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Invited Review

Ultrasound evaluation of interstitial lung disease in rheumatoid arthritis and autoimmune diseases

Esther F. Vicente-Rabaneda[1], David A. Bong[2,3], Noemí Busquets-Pérez[4], Ingrid Möller[3,5]

Abstract

The interpretation of lung ultrasound (US) is the result of the analysis of artifacts, rather than exact representations of anatomical structures, which appear when changes in the physical properties of the lung occur. Its application to the study of interstitial lung disease (ILD) associated with autoimmune diseases has aroused great interest in the last 10 years, as evidenced by a growing number of publications studying its usefulness in the diagnostic process, as a prognostic marker, and as an aid in monitoring of patients. The main elements in lung US interpretation in ILD are the B lines and the changes in the pleural line. B lines are vertical artifacts that are generated when there is a partial decrease in the air content of the lung parenchyma and/or the volume of the interstitial area expands. Pleural line alterations that can be seen are irregularities, thickening, fragmentation, or subpleural nodules. Both the B lines and the changes in the pleural line have shown a significant positive correlation with the evidence on chest computed tomography (high-resolution computed tomography [HRCT]) of ILD associated with autoimmune diseases, with sensitivity and negative predictive values of up to 100%. These results, together with the safety, accessibility, and low cost of lung US, support this imaging technique as a promising screening method for optimizing the indication for HRCT. The role of lung US regarding sensitivity to change needs further investigation with multicenter prospective studies.

Keywords: Lung ultrasound, interstitial lung disease, rheumatoid arthritis, systemic sclerosis autoimmune diseases

ORCID iDs of the authors:
E.F.V.R. 0000-0001-6823-4194;
D.A.B. 000-0002-6691-7968;
N.B.P. 0000-0003-2070-4876;
I.M. 0000-0002-9225-2568.

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[1] Department of Rheumatology, Hospital Universitario de la Princesa, Madrid, Spain
[2] Faculty of Medicine, University of Barcelona-Bellvitge Campus, Barcelona, Spain
[3] Instituto Poal de Reumatologia, Barcelona, Spain
[4] Department of Rheumatology, Hospital de Granollers, Granollers, Barcelona, Spain
[5] University of Barcelona (Anatomy), International University of Catalunya (Medical Image), Barcelona, Spain

Address for correspondence:
Ingrid Möller; Instituto Poal de Reumatologia Barcelona, University of Barcelona (Anatomy), International University of Catalunya (Medical Image), Castanyer 15, 08022, Barcelona, Spain

E-mail: ingrid.moller@ipoal.com

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Introduction

The use of diagnostic ultrasound (US) has become an essential component of rheumatologic practice as attested to by this current edition of the *European Journal of Rheumatology*. Lung ultrasound (LUS) has been used and is validated in the diagnosis and treatment of critically ill patients over the past 20 years,[1] in the diagnosis of respiratory failure, circulatory failure, and cardiac arrest. More recently, attention has turned to the use of this invaluable technique in the evaluation of one of the most challenging and debilitating manifestations of rheumatic disorders affecting the lung parenchyma, that of interstitial lung disease (ILD). ILD can complicate the course of most of the connective tissue diseases (CTDs) as polymyositis/dermatomyositis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma (SSc), or mixed CTD, and is the second leading cause of morbidity and mortality in SSc and RA.[2]

For the rheumatologist-sonologist who is practiced in examining the detailed morphology of the musculoskeletal system, performing US of an air-filled tissue enclosed in a bony case would seem counterintuitive. Not only does the presence of air cause a large acoustic mismatch and complete reflection of the US signal, but also a large portion of the surface has an impenetrable bony covering—the ribcage. Even the hyperechoic linear representation of the pleural line is controversial and thought to possibly represent an artifact caused by the high impedance between intrapulmonary air and thoracic wall soft tissues rather than the pleura itself. From a technical standpoint, LUS is only comparable to musculoskeletal ultrasound (MSKUS) when scanning the superficial chest wall. Thus, what we see of the actual lung on LUS is not a true anatomic or morphologic representation but rather "artifacts" created by the superficial soft tissues of the chest wall and alterations to these artifacts reflecting changes in the "density" of the underlying tissue whether due to increased fluid, an inflammatory response, or a fibrotic process relatively close to the pleural surface.

