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Advances in the validation of lung ultrasound for the detection of interstitial lung disease associated with rheumatoid arthritis

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Abstract

Interstitial lung disease (ILD) is one of the most important extra-articular manifestations of rheumatoid arthritis (RA) due to its associated significant mortality. The availability of pharmacological treatments capable of slowing its progression, especially when initiated early, makes early diagnosis an essential part of its management. The low sensitivity of chest X-ray or lung function tests to identify RA-ILD in the early stages of the disease, together with the cost, accessibility, and ionizing radiation limitations of high-resolution computed tomography (HRCT), especially when serial screening or follow-up studies are required, has prompted the study of lung ultrasound (LUS) as an additional aid for the screening, diagnosis, and/or follow-up of RA-ILD. Based on the safety, low cost, and accessibility of LUS, and the encouraging results of research into this technique in ILD associated with systemic sclerosis, progress has been made in its validation process with research addressing aspects such as its accuracy, feasibility, and reliability. Negative predictive value and sensitivity values exceeding 80–90% have been reported, suggesting its potential utility. Feasibility has been suggested since LUS scan can be performed in less than 10 minutes, and intra- and inter-observer or examiner reliability shows values in the good to excellent range. However, there are still aspects that require further investigation, such as the standardization of the LUS scanning protocol or the requirements to ensure an effective learning curve before applying the technique in clinical practice. It is necessary to recognize the inherent limitations of LUS and understand that it should be considered a tool to aid in the early identification of patients who require HRCT, which is currently the diagnostic gold standard.

Keywords

rheumatoid arthritis, interstitial lung disease, lung ultrasound, accuracy, reliability

Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory joint diseases in our country, with a prevalence ranging from 0.5% to 1%, depending on the geographic area [1]. Its initial manifestations are usually pain and swelling of the peripheral joints, which can lead to the appearance of erosions that are associated with structural deterioration, functional limitation, and loss of quality of life. Although the predominant manifestations are at the level of the musculoskeletal system, RA is a systemic disease that can present extra-articular manifestations that worsen its prognosis. With the advances that have occurred in the therapeutic field with the emergence of biological and targeted directed therapies, as well as the implementation of tight control by objectives or "treat to target" strategies, some of the extra-articular manifestations have shown a substantial decrease in their incidence. However, pulmonary involvement and, specifically, interstitial lung disease (ILD), are currently one of the main causes of morbidity and mortality after cardiovascular diseases [2, 3].

Studies on the prevalence of RA-ILD show a wide range of values, 1–58%, due to differences in the characteristics of the populations studied and the diagnostic methods used [2, 4]. RA-ILD usually appears late, although it is important to remember that this manifestation can occur at any time throughout the evolutionary course of the disease, even before the joint manifestations (10–18%). The predominant pattern of affectation is that of usual interstitial pneumonia (UIP), unlike systemic sclerosis (SSc) and most other autoimmune rheumatic diseases (AIRD) in which the non-specific interstitial pneumonia (NSIP) pattern is more frequent [5].

The progression of RA-ILD is usually slower than that of ILD associated with SSc (SSc-ILD). Paucisymptomatic or subclinical forms can be identified by chest high-resolution computed tomography (HRCT) screening protocols that remain stable for long periods of time without requiring specific treatment. However, RA-ILD is not a trivial manifestation. In some patients (40%), the disease evolves into a rapidly progressive fibrosing condition and leads to a worsening of the patient's quality of life, an increase in social and healthcare costs and a decrease in survival, with average values of less than 10 years [5–7]. Patients with RA-ILD have a 3- to 10-fold increased mortality rate compared to the general population and to patients with RA without ILD [2, 4, 8]. Furthermore, the UIP pattern has been associated with a worse prognosis than the NSIP pattern, worse therapeutic response, and higher morbidity and mortality, especially in the case of late diagnosis [5].

In recent years, there has been growing evidence on the beneficial effect of some biological, targeted, directed, or antifibrotic therapies in slowing the progression of RA-ILD, especially when treatment is started early [9–11]. In this scenario, it is crucial to establish strategies for early detection or screening of RA-ILD. There is still a lack of consensus on which patients should be screened, what the best algorithm is, when the search should begin, how often re-evaluations should be carried out, and what are the most appropriate tools to use at each stage. In this narrative review of the literature, we will present the current evidence on the usefulness of lung ultrasound (LUS) for screening and early diagnosis of RA-ILD.

