Chest ultrasound findings in usual interstitial pneumonia patterns: a pilot study

Laetitia Joërg[1], Tiffany Trouillon[1], Carole Jalaber[2], Isabelle Court Fortune[1], Antoine Luchez[1], Claire Boutet[2], Jean Michel Vergnon[1], Laurent Bertoletti[3], Marios E. Froudarakis[1]

[1]Department of Pneumonology and Thoracic Oncology; [2]Department of Radiology; [3]Department of Vascular Medicine and Therapeutics, North Hospital, University of St Etienne, France

Abstract

It is unknown what role chest ultrasound plays in distinguishing the various usual interstitial pneumonia (UIP) patterns of high-resolution chest tomography (HRCT). The purpose of this study was to see if there was a link between the results of chest ultrasound (u/s) and HRCT in patients with idiopathic pulmonary fibrosis (IPF). We performed chest u/s in 16 patients with UIP and probable UIP patterns to indeterminate UIP and alternative diagnosis patterns in this single center prospective study to determine any possible relationship with the HRCT findings. A chest radiologist reviewed each HRCT to determine the pattern in accordance with the American Thoracic Society (ATS) / European Respiratory Society (ERS) Guidelines. The local multidisciplinary committee validated the patients' diagnoses before they were included. When compared to the indeterminate for UIP or alternative diagnosis pattern group, there was a trend (p=0.07) toward the presence of more B-lines in UIP or probable UIP patterns. There was no statistically significant difference in the presence of small, large, white lung, or pleural line thickening >5 mm. Subgroup analysis revealed that patients with honeycombing were more likely to have a fragmented pleural line (p=0.04). To summarize, in our pilot study, chest u/s appears unable to differentiate UIP and probable UIP patterns from indeterminate UIP and alternative diagnosis patterns. However, it appears that this technique can be used to recognize the honeycombing pattern.

Correspondence: Marios E. Froudarakis, MD, PhD, Department of Pneumology and Thoracic Oncology, North Hospital, University Hospital of Saint Etienne, 42055 CEDEX2 Saint Etienne, France.
E-mail: marfroud@gmail.com

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Introduction

Interstitial lung diseases (ILD) are a heterogeneous group of the lower respiratory tract, sharing common pathways by accumulation of collagenous scar tissue which leads to increasingly severe impairment of ventilation and gas exchange. Interstitial lung diseases (ILD) include diffuse parenchymal lung diseases of known causes (autoimmune disease, occupational or environmental exposures, drug-induced lung toxicity, collagen vascular disease), and of unknown causes, such as idiopathic interstitial pneumonias, granulomatous lung disorders such as sarcoidosis, and other rare entities such as lymphangioleiomymatosis, pulmonary Langerhans' cell histiocytosis and eosinophilic pneumonia [1].

Idiopathic pulmonary fibrosis (IPF) is the most common and severe form of idiopathic interstitial pneumonia [2]. Early diagnosis of IPF is crucial for prognosis and initiation of therapy [3,4]. Velcro crackles have been considered the key for early diagnosis [5]. The disease affects more frequently males of over 60 years old. 4 Diagnosis of IPF is sustained after excluding the alternative causes of fibrotic ILDs, and a typical high resolution computed tomography (HRCT) pattern of usual interstitial pneumonia (UIP) or after a thoracoscopic lung biopsy, if doubt [6].

Although HRCT is the reference imaging technique for ILDs, an increasing role of chest ultrasound (u/s) as a non-radiating tool in lung assessment has emerged. Research has focused on the pul-

monary involvement of patients with systemic sclerosis (SSc) and rheumatoid arthritis (RA) because pulmonary involvement is the leading cause of related morbidity and mortality of these entities [7].

