



## Original Article

## Impact of obstructive sleep apnea on severe asthma exacerbations

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## ABSTRACT

**Background:** Patients with asthma have a higher incidence of obstructive sleep apnea (OSA). However, the association between OSA and the exacerbation of severe asthma remains unclear. In this study, we aimed to investigate the prevalence of OSA in a cross-sectional study of asthma patients and to prospectively examine the significance of the effect of OSA on severe asthma exacerbations.

**Methods:** One hundred and forty-six patients with asthma and 157 matched-controlled individuals were enrolled in this study. The patients with asthma were prospectively studied for one year, and exacerbation episodes were identified based on the patients' medical histories. Lung function and the percentages of eosinophils in induced sputum samples were determined, and the frequencies of severe asthma exacerbations during the previous year were evaluated in the group of patients with asthma.

**Results:** The rates of OSA were 19.2% (28/146) among the patients with asthma and 9.6% (15/157) among the control individuals ( $p = 0.016$ ). The frequency of severe asthma exacerbations was significantly higher among the asthma patients with OSA compared with those who did not have OSA ( $p < 0.001$ ). The apnea–hypopnea index (AHI) correlated significantly with the number of severe asthma exacerbations ( $r = 0.507$ , 95% confidence interval [CI] 0.357–0.637,  $p < 0.001$ ). Logistic regression analyses determined that the AHI was significantly associated with the occurrence of severe asthma exacerbations (odds ratio 1.322, 95% CI 1.148–1.523,  $p < 0.001$ ).

**Conclusions:** Patients with asthma had a high prevalence of OSA, which was an important factor associated with severe asthma exacerbations.

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## 1. Introduction

Asthma is a common chronic disease of the respiratory system that involves complex interactions among airflow obstruction, airway hyper-responsiveness, and inflammation. It is estimated that about 300 million people of all ages suffer from asthma [1] and, in 2011, more than half of these asthma patients experienced asthma attacks [2]. Severe asthma exacerbations increase the usage of health care resources and families' social and economic burdens. These attacks are associated with reductions in assessed quality of life and are potentially life-threatening [3,4]. Reducing the risk of exacerbations is a crucial/highly necessary treatment goal within asthma management guidelines. Therefore, identifying the risk factors for

exacerbations could lead to appropriate early interventions and greatly benefit patients. While the findings from previous studies have identified that previous asthma exacerbations, the use of bronchodilator therapy, reduced pulmonary function, chronic sinusitis, gastroesophageal reflux disease, and the need for larger amounts of controller therapy are among the risk factors for asthma exacerbations [5–10], comorbid conditions have received far less attention.

Findings from studies suggest a bidirectional relationship between obstructive sleep apnea (OSA) and asthma. The findings from epidemiological studies have demonstrated that patients with asthma have a higher prevalence of OSA [11,12]. A population-based cohort study discovered that the overall incidence of OSA was 2.51 times greater in the cohort of patients with asthma than in the comparison cohort [11]. The findings from a population-based prospective epidemiological study demonstrated that asthma was associated with both new-onset OSA and OSA with habitual sleepiness [12]. Likewise, patients with OSA have been reported to display many of the symptoms associated with asthma. Alharbi et al. reported that patients with OSA had a high prevalence of asthma (35.1%) [13]. The findings from a 14-year prospective study also suggested a pathogenic role for asthma in sleep-disordered breathing [14]. Accumulating evidence suggests that OSA contributes to poor asthma

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control [10,15–17], while continuous positive airway pressure treatment can improve the quality of asthma patients' lives [17].

However, it remains unclear whether OSA affects severe exacerbations in patients with asthma. Understanding the impact of OSA on severe asthma exacerbations is a necessary element in the efforts to reduce the burden of both OSA and asthma. Therefore, we performed a prospective cross-sectional study to investigate the prevalence of OSA among patients with asthma as well as the associations between OSA indices and severe asthma exacerbations.

## 2. Methods

### 2.1. Ethical approval and informed consent

The study's protocols and the patient consent documents were approved by the ethics committee at Xiangyang Hospital, Hubei University of Medicine and Renmin Hospital, Wuhan University. All of the participants were able and willing to provide informed consent and to complete our study.

