Clinical factors predicting the severity of obstructive sleep apnea in interstitial lung disease

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Research Article

Keywords: Interstitial lung disease, Sleep disorder, Sleep apnea

Posted Date: February 21st, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1319968/v1>

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Abstract

Background and Objectives: Obstructive sleep apnea (OSA) is known to be one of the common complications of interstitial lung disease (ILD). Although it is suspected that the incidence of OSA and the progression of ILD are closely related to each other, the clinical features of ILD with such complications are not fully understood. The aim of this study is to clarify specific clinical factors in ILD patients that predict the complication and the severity of OSA.

Study Design and Method: ILD patients in our institute were prospectively investigated for the incidence of OSA by polysomnography (PSG).

Results: All 33 patients were diagnosed with OSA. Univariate regression analysis showed a lower Diffusing capacity of the lung for carbon monoxide (DLco) and a lower respiratory rate (RR) predicted a higher HI and a higher AI, respectively. Multivariate regression analysis showed a lower DLco and a lower RR also predicted a higher apnea hypopnea index (AHI).

Conclusions: A high prevalence of OSA was exhibited in our study of ILD patients. Lacking rapid breathing pattern and impaired diffusing capacity were predictive factors for the severity of OSA. The examination of sleep disorders should be actively considered for these patients.

Short title: The relationship between ILD and OSA

Introduction

Interstitial lung disease (ILD) is a diffuse lung parenchymal disease that presents restrictive disorders derived from various etiologies¹. Several complications, including lung cancer, pulmonary hypertension, and gastroesophageal reflux, are known to have impacts on their clinical course and prognosis^{2,3}. Obstructive sleep apnea (OSA) is one of the common complications of ILD. Previous reports have shown evidence of a high incidence rate of OSA in 59–90% of ILD patients^{4–8}.

The underlying mechanisms of how ILD develops the complication of OSA have not been fully clarified. However, there has been some evidence that the incidence of OSA affects the progression of ILD. For example, reactive oxygen species are known to be generated by nocturnal intermittent hypoxia of OSA. The excessive production of reactive oxygen species leads to cellular dysfunction and tissue damage, resulting in the deterioration of ILD⁹. Forced respiratory efforts against airflow obstruction in OSA possibly cause recurrent tractional injury to the periphery of the lung, which is also expected to cause lung damage and aggregate ILD¹⁰. Moreover, it is known that nocturnal hypoxia is strongly related to the presence of pulmonary hypertension^{11,12}.

Therefore, early detection of OSA is crucial for preventing the progression of ILD. OSA is sometimes asymptomatic in ILD patients and goes undiagnosed. Herein, our study aimed to clarify the clinical features predicting the incidence and severity of OSA.

Methods

Study subjects

Patients who were admitted for the examination of ILD in our institute between January 1st in 2019 and June 31st in 2021 were prospectively evaluated. Eligible patients were recruited regardless of whether they were symptomatic of sleep disorders, while those who needed urgent hospitalization or needed oxygen supply during sleep were excluded. All eligible patients underwent PSG using SOMNOtouch™ RESP (SOMNOmedics).

Patients' characteristics

Age, sex, and obesity, which were evaluated by body mass index (BMI), were investigated. Respiratory rate (RR), spirometry data, blood gas analysis, serum biomarkers such as Krebs von den Lungen-6 (KL-6) and surfactant protein D (SP-D), results of the 6-minute walk test, and the diagnosis were included in the ILD characteristics. The respiratory rate (RR) was determined by the average rate during the 5 minutes just after setting up PSG and before the patient slept.

Definition of the sleep disorder

The diagnosis of OSA was made by more than 5 apnea hypopnea index (AHI). Apnea was defined as cessation of breathing for more than 10 seconds. Hypopnea was defined as a more than 30% reduction in airflow with more than 4% desaturation, which lasted more than 10 seconds. An oxygen desaturation index 4% (ODI4%) was defined as a frequency of desaturation greater than 4% per hour. The percentage of total sleep time spent with SpO₂ < 90% (%TST90) was defined as the percentage of the time of SpO₂ under 90% per sleep time.

Statistical analysis

Data are presented as the mean ± standard deviation for continuous variables. Univariate and multivariate regression analyses were undertaken to explore the potential risk factors for the increase in apnea index (AI), hypopnea index (HI), AHI, and ODI4%. All statistical analyses were carried out using Stata 17.0 (Stata Corp., College Station, TX, USA), and p values of < 0.05 were considered significant.