Recent studies reported that the use of chest u/s helps in the diagnosis of ILDs after detection of B-lines (called "ultrasound lung comets") [8,9], which are classically also present in patients with congestive heart failure [10,11]. Data have confirmed that B-lines are significantly correlated with HRCT findings in patients with ILDs. Indeed, Barskova *et al*., showed that chest u/s evaluation of B-lines may help in the screening for lung involvement in patients with early SSc [12]. Gargani *et al*. found a significant positive linear correlation between ultrasound lung comets and Warrick scores [9]. Gigante and associates reported that the presence of B-lines correlated with HRCT score and diffusing capacity for carbon monoxide (DLCO) decrease in patients with SSc [13]. Moreover, chest u/s may detect some pleural abnormalities, such as thickening and subpleural nodules in this patient population. Sperandeo and collaborators [14] in patients with SSc, showed that an ultrasound pleural line thickness between 3.0 and 5.0 has a good sensitivity and specificity for a HCRT reticular-nodular pattern. Also, chest u/s detects subpleural nodules in a large number of patients with reticular-nodular pattern [15]. Buda *et al*. [16], in patients with pulmonary fibrosis, assessed changes of the pleural lines (irregular, fragmented, blurred pleural line), artifacts (B-lines, white lung, A lines), and consolidations. They described two new ultrasound findings of pulmonary fibrosis: a blurred pleural line in severe cases and Am lines as a subpleural horizontal and numerous reverberation artifacts. They also showed a statistically significant correlation between Am lines in chest u/s and subpleural cysts and honeycombing in HRCT [16].However, few data exist, regarding the use of chest u/s in IPF. Manolescu and associates [17] showed that B-lines and the average thickness of the pleural line are highly and positively correlated with HRCT findings, forced vital capacity (FVC) and DLCO. Smargassiassi and colleagues [18], demonstrated some level of agreement between chest u/s patterns and HRCT grades of peripheral fibrotic changes. In a small cohort, Manolescu *et al*. [19] suggested that chest u/s could distinguish lung interstitial patterns (UIP; possible UIP; non-specific interstitial pneumonia - NSIP). Although the pattern of a typical UIP in HRCT is easily recognized, variations may exist.

Therefore, we designed a prospective study with the aim to assess whether there is a relationship between the findings of chest u/s and HRCT in patients with different UIP patterns in comparison to other ILDs (pneumopathies interstitielles diffuses en echographie: "PIDECHO").

Methods

Study design

We compared the findings of chest u/s to the HRCT pattern in patients presenting typical UIP, probable UIP, indeterminate for UIP or alternative diagnosis pattern, with the aim to determinate whether we can distinguish any difference in the u/s patterns in relation to the HRCT findings. We define UIP pattern, probable UIP pattern, indeterminate for UIP pattern and alternative diagnosis pattern as according to the international guidelines for diagnosis of IPF [20].

This study is a prospective, single center study. Patients were included in the study no later than one month after their HRCT and the final diagnosis of ILD, which was set by the local interdisciplinary committee. Both a highly experienced in chest u/s senior respiratory physician who performed the chest u/s and a fellow who assisted for data collection were blinded of the final diagnosis and the HRCT findings. Patients' age for inclusion was >18 years. Patients were excluded if they had a history of congestive heart failure, an acute exacerbation or other complications of their lung disease, a combined pulmonary fibrosis and emphysema (CPFE), a carcinomatous lymphangitis, and were <18 years old. The study was performed in the Department of Pneumonology of Saint Etienne University Hospital after approval of the Internal Review Board (IRBN462019/CHUSTE) from July 2019 to June 2020. All patients were included after signing a written informed consent.

Chest ultrasound technique

A VIVID S5 u/s (GE Health care, Chicago, USA) with a convex probe (7 Hz) and linear probe (4 Hz) was used. Imaging parameters was adjusted to ensure maximal contrast between the examined structures. The assessment included a comprehensive protocol with 64 lung intercostal spaces. Patients were examined in the seated position for the posterior scanning and in the supine position for anterior scanning (Figure 1). Ultrasound examination was obtained by moving the probe along anatomical reference lines (parasternal, mid-clavear, anterior axillary, mild axillary, posterior axillary, scapular and paravertebral lines). In each intercostal space, we evaluated the thickness of pleural line (<3 mm, 3-5 mm, >5 mm) and the regularity of pleural line (normal, irregular, fragmented, blurred) (Figure 2). Then, we evaluated the presence of more than 3 B-lines, small consolidations (<5 mm), large consolidations (≥5 mm), and other artifacts (white lung, Am lines) (Figure 3).

