

Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis

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Objective. To assess the correlation between ultrasound lung comets (ULCs, a recently described echographic sign of interstitial lung fibrosis) and the current undisputed gold-standard high-resolution CT (HRCT) to detect pulmonary fibrosis in patients with SSc.

Methods. We enrolled 33 consecutive SSc patients (mean age 54 ± 13 years, 30 females) in the Rheumatology Clinic of the University of Pisa. We assessed ULCs and chest HRCT within 1 week independently in all the patients. ULC score was obtained by summing the number of lung comets on the anterior and posterior chest. Pulmonary fibrosis was quantified by HRCT with a previously described 30-point Warrick score.

Results. Presence of ULCs (defined as a total number more than 10) was observed in 17 (51%) SSc patients. Mean ULC score was 37 ± 50 , higher in the diffuse than in the limited form (73 ± 66 vs 21 ± 35 ; $P < 0.05$). A significant positive linear correlation was found between ULCs and Warrick scores ($r = 0.72$; $P < 0.001$).

Conclusions. ULCs are often found in SSc, are more frequent in the diffuse than the limited form and are reasonably well correlated with HRCT-derived assessment of lung fibrosis. They represent a simple, bedside, radiation-free hallmark of pulmonary fibrosis of potential diagnostic and prognostic value.

KEY WORDS: Chest sonography, High-resolution computed tomography, Ultrasound lung comets, Systemic sclerosis.

Introduction

Pulmonary fibrosis is a common manifestation in SSc and is the second cause of death after cardiac involvement and pulmonary hypertension [1]. High-resolution CT (HRCT) of the chest has been found to be a sensitive and reproducible method to assess the extent and the pattern of pulmonary fibrosis [2, 3]. The HRCT signs of SSc are well documented, the main findings being a fine reticular pattern involving the subpleural regions of the lower lobe. Other common findings include ground-glass opacities, honeycombing and parenchymal micronodules [4]. Chest HRCT is presently considered as the diagnostic gold standard to assess pulmonary fibrosis [5].

The lung has always been considered poorly accessible to ultrasound, as air prevents the progression of the ultrasound beam [6]. This is true in a normal, aerated lung, but the presence in the lung of other structures besides air, opens the pulmonary acoustic window and allows one to gain an insight into pulmonary oedema and fibrosis that can be directly imaged and quantified. 'Ultrasound lung comets' (ULCs) are an echographic image detectable with chest sonography [7]. This image consists of multiple comet tails fanning out from the lung surface. They originate from water-thickened or fibrosis-thickened interlobular septa: the latter has been found in different forms of interstitial lung disease (ILD), i.e. pulmonary fibrosis and sarcoidosis [8]. The present study hypothesis was that chest ultrasound detection of ULCs may provide a feasible and accurate non-ionizing bedside estimation of fibrosis involvement in patients with SSc, compared with the diagnostic gold standard of chest HRCT.

Methods

Patient population

From May 2006 to March 2008, 33 consecutive patients (mean age 54 ± 13 years, 30 females) admitted to the Rheumatology Clinic of the University of Pisa were included in the study. The inclusion criteria were (i) previous diagnosis of SSc according to the ACR classification criteria for SSc [9] and (ii) chest sonography for specific assessment of ULCs, performed within a week of a clinically driven HRCT. All examinations were read by independent operators, unaware of the results of the other test. In all patients, a modified Rodnan skin score was assessed, as previously described [10].

The review board of the institute approved the study, and written informed consent was obtained from the patients. All patients gave their oral informed consent to undergo chest sonography.

Pulmonary function tests

Standard spirometry and lung volume measurements were performed in all patients by means of a fully equipped computerized spirometric system (CPL Morgan Transflow Test PFT System, Morgan Scientific, Haverhill, MA). Single-breath diffusing capacity for carbon monoxide (DL_{CO}) was also measured. Actual DL_{CO} values were corrected for haemoglobin and CO levels. The results were expressed as a percentage of predicted values [11, 12].

