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Utility of lung ultrasound to identify interstitial lung disease

An observational study based on the STROBE guidelines

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Abstract

Lung ultrasound (LUS) has recently been used to identify interstitial lung disease (ILD). However, data on the role of LUS in the detection of ILD remain limited. The aim of this study was to investigate the diagnostic value of LUS compared with high-resolution computed tomography (HRCT) in patients with ILD.

The retrospective study was carried out by reviewing the medical records of patients with respiratory signs and symptoms discharged from the respiratory ward. Only patients with suspected ILD who underwent HRCT and LUS within a week were selected. ILD was identified with a semi-quantitative score of B-lines >5 and a Warrick score >0 points. The endpoints of LUS in diagnosing ILD (i.e., sensitivity, specificity, positive likelihood ratio [PLR], negative likelihood ratio [NLR], positive predictive value [PPV], and negative predictive value [NPV], and receiver operating characteristic [ROC] curve) was compared with that of HRCT. The reference standard used for the diagnosis of ILD was based on history, clinical findings and examination, and laboratory and instrumental tests, including pulmonary function tests, lung histopathology, and HRCT (without LUS findings).

The final clinical diagnosis of ILD was 55 in 66 patients with suspected ILD. HRCT was positive in 55 patients, whereas LUS detected ILD in 51 patients. Four patients with negative LUS findings were positive on HRCT. The results showed 93% sensitivity, 73% specificity, 3.40 PLR, 0.10 NLR, 94% PPV, and 67% NPV for LUS, whereas 100% sensitivity, 82% specificity, 5.49 PLR, 0.01 NLR, 97% PPV, and 100% NPV for HRCT. Comparison of the 2 ROC curves revealed significant difference in the diagnostic value of the 2 methods for the diagnosis of ILD ($P = .048$).

Our results indicated that LUS is a useful technique to identify ILD. Considering its non-radiation, portable and non-invasive advantages, LUS should be recommended as a valuable screening tool in patients with suspected ILD.

Abbreviations: CI = confidence interval, HRCT = high-resolution computed tomography, ICS = intercostal space, ILD = interstitial lung disease, LUS = lung ultrasound, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value, ScS = scanning sites.

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

1. Introduction

Interstitial lung disease (ILD) is a group of diseases characterized by diffuse pulmonary parenchymal and alveolar inflammation and interstitial fibrosis; it is also known as diffuse parenchymal lung disease.[1] ILD treatment lacks effective drugs, and the disease progresses rapidly, seriously threatening human health. High-resolution computed tomography (HRCT) is an important screening tool for the diagnosis of ILD. It can assess the extent of lesions and suggest possible pathological types. The specificity and sensitivity are as high as 80% or more.[2] However, CT examination of the patient involved radiation of the patient.

It cannot be repeated multiple times and performed during bedside examinations, and it entails prohibitive costs,[3] and is particularly challenging for patients with limited mobility (e.g., those in emergency and intensive care units), for pregnant women with diffuse lung disease, and patients requiring rapid monitoring due to rapid disease progression. Hence, an imaging technology that is simple, fast, inexpensive, and radiation-free is needed.

With the outbreak of viral infections in the respiratory system, lung ultrasound (LUS) has received increasing attention because the virus invades the lungs, causing interstitial changes. In recent years, LUS has been used to localize and guide pleural biopsy in traditional pleural effusions, thereby revolutionising the imaging of lung parenchymal diseases. In ILD patients, the accumulation of collagen fibres and fibroblasts leads to subpleural interlobular

Editor: Rahul Khosla.

This work was supported by a grant from the Health and Family Planning Commission of Shandong Province (No.2017WS366), the Science and Technology Plan Project of Binzhou Medical University (No. BY2017KJ30).

The study protocol was approved by the Institutional Ethics Committee of Binzhou Medical University Hospital (No. 2018-BY2017KJ30–01). Informed written consent was obtained from all the participants.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Yan JH, Pan L, Gao YB, Cui GH, Wang YH. Utility of lung ultrasound to identify interstitial lung disease: an observational study based on the STROBE guidelines. Medicine 2021;100:12(e25217).

Received: 1 May 2020 / Received in final form: 22 February 2021 / Accepted: 23 February 2021

http://dx.doi.org/10.1097/MD.0000000000025217

septal thickening, often involving peripheral lung tissues; thus, LUS is a completely feasible method of examination. Many scholars have conducted meaningful research on the application of LUS in patients with pulmonary fibrosis;[4–6] however, data on the role of LUS in the diagnosis of ILD remain limited. In this study, we aimed to investigate the diagnostic value of LUS compared with HRCT in patients with ILD.