That being said, with these limitations, why resort to LUS when we already have the "gold standard" of lung imaging in high-resolution computed tomography (HRCT), which gives us morphologic and panoramic views of the lung? The answer is rather simple and straightforward. LUS is portable and can be performed relatively quickly in the office or at the bedside. It is inexpensive and uses basic "low-tech" US equipment, avoids ionizing radiation, and is well tolerated by the patient. The skills and knowledge required to perform and interpret it are assimilated rapidly especially if one is already doing MSKUS.

What exactly is an US "Artifact" and how is it produced?

An US artifact is a pattern on an US image that does not correlate with the actual morphology of the tissue or object being scanned. We see many artifacts in everyday US practice, including the reverberating images below the actual image produced by a needle as we perform an US-guided infiltration or the black anechoic shadows on each side of the short axis view of the rounded flexor tendon bundle of the fingers, so-called "edge shadowing."

To understand the generation of artifacts in the lung, it is important to realize that we are studying a balance between the lung content of air, liquid, and solid. Therefore, we need to have a basic knowledge of lung anatomy. The lung has two main components: the *alveoli* tiny air-filled sacules (containing air) and the *interstitium (containing solid and liquid)*. The alveoli (air) are located within the basic structural lung unit of the lung—the so-called *pulmonary lobule*. The "lobule" is demarcated by the interlobular septa (solid), has a diameter of 1-2.5 cm, a polyhedral shape, and is actually seen on HRCT. Filling each lobule and forming the lung parenchyma are an aggregation of three to five acini. An acinus, the basic lung respiratory unit, is made up of a "bunch" of 400 *alveoli*. Penetrating each lobule is a pulmonary arteriole (liquid), a lobular bronchiole, and peribronchiolar lymphatics (liquid), which connect to the acini. The septa give the lobule its polyhedral shape and contain lymphatic structures and the pulmonary veins. The *interstitium* is made up of both a peripheral interstitial fiber system and an "axial fiber system." The peripheral interstitial fiber system envelops the lung and then penetrates the lung parenchyma forming the *interlobular septa*. The "axial fiber system" extends out from the bronchi and pulmonary arteries to surround the centrilobular bronchioles and arteries.

With LUS, we are unable to "see" the true morphology of the lung parenchyma unless it has undergone pathologic consolidation and is in contact with the pleural surface. Thus, it is the pleural line, and the alteration of the pleural line together what increases the parenchymal "density" (by various pathologic processes that produce both normal and pathologic artifacts by altering the "air/solid/liquid balance").

What are the basic technical aspects of the LUS exam?

The starting position is with the probe placed in a longitudinal axis to the body perpendicular to the ribs to evaluate the superficial and deep aspects of the lung. The systematic examination of accessible lung tissue divides the chest wall into the right and left anterior, and lateral and posterior regions. The anterior region is defined by the sternal border and the anterior axillary line (AAL). Over the left anterior region, scanning is performed between the second and fourth intercostal spaces from the sternal border and the AAL. On the right anterior region, it is performed between the second and fifth intercostal spaces from the sternal border and the AAL. The lateral region is limited by the anterior and posterior axillary lines (AAL and PAL). The right and left posterior chest regions are demarcated by the paravertebral line, the medial scapular line, and the PAL. These regions are, in turn, further subdivided by the superficial anatomical features of the chest wall: anterior by the midclavicular line and nipple; lateral by the midaxillary line; posterior by the scapular angle. From these arbitrary divisions anywhere from 10 to 72, individual intercostal spaces (LIS) can be assessed depending on the desired protocol.[3,4]

The anterior region is examined with the patient supine. With the lateral regions, the patient is in the lateral decubitus position with the arm abducted over the head. The patient is seated for the evaluation of the posterior region.

Ultrasound scanners have been used from high-end to other pocket notebooks[5] and various types of probes such as cardiological,[4,6,7] linear[3,8-12] or convex,[5,13-19] or a combination of several.[20-23] Regarding the equipment and settings, generally we use a curvilinear probe and low frequency for the study of the parenchyma and a linear probe and high frequency for the study of the pleura, but it depends on patient size and probe availability. For the evaluation of the parenchyma, harmonics are eliminated, and attention to the depth, gain, and frequency adjustments is essential. Doppler is not utilized.