The role of LUS in the early detection of RA-ILD

Risk factors associated with the onset of RA-ILD, such as male sex, advanced age, late-onset RA, advanced disease with persistent inflammatory activity, smoking, *MUC5B* gene polymorphisms, or positivity for rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (ACPA), especially when present at high titers, have been described in the literature [12, 13]. Other biomarkers such as the Krebs von den Lungen-6 (KL-6) glycoprotein or genes associated with telomere shortening have also been investigated [14]. On this basis, multiple clinical-analytical scores have been proposed to predict the risk of RA patients of developing ILD, although they are pending validation [15–19].

Given the prevalence and incidence of RA-ILD and its presentation pattern, universal screening of all patients with RA does not seem justified. While a unanimous consensus is awaited, several scientific societies have proposed criteria, pending validation, not only for investigating the presence of RA-ILD in patients with respiratory symptoms, but also for screening asymptomatic patients with high-risk factors [20, 21].

In conventional clinical practice, the investigation of RA-ILD is based on chest X-rays and pulmonary function tests (PFT), with spirometry and diffusing capacity for carbon monoxide (DLCO) as the initial assessment, followed by HRCT, which is the gold standard for diagnosis. However, these tools have limitations. The first two have demonstrated low sensitivity (Se) in the early stages of the disease. Regarding HRCT, its limitations are due to problems of access, cost, and ionizing radiation, especially when serial evaluation is required during follow-up.

Due to these limitations, the criteria agreed upon by the Spanish Society of Rheumatology (SER) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) propose directly requesting HRCT, instead of chest X-ray, in patients with Velcro-like crackles on auscultation or with ≥ 7 risk factors [20]. More recently, the 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the screening and monitoring of ILD in people with systemic AIRD recommends screening with PFT and HRCT in patients with risk factors, which can be repeated annually if the result is negative [21].

In this context, it is desirable to have an additional tool that is safe, affordable, accessible, and allows for reliable monitoring over time, with the aim of facilitating the identification of patients who are candidates for HRCT to screen for RA-ILD. This is one of the main reasons why research into the usefulness of LUS for this purpose has grown substantially in recent years, allowing significant progress in its validation process.

Search methodology of this narrative review

Given the narrative nature of this review about the advances in the validation of LUS for the detection of RA-ILD, the search strategy was designed to identify representative and clinically relevant studies rather than exhaustively capture all available literature. We performed a search of the published literature on this topic in PubMed until the 19th of October 2025, using the following keywords and search strategy: (connective tissue diseases [Title/Abstract] OR rheumatoid arthritis [Title/Abstract]) AND lung ultrasound [Title/Abstract]. Only original articles that focused exclusively on RA were selected after reading the abstract. Original manuscripts that included patients with additional connective tissue diseases, reviews of any kind, and meta-analysis were excluded, although these papers were read to search for relevant manuscripts that could not have been identified by the performed search.

What LUS findings suggest RA-ILD?

The identification of the interstitial involvement pattern by LUS is based on the detection of multiple vertical artifacts called B lines and/or irregularities of the pleural line [22]. The ultrasound lung pattern associated with normality is characterized by the presence of a thin, regular, hyperechoic pleural line that has a lung sliding movement, together with the visualization of horizontal artifacts called A lines, which appear as hyperechoic lines parallel to the pleural line in depth as equidistant replicas.

On the contrary, when lung aeration decreases at the subpleural level, either due to inflammatory, edematous, or fibrotic contents, B lines appear as hyperechoic vertical lines from the pleural line to the bottom of the screen without fading. They blur the A lines and move synchronously with lung sliding. Additionally, in ILD, the pleural line may show an irregular appearance with focal, diffuse, linear, or nodular thickening. Recently, these consensual definitions of the sonographic findings in ILD have reached a high level of agreement (84.2% for B lines and 82.6% for pleural line irregularity) in a Delphi process and web-reliability exercise by the Outcome Measures in Rheumatology (OMERACT) Ultrasound Working Group, using video-clips of LUS from patients with SSc with and without ILD that had been acquired by the experts [23].

Accuracy of LUS to detect RA-ILD

The investigation of the usefulness of LUS to detect the presence of ILD in AIRD began in SSc, a disease in which clinical guidelines advocate screening for SSc-ILD at diagnosis by HRCT due to its high prevalence and risk of progressive fibrosis. Published studies suggest the potential usefulness of LUS as a screening technique due to its high Se and negative predictive value (NPV) when compared with HRCT, with values close to 90–100% [24, 25].