Chest sonography

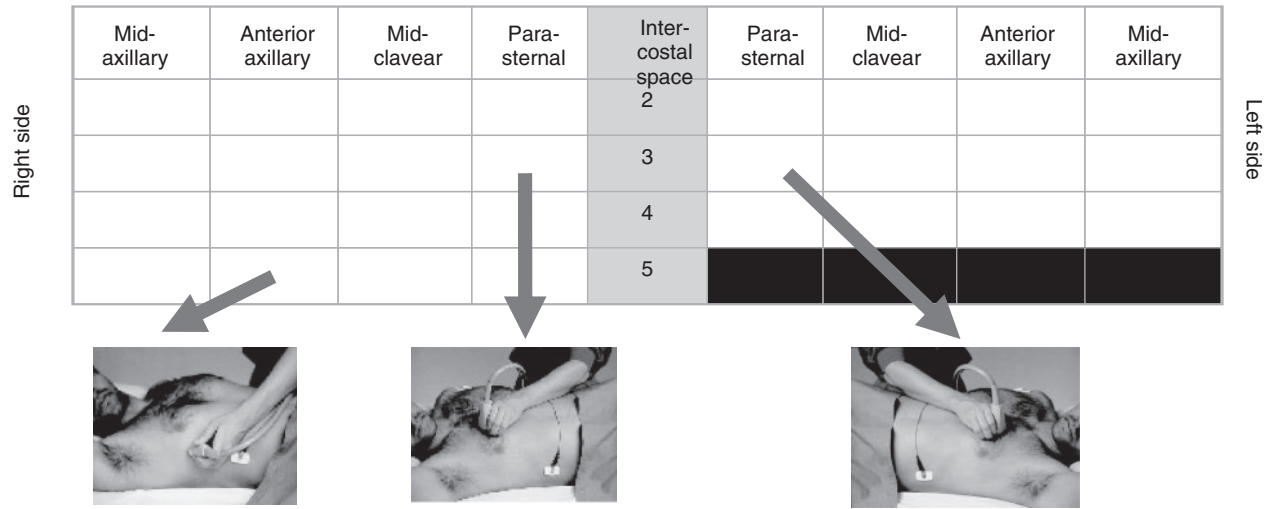
Commercially available echographic equipment with a 2.5–3.5 MHz cardiac sector transducer (2.5 cm long) was used [Optigo, HP Sonos 7500 and IE33 (Philips Medical Systems, Andover, MA, USA), Famiglia Mylab25 (Esaote, Genoa, Italy)]. The investigators were unaware of chest HRCT results and clinical data of the patients. The echographic examinations were performed with patients in the supine or near-supine position for the anterior scanning, and in the sitting position for the dorsal scanning. Ultrasound examination was obtained moving the probe longitudinally along anatomical reference lines, as previously described for the anterior chest [13] (Fig. 1A), whereas

