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The overlooked impact of sleep-related breathing disorders in patients with interstitial lung disease

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Abstract

English:

Sleep-related breathing disorders (SRBDs) significantly contribute to the quality of life (QoL) and disease progression of interstitial lung disease (ILD), but have not been thoroughly addressed in ILD management. This review aims to summarise the current literature addressing obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and nocturnal hypoxaemia (NH) in patients with ILD and to highlight existing/novel treatment strategies, as untreated SRBDs worsen symptoms such as chronic fatigue, excessive daytime sleepiness (EDS) and dyspnoea, leading to a vicious cycle that reduces functional capacity and psychological well-being. Validation of the possible role of SRBDs in ILD patients and the correlation of the postulated mechanisms with disease progression will open pathways to perform studies with a larger number of subjects to establish the reliability of biomarkers for early diagnosis and sustained benefits from therapeutic interventions. Polysomnography (PSG) combined with validated questionnaires should be implemented for early screening. Clinicians could address these disturbances in a multidimensional way while minimising disease progression and improving clinical outcomes and QoL. More research is needed to define the diagnostic criteria, implement targeted therapies and establish evidence-based recommendations for the management of sleep disorders in patients with ILD.

Keywords

sleep-related breathing disorders • interstitial lung disease • obstructive sleep apnoea • sleep quality

Impactul neglijat al tulburărilor respiratorii legate de somn la pacienții cu boală pulmonară interstițială

Rezumat

Romanian:

Tulburările respiratorii din timpul somnului contribuie în mod semnificativ la calitatea vieții și la progresia bolii pulmonare interstițiale (ILD), dar nu au fost abordate pe deplin în managementul ILD. Acest referat științific își propune să sistematizeze literatura medicală actuală care abordează apneea obstructivă în somn (OSA), apneea centrală în somn (CSA) și hipoxemia nocturnă (NH) la pacienții cu ILD și să evidențieze strategiile curente și noi de tratament, întrucât SRBD netratate agravează simptome precum oboseala cronică, somnolența diurnă excesivă și dispneea, fapt ce determină crearea unui cerc vicios care reduce capacitatea funcțională și starea de bine. Validarea posibilului rol al SRBD la pacienții cu ILD și corelarea mecanismelor postulate cu progresia bolii va deschide căi de realizare a unor studii cu un număr mai mare de pacienți, care ar putea stabili fiabilitatea biomarkerilor pentru diagnosticul precoce și beneficiile susținute ale intervențiilor terapeutice. Polisomnografia combinată cu chestionare validate ar trebui implementată pentru screening-ul precoce. Astfel, clinicienii ar putea aborda aceste tulburări într-un manieră multidimensională, reducând progresia bolii, îmbunătățind rezultatele clinice și calitatea vieții pacienților. Sunt necesare mai multe cercetări pentru a defini criteriile de diagnostic, a implementa terapii direcționate și a stabili recomandări bazate pe dovezi pentru gestionarea tulburărilor de somn la pacienții cu ILD.

Cuvinte-cheie

tulburări respiratorii legate de somn • boală pulmonară interstițială • apnee obstructivă în somn • calitatea somnului

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Introduction

Sleep disorders are a substantial and underappreciated component of interstitial lung disease (ILD) care, affecting quality of life (QoL) and even disease progression and prognosis. ILD encompasses a spectrum of diseases marked by pulmonary inflammation and/or fibrosis, resulting in impaired gas exchange and restrictive lung physiology. Although ILD management has long focussed on pulmonary function and radiographic progression, newer data emphasise the importance of extrapulmonary manifestations, notably sleep-related breathing disorders (SRBDs) such as obstructive sleep apnoea (OSA), central sleep apnoea (CSA) and nocturnal hypoxaemia (NH), on clinical outcomes.

