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Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea Overlap Syndrome: Narrative Review

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) are among the most common respiratory disorders, and their coexistence, termed COPD-OSA Overlap Syndrome (OVS), poses unique diagnostic and therapeutic challenges. OVS affects approximately 1% of adults, yet it's true prevalence is likely underestimated due to variable diagnostic criteria and under recognition. The combination of chronic airflow limitation, recurrent nocturnal hypoxia, and sleep fragmentation creates a synergistic pathophysiological burden characterized by heightened systemic inflammation, oxidative stress, endothelial dysfunction, and autonomic imbalance. These mechanisms contribute to an increased risk of pulmonary hypertension, right-sided heart failure, arrhythmias, and overall cardiovascular morbidity and mortality compared with either disease alone. Clinically, OVS patients experience more profound nocturnal desaturation, greater daytime hypercapnia, and a higher frequency of exacerbations and hospitalizations. Diagnosis relies on screening tools such as the STOP-Bang or NoSAS questionnaires, with confirmation by polysomnography, though oximetry and capnometry remain valuable alternatives in resource-limited settings. Optimal management integrates aggressive treatment of COPD, lifestyle modification, and positive airway pressure therapy, particularly continuous positive airway pressure, which improves oxygenation, reduces exacerbations, and restores survival rates comparable to those of COPD-only patients. Despite its clinical importance, OVS remains understudied, underscoring the need for standardized diagnostic criteria, multicenter prospective trials, and a phenotype-based approach to guide individualized management and improve outcomes in this high-risk population.

Introduction

Chronic obstructive pulmonary disease (COPD) and Obstructive sleep apnea (OSA) are among the most prevalent respiratory conditions [1]. When both disorders coexist in the same individual, the condition is referred to as COPD-OSA Overlap syndrome (OVS), a term originally described in 1985 [2]. COPD is marked by persistent, incompletely reversible airflow limitation and impaired ventilation, while OSA is caused by complex changes in airway causing recurrent upper airway obstruction during sleep, leading to intermittent apneas and hypopneas, with subsequent oxygen desaturation [3]. Common symptoms include loud snoring, gasping or choking during sleep, and excessive daytime sleepiness [4]. Reported prevalence rates of OVS vary significantly across studies, likely due to differences in diagnostic criteria and study populations [5].

When COPD and OSA coexist, they can contribute to more severe and prolonged nocturnal oxygen desaturation than either condition alone, potentially heightening the risk for a range of associated comorbidities [6,7]. In OSA, intermittent episodes of oxygen deprivation trigger a cascade of biological responses, including oxidative stress, autonomic imbalance, systemic inflammation, and endothelial dysfunction, mechanisms that have been implicated in the development of cardiovascular complications [8,9]. Similarly, COPD is linked to cardiovascular disease through mechanisms such as heightened sympathetic activity and chronic, low-grade inflammation [10]. While both conditions independently elevate cardiovascular risk, their combined effect, whether additive or synergistic, remains to be fully clarified. However, existing evidence suggests that patients with OVS experience poorer health-related quality of life, a greater burden of comorbidities, more frequent exacerbations, and higher mortality compared to those with either disease alone [11-13]. These findings highlight the importance of early identification and support routine screening for OSA in patients with COPD to enable timely diagnosis and targeted management of OVS. This review aims to explore the underlying pathophysiological mechanisms, clinical consequences, and diagnostic and therapeutic challenges associated with this complex condition.

