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REVIEW

Diagnosis and Management of Overlap Syndrome (COPD-OSA): Evidence, Challenges and Prospects

Xiaotong Wei[1], Xiaoyu Zhang[2], Siping Wang[1], Xin Tong[3], Chuang Wu[1], Shaodan Hu[2], Li Shi[2]

[1]College of Traditional Chinese Medicine, Changchun University of Chinese Medicine, Changchun, People's Republic of China; [2]Department of Pneumology, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, People's Republic of China; [3]College of Integrated Traditional Chinese and Western Medicine, Changchun University of Chinese Medicine, Changchun, People's Republic of China

Correspondence: Li Shi; Shaodan Hu, Department of Pneumology, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, People's Republic of China, Email shili0648@163.com; 734168300@qq.com

Abstract: The overlap syndrome (OVS), characterized by the co-existence of obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), presents a significant clinical challenge due to its association with serious cardiopulmonary consequences and increased mortality. The complex pathophysiology and absence of standardized treatments often lead to underdiagnosis, aggravating its disease burden. Therefore, early and precise diagnosis is crucial. Beyond monitoring carbon dioxide levels as a key indicator of ventilatory limitation, a comprehensive diagnostic approach should integrate subjective assessments and objective examinations. Advances in precision medicine are shifting research focus towards biomarkers, including systemic inflammation ratios and vascular injury markers, to facilitate early detection and risk stratification. In terms of treatment, non-invasive ventilation (NIV) remains the cornerstone for maintaining airway patency, though its effectiveness is constrained by suboptimal adherence and inherent limitations. This has prompted the exploration of pharmacological strategies as alternatives or adjuncts, yet their application requires careful risk-benefit evaluation. For instance, benzodiazepines may worsen upper airway muscle tone and blunt hypercapnic arousal responses. Promising directions include novel pharmacotherapies inspired by recent advances in OSA treatment, alongside weight-loss agents that act through weight management and metabolic regulation. Adjunctive strategies such as mild intermittent hypoxia (IH) conditioning are being investigated to enhance positive airway pressure (PAP) therapy, while targeted agents like thioredoxin (TRX) demonstrate potential by mitigating oxidative stress and neutrophilic inflammation. However, the clinical translation of these innovations faces a major bottleneck the scarcity of large-scale randomized controlled trials (RCTs) to confirm their efficacy and safety. This review synthesizes current evidence to address these gaps and inform the future precision management of OVS.

Keywords: obstructive sleep apnea, chronic obstructive pulmonary disease, overlap syndrome, interventions, potential markers

Introduction

Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are two highly prevalent chronic respiratory disorders worldwide. Their coexistence leads to a clinically distinct entity termed overlap syndrome (OVS), which is associated with significantly worse clinical outcomes.[1] Compared to individuals with either condition alone, OVS patients exhibit more pronounced nocturnal hypoxemia, daytime hypercapnia, and systemic inflammation.[2–4] Additionally, they face substantially higher risks of pulmonary hypertension, cardiovascular events, and all-cause mortality, contributing to considerable burdens on both individual health and healthcare systems.[5–7] The management of OVS remains particularly challenging due to the profound pathophysiological interplay between COPD and OSA. Airflow limitation and impaired gas exchange in COPD can exacerbate upper airway collapse, respiratory effort-related arousals, and sleep fragmentation caused by OSA, thereby establishing a self-perpetuating vicious cycle. Consequently, single-disease management strategies such as bronchodilators for COPD or continuous positive airway pressure (CPAP) for OSA often show limited efficacy in patients with OVS.

Nevertheless, evidence-based systematic interventions for OVS remain relatively underdeveloped, with current clinical guidelines largely derived from expert consensus or evidence targeting single diseases. Significant knowledge

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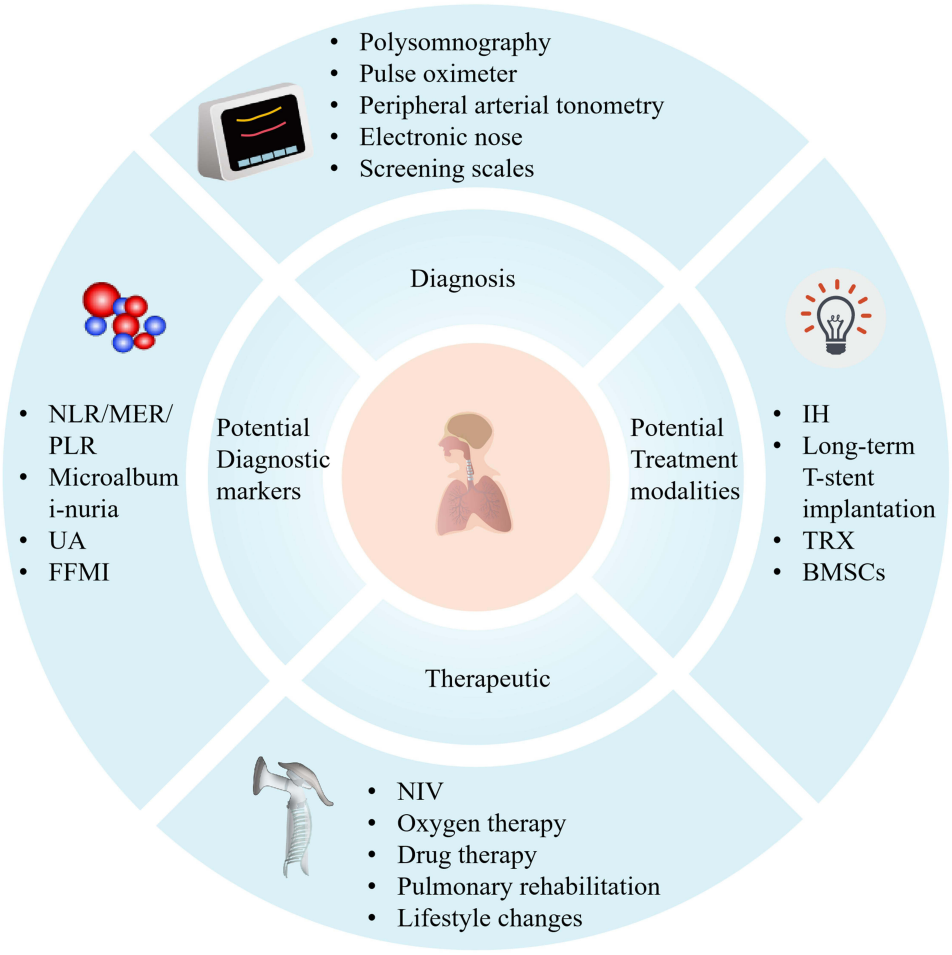
Graphical Abstract



gaps persist concerning the complex needs of this patient population, including issues related to CPAP adherence, optimal oxygen therapy regimens, and the integration of pulmonary rehabilitation with sleep-focused management. Thus, a comprehensive analysis and critical appraisal of the available evidence are urgently required, together with the identification of barriers to implementation and key priorities for future research. This review systematically evaluates interventional strategies for OVS management, covering CPAP optimization, oxygen therapy, pharmacotherapy, pulmonary rehabilitation, and behavioral interventions. It also assesses current biomarkers and promising treatment modalities, while proposing future strategies to promote personalized and integrated care frameworks for OVS.

