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Transthoracic ultrasonography in the assessment of interstitial lung disease in patients with systemic sclerosis

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ABSTRACT

Background: Transthoracic ultrasonography was considered, sometimes in the past as unsuitable for the assessment of lung but it eventually emerged as an important tool in the diagnosis and in guiding treatment of various lung and pleural diseases. Several studies in the past proved it to be a useful complementary tool in the detection of interstitial pulmonary fibrosis. **Aims and Objectives:** This study aims to assess the utility of transthoracic uultrasonography (TUS) in comparison to high-resolution computed tomography (HRCT) thorax in the detection of interstitial lung disease (ILD) in systemic sclerosis (SSc) patients. **Materials and Methods:** SSc patients with HRCT proven ILD were identified and classified according to Warrick's score. Sonographic evidence of ILD in these patients were judged by the presence of B-lines or ultrasonic lung comets (ULCs). Each procedure was studied and interpreted by two independent examiners blinded about the patient's clinical and radiological features. Standard spirometric measurements were performed in all patients. **Results**: A highly significant positive linear correlation between ULCs and Warrick's score was found in this study ($r = 0.83$, $P \leq 0.001$). ULC score had moderate negative correlation with forced expiratory volume in 1 s (FEV1) % p ($r = -0.60$, $P = 0.001$) and weak negative correlation with forced vital capacity (FVC) % p ($r = -0.45$, $P = 0.01$) and FEV1/FVC % ($r = -0.42$, $P = 0.02$). **Conclusion**: USG lung can be suggested as a useful non-invasive tool in the detection of ILDs in scleroderma patients.

Key words: Lung ultrasonography; Interstitial lung disease; Systemic sclerosis; B-lines; Ultrasound lung comets; Warrick's score

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INTRODUCTION

Interstitial lung disease (ILD) is an important complication of connective tissue diseases (CTDs) causing high morbidity and mortality. Scleroderma, among the CTDs is a leading cause of ILDs.[1] Patients with ILDs present with progressive exertional breathlessness and/or cough and can be suspected on the basis of an abnormal Chest X-ray. However, chest X-ray is relatively insensitive for early detection of ILDs. Pulmonary function tests (PFTs), showing restrictive defect aids in diagnosis. High-resolution computed tomography (HRCT), considered the gold standard is more useful for early detection and confirmation of suspected ILDs.[2-5] Lung ultrasonography emerged as a corroborative and complementary tool in the detection of interstitial pulmonary fibrosis as evidenced by several studies conducted in the last decades.[6-10]

Lung ultrasonography (LUS), sometimes in the past was considered unsuitable for the study of lung diseases because of the attenuating effect of air and bone on the propagation of ultrasound beam but eventually came out to be a useful tool in the diagnosis and in guiding treatment of various lung and pleural diseases.[7] In a sonogram of a normal lung,

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the chest wall representing the muscle and facial planes appear as a series of echogenic soft-tissue layers, the ribs appear as curvilinear or convex hyperechoic lines when the chest is scanned along the long axis[11] (Figure 1a).

A horizontal hyperechoic line, about half a centimeter below the rib line, is the pleural line (Figure 1a). Beyond the pleural line, the lung is represented by a zone of artefact with hyperechoic horizontal lines or A lines, spaced at constant intervals, indicating multiple reflections of the pleural line (Figure 1a).[11,12] The visceral and parietal pleurae, normally closely opposed with a minute amount of fluid in between, slide over one another with respiration and produce artefacts (white or black lines a few millimeters below the pleural line). known as lung sliding.[6] The ultrasonic hallmark of ILD is B-lines or ultrasonic lung comets (ULCs). B-lines are long, discrete, hyper echoic vertical artifacts arising from the pleural line and extending to the bottom of the screen without fading. They look like comet tails, erase the A-lines and move with lung sliding.[7-9] They are generated by the reflection of the ultrasonic beam from thickened subpleural interlobular septa with water or fibrosis and are detectable when the lung is probed in between the intercostal spaces[6,12,13] (Figure 1b).

