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Overview of Diagnostic Modalities Used for Screening and Monitoring Systemic Sclerosis-related Interstitial Lung Disease

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ABSTRACT

Background: Systemic sclerosis-associated interstitial lung disease (SSc-ILD) presents a significant challenge in clinical practice due to its high morbidity and mortality rates. This review evaluates various diagnostic modalities essential for screening and monitoring SSc-ILD, emphasizing their clinical utility and limitations. Pulmonary function tests (PFTs), including spirometry and diffusion capacity for carbon monoxide (DLCO), are primary tools for initial assessment and longitudinal monitoring. While DLCO demonstrates higher sensitivity, serial changes in forced vital capacity (FVC) predict disease progression and mortality more reliably. High-resolution chest CT (HRCT) scans provide superior sensitivity in detecting early structural abnormalities and guiding therapeutic decisions despite concerns over radiation exposure. Although widely used, the 6-minute walk test (6MWT) lacks specificity compared to advanced assessments like DLCO during exercise. Lung ultrasound (LUS) emerges as a promising, radiation-free alternative for early ILD detection, correlating well with HRCT findings. Mean pulmonary arterial pressure (MPAP), assessed via echocardiography and right heart catheterization, aids in identifying pulmonary hypertension complications in SSc-ILD patients. Bronchoalveolar lavage (BAL) and surgical lung biopsy offer additional insights in challenging cases, yet their routine use remains contentious due to invasiveness and limited impact on clinical outcomes. Integrating these diagnostic approaches optimizes screening accuracy and facilitates timely intervention in SSc-ILD management. Future research should focus on standardizing protocols and exploring novel biomarkers to enhance diagnostic precision and therapeutic efficacy.

Keywords: Bronchoalveolar lavage; chest radiography; DLCO; HRCT; interstitial lung disease; lung ultrasound; mean pulmonary arterial pressure; pulmonary function tests; systemic sclerosis; 6-minute walk test.

INTRODUCTION

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) ranks as the primary contributor to morbidity and mortality among individuals with SSc, with up to 70% of them exhibiting histological signs of lung involvement.[1] Severe organ complications in patients with diffuse scleroderma tend to manifest early in the disease course, significantly reducing survival rates. Therefore, close monitoring for signs and symptoms of potentially deteriorating organ involvement is crucial during the initial three years following diagnosis.[2]

Several modalities can be used to diagnose and monitor interstitial lung disease, including pulmonary function tests, 6-minute walk tests, high-resolution CT scans, chest radiography, surgical lung biopsy, and bronchoalveolar lavage. Recently, there has been ongoing research about the possible use of lung ultrasound as a screening instrument for ILD. Assessment of pulmonary arterial pressure could be an important predictive tool for identifying lung involvement in systemic disease. We now review the diagnostic value of each screening method and the clinical and scientific rationale behind using them.

Different Diagnostic Modalities

Pulmonary function tests

Repetitive cycles of inflammation and progressive fibrosis accompanying systemic sclerosis can lead to decreased lung compliance and volumes, marked impairment of gas diffusion across the alveolar membranes with subsequently increased alveolar-arterial gradient, respiratory failure, and hypoxia. Based on studies, up to 90% of patients diagnosed with SS reveal functional abnormalities of the lung, primarily associated with ineffective gas transfer.[1]

Pathogenic mechanisms involving air-filling difficulties caused by abnormally stiffened lung tissue and loss of diffusion capability in SSc patients reflect the importance of pulmonary function tests as a screening modality for early identification and further monitoring of interstitial lung disease. Spirometry, lung volumes, and diffusing capacity for carbon monoxide (DLCO) are the most commonly implemented PFTs for diagnosing ILD. FVC measured via spirometry and DLCO are precious screening tools, considering their noninvasive, easily accessible, cost-effective, and susceptible diagnostic properties.

