Predictors of Subclinical Interstitial Lung Disease in Patients with Obstructive Sleep Apnea

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Abstract

Rationale: The association between interstitial lung disease (ILD) and obstructive sleep apnea (OSA) is commonly encountered in clinical practice. ILD diagnosis can be easily missed in those patients. **Objective:** To investigate for predictors of ILD in patients with OSA.

Methods: This is a prospective observational study. 309 patients presented to polysomnography (PSG) unit in Assiut University Hospital, diagnosed as OSA (Respiratory Disturbance Index (RDI) more than 5) were reviewed. HRCT Chest was done for all included patients to screen for ILD. Spirometry was done to evaluate the severity of restriction. Echocardiography was performed by a cardiologist to screen for pulmonary hypertension. **Results:** 228 (73.8%) patients had normal HRCT. Eighty one cases (26.2%) were found to have features of ILD in HRCT chest. Patients with subclinical ILD (73 cases, 90.1%) had significantly higher RDI when compared with known cases of ILD (8 cases, 9.9%). Their level of PO2 and FVC were significantly reduced (P=0.003, and <0.001 respectively). There was significant negative correlation between RDI and Desaturation Index (DI) (r= - 0.476, p<0.001), PO2 (r = - 0.598, p<0.001), and FVC (r = - 0.576, p<0.001). Younger age at admission, higher RDI, lower FVC, and prolonged FEV1/FVC are significant predictors for subclinical ILD among patients with OSA.

Conclusions: ILD is a notable association in patients with OSA. The younger age at diagnosis, higher RDI, lower FVC, and higher ratio of FEV1/FVC are significant predictors for subclinical or undiagnosed ILD among patients with OSA.

Clinical trial.gov: NCT06058052

Keywords: Obstructive Sleep Apnea, Intestinal Lung Disease, High Resolution Computed Tomography.

Background

Interstitial lung diseases (ILDs) are a set of heterogeneous disorders with various degrees of fibrosis and inflammation of the lung parenchyma (1). Obstructive sleep apnea is caused by blockage or narrowing of the upper airway that is characterized by recurrent bouts of hypopnea and apnea during sleep (2). The overall incidence of sleep related breathing disorders and OSA in patients with ILD ranges from 47% to 83%) (3). Repetitive forced inspirations against an entirely or partially blocked upper airway, which can happen hundreds of times a night, are the hallmark of OSA (4). Wide variations in pleural pressure associated with obstructive events may apply local strain stresses at the lung's periphery, causing alveolar epithelial cells (AECs) to undergo cyclical deformation and stretching even in the absence of changes in lung volume (5). Additionally, following an obstructive apnea, sudden increases in alveolar volume may stretch the alveolar walls and put stress on the alveolar epithelium. These strain and stress pressures are known to generate AEC damage and inflammation, which have been linked to individuals who are predisposed to lung fibrosis (6). Another possible connection between OSA and AEC damage is oxidative stress and inflammation caused by intermittent hypoxia (7). It was found that OSA is associated with subclinical ILD even in non-obese individuals (8). This association was postulated to be due to remodeling in extracellular matrix and injury to epithelial cells (8). Furthermore, exercise desaturation and higher apnea/hypopnea index in patients with OSA were independent predictors of ILD (9).

Many studies discussed sleep related breathing disorders in patients with ILD, while only few studies discussed the occurrence of ILD in patients with OSA. Furthermore, diagnosis of ILD could be challenging in patients with OSA and might be easily missed. Majority of those patients are obese and their clinical chest examination is commonly unremarkable. There is no sufficient data about the predictors of ILD in patients suffering from OSA. This study was conducted to elucidate the characteristics of patients with OSA that could have undiagnosed (subclinical) ILD.

