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ORIGINAL RESEARCH

Arousal Threshold Score: A New Indicator for Examining the Relationship Between Obstructive Sleep Apnea and Overlap Syndrome — A Retrospective Study

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Objective: A low arousal threshold (AT) appears to contribute to obstructive sleep apnea (OSA) pathogenesis. However, the role of low AT in OSA and overlap syndrome (OVS) is still unclear. This study is aimed to investigate the value of the AT score, a new method for qualifying AT, for examining the relationship between OSA and OVS, including chronic obstructive pulmonary disease (COPD) and asthma.

Methods: In this retrospective study, a total of 3400 adults diagnosed with OSA at a sleep medicine center were finally included. All patients were stratified into low-, high- and very high-AT score groups according to the previous logistic regression for qualifying AT. Multivariate logistic regression was conducted to evaluate the association between AT score and OVS prevalence. We compared this association with that of the apnea hypopnea index (AHI).

Results: 40.3%, 42.9% and 16.8% of OSA patients had low-, high- and very high AT score, respectively. Compared with the very high AT score, the low AT score was independently associated with the prevalence of COPD (OR = 2.17, 95% CI = 1.09–4.32) and asthma (OR = 4.54, 95% CI = 2.52–8.17). With decreasing AT score, the adjusted ORs of the comorbidities increased stepwise, particularly in some subgroups based on sex, age and BMI. Conversely, the classification of AHI did not show similar values.

Conclusion: In individuals with OSA, low AT is a common pathophysiological feature associated with COPD and asthma. The AT score is a new and effective indicator for evaluating the relationship between OSA and OVS.

Keywords: asthma, chronic obstructive pulmonary disease, obstructive sleep apnea, overlap syndrome, arousal threshold, sleep-disordered breathing

Introduction

Obstructive sleep apnea (OSA) is a chronic sleep-disordered breathing disease characterized by a complex pathogenesis and a systematic association with comorbidities.[1] Several specific chronic respiratory disorders, including chronic obstructive pulmonary disease (COPD) and asthma, have been found to coexist with OSA and exacerbate sleep-related breathing disturbances. Specifically, the description of this synergistic connection between OSA and these respiratory disorders is commonly denoted as overlap syndrome (OVS).[2] The estimated prevalence of OSA was 23.6% in middle-aged adults in China, while the burden of OVS remains under-recognized due to the lack of systematic screening and limited integration of respiratory diagnostics in sleep medicine center.[3] In patients with OSA, the overall prevalence of COPD and asthma are reported to be 2.9–65.9% and 5–35%, respectively.[4–6] Previous studies have

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demonstrated that OVS (OSA with COPD) was associated with a greater prevalence of hypertension, peripheral vascular disease, diabetes mellitus and obesity, increasing risk of arrhythmias like atrial fibrillation, and resulted in higher hospitalization rate and worse mortality, compared with COPD or OSA alone.[7] On the other hand, there is a bidirectional interaction between OSA and asthma with shared risk factors such as gastroesophageal reflux disease, rhinitis and obesity, which can be further exacerbated by the combined impact of OVS (asthma).[8] Undeniably, OVS has emerged as a significant public health concern, necessitating the development of more comprehensive indicators and therapeutic strategies for effective clinical management.

The etiology and pathophysiology of OSA are considered to be complex and multifactorial with high heterogeneity. In addition to anatomical factors, non-anatomic factors such as high loop gain, ineffective upper-airway dilator muscles and low respiratory arousal threshold (AT), also referred to as the endotype, significantly contribute to OSA.[9] A low AT can be a major pathogenic factor in patients with a nonobvious anatomical predisposition factor, which is present in 30–50% of all patients with OSA.[10] Most researchers believe that AT is defined as the average nadir epiglottic pressure immediately before cortical arousal from apneas or hypopneas.[11] Although arousals are beneficial for upper airway reopening, airflow restoration and reoxygenation, low AT may lead to premature arousal, which is closely linked to increasing respiratory instability, preventing more stable sleep, and subsequently worsening OSA in patients with better anatomy.[12] Several studies have shown a greater prevalence of low AT in patients with OVS, and researchers subsequently considered low AT to be an important factor in OSA pathogenesis in patients with OVS.[13–15] The concrete relationship between OSA and OVS is currently unclear, but a low AT may be a potential indicator for evaluating the condition of coexistence.

