# Existence and pattern of sleep-related breathing disorders in patients diagnosed with bronchial asthma

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## Abstract

Asthma and obstructive sleep apnea (OSA) are commonly prevalent diseases, and both can co-exist to result in an alternate overlap syndrome, where a bidirectional relationship can adversely affect each other. This study aimed to determine the existence and pattern of sleep-related breathing disorders in subjects with bronchial asthma. It was prospectively conducted at the National Institute of Tuberculosis and Respiratory Diseases, New Delhi, in diagnosed cases of bronchial asthma. A subjective assessment of sleepiness was done using the Epworth Sleepiness Scale (ESS). All subjects underwent overnight polysomnography (PSG) in the Sleep Laboratory of the Institute.

A total of 70 subjects were screened, and among them, finally, 30 were enrolled. The mean age of the subjects was 37.53±11.21 years, the mean body mass index (BMI) was 26.4±5.58 kg/m², the mean ESS score was 3.1, and 80% of the subjects were male. After PSG, OSA, (apnea hypopnea index >5/hour) was found in 63% (19/30) of the patients, of whom 43% had mild OSA, 10% had moderate OSA, and 10% had severe OSA. 10% (3/30) had nocturnal oxygen desaturation, while none had sleep hypoventilation. Patients with OSA compared to those without OSA, had a higher BMI, more comorbid allergic rhinitis, severe bronchial asthma, and a worse percentage of predicted forced expiratory volume in the first second. The study showed high detection rates of OSA in bronchial asthma patients. Hence, asthma patients should be evaluated for OSA.

## Introduction

Asthma is a heterogeneous disease, usually characterised by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Asthma, a diverse condition, affects 1-18% of the global population [1]. An Indian study on the Epidemiology of Asthma, Respiratory Symptoms, and Chronic Bronchitis (INSEARCH), involving 85,105 men and 84,470 women from 12 urban and 11 rural locations, revealed an estimated asthma prevalence of 2.05% among those aged >15 years. This corresponds to an estimated national burden of 18 million people with asthma [2]. Similarly, the prevalence of obstructive sleep apnea (OSA) ranges from 3% to 7% in adult men and 2% to 5% in adult women globally [3]. In India, various studies report OSA prevalence between 4.4% and 13.7% [4].

A mutual relationship exists between OSA and bronchial asthma, with each condition negatively influencing the other. They share a common underlying pathophysiology characterized by

increased airway resistance, involving both local and systemic inflammation, as well as coexisting with comorbidities such as gastroesophageal reflux, obesity, and rhinitis [5]. The simultaneous presence of OSA and bronchial asthma is termed alternate overlap syndrome, distinguishing it from the overlap syndrome associated with chronic pulmonary disease and OSA [6].

Due to a lack of sufficient literature in the Indian context, the current study was undertaken to investigate the relationship between asthma and OSA.

## Materials and Methods

### Study design

The study was conducted prospectively at the National Institute of Tuberculosis and Respiratory Diseases in New Delhi, following ethical clearance from the Ethics Committee. Written informed consent was obtained from all participants. Asthma diagnosis relied on a history of respiratory symptoms such as wheezing, chest tightness, cough, and shortness of breath. Objective signs of reversibility were demonstrated on spirometry, with a change in volume of >12% and 200 mL or more in forced expiratory volume in the first second

(FEV1) after the inhalation of 400 µg of salbutamol, in accordance with the Global Initiative for Asthma (GINA) Guidelines [1]. Asthma was categorised into: i) mild asthma – asthma that is well controlled and requires reliever medication alone, or with low-intensity controller treatment such as low-dose inhaled corticosteroids (ICS), leukotriene receptor antagonists, or chromones; ii) moderate asthma – asthma that is well controlled with low-dose ICS/long-acting β-agonist (LABA); iii) severe asthma – asthma that necessitates high-dose ICS/LABA to prevent it from becoming "uncontrolled" or asthma that remains "uncontrolled" despite this treatment.

The study enrolled stable cases of bronchial asthma aged over 18 years but less than 60 years between September 2018 and May 2019. Exclusion criteria comprised patients with comorbidities (diabetes mellitus, hypertension, coronary artery disease), pregnant or lactating mothers, individuals with significant cognitive impairment, and those experiencing respiratory failure. Out of the initial 70 diagnosed cases of bronchial asthma, 30 underwent the sleep study, while the remaining 40 could not proceed due to reasons specified in Figure 1.