In 2014, the Scleroderma Foundation and Pulmonary Hypertension Association published high-quality evidence regarding recommendations for screening and detection of connective tissue disease that all patients with SSc and scleroderma-spectrum disorders should undergo PFT-spirometry with lung volumes and diffusion capacity carbon monoxide (DLCO).[3] Restrictive syndrome is generally characterized by a total lung capacity and/or FVC < 80% and/or DLCO <75%.[4] Assessing the baseline FVC within the initial three years of disease onset may predict a future decline in pulmonary function among scleroderma patients -

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those initially exhibiting normal pulmonary function have a relatively low likelihood of experiencing significant deterioration later in the disease course.[5] Furthermore, baseline FVC below 70% was associated with an increased risk of mortality.[6] Interestingly, the same research showed that FVC could distinguish among the SS patients treated with Cyclophosphamide versus placebo, which makes it an effective tool to monitor treatment response in individuals with SS. Another evidence based on data from Scleroderma Lung Studies discovered that a decrease in FVC over two years proved to be a superior predictor of mortality compared to the baseline FVC.[7] Other studies also pointed out the importance of observing the serial change in FVC as the most effective monitoring tool of ILD.[8] High-quality evidence indicates that the disease progression, characterized by either a decline in FVC of ≥10% from baseline or a decline in FVC of 5–9% coupled with a DLCO decline of ≥15%, was correlated with an elevated risk of mortality.[9,10]

A systemic review reported that in systemic sclerosis-associated interstitial lung disease (SSc-ILD), DLCO demonstrated a more consistent association with mortality compared to FVC.[11] There is scientific data about DLCO possibly being a more sensitive marker for ILD than FVC: according to Hoffman, measured DLCO < 80% and DLCO < 70% had respectively 83.6% and 67.2%sensitivity for identifying ILD, which is superior to the remaining commonly used PFTs, including FVC < 80%, FEV1 < 80%, TLC < 80%, and TLCO < 80%.[12] SSc cohorts revealed that DLCO is the most accurate overall indicator of lung damage evidenced by HRCT in patients without pulmonary hypertension.[13] Wells pointed out the importance of measuring DLCO during routine evaluations as it provides the most reliable assessment of the extent of fibrosing alveolitis.[8]

There is a strong correlation between the changes in DLCO and radiographic evidence of lung tissue damage: Tashkin and Volkman showed that DLCO was an effective tool for predicting both the extent of lung fibrosis and total interstitial lung disease. At the same time, FVC failed to do so.[13] Suliman also observed that only about half of the patients with significant ILD on high-resolution chest CT scans had FVC <80% of predicted.[14] Although a sensitive marker, measured DLCO can be confounded by several factors, especially when the disease involves pulmonary vasculature. FVC < 80%, FEV1 < 80%, TLC < 80%, and TLCO <80% showed higher specificity than DLCO <80% or <70%.[12] Serial gas transfer patterns have limited predictive significance in idiopathic pulmonary fibrosis and could be influenced by pulmonary vascular disease in systemic sclerosis.[8] The reason for that is the inability of DLCO to differentiate between parenchymal and vascular disease of the lung since gas diffusion gets impaired in both settings.[15] More consistency was noted between repeated measurements of FVC than DLCO due to technical difficulties and variables influencing measured DLCO levels, making FVC a more reproducible diagnostic tool. Moreover, unlike FVC, DLCO could not assess treatment efficacy in clinical trials involving SSc-ILD patients since it failed to differentiate between the patients treated with a placebo or active drug.[6]

Since different PFTs have their strengths and limitations, it is no surprise that the best prognostic value for identifying disease onset and progression is achieved using them combined. The most commonly used combinations would be a decrease in FVC and DLCO values by 10-15%.[16] It is important to note that while PFTs are handy diagnostic tools and a significant part of assessing SS-related ILD, they can be unreliable when used as isolated modalities during screening for ILD. There is evidence that extensive fibrosis can stay undetected since normal levels of PFTs do not exclude clinically significant disease, making it essential to perform imaging studies, especially HRCT and make them part of routine screening algorithms when approaching patients with possible SS-related ILD.[14,17] Using chest x-ray along with DLCO level < 80% increased its sensitivity by approximately 10 %, same is true for HRCT with additional almost double gain in specificity and improved negative and positive predictive values.[12]

