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SCIENTIFIC INVESTIGATIONS

Patients with idiopathic pulmonary fibrosis with and without obstructive sleep apnea: differences in clinical characteristics, clinical outcomes, and the effect of PAP treatment

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Study Objectives: Obstructive sleep apnea (OSA) in patients with idiopathic pulmonary fibrosis (IPF) is associated with worse mortality and clinical outcome. We aimed to assess differences between patients with IPF with and without OSA and the effect of positive airway pressure treatment on sleep and overall life quality, morbidity, and mortality in these patients.

Methods: Forty-five patients with newly diagnosed IPF underwent polysomnography. Using an apnea-hypopnea index ≥ 15 events/h for OSA diagnosis resulted in 16 patients with IPF and 29 with IPF-OSA. The patients completed the Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Functional Outcomes in Sleep Questionnaire, Fatigue Severity Scale, Short Form-36 life questionnaire, and Beck Depression Inventory before and at the end of the follow-up period.

Results: Patients with IPF-OSA showed the most severe functional impairments in questionnaires, especially for General Health component of the Short Form-36 life questionnaire (37 vs 58, $P = .03$). At the 7-year follow-up, 16 (36%) patients had died, 6 (38%) in the IPF group and 10 (35%) in IPF-OSA group. Patients with ≥6-hour positive airway pressure use had better survival compared with patients with <6-hour use ($P = .04$). Significant improvement was also observed in Epworth Sleepiness Scale (3 vs 6, $P = .03$), Pittsburgh Sleep Quality Index (5 vs 8, $P = .01$), and Fatigue Severity Scale (37 vs 48, $P = .008$) score in patients with ≥4-hour positive airway pressure use.

Conclusions: OSA plays a significant role on clinical features and quality of life in patients with IPF. Effective positive airway pressure treatment results in a significant improvement in sleepiness, fatigue, sleep quality, and mortality.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: CPAP Therapy in Patients With Idiopathic Pulmonary Fibrosis and Sleep Apnea; URL: https://clinicaltrials.gov/ct2/show/record/NCT01637831; Identifier: NCT01637831.

Keywords: obstructive sleep apnea; idiopathic pulmonary fibrosis; positive airway pressure; treatment; life quality; mortality

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BRIEF SUMMARY

Current Knowledge/Study Rationale: There are data suggesting that the presence of obstructive sleep apnea in patients with idiopathic pulmonary fibrosis is associated with worse prognosis in terms of mortality and clinical deterioration. This study aimed to investigate clinical characteristics and outcomes between patients with idiopathic pulmonary fibrosis with and without obstructive sleep apnea and the effect of positive airway pressure treatment on sleep and overall life quality parameters, morbidity, and mortality in these patients.

Study Impact: Our results show that management of obstructive sleep apnea in idiopathic pulmonary fibrosis is important because of its significant impact in life expectancy and quality of life. These findings underline the importance of comorbid obstructive sleep apnea awareness and effective treatment in patients with idiopathic pulmonary fibrosis.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) represents a specific form of interstitial lung diseases of unknown cause, with a fatal prognosis.[1] Although IPF is limited to the lungs, many comorbid conditions may influence the prognosis and modify the natural course of the disease.[2] Importantly, sleep-related disorders, such as obstructive sleep apnea (OSA), have been recognized as an important comorbidity in the latest official guidelines for the diagnosis and management of IPF.[1,3–5] Moreover, the prevalence of OSA on IPF has been reported from 50% to 90%,[3–10] which is higher than in the general population. Most of these patients have moderate to severe OSA (apnea-hypopnea index [AHI] > 15 events/h).[4,5,8]

It is worth noting that the presence of OSA in patients with IPF has been associated with worse prognosis in terms of mortality and clinical deterioration.[6] In addition, severe OSA was strongly associated with ischemic heart disease in newly diagnosed patients with IPF compared with patients with no or mild-to-moderate OSA.[8] Despite these adverse clinical outcomes, few patients with IPF are evaluated for OSA.[9]

As with the general population, moderate-to-severe OSA in patients with IPF should be treated with positive airway pressure (PAP), which has been shown to improve quality of life and sleep.[3,11,12] However, PAP nonadherence is common for a variety of reasons such as claustrophobia, irritating cough during sleep, insomnia, and depression.[11] Previously, we showed that PAP therapy reduced mortality and resulted in significant improvement in all used quality-of-life and sleep instruments in treatment-naïve patients with IPF after 1 year of effective PAP treatment.[3] However, new prospective clinical trials are needed in the long term about the impact of this treatment in the prognosis of the disease. Therefore, the aim of our study was to assess (1) clinical characteristics and outcomes between IPF patients with and without OSA and (2) the effect of PAP treatment on sleep and overall life quality parameters, morbidity, and mortality in these patients.

METHODS

Study patients

We conducted a single-center, prospective, long-term follow-up study of newly diagnosed IPF. Between January 2013 and January 2020, consecutive patients with IPF between 55 and 83 years of age were admitted to the Sleep Disorders Center, Department of Respiratory Medicine, University of Crete Medical School, for evaluation of suspected sleep-disordered breathing. Patients were eligible for the study if they had histologically proven IPF (usual interstitial pneumonia) on surgical lung biopsy, or, in the absence of surgical biopsy, they fulfilled the recent American Thoracic Society, European Respiratory Society and American College of Chest Physicians criteria for the diagnosis of IPF.[1] To be included in the study, patients had to be clinically stable for at least 4 weeks before enrollment. In addition, all included patients had to have an above-elementary school education. The exclusion criteria were as follows: refusal to participate, central sleep apnea syndromes, severe congestive heart failure, a history of life-threatening arrhythmias, severe cardiomyopathy, significant chronic kidney disease, untreated hypothyroidism, family or personal history of mental illness, drug or alcohol abuse, sedative use, severe cognitive impairment, concurrent oncologic diseases, history of narcolepsy, or restless legs syndrome.

All participants provided written informed consent and ethical approval was provided by the University Hospital Ethics Committee (Protocol 4222).

Measurements

All patients underwent a detailed evaluation that included age, measurement of body mass index (BMI), medical history focused on sleep-related symptoms, associated conditions and comorbidities, smoking history, and alcohol intake. In addition, we performed pulmonary function tests (PFTs), 6-minute walking distance test (6MWT), overnight attended polysomnography (PSG), and arterial blood gases.

