Overnight desaturation in interstitial lung diseases: links to pulmonary vasculopathy and mortality

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Abstract

Background Overnight desaturation predicts poor prognosis across interstitial lung diseases (ILDs). The aim of the present study was to investigate whether nocturnal desaturation is associated with pulmonary vasculopathy and mortality.

Methods A retrospective single centre study of 397 new ILD patients was carried out including patients with idiopathic pulmonary fibrosis (IPF) (n=107) and patients with non-IPF fibrotic ILD (n=290). This is the largest study to date of the effect of significant nocturnal desaturation (SND) (⩾10% of total sleep time with oxygen saturation ⩽90% measured by pulse oximetry).

Results The prevalence of SND was 28/107 (26.2%) in IPF and 80/290 (27.6%) in non-IPF ILD. The prevalence of SND was higher in non-IPF ILDs than in IPF (p=0.025) in multivariate analysis. SND was associated with noninvasive markers of pulmonary hypertension (PH): tricuspid regurgitation velocity (TRV) (p<0.0001), brain natriuretic peptide (p<0.007), carbon monoxide transfer coefficient (p<0.0001), A–a gradient (p<0.0001), desaturation >4% in 6-min walking test (p<0.03) and pulmonary artery diameter (p<0.005). SND was independently associated with high echocardiographic PH probability in the entire cohort (OR 2.865, 95% CI 1.486–5.522, p<0.002) and in non-IPF fibrotic ILD (OR 3.492, 95% CI 1.597–7.636, p<0.002) in multivariate analysis. In multivariate analysis, SND was associated with mortality in the entire cohort (OR 1.734, 95% CI 1.202–2.499, p=0.003) and in IPF (OR 1.908, 95% CI 1.120–3.251, p=0.017) and non-IPF fibrotic ILD (OR 1.663, 95% CI 1.000–2.819, p=0.041). Separate models with exclusion of each one of the diagnostic subgroups showed that no subgroup was responsible for this finding in non-IPF ILDs. SND was a stronger marker of 5-year mortality than markers of PH.

Conclusion SND was associated with high echocardiographic probability and mortality and was a stronger predictor of mortality in IPF and non-IPF ILDs grouped together to power the study.

Introduction

Nocturnal desaturation with or without associated obstructive sleep apnoea (OSA) is common in interstitial lung diseases (ILD) and is an independent predictor of poorer prognosis [1, 2]. To date, routine screening of all ILD patients for OSA is not justified. Sleep studies tend to be reserved for patients with daytime somnolence and severe fatigue. However, repetitive desaturation and associated sympathetic nervous system activation may play a role in the development of pulmonary hypertension (PH) and can potentially contribute to increased mortality [2, 3]. Furthermore, intermittent hypoxaemia worsens lung fibrosis in

animal models, suggesting links between nocturnal desaturation and disease progression and survival [4–6]. Thus, assessment for nocturnal hypoxaemia with simple overnight oximetry appears reasonable as part of the workup of ILD patients with a view to treat nocturnal hypoxia with supplementary oxygen in patients without OSA.

Fibrotic ILDs may develop a progressive phenotype characterised by declining lung function, worsening symptoms, loss of quality of life and early mortality [7]. Along with these clinical similarities, progressive fibrotic ILDs may share pathobiological pathways representing a common fibrotic response to tissue injury [8, 9]. We hypothesised that nocturnal desaturation might be a marker of a pulmonary vasculopathy pathway, common to fibrotic ILD and associated with poor outcome, and we therefore compared nocturnal desaturation and its association with PH and mortality in idiopathic pulmonary fibrosis (IPF) and non-IPF fibrotic ILDs.

Research into pulmonary hypertension in ILD (PH-ILD) has been hampered by two perceptions. Firstly, there is a view that in clinical studies of PH-ILD, every patient should undergo a right heart catheterisation (RHC) study to confirm or exclude PH-ILD. However, this effectively precludes observational studies in large ILD cohorts due to the absence of validated PH-ILD therapies justifying routine RHC in suspected PH-ILD. For this reason, the linkage between noninvasive markers of PH-ILD and nocturnal desaturation was evaluated in the current study [10]. Secondly, a perception exists that every individual ILD should be studied separately. However, PH complicates individual non-fibrotic ILDs in a minority of patients, leading to powering difficulties. Therefore, we studied all non-IPF fibrotic ILDs as a single group but re-evaluated findings with the exclusion of each diagnostic group in turn to ensure that observed associations were generalisable. The lumping of individual ILDs in PH-ILD studies has been applied in PH-ILD treatment studies [11–13] and also in anti-fibrotic trials [14, 15].

In the present study we used significant nocturnal desaturation (SND), a marker of nocturnal hypoxaemia, and explored its links with vasculopathy and mortality in a large group of ILD patients. This study follows a previous one and attempts to take the results further [16].

