



## Monaldi Archives for Chest Disease

eISSN 2532-5264

<https://www.monaldi-archives.org/>

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Monaldi Arch Chest Dis 2024 [Online ahead of print]

*To cite this Article:*

Prakash V, Kumar A, Saini LK, et al. **Proportion of sleep-related breathing disorders and their association with echocardiographic parameters in stable patients with chronic obstructive pulmonary disease: a cross-sectional observational exploratory study.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.2815

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**Proportion of sleep-related breathing disorders and their association with echocardiographic parameters in stable patients with chronic obstructive pulmonary disease: a cross-sectional observational exploratory study**

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**Contributions:** VP, LKS, RG, BK, GS, MM, conception and design of the study; VP, AK, BK, PS, RD, data collection; VP, AK, RG, LKS, MM, data analysis; VP, RG, MM, LKS, GS, RD, PS, writing and proof-reading of the manuscript.

**Conflict of interest:** the authors declare no potential conflict of interest.

**Ethics approval and consent to participate:** the present study was approved by institute's ethical committee vide letter no. AIIMS/IEC/20/528.

**Informed consent/Patient consent for publication:** a written informed consent was taken from all the participants to participate in the present study.

**Funding:** none.

**Availability of data and materials:** the data and material related to present study are available with the first author.

**Additional information:** this work was carried out at the Department of Pulmonary Medicine, All India Institute of Medical Sciences Rishikesh, Uttarakhand, India.

## **Abstract**

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. The coexistence of COPD and obstructive sleep apnea (OSA) (*i.e.*, overlap syndrome) has been reported in several studies. Both disorders independently increase the risk of cardiovascular complications. Hence, there is a theoretical possibility that cardiovascular parameters may be worse in patients with overlap syndrome compared to those with only COPD. However, this has been sparsely assessed in the literature. This study aimed to compare the clinical characteristics, echocardiography, and sleep parameters amongst COPD patients with and without sleep-related breathing disorders (SRBD).

This observational, cross-sectional study included 30 patients with stable COPD. All participants underwent a detailed clinical evaluation, followed by level 1 polysomnography (PSG). Each participant underwent echocardiographic evaluation to estimate mean pulmonary artery pressure from right ventricular systolic pressure (RVSP). Based on their PSG findings, participants were classified into non-SRBD and SRBD groups. Both groups were further compared with respect to clinical characteristics, echocardiographic, and PSG parameters. We found that most of the participants (93.3%) were male, and the mean age of the study population was  $56 \pm 8.2$  years. The only SRBD identified in this study was OSA, which was observed in 80% of participants. In this group, OSA was not associated with obesity. Systemic hypertension (50%) was the most common comorbidity, followed by diabetes mellitus (26.67%), but both were not significantly different between the groups. The mean RVSP was significantly higher amongst OSA patients than non-OSA patients ( $41.25 \pm 14.98$  versus  $30.83 \pm 5.84$ , respectively;  $p=0.01$ ). OSA was seen in 80% of participants with stable COPD, even in the absence of obesity. The presence of OSA was associated with a higher RVSP in this patient group.

**Key words:** chronic obstructive pulmonary disease, echocardiography, obstructive sleep apnea, overlap syndrome, polysomnography, pulmonary hypertension.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality throughout the world. It is currently the third leading cause of death worldwide, causing 3.23 million deaths in 2019, with more than 80% of these deaths being reported from low- and middle-income countries [1]. COPD may be associated with various cardiovascular conditions like pulmonary hypertension (PH), ischemic heart disease and cardiac remodeling [2,3]. Of these, the presence of PH in COPD is strongly associated with higher mortality [4], and reduced functional status, leading to worse outcomes [5]. The factors leading to PH in COPD include hypoxia, systemic inflammation and toxic effects of cigarette smoke [3].

Obstructive sleep apnea (OSA), a type of sleep-related breathing disorder (SRBD), is characterized by nighttime symptoms like snoring, snorting, and apneas as observed by bed partners, and daytime symptoms like non-refreshing sleep, fatigue, tiredness and daytime sleepiness. The diagnosis of OSA is established by identifying five or more obstructive respiratory events per hour of sleep during polysomnography (PSG) [6].

