Diagnostic value of lung ultrasound in patients with interstitial lung disease: a retrospective study

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Abstract

Background Interstitial lung disease (ILD) is a serious threat to human health due to its difficult diagnosis and lack of effective treatment. Lung ultrasound (LUS) has recently been applied to the detection of ILD, and but the data on its role in the diagnosis of ILD remain limited. The aim of this study was to explore the value of LUS in the diagnosis of ILD.

Methods This retrospective study was carried out by reviewing the medical records of patients admitted to a respiratory ward from June 2018 to July 2019. Only patients discharged with a clinical diagnosis of ILD and underwent high-resolution computerised tomography (HRCT) and LUS within a week were selected. Basic information about the patients, laboratory data, characteristic mages of LUS scans and diagnosis results of HRCT and LUS were collected. The sensitivity of LUS and HRCT in the diagnosis of ILD was calculated, and clinical diagnosis was applied as the gold standard.

Results A total of 32 patients with a clinical diagnosis of ILD were enrolled. Out of the 32 patients, 5 patients (15.63%) had false negative results in LUS, and 3 (9.38%) had false negative results in HRCT. False positive cases were not observed. All patients were diagnosed with ILD, and thus, the specificity of the examination could not be counted. With the clinical diagnosis of ILD as the gold standard, the sensitivity values of LUS and HRCT for the diagnosis of ILD were 0.84 (0.67–0.95) and 0.91 (0.75–0.98), respectively. No significant difference in sensitivity was observed between the two groups ($P = 0.4795$).

Conclusions LUS is not inferior to HRCT in the diagnosis of ILD. Considering its safety, low cost, portability and practicability, LUS should be considered as the first-line imaging tool for patients with suspected ILD.

Background

Interstitial lung disease (ILD) is a group of diseases characterised by diffuse pulmonary parenchyma, 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 computerized tomography (HRCT) is an important screening tool for the diagnosis of ILD. It can assess the extent of lesions and suggest possible pathological types. Specificity and sensitivity are as high as 80% or more [2]. However, CT is radioactive, it cannot be repeated multiple times, it cannot be performed during bedside examinations, and it entails prohibitive costs [3]; CT is particularly challenging for patients with limited mobility (e.g. those in emergencies and intensive care units), 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.

In recent years, lung ultrasound (LUS) has been used to localise and guide pleural biopsy intraditional pleural effusions, thereby revolutionising the imaging of lung parenchymal diseases. In ILD, the accumulation of collagen fibres and fibroblasts leads to subpleural interlobular septa and interlobular septal thickening, often involving peripheral lung tissues; thus, LUS is a completely feasible method of

examination. A total of 32 patients with clinically diagnosed ILD in our hospital were enrolled in the study. All patients underwent LUS and HRCT. The pleural and pulmonary parenchymal ultrasound images were retrospectively analysed. We aimed to compare the sensitivity levels of LUS and HRCT in the diagnosis of ILD and to explore the diagnostic value of LUS in patients with ILD.

Methods

Study design and setting

The present retrospective study was performed on patients presented to the Department of Respiratory and Critical Care Medicine of Binzhou Medical University Hospital between June 2018 and July 2019. The methodology of the present study was approved by the ethics committee of Binzhou Medical University Hospital. The researchers adhered to the ethical principles presented in the Helsinki declaration and maintained the confidentiality of data.

Study participants

Adult patients (over 18 years of age) with clinically diagnosed ILD were from the Department of Respiratory and Critical Care Medicine. No sex limitation was applied in the study. The diagnosis of ILD was based on clinical findings, serological tests, pulmonary function tests, lung histopathological biopsy and dual-source HRCT. All patients were diagnosed with ILD according to the 2015 American Thoracic Society/ATS/ERS[1], and all received LUS and HRCT examinations. Informed consent was obtained from all patients or/and their families.

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 oedema; (3) severe renal, heart and liver dysfunction; (4) lung function for contraindications (such as recent massive haemoptysis, angina or myocardial infarction, severe cardiac dysfunction, pneumothorax or proneness to pneumothorax and severe bullous bullae).

