Original Article

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Lung Ultrasound in Diagnosis of Interstitial Lung Disease

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ABSTRACT

Background: Interstitial lung disease denotes a group of disorders which mainly affects pulmonary interstitium consisting of connective tissue fibers that support the lungs. High-resolution computed tomography is currently the main imaging modality of diagnosis, however except for few major cities in the country, availability of computed tomography scan facility is sparse in remote areas; thus relevant use of lung ultrasound in patients with suspected interstitial lung disease could be rewarding.

Methods: A single center cross-sectional clinical diagnostic study was carried out at department of Radiology and Imaging, Patan Academy of Health Sciences after approval from institutional review committee. Lung ultrasound was done prior to patients undergoing high-resolution computed tomography chest. Senstivity, specificity, positive predictive value , negative predictive value , and accuracy of different echographic criteria–positive chest area score, total B lines score 5 and total B lines score 10 were calculated. Association of non-homogeneity of B lines and pleural line abnormalities with presence of interstitial lung disease, and association between B3 and B7 lines with alveolar and interstitial pattern were derived.

Results: Sensitivity (97.4%) and negative predictive value (97.9%) of total B lines score 5 was the highest. Maximum specificity (70.7%), PPV (61.4%) and accuracy (77.2%) was ofpositive chest area score. Pleural line abnormalities showed highly significant association with interstitial lung disease($p=0.003$). B3 and B7 lines illustrated very highly significant association with alveolar and interstitial pattern respectively ($p<0.001$).

Conclusions: Lung ultrasound can be a valid and reliable additional imaging method in evaluation of ILD in appropriate clinical scenario.

Keywords: B lines; high-resolution computed tomography; interstitial lung disease; lung ultrasound

INTRODUCTION

Interstitial lung disease (ILD) denotes a group of disorders which mainly affects pulmonary interstitium consisting of connective tissue fibers that support the lungs.[1]Sonographic appearance of ILD is characterized by presence of multiple diffuse bilateral B lines.[2] Various studies worldwide have demonstrated high sensitivity and negative predictive value, ranging from 80 to 100%, of lung ultrasound (US) in diagnosing ILD as compared to High-resolution computed tomography (HRCT) chest.[3,4]Few research have been carried out in Nepal about diagnostic utility of lung ultrasound in ILD, though presence of B lines have been mentioned in interstitial lung syndrome.[5]

HRCT is currently the main imaging modality of diagnosis of ILD.[1]Availability, easy for carrying out, inexpensive and free of ionizing radiation are advantages of lung US over computed tomography (CT) scan.

This study aims to assess whether and to what extent lung US can correctly identify ILD in patients with HRCT diagnosed ILD.

METHODS

This was a single center cross-sectional clinical diagnostic study carried out at department of Radiology and Imaging, Patan Academy of Health Sciences (PAHS) from January to December 2020.The study was commenced after approval letter was received from institutional review committee of PAHS; IRC reference number PMR2001031334.

A written informed consent was taken with patients. While performing lung ultrasound of female patients, one of the female staffs in the department was present

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as a chaperone during the whole period.

All patients aged 18 years or more, coming for HRCT chest at department of Radiology and Imaging, PAHS were enrolled in the study. Patients with known lung cancer and those undergoing HRCT chest for metastatic workup were excluded.

Using the sample size calculation formula $Z_\alpha^2 p(1-p)/d^2$; and taking sensitivity of lung ultrasound in diagnosing ILD as 92% as mentioned by Vizioli L et al. in 'Integrated Use of Lung Ultrasound and Chest X-Ray in the Detection of Interstitial Lung Disease'[4] and considering Z_α 1.96 at 95% confidence interval and margin of error 5%, the required sample size of the study was calculated to be 114 (113.09).

Consecutive sampling of first 114 patients who came for HRCT chest in the department of Radiology and Imaging, PAHS starting from October 2019 was done.HRCT chest reportings were done by consultant radiologists who were blinded to the prior lung US.

Philips Affiniti 50 ultrasound machine was used to carry out lung ultrasounds. Curvilinear probe of 2-6 MHz frequency was used for analysis in 2D B-mode with tissue harmonics and preset sonographic penetration of 14 cm depth.Total of 24 chest areas were analyzed in every patient; 12 in each side (Figure 1).