Materials and methods

This is a retrospective single centre study. Consecutive new ILD patients admitted for an ILD work-up between 1 January 2010 and 31 December 2013 at the Royal Brompton Hospital, London, UK, were studied. During this time period, it was our routine practice to perform overnight oximetry. Patients were followed to death or to 31 December 2016. Vital status at the closing date was known in all cases included in the analysis, confirmed with general practitioners when appropriate. The diagnosis of IPF and non-IPF ILD was confirmed at a multidisciplinary team meeting. The non-IPF ILD group included connective tissue disease-associated interstitial lung diseases (CTD-ILD), hypersensitivity pneumonitis (HP), idiopathic nonspecific interstitial pneumonia (i-NSIP), unclassified ILD (u-ILD) and other fibrotic ILDs (sarcoidosis, drug-induced ILD and occupational ILD). Ethical approval was obtained (ID:244621).

Overnight oximetry

The Konica-Minolta Pulsox-300i oximeter was used in all cases. Data were interpreted using Download 2001 (version 2.8.0; Stowood Scientific Instruments Ltd) software. Oximetry was performed on room air, unless patients were using continuous oxygen supplementation. SND was considered as $\geqslant$10% of total sleep time with oxygen saturation measured by pulse oximetry (S_{pO_2}) $\leqslant$90% (TST90 $\geqslant$10%) [16].

Echocardiography

Trans-thoracic echocardiography (TTE) was performed in patients with suspected PH-ILD. High echocardiographic probability of PH was defined as tricuspid regurgitation velocity (TRV) >2.9 $m \cdot s^{-1}$ with other echocardiographic signs of PH according to the 2022 European Society of Cardiology/European Respiratory Society guideline document for the diagnosis and treatment of PH [17].

Pulmonary function testing

Pulmonary function measurements included total lung capacity, spirometric volumes and diffusing capacity of the lung for carbon monoxide/K_{CO}. The composite physiologic index (CPI) was calculated as previously described [18].

Markers of PH

Noninvasive markers of PH such as TRV (measurements made, n=224), brain natriuretic peptide (BNP) (n=394), K_{CO} (n=389), A–a gradient (alveolar–arterial gradient) (n=387), 6-min walking test (6MWT),

desaturation (>4%) (n=106) [19, 20], pulmonary artery diameter ⩾29 mm (n=306) and baseline oxygen saturation (n=394) were associated with SND.

Statistical analysis

Data were analysed using SPSS 25 (IBM) software. Subgroup comparisons were made using independent t-test and Pearson's chi-square test for continuous and categorical variables respectively.

The threshold of ⩾10% of sleep with S_{pO_2} ⩽90% was classified as SND and was used as a categorical variable.

Prevalence analysis

Stepwise regression analysis and adjustment for age, sex and baseline CPI was used to compare SND prevalence between IPF and non-IPF ILDs.

SND and association with markers of PH

A t-test was used to assess differences in markers of PH between SND positive and SND negative patient categories. A Mann–Whitney test was used for variables with non-normal distribution.

Separate logistic regression models with adjustment for the CPI (as the primary measure of ILD functional severity) were used to show that greater abnormalities of noninvasive markers of pulmonary vasculopathy remained independently associated with the presence of SND.

Subsequently, univariate and multivariate (adjustment for age, sex, body mass index (BMI), CPI) logistic regression analysis was performed to determine the association of SND (as a categorical variable of ⩾10% of sleep with S_{pO_2} ⩽90%) with markers of PH (each one used as categorical variable). This was performed initially for the entire group and then in IPF and non-IPF ILDs separately.

To exclude that any single non-IPF ILD subgroup was driving the association, separate models were evaluated with exclusion of each one of the five diagnostic subgroups in turn (CTD-ILDs, HP, NSIP, Unclassifiable and Other ILDs).

Survival analysis

A Cox proportional hazards model was used to assess the impact of SND on survival in the entire group. Both unadjusted and adjusted analysis were performed.

To exclude whether a single group was driving the association with survival we performed a Cox proportional hazard analysis including SND and diagnostic group category (IPF *versus* Non-IPF) as well as an adjusted model for age, sex, BMI and CPI. To further exclude that a single ILD subgroup in the Non-IPF ILD group was driving the results, separate models were conducted with exclusion of each one of the five diagnostic subgroups in turn (CTD-ILDs, HP, NSIP, Unclassifiable and Other ILDs).

Univariate survival models were used to investigate associations of individual markers of PH (BNP, TRV, Pulmonary artery diameter, K_{CO}, S_{pO_2}, A–a gradient) with survival. Subsequently, we performed separate multivariate survival models with inclusion of SND and individual markers of PH to investigate if SND was a stronger predictor of survival than markers of PH.

Unless otherwise stated, values were expressed as mean±SD. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

The entire cohort included patients with IPF (n=107), CTD-ILD (n=54), HP (n=56), i-NSIP (n=52), unclassified ILD (u-ILD) (n=20) and other fibrotic ILDs (which included sarcoidosis, drug-induced ILD and occupational ILD) (n=108). We divided our cohort into two major groups (IPF and non-IPF fibrotic ILDs) and compared the baseline characteristics (table 1); we further divided into SND negative and SND positive groups (table 2). The median observation period was 46.5 (21–60) months.

