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Ultrasound B-lines in the evaluation of interstitial lung disease in patients with systemic sclerosis
Cut-off point definition for the presence of significant pulmonary fibrosis

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Abstract

The aim of this study was to establish the cut-off point of ultrasound (US) B-lines number for detecting the presence of significant interstitial lung disease (ILD) in patients with systemic sclerosis (SSc) (SSc-ILD) in relation to high-resolution computed tomography (HRCT) findings.

Consecutive SSc-ILD patients underwent chest HRCT, lung US (LUS), pulmonary function test, and clinical assessment. Exclusion criteria were represented by the presence of a coexisting congestive heart failure and a clinical history suggestive of lung or pleural diseases. HRCT images were scored for the presence of ILD by 2 readers, in accordance with the Warrick scoring system. US assessment was performed by a US skilled rheumatologist, blinded to HRCT results and clinical data, and included the bilateral evaluation of 14 lung intercostal spaces (LIS). In each LIS, the number of B-lines was recorded and summed. To test discriminant validity, we used the receiver operating characteristic (ROC) curve analysis applying a Warrick score of 7 as external criterion for the presence of SSc-ILD.

Forty patients completed the study. The US B-lines number and the Warrick score confirmed excellent correlation (Spearman rho: 0.958, $P = .0001$). The ROC curve analysis revealed that the presence of 10 US B-lines is the cut-off point with the greatest positive likelihood ratio (12.52) for the presence of significant SSc-ILD.

The detection of 10 B-lines is highly predictive for the HRCT presence of significant SSc-ILD. In SSc patients, the LUS assessment as first imaging tool may represent an effective model to improve the correct timing of chest HRCT.

Abbreviations: AUC = area under the curve, CIs = confidence intervals, DLco = diffusion capacity of carbon monoxide, FEV1 = forced expiratory volume in the first second, FVC = forced vital capacity, HRCT = high-resolution computed tomography, HRQoL = health-related quality of life, ILD = interstitial lung disease, KL-6 = Krebs von den Lungen-6, LIS = lung intercostal spaces, LUS = lung ultrasonography, MCS: mental component summary scale score, PCS = physical component summary scale score, PFTs = pulmonary function tests, ROC = receiver operating characteristic, SF-36 = Short-Form 36 questionnaire, SP-D = surfactant protein D, SSc = systemic sclerosis, UIP = usual interstitial pneumonia, US = ultrasound.

Keywords: B-lines, high resolution computed tomography, interstitial lung disease, systemic sclerosis, ultrasound

1. Introduction

Interstitial lung disease (ILD) is a common manifestation in patients with systemic sclerosis (SSc).[1,2] The severity of lung involvement may vary considerably and, in some cases, it can lead to respiratory failure and eventually to death.[3] Although high-resolution computed tomography (HRCT) abnormalities are

common, only 13% of patients with SSc have a severe ILD (SSc-ILD), with a reduction of forced vital capacity (FVC) of 50% of predicted in pulmonary function tests (PFTs).[4] The assessment of presence and severity of SSc-ILD and the choice of the correct treatment are 2 mandatory steps in the daily clinical practice of each rheumatologist who takes care of SSc patients.

Chest HRCT is considered the reference technique for noninvasive diagnosis of ILD.[5] In fact, HRCT provides for a detailed morphologic depiction of an even minimal lung involvement, also in those patients without any alteration in lung volumes and in diffusion capacity of carbon monoxide (DLco). However, exposure to X-ray and costs are relevant limits for its use, especially in disease evaluation and monitoring. The disease extension is commonly evaluated by HRCT, using conventional visual reader based score scoring systems. The Warrick score is the most frequently employed.[6]

Diot et al[7] correlated Warrick HRCT-score with PFTs, obtaining a HRCT score of 7 as the value that correspond to the best compromise between sensitivity and specificity to predict significant PFTs abnormalities in patients with SSc-ILD.