As with COPD, PH may be associated with OSA too, and its occurrence is multifactorial [4,7,8]. PH may be observed in nearly half of the cases of OSA; however, the actual prevalence in OSA is still unknown due to a dearth of population-based prospective studies [4,5,9].

One prospective and two retrospective studies have also found OSA in a proportion greater than the population prevalence among patients with COPD [10-15]. However, significant limitations of these studies included the absence of attended PSG for diagnosing OSA or the non-use of pulmonary function tests for diagnosing COPD. On the other hand, the Sleep Heart Health study found no significant increase in OSA risk among patients with COPD compared with matched controls [16]. However, since the authors studied patients with mild subclinical disease, the findings may not generalize to clinical cohorts.

COPD and OSA both lead to decreased arterial oxygen tension due to their synergistic effects. The coexistence of COPD and OSA is known as overlap syndrome [17]. The prevalence of overlap syndrome in the general population ranges from 1.0–3.6%, in OSA patients from 7.6–55.7%, and COPD patients from 2.9–65.9% across various studies [16,18,19]. A recent study reported that the prevalence of PH in patients with overlap syndrome was higher (31%) than in those with OSA (4.5%) or COPD (17.1%) alone [18]. Also, an increased risk of mortality has been seen in patients with overlap syndrome due to higher chances of developing cardiovascular complications, including PH [20,21]. However, most of these conclusions emerge from retrospectively analyzed data.

The present study has tried to address the limitations of previous studies by including stable COPD patients after PFT, and OSA was assessed using attended in-lab PSG. The study's primary objective was to ascertain the proportion of sleep-related breathing disorders among

patients with stable COPD. As a secondary objective, we also studied cardiovascular parameters and the presence of PH in view of a recent American Thoracic Society /European Respiratory Society statement suggesting that observational studies must be conducted to compare cardiovascular outcomes among individuals with overlap syndrome compared to OSA or COPD [22].

## **Materials and Methods**

This was a cross-sectional observational exploratory study. Since the prevalence of Overlap syndrome among COPD varies across the literature, the population prevalence of OSA was considered for the sample size calculation [18,23]. Sample size was calculated assuming the prevalence of OSA as 2.4% with the power of study as 0.80 and alpha as 0.05 (confidence interval 95%), which resulted in a sample size of 36. However, owing to COVID-19 pandemic waves, that could not be achieved and the sample size was reduced to 30 after institutional scientific committee approval.

Thirty consecutive adult participants aged 40 years or more diagnosed with stable COPD using Spirometry as per the GOLD 2019 criteria in the Pulmonology OPD, who did not require long-term oxygen therapy, home bilevel positive airway pressure and were normocapnic, were enrolled [24]. However, participants having insomnia, history of thromboembolic disease, cardiomyopathies, ischemic heart disease, chronic kidney disease, chronic liver disease or other respiratory comorbidities were excluded from the study. Participants not willing to provide written informed consent were also excluded.

## ***Clinical assessment***

Each participant underwent clinical evaluation with history taking, physical and anthropometric examination. This was followed by video-synchronized attended level 1 PSG as per the American Academy of Sleep Medicine 2017 guidelines [25], and manual scoring of data as per the AASM manual, version 2.5 [26]. Based on their PSG findings, participants were grouped as either not having or having an SRBD. Those with SRBDs were further classified into subgroups of OSA, central sleep apnea, obesity hypoventilation syndrome or sleep-related hypoxemia.

## ***Protocol for PSG***

Each participant was subjected to full-night in-lab PSG monitoring (SOMNOscreen™ plus, Somnomedic GmbH, Germany) after acclimatization. Six electroencephalography channels, two electrooculography channels, and chin electromyography (EMG) were recorded and used for scoring sleep stages. One lead of electrocardiography (Lead II) was used to score

arrhythmias. Respiratory parameters included assessment of airflow using a pressure transducer and thermistor, respiratory effort using respiratory inductance plethysmography belts on the chest and abdomen and recording of overnight oximetry. Snoring was recorded using a microphone. Limb movements from both legs were recorded using anterior tibialis EMG. Lastly, body position was recorded throughout the study.

Raw data of PSG was scored manually by trained scorers following the standard scoring manual [26]. The severity of sleep-disordered breathing was calculated using the apnoea hypopnoea index (AHI) and the time spent with oxygen saturation below 90% (T90). Sleep quality was assessed using sleep efficiency (Total Sleep Time/time in bed) and arousal index (number of arousals per hour of sleep) as surrogate markers.

