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Pleural Irregularities: a new ultrasound marker for lung involvement in primary Sjögren's disease

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Bullet points:

- Lung ultrasound potentially allows early detection of ILD in Sjögren's Disease (SjD)
- Pleural Irregularities (PI) scores on lung ultrasound strongly correlate with HRCT and PFT
- PI scores are higher in SjD patients with ILD compared to non-ILD lung involvement
- Lung ultrasound assessment may be limited to the postero-inferior fields for SjD-ILD screening

Objectives: Lung ultrasound (LUS) has been proposed as a useful tool for the assessment of interstitial lung disease (ILD) in connective tissue diseases. However, there are no studies investigating the significance of pleural irregularities (PI) on LUS in primary Sjögren's disease (SjD) patients. The aim of this study was to explore the role of PI for the assessment of SjD-related

lung involvement.

Methods: All primary SjD patients who had undergone a chest CT scan in the lasts 2 months from the start of the study were enrolled, including both SjD patients with known ILD and SjD patients without known lung involvement who underwent a chest CT due to clinical indications other than ILD screening. LUS was performed for all patients and PI total and partial scores were assigned from 0 (normal) to 2 (major changes). Based on CT scans results SjD patients were divided into 5 groups: normal CT scan, non SjD-related lung abnormalities, SjD-related non-ILD lung abnormalities, established ILD, newly diagnosed ILD.

Results: nineteen SjD patients with established ILD and 42 without known lung involvement who had undergone a CT scan were included. Among the latter, CT allowed the diagnosis of 4 new ILD cases. Both total and postero-inferior PI scores were comparable between established ILD and newly diagnosed ILD patients and significantly higher compared to patients with normal CT scan and SjD related non-ILD lung abnormalities. The AUC for ILD diagnosis was significantly higher for the PI postero-inferior score compared to the PI total score. A cut-off score of 15 for the PI postero-inferior score resulted in a sensitivity of 86.6% and specificity of 84.2% for SjD-ILD diagnosis. Both PI total and postero-inferior scores strongly correlated with HRCT Warrick score (r= 0.809 and r= 0.854). The correlation between PFT and both total and postero-inferior PI scores was higher than that observed between PFT and the Warrick HRCT score.

Conclusions: PI may represent a valid tool for the assessment of lung involvement in SjD, particularly for the screening of ILD. PI limited to postero-inferior lung fields seem to maintain good diagnostic accuracy, allowing to save time in clinical practice.

Introduction:

Primary Sjögren's disease (SjD) is generally regarded as a slow-progressive autoimmune disorder, characterized by clinical symptoms and signs resulting from exocrine glands lymphocytic infiltration and mild organ damage (1, 2). Recently, a growing interest has arisen for SjD-related lung involvement, focusing on its negative impact on long-term disease outcome (3, 4). Indeed, the most frequent pulmonary manifestations are benign and related to airways involvement, with a functional respiratory pattern of obstructive lung disease (OLD) (5, 6). However, some patients may develop an Interstitial Lung Disease (ILD) that can be particularly severe, potentially leading to a four-fold increased risk of mortality in the long-term follow-up (7-9). An early diagnosis of SjD-ILD is often hampered by a symptom-driven screening strategy, which may not be suitable to detect a great proportion of patients remaining asymptomatic for a long time (10). Moreover, even though lung involvement has a prevalence of 9-20% in selected cohorts of SjD patients, lung abnormalities

