



Screening value of lung ultrasound in connective tissue disease related interstitial lung disease



Yupeng Huang^{a,§}, Tao Liu^{b,§}, Songya Huang^c, Li Qiu^c, Fengming Luo^d, Geng Yin^{a,*}, Qibing Xie^{b,*}

^a Department of General Practice, General Practice Medical Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

^b Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

^c Department of Medical Ultrasound, West China Hospital, Sichuan University, Chengdu, Sichuan, China

^d Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan, China

ARTICLE INFO

Article History:

Received 29 May 2022

Revised 16 September 2022

Accepted 19 September 2022

Available online 28 September 2022

Key words:

CTD-ILD
Lung ultrasound
HRCT
Screening value

ABSTRACT

Background: Interstitial lung disease (ILD) is a common pulmonary complication of connective tissue disease (CTD) that can lead to poor quality of life and prognosis.

Objectives: To explore the screening value of lung ultrasound (LUS) for connective tissue disease-associated interstitial lung disease (CTD-ILD).

Methods: Data of patients with CTD were collected, and each patient underwent LUS, high-resolution computed tomography (HRCT), and pulmonary function tests. Considering HRCT is the gold standard for diagnosing CTD-ILD, patients were divided into CTD-ILD and CTD-non-ILD groups. The LUS and HRCT results were assessed using semiquantitative and Warrick scores, respectively. Pulmonary function results were also collected. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of LUS diagnosis. Spearman correlation analysis was used to analyze the correlation between LUS, HRCT, and lung function indices.

Results: A total of 88 patients (65 with CTD-ILD and 23 with CTD-non-ILD) were included in this study. The sensitivity and specificity of LUS for the diagnosis of CTD-ILD were 86.60% and 82.60%, respectively, which was consistent with the HRCT results ($P < 0.05$). The LUS results (total number of B-lines, frequency of B-line, pleural thickness, and pleural-line irregularity) were positively correlated with the HRCT Warrick score ($r = 0.77, 0.76, 0.65$ and $0.71, P < 0.05$).

Conclusions: LUS may be a promising tool for screening patients with CTD-ILD.

© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Abbreviations: ILD, interstitial lung disease; CTD, connective tissue diseases; IIM, idiopathic inflammatory myopathy; SSc, systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; BD, Behcet's disease; AAV, ANCA-associated vasculitis; UCTD, undifferentiated connective tissue disease; HRCT, high resolution computer tomography; LUS, lung ultrasound; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; BMI, body mass index; AI, alveolitis index; FI, fibrosis index; FVC, forced vital capacity; FEV1, first second forced expiratory volume; TCL, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; Reff, expiratory resistance raw eff; Sgaw eff SG, specific airway conduction; SD, standard deviation; ROC, receiver operating characteristic; AUC, area under the curve; UIP, usually interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; DIP, desquamative interstitial pneumonitis; OP, organizing pneumonia

* Corresponding authors at: 37 Guoxue Xiang, 610041.

E-mail addresses: yingeng1975@163.com (G. Yin), xieqibing1971@163.com (Q. Xie).

§ Yupeng Huang and Tao Liu contributed equally to this paper

<https://doi.org/10.1016/j.hrtlng.2022.09.011>

0147-9563/© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Interstitial lung disease (ILD) is a common manifestation of connective tissue diseases (CTD), including idiopathic inflammatory myopathy, systemic sclerosis (SSc), rheumatoid arthritis (RA), Sjogren's syndrome, systemic lupus erythematosus, mixed connective tissue disease, Behcet's disease, and undifferentiated connective tissue disease.^{1,2} It occurs in about 40% of patients with CTD³ and is one of the leading causes of death.⁴ A proportion of patients with CTD-ILD may develop a progressive fibrosing phenotype characterized by increasing fibrotic abnormalities, worsening dyspnea, irreversible respiratory failure, and high mortality. ILD may even be the first manifestation of CTD.^{5–7}

However, the pathogenesis of CTD-ILD remains unclear although it is associated with alveolar inflammation caused by environmental and immune factors. Studies have suggested that alveolar inflammation in the early stages of CTD-ILD is treatable and reversible, but progressive fibrosis in later stages is difficult to treat.^{8,9} Therefore, early

screening and diagnosis of CTD-ILD are essential. The tools used for the screening and diagnosis of CTD-ILD include chest radiography, high-resolution computed tomography (HRCT), pulmonary function tests, and lung biopsy. HRCT is the gold standard for diagnosing CTD-ILDs as it can detect early subclinical ILD, determine the extent and degree of the lesion, and evaluate the treatment and prognosis. However, the radiation dose of HRCT is large, which is not conducive to the long-term follow-up of patients (especially adolescents and pregnant women).^{10,11} Pulmonary function tests can assess ventilatory and diffusion dysfunction in patients with ILD; however, pulmonary function in the early stage of ILD is often normal and cannot be used to determine the extent of the lesion. Lung biopsy is an invasive procedure that may result in false-negative results. Ordinary chest radiography has poor sensitivity, which is not conducive to early diagnosis and screening of CTD-ILD.

