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Original Article

Lung ultrasound in the assessment of interstitial lung disease in patients with connective tissue disease: Performance in comparison with high-resolution computed tomography

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Running title: Lung ultrasound for the assessment of CTD-ILD

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ABSTRACT

Objective: To investigate clinical relevance of performing lung ultrasound (LUS) in patients with connective tissue disease (CTD)-associated interstitial lung disease (ILD) in comparison with high-resolution computed tomography (HRCT).

Methods: This single-centre study enrolled eligible patients with CTD-ILD from the prospective LUS registry. Total B-lines were detected by assessment at 14 sites via LUS. Forced vital capacity, diffusing lung capacity for carbon monoxide (DL_{CO}), DL_{CO}/alveolar volume, 6-minute walking distance, and the ILD-GAP index were used as ILD prognostic parameters. Correlations were examined using single and multiple regression analyses.

Results: Sixty-seven patients were enrolled, including 29 with idiopathic inflammatory myopathy or anti-synthetase syndrome, 25 with systemic sclerosis (SSc), 10 with rheumatoid arthritis, and 3 with mixed connective tissue disease. The total number of B-lines correlated with ILD extent on HRCT in patients with CTD-ILD ($r = 0.66$; $P < 0.001$), particularly in patients with SSc-ILD ($r = 0.78$; $P < 0.001$). Total B-lines and ILD extent on HRCT showed comparable correlations with prognostic parameters, while multiple regression analysis revealed the limited benefit of performing LUS in addition to HRCT in predicting correlations with prognostic factors.

Conclusions: LUS serves as an alternative tool for assessing the severity and prognosis of patients with CTD-ILD.

KEYWORDS

lung ultrasound; interstitial lung disease; high-resolution CT; systemic sclerosis; myositis

INTRODUCTION

Connective tissue disease (CTD) comprises a group of systemic autoimmune rheumatic diseases that affect multiple organ systems, such as the skin, joints, muscles, heart, lungs, and kidneys. Among these manifestations, interstitial lung disease (ILD) is a leading cause of mortality in patients with many CTDs, including systemic sclerosis (SSc), idiopathic inflammatory myopathy (IIM), rheumatoid arthritis (RA), and mixed connective tissue disease (MCTD) [1–4]. Treatment options have long been limited to glucocorticoids and nonspecific immunosuppressive agents, but recently, antifibrotic treatment and molecular-targeting drugs have been shown to prevent the progression of ILD [5–8]. The poor outcome is most notable in patients with ILD with a progressive phenotype, but the disease behaviour is highly variable and often unpredictable [9]. To implement appropriate management, it is essential to evaluate ILD severity and risk for progression accurately during the disease course.

The evidence-based Japanese consensus statements for CTD-ILD recommend high-resolution computed tomography (HRCT) of the chest as an effective and useful tool for screening, diagnosing, and assessing the severity of ILD [10]. In this regard, the extent of ILD on chest HRCT, which is supplemented with forced vital capacity (FVC) in patients with indeterminate ILD extent on HRCT, is used to predict mortality in patients with ILD associated with SSc or RA [11–13]. Recently, lung ultrasound (LUS) has attracted increased amounts of attention as a noninvasive, convenient, and readily available imaging tool for detecting ILD. Specifically, a B-line detected by LUS, which reflects fluid accumulation and/or fibrosis in thickened interlobular

septa, was shown to be useful in detecting ILD in SSc patients [14]. Since this report, a growing number of studies have reported the utility of LUS in screening for ILD in patients with CTD, especially in those with SSc [15,16]. In addition, a correlation between LUS parameters and semiquantified HRCT scores has also been demonstrated [15–20]. However, how to implement LUS in the clinical practice of CTD remains unclear. In this study, we used a single-centre LUS registry of patients with CTD-ILD to investigate whether the number of B-lines (total B-lines) measured by LUS correlated with semiquantified HRCT scoring. In addition, the correlations of the total B-line count determined by LUS with known ILD prognostic parameters were assessed via comparison with the ILD extent determined by HRCT.