Epidemiology

From an epidemiological perspective, COPD ranks as the third leading cause of death worldwide, affecting more than 400 million individuals.[8] OSA is also highly prevalent, with recent systematic analyses estimating that nearly one billion people are affected globally.[9] Although each disease individually contributes to a substantial health burden, the exact frequency of their coexistence remains incompletely understood. Recent meta-analyses have provided clearer insights into the epidemiological characteristics of OVS. One analysis involving 41 studies and 1,871,071 participants reported a global OVS prevalence of 28.3%, indicating that approximately one-third of COPD patients also have OSA. Prevalence estimates vary according to study design and geographical region, with cross-sectional studies reporting higher rates (30.7%) than cohort studies (21.2%), and the highest prevalence observed in Asia (37.9%). The diagnostic criteria for

OSA also influence these estimates, as using an apnea-hypopnea index (AHI) threshold of ≥5 events per hour yields a higher OVS prevalence compared to a threshold of AHI ≥10 events per hour.[10] These findings are corroborated by another meta-analysis of 60 studies, which reported an OSA prevalence of 29.1% among COPD patients.[11]

Collectively, the available evidence indicates that OVS is a common condition with considerable clinical significance. These epidemiological findings underscore the importance of screening for OSA in patients with COPD and evaluating COPD in those with OSA. They also highlight the need for targeted management strategies to improve clinical outcomes in this patient population.

Clinical Symptoms

The current literature has established clear indications for sleep assessment in patients diagnosed with COPD. Key clinical features prompting evaluation include sleep-related symptoms such as snoring, gasping, or sensations of choking, alongside nocturia or morning headache. Other significant indicators comprise worsening daytime sleepiness, obesity, daytime oxygen saturation below 93% at rest or during exertion, daytime hypercapnia, and signs of pulmonary hypertension or right heart failure, such as peripheral edema and polycythemia. Furthermore, the use of opioid medications or hypnotics, together with comorbidities including atrial fibrillation, end-stage renal disease, type 2 diabetes, heart failure, resistant hypertension, and stroke, also constitute important justification for conducting sleep studies in this patient population.[12]

When COPD patients present with the aforementioned clinical indicators, sleep monitoring is warranted. If OVS is diagnosed, priority should be given to assessing blood oxygen and carbon dioxide levels. The underlying pathophysiological mechanism lies in the shared ventilatory limitation of both disorders, which can lead to inadequate carbon dioxide elimination, resulting in carbon dioxide retention and the development of hypercapnia.[13] This hypercapnia, in turn, exacerbates sleep-related hypoxemia and worsens gas exchange function. This pathophysiological process frequently presents with hypoxemia or hypercapnia that is disproportionate to the measured lung function values, particularly the forced expiratory volume in one second (FEV1).[14]

Beyond gas exchange abnormalities, cardiovascular comorbidities are particularly common in OVS patients. For instance, resistant hypertension with elevated nocturnal or morning blood pressure, along with signs of pulmonary hypertension or cor pulmonale, should raise suspicion for OVS even in patients exhibiting only mild airflow limitation.[15–17] Moreover, accumulating evidence indicates that OVS is associated with various extra-pulmonary manifestations, including cognitive impairment, anxiety, depression, and an increased risk of falls.[18–21] Given the broad spectrum of potential clinical consequences associated with this syndrome, comprehensive and multidimensional clinical evaluation is essential for patients with confirmed or suspected OVS.

Pathophysiology

During sleep, reduced neural input from higher centers to the brainstem leads to a generalized decrease in respiratory drive,[22] disappearance of accessory respiratory muscle activity (excluding the diaphragm), and diminished tone of the upper airway dilator muscles,[23] predisposing the oropharynx to collapse. This physiological state results in a mild decline in arterial oxygen partial pressure and a slight rise in carbon dioxide partial pressure,[24] thereby increasing the reliance of respiratory control on peripheral and central chemoreceptors.[25] When patients with COPD face these physiological challenges, their underlying pathological alterations significantly exacerbate the condition. Sleep-related reductions in functional residual capacity worsen pre-existing ventilation-perfusion mismatch and gas exchange impairment, which, combined with weakened accessory muscle activity, collectively contribute to severe nocturnal hypoxemia, particularly during rapid eye movement sleep (REM).[23,26–28] The core defect in OSA lies in the collapse of the upper airway during sleep, triggering recurrent apnea, intermittent hypoxia (IH), hypercapnia, and sleep fragmentation.[29,30] When COPD and OSA coexist as OVS, they interact synergistically, creating a vicious cycle. The impaired gas exchange in COPD limits compensatory responses to acute hypoxic events induced by OSA, leading to more severe and prolonged oxygen desaturation.[31–34] Meanwhile, OSA-related blunted chemosensitivity combines with the inherently reduced ventilatory drive in COPD, resulting in dual suppression of ventilation.[35] In addition, COPD-associated systemic inflammation and blood gas abnormalities may further aggravate OSA. This synergistic interaction transforms nocturnal hypoxemia from

intermittent to persistent in OVS patients, accompanied by more pronounced and refractory hypercapnia,[4,36] ultimately increasing the diagnostic complexity of these cases.

Carbon Dioxide Monitoring

In patients with OVS of COPD and OSA, abnormal gas exchange represents a core pathophysiological feature, rendering accurate assessment of carbon dioxide levels clinically essential. A combination of invasive and non-invasive techniques offers complementary advantages for precise clinical management.

Arterial blood gas analysis remains the gold standard for measuring arterial partial pressure of carbon dioxide ($PaCO_2$). Blood samples obtained at the beginning and/or end of sleep enable evaluation of alveolar ventilation during sleep. This method not only directly and accurately determines $PaCO_2$ and oxygen partial pressure but also simultaneously assesses pH, bicarbonate levels, and base excess, providing a comprehensive overview of acid-base balance.[37,38] Studies have shown that in hypoxemic patients, invasively measured arterial oxygen saturation (SaO_2) (mean 84.41 ± 4.24) differs significantly from readings obtained by non-invasive pulse oximetry (mean 80.58 ± 5.77), with the accuracy of the latter further declining when saturation falls below 90%. Therefore, arterial blood gas analysis remains indispensable when hypoventilation is suspected.[39] However, the technique has notable limitations. As one of the more painful routine procedures,[40] it may cause awakening due to discomfort, potentially interfering with accurate measurement of sleep-related $PaCO_2$ levels. It also carries risks of complications such as bleeding, hematoma, and infection,[41] with thrombosis or embolism being most frequent (49.0%), followed by aneurysm formation (15.4%), nerve injury (1.5%), and arteriovenous fistula (0.6%). Patients receiving antithrombotic therapy face significantly higher risks, with an odds ratio of 1.31.[42]

Given these limitations, non-invasive monitoring techniques have become essential alternatives or supplements. For oxygen monitoring, pulse oximetry serves as a widely adopted non-invasive screening tool,[43] though its accuracy decreases markedly when SaO_2 falls below 90%, limiting its standalone utility in severe hypoxemia.[44,45] Nevertheless, this method can analyze heart rate variability to compute approximate entropy, which quantifies irregularity in physiological signals. Studies indicate that OVS patients exhibit significantly higher approximate entropy than those with COPD alone, with a diagnostic sensitivity of 71.2% and specificity of 78.9%. The positive correlation between approximate entropy and the AHI supports its potential as an auxiliary diagnostic tool.[46] Portable oximetry further simplifies screening and demonstrates good diagnostic consistency and accuracy in both laboratory and home settings, making it suitable for initial identification of moderate to severe OSA.[47]

For dynamic carbon dioxide monitoring during sleep, end-tidal CO_2 monitoring employs infrared analyzers to provide breath-by-breath estimates of gas exchange. It offers high temporal resolution and is well-suited for clinical scenarios requiring real-time feedback, such as anesthesia, mechanical ventilation, and sleep analysis, though its accuracy is generally slightly lower than that of transcutaneous monitoring.[48] Transcutaneous CO_2 monitoring, based on the principle of transcutaneous diffusion, continuously measures tissue-level partial pressure of CO_2 and is more appropriate for tracking long-term trends in alveolar ventilation. Research indicates that under stable conditions, properly calibrated transcutaneous values correlate well with $PaCO_2$, making this method particularly suitable for long-term follow-up, although its reliability may be reduced in acute pathological states.[49]

The integration of these monitoring modalities enables a more comprehensive understanding of gas exchange abnormalities in OVS. This multifaceted assessment is fundamental to guiding personalized treatment strategies, ultimately aiming to improve long-term patient outcomes.