LUS

A GE-E9 colour Doppler ultrasound system with a line array probe was used. The operator selected the lateral or sitting position according to the condition and divided the lungs into the anterior, lateral and posterior segments. The four chest areas per side considered for complete eight-zone by LUS examination were shown in Figure 1. In detail, areas 1 and 2 refer to the upper anterior and lower anterior chest areas, respectively. Areas 3 and 4 refer to the upper lateral and basal lateral chest areas, respectively [4]. On the back, areas 1, 2 and 3 refer to the medial upper posterior, medial middle posterior and medial lower posterior back areas, respectively. Areas 4, 5 and 6 refer to the lateral upper posterior, lateral middle posterior and lateral lower posterior back areas, respectively [5].

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 proposed by Gutierrez *et al.* in 2011[6]. The B-lines

score of ILD by LUS was shown in Table 1. The total scores of B-lines were calculated as the sum of the B-lines counted in each area. In the present study, ILD was identified with a total score of B-lines >10 [7]. In addition to the B line, we also observed other important indicators including the pleural line [8], the existence of a hypoechoic area under the pleura and the existence of fluid in the chest.

HRCT

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 pulmonary fibrosis score of HRCT was measured by the Warrick score [9]: imaging results included diffuse lesions of the lungs, subpleural arc shadows, irregular linear shadows, irregular linear mesh shadows, lung consolidation and nodules. One or more shadows, a cystic change, a honeycomb shadow, a ground glass change and a bronchiectasis were observed. The interval time between LUS and HRCT was not longer than one week, and two examinations were performed by the same experienced physician.

Statistical analysis

Descriptive data were presented as means ($\pm$ SD) for continuous variables, where as categorical variables were expressed as counts and percentages. Data analysis was performed using SPSS software package version 19 (SPSS, Chicago, IL, USA) to calculate the sensitivity levels of LUS and HRCT for the diagnosis of ILD. Statistical analysis of the specificity of the test was not possible because all patients were clinically diagnosed with ILD. The chi-square test was used to compare the rates, and the difference was deemed statistically significant at $P<0.05$.

Results

Baseline characteristics of patients

A total of 102 consecutive patients with suspected ILD who were hospitalised in Binzhou Medical University Hospital were initially enrolled. Forty-six patients were diagnosed with ILD, 14 did not undergo LUS, and 32 patients with ILD were eventually enrolled. A detailed flowchart was presented in Figure 2.

Baseline characteristics of patients were presented in Table 2. Of the 32 patients aged 48–82 years, 22 were male, and 10 were female. Amongst the aetiology of ILD, connective tissue disease-related interstitial lung (CTD-ILD) was noted in 17 patients (53.13%), and idiopathic pulmonary fibrosis (IPF) was noted in 8 patients (25%). The lung Warrick score of 29 patients with ILD diagnosed via HRCT was (14.26 ± 8.08) points. The B line score of 27 patients with ILD diagnosed via LUS was (15.44 ± 4.06) scores. A total of 27 (100%) patients had bilateral pleural effusions, and 20 (74.07%) patients had lung consolidation. In 27 patients with ILD diagnosed via LUS, several typical interstitial changes were noted in the 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 product.

Lung function tests showed that all patients had restrictive ventilatory dysfunction, and the severity of the diffusion function was graded from mild to severe.

Sensitivity of LUS and HRCT for the diagnosis of ILD

With the clinical diagnosis of ILD as the gold standard, the sensitivity of LUS in the diagnosis of ILD was 0.84 (95% confidence interval (CI): 0.67–0.95). The sensitivity of LUS in the diagnosis of ILD was not statistically different from the clinical diagnostic gold standard ($\chi^2=3.2$, $P=0.0736$) (Table 3). The sensitivity of HRCT for ILD diagnosis was 0.91 (95% CI: 0.75–0.98). The sensitivity of HRCT for ILD diagnosis was not statistically different from the clinical diagnostic gold standard ($\chi^2=1.33$, $P=0.2488$) (Table 4). No significant difference in sensitivity was observed between LUS and HRCT ($\chi^2=0.50$, $P=0.4795$).

