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Imaging in Systemic Sclerosis-Associated Interstitial Lung Disease: Comparison of Transthoracic Lung Ultrasound and HR Chest CT in Detecting Characteristic Patterns

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Abstract: Background/Objectives: Even today the interstitial lung disease (ILD) is diagnosed by chest high-resolution computed tomography (lung HR-CT). A large amount of data is available about the usefulness of lung ultrasound (LUS) in ILD. The aim of this study is to evaluate the LUS capacity to discriminate different ILD patterns in systemic sclerosis (SSc) patients, such as UIP, NSIP with GGO, and NSIP with GGO and reticulations, and then the possibilityto identify the progressive fibrosing ILD. **Methods**: All SSc-patients with recent HRCT performed underwent LUS. **Results**: ILD was observed in 99 (63.5%) patients (25% with UIP pattern, and 75% with NSIP pattern (46 with GGO, 28 with GGO and reticulations). By ROC curve analysis, that higher accuracy, sensitivity, and specificity were found for pleural line irregularity (0.68, 95.8%, and 41.5%, p=0.004), pleural line thickness (0.72, 70.8%, and 73.2%, p=0.001), and subpleural cyst (0.68, 58.3%, and 78.9%, p=0.004) to detect UIP pattern. The best performance among LUS signs for NSIP with GGO pattern was observed for B-lines (accuracy: 0.73, sensitivity: 92.9% and specificity: 54.3, p=0.0001). LUS signs with higher accuracy, sensitivity, and specificity for NSIP with GGO and reticulations were pleural line irregularity (0.69, 96%, and 42.1%, p=0.002), pleural line thickness (0.69, 65.4%, 72.7%, p=0.002), and B-lines (0.72, 96.2%, 48.8%, p=0.0001). Furthermore, a total number of B-line > 10 maximises LUS performance with 92.3% sensitivity, and an accuracy of 0.83 (p=0.0001) to detect the NSIP pattern, particularly GGO. A sample-restricted analysis (66 SSc patients) evidenced the presence of progressive fibrosing ILD in 77%. By binary regression analysis, that the unique LUS sign associated with progressive fibrosing ILD was the presence of pleural line irregularity (OR: 3.6; 95% CI 1.08-11.9; p= 0.036). **Conclusions**: Our study demonstrated that the LUS presented a high capacity to discriminate the different patterns of SSc-ILD. Therefore, the hypothesis of using transthoracic LUS as a screening method for the evaluation of the presence of SSc-ILD and to establish the correct timing for the execution of chest HR-CT, in order to avoid patients from excessive exposure to ionising radiation is supported.

Keywords: Interstitial lung disease; usual interstitial pneumonia; non-specific interstitial pneumonia; lung ultrasound (LUS); B-lines

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1. Introduction

Interstitial lung disease (ILD) is one of the most frequent clinical features in systemic sclerosis (SSc), estimated in 53% of patients with SSc with a diffuse cutaneous subset and in 35% of patients with a limited cutaneous subset. [1] Together with pulmonary arterial hypertension, despite advances in therapeutic management, it currently represents the most frequent cause of death in patients with SSc (28%). [2–7]

The gold-standard instrumental method for diagnosing and following SSc-ILD is chest high-resolution computed tomography (lung HR-CT). Given the subclinical onset and the need to diagnose SSc-ILD as early as possible, in order to try to slow down its progression through pharmacological therapy, lung HR-CT is recommended to be performed periodically. [8–14]

The most frequent lung CT pattern of ILD in SSc, above all in early phases of the disease, is the nonspecific interstitial pneumonia (NSIP) characterised by the presence of ground glass opacities (GGO) and reticulations, and less recurrent usual interstitial pneumonia (UIP), identified by honeycombing and traction bronchiectasis. [8–15]

In the last decade, however, the issues of high cost and the risk related to excessive exposure to ionising radiation, which every CT scan induces, and the increased risk of developing neoplasms (especially breast carcinomas) in patients with SSc [16], has induced the scientific community to search for new instrumental methods that are less harmful to the patient. Among these, transthoracic lung ultrasound (LUS) has assumed considerable importance, due to preliminary data supporting a positive association between LUS signs and CT findings [17–25]

This study aims to evaluate the LUS capacity to discriminate different ILD patterns in SSc patients, such as UIP, NSIP with GGO, and NSIP with GGO and reticulations. Furthermore, we wanted to evaluate the presence of any characteristic LUS signs to identify progressive fibrosing ILD.