### ***Echocardiography***

Participants of each group underwent transthoracic echocardiographic examination by an expert cardiologist using Philips Epiq 7 echocardiography equipment. Subjects were placed in the left lateral decubitus position, and complete interrogation of the right heart [right atrium (RA), right ventricle (RV), pulmonary artery (PA)] and left heart structures was done for two-dimensional images, color images and continuous wave (CW) Doppler signals, and images archived. A pulmonary regurgitation (PR) signal was obtained in the parasternal short-axis view using the color Doppler. CW Doppler at a sweep speed of 100 mm/s was used to measure the peak of diastole PR velocity ( $PRV_{peak}$ ). Mean PA Pressure (mPAP) was calculated using the following formula based on the simplified Bernoulli equation:  $mPAP = 4(PR_{peak} \text{ velocity})^2 + RA \text{ pressure (RAP)}$ . RAP was estimated using inferior vena cava diameter and collapsibility as per recommendation [27]. This method has been validated against gold-standard invasive cardiac catheterization measurements [28,29]. RVSP, left ventricular (LV) systolic function (LV ejection fraction, LVEF), and regional wall motion abnormality (RWMA) were also assessed. RVSP, which is equal to systolic PA pressure in the absence of RV outflow tract obstruction or pulmonary stenosis, was estimated by calculating peak TR velocity on continuous wave Doppler using a simplified Bernoulli equation ( $P = 4[TRV_{max}]^2 + RAP$ ) [30]. A peak TR velocity value of 2.8 m/s is considered normal. The mPAP can also be estimated using the formula  $mPAP = 0.61 \times RVSP + 2 \text{ mmHg}$  [30]. Based on RVSP, patients were categorized into four groups: No PH (<40 mmHg), mild PH (40-50 mm Hg), moderate PH (51-60 mm Hg), and severe PH (>60 mm Hg) [31]. Cardiovascular parameters described above were compared between the two groups.

### ***Statistical analysis***

Statistical analysis was conducted using SPSS v 28.0 for Mac. (IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp). Descriptive statistics were calculated. The probability of strength of association of categorical variables was compared using the Chi-square test or Fisher's exact test. Continuous variables between two groups were compared using the Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. For further comparison among subgroups, the Kruskal-Wallis test was applied wherever appropriate.

### **Results**

There were 6 participants in the non-SRBD group and 24 in the SRBD group (Table 1). The only SRBD identified in this study was OSA. Among 24, mild, moderate and severe OSA was present in 10, 7 and 7 patients, respectively. Most subjects (n=28, 93.3%) were male, and the mean age of the study population was  $56 \pm 8.2$  years. The mean oxygen saturation at room air was  $98.06 \pm 1.72$  %. Systemic hypertension was the most common comorbidity in this study (n=15, 50%), followed by diabetes mellitus (n=8, 26.67%) and coronary artery disease (n=1, 3.33%).

Both the groups were comparable concerning their demographic, anthropometric parameters and surrogate markers for sleep quality. (Table 1)

### ***Comorbidity***

In the non-SRBD group, 2 out of 6 subjects (33.33%) were hypertensive as compared to 13 out of 24 subjects (54.2%) in the SRBD group. Similarly, only 1 out of 6 subjects (16.7%) in the non-SRBD group was diabetic, compared to the SRBD group, in which 7 out of 24 subjects (29.2%) were diabetic. However, there was no statistically significant difference between the two groups regarding the presence of hypertension (p-value 0.470) or diabetes (p-value 0.132).

### ***Echo parameters***

A total of 11 subjects (36.77%) were diagnosed with PH. Mild, moderate and severe PH was found in 5 (16.67%), 2 (6.67%) and 4 (13.33%) subjects, respectively. Out of these 11 subjects, one was in the non-SRBD group, while 10 were in the SRBD group, and the difference was statistically significant (p-value 0.009). Mean RVSP was significantly higher amongst SRBD subjects than non-SRBD subjects (Table 1). Estimated mPAP was also higher in the SRBD group; however, the difference did not meet the level of statistical significance. The distribution of subjects with different severity of pulmonary hypertension varies according to the severity of COPD and OSA (Figure 1). As the severity of COPD or OSA increases, the percentage of

participants with higher grades of pulmonary hypertension likewise increases.

