Obstructive Sleep Apnea: a risk for uncontrolled and more severe asthma in adults that we should keep an eye on

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ABSTRACT

Background. Asthma control can be influenced by several factors, including obstructive sleep apnea (OSA). The literature reports variable prevalence and magnitude of OSA impact on asthma outcomes. The aim of our study is to analyze the frequency of high-risk for OSA in asthma patients and its impact on disease severity and control.

Methods. We conducted a cross-sectional study at an Allergy Department with adult asthma patients recruited while undergoing routine lung function tests. Data on sex, age, body mass index, allergen sensitization, smoking habits, risk of OSA (using the Berlin questionnaire), rhinitis control (through CARAT), asthma severity (based on GINA 2023),

asthma control (using the ACT), adherence to asthma treatment (through Treatment Adherence Measure) and pulmonary function test results were collected.

Results. We included 216 patients, predominantly women (70.4%), with a median (P25-P75) age of 29.0 (21.0-45.0) years, of whom 28.2% were on GINA treatment levels 4-5. In 75.5% of cases asthma was controlled. High-risk for OSA was identified in 21.8% of patients. Asthma patients with high-risk for OSA were more likely to have uncontrolled [(47.8%; n=22) vs (15.8%; n=26); p<0.001] and more severe disease [(44.7%; n=21) vs (23.7%; n=40), p=0.006]. In multivariable analysis, high-risk for OSA (OR: 2.81 [95%CI: 1.1.28-6.17], p=0.010), sex (women) (OR: 5.21 [95% CI: 1.70-15.96], p=0.004), uncontrolled rhinitis (OR: 3.65 [95%CI: 1.38-9.64], p=0.009) and GINA asthma treatment steps 4-5 (OR: 2.46 [95% CI: 1.15-5.26], p=0.020) were associated with uncontrolled asthma.

Conclusions. It is crucial to actively investigate OSA, especially in patients with uncontrolled and more severe forms of asthma.

Key words

Asthma; comorbidity; obesity; respiratory function tests; sleep apnoea syndromes

IMPACT STATEMENT:

Obstructive sleep apnoea is an underrecognized comorbidity that can have a detrimental influence on asthma outcomes. Our study showed an association between obstructive sleep apnoea and uncontrolled and more severe asthma; therefore, it is imperative to proactively assess this comorbidity in these patients.

INTRODUCTION

Asthma is a heterogeneous disease usually characterized by chronic inflammation of the airways. It is defined by respiratory symptoms that vary in time and intensity, associated with variable expiratory airflow limitation (1).

Many factors can contribute to poor control of the disease, including comorbidities. All comorbidities must be assessed when treating patients with asthma, including obstructive sleep apnea (OSA) (1).

OSA is a breathing disorder characterized by narrowing of the upper airway that interferes with normal ventilation during sleep (2). The prevalence of OSA varies considerably depending on the population studied (2). It is higher in disease-specific populations, including patients with coronary artery disease, congestive heart failure, cardiac arrhythmias, refractory hypertension, type 2 diabetes, polycystic ovary disease or asthma (2–4). In general, the prevalence of OSA in asthma patients appears to be about two to three times higher than in patients without asthma (3). A recent systematic review found an estimated prevalence of OSA in asthma patients of 8%–52.6%, which is even higher (50-95%) in patients with severe asthma (5). Despite the higher prevalence in patients with asthma, especially those with severe asthma, different prevalence estimates are reported in the literature (3,4).

OSA is an underestimated comorbidity that can have a negative impact on asthma outcomes. In most published studies, the presence of OSA is associated with poorer asthma control, more exacerbations and more emergency department visits, hospital admissions and ICU admissions (6–8). On the other hand, some studies showed no

significant association between asthma severity or control and the presence of OSA (4,9).

In this study, we aimed to analyze the frequency of high-risk for OSA in patients with asthma and assess its impact on disease severity and control.

MATERIALS AND METHODS

Study design, setting and participants

This cross-sectional study was conducted in the Allergy and Clinical Immunology Department of a tertiary hospital in Lisbon, Portugal.

