Integrated Use of Lung Ultrasound and Chest X-Ray in the Detection of Interstitial Lung Disease

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Keywords

Chest radiography · Chest ultrasound · Computed tomography · Dyspnea · Interstitial lung diseases · Lung diagnosis

Abstract

Background: Current data have shown that lung ultrasound (LUS) may be useful in the detection of interstitial lung disease (ILD) by the evaluation of B-lines, the sonographic marker of pulmonary interstitial syndrome. Nevertheless, no prospective study has compared LUS to chest X-ray (CXR) for ILD assessment, and there is no general agreement on the specific echographic diagnostic criteria for defining ILD. **Objectives:** The aims of this study were (1) to compare the accuracy of LUS and CXR in the detection of ILD using high-resolution CT (HRCT) as the gold standard and (2) to compare the accuracy of different echographic diagnostic criteria for ILD diagnosis. **Methods:** LUS was performed on 104 patients undergoing HRCT for suspected ILD. In 49 patients, a CXR scan performed within 3 months of HRCT was analyzed. ILD was defined as the presence of ≥ 5 B-lines in ≥ 3 chest areas. A total B-line score (TBLS) was also calculated, as in previous studies. The observers evaluating LUS and CXR were blinded

to the HRCT results and clinical data. **Results:** On HRCT, ILD was assessed in 50 patients. CXR was specific (91%; 95% CI 80–100) but not sensitive (48%; 95% CI 28–67). Conversely, LUS showed high sensitivity (92%; 95% CI 84–99) and low specificity (79%; 95% CI 69–90). Using a TBLS, sensitivity did not change, while specificity decreased. **Conclusions:** LUS could be a sensitive tool for ILD detection. CXR and LUS have different but complementary features, and their combined use could reduce the need for HRCT. The use of different diagnostic criteria for defining ILD does not affect sensitivity but influences specificity.

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Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of acute and chronic disorders of the lower respiratory tract that mainly affect the lung parenchyma [1, 2]. Their heterogeneity concerns clinical features, radiologic patterns, etiology, histology, and prognosis. ILDs could have a known origin (drugs, infections, environmental exposures, or other forms) or could be idiopathic (idiopathic interstitial pneumonias, sarcoidosis, or other

forms) and have great clinical relevance for their impact on patient prognosis [1–4]. The recent literature and guidelines emphasize the importance of an early diagnosis based on clinical history and examination, lung functional assessment, biochemical analysis with blood gas analysis, imaging, bronchoscopy with bronchoalveolar lavage, and, if necessary, transbronchial or surgical lung biopsy [5–8].

Among the imaging techniques, chest X-ray (CXR) still plays an important role in the diagnostic workup of ILD, especially in the initial evaluation of lung abnormalities, during follow-up, and in the detection of comorbidities [8, 9]. CXR is inexpensive and easily available and uses lower doses of ionizing radiations than high-resolution CT (HRCT). However, CXR is inaccurate for ILD detection, mainly because it lacks sensibility [10–14]. HRCT is currently considered the gold-standard imaging technique for ILD assessment [5–9], despite the higher costs and radiation exposure compared to CXR. Therefore, there is need for an accurate, nonionizing, and low-cost diagnostic tool for ILD detection.

In the last decade, the use of lung ultrasound (LUS) in clinical medicine has increased. LUS is an accurate tool for the diagnosis of pneumonia, pneumothorax, acute pulmonary edema, and pleural effusion [15, 16]. LUS may also be useful in the detection of ILD by the evaluation of B-lines, the sonographic hallmark of the interstitial syndrome, and by the assessment of pleural abnormalities [17, 18]. However, evidence in this field is limited to few studies comparing LUS to HRCT in patients with rheumatologic diseases [19–24], and no prospective study compared LUS to CXR for ILD assessment. Moreover, there is no general agreement on the specific echographic diagnostic criteria for defining ILD; previous studies differed in scanning technique (subdivision into chest areas or rib interspaces) and in scoring system (number of B-lines to indicate a positive examination result) [19].

Taking into account this background, the main aims of this study were (1) to compare the accuracy of LUS and CXR in the detection of ILD, using HRCT as the gold standard, and (2) to compare the accuracy of different echographic diagnostic criteria for the assessment of ILD.