2. Materials and Methods

One hundred fifty-six patients were consecutively recruited for this study, followed at the outpatient clinic of the Rheumatology Unit of Policlinico of Foggia and the Rheumatology Unit of Policlinico of Bari. All patients satisfied ACR/EULAR 2013 classification criteria for SSc. [26] The clinical examination at enrolled visit includes age, disease history, medications, visceral involvement, and laboratory test for reactants of the acute phase of inflammation (erythrocyte sedimentation rate, C-reactive protein), antinuclear antibodies (assessed by immunofluorescence) and extractable nuclear antigens antibodies (evaluated by immunoblotting), the presence of ILD and its pattern at CT lungs, the respiratory capacity by pulmonary function test, evaluation of the presence of main LUS signs of ILD, the assessment of nailfold capillaroscopy patterns. The extent and severity of skin thickening were evaluated by the modified Rodnan skin score.

Inclusion criteria were: age older than 18 years, the satisfaction of ACR/EULAR 2013 classification criteria for SSC; chest CT scan within three months before or three months after LUS evaluation; and availability of recent and complete pulmonary function test with FVC, DLCO and FEV1.

Exclusion criteria were: history or recent reactivation of chronic obstructive pulmonary disease, lung cancer, lung infection, heart failure, pulmonary oedema, pulmonary arterial hypertension, acute respiratory distress syndrome and diffuse alveolar haemorrhage and thoracic surgery.

2.1.1. Chest High-Resolution Computed Tomography

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Chest high-resolution computed tomography (lung HRTC) evaluation was performed with a high-resolution spiral technique at the patients' reference centres. Each exam, recorded in digital format, was acquired and subsequently examined by the same operator. The lung field was divided into three segments: basal, middle and apical, which did not correspond to the lung lobes. The inferior angle of the scapula was considered a landmark for the subdivision between basal and middle segments, while the middle and apical segments were divided to be constituted by the same number of intercostal spaces. The segmentation was used to standardize the subdivision of LUS areas and tomographic lung segments. For each lung field, was assessed the presence of characteristic lesions (covering at least 20% of the segment area) for NSIP with GGO only, NSIP with GGO and reticulations, and UIP. [27] In patients with ILD, the lung segments characterized by the presence of lesions were considered and compared with the LUS findings.

The presence of progressive fibrosing ILD was defined as suggested by Raghu G et al. [28]

2.1.2. Transthoracic Lung Ultrasound

Transthoracic lung ultrasound (LUS) was assessed according to the principal recommendation [29], evaluating all scanning lung fields on the anterolateral (28-site) and the posterior thorax (30 sites). The examination was conducted with the patient sitting and his hands resting on his knees for posterior scanning and a supine position for anterolateral acquisitions. The LUS was performed, by an expert sonographer, with Philips Epiq 7 ultrasound systems (Philips Ultrasound; Bothell, WA, USA), using a Convex probe (3.5–5 MHz) or a linear transducer (8.0–12.0 MHz), where appropriate, to improve the identification of pleural alterations.

In each intercostal space examined, the following ultrasonographic characteristics of the pleural line were evaluated:

- thickness of pleural line, abnormal if > 2,8 mm (Figure 1 a and b) [30].
- irregularities of pleural line, abnormal if extended more than 3 mm (Figure 1 a and b) [30,31]
- mobility of pleural line, in particular, the presence of sliding sing;
- the presence and the total number of B-lines (abnormal in the presence of 3 or more B-lines in at least two consecutive scans or the presence of at least 5 B-lines in the entire intercostal space examined) (Figure 1 c) [30; 32]. The total number of B-lines was given by the sum of all the B-lines found in the different fields examined;
- the presence of almost one subpleural cyst (Figure 1 d), defined as hypo-echoic lesions that interrupt the pleural line;
- the presence of the pleural effusion.