METHODS

Study subjects

Eligible patients with CTD-ILD for this study were selected from the NMS-LUS registry and included consecutive patients who underwent LUS at the Scleroderma/Myositis Centre of Excellence, Nippon Medical School Hospital, Tokyo, Japan, which was launched in April 2019. The inclusion criteria were as follows: (i) satisfied at least one of the classification criteria for IIMs [21], anti-synthetase syndrome (ASS) [22], SSc [23], MCTD [24], or RA [25]; (ii) ILD confirmed by chest HRCT [26]; (iii) LUS data obtained at 14 intercostal sites [27]; and (iv) available chest HRCT and LUS images within an interval of less than 3 months. Patients with concomitant lung conditions, such as pulmonary hypertension, bronchial asthma, chronic bronchitis, chronic obstructive pulmonary disease, lung cancer, pneumoconiosis, radiation pneumonitis, or pulmonary oedema, were excluded. Patients who satisfied the classification criteria for IIM and/or ASS were regarded as the IIM/ASS group, while patients who satisfied the diagnostic criteria for MCTD were regarded as having MCTD irrespective of whether they met other classification criteria. Rapidly progressive ILD was defined as ILD presenting with progressive dyspnea and progressive hypoxemia, and a worsening of interstitial change on the chest radiograph within 1 month from the onset of respiratory symptoms [28]. This study was approved by the ethics committee of Nippon Medical School Hospital (B-2020-203), and written informed consent was obtained *a priori* from all patients.

Clinical data collection and prognostic parameters

Demographic and clinical data at the time of the first LUS examination were obtained from the NMS-LUS registry and included age, sex, body mass index (BMI), smoking history, underlying CTD, disease duration

(weeks) at CTD diagnosis, follow-up period (weeks) after confirmed diagnosis of ILD, modified Medical Research Council (MRC) dyspnoea scale, 6-minute walking distance (6MWD), and serum Krebs von den Lungen-6 (KL-6) level. Pulmonary function test parameters included forced vital capacity (FVC), diffusing lung capacity of the lung for carbon monoxide (DL_{CO}), DL_{CO}/alveolar volume (V_A), and total lung capacity (TLC), which were expressed as percentages of the predicted values. The ILD-GAP index was calculated as described previously [29]. FVC, DL_{CO}, the DL_{CO}/V_A ratio, the FVC/DL_{CO} ratio, the 6MWD, and the ILD-GAP index were regarded as prognostic factors based on previous studies conducted in patients with CTD-ILD [12,29–33].

Chest HRCT scoring

HRCT was performed with a slice thickness of 1.25 mm. Images were acquired from the apex to the base of the lungs, at the end of inspiration, in spine decubitus. No intravenous contrast material was administered. Chest HRCT was assessed by two evaluators (SY and MS) blinded to the information of LUS. The morphological pattern of ILD was classified based on the official American Thoracic Society/European Respiratory Society statement [34]. The extent of ILD was assessed semiquantitatively using the average of approximate area ratios (expressed in 5% units) occupied by all lesions associated with ILD in 5 slices according to the procedure proposed by Goh et al. [11]. The range of the extent was 0-100%, and the higher proportion meant broader areas affected by ILD. The ICC of the extent of ILD on HRCT by two evaluators was 0.78, indicating acceptable interrater reliability.

LUS assessment

LUS was performed by two trained assessors (SW and KY) blinded to the information of chest HRCT, using a Hitachi Noblus instrument equipped with a microconvex probe (4–8 MHz) (Hitachi, Tokyo, Japan). B-lines were identified according to Lichtenstein's definition, i.e., comet-tail artefact, arising from the pleural line, moving in concert with lung sliding, long and extending to the edge of the screen, resembling a laser beam, obliterating A-lines, or hyperechoic like the pleural line [35]. The number of B-lines at each intercostal site was scored according to international evidence-based recommendations: the number of B-lines was counted from zero to ten, or if confluent, the percentage of the rib space occupied by B-lines was assessed and divided by ten [36]. The total number of B-lines was calculated by summing the number of B-lines at the predefined 14 intercostal sites in both lungs [27]. The range of the number of total B-lines was 0-140, and the higher number meant broader areas

affected by ILD. The interrater reliability of the total B-line measurements was excellent, and the intraclass correlation coefficient (ICC) of the two evaluators was 0.93.

Representative LUS and HRCT images of a patient with SSc-ILD are shown in Figure 1. The intercostal site evaluated by LUS was matched with the HRCT slice. A B-line is identified as a hyperechoic signal that is similar to the pleural line and extends vertically from the pleura, corresponding to a slice of typical ILD features on HRCT. In the area of extensive ILD on HRCT, LUS demonstrated a hyperechoic 'white' signal generated by confluent B-lines below the pleural line. There was no B-line at areas corresponding to the slice with no apparent ILD on HRCT.

Statistical analysis

Continuous variables are shown as medians (interquartile ranges [IQRs]), while categorical variables are shown as percentages. The Mann–Whitney test was used to compare continuous variables between two groups, while the chi-square test or Fisher's exact probability test was used to compare proportions, as appropriate. The total number of B-lines or the extent of ILD on HRCT were used as explanatory variables, and their correlations with prognostic parameters were examined using single regression analysis with the Pearson correlation coefficient (r). Multiple regression analysis was conducted using total B-lines and ILD extent on HRCT together as explanatory variables to evaluate correlations with individual prognostic factors. The standardized partial regression coefficient (β) was used as an index of contribution to the correlations. Missing values were not imputed. $P < 0.05$ (two-tailed) was considered to indicate statistical significance. All the statistical analyses were performed with RStudio (2022.12.0+353; RStudio PBC, Vienna, Austria).