Prevalence of SND in IPF and non-IPF ILDs

In the entire group the prevalence of SND was 108 out of 397 (27.2%). The prevalence of SND was 28 out of 107 (26.2%) in IPF and 80 out of 290 (27.6%) in non-IPF ILDs. In the individual non-IPF ILD subgroups the prevalence of SND was: CTD-ILD 17 out of 54 (31.5%), HP 21 out of 56 (37.5%), i-NSIP

TABLE 1 Patient characteristics in the entire group and in the subgroups of IPF and non-IPF fibrotic ILDs

	Entire group	IPF	Non-IPF ILDs	p-value
Patients n	397	107	290	
Age years	65±12	73.7±8.3	62±12.1	0.0001
Sex (male/female)	188/209	89/18	99/191	0.0001
Smoking history				0.0001
Never	189 (47.6)	38 (35.5)	151 (52.1)	
Ever	208 (52.4)	69 (64.5)	139 (47.9)	
SND	108 (27.2)	28(26.2)	80 (27.6)	NS
FVC L	73.8±20.5	69.7±20.1	75.4±20.5	0.01
D_{LCO} mmol·min^{-1}·kPa^{-1}	43.7±16.5	38.3±13	45.8±17	0.01
CPI	48.7±15.9	54.6±12.5	46.5±16.5	0.0001
BMI kg·m^{-2}	29.5±11.7	27.4±5.3	30.2±13.2	0.03
Baseline S_{pO_2}%	95.2±1.7	94.7±1.6	95.4±1.7	0.0001
A–a gradient mmHg	3.8±2.3	4±1.5	3.7±2.6	NS
T-90 %	3 (0.6–11)	2.6 (0.9–10.3)	3.1 (0.5–11)	NS#
Mean overnight S_{pO_2} %	94 (92–95)	93.8 (91.7–95.3)	94.2 (93–95)	NS#
BNP ng·L^{-1}	59 (25–101)	59 (42–109)	42.2 (25–85)	0.04#
TRV m·s^{-1}	2.7 (2.4–3)	2.8 (2.4–3.2)	2.6 (2.3–3)	NS#
Pulmonary artery diameter mm	27±6	28.3±5.8	26.3±6.1	0.01
PASP mmHg	38.2±12.1	38.1±10.2	38.2±13	NS

Data are presented as n (%), median (IQR) or mean±SD unless indicated otherwise. Patients with non-IPF ILD were younger, had less significant smoking history and had milder disease than patients with IPF. IPF: idiopathic pulmonary fibrosis; ILDs: interstitial lung diseases; SND: significant nocturnal desaturation; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; CPI: composite physiologic index; BMI: body mass index; S_{pO_2}: oxygen saturation measured by pulse oximetry oximetry; A–a gradient: alveolar–arterial gradient; T-90: percentage of sleep with saturations below 90%; BNP: brain natriuretic peptide; TRV: tricuspid regurgitation velocity; PASP: pulmonary artery systolic pressure; NS: nonsignificant. #: Mann–Whitney test.

TABLE 2 Patient characteristics related to the presence of SND and differences in noninvasive markers of pulmonary vasculopathy between the SND positive and negative subgroups

	SND negative	SND positive	p-value
Patients n	289	108	
Age years	64.6±12	67±11.8	NS
Sex (male/female)	132/157	56/52	NS
Smoking history			NS
Never	146 (50.6)	43 (39.8)	
Ever	133 (46.6)	65 (60.2)	
BMI kg·m^{-2}	29±13	30.5±6	NS
FVC L	75.1±21	70.3±18.6	0.04
D_{LCO} mmol·min^{-1}·kPa^{-1}	45.9±16.6	38.2±14.7	0.0001
K_{CO} mmol·min^{-1}·kPa^{-1}·L^{-1} (n=389)	75±17.4	67.3±16.8	0.0001
TRV m·s^{-1} (n=224)	2.6±5.8	3±5.6	0.0001
PASP mmHg (n=155)	37±11.4	42.8±14	0.001
BNP ng·L^{-1} (n=394)	47 (25–93)	59.2 (34–114)	0.007#
Baseline S_{pO_2} % (n=394)	95.6 (94.7–96.9)	94.8 (92.5–96)	0.0001#
A–a gradient mmHg(n=387)	3.4 (2.5–4.4)	4.3 (3.1–5.3)	0.0001#
Pulmonary artery diameter⩾29 mm (n=306)	67/147 (45.6)	44/92 (47.8)	0.005
6MWT desaturation >4% (n=106)	66/106 (62.2)	31/38 (81.6)	0.03

Data are presented as n (%), median (IQR) or mean±SD unless indicated otherwise. SND: significant nocturnal desaturation; BMI: body mass index; FVC: forced vital capacity; D_{LCO}: diffusing capacity for carbon monoxide; K_{CO}: carbon monoxide transfer coefficient; TRV: tricuspid regurgitation velocity; PASP: pulmonary artery systolic pressure; BNP: brain natriuretic peptide; S_{pO_2}: baseline oxygen saturation measured by pulse oximetry oximetry; A–a gradient: alveolar–arterial gradient; 6MWT: 6-min walking test. #: Mann–Whitney test.

