

# Association between Nocturnal Hypoxemia and COPD Severity: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Globally, Chronic Obstructive Pulmonary Disease (COPD) is the third most common cause of mortality. More than 80% of these fatalities happened in low- and middle-income nations. Transient desaturation during sleep occurs in healthy persons during Rapid Eye Movement (REM) sleep. This phenomenon is aggravated in COPD patients. As Nocturnal Desaturation (NOD) in COPD has been suggested to increase mortality, its early identification will aid in early initiation of treatment and prevention of associated complications.

**Aim:** To estimate the prevalence of nocturnal hypoxemia in COPD and determine its association with COPD severity.

**Materials and Methods:** A cross-sectional study was carried out at the Department of General Medicine, Apollo Hospitals, Guwahati, Assam, India during January to December 2021 involving 100 patients who had COPD symptoms. Continuous oxygen saturation monitoring with transcutaneous finger probe was done for the entire duration of sleep at night. Patients whose oxygen saturation falls below 90% for at least 30% of recording time in sleep were classified as desaturators. Statistical Package for Social Sciences (SPSS) Version 26.0 was used for data

analysis. Using the Chi-square test, the relationship between the qualitative variables was evaluated. The Mann-Whitney test or the unpaired t-test was used to analyse the quantitative data between the two groups. A p-value of less than 0.05 was considered significant.

**Results:** Prevalence of NOD among cases of COPD was observed as 26% in present study. A significant association was observed between presence of NOD in COPD cases with severity of COPD and with desaturation in 6-Minute Walk Test (6-MWT) ( $p < 0.01$ ). Severe cases had a prevalence of NOD as 65% as compared to 28.2% and 4.9% in moderate and mild cases respectively ( $p < 0.01$ ). A total of 61.9% cases with desaturation during 6-MWT showed NOD as compared to 38.1% without desaturation ( $p < 0.01$ ).

**Conclusion:** One fourth of the normoxemic COPD patients had significant NOD. NOD episodes were observed to be positively associated with increasing severity of COPD. Assessing variations in oxygen saturation during a 6-MWT can be helpful in identifying COPD patients who may be at risk for severe night time desaturation.

**Keywords:** Chronic obstructive pulmonary disease, Oxygen saturation, Pulmonary disease, Walk test

## INTRODUCTION

The COPD is a widespread, treatable, and avoidable illness marked by ongoing respiratory symptoms and restricted airflow because of abnormalities in the airways and/or alveoli, which are typically brought on by prolonged exposure to harmful particles or gases [1]. Common respiratory symptoms include dyspnoea, cough and/or sputum production. Smoking tobacco is the primary risk factor for COPD, however exposure to other environmental factors such as air pollution and biomass fuels may also be involved. A person's susceptibility to COPD is influenced by host factors such as rapid ageing, aberrant lung development, and genetic abnormalities [2].

In the world, COPD ranks third in terms of cause of death, accounting for 3.23 million deaths in 2019. More than 80 percent of these fatalities took place in low- and middle-income nations [3]. India's contribution to the global total of 27,756,000 Disability-Adjusted Life Years (DALYs) and death from COPD 102.3/100,000 is very considerable, hence negatively impacting the country's health-related quality of life [4].

For the diagnosis of COPD in symptomatic patients with risk factors, spirometry is necessary; postbronchodilator Forced Expiratory Volume 1/Forced Vital Capacity (FEV1/FVC)  $< 0.70$  indicates the existence of persistent airflow limitation [5]. The severity of the spirometric abnormalities, the extent of the patient's symptoms, the risk of future exacerbations and the history of moderate to severe exacerbations are all taken into account when assessing COPD [2].

The only therapies that have been shown to increase the survival of people with COPD are quitting smoking, oxygen therapy for

patients who are persistently hypoxic, and lung volume reduction surgery for certain emphysema patients [6]. Supplemental oxygen has been shown to significantly reduce mortality in patients with resting hypoxemia (resting O<sub>2</sub> saturation  $\leq 88\%$  in any patient or  $\leq 89\%$  in patients with signs of pulmonary hypertension or right heart failure) [6].

Transient desaturation during sleep occurs in healthy persons during REM sleep [7]. This phenomenon is aggravated in COPD patients [8,9]. The degree of desaturation that occurs during sleep may have an impact on the natural development of COPD to its last stages of severe hypoxemia, right heart failure, and mortality [10,11]. Sleep-related hypoxemia is corrected by long-term continuous oxygen therapy (15 hours or more per day to reach a saturation of 90% or more) which takes sleep duration into account [12].