Following these encouraging results, a growing number of studies have been published in recent years investigating the usefulness of LUS for the identification of RA-ILD [25–41]. These studies are heterogeneous in terms of the populations included, the ultrasound examination protocols used, the type of probe, the sonographic lesions assessed, their quantification, and the cutoff points chosen to define sonographic ILD. It must be considered that these methodological differences among studies, as well as the limitations of LUS reproducibility across centers, may affect reproducibility and generalizability of their results and must be seen as an important limitation regarding clinical implementation of LUS. Furthermore, they are observational studies, with limitations in their design and some of them with a small sample size, which gives them a level of evidence 4 according to the criteria of the Centre for Evidence-Based Medicine of Oxford [42], and a low quality of evidence according to the GRADE system [43]. Despite this, all the studies suggest the potential of LUS as an aiding tool in the diagnostic algorithm for RA-ILD, especially for identifying patients who are candidates for HRCT (currently the gold standard for its diagnosis), which provides consistency. Cross-sectional and retrospective studies on the accuracy of LUS to detect ILD are shown in Table 1, whereas case-control studies are displayed in Table 2.

B lines are the most studied elementary lesion, although irregularity in the pleural line is being progressively incorporated in the most recent manuscripts, which have also increased the sample size to about 200 patients. The discriminatory capacity of LUS has been analyzed in case-control studies, in which the presence and number of B lines in patients with RA-ILD were significantly higher than those found in both healthy controls and in RA patients without ILD [26–30]. Analogous results were found when evaluating pleural line abnormalities [26, 28]. Besides, pleural line abnormalities might have a greater discriminatory capacity than B lines because, while the latter have been identified in 7% of healthy controls, Moazedi-Fuerst et al. [26] did not find pleural line thickening in any of the healthy controls.

A significant positive correlation has been described between the detection of RA-ILD by LUS and HRCT, with concordances over 83%. Most works have defined the suspicion of sonographic ILD by the presence of B lines above a certain cut-off point calculated by ROC curve analysis. The high Se and NPV values found (60–100% and 70–99%, respectively), with cut-off points ranging from 5–12 B lines according to the LUS protocol used, make LUS an attractive tool for the screening or early diagnosis of RA-ILD (Tables 1 and 2).

Studies evaluating the accuracy of LUS have mostly included patients with known RA-ILD or consecutively recruited patients with RA regardless of respiratory symptoms, although most of them were symptomatic [27–40]. However, other researchers have focused their analyses on a context closer to real-world clinical practice, selecting patients with suspected RA-ILD [32, 34]. Santos-Moreno et al. [34] included 192 patients with clinical suspicion of RA-ILD (respiratory symptoms, Velcro crackles, and/or abnormal PFT). HRCT identified RA-ILD in 60.9% of patients, and LUS showed a Se of 98.3% and a NPV of 84.6%. However, the specificity (Sp) was low (14.7%), with discrepancies due to false positives of LUS conditioned by the existence of other pathologies related to RA or its comorbidities. Importantly, the data seem to suggest that LUS may be a more interesting tool for screening than chest X-ray, which showed worse Se and NPV values (29.9% and 46.4%, respectively), despite its Sp being higher (94.7%) [34].

This better performance of LUS compared to chest X-ray has also been described by Otaola et al. [33], who also found superiority of LUS over DLCO and Velcro crackles (Table 1). Along these lines, Vermant et al. [38] found that the number of B lines had a better predictive performance for ILD in HRCT than cough and dyspnea. Furthermore, Schneeberger et al. [37] observed that the association of a positive LUS (cutoff ≥

Table 1. Cross-sectional and retrospective studies on the accuracy of LUS.