Chest HRCT

Each examination was reviewed by a radiologist to determine the HRCT pattern with a thorough report of any presence of ground glass opacities, honeycombing, reticulation, bronchiectasis, cysts and consolidation, according to the American Thoracic Society (ATS) / European Respiratory Society (ERS) / Japanese Respiratory Society (JRS) / Asociacon Latinoamericana de Torax (ALAT) clinical practice guidelines (UIP; probable UIP; indeterminate for UIP, alternative diagnosis) [20] and was validated the session of the multidisciplinary review committee.

Statistical analysis

Standard descriptive results were expressed as means and standard deviation. The presence of more than 3 B-lines by intercostal

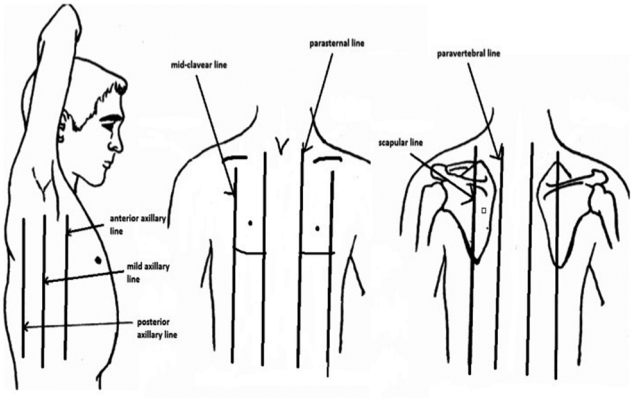

Figure 1. Representation of the exploration for anatomical reference lines in chest ultrasound.

space (> 3 B-lines), normal pleural line, irregular pleural line, fragmented pleural line and blurred pleural line are expressed as a percentage of intercostal spaces observed. White lung, small consolidation, large consolidation and thickness more than 5 mm are binary parameters (presence or not in one or more intercostal spaces). We used Wilcoxon test to compare quantitative parameters and Fisher's exact test for qualitative parameters. Subgroup analysis was performed for patients presented with honeycombing using with Wilcoxon test and Fishers exact test. Statistical analysis was performed using SAS 9.4® statistical package (SAS Campus Drive, Cary, USA) with a $p<0.05$ considered as statistically significant.

Results

Population

Sixteen patients (11 males and 5 females) with a diagnosis of ILD were included in our study: 6 IPF, 3 hypersensitivity pneumonitis, 2 sarcoidosis with pulmonary fibrosis, 2 connective tissue disorders, 1 asbestosis, 1 drug-induced ILD, 1 unknown cause (Figure 4). Demographic and pulmonary function data are reported in Table 1. The mean age was 70±10.3 years. There was no statistically significant difference in age, body mass index (BMI), or functional pulmonary tests between the different groups. The mean time delay between chest u/s and HRCT was 20±24 days.

HRCT findings

In our group, 8 patients (53.3%) had honeycombing, 15 (93.7%) had bronchiectasis, 7 patients (46.7%) had ground glass opacities, all patients had reticulations, 2 (13.3%) patients had cysts and one patient (6.7%) had consolidation. After HRCT evaluation, 3 patients showed a UIP pattern, 1 patient showed a probable UIP pattern, 4 showed an indeterminate for UIP pattern and 7 showed an alternative diagnosis pattern (Figure 4).