2. Materials and methods

2.1. Study design and setting

The present retrospective study was performed in the Department of Respiratory Diseases of Binzhou Medical University Hospital between September 2018 and December 2019. The methodology of the present study was approved by the Institutional Ethics Committee of Binzhou Medical University Hospital (No. 2018-BY2017KJ30-01). Informed consent was obtained from all patients and/or their families. The researchers adhered to the ethical principles presented in the Declaration of Helsinki and maintained the confidentiality of the data. Additionally, the authors had access to information that could identify individual participants during or after data collection.

2.2. Study participants

Adult patients (aged >18 years) with suspected ILD were selected from the respiratory ward. No sex limitations were included in the study. The diagnosis of ILD was based on history, clinical findings and examination, and laboratory and instrumental tests, including pulmonary function tests, lung histopathology, and HRCT. All patients were diagnosed with ILD according to the 2015 American Thoracic Society/ATS/ERS,[1] and all patients underwent LUS and HRCT.

Patients were excluded from the study if they had any of the following:

1. mental dysfunction;
2. acute respiratory distress syndrome, bronchial asthma, bronchiectasis, pulmonary bullae, and cardiogenic pulmonary edema;
3. severe renal, heart, and liver dysfunction;
4. lung function contraindications, such as recent massive hemoptysis, angina or myocardial infarction, severe cardiac dysfunction, pneumothorax or proneness to pneumothorax, and severe bullous bullae.

2.3. LUS technique

All LUS examinations were performed by the same attending physician with 5 years of experience in LUS. The physician was blinded to all clinical data and HRCT data. A commercially available GE-E9 Doppler ultrasound machine (GE Healthcare, Milwaukee, WI, USA) with a line array probe was used. The operator selected the lateral or sitting position according to the condition and divided the lungs into anterior, lateral, and posterior segments. Anatomical sites were assessed using simplified LUS B-line assessment.[7] Fourteen intercostal spaces (ICS) of the LUS examination are shown in Table 1.

Based on the analysis of the ultrasound images of the pleura and lung parenchyma, the LUS criteria for ILD according to the simplified B-line scoring system was proposed by Gutierrez et al in 2011.[7] The B-line scores for ILD by LUS are shown in Table 2.

Table 1

Anatomical sites assessed simplified LUS B-lines assessment.

Anatomical line	Right (7 ScS)	Left (7 ScS)
Anterior		
Parasternal	2nd ICS	2nd ICS
Mid-clavicular	4th ICS	4th ICS
Lateral		
Anterior axillary	4th ICS	4th ICS
Mid-axillary	4th ICS	4th ICS
Posterior axillary	8th ICS	8th ICS
Posterior		
Sub-scapular	8th ICS	8th ICS
Paravertebral	8th ICS	8th ICS

ICS = inter-costal space, LUS = lung ultrasound, ScS = scanning sites.

The total scores of the B-lines were calculated as the sum of the B-lines counted in each area. In the present study, ILD was identified using a semi-quantitative score of B-lines >5.[7] The semi-quantitative score was 0 = normal (<5 B-lines), 1 = mild (from 6–15 B-lines), 2 = moderate (from 16–30 B-lines), and 3 = severe (>30 B-lines). In addition to the B line, we also observed other important indicators, including the pleural line[8] and the existence of a hypoechoic area under the pleura in the chest.

2.4. HRCT technique

A dual-source CT scan with a scan pitch of 5.1 mm and a layer thickness of 5 mm was used. Pulmonary imaging findings were recorded for all patients. The HRCTs were initially performed by the radiologists on duty, but were also evaluated the following day by an expert radiologist with 20 years of experience, who classified the findings by the Warrick score,[9] which included diffuse lesions of the lungs, subpleural arc shadows, irregular linear shadows, irregular linear mesh shadows, lung consolidation, and nodules. One or more shadows, cystic changes, honeycomb shadows, ground glass changes, and bronchiectasis were observed. With reference to the Warrick score, different degrees of pulmonary fibrosis were evaluated using a semi-quantitative score (0 points: normal, <8 points: mild, 8–15 points: moderate, >15 points: severe).

In the present study, the radiologists were blinded to the LUS findings. The LUS was performed independently either before or after the HRCT, and the 2 examinations were performed within 1 week of each other.