might be detected in up to 50% of asymptomatic patients on imaging (11, 12).
High Resolution Computed Tomography (HRCT) is currently the gold standard for the diagnosis of SjD-ILD and allows definition of the imaging pattern (10, 13-16).
However, HRCT application presents various throwbacks, including radiation exposure, high costs and scarce availability that may limit its use in everyday clinical practice for the screening and follow-up of SjD-ILD, particularly for asymptomatic patients. The increasing awareness of these obstacles prompted the investigation of novel imaging tools that could improve lung assessment in SjD patients.
In this scenario, Lung Ultrasound (LUS) may represent a useful, not invasive, radiation-free, easily repeatable tool for the detection of ILD, as already shown in primary and secondary forms of ILD (17, 18). B-lines, a vertical hyperechoic artifact arising from the pleural line and extending to the bottom of the screen without fading are a well-known marker for lung interstitial syndrome, potentially corresponding to pulmonary edema, inflammation and fibrosis, and have been extensively studied in patients with Connective Tissue Diseases (CTDs), including one report in patients with SjD (19, 20). On the other hand, pleural irregularities (PI) have been proposed as a more specific marker for ILD, and their role has been already explored in patients with Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Systemic Sclerosis (SSc) and anti-Synthetase Syndrome (aSS) (21, 22). However, so far PI have not been investigated in SjD patients. Notably, in comparison with other CTDs, the clinical evaluation of lung involvement in SjD is particularly challenging due to the relatively high prevalence of nonspecific respiratory symptoms, possibly related to respiratory airways dryness. On the other hand, SjD-related ILD may present a long preclinical phase and only mild impairment on PFTs.
Therefore, the aim of this study was to explore the potential role of PI for the evaluation of lung involvement in SjD patients with known, established ILD and their correlation with HRCT patterns and spirometry. We also evaluated the role of PI as a screening and assessment tool in SjD patients without known lung involvement.

Methods

Patients: eligibility criteria

In this single-center cross-sectional study we consecutively enrolled all SjD patients who had undergone a chest CT scan in the lasts 2 months, including both SjD patients with known ILD (*established ILD group*) undergoing HRCT for follow-up purposes and SjD patients without known lung involvement, who had undergone a chest CT scan for clinical indications not related to ILD suspicion. These indications were mostly represented by the suspect of lymphoproliferative disease,

other neoplasms and infections.

All enrolled patients satisfied the ACR/EULAR 2016 classification criteria for SjD (23), and regularly attended the Sjögren's Clinic of the Rheumatology Unit of Pisa, Italy. All patients were enrolled between January 2019 and December 2023, out of single center SjD cohort of 480 patients. Patients receiving active immunosuppressive treatment (GC treatment >7.5mg/die prednisone equivalent dose for more than 7 days or immunosuppressive treatment for more than 14 days at the time of enrollment) which could modify pulmonary findings from the time of chest CT assessment were excluded.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethical Committee "Comitato Etico Regione Toscana – Area Vasta Nord Ovest (CEAVNO)" (protocol code: AIS-ILD; date of approval: 23/05/2024). All the patients signed their informed consent to participate to this study.

Clinical and laboratory assessments

All patients included in the study underwent a complete rheumatologic evaluation aimed at collecting information on demographics, disease duration and cumulative SjD-related glandular and extra-glandular manifestations. The latter were recorded by using an ad hoc clinical chart elaborated on the basis of the ESSDAI (24). In all cases, in addition to routine biological tests, we recorded patients' complete serological data.

At enrollment, we further investigated respiratory history, in particular chronic cough (defined as persistent cough for more than 8 weeks, according to the *European Respiratory Society* (25, 26)), dyspnea (defined as present for a score ≥ 2 according to the modified Medical Research Counsil dyspnea scale (27, 28)) and previous clinical and functional diagnosis of OLD. Moreover, we recorded smoke exposure and concomitant diagnosis of Chronic Obstructive Lung Disease (COPD), bronchial asthma and Gastroesophageal Reflux Disease (GERD), to better evaluate risk factors for ILD and rule out other possible causes of lung damage and respiratory symptoms. Finally, presence of abnormalities on lung auscultation was recorded.

Lung Ultrasonography: pleural irregularities (PI)

LUS was performed for all enrolled patients by a single expert operator, blind to the CT scan results, using a MyLab Class C (Esaote), 10-15 MHz, 5 cm linear probe. The 72 sonographic points corresponding to the anatomical distribution defined by Gargani were explored (29). PI were defined as the loss of the normal hyperechoic linear pleural contour. A semi-quantitative score was employed, scoring 0 for normal pleural line, 1 for moderate and 2 for severe irregularities,

according to Pineal-Fernandez (22) (**Figures 1a-c**). Partial scores were assigned to each of 3 lung fields: anterior, postero-superior and postero-inferior, bilaterally. Finally, PI total score (potentially ranging from a minimum of 0 to a maximum of 2x72= 144) was calculated as the sum of partial scores.

Lung HRCT and functional tests

HRCT of both SjD patients with known ILD (*established group*) and SjD patients without known lung involvement were evaluated blindly by two thoracic radiologists, expert in diffuse pulmonary parenchymal diseases.