Ultrasound evaluation of the lung (LUS) has been extensively explored in the last decade.[8–11] It is stated that LUS is superior to conventional chest radiography for detecting ILD, in particular

considering its very high negative predictive value.[12] It is indeed considered a basic technique for the diagnosis of ILD.[13] In 2011, we proposed a simplified US assessment to evaluate the presence of B-lines in connective tissues diseases,[14] and we found a significant correlation with Warrick HRCT-score.

The main aim of the present study was to determine a cut-off value of LUS-score predictive of significant interstitial abnormalities on HRCT, evaluated with a conventional visual reader-based score, namely the Warrick method. Second, the differences in PFTs and health-related quality of life (HRQoL) aspects were evaluated in the 2 groups of patients, categorized in significant or not-significant interstitial abnormalities according to the derived LUS cut-off value.

2. Materials and methods

2.1. Study population

From April 2016 to June 2017, consecutive SSc patients attending the outpatient and inpatient clinics of the Rheumatological Clinic of Università Politecnica delle Marche (Jesi, Italy) have been enrolled. The inclusion criteria were the following: age >18 years and a defined diagnosis of SSc, made according to the international criteria for SSc.[15] Exclusion criteria were the presence of a personal history of pulmonary diseases different from secondary ILD, heart failure, previous pulmonary surgical procedures, and absence of recent or current respiratory infections.

2.2. Study protocol

All patients underwent the following procedures in the same day: a complete clinical evaluation by an expert rheumatologist (MDC), comprehensive of Rodnan skin score assessment. HRQoL was evaluated using the validated Italian version of the self-administered Medical Outcomes Study Short-Form 36 (SF-36; IQOLA SF-36 Italian Version 1.6)[16]; PFTs and DLco measure; and LUS assessment. HRCT examinations were carried out at the Clinic of Radiology of the same University and performed within the 7 days after LUS assessment.

All patients signed the informed consent for the anonymous analysis of the data. In accordance with the policy of our University, local ethics committee approval is not required, as all patients underwent to clinical and instrumental examination (nonintervention) according to our standard of care for SSc patients.

2.3. Pulmonary function tests

Standard spirometric measurements of lung volumes, flow indices, and DLco were performed in the Lung Function Laboratory of the Pulmonary Department (Ospedale "Carlo Urbani", Jesi, Italy). FVC and forced expiratory volume in the first second (FEV1) were measured with a computerized lung analyzer (Masterscreen PFT-PRO; Viasys Jaeger, Höchberg, Germany). The DLco was determined as the single-breath diffusing lung capacity and corrected for hemoglobin and CO levels. The results were expressed as percentages of predicted values.

2.4. LUS assessment

LUS examinations were performed using a MyLab Twice (Esaote S.p.A., Genoa, Italy), equipped with a 4 to 13 MHz broadband linear transducer, according to the recently published data.[17] The examinations were carried out by a rheumatologist expert in

LUS (MT), blinded to clinical and PFTs findings. LUS simplified score was obtained summing the number of US B-lines found in each intercostal space, as described by Gutierrez et al.[14] Briefly, this assessment include 14 lung intercostal spaces (LIS): for the anterior chest the second LIS along the para-sternal lines and the fourth LIS along the mid-clavear, anterior axillary and mid-axillary lines; for the posterior chest, the eighth LIS along the paravertebral, sub-scapolar, and posterior axillary lines. Few B-lines were simply counted. If they were confluent, the semiquantification rule suggested by Gargani and Volpicelli was considered, that is, the percentage of scanning site occupied by B-lines divided by 10 (i.e., 30% of white screen corresponds to 3 B-lines, 40% to 4 B-lines, and so on).[18] Figure 1 provides an example of the classic B-line pattern in comparison with the normal lung.