2.5. Statistical analysis

Descriptive data are presented as means ± SD for continuous variables, and categorical variables are expressed as counts and percentages. All statistical analyses were performed using SPSS

Table 2

The simplified assessment the semi-quantitative B-lines score of ILD by LUS.

Grade	Number of B-lines	Score
Normal	<5 B-lines	0
Mild	6–15 B-lines	1
Moderate	16–30 B-lines	2
Severe	>30 B-lines	3

ILD = interstitial lung disease, LUS = lung ultrasound.

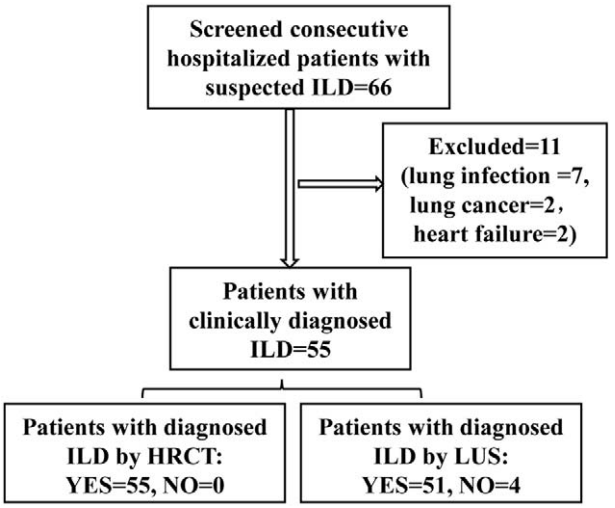

Figure 1. Study flowchart. ILD = interstitial lung disease; HRCT = high-resolution computed tomography; LUS = lung ultrasound.

version 19 (SPSS, Chicago, IL) and MedCalc (MedCalc Software, Mariakerke, Belgium). Receiver operating characteristic (ROC) curves were created to assess the diagnostic accuracy of either HRCT or LUS for the diagnosis of ILD. Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) were also calculated. ROC curves were compared to detect possible differences in the diagnostic performance. The Chi-Squared test was performed to compare the rates, and a two-tailed $P < .05$, was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

A total of 66 patients with suspected ILD who were hospitalized at the Binzhou Medical University Hospital were initially enrolled. A detailed flowchart was presented in Figure 1. The baseline characteristics of the 55 patients with ILD are provided in Table 3. Of the 55 patients, 36 were male and 19 were female. The Warrick scores were (11.02 ± 1.77) scores, and the B line scores were (16.26 ± 5.44) scores for 55 patients. In 51 patients with ILD diagnosed via LUS, several typical interstitial changes were noted on ultrasound, and these changes included several B lines, pleural rough, pleural line discontinuity, surface irregularities, pleural thickening, subpleural nodules, aurora signs, and a small amount of pleural effusion. Lung function tests showed that all patients had restrictive ventilatory dysfunction, and the severity of the diffusion function was graded from mild to severe.

Moreover, 55 patients were finally diagnosed with ILD. HRCT was positive in 55 patients, whereas LUS detected ILD in 51 patients. Four patients with negative LUS findings were positive on HRCT. Table 4 summarized the diagnostic performance of HRCT and LUS in the diagnosis of ILD.

Table 3

Demographic data of 55 patients with ILD.

Variable	Study patient (%) (n = 55)
Age (yr)	66.40 ± 10.04
Male/Female	36/19
Number of cases diagnosed by HRCT	55 (100.00%)
Warrick score	11.02 ± 1.77
Number of cases diagnosed by LUS	51 (92.73%)
B-lines score	16.26 ± 5.44
Left pleural thickness (mm)	2.53 ± 0.98
Right pleural thickness (mm)	2.50 ± 0.90
Number of lung consolidation	29 (55.77%)
Lung function	
DLCO% Pred	40.77 ± 10.99
FVC% Pred	62.05 ± 10.56

Data are expressed as mean ± SD or number (%); DLCO = diffusion lung capacity for carbon monoxide, FVC = forced vital capacity, HRCT = high-resolution computed tomography, ILD = interstitial lung disease, LUS = lung ultrasound.

