Transthoracic ultrasonography in patients with interstitial lung disease

Govind Narayan Srivastava¹, Aarushi Chokhani¹, Ashish Verma², Zeeshan Siddiqui²

¹Department of Tuberculosis and Respiratory Diseases, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, ²Department of Radiodiagnosis and Imaging, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

ABSTRACT

Background: Transthoracic ultrasonography (TUS) is suggested as a noninvasive, radiation-free method for the assessment of interstitial lung disease (ILD). This study was designed to study TUS features of ILD. Furthermore, possible correlations of these features with parameters of spirometry, arterial blood gas (ABG) analysis and 6-min walk test (6MWT) were assessed. Materials and Methods: Fifty patients with ILD were diagnosed based on history, examination, chest X-ray/high-resolution computed tomography, and spirometry. Each patient underwent 6MWT, ABG analysis, and TUS. TUS was also performed on 20 healthy volunteering controls. Results: The TUS features among patients were B pattern in 40 patients (80.0%, P < 0.001), decreased lung sliding in 22 patients (44.0%, P < 0.001), pleural line thickening in 28 patients (56.0%, P < 0.001), pleural line irregularity in 39 patients (78.0%, P < 0.001) and subpleural changes in 22 patients (44.0%, P < 0.01). Increasing pleural line thickness was inversely correlated with forced vital capacity (FVC) percent predicted (r = −0.345, P < 0.05), pO₂ (r = −0.335, P < 0.01), SpO₂ at rest (r = −0.444, P < 0.01), 6-min walk distance (6MWD) (r = −0.554, P < 0.001) and distance-saturation product (DSP) (r = −0.572, P < 0.001). Increasing distance between B lines also correlated inversely with FVC percent predicted (r = −0.278), pO₂ (r = −0.207), SpO₂ at rest (r = −0.170), 6MWD (r = −0.209), and DSP (r = −0.214); however these correlations were not statistically significant (P > 0.05). Conclusion: TUS seems to be a useful imaging method for the diagnosis of ILD. It can be used to estimate the severity of ILD. It is simple, bedside, cost-effective, and radiation-free. It may be especially useful in the follow up of patients in low resource settings, pregnant females, and bed-ridden or unstable patients who cannot be shifted to radiology suite.

KEY WORDS: B-pattern, interstitial lung disease, pleural irregularity, transthoracic, ultrasonography

Address for correspondence: Dr. Aarushi Chokhani, Department of Tuberculosis and Respiratory Diseases, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. E-mail: aarushi.chokhani@gmail.com

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INTRODUCTION

Interstitial lung disease (ILD) is a group of heterogeneous lung disorders in which the alveoli, alveolar epithelium, interstitium, capillary endothelium, perivascular tissue, or lymphatic tissue can be affected. They are grouped together as they share common clinical features, radiological appearances, and pathological findings. ILD usually presents with progressive dyspnoea, cough, diffuse bilateral infiltrates on chest X-ray, restriction on spirometry, and reduced diffusion capacity to carbon monoxide (DLCO). A high-resolution computed tomography (HRCT) is often required to identify the type
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of ILD. Histopathological examination of lung tissue, however, remains the gold standard.

Although chest X-ray is useful in categorizing the type of opacities into nodular, reticular, and cystic and identifying the distribution of the opacities, the definite diagnosis is more accurate with HRCT than X-ray. However, the high cost and the high radiation exposure associated with HRCT limits its repeated use. Surgical lung biopsies yield a definite diagnosis in 89% samples, but are associated with procedural mortality in 1.7% cases and other undesired complications such as respiratory infection, exacerbation, bleeding, prolonged air leak, neuropathic pain, and delayed wound healing. Because of the high cost, apparent fear, reluctance, hesitancy and uncertainty regarding surgical lung biopsy, a conservative approach to diagnose ILD is followed by most physicians. Transbronchial lung biopsy, though safer, provides adequate samples only in 77.6% of cases and leads to a definite diagnosis in only 36% of patients.

