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RESEARCH

Diagnosis of interstitial lung disease (ILD) secondary to systemic sclerosis (SSc) and rheumatoid arthritis (RA) and identification of 'progressive pulmonary fibrosis' using chest CT: a narrative review

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Abstract
Interstitial lung disease (ILD) is a frequent manifestation of connective tissue diseases (CTDs), with incidence and prevalence variously assessed in the literature but reported in up to 30% of patients, with higher frequency in rheumatoid arthritis (RA) and systemic sclerosis (SSc). Recent years have seen a growing interest in the pulmonary manifestations of ILD-CTDs, mainly due to the widening of the use of anti-fibrotic drugs initially introduced exclusively for IPF, and radiologists play a key role because the lung biopsy is very rarely used in these patients where the morphological assessment is essentially left to imaging and especially HRCT. In this narrative review we will discuss, from the radiologist's point of view, the most recent findings in the field of ILD secondary to SSc and RA, with a special focus about the progression of disease and in particular about the 'progressive pulmonary fibrosis' (PPF) phenotype, and we will try to address two main issues: How to predict a possible evolution and therefore a worse prognosis when diagnosing a new case of ILD-CTDs and how to assess the progression of an already diagnosed ILD-CTDs.

Keywords Intersitial lung disease · Pulmonary fibrosis · Connective tissue disease · Systemic sclerosis · Rheumatoid arthritis · Chest CT

Introduction

Connective tissue diseases (CTDs) are an important cause of interstitial lung disease (ILD), up to 30% of the cases, with a significant higher frequency in rheumatoid arthritis (RA) and systemic sclerosis (SSc); their clinical manifestations can be very significant, even with multi-compartmental involvement (e.g. interstitium, pleura, pulmonary arteries), and affect patients' survival [1]. CTD fibrosing lung diseases are included by pathologists in the group of secondary fibrosis, as well as fibrotic hypersensitivity pneumonitis (fHP) and others, and the thoracic manifestations may precede the onset of other signs and symptoms, such as skin, digestive and joint manifestations [2]. Incidence and prevalence of ILD-CTDs are variously assessed in the literature, depending on whether they are detected by clinical-functional tests or by imaging. Imaging assessment by HRCT is generally the most used option, considering the lack of sensitivity and specificity of chest radiography and since it can reveal the presence of ILD before pulmonary function tests (PFTs) become positive [2]. Likewise, the extension assessment based on lung ultrasound proposed in the literature [3–5] is neither less subjective nor more specific than the HRCT assessment, moreover, it has been applied almost only on SSc-ILD where it demonstrates its limitations the most, as in SSc the prevalent pattern is characterised, in 20–50% of cases, by reticulations that spare the visceral pleura and therefore cannot be detected with ultrasound [4, 5].

Also, in the assessment of progression, PFTs are probably less accurate than HRCT scores, and present problems of interpretation and reproducibility, as well as various limitations (e.g. in case of multi-compartmental pathology), so that they should always be combined with all available evidence. HRCT and PFTs, however, give distinct and complementary information with the best correlation between HRCT scores and DLCO [2, 6]. The assessment of progression of disease is one of the main issues in approaching these patients because, though ILD-CTD have a relatively

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slower and less aggressive course than idiopathic forms, also in these patients it is possible the development of progressive pulmonary fibrosis (PPF) characterized by a rapid deterioration of respiratory function and significant increase in mortality [7].

In this narrative review, we will refer to the two main forms of ILD-CTD, those secondary to RA and SSc, and we will discuss from the radiologist's point of view the most relevant findings reported in literature in the last years. In particular, we will focus on the diagnosis and quantification of lung involvement with special attention to the progression of disease and the progressive pulmonary fibrosis (PPF) pattern.

Incidence and radiologic features of ILD-CTD

As mentioned above, incidence and prevalence of ILD-CTDs are variously assessed in the literature.