All adult patients scheduled for an examination in our center's lung function test laboratory due to their asthma between January 2022 and December 2022 were invited to participate. Participation eligibility conditions were to be ≥18 years-old, to have a medical diagnosis of asthma, to present an asthma A2 score≥2, and be able to perform a spirometry. Exclusion criteria were the inability to understand the consent form or the questionnaires.

This study was approved by the Ethics Committee of the *Centro Hospitalar Universitário de Lisboa Central*. All participants provided written informed consent to participate in this study.

Data Collection

Data were collected using a self-administered standardized questionnaire that included questions on sociodemographic data, medical history, OSA risk (Berlin Questionnaire), rhinitis control (Control of Allergic Rhinitis and Asthma Test, upper airway subscore -

CARAT-UA), asthma control (Asthma Control Test - ACT) and treatment adherence (MAT - Treatment Adherence Measure). The lung function test results conducted on the questionnaire's day were recorded. Daily prescribed asthma medications and information about sensitization to airborne allergens were obtained from electronic medical records. Asthma severity was defined according to the Global Initiative for Asthma (GINA) 2023 classification (steps 1-5).

The A2 score comprises eight questions, being the score the sum of positive answers. It can be used to rule in/rule out asthma in epidemiological studies and clinical screenings. Asthma can be excluded for results of 0 to 1 (10).

The Berlin Questionnaire is an OSA screening questionnaire with ten questions organized in three categories: the first comprises five questions on snoring and cessation of breathing, the second includes four questions about daytime sleepiness and fatigue/tiredness, and the last comprises information about arterial hypertension and obesity. A score of at least two is warranted for categories one and two to be considered positive. The third category is positive if there is a history of high blood pressure or a body mass index>30 kg/m^2. Patients with a positive score in two or three categories are considered to have high-risk for OSA (11–13). The Berlin Questionnaire has a sensitivity, specificity, positive predictive value and negative predicted value of 72.1%, 50%, 87.7% and 26.7%, respectively, for an apnea-hypopnea index>5; of 82.6%, 44.8%, 58.4% and 73.3% for an apnea-hypopnea index>15; of 88.4%, 39.1%, 35.4% and 90% for an apnea-hypopnea index>30 (13).

The CARAT-UA encompasses the first four questions of CARAT answered on a 4-point Likert that address upper airway symptoms over a four-week period, with a total possible score ranging from 0 (minimum control) to 12 (maximum control) (14).

The ACT Questionnaire contains five questions about the frequency of asthma symptoms and required rescue medication use during the previous four weeks. The scores range from 5 (worse control) to 25 (total control), with a cut-off value for asthma control of 20 (15).

The MAT comprises seven questions that assess patient behavior patterns associated with the use of medicines. The answers are rated on a six-point scale, and the result is expressed as the sum of the score of all questions divided by seven, ranging from 1 (minimum adherence) to 6 (maximum adherence). The patient is considered to have good medication adherence if MAT≥5 (16).

Lung Function tests

Global Lung Function Initiative (GLI) reference equations for spirometry were used. The lower limit of normal (LLN) was defined as the 5^{th} percentile (corresponding to a z-score of −1.645).

Sample size

Considering n=1000 as the number of adult patients with asthma assessed in our lung function test laboratory each year, and assuming a 25% prevalence of OSA, for a confidence level of 95% and a 5% margin of error, we would need to include 224 participants.

Variables

The primary outcome variable of the regression analysis was the presence of non-controlled asthma (ACT<20). High-risk for OSA, obesity (body mass index≥30 kg/m^2), non-controlled rhinitis, to be on GINA treatment steps 4-5, current allergy sensitization to house dust mites, pollens, pets or mold evaluated by skin prick tests, low treatment adherence (according to MAT), former or current smoker, pre/post-bronchodilator FEV_1 and FEV_1/FVC<LLN were considered as potential risk factors for non-controlled asthma and sex and age were considered potential confounders.

An additional regression analysis was also conducted, considering asthma severity (GINA treatment steps 4-5) as the main outcome.