In view of the restrictions of the above methods, studies have shown that lung ultrasound (LUS) can also be used as a screening method for CTD-ILD.^{12–14} In clinical practice, ultrasound is commonly used in the chest to detect pleural effusion, tumors, or pneumothorax, and to conduct ultrasound-assisted thoracentesis or biopsy. However, in recent years, LUS has developed from a traditional application to the exploration of the lung parenchyma and has been gradually applied to evaluate diseases such as pneumonia and pulmonary edema.^{15,16} It is widely used by physicians in emergency departments, respiratory departments, and intensive care units.

In 2009, Reissig and Görg¹⁷ used LUS to assess patients with SSC-ILD and found three specific signs: B-line, pleural-line, and subpleural changes. These three specific findings are important for the assessment of ILD using LUS. The B-line originates from the pleural line and is a laser-like hyperechoic vertical reverberation artifact that extends to the bottom of the screen without attenuation and synchronizes with respiration. In ILD, the B-line, as the main ultrasonographic sign, can be used for the diagnosis and assessment of CTD-ILD. In addition, the B-line can also be seen in other diseases, such as pulmonary edema, pneumonia, and acute respiratory distress syndrome. Normally, the pleural line is an echogenic structure formed by the parietal and visceral pleura, representing the lung surface, and the normal pleural line is regular, smooth, and non-thickened. Pleural line changes, first proposed by Wohlgenannt in 2001,¹⁸ are another abnormal ultrasonographic sign associated with ILD in addition to the B-line. Reissig and Görg further described pleural-line alterations including irregularity, thickening, and fragmentation.¹⁷ Subpleural changes are mainly characterized by small areas of hypoechogenicity,¹⁹ which appear less frequently in the literature and have been reported in RA-ILD and sarcoidosis.²⁰ At present, no study has elucidated the principle of ultrasound formation of pleural line changes and subpleural changes, but they often occur at the same time as the B-line.

Thus far, HRCT remains the reference tool for diagnosing ILD. Under normal conditions, ultrasound beams cannot pass through the air because of the presence of air in the lungs; thus, ultrasonic examination is not useful for lung imaging. However, in the disease state, air within the lung may be replaced by fluids or solid tissue, which can be visualized.²¹ Given the anatomical structure of the lung, LUS only assesses 70% of the lung surface, and only changes close to the pleural surface can be seen^{17,22} and LUS cannot identify the central perihilar, or subpleural regions.²³ When compared to HRCT, chest radiography, pulmonary function test, and lung biopsy, LUS is a low-cost, noninvasive, radiation-free, and portable tool, and could represent a complementary screening approach.²²

Although research on the application of LUS in CTD-ILD is still in its early stages, previous studies have suggested that LUS may be helpful for early screening, diagnosis, and evaluation of CTD-ILD.^{20,13,24} However, the types of CTD involved in these studies were limited to RA, SSC, and idiopathic inflammatory myopathy, with a small number of cases, and obvious limitations in the research

scheme designs. This study aimed to systematically explore the screening value of LUS in detecting multiple forms of CTD-ILDs.

Method

Population

Patients enrolled in this study were >18 years of age, diagnosed with CTD, met the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria, attended the out and inpatient departments of Rheumatology and Immunology in West China Hospital, and had a stable condition for more than one month. Patients with the following factors were excluded: (1) inability or refusal to sign informed consent; (2) non-CTD-related ILD; (3) pulmonary infection, chronic obstructive pulmonary disease, sarcoidosis, IgG4 related diseases, lung tumor, pleural effusion, alveolar syndrome, etc.; (4) lymphoproliferative diseases and other hematological diseases; (5) history of chest radiotherapy and chemotherapy; (6) heart diseases that affect lung function, such as left ventricular dysfunction and right ventricular dysfunction; and (7) inability to perform pulmonary function tests. All the patients underwent HRCT, pulmonary function tests, and ultrasonography. The interval between each examination did not exceed one month. HRCT was used as the gold standard for the diagnosis of CTD-ILD, and all patients were divided into CTD-ILD and CTD-non-ILD groups according to HRCT. HRCT, LUS, and lung function data were collected to evaluate the sensitivity and specificity of LUS in diagnosing CTD-ILD and to analyze the relationship between HRCT, LUS, and pulmonary function tests. Patient characteristic's such as name, age, sex, smoking history, disease duration, and BMI were also collected.

This study was approved by the Medical Ethics Committee of West China Hospital, Sichuan University (ethical approval number:2019–246) and all participants provided written informed consent.

Lung ultrasound

In this study, an Aixplorer ultrasonic diagnostic instrument (Supersonic Imagine, France) was used, and a 2–10 MHz high frequency linear array probe was selected. LUS was performed by professional ultrasound doctors who had received lung ultrasound training and were blinded to the HRCT results. The examination included B-line number, B-line position number, pleura thickness, subpleural nodule, discontinuous pleura-line, irregular pleura-line, blurred pleura line, and other parameters. At present, there is no clear consensus on the ultrasound methodology. We used the method described in a previous study²⁴ to systematically explore each patient. In the supine position (90° abduction of both upper limbs), the parasternal line, midclavicular line, anterior axillary line, and midaxillary line were examined, and in sitting and standing positions, the posterior axillary line, paraspinal line, and subscapular line were examined. If the total number of B-lines in all areas was >10, it was considered ILD. The severity of CTD-ILD was evaluated by semi-quantitative evaluation of LUS, that is, 0=normal (<10 B-lines), 1=mild (11–20 B-lines), 2=moderate (21–50 B-lines), and 3=severe (>50 B-lines).²⁵

