Supplementary materials

Computed tomography (CT) features suggestive of vasculopathy

Apparent interstitial lung abnormalities on HRCT were interpreted as suggestive of vasculopathy, when the following findings were observed: 'either diffuse centrilobular ground glass opacities or non-subpleural conspicuous interlobular septal thickening, in the absence of HRCT features of fibrotic lung disease (e.g. honeycombing, subpleural reticulation with traction bronchiectasis)', adopting the description proposed for SSc-associated pulmonary veno-occlusive disease [1, 2]. As indirect support for the presence of a predominant vasculopathy in the 40 excluded patients, a "vascular" lung function profile was observed in this group [3], with an isolated marked reduction in DLco % (mean value 49.52 ± 23.99%) and preserved lung volumes (FVC%: mean value 91.01±27.88%), as expected for patients with little or no ILD and predominant pulmonary vasculopathy.

CT Protocols

The CT scans were obtained using a 64-slice multiple detector CT scanner (Somatom Sensation 64, Siemens, Erlangen, Germany, at Royal Brompton Hospital; GE light speed VCT 64, GE healthcare, US , at Ancona Hospital) or a 4-slice multiple detector CT scanner (Siemens Volume Zoom, Siemens, Erlangen, Germany).

All patients were scanned from lung apices to bases, supine, at full inspiration, with 1· 0 mm section thicknesses using a peak voltage of 120kVp with tube current modulation (range 30-140 mA). Images were viewed at window settings optimized for the assessment of the lung parenchyma (width 1500 H.U.; level -500 H.U.).

Qualitative and quantitative assessment of total ILD extent, PPFE features and airways abnormalities

i) Total interstitial lung disease extent scoring:

ILD extent on HRCT was scored using a continuous scale at five representative axial levels. The chosen anatomical levels included: (1) the origin of the great vessels from the aorta, (2) the main carina, (3) the pulmonary venous confluence, (4) a point halfway between level 3 and 5, (5) immediately above the dome of the right hemidiaphragm. At each level, the total extent of ILD was

estimated to the nearest 5%. The extent of PPFE was not included in the total ILD extent. The scores for the five sections were averaged to generate overall ILD extent.

ii) PPFE scoring

The presence of PPFE was identified on a lobar basis according to previously defined CT criteria [4]. PPFE extent was scored on a 4-point categorical scale as: 0 = absent, 1 = mild, affecting < 10% of the pleural surface, 2 = moderate, affecting 10–33% of the pleural surface, 3 = severe, affecting > 33% of the pleural surface. Lobar PPFE scores were summed for each patient to create an overall 18-point (potential scores of 0–18) scale for total PPFE. Severity of total PPFE scores was categorized as follows: limited = ≤2; extensive >2 (examples reported in Figure 2 A-B) [5].

iii) Airway scoring and emphysema

Freestanding bronchial abnormalities (in areas separate from the PPFE and from ILD changes), were evaluated on a three-point categorical scale, using the following scoring system: bronchial wall thickening: 0 = absent, 1 = mild, 2 = severe; bronchial dilatation: 0 = absent, 1 = dilatation not reaching CT criteria for bronchiectasis, 2 = dilatation reaching CT criteria for bronchiectasis [5-8]

Emphysema extent was assessed on a three-point categorical scale, as follows:0 = absent, 1 =trivial (<10%), 2 = moderate/severe (≥ 10%) [9,10]. Pleural thickening was evaluated on a three-point categorical scale:0 = absent, 1 = 25%, 2 = ≥ 25%.

The presence/absence of an obvious suprasternal depression was also recorded.

iii) Consensus formulation

Given that PPFE is a relatively new radiological sign, deriving a consensus for the PPFE scores of the two radiologists was achieved with a third experienced scorer (S.P.) with over 15 years of thoracic imaging experience. Any case in which only one of the original two scorers had identified PPFE features in the lungs (presence versus absence of PPFE) was arbitrated by the third scorer. Furthermore, any case with maximum lobar PPFE extent <10% (Grade 1/trivial PPFE) by both scorers was also consensed by the third scorer to avoid over-estimation of PPFE. Once a consensus for all the lobar scores had been reached, the lobar scores were summed for each patient (PPFE extent).

Goh et al staging system evaluation:

HRCT disease extent thresholds of 10% and 30% is used to identify patients readily classifiable as having limited or extensive disease (HRCT ≤ 10%: limited; HRTC extent > 30%: extensive).When HRTC disease extent lay between 11 and 30%, a threshold of FVC levels (< or ≥70% predicted) is used for classifying as limited or extensive disease. In other words, in presence of a HRCT disease

extent between 11 and 30%, the disease is defined as limited if FVC is ≥ 70% predicted, while as extensive if FVC is <70% predicted [11].

Comparison between cohort excluded due to the absence of HRCT and included cohort

To explore potential selection bias, we compared lung function parameters between patients excluded due to the absence of HRCT (n=261) and those included (N= 359), and we did not find substantial differences. Mean FVC% predicted and mean DLco% predicted were respectively 82.06 (±23.34) % and 54.01 (±19.09)% in the excluded cohort and not significantly different from those of included cohort (mean values FVC% 78% and Dlco 50%; p=0.3).

Comparison of CPI values at baseline according to treatment status

CPI of "intention to treat" subgroup: 51.10 ± 14.96; CPI of "Intention to observe" subgroup: 31.47 ±13.72; p <0.00001

FEV1 and Tiffenau values in subjects with freestanding bronchial abnormalities

FEV1 % predicted mean value: 79.94 ±21.81

Tiffenau (FEV1/FVC) mean value: 0.95 ± 0.14

Type of treatment at baseline *	**Whole cohort (n=317)**	**RBH cohort (n=186)**	**Ancona cohort (n=131)**
None	150 (48)	40 (21)	110 (85)
Oral corticosteroids only	43 (14)	37 (19)	6 (4)
Conventional Immunosuppressants only **	39 (12)	36 (20)	3 (2)
Biologics only ***	8 (2)	4 (2)	4 (3)
Oral corticosteroids + conventional immunosuppressants	77 (24)	69 (38)	8 (6)

Table 1 S. Type of treatment of the whole cohort and by center

* Treatment at baseline was considered the treatment instituted within 3 months since or continuation of pre-existing treatment up to three months

**Cyclophosphamide, methotrexate, mycophenolate, azathioprine, hydroxychloroquine, ciclosporin

*** Rituximab, Infliximab, Imatinib

Table 2.S. Mortality, expressed as hazards ratio with 95% confidence intervals, in relation to baseline data (univariable analysis)

	Univariable analysis		
Characteristics	**HR**	**95%CI**	***p***
PPFE	1.57	1.02-2.40	0.04
- *PPFE limited*	1.54	0.78-3.05	0.21
- *PPFE extensive*	1.42	0.89-2.31	0.16
Age (yrs)	1.03	1.02-1.05	<.0001
Gender (female)	1.97	1.32-2.93	0.0008
Cohort (Italian)	0.37	0.24-0.58	<.0001
% predicted FVC	0.97	0.96-0.98	<.0001
% predicted DLco	0.95	0.94-0.96	<.0001
ILD extent	1.02	1.01-1.03	<.0001
CPI	1.05	1.03-1.06	<.0001
Goh et al staging system	2.31	1.52-3.52	<.0001
Smoking history	1.06	0.71-1.56	0.76
Active treatment	2.62	1.72-4.00	<.0001

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