In RA, ILD is reported in 8–20% of cases and an interstitial lung abnormality (ILA), which may precede the development of true ILD, in 20% [6]; RA-ILDs are mainly observed in males, elderly and with a history of smoking [8]. At four years after diagnosis, 40% of cases are progressive but cases of 'long-term stability' are also reported [6]. In RA, the pattern 'UIP-typical' is the most common and is associated with a lower 6-year survival compared to cases with non-UIP pattern [9]. Usually, according to several Authors [10–13], RA-associated UIP has a less aggressive clinical course than UIP secondary to Idiopathic pulmonary fibrosis (IPF). About twenty years ago, a pathological study showed that patients with CTD and UIP patterns have fewer fibroblastic foci than those with UIP/IPF, and this observation could explain the relatively more benign evolution [14].

In SSc, the presence of ILD is even more common ($\geq 80\%$); in addition, pulmonary hypertension (PH), also in the absence of diffuse lung disease, can be demonstrated by cardiac catheterisation in 10% of cases. These conditions are the two main prognostic factors for SSc patients, in fact 40% of deaths in SSc are attributable to pulmonary pathology [15]. In 20% of patients with SSc, PFTs are still within normal range at the time of diagnosis but HRCT is already positive. 20% of SSc-ILDs turn out to have a progressive course [16].

In SSc-ILDs, the 'UIP probable' pattern prevails, which generally corresponds to a pathologic fibrosing NSIP pattern but cases with a typical or even mixed UIP pattern (UIP in one lung, NSIP in the other) are also reported [17, 18]. Cases with UIP patterns have a prognosis similar to that observed in RA but even here, cases of 'long-term' stability can be observed [2, 17–20]. The absence of ILD at the time of diagnosis in SSc is considered a favourable prognostic factor, because these patients remain free of lung disease in about 90% of cases [21].

It is important to highlight that the morphological assessment is essentially left to imaging, and mainly to HRCT, as lung biopsy is rarely performed in ILD-CTDs. In principle, this activity is similar to that required in idiopathic ILDs, except for a few particular aspects [2, 22] that allow the radiologist to point towards the diagnosis of CTD, in addition to well-known accessory signs such as oesophageal or pleural pathology. Recently, three HRCT signs suggestive of fibrosis CTD-related have been described: *Exuberant honeycombing*, (defined as extension of honeycombing greater than 70% of fibrotic portion of the lung), *anterior upper lobe fibrosis* (defined as concentration of fibrosis within the anterior aspect of the upper lobes) and the *straight-edge sign* (defined as isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane), all of which are more specific than sensitive [23, 24].

The prevalent pattern and other main HRCT features are summarized in Table 1.

Table 1 HRCT prevalent patterns and ancillary findings in ILD secondary to RA and SSc

HRCT features	RA	SSc
Prevalent pattern	*UIP-typical* honeycombing with or without traction bronchiectasis/bronchiolectasis; subpleural and basal predominant; distribution often heterogeneous, occasionally diffuse	*UIP-probable* reticular pattern with peripheral traction bronchiectasis/bronchiolectasis; may have mild GGO; subpleural and basal predominant; distribution often heterogeneous *NSIP* higher extent of GGO and lower extent of reticulation, more uniform and diffuse distribution, may be peribronchovascular predominant with subpleural sparing
Ancillary findings	Exuberant honeycombing Anterior upper lobe fibrosis Rheumatoid nodules Airway disease with bronchiolitis Pleural effusion (rheumatoid pleuritis)	Straight edge sign Pulmonary hypertension Esophageal dilatation May develop PVOD

HRCT High-resolution computed tomography; *RA* Rheumatoid arthritis; *SSc* Systemic sclerosis; *UIP* Usual interstitial pneumonia; *NSIP* Non-specific interstitial pneumonia; *GGO* Ground-glass opacity; *PVOD* Pulmonary veno-occlusive disease

Progression and quantification of ILD-CTD

The great renewed interest in pulmonary manifestations of CTDs arises from the fact that anti-fibrotic drugs, initially introduced for UIP/IPF, can probably be used with similar effects in ILD-CTDs (slowing down functional decline) [25–27]. There are also those who support the use of antifibrotics treatment before functional decline is even apparent [27], but the evidence to date is rather weak and based on heterogeneous series [28]. The definition of these forms also varies between Authors, often based on arguable and rather arbitrary criteria. For example, in the INBUILD study, participants had to have an HRCT score of fibrosis of at least 10% of lung volume to be enrolled [16, 29]. However, the drift that the literature has taken in this area, which is now enthusiastic, is hardly compatible with repeated observations, rigorous controls and in-depth reflections, e.g. on specific mortality in randomised groups with or without antifibrotic therapy [16, 30]. The assessment of the presence, severity and progressive nature of ILD-CTD, as for idiopathic forms, can no longer be left to a single specialist, however experienced. Here too, multidisciplinary discussion (MDD) must be used, which has its limitations but has proved to be until today an irreplaceable tool [31].