HRCT

HRCT was performed using a spiral CT scanner (UCT780, United Imaging, China). All patients were in the supine position and examined from the apex to the bottom of the lung after full inhalation. The thickness of each layer is 1 mm. The images were analyzed by an experienced radiologist, who were blinded to the LUS results, to determine and classify ILD. The severity of HRCT was evaluated according to the Warrick score.²⁶ To better distinguish the degree

and type of ILD, the Warrick score was divided into two categories: the alveolitis index (AI) score and fibrosis index (FI) score. In AI, the minimum score is 0 and the maximum score is 4; in FI, the minimum score is 0 and the maximum score is 26.²⁷

Pulmonary function test

Pulmonary function tests were performed using a MasterScreen pulmonary function measurement system (Jaeger, Wuertzburg, Germany). The results of the pulmonary function test examination included: ventilation function, forced vital capacity (FVC, ml), first second forced expiratory volume (FEV1, ml), and FEV1 / FVC%; total lung capacity (TCL, ml); and diffusion capacity of the lung for carbon monoxide (DLCO, mmHg). The actual DLCO was corrected for hemoglobin levels.

Statistical analysis

SPSS software (version 26.0) was used for the statistical analysis. Continuous variables were expressed as median and mean \pm standard deviation (SD). Categorical variables were expressed as counts and percentages. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of LUS diagnosis, and the results were expressed as the area under the curve (AUC) with 95% confidence intervals for this area. Spearman correlation analysis was used to analyze the correlation between the LUS, HRCT, and lung function indices. The Kruskal-Wallis H test was used to test the differences between groups and an independent samples T test was used to compare the two groups. The kappa consistency test was used to evaluate the diagnostic value of LUS and HRCT and the kappa value was calculated. Statistical significance was set at $P < 0.05$.

Results

Population

Eighty-eight patients with CTD (65 with ILD and 23 without ILD, assessed by HRCT) were included, including 29 males (33%) and 59 females (67%). The average age was 48.2 ± 11.5 years. Demographic data are presented in Table 1.

LUS and HRCT

HRCT was used to evaluate the diagnostic value of LUS for CTD-ILD. During LUS examination, the total number of B-lines in all examined areas was recorded, and, ILD was considered if the B-line was > 10 . The sensitivity, specificity, positive predictive value, and negative predictive value of LUS were 86.60%, 82.60%, 91.70%, and 94.30% respectively. The ROC curve showed the accuracy of the total number of B-lines in the diagnosis of ILD, with an AUC of 0.908 (95% CI 0.846–0.970), $P < 0.001$ (Fig. 1A). The diagnostic results of LUS and HRCT were consistent ($P < 0.05$) (Fig. 1B). The HRCT Warrick score was positively correlated with the total number of B-lines, B-line points (the site at which the B-line appears), pleural thickness, and pleural irregularities in LUS results ($P < 0.05$) (Fig. 2). We conducted pre- and post-comparisons of HRCT and LUS images of the same site in follow-up patients, which showed good consistency (Fig. 3).

The severity of CTD-ILD was stratified using the LUS semi-quantitative score and HRCT Warrick score. The results showed that the Warrick and LUS semi-quantitative scores were consistent in judging the severity of the patients ($P < 0.05$) (Fig. 4).

LUS and pulmonary function test

There was a negative correlation between B-line points and TCL ($r = -0.28$, $P = 0.04$) and no correlation between pleural thickness and

Table 1
Demographic information of patients included.

	CTD-ILD	CTD with non-ILD	All
N	65	23	88
Gender	Male n(%)	17(26)	29(33)
	Female n(%)	48(74)	59(67)
Age (year)	49.8 ± 10.5	43.7 ± 13.3	48.2 ± 11.5
Duration (year)	2.0(1.0–7.0)	3.0(1.0–8.0)	2.0(1–7.75)
BMI (kg/m ²)	22.8 ± 3.47	21.1 ± 3.3	22.4 ± 3.5
Smoke	Yes n(%)	7(11)	12(14)
	No n(%)	58(89)	18(78)
Type of CTD	SSc n(%)	21(32)	3(13)
	IIM n(%)	27(41)	5(22)
	SS n(%)	4(6)	3(13)
	RA n(%)	1(1)	2(8)
	SLE n(%)	1(1)	5(23)
	MCTD n(%)	7(11)	1(4)
	UCTD n(%)	3(5)	3(13)
	AAV n(%)	1(1)	–
	BD n(%)	–	1(4)

Note: Data are presented as mean \pm standard deviation when normally distributed, and median and interquartile range when non-normally distributed.

Abbreviations: ILD: Interstitial lung disease, CTD: connective tissue diseases, BMI: body mass index, SSc: systemic sclerosis, IIM: inflammatory myopathy, SS: Sjogren's syndrome, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, MCTD: mixed connective tissue disease, UCTD: connective tissue disease, AAV: ANCA-associated vasculitis, BD: Behcet's disease.

TCL ($r = -0.29$, $P = 0.034$). Pleural irregularities were negatively correlated with FVC, FEV1, TCL, and DLCO ($P < 0.05$) (Table 2).