Author, year of publication	Study characteristics	LUS protocol	Results
Otaola et al., 2025 [41]	Multicenter (5 centers), cross-sectional study including RA without respiratory symptoms (*n* = 203)	Convex probe and linear probe 14 ICS; BL numbers and PI ILD by LUS: BL score ≥ 5	• LUS for ILD diagnosis: Se 83%, NPV 93.1% • DLCO for ILD diagnosis: Se 52%, NPV 78.6%
Zheng et al., 2025 [39]	Monocentric, retrospective study including RA, regardless of respiratory symptoms (*n* = 120)	Cardiac sector probe (2.5–3.5 MHz) 50 ICS; BL score = sum of BL Sonographic ILD: BL > 10	• Concordance rate between LUS and HRCT 83.33% • LUS accuracy: Se 86.84%, NPV 77.27% • Optimal cutoff: 12 BL (AUC = 0.89, $p < 0.001$) • BL scores were significantly higher in patients with ILD vs. non-ILD, and in the UIP vs. NSIP pattern
Vermant et al., 2025 [38]	Monocentric, cross-sectional study including RA, regardless of respiratory symptoms (*n* = 116)	Curved array probe (3.5 MHz) 72 ICS Number of BL	• Number of BL was the most strongly associated with the clinical-radiological score[#] • BL cutoff = 5: outperformed mMRC, dyspnoea, or cough • LUS accuracy: Se 90–100%, NPV 0.96–1
Schneeberger et al., 2025 [37]	Monocentric, cross-sectional study including RA, regardless of symptoms (*n* = 107)	Convex probe (1–8 MHz) 14 ICS Total BL score[$]	• LUS cutoff ≥ 5 BL: AUC 0.86, Se 87.1%, Sp 74.3% • Clinical score[†] cutoff ≥ 5.5: AUC 0.80, Se 75%, Sp 71% • Clinical score including LUS (≥ 5 BL) cutoff ≥ 7.5: AUC 0.88, Se 84.4%, Sp 75%
Reichenberger et al., 2024 [36]	Monocentric, cross-sectional study including asymptomatic RF/ACPA-positive RA (*n* = 67)	Convex probe (3.5 MHz) 14 ICS; PI and BL > 5 Suspected ILD: LUS and PFT	• ILD suspicion by LUS and PFT: Se 60%, NPV 71% • ILD suspicion by LUS: Se 71%, NPV 75% • ILD suspicion by PFT: AUC 0.26
Tanten Zabaleta et al., 2024 [35]	Monocentric, cross-sectional study including consecutive RA patients, regardless of symptoms and previous ILD (*n* = 104)	Multifrequency linear probe (8–18 MHz) and convex probe (4–8 MHz) 14 ICS Total number of BL and PI	• Patients with ILD had more BL and PI ($p < 0.001$) than patients without ILD • Best cutoffs for significant ILD were 8 BL and 7 PI • BL ≥ 8: Se 80.9%, NPV 94.3%: PI ≥ 7: Se 80.9%, NPV 94%
Santos-Moreno et al., 2024 [34]	Monocentric, cross-sectional study including RA patients with clinical ILD suspicion (*n* = 192)	Convex probe (2–5 MHz) 72 ICS BL and PI, semiquantitative and binary scores	• LUS for ILD diagnosis: Se 98.3%, NPV 84.6% • BL cutoffs for ILD: 11.5 BL • Chest X-ray for ILD diagnosis: Se 29.9%, NPV 46.4%
Otaola et al., 2024 [33]	Cross-sectional study including RA patients, regardless of respiratory symptoms (*n* = 106)	Convex probe (1–8 MHz) 14 ICS Total number of BL LUS positive if BL ≥ 5	• LUS for ILD diagnosis: Se 90.6%, NPV 94.7% • LUS accuracy was superior to PFT, chest auscultation, and chest X-ray

Table 1. Cross-sectional and retrospective studies on the accuracy of LUS. (*continued*)

Author, year of publication	Study characteristics	LUS protocol	Results
Di Carlo et al., 2022 [32]	Monocentric, cross-sectional study including RA patients with suspicion of ILD (*n* = 72)	Linear probe (4–13 MHz) 14 ICS Total number of BL	• Good positive correlation between the number of BL and the percentage of chest HRCT fibrosis • BL cutoff of 9 to identify significant ILD • LUS accuracy: Se 70%, Sp 97.6%
Cogliati et al., 2014 [31]	Monocentric, cross-sectional study including RA patients with suspicion of or known ILD (*n* = 39)	Experienced and short-trained examiners, with convex and phased array probes Standard and pocket-sized machines, 72 ICS and 8 ICS	• BL score significantly correlated with HRCT Warrick score (*r* = 0.806) • Kappa value: 0.78

#: Clinical-radiological score: included medical record data, radiological assessment, PFT, and HRCT into a 4-point score: 0 = normal, 1 = non-specific abnormalities, 2 = subclinical interstitial lung changes, and 3 = advanced ILD; $: total B-line score (TBLS): counting the number of BL if < 5, assigning a value of 5 if BL ≥ 5, and a value of 10 if the presence of white lung. LUS was considered positive if TBLS > 5; ↟: clinical score of 5 variables: male sex (3 points), crackles (3 points), age ≥ 60 years (2 points), positive RF (2 points), and ACPA positive antibodies (1 point); ACPA: anti-cyclic citrullinated peptide antibodies; AUC: area under the curve; BL: B lines; DLCO: carbon monoxide diffusion capacity; HRCT: high-resolution computed tomography; ICS: intercostal spaces; ILD: interstitial lung disease; LUS: lung ultrasound; mMRC: modified Medical Research Council; NPV: negative predictive value; NSIP: non-specific interstitial pneumonia; PFT: pulmonary function tests; PI: pleural ultrasound irregularities; RA: rheumatoid arthritis; RF: rheumatoid factor; Se: sensitivity; Sp: specificity; UIP: usual interstitial pneumonia.