Patients and Methods:

This is an observational cross sectional study. During the period from January 2023 till February 2024, 309 patients presented to polysomnography unit in Assiut University Hospital, diagnosed as OSA, based on PSG (RDI> 5) were reviewed. Patients were excluded if they were younger than 18 years old, needed ICU admission or refused to sign the informed consent. HRCT chest was done for all patients. 228 patients had normal HRCT. Eighty one cases (26.2%) found to have features of ILD in HRCT chest were analyzed. The consort flow chart of the study is illustrated in figure 1. Standard 12 channel Polysomnography (PSG) was performed using "SOMNOscreen TM Plus PSG+. OSA was diagnosed if respiratory disturbance index (RDI) > 5/hour. Spirometry was performed

using standard techniques according to ATS and the European Respiratory Society (ERS) criteria 2019 (10). Spirometry device used was “ZAN 300, NSPIRE HEALTH GMBH Co.”. Based on reference values for healthy adults, the percentage predicted values (%pred) was computed. Every patient had spirometry performed in a repeatable manner, with the best results being recorded. International acceptability and repeatability requirements were fulfilled. HRCT chest imaging was done in suspended full inspiration in supine position. There were two stages included in the visual HRCT chest analysis. In stage 1, Using a sequential reading procedure, three readers—two pulmonologists and one chest radiologists—evaluated HRCT scans. The term "interstitial lung abnormalities" referred to nondependent alterations that affected over 5% of any lung zone. These included traction bronchiectasis, honeycombing, centriacinar nodules, cysts, and ground-glass (non-dependent) or reticular abnormalities (11). Findings such as ground-glass attenuation (found in < 5% of the lung), unilateral or focal ground-glass abnormalities, and patchy or unilateral reticular findings were considered unclear. When estimating interstitial lung anomalies, areas that satisfied features consistent with emphysema was excluded.

Four main radiographic subtypes were used to categorize the subjects with interstitial lung abnormalities in stage 2 of the visual HRCT analysis: ground-glass opacities in a mostly subpleural distribution that are reticular, nodular, or centrilobular in nature, sparing the peripheral lung parenchyma. In accordance with the standards of the ATS and ERS, mixed centriacinar and subpleural abnormalities and widespread radiographic changes consistent with sure evidence of ILD diagnosis (12). The four radiographic categories for participants with interstitial lung anomalies were determined by the three readers' consensus, without knowledge of the clinical characteristics of each individual. Echocardiography was performed by a cardiologist to screen for pulmonary hypertension, assess the right side of the heart and to exclude left sided heart disease.

Ethical Considerations:

Informed consent was taken from all patients before enrollment. The study followed the instructions of the ethical committee of faculty of Medicine, Assiut University. It was approved be the institutional review board (IRB: 04-2023-300173). It was registered on clinical trials.gov (NCT06058052).

Statistical Analysis:

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was used for all statistical computations. The data were analyzed using statistical methods such as mean ± standard deviation (±SD), median and range, and compared using the Mann Whitney U test. Data were provided as percentages and compared using the Chi square ($\chi 2$) test or the Fisher Exact

test. Pearson correlation test was used to determine the correlation between different variables. Using Receiver Operating Characteristic Curve (ROC) analysis, the optimal cut-off values were determined in order to validate the ILD prediction. To predict the development of ILD, an odds ratio (OR) with a 95% Confidence Interval (CI) and logistic regression were computed. P-value ≤ 0.05 considered significant.

Results

The study was a prospective observational cross sectional one. 309 patients presented to polysomnography unit diagnosed as OSA, based on PSG (RDI> 5) were reviewed. HRCT chest was done for all patients. 228 patients had normal HRCT chest. Eighty one cases (26.2%) found to have features of ILD in HRCT chest were analyzed. 73 cases (90.1%) were newly discovered to have ILD, and eight cases (9.9%) were known cases of ILD.

It was observed that newly diagnosed patients with ILD (subclinical ILD) were younger than those with known cases of ILD (62.92 ± 6.86 vs. 52.50 ± 0.54, P<0.001) respectively. Hypertension was more prevalent among previously diagnosed ILD cases (46.6% vs. 100.0%, P=0.006 respectively). RDI was significantly lower among subclinical ILD (24.56 ± 12.68 vs. 41.00 ± 1.07, P<0.001). While desaturation index (DI) was significantly higher in the same group (76.37 ± 11.83 vs. 70.00 ± 1.07, P=0.042) respectively.