15 out of 52 (28.8%), u-ILD seven out of 20 (25%) and other ILDs 20 out of 108 (18.5%). There was no difference in the prevalence of SND between IPF and non-IPF groups (p=0.778). In stepwise regression analysis, after adjustment for age, sex and baseline CPI, the prevalence of SND in non-IPF ILDs was higher than in IPF (p=0.025). As shown in figure 1, SND was not observed in IPF patients with mild disease (CPI <40), whereas in non-IPF ILDs, SND occurred across the whole spectrum of disease severity. To ensure that no single non-IPF ILD subgroup was driving the association, separate models were evaluated with exclusion of each one of the five diagnostic subgroups in turn. There was no diagnostic group responsible for the increased prevalence of SND in the non-IPF population (p<0.05 in all five models).

Nocturnal desaturation and markers of PH

In the entire group, 224 patients had an echocardiogram at inclusion and 88 (39.2%) had high echocardiographic probability of PH. The prevalence in IPF was 35 out of 70 (50%) and in non-IPF ILDs was 53 out of 154 (34.4%) (p=0.04). In the non-IPF ILD subgroups the prevalence was: CTD-ILD 10 out of 31 (32.3%), in HP nine out of 28 (32.1%), in i-NSIP 12 out of 30 (40%), in u-ILD three out of 14 (21.4%) and in other ILDs 19 out of 51 (37.3%).

The presence of SND was significantly associated with greater abnormalities in noninvasive markers of PH, including TRV, BNP, K_{CO}, A–a gradient, baseline S_{pO_2}, desaturation >4% in 6MWT and pulmonary artery diameter (table 2). With adjustment for the CPI (as the primary measure of ILD functional severity), greater abnormalities of noninvasive markers of pulmonary vasculopathy (each examined in a separate logistic regression model) remained independently associated with the presence of SND.

In unadjusted analysis SND was associated with high echocardiographic probability of PH in the entire group (OR 3.364, 95% CI 1.856–6.097, p<0.0001). After adjustment for age, sex, BMI and CPI, SND remained associated with high echocardiographic probability of PH (OR 2.865, 95% CI 1.486–5.522, p<0.002).

SND was associated with high echocardiographic probability of PH in non-IPF ILDs (OR: 4.022, 95% CI 1.964–8.238, p<0.0001), whereas the association was only marginally significant in IPF (OR 3.130, 95% CI 0.966–10.149, p=0.06). After adjustment for age, sex, BMI and CPI, SND remained associated with a high echocardiographic probability of PH in non-IPF ILDs (OR 3.492, 95% CI 1.597–7.636, p<0.002) but not in IPF (OR 1.395, 95% CI 0.330–5.899, p=0.61). We performed an analysis in which the five groups were excluded one by one, which suggested that no single diagnostic group drove the effect in the overall population (figure 2).

Effect of SND on survival in the combined cohort

During the observation period 73 IPF and 59 non-IPF patients died.

SND carried an almost two-fold risk of death at 5 years in the entire group in unadjusted analysis (OR 1.791, 95% CI 1.258–2.551, p<0.001) (figure 3a). SND remained independently associated with worse