### ***Sleep parameters***

The mean total sleep time of the population under study was  $6.05 \pm 1.14$  hours, while mean sleep efficiency was  $76.79 \% \pm 11.78 \%$ . AHI and time spent in sleep below 90% SPO<sub>2</sub> were significantly higher in the SRBD group, while baseline SPO<sub>2</sub> and minimum SPO<sub>2</sub> were significantly higher in the non-SRBD group. These and other sleep architecture characteristics between the two groups are depicted in Table 1. Also, the mean AHI in this study was  $27.5 \pm 32.25$ , representing a wide variability amongst subjects for this parameter.

### ***BMI and OSA***

The likelihood of identifying OSA in COPD was independent of the BMI of the subjects, as depicted in Figure 2.

### **Discussion**

This study fills the gap by improving the methodological limitations of the previous studies, e.g., diagnosis of COPD and OSA using spirometry and in-lab-attended PSG, respectively, following the standard diagnostic criteria [6,24,26]. The proportion of stable COPD patients having OSA is considerable (80%) given the adverse effects of OSA and COPD together on cardiovascular parameters like pulmonary artery pressure. This study also found a higher proportion of PH in the SRBD group (40%) than in the non-SRBD group (16%).

In contrast to earlier studies, the present study showed a greater prevalence of SRBD (OSA) among patients having stable COPD [18,32,33]. The greater proportion of OSA found among the stable COPD patients in the present study could be attributed to several reasons. First, the characteristics of the participants were different from the present study, e.g. Machado et al. [32] included hypoxemic COPD patients who are on long-term oxygen therapy, while Venkateshwaran et al. [33] excluded patients already diagnosed with OSA and patients having BMI  $>30 \text{ kg/m}^2$ . The use of oxygen therapy can improve the oxygen saturation in patients with OSA, leading to the underscoring of hypopneas and resulting in misdiagnosis or reduced severity of OSA [34]. Similarly, the exclusion of already diagnosed OSA cases and those with high BMI can lead to an underestimation of the proportion of COPD patients with OSA. Second, diagnostic techniques and criteria for diagnosing OSA can influence the results. While the previous studies used AHI as a primary determinant of OSA and the cutoff of the AHI also varied across studies, e.g. AHI  $>15$  [32], and AHI  $>10$  [35], this could have led to the underestimation of OSA. Using different criteria for scoring hypopnea, e.g. at least a 50% reduction in flow with 3% or more desaturation used by Solar et al. [10] can also lead to an



underestimation of the diagnosis and severity of OSA [36]. Third, Machado et al.[32] used a split night study, Steveling et al. [35] used level 3 PSG. Both these techniques can lead to underestimating OSA because of less time spent in REM sleep and using time in bed or total recording time instead of total sleep time in the calculation of AHI, respectively [37,38].

Like the present study, previous studies also found a higher prevalence of PH in patients having COPD with OSA compared to COPD without OSA (21.1% vs 7.3%, respectively) and (25% vs 20%, respectively) [39,40]. However, the absolute prevalence in both groups was lesser in Dotan et al.'s [39] study and in COPD with OSA group in Sun et al.'s[40] study. This difference could be related to the fact that the former study was a chart review; hence, the uniformity of the diagnostic techniques used for the assessment of PH couldn't be ensured, and the later study used a different method for diagnosis of PH (Tricuspid regurgitation velocity >2.8 m/s and systolic PAP >36 mmHg). In the present study, mPAP was calculated from RVSP and the severity of PH was determined based on the level of RVSP. RVSP was significantly higher in the SRBD group than in the non-SRBD group. On subgroup analysis, there was a significant increase in RVSP with increasing severity of OSA (p-value 0.002). This finding is consistent with the findings of another study in which patients with overlap syndrome were found to be at higher risk of developing PH even if their obstructive ventilatory defect was not severe [19]. In addition, Sun et al.[40] used the level 3 sleep study to diagnose OSA, and the OSA was defined as AHI > 10 events/hour. On the contrary, Dotan et al. [39] used the 4% desaturation criterion for scoring hypopnea. Issues arising out of different levels of sleep studies and scoring criteria have already been discussed above.