What is the basic vocabulary of the LUS image?

First of all, the basic vocabulary describes superficial and deep artifacts which are either static or dynamic. Superficially, when the probe is placed perpendicular to the ribs over an intercostal space, we have the hyperechoic and rounded signal of the two ribs and between them a hypoechoic muscular US pattern that is directly above a hyperechoic "pleural line" (representing the interface of the parietal and visceral pleura), a shimmering and sparkling hyperechoic line that moves back and forth simultaneously with the patient's respiratory movements. This movement is called "lung sliding," and its presence assures us that the pleural surfaces are in contact with nothing interposed such as air (pneumothorax) or fluid (effusion) (Figure 1). When the patient stops breathing, "lung sliding" stops, and it is possible to detect a subtle pulsatile movement of the pleural line coinciding with the heartbeat—the "lung pulse" reassuring us that the pleural layers are in contact (Figure 2). The most important linear artifacts include A lines, B lines, pleural line irregularity, and Z lines.

A-lines are parallel horizontal lines (reverberation artifacts) visualized below the pleural line at multiples of the distance between the US probe and the pleural line (Figure 3).

B-lines are defined as long, well-defined, laser-like, hyperechoic vertical artifacts perpendicular to the pleural line. B-lines move synchronously with the breath, originate at the pleural line, and penetrate to the depth of the image without fading. B-lines are counted between two ribs in one LIS (Figure 4) and are related to the thickening of the interlobular septum (e.g., fibrosis in ILD or edema). B-line presence, number, location, homogeneity, confluence, and the presence or absence of pleural line irregularity define the LUS image of "interstitial syndrome."

Pleural line irregularity is characterized by the loss of its linear pattern with thickening or fragmentation (Figure 5).

Z-lines are defined as localized vertical reverberation artifacts that do not reach depth, and they do not have a specific pathological meaning.

Main Points

- LUS is a promising screening method for ILD in autoimmune diseases.
- LUS may help optimize the use of HRCT.
- Preliminary data about the role of LUS to monitor ILD of autoimmune diseases are promising.

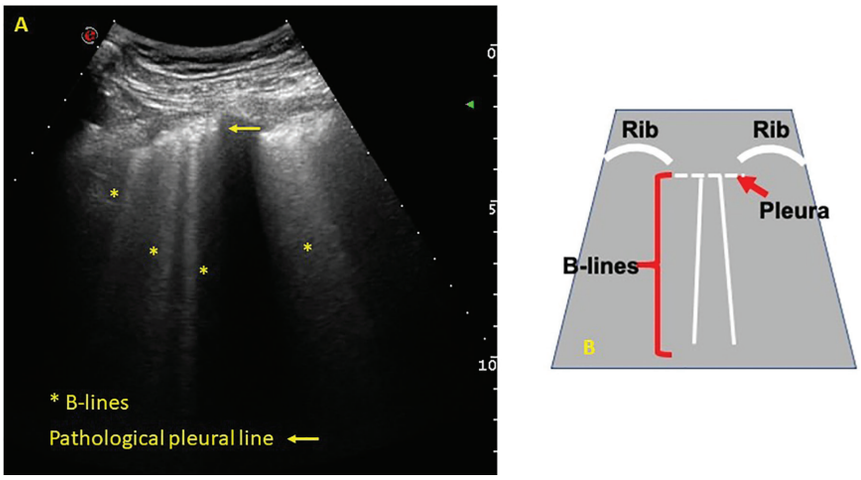

Figure 4. a, b. (a) Ultrasound image of B-lines defined as long, well-defined, laser-like, hyperechoic vertical artifacts perpendicular to the pleural line, which originate at the pleural line and penetrate to the depth of the image without fading. (b) Schematic graphic of B-lines.

of fibrosis in the HRCT ($P < 0.01$), whereas Gargani et al[4] found a positive linear correlation between pathological LUS and the Warrick score.[31] Thus, they found a good agreement between the patterns of LUS severity (according to the number of B-lines) and those of fibrosis severity in HRCT. In a follow-up study, the performance of linear probes in 25 of these patients was investigated.[32] They found a significant intraclass correlation (ICC) between the cardiac and linear transducers. The ICC between the two probes and the HRCT was moderate to good (cardiac probe, ICC = 0.547 and linear, ICC = 0.600). Regarding HRCT, the cardiac probe showed a better sensitivity than the linear one (70% vs. 60%), but a similar specificity (85% for both).