Statistical analysis

An exploratory analysis was carried out for all variables. Categorical data were presented as prevalence rates (with 95 % confidence intervals - 95% CI) and continuous variables as median (with 25^{th} - P25 and 75^{th} - P75 percentiles).

Logistic regression models were used to explore the association between non-controlled asthma (outcome) and the above-mentioned risk and confounding factors. Covariates with a p-value<0.25 were selected as candidates for the multivariable analysis, and a purposeful selection was used to choose the variables in the final model.

Crude regression coefficients and corresponding odds ratio (OR) with 95% CI were calculated first. Adjusted ORs were obtained as a result of fitting the multivariable logistic regression models to the data. The level of significance was α=0.05. Data analysis was performed using IBM SPSS Statistics version 26 (New York, USA).

RESULTS

Characterization of the population

We included 225 patients, but due to missing data, only 216 were included in the analysis. The majority were women (70.4%; n=152), with a median age of 29.0 (P25-P75: 21.0-45.0) years and a median BMI of 24.6 (P25-P75: 21.6-29.1) kg/m^2. Regarding asthma severity, 28.2% (n=61) of patients were taking medication corresponding to GINA steps 4-5. Rhinitis was controlled in 34.7% of patients (n=74) and asthma was controlled in 75.5% of patients (n=163). High-risk for OSA was considered in 21.8% of patients (n=47).

The baseline characteristics of our sample are described in Table I.

High-risk for OSA patients' characteristics

High-risk for OSA patients were mostly women [(83.0%; n=39) vs (66.9%; n=113), p=0.046], older [41.0 (26.0-49.0) vs 28.0 (21.0-42.5) years, p=0.001] and had a higher body mass index [31.8 (29.0-34.0) vs 24.0 (21.2-27.1), p<0.001] than patients without a high-risk for OSA, as expected, since obesity is part of the Berlin questionnaire. Obesity was present in 70.2% (n=33) of high-risk for OSA patients.

High-risk for OSA patients also presented more frequently uncontrolled rhinitis [(89.1%; n=41) vs (58.7%; n=98), p<0.001], uncontrolled asthma [(47.8%; n=22) vs (15.8%; n=26), p<0.001] and with asthma on GINA asthma treatment steps 4-5 [(44.7%; n=21) vs (23.7%; n=40), p=0.006]. Regarding lung function, high-risk for OSA was not associated with significant variations in pre-bronchodilator or post-bronchodilator FEV_1 and FEV_1/FVC.

High-risk for OSA: Association with uncontrolled asthma

Patients with uncontrolled asthma were more frequently classified as having high-risk for OSA compared to patients with controlled disease [(45.8%; n=22) vs (14.7%; n=24), p<0.001].

In the univariable analysis, women sex, obesity, sensitization to airborne allergens, uncontrolled rhinitis, GINA asthma treatment steps 4-5 and high-risk for OSA were associated with uncontrolled asthma (Table II).

In the multivariable analysis, after adjusting for other variables, high-risk for OSA persisted as a risk factor for uncontrolled asthma in the final model together with female sex, uncontrolled rhinitis, and GINA treatment steps 4-5 (Table II).

High-risk for OSA: Association with higher asthma severity

Patients on GINA asthma treatment steps 4-5 had a greater frequency of high-risk for OSA compared to patients with lower asthma severity [(34.4%; n=21) vs (16.8%; n=26), p=0.006].

In the univariable analysis, age, obesity, ACT<20, high-risk for OSA, pre-bronchodilator FEV_1<LLN, pre-bronchodilator FEV_1/FVC<LLN and post-bronchodilator FEV_1/FVC<LLN were associated with more severe asthma (Table III).

In the multivariable analysis, after adjusting for other variables, only high-risk for OSA, uncontrolled asthma and post-bronchodilator FEV_1/FVC<LLN remained significantly associated with more severe asthma in the final model (Table III).

DISCUSSION

Our study showed that asthma patients with high-risk for OSA were likelier to have uncontrolled asthma and more severe disease.