It has been proposed that nocturnal oxygen desaturation in COPD increases mortality [13]. NOD often occurs in patients not qualifying for continuous oxygen [8,14-18]. But little research has been done on the proportion of stable COPD patients who are ineligible for Long-Term Oxygen Therapy (LTOT). Many such patients are prescribed nocturnal supplemental oxygen although its benefits are yet to be established [19,20]. It is therefore important to find the prevalence of nocturnal hypoxemia and its association with COPD severity in stable COPD patients not on continuous oxygen before initiating clinical trials for nocturnal oxygen therapy. Literature has been available regarding prevalence of NOD among cases of COPD [21-26]. However, literature regarding association of NOD with severity of COPD and 6-MWT is sparse [21]. The findings in this

study can give an insight regarding requirement of nocturnal oxygen therapy in stable COPD cases.

## MATERIALS AND METHODS

A cross-sectional study was done at a tertiary care centre, in the Department of General Medicine, Guwahati, Assam, India during January to December 2021. Due clearance was taken from Institutional Ethical Committee (Letter No. AHG/IEC/2020- 52) before commencement of the study.

**Inclusion and Exclusion criteria:** Study included 100 cases with symptoms of COPD attending the hospital. The symptomatic assessment was done using COPD Assessment Test (CAT) [27]. COPD cases on LTOT or in exacerbation/with history of exacerbation within four weeks or who had co-morbidities like obstructive sleep apnoea, interstitial lung disease, tuberculosis, bronchiectasis, cor pulmonale, malignancy, morbid obesity {Body Mass Index (BMI) >40} or any other disease that could affect the study outcome were excluded.

**Sample size calculation:** The following formulae was used for sample size calculation:

$$n = (Z_{\alpha/2})^2 * (PQ) / E^2$$

where;

n=Sample size

Z<sub>α/2</sub>=Z value at 5% error (1.96)

P=Taken as 39% (prevalence of NOD in COPD) [21]

Q=1-P

E=Absolute error (taken as 10%)

$$n = \frac{(1.96)^2 * (0.39 * 0.61)}{(0.01)^2}$$

n=92

By rounding off, the authors decided to include a total of 100 patients.

## Study Procedure

A pre-formed structured format was used for data collection. A detailed history was taken from all cases including: age, gender and smoking habits. An adult who has “smoked at least 100 cigarettes in his or her lifetime but who had quit smoking” at the time of interview was taken as ex-smoker [28]. The following formula was used to generate the smoking index, a measure of long-term cigarette usage: “smoking index=Cigarettes Per Day (CPD) × years of tobacco use”. Smoking index categories were non smoker, <400, 400-799, and ≥800 [29]. BMI was calculated using formulae: weight (kg) divided by square of height in metres. Duration of COPD was taken from the day of diagnosis till day of interview.

The COPD severity was assessed as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [2]. This is followed by 6-MWT where significant desaturation was defined as >4% fall, from the baseline SpO<sub>2</sub> for >5 min [30]. Continuous oxygen saturation monitoring with transcutaneous finger probe was done for the entire duration of sleep at night between 10:00 pm and 6:00 am while breathing in room air. At least four hours of continuous sleep oximeter recording was considered for analysis [31]. Patients whose oxygen saturation falls below 90% for at least 30% of recording time in sleep were classified as desaturators [32]. The patients were then grouped into two groups i.e., desaturators and non desaturators for analysis. MIR Spiro bank II was used for Spirometry, 6-MWT, and nocturnal oximetry.

## STATISTICAL ANALYSIS

The frequency and percentage representations of the qualitative data were used. Mean±Standard Deviation (SD) was used to represent quantitative data. Using the Chi-square test, the relationship between the qualitative variables was evaluated. When analysing quantitative data comparing the two groups, the Mann-Whitney U test was used if

the data failed the “Normality test,” and the unpaired t-test was used if the data passed. The p-value of less than 0.05 was considered significant. SPSS Version 26.0 was employed to analyse the data.

## RESULTS

The study patients had an average age of 61.62±5.57 years, and more than half of them 59 (59%) belonged to the elderly age category (>60 years). In the study group, there was a male predominance with 88 (88%) males and 12 (12%) females, translating to a male to female ratio of 7.33:1. A total of 41 (41%) cases were of mild COPD as per GOLD grade while 39 (39%) and 20 (20%) were of moderate and severe grade. Prevalence of NOD among cases of COPD was observed as 26 (26%) in present study. A total of 57 (57%) cases were current smokers. A 35 (35%) were ex-smokers and 8 (8%) were non-smokers. Mean duration of COPD was 9.12 years. No association was observed between presence or absence of NOD in COPD cases with increasing age (62.73 vs 61.23 years; p=0.24), male or female gender (23.9% vs 41.7% desaturators; 0.29), BMI (25.81 vs 26.47 Kg/m<sup>2</sup>; 0.33), history of smoking or no smoking (26.6% vs 25% desaturators; 0.37), COPD duration (8.35 vs 9.88 years; 0.094) and baseline oxygen saturation (96.31% vs 96.88%; 0.054) [Table/Fig-1].