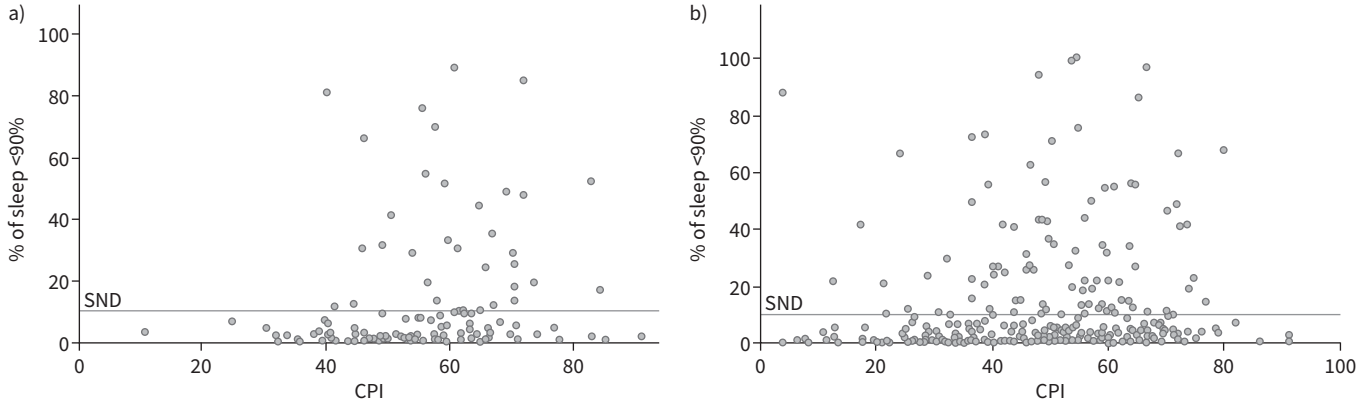

FIGURE 1 Scatter plots of SND defined as ⩾10% of total sleep time with S_{pO_2} ⩽90% (TST90 ⩾10%) *versus* CPI in a) IPF and b) non-IPF ILDs showing that SND was not observed in IPF patients with mild disease (CPI <40) whereas in non-IPF ILDs, SND occurred across the whole spectrum of disease severity. SND: significant nocturnal desaturation; S_{pO_2}: oxygen saturation measured by pulse oximetry oximetry; CPI: composite physiologic index; IPF: idiopathic pulmonary fibrosis; ILDs: interstitial lung diseases.

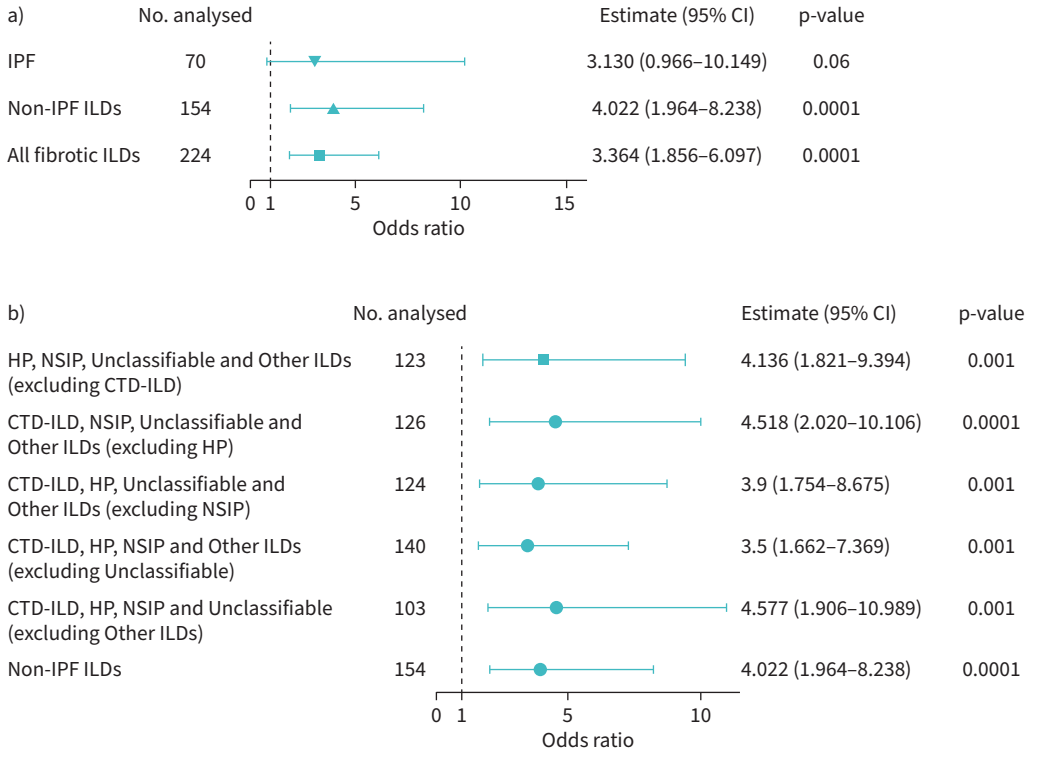

FIGURE 2 a) Association of significant nocturnal desaturation with echocardiographic probability of PH. b) Separate models were evaluated with exclusion of each of the five diagnostic groups in turn. IPF: idiopathic pulmonary fibrosis; ILDs: interstitial lung diseases; HP: hypersensitivity pneumonitis; NSIP: nonspecific interstitial pneumonia; CTD-ILD: connective tissue disease-associated interstitial lung diseases.

survival after adjustment for age, sex, BMI, CPI and diagnostic subgroup (IPF *versus* non-IPF) (OR 1.734, 95% CI 1.202–2.499, p<0.003).

SND had an independent effect on mortality in bivariable analysis when BNP, pulmonary artery diameter, K_{CO} and A–a gradient were included but no longer had an independent effect when TRV and S_{pO_2} were included (table 3).