Diagnostic Approaches

Screening Scales

Screening questionnaires provide a method for subjective assessment in OVS research. Instruments such as the Pittsburgh Sleep Quality Index (PSQI), STOP-Bang, and Berlin questionnaires are commonly used to identify individuals at high risk of OVS among populations diagnosed with COPD or OSA. This approach offers an efficient and cost-effective strategy that facilitates subsequent investigations into disease prevalence, severity, and prognosis.

The PSQI is particularly useful for evaluating subjective sleep quality in clinical settings.[50] Studies have confirmed its good reliability and validity across different populations, supporting its use in screening for sleep disturbances.[51] In obese populations, for example, PSQI scores have shown significant correlations with metabolic parameters such as body mass index, neck circumference, and insulin resistance, while also identifying a considerable number of individuals at high risk of OSA.[52] In patients with sleep bruxism, PSQI assessments revealed a notable association between subjective sleep quality and bruxism episodes, a contrast to the lack of intergroup differences observed in objective polysomnographic parameters.[53] By quantifying sleep disturbances across multiple dimensions, the PSQI effectively captures the compounded impact of conditions such as OVS on sleep, offering valuable supplementary information for clinical evaluation and treatment monitoring.

In addition to the PSQI, other screening instruments are available for detecting sleep-disordered breathing. Commonly used tools include the Epworth Sleepiness Scale (ESS), Sleep Apnea Clinical Score (SACS), Berlin Questionnaire (BQ), and STOP-Bang Questionnaire (SBQ). Evaluations of these instruments for OSA screening in COPD patients have revealed distinct performance characteristics. Comparative analyses indicate that the SBQ demonstrates superior predictive capability relative to the ESS, SACS, and BQ, as evidenced by optimized cut-off points, improved sensitivity, greater specificity, and higher AUC (area under the curve values).[54] Complementary research has established that the SACS outperforms both the BQ and ESS in predicting OSA onset among COPD patients, achieving better accuracy and higher AUC values.[55] As efficient subjective screening tools, questionnaires play a key role in supporting initial screening in OVS research.

Polysomnography

Polysomnography (PSG) is established as the gold standard for diagnosing sleep apnea, delivering a comprehensive evaluation of respiratory effort, airflow, and oxygen saturation to objectively quantify the frequency, duration, and severity of respiratory events. While subjective questionnaires serve as useful instruments for initial screening, PSG supplies the definitive objective data necessary for diagnosis. This role is illustrated by a study involving stable COPD patients, in which initial screening with the ESS using a cutoff score above 10 identified 15.6% of patients with daytime sleepiness. Subsequent PSG evaluation diagnosed OSA in 72.3% of these symptomatic individuals, resulting in an overall OSA prevalence of 10.9% within the COPD cohort. These findings confirm PSG as an indispensable objective tool for definitive diagnosis.[56]

In addition to its diagnostic role, PSG supports the management of chronic respiratory failure. A RCT demonstrated greater reductions in $PaCO_2$ (−0.36 kPa) by PSG-guided titration in comparison to $PaCO_2$ (−0.88 kPa) with limited respiratory monitoring, confirming PSG's role in guiding NIV efficacy in COPD-OSA.[57] Furthermore, PSG aids in distinguishing OVS from OSA alone by uncovering distinctive polysomnographic characteristics, such as elevated severity indices, more marked disruption of sleep architecture, and higher arousal indices. These attributes not only strengthen the clinical value of PSG but also facilitate early detection of OVS and may contribute to predicting patient-reported outcomes.[58]

Notwithstanding its recognized diagnostic importance and broad utilization in sleep medicine, the use of PSG is constrained by challenges including cumbersome equipment, substantial cost, and interpretive subjectivity. In light of these limitations, investigators are actively pursuing the development of alternative diagnostic tools and streamlined approaches to overcome these constraints.[59]

Home Sleep Apnea Testing

Home Sleep Apnea Testing (HSAT) serves as a screening tool for assessing sleep quality in patients with COPD and OSA. Devices employing an apnea–hypopnea index (AHI) threshold of ≥5 events per hour demonstrate high diagnostic performance for OSA in adults with COPD, showing a sensitivity of 95%, specificity of 78%, positive predictive value of 88%, and negative predictive value of 89% relative to PSG. However, significant discrepancies persist in oxygenation parameters. Mean oxygen saturation measurements varied considerably, with values of 93.2%±3.7% for PSG, 91.0% ±3.3% for in-laboratory portable monitoring (PM), and 90.8%±4.0% for HSAT ($P<0.001$). Similarly, the percentage of sleep time with oxygen saturation ≤88% was higher in both HSAT (17.9%±26.4%) and in-laboratory PM (17.4%±25.5%) than in PSG (10.0%±21.1%, $P<0.001$).[60] Overall, HSAT provides a cost-effective diagnostic alternative for identifying OSA in patients with COPD.

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Peripheral Arterial Tonometry

Peripheral arterial tonometry (PAT) represents a portable method for diagnosing OSA and COPD.[61,62] Evidence from cohort studies illustrates its application in sleep evaluation for COPD patients. A study involving 104 subjects revealed that 49 (47%) had moderate-to-severe OSA. Patients with overlapping OSA and COPD (OVS), who were predominantly male, showed significant differences from those with COPD alone, including increased age, higher BMI, greater hypertension prevalence, and concurrently reduced deep sleep duration and mean nocturnal oxygenation.[63] Validations of the WatchPAT device indicate moderate sleep-stage agreement with PSG but a strong correlation in AHI, yielding 93% sensitivity and 86% positive predictive value for OSA detection in COPD cohorts.[62] It is noteworthy that while WatchPAT shows no significant difference in REM/non-rapid eye movement sleep AHI compared to PSG, it consistently overestimates total sleep time, REM sleep duration, and sleep efficiency, warranting interpretive caution.[64] In conclusion, PAT-based devices provide supplementary tools that can enhance OVS surveillance.

Electronic Nose

Electronic nose (e-nose) technology allows for the profiling of volatile organic compounds (VOCs) in the context of respiratory diseases. A cross-sectional investigation enrolled 13 patients with OSA, 15 with COPD, and 13 with OVS. Their exhaled breath was collected via validated methods and analyzed using a Cyranose 320 device for VOC profiling. After principal component reduction, the raw data were processed by canonical discriminant analysis. The results showed clear clustering, distinguishing OSA patients from OVS (cross-validation accuracy, CVA=96.2%) and COPD (CVA=82.1%) groups. In contrast, the VOC patterns of OVS and COPD patients overlapped significantly (CVA=67.9%). An external validation using a new cohort of 18 patients (6 per group) and the pre-trained models confirmed this pattern. The study concludes that e-nose technology precisely discriminates exhaled VOC profiles among these patient groups, justifying further research into its role in non-invasive sleep apnea detection.[65]

In summary, current research has confirmed that questionnaires and various tools can be used for the diagnosis and screening of OVS. However, each method has certain limitations. Therefore, future studies should focus on integrating the strengths of different approaches to establish more efficient diagnostic pathways, thereby optimizing early identification and personalized management strategies for OVS (Table 1).