Regarding progression, we can imagine two types of scenarios that we will try to describe from the radiologist's point of view.

What characteristics can help us to predict a possible evolution, and therefore a worse prognosis, when diagnosing a new case of ILD-CTD or an IPAF (interstitial pneumonia with autoimmune features), which evolves into an overt ILD in 20% of cases?

Presence of a UIP-pattern at HRCT [8, 32]

As already mentioned, CTD-related UIPs often include less aggressive forms than idiopathic ones, which are characterised by 'long-term stability' [20]. In this regard, however, there are some clarifications to be made and open problems. In IPF, there is a tendency to give traction bronchiolectasis and bronchiectasis the same value as honeycombing, with a 'de facto' unification of UIP-typical and UIP-probable forms of fibrosis but, concerning idiopathic forms, there is not full agreement in the literature. (In fact, the prognosis of UIP-probable fibrosis, in particular of fibrotic NSIPs, remains better than that of UIP-typical pattern.) This assessment in ILD-CTDs is even more complicated [33, 34], in particular it is unclear what prognostic value should be given to cases in which there is a discordance between pattern and extent of disease (e.g. UIP pattern, usually associated to a worse prognosis, with < 10% extent, usually associated to a better prognosis).

Presence of emphysema

The combination of pulmonary fibrosis and emphysema (CPFE) in CTDs, as in idiopathic forms, increases the risk of mortality and reduces survival [35].

Extension of ILD at baseline HRCT [8, 27]

The principle is that it is likely that patients who have extensive disease at the baseline HRCT (i.e. those with more advanced forms at the onset) are also at higher risk of progression and have a worse prognosis [36]. But the problem is: How to assess this extension? Among the quantitative computed tomography (QCT) software, those based on texture analysis, such as CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Ratings), seem to be the most promising, overcoming the limitations of those based on threshold-analysis, which do not discriminate different parenchymal alterations characterised by the same attenuation range (e.g. reticulations and consolidations), thanks to the possibility of extracting different morphological aspects that characterise lung pathologies [37, 38]. The main advantages of QTC tools are the ability to objectively and reproducibly quantify the presence of lung pathology, along with its spatial distribution, even before PFTs abnormalities are evident; moreover, QTC would appear to perform better than radiologist's visual analysis in quantifying small variations in the extent of disease [37]. However, the applications of artificial intelligence and deep learning are still limited to a few research centres, particularly the use of the CALIPER programme [39], and in daily clinical practice, the visual score (VS) method is still widely used. The VS can be obtained by dividing each lung into four zones (lung apex to aortic arch/aortic arch to carina/carina to right inferior pulmonary vein / right inferior pulmonary vein to lung bases) and evaluating the extent of lung abnormalities in each zone for each side using a 5-point scale (0: no involvement/1: 1–25% involvement/2: 26–50%/3: 51–75%/4: 76–100%); the average score corresponds to the final score, that is expressed as a percentage of total lung volume. The VS presents a certain interobserver variability, however with an acceptable value of $K = 0.4–0.58$; 0.56–0.65 according to several Authors [17, 40]. Moreover, it is known that the UIP pattern at HRCT can be caused by different pathologies, especially NSIP but also fibrosing hypersensitivity pneumonitis (fHP) and sarcoidosis [41–43]. Best results can be obtained with a double reading, final agreement in case of discordance between the two initial readings and a rigorous study methodology, including side-by-side comparison with previous HRCT examinations.