2.5. HRCT assessment and disease quantification

HRCT examinations were performed according to standard protocol using a CT 64 General Electric Light Speed VCT power scanner (GE Healthcare) with a rotation tube scanning time of 0.65 s. Scans were obtained at full inspiration from the apex to the lung base with the patients in the supine position, at 120 kV and 300 mAs and slice thickness and spacing of scans of 1.25 and 7 mm, respectively. HRCT assessment did not include the use of contrast media agents. The parenchymal abnormalities on HRCT were coded and scored by 2 blinded independent readers, according to Warrick et al.[6] The scoring system of this method is the following. For each abnormality is given a value: ground-glass appearance = 1, irregular pleural margins = 2, septal/subpleural lines = 3, honeycombing = 4, subpleural cysts = 5. In each HRCT examination, the "severity of disease" score is get adding the single point values. The "extent of disease" score was obtained by counting the number of bronchopulmonary segments involved for each abnormality: 1 to 3 segments scored as 1; 4 to 9 segments scored as 2; more than 9 segments scored as 3. The severity and extent of disease are then calculated as total HRCT score (range from 0 to 30). The HRCT images were scored by a radiologist (MC), with more than 15 years of experience in general and thoracic radiology, and by a rheumatologist (FS), with experience with the Warrick scoring method. Both of them were blinded to the clinical, PFTs, and LUS findings. The agreement between the 2 readers on the Warrick method was good (intraclass correlation coefficients: 0.80),[19] and the final score was obtained from a consensus between the 2 readers.

2.6. Statistical analysis

All data were entered into a Microsoft Excel database developed for the management of all data. The data were analyzed using the MedCalc version 16.0 (MedCalc Software, Mariakerke, Belgium). Values in this study were expressed both as means ± standard deviations (SDs) and medians (interquartile ranges, IQRs). The relationships among the HRCT segmentation analysis, the LUS results, the PFTs values, and the clinical variables were calculated using the Spearman rank correlation coefficient (rho coefficient). Furthermore, to establish the cut-off point of the US B-lines number for detecting the presence of significant SSc-ILD in relation to HRCT scoring, we used the receiver operating characteristic (ROC) curve analysis. As ROC analysis requires a dichotomous external criterion, patients were divided in 2 groups, respectively, Warrick score ≥7 or <7. ROC curves were created by plotting the true-positive proportion
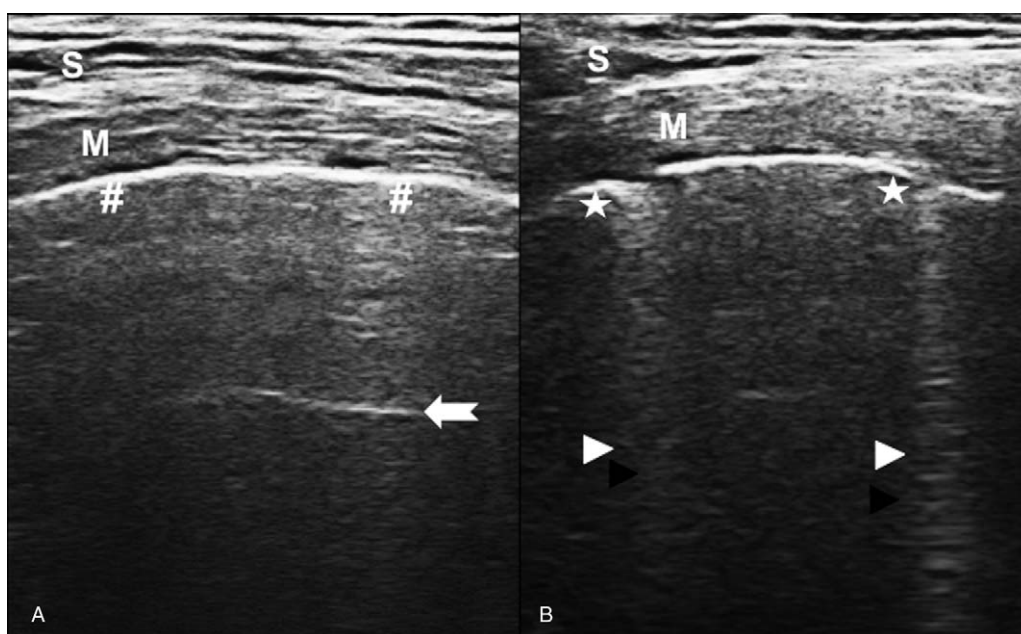
Figure 1. Ultrasonographic scans (4–13 MHz broadband linear transducer) at the level of the eighth right paravertebral lung intercostal space. (A) Normal lung with the typical reverberation artifact (line A, arrow); the normal pleural line (#) is regular. (B) Pathological lung with the presence of 2 ultrasound B-line (arrowheads), and the loss of A-line; the pathological pleural line shows irregularities (★). M = muscle of chest wall, S = subcutaneous tissues.