Recently, Edwards and his et al proposed a simple and efficient method to evaluate the AT based on polysomnography.[16] In this study, the authors initially quantified the AT as the nadir epiglottic pressure immediately preceding arousal and subsequently used multiple linear regression to establish a screening model for low AT based on demographic characteristics and polysomnography (PSG) parameters. Although the final three criteria for identifying low AT have become widespread, the clinical value of the AT score quantified by the regression model in their study has not been verified. The classification and severity of OSA are traditionally based on the apnea–hypopnea index (AHI), but the AHI exhibited limited capacity for providing a comprehensive assessment of the association between OSA and other comorbidities in many previous studies.[17,18] At present, few studies have investigated the relationship between the arousal threshold and comorbidities in patients with OSA and OVS. In this study, we hypothesized that a low AT is significantly associated with COPD (or asthma) in patients with OSA, and the AT score would serve as a superior indicator for assessing the connection between OSA and OVS in comparison to the AHI.

Materials and Methods

Study Population

In this retrospective study, all participants were recruited from the Sleep Medical Center of the First Affiliated Hospital of Guangzhou Medical University from Dec 2022 to Dec 2023, including adults referred for PSG evaluation due to suspected sleep disordered breathing by their attending physicians or self-requested check-up. The study used data from the same sleep center database, which contained data on 3,400 patients. Although the database has been used to publish a study on the relationship between OSA, hypertension and diabetes,[18] but different analytical methods and research hypotheses were used in this study to explore the unique relationship between OSA and OVS. This study complies with the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University with Ethical Approval No. 183, 2022, and all patients gave and signed their informed consent. The inclusion criteria were (1) age > 18 years; (2) complete independent behaviour and cognitive abilities; and (3) have electronic or paper records of past medical history for diagnosing other comorbidities. The study flowchart and exclusion criteria are displayed in Figure 1.

Data Extraction

Extracting baseline data of all patients from the medical electronic system and history records, including demographic characteristics such as age, gender and body mass index (BMI); The comorbidities cases in the study were identified by

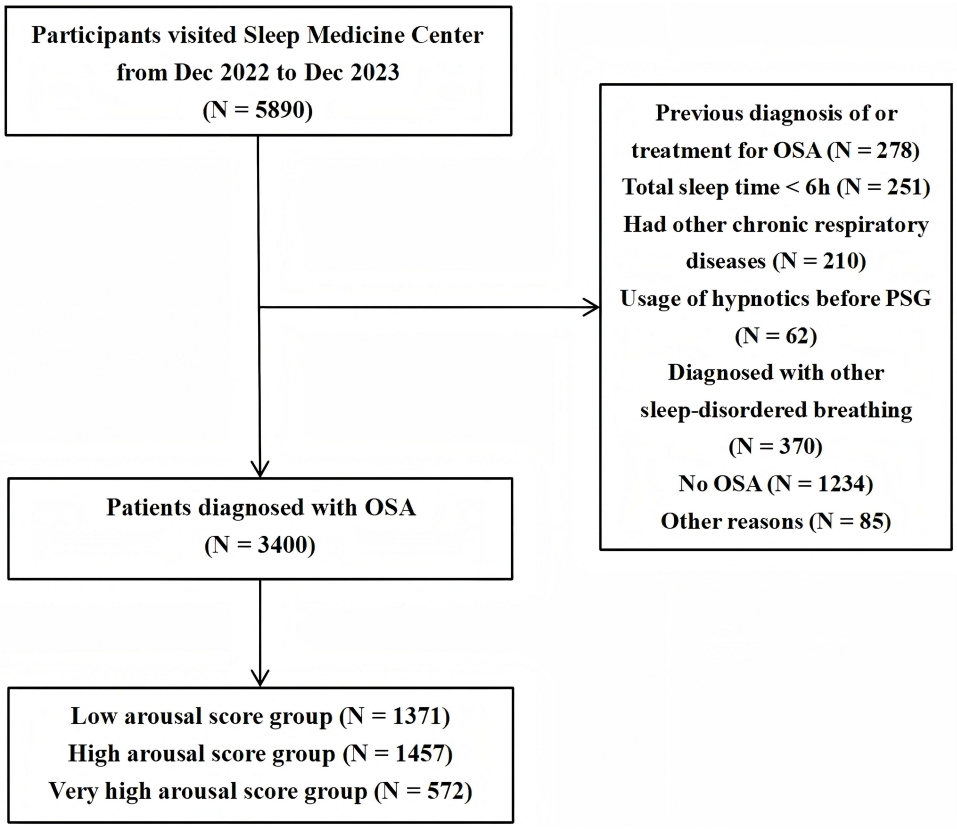

Figure 1 Study flowchart.