Transthoracic ultrasonography (TUS) was initially not considered as a useful lung imaging modality as ultrasound beams do not pass through air. However, because of the presence of air in the lungs, there is a generation of certain artifacts. In a diseased state, the air within the lung parenchyma may be replaced by fluids or solid tissue, which can either cause changes in the lung artifacts or lead to actual visualization of the diseased lung.

While examining the acoustically impermeable air-filled normal lung parenchyma, the solid pleural surface acts as a reflector. The reverberation of an ultrasound beam between the pleural surface and the surface of the ultrasound probe gives rise to the equidistant horizontal artifacts known as A-lines.

The presence of interstitial fluid, cellular infiltration, and fibrosis in various ILDs leads to high impedance acoustic discontinuities between closely apposed fluid and air or solid and air. This leads to the perception of very strong echoes by the ultrasound machine every time the ultrasound beam strikes the highly reflective air, which appears on the screen as B-lines. B-lines, also called comet tail artifacts, are discrete laser-like vertical hyperechoic artifacts that arise from pleural line and extend to the bottom of the screen without fading. B-lines move synchronously with lung sliding. The presence of three or more B-lines between two ribs in two or more regions bilaterally is called B-pattern. Otherwise, the B-lines are called focal B-lines and may be present in pneumonia, atelectasis, cancer, or infarction. In up to 20% of normal individuals, focal B-lines may be present in the dependant lateral-basal regions.

Lung sliding is the regular rhythmic movement of visceral pleura against the parietal pleura, which can normally be seen as a shimmering line synchronous with respiratory movements. Loss of the normal hyperechoic linear pleural contour leading to a fragmented and irregular appearance is called pleural line irregularity. Subpleural changes refer to small echo-poor areas beneath the pleural line in the lung parenchyma. Pleural thickenings are focal or diffuse echogenic lesions >3 mm in thickness, which arise from either parietal pleura or visceral pleura.

TUS has been found to be a good tool in diagnosing pneumonia, and a meta-analysis reported a sensitivity and specificity of 94% and 96%, respectively, for TUS against pneumonia diagnosed by chest X-ray or computed tomography (CT) scan, clinical criteria and microbiological laboratory results. Another meta-analysis has reported TUS as a useful tool for diagnosing community-acquired pneumonia in the emergency department with a sensitivity and specificity of 92% and 93%, respectively. However, there is limited data regarding the use of TUS for the diagnosis of ILD.

There is strong (level B) evidence that TUS is superior to chest X-ray for ruling in ILD, and the absence of TUS findings is superior to chest X-ray in ruling out ILD. Pleural line irregularities, subpleural abnormalities, diffuse B-lines, pleural thickening, and reduction or absence of lung sliding have been suggested as possible findings in ILD. A meta-analysis reported that the sensitivity and specificity of TUS with respect to HRCT for diagnosing connective tissue disease-related ILD were 91.5% and 81.3%, respectively. There is evidence that the number of B-lines/B-line scores correlates with the severity of disease on DLCO and HRCT.

The current study was designed to study the TUS features of ILD. Possible correlations between TUS features (pleural line thickness and distance between B-lines) with parameters of spirometry (forced vital capacity [FVC] percent predicted), arterial blood gas (ABG) analysis (pO2 at room air) and 6-min walk test (6MWT) (SpO2 at rest, 6-min walk distance [6MWD] and distance-saturation product [DSP]) were assessed. Since TUS is a noninvasive, radiation-free, and bedside imaging modality, these correlations could help in assessing whether TUS could be used as an imaging modality during follow-up to monitor the progress of ILD.

**MATERIALS AND METHODS**

This was a cross-sectional study involving fifty patients diagnosed with ILD based on history, examination, chest X-ray/HRCT, and spirometry, conducted in the out-patient Department of Tuberculosis and Respiratory Diseases and the Department of Radiodiagnosis and Imaging. The study period extended from September 2017 to June 2019. This study was approved by the Ethics Committee of our Institute. Informed consent was taken before enrolment from all eligible participants.
Inclusion criteria
The patient presenting with both of these:

1. Respiratory symptoms such as shortness of breath and/or cough
2. Bilateral abnormalities in X-ray/HRCT of the thorax suggestive of ILD.