The normal lung contains mostly air and little water and there is no reflection of the ultrasonic beams and B-line is not expected to appear except in old ages.[13] The presence of bilateral pathological B-lines (≥3 in USG images between two ribs) is indicative of "interstitial syndrome and can be observed in conditions such as cardiogenic pulmonary edema, acute or chronic ILDs, or acute respiratory distress syndrome.[13-15] Patients history, clearance of B lines with diuretics in serial sonographic examinations will differentiate lung fluid accumulations from fibrotic conditions.[14-16] The lung ultrasonography (LUS) signs suggestive of ILD are pleural line abnormalities (such as irregularities, fragmentations, and thickening), subpleural abnormalities (small echo-poor areas), and the non-homogeneous and bilateral distribution of B-lines.[15]

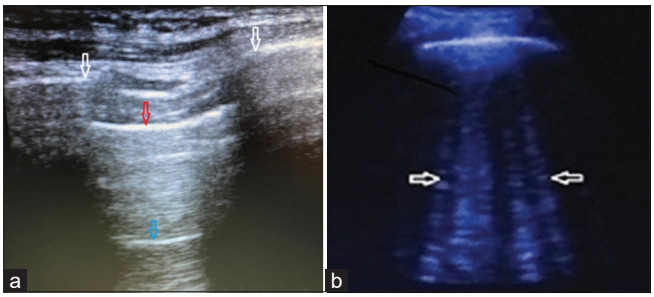

Figure 1: (a) USG lung showing the upper and lower ribs (upper white arrows), the pleural line (red arrow). The A-line (lower green arrow) is the repetition of the pleural line. (b) Showing B-lines or ultrasonic lung comets (white arrows)

Aims and objectives

This study aims to find out the utility of lung ultrasonography (LUS) compared to HRCT chest in identifying and quantifying ILD in systemic sclerosis (SSc) patients.

MATERIALS AND METHODS

Study design

This was a cross-sectional study carried out over a period of 1½ years (February 2014–August 2015) in the department of medicine and rheumatology in a tertiary care hospital, Kolkata.

Ethical clearance and approval

The study was approved by the "Research Oversight Committee (Institutional Ethics Committee), IPGME & R, Kolkata," Ref. No Inst/IEC/460, Dated January 11, 2014. Written informed consents were taken from all the studied patients after getting them assured the anonymity and confidentiality of the study.

Inclusion criteria

SSc patients as per the American College of Rheumatology classification criteria were included in the study.

Exclusion criteria

Patients with CTDs other than SSc, SSc patients without ILD, with pregnancy or with heart failure, and those who refused to participate were excluded from the study.

HRCT Thorax

Chest HRCT was performed by standard protocol. Scans were obtained in full inspiration from the lung apex to the base with the patient in the supine position. The scan was taken in sequential mode with 1 mm collimation, 10 mm interval, 180–260 mA average tube current (depending on body builds), and 120–140 kV tube voltage. No intravenous contrast material was used. Pulmonary interstitial fibrosis was identified and categorized as per Warrick' score (Table 1). The total HRCT Warrick score was obtained by taking into account the type of lung parenchymal and pleural alterations and the number of segments involved ("severity score" and an "extent score") and summing up the point values thereof (range 0–30 total; 0–15 for each lung).[17] The calculated score was expressed as normal - 0 point, mild <8, moderate 8–15, and severe >15 points.[18] Two radiologist conversant with HRCT Warrick's score worked up the values separately, both being blinded to the clinical, PFT, and X-ray Chest findings. The agreement between the two readers was strong (Kappa 0.81) and the final Warrick's score was worked out by consensus.

Chest ultrasonography

This was performed preferably within 7 days following the HRCT scan by using 2.5–5 MHz convex probe

Table 1: Warrick's score

Severity score		Extent score	
Lung parenchymal alteration	**Grading**	**Bronchopulmonary segments involved**	**Grading**
Ground glass opacities	1	1–3 segments	1
Irregular pleural margin	2	4–9 segments	2
Septal or subpleural lines	3	>9 segments	3
Honeycombing	4		
Subpleural cyst	5		

and 7.5–10 MHz linear probe to visualize lung and pleura. Patients were examined in the supine and sitting position on a series of scan lines along the chest wall in accordance with a simplified method.[18] For the anterior chest 2nd intercostals space (ICS) on the parasternal line, each 4th ICS on the midclavicular, anterior axillary, and mid axillary lines, and for the posterior chest 8th ICS on the paravertebral, subscapular, and on posterior axillary line - total 14 reference points on both sides combined (7 sites on each side) were scanned.

