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Review Article

The Role of Lung Ultrasound in Early Diagnosis of Systemic Sclerosis-Related Interstitial Lung Disease

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Abstract

Interstitial lung disease (ILD) is a major extra-articular manifestation of systemic sclerosis (SSc), significantly contributing to morbidity and mortality. Early detection and close monitoring of patients at high risk of progression are critical for establishing the need for targeted treatment with immunomodulatory and antifibrotic drugs that have the potential to alter the course of the disease. Although the predictive value of high-resolution computed tomography (HRCT) is undeniable, it increases the risk of cancer in SSc-ILD patients with a propensity for developing cancer due to medication overuse and radiation exposure. Lung ultrasonography (LUS) is an intriguing alternative technology in this context, providing a non-invasive and non-radiating evaluation that can be performed prior to other imaging techniques, such as a CT scan, to detect interstitial abnormalities within the subpleural space. Vertical artifacts such as B lines and pleural line modifications have a strong link with the presence of ILD on HRCT and the extent and severity of the disease, with sensitivity and negative predictive values of up to 100%. In the past decades, LUS has been shown to be a cost-effective and repeatable procedure when combined with pulmonary function tests as a primary assessment, limiting the frequency of HRCT application and minimizing radiation exposure that contributes to the probability of cancer development and progression. In this review, we have provided an etiological background for pulmonary involvement in SSc, screening modalities for ILD in SSc, and a thorough description of LUS findings and scoring systems as a point-of-care diagnostic tool in SSc-ILD.

Keywords: Interstitial Lung Disease; High-Resolution Computed Tomography; Lung Ultrasound; Systemic Sclerosis; Scleroderma

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Introduction

Systemic sclerosis (SSc), also known as scleroderma, refers to a spectrum of heterogeneous and autoimmune disorders characterized by abundant production and progressive deposition of fibrous tissue in the skin, joints, and several internal organs, especially the esophagus, lower alimentary tract, lungs, heart, kidneys, and the nervous system (1, 2). Scleroderma may be either localized (localized scleroderma (LS), also named Morphea) or systemic (systemic scleroderma (SSc)). Multi-system involvements are more likely associated with the systemic form. There is a substantially increased mortality risk in patients with diffuse cutaneous involvement and those with pulmonary or cardiac complications (3, 4). SSc is traditionally sorted into subtypes based on the proportion of skin involvement and the systemic complications. These include limited cutaneous (lcSSc or CREST syndrome calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias), diffuse cutaneous (dcSSc), sine scleroderma (ssSSc, which is characterized by no skin tightening), and SSc overlap syndrome (5, 6). SSc is a relatively uncommon disorder with disparate reported prevalence identified across studies. It affects approximately one in 100,000 individuals worldwide (7).

The discrepancy in annual incidence and prevalence of SSc originates from differences in statistical methodology, criteria of diagnosis, and various study populations and periods (8). SSc is more common in women (with a recorded female/male ratio of 3:1 to 14:1), and the highest incidence rate is in the age group of 45 to 54 years (9). Regardless of its low prevalence, high mortality and morbidity rates highlight the importance of timely diagnosis and prompt initiation of treatment in SSc (10–14).

With the ability to estimate the pattern and extent of ILD, HRCT is the most effective screening method in this population for SSc-ILD, outperforming lung function testing in terms of sensitivity and specificity. HRCT imaging exposes patients to radiation, and its use as a screening tool in asymptomatic patients is not uniformly recognized. Innovative non-invasive screening technologies can serve as alternate screening methods for SSc-ILD. Ultrasound imaging of air-filled, poorly echogenic lungs has risen in popularity during the past decade as a method for analyzing the lungs' structure (15, 16). In this review, we will discuss the details of the application of LUS in SSc-ILD.

Etiology of SSc and Pulmonary Involvement in SSc

SSc Etiology

The etiology of SSc is not entirely understood. Genetic and environmental risk factors (e.g., exposure to silica or organic solvents) appear to influence the susceptibility to the disease and innate homeostasis disturbances. In developing SSc, specific autoantibodies may assist in stimulating tissue fibrosis. As a result of immune-mediated responses and small vessel fibroproliferative vasculopathy brought on by the high concentration of plasma von Willebrand factor (vWF) in the blood circulation, these antibodies are released (17, 18)**(Figure 1)**.