It was found that PO2 and FVC were significantly reduced in known cases with ILD (P=0.003, and <0.001 respectively) when compared to subclinical ILD patients. FEV1/FVC was significantly lower among subclinical ILD cases (P<0.001). Other variables were comparable between both groups with no significant difference between them.

Correlations between RDI and patient's characteristics among the studied cases are presented in **Table 2** and **Figures 1 - 3**. RDI show significant negative correlation with DI (r= - 0.476, p<0.001), PO2 (r = - 0.598, p<0.001), and FVC (r = - 0.576, p<0.001), and significant positive correlation with FEV1/FVC (r = 0.331, p=0.003).

Table 3 and Figure 2 show the predictive ability of RDI for detection of ILD by using the ROC curve analysis. At a cutoff value of ≥ 40; the areas under the ROC curves was 99.5% (95%CI: 0.909 – 1.0, P<0.001) with a sensitivity of 100.0%, a specificity of 94.5%, and accuracy of 95.1%.

Table 4 shows that the younger age at admission, higher RDI, lower FVC, and prolonged FEV1/FVC are significant predictors for ILD among OSA studied cases. For every one-year decrease in patients age the probability of developing ILD was increased by 43.9% (OR=0.561, 95% CI 0.358 – 0.880, P=0.012), and for every one unit increase in RDI the probability of developing ILD was

increased by about 41% (OR=1.407, 95% CI 1.100 – 1.799, P=0.007). Furthermore, for every one unit decrease in FVC the probability of developing ILD was increased by 28.1% (OR=0.719, 95% CI 0.585 – 0.885, P=0.002), and for every one unit increase in FEV1/FVC the probability of developing ILD was tripled (OR=3.121, 95% CI 11.439 – 6.768, P=0.004).

Discussion

One of the most prevalent comorbidities in people with ILD is obstructive sleep apnea. Numerous mechanisms have been proposed to explain the pathologic and physiological connections between ILD and OSA, making these linkages complex and potentially bidirectional. Prior research has mostly assessed OSA prevalence in individuals with IPF (13-15), other studies additionally include other ILD subtypes (16-18). Previous studies have reported an incidence of OSA ranging from 17 to 88% (19-21). ILD and OSA are not only overlapping, but also both are treated by similar treatment modalities. It was noted in studies that noninvasive ventilation is a treatment option not only for OSA but also for critically ill patients with ILD (22, 23). This refers to a common pathophysiologic mechanisms. In the literature, there are few studies about ILD in sleep-related breathing disorder. So we aimed in this study to test the suggestion that OSA severity among obese patient is associated with interstitial lung abnormality on CT and worse pulmonary function or not.

Previous research proposed a number of potential methods by which OSA could lead to early AEC damage. For instance, cyclic hypoxia-reoxygenation during OSA patients' intermittent breathing (24, 25) may be contributed to the inflammation and oxidative damage of the alveolar epithelium (26). Furthermore, stretch-mediated AEC damage may result from obstructive apneas and hypopneas (27).

Inhibitory resistive loading, which is similar to obstructive apnea, damages AEC and increases lung inflammation in mice, providing evidence in favor of this theory (28). In vitro, AECs respond to strain and deformation by producing IL-8 and monocyte chemotactic protein-1 (8, 29), These responses may serve as potential pathways connecting lung inflammation and the stretch forces caused by obstructed respiratory episodes. Lastly, it has been suggested that OSA may exacerbate gastric reflux disease (30), which has been linked to IPF (31). Gastroesophageal reflux disease, however, may not develop during OSA, according to evidence (32-34), which minimizes the likelihood that it is a mediator of the relationship we have shown between OSA and preclinical ILD.

The study was a prospective observational one. It included 81 patients diagnosed as OSA; according to the HRCT finding, we divided the studied cases into 73 cases (90.1%) with subclinical or undiagnosed ILD, and eight cases (9.9%) with ILD. By comparing the baseline data between both studied groups we observed that, patients with ILD were younger than those with subclinical ILD. Furthermore, hypertension was more prevalent among ILD cases. In agreement with Raghu et al.