Subjects and Methods

Subjects and Study Design

From April 2014 to March 2015, we evaluated consecutive outpatients aged ≥ 18 years admitted to the Radiology Unit of the Sant'Orsola-Malpighi Polyclinic of Bologna to undergo HRCT of the chest. The inclusion criteria were (1) a suspected new diagnosis

Fig. 1. Scanning technique: subdivision into chest areas. MUA, medial upper anterior; LUA, lateral upper anterior; MLA, medial lower anterior; LLA, lateral lower anterior; UL, upper lateral; LL, lower lateral; MUP, medial upper posterior; LUP, lateral upper posterior; MMP, medial middle posterior; LMP, lateral middle posterior; MLP, medial lower posterior; LLP, lateral lower posterior.

of ILD (dyspnea on exertion, chronic cough, or restrictive pulmonary function tests), (2) being asymptomatic with risk factors for ILD (professional exposure, smoking habit, history of connective tissue disease, immunodeficiency, and drugs), or (3) a medical history of ILD. On the same day as HRCT was performed, recruitable patients were proposed to undergo LUS of the whole thoracic surface.

To avoid additional ionizing radiation, the patients were not proposed to undergo CXR *ex novo* but only asked for their permission to use the available data from previous CXR scans – if performed within 3 months of the HRCT scan. Therefore, we excluded patients with an acute onset of respiratory symptoms (< 2 weeks), because their unstable condition would have necessitated the application of the 3 imaging techniques at the same time.

Two different observers evaluated the LUS (L. Vizioli and M. Giovagnoli), CXR (A.M. Chiesa and M. Mugghetti), and HRCT (F. Ciccarese and M. Zompatori) results, each of them blinded to the results of the others and to the patients' clinical data. Disagreements were resolved by consensus. The observers evaluating the LUS results have several years of experience in LUS interpretation; all chest examinations (HRCT and CXR) were evaluated by well-experienced chest radiologists who were familiar with ILD. An independent observer recorded the demographics, clinical data, and risk factors for ILD, such as professional exposure (especially to asbestos, silica, and metal dusts), smoking habit, history of connective tissue disease, and immunodeficiency (due to HIV infection, exposure to immunosuppressive drugs, solid organ transplantation, stem cell transplantation, and malignancies).

Fig. 2. Study population. Flowchart of the patient inclusion process.

The study was approved by the Institutional Ethics Committee of the Sant’Orsola-Malpighi Polyclinic of Bologna (project approval No. 38/2014/O/Sper), and the patients gave written consent to their enrollment in the study. The patient data were deidentified after enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki for clinical research involving human subjects.

Lung Ultrasound

LUS was performed on the same day as HRCT, using Mylab 70 XVG echographic equipment (Esaote, Genoa, Italy). Both a linear (5–8 MHz) and a convex (2–5 MHz) probe were used for analysis. The linear probe was used to study the pleural line. Twenty-four chest areas were analyzed per patient, 12 per side (Fig. 1) – 6 per side with the patient in supine decubitus position to study the anterolateral lung fields, and 6 per side with the patient in the seated position for analysis of the posterior lung fields. For each area, the observers recorded the presence of B-lines, consolidations, pleural line abnormalities, and pleural effusion, defined according to the recommendations of the International Consensus Conference on Lung Ultrasound [15]. The B-line distribution (focal or diffuse), the sonographic pattern (homogeneous or not), and the presence and characterization of pleural line abnormalities (fragmentation, irregularity, swelling, and subpleural consolidations) were also evaluated.

An assessment of B-line features (distribution and pattern) and of the pleural line aspect (normal vs. with abnormalities) is indispensable for differential diagnostic considerations [15, 19]; these evaluations are particularly fundamental for differentiating acute pulmonary edema (diffuse and bilateral B-lines with a homogeneous pattern but without pleural abnormalities) from other causes of B-line generation. The general echographic feature of ILD is the presence of multiple and nonhomogeneous B-lines with pleural line abnormalities, especially swelling and subpleural consolidations. However, there is no general agreement on the specific diagnostic criteria for defining ILD [19]. Most of the previous studies calculated a total B-line score (TBLS), i.e., a complete count of B-lines on the entire thoracic surface, defining ILD as a TBLS >5 [22] or >10 [21, 23, 24]. Nevertheless, B-lines are artifacts [25] and the reproducibility of their count is debated [26], even if it has been

reported to be good for a maximum of 5 B-lines in a single scan [23]. We tested a different diagnostic criterion which is not based on the TBLS, considering LUS to be positive for ILD if ≥ 5 B-lines were present in ≥ 3 chest areas (not necessarily contiguous ones). For B-lines ≥ 5 , the observer did not count the B-lines but only recorded if they were confluent or not and if white lung (completely coalescent B-lines) was present.