Background

PREVALENCE

Chronic obstructive pulmonary disease (COPD) affects about 5-10% of global population and about 5% of the US population (estimated 13.7 million people). Its increasing prevalence is explained by high rates of smoking, rising environmental pollution and an ageing population [1]. The prevalence of OSA varies, but most studies report rates of approximately 17–24% in middle-aged males (50–75 years old) and 9% in middle-aged females [14-16]. OVS, characterized by the coexistence of COPD and OSA, affects approximately 1% of adults [17]. However, the true prevalence of one condition in the presence of the other remains a subject of ongoing debate, as it largely depends on the specific criteria used to define COPD and OSA [6,17]. Studies report varying estimates, with the prevalence of COPD among individuals diagnosed with OSA ranging from 8% to 16% [18,19]. Conversely, the prevalence of OSA among individuals with COPD demonstrates a much broader range, between 5% and 65% [1,20,21]. These discrepancies may be attributed to differences in study populations, diagnostic methods, and thresholds used to identify each condition [1,22]. Approximately 1 in 10 patients with one entity will have other by chance and causal association is not implied. Most of the studies for OVS that depict a lower prevalence looked at individuals with milder COPD [3,23]. A study looking at moderate to severe COPD patient demonstrated the prevalence of 66% in these individuals [1]. This variability highlights the complexity of accurately characterizing OVS and underscores the need for standardized definitions and diagnostic approaches to better understand its true burden in the general population [24].

UNDERSTANDING COPD AND OSA

Chronic obstructive pulmonary disease (COPD) is defined by long-standing limitations in airflow that show limited reversibility and are linked to atypical inflammatory activity within the pulmonary system [24,25]. It refers to a spectrum of related respiratory disorders, such as chronic bronchitis and emphysema, that predominantly impact the airways, though the lung tissue and blood vessels may also be affected based on the underlying disease mechanism [25]. These pathophysiologic changes are often more pronounced during physiological stressors, such as exercise or sleep, where the respiratory system is further challenged [24]. The pathological effects of COPD are multifaceted and include mucous hypersecretion, which contributes to airway obstruction, and ciliary dysfunction, impairing the clearance of mucus and debris from the respiratory tract [26]. Airflow obstruction and hyperinflation further compromise respiratory efficiency, while gas exchange abnormalities lead to impaired oxygenation and carbon dioxide elimination [25,27]. Additionally, COPD can result in pulmonary hypertension due to increased vascular resistance and strain on the pulmonary circulation [27]. Systemic effects, such as cachexia and polycythemia, also manifest in advanced stages, reflecting the widespread impact of the disease beyond the lungs [26]. The mechanisms underlying respiratory dysfunction in COPD can be broadly categorized into two primary groups: mechanical impairment and ventilatory dysfunction. These categories represent distinct pathways that contribute to respiratory compromise, providing valuable insight into the diverse factors driving disease progression [24-27]. Sleep in COPD patient presents physiological changes that further challenges the pulmonary mechanics. Loss of drive to breath during wakefulness, hypoventilation, worse elastic loading and inability to shorten the expiratory phase led to marked disturbances in breathing during sleep and hence, a poorer sleep quality [3]. Figure 1, adapted and from Malhotra et al. [3], summarizes these mechanisms, illustrating how reduced ventilatory drive, upper airway instability, airflow limitation, and dynamic hyperinflation contribute to sleep-related breathing disturbances and promote arousals, ventilatory overshoot, and further instability during sleep.