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A



B

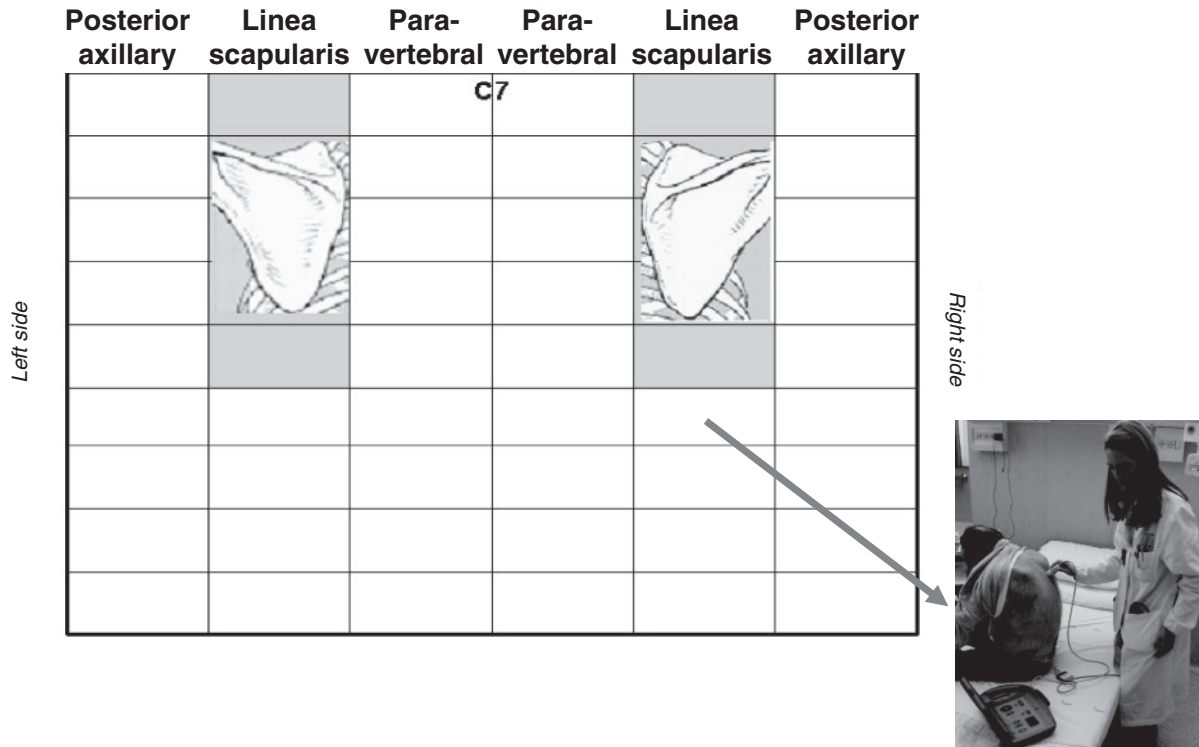


FIG. 1. (A) The pre-defined scanning sites on the anterior chest. Modified from Ref. [13] with kind permission from the *American Journal of Cardiology*. (B) The pre-defined scanning sites on the posterior chest.

for the posterior chest, the ultrasound examination was obtained by scanning along the paravertebral, scapular and posterior axillary lines (Fig. 1B). The ULC sign was defined as an echogenic, coherent, wedge-shaped signal with a narrow origin in the near field of the image [7]. In each intercostal space, the number of ULCs was recorded. The sum of ULCs yielded a score denoting the extent of pulmonary fibrosis diffusion. Presence of ULCs was defined by a total number of ULCs more than 10, considering all scanning sites on anterior and posterior chest. Zero was defined as a complete absence of ULCs in all scanning sites. The full white screen in a single scanning site was considered as corresponding to

10 ULCs. Two different observers (L.G. and F.F.), with dedicated training and previous experience in joint reading, acquired and analysed all chest sonography studies. Both readers were blinded to chest HRCT results and clinical data. The intra- and inter-observer variability of ULCs assessment is 5.1 and 7.4%, respectively, in our laboratory [13].

Chest HRCT

CT examinations were performed on a spiral CT/I Highspeed GEMs (General Electrics Medical Systems) scanner with one

row of detectors and a 1-s rotation time. All patients underwent an A-P and L-L scout. After this, 35–55 scans were acquired at the end of inspiration, in apnoea, from the apex to the lung base, either in supine or in prone decubitus. The acquisition parameters were as follows: sequential mode, 1-mm collimation and 10-mm interval, 180–260 mA average tube current (it depended on the build of patient) and 120–140 kV tube voltage. A bone plus reconstruction with lung window was used. No intravenous contrast material was administered. The duration of the CT acquisition was ~35–45 s. Matrix was 512 × 512. Absorbed dose was in the range 5–7 mSv. Pulmonary involvement was evaluated by topographically dividing the lung into segments, using the score proposed by Warrick *et al.* [14] as previously described (Table 1). This index includes a ‘severity score’, ranging from 0 (normal) to 15 (all lesions present), and an ‘extension score’, ranging from 0 (normal) to 15 (more than nine pulmonary segments involved). A total Warrick score was obtained by summing the severity and the extension scores.

Statistical analysis

Continuous variables are expressed as mean ± s.d. Categorical variables are presented as counts and percentages. Univariate comparisons were made with χ^2 or two-sample *t*-tests, as appropriate. Correlation between parameters was assessed with non-parametric Spearman correlation coefficient analysis or with Pearson correlation, as appropriate. A *P*-value of <0.05 was considered as statistically significant. All statistical analyses were performed using the SPSS/PC software package version 13 (SPSS, Chicago, IL, USA).

Results

Chest sonography examination was performed in all patients, and feasibility was 100%. The time needed for chest scan and analysis was always <10 min. Chest sonography was performed by

Optigo in 17 (52%) patients, by HP Sonos 7500 in 7 (21%), by IE33 in 6 (18%) and by Famiglia Mylab25 in 3 (9%). ULCs were absent (less than 10) in 16 patients and present (more than 10) in 17. The clinical, spirometric and immunological features of the 33 patients, separated on the basis of ULC presence, are reported in Table 2. A significant positive linear correlation was found between echographic ULC score and Warrick score ($r=0.72$; $P<0.001$; Fig. 2), with good concordance at individual patient analysis between CT and chest sonography patterns of normal, mildly fibrotic and severely fibrotic lung (Fig. 3). ULCs were higher in the diffuse than in the limited form (73 ± 66 vs 21 ± 35 ; $P<0.05$). We found a significant correlation between ULC number and values of DL_{CO} ($r=-0.60$; $P<0.05$).