### 2.2. Subjects

Subjects aged 18–65 years who had asthma, which was defined as a minimum 12% increase in the post-bronchodilator forced expiratory volume in 1 s (FEV1) and >200 mL of the FEV1, or a positive methacholine challenge test reaction, were recruited from in-patients who had been discharged from the hospital and returned for routine follow-up visits. The study also included subjects who were out-patients with physician-diagnosed asthma, were being treated with inhaled glucocorticoids (400 mg of fluticasone or its equivalent), and had not changed their controller therapy for at least eight weeks before they were enrolled to participate in the study at Xiangyang Hospital and Renmin Hospital. Healthy matched-controlled subjects were recruited from health centers based on their ages, body mass indices (BMIs), and sex. Subjects were excluded if they had comorbidities that included respiratory disorders other than asthma, active gastro-esophageal reflux disease, or histories of malignant diseases within five years of the study commencing, if they had an FEV1 that was <50% of the predicted value, had initiated and withdrawn asthma medications during the follow-up period, had used systemic corticosteroids daily, or had used long-term oxygen therapy.

We collected data about the patients' medical histories, and about their physical examinations, asthma control assessments, and spirometry tests that were undertaken at each clinic visit between January 2012 and December 2015. In total, 146 patients with asthma and 157 control individuals met the study's entry criteria and completed this study.

### 2.3. Definition of a severe asthma exacerbation

A severe asthma exacerbation was defined as asthma symptoms that required an urgent health care visit, a visit to a physician's office, systemic corticosteroids, or an increase from the stable maintenance dose for at least three days or hospitalization [18]. The numbers of severe asthma exacerbations that occurred between January 2012 and December 2015 were recorded, and we determined the severe acute exacerbation frequencies within the preceding year.

### 2.4. Obstructive sleep apnea evaluation

All of the subjects underwent full-night PSG at the sleep laboratories at Xiangyang Hospital using a digital system (Compumedics E-series EEG/PSG Recording System, Abbotsford, Victoria, Australia).

As recommended by the American Academy of Sleep Medicine (AASM), the following factors were assessed simultaneously and continuously: airflow via a thermocouple and nasal pressure, electroencephalograms, electro-oculograms, electrocardiograms, electromyograms of the chin and leg muscles, thoracic and abdominal respiratory efforts using inductance plethysmography, snoring, body positions, oxyhemoglobin saturation (SpO<sub>2</sub>), and the pulse rates. The findings were scored using the criteria outlined in the 2007 AASM Manual for Scoring Sleep and Associated Events, version 1 [19]. Hypopnea was defined as an event with a  $\geq 30\%$  decline in the baseline amplitude of the nasal pressure for  $\geq 10$  s accompanied by a  $\geq 4\%$  decrease in the SpO<sub>2</sub> based on the pre-event baseline value. Data describing the apnea–hypopnea index (AHI), the mean oxygen saturation level, and the percentage of the time that the oxygen saturation was <90% (T<sub>Sat90</sub>) were recorded.

### 2.5. Sputum induction and processing

In accordance with the European Respiratory Society's recommendations [20], the subjects with asthma were pre-treated with salbutamol (200 mg) that was inhaled using a metered-dose inhaler, then, 10 min later, saline (3%) was nebulized for 20 min for sputum induction. Each sample collected was processed immediately as described next. The contaminating saliva was separated from the sample, then, 0.1% dithiothreitol was added to the sputum at a ratio of 1:4. The mixture was then placed in a shaking water bath at 37 °C for 20 min, and it was homogenized. The sample was further diluted with an equal volume of phosphate buffered saline. After filtering the suspension through gauze to remove any mucus and centrifugation, the differential cell count was determined and at least 400 non-squamous cells were counted that had been stained using the May Grunwald Giemsa method. Only samples with cell viabilities of >50% and squamous cell contamination of <20% were considered adequate. The slides were read by two independent investigators.

### 2.6. Statistical analysis

All of the statistical analyses were performed using IBM® SPSS® version 19.0 (IBM Corporation, Armonk, NY, USA.). The data are presented as the means  $\pm$  standard deviations or as the medians (interquartile ranges [IQRs]), based on whether the variables were normally distributed or non-normally distributed. Descriptive statistics were used to characterize the subjects within the asthma groups and control groups. The differences between groups were analyzed using Student's *t* test for the parametric variables and the Mann–Whitney test for the non-parametric variables. Spearman's rank correlation test was used when appropriate. Logistic regression analysis was used to determine whether individual factors were associated with asthma exacerbations. The relationship between the groups was evaluated using the  $\chi^2$  test. A value of *p* < 0.05 was considered statistically significant.

## 3. Results

One hundred and forty-six patients with asthma and 157 control individuals completed this study. Table 1 shows the subjects' baseline characteristics. There were no significant differences between the groups in relation to age, sex, the FEV<sub>1</sub>, the forced vital capacity (FVC), the AHI, the BMI, the mean oxygen saturation level, the minimum oxygen saturation level, and the T<sub>Sat90</sub>.