Research suggests that up to 70% of patients with ILD have OSA, with many also experiencing NH, although not all have overt sleep apnoea. These disturbances are caused by decreased lung compliance, altered ventilatory control and upper airway collapse, which are aggravated by lung fibrosis (1). NH is independently associated with disease progression, increased mortality and the deterioration of health-related QoL (HRQoL) (2, 3). SRBDs may worsen daytime sleepiness, fatigue and dyspnoea, leading to a vicious cycle that further compromises functional capacity. Furthermore, untreated sleep disorders could worsen cardiovascular comorbidities, including pulmonary hypertension (PH) and right heart failure (1, 4, 5).

Current ILD management guidelines may not provide detailed recommendations for the assessment and treatment of SRBDs, indicating a substantial gap in clinical practice (6). There is increasing evidence to support interventions such as continuous positive airway pressure (CPAP) therapy and supplemental oxygen, which would improve nocturnal oxygenation, reduce symptoms and even slow disease progression (1, 2).

This review aims to summarise the current literature related to sleep disorders in ILD patients and current/novel treatment strategies. By providing an overview of this underappreciated aspect of ILD, this review aims to highlight the need for the inclusion of sleep medicine in the interdisciplinary care of ILD patients as well as propose directions for future research.

Methods and materials

We conducted a comprehensive literature review using PubMed/MEDLINE and Google Scholar to identify studies and publications that present evidence on the prevalence, pathophysiological mechanisms and clinical consequences of sleep disorders in patients with ILD. In addition, we aimed to explore current and novel therapeutic modalities. The search

terms were 'sleep disorders in ILD', 'nocturnal hypoxemia', 'sleep quality' and 'pathophysiology' in different combinations. The review included observational studies, including prospective and retrospective cohort studies, cross-sectional studies, case series, systematic reviews, pilot studies, randomised crossover trials and meta-analyses.

Results

ILD-related sleep disorder pathophysiology

Hypoxaemia during sleep and fragmentation of sleep

The pathophysiology of sleep disturbances in patients with ILD is multifactorial, including structural, mechanical and physiological alterations. This causes nocturnal hypoxaemia to become severe, particularly during rapid eye movement (REM) sleep, due to decreased muscle tone and ventilatory response during lung expansion (7). This contributes to frequent arousals, sleep fragmentation and poor sleep quality, worsening daytime symptoms such as fatigue and dyspnoea (8). A decrease in ventilatory drive and functional residual capacity (FRC) during sleep is a physiological phenomenon that worsens ventilation-perfusion (V/Q) mismatching, leading to oxygen desaturation. Fibrotic alterations towards the lung parenchyma further raise alveolar-arterial oxygen gradients, exacerbating hypoxaemia (2).

Physiological constraints on lung function

Another important contributor is the mechanical constraint on lung capacity in ILD. Reduced lung compliance and increased elastic recoil elevate the work of breathing, especially at night when respiratory drive is diminished. This can contribute to hypercapnia and exacerbate sleep-disordered breathing, including OSA and overlap syndromes (9). PH, which often accompanies ILD, also causes sleep disturbances by adding right ventricular (RV) work and worsening gas exchange (1, 4).

OSA and CSA

The increased prevalence of OSA in individuals with ILD is implicated in the collapsibility of the upper airway as a result of modified respiratory mechanics and the development of negative intrathoracic pressure during inspiration (10). The association between OSA and ILD is complex and probably bidirectional. ILD may predispose patients to OSA by compromising lung volumes and airway stability, particularly during REM sleep when muscle atonia exacerbates airway collapse. On the other hand, OSA significantly worsens oxidative stress, systemic inflammation and tissue injury through a mechanism quite similar to that of lung fibrosis involving profibrotic cytokines such as TGF- β . Hypoxic episodes due to OSA also increase lung injury and fibrosis

biomarkers and worsen pulmonary arterial hypertension and adverse outcomes in patients with ILD. In addition, CSA may also develop, particularly in advanced ILD, due to chemoreceptor hypersensitivity and instability of ventilatory control mechanisms. It can be worsened by chronic hypoxaemia and hypercapnia (11).