Variables	n	Nocturnal Desaturation (NOD)				p-value	
		No (n=74)	Yes (n=26)				
Age (years)	41-50	11	9	81.8%	2	18.2%	0.24
	>50-60	31	25	83.3%	6	16.7%	
	>60-70	60	40	67.8%	20	32.2%	
Gender	Female	12	7	58.3%	5	41.7%	0.29
	Male	88	67	76.1%	21	23.9%	
BMI (Mean±SD)			26.47±3.14		25.81±2.61		0.33
Smoking history	Current smoker	57	45	78.9%	12	21.1%	0.37
	Ex-smoker	35	23	65.7%	12	34.3%	
	Non-smoker	8	6	75.0%	2	25.0%	
Smoking index*	<400	33	30	90.9%	3	9.1%	<0.01
	400-799	49	36	73.5%	13	26.5%	
	≥800	10	2	20.0%	8	80.0%	
Duration of COPD in years (Mean±SD)			9.88±4.18		8.35±3.22		0.094
GOLD grade	Mild	41	39	95.1%	2	4.9%	<0.01
	Moderate	39	28	71.8%	11	28.2%	
	Severe	20	7	35.0%	13	65.0%	
Baseline oxygen saturation (Mean±SD)			96.88±1.25%		96.31±1.195		0.054
6-Minute walk distance in metres (Mean±SD)			230.42±23.82		210.68±16.17		<0.01
Significant desaturation in 6-min Walk Test (6-MWT) (>4%)	No	58	58	100.0%	0	0.0%	<0.01
	Yes	42	16	38.1%	26	61.9%	

**[Table/Fig-1]:** Association of Nocturnal Desaturation (NOD) with demographic and clinical parameters.  
\*Non-smokers (n=8) were excluded

A significant association was observed between presence of nocturnal saturation in COPD cases with consumption of cigarettes over a period of time, severity as per GOLD grade and cases having significant desaturation in 6-MWT (p<0.01). Cases with smoking index of ≥800 had a prevalence of NOD as 80% as compared to 9.1% in cases with index <400. Severe cases had a prevalence of NOD as 65% as compared to 28.2% and 4.9% in moderate and mild cases respectively (p<0.01). Distance in 6-MWT was significantly less in cases with NOD (230.42 vs 210.68; p<0.01). A total of 61.9% cases with desaturation during 6-MWT showed NOD as compared to 38.1% without desaturation (p<0.01) [Table/Fig-1].

## DISCUSSION

In present study, prevalence of NOD among cases of COPD was observed as 26%. Moses R and Narayanan P, studied 103 patients with COPD [21]. On continuous oxygen saturation monitoring, NOD was present among 39% participants. Lacasse Y et al., in their study observed prevalence of NOD among cases of COPD as 38% [22]. Thomas VD et al., in their study observed that the rate of occurrence of NOD in COPD patients was 46.6% [23]. Fletcher EC et al., in another similar study observed prevalence of NOD among cases of COPD as 27% [24]. Lewis CA et al., and Das A et al., in their studies observed the prevalence as 49.2% and 58%, respectively [25,26]. The comparison of present study findings with that of other studies is shown in [Table/Fig-2] [21-26].

with desaturation during 6-MWT showed NOD as compared to none in non desaturation group ( $p < 0.01$ ). In the study by Moses RJ et al., desaturation reported in the 6-MWT was found to be a significant predictor of NOD [21]. Distance in 6-MWT was significantly less in cases with NOD (238.03 vs 271.3;  $p < 0.01$ ). A total of 78.1% cases with desaturation during 6-MWT showed NOD as compared to 21.9% in non-desaturation group ( $p < 0.01$ ). The present study findings were further support by observations made by Garcia-Talavera I et al., and Moreira MA et al., which determined that the 6-MWT is a significant predictor of nighttime desaturation and COPD prognosis [33,34].

Thus, to summarise, one in four normoxemic COPD patients had significant NOD. NOD episodes were observed to be positively