participant questionnaires whether they had ever been diagnosed with rhinitis, COPD and asthma by doctor. We collected the parameters from PSG such as AHI, minimum peripheral oxygen saturation (min. SpO_2) and fraction of the respiratory events that were hypopnea ($F_{hypopnea}$).

Arousal Threshold and Arousal Threshold Score (AT Score)

The patients with OSA were categorized into low AT group if they had a score of ≥ 2 on the following 3-point scale: (1) AHI < 30 events/h sleep, (2) LSaO2 > 82.5% and (3) $F_{hypopnea}$ > 58.3%.[12] Otherwise, they were classified into the high AT group.

The method for determining AT score was as follows (where male sex = 1 and female sex = 0):[12,19] AT score = 0 − [−65.39 + (0.06 * age) + (3.69 * sex) − (0.03 * BMI) − (0.11 * AHI) + (0.53 * LSaO2) + (0.09 * $F_{hypopnea}$ * 100%)]. In the study by Edwards et al, they defined a low AT as an overall AT less negative than −15 cm H_2O and a high AT as more negative than −15 cm H_2O in epiglottis pressure measurement. To better clarify and understand the relationship between the AT score and different variables, we convert the AT score to a positive number. To allow further stratification and facilitate dose–response analyses, we introduced a second cutoff at an AT score of 30. However, we acknowledge that this upper threshold (30) was chosen primarily to create equal intervals for exploratory purposes, without direct physiological validation, and thus should be interpreted cautiously. Accordingly, we classified the AT score into three degree: low AT score = AT score ≤ 15; high AT score = 15 < AT score ≤ 30; very high AT score = 30 ≤ AT score.

Polysomnography and OSA

All participants underwent overnight polysomnography monitoring with an Alice 5 PSG (Philips Wellcome, USA) for at least 7 hours, and were analyzed with Sleepware G3 sleep diagnostic software. The raw data were automatically read by the instrument. Two trained sleep professionals separately manually analyzed the parameters, such as sleep duration and sleep breathing events, based on the Manual for the Scoring of Sleep and Associated Events published by the AASM in

2017. Apnea was classified from a drop ≥ 90% of baseline airflow lasting at least 10 s, while hypopnea was classified from a ≥ 30% pre-event drop over ≥ 10 s associated with desaturation of oxygen ≥ 3% or an arousal.[20] Patients with an AHI score of ≥ 5 events/h were defined as having OSA. AHI ≥ 5 and < 15 events/h, AHI ≥ 15 and < 30 events/h and AHI ≥ 30 events/h were classified as low, moderate and high, respectively.

Statistical Analysis

We compared the demographic characteristics, PSG parameters and comorbidities among the low-, high- and very high AT score groups. The continuous data were presented as medians (interquartile ranges (IQRs): P25, P75). Nonparametric tests and the Mann–Whitney *U*-test were used to compare group differences and pairwise differences, respectively. Categorical variables are expressed as counts (%) and were compared between groups using the chi-square test for valuating the unadjusted odds ratio (OR). Multiple logistic regression models with enter method were used to examine the adjusted ORs for COPD and asthma in patients with low AT (reference for high AT), low AT score (reference for very high AT score) and low AHI (reference for high AHI). The ODI and T90% were selected as confounding factors for adjustment for indicators of hypoxia. The basic models (Model 1) were adjusted for age, BMI, male sex, smoking status, alcohol consumption, ODI and T90%. To exclude the confounding factors of other comorbidities, the final model (Model 2) for COPD and asthma was additionally adjusted for asthma and rhinitis, respectively. The statistical analysis was performed using SPSS 26.0 software. A two-sided *P* value < 0.05 was considered to indicate statistical significance.