Table 2. Case-control studies on the accuracy of LUS.

Author, year of publication	Study characteristics	LUS protocol	Results
Tüzün et al., 2025 [30]	Monocentric, case-control study RA with ILD (*n* = 35) and RA without ILD (*n* = 34)	Multifrequency linear probe (6–18 MHz) 12 ICS Coalescent LUS score*	• Significant correlation between coalescent LUS score and Warrick score (*r* = 0.838)
Gutierrez et al., 2022 [29]	Multicenter (2 centers), case-control study RA patients, regardless of symptoms (*n* = 74) and healthy controls (*n* = 74)	Linear probe (5–13 MHz and 4–12 MHz) 14 ICS Semiquantitative BL score[&]	• Significantly higher LUS signs of ILD in patients than in controls • Positive correlation between US and HRCT findings • LUS for ILD diagnosis: Se 92%, NPV 95%
Mena-Vázquez et al., 2021 [28]	Monocentric, case-control study RA patients with (*n* = 35) and without ILD (*n* = 36)	Convex probe (1–8 MHz) 72 ICS Total number of BL and PI	• The number of BL and PI is significantly higher in patients with RA-ILD than in controls • LUS cutoffs and accuracy for different LUS scores • Positive correlation of BL with ACPA, DAS28, and HAQ, and negative association with DLCO
Fotoh et al., 2021 [27]	Monocentric, case-control study RA patients with (*n* = 75) and without ILD (*n* = 75)	Linear probe (4–13 MHz) 14 ICS Total number of BL Semiquantitative BL score[&]	• LUS score and serum KL-6 were significantly higher in RA-ILD than in controls • Positive correlation between LUS, KL-6, and HRCT. Negative correlation with PFT

Table 2. Case-control studies on the accuracy of LUS. (*continued*)

Author, year of publication	Study characteristics	LUS protocol	Results
Moazedi-Fuerst et al., 2014 [26]	Monocentric, case-control study RA patients without respiratory symptoms (n = 64) and healthy controls (n = 40)	Convex probe (3.5 MHz) and linear probe, 18 ICS LUS positive if BL in > 2 locations, pleural line thickening or fragmentation, subpleural nodules, and negative lung sliding	• ILD diagnosis in 26.5% of patients • LUS accuracy: Se 97.1%, NPV 98.6%

*: coalescent LUS score: score 0: presence of A lines or BL ≤ 2; score 1: BL ≥ 3; score 2: coalescent BL; score 3: tissue-like pattern; &: semiquantitative BL score: 0 = normal (≤ 5 BL), 1 = mild (≥ 6 and ≤ 15 BL), 2 = moderate (≥ 16 and ≤ 30 BL), and 3 = severe (≥ 30 BL); ACPA: anti-cyclic citrullinated peptide antibodies; BL: B lines; DLCO: carbon monoxide diffusion capacity; HAQ: Health Assessment Questionnaire; HRCT: high-resolution computed tomography; ICS: intercostal spaces; ILD: interstitial lung disease; KL-6: Krebs von den Lungen-6; LUS: lung ultrasound; NPV: negative predictive value; PFT: pulmonary function tests; PI: pleural ultrasound irregularities; RA: rheumatoid arthritis; Se: sensitivity.

5 B lines) with a 5-variable RA-ILD clinical risk score (sex, Velcro crackles, age ≥ 60 years, and positive RF or ACPA) improved its accuracy (Table 1). However, the combined LUS-clinical score did not exceed the accuracy of LUS alone (Table 1).

Di Carlo et al. [32] focused on high suspicion of RA-ILD defined by either the presence of respiratory symptoms or Velcro crackles, or the presence of at least two risk factors for RA-ILD, such as male sex, age > 65 years, smoking, positive RF or ACPA, in the absence of the former. RA-ILD was identified in 34.7% of patients, with favorable LUS accuracy values (Table 1). Furthermore, LUS showed a significant negative correlation with PFT, and the number of B lines was significantly higher in men [32].