Discussion

ULCs observed with chest sonography are correlated with presence and severity of pulmonary fibrosis as assessed by chest HRCT in patients with SSC.

Biophysical mechanism of fibrotic ULCs

As previously discussed in detail [7, 15], ULCs are generated by the reflection of the ultrasound beam from thickened subpleural interlobular septa. In patients with heart failure, interlobular septa are thickened by water, and ULCs represent an early sign of pulmonary interstitial oedema, well related to the increase in cardiac peptides [16], radiographic signs of pulmonary congestion [13], invasive measurement of extravascular lung water and pulmonary capillary wedge pressure [17]. In pulmonary fibrosis,

TABLE 1. Warrick score, as previously described [14]

	Severity score
Parenchymal alteration	
Ground glass opacities	1
Irregular pleural margins	2
Septal/subpleural lines	3
Honeycombing	4
Subpleural cysts	5
No. of lung segments	
1–3	1
4–9	2
>9	3

Table adapted from Ref. [14] with kind permission from the *Journal of Rheumatology*.

TABLE 2. Clinical and immunological features

Characteristics	ULCs absent (less than 10), <i>n</i> =16	ULC present (more than 10), <i>n</i> =17	<i>P</i> -value
Age, mean ± s.d., years	55 ± 13	53 ± 14	0.74
Female, <i>n</i> (%)	14 (87)	15 (94)	0.89
Duration of disease, mean ± s.d., years	4 ± 5	8 ± 7	0.15
Former or current smokers, <i>n</i> (%)	3 (19)	2 (12)	0.78
Diffuse form of the disease, <i>n</i> (%)	3 (19)	7 (41)	0.26
Skin score, mean ± s.d.	5.4 ± 8.1	8.3 ± 8.4	0.33
ANA, <i>n</i> (%)	4 (25)	4 (23)	0.92
ACA, <i>n</i> (%)	8 (50)	6 (35)	0.72
Scl-70, <i>n</i> (%)	4 (25)	5 (29)	0.70
TLC, mean ± s.d.	97 ± 21	82 ± 19	<0.05
VC, mean ± s.d.	112 ± 27	85 ± 30	<0.05
DL_{CO} , mean ± s.d.	83 ± 22	66 ± 22	<0.05
ULCs, mean ± s.d.	3 ± 3	69 ± 52	<0.001
Warrick score, mean ± s.d.	1.6 ± 2.5	6.9 ± 4.1	<0.001

Scl-70: anti-topoisomerase autoantibodies; TLC: total lung capacity; VC: vital capacity.

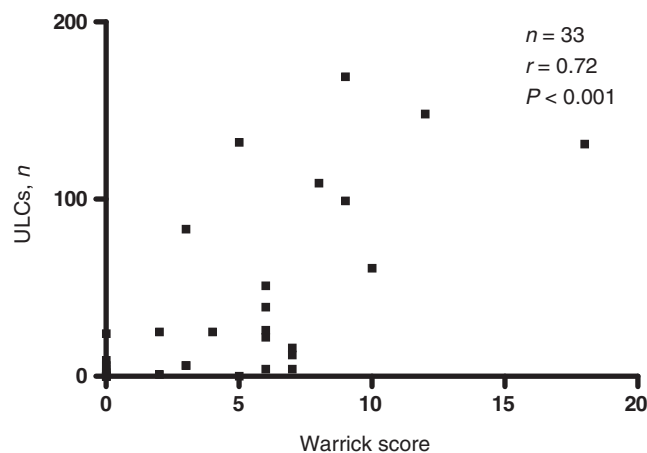


Fig. 2. Correlation between ULC number and Warrick score in identifying pulmonary interstitial fibrosis.