The difference of lus in the diagnosis of CTD-ILD

The total number of B-lines were 58.00 and 2.00 in the CTD-ILD and CTD-non ILD groups respectively. B-line points were 22.00 in the CTD-ILD group and 2.00 in the CTD-non ILD group. Pleural thickness were 2.92 ± 0.53 mm and 1.48 ± 0.12 mm and pleural irregularities were 7.00 and 0.00, in the CTD-ILD and CTD-non ILD groups, respectively ($P < 0.05$). In our study, patients were grouped according to types of ILD. Of these, there were 36 UIP (55.38%), 15 NSIP (23.07%), six DIP (9.23%), three OP (4.62%), and five other types (7.69%). There were significant differences in the total number of B-lines and pleural irregularities among the different CTD-ILD types (Table 3).

Discussion

ILD is one of the most serious organ complications in CTD, which significantly affects the prognosis of patients with CTD. In recent years, as a non-invasive, non-ionizing radiation, and convenient examination method, LUS has gradually expanded its application in the evaluation of lung parenchymal lesions. In our study, two models were used in the evaluation of CTD using LUS: the B-line and pleural line models. In an initial study using LUS to evaluate CTD-ILD, Picano et al.²⁷ proposed that a total number of > 5 B-lines was used as the cut-off value. Gargani et al.¹⁴ modified the cutoff value to the total number of > 10 B-lines and found that the LUS results were positively correlated with HRCT and lung function. In this study, we used the same method as Gargani et al. In 2013, Barskova et al. used LUS to assess 58 patients with SSc, including 32 patients with very early SSc. When the truncation value of SSc-ILD is B-line ≥ 5 , the sensitivity and specificity of LUS diagnosis are 100% and 55%, respectively. However, when the truncation value is B-line ≥ 20 , the sensitivity and specificity are 83% and 96% respectively.¹³ In our study, the sensitivity and specificity of LUS were 86.6% and 82.6%, respectively. Studies have also shown that portable LUS equipment or a simplified LUS evaluation method can provide a preliminary assessment of ILD.^{24,28} Thus,

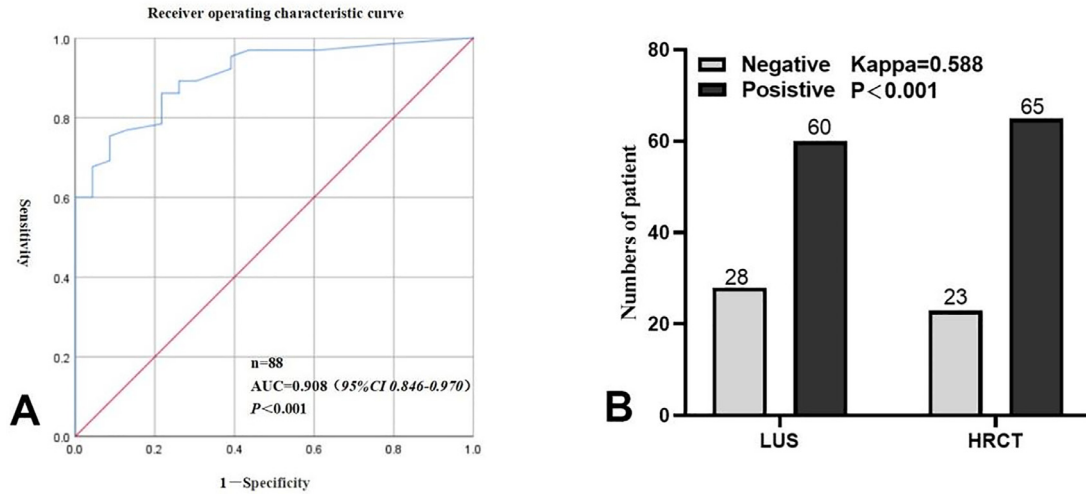


Fig. 1. The diagnosis value of LUS in CTD-ILD: A, ROC curve of diagnostic ILD for total number of LUS B lines; B, Consistency between LUS and HRCT in the diagnosis of CTD-ILD.

it is suggested that LUS can sensitively detect ILD in early SSc (HRCT is normal), which may be a reliable screening tool for ILD.

LUS and HRCT

HRCT is considered the gold standard for ILD diagnosis. However, the examination is limited by the equipment, and long-term follow-up patients cannot undergo HRCT frequently. A considerable number of critically ill patients cannot undergo HRCT, which restricts clinicians' understanding of CTD-ILD condition changes. Therefore, a rapid and accurate method without ionizing radiation is needed to evaluate CTD-ILD.