Results

Demographic Characteristics

A total of 3400 patients diagnosed with OSA were eventually enrolled in this study. All patients were categorized into three groups: low AT score (n = 1371), high AT score (n = 1457), very high AT score (n = 572). Among all patients, 78.9% were male, and the average age was 47.0 (37.0, 58.0) years old. The average BMI was 26.9 (24.6, 29.4) kg/m². The patients with very high AT score were the youngest. BMI, neck circumference, and waist circumference increased with increasing AT score, exhibiting statistically significant differences. The *P* values of all the results are both < 0.001 (as shown in Table 1).

PSG Parameters

Among the 3400 patients, the AHI significantly differed among the three groups, which were 12.7 (8.1, 20.1), 34.7 (20.4, 50.6) and 69.6 (58.5, 78.7), respectively. In terms of sleep architecture, the patients in the low AT score group had the minimum median TST, lowest sleep efficiency and highest WASO. Additionally, although patients in the very high AT score group had more sleep time, they had less REM sleep and were more difficult in reaching slow wave sleep, compared to other two groups. The final median AT score of each group were 10.9 (8.6, 13.0), 20.5 (17.3, 24.5) and 36.0 (32.8, 40.3), respectively. The data are shown in Table 1.

Comparison of Various Characteristics Among the Groups with COPD, Asthma and COPD & Asthma

Among 3400 patients with OSA, 130 (3.8%), 191 (5.6%) and 113 (3.3%) had comorbid COPD, asthma and COPD and asthma, respectively. Compared with those in the COPD group, the prevalence of chronic cough and rhinitis in the COPD and asthma group were greater; however, comparisons of the other results revealed no statistically significant differences. In terms of baseline characteristics, the asthma group had a significantly greater proportion of females and younger patients, with a significant difference observed among the three groups. In comparison of PSG parameters, the patients in COPD & asthma group had the most hypopnea events (78%) and the lowest median AT score [(10.7 (7.2, 17.3)], accompanied by the lowest median AHI [16.4 (10.4, 28.3) events/h] and almost no N3 sleep time. The other results are shown in Supplementary Table S1.

Table 1 The Characteristics of Included Patients Classified by Arousal Threshold Score

	Low AT Score (n=1371)	High AT Score (n=1457)	Very high AT Score (n=572)	*P* value
Demographic and clinical characteristics				
Age, years	50.0 (38.0, 60.0)	48.0 (37.0, 58.0)	40.0 (34.0, 50.0)	<0.001
BMI, kg/m^2	26.0 (23.8, 28.3)	26.9 (24.8, 29.4)	29.3 (27.0, 31.6)	<0.001
NC, cm	38.0 (36.0, 40.0)	39.0 (37.0, 41.0)	41.0 (38.5, 43.0)	<0.001
WC, cm	93.0 (87.0, 100.0)	96.0 (90.0, 103.0)	100.0 (94.0, 107.0)	<0.001
Male, n (%)	1052 (76.7)	1119 (76.8)	510 (89.2)	<0.001
Smoking, n (%)	407 (29.7)	480 (32.9)	263 (46.0)	<0.001
Alcohol consumption, n (%)	362 (26.4)	400 (27.5)	191 (33.4)	0.006
PSG parameters				
AHI, events/h	12.7 (8.1, 20.1)	34.7 (20.4, 50.6)	69.6 (58.5, 78.7)	<0.001
ODI, events/h	16.1 (9.5, 28.9)	39.2 (23.3, 56.8)	64.1 (39.1, 76.5)	<0.001
T90%, min	1.3 (0.2, 5.3)	13.3 (3.9, 37.9)	74.7 (41.5, 186.5)	<0.001
MAI, events/h	13.0 (8.4, 19.6)	22.0 (13.6, 34.6)	45.9 (30.7, 61.0)	<0.001
Min. SpO_2, %	86.0 (83.0, 88.0)	76.0 (70.0, 80.0)	56.0 (50.0, 61.5)	<0.001
TST, min	409.2 (355.3, 452.0)	424.0 (379.0, 463.0)	443.0 (395.4, 484.0)	<0.001
WASO, min	41.0 (17.0, 84.0)	34.0 (13.5, 71.5)	31.3 (11.6, 65.9)	<0.001
Sleep efficiency, %	86.6 (77.4, 93.0)	87.7 (79.4, 93.6)	91.6 (84.5, 96.3)	<0.001
N1, %	16.8 (10.3, 27.8)	19.6 (10.6, 35.7)	19.8 (10.5, 35.7)	<0.001
N2, %	56.3 (44.4, 65.9)	55.0 (40.8, 66.6)	58.1 (43.9, 70.7)	0.002
N3, %	7.6 (0.8, 14.6)	6.4 (0.0, 13.4)	0.35 (0, 7.9)	<0.001
REM, %	15.0 (10.1, 19.6)	13.9 (8.6, 18.8)	13.6 (9.8, 18.0)	<0.001
$F_{hypopnea}$, %	75.0 (53.4, 88.9)	35.5 (18.4, 58.1)	13.3 (3.5, 31.7)	<0.001
AT Score	10.9 (8.6, 13.0)	20.5 (17.3, 24.5)	36.0 (32.8, 40.3)	<0.001
Comorbidities				
Rhinitis	474 (34.6)	447 (30.7)	163 (28.5)	0.014
COPD, n (%)	146 (10.6)	81 (5.6)	15 (2.6)	<0.001
Asthma, n (%)	184 (13.4)	100 (6.9)	21 (3.7)	<0.001