For SjD-ILD patients, HRCT patterns were defined according to the latest definitions from international pulmonary societies (30, 31). Extension and severity of ILD were quantified by Warrick score (32).

Non-ILD lung abnormalities described in the spectrum of SjD pneumopathy were also recorded, including: mild peri-bronchial fibrotic changes, bronchial wall thickening, micro/macro-nodularities, disventilatory striae and/or medium-lobe syndrome, bronchiectasis and bronchioloectasis, atypical emphysema (33, 34). These findings were regarded as SjD-related only in enrolled patients without a smoking history. Finally, aspecific CT abnormalities in patients with smoking history where considered as non-SjD related.

Patients with SjD-ILD underwent pulmonary function tests (PFT) for the monitoring of lung involvement. Both dynamic (forced vital capacity -FVC-, forced expiratory volume within 1 second -FEV1-, FEV1/FVC) and static (total lung capacity -TLC-) lung volumes were evaluated. Diffusing capacity of the lung for carbon monoxide (DLCO) was assessed as well.

Study design

This was a single-center cross-sectional study.

Based on CT findings and clinical history, all enrolled SjD patients were classified into 5 categories:

- Group 0: normal lung CT;
- Group 1: aspecific, non SjD-related lung abnormalities;
- Group 2: SjD-related non-ILD lung abnormalities;
- Group 3: SjD patients with known ILD (*established group*);
- Group 4: SjD patients with a new diagnosis of ILD on HRCT

Both PI total and partial scores were then compared between the various groups.

Finally, we analyzed PI scores correlation with HRCT and PFT parameters of SjD-ILD patients.

Statistical analysis

Qualitative variables were described as absolute frequencies and percentages whereas continuous variables were expressed as mean, standard deviation (SD), or as median values (25th-75th percentiles). For the analysis of continuous variables, we employed Student's T-test or Mann–Whitney U-test depending on their distribution. For the analysis of categorical variables, a chi-squared test or a Fisher's exact test were employed. Pearson and Spearman r correlation tests were employed to analyze the degree of association between parametric and non-parametric variables respectively. Receiver operating characteristic (ROC) curves were used to analyze the performance of PI total and partial scores in diagnosing ILD. The area under the curve (AUC) with the 95% confidence interval (CI) was calculated to assess the diagnostic accuracy. The chi-square test was used to compare the AUCs of PI total score with that of partial scores. Youden's index was employed to establish the optimal PI score cut-off to diagnose ILD.

Results

Established ILD group

Nineteen SjD patients with established ILD were included in the study and underwent LUS evaluation, including PI analysis, within 2 months from the available HRCT scan. Enrolled patients were mainly female (F:M=15:4), with a mean age of 73.2 (±8.4) years and a mean disease duration of 12.6 (±18.9) years.

Regarding the pulmonary picture, 12/19 (63.2%) patients complained of dyspnea and 5/19 (26.3%) of chronic cough at enrollment. A previous diagnosis of OLD was formulated in 2/19 patients. No patients were smokers, while 31.6% had a concomitant GERD.

Clinical and serological features of SjD-ILD patients are summarized in **Table S1**.

Patients without known ILD

In addition to patients with known ILD, 42 additional SjD patients without known lung involvement who had performed a chest CT for various clinical indications (other than ILD screening) were enrolled and underwent LUS examination within 2 months from the CT scan.

When compared to SjD patients with established ILD, SjD patients without known lung involvement presented similar gender distribution (p non significant) disease duration (p non significant) and clinical characteristics. However, SjD-ILD patients were significantly older ($p<0.001$) and presented less frequently presence of anti-SSA/Ro60 ($p<0.05$), anti-La/SSB

antibodies (p<0.05), RF (p<0.01), and hypergammaglobulinemia (p<0.01). As expected, a significantly higher percentage of SjD patients in the *established ILD group* complained of dyspnea compared to patients without known ILD (p<0.01) (**Table S1**).