Exclusion criteria
1. Any infectious or malignant diseases
2. Left heart failure
3. Hemodynamically unstable patient
4. Pregnant females.

We enrolled 50 consecutive ILD patients. Twenty controls from volunteering attendants with no symptoms or signs suggestive of respiratory disease and a normal chest X-ray in posteroanterior view were also taken.

All patients were subjected to the following:

1. Clinical assessment – it included symptoms and signs, comorbidities, current or past occupational or hobbies-related exposure, domestic environmental conditions, relevant drug history, and family history.
2. Spirometry was done to assess the pattern and severity of the disease. The ATS/ERS recommended acceptability and reproducibility criteria was followed, such that there were 3 or 2 acceptable readings (Grade A and B) with repeatability within 100 ml or 10% of the highest value, whichever was greater;[12]
3. A posteroanterior chest X-ray was done for all patients. HRCT scanning was performed using Multi-detector row 128-slice CT scanner (Light speed, General Electric Medical Systems, Milwaukee, WI) in the Department of Radiodiagnosis and Imaging, Sir Sunderlal Hospital. 1 mm cuts were taken. CT findings were interpreted by a team consisting of two doctors, each from the Department of Tuberculosis and Respiratory Diseases, and the Department of Radiodiagnosis and Imaging.
4. ABG analysis was performed with a 1 ml blood sample collected in a heparinized syringe from the radial artery.
5. 6MWT was conducted after recording the baseline pulse rate, SpO₂ and dyspnea as per Borg’s scale. Patients were asked to walk for as long as possible along a flat course of 30 m in 6 min at their own pace. If they stopped due to breathlessness or fatigue, they were encouraged to resume walking.

Their pulse rate and SpO₂ were monitored with a pulse oximeter throughout the course of the test, and the lowest pulse rate and oxygen saturation during the test were noted. A fall of SpO₂ by 4%–<89% was considered as significant desaturation. Walking distance was recorded in meters. DSP, given in m%, is defined as the product of the final distance walked in meters and the lowest SpO₂ when breathing air.[13]

Transthoracic ultrasound scans were performed in all the cases and the controls using either Sonoline G20 (Seimens) or Philips IU22 (both equipped with 3.5 MHz curvilinear probes and 7.5–10 MHz linear probe). Subjects were examined in a sitting or supine position with arms raised above their head. Each hemithorax was divided into eight regions with the help of parasternal line, midclavicular line, anterior axillary line, posterior axillary line, and mammary line (extending laterally and posteriorly). Hence, each hemithorax had upper anteromedial, lower anteromedial, upper anterolateral, lower anterolateral, upper lateral, lower lateral, upper posterior, and lower posterior regions. Transducer was oriented either perpendicular or transverse to the chest wall.

Lung parenchyma was examined to look for B-lines. The presence of three or more B-lines between two ribs in two or more regions bilaterally was called B-pattern.[3] Pleura was examined to look for pleural line irregularity (defined as loss of the normal linear pleural contour leading to a fragmented and irregular appearance).[3] pleural line thickenings (focal or diffuse echogenic lesions >3 mm in thickness which arise from either parietal pleura or visceral pleura),[4] subpleural changes (small echo-poor areas beneath the pleural line in the lung parenchyma)[3] and lung sliding (regular rhythmic movement of visceral pleura against the parietal pleura, which can normally be seen as a shimmering line synchronous with respiratory movements).[3]

Statistical analysis
All the collected data were analyzed using SPSS version 16 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Normally distributed numeric data are described as mean ± standard deviation, and nominal data are described as frequency and percentage. Correlation between variables is derived using scatter plots and Pearson and Spearman correlation analysis. P < 0.05 is considered significant.

