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A clue for obstructive sleep apnea hidden in tomographic images of idiopathic pulmonary fibrosis patients

Sezgi Şahin Duyar[1], Hakan Ertürk[2], Selma Fırat[1], Deniz Çelik[3]

[1]Sleep Disorders Center, University of Health Sciences, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey
[2]Department of Radiology, University of Health Sciences, Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey
[3]Department of Pulmonology, Alanya Alaaddin Keykubat University, Medical Faculty, Alanya, Turkey

ABSTRACT

Objectives: The most common opinion about apnea/hypopnea formation in restrictive pulmonary diseases is based on decreased lung volumes causing upper airway collapse. This study targets to reveal some evidence for this pathophysiological pathway in patients with idiopathic pulmonary fibrosis (IPF) and obstructive sleep apnea (OSA).

Methods: The clinical, demographical, and polysomnographic characteristics of 19 patients with OSA and IPF who underwent all-night polysomnography (PSG) were retrospectively evaluated for investigating the correlations between lung volumes calculated on the images of high-resolution computed tomography (HRCT) and polysomnographic findings. Supine HRCT images performed at the time of diagnosis of IPF were used for the calculation of total lung volume and low attenuation areas of the lung (LAA). The results were compared with the results of the PSG and pulmonary function tests (PFT).

Results: The study group comprised 19 patients (3 female, 16 male) with a median apnea-hypopnea index (AHI) of 23.5/h. AHI in this IPF cohort was not correlated with body-mass index, neck circumference, age, or PFT. However, overall AHI and non-rapid eye movement (non-REM) AHI had a trend of positive correlation with LAA. We also showed a positive correlation between the LAA and forced vital capacity (FVC) ($r = 0.682$ and, $p = 0.003$).

Conclusions: The severity of OSAS in IPF patients is well correlated with LAA. This result supports the gravitational and the volumetric effect of the lung in apnea-hypopnea formation.

Keywords: idiopathic pulmonary fibrosis; low attenuation areas of the lung; obstructive sleep apnea; pulmonary function tests; quantitative imaging

Obstructive sleep apnea syndrome (OSAS) was defined as one of the comorbidities of idiopathic pulmonary fibrosis (IPF) which is the most common type of idiopathic interstitial pneumonia [1]. Sleep disorders accompanying obstructive or restrictive lung diseases were classified under 'Sleep-Related Hypoventilation/Hypoxemia Due to Medical Condition' in the "International classification of sleep disorders-3" which was published in 2014 [2]. Rather than being a coincidence, OSAS and IPF may have a role in the pathogenesis of each other. Gastroesophageal reflux disease, oxidative distress, and nocturnal desaturations are seen in OSAS may cause alveolar damage leading to IPF [3]. Mutually, the reduction of lung volumes in

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Address for correspondence: *Deniz Çelik, MD., Alanya Alaaddin Keykubat University, Medical Faculty, Department of Pulmonology, Alanya, Turkey*
E-mail: drdenizcelik@hotmail.com, Tel: +90 552 4036040

IPF facilitates apnea/hypopnea formation by increasing the collapsibility of upper airways due to the decrease in the caudal retraction effect of lungs over upper airways [3].

However previous studies investigating the relationship between forced vital capacity (FVC), forced expiratory volume during the first second (FEV1) and severity of OSAS reported conflicting results [4]. The results of the study held by Lancaster *et al*. [5] could not support the previous evidence indicating a negative correlation between pulmonary function tests and apnea-hypopnea index. Pulmonary function tests performed at the sitting position may conceal the real fact of pulmonary function impairment on polysomnography obtained during sleep in the supine position. Therefore, the radiologic calculation of lung volumes by using tomographic images taken in supine position before the treatment can be more informative than conventional pulmonary function tests in uncovering the pathophysiology of OSA in restrictive lung diseases.

This study is conducted to enlighten the correlations between total lung volumes (total lung volume and low attenuation areas of the lung) on high-resolution computed tomography (HRCT) and the severity of OSAS in IPF patients.

METHODS

Study Population

The study protocol was approved by the institutional review board of our hospital (decision no: 610 decision date: 02/11/2018). All procedures performed in this study comply with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments. We analyzed only records of patients who agreed to the use of their data.