Chest ultrasound

The mean intercostal spaces evaluated per patient was 52±7.6. The mean percentage of intercostal space with more than 3 B-lines was 88.2±8.3% in the UIP or probable UIP pattern group and 72±18.4% in the indeterminate for UIP or alternative diagnosis pattern group. There was a trend towards the presence of more B-lines in UIP or probable UIP pattern compared to the indeterminate for UIP or alternative diagnosis pattern group ($p=0.07$). The mean percentage of intercostal space with normal, irregular, fragmented, or blurred pleural line was respectively 9.3±5%, 15.3±10.2%, 53.5±37.5%, 22.0±23.5% in the UIP or probable UIP pattern group and 19.6±12.6%, 18.8±13.1%, 41.4%±22.3%, 20.6±16.4% in the indeterminate for UIP or alternative diagnosis pattern group (Figure 5A). The pleura line looked more frequently normal in the indeterminate for UIP or alternative diagnosis pattern group than in the group of UIP or probable UIP pattern, yet this difference was not statistically significant ($p=0.16$). Among the 12 patients with indeterminate for UIP pattern or alternative diagnosis pattern, 25% had white lung, 83% had small consolidations, 42% had large consolidations and 25% had a pleural line thickening >5 mm. Among the 4 patients with UIP pattern or probable UIP pattern, 50% had white lung, 100% had small consolidations, 50% had large consolidations and 25% had a pleural line thickening >5 mm. There was no statistically significant difference between the different patterns (Figure 5B). The mean percentage of intercostal space with thickening >3 mm was 0.25±0.31% in the UIP or probable UIP pattern group and 0.16±0.15%, in the indeterminate for UIP or alternative diagnosis pattern group and no statistically significant difference was noted between the two groups ($p=0.95$). We found only one Am lines (subpleural horizontal and numerous reverberation artifacts) in one patient with alternative diagnosis pattern and cysts in HRCT. Subgroup analysis (Figure 5C) showed statistically significant ($p=0.04$) more frequently the presence of a fragmented pleural line if patient had honeycombing in HRCT. Also, we found a statistically limited significance ($p=0.05$) towards the presence of an irregular pleural line and a trend ($p=0.08$) towards the presence of a thickening >5 mm in favor of honeycombing in HRCT. Moreover, there was no significant difference in the presence of white lung in chest u/s if patients had ground glass in HRCT ($p=1$) (Figure 5D). A receiver operating characteristic (ROC) curve (Figure 6) was generated using B-lines value and the best cut-off value predictive for UIP or probable UIP patterns was 87% of intercostal spaces with >3 B-lines, with sensitivity of 75% and specificity of 83%.

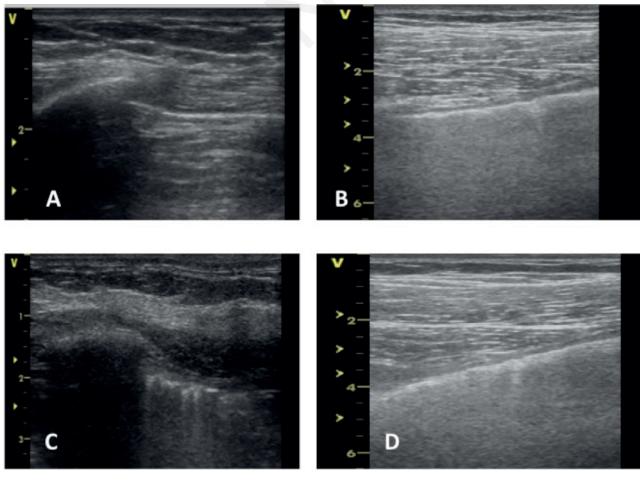

Figure 2. Main chest ultrasound pleural findings. A) Normal pleural line. B) Irregular pleural line. C) Fragmented pleural line. D) Blurred pleural line.