Consequently, PFTs are a crucial part of screening and monitoring SS-associated ILD. DLCO harbors more sensitivity but less specificity than FVC. At a point in time, DLCO has more prognostic value in predicting the severity and mortality of the disease. In contrast, serial FVC measurements have superior diagnostic strength than serial DLCO alterations during monitoring ILD progression.[6] Their sensitivity, specificity, NPV, and PPV increase when combined with imaging studies, especially HRCT. The progression of ILD should be monitored using PFTs every six months or more often if there is a decline in clinical condition without any other identifiable cause.[18]

6-minute walk test

The 6-minute walk test (6MWT) is a valuable tool in objectively gauging functional exercise capacity, prognostic evaluation, and treatment response within various clinical contexts.[19,20] Its historical prominence lies in its frequent utilization in pulmonary arterial hypertension (PAH) trials, though alternative assessments like shuttle walks and cardiopulmonary exercise tests exist.[21] Despite the availability of other metrics, the 6MWT remains the most extensively applied measure in clinical trial scenarios.[22,23] Its relevance extends to chronic respiratory ailments such as COPD and interstitial lung diseases (ILDs), suggesting a broader utility beyond its original scope.[20]

Notably, its potential to recognize the central pathophysiological mechanism in systemic sclerosis (SSc), particularly the exercise-aggravated impairment of gas exchange, has been proposed.[24] Evidence indicates that desaturation post-6MWT is a pertinent marker for pulmonary involvement in SSc.[25]

While reviewing the literature, our findings underscored a robust correlation between 6MWT performance and pulmonary function, anti-topoisomerase-I positivity, NYHA functional class, disease duration, and age. Given its simplicity

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and cost-effectiveness, the 6MWT is a valuable tool for identifying SSc patients at risk for adverse outcomes in clinical settings. Prospective studies are warranted to validate these observations.[26,27]

Despite its widespread use, the 6MWT's interpretative value in SSc is limited. It reflects the overall function of multiple organ systems involved in exercise yet fails to delineate the individual contributions or underlying mechanisms of exercise limitations, particularly in the context of SSc-related skin and musculoskeletal involvement. Additionally, its ability to gauge the severity of SSc-associated parenchymal lung disease, even when coupled with oxygen desaturation, remains inconclusive in specific case series of undifferentiated SSc patients.

The universal applicability of the 6MWT across diverse SSc patient profiles underscores its relative significance despite some limitations. Despite its advantages of versatility and simplicity, the 6MWT lacks the specificity and precision offered by more complex assessments like cardiopulmonary exercise testing (CPET) and diffusion capacity for carbon monoxide (DLCO) measured during exercise. While these advanced tests hold promise in early diagnosis and stratification of lung involvement severity, their intricate nature and higher demand for patient compliance pose challenges, particularly in the context of SSc patients.[28,29]

Thus, while initial evidence suggests promising avenues for CPET and DLCO in SSc management, complete replacement of the 6MWT seems premature. Instead, a comprehensive approach combining 6MWT with DLCO and supplementary parameters such as the SHAQ (scleroderma health assessment questionnaire) scores may offer enhanced insights, particularly in monitoring SSc-ILD patients, especially those positive for anti-Scl-70 autoantibodies, to identify those at heightened risk of developing pulmonary hypertension.[30]

High-resolution chest CT

As mentioned above, PFTs are essential tools to monitor the progression of SS-related ILD. However, due to insufficient sensitivity, they might fail to identify the appearance of pathological changes, especially during the early stages of SSc-ILD.[31] According to studies, many individuals with early SSc-ILD might maintain average lung volumes despite apparent structural lung abnormalities detected through HRCT scans.[14] Asymptomatic patients at high risk for developing clinically significant ILD can stay undiagnosed, especially if they have preserved lung volumes on routine screening. In contrast, CT can detect the disease's earliest, even subclinical forms.[32] Furthermore, HRCT findings might help differentiate between interstitial lung diseases of different etiology, highlighting its high specificity.