Other authors have also analyzed the association of LUS with RA-ILD risk factors, describing a significant association between the number of B lines and disease activity, RF, ACPA, age, male sex, or the Health Assessment Questionnaire, and an inverse correlation with DLCO [27–29, 35, 44]. A significant correlation (r = 0.97) has also been found between LUS and KL-6, identifying that cut-off values of KL-6 and LUS of 277.5 U/mL and < 5.5, respectively, had a Se of 86.7% and 100%, and a Sp of 88% and 100%, respectively [27].

Due to the importance of early diagnosis of RA-ILD, it is key to discuss the performance of LUS as a screening tool in asymptomatic patients with RA, although existing data are still very scarce. Moazedi-Fuerst et al. [26] evaluated 64 asymptomatic patients with RA and identified B lines in 28%, subpleural nodules in 18%, and fragmented pleural lines in 4%. Eighty-nine percent of cases showed concordant findings on HRCT. Of great interest is the recent study by Otaola et al. [41], who evaluated 203 patients with RA, asymptomatic at the respiratory level, with LUS and HRCT, finding subclinical ILD in 26%, predominantly NSIP (45.3%), and with an extension < 20% (75.5%). The accuracy of LUS in this setting surpassed that of DLCO, although not all patients had PFT (Table 1). Furthermore, NPV was greater than 90% regardless of the number of RA-ILD risk factors in patients [41].

Usefulness of LUS to assess the severity of RA-ILD

B-line quantification, either numerically by adding the total number of B lines in each of the examined intercostal spaces (ICS) or by semi-quantitative scores, has been shown to be significantly associated with the severity of RA-ILD determined on HRCT using the Warrick or Goh scores. Correlation coefficients of 0.806–0.838 postulate the usefulness of LUS to estimate ILD severity [29–31, 38]. Additionally, Di Carlo et al. [32] reported a good positive correlation (r = 0.559, p < 0.0001) between the number of B lines and the percentage of HRCT fibrosis measured by a computer-aided method, selecting a cutoff value of 9 B-lines to identify significant ILD on HRCT.

Reliability of LUS in RA-ILD

Reliability is one of the aspects of LUS validation that is in a more preliminary phase, with still little evidence in the literature. Most studies have evaluated the intra- and inter-observer reliability of either B lines or pleural irregularity [26, 31, 38, 44]. For the evaluation of B lines, intra-observer kappa values of 0.76–0.98 and inter-observer values of 0.73–0.96 have been reported, with the corresponding intraclass correlation coefficients (ICC) of 0.76–0.90 and 0.86–0.97, respectively [26, 35, 38, 44]. The ICC values reported for pleural irregularities were 0.79–0.9 and 0.79–0.84, respectively [35, 44].

A first approach to assessing the impact of reader experience was made by Bandinelli et al. [44], who analyzed the inter-reader reliability of residents who had been trained by an expert for 3 months (ICC 0.86–0.94 for B lines and 0.82–0.84 for pleural line abnormalities). The authors argued that the favorable results could suggest a short learning curve for LUS, although this conclusion could be biased since the examinations had been recorded by the expert.

The type of score used could also impact reliability. In this regard, Vermant et al. [38] found higher kappa values when assessing the presence/absence of B lines than when quantifying their number.

More relevant to clinical practice are the intra- and inter-explorer studies. Cogliati et al. [31] described an inter-explorer kappa of 0.78 between assessments made by an expert sonographer using a standard machine versus a less experienced explorer using a pocket-sized machine, suggesting that the technological requirements for LUS may be less demanding than for musculoskeletal ultrasound.

Recently, Vicente-Rabaneda et al. [40] published a pilot study focused on the intra- and inter-explorer reliability of different B-line and pleural irregularity scores. In this study, three experienced sonographers blindly performed LUS in 14 patients with suspected RA-ILD. The intra-explorer kappa values for B-line (global 0.73–0.82 and binary 0.80–0.90) and pleural line (semiquantitative 0.88–0.91 and binary 0.77–0.84) scores, as well as the inter-explorer kappa values for B-line (global 0.93 and binary 0.90) and pleural line (semiquantitative 0.84 and binary 0.84) scores, were good to excellent. These findings suggest that LUS reliability can be high when performed by adequately trained experts, underscoring the need for proper operator training, which remains to be defined, as recognized in a recent consensus on the use of LUS [45].