Diagnostic Marker

The evolving paradigm of precision medicine is catalyzing the exploration and application of novel biomarkers, facilitating early detection and stratified management of OVS (Table 2 and Figure 1).

Systemic Inflammation

Systemic inflammatory biomarkers show potential but varying performance in managing OVS. Evidence indicates that the neutrophil-to-lymphocyte ratio (NLR) exhibits moderate diagnostic utility for OVS.[66] This is supported by a cross-sectional analysis of 115 patients with chronic dyspnea (64 with OSA alone and 51 with OVS), which aligns with findings from Yang et al regarding the diagnostic significance of NLR.[67,68] Notably, NLR demonstrates superior prognostic performance, showing moderate predictive strength for the 6-month readmission risk in OVS patients at a cutoff of 3.567 (sensitivity 0.80, specificity 0.732). In contrast, the diagnostic value of the platelet-to-lymphocyte ratio (PLR) remains contentious. While studies report significantly elevated PLR in OVS compared to healthy controls, its standalone diagnostic efficacy is suboptimal. Beyond NLR, emerging data highlight the monocyte-to-eosinophil ratio (MER) as a prognostically significant biomarker. MER levels are markedly higher in OVS cohorts, and critically, each unit increase correlates with a doubled readmission risk for acute exacerbations during a 90-day follow-up. This robust association establishes MER as an independent prognostic indicator for COPD exacerbations.[69] Consequently, NLR serves as both a diagnostic adjunct and a short-term prognostic tool for OVS, whereas MER specifically holds clinical potential for exacerbation risk stratification. Prospective cohort studies are warranted to validate standardized applications of these inflammatory ratios.

Table 1 Screening Scales and Diagnostic Tools

Diagnostic Tool	Type	Core Indicators	Advantages	Limitations	References
PSQI	Screening Scale	Subjective sleep quality assessment tool	• Standardization and high reliability and validity • Comprehensiveness and multidimensionality	Subjective	[50–53]
SBQ	Screening Scale	Optimal AUC value High sensitivity/specificity	• Best predictive performance • Optimized cutoff point	Moderate specificity	[54]
SACS	Screening Scale	High AUC value High accuracy for specific differentiations	High predictive accuracy	\	[55]
BQ	Screening Scale	\	Extensively validated	Inferior performance compared to SBQ/SACS	[54,55]
ESS	Screening Scale	\	Simple and easy to use	Lowest performance for OVS screening	[54,55]
PSG	Gold Standard	Sleep architecture, arousal indices	• Predictive value • Guides therapy • Enables early identification	Bulky, costly, and interpretation can be subjective	[56–59]
HSAT	Portable Device	Differences in oxygenation measurement	• Lower cost • Simplified implementation	Systematic differences in oxygenation measurement compared to PSG	[60]
PAT	Portable Device	OVS patients exhibited lower deep sleep duration and mean nocturnal oxygenation than COPD-only patients.	Portable sleep assessment	\	[63]
WatchPAT Device	PAT-derived Device	Sensitivity: 93% Positive Predictive Value (PPV): 86%	• Automated algorithm analysis • Strong AHI correlation	Overestimates total sleep time and REM duration	[62]
eNose	Exhaled Breath Analysis	OSA-OVS differentiation: CVA=96.2% OSA-COPD differentiation: CVA=82.1%	• Non-invasive detection • High accuracy for specific differentiations	Limited differentiation between OVS and COPD (CVA=67.9%)	[65]

Note: "\": Indicates that the item was not specified in the study.

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; SBQ, STOP-BANG Questionnaire; SACS, Sleep Apnea Clinical Score; BQ, Berlin Questionnaire; ESS, Epworth Sleepiness Scale; PSG, Polysomnography; HSAT, Home Sleep Apnea Test; PAT, Peripheral Arterial Tonometry; eNose, Electronic Nose; AHI, Apnea-hypopnea index; AUC, Area under the curve; CVA, Cross-validation accuracy; REM, Rapid eye movement sleep; OVS, Overlap syndrome; COPD, Chronic obstructive pulmonary disease.

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Table 2 Early Detection and Stratified Management of OVS

Name of Marker	Attribution	Study Type	Functional Role	References
NLR	Systemic inflammation	Clinical study	Diagnostic inflammatory markers	[66–69]
PLR	Systemic inflammation	Retrospective clinical study	Inflammatory markers, poor efficacy	[66–69]
MER	Systemic inflammation	Clinical study	Predict the next attack of the disease	[66–69]
Microalbumin	Vascular endothelium and markers of multiple organ damage	Retrospective clinical study	Systemic vascular injury and endothelial function impairment	[70]
UA	Metabolic Markers	Clinical study	Markers of hypoxia	[71,72]
FFMI	Body composition and metabolic reserve markers	Cohort study	Early identification and severity stratification	[73]

Abbreviations: OVS, Overlap syndrome; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; MER, Monocyte-to-eosinophil ratio, UA, uric acid; FFMI, Fat-Free Mass Index.

Vascular Endothelium and Markers of Multiple Organ Damage

Endothelial dysfunction represents a primary pathological mechanism driving cardiovascular disease in patients with OVS. Pathophysiologically, microalbuminuria reflects systemic microvascular endothelial damage driven by oxidative stress and pro-inflammatory cytokine activation in OVS. A clinical study initially demonstrated a significant association between OVS and elevated microalbuminuria (odds ratio 2.61; 95% CI 1.02–6.38; P = 0.047). However, this association was no longer statistically significant after adjustment for confounding factors (adjusted OR 2.54; 95% CI 0.93–6.72; P = 0.070). Notably, three months of CPAP therapy significantly reduced albumin-to-creatinine ratios in adherent patients, whereas no improvement was observed in non-adherent individuals, further underscoring the role of the hypoxia-endothelial dysfunction pathway. Overall, these findings indicate a higher prevalence of microalbuminuria in OVS cohorts compared to those with OSA alone, establishing it as a dynamic biomarker reflecting the severity of vascular injury.[70]

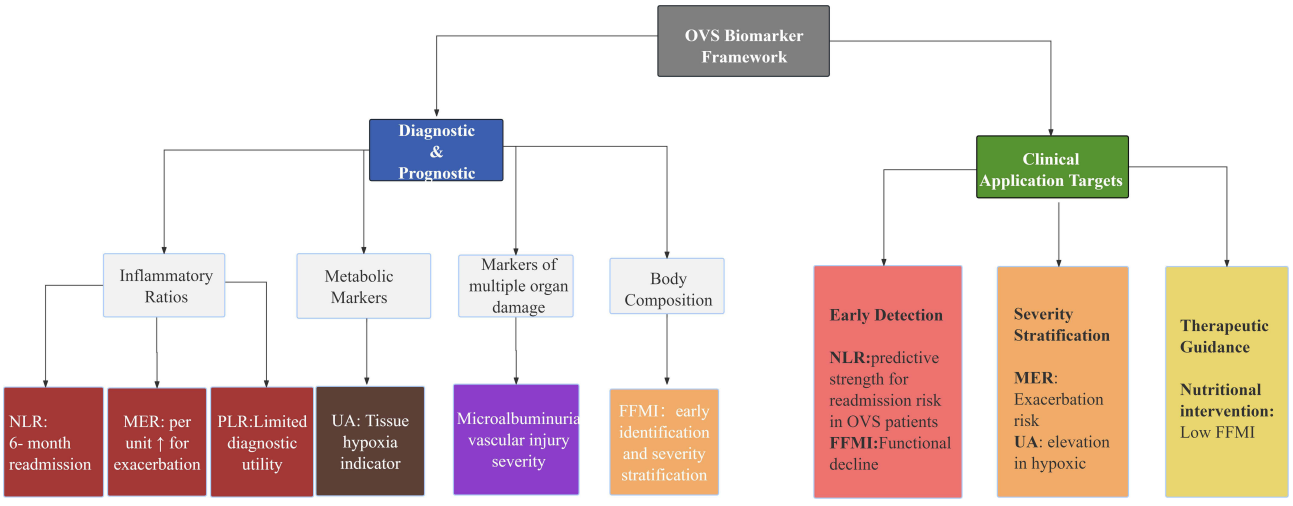

Figure 1 Summary of potential biomarkers.
Abbreviations: OVS, Overlap Syndrome; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; MER, monocyte-to-eosinophil ratio; UA, uric acid; FFMI, Fat-Free Mass Index.