(2015) (35) which proved that hypertension is a common risk factor for the development of ILD in patients with OSA.

This study found that RDI was significantly higher among ILD cases. While, DI was significantly lower among ILD cases. This finding comes in agreement with a study by Gille et al. (2017) (36) who demonstrated that IPF patients had more prevalent moderate-to-severe OSA. Furthermore, a study by Mermigkis et al. in 2007 (25) demonstrated that patients with IPF and coexisting sleep disordered breathing had lower RDI values, indicating more severe respiratory disturbances during sleep.

In this study it was found that RDI was significantly higher among ILD cases. While, DI was significantly lower among ILD cases. On the other hand, According to Aydogdu et al. (2006), who examined a mixed sample of patients with various ILD diagnosis, the majority of OSA cases were mild (19). Another study included 34 IPF patients; the frequency of OSA was 59%, and moderate OSA was frequently observed (44%) (37). Nonetheless, OSA severity was classified as primarily severe in two trials (20, 25). Our research supports the findings of Mermigkis et al., who showed that 61% of IPF patients had OSA and that 45% of their OSA patients had severe OSA (25). Only patients who were referred to the sleep laboratory because there was a significant clinical suspicion of OSA were included in this retrospective analysis. These conditions may be the cause of the increased incidence of severe OSA.

In the current study we found that the predictive ability of RDI for detection of ILD by using the ROC curve analysis at a cutoff value of ≥ 40; the areas under the ROC curves was 99.5% (95%CI: 0.909 – 1.0, P<0.001) with a sensitivity of 100.0%, a specificity of 94.5%, and accuracy of 95.1%. No previous studied address the predictive ability of RDI for detection ILD, so further studies are warranted to prove or deny this result.

This study show the younger age at admission, higher RDI, lower FVC, and prolonged FEV1/FVC are significant predictors for developing ILD among OSA studied cases. This in contrast to the study done by Jae Ha Lee et al 2020 (38) which found that independent predictors of OSA in patients with ILD were older age, obesity, and diabetes mellitus. The difference in results between studies can be explained by difference in study designs, heterogeneity is studied population and sample size.

This study was one of few studies that highlighted the incidence of ILD in patients with OSA. The results of this study provide significant support to the unique idea that OSA may be a modifiable

risk factor for ILD. On the other hand, one of the limitations of this study being an observational one. There is great need for case control studies with larger sample size to elucidate the complex inter-relation between ILD and OSA. This is actually a second limitation. It was better to exclude patients with comorbidities to clarify the exact effect of OSA which may contribute in the pathogenesis of ILD. However, comorbidities of OSA is so frequent that it would be hard to collect the suitable sample size. Collaboration between researches and conduction of multicenter studies is crucial. It would be more beneficial if comparison was made between patients suffering from both OSA and ILD with those without ILD. Further researchers should try to answer the question whether OSA is caused by an antecedent incident and whether it comes first or later in subclinical ILD.

Conclusion:

Patients with OSA had commonly features of ILD in HRCT chest imaging. This category of patients have worse pulmonary function results. Predictors of ILD in patients with OSA include: younger age at presentation, higher RDI, lower FVC, and higher ratio of FEV1/FVC.

Recommendations:

Screening for ILD is highly recommended in patients with OSA. Many factors contribute to missed ILD diagnosis in those patients. Dyspnea can be attributed to obesity. Dry crepitations, which is commonly faint and could be the only sign found in clinical examination, can be hardly heard due to thick chest wall due to obesity. On the other hand, diagnosis of ILD in patients with OSA should be made with caution. Exclusion of conditions that mimic ILD in HRCT chest such as mosaic perfusion which occur with pulmonary hypertension. Images taken at low lung volume (at expiration), respiratory motion artefacts could be misinterpreted as ILD, as well. Further multicenter studies with larger sample size is needed to accurately differentiate ILD from its previously mentioned mimickers in HRCT. Prompt and effective treatment of OSA is crucial in patients suffering from ILD as well.