Pulmonary Involvement in SSc

A vast majority of patients with SSc develop pulmonary system involvement. Due to the complicated nature of the SSc, the pattern of respiratory symptoms varies widely among affected individuals. SSc's pulmonary manifestations are divided into two major categories, namely interstitial lung disease (ILD) and pulmonary vascular disease (e.g., pulmonary arterial hypertension (PAH) and veno-occlusive disease (VOD)), which may occur separately or concurrently. However, fibrous tissue deposition is not restricted to the interstitial or vascular compartments (8).

Isolated PAH has a prevalence of 13–35% in SSc (19–21). Anti-Scl-70 (anti-topoisomerase I) antibodies are more commonly detected in patients with SSc-ILD, whereas anti-centromere antibodies are more frequently found in those with SSc-PAH (7, 9, 22).

Coexistence of ILD and PAH was reported in a significant subgroup of patients, which predominantly occurs secondary to newly-diagnosed SSc-ILD, particularly in those with diffuse SSc. This sheds light on the importance of carrying out initial assessments (e.g., trans-thoracic echocardiography (TTE) or right heart catheterization) for any comorbid conditions in ILD patients, including PAH (23–27).

SSc-Related ILD

SSc-ILD, which indolently affects a vast majority of SSc patients, is a leading cause of death in SSc, with a reported 10-year mortality of up to 40% (28). ILD was found responsible for 35% of SSc-related deaths (26% due to PAH and 26% due to cardiac reasons)(29). Mortality is approximately three times higher in SSc patients who present with lung fibrosis (30). The estimated prevalence of SSc-ILD varies from 30% to 90% based on different screening algorithms (31). Although SSc is more predominant in females, the male gender is more prone to be affected by SSc-ILD. A vicious cycle of constitutive fibroblasts activation, as a matter of excessive exposure to injury, primarily reactive oxygen species (ROS), and the complex interplay between overly-expressed proteins and dysregulation of the immune system is a crucial concept in the deterioration of lung function (13, 17).

Pulmonary involvement adversely affects the clinical course and therapeutic outcomes. There are no verified and globally accepted guidelines for the optimal type and timing of treatment in SSc-ILD, and the limited medication options draw heavily from previous experimental and clinical research. However, long-term survival rates are still dissatisfying. Patients with pulmonary or cardiovascular involvement have a 3-year survival rate of slightly more than 50%. This highlights the necessity of early SSc-ILD diagnosis and timely initiation of treatment (32, 33).

Factors that accompany the progressive forms of the SSc-ILD include African-American ethnicity, early-onset ILD, diffuse cutaneous SSc, older age, the detection of anti-Scl-70/anti-topoisomerase I antibody (ATA), and the absence of anti-centromere antibody (ACA). Additionally, high serum creatinine and creatine phosphokinase levels, lower baseline forced vital capacity (FVC) or diffusing capacity of the lungs for carbon monoxide (DLCO), elevated C-reactive protein (CRP) level, muscle weakness, hypothyroidism, and cardiac involvement are other reported risk factors for SSc progression (34–36).

In a study using data from the European Scleroderma Trials and Research group (EUSTAR) database over long-term follow-up, male gender, presence of gastroesophageal reflux (GER), dysphagia, and widespread involvement of skin at