LUS and HRCT diagnosis of typical ILD image

Figure 3 showed several typical ILD changes in a patient, such as pulmonary fibrosis. Traction bronchiectasis and cellular changes around the upper lung were found in the HRCT (Figure 3B, black arrow), and the corresponding changes for LUS presented as numerous B lines (Figure 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 (Figure 3D, 3E, red ellipse), and the corresponding changes for LUS presented as the thickened and irregularly fragmented pleural line (Figure 3F, red ellipse), as obtained using a high-frequency probe.

Safety

No adverse events were reported in the present study.

Discussion

Our findings show that LUS is highly sensitive in detecting ILD and that it may be a reliable tool for screening and diagnosing patients with ILD, although the sensitivity of LUS in ILD detection is slightly lower than that of HRCT.

The lung is a gas-containing organ and has always been a blind spot of ultrasound. With the deepening research into 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. 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 the interstitial thickening of the lobule of the lung; such relationship enables the ultrasound detection of interstitial pulmonary oedema [10]. The pathological

process of ILD is roughly divided into four stages: (a) lung parenchymal lesions and alveolitis, (b) alveolar septum and increased fibre components, (c) thickened alveolar wall and interlobular septa and (d) alveolar wall structure destruction caused by progressive acinar lesions and resulting in cystic and honeycombformation. This pathological changes of LUS scans show a gradual increase in the number of B lines and an increase in the pleural line index[11].

In lung diseases, the alveolar gas content increases, the fluid in the lung interstitial and alveolar increases, and the thickened interlobular septum forms 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 would be received by the ultrasonic probe to display the characteristic 'appendix sign artefact', also called the B line [12, 13]. The value of the diagnosis of ILD on the B line has been verified, but the irregularity of the pleural line needs further verification [14]. 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 [15]. 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 [16]. However, further study of large sample subjects is needed to clarify the diagnostic value of LUS for CTD-ILD [16].

In our study, 32 patients with clinically diagnosed ILD were examined by LUS and HRCT. The influence characteristics of LUS and HRCT were recorded. The clinical diagnosis of ILD was used as the gold standard. The sensitivity of LUS and that of HRCT were compared to investigate the diagnostic value of LUS. Our results suggest that the sensitivity of LUS is not inferior to that of HRCT. Numerous B lines formed by thickened leaflet spacing were observed by 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 0.7–4.6 mm, and the left lung was slightly thicker than the right pleura. The specific reasons are not clear and must be further investigated. In addition, LUS can clearly show pleural and subpleural lesions, and a small amount of pleural effusion can be found. Pleural effusion is often mistaken for pleural thickening in HRCT; such aspect makes LUS better than HRCT. However, LUS cannot easily display thickened and distorted interstitial lesions in the deep lung tissue, such as the vascular bronchial bundle, the small nodules distributed around the bronchial vessels, the deep ground glass or small nodules and the mediastinal lymph nodes, where as HRCT can completely display. 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, LUS sonogram was neither typical nor sufficient to diagnose ILD. Therefore, the above points must be investigated in further studies.

The present study had several limitations. Firstly, it was a retrospective study with a small population. In the future, a large prospective study is needed. Secondly, all patients were clinically diagnosed with ILD, and a statistical analysis of the specificity of the test was not possible. Thirdly, the causes of ILD amongst the patients in this study were numerous. Different causes of ILD may affect the diagnosis of ILD by LUS. A subgroup analysis was not conducted, and the diagnostic value of LUS may not be fully explained owing to the limited number of cases. Finally, the lack of a control group may affect the results. Control methods can be used in a future study to illustrate the diagnostic value of LUS and HRCT.

Conclusions

In summary, LUS has a typical characteristic sonogram in ILD. Compared with HRCT, LUS has many advantages, such as zero radiation, multiple repeatability detection, good mobility and low cost. As a portable and non-radioactive imaging method, LUS is expected to be a primary screening tool for patients with suspected ILD. It offers important clinical value and deserves in-depth study.