From the demographic perspective, 93.3% of patients were male. This observation can be due to the relatively lower incidence of smoking and COPD amongst females [41]. There was no significant difference between the groups concerning BMI and weight, showing that the occurrence of OSA in COPD is independent of BMI. A possible reason for this finding could be the chronic systemic inflammatory state in COPD, leading to low BMI. Recent studies have also shown a higher prevalence of OSA in COPD patients with low BMI [42,43]. Further, the increased risk of OSA in COPD could be due to COPD-associated skeletal muscle myopathy, impaired upper airway and dilator muscle reflex, and pharyngeal muscle myopathy associated with inhaled corticosteroid use in these patients [43].

The mean sleep efficiency in our study was  $76.79 \pm 11.78\%$ , which is lower than the normal sleep efficiency (>85%) but higher as compared to that noted by Karachaliou F et al. [44] in COPD patients. This difference can be due to different population characteristics, differences in sample size, and the inclusion of other sleep disorders in their study, such as insomnia, which were excluded from our study. In another questionnaire-based study on 377 COPD patients, 53% experienced poor sleep quality; the mean sleep efficiency was 73%. This is

comparable to the sleep efficiency in our study; however, their study population did not undergo PSG [45]. Sleep efficiency in COPD with SRBDs was low (75.3%) compared to COPD without SRBDs (82.7%), although statistically insignificant (Table 1). Decreased sleep efficiency is an expected finding in COPD and OSA, so it is likely that in overlap syndrome, the sleep efficiency should be even lower, which is consistent with our results.

COPD patients are at an increased risk of nocturnal hypoxemia due to co-existent SRBDs as compared to the general population. In REM sleep, increased airway resistance and diminished ventilatory drive lead to decreased oxygenation, which is usually clinically insignificant in normal individuals. However, in COPD, due to a lower baseline PaO<sub>2</sub>, this normal physiological change during sleep can lead to significant hypoxemia. Interestingly, COPD patients may be relatively protected from potential deleterious effects of REM sleep because of their poor quality of sleep and sleep fragmentation, leading to reduced durations of slow-wave and REM sleep [46].

Our study has a few important limitations. First, the sample size was small, which might not represent the entire COPD population. Second, though the gender difference represents the population in our clinic, women still do not have adequate representation; hence, findings cannot be generalized to both genders. Third, for the evaluation of PH, the ideal method is pulmonary vascular catheterization, which was not done, and the assessment of PH was done by 2D Echocardiography, considering the noninvasiveness and safety of the later procedure compared to pulmonary vascular catheterization.

The strength of our study was that the evaluation of sleep was done by level 1 polysomnography and the manual scoring of the sleep data of all the participants to ensure the exclusion of comorbid sleep disorders and detailed evaluations of sleep parameters that were missing in many previous studies on Overlap syndrome patients.

## **Conclusions**

The only SRBD identified in our study population of stable COPD patients was OSA, the occurrence of which was unrelated to the BMI of these patients. Overlap syndrome patients showed a higher prevalence and severity of PH than COPD patients without OSA. Also, overlap syndrome patients had significantly higher sleep-related oxygen desaturation and AHI compared to COPD patients without OSA. Due to the rising prevalence as well as awareness of both COPD and OSA, overlap syndrome is an increasingly common occurrence. Hence, a high index of suspicion is required to diagnose these patients. As overlap syndrome patients had more frequent COPD exacerbation, higher cardiovascular events, poorer quality of life, increased medical costs and mortality, physicians should be more vigilant in screening COPD patients for OSA to prevent such outcomes.