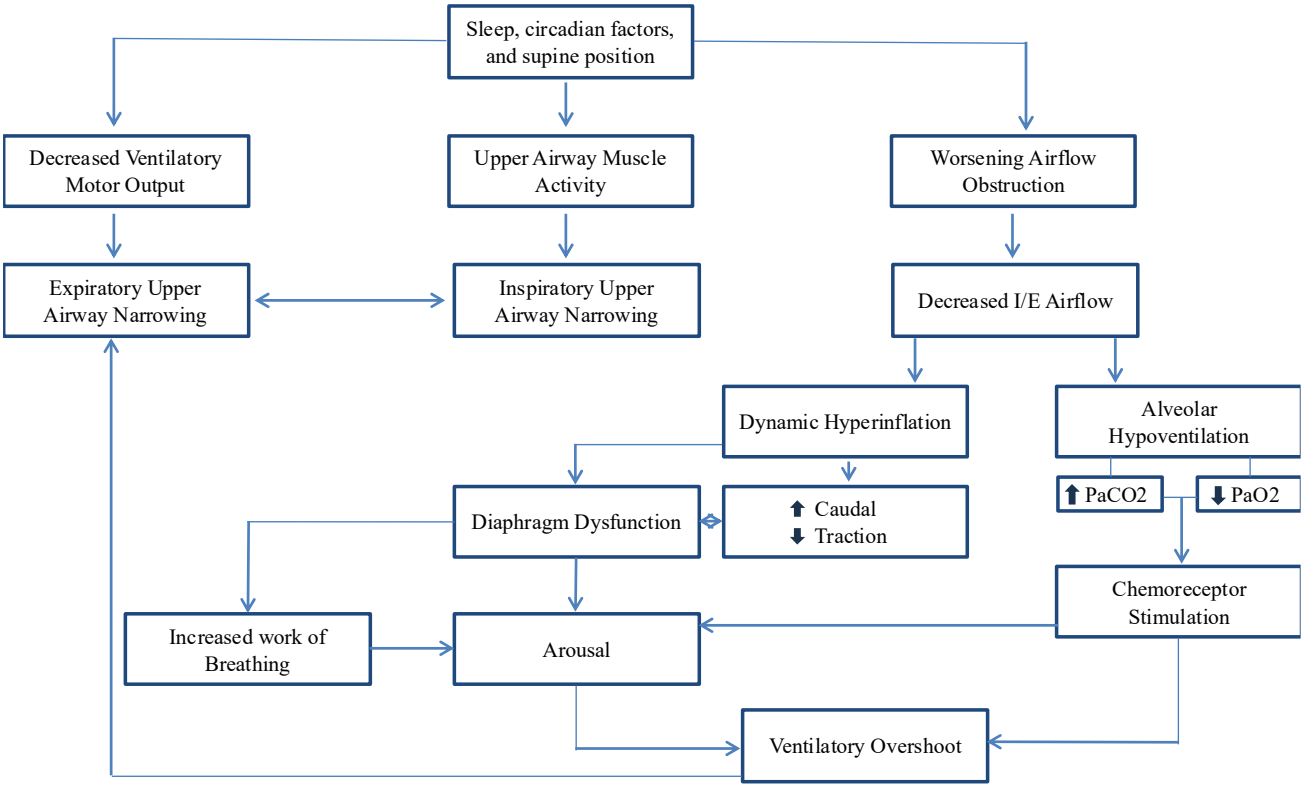

Figure 1: Sleep Cycle Disruptions in Chronic Obstructive Pulmonary Disease
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Malhotra A, et al. Research priorities in pathophysiology for sleep-disordered breathing in patients with chronic obstructive pulmonary disease: an official American Thoracic Society research statement. Am J Respir Crit Care Med. 2018;197(3):289-299.

Obstructive sleep apnea (OSA) is a condition marked by repeated narrowing or closure of the pharyngeal airway during sleep, leading to periodic reductions in oxygen saturation and disrupted sleep patterns [28]. During sleep, there is a physiological decline in respiratory drive compared to wakefulness, leading to decreased neuromuscular output to respiratory muscles [28,29]. This attenuation particularly affects pharyngeal dilator muscles, such as the tensor palatini and genioglossus, which are essential for keeping the upper airway open [29]. In at-risk individuals, these changes result in pharyngeal airway narrowing, increasing vulnerability to central apnea and airway collapse [30]. Airway narrowing leads to increased upper airway resistance and turbulent airflow, which causes oscillations of soft tissues, such as the soft palate, during sleep [30,31]. This increased resistance imposes an internal mechanical load on the lungs, which is compensated for by elevated respiratory effort during wakefulness [31]. Recurrent respiratory events associated with OSA are characterized by cycles of hypoventilation and hyperventilation, leading to fluctuations in end-tidal CO2 and variable oxygenation [32]. These events exacerbate oxidative stress and create significant gradients in partial oxygen pressure between the proximal and distal airways [33]. This process can further impair oxygen delivery and contribute to systemic complications [32].