PFTs

All patients underwent PFTs and recording of O_2 saturation (SpO_2) by noninvasive pulse oximetry. Spirometry and assessment of the carbon monoxide diffusing capacity of the lung were performed using standardized procedures.[13,14] Spirometry was performed with the patient in the upright and supine position. In addition, to summarize the clinical-functional severity in patients with IPF, we used the gender-age-physiology (GAP) index, a multidimensional prognostic staging system based on clinical and physiologic variables (sex, age, forced vital capacity [FVC], and carbon monoxide diffusing capacity of the lung).[15] Patients were classified in 3 stages according to GAP index: stage 1 (GAP index 0–3, 24 patients), stage 2 (GAP index 4–5, 15 patients), and stage 3 (GAP index > 5, 6 patients).

Questionnaires

The patients completed the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes in Sleep Questionnaire (FOSQ), Fatigue Severity Scale (FSS), quality-of-life questionnaire (Short-Form-36 [SF-36]), and Beck Depression Inventory before and at the end of the follow up period.

FOSQ

The FOSQ is a 30-item self-administrated questionnaire designed to measure the impact of excessive sleepiness on multiple activities of daily life. Lower scores indicate greater dysfunction.[16,17]

PSQI

A self-reported assessment of sleep was determined using the PSQI questionnaire, which is a standard instrument that has been validated as differentiating poor from good sleep. The higher the score, the greater the negative impact on sleep quality. A global score of 6 indicates poor sleep.[18,19]

ESS

The ESS is currently the most widely used self-reported test of daytime sleepiness in clinical practice. It is a simple, self-administered, 8-item questionnaire that measures the risk of falling asleep in 8 specific situations that are commonly encountered. A score of 10 is considered normal. The higher the score (from 10 to 24), the greater the reported self-reported daytime sleepiness.[20]

FSS

In this scale, individuals rate their agreement (range, 1–7) with 9 statements concerning the severity, frequency, and impact of fatigue on daily life (physical functioning, exercise and work, and family or social life). A total score of less than 36 is considered normal. A score above that limit (maximum score 63) is suggestive of a significant negative impact of fatigue on daily life activities.[21]

SF-36 Health Survey

This 36-item questionnaire is a reliable and validated tool for the assessment of general (physical and mental) health and quality of life.[22] The SF-36 encompasses 8 domains, each of which is scored separately from 0 (worst) to 100 (best). The SF-36 scales are summarized into 2 dimensions: the physical health dimension and the mental health dimension. The score ranges

from 0 to 100, with the best quality of life corresponding to 100 and the worst to 0.

Beck Depression Inventory

This 21-item questionnaire is a widely used and well-validated self-reported inventory of depressive symptoms.[23] The Beck Depression Inventory (BDI) measures the severity of depressive symptoms over the preceding week. For each item, the respondent chooses 1 or more options rated from 0 (absence of symptoms) to 3 (most severe level). Total scores range from 0 to 63 and represent the sum of the highest level endorsed on each item. Scores below 10 are considered normal.

Sleep study and PAP treatment

PSG

All patients underwent a single-night full diagnostic PSG study (Alice 5 Diagnostics System; Respironics, Murrysville, Pennsylvania) according to standard techniques, with monitoring of the electroencephalogram (using 3 electroencephalogram derivations: frontal, central, and occipital), electro-oculogram, electromyogram, flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort (by respiratory inductance plethysmography), pulse oximetry (SpO_2), and body position monitoring. Snoring was recorded by a microphone placed on the anterior neck. The definition of apnea and hypopnea followed the American Academy of Sleep Medicine standard criteria.[24] The AHI, calculated as the number of apnea and hypopnea events per hour of sleep, was used to diagnose OSA and assess its severity. OSA was considered mild at AHI of 5 to < 15 events/h, moderate at AHI of 15 to < 30 events/h, and severe at AHI ≥ 30 events/h.

PAP titration

During in-laboratory PAP titration with full PSG, the appropriate PAP settings were established. All patients received education before the PAP titration night and completed a questionnaire at the end of the first night, reporting their quality of sleep under PAP titration and any side effects. Furthermore, heated humidification was added to all patients during the titration study and thereafter from the first PAP initiation to to improve dry nocturnal cough.

Follow-up

All study groups received individual counseling during scheduled clinic appointments, at their initial sleep clinic consultation, and after the completion of overnight in-laboratory PSG. Once PAP therapy was started, patients were followed up in the outpatient sleep clinic at 1 month and then in 3-month intervals during the first year and every 6 months thereafter. Patients were advised to bring their PAP device and interface to every sleep clinic visit. The importance of good adherence to PAP therapy was emphasized, encouraging the patients to use PAP therapy throughout the entire sleep period every day. The study was designed to follow patients for at least 5 years.

PAP adherence

PAP use data included mask type (nasal or full face), number of nights on PAP, average use per night (hours), air leakage, and air pressure delivered. Regular PAP adherence (good adherence) was defined as using PAP therapy for an average of 4 hours a night for at least 70% of the nights.

Statistical analysis

Results are presented as mean ± standard deviation for continuous variables if normally distributed and as median (25th–75th percentile) if not. Qualitative variables are presented as absolute number (percentage). For comparisons between groups, a 2-tailed *t* test for independent samples (for normally distributed data) or a Mann–Whitney *U* test (for nonnormally distributed data) was used for continuous variables, and the χ^2 test was used for categorical variables. To compare changes from baseline to follow-up, the paired samples *t* test (for normally distributed data) and the Wilcoxon signed rank test (for nonnormally distributed data) were used. Correlation coefficients were calculated using the Pearson or Spearman (for nonnormally distributed data) correlation test for all the independent predictors of OSA severity. Only the variables that were found to be significant were further analyzed. Multivariate linear regression analysis was used to examine any association between potential confounders with respiratory function indices recorded during wakefulness and sleep and questionnaire scores. All models were adjusted for potential explanatory variables, including age, BMI, AHI, smoking status, and comorbidities. We checked multicollinearity among the predictors using collinearity statistics to ensure that collinearity between predictor variables was in the acceptable range as indicated by the tolerance value variance inflation factor. However, Bonferroni adjustments were not conducted because of the small sample size. The Kaplan–Meier method of survival analysis was applied for the calculation of survival rates, and log-rank analysis was used to detect differences between groups. Clinically relevant variables were entered into a Cox proportional hazard model analysis to determine the variables independently associated with mortality in the 2 study groups. The following variables were finally selected to enter in the Cox model: age, BMI, smoking habit, arterial hypertension, diabetes mellitus, previous coronary heart disease, OSA diagnosis, and GAP classification. $P < .05$ was considered statistically significant. Data were analyzed using SPSS software (version 25; SPSS Inc., Chicago, IL).