The study group comprises 23 IPF patients who were consecutively referred to sleep disorders center due to clinical suspicion of OSA and underwent all-night polysomnography (PSG) between March 2016 and June 2017. The diagnosis of IPF (either radiological or pathological) was based on the final decision of the multidisciplinary council for interstitial lung diseases at our hospital as recommended in the available guideline published for the diagnosis of IPF [1]. Medical records of 23 patients were retrospectively evaluated. OSA was defined as an apnea-hypopnea index (AHI) of ≥ 5 events/h on PSG [2]. Out of 23 patients who were polysomnographically diagnosed as OSAS, one patient with congestive heart failure and three patients whose HRCT scans were not available were excluded. The remaining 19 patients were sleep-modifying drugs free and at the time of the computed tomography (CT) scan, either corticosteroids or antifibrotic drugs had not been initiated yet. The patients did not have any comorbidity like cerebrovascular diseases or obstructive lung diseases, which could affect the results of the study.

A pulmonary function test (PFT) was performed for all capable patients. Measurements including spirometry (n = 17) and diffusing capacity of the lung for carbon monoxide divided by the alveolar volume (DLCO/VA) (n = 12) by the single breath technique were performed according to current guidelines, in the seated position [6].

Age, gender, body mass index (BMI), symptoms, neck circumference (NC), smoking status, and scores on the Epworth Sleepiness Scale (ESS) and the results of PSG were obtained from the medical records of the remaining 19 patients.

Polysomnography

PSG including four channels of electroencephalography, two channels of electrooculography, one channel of chin electromyography, thermistor and nasal pressure transducer monitoring to measure airflow, thoracic and abdominal wall motion monitoring to measure respiratory effort, pulse oximetry to measure oxygen saturation, electrocardiography, and a microphone to record snoring was performed using a digital system (Neuron-Spectrum EEG and EP neurophysiological system version 1.6.9.6, Neurosoft, Russia). The records were manually scored based on the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2 by a sleep specialist [7].

High-Resolution Computed Tomography Imaging

HRCT examinations were performed in the supine position and deep inspiration by using Siemens Emotion 6 (Siemens AG, Erlangen, Germany) and Toshiba Alexion 16 (Nasu, Japan) for the diagnosis of IPF. No contrast medium was injected. CT images were re-

viewed by using the picture archiving and communication system (PACS). Parameters were each set to 80-135kV, 50-300 mA with dose modulation, a 1 mm and -1.25 mm thickness, and reconstruction. All axial and reconstructed CT images were reviewed in the PACS by using mediastinal (width, 340 HU; level, 50 HU) and lung (width, 1500 HU; level, −500/-600 HU) window settings. After CT scanning, images were reconstructed by using a pre-installed post-processing program (General Electric GEAW Server 3.2 Thoracic VCAR). Thoracic VCAR is a non-invasive CT image analysis software package, by which areas of the lung with a preset value of Hounsfield Units (HU) can be determined in conjunction with CT lung images. These areas are shown color (blue) for the assessment of the lung diseases [8]. The percentage and volume of low attenuation areas of the lung (LAA) were calculated by the density mask method which was set to show lung voxels with a density lower than 950 HU [9]. (Fig. 1) Total lung volume (TLV), which was reported by this software was also analyzed.

Statistical Analysis

Data were analyzed using SPSS for Windows 15 software. Normality for the continuous variables was analyzed using the Shapiro-Wilk test. Descriptive statistics were presented as mean ± standard deviation for the normally distributed variables and median (minimum-maximum) for randomly distributed variables. Nominal variables were presented as the number and percentage of cases. Most of the variables were randomly distributed and the study comprised a small number of patients. Hence, the Spearman correlation coefficient (r) was employed to examine the relationship between lung volumes and results of PSG, demographic characteristics, or PFT. A multiple linear regression model was used to identify the predictive value of LAA (L) and BMI for AHI. Before the analysis, the logarithmic transformation of the non-normally distributed data was performed to obtain a normal distribution. The model fit was assessed using appropriate residual and goodness-of-fit statistics. *P*-value < 0.05 was considered as statistically significant.