(sensitivity) versus the false-positive proportion (100-specificity). The area under the ROC curve (AUC) was calculated to quantify the discriminative accuracy. In accordance to Swets,[20] AUC from 0.50 to about 0.70 represent poor accuracy, those from 0.70 and 0.90 are "useful for some purposes," and higher values represent high accuracy. From the ROC curves, the optimal cut-off point corresponding to the maximum sum of sensitivity and specificity was computed. We computed ROC curves on 1000 bootstrapped samples, using nonparametric resampling and the bias-corrected and accelerated method to compute 95% confidence intervals (95% CIs).

Then, subjects were separated into 2 groups, according to the LUS cut-off obtained for significant or not significant interstitial abnormalities, and compared using the Student t test (parametric) or the Mann–Whitney U test for continuous variables (nonparametric), and the Chi-squared test for categorical variables.

Table 1

Demographic, clinical, and health-related quality of life variables, pulmonary function tests characteristics, Warrick score, and lung ultrasound findings.

	Mean	SD	Median	25–75 P
Age	56.40	13.42	56.50	50.00–66.50
Disease duration, mo	78.00	81.52	54.00	9.00–132.00
DLco (%)	67.94	21.69	68.90	51.20–85.80
FEV1 (%)	90.10	24.62	86.05	75.60–102.95
FVC (%)	88.87	28.43	88.60	63.15–110.30
Rodnan skin score	8.85	7.96	6.50	3.00–10.50
SF-36 physical activity	53.72	22.11	55.00	35.00–78.00
SF-36 social activity	50.62	19.74	43.50	37.00–62.00
SF-36 pain	58.87	25.11	41.00	41.00–82.50
SF-36 emotionality	47.60	32.64	41.50	33.00–66.00
SF-36 physical limitation	53.00	37.83	25.00	25.00–100.00
SF-36 psychological health	50.40	19.25	44.00	32.00–66.00
SF-36 physical health	42.35	16.95	45.00	30.00–49.50
SF-36 vitality	50.97	13.31	50.00	35.00–60.00
SF-36 MCS	50.08	16.36	48.30	37.30–61.50
SF-36 PCS	43.36	15.58	42.60	29.70–56.10
Total LUS score	21.17	15.29	19.50	5.50–32.00
Warrick score extension	7.30	5.05	8.00	3.00–9.00
Warrick score severity	6.25	5.02	6.00	3.00–6.50
Warrick score total	13.57	9.97	13.50	6.00–15.00

DLco = diffusion capacity of carbon monoxide, FEV1 = forced expiratory volume in the first second, FVC = forced vital capacity, LUS = lung ultrasound, MCS = Mental Component Summary Scale Score, P = percentile, PCS = Physical Component Summary Scale Score, SD = standard deviation, SF-36 = Short Form 36 questionnaire.

Table 2

Receiver operating characteristic curve analysis applying a Warrick score of 7 as external criterion for the presence of interstitial lung disease.

Number of B-lines	Sensitivity	95% CI	Specificity	95% CI	LR+
≥2	100.00	87.2–100.0	0.00	0.0–24.7	1.00
>2	100.00	87.2–100.0	15.38	1.9–45.4	1.18
>3	100.00	87.2–100.0	46.15	19.2–74.9	1.86
>4	100.00	87.2–100.0	61.54	31.6–86.1	2.60
>5	100.00	87.2–100.0	69.23	38.6–90.9	3.25
>8	100.00	87.2–100.0	76.92	46.2–95.0	4.33
>9	96.30	81.0–99.9	84.62	54.6–98.1	6.26
>10	**96.30**	**81.0–99.9**	**92.31**	**64.0–99.8**	**12.52**
>11	92.59	75.7–99.1	92.31	64.0–99.8	12.04
>14	88.89	70.8–97.6	92.31	64.0–99.8	11.56
>15	85.19	66.3–95.8	92.31	64.0–99.8	11.07
>16	81.48	61.9–93.7	92.31	64.0–99.8	10.59
>19	70.37	49.8–86.2	92.31	64.0–99.8	9.15
>20	59.26	38.8–77.6	92.31	64.0–99.8	7.70
>21	55.56	35.3–74.5	92.31	64.0–99.8	7.22
>22	51.85	31.9–71.3	92.31	64.0–99.8	6.74

CI = confidence interval, LR+ = positive likelihood ratio.
Bold is used to emphasize the 10 B-lines.