Individuals with optimal upper airway anatomy generally maintain normal oxygen saturation and sleep patterns despite mild hypercapnia [34]. However, anatomical predispositions such as inspiratory flow limitation, snoring, or structural airway collapse increase the risk of OSA, with snoring serving as a clinical marker [35]. In obesity, excess adipose tissue around the pharyngeal airway, particularly in those with larger neck circumferences, further heightens the risk of airway collapse[34]. These factors underscore the intricate relationship between anatomy, respiratory mechanics, and risk factors in the pathogenesis of OSA [32,34].

CLINICAL FEATURES AND RISK FACTORS OF OVS

Despite the uncertainty regarding which conditions overlap, the term "OVS" emphasizes that the resulting pathophysiology is more intricate than would be anticipated if the conditions were entirely separate, thereby justifying its classification as a syndrome. The clinical features of OVS frequently appear alongside the typical manifestations of both COPD and OSA [2]. In addition to the hallmark symptoms of COPD and OSA, patients with OVS often exhibit more severe and prolonged hypoxemia, increased daytime hypercapnia, and metabolic derangements, including acidemia [36,37]. Clinicians must recognize and distinguish between nocturnal hypoxemia caused by COPD and hypoxemia

resulting from obstructive airway hypoventilation in OSA [36]. As a result, they may present with morning headaches due to hypercapnia, cyanosis from hypoxemia, and peripheral edema, highlighting additional clinical findings associated with OVS [38].

There is evidence indicating a reciprocal relationship between OSA and COPD, where OVS may arise in individuals with COPD who later develop OSA or in those with OSA who are subsequently diagnosed with COPD [39]. Factors linked to its development include older age, male gender, cigarette smoke and alcohol exposure, reduced physical activity, and obesity [2,40]. Smoking, a shared risk factor for both COPD and OSA, exacerbates these conditions through oxidative stress and airway inflammation [38].

PROMOTING AND PROTECTIVE MECHANISMS IN OVS

In individuals with COPD, several factors can either promote or protect against the development of OSA [41]. Promoting factors include coexistent cor pulmonale with fluid retention. The rostral shift of peripheral edema, where fluid redistributes from the lower extremities to the neck and upper airway during sleep, compromising airway patency [41,42]. Other contributors include upper airway and skeletal myopathy associated with advanced COPD which reduces upper airway stability during sleep. Moreover, the use of corticosteroids, frequently prescribed in COPD, can further weaken muscles and promote weight gain, thereby increasing the risk of airway obstruction [42,43]. Additionally, chronic cigarette smoking, commonly associated with COPD, contributes to airway inflammation, remodeling, and dysfunction, increasing the susceptibility to OSA [44].

Conversely, certain factors appear to protect individuals with COPD from developing OSA. A low body mass index (BMI), often seen in severe COPD due to increased metabolic demands and cachexia, reduces fat deposition in the upper airway, lowering the likelihood of obstruction [45]. Lung hyperinflation, a characteristic feature of COPD, may mechanically stabilize the upper airway due to tracheal traction and reduce its collapsibility during sleep [46]. Additionally, diminished REM sleep, a stage when OSA events are most prominent, decreases the exposure to periods of airway collapse [47]. Other protective factors include older age, which paradoxically reduces OSA severity due to age-related changes in airway structure [48].

The influence of these promoting and protective factors can vary depending on the underlying COPD phenotype. For instance, patients with emphysema typically have hyperinflated lungs and lower BMI due to increased work of breathing, which may reduce their risk of OSA [38,46]. In contrast, patients with chronic bronchitis often present with higher BMI, increasing the likelihood of OSA due to adipose tissue accumulation around the neck [46]. Moreover, environmental and occupational exposures that drive the progression of COPD, particularly in resource-limited settings, can accelerate COPD progression and further influence the risk of OSA [49].