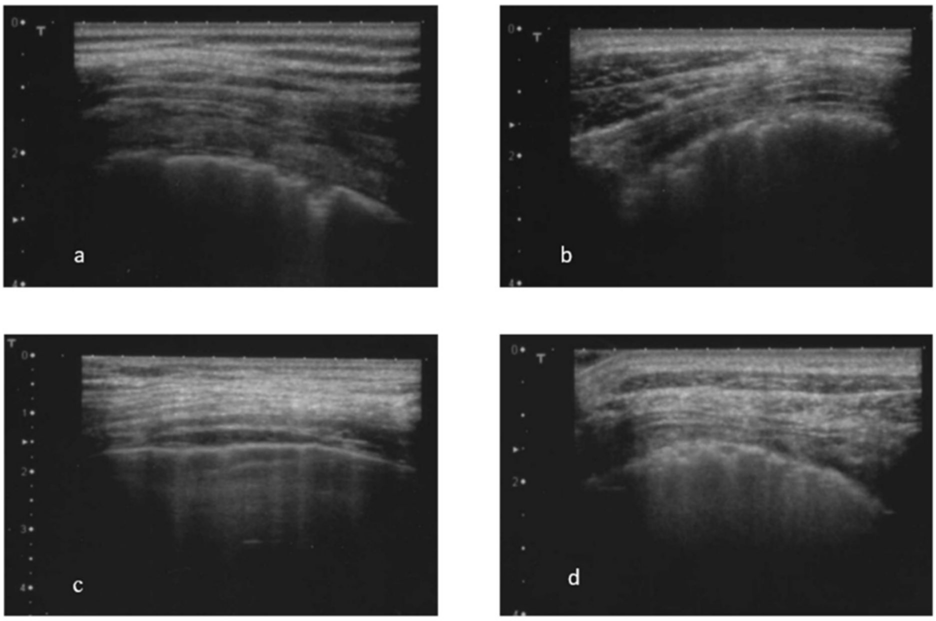

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Figure 1. Echograms: signs detected by transthoracic lung ultrasound (linear probe between 7-10 MHz). a) thickening and irregularity of the pleural line; b) thickening and irregularity of the pleural line; c) B-lines; d) subpleural cysts.

Statistical Analysis.

The results were expressed as means (m) ± standard deviation (sd); categorical variables were expressed as numbers (percentage). The normality of the distribution of the study variables was verified with the Kolmogorov-Smirnov test.

Statistical differences between the two groups were analyzed with the t-student for unpaired data. Multiple comparisons of continuous variables were analyzed with analysis of variance (ANOVA) followed by the Bonferroni test.

Pearson $\chi 2$ and Fisher's exact test, followed by Z-test, were used to compare categorical variables and percentages.

The ROC curve was used to compare the diagnostic performance of each US sign with lung CT patterns of ILD as NSIP with GGO, NSIP with GGO and reticulations, and UIP, assessing the area under the curve (AUC). The AUC values of 0.50–0.59, 0.60–0.69, 0.70–0.79, and ≥0.80 are defined as none, poor, acceptable, and excellent accuracy, respectively

Binary logistic regression was used to evaluate predictors of progressive fibrosing ILD.

Statistical significance was defined as a value of $p \leq 0.05$.

Statistical analysis was performed with IBM SPSS Statistics 26.

Ethics Approval.

Our study was approved by the local Ethics Committee (115/C.E.). All participants gave their informed consent to participate in this study and undergo a computed tomography scan.

3. Results

One hundred and fifty-six Caucasian patients diagnosed with SSC (mean age 59.0 ± 12.4 years; and mean disease duration 32 ± 10.8 years) satisfied the inclusion criteria. The ILD at lung CT was detected in 99 (63.5%) studied patients, of which 25 (25%) with UIP pattern, and 74 (75%) with NSIP pattern (46 with GGO alone, and 28 with GGO and reticulations).

The comparison between the study groups of the main demographic and clinical characteristics is shown in Table 1. A higher presence of anti-Scl-70 antibodies was found in patients with ILD (any CT patterns) compared with no-ILD patients. Lower values of FVC at pulmonary function tests are detected in UIP (84.8 ± 18.3) and NSIP with GGO and reticulations (84 ± 19.4) groups. As regards other specific CT lung abnormalities, a higher rate of micro-nodules was found in NSIP with GGO group (56.5%). More extensive and severe ILD, assessed by Warrick Score, was recognized in UIP (10.2 ± 4) and NSIP with GGO and reticulations (10.8 ± 1.7) groups (Table 1).