RESULTS
This study was carried out in 50 patients with ILD. Their ages ranged from 18 to 81 years, with a mean age of

Table 1: Demographic data

| Variables                        | Cases, n (%)  | Controls, n (%) |
|----------------------------------|---------------|-----------------|
| Age (years), mean±SD             | 51.28±14.74   | 50.50±15.50     |
| Sex                              |               |                 |
| Females                          | 26 (52)       | 9 (45)          |
| Males                            | 24 (48)       | 11 (55)         |
| Smoking                          |               |                 |
| Smoker                           | 13 (26)       | 4 (20)          |
| Nonsmoker                        | 37 (74)       | 16 (80)         |
| Significant occupational or domestic exposure (at least 1) |               |                 |
| Present                          | 46 (92)       | 6 (30)          |
| Absent                           | 4 (8)         | 14 (70)         |

1Occupations associated with significant exposures include cattlemaker, farmer, stone blaster, blacksmith, coal mine worker, teacher, carpet maker, and flour mill worker. Domestic exposures were associated with exposure to birds, mold, cooler, air-conditioner, biomass fuel, and visible dust. SD: Standard deviation
51.28 ± 14.74 years [Table 1]. There were 26 (52%) females and 24 (48%) males. The mean age of the 20 controls was 50.50 ± 15.50 years. Among controls, 9 (45%) were females and 11 (55%) were males. Thirteen (26%) out of the fifty patients were smokers and 46 (92%) had at least one significant domestic or occupational exposure. Cough (n = 47, 94%) and breathlessness (n = 46, 92%) were the most common symptoms and bilateral crepitations (n = 45, 90%) was the most common sign [Table 2].

Hypersensitivity pneumonitis was the most common (n = 13, 26%) ILD, followed by connective tissue disease-related ILD (n = 12, 24%), idiopathic pulmonary fibrosis (IPF, n = 8, 16%), pneumoconiosis (n = 4, 8%), sarcoidosis (n = 3, 6%), idiopathic nonspecific interstitial pneumonia (n = 2, 4%), and diffuse alveolar hemorrhage (n = 2, 4%). Pulmonary alveolar proteinosis, eosinophilic pneumonia, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, Langerhans cell histiocytosis and Lymphangioleiomyomatosis were diagnosed in one patient each.

On TUS, B-pattern was present in 40 out of 50 (80%, P < 0.001) patients, pleural line irregularity in 39 (78%, P < 0.001), pleural thickening was present in 28 (56%, P < 0.001), subpleural changes in 22 (44%, P < 0.01) and decreased lung sliding in 22 (44%, P < 0.001) patients [Table 3]. Pleural line irregularity was present in 2 (10%) out of 20 controls, pleural thickening in 1 (5%) and subpleural changes in 1 (5%) control. At least one TUS finding was present in 46 (92%) of the 50 patients and 4 (20%) of the 20 controls. The mean distance between B lines in patients was 5.17 ± 1.94 mm. Mean pleural thickness in cases was 2.99 ± 1.81 mm compared to 1.10 ± 0.57 mm in controls (P < 0.001). The TUS features in different types of ILD in our study are summarized in Table 4.

Increasing pleural line thickness had a statistically significant inverse correlation with FVC percent predicted (r = -0.345, P < 0.05), pO_2 (r = -0.335, P < 0.01), SpO_2 at rest (r = -0.444, P < 0.01), 6MWD (r = -0.554, P < 0.001), and DSP (r = -0.572, P < 0.001) [Table 5 and Figure 1]. Increasing distance between B lines also inversely correlated with FVC percent predicted (r = -0.278), pO_2 (r = -0.207), SpO_2 at rest (r = -0.170), 6MWD (r = -0.209) and DSP (r = -0.214), however these correlations were not statistically significant (P > 0.05).