For each area, the observer recorded presence and number of B lines. B lines are defined as a type of reverberation artifact secondary to reflection of sound waves at the interlobular septa, which have distinct characteristics of being vertical, strongly hyperechoic, laser-like, with sharp margins and originating at the pleural line and extending to the edge of the ultrasound screen.[2] If B lines were present, interspace distance between the B lines were also measured, and were classified as B7 lines (B lines that are 7 mm apart) and B3 lines (B lines that are apart 3 mm or less). In conditions when both B3 and B7 lines were present, the predominant pattern was recorded. The B line sonographic pattern (homogeneous or heterogeneous), and the presence and characterization of pleural line abnormalities (fragmentation, irregularity, swelling, and subpleural consolidations) were also evaluated. These evaluations are particularly fundamental for differentiating acute pulmonary edema (bilateral B lines with a homogeneous pattern but without pleural abnormalities) from ILD.

In this study, three different diagnositc criteria in lung ultrasound were used for ILD which were as follows; Positive Chest Area Score (PCAS): Considering lung ultrasound to be positive for ILD if ≥5 B lines were present in ≥3 chest areas (not necessarily contiguous ones), Total B lines score 5 (TBLS 5): Considering lung ultrasound to be positive for ILD if ≥5 B lines were present in the entire thoracic surface, and Total B lines score 10 (TBLS 10): Considering lung ultrasound to be positive for ILD if ≥10 B lines were present in the entire thoracic surface. If there was complete white out area of the lung, all these scorings were considered as positive.

Philips Multislice CT scan Ingenuity Core 128 was used to carry out HRCT of the chest. All the examinations were performed with patients in supine position with both arms raised over the head, during a deep inspiratory breath hold, and without intravenous injection of a contrast agent.Volumetric acquisition of axial cross sectional imaging of the chest was obtained with standard parameters used as follows: slice thickness of 0.625 mm, rotation time of 0.8 seconds, 140 Kilo-voltage (kV), 300 milli-ampere second (mAs), collimation of 1.5-3 mm, matrix size of 768 x 768 and field of view (FOV) of 35 cm. Post processing with high spatial frequency reconstruction algorithm was carried out for HRCT images.Reportings were done by assessment in lung window with window level (WL) of -600 and window width (WW) of +1600 as well as mediastinal window (WL +60; WW +350). Presence or absence of ILD was diagnosed in HRCT by consultant radiologists.Alveolar or interstitial pattern of involvement was also noted. In cases where both alveolar and interstitial patterns were present, the predominant pattern was taken into consideration.

Data entry was carried out in Epi-Info version 7.2.2.6 and analysis was done in EZR version 1.36, both of which were licensed freeware.Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of lung US in diagnosing ILD were calculated with HRCT chest as the gold standard investigation along with comparision between different echographic diagnostic criteria (PCAS, TBLS 5 and TBLS 10). Minimum number of B lines required for greatest positive likelihood ratio for the presence of ILD was also calculated. Association of non-homogeneity of B lines and pleural line abnormalities with presence of ILD in HRCT in patients with positive B lines in lung ultrasound was done. Association between B3 and B7 lines with alveolar and interstitial pattern of ILD in HRCT was also calculated. Fischer's exact test was used for measure of association with p value$\leq$0.05 taken as significant, $\leq$0.01 taken as highly significant and $\leq$0.001 taken as very highly significant.

RESULTS

Total of 114 patients were enrolled in the study among which 64(56.1%) were female and 50(43.9%) were male. ILD was diagnosed in HRCT chest in 39(34.2%) cases. Median age of patients enrolled in the study was 56 years. Median age of patients with ILD was 62 years and those without ILD was 50 years. B lines were seen in 91(82.4%)out of total 114 patients enrolled in the study (Figures 2 and 3).