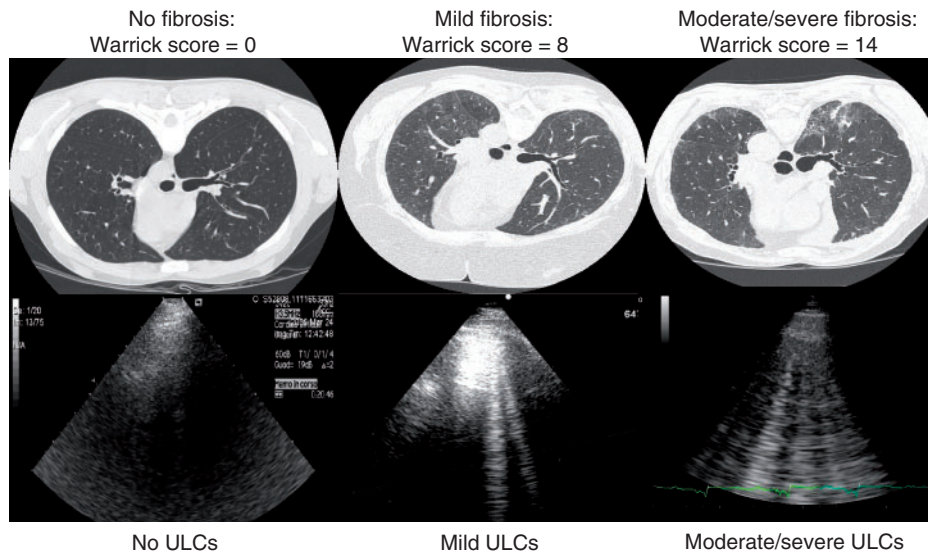


FIG. 3. Different CT and chest sonography patterns of absent, intermediate and severe fibrotic involvement.

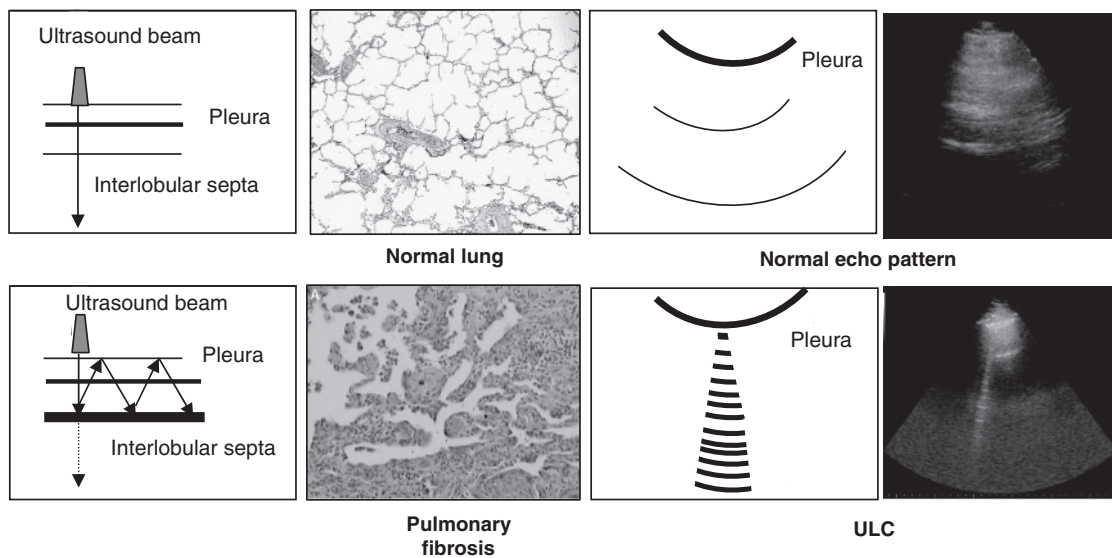


FIG. 4. The hypothesized physical and anatomic basis of ULCs. Reflections of the ultrasound beam by thickened interlobular septa give rise to ULCs. Modified from Ref. [13] with kind permission from the *American Journal of Cardiology*.

interstitial lobular septa are thickened by collagen tissue accumulation and, therefore, ULCs are generated by the same anatomical interface as in heart failure, i.e. a thickened subpleural interlobular septa, although the physical scatterers are represented by lung air fibrosis and not by air–water impedance mismatch (Fig. 4).

Clinical implications

Detection, characterization and quantification of lung changes in patients with SSc are important for several reasons. First, it may help to identify early changes in asymptomatic patients establishing the need of follow-up and treatment [18]; secondly, it may have an important prognostic significance [4, 19]; finally, it can provide support when monitoring lung disease progression in a single patient with or without therapy [20]. Actually, HRCT is the gold-standard technique for assessing pulmonary fibrosis in these patients, also able to detect early stages of the disease [21, 22]. For such reasons, these patients underwent HRCT scans annually.