RESULTS

Out of 23 patients with IPF whose PSG results revealed accompanying OSAS, 19 patients (3 female, 16 male) were included in the analysis. The baseline

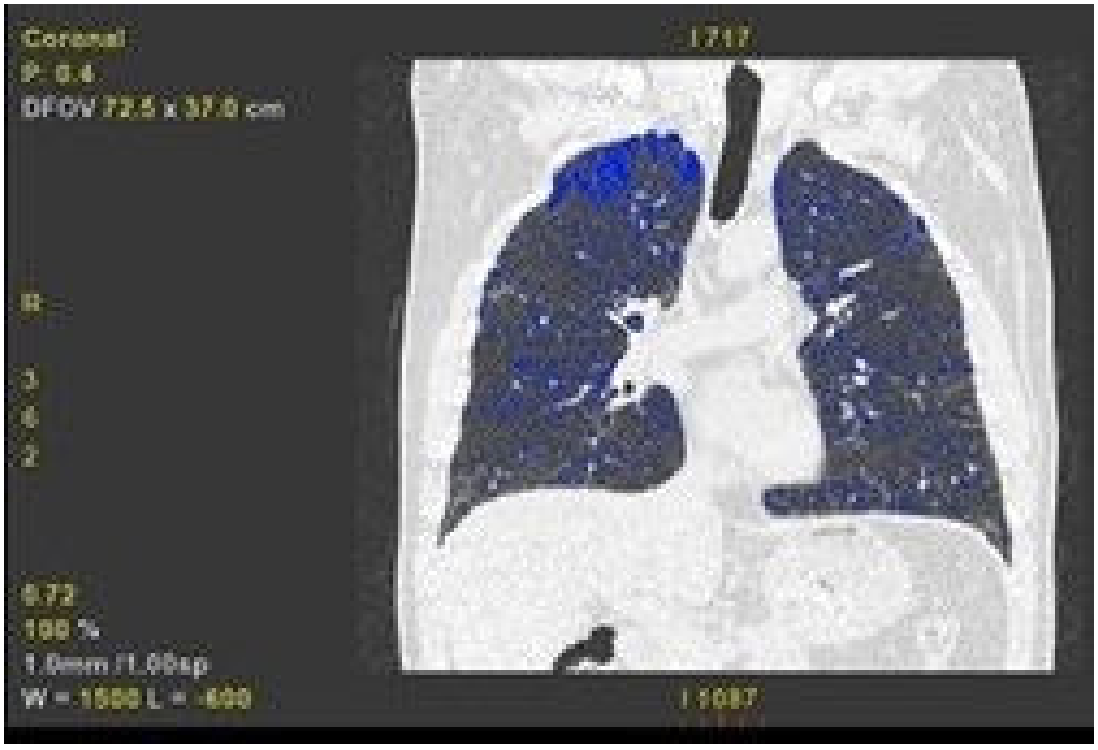

Fig. 1. Representative HRCT scan of a patient. A male patient, 56 years old. The percentage of low attenuation areas (shown as blue) was 10.2%.

characteristics of the study subjects were shown in Table 1. Most patients had moderate/severe OSAS (n = 16, 84.2%) and the median AHI was 23.5/h. The details of PSG results were represented in Table 2. It was found that an averagely of 89.1% of respiratory events comprised hypopneas.

The correlation coefficients (r values) between the parameters of PSG and demographic characteristics, pulmonary function tests, or quantitative CT results were shown in Table 3. Correlation analysis showed that age was positively correlated with nREM1% (p = 0.019 and r = 0.531). The amount of smoking (packages/year) was correlated negatively with REM% (r = -0.657) and the percentage of slow-wave sleep (nREM3%) (r = -0.728) and positively with nREM1% (r = 0.858), nREM2% (r = -0.728) ($p < 0.05$). The ratio of FEV1/FVC had a positive correlation with REM% and nREM3% (r = 0.523 and, r = 0.610, respectively).

Table1. Clinical and demographical characteristics of the patients

	(n = 19) mean ± SD median (25th -75th percentile) n (%)
Age	66.4 ± 9.4
Gender	
Female	3 (15.8%)
Male	16 (84.2%)
BMI	26.7 ± 3.7
Smoking status	
none smoker	6 (31.6%)
quitted/active smoker	13 (68.4%)
Smoking (packages/year)	45 (20-55)
Diagnosis	
Clinical-radiological	15 (78.9%)
VATS	3 (15.8%)
Open lung biopsy	1 (5.3%)
PFT (n = 17)	
FVC	2.4 ± 0.85
FVC (%)	69.7 ± 19.6
FEV1	1.6 (1.42-2.62)
FEV1 (%)	73.6 ± 21.8
FEV1/FVC	83.2 ± 8.8
DLCO (%) (n = 10)	51.5 (24.5-82.8)
DLCO/VA (%) (n = 12)	79.7 ± 39.9
Neck circumference (cm)	38.8 (37.5–41)
ESS (n = 17)	4 (2-6,5)
Total lung volume (L)	3.37 ± 1.38
LAA (L)	0.22 (0.16-0.65)
LAA (%)	9.2 (6.2-15.4)