CT findings

Among SjD patients in the *established ILD group,* HRCT pattern was defined as NSIP in 9 cases, NSIP-OP in 2 cases, OP in 1 case and UIP in 7 cases. Mean Warrick score was 13.3 (±16.7). Notably, among patients without known ILD, lung CT evaluation allowed a new diagnosis of ILD in 4 patients. CT pattern was defined as NSIP in all cases and the mean Warrick score tended to be inferior to that observed in SjD patients with established ILD (i.e 7.3±6.0 vs 13.3±6.7; p= 0.055). Only in 1 out of these four cases (25%) pulmonary auscultation had revealed inspiratory crackles on lung bases. Moreover, on CT scan 6/42 (14.3%) SjD patients without known ILD presented typical emphysema and/or aspecific lung abnormalities mainly related to smoke exposure, while 22/42 (52.3%) presented SjD-related non-ILD lung abnormalities, the most frequent being mild peri-bronchial fibrotic changes associated to bronchial wall thickening (19/22, 86.4%), nodularites (13/22, 59.1%) and disventilatory abnormalities (13/22, 59.1%) (**Figure S1**).

Based on CT findings and clinical data, enrolled SjD patients were further categorized as follows:

- Group 0 (normal lung CT) = 10 patients
- Group 1 (aspecific, non SjD-related lung abnormalities)= 6 patients
- Group 2 (SjD-related non-ILD lung abnormalities)= 22 patients
- Group 3 (SjD patients with known, established ILD)= 19 patients
- Group 4 (SjD patients with a new diagnosis of ILD on CT)= 4 patients

Pleural Irregularities assessment

The mean PI total score in SjD with established ILD was 54.2 (±25.5), with a mean postero-inferior score of 21.7 (±8.3), mean postero-superior score of 15.2 (±8.1) and mean anterior score of 17.7 (±11.3).

Compared to SjD patients in the *established ILD group,* SjD patients without known ILD presented significantly lower PI total score and partial scores (p < 0.001).

Comparing mean PI scores between subgroups with multiple comparison analysis, both total and postero-inferior scores were significantly higher in both established (group 3) and newly-diagnosed ILD patients (group 4) compared to normal CT patients (group 0) (p< 0.001). No differences were observed in patients with established ILD (group 3) and with newly-diagnosed ILD (group 4)

regarding both PI total and postero-inferior scores. Moreover, both mean PI postero-inferior and total scores were significantly higher in patients with established ILD (group 3) compared to patients with SjD-related non-ILD lung abnormalities (group 2) ($p<0.001$). Mean PI postero-inferior, but not total score, was significantly higher in patients with newly-diagnosed ILD (group 4) compared to patients with SjD-related non-ILD lung abnormalities (group 2) ($p<0.05$) as well as in patients with established ILD (group 3) compared to patients with non SjD-related lung abnormalities (group 1)($p<0.05$).

Finally, PI total score resulted significantly higher in patients with non SjD-related lung abnormalities (group 1) compared to patients with normal lung CT (group 0) ($p<0.05$); while the postero-inferior score was significantly higher in patients with SjD-related non-ILD lung abnormalities (group 2) compared to group 0 ($p<0.05$). (**Figures 2a and 2b**).

The AUC for ILD diagnosis was significantly higher for the PI postero-inferior score (0.912, 95% CI: 0.842-0.982) compared to the PI total score (0.837, 95% CI: 0.724-0.937; $p<0.05$) (**Figure 3**).

The cut-off score maximizing the Youden's Index for the PI postero-inferior score was 15. This cut-off for the PI postero-inferior score resulted in a sensitivity of 86.6%, specificity of 84.2%, negative predictive value of 0.89 and positive predicted value of 0.76 for SjD-ILD diagnosis. Interestingly, lowering the PI postero-inferior cut-off score to 8 resulted in a sensitivity of 95.7% at the expense of a reduced specificity of 55.3% (complete data shown in Table S3).

Correlation of PI with HRCT and PFT features of SjD patients with established ILD

In SjD patients with established ILD, all PI partial scores and the total score were strongly correlated with ILD extension on HRCT measured by Warrick score. Of note, total and postero-inferior scores displayed the strongest correlation with Warrick score ($r= 0.809$ and $r= 0.854$, respectively) (**Figures 4 and 5**).

Moreover, all PI partial scores and the total score were inversely correlated with FVC, FEV1, TLC and DLCO on PFT. Remarkably, the correlation between PFT parameters and both PI and postero-inferior scores was stronger compared to the correlation between PFT and Warrick score. These data are summarized in **Table 1**.

Regarding HRCT pattern, we found that UIP patients presented significantly higher mean PI total score ($p<0.05$) and postero-inferior score ($p<0.05$) compared to non-UIP patients, in line with a greater severity of the pulmonary picture documented by a higher Warrick score and more impaired FVC, TLC and DLCO. In **table S2** we compared PI scores, Warrick score and PFT findings

between UIP and non-UIP patterns.