According to the present study, chest sonography has the potential to identify and quantify pulmonary fibrosis accumulation, as assessed by CT. The clinical impact of this information is magnified by the low cost of this method, which can also be performed at the bedside with a hand-held device, its very easy acquisition, learning and interpretation of curves [23] and its quick performing time (<10 min for a total chest assessment). Moreover, the technique is non-ionizing, and chest sonography can easily be coupled with standard echocardiography, that evaluates the other major prognostic determinant in these patients, i.e. pulmonary hypertension [4]. Obviously, chest HRCT remains the gold-standard technique for assessing pulmonary fibrosis, also because it is the only tool that allows the evaluation of the whole lung, and not only the subpleural interstitial lobular septa. Nevertheless, ULCs can be useful to support CT, especially for the follow-up of SSc patients during treatment, and to reduce radiation exposure, a quite relevant issue in patients who need serial examinations for monitoring disease progression,

especially in young women who have a 37% higher cancer risk than men for any radiation [24]. A reduction of radiation exposure could also be achieved by low-dose chest CT or chest MRI, which are, however, more costly and less widely available than chest sonography [25].

From the scientific viewpoint, ULCs are attractive as a specific, proximal biomarker of lung fibrosis, of special interest in viewing the ongoing development of novel methods to prevent scarring and alleviate the symptoms of fibrosis [26]. A direct, quantitative, early and radiation-free imaging biomarker would greatly facilitate the presence of validation of new therapies in this field [27].

Comparison with previous studies

This is the first study evaluating the presence of a chest sonography sign of interstitial fibrosis in patients with SSc, in comparison with the gold-standard HRCT. Previous studies had evaluated this sign in different forms of ILD, including pulmonary fibrosis and sarcoidosis, underlining that diffuse parenchymal lung disease should be considered in presence of multiple ULCs distributed over the whole surface of the lung [8]. Because diffuse parenchymal lung disease was defined on the basis of chest X-ray, our study represents the first quantitative comparison between chest sonography and radiographic signs of pulmonary fibrosis on HRCT.

We found higher values of ULCs to be associated to the diffuse form of the disease, compared with the limited form, and a correlation between ULC number and values of DL_{CO}. It is established that patients with the dcSSc compared with the lcSSc subgroup have a higher prevalence of interstitial lung fibrosis documented on HRCT, a reduced lung diffusing capacity [28] and a significant decrease in the mean percentage of forced vital capacity and total lung capacity [29].

Chest sonography is more often performed by medium- to low-frequency transducers, such as convex, micro-convex or cardiac probes, whereas high frequency linear probes are considered to be the best tool for visualization and measurement of the pleural line. We employed cardiac probes, which allow a clear visualization of ULCs and are very easy to handle along patients' intercostal spaces. However, it is likely that similar results would have been found by using a convex or micro-convex probe [30, 31].

Limitations

Some limitations of the proposed chest ultrasound method should be acknowledged. A limit of ULCs may arise from the differential diagnosis between cardiogenic and fibrotic ULCs. Cardiogenic watery ULCs may be difficult to distinguish from pneumogenic fibrotic ULCs, which can be typically found in ILD. Usually, diagnosis is obvious from patient's history and/or from dynamic, serial evaluation, since only cardiogenic comets are cleared by diuretic therapy [7]. However, in the present study only the fibrotic origin has been considered as the possible origin of abnormal signal, given the clinical context. In a less well-selected patient population, problems of differential diagnosis between fibrotic and watery ULCs may arise [7].

The sample size was limited and, moreover, only a few patients had important pulmonary fibrosis and nobody had a very high Warrick score, potentially influencing ULC accuracy. This was a pilot study; additional studies, including a higher number of patients with the whole range of degrees of pulmonary fibrosis, will be needed to provide more accurate information on sensitivity and specificity, as well as reproducibility and feasibility for patients' follow-up.

As always, the reading of ultrasound was subjective and qualitative. Although a semiquantitative index of ULCs was generated, there is no doubt that quantitative radiological imaging provides a more established and robust quantitative support to the diagnosis of lung fibrosis. It is also unquestionable, however, that a

user-friendly, easy and fast approach of chest sonography may be appealing in the initial characterization and follow-up of these patients in a cost- and risk-conscious perspective [32–35].

Rheumatology key messages

- ULCs are well correlated with HRCT signs of pulmonary fibrosis.
- ULCs represent a simple, bedside, radiation-free hallmark of pulmonary fibrosis.

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