An Integrated Approach Toward the Clinical and Polysomnographic Characteristics of OSA Accompanying IPF

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis and a median survival of 2–5 years [1]. IPF may reveal complications and comorbidities such as acute exacerbation, pulmonary hypertension (PHT), gastroesophageal reflux disease (GERD), obesity, emphysema, and obstructive sleep apnea (OSA). Whether management of these comorbidities could contribute to the quality of life and prognosis of IPF remains unclear [2]; however, certain studies propose positive airway pressure for IPF patients with OSA for a better quality of life [3, 4].

The prevalence of OSA is estimated to be between 9% and 38% in the adult population [5]. IPF and OSA have some shared comorbidities like PHT and GERD. These diseases can have certain common pathways, which may indicate important implications in clinical management. Therefore, the clinical and demographical characteristics of patients with IPF and OSA must be clearly identified. This study aims to contribute to this area by a retrospective analysis of 22 patients with OSA and IPF who underwent nocturnal polysomnography (NPSG).

MATERIALS AND METHODS

Patients and Study Design

Our study included 22 patients who were previously diagnosed with IPF according to the latest American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association (ATS/ERS/JRS/ALAT) statement published in 2011 [2]. These patients were referred to our sleep disorders center in Turkey between March 2016 and December 2016 due to clinical suspicion of OSA. Three patients were excluded as two were aged above 80 years and one suffered congestive heart failure. The remaining 19 patients revealed no cerebrovascular diseases or obstructive lung diseases, which could complicate the study results. None of these patients were on sleep-modifying medications.

OBJECTIVES: Coincidence of idiopathic pulmonary fibrosis (IPF) and the obstructive sleep apnea syndrome (OSA) may have important effects on the pathogenesis of each other. Our aim is to define clinical characteristics of patients with IPF and OSA and to identify a combined index to determine the severity of both diseases together.

MATERIALS AND METHODS: The clinical and polysomnographic characteristics of 22 patients with OSA and IPF who underwent nocturnal polysomnography (NPSG) were retrospectively evaluated and compared with 23 OSA patients without any other pulmonary comorbidities.

RESULTS: We demonstrated high frequency of OSA within our study group (94.7%) all of whom had at least one of the major symptoms of OSA. Lower AHI, lower neck circumference, higher percentage of deep sleep (nREM3) and less comorbidities were observed in the study group when compared to OSA with no other pulmonary comorbidities (p<0.05). When restaged into a compound index according to the gender, age and physiology (GAP) index, the patients with mild IPF and OSA showed the same life and sleep quality with the patients who have higher GAP index.

CONCLUSION: All patients with IPF must be questioned for the major symptoms of sleep related breathing disorders (SRBD). Clinical suspicion for OSA must prompt NPSG. With the presence of moderate-severe OSA, the life and sleep quality of patients with mild IPF can be at the same level of patients with severe IPF.

KEYWORDS: Idiopathic pulmonary fibrosis, interstitial lung diseases, obstructive sleep apnea, overlap syndrome

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drugs or corticosteroids. One patient was being treated with pirfenidone.

The age- and gender-matched control group included 23 patients who consecutively visited our outpatient sleep disorders clinic for routine care between May and July 2017. The patients were listed according to their visit date, and the first 23 patients matching with the study group in terms of age and gender were selected as control group. Patients with other pulmonary comorbidities were excluded.

The study protocol was approved by the Institutional Review Board at our facility (decision number:563, decision date:02.08.2017). The study design was retrospective, therefore, approval of the ethical committee was not required. All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board and with the Declaration of Helsinki, 1964 and its later amendments.

Measurements
The clinical and demographical characteristics of the patients were retrospectively extracted from their medical records.

Pulmonary function test (PFT) was performed for all patients prior to the diagnosis of OSA according to approved standards [6]. Age, gender, body mass index (BMI), symptoms, neck circumference (NC), smoking status, daytime oxygen saturation (SpO2), upper airway pathology, comorbidities, and scores on the Epworth Sleepiness Scale (ESS) were obtained for both study and control groups [7]. Level of dyspnea measured by the modified Medical Research Council (mMRC) dyspnea scale [8], the distance for the 6-minute walking test (6MWT) [9], the pulmonary artery pressure (PAP) measured by transthoracic echocardiography [10], and the St. George’s Respiratory Questionnaire total scores (SGRQ) [11] were accessible for the study group.