EVALUATION

Currently, no definitive guidelines exist for screening patients with COPD for OSA [50]. However, the STOP-Bang Questionnaire (SBQ), which evaluates factors such as snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, and gender, is recommended as an initial screening tool for all COPD patients [51]. Diagnostic testing is advised for patients identified as having an intermediate-to-high risk of OSA based on SBQ scores [50]. Additional screening tools include the NoSAS Questionnaire, which assesses neck circumference, obesity, snoring, age, and sex, and the Berlin Questionnaire, both of which aid in identifying patients at increased risk for sleep apnea [52,53].

Polysomnography remains the gold standard for evaluating sleep disturbances in patients with OVS, offering the most comprehensive assessment of sleep and breathing patterns [50,54]. However, sleep studies have limitations in this scenario as well. Given the variety of physiological airway changes and sustained and severe hypoxemia in COPD patients, the apnea-hypopnea index (AHI), might be underestimation in prolonged hypoxic events [55]. Moreover, sleep disturbances associated with hyperinflation, poor sleep quality, and nocturnal cough can likely cause breathing disturbances being misinterpreted as respiratory events [56]. Conversely, frequent arousals might not lead to adequate desaturation and might lead to underestimation of hypopneas [55]. Additionally, the correlation on AHI with clinical outcomes, including cardiovascular outcomes, symptom severity, and mortality, remains unknown [57]. In COPD patients, sleep indices that determine hypoxemic load (e.g. deoxygenation nadir, duration of hypoxia, area under oxygen desaturation curve) might predict clinical outcomes, and further research is warranted in this field [3].

In resource-limited settings, oxygen desaturation monitoring and overnight oximetry may suffice for clinical evaluation [58]. The American Thoracic Society (ATS) and European Respiratory Society (ERS) recommend overnight polysomnography for patients with mild COPD and clinical evidence of pulmonary hypertension to evaluate for OSA [7,50]. While overnight oximetry can be a valuable screening method, particularly in resource-constrained settings where a sawtooth pattern on oximetry often indicates OSA in COPD patients, confirmation with polysomnography remains essential [59,60].

Comparison of other methods of nocturnal gas-exchange beyond pulse oximetry is an area of interest in COPD patients. Capnometry, in addition to sleep study, might help detect potential hypoventilation and help guide treatment choices as well [3].

SEVERITY AND PHYSIOLOGICAL IMPAIRMENTS IN OVS

Patients with OVS often exhibit higher scores on the COPD Assessment Test and the Epworth Sleepiness Scale compared to patients with COPD alone, reflecting greater symptom burden and sleep-related impairments [61]. These clinical findings are closely associated with physiological changes, such as lung hyperinflation, which significantly impacts pulmonary function in OVS [62]. A reduced inspiratory capacity to total lung capacity

(IC/TLC) ratio is indicative of more severe hyperinflation and is considered a more accurate marker of disease severity than forced expiratory volume (FEV_1) [63]. Hyperinflation can impair sleep quality by increasing the work of breathing in the recumbent position, though this mechanism requires further investigation [62]. Additionally, the severity of airflow obstruction, measured by the forced expiratory volume/forced vital capacity (FEV_1/FVC) ratio, correlates with a higher likelihood of persistent hypoxemia [64]. However, data comparing pulmonary function testing in OVS versus COPD alone remain limited.

Patients with OVS are especially prone to oxygen desaturation during sleep [38]. Notably, even in the absence of upper airway obstruction, individuals with COPD and an awake oxygen saturation (SaO_2) between 90% and 95% are prone to substantial nocturnal desaturation. This is particularly pronounced during rapid eye movement (REM) sleep and is attributed to alveolar hypoventilation, impaired ventilation-perfusion matching, and reduced end-expiratory lung volume [36]. Continuous overnight monitoring of oxygen saturations, with an emphasis on the oxygen desaturation index (ODI), is critical, particularly in resource-limited settings where polysomnography may not be available. The ODI, which reflects intermittent hypoxemia, is considered a more reliable predictor of systemic inflammation and cardiovascular comorbidities than the apnea-hypopnea index (AHI) [58].