3. Results

Forty patients (34 women, 6 men) with a defined diagnosis of SSc were included in our study. Demographic and clinical data are reported in Table 1. The mean time to perform the LUS examination was 8.7 ± 1.3 minutes. In our cohort, we found a mean LUS-score of 21.17 (SD $\pm$ 15.29), and a median of 19.5. The mean HRCT Warrick score resulted 13.57 (SD $\pm$ 9.97), and median 13.5. Twenty-seven patients had a total Warrick score ≥7. From this cut-off value, which defines a significant ILD, we derived the LUS cut-off value of B-lines. Thus, using a Warrick score ≥7 as external criterion, the ROC curve analysis showed that the presence of 10 US B-lines is the cut-off point with the greatest positive likelihood ratio (LR+ 12.52) for the presence of significant SSc-ILD (Table 2, Fig. 2). This value represents the

best compromise between the best sensitivity (96.3%) and specificity (92.3%).

The analysis of the degree of relationship among the variables showed a very strong correlation between the total LUS score and the Warrick score (rho = 0.819, $P < .001$). A strong correlation between LUS score and DLco (rho = 0.600, $P < .001$) was also observed, while a moderate correlation was seen with SF-36 mental component summary scale score (MCS), SF-36 physical component summary scale score (PCS) (respectively rho = 0.529, $P < .001$; and rho = 0.560, $P < .001$), and with FVC (rho = 0.507, $P = .001$). A weak correlation was found with disease duration and Rodnan skin score (respectively rho = 0.344, $P = .030$; rho = 0.033; $P = .842$) (Table 3).

Compared with the patients with a lower number of B-lines, the presence of a LUS score ≥10 results in lower mean values of DLco (64.64 ± 21.68 vs 84.77 ± 13.56, $P = .005$), FVC (92.07 ± 30.92 vs 107.64 ± 12.67, $P = .005$), and in worse outcomes in almost all the domains of SF-36 (Fig. 3).

4. Discussion

During the last years, a growing interest on the role of LUS in the detection of SSc-ILD raised.[10–14,21–24] However, up to now, the right placement of LUS in the diagnostic or follow-up route of SSc-ILD patients has not been clarified. In this work, a cut-off point for LUS was defined: if 10 B-lines are detectable, there is a high probability to face a SSc-ILD deserving a HRCT scan. To the best of our knowledge, this is the first study that proposes a prognostic threshold for LUS in patient with SSc-ILD. The definition of a cut-off may be useful to standardize the clinical decisional making process in an otherwise confusing scenario.[25]

Thus, in our opinion, the opportunity to use LUS like a referral model in clinical practice is conceivable and, theoretically, LUS could be placed as first pulmonary imaging technique in subjects with suspected SSc-ILD.