Metabolic Markers

Uric acid (UA), the end metabolite of adenosine triphosphate degradation, accumulates under hypoxic conditions. In obese men with OSA, elevated serum UA levels demonstrate significant pathophysiological relevance. A cohort study of 260 such patients identified hyperuricemia (UA >7 mg/dL) in 56.2%, with prevalence increasing concurrently with three clinical variables: severity of obesity, magnitude of nocturnal oxygen desaturation, and frequency of COPD comorbidity. This pattern of increase indicates UA's primary association with adiposity and nocturnal hypoxemia in OSA. Mechanistically, COPD exacerbates this process through sustained oxygen desaturation, which upregulates xanthine oxidase activity to accelerate UA production while suppressing renal urate transporters such as URAT1.[71] Within this framework, Ozanturk et al established urinary UA excretion as a validated marker of tissue hypoxia severity in patients with OSA-COPD overlap.[72] In summary, UA dynamics offer critical insights for predicting clinical deterioration and stratifying progression risk in OVS.

Body Composition and Metabolic Reserve Markers

The Fat-Free Mass Index (FFMI), a key metric for evaluating body composition, is calculated as fat-free mass divided by the square of height (kg/m²). A cohort study involving 364 COPD patients (203 with COPD alone and 161 with OVS) analyzed clinical characteristics, pulmonary function, and sleep apnea parameters to assess the potential of FFMI for early OVS identification and severity evaluation. Using a predefined FFMI threshold, the OVS group was stratified into low- and normal-FFMI subgroups. Results showed that the low-FFMI subgroup had a significantly higher frequency of acute exacerbations and hospitalizations in the preceding year than the normal-FFMI subgroup. Moreover, the OVS group exhibited distinct comorbidity profiles compared to the COPD-only group. OVS patients were characterized by pulmonary function decline that correlated with FFMI levels. Significant differences in pulmonary function indices and sleep parameters were observed between the FFMI-based OVS subgroups. FFMI was strongly correlated with impaired pulmonary function, severity of sleep-disordered breathing, and exacerbation frequency. Together, these findings identify FFMI as a potential biomarker for the early detection and severity stratification of OVS, including in cases where no significant BMI differences are present.[73]

Treatment

Currently, treatments for OVS, including non-invasive positive pressure ventilation (NIV), oxygen therapy, pharmacotherapy, and lifestyle interventions, have been investigated. This section summarizes findings from existing research (Table 3).

Table 3 Current and Potential Treatment Modalities for OVS Patients

Intervention Category	Representative Therapy	Key Mechanism/Action	Core Efficacy Evidence/Unique Advantages	OVS Clinical Context
NIV	CPAP[74–76]	Maintains airway patency; improves ventilatory/gas exchange impairment	↓ Invasive intubation within 48h (9.2% vs 20.9%) ↓ Cardiovascular/cerebrovascular mortality	First-line therapy for all OVS patients
	BiPAP[77–81]	Maintains airway patency; improves ventilatory/gas exchange impairment	It effectively relieved symptoms; Improved treatment tolerance; Normalized arterial carbon dioxide levels	It is suitable for patients with poor CPAP compliance; Chronic hypoventilation patients with hypercapnic respiratory failure
	Auto-trilevel PAP[82–84]	Synchronized elimination of obstructive events and CO_2 retention	↑ Sleep quality; ↓ Daytime sleepiness	Hypercapnic patients failing CPAP/BiPAP
Oxygen Therapy	HFNO[85]	High-flow nasal cannula oxygen delivery	↓ AHI (5.4 vs 19.4 events/h); ↑ Nocturnal SaO_2 (93.9% vs 91.8%)	OVS with PAP intolerance

(*Continued*)

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Table 3 (Continued).

Intervention Category	Representative Therapy	Key Mechanism/Action	Core Efficacy Evidence/Unique Advantages	OVS Clinical Context
Sedative Alternative	Zaleplon[86]	Safety in mild-moderate COPD/OSA without hypercapnia	Short-acting non-benzodiazepine sedative	Stable patients requiring sedation
Bronchodilators[87]	\	Dual-pathway airway smooth muscle relaxation	↑ Exercise tolerance; ↑ Nocturnal oxygenation (with CPAP)	/
Anti-inflammatory/ Bronchodilator[88,89]	ICS/LABA/LAMA triple therapy	Anti-inflammatory + dual bronchodilation synergy	↑ FEV_1 Potential sleep architecture modulation	/
Pulmonary rehabilitation[90]	Moderate-intensity aerobic exercise	The change in blood oxygen saturation	↑ physiological resilience, restoring functional autonomy, ↓respiratory burden	OVS
Lifestyle changes	Smoking cessation[91]	Relief of dyspnea Improved oxygenation	↓ Viscous airway resistance ↓ Airway inflammation	Targets synergistic inflammation in COPD-OSA overlap
	Behavioral weight management[92–94]	Reduced symptom burden Enhanced exercise tolerance	↑oxygen saturation, ↓sleep fragmentation, ↑ pulmonary function	(OSA-COPD)
	Structured physical activity[95]	Improved functional capacity	↑ Endothelial function	Counters OVS-specific deconditioning
Potential treatment modalities	Long-term T-tube Stent Implantation[97]	• Mechanical airway support • Maintenance of luminal structural stability • Reduction of soft tissue collapse	• Restoration of vocal function • Simultaneous resolution of stenosis and apnea • Applicable to patients with disrupted anatomy	Patients with permanent tracheostomy COPD-OSA with severe comorbidities (Case report - Innovative application))
	TRX[98]	• Regulation of redox homeostasis • ROS scavenging • Inflammation inhibition	• Targets core mechanism of oxidative stress • Avoids immunosuppressive side effects of corticosteroids • Modulates circadian-related oxidative damage	Inflammatory respiratory diseases (COPD, OSA) (Review)
	BMSCs (Preclinical research[99,100]	• Multidirectional differentiation (pulmonary epithelial/endothelial cells) • Mitigation of lung tissue injury and fibrosis	• Tissue regenerative potential • Immunomodulatory function	Animal model studies: Emphysema in OVS model Preclinical research (Validated in animal models)

Note: "\": Indicates that the item was not specified in the study.
Abbreviations: OVS, Overlap syndrome; OSA, Obstructive sleep apnea; COPD, Chronic obstructive pulmonary disease; CPAP, Continuous positive airway pressure; NIV, Non-invasive ventilation; BiPAP, Bilevel positive airway pressure; PAP, Positive airway pressure; HFNO, High-flow oxygen therapy; AHI, Apnea-hypopnea index; IH, Intermittent hypoxia; TRX, Thioredoxin; BMSCs, Bone Marrow Mesenchymal Stem Cells; ICS, Inhaled Corticosteroids; LABA, Long-Acting β_2-Adrenoceptor Agonists; LAMA, Long-Acting Muscarinic antagonist; FEV, Forced Expiratory Volume; SaO_2, Arterial Oxygen Saturation.