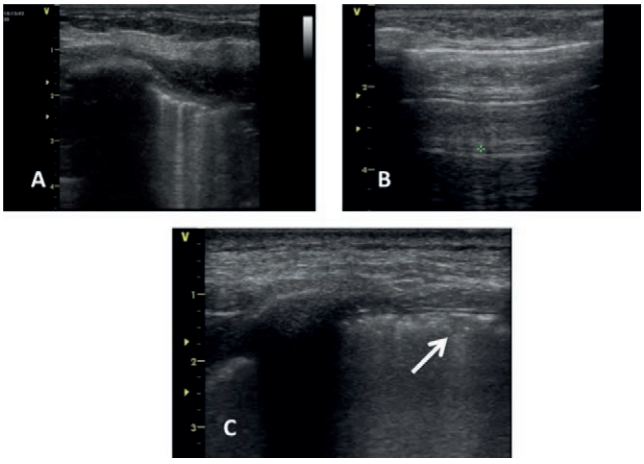

Figure 3. Main chest ultrasound lung findings. A) B-lines. B) Am lines. C) Large consolidation.

Discussion

Our study showed some major ultrasound signs for UIP or probable UIP pattern. We found more B-lines, more fragmented pleural line, more consolidations, and more white lungs but no statistically significant difference was noted between the two groups. These findings can simply be related to the sub-pleural predominance in UIP and probable UIP pattern. There was no difference in the severity of the disease on lung function data that could explain more extensive lesion, but we did not compare the extent of the lesions in HRCT. Although HRCT is the gold standard diagnostic technique in ILDs, an increasing role of chest u/s has emerged in the recent years. Chest u/s has some advantages over HRCT such as low-cost, les time-consuming bedside technique, no radiation exposure. As IPF is a disease with a relatively low incidence and prevalence, the role of chest u/s in the assessment of IPF remains less investigated compared to other ILDs. Reticulation and honeycombing with basal subpleural predominance are the main HRCT criteria of UIP or probable UIP pattern required for IPF diagnosis [20]. If chest u/s was able to recognize these patterns, it could help in the diagnosis of IPF and the patient may avoid HRCT and referral for thoracoscopic lung biopsy.

Manolescu *et al.* [17] who studied IPF in chest u/s, found a high prevalence of B-lines and pleural line thickness in the posterior lung zone. They found a linear correlation between chest u/s and HRCT by overlapping the distribution map and severity score with a cut-off value of 2.4 mm for the pleural line thickness as the IPF severity indicator. Sperandeo *et al*. [14] studied reticular nodular with honeycombing pattern in Scc. They found that major pleural line thickening ≥5 mm had a good sensitivity (90%) and good specificity (99%) for reticular-nodular and honeycombing pattern. Their study also showed that the quantity of B-lines superior to 3 was highly prevalent at all severity grade of pulmonary fibrosis but was not able to discriminate severe nodular and honeycomb forms. In our study, we also found more pleural line thickening >5 mm if patient had honeycombing but this was not associated with UIP or probable UIP pattern. B-lines >3 may be predictive of UIP or probable UIP pattern with a cut-off of 87% of intercostal spaces affected as shown in our ROC analysis.

As opposed to UIP pattern, no specific interstitial pattern in HRCT is shown as prominent areas of ground glass opacity [21]. Few studies proposed the hypothesis that white lung in chest u/s can be caused by the presence of ground glass opacity in HRCT [18,19]. In our study, ground glass opacities were not associated with white lung in chest u/s. Buda *et al*. [16] introduced the concept of fragmented and blurred pleural line. They found a significant correlation between a blurred pleural line in chest u/s and honeycombing in HRCT. In our study, complementary analysis showed the presence of a fragmented pleural line significantly (p=0.04) more frequent if patient had honeycombing in HRCT. This finding needs to be explored in further studies with more attention to the inter-observer correlation to limit the operator's bias of subjectivity. Smaghessi *et al*. [18] tried to correlate u/s patterns with peripheral parenchymal fibrotic changes in HRCT for patients affected by IPF, demonstrating some level of agreement between u/s patterns and HRCT grades of peripheral fibrotic alterations. According to these findings, we may consider chest u/s as a possible relevant tool to highlight the evolution in IPF. Furthermore, chest u/s might be useful in the follow-up of patients with IPF after treatment initiation [22]. Indeed, in the recent INBUILD trial [22] that evaluated the safety and efficacy of nintedanib in patients with progressive fibrosing ILD, the authors found that patients who received nintedanib had a slower rate of progression, independent of the fibrotic pattern on HRCT. Chest u/s may not be able to distinguish the various IPF patterns, but it might be able to identify patients with progression to honeycombing [18,23] and therefore be an interesting tool in the patient's treatment strategy.