3.2. Endpoints comparison of LUS and HRCT

Table 5 showed the endpoints comparison of LUS and HRCT in detail. The sensitivity of LUS and HRCT in the diagnosis of ILD was 93% (95% confidence interval [CI]: 0.82–0.98) and 100% (95% CI: 0.94–1.00). The sensitivity of LUS in the diagnosis of ILD was not statistically different from that of HRCT ($\chi^2 = 2.25$, $P = .13$). The specificity of LUS (73%) in the diagnosis of ILD was also not statistically different from that of HRCT (82%) ($\chi^2 = 0.00$, $P = 1.00$). The PLR was 3.40 (95% CI: 1.29–8.95) and 5.49 (95% CI: 1.58–19.27) for LUS and HRCT, respectively. The NLR of LUS and HRCT was 0.10 (95% CI: 0.04–0.27) and 0.01 (95% CI: 0.00–0.18). The PPV was 94% (95% CI: 0.87–0.98) and 97% (95% CI: 0.89–0.99) for LUS and HRCT, respectively. The NPV of LUS and HRCT was 67% (95% CI: 0.42–0.85) and 100% (95% CI: 0.96–1.00). Additionally, we calculated the positive and negative likelihood ratios and positive and negative predictive values of HRCT and LUS, respectively. Finally, comparison of the 2 ROC curves revealed significant difference in the diagnostic value of the 2 methods ($P = .048$, Fig. 2).

Table 4

Comparison of HRCT and LUS results.

	ILD + (n = 55)			ILD − (n = 11)		
	HRCT			HRCT		
	+	−	Total	+	−	Total
LUS						
+	51	0	51	2	1	3
−	4	0	4	0	8	8
Total	55	0	55	2	9	11

+ = positive, − = negative, HRCT = high-resolution computed tomography, LUS = lung ultrasound. The diagnosis of ILD was based on history, clinical findings and examination, and laboratory and instrumental tests, including HRCT (without LUS findings).

Table 5

Diagnostic accuracy of LUS and HRCT in detection of ILD.

	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	PPV (95% CI)	NPV (95% CI)
LUS	0.93 (0.82–0.98)	0.73 (0.39–0.94)	3.40 (1.29–8.95)	0.10 (0.04–0.27)	0.94 (0.87–0.98)	0.67 (0.42–0.85)
HRCT	1.00 (0.94–1.00)	0.82 (0.48–0.98)	5.49 (1.58–19.27)	0.01 (0.00–0.18)	0.97 (0.89–0.99)	1.00 (0.96–1.00)
χ^2	2.25	0.00				
P	0.13	1.00				

CI = confidence interval, HRCT = high-resolution computed tomography, LUS = lung ultrasound, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value.

3.3. Images comparison of LUS and HRCT

Figure 3 showed several typical changes in patients with idiopathic pulmonary fibrosis. Traction bronchiectasis and cellular changes around the upper lung were observed on HRCT (Fig. 3B, black arrow), and the corresponding changes for LUS presented as numerous B lines (Fig. 3A, 3C, white arrow), as obtained using a low-frequency probe. The HRCT longitudinal window of the patient suggested thickening of the left pleural pleura (Fig. 3D, 3E, red ellipse), and the corresponding changes for LUS presented as a thickened and irregularly fragmented pleural line (Fig. 3F, red ellipse), as obtained using a high-frequency probe.

3.4. Safety

No adverse events were reported in the present study.

4. Discussion

The present study was carried out by reviewing the medical records of patients with suspected ILD to evaluate the value of LUS compared to HRCT. Our findings showed that LUS is a useful technique to identify ILD. Given its safety, low cost, portability, and non-invasiveness, LUS should be considered as a valuable imaging tool for screening ILD in suspicious patients.

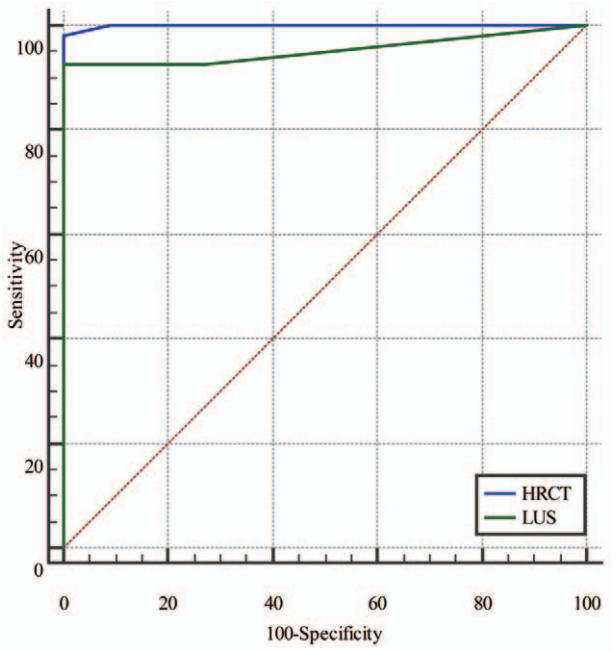

Figure 2. Receiver operating characteristic curves comparison between LUS and HRCT reveals no difference between the diagnostic values of the 2 methods for the diagnosis of ILD.