LUS can dynamically image the lungs without radiation exposure and is thus useful for children and pregnant women. LUS can detect bilateral, subpleural, and posterobasal interstitial-alveolar

damage.^{29,30} LUS can also be effectively used to detect lesions in the pleural or subpleural regions, including pleural effusions and subpleural and chest wall lesions.²¹ As such, LUS has been applied in screening for CTD-ILD in recent years. Dovcric et al. first evaluated the performance of LUS in SSc and found that LUS may have a similar function as HRCT.³¹ In 2009, Gargani et al. found a strong correlation between the total number of B-lines and the HRCT Warrick score.¹⁴ Moreover, Tardella et al. reported a strong correlation between LUS and HRCT.³² Our study found that two LUS evaluation models (B-line and pleural line models) correlated with HRCT. The total number of B-lines, number of B-line points, pleural thickness, and pleural line abnormalities showed a strong positive correlation with the HRCT Warrick score. The above results show that LUS can draw conclusions similar to HRCT when evaluating various types of CTD-ILD. We also evaluated the severity of CTD-ILD with LUS semi-quantitative scores

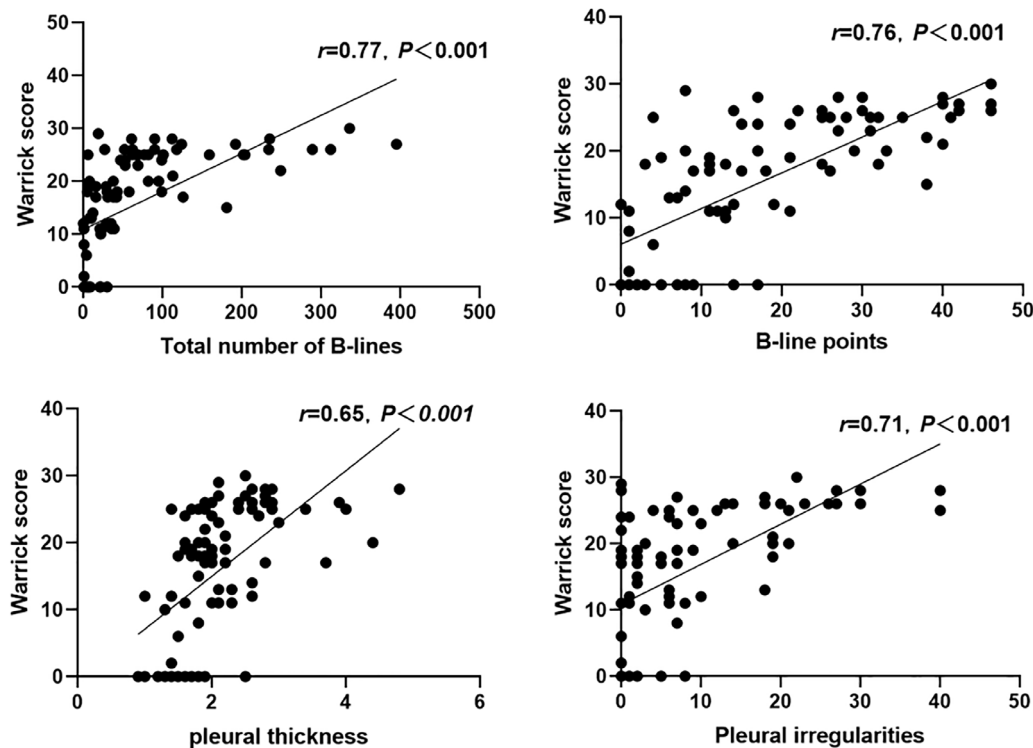


Fig. 2. Correlation between LUS and HRCT Warrick score.

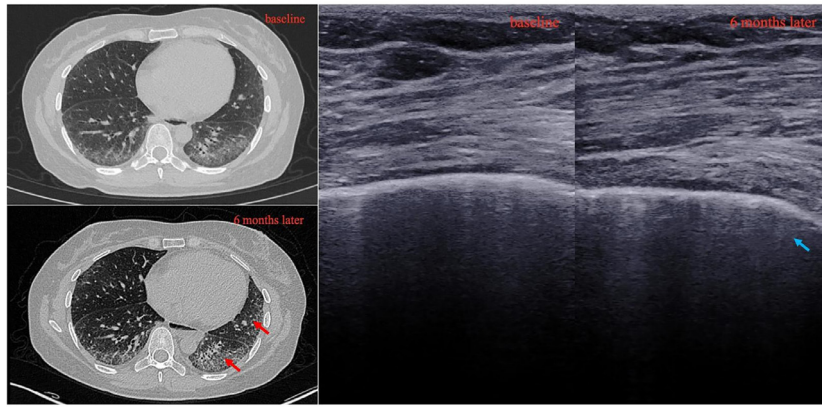


Fig. 3. Comparison of LUS and HRCT of a follow-up patient before and after 6 months.

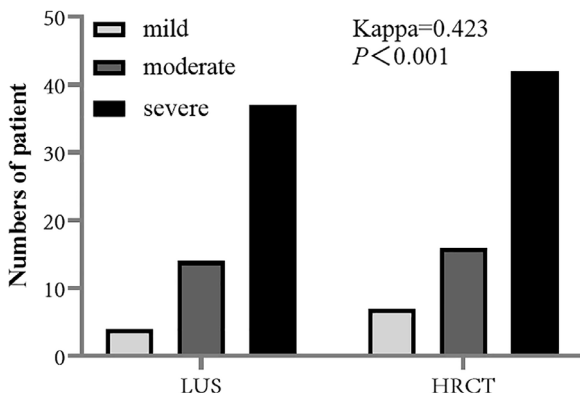


Fig. 4. Consistency between LUS and HRCT in judging the severity of CTD-ILD.

and HRCT Warrick scores and found that the results of the two methods were consistent. In view of the consistency of LUS and HRCT results, LUS can be a powerful supplement to HRCT in screening for CTD-ILD, as well as assessing the disease severity. Buda et al.³³ suggested that irregular pleural lines are associated with honeycomb-like changes in HRCT, which directly indicates the severity of pulmonary interstitial lesions. In addition, Sperandeo et al. suggested that pleural thickness can also be used to determine the severity of ILD,³⁴ and has a good correlation with HRCT. However, we did not find similar results in our study. The reason may be that our study included multiple types of CTD, whereas previous studies only included a single CTD.