RESULTS

Clinical characteristics

Of the 100 patients enrolled in the NMS-LUS registry as of March 2022, 67 patients with CTD-ILD were eligible for this study. As shown in patient flow diagram (Figure 2), 33 patients were excluded due to the absence of ILD by chest HRCT (n = 22), LUS conducted in areas inconsistent with the predefined sites (n = 9) or no chest HRCT performed within 3 months of LUS evaluation (n = 3). There was no difference in demographic and clinical characteristics between patients included and those excluded, except prevalence of ILD (100% versus 33%, respectively). Table 1 shows the clinical characteristics of the patients at the time of LUS evaluation. The underlying CTDs included IIM/ASS (43%), SSc (37%), RA (15%), and MCTD (5%). The prevalent

morphological patterns on HRCT were nonspecific interstitial pneumonia (NSIP) (57%) and fibrosing organized pneumonia (FOP) (28%), while usual interstitial pneumonia (UIP) was found in only 6 patients (9%). The HRCT patterns of the remaining patients included organizing pneumonia, respiratory bronchiolitis-associated interstitial lung disease and diffuse alveolar damage. NSIP was observed in patients with various CTDs, including IIM/ASS, SSc, and RA, but FOP was detected predominantly in patients with IIM/ASS (16/19 [84%]). Patients with the UIP pattern included one with IIM/ASS, 3 with SSc, and 2 with MCTD. In general, the restrictive ventilatory impairment was mild, and exercise tolerability assessed by the 6MWD was preserved. At the time of LUS, the majority of patients were untreated (37/67 [55%]).

Total B-lines identified by LUS and their correlation with ILD extent on HRCT

In 67 patients with CTD-ILD, the total number of B-lines evaluated by LUS ranged from 3 to 112, and the ILD extent on HRCT ranged from 0.5% to 57.5%, clearly indicating that patients with variable degree of CTD-ILD were included (Supplementary Table 1). The median (interquartile range) interval between HRCT and LUS was 8 (1–22) days in all cases, and 4 (2–6) days in 7 patients with RP-ILD. As shown in Figure 2, total B-lines and the ILD extent were positively correlated with each other in the overall CTD population ($r = 0.66$, $P < 0.001$). When patients were stratified by underlying CTDs, there was a trend towards a better correlation in patients with SSc-ILD ($r = 0.78$, $P < 0.001$) than in those with IIM/ASS-ILD ($r = 0.56$, $P = 0.001$). A correlation between total B-lines and ILD extent was also observed in patients with the NSIP pattern ($r = 0.58$, $P < 0.001$) and in those with the FOP pattern ($r = 0.67$, $P = 0.002$).

Correlations of total B-lines with prognostic parameters

To investigate the clinical relevance of the quantitative results of LUS total B-lines, we next examined whether total B-lines were correlated with known ILD prognostic parameters, including FVC, DL_{CO}, DL_{CO}/V_A, the FVC/DL_{CO} ratio, the 6MWD, and the ILD-GAP index, using single regression analysis (Table 2). The same analysis was conducted using the extent of ILD on HRCT as the explanatory variable. As a result, both the LUS total B-lines and the ILD extent determined via HRCT showed almost equal performance in predicting all prognostic parameters except the 6MWD in all patients with CTD-ILD. Similar correlations between total B-lines and ILD extent and prognostic parameters were observed in patients with SSc-ILD, but there were almost no correlations between total B-lines or ILD extent and prognostic parameters in patients with IIM/ASS-ILD. Differences in correlation with prognostic parameters between the LUS and HRCT indices were found for the

FVC; i.e., the ILD extent was greater in patients with SSc-ILD, whereas the total number of B-lines was greater in patients with IIM/ASS-ILD. When the patients were stratified by the morphologic pattern on HRCT, there was no correlation between the total number of LUS B-lines and any prognostic parameter in patients with the NSIP pattern. On the other hand, the extent of ILD on HRCT correlated with the FVC, DL_{CO}, and ILD-GAP indices. In patients with FOP patterns, the total number of B-lines and the extent of ILD did not correlate well, and a significant correlation was found between the total number of B-lines and the FVC. Taken together, these findings indicate that the performance of the LUS total B-line and ILD extent on HRCT in correlating with known prognostic factors was almost comparable in patients with CTD-ILD. However, the ILD extent determined via HRCT was greater in patients with the NSIP pattern, while the LUS total B-line was better correlated with the FVC in patients with IIM/ASS-ILD and the FOP pattern.