Ethics approval and participant consent

The authors conducted this research in full accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Tokyo Medical and Dental University (approval number; M2018-189) and supported by a grant from Fukuda Foundation for Medical Technology. Informed consents were obtained from all the patients.

Results

Patients' characteristics

Thirty-three patients with ILD (26 males and 7 females, mean age 69.8 ± 9.2) were studied (Table 1). The mean BMI was 23.9 ± 4.6 , and the breakdown of obesity was underweight (BMI < 18.5) in 3, normal weight ($18.5 \leq \text{BMI} < 25$) in 20, overweight ($25 \leq \text{BMI} < 30$) in 7, and obese (BMI ≥ 30) in 3, according to the WHO criteria. The mean RR was 22.6 ± 6.2 . The mean forced vital capacity (FVC) was $71.1 \pm 19.9\%$ predicted, and the mean diffusing capacity of the lung for carbon monoxide (DLco) was $63.5 \pm 21.3\%$ predicted. Blood gas analysis presented a mean pH of 7.41 ± 0.02 , a mean PO₂ of 85.3 ± 12.6 mmHg, and a mean PCO₂ of 40.0 ± 4.8 mmHg. The other parameters of ILD were evaluated, including KL-6 (1256.8 ± 602.5 U/ml), SP-D (288.8 ± 215.9 ng/ml) and 6-minute walk distance (387.3 ± 113.0 m). The breakdown of the diagnosis was 16 idiopathic interstitial pneumonias including 1 idiopathic pulmonary fibrosis and 1 interstitial pneumonia with autoimmune features, and 17 fibrotic hypersensitivity pneumonias.

Table 1
Patients' characteristics

	n = 33
Age	69.8 ± 9.2
Male	26 (78.8%)
BMI (kg/m ²)	23.9 ± 4.6
underweight/ normal/ overweight/ obese	3/20/7/3
RR (/minute)	22.6 ± 6.2
FVC (%)	71.1 ± 19.9
DLco (%)	63.5 ± 21.3
pH	7.41 ± 0.02
PO ₂ (mmHg)	85.3 ± 12.6
PCO ₂ (mmHg)	40.0 ± 4.8
KL-6 (U/ml)	1256.8 ± 602.5
SP-D (ng/ml)	288.8 ± 215.9
6MWD (m)	387.3 ± 113.0
Diagnosis (IIPs/ Fibrotic HP)	16/17
BMI, body mass index; RR, respiratory rate; FVC, Forced vital capacity; DLco, Diffusing capacity of the lung for carbon monoxide; KL-6, Krebs von den Lungen-6; SP-D, Surfactant protein-D; IIPs, Idiopathic interstitial pneumonias; HP, Hypersensitivity pneumonia.	

Sleep architecture and questionnaires

All 33 patients had OSA (mean AHI was 28.6 ± 17.0 , 7 for mild, 13 for moderate, and 13 for severe OSA) (Table 2). Other parameters reflecting the sleep disorder were 11.9 ± 9.0 /h of ODI4%, $9.6 \pm 19.2\%$ of %TST90, $15.3 \pm 1.2\%$ of REM sleep, $2.4 \pm 4.3\%$ of N3 sleep, and 24.0 ± 9.6 /h of arousal response. Sleep questionnaires revealed Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) scores of 4.9 ± 2.0 and 6.0 ± 3.0 , respectively.

Table 2
Sleep architecture and questionnaires

	n = 33
AHI (/h)	28.6 ± 17.0
No OSA/ Mild OSA/ Moderate OSA/ Severe OSA	0/7/13/13
AI (/h)	11.9 ± 14.4
HI (/h)	16.5 ± 7.9
Obstructive (/h)	23.0 ± 13.3
Central (/h)	0.7 ± 1.34
Mixed (/h)	1.1 ± 2.4
ODI4%	11.9 ± 9.0
%TST<90 (%)	9.6 ± 19.2
REM sleep (%)	15.3 ± 1.2
N3 sleep (%)	2.4 ± 4.3
Arousal response (/h)	24.0 ± 9.6
ESS	4.9 ± 2.0
PSQI	6.0 ± 3.0
AHI, Apnea hypopnea index; OSA, Obstructive sleep apnea; AI, Apnea index; HI, Hypopnea index; ODI4%, Oxygen desaturation index $\geq 4\%$; %TST<90, Percent of total sleep time < 90% of SpO ₂ ; REM, Rapid eye movement; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.	