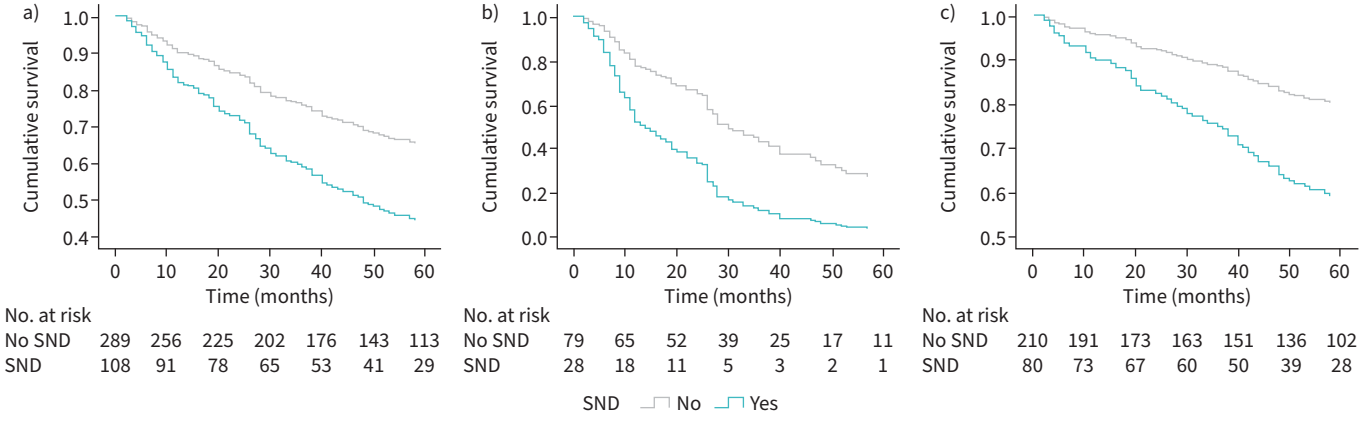

FIGURE 3 5-year survival in a) the entire group, b) idiopathic pulmonary fibrosis (IPF) group and c) non-IPF ILD group. SND: significant nocturnal desaturation.

TABLE 3 Univariate and multivariate predictors of survival

	OR (95% CI)	p-value
Univariate predictors of survival		
BNP	1.000 (1.000–1.001)	0.01
TRV	1.008 (1.004–1.011)	0.0001
Part diameter	1.080 (1.038–1.123)	0.0001
K_{CO}	0.992 (0.928–1.002)	0.1
A–a gradient	1.097 (1.046–1.151)	0.0001
S_{pO_2}	0.756 (0.689–0.830)	0.0001
SND	1.791 (1.258–2.551)	0.001
Multivariate predictors of survival[#]		
BNP	1.000 (1.000–1.001)	0.01
SND	1.659 (1.150–2.395)	0.007
TRV	1.008 (1.004–1.011)	0.0001
SND	1.144 (0.712–1.839)	0.5
Part diameter	1.071 (1.028–1.114)	0.001
SND	1.624 (1.096–2.408)	0.016
K_{CO}	0.995 (0.985–1.005)	0.3
SND	1.750 (1.218–2.515)	0.002
A–a gradient	1.089 (1.027–1.137)	0.003
SND	1.615 (1.101–2.368)	0.01
S_{pO_2}	0.776 (0.703–0.856)	0.001
SND	1.364 (0.920–2.021)	0.1

BNP: brain natriuretic peptide; TRV: tricuspid regurgitation velocity; Part diameter: pulmonary artery diameter; K_{CO}: carbon monoxide transfer coefficient; A–a gradient: alveolar–arterial gradient; S_{pO_2}: baseline oxygen saturation measured by pulse oximetry oximetry; SND: significant nocturnal desaturation; BMI: body mass index; CPI: composite physiologic index. [#]: adjustment for age, sex, BMI and CPI and diagnostic subgroup.

Effect of SND on survival: IPF versus other ILDs

In subgroup analysis, SND was associated with poor survival in unadjusted analysis in IPF (OR 2.409, 95% CI 1.456–3.985, p=0.001) and non-IPF (OR 2.204, 95% CI 1.318–3.686, p=0.003). The result remained significant after adjustment for age, sex, BMI, CPI in IPF (OR 1.908, 95% CI 1.120–3.251, p=0.017) and non-IPF ILDs (OR 1.663, 95% CI 1.000–2.819, p=0.041) (figure 3b, c). To exclude that a single non-IPF ILD subgroup was driving the association, separate models were evaluated with exclusion of each one of the five diagnostic subgroups in turn. There was no diagnostic group responsible for this finding in the non-IPF population ($p<0.05$ in all five models) (figure 4).

Discussion

In this study, nocturnal desaturation was associated with evidence of pulmonary vasculopathy, based on associations between the presence of SND and noninvasive PH markers, with all associations remaining significant after adjustment for the functional severity of ILD. Moreover, SND was associated with increased mortality on univariable analysis, and remained independently associated with mortality, with the inclusion of noninvasive markers of pulmonary vasculopathy in multivariate analysis, with the exception of TRV and S_{pO_2}. SND was more prevalent in non-IPF ILDs where it occurred across the whole spectrum of disease severity, unlike IPF where SND was not observed in patients with milder disease.