The lung is a gas-containing organ that has always been a blind spot for ultrasound. With the deepening research in this field, ultrasound has been found to have high sensitivity and specificity for the diagnosis of lung diseases. In recent years, LUS has been used to locate and guide pleural disease tissue biopsy from traditional pleural effusions and to revolutionise the imaging of lung parenchymal diseases. Wojsyk-Banaszak et al believed that LUS should be considered a supplementary radiographic examination in the monitoring of patients with cystic fibrosis.[10] In patients with ILD, the accumulation of collagen fibres and fibroblasts leads to subpleural interlobular septa and interlobular septal thickening, often involving peripheral lung tissue; thus, LUS is a completely feasible method of examination. In 1997, Lichtenstein et al first reported the relationship between the ultrasound pulmonary stellate tail and interstitial thickening of the lobule of the lung; such a relationship enables the ultrasound detection of interstitial pulmonary edema.[11] The pathological process of ILD is roughly divided into 4 stages: (a) lung parenchymal lesions and alveolitis, (b) alveolar septum thickening and increased fibre components, (c) thickened alveolar wall and interlobular septa, and (d) alveolar wall structure destruction caused by progressive acinar lesions, resulting in cystic and honeycomb formation. The pathological changes in the LUS scans showed a gradual increase in the number of B lines and an increase in the pleural line index.[12]

In lung diseases, the alveolar gas content increased, and the fluid in the lung interstitium and alveoli increased; subsequently, the thickened interlobular septum formed a reflective interface with gas due to various damage factors. Given the large difference in acoustic impedances, when the ultrasonic wave contacts the interface, a reflection forms, and the reflection of the round-trip multiple back and forth is received by the ultrasonic probe to display the characteristic "appendix sign artefact," also called the B line.[13,14] The value of the diagnosis of ILD on the B line has been verified, but the irregularity of the pleural line needs further verification.[15] Lung consolidation is usually composed of alveolar septal infiltration caused by lymphocytes and plasma cells, which seem to be patchy, and the subpleural nodular hypoechoic area might be related to pulmonary fibrosis.[16] A meta-analysis of 249 patients showed that LUS has a high diagnostic accuracy for CTD–ILD with sensitivity and specificity of 91.5% and 81.3%, respectively.[17] However, further studies with a larger sample size are needed to clarify the value of LUS for ILD, not just CTD–ILD.

In our study, 55 patients with clinically diagnosed ILD were examined using LUS and HRCT. The influence characteristics of

