

Prevalence of Pulmonary Hypertension in Obstructive Sleep Apnea and Overlap Syndrome Patients Living in Rural and Suburban Areas of North India

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is a neglected and underdiagnosed disease in rural and suburban India. Chronic obstructive pulmonary disease (COPD) associated with OSA is termed overlap syndrome. OSA and COPD both cause pulmonary hypertension (PH) that further aggravates nocturnal hypoxia.

Aim and objective: To estimate the prevalence of PH in OSA and overlap syndrome.

Materials and methods: Patients coming to our outpatient department with symptoms of OSA were selected by STOP-BANG criteria for polysomnography (PSG). One hundred patients with apnea–hypopnea index (AHI ≥ 5) with symptoms and AHI ≥ 15 without symptoms were taken for pulmonary function test (PFT) and chest X-ray to rule out COPD. Thereafter, 2D echocardiography (2D-echo) was done to check cardiac changes and the assessment of pulmonary artery pressure.

Results: Out of 100 patients in the study group, 10% ($n = 10$) had mild, 12% ($n = 12$) had moderate, and 78% ($n = 78$) had severe OSA. Overlap syndrome was present in 60% ($n = 60$) of the patients. PH was present in 24% ($n = 24$) of cases—mild ($n = 10$) and moderate ($n = 10$) PH each was 10%, and severe ($n = 4$) PH was present in 4% of the cases. PH was present in 36.67% ($n = 22$) of the patients with overlap syndrome and only 5% ($n = 2$) of the patients with OSA.

Conclusions: Nearly, one-fourth of the patients with OSA and overlap syndrome have PH. Prevalence of PH is seven times higher in overlap syndrome than in OSA alone.

Keywords: Obstructive sleep apnea, Overlap syndrome, Pulmonary hypertension.

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INTRODUCTION

Obstructive Sleep Apnea¹

Obstructive sleep apnea (OSA) is defined by the presence of repetitive episodes of upper airway obstruction during sleep. An apnea–hypopnea index (AHI) of equal to or greater than 5 events/hour is defined as OSA, with obstructive or mixed (rather than central) events comprising more than 50% of the total. The obstructive sleep apnea syndrome is defined as AHI equal to or greater than 5 events/hour and persistent complaints of excessive daytime somnolence, unrefreshing sleep, or fatigue.

Apnea¹

- A respiratory event is called apnea when:
 - There is a fall in peak signal by $\geq 90\%$ of pre-event baseline using an oronasal thermistor, positive airway pressure (PAP) device flow, or alternative apnea sensor.
 - Duration of the $\geq 90\%$ drop in signal is ≥ 10 seconds.
- An obstructive apnea is associated with continued or increased inspiratory effort throughout the entire event, but airflow is absent.
- A central apnea is characterized as the absence of inspiratory effort and airflow throughout the entire event.
- A mixed apnea is absent inspiratory effort in the initial part of the event, followed by resumption of inspiratory effort in the later part of the event.

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Hypopnea¹

- A respiratory event is called hypopnea when—(RECOMMENDED):
 - There is a fall in peak signal by $\geq 30\%$ of pre-event baseline using an oronasal thermistor, PAP device flow, or alternative apnea sensor.
 - Duration of the $\geq 30\%$ drop in signal is ≥ 10 seconds.
 - Oxygen desaturation is $\geq 3\%$ from pre-event baseline or the event is associated with an arousal.
- A respiratory event is called hypopnea when—(ACCEPTABLE):
 - There is a fall in peak signal by $\geq 30\%$ of pre-event baseline using an oronasal thermistor, PAP device flow, or alternative apnea sensor.

- Duration of the $\geq 30\%$ drop in signal is ≥ 10 seconds.
- Oxygen desaturation is $\geq 4\%$ from the pre-event baseline.

Respiratory Effort-related Arousal¹

Respiratory effort-related arousal (RERA) is a sequence of breaths lasting ≥ 10 seconds characterized by increasing respiratory effort or flattening of the inspiratory portion of the nasal pressure waveform leading to arousal from sleep when the sequence of breaths does not meet the criteria for an apnea or hypopnea.

ICSD-3 Diagnostic Criteria for OSA in Adults¹

(A and B) or C satisfies the criteria.