For all the participants included in the study, a comprehensive sleep questionnaire was completed, covering sleep-related history, comorbidities, physical examination, and laboratory assessments, which included a complete blood count. Additionally, spirometry
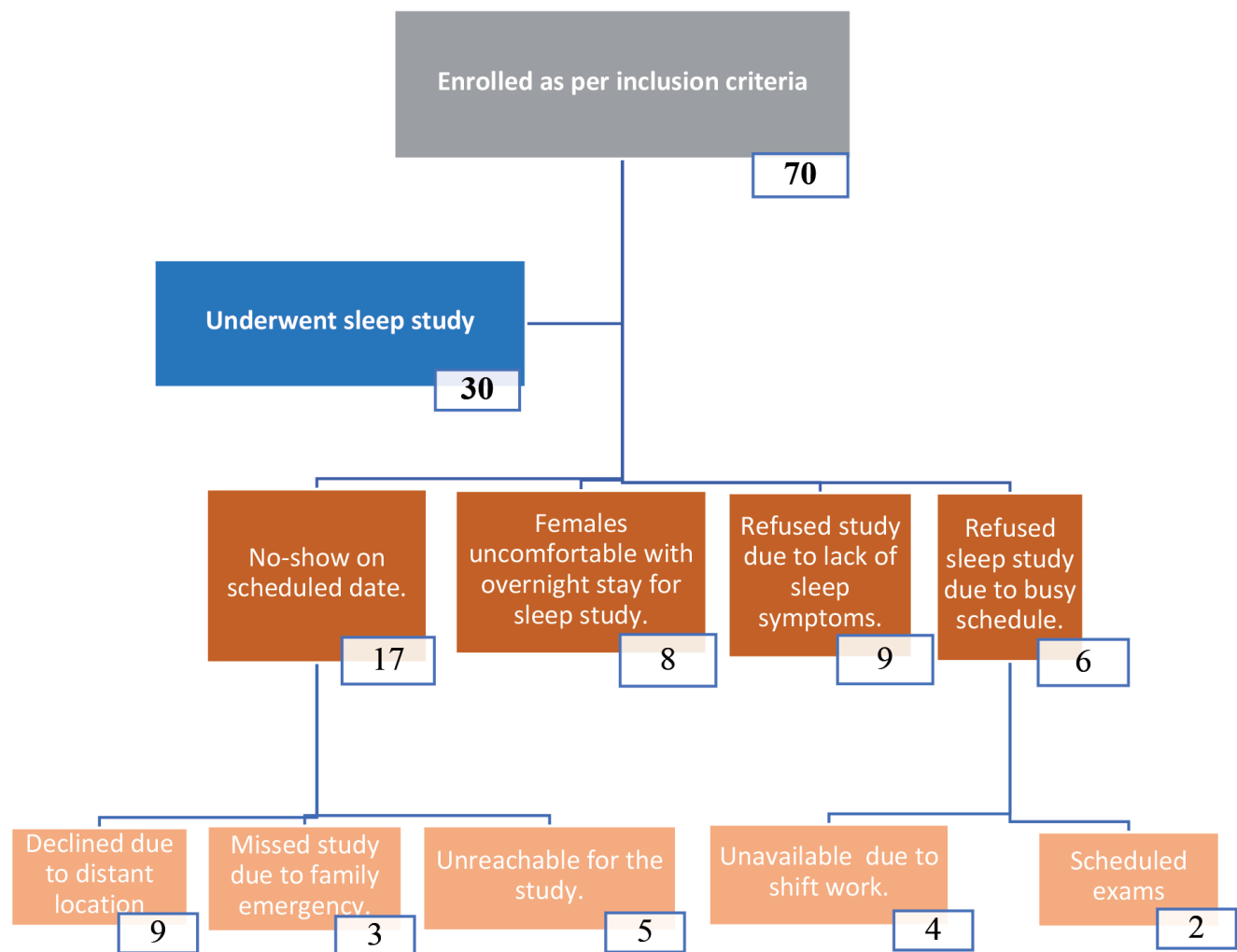


**Figure 1.** Flowchart describing the details of a patient enrolled in the study.

with reversibility, electrocardiogram, lipid profile, thyroid function test, and random blood sugar were conducted. Subsequently, an in-lab diagnostic polysomnography (PSG) study was performed. The Epworth Sleepiness Scale (ESS) was administered to all participants, with scores ranging from 0 to 24. Scores exceeding 10 were indicative of the presence of excessive daytime sleepiness [7].

The determination of the sample size was grounded on the reported prevalence of OSA in individuals with bronchial asthma in the Indian population. The calculation employed the formula (Z95)2*p(1-p)/d2, where n represents the sample size, p denotes prevalence, z signifies the confidence interval, and d stands for precision. The computed sample size was found to be 24.