NC was measured with a tape, which was placed immediately below the most prominent protrusion of the thyroid cartilage.

NPSG was performed using a digital system (Neuron-Spectrum EEG and EP Neurophysiological System Version 1.6.9.6, Neurosoft, Russia). Testing included four channels of electroencephalography, two channels of electrocogulography, one channel of chin electromyography, a thermistor and nasal pressure transducer monitoring system 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. All NPSGs were manually scored based on the criteria of the American Academy of Sleep Medicine (AASM) Scoring Manual Version 2.2 [12] by one of the three pulmonologists who have a sleep medicine certificate from the Sleep Society in Turkey. OSA was defined as an apnea-hypopnea index (AHI) of ≥5 events per hour. OSA was considered mild if the AHI was ≥5 per hour but <15 per hour, moderate if ≥15 per hour but <30 per hour, and severe if ≥30 per hour. The oxygen desaturation index (ODI) was defined as the average number of at least 3% decreases in the mean oxygen saturation over the last 120 seconds for at least 10 seconds per hour during sleep.

The Gender-Age-Physiology (GAP) index was used to stage the mortality risk in patients with IPF. According to GAP index, male patients and patients older than 60 years are given higher points whereas physiology is assessed with two criteria—forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Three stages (Stage 1: 0-3 points; Stage 2: 4-5 points; and Stage 3: ≥6 points) were identified. Higher GAP stages indicate a higher risk for 1-year mortality and a greater need for transplantation [13]. A total of 17 patients with moderate-to-severe OSA were restaged into compound indexes (CIs) A and B according to the GAP stage. The CI-A group included patients with IPF with GAP Stage 1 (n=7), and the CI-B group comprised patients with GAP Stages 2 and 3 (n=10).

Statistical Analyses
Data were analyzed using the Statistical Package for Social Sciences for Windows version 20 software (IBM SPSS Corp.; Armonk, NY, USA). 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 non-normally distributed variables. Nominal variables were presented as the number and percentage of cases. The Mann-Whitney U test or the Student’s t-test was performed to compare the distribution of the two groups for numerical data. Chi-square test was used to examine the differences between groups for categorical variables. p value <0.05 was considered as statistically significant. Clinical, demographical, and polysomnographic characteristics of the study group were compared with the control group.

RESULTS
Out of 19 patients (3 female, 16 male) who were diagnosed either clinically (66.7%) or pathologically (33.6%) with IPF with a median follow-up time of 7.5 months, only 1 patient revealed AHI <5 per hour. A high incidence of OSA was found in the study group (94.7%), in which each revealed at least one major symptom of OSA, including snoring, and witnessed apnea and excessive daytime sleepiness (EDS). Only 1 patient (5.6%) had mild OSA, 7 (38.8%) had moderate OSA, and 10 patients (55.3%) had severe OSA. No person in the study group revealed a severe obstruction in the upper airway that would require surgery.

Clinical and demographical data of the study and control groups are summarized in Table 1. The age- and gender-matched control group was identical to the study group.
with IPF patients in terms of BMI, smoking status, and pulmonary functions. Snoring was the most common symptom in both groups, whereas witnessed apneas and EDS were quite rare in the study group. The patients with IPF appeared to have smaller NC, less comorbidities, and lower ESS score (Table 1). A total of 19 patients in the control group (82.6%) exhibited at least one comorbidity, including hypertension, diabetes mellitus, and coronary artery disease; however, these comorbidities were noted in only 50% of the patients with IPF.

NPSG revealed that the patients with IPF had hypopnea-predominant OSA with a lower AHI and higher ratio of deep sleep (non-rapid eye movement sleep Stage 3). ODI was found to be lower in the study group, including IPF patients (Table 2).

When patients were regrouped into CI-A and CI-B according to the GAP stage, both groups revealed almost the same polysomnographic characteristics and clinical features, including the quality of life, the dyspnea level, the distance covered in 6MWT, PFT, NC, and the scores of ESS (Tables 3 and 4); predictably, the pulmonary artery pressure (PAP) was higher in the CI-B group (p=0.032).