On the other hand, functional tests and multidimensional scores, such as the GAP index (gender, age,

physiology), initially proposed for IPF, demonstrated usefulness in the evaluation of prognosis in large cohorts [17] but have not yet been shown to reliably quantify the risk in individual patients, as pointed out by Wells et al. [43]. Many other scores, including HRCT assessment and radiological indices employing more or less accurate quantitative assessment have been proposed in the literature [6, 19, 35, 44–46]; of these, the most widely used is Goh's composite score, initially developed to assess the progression of SSc-ILD but also used in patients with other CTD, such as RA and Sjogren syndrome [33]. However, even this score is limited by a certain intra- and interobserver variability.

A large extent of interstitial disease at diagnosis and the UIP-pattern thus have an unfavourable prognostic value. On the other hand, a normal HRCT at the time of diagnosis of a CTD, and in particular of an SSc, has a favourable prognostic value because it makes the subsequent development of ILD less likely [2]. More than 50% of SSc patients with visible interstitial disease on the initial HRCT still have spirometry within normal ranges. In turn, PFTs are moderately sensitive, rather non-specific and may be inaccurate in various situations, for example are limited in the evaluation of multi-compartmental pathology (e.g. restrictive physiology as a result of pulmonary, pleural and musculoskeletal involvement) [47]; furthermore, during follow-up, it is difficult to detect variations in PFTs of the order of 5–10%.

How can we assess the progression of an already diagnosed ILD-CTD?

In this scenario, the issue is to identify cases of interstitial progressive fibrosis CTD-related (PF-CTDs), accounting for about 30% of all ILD-CTDs, with an average survival of 60% at 5 years, but the frequency of PF is higher in RA and SSc [17, 44].

The progression criteria are similar to those applied in IPF [13, 48]. At least two out of three criteria must be fulfilled in the last year, in the absence of alternative causes: Worsening of symptoms (not better defined), worsening of PFTs, with the limitations we mentioned above and worsening of HRCT [49]. From a radiological point of view, the progressive pulmonary fibrosis (PPF) phenotype is characterised by an increase in the extent of disease at HRCT, by VS, of 10% or more to compensate for interobserver variability [3] (Figs. 1, 2 and 3) but recent guidelines recommend to use only a visual score, without any quantitative automatic quantification [49]. It should be recommended to compare the current HRCT not only with the immediate previous study but also with studies further back in time, to better detect small variations, always at the same anatomical levels. Recent studies report that among the clinical, functional and radiological criteria for PPF, the most reliable parameter, even in non-IPF ILDs, remains a decline in FVC $\geq$ 5%, which has been found to be the strongest predictor of a reduced transplant-free survival (TFS) [48, 50]. However, in the absence of such a