Subsequent studies conducted in patients with SSc have used the Warrick index almost unanimously to quantify the involvement of ILD in HRCT.[3,7-10,13,14] However, LUS protocols have varied widely both in the number of LIS examined, as well as in the definitions of normality and the type of scores. Mohammadi et al[3] evaluated 70 patients with SSc with a linear multifrequency probe, examining 10 LIS, chosen for having a higher prevalence of ILD in SSc and greater accessibility. He found a significant correlation between LUS and the severity of lung involvement with a Spearman correlation coefficient of 0.695 ($P < 0.001$) and a likelihood ratio (LR) of 74.36 ($P < 0.001$), calculating a sensitivity of 73.58%, a specificity of 88.23%, a positive predictive value (PPV) of 95.12%, and a negative predictive value (NPV) of 51.72%. Similar findings were described by Gigante et al[13] and Tardella et al[8] Furthermore, Çakir et al[9] evaluated 14 LIS bilaterally with a linear multifrequency probe. These authors also found a significant correlation between LUS and HRCT (r = 0.89, $P = 0.0001$), with a sensitivity of 100%, a specificity of 84.2%, a PPV of 90.6%, an NPV of 100%, and precision of 93.7%. Recently, Hassan et al[14] have published their results after evaluating 67 SSc patients (63% lSSc) with respiratory manifestations (67%), mainly dyspnea (48%) and cough (6%). In this population, LUS had a sensitivity and an NPV of 100%, with a specificity of 34.21% and a PPV of 53.7% (AUC, 0.80; 95% CI, 0.69-0.90).

Controlled studies with healthy individuals are rare. Moazedi-Fuerst et al[20] were the first to conduct a pilot study in 25 patients with SSc versus a control group of 40 healthy individuals matched for age and gender. Forty-four percent of SSc patients had B-lines, but they were only present in 7% of controls ($P < 0.001$), with higher LUS rates in SSc patients with ILD confirmed by HRCT than in those SSc without radiological evidence of ILD. The analysis of the baseline characteristics of the populations of patients with SSc described in most of these works reflects that they have included patients with evolved forms of the disease, with a mean duration of 4.09-8.5 years.

Given the importance of the early diagnosis of the disease, one aspect of great interest is to know the behavior of the LUS in detecting subclinical involvement of the ILD. Barskova et al[7] shed light on this issue by including 58 SSc patients, of whom about half (n = 32) had very early forms of SSc, with an average duration of disease of 1.9 ± 3.2 years. The prevalence of ILD by HRCT was 41% in patients with very early SSc. LUS detected a lower number of B-lines in the early SSc (18 ± 21 vs. 66 ± 57, $P < 0.001$). The patients with ground glass in HRCT had a greater number of B-lines than those without it (63 ± 47 vs. 33 ± 40, $P < 0.05$), and, in the individual analysis of the patients, LUS and HRCT showed an agreement of 83% in the global population, with a sensitivity of 100%, a specificity of 55%, a PPV of 78%, and an NPV of 100%. Recently, Reyes-Long et al[10] have evaluated the role of LUS for ILD screening in 68 SSc asymptomatic patients; of whom, there was no previous evidence or diagnosis of ILD, controlled with healthy controls matched for age and