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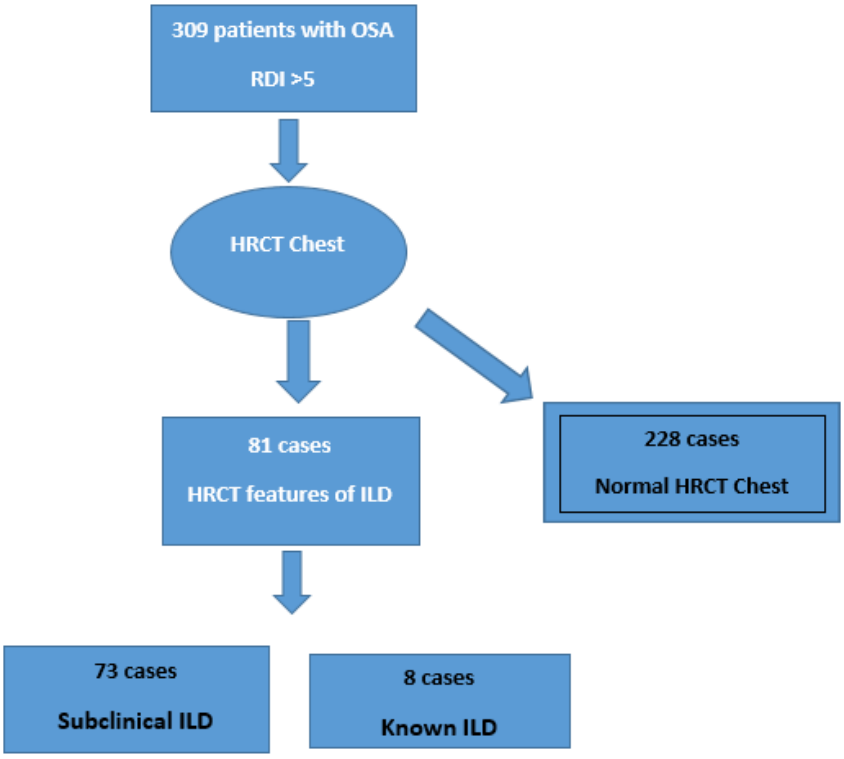

Figure (1): Consort flow chart of the study

Table 1: Baseline data of study participants

Variable name		Subclinical ILD, n=73	ILD, n=8	P value
Age (years)	Mean ± SD	62.92 ± 6.86	52.50 ± 0.54	**<0.001**
	Median (range)	60 (51 – 73)	53 (52 – 53)	
Sex	Male	24 (32.9%)	0 (0.0%)	0.097
	Female	49 (67.1%)	8 (100.0%)	
Associated comorbidities	DM	16 (21.9%)	4 (50.0%)	0.098
	HTN	34 (46.6%)	8 (100.0%)	**0.006**
RDI	Mean ± SD	24.56 ± 12.68	41.00 ± 1.07	**<0.001**
	Median (range)	28 (5 – 46)	41 (40 – 42)	
DI	Mean ± SD	76.37 ± 11.83	70.00 ± 1.07	**0.042**
	Median (range)	78 (36 – 90)	70 (69 – 71)	
PH	Mean ± SD	7.43 ± 0.06	7.46 ± 0.03	0.158

	Median (range)	7.4 (7.4 – 7.5)	7.5 (7.4 – 7.5)	
PCO2	Mean ± SD	46.51 ± 5.66	44.50 ± 2.67	0.280
	Median (range)	46 (33 – 58)	45 (42 – 47)	
PO2	Mean ± SD	57.32 ± 8.56	46.25 ± 8.01	**0.003**
	Median (range)	57 (33 – 76)	49 (33 – 55)	
FVC	Mean ± SD	65.03 ± 7.09	39.38 ± 3.42	**<0.001**
	Median (range)	68 (34 – 73)	39.5 (33 – 45)	
FEV1/FVC	Mean ± SD	78.44 ± 3.12	85.50 ± 1.60	**<0.001**
	Median (range)	79 (74 – 87)	85.5 (84 – 87)	
EF (%)	Mean ± SD	59.90 ± 7.23	62.25 ± 7.19	0.445
	Median (range)	62 (41 – 71)	62 (48 – 71)	
PASP	Mean ± SD	52.88 ± 15.43	60.13 ± 6.01	0.715
	Median (range)	61 (20 – 86)	60 (55 – 73)	