#### Table 1. The difference of clinical and demographic variables between patients with and without IPF in a population with OSA

| Variables                  | OSAS with IPF (n=18) | OSAS w/o IPF (n=23) | p   |
|----------------------------|----------------------|---------------------|-----|
| Age (years)                | 64.1±8.9             | 64.4±7.2            | 0.88|
| Gender                     |                      |                     |     |
| Female                     | 17%                  | 17.40%              | 0.99|
| Male                       | 83%                  | 82.60%              |     |
| BMI                        | 28.4±5.7             | 31.9±7.1            | 0.09|
| Smoking status             |                      |                     |     |
| None smoker                | 27.8%                | 43.5%               |     |
| Quitted/active             | 72.2%                | 56.5%               | 0.30|
| Smoking (packages/year)    | 22 (0-72)            | 15 (0-40)           | 0.69|
| PFT                        |                      |                     |     |
| FVC (lt)                   | 2.35±0.79            | 2.89±0.99           | 0.07|
| FEV1 (lt)                  | 2.01±0.68            | 2.38±0.84           | 0.14|
| FEV1/FVC                   | 85.6±7.7             | 82.3±5.1            | 0.11|
| Neck circumference (cm)    | 39.5 (36-52)         | 42 (39-50)          | 0.01|
| ESS                        | 4.0±2.6              | 6.6±4.5             | 0.046|
| Symptoms                   |                      |                     |     |
| Snoring                    | 83.3%                | 100%                | 0.08|
| EDS                        | 11.1%                | 56.5%               | 0.01|
| Witnessed apnea            | 11.1%                | 60.9%               | 0.001|

The results were shown as n (%), mean±standard deviation or median (25%-75% percentile).

BMI: body mass index; EDS: excessive daytime sleepiness; ESS: Epworth Sleepiness Scale; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; PFT: pulmonary function test

#### Table 2. Polysomnographic characteristics

| Variables                  | OSAS with IPF | OSAS w/o IPF | p   |
|----------------------------|---------------|--------------|-----|
| TRT                        | 485.1 (458-621)| 461.9 (301.9-485.5)| 0.01|
| Sleep efficiency (%)       | 66.0±15.8     | 72.2±11.6    | 0.15|
| Sleep latency              | 14.7 (4-65)   | 24 (2.5-46)  | 0.67|
| REM sleep (%)              | 14.4±7.6      | 12.8±8.1     | 0.53|
| nREM1 (%)                  | 8.1±5.4       | 13.1±9.1     | 0.03|
| nREM2 (%)                  | 56.6±12.5     | 63.3±10.5    | 0.07|
| nREM3 (%)                  | 20.1±12.5     | 10.6±10.1    | 0.01|
| AHI                        | 33.8±17.1     | 56.3±23.7    | 0.002|
| Hypopnea (%)               | 87.1 (15.7-100)| 65 (24-99)   | 0.03|
| ODI                        | 19.7 (7.2-62.8)| 46.4 (14.2-97.9)| <0.001|

The results were shown as mean ± standart deviation or median (25%-75% percentile).

AHI: apnea-hypopnea index; ODI: oxygen desaturation index; REM: rapid eye movement; TRT: total recording time

#### DISCUSSION

Sleep hypoventilation is a physiological characteristic that occurs during rapid eye movement (REM) sleep; however, it may not be tolerated if obstructive or restrictive lung diseases exist. Additionally, it may worsen the underlying lung disease, and limitations in lung function may lead to sleep disorders [14]. This co-occurrence of lung diseases and sleep disorders was originally described as “overlap syndrome” until a new category called “sleep-related hypoventilation due to a medical disorder” was added to International Classification of Sleep Disorders (ICSD) in 2014 [15]. The most frequently occurring medical disorder in this category is chronic obstructive pulmonary disease. Limited data are available on sleep patterns in patients with IPF. Most of the studies consider fewer patients with different interstitial lung diseases. Moreover, the previous research between the mid-1980s and the 1990s had certain methodological differences about the diagnostic criteria for IPF and the definition of hypopnea.