**DISCUSSION**

There is an unmet need for a reproducible, cost-effective, and radiation-free investigation modality which could be used to diagnose and follow up patients with ILD. When used in an appropriate clinical setting, TUS could help in selecting those patients who need HRCT for diagnosis, effectively avoiding unnecessary radiation exposure in those who are unlikely to have ILD. It could help in avoiding radiation exposure to pregnant females for the purpose of diagnosis also. Furthermore, we have tried to find possible correlations between TUS features (pleural line thickness and distance between B lines) with FVC percent predicted, pO_2 SpO_2 at rest, 6MWD and DSP to assess whether TUS could be used to monitor the disease progression as a noninvasive, radiation-free and bedside imaging modality. This could be extremely helpful in assessing the disease progression in unconscious patients in emergency or intensive care units, and those who are too breathless to perform pulmonary function tests (PFT).

In our study, we found that B-pattern was present in 40 out of 50 (80%) patients, pleural line irregularity in 39 (78%), pleural line thickening in 28 (56%), subpleural changes in 22 (44%) and decreased lung sliding in 22 (44%) patients. Reissig and Kroegel conducted TUS in 53 patients with ILD and reported B-lines in 98.1%, irregular pleural line in 98.1%, and subpleural alterations in 37.7% of patients [Table 6]. Said and Sayed found B-lines in 73.8% of their 42 patients with ILD, irregular pleura in 47.6%, thickened pleura in 35.7%, subpleural lesions in 38.1%, and abolished lung sliding in 23.8%. Mansour et al. examined 40 patients with IPF and reported that 100% of patients had B-lines, 85% had pleural irregularity, 77.5% had pleural thickening, subpleural lesions in 7.5%, and absent lung sliding in 17.5%. Hasan and Makhloff reported B lines in all of their 61 patients with ILD. In 84 patients with pulmonary fibrosis, Sperandeo et al. found irregular thickening of the pleural line in 100% patients, subpleural cysts in 68%, and reduction or absence of gliding sign in 39% patients. Targhetta et al. found...
In fact, pleural

\[ r = -0.664, \quad P < 0.001 \]

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correlation between increasing distance between B-lines and FVC percent predicted. In the current study, we also found that increasing distance between B-lines inversely correlated with FVC percent predicted, \( \text{pO}_2 \), at room air, \( \text{SpO}_2 \) at rest, 6MWD, and DSP [Table 4], however, these correlations were not statistically significant. Mansour et al. have also reported a statistically insignificant negative correlation of distance between B-lines with \( \text{FVC} \), and \( \text{Pao}_2 \). Gayserini et al. monitored 41 patients with Systemic sclerosis-related ILD for 1 year and found that the number of B-lines increased with worsening of ILD based on HRCT score, DLCO, and progression of digital microvascular damage.

Table 4: Transthoracic ultrasonography findings in different types of interstitial lung disease in our study

| Table 5: Correlation between transthoracic ultrasonography findings and forced vital capacity percentage predicted, \( \text{pO}_2 \), \( \text{SpO}_2 \) at rest, 6-min walk distance and distance-saturation product |

| Pleural line thickness | Distance between B lines |
|-----------------------|--------------------------|
|                       | FVC percent predicted    | \( r \) | \( P \) | \( r \) | \( P \) |
|                       | \( -0.345 \) | <0.05 | -0.278 | 0.118 |
| \( \text{pO}_2 \) at room air | -0.335 | <0.01 | -0.207 | 0.119 |
| \( \text{SpO}_2 \) at rest | -0.444 | <0.001 | -0.170 | 0.294 |
| 6MWD                  | -0.554 | <0.001 | -0.209 | 0.336 |
| DSP                   | -0.572 | <0.001 | -0.214 | 0.333 |

DSP: Distance-saturation product, 6MWD: 6-min walk distance, FVC: Forced vital capacity

that irregular pleural surfaces and B-lines were present in all their 12 patients with Sarcoidosis.