Forty-three patients were diagnosed with OSA using PSG, comprising 28 patients with asthma and 15 control individuals (Table 2). OSA was significantly more prevalent among the patients with asthma than among the control subjects, and the relative risk was 2.25 (95% confidence interval [CI] 1.15–4.40, *p* = 0.016) (Table 2).

**Table 1**

Baseline characteristics of the study subjects.

| Characteristic                                 | Asthma group (n = 146) | Control group (n = 157) | p value |
|------------------------------------------------|------------------------|-------------------------|---------|
| Age (years)                                    | 46.7 ± 7.3             | 46.6 ± 6.5              | 0.91    |
| Sex, n (male:female)                           | 102:44:00              | 121:36:00               | 0.155   |
| Smoking status, n (current:former:never)       | 42:58:46               | 49:60:48                | 0.898   |
| Number of packs of cigarettes smoked per year  | 14.3 ± 13.6            | 13.2 ± 15.9             | 0.321   |
| FEV <sub>1</sub> (L)                           | 2.49 ± 0.74            | 2.60 ± 0.68             | 0.142   |
| FVC (L)                                        | 2.69 ± 0.89            | 2.86 ± 0.80             | 0.092   |
| Medication                                     |                        |                         |         |
| Statins, n                                     | 17                     | 20                      | 0.771   |
| Inhaled long-acting beta-agonists, n           | 107                    | 0                       |         |
| Inhaled corticosteroids, n                     | 96                     | 0                       |         |
| BMI (kg/m <sup>2</sup> )                       | 24.1 ± 4.3             | 24.0 ± 3.4              | 0.842   |
| Apnea–hypopnea index                           | 2.85 (1.46–4.56)       | 3.30 (1.94–4.28)        | 0.187   |
| Minimum O <sub>2</sub> saturation, %           | 84.8 (79.8–88.4)       | 84.6 (77.8–87.5)        | 0.32    |
| Mean O <sub>2</sub> saturation during sleep, % | 95.6 (94.6–96.6)       | 95.9 (95.2–96.6)        | 0.108   |
| T <sub>Sat90</sub>                             | 0.26 (0.02–1.31)       | 0.19 (0.03–1.12)        | 0.968   |
| Epworth Sleepiness Scale                       | 5.0 (2.0–9.0)          | 5.0 (3.0–8.5)           | 0.588   |

The data are presented as the numbers of subjects, means ± standard deviations, or the medians and interquartile ranges. FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; BMI, body mass index; T<sub>Sat90</sub>, percent night time with oxygen saturation <90%.

Although there were no significant differences between the asthma patients who did and did not have OSA with respect to age, sex, the FEV<sub>1</sub>, and the FVC, the Epworth Sleepiness Scale (ESS) score, the BMI, and the T<sub>Sat90</sub> were significantly higher, and the mean and minimum oxygen saturation levels were significantly lower among the asthma patients who had OSA compared with the asthma patients who did not have OSA. There was a significantly higher prevalence of severe asthma exacerbations among the patients with OSA compared with the subjects who did not have OSA, and the relative risk was 14.23 (95% CI 4.60–44.04,  $p < 0.001$ ) (Table 3). The overall number of severe asthma exacerbations was 0 (IQR 0–1.0) in all of the subjects, and those patients who had asthma and OSA experienced significantly more episodes than those asthma patients who did not have OSA (1.0 [IQR 1.0–2.0] vs. 0 [IQR 0–1.0],  $p < 0.001$ ). The incidence of severe asthma exacerbations increased as the AHI and the T<sub>Sat90</sub> increased, and it declined as the mean SpO<sub>2</sub> and the minimum SpO<sub>2</sub> increased. The AHI was significantly correlated with the number of exacerbations ( $r = 0.507$ , 95% CI 0.357–0.637,  $p < 0.001$ ) (Fig. 1).

To examine whether the known confounding factors impacted upon the prevalence of severe asthma exacerbations, we compared the asthma patients with and without OSA with respect to their demographic and clinical characteristics (Table 4). There were no significant differences between the groups in relation to age, gender, smoking status, lung function, chronic sinusitis, and their medical histories. The percentages of eosinophils in the induced

sputum samples were similar in the asthma patients who had and did not have OSA. There were significant differences between the groups with respect to the BMI, min SaO<sub>2</sub>, mean SaO<sub>2</sub>, T<sub>Sat90</sub>, ESS, and the frequency of previous severe acute exacerbations. The logistic regression analysis determined that a history of severe exacerbations was a risk factor for severe asthma exacerbations.