We further examined whether correlations with individual prognostic parameters were improved by combining LUS total B-lines and ILD extent on HRCT as exploratory variables via a multiple regression model (Table 3). Unfortunately, LUS and HRCT combined had little benefit in predicting the correlation with prognostic factors. The extent of ILD on HRCT contributed predominantly to the correlations in overall patients with CTD-ILD, in patients with SSc-ILD, and in patients with the NSIP pattern. On the other hand, the LUS total B-lines contributed predominantly to the correlation with the FVC in patients with IIMs/ASSs and in patients with FOP pattern.

DISCUSSION

In this study, we demonstrated that total B-lines measured by LUS were correlated with the extent of ILD on HRCT and that the performance of LUS was comparable to that of chest HRCT in correlating with the known prognostic parameters in patients with CTD-ILD, suggesting that LUS serves as an alternative tool to chest HRCT for assessing ILD severity and risk of progression. However, we failed to demonstrate any additional benefit in performing LUS in addition to HRCT. Because of its performance comparable to that of HRCT, LUS can be useful for monitoring ILD severity as a complement to HRCT, which is difficult to repeat in the short term due to potential harm from radiation exposure and high medical cost.

A better correlation between LUS total B-lines and ILD extent on HRCT was found in patients with SSc-ILD than in those with IIM/ASS-ILD. In this regard, the correlation between B-lines and semiquantitative HRCT score in patients with SSc has been shown in many studies [15–19]; however, only one study has shown the correlation between B-lines and semiquantitative HRCT score in patients with IIM/ASS [20], and one study

involving ASS patients failed to show a significant correlation [37]. In principle, B-lines are detected by LUS to indicate subpleural, interlobular septal thickening, which is one of the characteristics of the fibrotic NSIP pattern, a predominant HRCT morphologic pattern in patients with SSc-ILD [38,39]. In addition, 14 sites in the lower lung fields of the back were used as the evaluation sites for LUS in this study and were consistent with the most commonly affected area of SSc-ILD. Taken together, these morphological features of SSc-ILD may explain the better correlation between LUS total B-lines and ILD extent on HRCT and the equal performance of LUS and HRCT indices in correlating with prognostic parameters in patients with SSc-ILD.

On the other hand, in patients with IIM/ASS-ILD, the correlation between the LUS total B-lines and the ILD extent determined via HRCT was low, and the LUS total B-line count was poorly correlated with the prognostic parameters. HRCT in patients with IIM/ASS-ILD frequently presents with the cellular NSIP pattern characterized by reticulation and ground-glass opacities, which are distributed not only peripherally but also around bronchovascular bundles [40,41]. The FOP pattern, which is characterized by overlapping consolidation and the cellular NSIP pattern, is another predominant HRCT morphological pattern in patients with IIM/ASS-ILD [40,41]. Since the ultrasound signal attenuates with distance, changes in signals around central bronchovascular bundles may not be properly evaluated by LUS. In addition, consolidation on HRCT often presents a tissue-like pattern rather than B-lines on LUS [42]. This is a potential limitation in evaluating LUS B-lines and may explain the poor correlation between LUS total B-lines and prognostic parameters in patients with the overall NSIP pattern and those with the FOP pattern in this study. A new LUS scoring system may be necessary to accurately assess tissue-like patterns on HRCT, which are often observed in patients with IIM/ASS-ILD.

Paradoxically, LUS total B-lines performed better than ILD extent on HRCT in correlation with FVC in patients with IIM/ASS-ILD and in those with FOP patterns according to single and multiple regression analyses. These findings need to be assessed for reproducibility in independent validation cohorts, but it is interesting to examine the mechanisms underlying the potential correlation between imaging features captured as B-lines by LUS and restrictive ventilatory dysfunction in patients with IIM/ASS-ILD and in those with the FOP pattern. It has been shown that B-lines by LUS reflect the increased density of interlobular septal thickening due to fibrosis and/or inflammation [43], but it is difficult to discriminate fibrosis from inflammation. Nevertheless, an increased number of total B-lines in conjunction with restrictive ventilatory dysfunction might suggest predominant fibrotic changes in patients with IIM/ASS-ILD and in those with the FOP pattern.

In the context of the recommendation of chest HRCT as the gold standard for diagnosing ILD according to evidence-based consensus statements [10], a single LUS has limited utility in assessing CTD-ILD.

Furthermore, information on the morphological pattern obtained by HRCT (i.e., UIP versus non-UIP pattern) is indispensable for predicting disease behaviour and prognosis [12,44,45]. On the other hand, LUS has the advantage of being repeatable in the short-term due to its low cost, lack of radiation exposure, and easy accessibility [46]. Although HRCT is the gold standard for diagnosing and assessing the severity of ILD, LUS is considered an imaging modality useful for monitoring ILD since it provides information on ILD severity comparable to that of HRCT.

