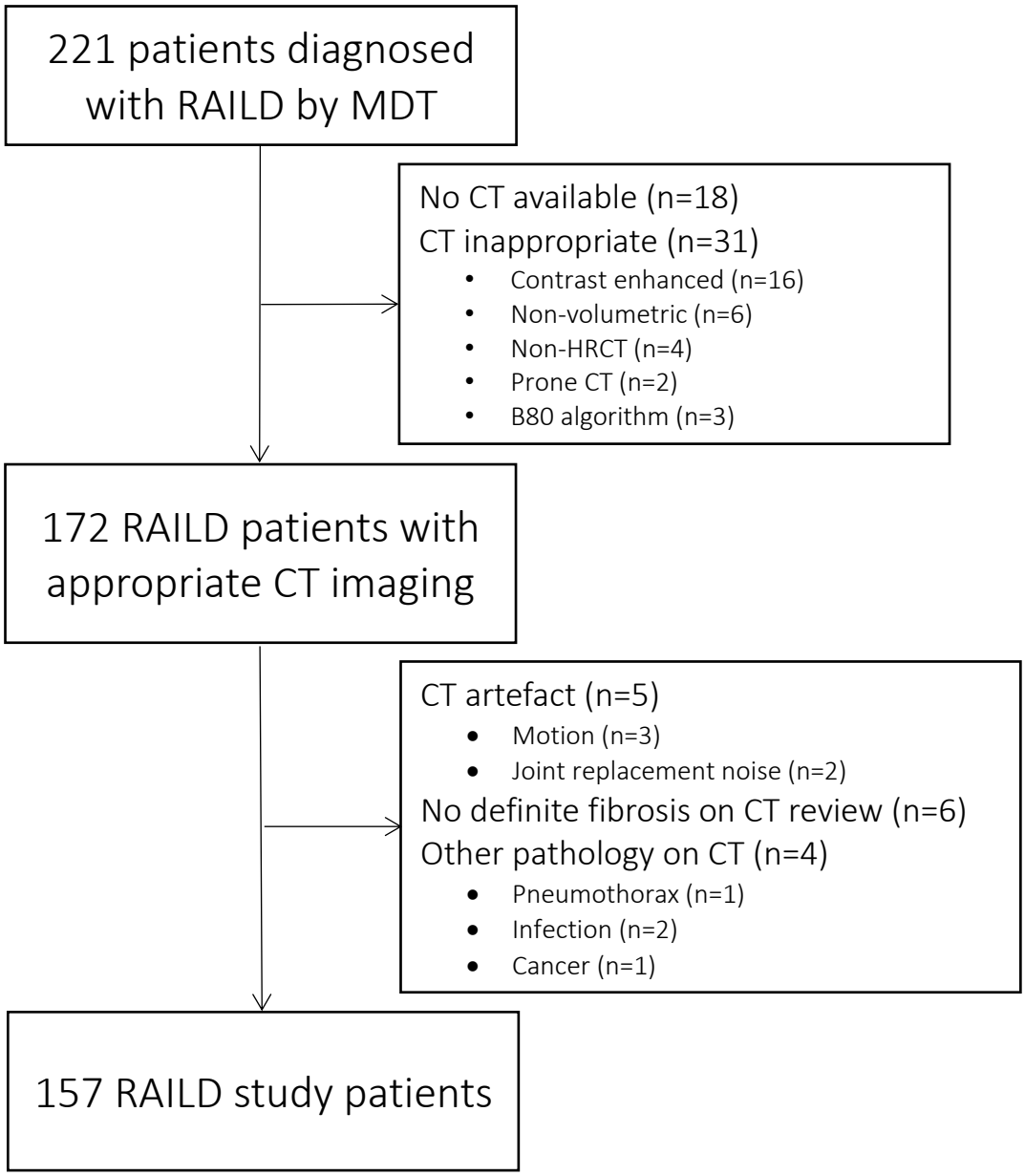
Supplementary Table S2. Variation in visual scores of CT parenchymal patterns between the two scorers for the rheumatoid arthritis-related interstitial lung disease patients, calculated using the single determination standard deviation. CT = computed tomography.

Variable	RAILD Cohort (n=157)	IPF Cohort (n=284)	Cohort differences
Median Age (range)	65 (30-85)	69 (37-92)	0.004^
Male/female	71/86	225/59	<0.0001*
Survival (alive/dead)	103/54	95/189	<0.0001
FVC % predicted	84.4 ± 24.1 (154)	74.2 ± 19.5 (283)	<0.0001
Visual ILD extent	25.1 ± 17.0	29.1 ± 12.1	0.01
Visual TxBx severity (max score 18)	7.7 ± 3.6	10.2 ± 3.2	<0.0001
CALIPER ILD extent	15.7 ± 16.0	23.5 ± 16.3	<0.0001
CALIPER Vessel-related structures	4.0 ± 1.8	5.3 ± 1.7	<0.0001

Supplementary Table S3. Patient age, gender and mean and standard deviations of forced vital capacity (FVC) and visually and CALIPER scored CT parameters in patients with rheumatoid arthritis-related interstitial lung disease (RAILD, Column 1), and idiopathic pulmonary fibrosis (IPF, Column 2). Data represent mean values with standard deviations. Comparisons were made with the Students t-test, unless indicated: ^=Mann Whitey U test, *=Chi-squared test. FVC=forced vital capacity, ILD=interstitial lung disease, TxBx=traction bronchiectasis.

Variable	Hazard ratio	95.0% Confidence Interval		P Value
		Lower	Upper	
Age	1.05	1.02	1.08	0.001
Male Gender	1.09	0.61	1.95	0.78
Smoking (never vs ever)	2.97	1.45	6.09	0.003
Scleroderma System	3.80	1.90	7.63	0.0002
4.4% VRS Threshold	2.43	1.28	4.60	0.007
Age	1.03	1.00	1.06	0.06
Male Gender	1.29	0.72	2.28	0.39
Smoking (never vs ever)	2.05	1.02	4.10	0.04
Fleischner System	1.65	1.14	2.40	0.008
4.4% VRS Threshold	3.93	2.21	7.02	<0.0001
Age	1.04	1.01	1.07	0.008
Male Gender	1.08	0.60	1.94	0.80
Smoking (never vs ever)	2.69	1.32	5.51	0.007
Progressive Fibrotic System	2.19	1.45	3.31	0.0002
4.4% VRS Threshold	2.57	1.36	4.87	0.004

Supplementary Table S4. Multivariable Cox regression analysis demonstrating mortality in patients with rheumatoid arthritis-related interstitial lung disease. Three staging systems (Scleroderma System, Fleischner System and Progressive Fibrotic System) were compared to the CALIPER vessel-related threshold (VRS) of 4.4% of the lung, after adjustment for patient age, gender and smoking status (never versus ever).



Supplementary Figure S1. CONSORT diagram illustrating the selection of rheumatoid arthritis-related interstitial lung disease (RAILD) patients for the study. CT = computed tomography.