RESULTS

Fifty-four consecutive patients with newly diagnosed IPF were prospectively recruited and were asked to participate in the study. Of those, 45 (30 males and 15 females; age, 72 ± 6 years) agreed to participate and were evaluated at the sleep center. Most patients with IPF had mild GAP scores (53%). Fourteen patients (31%) started antifibrotic treatment and 18 patients (40%) used long-term oxygen therapy after study initiation. Of the 45 patients who underwent overnight PSG, OSA was confirmed in 38 of 45 patients (84%; AHI ≥ 5 events/h). The severity distribution showed the presence of moderate-severe form in 29 (76%) patients with OSA. Specifically, 11 (24%) had an AHI within the normal range, 5 (11%) patients had an AHI

compatible with mild OSA, 13 (29%) had moderate OSA, and 16 (36%) patients had severe OSA. Respiratory events were mostly obstructive or mixed, with central representing less than 5% of scored events.

Differences in clinical characteristics of patients with IPF with and without OSA

Using AHI ≥ 15 events/h for OSA diagnosis resulted in 16 patients with IPF (36%) and 29 with IPF-OSA (64%). The clinical variables collected for the 2 groups are summarized in **Table 1** and **Table 2**. No significant differences were found for anthropometrics, comorbidities, PFTs, and arterial blood gases between groups. However, patients with IPF-OSA had lower oxygen saturation ($SpO_2 \leq 88\%$) before and at the end of a 6MWT. Concerning sleepiness, depressive symptoms, fatigue, and quality of life, patients with IPF-OSA showed the most severe functional impairments, which reached statistical significance only for the General Health component of the SF-36 (37 vs 58; $P = 0.03$). General Health was significantly correlated with AHI ($r = -.50$, $P = .001$), mean ($r = 0.30$, $P = .04$), and lowest SaO_2 during sleep ($r = 0.32$, $P = .039$), oxygen desaturation index (ODI; $r = -.4$, $P = .008$), and total sleep time with oxygen saturation < 90% (TST90; $r = -.43$, $P = .004$). In multiple regression analysis, AHI was the only significant independent predictor of the General Health ($\beta = -0.63$, $P = .015$).

The mean ESS score in the whole sample was low: most of the 13 patients (29%) who reported an ESS score > 10 belonged to IPF-OSA group. ESS was significantly correlated with AHI ($r = .29$, $P = 0.04$), mean ($r = -.30$, $P = .04$) and lowest SaO_2 during sleep ($r = -.31$, $P = .03$), and FVC (%) in supine position ($r = -.35$, $P = .03$). In multiple regression analysis, AHI (odds ratio [OR] = 1.123; 95% confidence interval [CI], 1.012–1.246; $P = .029$) and mean SaO_2 during sleep (OR = 0.621; 95% CI, 0.388–0.994; $P = .047$) were the only predictors of ESS > 10.

Forty-nine percent of patients (22 of 45) reported a BDI score ≥ 10, mostly in the IPF-OSA group (55%). Overall, the BDI score was significantly correlated with AHI ($r = .30$, $P = .04$), mean SaO_2 during sleep ($r = -.30$, $P = .04$), the amount of SWS sleep (%TST; $r = -.30$, $P = .04$), and FVC (%) in supine position ($r = -.34$, $P = .03$). In the stepwise multiple regression analysis, AHI (OR = 1.088; 95% CI, 1.012–1.246; $P = .029$) and mean SaO_2 during sleep (OR = 0.621; 95% CI, 0.388–0.994; $P = .047$) were the only predictors of BDI score ≥ 10.

Sixty percent of patients (27 of 45) reported a PSQI score > 5, 91% a FOSQ score < 18, and 74% a FSS score ≥ 36, mostly in the IPF-OSA group, although no statistical significances were noted between the groups ($P > .05$). Overall, the FOSQ score was significantly correlated with male sex ($r = .43$, $P = .005$) and age ($r = -.32$, $P = .04$), even after multiple regression analysis ($\beta = 2.8$, $P = .001$ and $\beta = -0.21$, $P = .003$, respectively). FSS was significantly correlated with BMI ($r = .34$, $P = .03$), AHI ($r = .38$, $P = .014$), mean SaO_2 during sleep ($r = -.37$, $P = .015$), ODI ($r = .36$, $P = .02$), and TST90 ($r = .36$, $P = .02$). Although mean SaO_2 during sleep was the only predictor of FSS score ≥ 36 after multiple regression analysis (OR = 0.628; 95% CI, 0.396–0.996; $P = .048$), no significant predictors were found for PSQI score.

Correlation between OSA and IPF

Sleep structure and sleep respiratory data are shown in **Table 3**. There was no correlation at baseline of AHI, ODI, and TST90 with any upright lung function variables, age, or comorbidities. However, AHI was correlated with BMI ($r = .33$, $P = .025$), WC ($r = .42$, $P = .008$), resting awake SpO_2 ($r = -.48$, $P = .001$), arterial PaO_2 ($r = -.33$, $P = .029$), supine FVC % ($r = -.37$, $P = .02$), and SpO_2 after 6MWT ($r = -.38$, $P = .013$). ODI was correlated with BMI ($r = .32$, $P = .032$), WC ($r = .40$, $P = .013$), arterial PaO_2 ($r = -.32$, $P = .033$), supine FVC % ($r = -.32$, $P = .04$), and SpO_2 after 6MWT ($r = -.37$, $P = .017$) as well. Nevertheless, correlation of AHI ($\beta = -0.34$, $P = .06$) and ODI ($\beta = -0.31$, $P = .12$) with supine FVC % disappears after adjustment for BMI.

Linear correlations between respiratory function indices recorded during wakefulness and sleep are showed in **Table 4**. In a stepwise multiple regression analysis, only TST90 ($\beta = -0.005$; 95% CI, −0.009 to 0; $P = .03$) and DLCO ($\beta = 0.024$; 95% CI, 0.006–0.043; $P = .012$) were identified as predictors of daytime SpO_2. Similarly, only TST90 was identified as predictor of nocturnal SpO_2 ($\beta = -0.006$; 95% CI, −0.01 to −0.002; $P = .006$).