Sensitivity and NPV of all these echographic criteria were found to be higher than specificity and PPV (Table 1). Sensitivity and NPV of TBLS 5 was the highest which was 97.4% and 97.9% respectively. PCAS criteria was found to be the most specific with value of 70.7%. The highest PPV of 61.4% and overall accuracy of 77.2% was for PCAS.Based on the confidence interval method of analysis, there was no statisically significant difference in sensitivity, specificity, PPV, NPV or accuracy of these echographic criteria of lung ultrasound. There were 22 false positive cases which were diagnosed as ILD by lung sonography using PCAS criteria. On HRCT imaging, these 22 cases comprised of 13 cases of infective etiology including four cases of pulmonary tuberculosis, three cases of lung fibrosis and pulmonary edema each, two of acute respiratory distress syndrome (ARDS) and one solitary case of pleural thickening.

Median number of B lines in patients with ILD in HRCT was 17 (IQR 13-20) and those without ILD in HRCT was 4 (IQR 0-11), p<0.001. Receiver operating characteristic curve (ROC) analysis was used to confirm the analytical relationship between the number of B lines and the presence of ILD at HRCT (Figure 4). It showed that presence of 11 sonographic B lines was the cut-off point with the greatest positive likelihood ratio for presence of ILD (AUC=0.84, 95%CI 0.77-0.92, p<0.001).

Table 1. Concordance table for different echographic criteria of lung ultrasound and HRCT chest in detection of interstitial lung disease.

Lung ultrasound		ILD in HRCT		Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive		Negative					
	n = 39		n = 75					
PCAS	Positive	35	22	89.7 (75.8-97.1)	70.7 (59.0-80.6)	61.4 (47.6-74.0)	93.0 (83.0-98.1)	77.2 (68.4-84.5)
	Negative	4	53					
TBLS 5	Positive	38	28	97.4 (86.5-99.9)	62.7 (50.7-73.6)	57.6 (44.8-69.7)	97.9 (88.9-99.9)	74.6 (65.6-82.3)
	Negative	1	47					
TBLS 10	Positive	35	23	89.7 (75.8-97.1)	69.3 (57.6-79.5)	60.3 (46.6-73.0)	92.9. (82.7-98.0)	76.3 (67.4-83.8)
	Negative	4	52					

Sensitivity, specificity, PPV, NPV and accuracy are expressed as percentage (%).Values in parenthesis denote 95%CI. PCAS-Positive Chest Area Score; TBLS 5-Total B Lines Score more than 5; TBLS 10-Total B Lines Score more than 10.

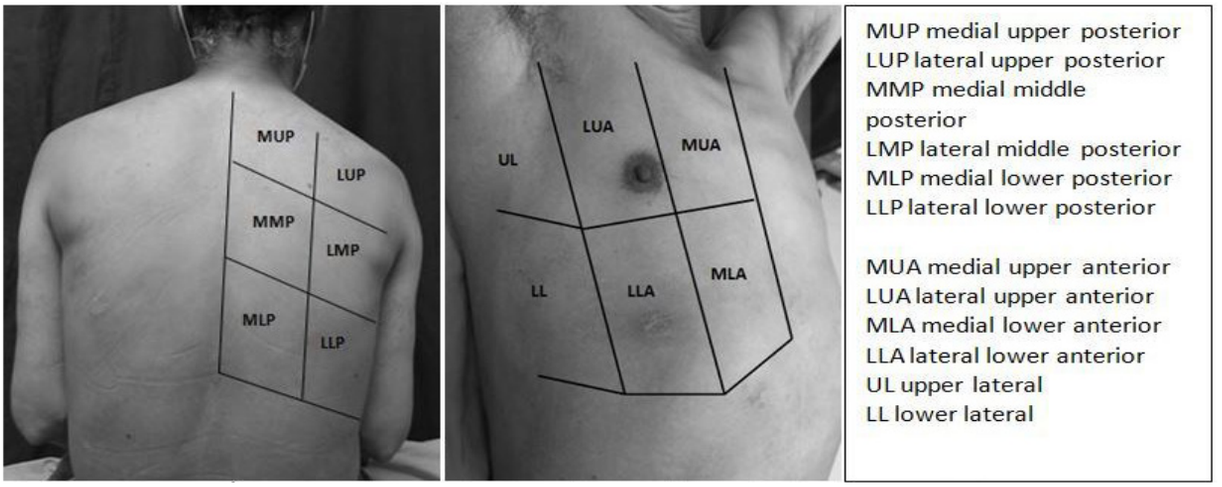

Figure 1. Division of anterolateral and posterior hemithorax (lung fields) into total of 12 ultrasound scan areas each.