Predictive factors of the AI

Age, male sex, BMI, KL-6, FVC, DLco, PCO₂, and RR were included in the univariate regression analysis for the AI increase (Table 3). A higher BMI predicted a higher AI (OR = 0.92, 95%CI -0.17 to 2.02, p = 0.10). A lower RR significantly predicted a higher AI (OR = -0.85, 95%CI -1.64 to -0.06], p = 0.04). Multivariate

regression analysis revealed that a lower RR predicted a higher AI (OR = -0.77, 95% CI -1.55 to 0.02, p = 0.05).

Table 3
Predictive factors of the AI increase

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.23 [-0.34, 0.79]	0.42		
Male	-1.8 [-14.5, 10. 9]	0.77		
BMI (kg/m ²)	0.92 [-0.17, 2.02]	0.10	0.77 [-0.29, 1.83]	0.15
KL-6 (U/ml) ^a	-0.44 [-1.30, 0.42]	0.31		
FVC (%)	0.22 [-0.04, 0.49]	0.09		
DLco (%)	0.03 [-0.35, 0.41]	0.87		
PCO ₂ (mmHg)	-0.86 [-1.91, 0.18]	0.10		
RR	-0.85 [-1.64, -0.06]	0.04	-0.77 [-1.55, 0.02]	0.05
FVC and PCO ₂ were not included in the explanatory variables in the multivariate regression analysis because their significant correlations with RR were seen (Not shown).				
OR, odds ratio.				
^a Per 100 increase.				

Predictive factors of the HI

The same explanatory factors were included in the univariate regression analysis for the HI (Table 4), which showed that a lower DLco significantly predicted a higher HI. Multivariate regression analysis also showed that a lower DLco predicted a higher HI (OR = -0.15, 95% CI -0.32 to -0.02, p = 0.08).

Table 4
Predictive factors of the HI increase

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	-0.02 [-0.33, 0.29]	0.90		
Male	-1.05 [-7.97, 5.88]	0.76		
BMI (kg/m ²)	0.46 [-0.14, 1.07]	0.13	0.23 [-0.53, 0.99]	0.53
KL-6 (U/ml) ^a	0.19 [-0.28, 0.67]	0.41		
FVC (%)	0.02 [-0.12, 0.17]	0.76		
DLco (%)	-0.17 [-0.33, -0.01]	0.04	-0.15 [-0.32, 0.02]	0.08
PCO ₂ (mmHg)	-0.21 [-0.79, 0.39]	0.49		
RR	0.10 [-0.36, 0.56]	0.65		
^a Per 100 increase.				

Predictive factors of the AHI and ODI4%

The RR, which predicted the AI, and DLco, which predicted HI, were included as the explanatory variables of a multivariate regression analysis of AHI and ODI4%. The results revealed that a lower DLco predicted a higher AHI (OR = -0.38, 95% CI -0.82 to -0.05, p = 0.08), and a lower RR significantly predicted a higher AHI (OR = -1.80, 95% CI -3.38 to -0.23, p = 0.03) and a higher ODI4% (OR = -1.27, 95% CI -2.13 to -0.40, p < 0.01) (Table 5).

Table 5
Predictive factors of the AHI and ODI4% increase

	AHI (Multivariate)		ODI4% (Multivariate)	
	OR (95% CI)	p value	OR (95% CI)	p value
DLco (%)	-0.38 [-0.82, 0.05]	0.08	-0.17 [-0.41, -0.07]	0.14
RR	-1.80 [-3.38, -0.23]	0.03	-1.27 [-2.13, -0.40]	< 0.01

Discussion

In our study, all 33 ILD patients were diagnosed with OSA. A lower RR predicted a higher AI, and a lower DLco predicted a higher HI. These parameters were also predictive factors for AHI and ODI4%. These results indicate that ILD patients who lack rapid breathing pattern and who reveal impaired diffusion

capacity are at a high risk of severe OSA. For such patients, clinicians should actively consider examinations of sleep disorders. Moreover, two other significant findings were present.

First, the high occurrence of OSA was not significantly related to BMI, while the high prevalence of this complication is consistent with previous reports^{4–8}. The mean BMI of the patients was 23.9 ± 4.6 , and either underweight or normal weight patients were the major population of this study (23 of 33 patients). It is noteworthy that the group with such a background exhibited 100% prevalence of OSA. Moreover, BMI was not a significant predictive factor for the severity of OSA. These results suggest that factors other than obesity are implicated in the occurrence of OSA in ILD patients. Previous reports have presented some hypotheses for the relationship of these diseases, such as craniocaudal traction of the trachea resulting from decreased lung volume, which increases the collapsibility of the upper airway lesion^{13,14}. Ventilatory control system instability also results from intermittent hypoxia, which possibly exacerbates this complication^{15,16}. However, no results supporting these hypotheses were obtained from our study.