Note: Values were expressed as median (interquartile range in brackets) or count (percentage).

Abbreviations: AT, arousal threshold; BMI, body mass index; NC, neck circumstance; WC, waist circumstance; PSG, polysomnography; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; T90%, cumulative percentages of time spent at arterial oxygen saturation below 90%; Min. SpO_2, minimum peripheral oxygen saturation; WASO, wake after sleep onset; MAI, microarousal index; TST, total sleep time; N1%, N2%, N3%, REM, the percentage of stage 1, 2, 3 and rapid eye movement sleep in total sleep time; $F_{hypopnea}$, fraction of the respiratory events that were hypopnea; COPD, chronic obstructive pulmonary disease.

The Relationship Between Low AT and the Prevalence of COPD and Asthma in Patients with OSA

Compared with the high AT group, the low AT group was significantly associated with COPD and asthma ($P < 0.001$). After adjustment with Model 1, the results were found to be stable, with similar ORs. When Model 2 was performed, the OR of low AT for COPD was significantly decreased to 1.45 (95% CI = 1.03–2.07, $P = 0.034$). After additionally adjusting for rhinitis, a low AT was still closely related to asthma (OR = 1.89, 95% CI = 1.36–2.62, $P < 0.001$). The results are shown in Table 2.

Table 2 Odds Ratio of Low AT for COPD and Asthma, Compared with High AT

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI) Model 1	*P* value	Adjusted OR (95% CI) Model 2	*P* value
COPD	2.20 (1.68–2.88)	<0.001	1.94 (1.40–2.68)	<0.001	1.45 (1.03–2.07)§	0.034
Asthma	2.37 (1.86–3.03)	<0.001	2.03 (1.53–2.70)	<0.001	1.98 (1.48–2.46)$^{\Psi}$	<0.001

Abbreviations: AT, arousal threshold; COPD, chronic obstructive pulmonary disease; CI, confidence interval; Model 1, Adjusted for age; BMI, male%, smoking, alcohol consumption; ODI and T90%; Model 2§: Model 1 + asthma; Model 2$^{\Psi}$: Model 1 + rhinitis.

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We conducted several exploratory subgroup analyses to determine whether sex, age and BMI had effects on the association between low AT and comorbidities (as shown in Supplementary Tables S2–S4). In Model 2, low AT was associated with COPD, only in the male subgroup, age < 60 years and BMI < 27 kg/m^2 (according to median values), and the ORs were 1.42 (95% CI = 1.08–2.05, P = 0.015), 1.55 (95% CI = 1.10–2.46, P = 0.012) and 1.47 (95% CI = 1.02–2.33, P = 0.046), respectively. According to the subgroup analyses of sex and BMI in Model 2, low AT was associated with asthma, with similar ORs in each subgroup. However, compared with age < 60 years (OR = 1.50, 95% CI = 1.06–2.11, P = 0.021), low AT was much more closely associated with asthma in patients with age ≥ 60 years (OR = 4.02, 95% CI = 2.20–7.37, P < 0.001) in Model 2.