## Polysomnography

Following the guidelines of the American Academy of Sleep Medicine (AASM) [8,9], all participants underwent overnight PSG using the Compumedics E series PSG machine in the Sleep Laboratory of the Institute. Monitored parameters included electroencephalogram, electrooculogram, chin electromyogram (EMG), electrocardiogram, oronasal airflow, snoring, respiratory effort, body position, leg movement (anterior tibialis EMG), and transcutaneous oxygen saturation. Electrode placement adhered to the 10-20 international system of lead placement.

Manual scoring was conducted for all studies in accordance with AASM guidelines the apnea, hyponea, and respiratory effort related arousal were followed. Sleep hypoventilation was defined as a >10 mmHg increase in partial pressure of arterial carbon dioxide during sleep compared to the awake state or an increase in arterial partial pressure of carbon dioxide to a value >55 mmHg for >10 minutes. Nocturnal oxygen desaturation (NOD) was considered present if the patient spent >30% of the total sleep recording time with a transcutaneous arterial oxygen saturation of <90%. The same was classified as per the Chicago criteria. Arterial blood gas analysis was conducted before and after the study for all patients.

## Body mass index

Body mass index (BMI) was computed by dividing the body weight in kilograms by the square of height in meters. The classification of BMI followed the Indian criteria for obesity: overweight was defined as a BMI of 23-24.9 kg/m², obesity as a BMI greater than 25 kg/m², and normal as a BMI less than 23 kg/m² [10].

## Statistical analysis

All measurements were recorded using a pre-designed form, and the data were subsequently entered into Microsoft Office Excel.

Descriptive statistics were presented as the mean and standard deviation. For quantitative data, the difference in means between the two groups was compared using the Student *t*-test, while categorical data analysis was conducted using the Fisher exact probability test. All statistical analyses were carried out using dedicated statistical software. Differences were considered statistically significant at a p-value of less than 0.05.

## Results

A total of 70 patients were initially screened for the study between 2018 and 2019, and among them, 30 patients met the eligibility criteria for enrollment. All patients underwent an assessment for sleepiness using the ESS, revealing that the majority (57%; 17/30) were asymptomatic regarding sleep. The most commonly reported sleep symptom was snoring (30%; 9/30), followed by easy fatigability (20%; 6/30), morning headaches (10%; 3/30), and unrefreshing sleep (10%; 3/30). Among these patients, only one exhibited excessive daytime sleepiness with an ESS score of 13.

Table 1 presents the demographic and clinical characteristics of all 30 subjects. The average age of the population was 37.53±11.21 years, with a predominance of male participants. Although the difference was not statistically significant (p=0.09), asthma patients with OSA tended to have a longer duration of disease compared to those without OSA. Asthma patients with OSA also exhibited a higher BMI (28.15±6.06 *vs*. 23.45±3.03 kg/m²), a higher prevalence of comorbid allergic rhinitis (AR) (11/19 *vs*. 0/11), a greater severity of bronchial asthma (10/19 *vs*. 0/11), and a lower FEV1% predicted (53.42±18.80 *vs*. 68.02±18.21) with statistically significant differences (p=0.023, p=0.001, p=0.004, and p=0.47, respectively). All three components of AR, obesity, and OSA were present in 23% (7/30) of patients. About 55% of mild asthmatics and 68% of those with moderate to severe asthma were found to have OSA.

Table 2 illustrates the PSG parameters during sleep. While there was no statistically significant difference in total sleep time, sleep latency, and sleep efficiency between those with and without OSA, the proportion of rapid eye movement sleep percentage and slow wave sleep was lower in the former compared to the latter. Subjects with OSA exhibited higher mean values of lowest saturation, snores per hour of sleep, apnea hypopnea index (AHI), and NOD compared to those without OSA. Notably, lowest oxygen saturation (p=0.006), snores per hour of sleep (p=0.022), and AHI per hour (p=0.011) showed statistically significant associations between the two groups. Arterial blood gas analysis was conducted before and after the study for all patients. No statistical correlation was observed between the two groups with and without OSA.