BMI = body mass index, DLCO/VA = diffusing capacity divided by the alveolar volume, ESS = Epworth Sleepiness Scale, FVC = forced vital capacity, FEV1 = forced expiratory volume during the first second, LAA = low-attenuation areas of the lungs PFT = pulmonary function test, VATS = Video-assisted thoracoscopic surgery

Table 2. **Polysomnographic characteristics**

	mean ± SD median (25^{th}-75^{th} percentile) n (%)
TST (min)	321.9 ± 70.3
Sleep efficiency (%)	66.0 ± 14
REM sleep (%)	11.5 ± 5.7
nREM1 (%)	9.6 ± 5.6
nREM2 (%)	59.3 ±14.1
nREM3 (%)	17.3 (5.8-27.3)
AHI	23.5 (16.6-43.4)

AHI = apnoea-hypopnea index, REM = rapid eye movement, TST = total sleep time

Table 3. **Correlations between polysomnographic and clinical/radiological variables**

Variables	LAA (L)		LAA (%)	
	r	*p* value	r	*p* value
Age	0.156	0.523	0.272	0.229
BMI (n = 18)	-0.173	0.494	-0.208	0.408
Smoking (pack year) (n = 13)	0.646	0.017	0.623	0.023
FVC (L) (n = 17)	0.682	0.003	0.587	0.013
FEV1 (L) (n = 17)	0.527	0.03	0.477	0.053
FVC (%) (n = 17)	0.466	0.06	0.434	0.082
FEV1 (%) (n = 17)	0.378	0.135	0.352	0.166
FEV1/FVC (n = 17)	-0.583	0.014	0.538	0.026
DLCO (%) (n = 10)	-0.179	0.558	-0.16	0.602
DLCO/VA (%) (n = 12)	-0.203	0.527	-0.189	0.556
NC (cm)	0.174	0.477	0.075	0.761
ESS (n = 17)	-0.009	0.974	0.048	0.855
TLV (L)	-0.184	0.45	0.166	0.497
Sleep efficiency	-0.161	0.509	-0.108	0.66
REM %	-0.311	0.195	-0.423	0.071
NREM 1%	0.518	0.023	0.477	0.039
NREM 2%	0.503	0.028	0.514	0.024
NREM 3%	-0.652	0.002	-0.574	0.01
AHI	0.543	0.016	0.526	0.021
ODI	0.445	0.064	0.457	0.056

*r values represent correlation coefficients. BMI = body mass index, DLCO = diffusing capacity of the lungs for carbon monoxide, DLCO/VA = diffusing capacity divided by the alveolar volume, ESS = Epworth Sleepiness Scale, FVC = forced vital capacity, FEV1 = forced expiratory volume during the first second, NC = neck circumference, LAA = low-attenuation areas of the lungs, REM = rapid eye movement, TLV = total lung volume