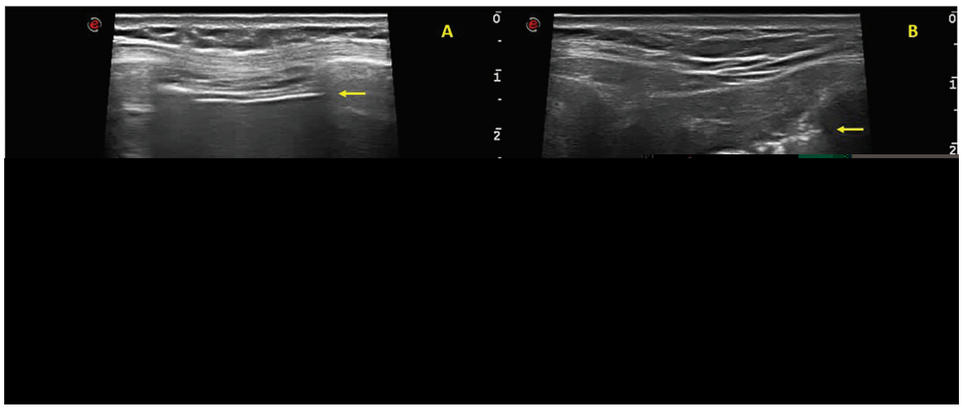

Figure 5. a, b. Ultrasound images of a normal pleural line (a), with its typical fine linear pattern and a pathological pleural line (b), characterized by its irregularity, with thickening and fragmentation, in a patient with ILD. Arrows identify the pleural line.

gender. Ultrasound involvement was higher in patients with SSc versus healthy controls (41.2% vs. 4.8%, $P = 0.0001$), presenting a positive correlation with HRCT (r = 0.80, $P = 0.0001$), with sensitivity (91.2%), specificity (88.6%), PPV (92.4%), NPV (87%), and AUC (0.899) values very favorable for LUS. These results support LUS as a potential screening method for ILD in SSc, given the high precision[9] and the sensitivity and NPV values of 100% reported.[7,9,14]

In RA, unlike with SSc, there are no accepted recommendations for the early LUS detection of ILD and no validated or agreed protocol for this purpose. Two studies focused on long-standing RA patients. Cogliati et al[5] studied 39 patients with RA using an extended and a simplified LUS protocol. The extended protocol showed results in line with previous SSc reports, with a sensitivity and a specificity of 92% (95% CI, 78-100) and 56% (95% CI, 38-75), respectively, and a significant correlation between the LUS and HRCT scores (r = 0.806). However, with the simplified score, the sensitivity decreased (69%; 95% CI, 44-94). Additional examination of 29 of the patients using a pocket US machine, carried out by an inexperienced examiner, showed fairly good results with a sensitivity of LUS against HRCT of 89% (95% CI, 68-100), a specificity of 50% (95% CI, 28-72), and a correlation coefficient with respect to the standard LUS of 0.78.

Moazedi-Fuerst et al[21] studied 64 patients with RA and compared the findings with 40 healthy controls matched for age and gender. Twenty-eight percent of the RA patients had HRCT incipient ILD changes and presented with alterations in the LUS with subpleural nodules (18%) or B-lines (28%) compared with only 10% of healthy controls (7% with B-lines and 2% with subpleural nodules). This same author has studied several CTD such as RA (n = 25), SSc (n = 14), and SLE (n = 6).[23] Twenty-eight percent of RA patients, 64% of SSc patients, and four of the six SLE patients had ILD on HRCT, noting pathological LUS pattern more frequent in patients who had ILD compared with those who did not show alterations in HRCT (100% vs. 12%, $P < 0.001$). With these results, the authors supported the use of LUS for screening for ILD in RA, even with the use of pocket devices or in outpatient settings.

Similar results have been reported in studies that included patients with different CTD such as SSc, RA, SLE, primary Sjögren's syndrome, ASS, dermatomyositis, or mixed or undifferentiated CTD, although all of them with a small sample size.[11,15,16,22,23]

LUS pleural line alterations compared to HRCT

LUS studies on pleural lesions in the diagnosis of ILD are less frequent than that published on B-lines. Pathological pleural line, irregularities, thickening, fragmentation, and subpleural nodules can be assessed (Figure 5). The initial study was published by Moazedi-Fuerst et al[20] in patients with SSc and controlled with healthy volunteers. To quantify LUS pleural involvement, they used a semiquantitative index analogous to that used for parenchymal evaluation and considered the presence of pleural irregularities with a thickening >2.8 mm as pathological. Patients with SSc had a greater thickness of pleural irregularities than healthy volunteers (3.2 mm vs. 1.3 mm, $P < 0.001$) and showed pleural fragmentation and pathological thickening in 8% and 36% of cases, respectively. Furthermore, the rates of pleural involvement were higher in patients with radiological evidence of ILD than in those without it. Interestingly, no pathological pleural LUS involvement was found in any control or any patient with SSc without HRCT findings of ILD. B-lines were present in 35% of these SSc patients. In a subsequent study with a similar design carried out by the same author in patients with RA,[21] 4% of the patients showed LUS pleural line alterations but none were found in healthy controls.