The prevalence of OSA in patients with interstitial lung disease (ILD) ranges from 17% to 88% due to different referral patterns, ethnicity, and inclusion or exclusion of patients with obesity or patients on corticosteroid treatment [14]. In our study, OSA was found in 94.7% of patients with IPF. Interestingly, a different methodology resulted in a much lower incidence of 22% in a recent study, which only included the patients who underwent unattended polysomnography in early stages of the disease [16]. Although our study population is free of corticosteroids, 27.7% of the patients have BMI≥30 kg/m², and each patient reveals at least one of the major symptoms of OSA. In a recent study, Bosi et al. [17] reported that sleep breathing disorders were indicated as an independent risk factor for progression and mortality in patients with IPF. Another study revealed a strong association between moderate-to-severe OSA and ischemic heart disease in patients with IPF [18]. These results emphasize the high prevalence of OSA in patients with IPF who have sleep disorder–related symptoms and underline the importance of inquiring about
these symptoms during pre-diagnosis of OSA in patients with IPF. The only symptom observed in 66.6% of our study group is snoring. The absence of witnessed apneas and minimal EDS cannot exclude OSA in this population. The mean ESS score of our study group is lower than the mean score of the control group. Likewise, Lanchester et al. [19] reported that ESS cannot be used to screen for OSA in patients with IPF. The question “Do you snore?” must be included in every routine evaluation of patients with IPF.

Our results reveal that the control group has larger NC, resulting in higher AHI and several comorbidities. Tseh et al. [20] noticed a correlation between NC and abdominal adiposity, especially in women. NC was also associated with the cardiometabolic risk factors, including serum total cholesterol, levels of low-density lipoprotein cholesterol and triglycerides, epicardial fat thickness, metabolic syndrome, insulin resistance, and clinical/subclinical atherosclerosis [21-25]. Therefore, large NC in the control group may contribute to the higher ratio of comorbidities. NC is also a reliable predictor for the presence and severity of OSA [26, 27]. Nevertheless, our results indicate that NC may be low in patients with IPF who also have moderate-to-severe OSA.

In contrast to our findings, several studies reported mild OSA in majority of the IPF patients [28-30]; however, Gille et al. [18] also observed moderate-to-severe OSA in 62% of the 45 patients newly diagnosed with IPF. Most of the patients in our study group are not obese (mean BMI=28.35±5.68 kg/m²); however, they all were clinically suspected to have OSA. As stated

| Variables | Compound index A (n=7) | Compound index B (n=10) | p |
|-----------|------------------------|------------------------|---|
| BMI (kg/m²) | 30.3±6.1 | 27.1±5.0 | 0.24 |
| Smoking (packages/year) | 23.9±23.4 | 26.5±27.4 | 0.83 |
| mMRC | 2 (25%) | 3 (30%) | 0.99 |
| ≥2 | 6 (75%) | 7 (70%) | 0.88 |
| SGRQ (n=15) | 57.8±23.0 | 55.6±32.4 | 0.17 |
| 6MWT (m) (n=11) | 420 (120-450) | 300 (83-540) | 0.27 |
| PFT | FVC (lt) | 2.6±0.8 | 2.2±0.7 |
| FVC (%) | 74.5±14.8 | 64.4±1.6 |
| FEV1 (lt) | 2.2±0.7 | 1.8±0.7 |
| FEV1 (%) | 79.4±15.0 | 70±23.8 |
| FEV1/FVC | 85.9±5.2 | 84.7±9.5 |
| PAP (mmHg) | 25 (19-35) | 30 (23-70) | 0.03 |
| Neck circumference (cm) | 38.6±2.6 | 41.1±4.2 | 0.16 |
| ESS (n=15) | 3.6±2.8 | 4.4±2.5 | 0.59 |

The results were shown as n (%), mean±standard deviation or median (25th-75th percentile)

BMI: body mass index; ESS: Epworth Sleepiness Scale; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; mMRC: modified Medical Research Council Dyspnea Scale; PAP: pulmonary artery pressure; PFT: pulmonary function test; 6MWT: 6-minute walking test.
in earlier studies, BMI may not be strongly correlated with AHI in patients with IPF [19, 28, 29]. These findings emphasize the importance of questioning the patients about major symptoms of OSA, regardless of anthropometric evaluation.

All of the previous studies compared the sleep quality of IPF patients with and without OSA. Distinctly, this study compares the overlapping of IPF and OSA with no other respiratory diseases. However, our results correlate with the previous studies on the predominance of hypopnea in patients with IPF [19, 28-30]. Hypocapnia and increased minute ventilation caused by the increased respiratory drive were proposed as protective factors against OSA in patients with IPF [31, 32]. We also proved hypopnea predominance in mild IPF (Table 4). This result suggests that there may be some other mechanisms having a protective effect on apnea formation for the underlying OSA in this population other than increased respiratory drive.