Scanning protocols and feasibility of LUS

LUS studies investigating RA-ILD show considerable heterogeneity in examination protocols. Linear, curved, and cardiac sector probes have been used. B lines have been studied, and in some cases, pleural line irregularities have been included. The scores used have been binary (presence/absence), numerical (sum of individual findings in the different ICS), or semiquantitative, with different cutoffs depending on the protocol used.

To increase the feasibility of LUS, the accuracy of simplified protocols has been investigated. Initially, examinations included 72 ICS, although later studies have found similar results scanning 8 or 10 ICS [28, 31]. The most used protocol includes 14 ICS due to the appropriate balance between examination length and performance time (8 minutes) [27, 29, 32, 33, 35–37, 41].

At present, many aspects of LUS remain to be investigated, such as machine settings, and a consensus on the optimal protocol to use has not yet been reached. Recently, the OMERACT Ultrasound Working Group recommended that B lines and pleural irregularity should be the key lesions to assess by LUS following three Delphi consensus rounds [23]. Further research is warranted [45].

The role of LUS in monitoring RA-ILD

One of the a priori advantages of LUS for monitoring RA-ILD is its safety and accessibility, which allows for repeat examinations without subjecting the patient to ionizing radiation. Studies on the Se to change of LUS in RA-ILD and the ideal protocol for this purpose are still lacking. A recent international consensus suggests that the same probe and protocol should be used in serial evaluations [45].

Fotoh et al. [27] have suggested that LUS could be a prognostic indicator. In the one-year follow-up of patients with RA-ILD in their study, 33% died, mainly due to ILD progression. In these patients, LUS showed

a higher number of B lines (> 28), with an odds ratio of progression of 1.5 (95% CI, 1.3–1.8). Despite LUS potentially being a promising tool to monitor RA-ILD, further investigation is required since Se to change has not been formally validated against HRCT progression.

Where to incorporate LUS into the RA-ILD assessment algorithm?

Various proposals have been made to incorporate LUS into the diagnostic and screening algorithm for RA-ILD. Wang et al. [46] have suggested screening RA patients from diagnosis using LUS and KL-6. In those patients with B lines > 10 or KL-6 ≥ 500 U/mL, regardless of respiratory symptoms, they recommend performing HRCT and PFT. If negative, they propose repeating LUS and KL-6 every 6 months. Below these thresholds for B lines and KL-6, the monitoring cadence would be determined by risk factors. Reichenberger et al. [36] proposed a radiation-free protocol with LUS, PFT, and screening for cardiac involvement with an echocardiogram and CPET on a treadmill. Gutiérrez et al. [29] suggested annual screening for RA-ILD from RA diagnosis, using LUS in asymptomatic patients, and with LUS and chest X-ray in symptomatic patients. HRCT would be performed if the results were positive.

Despite the current lack of consensus, considering the epidemiology of RA-ILD, it seems more reasonable to propose screening in high-risk patients, either due to symptoms or suspected signs or the presence of risk factors for RA-ILD in asymptomatic patients, as the recommendations of scientific societies are beginning to suggest [20, 21]. However, the role of LUS in these algorithms remains to be defined. It is important to emphasize that LUS should be considered a potential aiding tool to add to existing ones, and does not in any way replace HRCT, which remains the current gold standard for screening and diagnosis of RA-ILD. In Table 3, we display the main characteristics of LUS in comparison with the tools used in clinical practice to screen for ILD.

Table 3. Comparison of LUS with the diagnostic tools used to screen for interstitial lung disease.

Characteristics	LUS	PFT	HRCT
Accessibility	High	Moderate	Low
Cost	Low	Moderate	High
Availability of results	Immediate	Deferred	Deferred
Ionizing radiation	No	No	Yes
Operator-dependent	Yes	Yes	No
Type of information	Lung structure-related	Lung function-related	Lung structure-related
	Bidimensional	Spirometry/plethysmography	Three-dimensional
	Restricted to the subpleural region	DLCO	Whole lung
Diagnostic sensitivity*	60%–98%	52%	Gold standard

*: LUS and PFT data obtained from the following included studies: LUS [26–29, 31–41] and PFT [41]; DLCO: diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; LUS: lung ultrasound; PFT: pulmonary function tests.

Limitations of LUS

LUS has limitations that are important to understand. First, this technique can only assess pathological changes in the subpleural lung region, and lesions in other locations cannot be visualized, unlike HRCT, which can assess the entire lung parenchyma and rule out other processes such as infections or neoplasia. However, the fact that RA-ILD involvement often begins in this subpleural location makes LUS an interesting tool for its study.