Follow-up

At 7-year follow-up, 16 (36%) patients had died: 6 (38%) in the IPF group and 10 (35%) in the IPF-OSA group. Fourteen of all deaths were caused by respiratory failure related to their IPF, 1 patient had comorbid lung cancer either causing or contributing to his death, and 2 patients died because of acute chronic heart failure. Mean survival was 64 months for the cohort overall. There was a significant difference between survived or died patients for age (70 vs 75, $P = .01$), 6MWT (428 vs 200 m, $P < .001$), upright FVC % (77 vs 62, $P = .01$), supine FVC % (70 vs 58), DLCO (%) (60 vs 37, $P < .001$), TST90 (39 vs 124, $P = .007$), awake SpO_2 (96 vs 94, $P < .001$), and GAP category (100% vs 0% in GAP III, $P = .001$). Survival curves were similar in the 2 groups stratified according to OSA diagnosis (**Figure 1**; Mantel-Cox log-rank $\chi^2 = 0.003$; $P = .959$). Survival curves, however, were significantly different when patients were stratified for GAP Index as shown in **Figure 2** (Mantel-Cox log-rank $\chi^2 = 41.845$; $P < .001$). In Cox proportional hazards, multiple regression analysis identified the presence of coronary artery disease diagnosis (hazard ratio, 9.79; 95% CI, 1.2–83.2; $P = .03$), BMI (hazard ratio, 1.21; 95% CI, 1.021–1.442; $P = 0.03$), and GAP Stage III (HR, 300.2; 95% CI, 24.8–3634.1; $P < .001$) as predictors of mortality.

Effect of PAP use

Twenty-nine of 45 patients started PAP treatment. Of those, 11 (38%) had ≥ 4-hour PAP use per day (good adherence group) and 6 had ≥ 6-hour PAP use per day (21%). The overall survival of patients with IPF (**Figure 3**) with IPF-OSA who used PAP (good and poor PAP adherence groups) showed differences (2 deaths in the >4-hour group compared with 8 deaths in the <4-hour group), although not statistically significant at the end of follow up after PAP initiation (Mantel-Cox log-rank $\chi^2 = 1.75$; $P = .186$). However, patients with ≥6-hour PAP use had better survival (no deaths) compared with

Table 1—Baseline demographics, spirometric measurements, and ABG analysis results of the final sample.

Characteristics	All patients (n = 45)	IPF (n = 16)	IPF-OSA (n = 29)	*P*
Age (yr)	72 ± 6	73 ± 7	71 ± 6	.25
Sex, male (%)	30 (67%)	10 (63%)	20 (69%)	.66
BMI (kg/m^2)	30 ± 4	29 ± 4	31 ± 4	.13
Neck circumference (cm)	40 ± 3	40 ± 4	41 ± 3	.55
Smoking status, n (%)				
Current smokers	3 (7%)	1 (6%)	2 (7%)	.59
Ex-smokers	24 (53%)	7 (44%)	17 (59%)	
Comorbidities, n (%)				
Diabetes mellitus	11 (25%)	3 (19%)	8 (29%)	.47
Hypertension	31 (71%)	10 (63%)	21 (75%)	.38
Dyslipidemia	19 (43%)	8 (50%)	11 (39%)	.49
Ischemic heart disease	6 (14%)	2 (13%)	4 (14%)	.87
Compensated heart failure	2 (5%)	0	2 (7%)	.27
Hypothyroidism	6 (14%)	3 (19%)	3 (11%)	.46
COPD	9 (21%)	2 (13%)	7 (25%)	.32
GERD	15 (35%)	5 (31%)	10 (37%)	.7
GAP Index, n (%)				.58
Stage I	24 (53%)	9 (56%)	15 (52%)	
Stage II	15 (33%)	4(25%)	11 (38%)	
Stage III	6 (13%)	3 (19%)	3 (10%)	
PFT				
FEV1, % predicted	85 ± 20	89 ± 24	82 ± 17	.21
FVC, % predicted	82 ± 18	83 ± 23	81 ± 16	.74
FEV1/FVC	81 ± 8	85 ± 8	80 ± 8	.05
TLC (%)	75 ± 17	79 ± 22	73 ± 14	.28
DLCO (%)	60 (37–70)	58 (40–70)	62 (40–69)	.89
6MWD				
Distance (m)	400 (230–480)	480 (360–480)	380 (160–480)	.38
SpO_2 before %	76 ± 9	79 ± 10	73 ± 8	.04
SpO_2 after %	61 (52–76)	76 (56–86)	58 (49–71)	.013
PFT (supine)				
FVC, % pred, upright	72 ± 18	76 ± 18	70 ± 18	.37
FVC, % pred, supine	66 ± 18	72 ± 17	63 ± 17	.11
ABG				
pH	7.41 ± 0.02	7.41 ± 0.02	7.41 ± 0.02	.62
PCO_2 (mm Hg)	40.4 ± 3.7	39.8 ± 2.3	40.7 ± 4.3	.49
PO_2 (mm Hg)	75.6 ± 9.2	79.4 ± 10.0	73.5 ± 8.3	.06
HCO_3^- (mmol/L)	25.1 ± 2.3	24.6 ± 1.7	25.3 ± 2.5	.29

Data are presented as mean values ± standard deviation or median (25th–75th percentile), unless otherwise indicated. 6MWD = 6-minute walking distance, ABG = arterial blood gases, BMI = body mass index, COPD = chronic obstructive pulmonary disease, DLCO = predicted diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GAP = gender-age-physiology, GERD = gastroesophageal reflux disease, IPF = idiopathic pulmonary fibrosis, OSA, obstructive sleep apnea, PFT = pulmonary function test, SpO_2 = resting room air pulse oximetry, TLC = total lung capacity.

patients with <6-hour use (**Figure 4**; Mantel-Cox log-rank $\chi^2 = 3.35$; $P = .04$).

Concerning acute exacerbations of IPF, patients who experienced clinical exacerbation during follow-up showed higher baseline values of TST90 during sleep (94 vs 28, $P = .01$), higher GAP category (100% vs 0% in GAP III, $P = .02$), lower DLCO (%) (46 vs 62, $P = .008$), and PaO_2 before (81 vs 73, $P = .003$) and after 6MWT (59 vs 75, $P \leq .001$) than those without clinical deterioration. No differences were found for daytime respiratory function or the other PSG parameters.

Table 2—Questionnaires scores between groups.