Sonographic evidence of ILD was judged by the presence of ULCs (B-lines). Three or more ULCs in between rib spaces were taken as pathological. The complete absence of ULCs in all scanning sites combined was taken as zero score. A total of ≥10 ULCs taking all scanning sites together was considered suggestive of the presence of ILD. The full white screen on a single scanning site was considered as corresponding to 10 ULCs.[7]

A radiologist experienced on USG lung, blinded to the patient's clinical data, PFT and HRCT features, carried out the examination. To evaluate interobserver variation the USG lung was repeated on the same day by a USG lung-trained rheumatologist, also unaware of the patients clinical and radiological data, and the interobserver agreement was found good (Kappa 0.77).

PFT: Standard spirometry measurements were performed in all patients by means of a computerized spirometric system. The results were expressed as percentages of the predicted values.

Statistical tools

Statistical analysis was carried out with Epi Info TM 3.5.3 statistical software (CDC). Categorical data were expressed in numbers and frequencies (percentage) and quantitative data were presented as mean±standard deviation (SD). Chi-squared (χ^2) test was used to compare categorical or qualitative variables and Student's *t* test was used to compare quantitative or continuous variables. Pearson's correlation coefficient was calculated to measure the correlation between different variables. P≤0.05 was taken as statistically significant.

RESULTS

Thirty SSc patients with a mean age of 33.20 (SD 8.09) years were enrolled for the study (Table 2).

The male: female ratio was 1:5. All the male and 80% of female patients were <40 years. The mean age of the patients of diffuse cutaneous SSc (dcSSc) type was 33.22 (SD 7.74) years and that of limited cutaneous (lcSSc) one was 33.17 (SD 10.21) years with no significant difference in age distribution.

ULC score ≥10, considered suggestive of ILDs were present in 23 (77%) patients with the mean ULC score 13 (SD 2.04) and <10 ULCs were present in the rest 7 (23%) patients with a mean ULCs score 8.57 (SD 0.53) (P≤0.001).

Five patients (16.7%) had Warrick score ≤8 (mild ILD), 22 (73.3%) patients had 9–15 (moderate ILD) and 3 (10.0%) patients had Warrick score >15 (severe ILD). When Warrick's score was categorized with respect to the presence of <10 and ≥ 10 ULCs, the mean Warrick score in the corresponding patients were 8.29 (SD 1.70) and 13.04 (SD 2.20) respectively and a highly significant positive linear correlation between ULCs and Warrick's score and vice versa was observed (r=0.83, P≤0.001) (Figure 2).

The clinical, immunological, and other parameters with respect to ULC class of the patients were also categorized and compared and the difference was found significant with most of the variables (Table 3).

The ULC scores in diffuse SSc were significantly more than that of localized type (12.5 SD 2.58 vs. 9.83 SD 2.17, P=0.03). With regard to PFT parameters Warrick's score had a moderate negative correlation with forced expiratory volume in 1 s (FEV1) % p (r=−0.74, P≤0.001) and forced vital capacity (FVC) % p (r=−0.64, P≤0.001) and no correlation with FEV1/FVC % (r=−0.25, P=0.18). In comparison ULC score had moderate negative correlation with FEV1 % p (r=−0.60, P≤0.001) and weak negative correlation with FVC % p (r=−0.45, P=0.01) and FEV1/FVC % (r=−0.42,

Table 2: Patients profile

Total no. of patients	Male	Female	Total
	5 (16.7%)	25 (83.3%)	30 (100%)
Age (Years)	**All Patients**	**Male**	**Female**
Mean±SD	33.20±8.09	29.00±2.23	34.04±8.59
Range (Min.–Max.)	25–60	26–32	25–60
Median	30.0	29	32
Duration of disease (months)	**Mean±SD**	**Range (Min.–Max.)**	**Median at presentation**
	14.23±9.43	6–48	12
No of patients with smoking	**Present**	**Absent**	**Total**
	5 (16.7%)	25 (83.3%)	30 (100.0%)
Male	3	2	5
Female	2	23	25
Type of SSc	**Diffuse**	**Limited**	**Total**
	24 (80.0%)	6 (20.0%)	30 (100.0%)
	Positive	**Negative**	**Total**
ANA status	28 (93.3%)	2 (7.7%)	30 (100.0%)
Scl 70	24 (80.0%)	6 (20.0%)	30 (100.0%)
	Mean	**Range**	**Median**
FEV1% p	47.6±9.43	32–67	46.0
FVC % p	46.70±9.07	30.0–65	46.0
FEV1/FVC %	89.13	75–98	89.5
ULCs	11.96±2.61	8–17	12.0
Warrick's score	11.93±2.91	5–16	12.0