Sperandeo et al[17] evaluated pleural abnormalities in a prospective cohort of 175 patients with SSc and found an association between pleural thickening and different patterns of HRCT indicative of pulmonary fibrosis. In the analysis of the ROC curves, they identified the best pleural thickening cutoff points for each HRCT pattern. They also found correspondence between strictly basal or extensive involvement (including basal and superior areas) with both imaging techniques. When performing the same analysis with the B-lines, although the pathological LUS (>3 B-lines) showed good reliability to detect a pathological HRCT (sensitivity 0.940, specificity 0.952, LR+ 20, LR– 0.06), the number of B-lines did not allow discrimination between the reticular, reticulo-nodular, or honeycomb patterns of the HRCT.

Along these same lines, Pinal-Fernandez et al[12] found in patients with SSc and ASS that the evaluation of pleural irregularities, defined as a loss of linear and hyperechogenic pleural morphology and quantified as the percentage of lung affected areas, had a better performance than the B-lines to differentiate patients with and without ILD by HRCT. Patients with ILD had a higher rate of pleural irregularity than those without ILD (35.3% vs. 6%, $P < 0.001$).

In addition to thickening and pleural irregularity, the role of subpleural nodules has been evaluated. Moazedi-Fuerst et al[23] investigated in patients with RA, SSc, and SLE the presence of three patterns of US, that of the B-lines, the subpleural nodules, and the thickening of the pleural line. All patterns were observed more frequently in patients with ILD in HRCT than in those without ILD: 100% versus 12% for the B-lines pattern ($P < 0.001$), 55% versus 17% for the subpleural nodules ($P = 0.006$), and 95% versus 12.5% for pleural irregularities >3 mm ($P < 0.001$).

The sensitivity and specificity of lung US, related to either B-lines or pleural thickening or irregularity, compared to HRCT reported in previous studies is shown in Table 1.

These evidences have led some authors to suggest that the evaluation of the pleural line presents a better NPV for ILD and a better discrimination against healthy controls than B-lines.

LUS compared with PFT and clinical parameters of severity

Some authors have found a significant negative correlation between the number of B-lines and different parameters of the PFT, such as diffusing capacity of the lung for carbon monoxide (DLCO),[4,8,12,13,16,18,19] with forced vital capacity (FVC)[8,9,13,18] and with the DLCO/FVC ratio.[16] On the other hand, the presence of pathological LUS has also been significantly correlated ($P < 0.05$) with lower values of DLCO, total lung capacity, and vital capacity.[4] A significantly higher number of B-lines have also been described in patients with diffuse SSc versus localized SSc and with antitopoisomerase-I antibodies,[4,13,19] as well as with Rodnan skin score.[10,19] Another author has identified the anticentromere antibodies ($P = 0.005$) associated with the ILD findings by LUS.[10]

Other severity markers assessed in patients with SSc showing correlation with the number of B-lines include the Medsger SSc disease severity scale (r = 0.80, $P < 0.01$),[13] the progression of capillaroscopic damage[13,18] or its late pattern,[19] the presence of digital ulcers[13,18,19] and the ACR/EULAR score of SSc > 9, male gender, and functional class of New York Heart Association (NYHA) III or IV.[19] Some authors have even described an association between B-lines and the quality of life measured by the SF-36 questionnaire, both in its mental and physical component.[8]

Of special interest is the comparative study of LUS with other diagnostic tools such as chest X-ray, PFT, or pulmonary auscultation.[10] Although the chest X-ray and the PFT showed a higher specificity than LUS (98.1%

Table 1. Sensitivity and specificity of lung ultrasound.