A TBLS was calculated as well, as was done in previous studies [21–23], counting B-lines if <5 , assigning a default value of 5 points for areas with B-lines ≥ 5 without white lung and 10 points for areas with white lung.

High-Resolution CT

All the examinations were performed with multidetector CT (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA), with the patient either in supine or in prone position, during 1 deep inspiratory breath hold, and without intravenous injection of a contrast agent. The standard parameters were as follows: collimation = 0.625; pitch = 1.173; rotation time = 0.5 s; 120 kV; and 180 mAs. During postprocessing, the following were used: a slice thickness of 1 mm and a reconstruction increment of 0.5 mm with the window of the lung parenchyma (window: –600/1,600, filter yB), and a slice thickness of 2 mm and a reconstruction increment of 1 mm with the window of the mediastinum (window: 50–350, filter B). Classification of ILD was made referring to the most recent guidelines [3, 5].

Chest X-Ray

Only chest radiographs performed within 3 months of the HRCT scan were considered. The patients underwent digital radiography in P-A and R-L projection (Burgatti EIDOS 3000, Bologna, Italy). Images were obtained with the patient in orthostatism at full inspiration (120 kV, 2–3.5 mAs, depending on the patient’s size). Presence of ILD was defined referring to well-known and established radiological criteria from the literature [27].

Statistical Analysis

Descriptive data are presented as means ($\pm$ SD) or medians (with interquartile range [IQR]) for continuous variables, while

Table 1. Differences in demographic and clinical variables between patients with and those without ILD on HRCT

	Overall population (<i>n</i> = 104)	ILD absent on HRCT (<i>n</i> = 54)	ILD present on HRCT (<i>n</i> = 50)	<i>p</i> value
Age, years	65±13	65±13	65±13	0.799
Female	48 (46.2)	28 (51.9)	20 (40.0)	0.226
Connective tissue disease	24 (23.1)	12 (22.2)	12 (24.0)	0.830
Professional exposure	14 (13.5)	5 (9.3)	9 (18.0)	0.192
Immunodeficiency	9 (8.7)	3 (5.6)	6 (12.0)	0.243
Smoker	30 (28.8)	18 (33.3)	12 (24.0)	0.560
Ex-smoker	36 (34.6)	17 (31.5)	19 (38.0)	0.560
Nonsmoker	38 (36.5)	19 (35.2)	19 (38.0)	0.560
Asymptomatic	36 (34.6)	25 (46.3)	11 (22.0)	0.009
CXR available	49 (47.1)	24 (44.4)	25 (50.0)	0.571

Data are presented as means ± SD or *n* (%). ILD, interstitial lung disease; HRCT, high-resolution CT; CXR, chest X-ray.

Table 2. Concordance table for LUS, CXR, and HRCT and the diagnostic accuracy of LUS and CXR in the detection of interstitial lung disease

	HRCT		Sensitivity	Specificity	LR+	LR–	PPV	NPV	Overall accuracy
	posi- tive	nega- tive							
LUS			0.92 (0.81–1.00)	0.71 (0.53–0.89)	3.15 (1.67–5.94)	0.11 (0.02–0.43)	0.76 (0.61–0.91)	0.89 (0.75–1.00)	0.81 (0.70–0.92)
Positive	23	7							
Negative	2	17							
CXR			0.48 (0.28–0.67)	0.91 (0.80–1.00)	5.76 (1.43–23.08)	0.56 (0.38–0.84)	0.85 (0.67–1.00)	0.62 (0.46–0.78)	0.69 (0.56–0.82)
Positive	12	2							
Negative	13	22							

Values in parentheses denote 95% CI. CXR, chest X-ray; HRCT, high-resolution CT; LR–, negative likelihood ratio; LR+, positive likelihood ratio; LUS, lung ultrasound; NPV, negative predictive value; PPV, positive predictive value.

categorical variables are expressed as counts and percentages. Univariate comparisons were made with χ^2 or 2-sample *t* tests. The diagnostic accuracy of CXR and LUS is expressed as sensitivity, specificity, predictive values, and likelihood ratios. ROC (receiver operating characteristic) curves and AUCs (areas under curve) were used to analyze the accuracy of B-lines in recognizing the presence of ILD on HRCT. All statistical analyses were performed using the SPSS/PC software package version 21 (SPSS, Chicago, IL, USA).