Discussion

To our knowledge, this is the first study to have explored the potentialities of pleural irregularities on ultrasound for the assessment of lung involvement in SjD. We found that PI scores were comparable between SjD patients with established ILD and 4 SjD patients who underwent CT scan for clinical indications other than ILD screening and were newly diagnosed with ILD. Importantly, PI scores in both established ILD and newly diagnosed ILD patients were significantly higher when compared to patients with normal CT scan. Moreover, in this study we investigated for the first time the role of lung ultrasound for the evaluation of SjD-related non-ILD lung involvement, which represents the most common type of lung involvement in Sjögren's patients. Particularly, we found that PI scores differed significantly between SjD-patients with non-ILD lung abnormalities and SjD-ILD patients, thus providing a clue for the distinction of these conditions. Finally, we observed a strong correlation between PI scores and both lung HRCT findings and PFT parameters in SjD patients with established ILD.

The early recognition of ILD in SjD is challenging due to several reasons, including a long preclinical phase and the absence of validated organ-specific biomarkers, which can lead to delayed diagnosis and treatment (11, 35). Indeed, clinical and serological risk factors for ILD presence in SjD patients have been described, including elder age, smoking history, presence of Raynaud's phenomenon and positivity of anti-Ro52. However, the phenotypic characteristics of SjD associated to the development of ILD are still debated (36-40). According to literature data the incidence of ILD increases with disease duration in patients with established SjD diagnosis (41). Moreover, since ILD has been associated with increased morbidity and mortality in SjD patients, the possibility of using a non-invasive tool for the early identification of SjD-ILD in clinical practice is of crucial importance (7).

B-lines have been widely employed for the assessment of ILD in CTDs and have a role as a screening tool for the early detection of lung involvement, in particular in Systemic Sclerosis patients (42). More recently, PI have been explored as a potential LUS marker of ILD in different CTDs, demonstrating even better diagnostic performances compared to B-lines (17, 22). Particularly, PI appeared to be useful in discriminating B-lines false positivity due to age and pulmonary congestion in patients not affected by ILD (43, 44). Moreover, PI were shown to represent a valid tool to detect ILD in SSc, SLE, aSS and in RA (21, 22). Despite these findings, studies investigating PI assessment in CTD patients still represent a small minority compared to

those evaluating B-lines. Moreover, to the best of our knowledge there are no previous studies assessing the value of PI in SjD patients, while only one study specifically investigated the usefulness of B-lines for the screening of ILD in SjD patients, demonstrating a high correlation of LUS with HRCT (20).

In our study, in consecutive SjD patients without known ILD, PI provided valuable information potentially able to identify subclinical SjD-ILD cases that would deserve further investigation by HRCT, confirming the findings from Vasco and colleagues (20). Indeed, we found that established and newly-diagnosed ILD patients presented comparable total and postero-inferior PI scores, which were significantly higher compared to SjD patients with normal lung CT. Importantly only in 1 of the 4 newly diagnosed ILD cases inspiratory crackles were present on pulmonary auscultation. Interestingly, the AUC for ILD diagnosis was significantly higher for the PI postero-inferior score compared to the PI total score. Hence, we speculate that it could be possible to limit PI evaluation to the postero-inferior lung fields, allowing to save time in routine clinical practice, while preserving the accuracy of ILD assessment. The cut-off of 15 maximized the sensitivity (86.6%) and specificity (84.2%) of the PI postero-inferior score for SjD-ILD diagnosis. However, being LUS a screening test for ILD we would suggest to lower the cut-off score to 8, which results in a sensitivity of 95.7% at the expense of a reduced specificity of 55.3%. Indeed, we believe that the decision to perform a HRCT for ILD screening should not rely on LUS alone, but this should be properly integrated with the clinical context and PFTs results.

In addition, we found that PI scores were significantly different in ILD patients with UIP and non-UIP pattern. However, this difference is likely related to the greater extent and severity of interstitial changes in UIP patients (as documented by the higher Warrick score on CT).

