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Clinical science

Lung ultrasound compared to computed tomography detection and automated quantification of systemic sclerosis-associated interstitial lung disease: preliminary study

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Abstract

Background: Lung ultrasound (LUS) is a promising tool for detecting SSc-associated interstitial lung disease (SSc-ILD). Currently, consensus on the best LUS findings and execution technique is lacking.

Objectives: To compare qualitative and quantitative assessment of B-lines and pleural line (PL) alterations in SSc-ILD with chest CT analysis.

Methods: During 2021–2022, consecutive SSc patients according to 2013 ACR/EULAR classification criteria underwent pulmonary functional tests (PFTs). On the same day, if a CT was performed over a ± 6 months period, LUS was performed by two certified blinded operators using a 14-scans method. The ≥10 B-lines cut-off proposed by Tardella and the Fairchild's PL criteria fulfilment were selected as qualitative findings. As quantitative assessment, total B-lines number and the quantitative PL score adapted from the semi-quantitative Pinal-Fernandez score were collected. CT scans were evaluated by two thoracic radiologists for ILD presence, with further processing by automated texture analysis software (QCT).

Results: Twenty-nine SSc patients were enrolled. Both qualitative LUS scores were significantly associated to ILD presence on CT, with Fairchild's PL criteria resulting in slightly more accuracy. Results were confirmed on multivariate analysis. All qualitative and quantitative LUS findings were found to be significantly associated with QCT ILD extension and radiological abnormalities. Mid and basal PL quantitative score correlated with mid and basal QCT ILD extents. Both B-lines and PL alterations differently correlated with PFTs and clinical variables.

Conclusion: This preliminary study suggests the utility of a comprehensive LUS assessment for SSc-ILD detection compared with CT and QCT.

Keywords: interstitial lung disease, lung ultrasound, systemic sclerosis, chest computed tomography, quantitative analysis, automated analysis

Rheumatology key messages

- A comprehensive lung ultrasound assessment was significantly associated with systemic sclerosis-associated interstitial lung disease.
- Pleural line score showed an anatomical correlation with disease extension on quantitative chest tomography.
- Pleural line alterations appear to reflect fibrotic structural changes more than B-lines.

Introduction

Interstitial lung disease (ILD) is one of the most frequent complications of SSc, representing a leading cause of mortality in these patients. ILD diagnosis is traditionally based on chest CT and on reduction of forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO) at pulmonary functional tests (PFTs), although there is no complete agreement on the exact execution timing during follow-up [1].

SSc-associated ILD (SSc-ILD) mostly occurs as a non-specific interstitial pneumonia, characterized by ground-glass

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opacities on CT. Other possible findings are reticulations and traction bronchiectasis, defining a fibrotic phenotype. A usual interstitial pneumonia, defined by honeycombing, is less frequent in SSc-ILD [2].

Lung ultrasound (LUS) has been in use for more than a decade for detection of SSc-ILD and is currently under standardization [3]. LUS has the advantages of being radiation-free, fast, low cost, and accessible in an outpatient setting. LUS showed good diagnostic accuracy for ILD detection compared with the current gold standard of CT [4].

Different scanning techniques are described, with the 14 lung intercostal spaces (LIS) assessment proposed by Gutierrez showing a diagnostic accuracy comparable to all-intercostal spaces evaluation and being significantly less time-consuming [5].

Traditionally, ILD on LUS is identified by the vertical hyperechoic 'B-lines' artefacts [6]. Another LUS finding is pleural line (PL) artefact modifications, highly specific for ILD on CT [7].

Most studies focused on B-lines as the main findings, describing qualitative, semiquantitative and quantitative scoring systems [8]. Among these, the cut-off of $\geq$10 B-lines on a 14-scans assessment described by Tardella showed the greatest positive likelihood ratio for the presence of significant SSc-ILD [9].

Additionally, Pinal-Fernandez proposed a semi-quantitative score to assess PL irregularity (normal-minor, moderate and severe) based on the evaluation of 72 LIS, resulting in a higher performance to detect ILD than B-lines [10]. Recently, Fairchild proposed novel 14-scans LUS interpretation criteria for PL evaluation, showing very good sensitivity and reliability [11].

Nevertheless, there is currently no consensus about the more accurate US finding for SSc-ILD detection and even less for the disease follow-up [8]. Moreover, there is currently a lack of studies involving a comprehensive LUS assessment and comparing different LUS scores with CT, particularly with automated quantitative CT (QCT) assessment. QCT has proven to be effective in identifying SSc-ILD, resulting in being associated with worse PFTs values [12]. Furthermore, total pulmonary vascular volume assessed by texture analysis software was found to correlate with SSc-ILD [13]. Very recently, Bruni *et al.* described total B-lines count correlating with QCT densitometric indexes [14], but data on LUS against lung texture analysis are missing.