The Relationship Among AT Score, AHI and the Prevalence of COPD, and Asthma in Patients with OSA

In the Model 1, when a very high AT score served as reference, low- and high AT score were significantly related to COPD and asthma, and these associations were strengthened with decreasing AT (both P < 0.01, Figures 2 and 3, Tables 3 and 4). Nevertheless, compared with those in the high AHI group, although the odds of three comorbidities were greater in patients

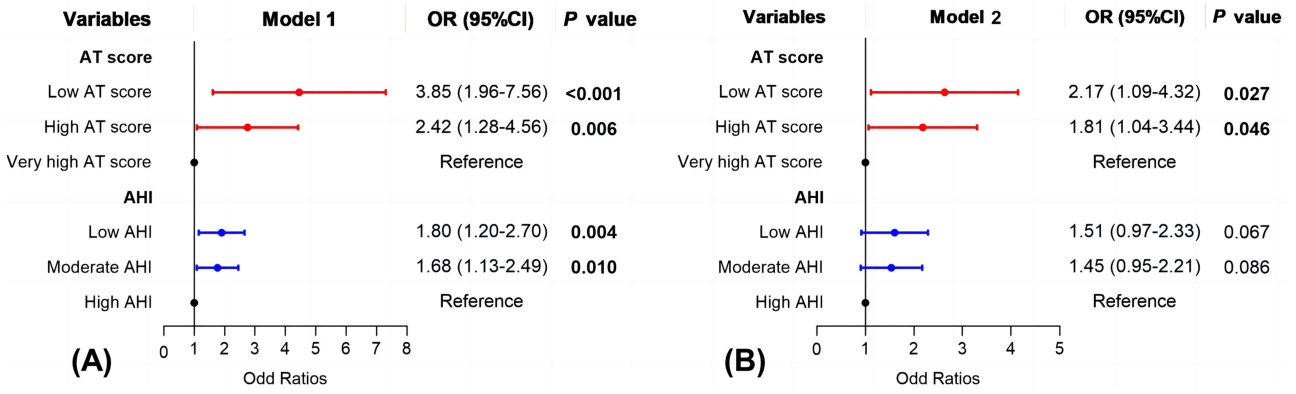

Figure 2 Odds ratio and 95% confidence interval of different levels of AT score and AHI for COPD. Notes: Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for COPD across AT score categories and AHI severity levels. Panels (**A** and **B**) show results from Model 1 (adjusted for age, sex and BMI) and Model 2 (further adjusted for cardiovascular comorbidities, smoking status and Epworth Sleepiness Scale score), respectively. The "very high AT score" group served as the reference category. Red markers represent comparisons across AT score groups; blue markers represent comparisons across AHI levels. Bold font indicate statistical significance, and P < 0.05 was considered statistically significant.
Abbreviations: AT, arousal threshold; AHI, apnea hypopnea index; COPD, chronic obstructive pulmonary disease.