Importantly, when evaluating SjD patients with established ILD PI total and postero-inferior scores showed the strongest correlation with Warrick score, reflecting the typical distribution of interstitial lung involvement in SjD. We also found that the correlation between PI scores and PFT values was stronger than that between spirometry and Warrick score, thus confirming data by Pineal-Fernandez in SSc- and aSS-related ILD (22). These findings suggest that PI evaluation could also be useful for the follow-up of SjD-ILD patients, integrating spirometry information, also with the advantage of being easily repeatable even during the outpatient visits.

Interestingly, we also found higher postero-inferior PI scores in patients with non-ILD SjD related lung involvement compared to SjD patients with normal CT. This might be counter-intuitive since PI are thought to reflect interstitial parenchymal changes. However, we speculate that PI in non-ILD SjD-related lung involvement likely reflect abnormalities such as dysventilatory striae and particularly small peri-bronchial fibrotic changes accompanying small airway involvement. These

findings, despite not configuring a defined ILD picture, still represent mild interstitial lung abnormalities (ILA) which have long been described both in radiologic and pathologic series of SjD patients, resulting from the well-known epithelitis targeting the small airways in SjD (5, 45-47). Finally, PI scores were comparable between newly diagnosed SjD-ILD cases and patients exhibiting non-SjD related lung abnormalities on CT. However, the typical bilateral distribution with apex-basal gradient of PI may help to discriminate ILD from aspecific abnormalities that can often be observed in smokers and older patients.

This study has different limitations. Firstly, LUS was performed for all patients once by a single experienced operator which did not allow us to calculate intra-observer nor inter-observer agreement. This limits the generalization of the results. Indeed, a recent Delphi exercise from the OMERACT ultrasound working group showed a Inter-reader and intra-reader agreement for PI of 0.58 and 0.75 respectively (19). Moreover, most of SjD patients without known ILD underwent a CT scan, rather HRCT, since the exam was performed for reasons other than ILD screening.

Nevertheless, we believe that our study has some points of strength. First of all, this is the first study investigating the role of PI in a homogeneous cohort of SjD patients with a longstanding disease. All enrolled SjD-ILD patients were well characterized and presented a long follow-up duration, allowing correlation of PI scores with complete clinical, functional and imaging data. Finally, this is the first study that evaluates the correlation between LUS findings and non-ILD SjD-related lung abnormalities, which represent the most common type of lung involvement in SjD.

Online material. Supplementary data

Supplementary data associated with this article can be found in the online version at …

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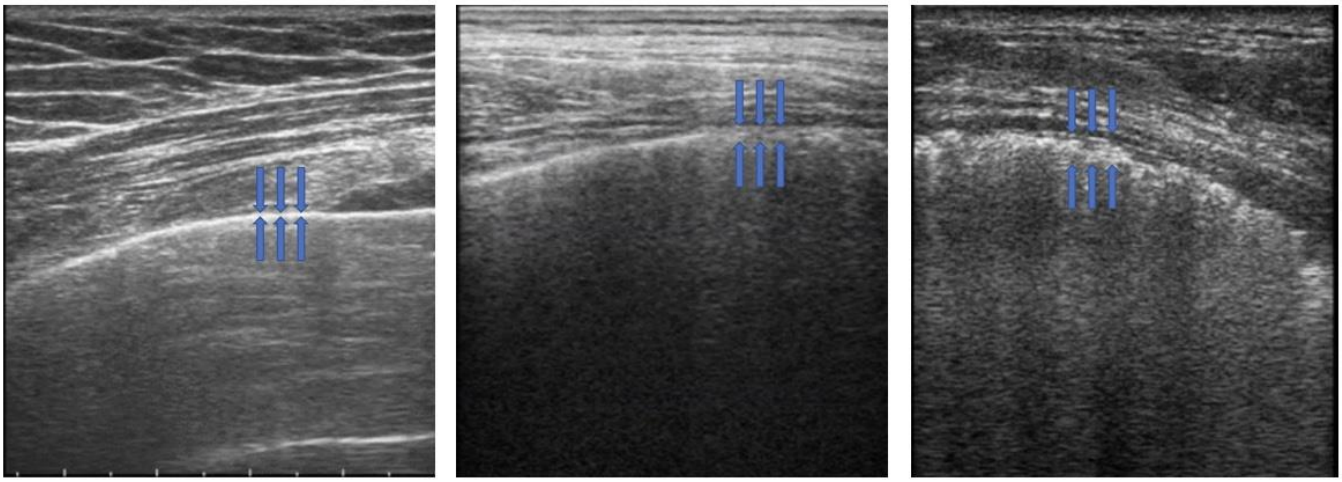