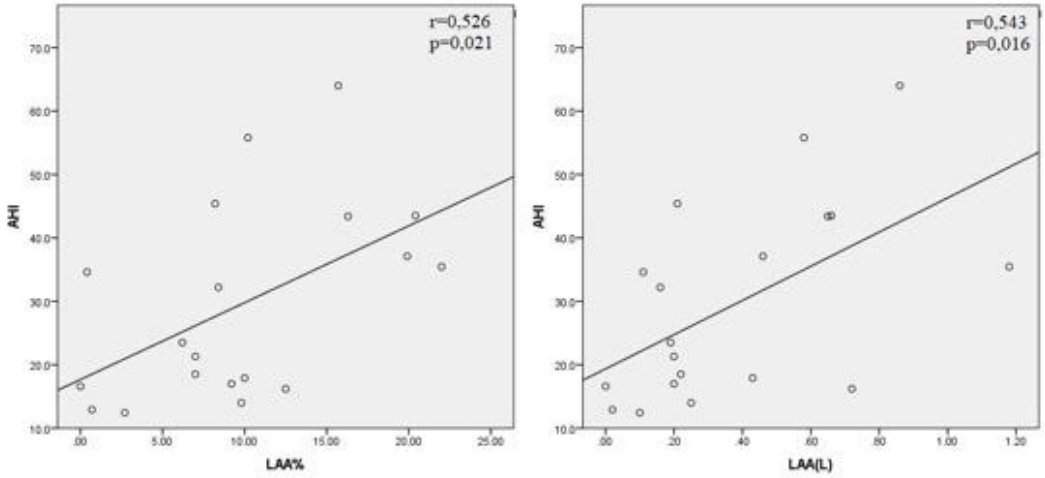

Fig. 2. a) Relationship between AHI and LAA%, b) Relationship between AHI and LAA(L). AHI = apnea-hypopnea index, LAA = low-attenuation areas of the lungs

DLCO or DLCO/VA was not correlated with any of the variables. There was a weak positive correlation between ESS scores and nREM1% (r = 0.498). Total lung volume was negatively correlated with the percentage of slow-wave sleep.

Any of the classical predictors of OSAS including BMI, neck circumference, age, pulmonary function tests, or radiologically calculated TLV did not demonstrate a correlation with AHI ($p > 0.05$). However, as shown in Fig. 2, the results indicated that AHI was positively correlated with LAA% and LAA (L) ($p = 0.016$, r = 0.526 and, $p = 0.021$, r = 0.543, respectively). After obtaining normal distribution for LAA (L) and AHI via logarithmic transformation a multiple linear regression model including log [LAA (L)] and BMI was performed. This analysis proved that log [LAA (L)] can be used to predict log (AHI) for IPF patients, regardless of BMI. As the values were shown in Table 4, log (AHI) can be calculated with this formula: log (AHI) =1.58 + 0.31x log [LAA (L)].

DISCUSSION

This study shows that LAA has a positive correlation with the severity of OSAS. Additionally, our results present proof for the clinical parameters effecting sleep architecture in patients with IPF.

Prior studies dating back to the mid-1980s pointed out poor sleep quality and oxygen desaturation during sleep in patients with interstitial lung diseases [10, 11]. The first study describing sleep-related disorders in a sole group of patients with IPF demonstrated a decrease in sleep efficiency, slow-wave sleep, and REM sleep with an overall AHI in the moderate range [4]. Likewise, the decrease in REM sleep (%11.5 ± 5.7) in our study group indicates the disruption of sleep architecture in IPF. Due to the increased respiratory

Table 4. Multivariate regression analysis for AHI

variables	B ± SH		
	constant		*p* value
Log (AHI score)	1.305		
BMI (kg/m^2)		0.011 ± 0.014	0.464
Log [(LAA (L)]		0.31 ± 0.109	0.013
Log [(LAA (L)]	1.582	0.31 ± 0.107	0.011
R^2:0.385, ***p = 0.033***			

* p-value for ANOVA test, β±SH = regression coefficient ± standard error

AHI = apnea-hypopnea index, dependent variable=AHI, BMI = body mass index, LAA = low-attenuation areas of the lungs

drive and hypocapnia which were suggested as the conservation mechanisms against apnea formation in IPF, the median AHI was in the moderate range and hypopnea predominant. Our data also showed the negative effect of smoking and age on sleep architecture in IPF patients. Smoking cessation may have a positive effect on sleep quality for IPF patients.

Additionally, our results pointed out a trend of a positive correlation between FEV1/FVC, and slow-wave sleep and REM sleep. Despite this impact of FEV1/FVC on sleep architecture, we could not show any correlations between pulmonary function tests and the severity of OSAS. For the general population age, BMI and NC are commonly accepted as predictors for the severity of OSAS [12, 13]. However, the most common opinion about apnea/hypopnea formation in restrictive pulmonary diseases is based on decreased lung volumes causing upper airway collapse, especially during REM sleep due to a decreased traction on the upper airway [4, 5]. This hypothesis was also supported by an animal study demonstrating that the caudal tracheal traction could decrease upper airway collapsibility by reducing extraluminal tissue pressure in rabbits [13]. Similarly, Mermigkis *et al*. [4] noted impairment in pulmonary function tests as potential predictors of OSA in IPF. However, two years later the contradictory results published by Lancaster *et al*. [5]could not indicate any correlations between spirometry or lung volumes with the AHI. A recent meta-analysis elucidated the influence of body position on PFT of the patients with heart, lung, neuromuscular disease, obesity, or spinal cord injury [14]. As PFT is performed while sitting upright and in the daytime, the results can not reflect the pathogenetic pathway of upper airway collapse in a supine position at night during sleep. The results of our study revealed that supine volumes calculated by quantitative analysis of HRCT scan well-correlated with AHI while conventional PFT, DLCO, and DLCO/VA failed to show any correlations in this group of IPF patients. The last guideline proposed the usage of radiologic findings of HRCT as the key factor for the diagnosis of IPF. The same statement called attention to comorbidities like pulmonary hypertension, gastroesophageal reflux disease, and OSAS for IPF patients [16]. Although the effects of these comorbidities need to be further evaluated, some evidence about the unfavorable effects of OSAS in disease progression and life quality of IPF patients has been published [17, 18].