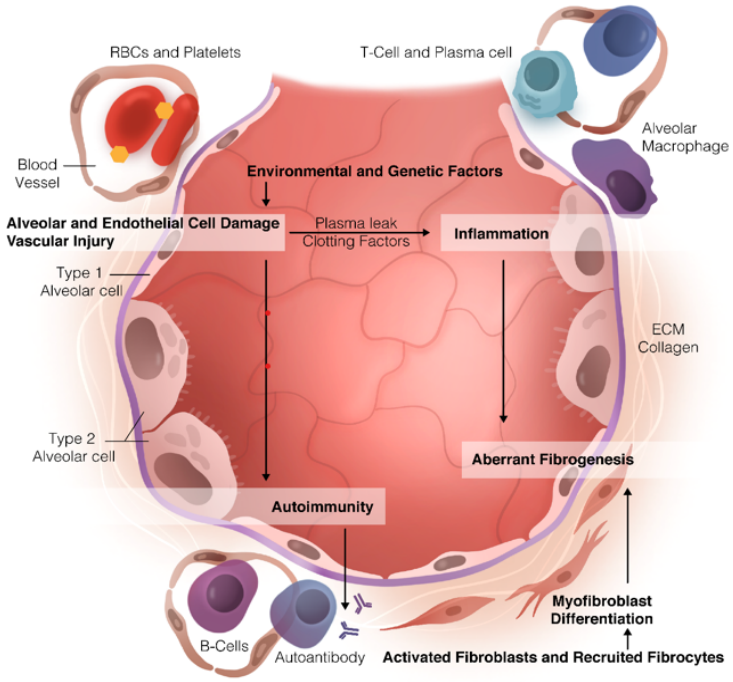

Figure 1. Pathogenesis of SSc-ILD. Environmental and genetic risk factors contribute to alveolar and endothelial cell damage, as well as microvascular injury. These factors lead to plasma leakage from the vasculature, which together with plasma clotting factors, causes inflammation and autoimmune activity. The resultant inflammatory response induces the recruitment of fibroblasts, together with the activation and differentiation of myofibroblasts. The excessive production and deposition of extracellular matrix by these myofibroblasts leads to aberrant fibrogenesis, and the subsequent fibrosis and remodeling of the alveoli is the characteristic pathological finding in SSc-ILD.

baseline (high baseline mRSS) are the most potent and time-dependent predictors of acceleration in 5-year FVC decline rate (27, 37). Nevertheless, significant heterogeneity of disease progression is still a challenging factor in determining the prognosis (13, 31, 37).

Lung Cancer in Patients Suffering from SSc

Several studies support that the prognostic utility of high-resolution computed tomography (HRCT) in SSc is undeniable. Moreover, several meta-analyses have pointed out that rheumatologic diseases, including SSc, are accompanied by an elevated risk of lung cancer (38, 39). Reports have shown that ionizing radiation may cause LS and worsen precedent SSc (40, 41).

In 2008, Wooten *et al.* declared that 3.6% to 10.7% of patients with SSc are at risk of developing at least one type of malignancy, the most frequent of which are lung cancer, followed by breast cancer (42). In a meta-analysis of 12,218 patients, a remarkably increased risk of lung cancer was observed (OR = 2.80, 95% CI = 1.55–5.03)(39). Several studies have shown that the risk for cancer development is increased by approximately 2.2 to 7.3 times in patients with SSc compared to the general population (39). Numerous studies justify the association between pulmonary fibrosis and lung cancer. Persistent inflammation, tissue remodeling, cell cycle dysregulation, and the sequestration of carcinogens by fibrosis due to damaged lymphatic drainage are all assumed to be possible causes. Likewise, inflammatory mediators have a major role in inducing changes in the genetic and epigenetic makeup of cell signaling pathways, disrupting the cell cycle's regulatory systems (27, 34, 42).

Several other factors might give rise to the subsequent malignancy, the most prominent of which is the early onset of SSc (38, 42, 43). It may imply that direct immune responses at the disease activity sites may make the involved cell more prone to malignant transformation (36). The central point is that malignant transformation in patients with SSc might be potentiated by the significant utilization of medications and exposure to ionizing radiation (38, 44). Lastly, promising deductions based on HRCT findings cannot be obtained unless performed repeatedly over time and at specified intervals. The principles of proper management of radiation dose to patients emphasize the critical role of a well-timed application of HRCT in the early recognition of ILD, and in identifying the prognosis of the disease (43, 45, 46).

ILD Screening and Monitoring

Early SSc-ILD may have no clinical manifestations. However, physicians should comprehensively assess any respiratory symptoms, such as dyspnea on exertion and persistent non-productive cough. Moreover, a complete history and physical examination, laboratory tests and serum biomarkers assessment, pulmonary function tests, and imaging should be performed on any patient recently diagnosed with SSc (47–49).

Pulmonary Function Tests (PFTs)

There is no clear consensus on a validated concept of progression in SSc. FVC, on the other hand, is the most often used variable, since it reflects the severity of restrictive pulmonary function impairment. These measurements are usually recorded within a year (50–52). It has been reported that the result of the PFT is more likely to be affected by external factors, including the season and time of testing, the patient's general well-being, and the operator's skill level (20). For instance, DLCO is the most sensitive variable of PFTs. However, it can be confounded by conditions like emphysema and pulmonary vascular diseases like PAH (14).