The main limitation of our study was the low number of enrolled patients. Indeed, IPF is a rare entity, and our data are collected prospectively, from a single center during a period of one year. However, it would be difficult to perform a multicenter study in this case as chest u/s is an imaging technique very much related to the operator experience and our major concern was to perform the same standardized procedure, which might not be the case for studies enrolling patients from many different centers with possible variances in the technique and its interpretation. Yet, our study is a pilot study generated by our concern to further test a less invasive tool, cost-effective, easy to perform at patient's bedside, which is widely and successfully utilized by a respiratory physician.

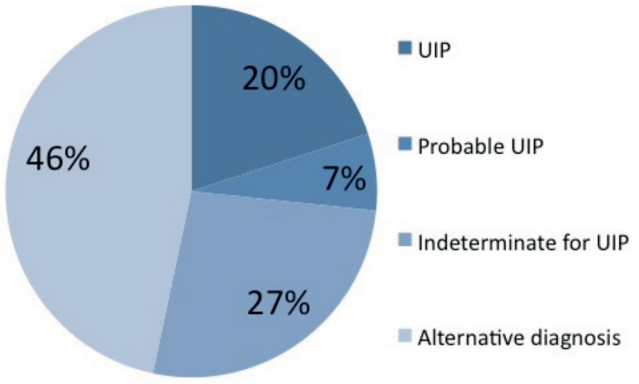

Figure 4. Pie chart for patient's distribution according to high-resolution chest tomography patterns.

Table 1. Demographics and pulmonary function data of our patient population according to usual interstitial pneumonia pattern. All values are expressed as mean±SD.

Parameters	UIP / probable UIP	Indeterminate for UIP / alternative diagnosis	p-value
Age (years±SD)	71+1	70+12	0.67
BMI (kg/m^2±SD)	26+4	28+6	0.63
VC (% of predicted value±SD)	85+18	69+16	0.18
FEV_1 (% of predicted value±SD)	87+16	67+14	0.06
KCO (% of predicted value±SD)	85+16	82+22	0.9

UIP, usual interstitial pneumonia; BMI, body mass index; VC, vital capacity; FEV_1, forced expiratory volume in the first second; KCO, carbon monoxide transfer coefficient.