Noteworthy, when performing chest CT, it is essential to choose an appropriate protocol adjusted for ILD evaluation, as the consensus guideline recommends.[33] Non-contrast volumetric imaging is usually performed to obtain supine end-inspiration and end-expiration scans, sometimes requiring additional prone inspiratory scanning to identify the presence of possible dependent atelectasis.

Radiological patterns of SS-related ILD on HRCT most commonly resemble those of Nonspecific Interstitial Pneumonia and Usual Interstitial Pneumonia.[34,35] Pulmonary fibrosis and ground glass opacities tend to be predominant features, sometimes accompanied by honeycomb cysts, especially in patients with limited SSc.[36] Development of honeycombing and traction bronchiectasis/bronchiectasis is often preceded by ground glass opacities on chest CT, which can serve as an early sign of developing lung fibrosis and might even dictate consideration of treatment initiation.[37] Furthermore, honeycombing, though often mild, is indicative of disease progression, marked by the transformation of ground-glass areas into honeycomb structures and the advancement towards "end-stage lung disease.[38] The "straight-edge" sign is a notable pattern marked by fibrosis confined to the lung bases with clear demarcation in the craniocaudal plane on coronal images without significant extension along the lateral margins of the lungs. It is more frequently observed in ILD and associated with SSc than in RA.[39] The "Four Corners" sign is a term used to describe focal or disproportionate inflammation and/or fibrosis affecting the bilateral anterolateral upper lobes and posterosuperior lower lobes in the form of reticular opacities, ground-glass attenuations, and/or honeycombing. It is also specific for SSc-ILD when confidently identified by readers.[40]

High attenuation areas (percentage of CT attenuation values between −600 and −250 Hounsfield units) are increasingly used as quantitative markers of subclinical ILD. (Podolanczuk AJ). The same study showed that increased high attenuation areas (HAA) correlate with biomarkers indicating inflammation (interleukin-6) and extracellular matrix remodeling (serum matrix metalloproteinase-7), diminished lung function (lower FVC and 6-min walk distance), interstitial lung abnormalities, and a heightened risk of mortality among community-dwelling adults.[41]

Thus, besides its susceptible and specific diagnostic properties, the information obtained from initial CT can have a predictive role in the future development/progression of the ILD: the majority (85%) of SS patients with normal baseline CT continued to have so after a five-year follow-up. In comparison, 68% of the ones with areas of isolated ground-glass opacities progressed to lung fibrosis.[37] The severity of pulmonary fibrosis observed on HRCT scans showed a notable inverse relationship with FVC, diffusing capacity of the lung for carbon monoxide, and total lung capacity.[38] A prospective cohort study also showed that initial HRCT can anticipate the onset and progression rate of fibrosis and the deterioration in pulmonary function among those with SSc.[42] The extent of disease visible on high-resolution computed tomography (HRCT) lung scans predict decline and mortality in systemic sclerosis-related interstitial lung disease (SSc-ILD). Extensive disease (over 20%) on baseline HRCT, assessed with a semi-quantitative grading system, is linked to a three-fold higher risk of deterioration or death compared to limited disease.[43]

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Also, those with NSIP patterns on HRCT showed longer survival time than the ones with UIP.[34] Quantitative Computed Tomography Indexes identify SSc patients who experience severe oxygen desaturation post-exercise and functional and other radiological outcomes. These indexes are generated using an algorithm, eliminating intra- or inter-reader variability, which increases their reliability for assessing SSc-associated ILD.[44]