**Table 1.** Demographic and clinical characteristics of the patients.

| Characteristics | Asthma with OSA (n=19) | Asthma without OSA (n=11) | p |
|---|---|---|---|
| Age [mean+SD (min-max)], years | 39.74±11.69 (18-58) | 33.73±9.64 (21-51) | 0.16 |
| Gender [female/male] | 3/16 | 3/8 | 0.64 |
| Duration of Asthma [mean+SD (min-max)], years | 7.42±5.95 (1-20) | 4.09±2.95 (1-12) | 0.09 |
| BMI [mean+SD (min-max)], kg/m² | 28.15±6.06 (18.24-41.86) | 23.45±3.03 (18.76+28.12) | 0.02 |
| Allergic rhinitis [present] | 11 | 0 | 0.001 |
| ESS [mean+SD (min-max)] | 3.53±3.22 (0-13) | 2.27±1.85 (0-7) | 0.24 |
| Severity of bronchial asthma [mild/moderate-severe] | 9/10 | 11/0 | 0.004 |
| FEV₁ (% predicated) [mean+SD (min-max)] | 53.42±18.80 (20.0-82.0) | 68.02±18.21 (44.0-104.2) | 0.04 |

OSA, obstructive sleep apnea; SD, standard deviation; BMI, body mass index; FEV₁, forced expiratory volume in the first second; ESS, Epworth sleepiness scale.

Table 3 presents the results of multivariate regression analysis examining factors predictive of the occurrence of OSA in asthmatics. The analysis reveals that the severity of bronchial asthma, coexistent AR, and BMI are significant independent predictors for the development of OSA in asthmatics, and each remains significant even when accounting for the others (p=0.001, p=0.006, and p=0.048, respectively).

## Discussion

In our study, we identified that the severity of asthma, the presence of AR, and a high BMI appeared to be independent predictors of OSA in patients with bronchial asthma, as indicated in Table 3.

In our study, we identified OSA in 63% of patients with bronchial asthma. Subjects with OSA exhibited a higher number of hypopneas than apneas, as shown in Table 2. Among them, 43% had mild OSA, 10% had moderate OSA, and 10% had severe OSA, while 10% exhibited NOD. These findings align with numerous studies conducted worldwide on the relationship between OSA and bronchial asthma. For instance, a study by Zidan *et al.* in Egypt, which investigated the overlap of OSA and bronchial asthma, reported OSA in 60% of subjects with asthma and 17% in the control group [11]. Similarly, an Indian study by Dixit *et al.*, involving 50 patients with bronchial asthma, found that 46% of the subjects had OSA [12].

In our study, we observed a higher prevalence of OSA in subjects with moderate to severe asthma compared to those with mild asthma, and this difference was significantly associated with the risk of OSA (p=0.004). Furthermore, this association was identified as an independent predictor for the development of OSA in asthmatics (p=0.001).

Similar findings were reported by Julien *et al.*, who studied subjects with moderate *vs.* severe asthma. They found that an AHI>5 (Wisconsin cohort study criteria) was present in 50% of subjects with severe asthma, 23% in subjects with moderate asthma, and 12% in control subjects [13]. Additionally, Zidan *et al.* noted that the percentage of OSA in asthma patients was 5.6% in well-controlled asthma patients, 61% in partially controlled, and 33.3% in uncontrolled asthma patients [11].

AR not only contributes to poor asthma control but also serves as an associated risk factor for OSA. A substantial population-based study conducted by Braido *et al.* between March and December 2011, involving 1941 subjects (58% males, mean age 48.2±15.2 years), found that rhinitis was associated with a 1.44 times higher odds ratio for having a risk of OSA syndrome [14]. In another study by Selsabil *et al.*, AR was identified in 47% of subjects with OSA compared to 27% in non-OSA subjects (p=0.17) [15]. Similar findings were reported in a cross-sectional study of asthma patients, revealing a significant independent association between diagnosed rhinitis and the risk of OSA, suggesting that rhinitis may be a risk factor for OSA in patients with asthma [16].

In our study, we observed that 58% (11/19) of subjects with OSA had comorbid AR, while none of the subjects in the group without OSA had AR. Consequently, coexistent AR emerged as a significant independent predictor for the development of OSA in asthmatics (p=0.009). This association may be attributed to nasal inflammation in AR, causing mucosal hyperemia, edema, nasal stenosis, and obstruction. These factors result in increased nasal resistance, leading to higher negative oropharyngeal pressure during inspiration and airway collapse [17].