3.1.1. LUS Signs and UIP Lung CT Pattern

As regards UIP at lung CT, the rate of presence of pleural line irregularity (96% vs 26%), sliding sign (20% vs 0%), pleural line thickness (72% vs 3.5%), B-lines (56% vs 17.5%), and subpleural cysts (58% vs 9%) were higher compared to the no-ILD group of patients (Table 1). Furthermore, the frequency of the presence of pleural thickness in the UIP pattern was higher than NSIP with GGO (72% vs 36%) (Table 1).

By ROC curve analysis in the UIP pattern, higher accuracy, sensitivity, and specificity were found for pleural line irregularity (0.68, 95.8%, and 41.5%, p=0.004), pleural line thickness (0.72, 70.8%, and 73.2%, p=0.001), and subpleural cyst (0.68, 58.3%, and 78.9%, p=0.004) (Table 2, Figure 2 a). No significance was observed regarding the presence or absence of B-lines and their number.

3.1.2. LUS Signs and NSIP with Ground Glass Lung CT Pattern

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Concerning NSIP with GGO pattern, the LUS signs observed with higher frequency were pleural line irregularity (76% vs 26%) (even though was significantly lesser than UIP pattern), B-lines (93.5% vs 17.5%) compared with no-ILD patients. In particular, there was a significant difference in the rate of the presence of B-line (93.5% vs 56%) and the total number of B-lines (69.5 ± 10.7 vs 29 ± 10.2; p=0.0001) between NSIP with GGO pattern and UIP pattern (Table 1).

By ROC curve analysis, the best performance among LUS signs for NSIP with GGO pattern was observed just for B-lines (accuracy: 0.73, sensitivity: 92.9% and specificity: 54.3, p=0.0001) (Table 2, Figure 2 b). As regards the cut-off of total B-lines numbers useful for discriminating the presence of NSIP with GGO pattern, a total number of B-line > 10 maximises the LUS performance with 92.3% of sensitivity, 65.3% of specificity, and accuracy of 0.83 (p=0.0001).

3.1.3. LUS Signs and NSIP with Ground Glass and Reticulation Lung CT Pattern

The NSIP with GGO and reticulation pattern was detected in 28 patients. The principal LUS sign assessed with a higher rate in patients with this pattern compared to no-ILD patients were sliding sign (18.5% vs 0%), pleural line irregularity (96% vs 26%), pleural line thickness (64% vs 3.5), B-lines (96% vs 17.5%), and subpleural cysts (48% vs 9%). In particular, the presence of B-lines and the number of B-lines were found to be statistically significant between NSIP with GGO and reticulations group and UIP group respectively 96% vs 56%, and 56.6 ± 11.8 vs 29 ± 10.2 (Table 1).

By ROC curve analysis, the LUS signs with higher accuracy, sensitivity, and specificity for NSIP with GGO and reticulations were pleural line irregularity (0.69, 96%, and 42.1%, p=0.002), pleural line thickness (0.69, 65.4%, 72.7%, p=0.002), and B-lines (0.72, 96.2%, 48.8%, p=0.0001). Concerning the cut-off numbers of B-lines, the presence of >10 B-lines maintains good sensitivity (91.3%) for the NSIP pattern with GGO and reticulation, but loses some points in terms of specificity (56.2%) and accuracy (0.72; p=0.001) compared to the NSIP pattern with GGO.

3.1.4. LUS Signs and NSIP with Ground Glass and Reticulation Lung CT Pattern

In 66 patients it was possible to do a comparative evaluation to establish the presence of progressive fibrosing ILD, and 77% of these patients presented the criteria for progressive fibrosing ILD. A higher rate of pleural line irregularities was found in the group of patients with progressive fibrosing ILD compared to those with ILD (71% vs 40%, p=0.033). No other significant differences in LUS signs were found between the group of patients with ILD and those with progressive fibrosing ILD.

By binary regression analysis, the unique LUS sign associated significantly with progressive fibrosing ILD was the presence of pleural line irregularity (OR: 3.6; 95% CI 1.08-11.9; p= 0.036). No significance was observed regarding the presence or absence of B-lines and their number.