Even though it is mandatory to use HRCT for initial ILD screening in SSc patients, there is an ongoing discussion about the rationale behind repeating scans for monitoring disease progression and the frequency of recurrent testing. While the clinical deterioration of the disease could warrant repeated scanning, there is no clear evidence of whether to use HRCT routinely, especially in individuals with normal radiologic findings on initial HRCT. 2023 American College of Rheumatology (ACR) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Disease conditionally recommends monitoring with HRCT for SARDs-ILD but does not guide frequency of routine HRCT scanning; however, suggests implementing it when clinically indicated.[45]

There is also an ongoing attempt to decrease radiation exposure risks by using a 9-slice, reduced chest HRCT protocol, effectively identifying even mild SSc-ILD at a threshold of 20% lung fibrosis with high sensitivity and specificity comparable to standard protocols.[46] This could increase its value as a routine monitoring tool with a relatively safe background. Using low-dose two mSv techniques instead of 7 mSv also significantly decreases radiation exposure.[47]

Since CT has superior sensitivity and specificity to all currently available diagnostic modalities, it remains the gold standard for screening and diagnosing ILD among Systemic sclerosis patients.

Chest x-ray

Like dozens of other pulmonary conditions, restrictive lung disease can be featured on routine chest radiograms, which so far remain an irreplaceable initial screening tool for numerable thoracic pathologies. Chest radiography could be important for identifying early changes in SS-related ILD before proceeding to HRCT since it is less invasive, cost-effective, and convenient for widespread use. Chest radiography is capable of detecting several patterns associated with lung involvement in connective tissue diseases such as reticular and ground-glass opacities, nodular lesions, presence of bronchiectasis, reduced lung volumes, and enhanced pulmonary vascular markings - reticulonodular infiltrates predominantly located in lower extended zones being especially characteristic for SS.[48] These findings can strongly suggest ILD and be helpful to guide physicians for further workup demonstrating as much as 93% specificity and positive predictive value of 90%.[49] Chest radiography fails to detect fibrotic ILD in many individuals. Data obtained from the Canadian Scleroderma Research Group registry showed that SSc-related ILD could be identified in only about a third of patients with HRCT evidence of the disease.[50] According to a study published by the American Thoracic Society, chest X-ray bears 63% sensitivity with a negative predictive value of 72%.[51] At the same time, abnormal findings prompt additional HRCT imaging; a normal chest X-ray does not exclude possible ILD. Therefore, there is a need for HRCT in patients diagnosed with SSc, decreasing the X-ray's reliability as a screening modality.[52]

The American College of Rheumatology guideline is consistent with these findings as it does not recommend using CXR for screening or monitoring SS-related ILD.[45]

Lung ultrasound

Despite the gaseous nature of the lungs, ultrasound has demonstrated noteworthy sensitivity and specificity in diagnosing lung diseases. In recent years, LUS has been employed for localizing pleural disease and, in cases of ILD patients, the accumulation of collagen fibers and fibroblasts has resulted in subpleural interlobular septa and interlobular septal thickening involving peripheral lung tissue.[53] LUS has shown a progressive increase in the number of B lines, characterized as hyperechoic narrow base reverberation artifacts extending like a laser beam up to the edge of the screen.[54]

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B lines have been validated as a valuable diagnostic indicator of ILD.[58,89] However, it is crucial to acknowledge that B-line artifacts have also been observed in conditions such as cardiogenic pulmonary edema, interstitial pneumonia (e.g., viral infection), acute respiratory distress syndrome (ARDS), and diffuse alveolar hemorrhage.[60-62] Nevertheless, B lines can still be utilized to assess the severity of pulmonary fibrosis based on their quantity. Research indicates a correlation between the number of B-line artifacts and High-Resolution Computed Tomography (HRCT) results, with more severe pulmonary involvement associated with increased B lines. This correlation often corresponds to worsened gas exchange in pulmonary function tests.[62-66] Consequently, distinguishing between different types of ILD is paramount, as evident in the significantly varying number of B lines and irregular pleura lines among different ILD types. Pleural irregularity, notably, was found to be significantly different between Usual Interstitial Pneumonia (UIP) and Nonspecific Interstitial Pneumonia (NSIP), suggesting its potential as a LUS index for distinguishing UIP from NSIP.[67]