Study, year (reference)	Sensitivity (%)/specificity (%)
Delle Sedie et al[32]	85/70 (cardiac sector probe) 85/60 (linear probe)
Aghadashi et al[11]	73.5/88.2
Barskova et al[7]	100/55 (global) 100/59 (>5 B-lines) 83/96 (≥20 B-lines)
Mohammadi et al[3]	73.5/88.2
Cogliati et al[5]	92/56 (standard device) 89/50 (pocket-size device)
Mozaedi-Fuerst et al[21]	97.1 /97.3
Pinal-Fernandez et al[12]	79/100 (pleural line)
Sperandeo et al[17]	80/99 (pleural line)
Cakir Edis et al[9]	100/84.2
Vasco et al[22]	100/89
Tardella et al[8]	96.3/92.3
Reyes-Long et al[10]	91.2/88.6
Hassan et al[14]	100/34.2
Gargani et al[19]	92/16 (≥5 posterior B-lines)

Sensitivity and specificity values refer to B-lines, except when it is specified that they relate to the pleural line.

and 98.3%, respectively), their sensitivity was much lower (2.5% and 8.7%, respectively). Regarding the auscultation of velcro-type crackles, it showed a lower sensitivity (27.5%) and specificity (77.3%) than LUS. Interestingly, the PPV, NPV, and AUC of LUS (92.4%, 87%, 0.899, respectively) were more favorable than those obtained for the other diagnostic methods including chest X-ray (66.6%, 40%, 0.503, respectively), PFT (64.7%, 41.4%, 0.524, respectively), and pulmonary auscultation (87.5%, 41.6%, 0.503, respectively).

Role of the LUS as a prognostic marker and for disease monitoring

Evidence on the role of LUS as a prognostic marker for the appearance or worsening of ILD and on its application for monitoring patients is still scarce and needs further investigation. Two studies focusing on B-lines have recently been published. In a study of 41 SSc patients, Gasperini et al[18] have shown that the number of baseline B lines has a good accuracy to predict the worsening of DLCO at 12 months (AUC 0.72; 95% CI, 0.56-0.88) and for the progression of capillaroscopic damage and digital ulcers. More significantly, Gargani et al[19] followed 396 patients with SSc for a mean of 28 (r: 11-44) months. At baseline, the average number of B-lines was 19 (r: 8-55), somewhat higher in the posterior LIS, with significant pleural alterations in 40% which was associated with a greater number of B-lines. During follow-up, 50 patients developed ILD or showed worsening of previous ILD in HRCT at a mean of 30.8 months and 20.8 months, respectively. The authors found that the baseline presence of ≥5 B-lines in posterior LIS was the best cutoff point to predict the onset or worsening of ILD.

With respect to pleural findings, Sperandeo et al[17] analyzed a prospective cohort of 175 patients with SSc for 2 years by LUS assessment of pleural thickening and HRCT. They found no change in patients with localized SSc. However, in patients with diffuse SSc showing increases in LUS pleural thickening, they observed corresponding changes in the HRCT. It should be noted that in patients who evolved from a normal LUS to LUS involvement in the basal LIS at follow-up, there was incipient changes in ILD in HRCT, without presenting abnormalities in PFT, 6MWT, or chest X-ray, supporting the role of the LUS for follow-up.

What is considered pathological and how to quantify/score it?

The heterogeneity of the published LUS evidence limits the establishment of cutoff points to define the disease.

The initial scores of B-lines utilizing up to 72 LIS were more comprehensive in order to obtain the maximum possible evidence.[4] These authors reported an exploration time of 10 minutes, although the duration increased in patients with more severe lung involvement. In an attempt to simplify the evaluation, Gutierrez et al[15] compared an extensive B-lines index of 50 LIS with a simplified one that evaluated 14 LIS bilaterally. They showed a significant correlation between the two scores ($P = 0.0001$) and of the simplified score with HRCT ($P = 0.0006$), with the consequent reduction in exam time from 23.3 ± 4.5 minutes to 8.6 ± 1.4 minutes ($P < 0.0001$). The lowest number of LIS utilized is that of Mohammadi et al[3] that evaluates only 10 LIS with an exploration time of 5.4 ± 1.8 minutes.

The definition of pathological score of B-lines is also quite variable. There are dichotomous scores (present/absent) above a threshold, which may refer to the entire examination,[4] to one region, to two adjacent regions, or to a combination of both.[7,9,13,20] Others are semiquantitative, establishing different severity scales.[3,4,6,9,10,14] Finally, there are also quantitative scores, adding the number of B lines of all the explored areas.[3,4,8-10,12,13,16,18,19,32] Some authors have evaluated all of them.

In relation to the assessment of the pleural line, the definition of pathology has been established as thickening above a certain threshold[17,23] or as irregularity with loss of its characteristic linear appearance,[12] although fragmentation or subpleural nodules have also been described.[17,21,23] Alterations have been quantified dichotomously (presence/absence),[17,21,23] with semiquantitative scores[20,23] or as a percentage of affected areas[12] and the probes used have been linear or convex.