Non-Invasive Positive Pressure Ventilation

Non-invasive Positive Pressure Ventilation (NIV) provides positive-pressure ventilatory support without an artificial airway, using interfaces such as nasal, oronasal, or full-face masks. Its primary modes include CPAP and bilevel positive airway pressure (BiPAP), which are widely employed in conditions characterized by impaired ventilation or gas exchange.[101] A retrospective study comparing patients with OVS and those with COPD alone reported a significantly lower rate of invasive intubation within 48 hours among OVS patients (9.2% vs 20.9%), along with longer durations of NIV use.[74,75] In addition, the combination of NIV with conventional therapy has been shown to reduce cardiovascular and cerebrovascular mortality in OVS patients.[76] These findings suggest that individuals with OVS derive particular benefit from NIV. Early initiation of NIV alongside conventional treatment significantly lowers the need for invasive interventions and improves long-term survival, establishing it as a cornerstone of management in this population.

Among NIV modalities, CPAP has demonstrated considerable clinical utility in OVS. Robust evidence indicates that CPAP improves lung function,[102] attenuates airway inflammation,[103] slows COPD progression, and reduces hospitalization and mortality rates.[104] It also enhances sleep quality and overall quality of life, while alleviating depressive symptoms and daytime manifestations.[105] However, these therapeutic effects depend critically on consistent adherence, which remains the major factor influencing outcomes.[106] Clinical data show that OVS patients who adhere to three months of CPAP therapy exhibit significant reductions in log-transformed urinary albumin-to-creatinine ratio, whereas non-adherent patients show no such improvement.[70] Radiographic evidence of hyperinflation has further been identified as a potential predictor of suboptimal PAP adherence in this population.[107] Therefore, clinicians should focus on optimizing modifiable barriers to adherence, including mask fit, interface comfort, and adequate nasal humidification, to maximize the benefits of CPAP in OVS.[108] It should be noted, however, that the widespread use of CPAP in OVS still requires further validation through high-quality randomized controlled trials (RCTs), particularly regarding its role in preventing acute exacerbations of COPD. A rigorous multicenter RCT is currently underway to address this evidence gap.[109]

Building on the importance of treatment adherence for CPAP efficacy, nasal continuous positive airway pressure (nCPAP) represents a specialized approach that delivers continuous positive pressure ventilation via nasal interfaces to maintain upper airway patency. Clinical evidence indicates that nCPAP stabilizes arterial blood gases and reduces mean pulmonary artery pressure in severe OSA patients and those with mild-to-moderate COPD following three months of therapy.[110] Additionally, integrated oxygen delivery through nasal cannula via mask interfaces optimizes patient comfort, improves oxygenation, and enables effective management of OVS at lower CPAP or BiPAP pressures. It should be noted, however, that these findings originate from case reports, and the broader clinical applicability of this approach requires further investigation.[4,111]

BiPAP is an established mode of NIV with specific clinical indications. Evidence supports BiPAP for complex OSA, particularly in patients with poor CPAP adherence resulting from high-pressure discomfort or mask-related problems.[77] BiPAP is also clearly indicated for chronic hypoventilation accompanied by hypercapnic respiratory failure, as seen in conditions such as obesity hypoventilation syndrome, neuromuscular disorders, and restrictive thoracic wall diseases.[78] For OVS patients presenting with hypercapnia, multiple studies demonstrate that transitioning to BiPAP following CPAP failure can effectively alleviate symptoms, improve treatment tolerance, and normalize arterial carbon dioxide levels.[79–81] Furthermore, in COPD management, the presence of nocturnal hypoxemia represents a valid indication for BiPAP consideration, regardless of concomitant OSA diagnosis.[31] By delivering separately adjustable inspiratory and expiratory pressures, BiPAP maintains upper airway patency while providing pressure support that increases tidal volume and alveolar ventilation. This mechanism reduces respiratory muscle load and improves gas exchange, thereby promoting treatment adherence.

Based on current evidence, BiPAP is recommended as the preferred second-line therapy following CPAP failure or intolerance, and serves as a core treatment for hypercapnic respiratory failure. Beyond conventional BiPAP, emerging modalities are under investigation. Preliminary data suggest that auto-trilevel PAP may offer improved patient-ventilator synchrony, better resolution of residual obstructive events and carbon dioxide retention, and enhanced sleep quality with reduced daytime sleepiness compared to standard BiPAP.[112] However, this technology has not yet been widely validated in clinical studies.

In summary, the available evidence supports NIV as a fundamental component of OVS management. Future research should aim to improve patient adherence and develop more effective assessment methodologies.[82–84]

Oxygen Therapy

Although PAP therapy is effective for OVS, treatment adherence remains suboptimal, especially among elderly patients. This challenge has led to the investigation of nasal high-flow oxygen therapy (HFNO) as an alternative nocturnal oxygen delivery method. Clinical evidence indicates that HFNO significantly reduces the AHI compared to both baseline and conventional oxygen therapy. The mean AHI decreased progressively from baseline under HFNO, with a substantial number of patients achieving an AHI below 5 during the intervention. HFNO also resulted in significant improvements in nocturnal oxygen saturation and a reduction in the percentage of sleep time spent with oxygen saturation below 90%,

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confirming its efficacy in enhancing oxygenation in elderly OVS patients.[85] As a nocturnal oxygen delivery modality integrated into long-term oxygen therapy, HFNO represents an important respiratory management strategy. This comprehensive approach contributes to improved survival, reduced hospitalization rates, alleviation of hypoxemia, and optimization of oxygenation parameters, which collectively lead to better clinical outcomes in OVS.[113]

Drug Therapy

Pharmacological Management of OVS

Recent advances in pharmacological treatment for OSA have evolved from monotherapy to combination strategies. Evidence indicates that the combination of atomoxetine and oxybutynin significantly reduces the AHI and improves nocturnal hypoxia.[114] Subsequent studies have explored alternative approaches, including the use of sustained-release antimuscarinic agents such as fesoterodine, which shows particular efficacy in patients with less severe pharyngeal collapsibility.[115] The introduction of sedating medications like trazodone helps counterbalance potential sleep architecture disruption caused by wake-promoting drugs.[116,117] Furthermore, the combination of viloxazine and trazodone demonstrates the effectiveness of this balanced approach, achieving both respiratory event reduction and sleep quality preservation.[118]

These pharmacological developments, however, remain primarily investigated in patients with OSA alone. Their applicability to OVS, defined as the coexistence of OSA and COPD, requires further systematic evaluation. Pharmacological management in OVS must consider its distinct risk profile, especially regarding sedative selection. Benzodiazepines may suppress upper airway muscle activity and respiratory drive, posing potential risks in OVS patients. In contrast, short-acting non-benzodiazepine agents such as zaleplon exhibit a more favorable safety profile in mild to moderate OVS cases.[86]

Conventional COPD medications also show promise in OVS management. Bronchodilators improve ventilation through airway smooth muscle relaxation, and clinical observations suggest potential synergistic effects with standard OSA treatments like CPAP. Case reports indicate that inhaled dual bronchodilators such as indacaterol/glycopyrronium can reduce lung hyperinflation and improve nocturnal oxygen saturation.[87] Additionally, triple therapy combining inhaled corticosteroids with long-acting β_2-agonists and long-acting muscarinic antagonists (ICS/LABA/LAMA) has established benefits in improving lung function, quality of life, and reducing exacerbation risk in COPD patients, while potentially exerting positive effects on sleep architecture.[88] This makes triple therapy a relevant consideration in OVS management, though its optimal application and patient selection criteria require further investigation in this specific population.[89]

In summary, current evidence supports pharmacological therapy as an adjunct approach in OVS management. However, the evidence remains limited, underscoring the need for large-scale RCTs to establish standardized treatment protocols and confirm the efficacy of various drug classes in OVS.