Systemic inflammation and associated comorbidities

Systemic inflammation, a hallmark of ILD, may serve to disrupt circadian rhythms and contribute to fatigue and insomnia, leading to sleep disturbance (12). It is relevant that comorbid conditions, especially gastroesophageal reflux disease (GERD) with its very high prevalence in ILD patients, are related to microaspiration and both nocturnal coughing and sleep disruption. Conversely, GERD was shown to be involved in the pathogenesis of a subset of ILD, idiopathic pulmonary fibrosis (IPF), which further complicated the relationship between sleep and lung disease (13–15). In addition, the chronic and progressive nature of ILD can be complicated by psychological disorders such as anxiety and depression. Such conditions can induce sleep loss and poor-quality sleep, leading to a vicious cycle that deteriorates mental health and respiratory symptoms (13, 16).

Circadian dysregulation

There is also emerging evidence suggesting that dysregulation of the circadian rhythm may be implicated in sleep disturbance in ILD. Circadian clocks regulate immune response and inflammation, and their disruption might aggravate ILD progression and sleep disorders (12). Third, corticosteroids and other drugs used for the management of ILDs can also contribute to sleep disturbances by inducing insomnia or changing sleep architecture (14).

Prevalence and clinical impact of sleep disorders in patients with ILD

A cross-sectional study by Cho et al. (17) provides a detailed analysis of sleep disturbances in patients with ILD. The study analysed 101 patients who presented to a pulmonary rehabilitation assessment clinic for evaluation, examining various sleep quality, daytime symptoms and psychological characteristics. The authors measured sleep quality using the Pittsburgh Sleep Quality Index (PSQI) scale, where a score >5 was classified as a poor sleeper. The results showed that 66% of the participants had poor sleep quality (PSQI >5 ; median PSQI: 8; interquartile range: 4–11). To investigate potential contributing factors, the study recorded data on lung function (measured using forced vital capacity and diffusing capacity for carbon monoxide), demographic characteristics and comorbid symptoms of anxiety, depression, and sleepiness. Interestingly, poor sleep quality had no significant association with demographic or physiological variables,

including lung function, age, sex or body mass index (BMI). Using multivariable logistic regression, we found that poor sleep quality was independently associated with increased symptoms of depression (Hospital Anxiety and Depression Scale) and greater daytime sleepiness (Epworth Sleepiness Scale [ESS]). In addition to this, the study found that complaints such as fatigue, difficulty maintaining sleep and early morning awakenings were common among patients with ILD. The results further highlighted that OSA could be an important contributing factor to sleep disturbance.

The reported prevalence of OSA in ILD patients is widely variable depending on the diagnostic criteria, methods used to score hypopnea events, and patient characteristics of the study population. Consequently, obtaining a definitive prevalence is difficult. For instance, the prevalence of OSA in the IPF has been shown to range from 47.2% to 88.8%, depending on the criteria for diagnosis and population characteristics (15). A meta-analysis estimated the prevalence of OSA in patients with IPF to be 76.4%, much higher than the rate of 25% in the general population (18). A meta-analysis and systematic review including 569 ILD patients showed that 61% had OSA: 32% had mild, 17% moderate and 9% severe disease (19).

In rheumatoid arthritis and interstitial lung disease (RA-ILD) patients, insomnia was found with a prevalence of 42.9% (RA with ILD vs. RA without ILD). RA-ILD patients also reported decreased sleep satisfaction, the study noted (20).

The findings emphasise the crucial role of the diagnosis of sleep disorders in patients with ILD, as well as the multifactorial relationships between psychological factors, OSA and sleep disturbances in patients with ILD.