Due to the rapid development of severe restrictive lung disease in the first 3-5 years of diagnosis, conducting PFTs every 4-6 months can be beneficial. Still, as mentioned previously, PFTs, e.g., FVC and DLCO, have restrictions for evaluating the initial stages of ILD and may not represent the actual extent of fibrosis (16). Additionally, observational studies have demonstrated that the rate of decline in PFTs could be pronounced or subtle. In an analysis of 102 patients with SSc, HRCT results demonstrated that 63% had interstitial abnormalities. At the same time, only 37.5% had decreased predicted FVC. In conclusion, spirometry is neither sensitive nor specific enough to detect early SSc-ILD (7, 8, 53).

HRCT as a Gold-Standard Imaging Modality for SSc Progression

Changes in the radiographic characteristics of

a chest HRCT scan is the gold-standard indicator of SSc progression (51, 53). Obtaining an HRCT scan is considered the most sensitive and non-invasive imaging technique for SSc-ILD screening. Interstitial abnormalities are prominent on HRCT and at autopsy in up to 80% and 90% of patients, respectively. However, only 30-40% are clinically symptomatic (28). Due to the broad spectrum of the disease manifestations, assessing baseline HRCT results and changes over time is needed to determine the course of the lung disease and the potential risks as a guide for applying the most suitable treatment (53).

HRCT Patterns of Lung Disease in SSc

HRCT patterns of lung disease in SSc are divided into three principal classes: interstitial, the most common class, alveolar, and vascular. The most commonly detected finding, nonspecific interstitial pneumonia (NSIP), is a form of idiopathic interstitial pneumonia characterized by varying degrees of inflammation and fibrosis (53–55). Fibrotic features on HRCT are typically dominant in the bases of the lungs. The fibrotic variant of NSIP is defined by the exhibition of traction bronchiectasis and honeycombing in addition to evolved reticular changes (56). Infrequently, the usual interstitial pneumonia (UIP) pattern, which is observed in approximately 10-15% of patients and associated with even worse prognosis, can be distinguished.

Whether the fibrotic patterns on HRCT or tissue biopsy (e.g., UIP versus NSIP) alters the prognosis of SSc-ILD is under investigation (17, 57). Sporadically, alveolar patterns, including diffuse alveolar damage (DAD), pulmonary hemorrhage, organizing pneumonia, aspiration pneumonia secondary to esophageal involvement, and drug-induced lung injuries, can be portrayed on HRCT (35, 58–60).

ILD Extension Based on Goh Criteria

Based on the extension of the disease represented on HRCT, the Goh criteria categorize ILD into extensive and limited subtypes, with a declared threshold of 70% for FVC (% predicted). If the extent of fibrosis on HRCT is a) less than 10%, it is defined as a limited disease, b) above 30%, it shows an extensive disease, and c) in the 10-30% range (indeterminate), the FVC limit indicates whether it is a limited or extensive disease (61). Extensive pulmonary fibrosis is a strong mortality prognosticator (HR=3.46, 95% CI: 2.19-5.46) (35, 48). An analysis of the HRCT of 203 patients suggested that a mean annual extension of ILD on serial HRCT (0.92 ± 0.36% per year) is statistically significant (p-value = 0.018)(62).

Lung ultrasonography (LUS) in ILD as an alternative modality

LUS has become embedded in monitoring ILD as a non-invasive and non-radiating examination that can detect any interstitial abnormalities in the sub-pleural space (14). Compared to musculoskeletal ultrasonography, it is worth noting that LUS findings are mostly artifacts and can only offer additional data on the most peripheral subpleural area (63).

LUS Techniques and Common Artifacts

In a comprehensive scanning of a normal lung with LUS, probe selection depends on the examination's purpose. Linear high-frequency probes (8–12 MHz) provide a reasonable resolution of superficial structures, permitting a better image of the pleura and lung sliding (also called gliding sign, which represents ventilation in the inspected area)(64–66). According to the study of Gutierrez *et al.* (67), while small surface probes operating at 3–3.5 MHz were optimal for LUS application, transducers operating at 5–7.5 MHz were also used in the common research settings.
Characteristic horizontal artifacts can be detected below the pleural level:

1) A-lines, representing the pleural line, are horizontal artifacts that are mainly appreciated during the insonation of inflated lungs. The air component (physiological or pathological free air like pneumothorax), just below the pleural line, can be elucidated by A-lines (35, 64, 68, 69), and

2) Artifacts from the chest wall's myofascial layers caused by slight reverberation phenomena and the mirror effect; The "curtain sign," or upward shifting of the subdiaphragmatic organs during expiration, appears in the posteroinferior lung intercostal spaces (LIS) at the costophrenic angles (63).