Objectives

This study aimed to evaluate the accuracy of LUS B-lines and PL alterations as qualitative assessment in SSc-ILD detection compared with CT and to evaluate the association of qualitative and quantitative LUS analysis with QCT via texture analysis software.

Methods

From May 2021 to May 2022, consecutive SSc patients according to ACR/EULAR 2013 classification criteria who underwent PFTs with DLCO were prospectively evaluated for enrolment. Inclusion criteria was an available CT performed $\pm$6 months the visit date. Patients with pulmonary arterial hypertension (also those with indirect signs evidenced at echocardiography), history of lower airways infection in the previous 6 months or chest radiating therapy were excluded. Written and oral consensus was obtained. The ethics committee of Policlinico Umberto I hospital has approved the study.

LUS assessment

On the same day as PFTs, LUS was performed by two blinded certified operators. An ESAOTE® MyLabGamma sonograph with a linear 3–13 MHz probe and a musculoskeletal presetting was used. For each patient, 14 LIS with sagittal scans were evaluated (Supplementary Table S1A, available at *Rheumatology* online). The total number of B-lines was collected (quantitative assessment) and the Tardella's cut-off of $\geq$10 B-lines was selected as qualitative analysis [9]. Regarding PL modifications, the Fairchild's criteria were applied as qualitative assessment [11] (Supplementary Table S1B, available at *Rheumatology* online). Due to the lack of a 14-scans quantitative PL score, we adapted the semiquantitative score from Pinal-Fernandez, by summing the PL score (0–2) value for each LIS [10]. LUS findings were further classified into apical, mid and basal to compare quantitative alterations with ILD extension on QCT (Supplementary Table S1C, available at *Rheumatology* online).

CT analysis

CT images performed on $\pm$6 months were collected and examined in agreement by two thoracic radiologists to determine ILD presence. CT scans were further analysed by Imbio® 'Lung Texture Analysis' (LTA) software, based on Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) technology. It characterizes and quantifies lung parenchymal patterns [ground-glass, reticular, honeycombing, total fibrosis score (combining honeycombing and reticulation) and total ILD score (combining ground-glass, reticular and honeycombing)] on CT scans (Supplementary Figure S1, available at *Rheumatology* online). Total lung volume is further divided into apical, mid and basal sections. The software has already been applied in SSc-ILD [13, 15].

Statistical analysis

Statistical analysis of the results was performed using GraphPad Prism 8 for Windows. Cohen's kappa (k) was used to assess the inter-operator agreement for qualitative variables. Bland-Altman plot was used to assess agreement for quantitative variables. Linear regression was performed to compare qualitative LUS scores with the extent of pulmonary involvement on CT scans, reporting β coefficient. Multivariate analysis models was generated to adjust the association between dependent variables (qualitative LUS scores) and independent variables for potential confounders. Logistic regression with the area under the curve (AUC) was used to evaluate the accuracy of LUS qualitative scores. Spearman's r index was adopted for correlations of quantitative score. A 95% CI and P-value <0.05 was chosen as significant.

Results

Eighty SSc patients were enrolled. After excluding those who had no CT available or performed in a time longer than six months and CT scans non-compatible with the software, the final study population consisted of 29 patients (23 female, 6 male). Median age (quartiles) was 59 (49; 70) years and

median disease duration was 8 (4; 12) years. Twenty (68.9%) of them had a diffuse cutaneous disease and 16 (55.1%) were positive for anti-topoisomerase I antibodies (Table 1).

LUS assessment

LUS assessment showed Fairchild's criteria fulfilment in 21 patients (72.4%) and ≥10 B-lines cut-off in 21 patients (72.4%). Median total B-lines number was 24 (8; 57) and the median quantitative PL score was 13 (4; 22) (Table 1). The agreement between two LUS operators was almost perfect for Fairchild's criteria [Cohen's kappa (k) 0.84] and substantial for the ≥10 B-lines cut-off (k 0.78). The Bland–Altman plot showed an average bias of 1.28 (-6.7–7.1 95% limits of agreement) for total B-lines number and 0.17 (-0.49–3 95% limits of agreement) for quantitative PL score. Both qualitative and quantitative scores resulted significantly associated to each other (Supplementary Table S2A and B, Available at *Rheumatology* online).