Specialised research investigating OSA in ILD

OSA is a common comorbidity in patients with ILD that negatively impacts sleep quality and health outcomes. Hagmeyer et al. (1) evaluated the prevalence and effect of OSA in IPF, one of the specific subtypes of ILD, by using overnight polysomnography (PSG). The authors found that nearly 81% of patients with IPF had OSA, which was associated with significant nocturnal hypoxaemia and sleep fragmentation. The results underscore the need to incorporate screening for OSA and treatment options (e.g., CPAP therapy) for IPF patients, as OSA may be contributing to disease progression via intermittent hypoxia and systemic inflammation.

In agreement with these results, Kim et al. (21) performed a *post hoc* longitudinal analysis within the Multi-Ethnic Study of Atherosclerosis (MESA) cohort to investigate the association between OSA severity and progression of ILD. By using PSG to determine apnoea–hypopnoea index (AHI) and using computed tomography (CT) scans to assess high-attenuation areas (HAAs) as potential markers for interstitial lung abnormalities, the researchers found that participants with moderate to severe OSA (AHI ≥ 15 events/hr) had significantly

greater increases in HAAs, greater declines in lung volumes and forced vital capacity over time. These associations remained significant when adjusting for potential confounders, including body habitus, suggesting that OSA might play a role in the early stages of ILD development. Taking into account body habitus, they concluded that a greater burden of hypoxia associated with obstructive events during sleep was associated with increased lung densities over time and a more rapid decline in lung volumes. The study results indicate that OSA could play a role in the early development of ILD.

These studies emphasise the instrumental role of PSG in the diagnosis of OSA or other SRBDs in ILD patients. They propose regular sleep evaluations with timely intervention, namely CPAP therapy, to ameliorate nocturnal oxygenation and minimise sleep fragmentation, all to attenuate disease progression and ultimately improve health outcomes and QoL for patients with ILD.

Nocturnal hypoxemia in ILD

Although OSA can contribute to overnight desaturation, many IPF patients will desaturate significantly without this condition. Papadogiannis et al. (22) found that there is a significant desaturation during sleep among well-characterised IPF patients without OSA, with common desaturations <90%. Similarly, a systematic review was conducted by Khor et al. (7), which included fifty-three studies with a total of 2590 participants, found that the most common definition for clinically significant nocturnal hypoxaemia was $\geq 10\%$ of total sleep time with an oxyhaemoglobin saturation <90%, with a pooled prevalence of 37%.

Nocturnal hypoxaemia is common in patients with IPF and other forms of ILD, presenting as severe nocturnal oxygen desaturation. A retrospective survey conducted by Margaritopoulos et al. (23) studied the presence of significant nocturnal desaturation (SND) ($\geq 10\%$ of total sleep time with oxygen saturation $\leq 90\%$ measured by pulse oximetry) and non-invasive PH markers in 397 newly ILD-diagnosed patients. The results showed that SND was associated with increased mortality. 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. Moreover, SND was associated with non-invasive markers of PH and with a high echocardiographic probability of PH in non-IPF ILDs. The obtained results emphasise the need for future studies to be done, which would identify SND as an early marker of pulmonary vasculopathy and determine whether treatments addressing SND might improve ILD outcomes.

Myall et al. (3) conducted a study of nocturnal hypoxemia (NH) in 102 patients with progressive fibrotic ILD. PSG was used to diagnose OSA in 31.4% of patients, with 19.6% having SND (TST <90%). NH was an independent risk factor for increased PH and higher mortality, suggesting that nocturnal hypoxemia

may contribute to disease progression and poor prognosis in individuals with ILD.

A prospective study by Lowery et al. (5) examined the relationship between sleep-related hypoxaemia and RV dysfunction in patients with PH. The study reported that higher nocturnal hypoxemia was significantly associated with increased RV systolic pressure (RVSP), a cardiovascular response to stress reflected in both cardiac capacity and workload that is associated with PH. Specifically, RVSP increased by a mean of 2.52 mm Hg for every 10% increase in percent sleep time (T90) with oxygen saturation <90%. T90 was also inversely correlated with RV ejection fraction and positively correlated with mean pulmonary artery pressure. There are also data that indicate that nocturnal hypoxemia is responsible for RV dysfunction and may have negative implications for outcomes in patients with PH.