LUS Findings in SSc-ILD

The interstitial changes due to SSc-ILD are

evidenced by identifying the multiple B-lines. B-lines are defined as vertical hyper-echoic and comet-tail artifacts fading to the field's bottom, moving concertedly along with lung-sliding and obliterating the A-lines. Although the exact basis of B-line generation is not obviously recognized, it is indicated by various studies that irregularly spaced B-lines reflect altered alveolar-interstitial features at the visceral pleural space tending to be affected in multiple conditions, which decrease the acoustic impedance between lung air and the soft tissues of the chest wall, (e.g., fibrosing lung disease, interstitial pulmonary edema, and reduction in lung parenchymal air content). This pattern indicates the hallmark of the "lung interstitial syndrome" (IS), recognized with an accuracy of 93% on LUS (63, 65).

The interstitial syndrome is described by finding at least three B-lines between two ribs per field of view in a single longitudinal scan with a distance of at most 7 mm from each other in both lungs. Lung-rockets refer to the presence of higher or equal to three B-lines in intercostal space. Sonographic terms of "septal" and "glass" rockets are depicted on LUS by up to four and higher or equal to five lines, respectively, and they can affirm a white lung pattern (68, 70–73). LUS can differentiate between the causes of interstitial syndrome (64). Additionally, pleural irregularity (PI), as a more recent LUS assessment sign, contributes significantly to the presentation of ILD in patients suffering from SSc. PI is described as thickening (>3 mm) or fragmentation of normal pleural contouring. These changes in pleural integrity are generally established in the more progressive stages of SSc (66, 73, 74).

Lung Ultrasound Scoring System (LUSS)

LUS score ranging from 0 to 36, is calculated by the sum of the points of each of the 12 ultrasound regions (6 regions per side, dividing each hemithorax into anterior, lateral, and posterior regions, and each region into upper and lower part). LUS score is categorized into normal, moderate, severe areation, and complete loss of aeration (75–78). The LUS score higher or equal to 10 B-lines is predictive for the existence of an extensive form of SSc-ILD (14, 79). Studies have shown that the total number of B-lines and morphologic features of the pleural line (e.g., blurriness or thickness) have a relatively high correlation with Warrick's semi-quantitative tomographic score, PFTs, and even clinical symptoms and variables **(Figure 2)** (70, 71, 80–82). A study of 39 patients with SSc revealed that the B-line score was inversely correlated with DLCO ($r = -0.63$, $p < 0.0001$), which confirms the previous data. In addition, the higher B-line scores were in concordance with diffuse cutaneous SSc (dcSSc), history of digital ulcer, and the Medsger scleroderma disease severity scale (DSS)(68, 83).

Utility of LUS as a Point-of-Care Diagnostic Tool

The utility of LUS as a point-of-care diagnostic tool, especially in critically ill and emergency patients, has expanded in the last few years (69, 84). Given its cost-efficacy, convenience, high feasibility, accuracy, and sensitivity, LUS can be clinically used as a bedside tool with a short execution time and without exposing patients to ionizing radiation, which can be interpreted simultaneously by the examiner (74). In a meta-analysis of 11 studies, compromising a total number of 487 patients, the sensitivity and specificity of LUS were estimated as 0.859 (95% confidence interval (CI) 0.812–0.898) and 0.839 (95% CI 0.782–0.886), respectively. Moreover, the calculated specificity and sensitivity may differ by assigning different methods of evaluating lung intercostal spaces (LIS) according to anatomical lines of the chest wall (73, 75).

Despite the poor specificity of B-lines, recent data have shown that the sonographic B-lines can be used as an indicator of the pulmonary interstitial syndrome, especially in high-risk patients for SSc-ILD, even without any established diagnosis of ILD. Besides, the presence of B-lines, as an alarming finding in combination with anti-topoisomerase I positivity, magnifies its predictive value (65, 69, 74). According to a recent study, LUS with B-line evaluation and serum Krebs von den Lungen-6 antigen (KL-6), as two non-ionizing and non-invasive biomarkers, have a strong correlation, have been demonstrated to be sensitive biomarkers for the early detection of connective tissue disease–associated interstitial lung disease (CTD-ILD)(85).