Second, lacking rapid breathing pattern and impaired diffusion capacity were significant predictive factors for the severity of OSA. Advanced ILD typically shows rapid and shallow breathing¹⁷, which means that RR rises in severe ILD. On the other hand, diffusing capacity is likely to be impaired along with the progression of ILD, resulting in a lower DLco. Namely, these parameters are likely to change in the opposite direction in a clinical course of ILD progression, as an increase in RR and a decrease in DLco. Therefore, the results of our study indicate that AI is likely to decrease with the progression of ILD, while HI is likely to increase. In other words, hypopnea may be the major constitutive factor of OSA in severe ILD (Figure 1). These results indicate the possibility that minimal pressure may be reasonable as an initial treatment with continuous positive airway pressure (CPAP) therapy for OSA complicated with ILD.

The underlying mechanism of the inverse relationship between RR and AI is unclear. However, progression of ILD leads to a decrease in FVC, which is known to exhibit a rapid and shallow breathing pattern responding to stretch receptor afferents from the periphery of the lung sensing mechanical load of increased lung elastance¹⁷. Under the condition that the afferent signal is strongly stimulated, transient cessation of respiration may be less likely to occur. Such a mechanism may explain the relationship between RR and AI, but this speculation lacks support from scientific evidence.

The causal relationship between lower DLco and higher HI suggests that impaired diffusing capacity is likely to exhibit a drop in PaO₂ only by a weak airflow limitation. Namely, craniocaudal traction of the trachea caused by restrictive lung disease or a shallow breathing pattern of ILD may lead to subtle airflow limitation. This may not be enough for a complete cessation of breathing but may lead to a more prominent drop in PaO₂, especially in patients with lower DLco. Moreover, if the diffusing capacity is severely impaired, the baseline PaO₂ is also likely to be lower. Such a condition means they are sitting on the steep slope of the oxygen dissociation curve, which also increases the likelihood of SpO₂ dropping.

Previously, several authors have investigated the relationship between OSA and ILD, while very few of them have clearly distinguished AI and HI. However, considering the preciseness of their definition, AI and

HI are strictly not synonymous parameters. Namely, AI reflects complete airflow cessation, HI reflects a likelihood of desaturation with subtle airflow limitation, and it seems that they correspond to different etiologies. Therefore, we investigated the relationship between ILD and OSA by distinguishing AI and HI, which was a unique point in this study.

There are some limitations of our study. First, this was a single-center study with a small sample size. Second, the study did not examine whether the treatment of ILD affects the severity of OSA. A future randomized control study is needed.

In conclusion, there was a high incidence rate of OSA in patients with ILD. RR and DLco were predictive factors of OSA severity. ILD patients should be actively evaluated for the presence of sleep disorders, especially when they lack rapid breathing pattern and reveal lower DLco.

Abbreviations

ILD interstitial lung disease

OSA obstructive sleep apnea

BMI body mass index

RR respiratory rate

KL-6 krebs von den Lungen-6

SP-D surfactant protein-D

AHI apnea hypopnea index

%TST90 percent of total sleep time < 90% of SpO₂

AI apnea index

HI hypopnea index

ODI4% oxygen desaturation index 4%

FVC forced vital capacity

DLco diffusing capacity of the lung for carbon monoxide

ESS Epworth Sleepiness Scale

PSQI Pittsburgh Sleep Quality Index

CPAP continuous positive airway pressure

Declarations

Authorship contribution;

Y.I. collected data, reviewed PSG results, and wrote the manuscript. M.T. and Y.M. designed and supervised the study, analyzed data, and wrote the manuscript. S.S., T.Y., S.S., R.S., M.E., T.H., T.M, T.S., T.O., H.F., and T.T. provided clinical data and supervised the study. All authors reviewed and approved the final manuscript.

Data availability;

Our secured database contains several information used in other research projects and patients' identifiers. Therefore, we cannot share it completely. However, if requested, we will consider providing raw data.

Funding; This study was supported by a grant from Fukuda Foundation for Medical Technology (grant number: none).

Competing interests; The authors declare no competing interests.

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Figures

Figure 1

The relationship between physiological changes and ILD progression and OSA severity

As the ILD progresses, RR increases and DLco declines. These changes influence the decrease in AI and the increase in HI. Consequently, hypopnea may become more prominent in the characteristics of sleep disorders of ILD than apnea.