Although LUS may be a promising tool, owing to its many limitations, it can only be used as a supplement to HRCT, not as a substitute. First, LUS imaging is affected by air in the lungs, and the detection range of LUS is also limited.^{17,22,23} In our study, B lines were an important evaluation index of LUS, which can be found under

physiological or pathological conditions such as aspiration, acute respiratory distress syndrome or various types of pneumonia. Therefore, B lines are not specific markers of ILD.^{23,35–37} Moreover, because ultrasound examination is subjective, the accuracy of the results of any ultrasound examination, including LUS, depends on the experience of the operator. The selection of the probe, the location of the examination, the ultrasonic scanning frequency, and the setting of the ultrasonic machine all affect imaging quality, especially the B lines.^{23,35,36,38} Operators with insufficient training and experience may lead to deviations in the results. According to Tinti et al.,³⁹ reliably obtaining B lines is based on freezing the ultrasound image and counting the lines each time the probe position is changed. Rea et al.^{40,41} and Sperandeo et al.^{35,38} highlighted the technical limitations of LUS. In addition, the imaging level and detection sensitivity of various equipment for LUS and HRCT are different. However, LUS is more operator-independent, and the results may be unstable.

LUS and ILD types

Different types of ILD have different prognoses. The response of nonspecific interstitial pneumonia NSIP to glucocorticoids and immunosuppressants is much better than that of usual interstitial pneumonia(UIP); therefore, distinguishing ILD types is very important. The total number of B-lines and irregular pleura lines was significantly different among the different types of ILD. Furthermore, we found that pleural irregularity was significantly different between UIP and NSIP ($P = 0.023$), suggesting that pleural irregularity can be used as a LUS index to distinguish UIP from NSIP.

LUS and pulmonary function test

FVC and DLCO are related to the prognosis and mortality of patients⁴³ as studies have shown that if the FVC predictive value is less than 70%, ILD mortality will increase threefold.⁴² Gargani et al.

Table 2 Correlation between LUS and pulmonary function test.

	FVC		FEV1		FEV1/FVC		TCL		IC		DLCO/SB		DLCO/VA	
	r	P	r	P	r	P	r	P	r	P	r	P	r	P
Total number of B-lines	-0.07	0.598	-0.09	0.505	0.04	0.767	-0.23	0.091	-0.25	0.186	-0.20	0.144	0.02	0.929
B-line points	-0.14	0.31	-0.14	0.326	0.10	0.476	-0.28	0.04	-0.30	0.11	-0.24	0.083	0.01	0.955
Pleura thickness	-0.13	0.358	-0.19	0.175	-0.01	0.942	-0.29	0.034	-0.11	0.568	0.05	0.701	0.06	0.749
Pleural irregularities	-0.47	0.00	-0.40	0.003	0.20	0.158	-0.47	0.00	-0.75	0.69	-0.33	0.02	-0.13	0.51

Note: Data was analyzed by Spearman correlation.

Abbreviations:FVC: forced vital capacity, FEV1: first second forced expiratory volume, IC: inspiration capacity, TCL: total lung capacity; DLCO: diffusion capacity of the lung for carbon monoxide; SB: single breath; VA: aveolar volume.

Table 3
Group differences of LUS indexes of different CTD types.

	UIP	NSIP	DIP	other	P
total number of	73.00	22.00	48	24.00	0.035
B-line	(43.25–125.50)	(5.00–99.00)	(15.75–80.00)	(7.00–182.00)	
B-line points	27.50	13.00	19.50	12.00	0.055
	(17.00–35.00)	(4.00–32.00)	(7.25–30.25)	(5.00–33.50)	
Pleural thickness	2.35	1.90	2.15	2.10	0.183
	(1.90–2.80)	(21.70–2.40)	(2.00–2.65)	(1.55–2.40)	
Pleural irregularities	11.00	3.00	9.50	6.00	0.022
	(6.00–20.75)	(1.00–6.00)	(6.75–19.00)	(1.00–6.00)	

Note: Data was analyzed by Kruskal-Wallis H test between multiple groups, and independent samples T test between two groups.

Abbreviations: UIP: usually interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, DIP: desquamative interstitial pneumonitis.

and Cakir et al. found that the total number of B-lines was negatively correlated with FVC and DLCO.¹⁴ Our study found that there was a negative correlation between the number of B-line points and TCL, but no significant correlation between the number of B-lines and lung function index. This difference may be due to the different participants: our study involved ILD patients with multiple CTD, while the above two studies were limited to SSC-ILD, and did not explore the relationship between irregular pleural lines and pulmonary function test. This study found that irregular pleural lines were negatively correlated with FVC, FEV1, TCL, and DLCO, indicating that an irregular pleural line may also be an effective indicator to judge the condition of ILD.