Early diagnosis and assessment of biomarkers

Early diagnosis of sleep disorders in ILD patients becomes essential for preventing the future progression of the disease and for managing the related complications. All sleep disturbances (e.g., OSA, nocturnal hypoxaemia, etc.) are common in the course of ILD and may aggravate symptoms such as hypoxia, fatigue, and systemic inflammation, resulting in poorer clinical outcomes. Recognising and managing these disorders early may optimise respiratory function, enhance QoL and decrease mortality risk. Additionally, early intervention may be relevant to the avoidance of PH development and other cardiovascular comorbidities that are often found to be associated with sleep-related hypoxaemia. Routine sleep screening and focussed therapeutic intervention are important considerations to be included in a multidisciplinary care model to improve the long-term outlook of ILD patients.

The reviewed literature highlights a significant emphasis on routine sleep assessment in IPF patients, especially early in the disease course, as this would allow for timely interventions (24). Additionally, possible pathophysiological links between the two disease processes are outlined, such as the role of intermittent hypoxia, oxidative stress and pulmonary vasculature remodelling (25). The authors emphasise the need for further assessment regarding biomarkers, epigenetic changes and targeted therapies to improve the management of sleep disorders and related comorbidities in IPF. The obtained data emphasise the value of a collaborative team approach to managing IPF needs, including both respiratory and sleep conditions, for enhanced care delivery and prognostic outcomes.

Biomarkers are used as important clinical tools in the diagnosis and treatment of diseases such as IPF and OSA, being used as indicators of biological processes or responses to treatment. The ideal biomarkers should be sensitive and specific to the disease, correlated with severity, involved in

causal pathways and detectable early in the disease course at low cost. However, there is currently no common biomarker for both IPF and OSA, and it remains a major challenge to identify ideal markers for both diseases (26, 27).

In addition, CCL18, which is a prognostic biomarker for IPF, has recently been associated with hypercapnia during sleep in patients with SDB, suggesting an important link between hypoventilation and disease progression. Unfortunately, the identification of validated biomarkers is complicated by confounding factors such as smoking, age, obesity, cardiovascular diseases and metabolic disorders that can change biomarker levels in both conditions (28, 29).

Many studies have documented that patients with OSA have higher exhaled nitric oxide (eNO) levels than healthy people, including fractional exhaled NO (FeNO) and airway NO flux (J'awNO), as well as lower alveolar NO concentration (CaNO). CPAP therapy restores these parameters to normal levels, indicating their potential as biomarkers of treatment response. Although OSA is highly prevalent among ILD patients, there are no data on eNO parameters in this population. Considering the potential impact of OSA on eNO and its known negative impact on prognosis, sleep quality assessment should be prioritised in ILD patients in order to realise better outcomes and treatment stratification (30).

In a cross-sectional study of 1690 community-dwelling adults from the MESA, Kim et al. (31) investigated the association between OSA and subclinical ILD. Obstructive AHI (oAHI) was assessed by in-home PSG and HAAs and interstitial lung abnormalities by thoracic CT. After adjusting for demographics and smoking status, the study found that an oAHI >15 events/hr was linked to a 4.0% increase in HAA and a 35% higher likelihood of interstitial lung abnormalities. These associations were stronger in those who had a BMI <25 kg/m². Moreover, increased oAHI was associated with increased serum surfactant protein-A and matrix metalloproteinase-7 – two biomarkers of alveolar epithelial injury and extracellular matrix remodelling. Moderate to severe OSA appears to play a role in the early development of ILD, especially in those who are of normal weight.

Current research on biomarkers in IPF and OSA is significantly limited due to small cohort size, retrospective designs, mixed cohorts and the absence of independent validation or longitudinal data. However, new multicentric studies with larger cohorts and enhanced methodologies bring hope for the discovery of reliable biomarkers. Such pivotal advances may help in early diagnosis, predict the disease course and enable individualised therapeutic strategies for both sleep disorders and ILD (26).