Besides the visual assessment of CT images, a quantitative method using digital data for calculating lung volumes and low attenuation areas of the lung has become a scientific attraction point recently. This method was recommended for representing macroscopic and microscopic emphysematous changes of the lung in chronic obstructive pulmonary disease (COPD) and asthma [19-21]. It was also proposed as a routine follow-up for chronic pulmonary emphysema patients with low radiation at a level of 25% of the routine [22]. LAA% seems to be correlated with pulmonary function tests in asthma and COPD [20, 21, 23].

Some researchers managed to reach positive results outlining the importance of some novel radiologic findings in the assessment of OSA patients. The evaluation of airway ellipticity, water content around the airway, and fat distributions by magnetic resonance imaging were proposed as quick alternatives for identifying the severity of OSA [24-26]. Additionally, CT images obtained during apneic episodes can be used for defining the level of obstruction [27]. In this study, a different radiologic finding was evaluated in an overlapping situation of OSA and IPF. Our results showed that the lung volumes obtained by software from HRCT scans at the supine position may enlighten the caudal traction hypothesis and expressed the effect of low attenuation areas on the severity of OSA for IPF patients. Hochhegger *et al*. [28] investigated air trapping in patients with IPF and other interstitial lung diseases quantitatively by using automated-software and found that air trapping on CT was a common finding for IPF patients as well. The previous studies indicated that the vertical gradient of lung density in the supine position was less at total lung capacity than at residual volume in healthy people. The vertical gradient of an emphysematous lung is less than that of normal healthy men, even at residual volume [29, 30]. Therefore, the higher volumes or percentages of LAA facilitate apnea-hypopnea formation in IPF due to the increase in collapsibility of upper airways.

Our results point out an easily available parameter for evaluating the OSA severity in IPF patients. It presents a new perspective for using radiologic findings in sleep medicine. These results also support the hypothesis of caudal retraction in the pathophysiology of apnea formation. Nevertheless, the small number of

patients and the lack of control group must be considered as the limitations of our study. Also, the effect of smoking must be highlighted in a larger scale study in which regression models with more variables can be established.

CONCLUSION

Although LAA may include either emphysematous or hyperinflated areas, the positive correlation between AHI and LAA supports the hypothesis for the pathophysiology of OSA overlapping with restrictive lung diseases. Despite the small number of patients, the results of this study are informative for explaining the effect of LAA on the severity of OSAS in IPF patients. The caudal traction hypothesis can be based on the density of the lung considering the mixture of areas with different densities. The quantitative HRCT results which can be easily calculated via software can be used to predict the severity of OSAS in IPF patients. It is known that OSA had an impact on the quality of life for IPF patients. All IPF patients undergo HRCT. However, due to the limited number of sleep laboratories with busy schedules, PSG may be delayed. LAA which can be easily calculated from sections of CT scans can be used as a predictive factor for OSA in this population. The effect of LAA in the diagnosis and treatment of OSAS must be further investigated especially in patients who smoke or with underlying lung diseases.

Authors' Contribution

Study Conception: SŞD, HE, SF, DÇ; Study Design: SŞD, HE, SF, DÇ; Supervision: SŞD, HE, SF, DÇ; Funding: SŞD, HE, SF, DÇ; Materials: SŞD, HE, SF, DÇ; Data Collection and/or Processing: SŞD, HE, SF, DÇ; Statistical Analysis and/or Data Interpretation: SŞD, HE, SF, DÇ; Literature Review: SŞD, HE, SF, DÇ; Manuscript Preparation: SŞD, HE, SF, DÇ and Critical Review: SŞD, HE, SF, DÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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