Based on a recent meta-analysis, our study is the largest among those evaluating the prognostic significance of SND in ILDs [21]. Overnight oximetry was evaluated in six studies [16, 22–26], with three adopting the definition of SND (TST90 ⩾10%) used in this study [16, 23, 25]. The combined number of patients included in these three studies (n=350) is lower than the number of patients included in our study (n=397). Moreover, the number of non-IPF ILDs in our cohort (n=290) was substantially higher than the total number of non-IPF cases in the three studies (n=120). In only one of these three studies was the association of SND with mortality investigated in a mixed population of patients with fibrotic ILDs (n=134) [16]. In that study, no separation between IPF and other ILDs was made. In a further study where the SND was defined as TST90 ⩾10% after the performance of polysomnography, SND was not associated with mortality in a mixed group of 92 ILD patients [27]. When a less strict criterion of nocturnal desaturation such as the time of total sleep below S_{pO_2} <90% was applied (TST90), the authors found an association with mortality on univariate and multivariate analysis. The size of our cohort allowed

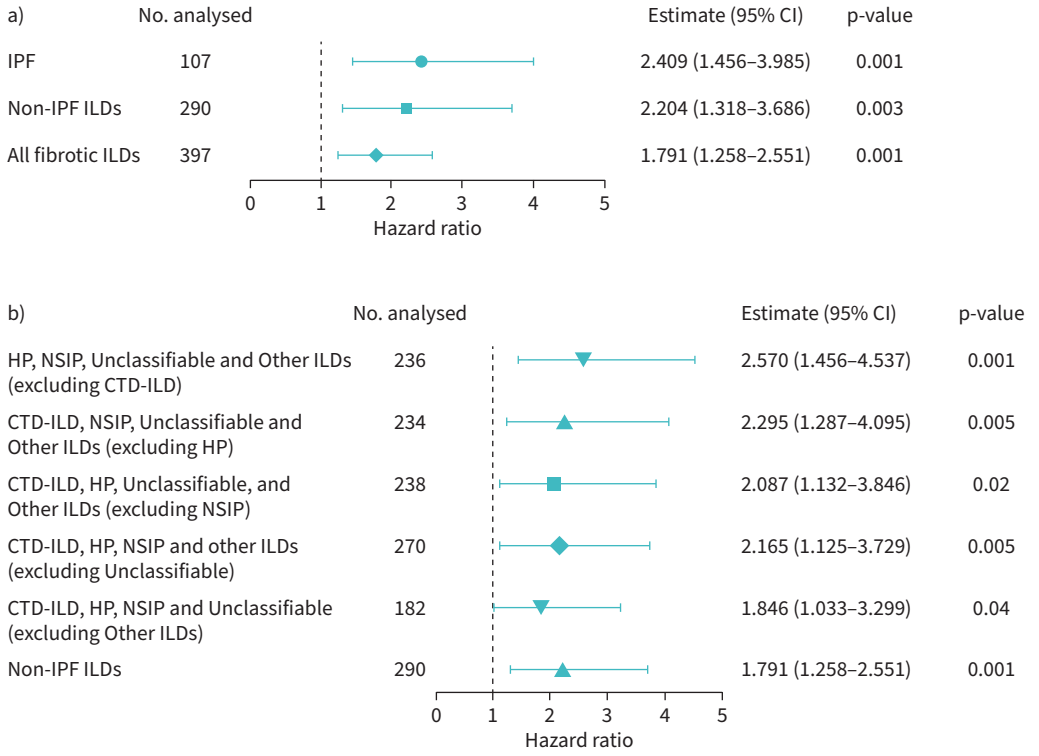

FIGURE 4 a) Association of SND with survival. b) Separate models were evaluated with exclusion of each of the five diagnostic non-IPF ILD groups in turn. IPF: idiopathic pulmonary fibrosis; ILDs: interstitial lung diseases; HP: hypersensitivity pneumonitis; NSIP: nonspecific interstitial pneumonia; CTD-ILD: connective tissue disease-associated interstitial lung diseases.

us to perform subgroup analysis on the prevalence, association with PH on echocardiogram and effect on survival of SND in IPF and non-IPF ILDs, which was not possible in earlier smaller cohorts.

The prevalence of SND was higher in non-IPF ILDs. SND was observed in non-IPF ILD across the whole spectrum of disease severity, in contrast with IPF, where SND was not observed in milder disease. SND was associated with noninvasive markers of PH and with a high echocardiographic probability of PH in non-IPF ILDs. With adjustment for the CPI (as the primary measure of lung function severity), noninvasive markers of pulmonary vasculopathy (each examined in separate logistic regression models) remained independently associated with the presence of SND.

Our findings do not have immediate implications for ILD management but raise two important issues that merit further prospective evaluation. Firstly, with regard to associations between markers of PH and SND, it should be emphasised that association is not synonymous with causation. It remains unclear whether SND might be a causative factor for, or a consequence of, pulmonary vasculopathy. It can be hypothesised that SND might contribute to a vasculopathy/endothelial pathway in the pathogenesis of PH-ILD. Endothelial pathways may be associated with sleep disorders: chronic intermittent hypoxia (CIH), defined as recurrent blood oxygen desaturation, a characteristic of sleep disorders, was associated with activation of inflammation [5]. In theory, SND could promote the development of PH through the upregulation of molecules involved in angiogenesis and by inducing an impaired endothelium-dependent vasodilatation and increased vasoconstrictor responsiveness [5]. However, it is also possible that SND might, in principle, represent pulmonary vasospasm as an early marker and, therefore, a consequence of pulmonary vasculopathy, as suggested by early studies in systemic sclerosis [28, 29], although this phenomenon may not exist in established PH [30]. A possible association between SND and pulmonary arterial vasospasm is likely to require the use of indwelling pulmonary artery catheters in a future study, as used in cardiac studies [31]. Without a clear understanding of the pathogenetic significance of SND, it is difficult to argue that it might be used as a future test to screen for pulmonary vasculopathy.