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Furthermore, due to the subjectivity inherent in ultrasound examinations, the accuracy of results, including those from LUS, hinges on the operator's experience. Factors such as probe selection, examination location, ultrasound scanning frequency, and machine settings can significantly impact imaging quality, particularly in visualizing B lines. More training and experience among operators may introduce deviations in the results.[67]

Several studies have highlighted LUS's high sensitivity in detecting Connective Tissue Disease-related ILD by identifying B lines, pleural thickening, and irregularities in the lung surface. Given LUS's advantages, including zero radiation exposure, repeatability in detection, cost-effectiveness, and portability, it emerges as a valuable screening tool for patients suspected of having ILD.

Mean pulmonary arterial pressure

Systemic Sclerosis (SSc) commonly stands out as the predominant Connective Tissue Disease (CTD) associated with Pulmonary Hypertension (PH). Furthermore, PH manifests in a substantial percentage, ranging from 19% to 53%, of patients diagnosed with Mixed Connective Tissue Disease (MCTD).[68-69] The emergence of PH in individuals with Interstitial Lung Disease (ILD) is linked to diminished survival rates and heightened morbidity, as noted by Song et al. PH often intervenes at various ILD stages, necessitating a routine, noninvasive, and cost-effective screening tool crucial for continual patient management and informed decision-making.[70]

Despite echocardiography being an excellent noninvasive screening method for PH, its accuracy in estimating proper ventricular systolic pressure within the context of ILD is limited. Typically utilized to assess PH risk rather than for definitive diagnosis, echocardiography falls short in providing detailed characteristics.[71-72] Right Heart Catheterization (RHC) emerges as a more comprehensive approach, enabling direct measurement of pulmonary artery pressure and offering specific insights into PH type and severity. RHC distinguishes between precapillary and postcapillary PH while revealing other prognostic hemodynamic factors, such as proper atrial pressure and cardiac index.[73] Given the prevalence of cardiac diseases and left ventricular failure in ILD patients, a recent study highlighted postcapillary PH in 20% of 157 diagnosed ILD and PH patients.[74-75]

Mild elevation of Mean Pulmonary Arterial Pressure (MPAP) is commonly observed in CTD-ILD patients with diverse CTD backgrounds. Notably, a higher MPAP during the initial assessment proves to be a significant independent predictor of survival in CTD-ILD cases. Evaluation of MPAP furnishes additional insights into disease status and aids physicians in predicting mortality in CTD-ILD cases. Historically, PH assessment in ILD patients was primarily conducted as part of lung transplantation considerations and to evaluate prognosis. However, the perceived costs and risks of screening, along with confirmatory RHC, for Pulmonary Hypertension-Interstitial Lung Disease (PH-ILD) outweighed potential benefits, except in the context of lung transplant evaluations.[19,79] While RHC remains the gold standard for PH diagnosis, its utility as a convenient screening tool is hindered by invasiveness, time consumption, cost implications, and an elevated risk of moderate sedation, particularly in individuals with baseline hypoxemia.[77]

Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) is a diagnostic tool occasionally employed in patients with Systemic Sclerosis (SSc) and suspected Interstitial Lung Disease (ILD), primarily to rule out alternative etiologies of ILD.[77-78] However, in cases where SSc patients exhibit symptoms such as fever, productive cough, hemoptysis, peripheral blood eosinophilia, or focal consolidation on chest imaging, bronchoscopy with BAL may be warranted. BAL fluid analysis in SSc-associated ILD often reveals elevated granulocyte counts, particularly neutrophils and eosinophils, with possible increases in lymphocytes and mast cells. However, the clinical significance of these findings remains debated.[80-82] While some centers utilize BAL to assess alveolitis severity and predict response to immunosuppressive therapy in SSc-associated ILD, a multicenter clinical trial has contested its routine use for identifying active or progressive ILD. This trial found no discrepancy in Forced Vital Capacity (FVC) change after 12 months between patients with BAL-defined alveolitis and those with normal BAL. BAL, integral to bronchoscopy, entails instilling and withdrawing sterile saline to sample cellular and acellular components from alveolar spaces. The abundance of BAL leukocytes, particularly granulocytes or lymphocytes, often termed "alveolitis," is thought to signify inflammatory processes in ILD patients, potentially influencing disease progression in SSc-ILD. Despite this, the role of BAL in ILD remains controversial due to its invasiveness and technical variability.[83] Existing literature on BAL in SSc-ILD assessment, mostly dated from the 1990s, needs more uniformity and comprehensive analysis. To address these gaps, future research should prioritize prospective clinical trials aiming to standardize BAL techniques, characterize BAL-detected alveolitis, explore novel molecular biomarkers, and correlate BAL findings with functional, High-Resolution Computed Tomography (HRCT) and histopathological data. Additionally, establishing correlations between BAL findings, treatment response, disease trajectory, and patient outcomes is essential for advancing the understanding and management of SSc-associated ILD.[84-85]

Surgical lung biopsy

As is true for HRCT scans, SSc patients with lung involvement usually exhibit NSIP and UIP patterns on histological examination.[34] Surgical lung biopsies that became less invasive after the introduction of the video-assisted thoracoscopic surgical (VATS) approach are presently considered the gold standard for acquiring histological samples in the diagnosis of interstitial lung disease (ILD) that

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cannot be classified based on clinical and radiological evaluations.[86]

Routine implementation of lung biopsies is not recommended in patients with already known underlying systemic diseases such as SSc since diagnosis of SSc-related ILD can be made based on findings obtained from clinical data, HRCT, and pulmonary function tests.[45,87] Same is valid for the monitoring of disease progression. They are predicting prognosis: The outcome is more strongly connected to the initial severity of the disease and the progression of DLCO trends over time than to the histopathologic findings.[88] On the other hand, studies are showing some correlation between histopathological patterns and prognosis of clinical disease: non-UIP patterns on lung biopsy were associated with improved 10-year survival rates in comparison with UIP morphology.[89] Interestingly, patients with the usual interstitial pneumonia pattern in collagen vascular disease-related subtypes have a more favorable prognosis than those with idiopathic pulmonary fibrosis, even though they share the same pathological pattern. In contrast, the prognosis does not differ significantly between the two groups in individuals featuring NSIP.[90] However, as mentioned above, these patterns can frequently be caught on HRCT as well and have inferior prognostic value compared with radiologic and functional studies, which are capable of detecting the extent of the disease as well as further deterioration during disease progression. For those reasons, the rationale behind invasive techniques does not validate exposing patients to an intervention unlikely to change the disease's diagnostic, monitoring, or management strategies.

CONCLUSION

Considering the potentially devastating nature of SSc-associated ILD, it is essential to rationally implement highly predictive diagnostic tools for early identification of pulmonary involvement as well as controlling the further progression of the disease. This could aid in both clinical decisions for treatment initiation and monitoring therapeutic response, along with planning future diagnostic surveillance strategies. Pulmonary function tests and HRCT remain the core disease screening and follow-up instruments. From PFTs, initial DLCO tends to have uppermost sensitivity for prognosis of the disease course and mortality. At the same time, serial FVC trends correlate with the disease progression in a most specific manner. This warrants regular PFT use at least every six months.

Nevertheless, limitations of functional studies necessitate HRCT in all patients with SSc at least once and then repeatedly as dictated by clinical scenario, possessing superior sensitivity and specificity to evaluate the disease extent and accurately indicate mortality and morbidity. Routine use of 6-MWT, chest x-ray, bronchoalveolar lavage, or lung biopsy are not recommended for either screening or monitoring SSc-associated ILD due to their limited impact on diagnostic or management strategies. LUS is a promising screening tool for assessing disease severity and progression based on changes in B-line quantity as a radiation-sparing instrumental modality. However, its diagnostic properties still need to be developed.

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