While Reissig and Kroegel defined B lines as the presence of 6 comet tail artifacts per scan such that a scan comprised of examination of all the ventral and posterior rib spaces, Mansour et al. defined a positive scan as the presence of more than 3 B-lines in one region such that each hemithorax was divided into six regions. The criteria for a positive examination of B-lines by Hasan and Makhlouf was the same criteria that we have reported as B-pattern. Since focal B-lines can be present in other diseases such as pneumonia, atelectasis, cancer, and infarction, we have reported our findings as B-pattern. Differences in the definition of a positive scan for B-lines and the differences in the type of ILD in the study population may be the reason for the varying results in different studies. If we consider only the small number of patients with IPF in our study (\( n = 8 \)), their TUS findings are comparable with those of Sperandeo et al. and Mansour et al. [Tables 4 and 6].

Hasan and Makhlouf have reported that the distance between B lines correlates inversely with FVC (\( r = -0.848, \quad P < 0.001 \)), total lung capacity (\( r = -0.664, \quad P < 0.001 \)) and DLCO (\( r = -0.817, \quad P < 0.001 \)). Similarly, Said and Sayed had also reported a negative correlation between increasing distance between B-lines and FVC percent predicted. In the current study, we also found that increasing distance between B-lines inversely correlated with FVC percent predicted, \( \text{pO}_2 \), at room air, \( \text{SpO}_2 \) at rest, 6MWD, and DSP [Table 4], however, these correlations were not statistically significant. Mansour et al. have also reported a statistically insignificant negative correlation of distance between B-lines with \( \text{FVC} \), and \( \text{Pao}_2 \). Gayserini et al. monitored 41 patients with Systemic sclerosis-related ILD for 1 year and found that the number of B-lines increased with worsening of ILD based on HRCT score, DLCO, and progression of digital microvascular damage.

Pinal-Fernandez et al. have reported that pleural irregularity has a higher diagnostic value for detecting ILD than B-lines. Manolescu et al. found a positive correlation between pleural line thickness and HRCT fibrotic score. In the current study, there was a statistically significant inverse correlation of increasing pleural line thickness with FVC percent predicted, \( \text{pO}_2 \), \( \text{SpO}_2 \) at rest, 6MWD and DSP [Table 5 and Figure 1]. In the study conducted by Mansour et al., there was a significant increase in the percentage of patients with irregular pleura, thickened pleura, and reduced lung sliding with increasing severity. In fact, pleural irregularity was found to be a sensitive tool to detect early sub-clinical lung alterations in patients with systemic sclerosis by Ferro et al.

Limitations

Our study has some limitations. No sample size determination was done before the study, and 50 patients and 20 controls were chosen arbitrarily by convenience sampling. The TUS was performed on patients who were already diagnosed with ILD based on clinical features, PFT and HRCT. The diagnosis was confirmed with a biopsy in only 30% of our patients. Blinding of the TUS operator was not done. The study was conducted at a referral center. However, this study was not designed to evaluate the diagnostic accuracy of TUS, but to assess the utility...
Strengths
This is probably the first study of its kind in our population. TUS findings were correlated with parameters of 6MWT, which might be closest to the functional limitations of the patient. Pleural line thickness has been shown to be a marker of disease severity, probably for the first time.

CONCLUSION
TUS is a useful imaging method for the diagnosis of ILD. The presence of B-pattern, pleural line irregularities, pleural line thickening, decreased lung sliding, and subpleural changes can be used to diagnose ILD in an appropriate clinical setting. It can help in selecting those patients who need an HRCT, effectively ruling out ILD, and avoiding unnecessary radiation exposure who are not likely to have the disease.

TUS can also be used to estimate the severity of the disease. It is a simple, bedside, cost-effective, and radiation-free imaging modality which can prove to be useful in low resource settings where CT machines cannot be installed. TUS could avoid repeated radiation exposure while monitoring the patient. It is especially useful when HRCT cannot be done in a patient too sick to be shifted to the radiology suite or during pregnancy and when the patient is too breathless to perform PFT during follow up.

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Conflicts of interest
There are no conflicts of interest.

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