- The presence of one or more of the following:
 - The patient complains of excessive sleepiness, nonrefreshing sleep, fatigue, or insomnia symptoms.
 - The patient wakes with choking or gasping.
 - Partner reports habitual snoring, breathing interruptions, or both during patient's sleep.
 - The patient has been diagnosed with hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, congestive heart failure, atrial fibrillation, mood disorder, or cognitive dysfunction.
- Polysomnography (PSG) or out-of-center sleep testing (OCST*) demonstrates the following:
 - Five or more obstructive events (obstructive or mixed apneas, hypopneas, or RERAs) per hour of sleep during PSG or per hour of monitoring in OCST.

Or
- PSG or OCST* demonstrates:
 - Fifteen or more obstructive events (obstructive or mixed apneas, hypopneas, or RERAs) per hour of sleep during PSG or per hour of monitoring in OCST.

Classification of OSA^{1,2}

Class	Apnea-hypopnea index
Normal	< 5
Mild	$5 \leq \text{AHI} < 15$
Moderate	$15 \leq \text{AHI} < 30$
Severe	≥ 30

Overlap syndrome is a condition where a patient has OSA with chronic obstructive pulmonary disease (COPD).^{3,4} This type of presentation of disease has a poorer prognosis and has a higher rate of hypoxemia, morbidity, and mortality.

Pulmonary hypertension (PH)^{4,5} is defined as a mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest. It can be due to diseases primarily associated with the pulmonary vasculature *per se*, as in pulmonary arterial hypertension (PAH), or a complication of other diseases, including hypoxemic pulmonary disorders (e.g., COPD), left heart disease (e.g., systolic, diastolic, or valvular dysfunctions), or thromboembolism. PH due to OSA and COPD both comes in class 3 of the etiological classification of PH.

COPD and OSA both cause PH, but the mechanisms are different. In COPD, PH is caused due to permanent structural changes that occur in the lung parenchyma, whereas in OSA, it is due to hypoxemia, systemic hypertension, and obesity.

Mechanism of PH in OSA⁶

Hypoxia-induced Vasoconstriction

- Serotonin-dependent vasoconstriction and vascular remodeling
- Hypoxia interrupting angiotensin 1-angiotensin receptor (Ang1-Tie2) signaling by preventing Ang1 from binding to receptor and causing pulmonary vasoconstriction.
- Endothelin-1-mediated vasoconstriction
- Chronic hypoxia causes suppression of endothelial-NO-synthase (eNOS) and impairment of endothelial NO-dependent vasodilation.

Systemic Hypertension Causing Left-sided Heart Failure

- Initial passive increase in pulmonary blood volume secondary to the hydrostatic forces in heart failure results in passive postcapillary PH with a normal transpulmonary pressure gradient and relatively normal pulmonary vascular resistance.

Obesity

- Because of metabolic dysregulation and vascular inflammation, obesity is associated with a greater risk of PAH, independent of OSA and left heart dysfunction.
- Circulating levels of adiponectin are decreased in individuals with both obesity and OSA. It is secreted from adipose tissues and has anti-inflammatory and vascular homeostatic functions.

MATERIALS AND METHODS

It was a prospective observational study conducted at a tertiary center involving patients coming from rural and suburban areas. Patients presenting with symptoms of OSA were screened for PSG by using STOP-BANG criteria. One hundred patients with AHI ≥ 5 with symptoms of OSA and AHI ≥ 15 without symptoms of OSA were taken for pulmonary function test (PFT) and chest X-ray, after proper history and examination, to rule out COPD. Thereafter, 2D echocardiography (2D-echo) was done for screening of pre-existing structural cardiac anomaly or any raise in pulmonary artery pressure.

Inclusion Criteria

- Patients with the symptoms of OSA with or without COPD.
- Patients with PH caused by OSA.
- Newly diagnosed OSA.