CT analysis

ILD presence was detected in 22 (75.9%) patients on CT. LTA reported median values of total ILD volume (cm^3) of 323 (70; 652) [8.2% of total lung (1.6; 18.6)] and total fibrosis volume of 56 (30; 121) [1.4% (0.7; 5.5)]. Detailed LTA data are reported in Table 1.

LUS assessment compared with CT

Fairchild's criteria showed a sensitivity (CI) of 91% (71, 99), a specificity of 86% (42, 99), a positive predictive value (PPV) of 95% (76, 99), a negative predictive value (NPV) of 75% (43, 92) and an accuracy of 90% (73, 98), with an AUC of 0.85. The ≥10 B-lines cut-off had 91% (71, 99) sensitivity, 57% (18, 90) specificity, 87% (74, 94) PPV, 67% (31, 90) NPV and 83% (64, 94) accuracy, with AUC of 0.77 (Fig. 1A).

Both Fairchild's criteria and ≥10 B-lines cut-off were found significantly associated with ILD presence on CT, after introducing confounders like age, disease duration, ongoing immunosuppressant therapy and current/ever smoking on multivariate analysis [respectively β_1 0.6106 (CI 0.3165, 0.9047), *P* 0.0003, and *P* 0.03, β_1 0.4346 (CI 0.044, 0.825)].

Both Fairchild's criteria and ≥10 B-lines cut-off were significantly associated with total ILD and total ground-glass volumes on QCT. Fairchild's criteria were also associated with

Table 1. Descriptive data of study population, LUS assessment and QCT LTA software analysis

Patients' characteristics	
Female/male, *n* (%)	26/3 (89.6/10.4)
Median age (years) [quartiles]	59 [49;70]
Median disease duration (years) [quartiles]	8 [4;12]
Diffuse/limited cutaneous disease, *n* (%)	20/9 (69/31)
ATA I/anti-centromere antibodies positivity *n* (%)	16/5 (55/17.2)
Digital ulcers presence, *n* (%)	6 (20.7)
Gastro-intestinal manifestations, *n* (%)	7 (24.1)
Immunosuppressive therapy, *n* (%)	15 (51.7)
Median FVC % [quartiles]	96 [78;110]
Median DLCO % [quartiles]	70 [54;84]
Median DLCO/VA % [quartiles]	88 [75;102]
Median TLC % [quartiles]	91 [75;100]
ILD presence on CT *n* (%)	22 (75.9)
NSIP/UIP CT pattern, *n* (%)	21/1 (95.5/0.05)
LUS assessment	
Fairchild's criteria for PL fulfilling, *n* (%)[a]	21 (72.4)
≥10 cumulative B-lines, *n* (%)[a]	21 (72.4)
Total B-lines (median [quartiles])	24 [8;57]
Total PL quantitative score (median [quartiles])	13 [4;22]
Apical lung fields B-lines (median [quartiles])	3 [0;8]
Middle lung fields B-lines (median [quartiles])	7 [1.5;19]
Basal lung fields B-lines (median [quartiles])	15 [4;27]
Apical lung fields PL quantitative score (median [quartiles])	2 [0;3]
Middle lung fields PL quantitative score (median [quartiles])	5 [1;8.5]
Basal lung fields PL quantitative score (median [quartiles])	7 [3;12]
QCT analysis	
Healthy lung volume (cm^3 / %) (median [quartiles])	3988 [1971;4254] / 87 [78;93]
PVV (cm^3) (median [quartiles])	91 [67;108]
Ground-glass (cm^3 / %) (median [quartiles])	179 [30;578] / 3.8 [0.65;15]
Reticulations (cm^3 / %) (median [quartiles])	47 [28;103] / 1.2 [0.6;5.2]
Honeycombing (cm^3 / %) (median [quartiles])	3.7 [0.5;10] / 0.1 [0;0.25]
Total fibrosis (cm^3 / %) (median [quartiles])	56 [30;121] / 1.4 [0.7;5.6]
Total ILD volume (cm^3 / %) (median [quartiles])	323 [70;652] / 8.2 [1.6;19]
Apical ILD (cm^3) (median [quartiles])	17 [2.4;54]
Middle ILD (cm^3) (median [quartiles])	85 [4.8;185]
Basal ILD (cm^3) (median [quartiles])	191 [51;305]

[a] Patients are not the same.