Secondly, with regard to management our findings do not establish whether SND should be treated and if so, how it should be corrected. A recent Delphi survey of international ILD experts identified consensus for the recommendation of supplemental oxygen therapy for treating nocturnal hypoxaemia in the absence of other causes [32]. SND was associated with mortality in both subgroups of the study and was a more powerful predictor of survival than some of the noninvasive markers of PH. CIH associated with sleep disorders may contribute to increased mortality in fibrotic ILDs by inducing fibrosis progression, suggesting that epithelial pathways may also be triggered by nocturnal desaturation. CIH results in overproduction of reactive oxygen species, reactive nitrogen species and oxidative stress, which are all well-known promoters of pulmonary fibrosis. Hypoxia-inducible factor 1a, which is increased in patients with intermittent hypoxia (IH), promotes epithelial proliferation and fibrosis through hypoxia-inducible factor 1a, deoxycytidine kinase expression pathway [33–36]. However, knowledge of a potentially important pathogenetic pathway linked to SND does not establish whether correction of nocturnal desaturation is best addressed by proactive identification and treatment of OSA or simply by supplemental oxygen therapy. Nor is it known whether these managements would necessarily prevent the excess mortality associated with SND. Our findings may provide helpful information for the design of a future interventional study as we have documented associations between SND and high probability PH and between SND and mortality, common to IPF and non-IPF ILDs.

Our study was limited by its retrospective nature and potential selection bias, as more severe cases were more likely to be referred to specialised tertiary referral centres. However, our cohort included a wide range of disease severity and ILD subgroups, and we suggest that the range of severity does reflect real-life clinical practice.

There are two significant limitations to our study related to the practicability of performing all tests in all patients in a large retrospective cohort of consecutive patients, and this especially applies to the performance of polysomnography (PSG) and to routine echocardiography.

Overnight PSG was not part of our routine clinical protocol and was performed only in occasional patients based on symptoms, without a standardised approach. Ideally, PSG should have been performed in all patients, or in all patients with nocturnal hypoxia, but this was not achievable in a large consecutive cohort in routine practice and was performed in a non-standardised way in only a small proportion of patients based on symptoms. It should be stressed that our findings relate to SND at large and are not specific to SND causation. In small prospective IPF cohorts (n=34, n=35), ND without OSA (AHI <5) has been documented [37, 38]. In a recent prospective cohort of 102 patients with fibrotic ILD, evaluated with a home nocturnal sleep study, SND (defined as in the current study) was associated with OSA in only 13 of 76 patients (17%) [39]. Importantly, the impact of SND on both quality of life and survival was virtually identical in patients with and without OSA, although powering of subgroups was a study limitation. These data suggest that pending a large cohort study with all patients undergoing PSG, our findings are likely to be relevant to SND, independently of OSA causation. In addition, our findings were independent of BMI, and this variable can be viewed as a marker associated with OSA, much as age can be viewed as a marker of age-related comorbidities.

Selection bias existed in the various analyses of markers of PH. Even with performance of a pulmonary function test (PFT) and, separately, CT, there was a handful of exclusions. This applied to a greater extent to 6MWT data and the performance of echocardiography. Owing to the size of the cohort and, therefore, the large patient throughput, TTE could not be performed routinely in all cases, but only in selected patients viewed at the time as having a realistic suspicion of PH, based on symptoms and PFT. In addition, we excluded patients with echocardiographic data from outside our institution due to lack of a standardised approach and questionable quality/lack of focus on possible PH.

All analyses comparing the prognostic impacts of SND and individual markers of PH were, by definition, confined to patients with available data for individual PH markers. However, due to selection bias in these analyses, the more robust conclusions in our study relate to links between nocturnal hypoxia and mortality in the whole cohort and are novel in their exploration in powered IPF and non-IPF subgroups. The analyses relating to markers of PH can be viewed as hypothesis-generating data, worthy of further evaluation.

In conclusion, we observed that SND is highly prevalent in both non-IPF ILD and IPF and is associated with worse survival and noninvasive markers of PH in both patient subsets. Our findings suggest that future studies of SND as an early marker of pulmonary vasculopathy may be fruitful, especially as treatments are developed for PH-ILD and earlier PH diagnosis has a higher future priority. The observed

associations with mortality provide a further stimulus for interventional studies to determine whether treatments addressing SND might improve ILD outcome.

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