Exclusion Criteria

- Pregnant females
- Patients taking treatment for OSA
- Any chronic pulmonary condition other than COPD
- Any neuromuscular disorder
- History of drug abuse and alcoholism

RESULTS

- The study involved 100 clinically and polysomnographically proven OSA patients with or without COPD. Data analysis was done by using SPSS version 20. *p*-value < 0.05 is considered as significant.
- Out of 100 OSA patients, 64% ($n = 64$) were males and 36% ($n = 36$) were females. Minimum and maximum ages were 34 and 84 years, respectively, whereas the mean age of the study group was 53.4 years. Mild, moderate, and severe OSA was,

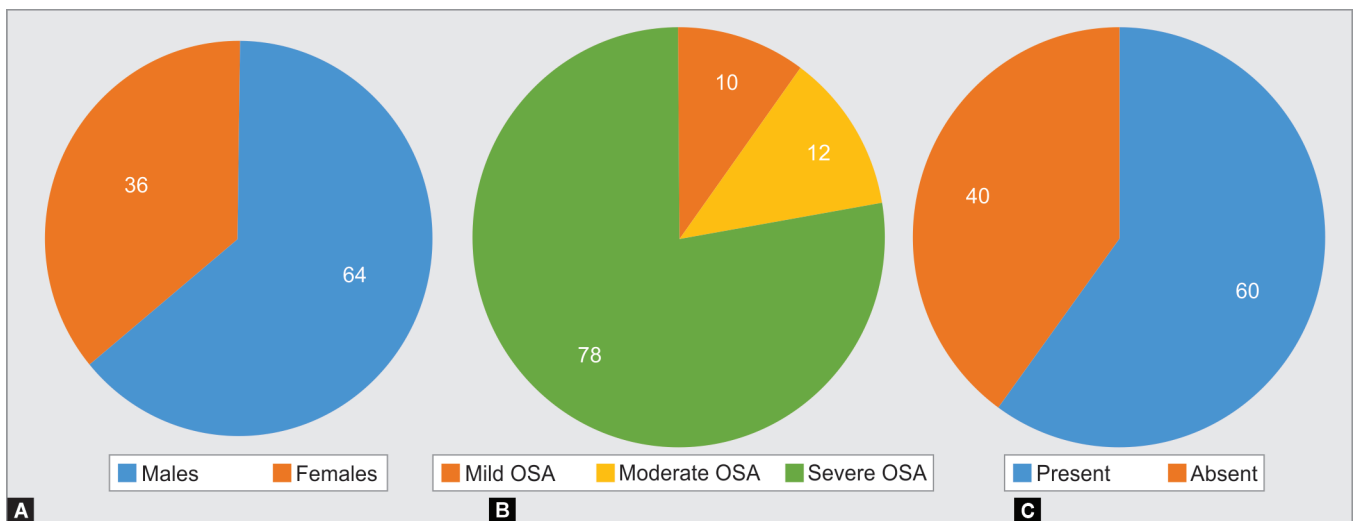
respectively, present in 10% ($n = 10$), 12% ($n = 12$), and 78% ($n = 78$) of patients in the study group.

- Sixty percentage of patients in our study group had overlap syndrome ($n = 60$), whereas 40% ($n = 40$) of the patients had OSA without COPD.
- In patients with OSA, PH was present in 24% ($n = 24$) of the patients. Mild PH was present in 10% ($n = 10$), moderate PH was present in 10% ($n = 10$), and severe PH was present in 4% ($n = 4$) of the patients.
- In patients with overlap syndrome, 36.67% ($n = 22$) were having PH. Mild PH was present in 13.33% ($n = 8$), moderate PH was present in 16.67% ($n = 10$), and severe PH was present in 6.67% ($n = 4$) of the patients.
- Of all the OSA patients without COPD, only 5% ($n = 2$) of patients had PH (Figs 1 and 2).