Abbreviations

ILD: interstitial lung disease; HRCT: high-resolution computerized tomography; LUS: lung ultrasound; CTD-ILD: connective tissue disease-related interstitial lung; IPF: idiopathic pulmonary fibrosis; COP: cryptogenic organizing pneumonia; DLCO: diffusion lung capacity for carbon monoxide; FVC: forced vital capacity.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee of Binzhou Medical University Hospital (reference number: 2018-BY2017KJ30-01). Informed written consent was obtained from all the participants.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author and/or the first author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

(I) Conception and design: JHY and YHW. (II) Administrative support: GHC and YHW. (III) Provision of study materials or patients: LP and YBG. (IV) Collection and assembly of data: JHY, LP and YBG. (V) Data analysis and interpretation: JHY, LP and GHC. (VI) Manuscript writing: All authors. (VII) Final approval of manuscript: All authors.

Acknowledgements

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Tables

Table 1 B-lines score of ILD by LUS

Grade	Number of B-lines	Score
Normal	< 10 B-lines	0
Mild	11 to 20 B-lines	1
Moderate	21 to 50 B-lines	2
Severe	> 50 B-lines	3

ILD: interstitial lung disease; LUS: lung ultrasound

Table 2 Demographic data of the present study

Variable	Study patient (%) (n = 32)
Age (years)	64.28±10.12
Male/Female	22/10
Cause of ILD	
IPF	8 (25%)
CTD-ILD	17 (53.13%)
COP	2 (6.25%)
Other forms of ILD	5 (15.63%)
Number of cases diagnosed by HRCT	29 (90.63%)
Warrick score	14.26±8.08
Number of cases diagnosed by LUS	27 (84.38%)
B-lines score	15.44±4.06
Left pleural thickness (mm)	2.63±1.09
Right pleural thickness (mm)	2.50±1.26
Number of pleural effusions	27 (100%)
Number of lung consolidation	20 (74.07%)
Lung function	
DLCO% Pred	41.57±12.60
FVC% Pred	64.91±10.81

Data are expressed as mean ± SD or number (%); ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-related interstitial lung; COP: cryptogenic organizing pneumonia; HRCT: high-resolution computerized tomography; LUS: lung ultrasound; DLCO: diffusion lung capacity for carbon monoxide; FVC: forced vital capacity.

Table 3 The sensitivity of LUS for the diagnosis of ILD

Clinical diagnosis	LUS			Sensitivity (95% CI)	c ²	P value
	Positive	Negative	Total			
Positive	27	5	32	0.84 (0.67-0.95)	3.2	0.0736
Negative	0	0	0			
Total	27	54	32			

Table 4 The sensitivity of HRCT for the diagnosis of ILD

Clinical diagnosis	HRCT			Sensitivity (95% CI)	c ²	P value
	Positive	Negative	Total			
Positive	29	3	32	0.91 (0.75-0.98)	1.33	0.2488
Negative	0	0	0			
Total	29	3	32			

Figures

Figure 1

Lung ultrasound examination areas. In the front chest (A), areas 1 and 2 refer to the upper anterior and lower anterior chest areas, respectively. Areas 3 and 4 refer to the upper lateral and basal lateral chest areas, respectively [4]. On the back (B), areas 1, 2 and 3 refer to the medial upper posterior, medial middle posterior and medial lower posterior back areas, respectively. Areas 4, 5 and 6 refer to the lateral upper posterior, lateral middle posterior and lateral lower posterior back areas, respectively [5].

Figure 2

Study diagram. ILD: interstitial lung disease; HRCT: high-resolution computerized tomography; LUS: lung ultrasound.

Figure 3

Lung ultrasound signs of ILD. Traction bronchiectasis and cellular changes around the upper lung were found in the HRCT (Figure 3B, black arrow), and the corresponding changes for LUS presented as numerous B lines (Figure 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 (Figure 3D, 3E, red ellipse), and the corresponding changes for LUS presented as the thickened and irregularly fragmented pleural line (Figure 3F, red ellipse), as obtained using a high-frequency probe.