Limitations of LUS Application

LUS application has its own noticeable barri-

ers to being used as an alternative and novel tool to HRCT. First, air-filled structures and thoracic cage bones undermine the penetration of ultrasound waves. Thus, except for some regions of the lungs, other parts cannot be easily examined. Dynamic properties of findings on LUS, as a consequence of respiratory movements, make the scanning more difficult. Static signs discovered on LUS are primarily artifacts (79, 86). LUS is applicable only for real-time exploration of the lung's pleural lines and adjacent regions where the early interstitial changes of SSc-ILD can be detected (66). In the most favorable condition, only 70% of the lung surface is appraisable (65). The deeper portion of the lung and the intra-parenchymal lesions cannot be investigated thoroughly by employing LUS (65). For instance, the distribution of UIP pattern (associated with honeycombing with or without traction bronchiectasis) is routinely characterized by reticular abnormalities and apicobasal gradient with a peripheral (sub-pleural) predominance, and it can be detected by LUS. Nonetheless, the NSIP pattern, a more common morphological pattern in SSc-ILD, is featured by bilateral ground-glass opacities and sub-pleural sparing and is more challenging to be spotted by LUS (70, 79).

The accuracy of sonography depends very much on the technical skill of the examiner (72, 74, 87). Moreover, an optimal probe (e.g., a linear high-frequency probe) is necessary for better specifying the pleural line. Patient-dependent limitations include obesity, rare in patients with SSc, and coexistence of any pathologies in which the sub-pleural air content is altered (e.g., emphysema or atelectasis)(65, 74).

According to the literature, critical aspects of LUS findings interpretation included the following: to begin, there is disagreement on the definition of elementary lesions during the examination. Additionally, there is a dearth of information regarding the acquisition method of LUS images (e.g., controversy on the optimal US transducer to use). Standardizing the scanning technique and strategy and defining the number of spots to investigate are crucial for the LUS assessment of the lung (i.e., intercostal spaces that should be evaluated). Intercostal spaces are currently documented in various studies, ranging from 10 to 72 per patient (67, 88, 89).

Thirdly, there is no agreement on measuring ILD using LUS-whether through a dichotomous approach or quantitative or semi-quantitative grading systems. The severity of ILD is determined using a variety of LUS B-line scores with varying cut-off values. There was no research that included a sample of individuals newly identified with ILD using LUS that could be followed over

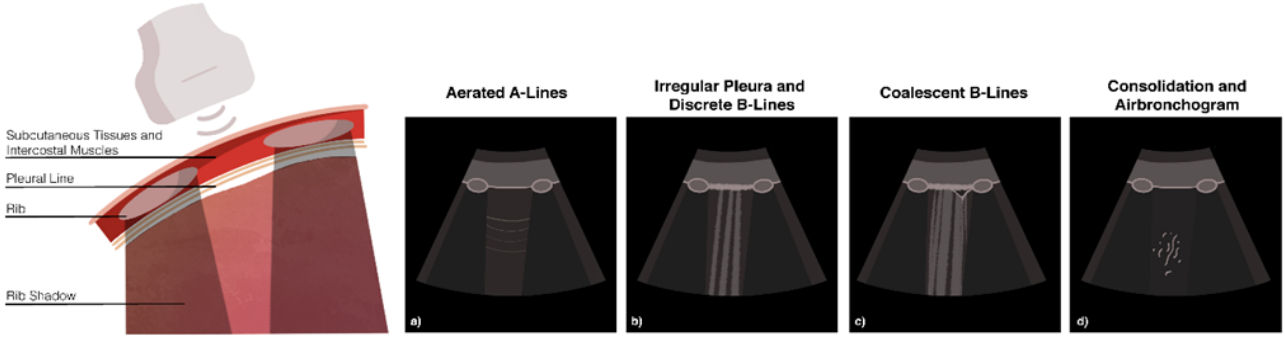

Figure 2. Common findings in LUS

a) Aerated A-lines. A-lines are hyper-echoic horizontal reverberation artifacts, seen deep to the pleural lines (PLs), which lose intensity the deeper they are seen in the field. PLs can be seen between the two surrounding ribs (also known as the bat sign) (97).