Are there "Patterns" of disease?

One of the questions of great importance to clinical practice is whether the appearance of B lines of cardiogenic origin can be differentiated from those of inflammatory/fibrotic origin, especially in autoimmune diseases where both processes can manifest. At this point, LUS imaging does not allow us to clearly discriminate between cardiogenic, inflammatory, or fibrotic phase of ILD.

In general, B-lines due to extravascular lung water tend to be multiple, diffuse, and bilateral, following a distribution related to gravity, with predominance in the most declining areas. However, those due to a thickening of the interlobular septa of the interstitial space due to collagen deposition are usually multiple and diffuse as well, although not necessarily bilateral, more numerous in the posterior basal LIS and generally associated with pleural line alterations.

Another question of clinical interest is whether it is possible to differentiate between the types of ILD in CTD by LUS. Moazedi-Fuerst et al[23] investigated this topic in patients with RA,

SSc, and SLE by evaluating characteristics of B-lines, subpleural nodules, and the thickening of the pleural line. All LUS characteristics were observed more frequently in patients with ILD confirmed by HRCT than in those without ILD: 100% versus 12% for the B-lines pattern ($P < 0.001$), 55% versus 17% for the nodules subpleural ($P = 0.006$), and 95% versus 12.5% for pleural irregularities >3 mm ($P < 0.001$). Regarding the differentiation by pathologies, the subpleural nodules were statistically higher in the RA (100%) compared with 22% of the SSc ($P = 0.003$) and 50% of the SLE ($P = 0.049$). However, the presence of a pleural line >3 mm, although more frequent in SSc and SLE (100%), was also present in 86% of RA patients. These findings indicate that LUS may be able to differentiate different types of ILD involvement in autoimmune diseases.

Regarding the differentiation of ILD related to CTD from that due to idiopathic pulmonary fibrosis (IPF), the study by Sperandeo et al[33] evaluates the pulmonary US findings in these patients and compares them with healthy controls. The authors do not refer differences related to the etiology of ILD, but rather to its degree of involvement. In patients with IPF, severe or moderate forms of ILD predominated, with mild or moderate forms of ILD being more frequent among patients with CTD. In all mild forms, an irregular thickening of the pleural line >3 mm at the lung bases was observed, often bilateral. This finding seems especially remarkable for detecting early ILD since it was the only US finding present and no control had a thickening >2.1 mm, regardless of gender and smoking. In the forms with more advanced fibrosis, the pleural thickening became more pronounced and extensive, accompanied by a proportional decrease in pleural gliding signs in the more severe forms.[33] This finding, if confirmed in studies with a sufficient sample size, could facilitate an early diagnosis and a more rational use of healthcare resources.

Is LUS a valid imaging tool?

The analysis of the reviewed publications shows us that the investigations on the validity of aspect, content or criteria, and feasibility are actually quite advanced. Other aspects have been less studied and need a further evaluation. Reliability has been investigated by a few authors, who have published interobserver[9,10,15-17,21] and intraobserver[3,5,15-17,22] values in the range from very good to excellent. The least analyzed aspect is sensitivity to change in which there is scarcity of prospective longitudinal studies. Much work remains to be done in terms of establishing consensus on the definition of elementary lesions to be assessed by LUS, on the examination protocol, the scores, and the most recommended equipment.

Conclusion

LUS appears to be a valuable screening method for ILD in autoimmune diseases based on the very good NPV that has reached 100% in some studies of systemic sclerosis series,[7,9,14] as all the patients who had normal LUS did not have findings of ILD in HRCT. It is noteworthy that these very favorable NPV data have been found both in patients with advanced forms of the disease[9,14] and in patients with very early systemic sclerosis,[7] reinforcing its potential as a screening method to detect early ILD. Consequently, the use of the widely available, economic, and innocuous LUS in conjunction with the currently recognized screening methods should be considered as it might result in earlier diagnosis and could represent an aid to optimize the use of HRCT, which is the gold standard for the diagnosis of the ILD. The role LUS in the prognosis or for monitoring progression remains to be clarified, but the preliminary results are promising.

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