The pathogenetic interaction between these two diseases is obvious. Reduced lung volume and corticosteroid treatment resulting in obesity may lead to OSA. Alternatively, the oxidative stress caused by nocturnal desaturations, alveolar damage caused by recurrent Müller’s maneuver occurring frequently during apneas, and GERD can be the underlying or aggravating factors for IPF [33, 34]. Smoking status, BMI, and age in both groups were similar; however, a statistically significant reduction in the forced expiratory volume in the first second (FEV1) or FVC could not be demonstrated in the study group. As PFT is performed while sitting upright and in the daytime, the results may not reflect the pathogenetic pathway of upper airway collapse in a supine position at night during sleep [19]. Nevertheless, the mean FVC of the control group is 54 ml, which is (8.6%) greater than the study group. This difference in FVC might be statistically significant if the supine values of lung volumes were evaluated in a study with a larger sample size.

Aydöğdu et al. [29] and Pihtili et al. [30] investigated the effects of the severity of ILD on sleep by using the clinical, radiological, physiological (CRP), and disease severity index. OSA was more frequent in patients with a disease severity index ≥3; however, the polysomnographic characteristics of patients with a CRP index ≥30 were identical to the patients with a CRP index <30. Both the studies included different types of ILD. In our IPF-specific study design, the GAP index is used within a homogenous OSA population.

In general, studies have reported certain changes in the micro- and macro-architecture of sleep in patients with IPF [14]; however, our study population with IPF reveals a better quality of sleep in terms of a higher ratio of deep sleep (nREM3). Furthermore, the CI-A group and the CI-B group indicated nearly similar polysomnographic characteristics, as well as the same clinical features, including the quality of life, the dyspnea level, the distance in 6MWT, and the scores of ESS. OSA may cause aggravated symptoms for patients with mild IPF which is more common in severe disease. Therefore, if there is a clinical discordance in means of levels of EDS, exercise capacity, dyspnea, life and sleep quality for patients with mild IPF; OSA as comorbidity must be questioned. Unexpectedly, ODI is much higher in the control group. Evidence indicates that ODI increases in patients with IPF and severe OSA [19, 29]. When the severities of the two diseases are evaluated collectively according to the CI model, ODI becomes equal with the same severity of OSA, regardless of the severity of IPF; predictably, PAP is higher in the CI-B group, which may emphasize the major effect of the severity of IPF on pulmonary hemodynamics. Kolilekas et al. demonstrated a correlation between survival and lowest oxygen saturation during sleep. They also indicated that maximal difference in oxygen saturation between wakefulness and sleep had a significant negative correlation with survival [35]. Bosi et al. [17] reported that higher rates of mortality and disease progression can be expected if both OSA and sleep-related hypoxemia accompany IPF. Conversely, in a recent study including patients during the early stages of IPF the time with SpO2<90% on baseline polygraphy of the patients with AHI>20 was not correlated with survival [16]. Presumably, the accuracy of polygraphy must be further investigated in this population, because more sensitive measurements may be needed due to hypopnea predominance.

In conclusion, when a patient with IPF is referred for a sleep-related breathing disorder, the clinician must be aware that patients with IPF are less symptomatic and may have smaller NC. NPSG may result in a lower AHI with more hypopneas than classical OSA, even with the same age and BMI. It is evident that sleep and quality of life are affected by the presence of OSA; therefore, NPSG must be performed if clinical suspicion exists. Evaluating the severity of both diseases collectively is essential, because if moderate-to-severe OSA is diagnosed in a patient with mild IPF (CI-A group), the quality of life and the level of dyspnea can be same as in a patient with severe IPF with moderate-to-severe OSA (CI-B group). The discordance between the severity of IPF and the symptoms of the patient must lead up to further evaluation for comorbidities like OSA.

Ethics Committee Approval: Ethics Committee approval for the study was obtained from the Institutional Review Board of Atatürk Chest Diseases and Chest Surgery Training and Research Hospital (decision number: 563, decision date: 02.08.2017).

Informed Consent: Written informed consent was obtained from the patients for the usage of their data.

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