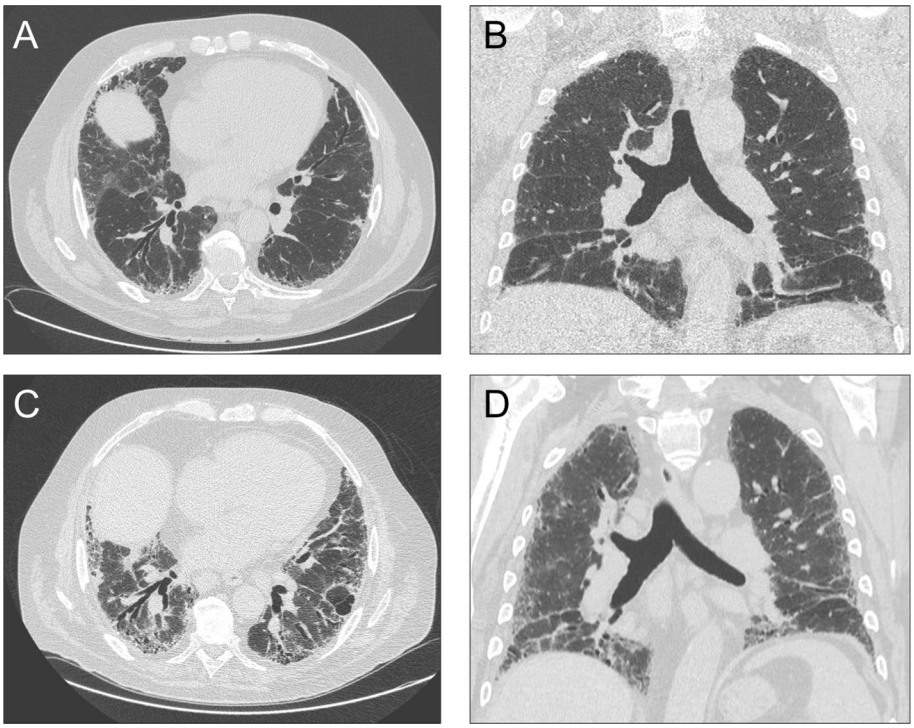

Fig. 1 A 66-year-old man with systemic sclerosis. Axial (**A**) and coronal (**B**) chest HRCT images obtained at the time of diagnosis show mild reticular interstitial thickening prevailing in subpleural regions of lower lobes associated to small traction bronchiectasis (UIP-probable pattern); CT images at the same level at 3-year follow-up **C** and **D** show reduction in lung volume associated to significant increase of septal thickening, interstitial reticulations and GGO with appearance of small subpleural microcysts in the dorsal regions of the lower lobes suggestive of initial honeycombing, evolution compatible with progressive pulmonary fibrosis (PPF) phenotype

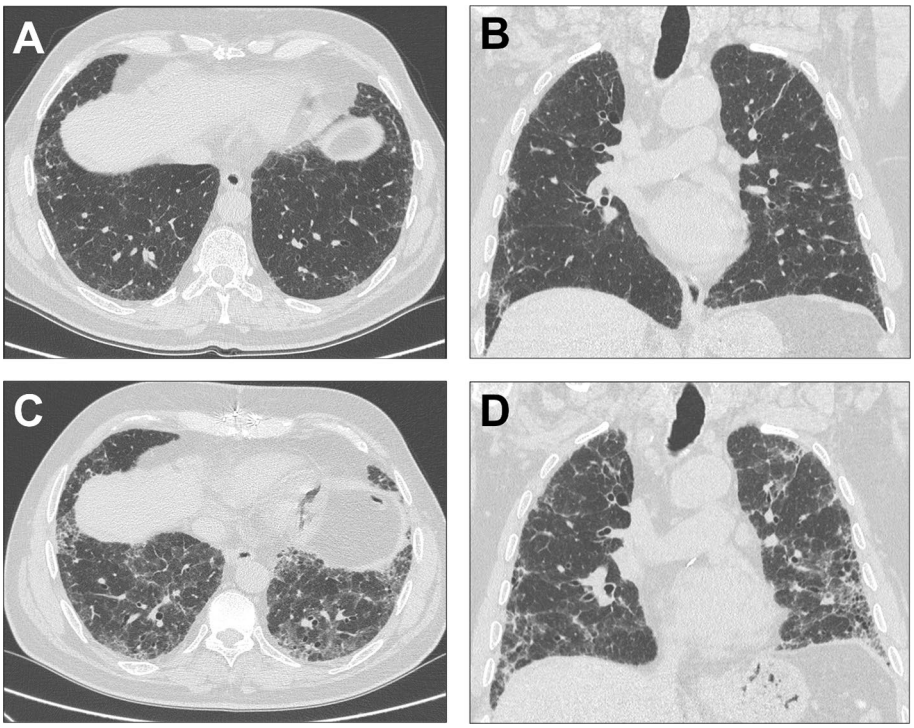

Fig. 2 A 68-year-old man with systemic sclerosis. Axial (**A**) and coronal (**B**) chest HRCT images obtained at the time of diagnosis show scattered areas of subpleural reticulation with interstitial thickening, with partial subpleural sparing and minimum GGO, prevalent in the lower lobes (NSIP pattern); CT images at the same level at 4-years follow-up **C**, **D** demonstrate significant progression of parenchymal fibrotic abnormalities with important increase of reticulation and GGO and appearance of traction bronchiectasis, evolution compatible with progressive pulmonary fibrosis (PPF) phenotype