It should not be forgotten that patients with a very early diagnosis of SSc are commonly young women, and any efforts to avoid the exposure to ionizing radiations are mandatory. In fact, in many fields of medicine, there is a large interest in reducing the radiation exposure in the management of chronic diseases.[26]
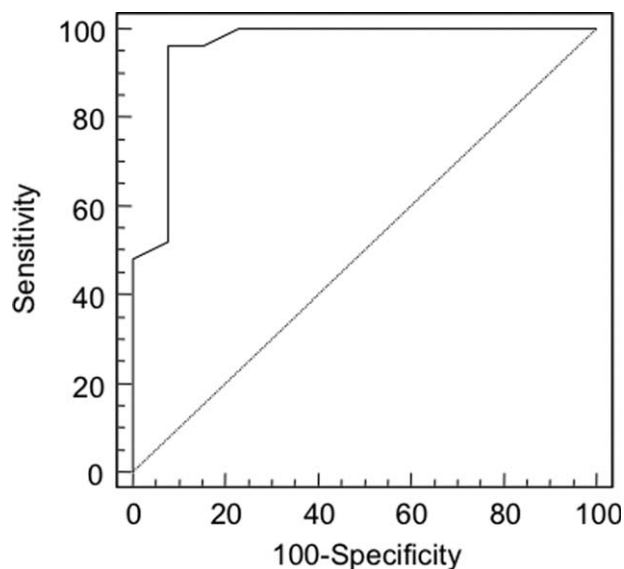
Figure 2. Area under the receiver operating characteristic curve (AUC-ROC) to discriminate the ability of lung ultrasonography (number of B-lines) to distinguish patients with not-significant or significant interstitial abnormalities applying a Warrick score ≥7 as external criterion for the presence of interstitial lung disease.

Table 3

Correlation table (Spearman rank correlation coefficient) among clinical and health-related quality of life variables, pulmonary function tests characteristics, Warrick score, and lung ultrasound finding.

		DLco (%)	FEV1 (%)	FVC (%)	Rodnan skin score	SF-36 MCS	SF-36 PCS	Total LUS score	Warrick total score
Disease duration, mo	Correlation coefficient (rho)	0.175	0.137	0.085	0.436	0.234	0.105	-0.344	-0.420
	Significance Level P	.279	.398	.602	.005	.147	.520	.030	.007
DLco (%)	Correlation coefficient (rho)		.757	0.793	0.152	0.501	0.636	-0.600	-0.725
	Significance Level P		<.001	<.001	.348	.001	<.001	<.001	<.001
FEV1 (%)	Correlation coefficient (rho)			0.873	0.034	0.555	0.588	-0.439	-0.678
	Significance Level P			<.001	.833	<.001	<.001	.005	<.001
FVC (%)	Correlation coefficient (rho)				0.062	0.461	0.548	-0.507	-0.682
	Significance Level P				.706	.003	<.001	.001	<.001
Rodnan skin score	Correlation coefficient (rho)					0.070	0.051	-0.033	-0.145
	Significance Level P					.666	.754	.842	.373
SF-36 MCS	Correlation coefficient (rho)						0.850	-0.529	-0.667
	Significance Level P						<.001	<.001	<.001
SF-36 PCS	Correlation coefficient (rho)							-0.560	-0.663
	Significance Level P							<.001	<.001
Total LUS score	Correlation coefficient (rho)								0.819
	Significance Level P								<.001

DLco = diffusion capacity of carbon monoxide, FEV1 = forced expiratory volume in the first second, FVC = forced vital capacity, LUS = lung ultrasound, MCS = mental component summary scale score, PCS = physical component summary scale score, SF-36 = Short Form 36 questionnaire.

LUS is very useful to explore the pleura and peripheral lung regions adjacent to the pleura, the areas in which the interstitial abnormalities related to SSc are earlier detectable.[27] The interstitial abnormalities early detectable under SSc-ILD are represented by B-lines. B-lines consist of discrete laser-like vertical hyperechoic reverberation artifacts, which are generated by the pleural line and extending to the bottom of the screen.[13] The presence of multiple B-lines represents the sonographic appearance of the "lung interstitial syndrome." These artifacts are generated by high-impedance discontinuities due to the close opposition between alveolar air and interstitial fluids.[28] Under the so-called "B-pattern" are included different syndromes: pulmonary edema, interstitial pneumonia, and diffuse parenchymal lung disease. The LUS signs suggestive of ILD are pleural line abnormalities (such as irregularities, fragmentations, and thickening), subpleural abnormalities (small echo-poor areas), and the nonhomogeneous and bilateral distribution of B-lines.[29]

Other advantages of LUS include easy to carry out, cheap, repeatable, and reproducible in outpatient evaluation.[10]