This study has several limitations. First, there were considerable number of missing data for some prognostic parameters, including 6MWD and DL_{CO}, indicating a potential role of partial verification bias in interpretation of the findings observed. Second, LUS was not performed on all CTD patients during the study period, indicating a potential selection bias. Third, we adopted total B-lines obtained at 14 intercostal sites because of the minimized patient burden. Since the 14 sites were located mainly in the lower lung field on the back, the total number of B-lines did not reflect changes in the lung architecture outside of the evaluable areas. Finally, we adopted a semiquantitative method for assessing the extent of ILD on chest HRCT; this method was shown to be useful for predicting mortality in patients with SSc-ILD and RA-ILD but has never been validated in patients with IIM/ASS-ILD.

In summary, the LUS serves as an alternative tool for assessing the severity and prognosis of patients with CTD-ILD. However, further studies are necessary to establish the optimal use of noninvasive, convenient LUSs in clinical practice.

Conflict of interest

SW received speaking fees from AbbVie, Asahi Kasei Pharma, Boehringer Ingelheim, and Janssen. KY, SY and MS declare no conflicts of interest. TG received a grant and a speaking fee from Janssen as well as speaking fees from Asahi Kasei Pharma, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Ono Pharmaceuticals, and Tanabe-Mitsubishi. MK has received research grants and personal fees from Boehringer Ingelheim, Ono Pharmaceuticals, and MBL and personal fees from Asahi Kasei Pharma, AstraZeneca, Chugai, Eisai, GlaxoSmithKline, Kissei, Janssen, Mochida, and Tanabe-Mitsubishi.

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Role of contributors

Research design, SW, TG, MK; data collection, SW, KY, SY, MS, TG; interpretation of the results: SW, TG, MK. All the authors have read and agreed with the published version of the manuscript.

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Figure legends

Figure 1. Comparison of LUS and HRCT images in corresponding areas of a patient with SSc-ILD

The areas of no (a), minimal (b), and extensive (c) ILD on HRCT slices and the corresponding LUS images obtained at the intercostal site are shown in the right panel. The B-lines were identified as a hyperechoic signal similar to the pleural line extending vertically from the pleura. The number of B-lines is shown in the upper-right of individual LUS images.

HRCT: high-resolution computed tomography; ILD: interstitial lung disease; LUS: lung ultrasound; SSc: systemic sclerosis.

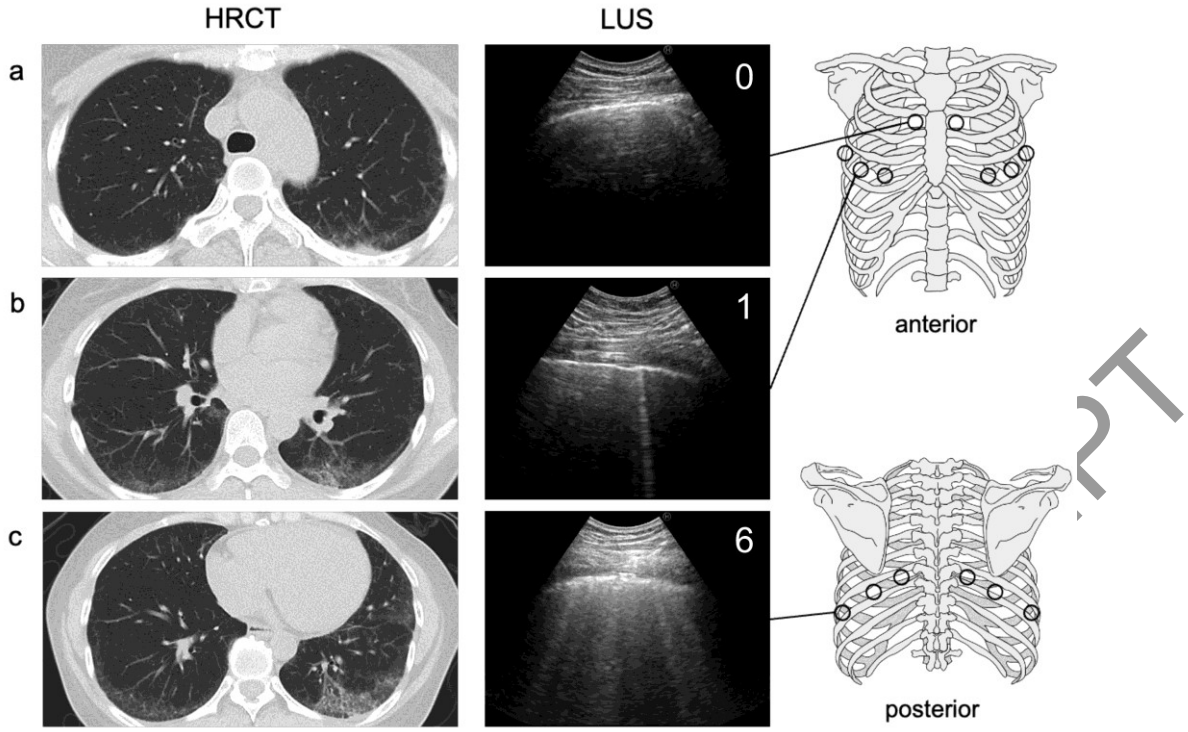

Figure 2. Patient flow diagram

CTD: connective tissue disease; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; LUS: lung ultrasound.