3.2. Figures, and Tables

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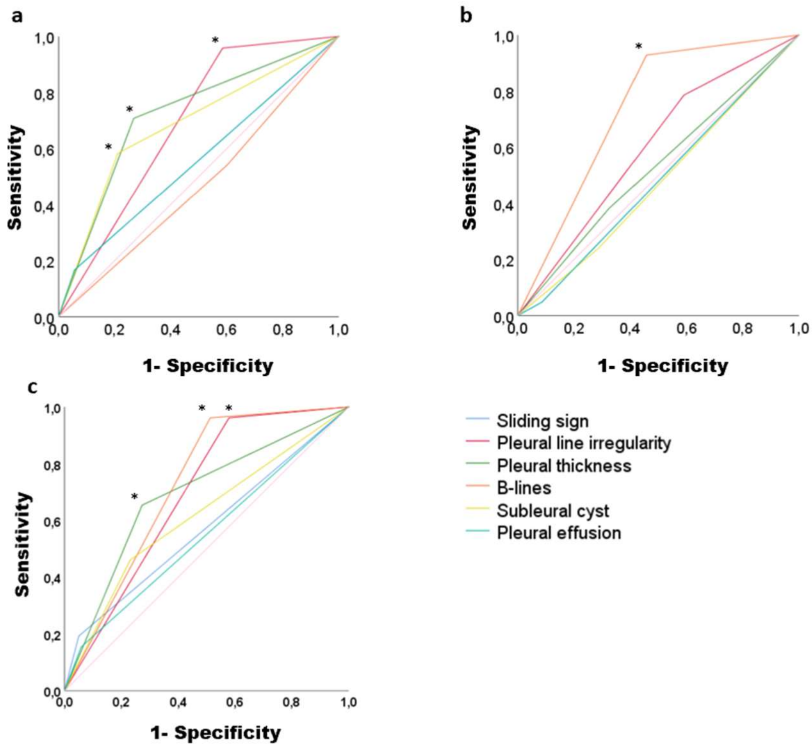

Figure 2. Graphical representation of ROC curve analysis of different LUS signs for detecting a) UIP CT ILD-pattern; b) NSIP with GGO CT ILD-pattern; c) NSIP with GGO and reticulation CT ILD pattern. *p≤0.05.

Table 1. Comparison among study groups of the main demographic, clinical and instrumental characteristics.

	No-ILD	UIP	NSIP with GGO	NSIP with GGO and reticulations	p-value
N (%)	57 (36,5%)	25 (16%)	46 (29,5%)	28 (18%)	
F/M	55 (96%) / 2 (3%)	23 (92%) / 2 (8%)	43 (93%) / 3 (6%)	27 (96%) / 1 (4%)	0.788
Age (years)	57.5 ± 14.4	60.4 ± 11.0	58.2 ± 11.5	62.2 ± 10.1	0.370
Disease duration (years)	9.7 ± 6.9	10.9 ± 5.9	7.4 ± 5.9	7.8 ± 7.7	0.479
BMI	25.9 ± 4.1	25.2 ± 6.1	25.2 ± 4.3	26.1 ± 4.5	0.170
ESR (mm/h)	19.3 ± 14.8	17.6 ± 14	17.7 ± 13.1	24.5 ± 14.4	0.242
CRP (mg/l)	4.8 ± 4.8	5.0 ± 1.1	7.5 ± 1.3	9.6 ± 1.8	0.238
ENA					
Anti CENP-B	42 (74%)	3 (12%)	6 (13%)	6 (23%)	0.0001^
Anti Scl-70	10 (17,5%)	19 (76%)	36 (78%)	17 (65%)	0.0001”
Nailfold Videocapillaroscopy					
Early scleroderma pattern	16 (32%)	4 (20%)	16 (40%)	4 (17%)	0.440
Active scleroderma pattern	24 (45%)	8 (40%)	15 (37%)	12 (52%)	0.786
Late scleroderma pattern	13 (24%)	8 (40%)	9 (22,5%)	7 (30%)	0.443
Cutaneous subsets					
Limited	49 (86%)	20 (80%)	34 (74%)	25 (89%)	0.292
Diffuse	8 (14%)	5 (20%)	12 (26%)	3 (11%)	0.296