Questionnaires	All patients (n = 45)	IPF (n = 16)	IPF-OSA (n = 29)	*P*
ESS	6 (3–11)	4.5 (3–8.5)	6 (3–8)	.21
ESS ≥ 10, n (%)	13 (29%)	3 (19%)	10 (35%)	.27
BDI	10 (5–19)	9 (5–13)	11 (5–13)	.49
BDI ≥ 10, n (%)	22 (49%)	6 (38%)	16 (55%)	.45
PSQI	6.6 ± 3.4	6.5 ± 3.5	6.6 ± 3.4	.92
PSQI ≥ 5, n (%)	27 (60%)	9 (57%)	18 (62%)	.97
FOSQ	13.4 ± 2.9	13.8 ± 3.0	13.1 ± 2.9	.47
FOSQ < 18, n (%)	38 (91%)	12 (86%)	26 (93%)	.59
FSS	46 (33–54)	41 (17–55)	47 (18–54)	.33
FSS ≥ 36, n (%)	31 (74%)	9 (64%)	22 (79%)	.32
SF-36				
PF	53.2 ± 30.1	57.1 ± 32.1	51.3 ± 29.5	.56
RP	38 (0–81)	50 (19–81)	25 (0–94)	.48
BP	79 (52–100)	67 (42–100)	100 (61–100)	.29
GH	45 (27–71)	58 (40–73)	37 (25–65)	.03
PCS	40 ± 11	42 ± 12	39 ± 10	.51
VT	50 ± 25	50 ± 27	50 ± 25	.97
SF	100 (50–100)	75 (50–100)	100 (50–100)	.64
RE	50 (33–100)	66 (33–100)	33 (33–100)	.99
MH	62 ± 21	63 ± 19	62 ± 23	.84
MCH	46 ± 11	46 ± 10	46 ± 11	.86

Data are presented as mean values ± standard deviation or median (25th–75 percentile), unless otherwise indicated. BDI = Beck Depression Inventory, BP = bodily pain, ESS = Epworth Sleepiness Scale, FOSQ = Functional Outcomes in Sleep Questionnaire, FSS = Fatigue Severity Scale, GH = general health, IPF = idiopathic pulmonary fibrosis, MCH = mental component, MH = mental health, OSA, obstructive sleep apnea PF = physical functioning, PSQI = Pittsburgh Sleep Quality Index, RE = role emotional, RP = role physical, SF = social functioning, SF-36 = Short-Form-36, PCS = physical component, VT = vitality.

Furthermore, in the IPF-OSA group, patients who experienced clinical exacerbation during follow-up showed lower PAP use (68% used PAP < 4 hours, $P = .39$).

Concerning quality of life, no statistically significant improvements in questionnaires scores at the end of the follow-up period were noted in all patients and separately in IPF and IPF-OSA groups apart from ESS ($P = .019$) and BDI ($P < .001$) which was improved in the IPF-OSA group (**Table S1** in the supplemental material). Related to adherence to PAP groups, statistically significant changes were noted in ESS, PSQI, and FSS only in the good adherence group (**Table 5**).

DISCUSSION

The identification and management of comorbidities, such as OSA, is an important element of the overall care of patients with IPF. We found that OSA is a common comorbidity in IPF in agreement with previous studies[3–10] and plays a significant role on quality of life in patients with IPF, as most of these patients believed that their health would be worsening. Effective PAP treatment resulted in a significant improvement in sleepiness, fatigue, sleep quality, and exacerbations in patients with IPF and OSA. Furthermore, PAP treatment improved life expectancy in long-term follow-up, providing the first evidence that OSA treatment may also influence mortality in IPF.

OSA seems to be a common disorder in patients with IPF, and our results show that 64% of patients with incident IPF had a moderate-to-severe OSA defined by an AHI ≥ 15 events/h. However, it is too early to characterize this as an overlap syndrome because further research is mandatory with larger number of patients. In contrast, OSA with prolonged sleep-related desaturation and disrupted sleep architecture has significant impact in life expectancy, clinical deterioration, and quality of life.[6,8,25–27] Concerning quality of life, in our study, significant differences were presented in the General Health domain of the SF-36, with most of the patients with OSA-IPF believing that their health would be worsening. Moreover, a considerable percentage of patients in both groups had depressive symptoms in accordance with previous studies reporting prevalence of depression ranges from 24.3% to 49.2%.[28–30] Specifically 55% of patients with IPF and OSA reported depressive symptoms compared with 38% of patients with pure IPF, although the difference was not statistically significant, probably because of the low number of patients in our study. However, we should keep in mind that depression scores in questionnaires are not always suggestive of clinically meaningful depression in these patients.[31–33] Despite that,

Table 3—PSG characteristics of IPF patients with and without OSA.

Characteristics	All patients (n = 45)	IPF (n = 16)	IPF-OSA (n = 29)	*P*
Sleep latency (min)	37 (26–66)	58 (33–70)	35 (25–58)	.07
Sleep efficiency (%)	56 (41–66)	50 (39–64)	61 (44–66)	.36
WASO (min)	149 (119–197)	175 (113–201)	142 (119–196)	.57
REM latency (min)	313 (178–371)	350 (190–379)	301 (178–356)	.30
TST (min)	241 ± 63	233 ± 70	244 ± 60	.58
N1 (% TST)	2.8 ± 1.3	2.9 ± 1.3	2.6 ± 1.4	.52
N2 (% TST)	81 ± 4.0	80.8 ± 4.8	80.3 ± 3.5	.78
N3 (% TST)	7.5 ± 2.7	7.8 ± 2.9	7.3 ± 2.7	.51
REM (% TST)	9.0 ± 2.9	9.3 ± 3.7	8.8 ± 2.5	.45
AI (events/h)	46 ± 14	35.6 ± 13.0	51.5 ± 11.2	<.001
AHI (events/h)	25 (6–38)	5 (2–8)	35 (20–49)	<.001
AHI REM (events/h)	27 (9–49)	5 (1–9)	39 (26–66)	<.001
ODI (events/h)	24 ± 19	5.3 ± 3.8	37 ± 18	<.001
TST90 (min)	30 (3–82)	2 (0–8)	47 (25–189)	<.001
Mean SpO_2 (%)	92 ± 4	94.1 ± 1.5	91.5 ± 4.7	.03
Lowest SpO_2 (%)	82 ± 8	87.4 ± 3.7	78.8 ± 7.8	<.001

Data are presented as mean values ± standard deviation or median (25th–75th percentile), unless otherwise indicated. AHI = apnea-hypopnea index, AI = arousal index, ODI = oxygen desaturation index, SpO_2 = resting room air pulse oximetry, TST = total sleep time, TST90 = sleep time with oxygen saturation < 90%, WASO = wake after sleep onset.