Fig 1a. PI score 0: normal, thin hyperechoic pleural line. **Fig 1b.** PI score 1: moderate pleural irregularities. **Fig 1c.** PI score 2: severe pleural irregularities

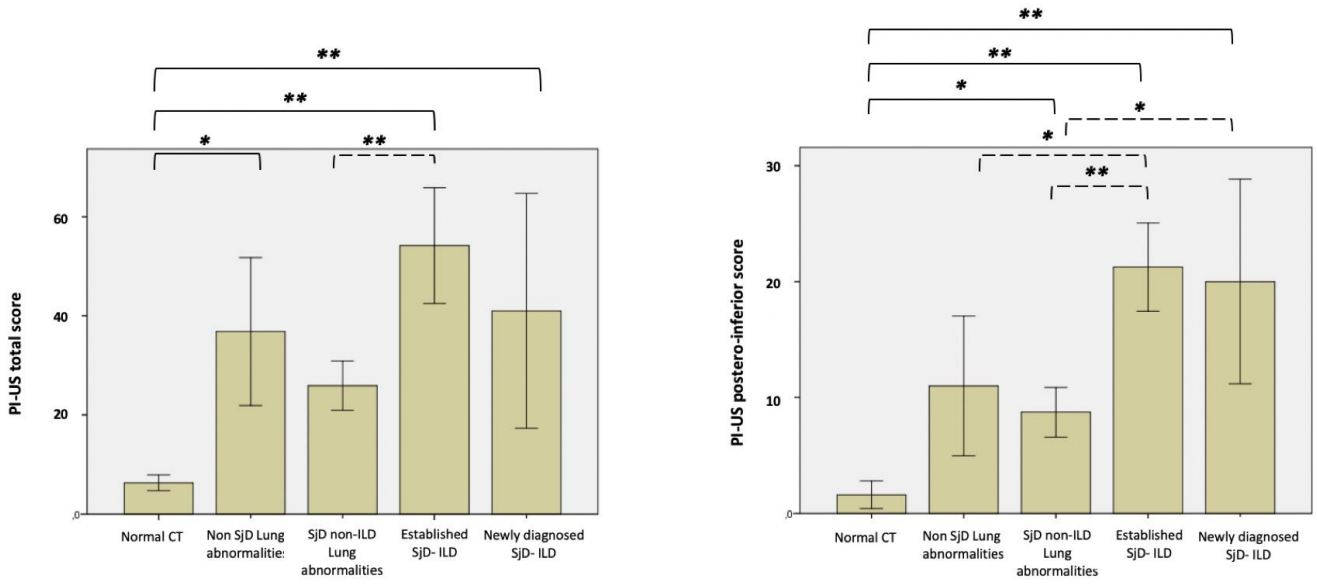

Figure 2a. Comparison of PI total score between subgroups of enrolled SjD patients; **2b.** Comparison of PI postero-inferior score between subgroups of enrolled SjD patients.

* p< 0.05; ** p< 0.001

Continuous lines: pathological subgroups vs normal CT group (—)

Dashed lines: between pathological subgroups (- - -)

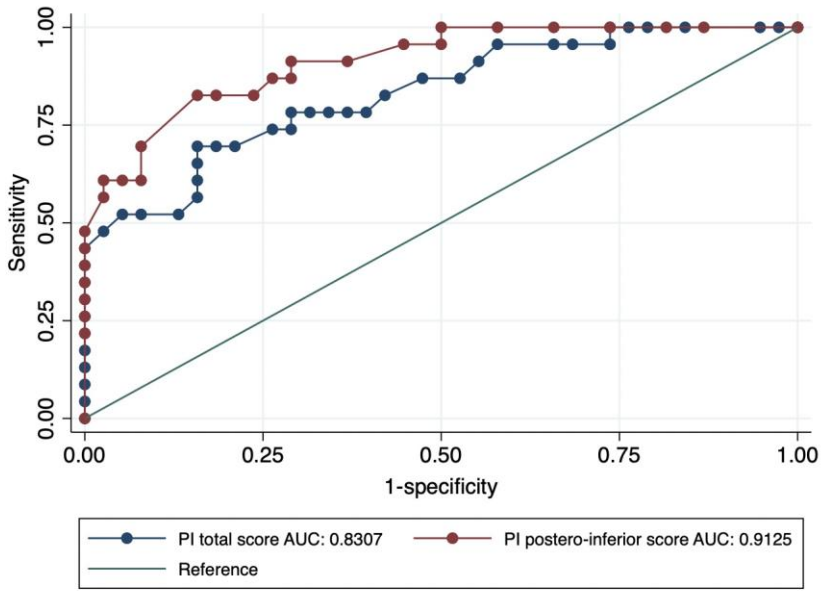

Figure 3. ROC curves of PI total score and PI postero-inferior score for SjD-related ILD diagnosis