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Presence of LUS abnormalities					
Sliding sign	0 (0%)	5 (20%)	2 (4%)	5 (18,5%)	0.002 §
Pleural line irregularity	15 (26%)	24 (96%)	35 (76%)	27 (96%)	0.0001^
Pleural thickness	2 (3,5%)	18 (72%)	16 (36%)	18 (64%)	0.0001°
B-lines	10 (17,5%)	14 (56%)	43 (93,5%)	27 (96%)	0.0001#
B-lines number	3.5 ± 16.1	29.0 ± 10.2	69.5 ± 10.7	56.6 ± 11.8	0.0001#
Subpleural cystis	5 (9%)	14 (58%)	10 (24%)	13 (48%)	0.0001@
Pleural effusion	2 (3,5%)	4 (16%)	2 (4%)	4 (14%)	0.103
PFT					
FVC% baseline	108.1 ± 14.4	84.8 ± 18.3	99.5 ± 15.4	84 ± 19.4	0.0001&
DLCO% baseline	77.1 ± 16.9	77.2 ± 17	77.7 ± 18	69.1 ± 18.5	0.627
TLC% baseline	101.6 ± 12.9	75.2 ± 11	92.9 ± 16.2	91.8 ± 33	0.059
Other lung CT abnormalities					
Micro nodules	6 (13%)	8 (32%)	26 (56.5%)	9 (32%)	0.0001*
Warrick Score	0.0 ± 0.0	10.2 ± 4.0	8 ± 3.4	10.8 ± 1.7	0.0001$

[1] BMI: body mass index; CRP: C-reactive proteins; CT: computed tomography; ENA: Extractable Nuclear Antigen; ESR: erythrocyte sedimentation rate; F: female; GGO: ground glass; ILD: interstitial lung disease; M: male; LUS: lung ultrasound; NSIP: non-specific interstitial pneumonia; PFT: pulmonary function tests; UIP: usual interstitial pneumonia. *NSIP with GGO vs UIP p≤0,05; NSIP with GGO vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05; UIP vs No-ILD p≤0,05, § UIP vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05, ^ NSIP with GGO vs No-ILD p≤0,05; UIP vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05, " No-ILD vs NSIP with GGO p≤0,05; No-ILD vs UIP p≤0,05; No-ILD vs NSIP with GGO and reticulations p≤0,05, ° UIP vs NSIP with GGO p≤0,05; NSIP with GGO vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05; UIP vs No-ILD p≤0,05, # UIP vs No-ILD p≤0,05; NSIP with GGO vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05; NSIP with GGO vs UIP p≤0,05; NSIP with GGO and reticulations vs UIP p≤0,05, @ UIP vs No-ILD p≤0,05; UIP vs NSIP with GGO p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05, & UIP vs No-ILD p≤0,05; NSIP with GGO vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05; UIP vs NSIP with GGO p≤0,05; NSIP with GGO and reticulations vs GGO p≤0,05, $ UIP vs No-ILD p≤0,05; NSIP with GGO vs No-ILD p≤0,05; NSIP with GGO and reticulations vs No-ILD p≤0,05; NSIP with GGO vs NSIP with GGO and reticulations p≤0,05.

Table 2. ROC curve analysis. Sensitivity, specificity, and accuracy of different lung ultrasound signs for detecting specific ILD CT lung patterns (UIP, NSIP with GGO, NSIP with GGO and reticulations).

	Sensitivity	Specificity	Accuracy	p-value
UIP CT lungs pattern				
Sliding sign	16.7%	95%	0.55 (0.42-0.68)	0.396
Pleural line irregularity	95.8%	41.5%	0.68 (0.58-0.78)	0.004
Pleural thickness	70.8%	73.2%	0.72 (0.60-0.83)	0.001
B-lines	54.2%	39.8%	0.47 (0.34-0.59)	0.643
Subpleural cyst	58.3%	78.9%	0.68 (0.56-0.81)	0.004
Pleural effusion	16,7%	95%	0.55 (0.42-0.68)	0.396
NSIP with GGO CT lungs pattern				
Sliding sign	48%	91.4%	0.48 (0.37-0.58)	0.719