Table 4—Linear correlations between respiratory function indices recorded during wakefulness and sleep.

Daytime SpO_2			Sleep SpO_2		
Variables	***r***	***P***	**Variables**	***r***	***P***
AHI	−0.48	.001	AHI	−0.48	.001
ODI	−0.49	.001	ODI	−0.33	.025
TST90	−0.52	<.001	TST90	−0.71	<.001
DLCO	0.38	.014	BMI	−0.30	.04
SpO_2 after 6MWT%	0.65	<.001	SpO_2 after 6MWT%	0.4	.007

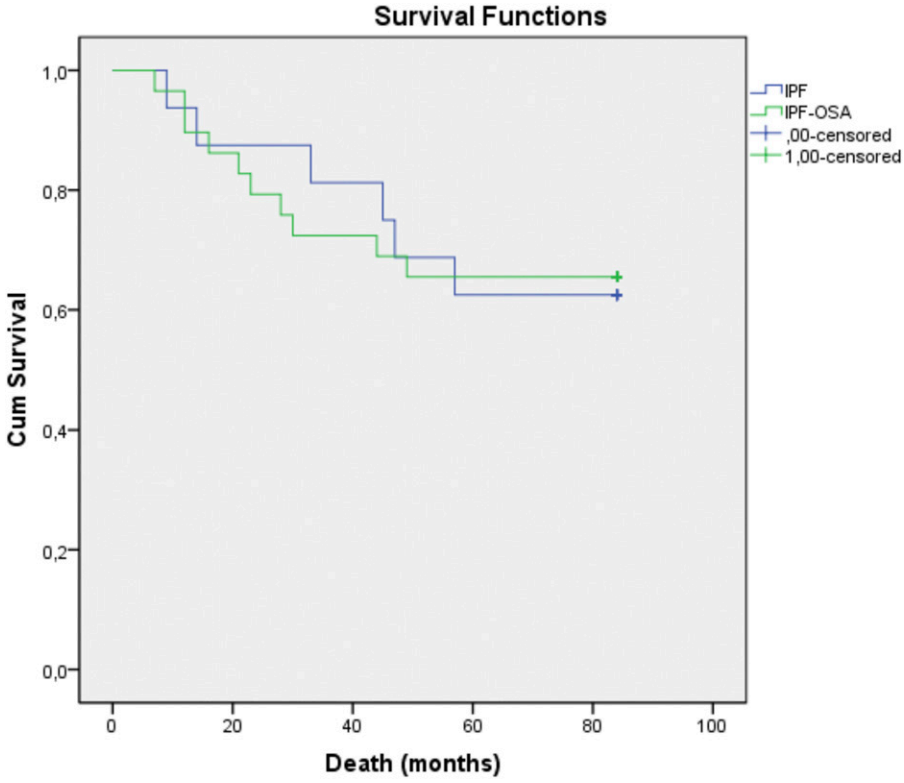
6MWD = 6-minute walking distance, AHI = apnea-hypopnea index, DLCO = predicted diffusing capacity of the lung for carbon monoxide, ODI = oxygen desaturation index, SpO_2 = resting room air pulse oximetry,TST90 = sleep time with oxygen saturation < 90%.

depression alters the perception of respiratory symptoms; has been associated with the severity of dyspnea, cough, and pulmonary dysfunction[34,35]; and influences quality of life.[33] Therefore, treatment of depression in these patients may improve not only mood but also dyspnea. Nonetheless, further studies are required to determine whether psychologic and pharmacologic treatment for depression can improve health outcomes such as quality of life, mortality, hospitalization, and exacerbation of symptoms in patients with IPF or even adherence to PAP therapy.

Another interesting point is that upright PFTs did not correlate with AHI. However, the association between sleep-disordered breathing and IPF is still questionable.[5,9] It could be expected that restrictive lung diseases, such as IPF, are characterized by decreased lung volumes that could induce upper airway instability and promote OSA. One possible explanation for the lack of correlation between the PFTs and the severity of OSA is that lung volumes were only mildly decreased, consistent with early-stage IPF. It has also been suggested using PFTs performed with the patient in the upright or standing position and not in the supine position may not be accurate at predicting sleep lung volumes. Although supine measurements were obtained in our study correlation of AHI with supine FVC was statistically borderline after adjustment for BMI, and furthermore, patient recruitment is required to determine exactly how PFTs affects OSA severity. AHI was correlated with BMI, in accordance with previous studies,[5,9] suggesting that obesity was a major risk factor for OSA in incident IPF.

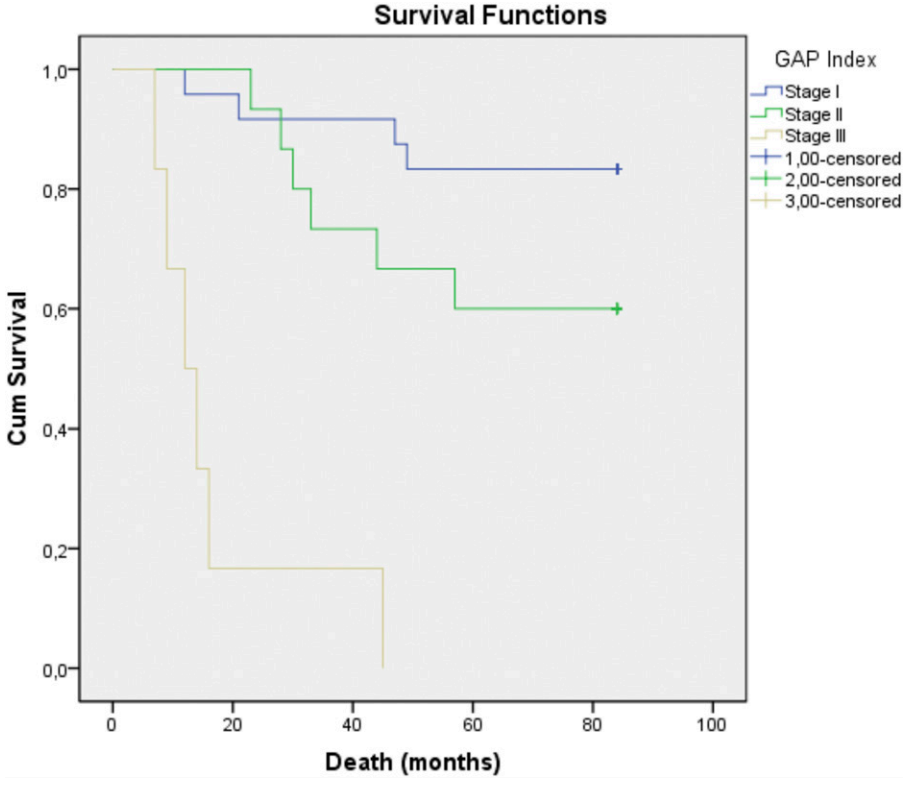
Patients with IPF with OSA should be treated with PAP as all other patients with OSA. PAP therapy is efficacious across a range of adverse outcomes and has been also shown to improve quality-of-life measures and sleep instruments in those with IPF.[3] Importantly, good PAP compliance resulted in significant improvement in all used quality-of-life and sleep instruments and reduced mortality after 1 year of PAP treatment.[3] This study provided the first evidence that treatment of comorbidities such as OSA may also influence mortality in a fatal disease, such as