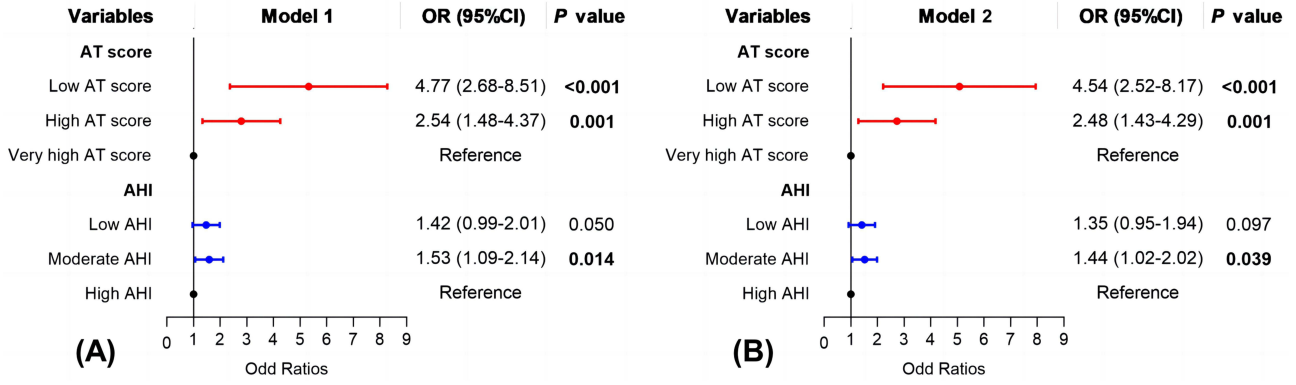

Figure 3 Odds ratio and 95% confidence interval of different levels of AT score and AHI for asthma. Notes: Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for asthma across AT score categories and AHI severity levels. Panels (**A** and **B**) represent Model 1 (adjusted for age, sex and BMI) and Model 2 (further adjusted for cardiovascular comorbidities, smoking status and Epworth Sleepiness Scale score), respectively. The "very high AT score" group was used as the reference category. Red markers indicate comparisons across AT score groups; blue markers indicate comparisons across AHI levels. Bold font indicate statistical significance, and P < 0.05 was considered statistically significant.
Abbreviations: AT, arousal threshold; AHI, apnea hypopnea index.

Table 3 Odds Ratio of Different Levels of AT Score and AHI for COPD and Asthma

	AT Score			AHI		
	Low	**High**	**Very high**	**Low**	**Moderate**	**High**
Model 1						
COPD	**3.85**** (1.96–7.56)	**2.42**** (1.28–4.56)	Ref	**1.80**** (1.20–2.70)	**1.68*** (1.13–2.49)	Ref
Asthma	**4.77**** (2.68–8.51)	**2.54**** (1.48–4.37)	Ref	1.42 (0.99–2.01)	**1.53*** (1.09–2.14)	Ref
Model 2						
COPD[§]	**2.17* (1.09–4.32)**	**1.81* (1.04–3.44)**	Ref	1.51 (0.97–2.33)	1.45 (0.95–2.21)	Ref
Asthma[Ψ]	**4.54** (2.52–8.17)**	**2.48** (1.43–4.29)**	Ref	1.35 (0.95–1.94)	**1.44* (1.02–2.02)**	Ref

Note: Very high AT score and high AHI were considered as the reference. Bold font indicate statistical significance, *indicated *P* value < 0.05, and **indicated *P* value < 0.01.

Abbreviations: AT, arousal threshold; AHI, apnea hypopnea index; COPD, chronic obstructive pulmonary disease; Ref, reference; CI, confidence interval; Model 1, Adjusted for age; BMI, male%, smoking, alcohol consumption, ODI and T90%; Model 2[§]: Model 1 + asthma; Model 2[Ψ]: Model 1 + rhinitis.

Table 4 The Relationship Between the AT Score and the Prevalence of COPD and Asthma

	Adjusted OR (95% CI) Model 1	***P* value**	**Adjusted OR (95% CI) Model 2**	***P* value**
COPD	1.056 (1.033–1.080)	0.008	1.032 (1.009–1.057)[§]	0.007
Asthma	1.066 (1.046–1.087)	0.001	1.066 (1.046–1.087)[Ψ]	<0.001

Note: *Indicated *P* value < 0.05, and **indicated *P* value < 0.01.

Abbreviations: AT, arousal threshold; COPD, chronic obstructive pulmonary disease; Model 1, Adjusted for age; BMI, male%, smoking, alcohol consumption, ODI and T90%; Model 2[§]: Model 1 + asthma; Model 2[Ψ]: Model 1 + rhinitis.

with low- and moderate AHI, the ORs were similar and of lesser magnitude in two groups (Figures 2, 3 and Table 3). The subgroup analyses of sex, age and BMI for the various AT score groups are displayed in Supplementary Tables S5–S7.