To exclude the confounding factors, binary logistic regression analysis was performed and it identified that the AHI was significantly associated with the occurrence of severe asthma exacerbations (odds ratio 1.322, 95% CI 1.148–1.523,  $p < 0.001$ ).

#### 4. Discussion

The findings from this prospective cross-sectional cohort study showed that the prevalence of OSA was significantly higher among patients with asthma compared with the control subjects. OSA is associated with an increased severity of acute asthma exacerbations among asthma patients, and the patients who had asthma and OSA showed a 14-fold increase in the risk of severe asthma exacerbations compared with the patients who had asthma but did not have OSA. These are novel findings that highlight the necessity of OSA assessments for patients with asthma who present with OSA indicators, such as snoring, obesity, and daytime sleepiness. This study confirms and extends the findings from previous studies [9,10] because it proves that OSA is an independent risk factor for asthma exacerbations.

The established risk factors for asthma exacerbations include exposure to cigarette smoke, chronic sinusitis, and an increase in the

**Table 2**

Presence of obstructive sleep apnea among the study subjects.

| Group   | Obstructive sleep apnea |             | p value |
|---------|-------------------------|-------------|---------|
|         | Positive, n             | Negative, n |         |
| Asthma  | 28                      | 118         | 0.016   |
| Control | 15                      | 142         |         |

**Table 3**

Associations between asthma exacerbations and symptoms in patients with obstructive sleep apnea.

| Obstructive sleep apnea | Severe asthma exacerbations |          | Exacerbation frequency over one year, n |
|-------------------------|-----------------------------|----------|-----------------------------------------|
|                         | Did not occur               | Occurred |                                         |
| Negative                | 83                          | 35       | 37                                      |
| Positive                | 4                           | 24       | 39                                      |
| P value                 | <0.001                      |          | <0.001                                  |

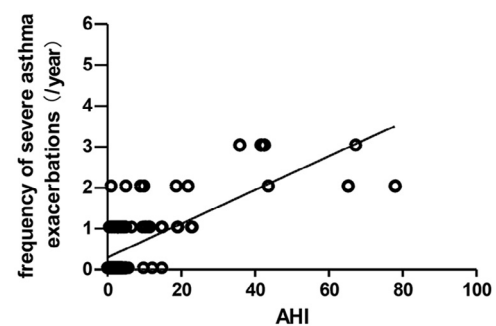


**Fig. 1.** The relationship between the apnea–hypopnea index (AHI) and severe exacerbation frequency ( $r = 0.507$ , 95% confidence interval 0.357–0.637,  $p < 0.001$ ). AHI, apnea–hypopnea index.

**Table 4**  
Baseline characteristics of the patients with asthma.

| Characteristic                                  | Patients with asthma and OSA<br>(n = 28) | Patients with asthma and<br>without OSA (n = 118) | p value |
|-------------------------------------------------|------------------------------------------|---------------------------------------------------|---------|
| Age (years)                                     | 46.6 ± 5.2                               | 46.8 ± 7.7                                        | 0.919   |
| Sex, n (male:female)                            | 24:4                                     | 78:40                                             | 0.071   |
| Smoking status, n (current:former:never)        | 6:11:11                                  | 36:47:35                                          | 0.518   |
| Number of packets of cigarettes smoked per year | 12.5 ± 12.3                              | 13.6 ± 14.3                                       | 0.442   |
| FEV <sub>1</sub> (L)                            | 2.73 ± 0.66                              | 2.43 ± 0.75                                       | 0.054   |
| FVC (L)                                         | 2.94 ± 0.64                              | 2.63 ± 0.93                                       | 0.097   |
| Medication                                      |                                          |                                                   |         |
| Statins, n                                      | 6                                        | 11                                                | 0.073   |
| Inhaled long-acting beta-agonists, n            | 18                                       | 89                                                | 0.231   |
| Inhaled corticosteroids, n                      | 15                                       | 81                                                | 0.131   |
| Chronic sinusitis                               | 11                                       | 29                                                | 0.117   |
| BMI (kg/m <sup>2</sup> )                        | 28.3 ± 4.3                               | 23.1 ± 4.6                                        | <0.001  |
| AHI                                             | 14.8 (10.2–32.6)                         | 2.40 (1.20–3.35)                                  | <0.001  |
| Minimum O <sub>2</sub> saturation, %            | 76.5 (72.3–80.0)                         | 86.5 (82.8–89.0)                                  | <0.001  |
| Mean O <sub>2</sub> saturation during sleep, %  | 94.1 (92.6–94.9)                         | 96.0 (95.2–96.7)                                  | <0.001  |
| T <sub>Sat90</sub>                              | 5.05 (1.92–10.37)                        | 0.11 (0.01–0.44)                                  | <0.001  |
| Epworth Sleepiness Scale                        | 7.5 (1.3–13.0)                           | 5.0 (2.0–8.0)                                     | 0.030   |
| Sputum eosinophils (%)                          | 11.5 ± 2.9                               | 10.4 ± 3.1                                        | 0.088   |
| Previous acute exacerbations                    | 0.0 (0.0–1.0)                            | 0.0 (0.0–1.0)                                     | 0.001   |