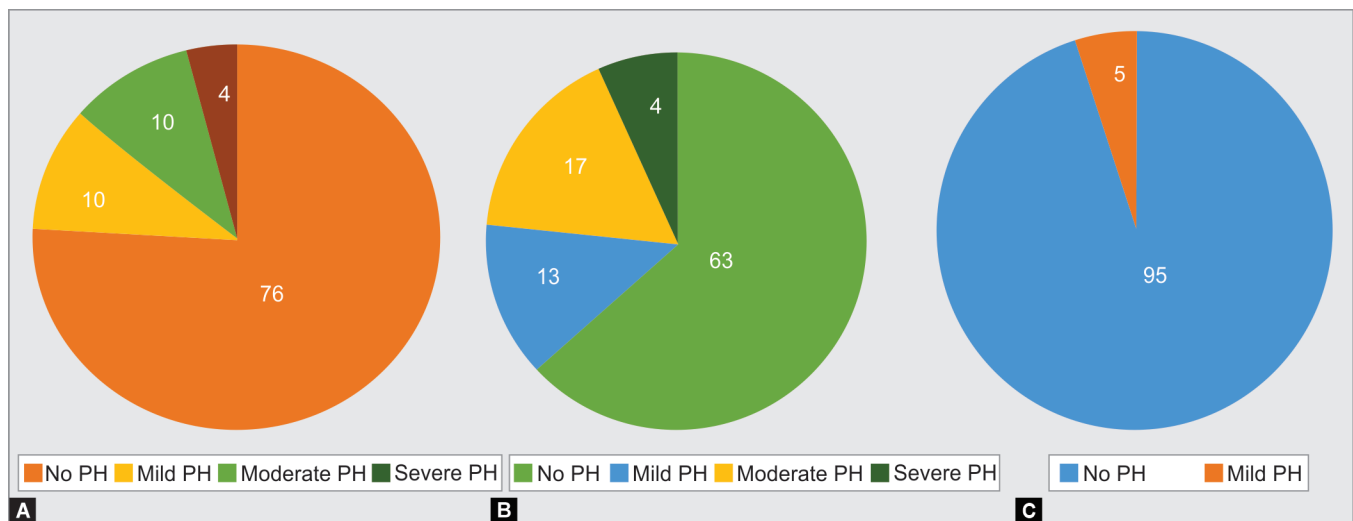
DISCUSSION

OSA is defined as repetitive episodes of upper airway obstruction during sleep. An AHI of equal to or greater than 5 events/hour is commonly used to define OSA, with obstructive or mixed (rather than central) events comprising more than 50% of the total. An OSA or hypopnea is characterized by a transient reduction or complete cessation of breathing due to upper airway collapse and is usually associated with sleep fragmentations, arousals, and reduction in oxygen saturation, which may eventually lead to the development of other significant comorbidities as well.

OSA and COPD are among the most common pulmonary diseases, so a large number of patients have both disorders; this “overlap syndrome” causes more severe nocturnal hypoxemia than either of the diseases alone. Patients with COPD and OSA have a



Figs 1A to C: (A) Gender distribution; (B) Severity of OSA; (C) Percentage of patients with overlap syndrome



Figs 2A to C: (A) Pulmonary hypertension in OSA patients with or without COPD; (B) PH in overlap syndrome patients; (C) PH in OSA patients without COPD

greater risk of morbidity and mortality, compared to those with either COPD or OSA alone.

Our study demonstrated that patients with COPD with OSA were more susceptible to PH, which might be associated with declining lung function and increased OSA severity. We did a clinical assessment of OSA patients and took the patients for PSG. All the OSA patients were checked for having COPD by doing PFT and chest X-ray, and smoking and biomass exposure history was also taken. All the OSA and overlap syndrome patients underwent 2D-echo to rule out PH.

Our study had a total number of 100 subjects, of which 64 were males (64%) and 36 were females (36%). Nearly, all the patients in our study group belonged to either middle or older age-groups. The youngest patient was 34 years old and the oldest was 84 years old. The majority of patients (68%) were middle-aged and belonged to 41–60 years age-group. Ten percent of all the subjects were younger than 40 years of age. Twenty percent of all the patients were between 61 years and 80 years, and 2% of patients were older than 80 years. The mean age of patients in our study group was 53.4 years.

Men have larger pharyngeal airway cross-sectional area and airway volumes than women but are more likely to develop OSA because men have longer, and thus more collapsible, pharyngeal airways compared to women. In our study as well, men were 1.7 times more commonly affected than women. So, the ratio of incidence of OSA in males and females is 1.7:1 in our study.

In our study group, 10% of the patients had mild OSA, 12% of patients had moderate OSA, and 78% of patients had severe OSA. In patients with mild OSA, 4% were males and 6% were females; in patients with moderate OSA, 8% were males and 4% were females; and in patients with severe OSA, 52 and 26% were males and females, respectively.