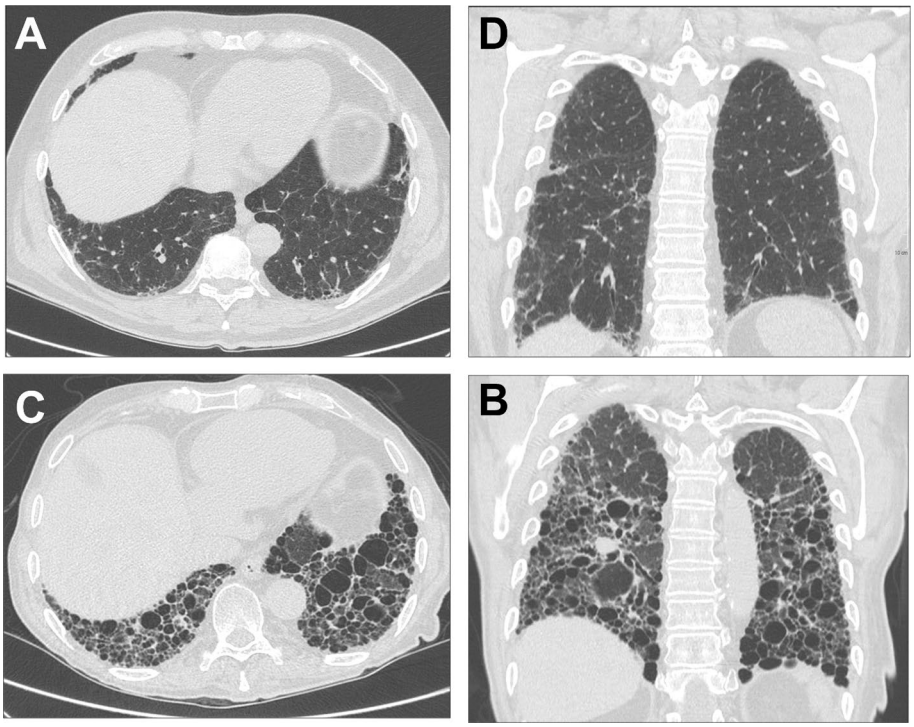

Fig. 3 A 69-year-old man with rheumatoid arthritis. Axial (**A**) and coronal (**B**) chest HRCT images obtained at the time of diagnosis show small subpleural band-like opacities and mild reticulations in the mid-lower lobes, with a circumscribed cluster of honeycombing in the left lower lobe (UIP pattern); CT images at the same level obtained 4 years later **C** and **D** show dramatic progression of fibrotic parenchymal abnormalities with florid honeycombing affecting more than 70% of the fibrotic areas classifiable as 'exuberant honeycombing', evolution compatible with progressive pulmonary fibrosis (PPF) phenotype

decline in FVC ≥ 5%, TFS among patients with non-IPF ILDs, fulfilling the other criteria for the PPF phenotype, varies considerably depending on the specific ILD. This variability was observed particularly for CTD-ILDs, which maintain an advantage in TFS in the presence of PPF criteria, except for FVC decline ≥ 5%, compared to the other subtypes of non-IPF ILDs [48]. This finding suggests that patients with CTD-ILD may need a different set of criteria to correctly assess the risk of progression and an individualised approach to patient management [48].

In the assessment of the progressive phenotype, some Authors suggest the use of a multi-domain assessment over a short observation period [49], others argue that PPF criteria requiring a combination of clinical, radiological and functional data can identify patients with an increased risk of death or transplantation but with a reduced sensitivity. Stand-alone components of these criteria, and among them CT progression, should be evaluated because they are associated with reduced TFS; in addition, CT progression of fibrosis is associated with a subsequent decline in FVC [48, 51]. The time criterion has recently been contested by Cottin [52], who claims that the timeline should be disassociated from both functional and radiological progression criteria ('Progression is progression, whether it occurs at 3 months or 3 years') and, indeed, even a slower decline may be relevant [25]. This may seem a simple common-sense statement, but it must be said that the margin of unpredictability in the course of ILDs in general, and of those associated with CTDs in particular, may hinder a correct interpretation of antifibrotic drug results.