New therapeutic approaches

Supplemental oxygen to address nocturnal hypoxemia and its associated complications holds potential clinical value,

particularly in delaying the progression of PH, as emphasised in the literature (5). The availability of evidence remains limited, particularly as there have not been large trials that demonstrate the effect of nocturnal oxygen therapy (NOT) on survival and QoL in patients with ILD. Khor et al. (7) found two small short-term intervention studies which demonstrated that supplemental oxygen of 1–3 L/min corrected nocturnal hypoxaemia, with improved heart rate control during in-laboratory observation and increased serum antioxidant levels after 1 month of therapy in ILD patients with SND.

In a recent randomised crossover trial, Han et al. (32) assessed OSA in patients with ILD before and after 1-night oxygen therapy. It showed that oxygen therapy had beneficial effects on SDB, sleep architecture, heart rate and nocturnal oxygenation by reducing AHI scores. The study highlights the importance of further randomised trials to evaluate long-term outcomes and develop effective treatment for sleep in this cohort. Although there are theoretical arguments suggesting that supplemental oxygen could contribute to increased oxidative stress, these concerns are outweighed by the potential benefits. NOT may be a reasonable empirical treatment option; however, it has been suggested for patients with severe nocturnal desaturation. Further studies are required to better define treatment thresholds and long-term outcomes. More comprehensive and well-designed research is urgently needed to determine whether correcting nocturnal hypoxemia will improve the survival and QoL of patients with ILD, especially in patients with IPF (7).

Whether CPAP adherence actually improves outcomes in ILD patients with OSA remains an open question. Hoffman and Grutters (33) detail the 'treatable traits' framework as it relates to progressive pulmonary fibrosis as well as OSA as a target for medical management. Data were collected retrospectively using a localised OSA database, and all patients were treated with CPAP therapy for OSA. It emphasises the CPAP role in the correction of repetitive nocturnal hypoxemia underlying PH and fibrosis, thus addressing a component of disease progression initiated by persistent nocturnal hypoxemia. The article highlighted the need for additional research to assess the benefits of treatment for OSA specifically in individuals with ILD.

In their pilot study, Bordaz-Martines et al. (11) explored the impact of CPAP and NOT in the treatment of SDB in IPF patients. In a cohort of 50 newly diagnosed IPF patients, PSG, lung function tests, blood analyses and QoL questionnaires were performed at baseline and one year later. SDB was identified in 70% of participants, including 36% with OSA, 22% with CSA and 12% with sleep-sustained hypoxaemia (SSH). Adherence to treatment was high, with CPAP use averaging 6.74 h per night. Significantly, following treatment, there was a marked reduction in the level of matrix metalloproteinase-1 (MMP-1), a biomarker of lung fibrosis in OSA and CSA

patients. CPAP and NOT are well tolerated in IPF patients, and physicians should consider regular monitoring of SDB. Likewise, Papadogiannis et al. (22) reported that CPAP treatment was associated with marked improvement of sleep quality, decreased sleepiness and fatigue, reduction of exacerbations and mortality in IPF patients. Adherence to CPAP was closely associated with better survival and quality-of-life outcomes (34).

Sleep and QoL in ILD patients

Over the past few years, QoL among patients with ILD has continued to be an area of interest. Many of these studies (10, 16, 24) seek to confirm the necessity of applying all the existing mechanisms that can offer an objective measurement of how this chronic pathology affects the everyday life of the sick. The aim is that this will make it easier for them to be incorporated into specialised pulmonary rehabilitation courses that would help improve their QoL.

The medical literature indicates that sleep quality is an important aspect of health status for patients with ILD. OSA, nocturnal hypoxemia and insomnia are common sleep disorders that contribute to more fatigue, cognitive problems, decreased exercise ability and worsening of dyspnoea, all of which can mean a major reduction in QoL (6, 35). The findings highlight the importance of early detection and appropriate treatment of sleep disorders in ILD, which could enhance symptoms, lung function and QoL.