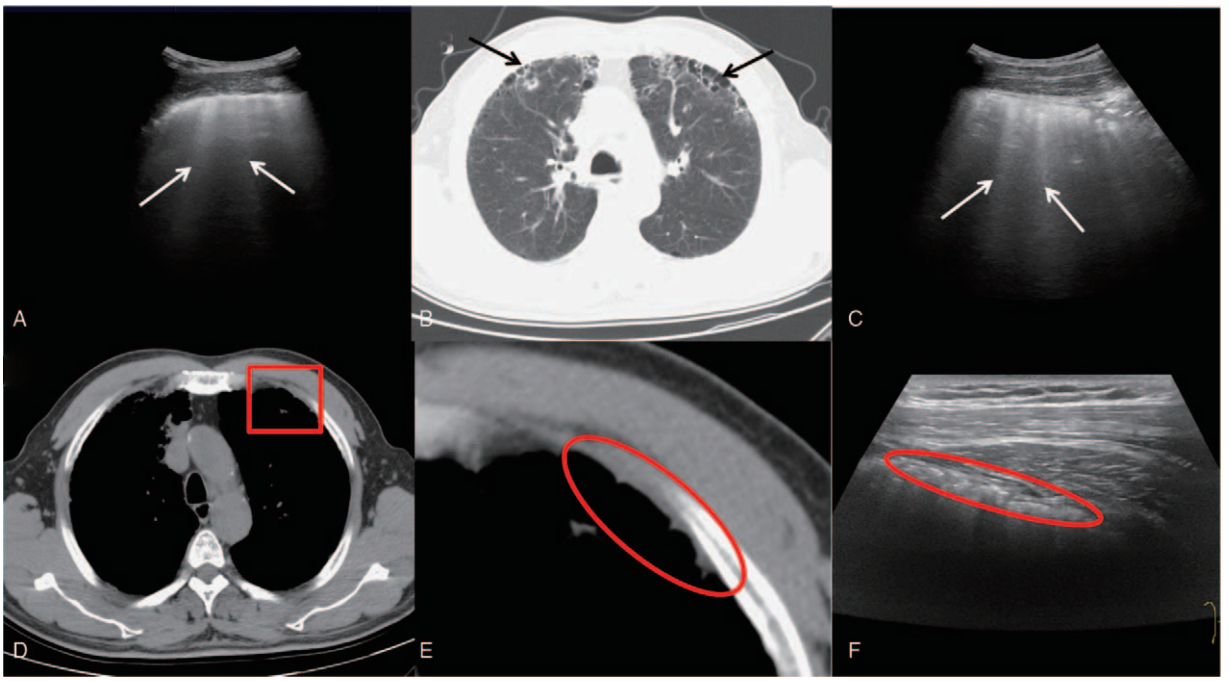

Figure 3. Lung ultrasound signs of ILD. Traction bronchiectasis and cellular changes around the upper lung were found in the HRCT (Fig. 3B, black arrow), and the corresponding changes for LUS presented as numerous B lines (Fig. 3A, 3C, white arrow), as obtained using a low-frequency probe. The HRCT longitudinal window of the above patient suggested a thickening of the left pleural pleura (Fig. 3D, 3E, red ellipse), and the corresponding changes for LUS presented as the thickened and irregularly fragmented pleural line (Fig. 3F, red ellipse), as obtained using a high-frequency probe.

LUS and HRCT were recorded. Our results suggested that LUS had a high sensitivity. Numerous B lines formed by thickened leaflets were observed using LUS. The normal pleural line thickness was less than 0.5 mm, and the surface was flat. The corresponding pathological changes appeared on the ultrasound sonogram as pleural thickening and irregular and uneven lung surface because the common pathological manifestations of ILD are pleural thickening, fibrosis, interstitial fibrosis, and fibrous scars, especially interlobular septal fibrosis. The results of our study suggest that the pleural thickness of all patients with ILD was between and 0.7 to 4.6 mm and that the left lung was slightly thicker than the right pleura. The specific reasons are not clear and require further investigation.

The PPV of LUS and HRCT was 94% and 97%, which stated that a positive LUS highly likely identifies an ILD and that an HRCT can be avoided in most patients if LUS is positive. The NLR of LUS and HRCT was 0.10 and 0.01, and the NPV of LUS and HRCT was 67% and 100%, which stated that a negative HRCT compared with LUS more highly likely rules out an ILD in patients with suspected ILD. Therefore, LUS can be used as a useful screening tool to identify ILD rather than a means of exclusion in suspicious patients.

In addition, LUS cannot easily display thickened and distorted interstitial lesions in the deep lung tissue, such as the vascular bronchial bundle, small nodules distributed around the bronchial vessels, deep ground glass or small nodules, and mediastinal lymph nodes. In contrast, HRCT can display them completely. We also found that LUS missed more ILD cases than HRCT, and these missed patients with ILD were all in the early stages. We believe that patients with interstitial lung changes in the early stages were atypical, and that the degree of pulmonary fibrosis was mild. However, the LUS sonogram was neither typical nor sufficient for diagnosing ILD. Therefore, these points must be investigated in future studies.

The present study had several limitations. First, a retrospective study with a small sample size may have affected the results. In the future, a prospective study with large-scale sample is needed. Second, there were numerous causes of ILD among the patients in this study. Except that HRCT can diagnose idiopathic pulmonary fibrosis independently, it is currently difficult to determine the aetiology of ILD when the 2 methods are used to identify ILD. Therefore, a subgroup analysis based on the aetiology of ILD was not conducted.

5. Conclusions

LUS has a typical characteristic sonogram in ILD. Considering that LUS has many advantages, such as zero radiation, multiple repeatability detection, good mobility, and low cost, LUS should be a valuable screening tool for patients with suspected ILD. However, further prospective studies with large-scale samples are needed to confirm our preliminary findings.

Author contributions

Conceptualization: Lei Pan, Yue-Heng Wang.
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Writing – original draft: Jun-Hong Yan, Lei Pan.
Writing – review & editing: Yue-Heng Wang.

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