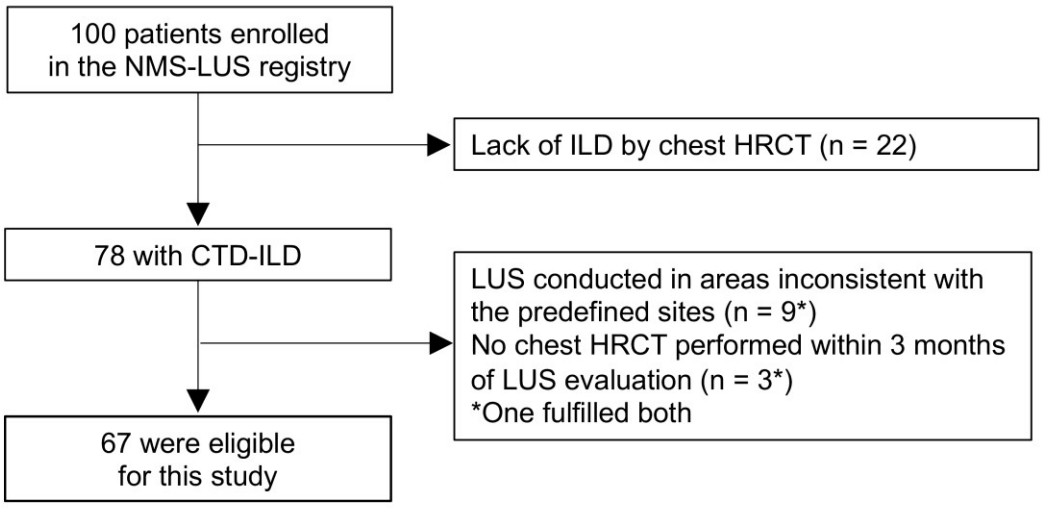

Figure 3. Correlations between total B-lines evaluated by LUS or ILD extent on HRCT

Single regression analysis was conducted to examine the correlation between total B-lines and ILD extent in patients with CTD-ILD (a), IIM/ASS-ILD (b), SSc-ILD (c), CTD-ILD with an NSIP pattern (d), and CTD-ILD with an FOP pattern (e).

ASS: anti-synthetase syndrome; CTD: connective tissue disease; FOP: fibrosing organizing pneumonia; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; LUS: lung ultrasound; NSIP: nonspecific interstitial pneumonia; *P*: p-value; SSc: systemic sclerosis.

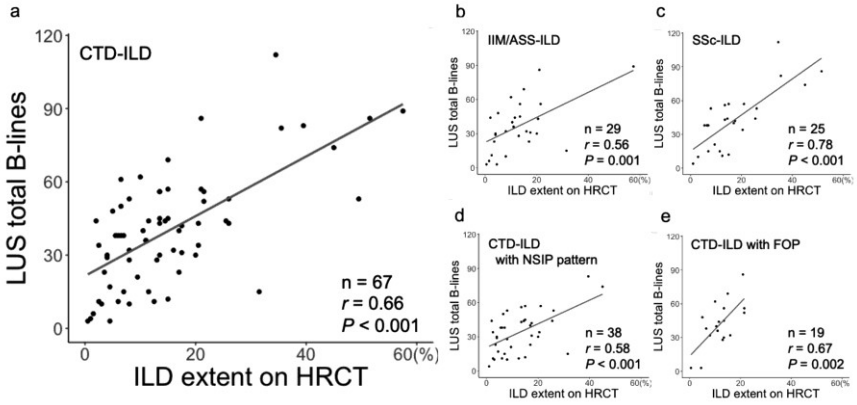

Table 1. Clinical characteristics in 67 patients with CTD-ILD at time of LUS evaluation