There are different perspectives from which sleep quality and its effect on health can be measured. While sleep quality cannot always be solely self-assessed, sleep satisfaction does refer to the patient's experience with sleep regarding quality, duration and restfulness. Insomnia is defined by trouble falling and/or staying asleep, which can leave you feeling tired and unrested. Hypersomnia is excessive daytime sleepiness (EDS) that can disrupt daily life and one's overall QoL. People with hypersomnia may sleep more than they need to, yet still feel constant tiredness and drowsiness during the day (36).

Silva et al. (6) investigated the association between sleep duration and daily physical activity in patients with IPF. They showed that patients with IPF had more limited profiles of physical activity than healthy control subjects. In addition, these patients had fewer daily steps and less moderate-to-vigorous physical activity. The study suggests that poor sleep may impair physical activity in patients with IPF and serve as a potential mediator of worse health and QoL status.

In a cross-sectional study (21), sleep quality was studied in 101 patients with different types of ILDs, including IPF, connective tissue disease-associated ILDs, non-specific interstitial pneumonitis, combined pulmonary fibrosis and emphysema, asbestosis and sarcoidosis. They found that 66% of the patients had poor sleep quality, most highly associated with symptoms of depression and sleepiness, and

not with physiological or anthropometric variables. Patients with poor sleep quality reported frequent awakenings, difficulty falling asleep, decreased sleep duration and more sensitivity to disturbances (such as pain, temperature, noise and light). However, overall, patients with poor sleep quality had no impairments in the sleep architecture. Most patients had normal ESS values despite higher sleepiness scores. Poor sleep was found to be associated with higher depression scores and longer sleep latency, highlighting the potential for clinical interventions such as cognitive behavioural therapy (CBT) to improve the quality of sleep, which may have a positive impact on their mental health and overall well-being. Comorbid OSA was cited as a potential contributor, impacting 59%–90% of ILD patients. PSG was not undertaken; however, there were elevated scores when using subjective measures (e.g. PSQI), which correspond with earlier research findings.

Myall et al. (3) found that NH was associated with a more rapid decline in both QoL as measured by the King's Brief Interstitial Lung Disease questionnaire and higher all-cause mortality at 1 year. Among 102 ILD participants, 19.6% demonstrated prolonged NH and 31.4% showed OSA.

The Mena-Vázquez et al. (20) study described patients with RA-ILD having significantly poorer sleep quality than those without ILD. These patients had a higher prevalence of insomnia and hypersomnia and lower overall sleep satisfaction. The study also found that ILD was an independent predictor of sleep problems in RA patients. Older age, higher disease activity (measured by DAS28-ESR), multiple comorbidities and the usual interstitial pneumonia (UIP) pattern on radiologic examination were associated with lower sleep satisfaction. Compared to the non-ILD group, insomnia had the following associations: increased disease activity, lower resilience, Charlson index, hypersomnia, older age and limited emotional independence. These findings highlight the important role of a multidisciplinary evaluation that would be able to identify and manage potential sleep disorders that may affect QoL and worsen disease progression in RA-ILD patients.

A recent study in *Respiratory Medicine* (37) investigated the effect of SDB on sleep quality and HRQoL in patients with IPF. A total of 34 subjects with the diagnosis of IPF participated in the study, all of them underwent overnight PSG and filled out validated questionnaires: PSQI, ESS, and St. George's Respiratory Questionnaire (StGQ). Patients were divided into three groups based on their diagnostic evaluation findings: no SDB, OSA without sleep-related hypoxaemia, and OSA with concomitant sleep-related hypoxaemia. The study showed that poor sleep quality is very common, with pathological PSQI scores found in 47% of patients. The most detrimental effects on sleep fragmentation and QoL occurred among patients with both OSA and hypoxaemia. Sleep fragmentation severity was correlated with greater respiratory disturbance

index (RDI) and worsening PSQI and StGQ scores. Multivariate regression revealed independent predictors of QoL, which explained 75% of its variability: PSQI, ESS, FVC% and DLco%. The study emphasises the implications of SDB in sleep quality and QoL, highlighting the need for better identification and management of SDB in patients with IPF.