The data are presented as the numbers of subjects, means ± standard deviations, or the medians and interquartile ranges. OSA, obstructive sleep apnea; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; AHI, apnea–hypopnea index; T<sub>Sat90</sub>, percent night time with oxygen saturation <90%.

levels of eosinophils in the sputum [2]. To investigate the associations between these factors and the exacerbation frequency, we compared patients with asthma and OSA with those who had asthma but did not have OSA, and there were no significant differences between the groups. These findings suggest that the OSA indices might have impacted severe asthma exacerbations within our study population.

The occurrence of OSA in our study population was similar to the results reported in a previous study [12]. The prevalence of OSA was significantly higher among the patients who had asthma compared with the control individuals. We also found that OSA was associated with an increase in acute asthma exacerbations and that the AHI was positively correlated with asthma exacerbations. The AHI index could be affected by symptoms that are associated with asthma comorbidities.

The underlying mechanisms that may explain the association between asthma and OSA are briefly described next. The findings from a few clinical studies that have involved exhaled nitric oxide [21], and induced sputum [22] assessments, have demonstrated that airway inflammation exists in patients with OSA. Airway inflammation can affect the thickness of the airway wall, airflow resistance, and the underlying airway hyper-responsiveness, which enhances susceptibility to acute asthma exacerbations. Repetitive episodes of intermittent hypoxia and re-oxygenation in OSA induce the oxidative stress cascade downstream and inflammation increases, leading to systemic inflammation that involves the airway and asthma aggravations. Many researchers have reported increases in the expression of inflammatory biomarkers in the circulation, including that of tumor necrosis factor- $\alpha$  [22], interleukin-6 [23], and C-reactive protein [23,24], which provides evidence for a systemic inflammatory reaction in patients with OSA. All of these cytokines may contribute to bronchial inflammation [25] and increase the risk of acute asthma exacerbations. The findings from recent studies indicate that patients with OSA have elevated concentrations of vascular endothelial growth factor [26], which may contribute to bronchial inflammation and airway hyper-responsiveness [27]. Furthermore, obesity appears to be a major risk factor for asthma [28], and OSA is mainly found among obese patients; obese male patients who had OSA exhibited higher levels of leptin than obese men who did not have OSA [29]. Elevated leptin concentrations are associated with airway hyper-responsiveness [30], which may be relevant to asthma exacerbations in OSA. Patients with OSA show

increases in their vagal tone during sleep, which could stimulate the muscarinic receptors located in the central airways and may lead to nocturnal asthma [31], thereby providing a role for the neural receptors.

Poor sleep quality has been reported in asthma patients [32] which may be attributed to their underlying respiratory disease, which may be under-reported. Moreover, many practitioners may attribute these sleep problems to poorly controlled asthma, and they may escalate treatment rather than assessing the patients for OSA. This may explain the increase in severe asthma exacerbations in our cohort.

Our study had some limitations, such as the difficulties that occur when determining whether OSA itself directly affects asthma exacerbations or whether it merely co-exists in patients who experience frequent exacerbations. The 14-fold increase in acute exacerbations among the asthma patients with OSA may have led to the observed rise in OSA among the patients with asthma. It remains unclear whether OSA alters pulmonary function, which is a risk factor for acute exacerbations. Further studies are needed to determine whether the observed increase in acute exacerbations arose as a consequence of differing incidences of OSA in asthma patients or whether OSA reduces lung function in asthma patients.

In conclusion, this study further substantiates the previously-reported association between OSA and asthma. We found that asthma patients with OSA were more likely to experience severe exacerbations than those without OSA. The AHI was significantly associated with the occurrence of severe asthma exacerbations. Our study highlights the importance of the need to be aware of the association between asthma and OSA, as well as the need to assess OSA in asthma patients who snore. Inattention to OSA evaluations in these patients may lead to diagnostic and treatment delays and to increases in the frequency of severe acute exacerbations. Thus, we hope that the findings from our study encourage practitioners to consider screening for OSA and its clinical outcomes.

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## Conflict of interest

This was not an industry-supported study, and there are no conflicts of interest to declare.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2016.06.013>.

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