b) Irregular pleura and discrete B-lines. B-lines are vertical hyper-echoic comet-tail artifacts, emerging from the PLs and fading indefinitely to the field's bottom, while obliterating the A-lines (98). Pleural Irregularity (PI) is described as thickening (>3 mm) or fragmentation of normal pleural contouring.

c) Coalescent B-lines. As thickened B-lines descend in the field, they may merge together, forming coalescent B-lines, which can be regarded as the ultrasound equal to HRCT's peripheral lung ground glass opacities (99,100).

d) Consolidation and air bronchogram. Consolidations in the lung appear as tissue-dense hypo-echoic areas in LUS, which may be penetrated by hyper-echoic lines that are air bronchograms (99).

time to determine how it progressed. LUS screening was 100 percent accurate in detecting ILD, according to the authors. These findings may serve as a springboard for further investigation of LUS's potential as an early detection tool for ILD-SSc (67).

Clinical Horizons

Prediction of Need for HRCT

Manolescu *et al.* stated that even assuming HRCT as the gold-standard modality for diagnosis and monitoring of ILD, LUS sensitivity is still high enough, approximately 89%, and variability in the estimated sensitivity due to the ultrasound devices used is neglectable (73). Clinically, an integrating approach of conducting LUS as a complementary method and evaluating other para-clinical tools can be beneficial, especially in younger female patients at the time of diagnosis whose cumulative rates of multiple or repeat imaging are high (80, 87).

Point-of-Care Lung Ultrasonography (POCUS) during the COVID-19 Pandemic

Some of the complications of COVID-19 are interstitial pneumonia and vascular impairment. Recent investigations demonstrate that COVID-19 and SSc may share similar radiological characteristics (90), such as B-lines, consolidation regions, and alterations to the pleural line. In case of severe COVID-19 pneumonia with serious consequences such as pneumothorax, ultrasonography can provide a real-time and dynamic examination. Other than that, there is little correlation between the emergence of these ultrasonic manifestations and the severity of interstitial lung disease (91).

The use of lung ultrasonography as an aid in the diagnosis of SARS-CoV-2 infection has been shown to be superior to auscultation and X-rays by numerous studies. A representative article demonstrated that the specificity, sensitivity, and diagnostic accuracy attained during a lung ultrasound exceeded 93%, whereas auscultation and X-rays yielded variable results (92). Ultrasound is regarded as the fifth pillar of physical examinations. It may aid in minimizing X-ray usage and doing selective CT scans during the COVID-19 pandemic and deeming the POCUS triage particularly beneficial. It allows medical professionals to examine and re-evaluate critically ill patients in real-time, saving time and money while reducing the risk of nosocomial infection from portable X-ray machines or non-selective transport to the CT scan room (65, 92, 93).

Conclusion

The high prevalence of ILD in SSc raises the unmet need for additional stratification tools for the early detection of lung parenchymal impairment (53). Lung involvement can exist in SSc, even in clinically asymptomatic patients or those without abnormal PFT findings. Hence, a systematic screening strategy at baseline and follow-up ensures that the patient is assigned suitable treatment (48, 50).

There is no doubt that HRCT provides an accurate assessment of the distribution and pattern of lung lesions, but radiation exposure still remains a concern. Measured radiation dose exposure is much higher than a routine chest scan, which can exceed the ultimate chest X-ray (CXR) 100 times, even if acquired with a reduced radiation scanning technique (86). In addition, there is no robust evidence of performing necessity and identified intervals for HRCT application in newly diagnosed cases of SSc (51). It was demonstrated that lung ultrasonography (LUS) is a cost-efficient, radiation-free, repeatable, and sensitive technique as a primary assessment along with pulmonary function tests. Due to its high sensitivity, it can be employed to legitimate HRCT application frequency and subsequently lower radiation exposure, contributing to the reduced likelihood of cancer progression (47, 74, 79, 81). In SSc patients with worsening PFTs and increasing reverberation artifacts (B-lines), the interval between the HRCTs can be reduced. Additionally, a low score of LUS based on B-lines eliminates the demand for HRCT (74, 94).

Finally, conducting supplemental investigations is essential to confirm the cut-off points and positive and negative predictive values (PPV and NPV, respectively) of the LUS score, assess its accuracy in detecting pulmonary fibrosis, and monitor the eventual response to therapeutic approaches. Therefore, enhancing the understanding of the strength and limitations of LUS can open avenues for the perfect appliance of LUS, a

complementary modality in SSc (73, 88, 95, 96).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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