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Pleural line irregularity	78.6%	41%	0.59 (0.49-0.69)	0.065
Pleural thickness	38.1%	67.6%	0.52 (0.42-0.63)	0.589
B-lines	92.9%	54.3%	0.73 (0.65-0.81)	0.0001
Subpleural cysts	23.8%	71.4%	0.47 (0.37-0.57)	0.653
Pleural effusion	4.8%	91.4%	0.48 (0.37-0.58)	0.719
NSIP with GGO and reticulation CT lungs pattern				
Sliding sign	19%	95%	0.57 (0.44-0.70)	0.254
Pleural line irregularity	96.2%	42.1%	0.69 (0.59-0.78)	0.002
Pleural thickness	65.4%	72.7%	0.69 (0.57-0.80)	0.002
B-lines	96.2%	48.8%	0.72 (0.63-0.81)	0.0001
Subpleural cyst	47.2%	76.9%	0.61 (0.49-0.74)	0.066
Pleural effusion	15.4%	42%	0.54 (0.42-0.67)	0.443

CT: computed tomography; GGO: ground glass; ILD: interstitial lung disease; LUS: lung ultrasound; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia.

4. Discussion

A large number of studies are available on the use of LUS in ILD, although a consensus has never been reached on its real clinical value, the coding and scoring system [14]. Our study adds to the other published works, introducing considerations regarding how LUS can differentiate specific lung HR-CT patterns such as NSIP, and UIP. Indeed, the present study highlights that transthoracic LUS is a enough sensitive and specific technique in evaluating the presence of typical SSc-ILD tomographic patterns and is also sufficiently accurate in discriminating its different and characteristic phases. The finding of B-lines on LUS was found to be significantly associated with the presence of active inflammatory phases of SSc-ILD, characterized by GGO, as observed in the NSIP pattern. [33–36] and that the finding of irregularities of the pleural line, of thickening of the pleural line and subpleural cysts is, instead, significantly associated with the presence of honeycombing and traction bronchiectasis, as in UIP pattern, and therefore of the fibrosis phase. So, principally, the presence or the absence of B-lines significantly differentiates the NSIP pattern from the UIP pattern.

The presence of LUS signs, such as the presence of irregularities of the pleural line, thickening of the pleural line, the presence of subpleural cysts, reduced mobility of the pleural line and the presence of B-lines, in patients with pulmonary fibrosis, was first described in 1997 [37] Other studies have evaluated the presence of these same LUS signs in ILD secondary to sarcoidosis, rheumatoid arthritis, SSc, mixed connective tissue disease, Sjogren's syndrome and primary biliary cirrhosis, demonstrating their presence also in these secondary forms of ILD [30], and highlighting, in particular, that the presence of B-lines distributed throughout the lung area is associated with more severe pulmonary fibrosis. [38] Concerning the LUS evaluation of ILD in connective tissue diseases, in previous studies, it has been observed that the greater number of B-lines could identify SSc-ILD [30; 38-39]; and, in particular, that the number of B-lines correlates with the tomographic Warrick Score, an index of severity of SSc-ILD [20]. Furthermore, the high sensitivity of B-lines in evaluating the presence of SSc-ILD has been described both in patients with a diagnosis of very early SSc [40] and those with a diagnosis of SSc. [32]

The high frequency and sensitivity, found in the present study, between the presence of B-lines and the tomographic pattern of NSIP with GGO, characteristic of active inflammatory processes

[41], could be attributed to the presence of inflammatory infiltrate that would determine a variation in acoustic impedance of the lung parenchyma, creating the air-water interface necessary for the generation of B-lines, as demonstrated in previous studies [42–44].

Concerning the cut-off of B-lines, the limit of >10 B-lines found to be sufficiently effective for recognising ILD, confirms what was previously found for ILD-SSc. [45,46]; but in our study we found a high sensitivity for the NSIP pattern, especially for the GGO-only pattern but also for the GGO and reticulations pattern. These findings have not been specifically evaluated in previous studies. However, few data support the presence of B-lines in both GGO and honeycombing patterns [14,47]. Still, no study has ever investigated the possible association between specific CT patterns, such as UIP and NSIP, and LUS signs. These results could indicate a greater sensitivity for the more inflammatory phases, which presuppose the presence of a greater inflammatory infiltrate with a subsequent increase in acoustic impedance.

In a previous study, a low specificity (55%) of B-lines was highlighted for SSc-ILD, despite a high sensitivity (100%); this finding was attributed to the probable presence of pulmonary oedema [32]; similar data was observed in our study, for both NSIP with GGO and NSIP with GGO and reticulations, but patients with pulmonary oedema, or other heart and lung diseases were excluded, so there could be other reasons yet to understand.