Our study had some limitations. First, because the number of patients completing follow-up was small, there may be bias in evaluating the consistency of HRCT and pulmonary ultrasound. Moreover, the time points of HRCT, LUS, and pulmonary function tests cannot be synchronized completely. Thus, changes in lung conditions in a short time may have affected the research results. In addition, LUS was performed in different patients by different doctors. Although our doctors received strict training according to uniform standards, bias can only be minimized and not eliminated. The findings of our study, contribute toward considering LUS a feasible method for screening patients with CTD-ILD. However, if more convincing results are to be obtained, future researches should pay attention to the following issues: (1) large cohorts of patients; (2) how to perform a standardized LUS examination; (3) consensus on the scoring system of LUS for CTD-ILD; (4) application of portable ultrasonic machine.

Conclusion

This study explored the use of LUS in evaluating CTD-ILD, suggesting that it may be a promising tool for screening patients. LUS could also reflect the severity of respiratory symptoms in patients with CTD-ILD, and it may be used to judge the condition of ILD. Considering the limitations of LUS, HRCT remains the tool of reference in the diagnosis of CTD-ILD. Further studies are necessary to confirm the screening value of LUS in patients with CTD-ILD.

Guarantor

The scientific guarantor of this publication is Qibing Xie.

Ethical approval

Institutional Review Board approval was obtained.
Study subjects or cohorts overlap:
No study subjects or cohorts have been previously reported.

Conflict of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Acknowledgments

This research was supported by Sichuan Science and Technology Program (Grant number: 2021JDRC0045, and 2021YFS0164), the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (Grant number: ZYJC18021), and Chengdu science and technology Bureau Project (Grant number: 2021-YF05-00677-SN).

References

- Salaffi F, Carotti M, Baldelli S, et al. Subclinical interstitial lung involvement in rheumatic diseases. Correlation of high resolution computerized tomography and functional and cytologic findings. *Radiol Med.* 1999;97:33–41.
- Spagnolo P, Distler O, Ryerson CJ, et al. Mechanisms of progressive fibrosis in connective tissue disease (CTD)-associated interstitial lung diseases (ILDs). *Ann Rheum Dis.* 2021;80(2):143–150.
- Fischer A, Strek M, Cottin V, et al. Proceedings of the American College of Rheumatology/Association of Physicians of Great Britain and Ireland Connective Tissue Disease Associated Interstitial Lung Disease Summit: a multidisciplinary approach to address challenges and opportunities. *Arthritis Rheumatol.* 2019;71:182–195.
- Mira-Avendano I, Abril A, Burger C, et al. Interstitial lung disease and other pulmonary manifestations in connective tissue diseases. *Mayo Clin Proc.* 2019;94(2):309–325.
- Fathi M, Dastmalchi M, Rasmussen E, et al. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. *Ann Rheum Dis.* 2004;63:297–301.
- Koduri G, Norton S, Young A, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology.* 2010;49:1483–1489.
- Zamora AC, Hoskote SS, Abascal-Bolado B, et al. Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome. *Respir Med.* 2016;118:39–45.
- Perelas A, Silver RM, Arrossi AV, et al. Systemic sclerosis-associated interstitial lung disease. *Lancet Respir Med.* 2020;8(3):304–320.
- Castelino FV, Moua T. detection and management of interstitial lung diseases associated with connective tissue diseases. *ACR Open Rheumatol.* 2021;3(5):295–304.
- Hoffmann-V AM, Aaløkken TM, Lund MB, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. *Arthritis Rheum.* 2015;67:2205–2212.
- Pignone A, Matucci-Cerinic M, Lombardi A, et al. High-resolution computed tomography in systemic sclerosis. Real diagnostic utilities in the assessment of pulmonary involvement and comparison with other modalities of lung investigation. *Clin Rheumatol.* 1992;11:465–472.
- Hassan RI, Lubertino LI, Barth MA, et al. Lung ultrasound as a screening method for interstitial lung disease in patients with systemic sclerosis. *J Clin Rheumatol.* 2019;25(7):304–307.
- Barskova T, Gargani L, Guiducci S, et al. Lung ultrasound for the screening of interstitial lung disease in very early systemic sclerosis. *Ann Rheum Dis.* 2013;72(3):390–395.
- Gargani L, Doveri M, D'errico L, et al. Ultrasound lung comets in systemic sclerosis: a chest sonography hallmark of pulmonary interstitial fibrosis. *Rheumatology (Oxford).* 2009;48:1382–1387.