Obesity Management

Obesity represents a significant exacerbating risk factor in OVS, which combines COPD and OSA. Consequently, effective weight management has become an important research focus. Bariatric surgery constitutes a fundamental therapeutic intervention in this context. Evidence confirms that surgical weight loss significantly ameliorates the severity of OSA, as reflected by substantial reductions in the AHI and body weight. Concurrently, it improves nocturnal oxygen saturation, sleep architecture, and key pulmonary function parameters such as forced vital capacity (FVC). These comprehensive improvements highlight the potential role of bariatric surgery in managing the complex pathophysiology of OVS.[92–94]

Complementing surgical approaches, pharmacological interventions, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs), exhibit considerable efficacy in treating both OSA and obesity. For instance, two Phase 3 RCTs indicated that tirzepatide significantly reduces the AHI, body weight, hypoxic burden, high-sensitivity C-reactive protein levels, and systolic blood pressure in patients with moderate to severe OSA and obesity, while also improving patient-reported sleep outcomes.[119] A meta-analysis further supports the role of GLP-1RAs, including tirzepatide and liraglutide, in reducing OSA severity and promoting weight loss and blood pressure reduction, with tirzepatide demonstrating superior efficacy compared to liraglutide.[120] Systematic reviews and network meta-analyses also reveal that various anti-

obesity medications, such as tirzepatide, semaglutide, and liraglutide, achieve significant weight reduction and ameliorate obesity-related complications.[121] Additionally, comparative studies highlight phentermine-topiramate and liraglutide as particularly effective for weight loss, though liraglutide is associated with a higher risk of adverse events.[122]

Although these findings underscore the potential of anti-obesity medications in OSA treatment, evidence regarding their application in OVS remains unavailable. Therefore, investigating the efficacy and safety of GLP-1RAs and other weight-loss agents in patients with OVS represents an important direction for future research, potentially informing personalized treatment approaches.

Pulmonary Rehabilitation

Pulmonary rehabilitation serves as an essential non-pharmacologic intervention complementary to pharmacologic strategies for improving outcomes in OVS. A recent prospective, single-blind RCT involving 79 OVS patients demonstrated that incorporating moderate-intensity aerobic exercise over 20 weeks alongside nightly PAP therapy yielded significantly greater improvements across multiple clinical domains compared to PAP therapy alone. The intervention group (n=40) showed superior enhancement in functional capacity measured by 6-minute walk distance, activities of daily living assessed with the Barthel Index, dyspnea perception evaluated using the modified Medical Research Council scale, body composition with reduced fat mass, and sleep-disordered breathing parameters through polysomnographic measures, with all outcomes reaching statistical significance ($p<0.01$). These findings solidly establish pulmonary rehabilitation as a synergistic approach that enhances PAP efficacy by improving physiological resilience, restoring functional autonomy, and alleviating respiratory burden in OVS management.[90]

Lifestyle Changes

Lifestyle modifications are fundamental to the management of OVS. In addition to weight reduction, smoking cessation yields clinically meaningful symptomatic benefits for OVS patients. Mechanistic studies demonstrate significant positive correlations among age, body mass index, smoking history, and airway resistance in this population,[91] offering a physiological rationale for these interventions. Physical activity represents a further distinct therapeutic strategy for improving functional capacity in OVS. Moderate-intensity exercise specifically addresses cardiovascular comorbidities, which are the most common in OVS, through the mitigation of endothelial dysfunction. This pathological process is a key mechanism in cardiovascular disease. Support for this mechanism comes from strong correlations of both daily step counts and moderate activity regimens with flow-mediated dilation ($\rho=0.77$, $p=0.04$ and $\rho=0.9$, $p=0.005$, respectively).[95] In conclusion, core therapeutic strategies for OVS include smoking cessation, moderate-intensity exercise, and weight reduction. These evidence-based lifestyle interventions collectively target underlying pathophysiological processes to alleviate symptoms and enhance functional status.

Potential Treatment Modalities

Intermittent Hypoxia

Mild intermittent hypoxia (IH) has evolved from a physiological phenomenon to a promising therapeutic approach with demonstrated efficacy in respiratory rehabilitation. As an adjunct to CPAP therapy, IH improves clinical management in patients with comorbid OSA and COPD. This synergistic strategy induces fundamental modifications in respiratory control mechanisms, where neural metaplasticity enhances ventilatory drive and concurrent neuromodulatory adaptations stabilize upper airway musculature. These changes yield significant clinical benefits. Critically, the accompanying neurophysiological adjustments enable a substantial reduction in the optimal CPAP pressure required for effective OSA management. The resultant decrease in therapeutic pressure intensity directly improves patient tolerance and treatment adherence. Moreover, by extending nightly therapy duration through enhanced comfort, this pressure optimization bolsters the long-term efficacy of CPAP. Current evidence therefore positions IH as a multidimensional intervention for managing sleep-disordered breathing and associated cardiopulmonary comorbidities.[96]

Long-Term T-Stent Implantation

Long-term T-stent implantation constitutes a viable intervention for selected complex OVS cases. As documented in one clinical case involving a permanently tracheostomized patient with severe comorbidities, this approach achieved

integrated outcomes, including structural airway stabilization, significant alleviation of OSA symptoms, and restoration of phonatory function. It demonstrates particular efficacy in managing concurrent airway compromise and vocal impairment in medically complex patients. For individuals with similar clinical profiles, the intervention offers dual benefits by providing structural airway support while facilitating vocal rehabilitation. However, its broader clinical adoption is constrained by procedural complexity and stringent patient selection criteria.[97]

Thioredoxin

Thioredoxin (TRX) represents a promising therapeutic strategy for COPD and OSA, owing to their shared pathophysiology of oxidative stress-driven inflammation. Mechanistically, TRX counteracts core pathological features of COPD-OSA overlap by directly scavenging reactive oxygen species to reduce airway oxidative damage, while simultaneously suppressing the activation of neutrophils and eosinophils to attenuate chronic inflammation. Crucially, TRX restores disrupted redox homeostasis in COPD-OSA comorbidity, wherein the recurrent hypoxia-reoxygenation cycles characteristic of OSA synergistically exacerbate oxidative injury in already compromised airways. This targeted mechanism contrasts sharply with that of conventional anti-inflammatory agents such as glucocorticoids, as TRX specifically modulates the redox-sensitive inflammatory pathways central to both conditions. In summary, TRX concurrently mitigates oxidative damage, suppresses granulocyte-mediated inflammation, and normalizes redox dysregulation through pathway-specific mechanisms distinct from standard therapies. However, extensive future studies are warranted to validate these therapeutic effects.[98]

Bone Marrow Mesenchymal Stem Cells

Animal studies demonstrate that bone marrow mesenchymal stem cells (BMSCs) alleviate emphysema progression in OVS models through endothelial differentiation, combined with the inhibition of endothelial apoptosis and oxidative stress. These findings provide a theoretical foundation for treating OVS-related cardiovascular disease.[99] Mechanistically, BMSCs selectively migrate to injured lung tissues and the aorta, where they differentiate into endothelial cells that integrate into alveolar walls. This process significantly suppresses emphysema progression, as evidenced by a reduced mean linear intercept and an increased mean alveolar number, while concurrently mitigating vascular damage through attenuated endothelial apoptosis and upregulated CD31 and VWF expression. Furthermore, BMSCs reverse systemic oxidative stress by decreasing malondialdehyde levels and enhancing superoxide dismutase activity. Collectively, these findings establish an experimental basis for BMSC-mediated tissue repair and cytoprotection against OVS-associated cardiovascular complications.[100] Given these promising preclinical results, further exploration through large-animal studies and early-phase clinical trials is warranted. This will advance the translational potential of BMSC-based therapies, particularly for OVS patients with progressive cardiovascular complications that remain challenging to treat.