In a cross-sectional study conducted in Portugal in 2014, the prevalence of OSA in the general population aged 25 years or older was estimated to be 0.89% (17). Different prevalence estimates have been reported for the higher incidence of OSA in patients with asthma. A systematic review found a prevalence of OSA (from thirteen questionnaire-based studies) in asthma patients ranging from 8% to 52.6% (5). In a meta-analysis by Kong et al. the prevalence of OSA in asthma patients was reported to be 49.5% (3). In our study we observed an estimated frequency of OSA of almost 20%, which is higher than the prevalence observed in the general population and consistent with previous studies conducted in asthma patients (8).

In our analysis, patients with high-risk for OSA were mostly women, older and had a higher BMI. Our results are consistent with the published literature on the general population, as higher BMI and age are major risk factors for OSA (18,19). Although we should emphasise that 30% of high-risk for OSA patients were not obese, suggesting that this single characteristic should not be considered synonymous with OSA.

In the general population, OSA is generally more common in men (18,19). In asthma patients, however, the dominance of sex varies (9,20,21). High-risk for OSA has not been associated with significant variations in lung function, which is consistent with other studies, such as that of Oyama et al. in which no significant correlation was found between lung function and the presence or severity of OSA, although OSA patients had more severe asthma (22).

In recent years, there is increasing evidence of a relationship between OSA, and asthma based on shared pathophysiological factors and bidirectional interactions (23,24). Although asthma and OSA share some similar risk factors, such as rhinitis, obesity and gastroesophageal reflux, there are specific characteristics that may contribute to this relationship (24). OSA is associated with increased bronchial hyperreactivity and inflammation (23). Chronic intermittent hypoxia associated with OSA has been shown to shift the inflammatory profile in the airways from type 2 to type 1 T helper cells, contributing to lung remodeling and airway dysfunction (24,25). This altered profile may lead to a reduced response to inhaled corticosteroid therapy (24,25). On the other hand, airway, and systemic inflammation together with the use of systemic and inhaled corticosteroids in asthma patients may contribute to the remodeling of pharyngeal structures and redistribution of adipose tissue, favoring its collapse (23,26).

According to our findings, it is crucial to screen asthma patients for OSA, especially those with uncontrolled asthma and uncontrolled rhinitis who are women and comply with GINA treatment levels 4-5. These findings are consistent with those of a study by Al-Lawati et al. in which the incidence of high-risk for OSA, also assessed by the Berlin questionnaire, was 46% in patients with uncontrolled asthma (20). Rhinitis is a common comorbidity in asthma patients, affecting most of them (1). Furthermore, rhinitis symptoms, particularly nasal congestion, have been linked to an increased risk of sleep breathing disorders in asthma patients, with longer and more frequent apneas in some studies (27), while in others this association is not as clear (4). We did not find an association between the presence of rhinitis and the risk of OSA, although patients with

uncontrolled rhinitis were at higher risk of OSA. Studies addressing the relationship between rhinitis control and OSA are currently lacking.

In our work, high-risk for OSA was associated with higher odds of uncontrolled asthma. Previous studies on asthma and OSA showed similar results, although the magnitudes of the effects varied. Teodorescu et al. examined the relationship between OSA risk (assessed by questionnaire) and asthma control (measured by the Asthma Control Questionnaire) in adults and concluded that high OSA risk was associated with 2.87-fold higher odds of uncontrolled asthma, even after adjustment for factors known to worsen asthma control (28).

In our study, high-risk for OSA was also associated with more severe asthma, especially in patients with bronchial obstruction and uncontrolled asthma. This result is consistent with other published studies that show crescent prevalence estimates based on asthma severity (3,5). Julien et al. compared the prevalence of OSA (assessed by polysomnography) in patients with severe and moderate asthma and in non-asthmatic patients (4). They showed that OSA was related to asthma severity, occurring in 88% of patients with severe asthma and 58% of patients with moderate asthma, compared with 31% in patients without asthma (4). Guven et al. found a prevalence of 74.5% of OSA (assessed by polysomnography) in patients with difficult-to-treat/severe asthma (21). In our work, the estimated frequency of OSA (34.4%) in patients with severe asthma was lower than in these studies (4). This could be explained by the definition of OSA (Berlin questionnaire) we used, and by different population characteristics. In the study by Al-Lawati et al. the prevalence of OSA (assessed by polysomnography) in patients with severe asthma was 32.4%, which is more in line with our results (20).