SSc: Systemic sclerosis, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, ULCs: Ultrasonic lung comets, SD: Standard deviation

Table 3: Clinical, immunological and other parameters in respect of ULC class

Characteristics/Variable	ULCs <10 (n=7)	ULCs ≥10 (n=23)	P-value
Age in years (Mean±SD)	35.29±8.0	32.57±7.12	0.45
Female - n (%)	7 (23%)	18 (60%)	<0.001
Male - n (%)	0 (0.0%)	5 (17%)	<0.001
Duration of disease in months (Mean±SD)	10.57±4.1	15.43±10.29	0.24
Smoker - (%)	0 (0.0%)	5 (17%)	<0.001
Diffuse cut, SSc - n (%)	4 (13%)	20 (67%)	<0.001
Limited cut, SSc - n (%)	3 (10%)	3 (10%)	0.02
ANA positive - n (%)	5 (83.33%)	23 (95.83%)	<0.001
Scl positive - n (%)	3 (12.5%)	21 (87.5%)	<0.001
FEV1- % predicted (Mean±SD)	56.86±6.0	44.78±8.34	<0.001
FVC - % predicted (Mean±SD)	53.14±5.3	44.74±9.12	0.01
FEV1/FVC %(Mean±SD)	92.71±3.4	88.04±6.39	0.02
Warrick's Score	8.29±1.70	13.04±2.20	<0.001

SSc: Systemic sclerosis, FEV1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, ULC: Ultrasonic lung comet, SD: Standard deviation

P=0.02). The relation of ULCs with the duration of the disease was not significant (r=0.21, P=0.27) in this study. Three males and two females, in total 5 out of 30 (16.7 %) patients were smokers. All the SSc patients who were smoker had >10 ULCs suggesting smoking may be a contributory factor of ILD in SSc patients.

DISCUSSION

USG lung is widely used nowadays as a non-invasive diagnostic modality and as a guide to invasive diagnostic and therapeutic procedures in pleural and lung parenchymal diseases especially located adjacent to pleura.[5] The utility of this tool in the assessment of ILD was studied by several investigators in the past.[7-10] We studied the diagnostic yield of lung ultrasonographic B-lines in comparison with Chest HRCT-Warrick's Score in identifying and quantifying pulmonary fibrosis in SSc patients and found a highly significant positive linear correlation between ULCs and Warrick's score (r=−0.83, P≤0.001).

Gargani et al., carried out one of the pioneering studies evaluating the role of USG in SSc patients and found ULCs were well correlated with HRCT-derived assessment of lung fibrosis. Taking ≥10 ULC score as an indication

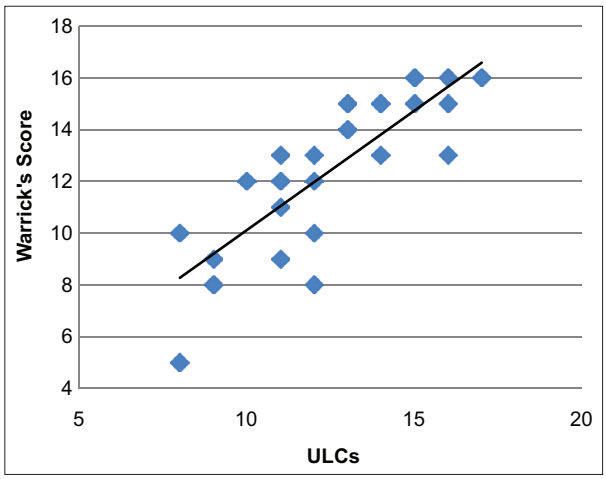

Figure 2: Scatter plot with trend line illustrating correlation between ultrasonic lung comets and Warrick scores

of ILD they found a significant positive linear correlation between ULC score and Warrick's score (r=0.72, P≤0.001) and concluded that USG lung could be a simple bedside, radiation-free hallmark of pulmonary fibrosis of potential diagnostic and prognostic value. The higher numbers of ULCs in the diffuse form of SSc than in the limited form as observed by them was similar to our findings corroborating the fact that dcSSc compared with lcSSc subgroup had a higher prevalence of ILD.[7]