ATA I: anti-topoisomerase I antibodies; CT: chest computed tomography; DLCO: diffusing capacity of carbon monoxide; FVC: forced vital capacity; ILD: interstitial lung disease; LTA: lung texture analysis; LUS: lung ultrasound; NSIP: non-specific interstitial pneumonia; PL: pleural line; PVV: pulmonary vessel volume; QCT: quantitative chest tomography; TLC: total lung capacity; UIP: usual interstitial pneumonia; VA: alveolar volume.

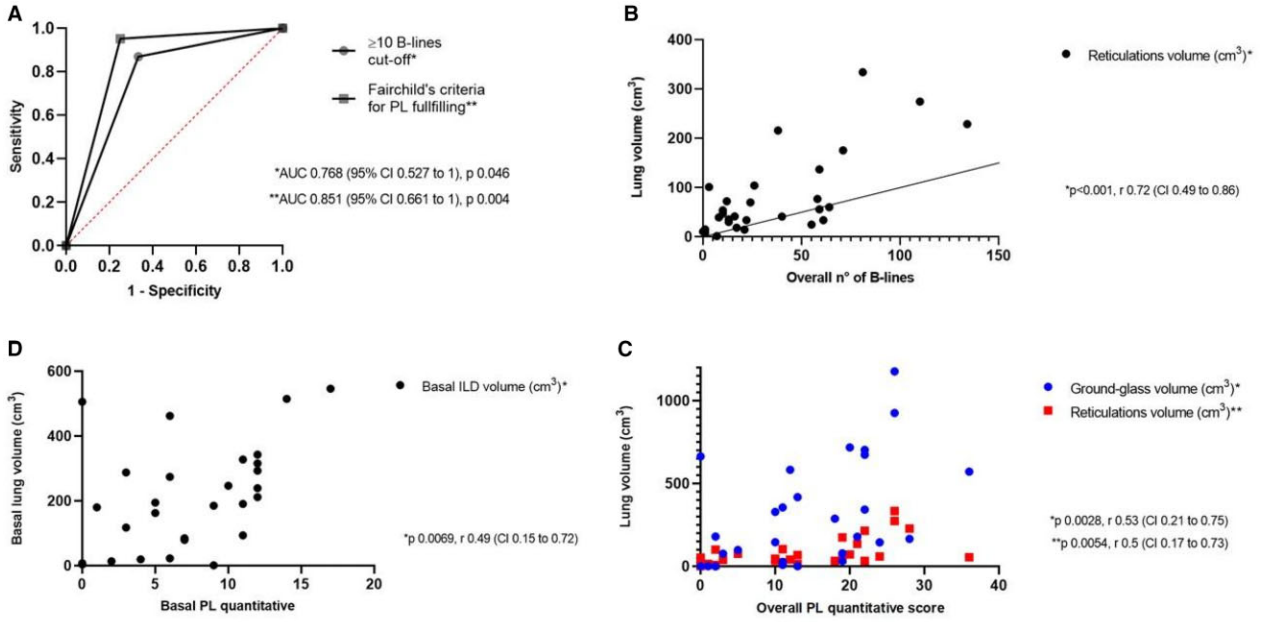

Figure 1. Significant associations of LUS scores with CT and automated QCT. (**A**) ROC curve of Fairchild's criteria and ≥10 B-lines cut-off accuracy to detect SSc-ILD as assessed by CT. (**B**) Correlation of overall B-lines number with reticulations volume. (**C**) Correlation of overall PL quantitative score with ground-glass and reticulations volumes. (**D**) Correlation of basal PL quantitative score with corresponding basal ILD volume. AUC: area under the curve; CI: 95% CI; CT: chest tomography; PL: pleural line; ROC: receiver operating characteristic; SSc-ILD: systemic sclerosis-associated interstitial lung disease

total fibrosis and total reticulation volumes (Supplementary Table S2A, available at *Rheumatology* online).

Both total B-lines number and total quantitative PL score positively correlated with total ILD, total fibrosis and reticulation volumes (Supplementary Table S2B, available at *Rheumatology* online, Fig. 1C). Total PL score positively correlated also with ground-glass volume (Fig. 1C).

No significant correlation of apical, mid and basal number of B-lines with ILD extension of corresponding QCT lung fields was found. Mid and basal lung PL score positively correlated with mid and basal ILD volume [respectively *P* 0.029, r 0.4 (0.44–0.67) and *P* 0.0069, r 0.49 (0.15–0.73) (Fig. 1D)]. Both basal B-lines number and basal PL score positively correlated with total ILD score, total fibrosis score and total reticulation volumes. Basal lung PL score also correlated with total ground-glass volume (Supplementary Table S2C, available at *Rheumatology* online).