The presence of OSA may be associated with worse outcomes in asthma patients, as a higher rate of severe asthma exacerbations, a higher risk of non-invasive positive pressure ventilation and longer length of hospital stay, a higher risk of readmission after hospitalization for an asthma exacerbation (8,29,30). Therefore, it is important to identify asthma patients with OSA, as its treatment has positive effects on asthma symptoms, asthma control and severity, as well as quality of life (31–36).

Our study has some limitations. First, it is a unicentric study and conducted in an Allergy and Clinical Immunology Department, so our results may not be generalizable to the general asthma patients. Second, it is a questionnaire-based study, so the identification of OSA patients may not have been entirely accurate, despite the Berlin Questionnaire being a validated OSA screening tool. Nevertheless, our findings highlight the need to actively look for the presence of OSA, a comorbidity that has a negative impact on asthma control, especially in those patients with uncontrolled and more severe asthma.

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AUTHORS' CONTRIBUTION

GMDS: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft

PSC: Conceptualization, Investigation, Methodology, Writing – original draft

JGM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing

SS: Investigation, Writing – original draft

SS: Investigation, Writing – original draft

AB: Investigation, Writing – original draft

PCM: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing

PLP: Methodology, Writing – review & editing

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Table I: Baseline characteristics of the participants (n=216)

CHARACTERISTICS	
Sex (women), % (95% CI)	70.4 (63.8-76.4)
Age - median (P25-P75), years	29.0 (21.0-45.0)
BMI - median (P25-P75), kg/m^2	24.6 (21.6-29.1)
Obesity, % (95% CI)	21.3 (16.0-27.4)
Past or current smoking habit, % (95% CI)	27.8 (21.9-34.3)
Rhinitis, % (95% CI)	97.2 (94.1-99.0)
Sensitisation to airborne allergen, % (95% CI)	89.4 (84.5-93.1)
House dust mites, % (95% CI)	84.7 (79.2-89.2)
Pollens, % (95% CI	58.8 (51.9-65.4)
Pets, % (95% CI)	51.4 (44.5-58.2)
Moulds, % (95% CI)	6.9 (3.9-11.2)
Controlled rhinitis (CARAT-UA >8), % (95% CI)	34.7 (27.5-40.5)
Asthma on GINA treatment steps 4-5, % (95% CI)	28.2 (22.3-34.8)
Controlled asthma (ACT ≥20), % (95% CI)	75.5 (69.2-81.1)
High-risk for OSA, % (95% CI)	21.8 (16.5-27.9)

Good asthma medication adherence (MAT ≥5), % (95% CI)	76.9 (70.7-82.3)
Pre-bronchodilator FEV_1 (z-score) <LLN, % (95% CI)	18.5 (13.6-24.4)
Pre-bronchodilator FEV_1/FVC (z-score) <LLN, % (95% CI)	18.1 (13.2-23.9)
Post-bronchodilator FEV_1/FVC (z-score) <LLN, % (95% CI)	6 (3.2-10.1)

ACT – asthma control test; BMI – body mass index; CARAT-UA – Control of Allergic Rhinitis and Asthma Test, upper airway subscore; CI – confidence interval; FEV_1 – forced expiratory volume in the first second; FVC – forced vital capacity; GINA – Global Initiative for Asthma; LLN – lower limit of normal; OSA – obstructive sleep apnoea

Table II: Associations with uncontrolled asthma (ACT<20)

Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value#
Sex				
Men	1			
Women	6.24 (2.14-18.23)	0.001	**5.21 (1.70-15.96)**	**0.004**
Age				
One-year increment	0.99 (0.96-1.01)	0.207	-	-
Obesity				
BMI <30 kg/m^2	1			
BMI ≥30 kg/m^2	2.76 (1.34-5.68)	0.006	-	-
GINA treatment steps				
Step ≤ 3	1			
Step 4-5	2.88 (1.47-5.66)	0.002	**2.46 (1.15-5.26)**	**0.020**
High-risk for OSA				
No	1			
Yes	4.90 (2.40-10.01)	<0.001	**2.81 (1.28-6.17)**	**0.010**
Former or current smoker				
No	1			

Yes	1.38 (0.69-2.77)	0.359	-	-
Rhinitis				
No	1			
Yes	0.188 (0.03-1.16)	0.071	-	-
Sensitisation to airborne allergens				
No	1			
Yes	0.38 (0.15-0.94)	0.037	-	-
Rhinitis control				
CARAT-UA ≤8	4.70 (1.89-11.70)	0.001	**3.65 (1.38-9.64)**	**0.009**
CARAT-UA >8	1			
Non-adherence to asthma medication				
MAT ≥5	1			
MAT <5	1.45 (0.64-3.32)	0.375	-	-
Pre-bronchodilator FEV_1 (z-score)				
≥LLN	1			
<LLN	1.50 (0.68-3.30)	0.316	-	-

Pre-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	1.33 (0.59-2.98)	0.495	-	-
Post-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	1.14 (0.30-4.39)	0.848	-	-

*: Adjusted for sex, age, obesity, GINA treatment step, OSA and sensitization to airborne allergens; #: Only variables with a p-value < 0.05 are reported; CARAT-UA - Control of Allergic Rhinitis and Asthma Test, upper airway subscore; FEV_1 – forced expiratory volume in the first second; FVC – forced vital capacity; GINA – Global Initiative for Asthma; LLN – lower limit of normal; MAT – Treatment Adherence Measure; OSA – obstructive sleep apnoea

Table III: Associations with higher asthma severity (asthma on GINA treatment steps 4-5)

Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value#
Sex				
Men	1		-	
Women	1.60 (0.81-3.17)	0.180	-	-
Age				
One-year increment	0.97 (0.95-0.99)	0.002	-	-
Obesity				
BMI <30 kg/m^2	1			
BMI ≥30 kg/m^2	2.15 (1.08-4.24)	0.028	-	-
Asthma control				
ACT ≥20	1			
ACT <20	2.88 (1.47-5.66)	0.002	**2.26 (1.09-4.72)**	**0.029**
High-risk for OSA				
No	1			
Yes	2.61 (1.33-5.12)	0.005	**2.51 (1.19-5.28)**	**0.015**
Former or current smoker				
No	1			

Yes	1.15 (0.60-2.22)	0.670	-	-
Rhinitis				
No	1			
Yes	0.248 (0.04-1.53)	0.133	-	-
Sensitisation to airborne allergens				
No	1			
Yes	0.57 (0.23-1.41)	0.224	-	-
Rhinitis control				
CARAT-UA ≤8	1.21 (0.64-2.29)	0.555	-	-
CARAT-UA >8	1			
Non-adherence to asthma medication				
MAT ≥5	1			
MAT <5	0.67 (0.28-1.57)	0.355	-	-
Pre-bronchodilator FEV_1 (z-score)				
≥LLN	1			
<LLN	3.76 (1.84-7.67)	<0.001	-	-
Pre-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			

<LLN	2.67 (1.30-5.47)	0.007	-	-
Post-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	6.53 (1.93-22.11)	0.003	**7.20 (2.01-25.79)**	**0.002**

*: Adjusted for sex, age, obesity, asthma control, GINA treatment step, OSA, sensitization to airborne allergens and pre- bronchodilator FEV_1 < LLN; #: Only variables with a p-value < 0.05 are reported; ACT - asthma control test; CARAT-UA – Control of Allergic Rhinitis and Asthma Test, upper airway subscore; FEV_1 - forced expiratory volume in the first second; FVC - forced vital capacity; GINA – Global Initiative for Asthma; LLN - lower limit of normal; MAT - Treatment Adherence Measure; OSA - obstructive sleep apnoea.