Variations in VS at HRCT correlate with those of PFTs and with mortality. In IPF, a VS ≥ 30% (i.e. a situation of high severity) corresponds to a very poor prognosis and this is also probably the case in ILD-CTD. More specifically, the PPF criteria in the literature were defined as follows [16, 28, 49, 53, 54]: Increased extent or severity of traction bronchiectasis and bronchiolectasis; new fibrotic ground-glass opacities (with contextual traction bronchiectasis); new reticular opacities; increased extension or coarsening of reticular opacities; increased or appearance of honeycombing; volume reduction of the affected lobes, usually the lower lobes, again with visual assessment (displacement of fissural planes or quantitative indices).

Implicit in these criteria is the fact that, over time, not only the extension but also the HRCT pattern can change, generally from 'probable' to 'typical' (with the appearance of honeycombing) but also (albeit more rarely) from 'indeterminate' to 'typical'. This transition occurs, within 2–3 years after diagnosis, in more than 20% of IPF cases [5] and can also be observed in ILD-CTD, although the frequency is unknown [24].

We must also consider other elements that may affect prognosis [18], such as pulmonary hypertension more frequent in SSc, not necessarily related to the presence and severity of ILD and that not infrequently occurs in the form of veno-occlusive disease; oesophageal pathology (always in SSc); neoplasms; coronary artery disease easily assessed on HRCT without contrast medium by the Agatston coronary artery calcification score (CAC) that has been shown to be a very important prognostic factor in IPF, where a CAC score ≥ 405 is a significant independent mortality factor [55] and probably also in CTD; pneumothorax, pleural effusion, pneumomediastinum; pulmonary embolism; over-infections; exacerbations of pulmonary fibrosis, which are certainly not exclusive to idiopathic forms and of which a classification and grading can be attempted on the basis of HRCT (in turn, exacerbations enter into differential diagnosis with pneumotoxicity from drugs, infections (including COVID-19), aspiration episodes, heart failure.

This is in summary what is possible to know so far. Predicting the risk of progression is difficult in idiopathic forms and even more so in secondary forms of ILD.s

The last topic worthy of at least a mention is that of interstitial lung abnormalities (ILAs), which can be found by chance in asymptomatic subjects, for example, in the context of lung cancer screening in smokers. By convention (but this, too, is a questionable criterion), ILAs must affect at least 5% of any lung area; they prevail in the elderly, smokers or ex-smokers and in persons with positivity for MUC-5B (mucin 5B, oligomeric mucus/gel-forming) [56, 57]. In the 1-to 4-year follow-up ILAs progresses in 40% of cases, especially if they present a 'UIP-typical' or 'UIP-probable' pattern with subpleural involvement at onset [49].

Interstitial lung disease with isolated pulmonary involvement can also be observed in the context of interstitial pneumonia with autoimmune features (IPAF) but the course of these subgroups is poorly known and, by definition, interstitial lung disease and not ILA should be mentioned in patients who are symptomatic. Clinical and functional controls, radiological follow-up and MDD are therefore necessary to identify the possible development of an autoimmune disease, which occurs in about 20% of cases [58]. Moreover, the management of minimally extended and asymptomatic lung disease in CTD patients is different from the rest of the population, as the detection of early abnormalities in this group is a risk factor for progression to an overt ILD [58]. Therefore, these patients should be actively monitored by repeating the PFTs at 3–12 months, and chest-CT at 12–24 months or earlier in case of clinical worsening [59–61].

However, many open problems remain. For example, the frequent overlap between early interstitial abnormalities and aspects of simple pulmonary senescence (the lung 'wrinkling' or lung aging) [60].

Conclusions

Much still remains to be understood about the natural history and prognosis of ILD-CTDs [60]. HRCT is to date the fundamental tool for the identification, morphological evaluation and progression assessment of ILD-CTDs, and in this sense it would be useful to adopt a structured report containing the basic information to characterize the disease, such as prevalent pattern, main ancillary signs, the visual score and any progression compared to previous examinations.

However, a more objective and quantitative assessment than visual assessment remains desirable and is likely to be achieved in the next future with the spread of deep learning algorithms, which promise to give results overlapping with those of an experienced radiologist and seem to correlate well with PFTs [62–64].

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Declarations

Conflict of interest The authors declare no competing interests.

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