LUS assessment compared with PFTs and clinical and laboratory data

Both total B-lines number and total PL quantitative score sum negatively correlated with predicted FVC% and TLC%. Total B-lines also negatively correlated with predicted DLCO% (Supplementary Table S2B, available at *Rheumatology* online).

Regarding clinical and laboratory data, Fairchild's criteria were found significantly associated with anti-topoisomerase I antibodies positivity (Supplementary Table S2A, available at *Rheumatology* online) and basal B-lines number positively correlated with the presence of digital ulcers and gastro-oesophageal reflux symptoms (Supplementary Table S2B, available at *Rheumatology* online).

Discussion

In our preliminary study, we comprehensively tested LUS findings with CT for defining ILD presence and with QCT by using texture analysis software for ILD extent assessment. As far as we are concerned, we were the first to assess SSc-ILD by the evaluation of both B-lines and PL alterations (qualitatively and quantitatively), also analysing the involvement of apical, mid and basal lung fields. Moreover, these LUS methods were tested for the first time against QCT, that overcomes the intra- and inter-reader variability of visual CT analyses [16].

Our results showed both Fairchild's criteria and B-lines cut-off having good sensitivity values, results associated with ILC on CT on multivariate analysis. However, Fairchild's criteria had higher specificity, positive predictive value and accuracy, presenting also higher reproducibility. Our results are similar to Fairchild's study and seem to confirm the reliability of this score for SSc-ILD detection [11].

Furthermore, both scores were significantly associated with total ILD and ground-glass volumes on QTC, with Fairchild's criteria result additionally associated with total fibrosis and reticulations volumes. It suggests that PL modifications might reflect a more progressive lung involvement, as described in a recent preliminary study of patients with different forms of ILD [17].

As regards quantitative findings, we collected the total B-lines number. Due to the lack of a specific 14-scans SSc-ILD scoring system for PL alterations, we adapted the semiquantitative score proposed by Pinal-Fernandez. It was found associated witch total lung ILD and correlated to all radiological abnormalities on QCT, proving to be a promising score for quantitative LUS evaluation of ILD, also due to its good

reproducibility. We also noticed that both basal B-lines and PL quantitative score were associated to total lung ILD. Moreover, mid and basal lung PL score positively correlated with mid and basal ILD volume on QCT, whereas B-lines showed no correlation for any lung fields. These results may indicate that both basal lung quantitative findings could be predictive of entire lung involvement. Furthermore, basal lung PL assessment could accurately reflect structural damage on CT, also due to its greater specificity for ILD compared with B-lines [7]. Therefore, our preliminary data suggest that quantitative PL alterations assessment may represent a more accurate sonographic indicator of SSc-ILD, rather than B-lines, although this needs to be confirmed in larger cohorts.

As regards correlations with PFTs, we obtained a negative correlation of quantitative PL findings with predicted FVC% and TLC%, whereas the total number of B-lines negatively correlated also with predicted DLCO%, confirming literature data [9, 12]. This would hypothesize that a combined evaluation by both LUS methods could be adopted as a surrogate of functional deterioration.

Lastly, Fairchild's criteria were found associated with ATA I positivity, notably linked to a worse prognosis and predictive of SSc-ILD [18].

Besides, basal B-lines number was associated with digital ulcers presence, as reported also by Gasperini *et al.* [19] and with gastro-oesophageal reflux symptoms, that was found associated to ILD worsening [20].

Our study has several limitations. The first limitation is the small study population number; therefore, our results need to be confirmed in larger population and in prospective cohorts. Another limitation is the CT scan timing within a 6-months interval from the LUS performance, which may have caused a slight discrepancy in structural and functional abnormalities. Moreover, a form of selection bias is present. In fact, CT scans could be performed either as a periodic check-up or because clinically required, led to a study population at higher risk of ILD. This may have affected positive and negative predictive values. Finally, as the CTs were collected retrospectively, we had to exclude some of them as not being compatible with the software acquisition requirements.

On the other hand, the strengths of our report are the quantitative and qualitative assessments of both LUS findings performed by two blind operators using the same evidence-based scoring systems and machine setting and the adoption of QCT texture analysis, as well as the confirmation of results by multivariate analysis.

Conclusion

This preliminary study suggests the usefulness of both LUS B-lines and PL alterations as valid tools for SSc-ILD assessment. However, PL alterations analysis seems to be more reliable in both SSc-ILD detection and quantification. On the other hand, a comprehensive LUS assessment might better reflect functional and clinical findings.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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