However, sonography has important limitations. Up to now, a unique way to perform the LUS does not exist, both in terms of the LIS to be evaluated, and both in terms of machine equipment. In this research, 14 LIS have been studied, in accordance to a simplified method,[14] with a linear 4 to 13 MHz probe. Moreover, LUS explores only the pleural and subpleural portions: indeed, it does not provide information of the deeper lung zones and cannot explore parenchymal details.
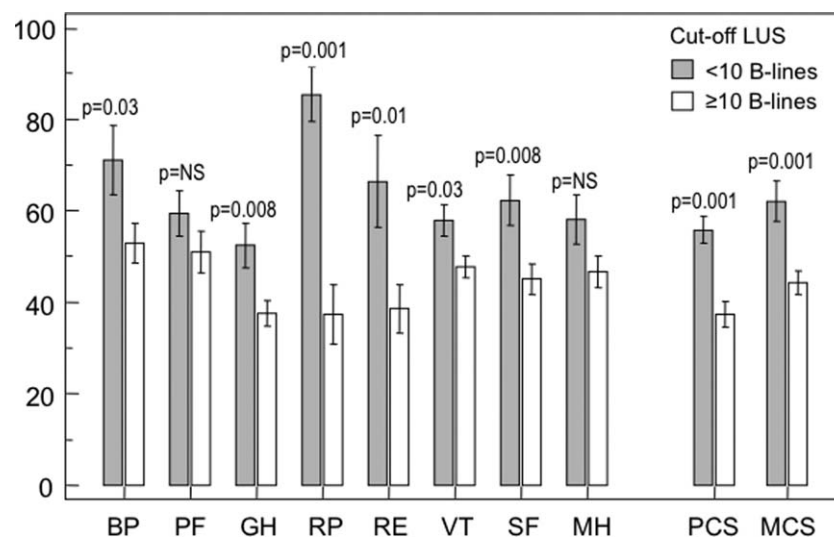

Figure 3. Histograms comparing the Short-Form 36 questionnaire subscales between patients with not-significant (<10 B-lines) or significant (≥10 B-lines) interstitial abnormalities. Differences determined by the Mann–Whitney U test. Means (error bars: 1 standard error of the mean). BP = bodily pain, GH = general health perception, MCS = mental component summary scale score, MH = mental health, PCS = physical component summary scale score; PF = physical functioning, RE = role-emotional, RP = role-physical, SF = social functioning, VT = vitality, .

Conversely, HRCT advantages are striking in the morphological representation of the lung and in the definition of a ILD pattern [usual interstitial pneumonia (UIP) or non-UIP]. Several computerized tools are currently available to automatically segment the lung with a consequent fast and precise quantitative estimation of disease extent.[29]

LUS should not be regarded as an alternative tool to HRCT, which demonstrated to correlate with lung histology and to predict the prognosis of the disease.[30]

Future studies also have to evaluate the correlation between LUS and the promising serum biomarkers, such as surfactant protein D (SP-D) and Krebs von den Lungen-6 (KL-6).[31,32] In particular, recent studies demonstrated that KL-6 reflects alveolitis and alveolar damage, and correlates positively with DLco, HRCT score, and honeycombing.[33]

Regarding the second aim of this study, a strong correlation between LUS total score and DLco, and a moderate correlation between LUS total score and SF-36 subscales have been demonstrated. Intuitively and in accordance with the data obtained in a previous study, [10] a major extension of ILD results in worse pulmonary exchanges and in a poor HRQoL.

The present study has some limitations, which have to be mentioned. The first one is that we did not assess a normal population as control group. This issue is difficult to be addressed: performing a HRCT in healthy people is not ethical. The second one is the limited number of patients enrolled.

5. Conclusion

Up to now, the perfect way to early detect SSc-ILD has not yet been defined, and probably will arise from the integration of imaging techniques and PFTs.[34]

Despite the absence of an unequivocal role and few data in current medical literature, LUS is a valuable diagnostic tool for SSc-ILD and may represent an important referral model. The presence of a LUS score superior or equal to 10 B-lines is predictive for the presence of significant SSc-ILD. The use of LUS as first imaging tool in the evaluation of SSc patients may represent an effective model to improve the correct timing of HRCT assessment.

Author contributions

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