OUTCOMES OF OVS AND IMPLICATION OF COMORBIDITIES

Individuals with both COPD and OSA are thought to face an elevated risk of cardiovascular disease due to shared and potentially synergistic pathological mechanisms [38]. These mechanisms include oxidative stress, systemic inflammation, vascular endothelial dysfunction, and accelerated atherosclerosis, which may interact in a way that exacerbates cardiovascular harm[65-67]. Supporting this hypothesis, multiple studies have demonstrated that OVS is associated with a higher cardiovascular risk and greater mortality compared to COPD or OSA alone [5,68]. However, whether the coexistence of these two conditions results in a truly synergistic effect on cardiovascular outcomes remains unclear [5]. OVS patients may experience more frequent and severe episodes of oxygen desaturation, deeper hypoxemia, and a higher incidence of cardiac dysrhythmias [6,69]. Mechanistic pathways indicate intermittent hypoxia leading to pulmonary vasoconstriction and right ventricular load leading to increased RV mass in patients with OVS as compared to COPD alone [70]. Myocardial fibrosis has been proven to be present with cardiac MRI imaging in patients with worse nocturnal hypoxia [71]. Synergistic mechanisms leading to increased inflammation and impaired metabolism in COPD and OSA lead to worse chronic inflammation in OVS [70,72].

Consequently, OVS patients are susceptible to developing pulmonary hypertension [73], right-sided heart failure, vascular endothelial dysfunction [65], and accelerated atherosclerosis [66]. These combined effects significantly increase the risk of long-term complications and reduce overall survival rates [5].

Interestingly, emerging evidence suggests that the severity of OSA may influence the impact of COPD on mortality and respiratory function [74]. For instance, severe OSA has been associated with a reduced contribution of impaired lung function to mortality, as well as decreased gas trapping and a lower burden of emphysema in smokers with concurrent OSA [74,75]. These findings highlight the complex interplay between COPD and OSA, particularly in how they interact to influence gas exchange, cardiovascular health, and overall mortality. Understanding these mechanisms, alongside the balance of promoting and protective factors, is critical for identifying individuals at high risk for OVS and optimizing their clinical management.

MANAGEMENT

Lifestyle Modifications and Exercise

Exercise and pulmonary rehabilitation improve sleep quality, symptoms, and quality of life in OVS, while smoking cessation reduces morbidity and mortality [7]. Weight loss benefits obese OSA patients, but cachexia in advanced COPD increases mortality [7,50].

Supplemental Oxygen

Supplemental nocturnal oxygen is necessary for persistent desaturations despite optimized medications and does not increase the risk of hypercapnia [50]. However, studies indicate it may elevate the risk of arrhythmias in COPD patients, particularly those with coronary artery disease or left ventricular dysfunction, requiring cautious use. Therefore, oxygen therapy alone is insufficient for managing OVS [76].

Pharmacologic Therapies

Long-acting bronchodilator therapies, including inhaled beta-agonist and anticholinergics, have demonstrated significant benefits in improving mean nocturnal oxygen saturation in COPD patients [77]. Both therapies reduce the time spent in hypoxemia during sleep, helping to mitigate nocturnal desaturation and related complications [38,77].

The effectiveness of inhaled corticosteroids (ICS) in managing OVS remains controversial [78]. Some studies suggest that ICS can improve the AHI, nocturnal oxygenation, daytime hypercapnia and lung function by reducing airway inflammation [78]. Conversely, other research indicates that ICS may contribute to an increased risk of myopathy, potentially exacerbating upper airway collapsibility [3,79].

Theophylline improves nocturnal oxygenation and reduces the AHI in OSA patients, likely by stimulating central respiratory drive, which may be particularly effective in central sleep apnea. However, its use is limited by potential side effects [80].

Sedatives, opioids, and respiratory stimulants like acetazolamide are not recommended for OVS due to potential risks and lack of clinical benefit [81,82].