Results

After exclusion of ineligible patients (Fig. 2), the study sample included 104 patients aged 24–90 years. The feasibility of LUS was 100%; the mean time needed for scanning was 8 ± 1 min (range 5–14). According to HRCT, ILD was present in 50 patients (Table 1). The HRCT patterns in the patients with ILD were reticular

(*n* = 17/50), ground glass (*n* = 9/50), nodular (*n* = 7/50), reticulonodular (*n* = 3/50), and mixed (*n* = 14/50). Patients with ILD on HRCT were more likely to have respiratory symptoms, but they did not differ in any other study variable. The most frequent symptoms were dyspnea (85.2%) and cough (33.8%), whereas other symptoms (e.g., hemoptysis and fever) accounted for <5%. One-third of the patients (*n* = 36) were asymptomatic; of these, 19 were ex-smokers, 4 were smokers, 15 had a connective tissue disease, 5 presented with immunodeficiency, and 4 had a history of professional exposure. Of these asymptomatic patients, 25 had negative LUS results (2 false negatives).

CXR availability was obtained for 49 patients. CXR availability did not differ between patients with and those without ILD on HRCT. In patients with available CXR scans, the median delay in LUS was 14 days (range 0–90).

Table 3. Accuracy of different echographic diagnostic scoring systems in the detection of interstitial lung disease

	PCAS (<i>n</i> = 104)	TBLS >10 (<i>n</i> = 104)	TBLS >5 (<i>n</i> = 104)
Sensitivity	0.92 (0.84–0.99)	0.92 (0.84–0.99)	0.92 (0.84–0.99)
Specificity	0.79 (0.69–0.90)	0.66 (0.54–0.79)	0.53 (0.40–0.67)
LR+	4.51 (2.64–7.70)	2.76 (1.87–4.06)	1.98 (1.47–2.67)
LR–	0.10 (0.03–0.25)	0.12 (0.05–0.31)	0.14 (0.05–0.39)
PPV	0.80 (0.70–0.90)	0.71 (0.60–0.82)	0.64 (0.53–0.75)
NPV	0.91 (0.83–0.99)	0.90 (0.80–0.99)	0.87 (0.76–0.99)
Overall accuracy	0.85 (0.78–0.92)	0.78 (0.71–0.86)	0.72 (0.63–0.80)

Values in parentheses denote 95% CI. LR–, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PCAS, positive chest area score; PPV, positive predictive value; TBLS, total B-line score.

Fig. 3. Dot plot. Differences in the number of positive chest areas (≥ 5 B-lines) between patients with and those without interstitial lung disease (ILD) on high-resolution CT. **Fig. 4.** ROC curve showing the accuracy of lung ultrasound in the detection of interstitial lung disease.

Comparison of the Accuracy of LUS and CXR

This analysis included only the 49 patients that underwent CXR within 3 months of HRCT scanning. Using HRCT as the gold standard, CXR had a lower sensitivity and a trend for a higher specificity than LUS (Table 2).

Comparison between Different Echographic Diagnostic Criteria

This analysis included all the 104 patients enrolled in the study. Using our diagnostic criterion (the presence of ≥ 3 positive chest areas), LUS showed high diagnostic accuracy (Table 3). Using the TBLS to identify a positive

LUS examination, sensitivity did not change (92.0%; 95% CI 84.0–99.0), while specificity decreased to 66.6% (95% CI 54.0–79.2) considering a TBLS >10 as positive [21, 23, 24] and to 53.7% (95% CI 40.4–67.0) considering a TBLS >5 as positive [22]. A statistically significant difference in the total number of positive chest areas was found between patients with and those without ILD on HRCT (median 0 [IQR 0–2] vs. 11 [5–23]; $p < 0.0001$; Fig. 3). This relationship was confirmed by ROC curve analysis (AUC = 0.90; 95% CI 0.84–0.96; $p < 0.0001$; Fig. 4).