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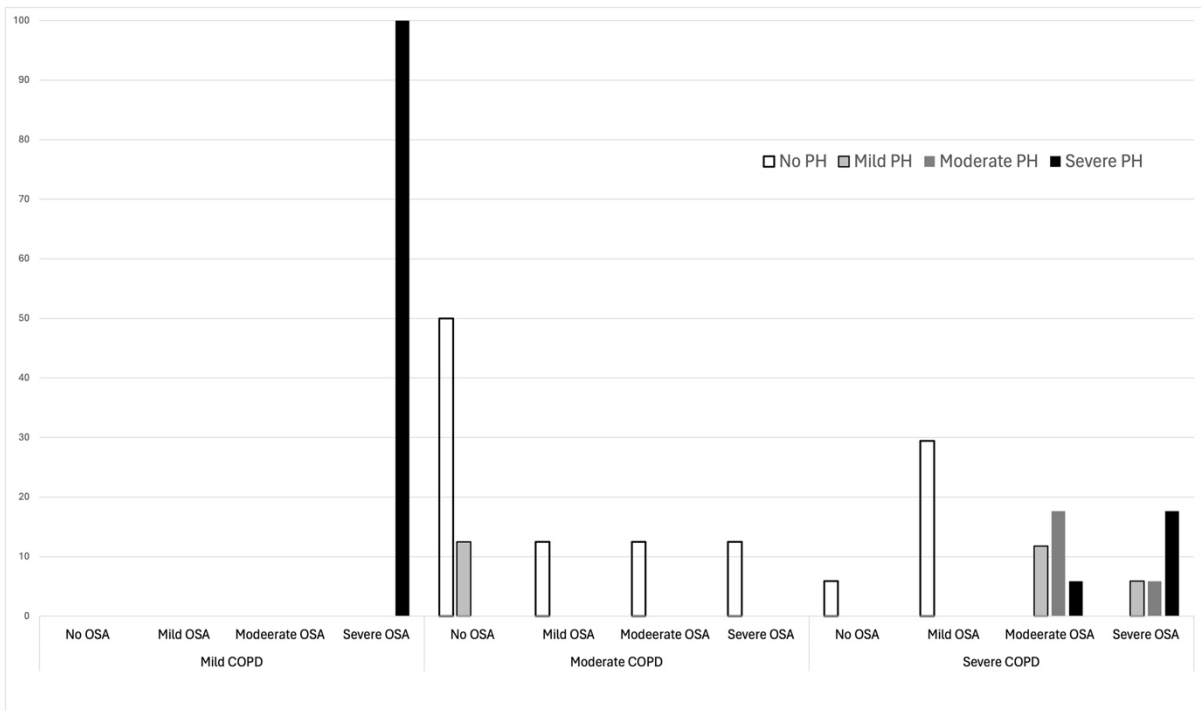
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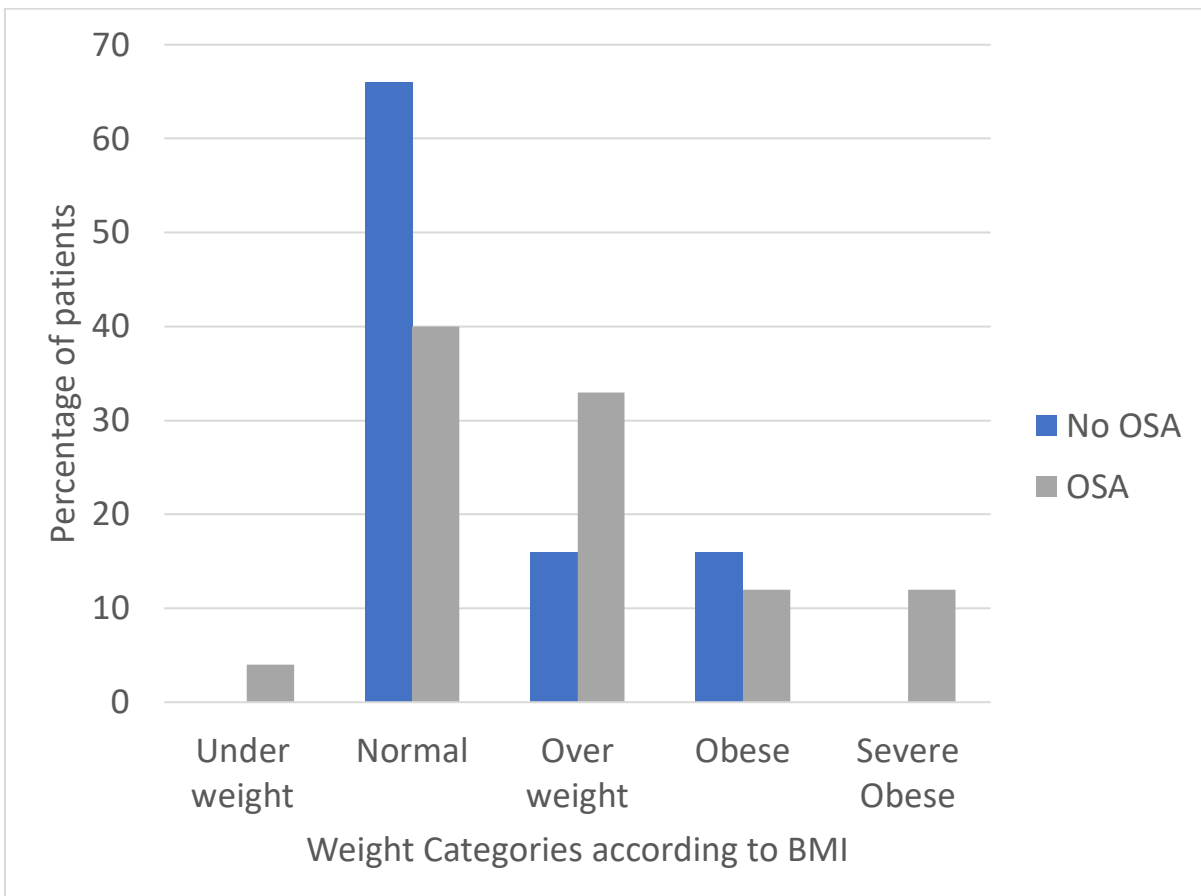
**Table 1. Demographic, echocardiographic and polysomnography parameters between non-SRBD and SRBD groups.**