Figure 1—Median survival of patients with IPF and IPF-OSA.



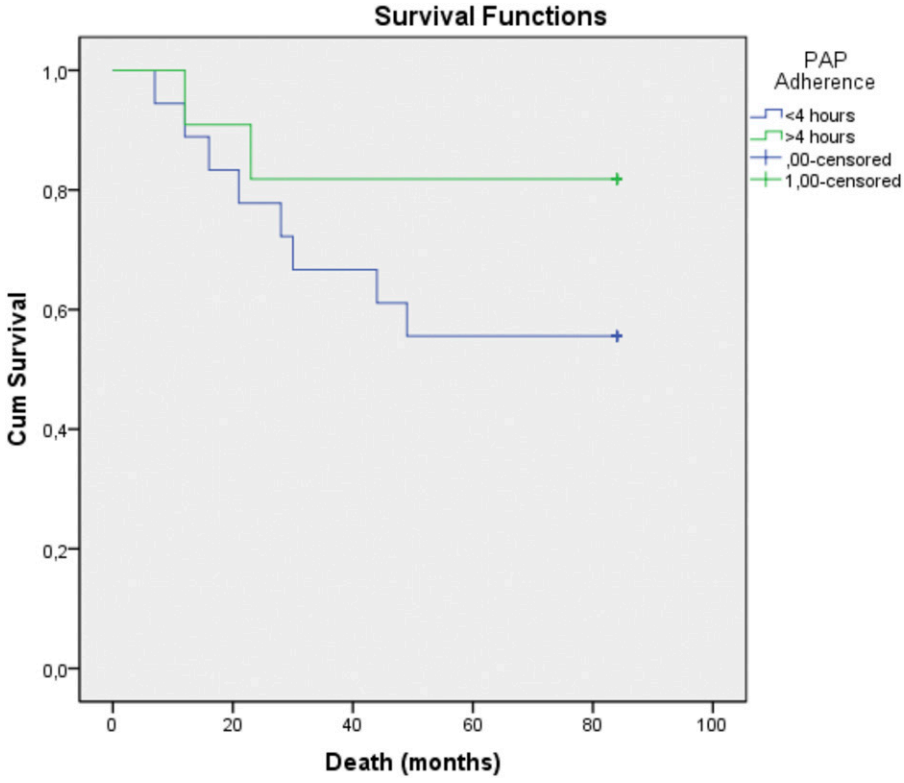
IPF = idiopathic pulmonary fibrosis, OSA, obstructive sleep apnea.

Figure 2—Median survival of patients with IPF according to GAP Index.



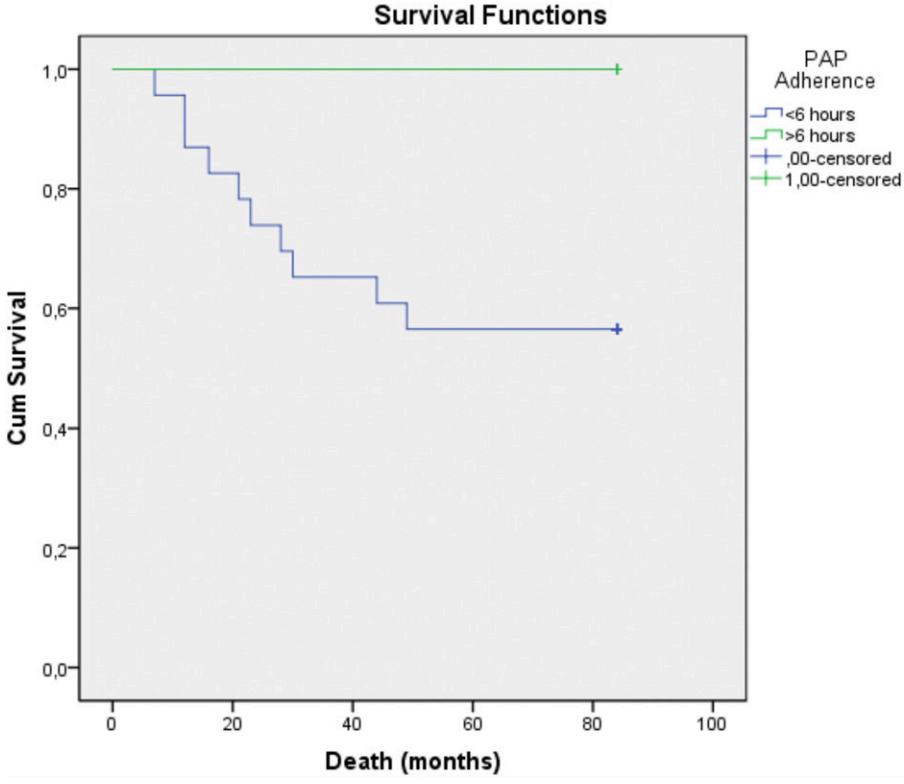
IPF = idiopathic pulmonary fibrosis, GAP = gender-age-physiology.

Figure 3—Median survival of patients with IPF-OSA according to PAP use (≥4 vs <4 hours of PAP use).



IPF = idiopathic pulmonary fibrosis, OSA, obstructive sleep apnea, PAP = positive airway pressure.