Ouyang et al. (35) showed that fatigue and EDS are more prevalent in patients with ILD than in the general population. This cross-sectional study assessed fatigue and EDS in 108 ILD patients as compared to 92 healthy controls using the Fatigue Assessment Scale (FAS) and ESS. Fatigue was associated with impaired pulmonary diffusion function, reduced exercise capacity and lower QoL. Fatigue was related to chest discomfort and decreased exercise capacity, while age, particularly >60 years, was one of the most important predictors of EDS. Despite its high prevalence, many patients with ILD do not report fatigue, reflecting inadequate awareness and detection by health care providers. Routine assessment with validated tools such as the FAS is recommended to better identify and manage this symptom. As discussed previously, fatigue causes decreased exercise capacity by decreasing physical activity, which in turn leads to further deconditioning. Pulmonary rehabilitation, which includes exercise training, has also shown benefits in fatigue, exercise capacity and potentially EDS. The interplay between EDS and depression highlighted the requirement for assessment and treatment of psychological features in ILD patients. Side effect profiles for drugs such as pirfenidone, nintedanib and corticosteroids can also lead to fatigue and sleep disruption, which must also be addressed.

Discussions

This systematic review draws attention to the considerable but often overlooked burden of sleep-related disturbances in patients with ILD. The pathophysiology of these disturbances is multifactorial, involving mechanical limitations of lung function, systemic inflammation, circadian rhythm dysregulation, psychological factors and co-morbid conditions including nocturnal hypoxaemia, OSA, CSA, PH and GERD. Untreated sleep disorders aggravate symptoms such as chronic fatigue, daytime sleepiness and dyspnoea, creating a vicious cycle that additionally reduces functional capacity and psychological well-being. A crucial goal for upcoming research is the unidirectional link between OSA and ILD, and the potential mechanisms (such as intermittent hypoxia, oxidative stress and systemic inflammation) that drive this relationship on both sides. This interdependence emphasises the importance of early diagnosis and targeted interventions. Validation of the potential role of sleep abnormalities in ILD

patients, and association of the explained mechanisms with disease progression, will pave the way for conducting studies with a larger number of subjects to ascertain the reliability of biomarkers for early diagnosis as well as long-term benefits from therapeutic interventions. Despite current evidence suggesting that interventions such as CPAP therapy and supplemental oxygen may improve nocturnal oxygenation, reduce symptom burden and even slow the disease's progression, a major limitation is the absence of large-scale randomised controlled trials. These investigations are important to develop specific guidelines for the management of sleep disorders in ILD patients based on evidence. Thus, this illustrates that sleep medicine should be part of the multidisciplinary approach for ILD patients to optimise clinical outcomes. Standardisation of a regimen, including PSG and validated questionnaire measurements (PSQI and ESS), should be included in the scope of care to promote early screening and treatment of sleep disorders. Moreover, psychological factors are prevalent among ILD patients and are likely to contribute to sleep disruptions and need to be addressed to enhance the QoL and overall well-being in the face of ILD, which is highly debilitating.

Conclusions

Sleep disturbances are an important but modifiable problem in the treatment of ILD. Clinicians armed with knowledge on the dual-headed nature of ILD can address these disturbances in a multifaceted manner, optimising clinical outcomes and improving quality-of-life measures while minimising disease progression. Further studies are needed to validate diagnostic criteria, develop focussed therapies and importantly, set evidence-based guidelines for those at highest risk who experience sleep-related disturbances.

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Informed consent statement

No informed consent was necessary.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest statement

The authors declare no conflict of interest.

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