Another important limitation is that LUS does not clearly discriminate against the pattern of lung involvement (UIP or NSIP) as HRCT does, although in fibrotic forms, there could be greater involvement of the pleural line. Furthermore, B lines are not pathognomonic of ILD since they may be present in other pathologies such as pneumonia, pleural diseases, or heart failure, which are frequent comorbidities in elderly patients with RA who are at risk of RA-ILD [25, 45].

Furthermore, B lines can also be present in healthy populations, especially in the elderly, further complicating their interpretation. This lack of Sp of LUS can lead to false positives, so its interpretation should always be based on a complete clinical assessment of the patient, including the necessary diagnostic tests. Emerging evidence suggests that pleural line irregularities may have higher diagnostic Sp than B lines, although data on pleural lines are still scarce. Some authors even suggest combining cardiac imaging or functional tests with LUS for a more comprehensive assessment [36].

Additionally, standardizing the evaluation protocol is essential if we want to increase the reproducibility of LUS and be able to apply it in clinical practice. It is not enough to define the basic lesions to be evaluated; it is also important to define how to quantify them, as well as the settings of the ultrasound system, the probe, and the ICS to scan, among others.

Finally, LUS is an operator-dependent technique that requires a learning curve that is not yet defined but is essential to achieve before it can be implemented in clinical practice. Furthermore, in addition to the limitations inherent in the technique, there are those derived from the level of evidence of the studies available to date, since most are small observational cross-sectional studies. Additionally, most of the studies were performed by highly trained sonographers in controlled research settings. Whether these reliability metrics can be reproduced in routine rheumatology clinics remains uncertain.

Conclusions

The progress made in recent years in the validation of LUS for the detection and screening of RA-ILD is considerable and shows very encouraging results in terms of accuracy, reliability, and feasibility. However, crucial aspects remain to be defined to ensure its reproducibility, such as the agreed-upon standardization of the examination protocol—the ICS to be scanned, the type of probes or the scoring methods to be used—and the learning curve prior to its implementation as a diagnostic tool, due to the technique's inherent limitations. Regarding the elementary lesions of LUS, further investigation is required to acknowledge whether pleural line irregularities may have higher diagnostic Sp than B lines and their potential to reduce the rate of false positives. At the technical level, it is necessary to advance our understanding of the physical origin of B lines, as well as to improve the characterization of B lines and pleural irregularity and their potential quantification, exploring whether artificial intelligence and automated B-line detection can facilitate this and enhance standardization. At the clinical level, multicenter studies with sufficient sample sizes are needed to address the knowledge gaps, increase the level of evidence, and complete the validation of LUS before widespread clinical adoption.

Further large patient-based intra- and inter-observer reliability exercises including both the entire spectrum of RA-ILD involvement as well as healthy controls and RA without ILD are needed. Multicenter and multimachine studies with a high number of patients with different degrees of ILD severity, including subclinical states, would be of great interest to provide more reliable information about the accuracy of LUS to detect and quantify RA-ILD. In the validation process of LUS in RA-ILD, it is also very important to investigate the Se to change of this technique through longitudinal studies, including patients with and without targeted treatment for ILD, and comparing the findings with the gold standard (HRCT).

In summary, future research agenda should focus on completing the validation process of LUS and reaching a consensus on the LUS protocols for RA-ILD screening, establishing algorithms to define when to begin screening and how to monitor disease progression and response to treatments.

Abbreviations

ACPA: anti-cyclic citrullinated peptide antibodies

AIRD: autoimmune rheumatic diseases

DLCO: diffusing capacity for carbon monoxide

HRCT: high-resolution computed tomography

ICC: intraclass correlation coefficients

ICS: intercostal spaces

ILD: interstitial lung disease

KL-6: Krebs von den Lungen-6

LUS: lung ultrasound

NPV: negative predictive value

NSIP: non-specific interstitial pneumonia

OMERACT: Outcome Measures in Rheumatology

PFT: pulmonary function tests

RA: rheumatoid arthritis

RF: rheumatoid factor

Se: sensitivity

Sp: specificity

SSc: systemic sclerosis

UIP: usual interstitial pneumonia

Declarations

Author contributions

EFVR: Conceptualization, Investigation, Validation, Writing—original draft, Writing—review & editing, Supervision. DB: Conceptualization, Investigation, Validation, Writing—review & editing. FGJN: Validation, Writing—review & editing. PSM: Validation, Writing—review & editing. SC: Conceptualization, Investigation, Validation, Writing—original draft, Writing—review & editing, Supervision. IM: Conceptualization, Investigation, Validation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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