Figure 2. B lines in lung sonography with corresponding HRCT image showing bilateral basal honeycombing in usual interstitial pneumonia type ILD.

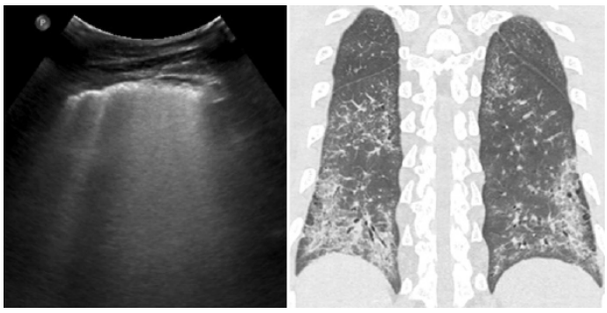

Figure 3. B lines along with white-out appearance in lung sonography with corresponding coronal reformatted HRCT image showing ground glass areas with subpleural sparring in bilateral basal segments in non-specific interstitial pneumonia type ILD.

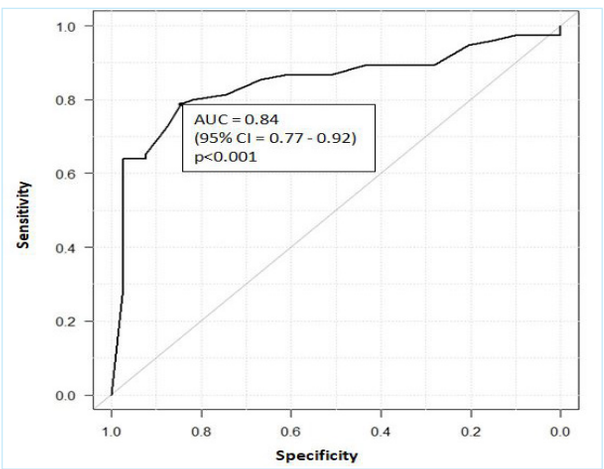

Figure 4. Receiveroperating characteristic curve to discriminate ability of lung ultrasonography (number of B lines) to distinguish whether patients had ILD in HRCT.

Among these patients in whom B lines were visualized in lung ultrasound, pleural line abnormalities showed statistically highly significant association with diagnosis of ILD in HRCT (p=0.003). However non-homogeneity of B lines did not show significant association with ILD in this study (p=0.137). B3 lines were associated with alveolar pattern and B7 lines were associated with interstitial pattern of ILD, which was found to be statistically very highly significant (p<0.001).

DISCUSSION

This study included all the patients visiting in department of Radiology and Imaging, PAHS for HRCT chest which thus included a near representative population of patients encountered in daily clinical practice where comorbidities also occur. The patients enrolled in the study underwent lung ultrasound just prior to HRCT of the chest, thus there was no time lag between these two procedures.

As all three echographic criteria used in the study-PCAS, TBLS 5 and TBLS 10, demonstrated high sensitivity and NPV, lung ultrasound can be used as an effective tool in a population for screening for ILD, especially considering its cost effectiveness, non-ionizing technique, very short execution time and therefore high patient compliance. Various studies have demonstrated sonographic B lines in different forms of ILD. Gargani L. et al. demonstrated positive linear correlation of ultrasound B lines in systemic sclerosis patients with HRCT-derived assessment of lung fibrosis.[6] A study in 2018 by Barbieri C et al. proved lung ultrasound as a reliable diagnostic technique for ILD with chest US sensitivity and NPV for the presence of ILD both accounting for 100% (95%CI 0.85-1, p<0.001).[3] A meta-analytical study in 2019 by Xie HQ et al. recorded pooled sensitivity and specificity of lung US as 86% (95%CI 0.81-0.89) and 84%(95%CI 0.78-0.88), respectively.[7] Since sensitivity is high, lung ultrasound would include ILD cases as positive result and thus patients could be further evaluated and managed accordingly based on the appropriate clinical setting. As the NPV is also very high, a negative test in lung ultrasound can confidently rule out ILD.