Demographic and clinical characteristics	The number of data available	
Age, years	67	53 (42–65)
Female, number (%)	67	47 (70%)
BMI, kg/m^2	67	21 (19–24)
Smoking history, number (%)	67	
Current		4 (6%)
Ever		23 (34%)
Never		40 (69%)
Underlying CTD, number (%)	67	
IIM/ASS		29 (43%)
SSc		25 (37%)
RA		10 (15%)
MCTD		3 (5%)
Disease duration, weeks	67	34 (11–195)
Follow-up period after ILD diagnosis, weeks	66	6 (1–136)
Modified MRC dyspnoea scale, number (%)	61	
0		22 (36%)
1		24 (39%)
2		9 (15%)
3		5 (8%)
4		1 (1%)
Total B-lines by LUS	67	38 (26–53)
ILD extent on HRCT, %	67	13 (7–20)
HRCT morphology, number (%)	67	
NSIP		38 (57%)
FOP		19 (28%)
UIP		6 (9%)
OP		1 (1%)
RB-ILD		1 (1%)
DAD		2 (3%)
KL-6, U/mL	66	728 (447–1081)
Pulmonary function test parameters		
FVC, %	52	88 (76–99)
DL_{CO}, %	49	69 (58–79)
DL_{CO}/V_A, %	49	88 (77–103)
FVC/DL_{CO} ratio	49	1.3 (1.1–1.5)
TLC, %	50	87 (72–101)
6MWD, m	35	456 (386–514)
ILD-GAP index, number (%)	63	
-2		10 (16%)
-1		18 (29%)
0		11 (17%)
1		10 (16%)
2		10 (16%)
3		2 (3%)
4		2 (3%)
Treatment for ILD	67	
Untreated, number (%)		37 (55%)
GC alone, number (%)		3 (4%)
MTX alone, number (%)		2 (3%)
MMF alone, number (%)		2 (3%)

Tacrolimus alone, number (%)	2 (3%)
Nintedanib alone, number (%)	2 (3%)
GC + Tacrolimus, number (%)	9 (13%)
GC + CYC, number (%)	3 (4%)
MTX + Nintedanib, number (%)	1 (2%)
AZA + Nintedanib, number (%)	1 (2%)
GC + Tacrolimus + CYC, number (%)	3 (4%)
GC + Tacrolimus + Nintedanib, number (%)	1 (2%)
GC + MMF + Nintedanib, number (%)	1 (2%)

Continuous values are shown as medians (interquartile ranges).

6MWD: 6-minute walking distance; ASS: anti-synthetase syndrome; AZA: azathioprine; BMI: body mass index; CTD: connective tissue disease; CYC: cyclophosphamide; DAD: diffuse alveolar damage; DL_{CO}: diffusing capacity for carbon monoxide; FOP: fibrosing organizing pneumonia; FVC: forced vital capacity; GC: glucocorticoid; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; LUS: lung ultrasound; MCTD: mixed connected tissue disease; MMF: mycophenolate mofetil; MTX: methotrexate; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; RA: rheumatoid arthritis; RB-ILD: respiratory bronchiolitis-associated interstitial lung disease; SSc: systemic sclerosis; TLC: total lung capacity; UIP: usual interstitial pneumonia; V_A: alveolar volume.

Table 2. Single regression analysis to evaluate correlations of LUS/HRCT measurements with prognostic parameters

Prognostic parameters	n	CTD-ILD		n	IIM/ASS-ILD		n	SSc-ILD		n	CTD-ILD with NSIP pattern		n	CTD-ILD with FOP pattern	
		r	*P*		*r*	*P*		*r*	*P*		*r*	*P*		*r*	*P*
Total B-lines by LUS															
FVC	52	-0.32	0.020*	18	-0.59	0.010*	24	-0.36	0.080	33	0.03	0.889	11	-0.73	0.011*
DL_{CO}	49	-0.53	<0.001*	17	-0.45	0.070	24	-0.63	0.001*	31	-0.20	0.283	10	-0.63	0.053
DL_{CO}/V_A	49	-0.33	0.022*	17	0.00	0.993	24	-0.52	0.010*	31	-0.06	0.747	10	-0.06	0.860
FVC/DL_{CO} ratio	49	0.47	0.001*	17	0.06	0.828	24	0.63	0.001*	31	0.18	0.334	10	0.37	0.298
6MWD	35	-0.18	0.301	16	-0.26	0.338	15	-0.39	0.153	19	-0.06	0.809	10	-0.11	0.755
ILD-GAP index	63	0.37	0.003*	29	0.31	0.100	23	0.61	0.002*	34	0.31	0.071	19	0.12	0.629
ILD extent on HRCT															
FVC	52	-0.46	0.001*	18	-0.28	0.266	24	-0.62	0.001*	33	-0.40	0.022*	11	-0.38	0.255
DL_{CO}	49	-0.58	<0.001*	17	-0.22	0.391	24	-0.79	<0.001*	31	-0.55	0.001*	10	-0.06	0.879
DL_{CO}/V_A	49	-0.30	0.035*	17	-0.25	0.330	24	-0.45	0.027*	31	-0.12	0.514	10	0.21	0.556
FVC/DL_{CO} ratio	49	0.42	0.003*	17	0.02	0.933	24	0.67	<0.001*	31	0.12	0.514	10	-0.12	0.736
6MWD	35	-0.11	0.520	16	0.12	0.667	15	-0.46	0.086	19	0.05	0.823	10	-0.24	0.498
ILD-GAP index	63	0.44	<0.001*	29	0.27	0.150	23	0.81	<0.001*	34	0.37	0.033*	19	0.17	0.499

Single regression analysis was used to determine the correlation between known prognostic parameters of ILD and total B-lines. *$P < 0.05$.