Positive Airway Pressure and Noninvasive Ventilation

Positive airway pressure (PAP) therapy is the most effective and widely recognized treatment for OVS. While PAP treatments have been proven to improve sleep quality and cardiovascular outcomes in OSA

patients, the use of non-invasive ventilation (bilevel positive airway pressure ventilation) has been shown to improve mortality in advanced COPD patients with hypercapnia [39].

Positive airway pressure treatment has been shown to decrease pro-inflammatory markers associated with cardiovascular disease, such as C-reactive protein (CRP) and tumor necrosis factor-α (TNF-α) [83], increase exercise capacity, respiratory and skeletal muscle strength [84,85], improve mean arterial pressure [86] and FEV1 [87]. Adherence to PAP therapy has been associated with fewer COPD exacerbations, reduced COPD-related hospitalizations, lower incidence of cardiovascular events, and decreased mortality [5].

The study by Marin et al. highlights the significant impact of long-term continuous positive airway pressure (CPAP) therapy on survival and hospitalization rates in patients with OVS[5]. Patients treated with CPAP had survival rates comparable to those with COPD alone, demonstrating that CPAP effectively mitigates the additional mortality risk associated with OVS. In contrast, patients not receiving CPAP had a 1.79-fold higher risk of mortality and were 1.70 times more likely to experience severe COPD exacerbations requiring hospitalization compared to COPD-only patients. These findings underscore the critical role of CPAP in improving long-term outcomes by reducing mortality, severe exacerbations, and hospitalizations in OVS patients [5,88,89].

Similarly, a study on CPAP and survival in moderate-to-severe OSA and hypoxemic COPD reinforces these conclusions, showing that long-term CPAP therapy significantly improves survival in OVS patients [90]. Individuals with moderate-to-severe OSA and hypoxemic COPD who adhered to CPAP therapy experienced better outcomes, including reduced mortality, compared to those who did not receive or adhere to CPAP treatment [90]. Albeit a small study with limited individuals, these results further emphasize CPAP's role in alleviating nocturnal hypoxemia and mitigating the combined risks of COPD and OSA, highlighting its importance in improving prognosis and long-term outcomes in this high-risk population [90].

Prognosis

Several studies have examined the prognosis of patients with OVS. For instance, a case-control study reported that the presence of COPD in patients with OSA was associated with a nearly sevenfold increase in mortality compared to those without COPD [12]. Similarly, Marin et al. found that among individuals with COPD, the coexistence of OSA significantly increased the risk of all-cause mortality, cardiovascular-related deaths, and hospitalizations due to COPD exacerbations [5]. Notably, treatment with CPAP is associated with improved survival and reduced hospital admissions [5].

Furthermore, patients with OVS tend to experience more frequent COPD exacerbations and hospitalizations with increased healthcare utilization. These patients experience greater sleep disruption, more severe nocturnal oxygen desaturation, lower health related quality of life indices and a higher burden of comorbidities than those with either condition alone[5,91,92]. These factors contribute to a significantly poorer health-related quality of life. Collectively, these findings highlight the importance of early recognition and management of OVS and support routine screening for OSA in patients with COPD.

Conclusion

Patients with OVS experience a higher burden of comorbidities, increased mortality, and reduced quality of life compared to those with COPD or OSA alone, contributing to both clinical and economic challenges. These patients often present with more severe nocturnal desaturation, systemic inflammation, oxidative stress, and endothelial dysfunction, all of which raise their risk for cardiovascular complications. CPAP remains the first-line therapy for OVS, offering improvements in oxygenation, sleep quality, and COPD exacerbation frequency. Despite evidence supporting CPAP's benefits, research on OVS remains limited and inconsistent, largely due to small sample sizes, regional differences, and the lack of large, multicenter prospective studies. Additionally, varying diagnostic criteria and the frequent exclusion of OVS patients from clinical trials hinder broader understanding and management. There is a clear need for standardized evaluation tools, phenotype-specific research, and stronger clinical guidelines to improve the prevention, diagnosis, and treatment of this underrecognized population.

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