S. No.	Author's name and publication year	Place of study	No. of subjects	Objectives	Conclusion
1	Fletcher EC et al., [24] (1987)	Houston, USA	135	To find prevalence of nocturnal oxyhaemoglobin desaturation in COPD	Prevalence of NOD was 27% among COPD cases.
2	Thomas VD et al., (2002) [23]	Pondicherry, India	30	To document NOD in COPD and to identify associated factors	14 patients (46.6%) experienced NOD. Lower awake oxygen saturation was seen among desaturators.
3	Lewis CA [25] (2009)	Auckland, New-Zealand	59	To assess NOD's clinical significance and prevalence in COPD	Significant night time desaturation was seen in twenty-nine (49.2%) of the fifty-nine subjects. No difference was observed between saturators and desaturators in terms of quality of life, sleep and daytime functions.
4	Lacasse Y et al., (2011) [22]	Toronto, Canada	128	To evaluate Nocturnal Oxygen Desaturation (NOD) in COPD	Nocturnal oxygen desaturation affects a sizable fraction (38%) of individuals with moderate-to-severe COPD who are not eligible for home oxygen therapy.
5	Das A [26] (2015)	Mumbai, India	50	Determining NOD and daytime oxygen saturation levels. 2. Correlating NOD with Severity of COPD, BMI, Pulmonary artery pressure and BODE Index	A total of 58% patients had NOD. NOD had significant correlation with the severity of COPD, daytime hypoxemia, Pulmonary artery systolic pressure and BMI.
6	Moses R and Narayanan P, [21] (2019)	Chennai, India	103	To evaluate the predictors of NOD in normoxemic patients with moderate to severe COPD	NOD was present among 39% of the study participants. Associated factors were desaturation in 6-MWT and RA/RV dilatation.
Present study		Guwahati, India	100	To find the prevalence of nocturnal hypoxemia in COPD and determine its association with COPD severity	Prevalence of NOD was 26% among COPD cases. A significant association was observed between presence of NOD in COPD cases with severity of COPD and with desaturation in 6-MWT.

**[Table/Fig-2]:** Comparison of present study findings with other studies in literature [21-26].

RA/RV: Right atrium/Right ventricle

In present study, a significant association was observed between presence of nocturnal saturation in COPD cases and consumption of cigarettes over a period of time ( $p < 0.01$ ). Cases with smoking index of  $\geq 800$  had a prevalence of NOD as 80% as compared to 9.1% in cases with index  $< 400$ . Lacasse Y et al., in their study observed similar results, authors reported a significant association between pack years of smoking and nocturnal saturation ( $p < 0.01$ ) [22]. The importance of smoking cessation is well established in preventing COPD and reducing mortality of COPD [6]. However, its association with nocturnal saturation still warrants more attention.

A significant association was observed between presence of nocturnal saturation in COPD cases and severity of COPD as per GOLD grade. Severe cases had a prevalence of NOD as 65% as compared to 28.2% and 4.9% in moderate to mild cases respectively ( $p < 0.01$ ). Das A et al., in their study aimed to correlate NOD with severity of COPD [26]. Study observed that severity of COPD is a good predictor of NOD in COPD. Severe cases had a prevalence of NOD as 100% as compared to 59.3% and 16.7% in moderate to mild cases respectively ( $p < 0.01$ ). In their investigation, Moses R and Narayanan P, measured the FEV1 both before and after giving bronchodilators [21]. It has been discovered that NOD is related to postbronchodilator FEV1. Lacasse Y et al., and Lewis CA et al., in their studies also observed a significant correlation between presence of NOD and spirometry parameters like FEV1 and FVC [22,25]. The comparison of present study findings with that of other studies is shown in [Table/Fig-2] [21-26].

Distance in 6-MWT was significantly less in cases with NOD (230.42 vs 210.68;  $p < 0.01$ ). A significant association was observed between presence of nocturnal saturation in COPD cases and significant desaturation in 6-MWT ( $> 4\%$ ). A total of 61.9% cases

associated with increasing severity of COPD and history of heavy smoking.

### Limitation(s)

Present study was a single centre study. Secondly, being a cross-sectional study, no follow-ups were made with patients in terms of management strategies used for cases with NOD and their outcomes.

### CONCLUSION(S)

From present study, it may be concluded that 26% of the patients with normoxemic COPD exhibited notable desaturation during the night. A significant association was found between the occurrence of NOD episodes and the history and severity of heavy smoking. The current study's results also indicated that tracking variations in oxygen saturation during a 6-MWT may be helpful in identifying COPD patients who may be at risk for severe NOD. Therefore, it will be possible to identify COPD patients who are more likely to experience nighttime desaturation by screening them for these indicators at the outpatient department. It will also be less expensive and time-consuming because it will eliminate the requirement for all-night polysomnography. Early detection will help prevent related consequences and enable early treatment, such as home oxygen therapy. This research laid the foundation for further studies, particularly exploring the potential benefits of oxygen therapy for stable COPD patients with NOD.

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**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

**PLAGIARISM CHECKING METHODS:** [Jan H et al.]

- Plagiarism X-checker: Nov 11, 2023
- Manual Googling: Nov 28, 2023
- iThenticate Software: Dec 18, 2023 (5%)

**ETYMOLOGY:** Author Origin**EMENDATIONS:** 7Date of Submission: **Nov 02, 2023**Date of Peer Review: **Nov 24, 2023**Date of Acceptance: **Dec 20, 2023**Date of Publishing: **Jan 01, 2024**