15. Volpicelli G, Elbarbary M, Blaivas M, et al. International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS): international evidence-based recommendations for point-of-care lung ultrasound. *Intensive Care Med.* 2012;38:577–591.
16. Kreuter M, Mathis G. Emergency ultrasound of the chest. *Respiration.* 2014;87:89–97.
17. Reissig A, Görg C, Mathis G. Transthoracic sonography in the diagnosis of pulmonary diseases: a systematic approach. *Ultraschall Med.* 2009;30(5):438–454.
18. Wohlgenannt S, Gehmacher O, Gehmacher U, et al. Sonographische Befunde bei interstitiellen Lungenerkrankungen [Sonographic findings in interstitial lung diseases]. *Ultraschall Med.* 2001;22(1):27–31.
19. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest.* 2008;134(1):117–125.
20. Moazedi-Fuerst FC, Kielhauser SM, Scheidl S, et al. Ultrasound screening for interstitial lung disease in rheumatoid arthritis. *Clin Exp Rheumatol.* 2014;32(2):199–203.
21. Volpicelli G, Elbarbary M, Blaivas M, et al. international evidencebased recommendations for pointofcare lung ultrasound. *Intensive Care Med.* 2012;38: 577591.
22. Tinti M, Rea G, Mirijello A, et al. Is there any role for thoracic ultrasound for interstitial lung disease underlying rheumatologic conditions? *Comment. Intern Emerg Med.* 2017;12(6):903–904.
23. Brogna B, Bignardi E, Brogna C, et al. A pictorial review of the role of imaging in the detection, management, histopathological correlations, and complications of COVID-19 pneumonia. *Diagnostics.* 2021;11(3):437.
24. Gutierrez M, Salaffi F, Carotti M, et al. Utility of a simplified ultrasound assessment to assess interstitial pulmonary fibrosis in connective tissue disorders—preliminary results. *Arthritis Res Ther.* 2011;13:R134.
25. Moazedi-fuerst FC, Kielhauser S, Brickmann K, et al. Sonographic assessment of interstitial lung disease in patients with rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus. *Clin Exp Rheumatol.* 2015;33:S87–S91.
26. Warrick JH, Bhalla M, Schabel SI, et al. High resolution computed tomography in early scleroderma lung disease. *J Rheumatol.* 1991;18:1520–1528.
27. Picano E, Frassi F, Agricola E, et al. Ultrasound lung comets: a clinically useful sign of extravascular lung water. *J Am Soc Echocardiogr.* 2006;19:356–363.
28. Mohammadi A, Oshnoei S, Ghasemi-Rad M. Comparison of a new, modified lung ultrasonography technique with high-resolution CT in the diagnosis of the alveolo-interstitial syndrome of systemic scleroderma. *Med Ultrason.* 2014;16:27–31.
29. Iodice V, Pisaturo M, Fusco FM, et al. Use of lung ultrasound in COVID-19: comparison with ultra-high-resolution computed tomography among 29 patients at “D. Cotugno” hospital, Naples, Italy. *Infez. Med.* 2020;28:346–350.
30. Lomoro P, Verde F, Zerboni F, et al. COVID-19 pneumonia manifestations at the admission on chest ultrasound, radiographs, and CT: single-center study and comprehensive radiologic literature review. *Eur J Radiol Open.* 2020;7: 100231.
31. Doveri M, Frassi F, Consensi A, et al. Ultrasound lung comets: new echographic sign of lung interstitial fibrosis in systemic sclerosis. *Reumatismo.* 2008;60:180–184.
32. Tardella M, Gutierrez M, Salaffi F, et al. Ultrasound in the assessment of pulmonary fibrosis in connective tissue disorders: correlation with high-resolution computed tomography. *J Rheumatol.* 2012;39(8):1641–1647.
33. Buda N, Piskunowicz M, Porzezińska M, et al. Lung ultrasonography in the evaluation of interstitial lung disease in systemic connective tissue diseases: criteria and severity of pulmonary fibrosis - analysis of 52 patients. *Ultraschall Med.* 2016;37(4):379–385.
34. Sperandeo M, Varriale A, Sperandeo G, et al. Transthoracic ultrasound in the evaluation of pulmonary fibrosis: our experience. *Ultrasound Med Biol.* 2009;35:723–729.
35. Sperandeo M, Carnevale V, Varriale A. Response to pleuro-pulmonary US Examination Artifacts: “Error in Images”. *Ultrasound Med Biol.* 2010;36:357.
36. Quarato CMI, Venuti M, Sperandeo M. Diagnosis of Coronavirus Disease (COVID-19) Pneumonia: is lung ultrasound the better choice? *Am J Roentgenol.* 2021;216: W5.
37. Sperandeo M, Rea G. Interstitial Lung Diseases. In: Feletti F, Malta B, Aliverti A, eds. *Thoracic Ultrasound and Integrated Imaging.* Berlin, Germany: Springer International Publishing; 2020:61–82.
38. Sperandeo M, Trovato G. Lung ultrasound in covid-19 patients—more shadows than information—letter to the Editor on the Article “W. LU et al. *Ultraschall in Med.* 2020 Apr 15. *Ultraschall Der Med.-Eur J Ultrasound.* 2020;41:439–440.
39. Tinti M, Rea G, Frongillo E, et al. The pathologic patterns detectable by transthoracic ultrasonography are only the pleural and subpleural ones and are not specific: why compare them with high-resolution computed tomography? *J Ultrasound Med.* 2018;37:1847–1848.
40. Rea G, Trovato GM. A Farewell to B-Lines: ageing and disappearance of ultrasound artifacts as a diagnostic tool. *Respiration.* 2015;90(6):522.
41. Rea G, D’Amato M, Ghittoni G. Pitfalls of the ultrasound diagnosis of pneumothorax. *Am J Emerg Med.* 2014;32(9):1126–1127.
42. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med.* 2008;177:1248–1254.
43. Goh NS, Hoyle RK, Denton CP, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* 2017;69:1670–1678.