Data are presented as mean ± SD and median (range), or number (percentage), Significance defined by $p < 0.05$. RDI: Respiratory Disturbance Index, DI: Desaturation Index, PH: Pulmonary Hypertension, pCO2: Partial Pressure of Carbon Dioxide, pO2: Partial Pressure of Oxygen, FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in One Second, EF: Ejection Fraction, PASP: estimated Pulmonary Artery Systolic Pressure.

Table 2 The correlation between RDI and demographic details and lung function of the studied cases (n=81).

Variable name		RDI
Age	r	0.022
	p	0.847
DI	r	-0.476
	p	**<0.001**
PH	r	-0.033
	p	0.773
Pco2	r	-0.041
	p	0.719
Po2	r	-0.598
	p	**<0.001**
FVC	r	-0.576
	p	**<0.001**
FEV1/FVC	r	0.331

	p	**0.003**	Significance defined by p < 0.05, r=correlation coefficient
EF	r	0.107	
	p	0.340	
PASP	r	-0.002	
	p	0.985	

Table 3 The best cut off, sensitivity and specificity for detection of ILD by RDI (n=81).

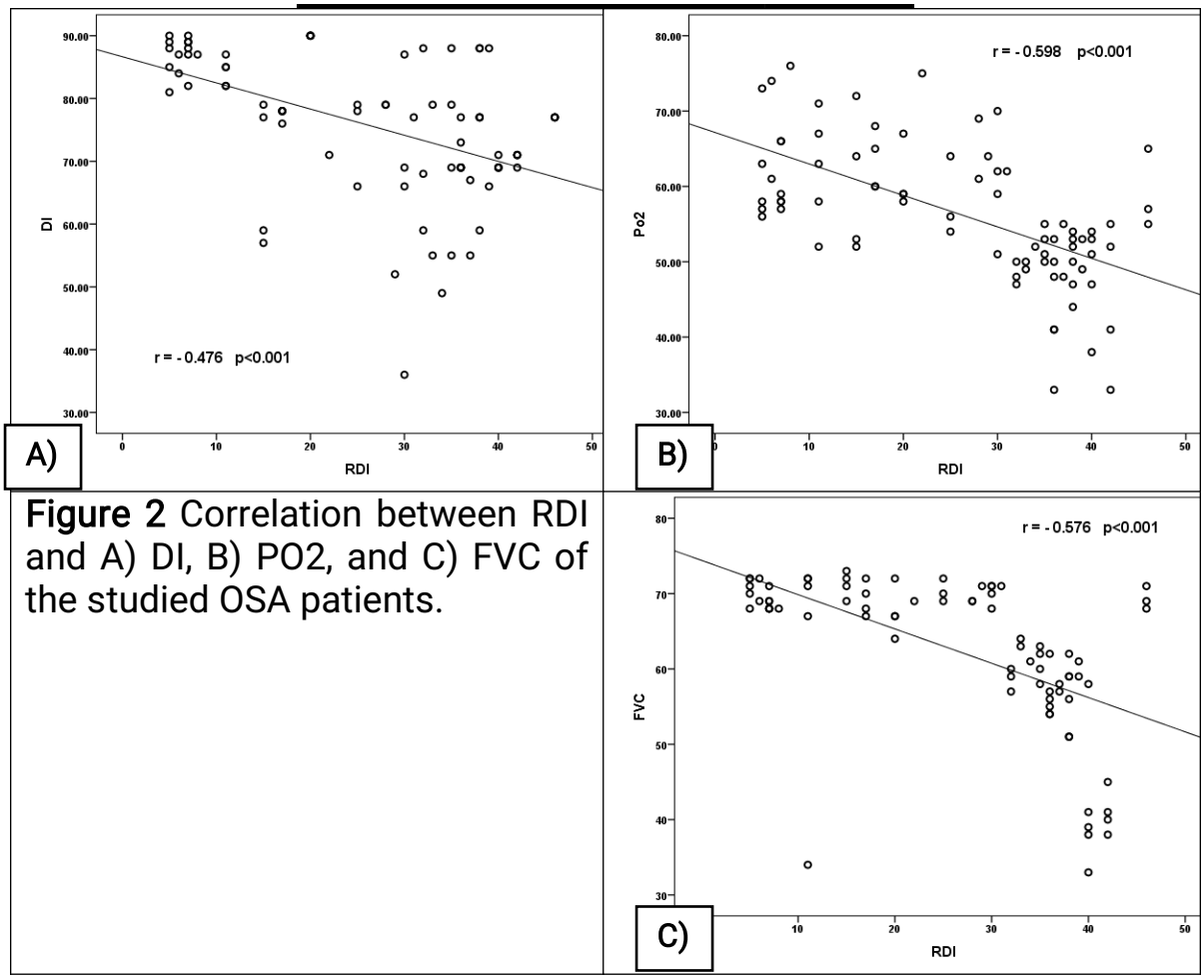