OSA and COPD are two very closely related diseases and are found together in many of the patients; it is termed as “overlap syndrome.”⁷ In our study, 60% of the patients had overlap syndrome, whereas 40% of the patients had OSA only. Of all the patients with overlap syndrome, 83.3% of the patients had severe OSA, whereas in patients with isolated OSA, only 70% of the patients had severe OSA. Thus, it can be said that OSA is more severe in overlap syndrome.

PH is associated with both of the diseases, OSA and COPD.^{8,9} PH in COPD is caused due to hypoxia and anatomical changes in the lungs, whereas in OSA, PH is due to hypoxia, systemic hypertension, and obesity. In general, high body mass index, older age, greater nocturnal desaturations, and poor pulmonary function are closely related to PH in OSA. Most studies have found that OSA-induced PH was mild to moderate, and some studies have challenged the effect of AHI on PH.^{8–10} In our study group, a total of 24% of the patients had PH, of which mild and moderate PH was present in 10% of patients each and severe PH was present in 4% of the patients. And 22.2% of females and 25% of males were having PH. None of the females had severe PH, and 6.25% of males had severe PH; 16.7% of females and 6.25% of males had moderate PH; and 5.5% of females and 12.5% of males had mild PH.

In patients with COPD, increased AP is an independent predictor of future exacerbations and life expectancy reduction. Decrease

in the pulmonary vasculature and chronic hypoxia are two main mechanisms of increased PVR and subsequent PH in COPD. In patients with overlap syndrome, it is very difficult to determine whether PH is due to intermittent hypoxemia caused by sleep apnea or persistent hypoxemia associated with chronic cardiopulmonary disease. Few studies have focused on PH in patients with COPD and OSA.^{8–10} The coexistence of OSA in patients with COPD may have a synergistic adverse effect on pulmonary hemodynamics leading to right ventricular dysfunction. The coexistence of COPD and severe OSA has a synergistic effect on cardiovascular events and mortality. We have found that patients with COPD with OSA developed more severe hypoxemia at night. In our study, 36.67% of the patients with overlap syndrome had PH, whereas only 5% of the patients with OSA had PH.

CLINICAL SIGNIFICANCE

PH is a consequence of both COPD and OSA. Sometimes, COPD and OSA are simultaneously present; this condition is known as overlap syndrome. The prevalence of PH is higher in overlap syndrome patients. The incidence of nocturnal hypoxemia, morbidity, and mortality is also higher in these patients. PH is a mortality predictor in OSA and overlap syndrome.

REFERENCES

1. Kryger M, Roth T, Dement WC. Principles and practice of sleep medicine. 6th ed. Philadelphia, PA: Elsevier; 2017.
2. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnoea: an American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017;13(3):479–504. DOI: 10.5664/jcsm.6506.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2021 report; 2021.
4. Darren B. Taichman, Jess Mandel, Kimberly A. Smith, Jason X.-J. Yuan, Pulmonary Arterial Hypertension, Fishman's pulmonary diseases and disorders. 5th ed. New York: McGraw-Hill Education; 2015.
5. Aaron B. Waxman, Joseph Loscalzo, Pulmonary Hypertension, Harrison's principles of internal medicine. 20th ed. New York: McGraw-Hill Education; 2018.
6. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. *Pulm Circ* 2015;5(2):220–227. DOI: 10.1086/679995.
7. Shawon MS, Perret JL, Senaratna CV, et al. Current evidence on prevalence and clinical outcomes of co-morbid obstructive sleep apnea and chronic obstructive pulmonary disease: a systematic review. *Sleep Med Rev* 2017;32:58–68. DOI: 10.1016/j.smrv.2016.02.007.
8. Hawrylkiewicz I, Sliwinski P, Gorecka D, et al. Pulmonary haemodynamics in patients with OSAS or an overlap syndrome. *Monaldi Arch Chest Dis* 2004;61(3):148–152. DOI: 10.4081/monaldi.2004.693.
9. Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *Am J Respir Crit Care Med* 1995;151(1):82–86. DOI: 10.1164/ajrccm.151.1.7812577.
10. Kendzerska TB, Smith PM, Brignardello-Petersen R, et al. Evaluation of the measurement properties of the Epworth sleepiness scale: a systematic review. *Sleep Med Rev* 2014;18:321–331. DOI: 10.1016/j.