Regarding the tomographic pattern of UIP, a high sensitivity of LUS signs was observed, such as thickening of the pleural line, the presence of irregularities of the pleural line and the presence of subpleural cysts. This finding could be due to the presence of structural subversion of the lung parenchyma (complete loss of the typical acinar structure of the lung) observed in cases of stabilized pulmonary fibrosis, characterized tomographically by the presence of honeycombing. [48]

No data are available on the use of LUS in progressive fibrosing ILD; for the first time in this study, we observed a strict association between this ILD pattern and the presence of pleural line irregularities. Probably the subversion of the parenchymal structure could explain the irregularities of the pleural line visible with LUS. Observational studies with larger patient samples would serve to confirm this finding.

In the group of patients enrolled in this study, the percentage of SSc-ILD (63%) is in line with what has been described in other studies [1,49]; and the ENA specificity found most frequently in these patients is anti-Scl-70, as observed previously [50].

Therefore, LUS, due to its versatility, ease of handling and low maintenance costs, could assume considerable clinical importance for evaluating SSc-ILD. Furthermore, the ease of interpretation of LUS images and the rapid execution times (minimum duration < 10 minutes [32] and maximum 23 minutes [46]) make LUS an efficient instrumental method from a clinical point of view.

The accuracy and completeness of the information provided by the tomographic images, currently not obtainable by other methods, still make the chest HR-CT the gold-standard instrumental technique for diagnosing SSc-ILD. Although, probably, LUS will probably not replace the chest HR-CT for the diagnosis of SSc-ILD, at least, at the moment, it could be considered a guide to establish the most appropriate timing to perform the chest HR-CT, minimising the risk of exposure to ionising radiation [32]. In recent decades, this latter risk and the need to contain the costs related to the diagnosis and clinical management of patients has led the scientific community to identify new imaging techniques and new predictors of disease. [17–25,51–56] A LUS score with a weighted score for each LUS sign would be desirable to improve the diagnostic ability of LUS for different HR-CT patterns of ILD. The clinical utility of recognizing early and without excessive exposure to ionizing radiation, the different patterns of ILD-SSc, could have important implications in the therapeutic management of patients with SSc. Probably with the advent of artificial intelligence software, it will probably be possible to design multifactorial scores that will meet the needs of clinicians.

There are some limitations to our study such as the distance between two consecutive B-lines was not reported. This parameter has been shown to correlate with the Warrick score in patients diagnosed with pulmonary fibrosis [57], but its evaluation was not considered useful for the purposes of our study. It would have been, furthermore, interesting to compare the ultrasound data of patients with SSc-ILD with healthy subjects and other groups of patients with pathologies complicated with ILD. However, in other studies conducted on this topic, the same LUS signs highlighted in this study were also found for other forms of ILD. [30,39,58]. We did not use the scoring system of LUS, as it

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has not yet been validated. As regards the progressive fibrosing ILD, it would have been useful to evaluate the LUS in an observational study, almost in two study-time points, in conjunction with the lung HR-CT, instead, we only have one LUS detection in conjunction with the last lung HR-CT performed.

5. Conclusions

The present study, comparing two instrumental methods, such as transthoracic LUS and lung HR-CT, demonstrates that there is a satisfying association between these two methods in evaluating the presence of specific patterns of ILD. In particular, LUS has shown high sensitivity in distinguishing different tomographic ILD patterns, such as UIP, with pleural line irregularities, pleural line thickness and the presence of subpleural cells; NSIP with GGO, characterised by B-lines; and NSIP with GGO and reticulations, characterised by pleural thickness, pleural irregularities, and B-lines. Therefore, the hypothesis of using transthoracic LUS as a screening method for the evaluation of the presence of SSc-ILD and to establish, therefore, the correct timing for the execution of chest HR-CT, in order to avoid patients from excessive exposure to ionising radiation is supported.

Observational studies should be performed to confirm LUS findings to characterize the pattern of progressive fibrosing ILD.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

BMI	body mass index
CRP	C-reactive proteins
ESR	erythrocyte sedimentation rate
GGO	Ground glass opacities
LUS	Lung ultrasound
ILD	Interstitial lung disease
Lung HR-CT	chest high-resolution computed tomography
NSIP	Non-specific interstitial pneumonia
PFT	pulmonary function tests
ROC	Receiver operating characteristic
SSc	Systemic sclerosis
UIP	Usual interstitial pneumonia

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