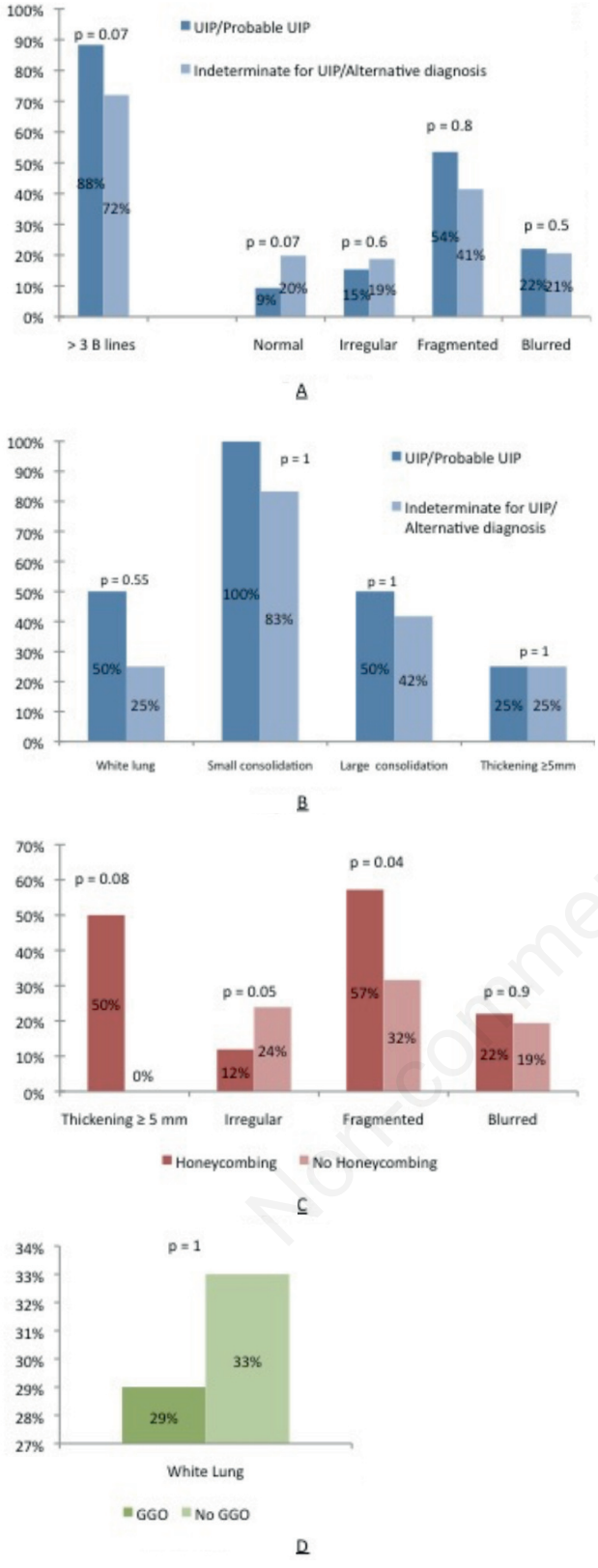

Figure 5 A) Chest ultrasound quantitative data compared by Wilcoxon test according to the high-resolution chest tomography (HRCT) classification. B) Chest ultrasound qualitative data compared by exact Fisher test according to HRCT classification. C) Chest ultrasound data of patients with honeycombing in HRCT. D) Chest ultrasound data of patients with ground glass opacities in HRCT.

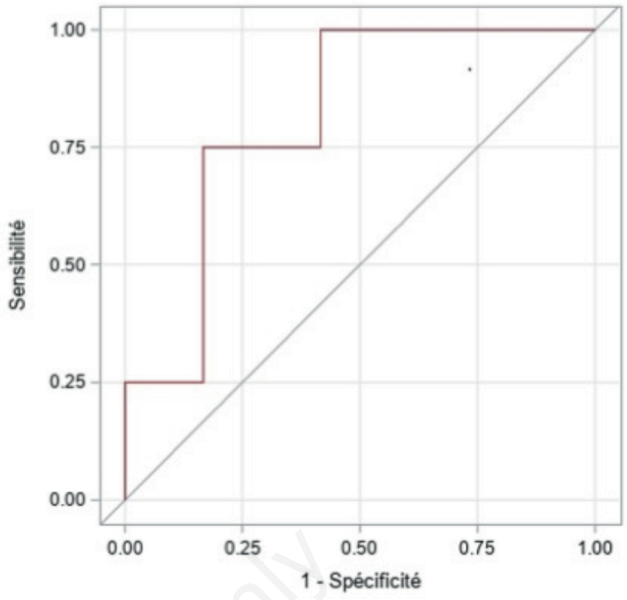

Figure 6. Receiver operating characteristic curve for B-lines.

To conclude, in our pilot study, chest u/s seems not to be able to distinguish UIP and probable UIP patterns to indeterminate for UIP and alternative diagnosis patterns. However, it seems that this technique may be useful in recognizing the honeycombing pattern. Larger studies are needed in this patient population, to further specify its role in the diagnosis and follow up of IPF patients.

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