The analysis of LUS misdiagnosis showed the following:

Fig. 5. **a** Chest CT scan showing the thickness of the interlobular septa and ground glass opacities in the right lower lobe as well as pleural thickness. **b** Chest X-ray was not able to detect any pathological findings or any signs of alveolar-interstitial involvement. **c** Lung ultrasound showed the presence of B-lines and pleural irregularities.

- False negatives ($n = 4$) – in all patients, HRCT showed mild inflammation of the small respiratory airways, not involving the pleura
- False positives ($n = 11$) – most of these patients were ≥ 64 years old ($n = 9$) and presented with the interstitial syndrome in the lower posterior lung fields ($n = 8$); none of these patients had white lung

Discussion

This study documented the high diagnostic accuracy of LUS in the detection of ILD. Previous studies compared LUS only with HRCT, and only in selected patients with rheumatologic disorders [21–24]. Some of these studies also excluded patients with known cardiac and pulmonary comorbidities [23, 24]. By contrast, we tested LUS in conditions similar to daily clinical practice, where comorbidities and confounding factors usually occur, thereby obtaining encouraging data. Figure 5 shows a case of correct LUS diagnosis of ILD, while CXR was not able to detect any pathological findings. Our findings support the use of LUS as a sensitive tool for ILD detection, especially considering that it is an inexpensive and nonionizing technique with a very short execution time. It is noteworthy that in our study sample, among the asymptomatic patients who underwent HRCT, negativity on LUS could have avoided the use of HRCT in 25 cases (with 2 false negatives).

Compared to LUS, CXR showed lower sensitivity but higher specificity, suggesting that LUS and CXR have complementary features. Moreover, unlike LUS, CXR permits a panoramic view of the thoracic surface, the de-

tection of abnormalities of the inner portion of the lung (perihilar area), and the identification of nodules or lung masses. Therefore, in this clinical setting, the combined use of LUS and CXR might be an effective approach to identify patients actually needing further investigation by HRCT, assigning asymptomatic patients with negative LUS and CXR results to follow-up. This integrated approach could reduce radiation exposure and costs, especially in young patients.

A further aim of this study was to test different echographic criteria for defining the presence of interstitial disease. Compared to previous studies, we used different echographic diagnostic criteria to identify a positive examination (presence of ILD). ILD was defined as the presence of ≥ 3 positive chest areas (≥ 5 B-lines), while previous studies defined ILD as a TBLS > 5 [22] or > 10 [21, 23, 24]. Moreover, B-lines were not counted if ≥ 5 . In fact, counting B-lines is debated [26]. In addition, the use of a TBLS easily generates false-positive diagnoses, as in the case of 6 normal zones with 2 B-lines (TBLS > 10) or a single zone of white lung (e.g., focal scar) associated with a normal zone with 1–2 B-lines (even in this case, TBLS > 10). The use of a different diagnostic approach (subdivision into positive chest areas) enabled us to maintain a high sensitivity while obtaining a better specificity. Furthermore, analyzing the false positives, we identified advanced age and isolated presence of nonconfluent B-lines in the lower posterior lung fields as characteristics associated with possible misdiagnosis. These findings confirm what we documented in a previous paper [28].

This study has several limitations. First of all, this was a single-center study. A second limitation is the time delay between CXR and both LUS and HRCT. Therefore,

we cannot exclude that the CXR results were more likely to be positive because of disease progression. We attempted to minimize this aspect by enrolling only clinically stable patients, which also might have caused a selection bias. Nevertheless, the spectrum of radiologic manifestations of ILD is similar in acute and in chronic patients [29]. A third limitation of our study is that we selected patients on the basis of the need for HRCT. Finally, the sample size was small, even if greater than in previous studies [20–24].

In conclusion, our study suggests that LUS can be used as a useful tool for ILD detection and, combined with CXR, can guide the use of the gold-standard technique, HRCT, thereby minimizing radiation exposure and costs. The use of different diagnostic criteria to define ILD does not affect sensitivity but influences specificity. These findings need further validation in large samples. Moreover, future studies should evaluate the role of LUS in the follow-up of ILD, for which, at present, no data are available yet.

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