6MWD: 6-minute walking distance; ASS: anti-synthetase syndrome; CTD: connective tissue disease; DL_{CO}: diffusing capacity for carbon monoxide; FOP: fibrosing organizing pneumonia; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; LUS: lung ultrasound; NSIP: nonspecific interstitial pneumonia; *r*: Pearson correlation coefficient; SSc: systemic sclerosis; V_A: alveolar volume.

Table 3. Multiple regression analysis to assess the contribution of LUS/HRCT measurements to prognostic parameters

Prognostic parameters	n	*R*	*P*	LUS total B-lines		ILD extent on HRCT	
				β	*P*	*β*	*P*
CTD-ILD							
FVC	52	0.46	0.003*	-0.035	0.839	-0.494	0.013*
DL_{CO}	49	0.61	<0.001*	-0.267	0.106	-0.458	0.013*
DL_{CO}/V_A	49	0.35	0.053	-0.233	0.231	-0.173	0.410
FVC/DL_{CO} ratio	49	0.49	0.002*	0.357	0.051	0.215	0.273
6MWD	35	0.18	0.587	-0.205	0.421	0.028	0.917
ILD-GAP index	63	0.45	0.001*	0.132	0.393	0.351	0.023*
IIM/ASS-ILD							
FVC	18	0.59	0.039*	-0.600	0.023*	-0.053	0.858
DL_{CO}	17	0.46	0.196	-0.544	0.116	-0.100	0.758
DL_{CO}/V_A	17	0.27	0.593	0.127	0.723	-0.361	0.315
FVC/DL_{CO} ratio	17	0.06	0.977	0.072	0.846	0.004	0.992
6MWD	16	0.45	0.234	-0.567	0.105	0.693	0.163
ILD-GAP index	29	0.33	0.215	0.230	0.313	0.145	0.523
SSc-ILD							
FVC	24	0.65	0.003*	0.355	0.206	-0.897	0.004*
DL_{CO}	24	0.79	<0.001*	0.006	0.977	-0.788	0.002*
DL_{CO}/V_A	24	0.52	0.037*	-0.424	0.181	-0.104	0.739
FVC/DL_{CO} ratio	24	0.69	0.001*	0.233	0.379	0.480	0.082
6MWD	15	0.46	0.243	-0.019	0.970	-0.392	0.360
ILD-GAP index	23	0.81	<0.001*	-0.056	0.796	0.858	0.001*
CTD-ILD with NSIP pattern							
FVC	33	0.48	0.018*	0.363	0.094	-0.605	0.005*
DL_{CO}	31	0.56	0.006*	0.132	0.522	-0.649	0.003*
DL_{CO}/V_A	31	0.12	0.811	0.005	0.983	-0.132	0.577
FVC/DL_{CO} ratio	31	0.18	0.623	0.175	0.471	0.041	0.861
6MWD	19	0.14	0.854	-0.191	0.611	0.179	0.617
ILD-GAP index	34	0.39	0.080	0.158	0.450	0.272	0.176
CTD-ILD with FOP pattern							
FVC	11	0.75	0.036*	-0.831	0.024*	0.211	0.442
DL_{CO}	10	0.77	0.043*	-1.115	0.016*	0.478	0.106
DL_{CO}/V_A	10	0.34	0.657	-0.379	0.488	0.352	0.385
FVC/DL_{CO} ratio	10	0.59	0.222	0.840	0.100	-0.495	0.172
6MWD	10	0.26	0.785	0.110	0.817	-0.277	0.545
ILD-GAP index	19	0.17	0.800	0.013	0.970	0.157	0.645

Multiple regression analysis was also conducted to evaluate the associations of LUS and HRCT indices with prognostic factors. *$P < 0.05$.

6MWD: 6-minute walking distance; ASS: anti-synthetase syndrome; CTD: connective tissue disease; DL_{CO}: diffusing capacity for carbon monoxide; FOP: fibrosing organizing pneumonia; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; LUS: lung ultrasound; NSIP: nonspecific interstitial pneumonia; *R*: multiple regression coefficient; SSc: systemic sclerosis; V_A: alveolar volume; *β*: standard partial regression coefficient.