Tardella et al., observed that lung ultrasonography (LUS) was a valuable diagnostic tool for SSc ILD and might represent an important referral model. The presence of a LUS score more or equal to 10 B lines was predictive of the presence of significant SSc ILD. The use of LUS as the first imaging tool in the evaluation of SSc patients might represent an effective model to improve the correct timing of HRCT assessment.[19]

ULCs or B-lines, the ultrasonic hallmark of ILD were generated by the reflection of the US beam from thickened interlobular septa especially from the subpleural lung parenchyma.[6,12,13] As the subpleural region was the site first affected in SSc ILD, USG chest could be a suitable noninvasive diagnostic modality in the early detection of ILD in SSc patients.[20]

Sometimes in the past, USG lung was performed in more than 50 intercostal sites (detailed or classic USG).[7,8,13,20] Gutierrez et al., carried out both detailed and simplified USG (14 intercostal spaces) and found positive correlation between B lines assessed by both methods and HRCT Warrick score (simplified USG vs. Warrick Score, P=0.0006) and between classic ultrasound (US) and simplified US (P=0.0001) in the assessment of lung fibrosis in CTDs.[18]

In this study, we used a simplified USG method and took a cutoff value of ≥10 ULCs for the presence of lung fibrosis.[7,19]

Barskova et al., noted that even when HRCT failed to detect anything suggestive of ILD, USG was found to be useful and concluded that USG lung was more sensitive than HRCT in the detection of ILD in early stage of SSc. As per their study the sensitivity, specificity, positive predictive value and negative predictive value of USG lung were 72%, 88%, 100% and 78%.[10]

Lichtenstein et al., Bouhemad et al., and Hasan and Makhlouf found that B-lines appeared clearly visible and widely separated from each other (7 mm) in the patients with well-established fibrosis showing reticular pattern or honeycombing in HRCT whereas B-lines with a narrow distance between those (3 mm) corresponded with the early alveolar-interstitial or ground glass state in HRCT and concluded that distance between two adjacent B-lines correlated with the degree of interstitial affection on chest HRCT (Warrick score).[21-23]

With regard to PFT parameters, we found ULCs had a moderate negative correlation with FEV1 % p and weak negative correlation with FVC % p and FEV1/FVC %. Warrick's score had nearly the same relations with those entities, a moderate negative correlation with FEV1% p and FVC % p, and no correlation with FEV1/FVC %.

Gutierrez et al., found a strong negative correlation between LUS score (ULCs) with diffusion capacity of the lung for carbon monoxide (DLCO) (r=−0.60, P<0.001). moderately negative with FVC (r=−0.51, P=0.001) and weak negative correlation with FEV1 (r=−0.44, P=0.005),[18] almost similar findings were observed by Ebru et al., showing that USG B lines were negatively correlated with DLCO (r=−0.56, P=0.0001) and FVC (r=−0.46, P=0.001).[24]

Limitations of the study

(i) The study was carried out among a small number of patients, (ii) SSc patients already diagnosed with ILD on the basis of HRCT chest might have a chance of uncalled-for bias on LUS findings, (iii) DLCO and total lung capacity were not measured, (iv) The sonographic reading was qualitative and might have potential of subjective variations.

CONCLUSION

USG lung is an effective method in the evaluation of pulmonary fibrosis with a potential clinical impact in view of the fact that it is a non-invasive, low-cost modality with no radiation effect. The presence of 10 or more ULCs or

B-lines are predictive of the presence of significant SSc-ILD. We propose that transthoracic USG may be used as a complementary tool along with PFT and HRCT in the management of ILD patients.

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Author's Contribution:
SSD- Implementation of study protocol, data collection, data analysis and preparation of first draft of manuscript; **SK-** Concept, study design, clinical protocol, manuscript preparation; **MKD**- Concept, manuscript revision and editing; **ACR-** Concept, study design and literature review**,** final preparation and critical revision of manuscript, submission of article; **KM-** manuscript revision, data analysis and interpretation; **PG-** Co-ordination and manuscript revision.

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