In summary, although promising therapeutic strategies continue to emerge, their clinical translation necessitates rigorous validation via large-scale clinical trials to establish comprehensive efficacy and safety profiles (Table 3).

Discussion

This review focuses on diagnostic and therapeutic strategies for the OVS of COPD and OSA. The pathophysiological interplay between these conditions leads to worse clinical outcomes than either disease alone, posing distinct challenges for clinical management. A key pathophysiological feature of OVS is ventilatory limitation, often manifesting as hypoxemia and hypercapnia. Accordingly, monitoring carbon dioxide levels constitutes an essential component of patient assessment. This review also discusses how combining invasive and non-invasive techniques may offer complementary advantages for precise clinical management. Given the complexity of OVS and its association with elevated morbidity and mortality, early identification and effective intervention are crucial for improving patient outcomes.[123,124]

In terms of diagnosis, questionnaires serve as initial screening tools, offering an efficient and cost-effective strategy for subsequent studies on disease prevalence, severity, and prognosis, although they carry inherent subjectivity. PSG is widely recognized as the gold standard for diagnosing sleep-disordered breathing. It provides critical diagnostic information by comprehensively monitoring respiratory effort, airflow, and oxygen saturation, thereby objectively quantifying the frequency, duration, and severity of apneic events. However, limitations such as cumbersome equipment

and high costs have motivated the exploration of alternative diagnostic modalities. These include HSAT, PAT and e-nose. Beyond technical approaches, potential biomarkers are also emerging as promising diagnostic substitutes. For instance, the NLR exhibits both diagnostic value and potential for short-term prognosis, while the MER shows unique promise in risk stratification for acute exacerbations. Other biomarkers, such as microalbuminuria (a dynamic indicator of vascular injury), serum uric acid (a predictor of disease progression), and the FFMI (an early stratification tool that overcomes the limitations of body mass index), warrant further investigation. Collectively, these developments open new avenues for the precise diagnosis and management of OVS.

As a first-line noninvasive therapy, CPAP effectively alleviates nocturnal hypoxemia and reduces cardiovascular risk. However, its benefits are constrained by suboptimal adherence and limited efficacy in correcting daytime hypercapnia. In contrast, BiPAP is specifically indicated for significant hypercapnia. Studies demonstrate that switching to BiPAP after CPAP failure improves symptoms, enhances tolerance, and normalizes arterial carbon dioxide levels in hypercapnic OSA patients. Beyond PAP therapies, comprehensive management strategies play an important role. These include pulmonary rehabilitation, enhanced smoking cessation interventions, and weight reduction programs, which provide synergistic benefits surpassing single-disease approaches. Emerging alternatives such as mild IH, T-stent implantation, and TRX demonstrate promising potential and growing research interest. However, their efficacy and safety require validation through large-scale RCTs, representing critical evidence gaps that challenge their translation into routine clinical practice.

The translation of evidence-based findings into routine clinical practice for OVS faces several significant challenges. A primary obstacle involves case identification and diagnostic complexity. Patients frequently present with nonspecific symptoms, and low clinical awareness combined with the need for multimodal assessments such as pulmonary function tests and sleep studies contributes to widespread underdiagnosis. Furthermore, comorbidities complicate pharmacotherapy and elevate the risk of drug interactions, while the management of multiple devices and complex treatment regimens creates substantial adherence barriers. Additional challenges arise from evidence gaps and considerable patient heterogeneity. High-quality intervention studies targeting specific overlap phenotypes remain limited, treatment responses vary significantly across patient subgroups, and existing clinical guidelines do not address all individual scenarios. These limitations underscore the urgent need for reliable biomarkers to guide personalized therapeutic strategies.

Despite these challenges, future efforts should prioritize overcoming existing barriers through multiple strategic directions. Advancing phenotype research and precision medicine represents a core approach, utilizing multi-omics technologies, advanced imaging, and data from wearable devices to decipher disease heterogeneity, identify biomarkers predictive of treatment response or prognosis, and establish a foundation for individualized care.[125] The integration of innovative technologies and remote management systems also plays a crucial role. Smartphone-based monitoring combined with AI algorithms enables real-time risk alerts and personalized feedback,[126] while the development of more comfortable, intelligent, and integrated therapeutic devices may significantly improve patient experience and adherence.[127] In addition, telemedicine substantially enhances the accessibility and continuity of follow-up care.[128] System-level optimization through integrated care models is equally important, requiring structured interdisciplinary pathways, collaborative platforms such as shared electronic health records, and multidisciplinary team discussions. The establishment of comprehensive management teams with dedicated care coordinators in primary care settings can further ensure continuity and efficiency. Concurrently, patient-centered empowerment remains essential, which involves implementing structured education programs tailored to patient needs, delivering behavioral theory-guided interventions to improve disease awareness and self-management skills, and incorporating patient-reported outcomes as core evaluation metrics.

In summary, the management of OVS is transitioning from reactive treatment to proactive, integrated care. Addressing its key challenges requires advancing scientific knowledge, integrating new technologies, and optimizing patient-centered care systems. Such coordinated efforts are essential to translate current evidence into better long-term outcomes and quality of life for these patients.

Abbreviations

OSA, Obstructive sleep apnea; COPD, Chronic obstructive pulmonary disease; OVS, Overlap syndrome; CPAP, Continuous positive airway pressure; PSG, Polysomnography; BMI, Body mass index; NIV, Non-invasive ventilation;

REM, Rapid eye movement sleep; RCT, Randomized controlled trial; HSAT, Home sleep apnea testing; ApEn, Approximate entropy; SaO_2, Arterial oxygen saturation; PAT, Peripheral arterial tonometry; VOC, Volatile organic compound; CVA, Cross-validation accuracy; ROC, Receiver operating characteristic; ESS, Epworth Sleepiness Scale; SACS, Sleep Apnea Clinical Score; BQ, Berlin Questionnaire; SBQ, STOP-BANG Questionnaire; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; MER, Monocyte-to-eosinophil ratio; UA, Uric acid; FFMI, Fat-Free Mass Index; BiPAP, Bilevel positive airway pressure; nCPAP, Nasal continuous positive airway pressure; PAP, Positive airway pressure; HFNO, High-flow oxygen therapy; AHI, Apnea-hypopnea index; FMD, Flow-mediated dilation; IH, Intermittent hypoxia; TRX, Thioredoxin; BMSCs, Bone marrow mesenchymal stem cells; PM, Portable monitoring; FEV1, Forced expiratory volume in one second; $PaCO_2$, Partial pressure of carbon dioxide; PSQI, Pittsburgh Sleep Quality Index; PM, Portable monitoring; e-nose, Electronic nose; FVC, Forced vital capacity; GLP-1Ras, Glucagon-like peptide-1 receptor agonists; AUC, Area under the curve values.

Data Sharing Statement

Data sharing is not applicable to this study as no new datasets were generated.

Author Contributions

Xiaotong Wei: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. Xiaoyu Zhang, Siping Wang: Writing – review & editing, Visualization, Investigation, Conceptualization. Xin Tong, Chuang Wu: Writing – review & editing, Conceptualization. Shaodan Hu, Li Shi: Writing – review & editing, Supervision, Conceptualization. All authors gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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