Figure 4—Median survival of patients with IPF-OSA according to PAP use (≥6 vs <5 hours of PAP use).



IPF = idiopathic pulmonary fibrosis, OSA, obstructive sleep apnea, PAP = positive airway pressure.

Table 5—Questionnaires scores before and at the end of the follow up period according to PAP use.

Questionnaires	PAP use < 4 hours (n = 18)			PAP use ≥ 4 hours (n = 11)		
	Baseline	Follow-up	*P*	Baseline	Follow-up	*P*
ESS	6 (4–11)	5 (3–6)	.20	6 (3–12)	3 (2–6)	.03
BDI	10 (6–20)	10 (7–15)	.80	11 (3–19)	10 (5–17)	.24
PSQI	6 ± 3	7 ± 4	.38	8 ± 4	5 ± 2	.01
FOSQ	13 ± 3	13 ± 3	.73	13 ± 3	14 ± 3	.47
FSS	46 (29–51)	50 (30–56)	.46	48 (40–59)	37 (30–48)	.008
SF-36						
PF	54 ± 25	52 ± 26	.59	46 ± 37	55 ± 27	.23
RP	50 (0–88)	38 (0–94)	.77	25 (0–100)	25 (0–50)	.75
BP	100 (61–100)	87 (64–100)	.50	84 (52–100)	74 (74–100)	.35
GH	45 (33–69)	41 (23–67)	.34	25 (20–60)	40 (20–57)	.41
PCS	40 ± 9	41 ± 9	.79	37 ± 12	35 ± 9	.48
VT	49 ± 25	55 ± 23	.38	53 ± 26	51 ± 30	.80
SF	100 (56–100)	100 (78–100)	.61	100 (37–100)	75 (50–100)	.92
RE	66 (17–100)	66 (0–100)	.27	33 (33–100)	66 (33–100)	.78
MH	64 ± 18	60 ± 21	.31	59 ± 30	61 ± 18	.65
MCH	47 ± 10	47 ± 10	.89	45 ± 14	46 ± 12	.88

Data are presented as mean values ± standard deviation or median (25th–75 percentile), unless otherwise indicated. BDI = Beck Depression Inventory, BP = bodily pain, ESS = Epworth Sleepiness Scale, FOSQ = Functional Outcomes in Sleep Questionnaire, FSS = Fatigue Severity Scale, GH = general health, MCH = mental component, MH = mental health, PAP = positive airway pressure, PF = physical functioning, PSQI = Pittsburgh Sleep Quality Index, RE = role emotional, RP = role physical, SF = social functioning, SF-36 = Short-Form-36, PCS = physical component, VT = vitality.

IPF. In another previous report, including 32 patients with IPF and OSA, adherence to PAP also improved survival after 5 years of PAP initiation.[36] Likewise, in our study, patients with ≥4 hours and especially ≥6 hours PAP use had better survival, as well as lower exacerbation rates, daytime sleepiness, fatigue, and improved sleep quality compared with patients with lower PAP use.

On the other hand, the absence of statistically significant improvement in questionnaires scores in the poor PAP adherence group suggests that this level of PAP use is not sufficient to accomplish significant changes and that regular encouragement to increase PAP use is recommended. However, one of the major challenges to control chronic diseases, such as OSA is the lack of adherence to the prescribed therapeutic regimen. For example, in the fight against hypertension and diabetes, individuals with low medication adherence have a high risk of uncontrolled blood pressure, poor glycemic control, and adverse outcomes that may arise.[37,38] In OSA treatment with PAP, despite the widespread adoption in clinical practice of a threshold approach of ≥4-hour PAP use for or 70% of the nights,[39] it is suggested that the greater the number of hours of PAP use per night the greater the improvement in a range of outcomes, including sleepiness, functional status, and blood pressure.[40] The adherence rate found in our study was 38% (≥4-hour PAP use per day; 21% in ≥6-hour PAP use), lower than the 67% observed in a previous study[3] and lower to the World Health Organization estimated 50% adherence to therapy for chronic diseases in developed nations.[41] These findings may have significant clinical implications for the estimation of the duration of PAP use that is needed to decrease the health risks associated with OSA in these patients.

It is worth noting that PAP initiation in these patients is often problematic because of claustrophobia, irritating cough during sleep, insomnia, and depression.[11] The possible high incidence of PAP nonacceptance or poor adherence could only be eliminated through intense follow-up. Furthermore, one central issue is to identify OSA in patients with IPF in the early stages of the disease and not in late stages and close to death, when the possibility of PAP nonadherence is high.

One limitation of the present study is the relatively small size of our cohort, which could explain the failure to detect statistically significant effects of many of the parameters measured, and additional studies are needed to confirm the results. However, IPF is a rare disease with some difficulty in recruiting large groups at a single center. Another limitation is probably the used definition of OSA in our study that includes those patients with an AHI above 15 respiratory events per hour of sleep. However, based on general accepted criteria, PAP coverage by insurance companies is accepted in patients with moderate-severe OSA, irrespective of symptoms. IPF is not included in comorbidities in which PAP therapy is covered, even with an AHI of 5–15 events/h. The initiation of PAP in patients with IPF with mild OSA might be a future interesting research field. Last, potential biases that are related to patient behaviors or underlying patient characteristics, such as healthy user effect and the healthy adherer effect,[42] were not included in our analysis and may have influenced the effect of PAP adherence on clinical outcomes.

In conclusion, OSA is a common comorbidity in IPF and plays a significant role on the clinical features and reduced quality of life in patients with IPF. Effective PAP treatment in these patients results in a significant improvement in sleepiness, fatigue, poor sleep quality, mortality, and exacerbations. Therefore, awareness of the potential for comorbid OSA in IPF and effective treatment is crucial.

ABBREVIATIONS

AHI, apnea-hypopnea index
BDI, Beck Depression Inventory
BMI, body mass index
CI, confidence interval
ESS, Epworth Sleepiness Scale
FOSQ, Functional Outcomes in Sleep Questionnaire
FSS, Fatigue Severity Scale
FVC, forced vital capacity
GAP, gender-age-physiology
ODI, oxygen desaturation index
OR, odds ratios
OSA, obstructive sleep apnea
PAP, positive airway pressure
PFTs, pulmonary function tests
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
SF-36, Short Form-36
SpO_2, resting room air pulse oximetry
TST, total sleep time
TST90, sleep time with oxygen saturation < 90%

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.