Categories	Parameters	Mean (SD)		p-value
		Non-SRBD group (n=6)	SRBD group (n=24)	
<b>Demographic characteristics</b>	Age (years)	58.8 (5.4)	55.29 (8.6)	0.35
	Height (cm)	159.8 (6.9)	162.6 (6.3)	0.35
	Weight (kg)	57.3 (17.3)	69.6 (21.8)	0.21
	BMI	22.1 (5.2)	26.2 (8)	0.25
<b>Spirometry parameters</b>	FEV1/FVC	58.16 (11.64)	51.28 (9.46)	0.13
	FEV1	56.0 (6.06)	47.50 (13.28)	0.14
	FVC	2.77 (0.13)	2.59 (0.22)	0.07
<b>Awake Oxygen Saturation</b>	SPO2	96.67 (1.03)	95.13 (2.49)	0.03
<b>2-D-Echo parameters</b>	RVSP (mm Hg)	30.8 (5.8)	41.2 (14.9)	0.01
	mPAP (estimated)	20.1 (4.4)	26.7 (9.2)	0.10
	LVEF %	60 (3.1)	58.3 (4.1)	0.36
<b>Sleep (PSG) parameters</b>	Sleep time (hours)	6.6 (.97)	5.9 (1.1)	0.16
	N1%	17.4 (5.8)	21.1(11.8)	0.46
	N2%	49.7(26.5)	47 (16.5)	0.75
	N3%	6.5 (4.7)	11.2 (10.6)	0.29
	REM%	16 (9.6)	15.9 (7.9)	0.97
	AHI	3.2 (1.7)	33.6 (33.4)	0.03
	Sleep efficiency %	82.7 (11.9)	75.3 (11.5)	0.17
	Baseline SPO <sub>2</sub> %	96.6 (1.0)	95.1 (2.4)	0.03
	Minimum SPO <sub>2</sub> % (during sleep)	92.1 (1.4)	81.9 (10.2)	0.02
	Time spent with <90% SPO <sub>2</sub> (minutes)	8 (36.4)	46.1 (92.8)	0.02

AHI, apnea hypopnea index; BMI, body mass index; LVEF, left ventricular ejection pressure; mPAP, mean pulmonary artery pressure; N1, N2, N3, non-rapid eye movement sleep stage 1, 2 and 3 respectively; PSG, polysomnography; RVSP, right ventricular systolic pressure; REM, rapid eye movement sleep stage; SRBD, sleep related breathing disorder; SD, standard deviation



**Figure 1. Distribution of Pulmonary Hypertension among different categories of obstructive sleep apnea and chronic obstructive pulmonary disease severity (bars represent percent of participants in each COPD Category)**



**Figure 2. Association between the categories of weight (based on body mass index) and obstructive sleep apnea.**