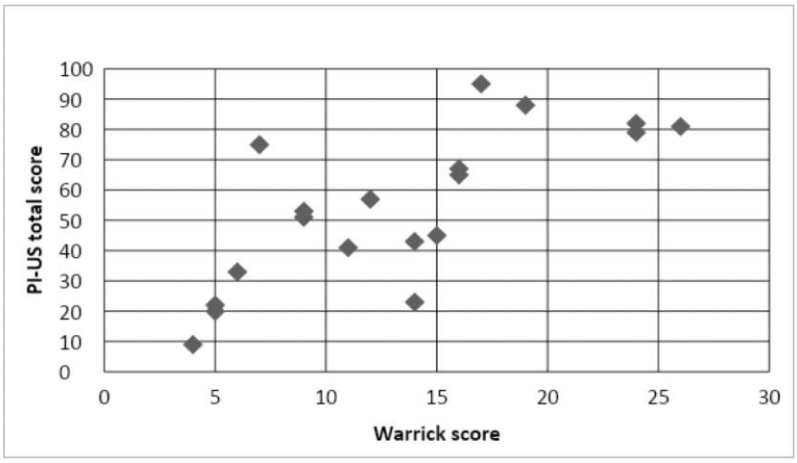

Figure 4. Correlation between PI total and Warrick scores

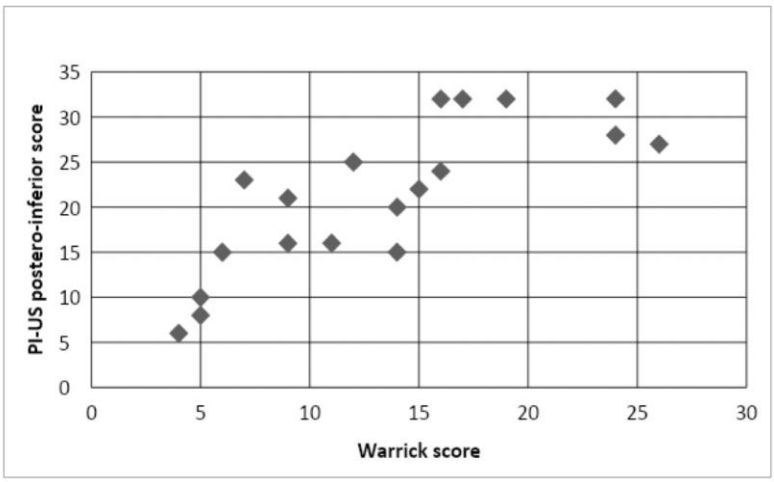

Figure 5. Correlation between PI postero-inferior and Warrick scores

Table 1. Correlation between PI scores, Warrick score and spirometry parameters in SjD patients with established ILD.

	Warrick score	FVC	FEV1	FEV1/FVC	TLC	DLCO
PI total score	p=0.000 r=0.809	p=0.000 r= -0.885	p=0.000 r= -0.831	p=0.033 r= 0.570	p=0.000 r= -0.982	p=0.000 r= -0.951
PI postero-inferior score	p=0.000 r= 0.854	p=0.000 r= -0.883	p=0.000 r= -0.865	p=0.089 r= 0.471	p=0.000 r= -0.943	p=0.000 r= -0.905
PI postero-superior score	p=0.005 r= 0.614	p=0.005 r= -0.701	p=0.009 r= -0.670	p=0.06 r= 0.508	p=0.000 r= -0.904	p=0.000 r= -0.813
PI anterior score	p=0.001 r= 0.706	p=0.001 r= -0.776	p=0.007 r= -0.683	p=0.03 r= 0.579	p=0.000 r= -0.904	p=0.000 r= -0.947