Figure 2 Correlation between RDI and A) DI, B) PO2, and C) FVC of the studied OSA patients.

Markers	Cut off	95%CI	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	p-value
RDI	≥ 40	0.909 – 1.0	100.0%	94.5%	66.7%	100.0 %	95.1%	0.995	**<0.001 ***

PPV: positive predictive value; NPV: negative predictive value; AUC: Area under the curve; CI: confidence interval. *Significance defined by p < 0.05

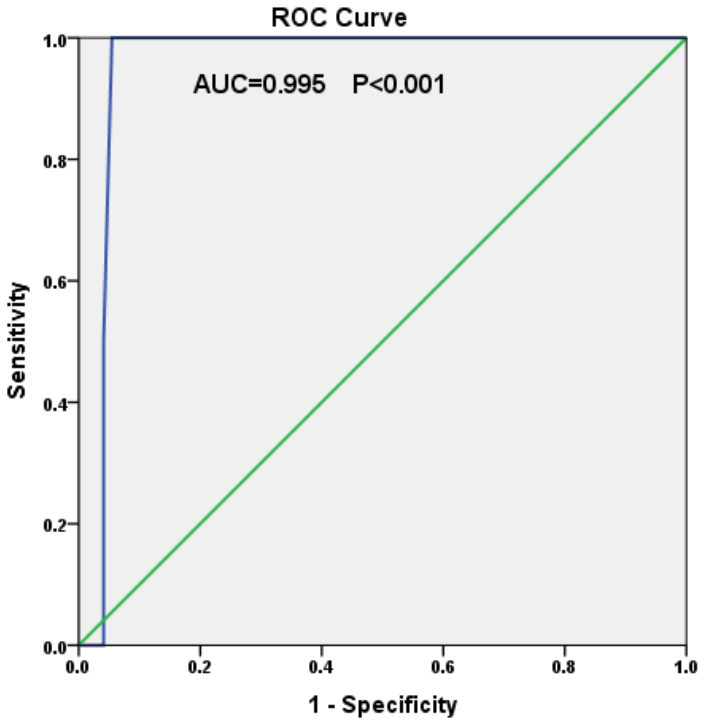

Figure 3: ROC curves for ILD detection in studied participants. RDI (blue), and reference line (green). Area under the curve = 0.995 (0.909 to 1.0), P value <0.001.

Table 4: Logistic regression analysis for prediction of ILD among the studied OSA cases

Variables	OR	95% CI	P value
Age	0.561	0.358 – 0.880	**0.012**
RDI	1.407	1.100 – 1.799	**0.007**
DI	0.957	0.903 – 1.015	0.143
PO2	0.931	0.806 – 1.074	0.326
FVC	0.719	0.585 – 0.885	**0.002**
FEV1/FVC	3.121	1.439 – 6.768	**0.004**

CI: Confidence interval; OR: Odds ratio. * P value is significant ≤0.05