Relative to sensitivity and NPV; specificity and PPV of lung ultrasound for all three echographic criteria are comparatively lower. Visualization of B lines in lung ultrasound was found to be non-specific finding for ILD in this study. Various other pathological lung conditions also showed presence of B lines-tuberculosis, lung fibrosis, pulmonary edema, ARDS and pleural thickening. Barskova T et al. in 2013 showed specificity of 55% and PPV of 78% in patients with early systemic sclerosis.[8] A study by Vizioli et al. showed low specificity (79%, 95%CI 0.69-0.90) for lung ultrasound in cases of ILD.[4]Fluid in the alveoli or consolidation, septal thickening due to interstitial fluid or fibrosis can give rise to B lines in lung

sonography.[9] Use of B lines has been well documented in other pathological conditions like neonatal RDS and pediatric pneumonia in various literatures. The Role of Lung Ultrasound in Diagnosis of Respiratory Distress Syndrome (RDS) in Newborn Infants by Lui J et al. demonstrated ultrasound as an effective tool to diagnose neonatal RDS by using B lines, white out lungs and consolidation as major determining parameters.[10] In 2018, Amatya Y et al. in a study at a tertiary care center in Nepal demonstrated sensitivity of lung ultrasound to be 91% and specificity to be 61% for pneumonia in children .[11] Use of B lines in bedside lung ultrasound in emergency (BLUE) and fluid administration limited by lung sonography (FALLS) protocol for assessing pulmonary edema and fluid overload have also been established.[12] All of these studies used B lines as the major determining factor diagnosis of RDS, pneumonia and pulmonary edema. Thus it is recommended that appropriate clinical scenario in the given setting is of utmost importance in utilization of lung ultrasound as a diagnostic investigation for lung pathologies.

More number of B lines was seen in patients with ILD than in those without ILD with statistical significant difference. In addition 11 sonographic B lines was the cut-off point with the greatest positive likelihood ratio for the presence of ILD. Near similar finding was seen in a study by Tardella M et al. that revealed that the presence of 10 US B lines as the cut-off point with the greatest positive likelihood ratio (12.52) for the presence of significant systemic sclerosis related ILD.[13]

As pleural line abnormalities which included fragmentation, irregularity or thickening of pleural line were found to be have positive association with diagnosis of ILD in HRCT ($p<0.01$), its use together with identification of B lines would have better value in diagnosing ILD than using B lines alone. Various literatures also provide compelling evidences in support of this finding. Saeed S et al. in 2016 showed that the sonographic features among ILD patients were B lines in 73.8%, irregular and thickened pleura in 47.6% and 35.7% respectively and subpleural lesions in 38.1%.[9]B3 lines correlated to alveolar pathology and B7 lines correlated to interstitial pathology with statistical significance. This was in agreement with a study by Hasan A et al. which showed that the distance between each of the two adjacent B lines correlated with the severity of the disease on chest HRCT where B3 correlated with ground glass opacity and B7 correlated with extensive fibrosis and honey combing.[14]

As this was a single center study in a tertiary level hospital in the capital city, this could indicate restrictions to generalize the findings to all the people of country. Also selection of patients was on the basis of the need for HRCT; therefore patients with mild symptoms probably would not have been enrolled in the study. This study was a one-time encounter cross sectional study with no data about patients' follow-up and exploration on role of ultrasound in monitoring of ILD. Use of chest sonography had dependency on both assessor as well as the patients, with obese patients being difficult to examine because of the thickness of their rib cage and soft tissues.

CONCLUSIONS

This study showed that sonographic B line assessment can be a valid and reliable additional imaging method in the evaluation of ILD. Given its very high sensitivity and NPV, LUS evaluation of B lines is helpful in the screening of ILD. In addition, characterization of B lines into B3 and B7 lines can further facilitate to determine alveolar or interstitial pathology of the lung as well. Given its easy availability, affordability, easy to carry out, non-ionizing and non-invasive imaging method of investigation, LUS can benefit the patients with suspected ILD. Especially in context of Nepal where CT is not available even at most major cities whereas ultrasound machines have reached the rural most areas, lung ultrasound can be a very effective tool in management of the patients. However given it's relatively lower specificity and PPV, correlation with the history of the patient and given clinical scenario is recommended for better interpretation of B lines in lung sonography.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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