In our study, a higher BMI was identified as a significant independent predictor for the development of OSA in asthmatics (p=0.048). Subjects with a BMI>25 kg/m$^2$ were classified as obese according to the Indian criteria for obesity [10]. Similar findings were reported in an Indian study by Dixit *et al.* [12]. Epidemiologic and observational studies have consistently demonstrated that obesity is a significant risk factor for incident asthma

**Table 2.** Polysomnography parameters of subjects with and without obstructive sleep apnea.

| Characteristics | Asthma with OSA (n=19) | Asthma without OSA (n=11) | p |
|---|---|---|---|
| Sleep latency - Mins | 9.8±8.3 | 22.6±28.0 | 0.07 |
| REM sleep % | 8.89±6.15 | 9.59±5.26 | 0.75 |
| Stage N1 % | 20.26±7.78 | 16.23±8.19 | 0.19 |
| Stage N2 % | 52.75±15.29 | 50.99±12.93 | 0.75 |
| Stage N3 % | 21.57±15.39 | 29.33±17.25 | 0.21 |
| Lowest saturation | 78.15±16.60 | 93.18±2.36 | 0.006 |
| Snores/hours of sleep | 197.93±213.11 | 39.02±47.41 | 0.02 |
| NOD % | 26.80±64.45 | 0.33±1.09 | 0.18 |
| Hyponea | 77.97±83.12 | 10.36±10.39 | 0.013 |
| Apena | 10.47±23.24 | 3.18±5.17 | 0.317 |
| RERA | 0.0±0.0 | 0.0±0.0 | N/A |
| AHI | 15.27±15.75 | 2.36±1.81 | 0.01 |

OSA, obstructive sleep apnea; SD, standard deviation; REM, rapid eye movement; NOD, nocturnal oxygen desaturation; RERA, respiratory effort related arousal; AHI, apnea hypopnea index.

**Table 3.** Multivariate regression analysis of factors predictive of the occurrence of OSA in asthmatics.

| Parameters | Regression coefficients±SD | p |
|---|---|---|
| Severity of bronchial asthma | 0.465±0.131 | 0.001 |
| Allergic rhinitis | 0.401±0.135 | 0.006 |
| BMI | 0.024±0.012 | 0.04 |

SD, standard deviation; BMI, body mass index.

and is associated with asthma severity [18]. Conversely, obesity is a predominant risk factor for OSA [19] and is often considered a surrogate marker for OSA in adult populations.

Obesity contributes to the development of OSA through various mechanisms, including the reduction of pharyngeal lumen size due to fatty tissue within the airway or in its lateral walls. Additionally, obesity leads to a decrease in the protective force of upper airway dilator muscles due to fatty deposits in the muscle, and a reduction in upper airway size secondary to the mass effect of a large abdomen on the chest wall and tracheal traction. These factors collectively increase the risk of developing OSA [19]. Excessive weight gain in asthma patients may be attributed to a limited ability to exercise, sleep deprivation leading to increased insulin resistance, or the use of oral steroids.

In our study, the total mean duration of asthma symptoms was found to be higher in the group with OSA compared to the group without OSA (7.42±5.95 *vs.* 4.09±2.95), although the difference did not reach statistical significance (p=0.09). Similar findings were observed in a study conducted in Turkey by Firat *et al.* [20]. They analyzed OSA in 47 difficult-to-treat asthma patients from an adult allergy clinic of a tertiary care hospital and noted that the duration of asthma symptoms was a risk factor for the development of OSA.

A bidirectional relationship exists between OSA and bronchial asthma, wherein each condition can adversely affect the other. The potential mechanism underlying their association involves both airway and systemic inflammation. Local inflammation plays a crucial role in the progression of increased airflow resistance, airway wall thickness, airway hyper-responsiveness, and the development of comorbidities such as asthma and chronic obstructive pulmonary disease.

Systemic inflammation in OSA, driven by factors like metabolic syndrome and oxidative stress induced by obesity, as well as repetitive episodes of intermittent hypoxia, may influence the onset and severity of asthma. Conversely, the compromised pulmonary function resulting from asthma can exacerbate the hypoxia associated with OSA. The presence of severe asthma can lead to poor sleep quality, lowering arousal thresholds, and causing frequent nocturnal arousals, ultimately increasing upper airway collapsibility.

Other contributing factors to the bidirectional relationship between OSA and asthma include gastroesophageal reflux disease, neuro-mechanical effects of recurrent upper airway collapse, changes in leptin levels, nasal obstruction, and weight gain due to asthma-controlling medications, particularly corticosteroids. The interplay of these factors highlights the complex and multifaceted nature of the relationship between OSA and bronchial asthma.

Small sample size and short duration of the study were some of the limitations in our study.

## Conclusions

This study emphasizes the importance of systematically assessing bronchial asthma patients, particularly those with severe disease, for OSA. The high detection rate of OSA in this population highlights the need for detailed sleep history and PSG evaluation to identify and manage sleep-related breathing disorders early. Community awareness campaigns are crucial to disseminate information about the bidirectional relationship between asthma and OSA. Larger community-based studies are recommended to validate and establish the prevalence and patterns of sleep-disordered breathing among Indian asthma patients.

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