After adding related comorbidities to Model 2 for adjustment, a decrease in the AT score was still strongly associated with a greater risk of asthma, especially in the low AT score group (Tables 3, 4 and Figure 3). Similarly, compared with those of patients with very high AT, the ORs for low and high AT scores for asthma were 4.54 (95% CI = 2.52–8.17, $P < 0.001$) and 2.48 (95% CI = 1.43–4.29, $P < 0.001$), respectively. Moreover, the subgroup analyses suggested that patients with low AT score had a significantly greater frequency of asthma in the female group (OR = 12.24) and age < 60 years (OR = 16.99) (as shown in Supplementary Tables S5 and S6). On the other hand, low AT score had a weaken association with COPD (OR = 2.17, 95% CI = 1.09–4.32, $P = 0.027$) after adjustment. The probability of comorbid COPD was increased with decreasing AT score, similar to that of asthma (Tables 3 and 4, Figures 2 and 3). In subgroup analyses for the low AT score, COPD was more frequently observed in subgroups of BMI < 27 kg/m^2 (OR = 2.86), age < 60 years (OR = 2.78) and male (OR = 2.30), in patients with a low AT score (Supplementary Tables S5–S7). Among the OVS, patients with COPD and asthma had a lowest AT score compared with either isolated COPD or asthma (Supplementary Table S1). Finally, when we stratified the samples according to the AHI, there were no significant differences among the low, moderate and high AHI groups (Table 3, Figures 2 and 3).

Discussion

To the best of our knowledge, this is the first study to examine the relationship between OSA and OVS with a quantified arousal threshold. Our study revealed that a low arousal threshold was closely associated with a greater frequency of COPD and asthma in patients with OSA, independent of hypoxia. Moreover, this association was significantly weakened for the AHI, suggesting that the AHI is unlikely to predict the coexistence of other respiratory comorbidities in patients with OSA. This study provides novel evidence that a low arousal threshold is an important pathophysiological mechanism in OVS and a potential indicator of OVS.

Low AT is considered a nonanatomical trait that contributes to the pathogenesis of OSA and is associated with minor respiratory events. Previous studies have demonstrated that the prevalence of respiratory events and the tendency to develop OSA are considerably reduced in deeper sleep, while frequent arousals influence the progression of sleep to deeper stages.[21] Frequent arousals, particularly in low AT phenotypes, may impair sleep architecture and contribute to cognitive dysfunction. This highlights the need to further explore neurocognitive consequences in OVS patients.[22] Repeated arousals may result in: 1) inadequate time for respiratory stimuli to recruit the pharyngeal muscles and reopen the airway before arousal (decreased dilator muscle responsiveness) and 2) induction of a strong ventilatory response, thereby fostering dynamic ventilatory instability (increased loop gain).[16] These effects can interact with each other, and eventually lead to recurrent respiratory events. In patients with OSA, a low AT can be a pathogenic factor or result, depending on individual differences, similar to arousal frequency (presented as arousal index or microarousal index). Our study indicates that the MAI in patients with low AT is lower, which is consistent with the results of study by Feng and his et al.[23] This indicates that the arousal frequency may not always correlate positively with the AT level. Patients with higher AT often experience more severe and prolonged obstructive events accompanied by greater respiratory effort and hypoxia, potentially resulting in increased respiratory-related arousals. Regardless, we should place significant emphasis on the presence of low AT, as AT is closely associated with various comorbidities, such as COPD, asthma, insomnia, and even an increased risk of mortality.[7,24–26] On the contrary, high AT represents more stable respiratory control state with reduced cortical arousability, and greater tolerance to ventilatory disturbances. While high AT may theoretically delay hypoxia-triggered arousals in isolated severe OSA, respiratory stability may have a protective effect on the pathophysiological mechanism of OVS. Therefore, we considered very high AT as the logical reference for evaluating pathological low AT, aligned with established literature (eg, Edwards et al 2014) that treats high AT as the comparator for abnormal AT.[15]

The AT score is a simple indicator that is composed of PSG parameters and demographic characteristics. In our study with a large clinical sample, the percentage of patients with a quantified low AT score (40.3%) was similar to that of patients with low AT (45.7%, based on the three criteria); both of these findings are consistent with the prevalence of 30–50% reported in previous studies.[10] Compared with those in the high- and very high-AT score groups, patients in the low-AT score group were older, less obese and had less total sleep time, more WASO and less sleep efficiency. Another study showed that after adjusted for demographic characteristics by propensity score matching, patients with low and high AT had similar slow-wave sleep durations (9.8% vs 9.3%, P = 0.285).[27] The findings from studies on hypnotics indicated that eszopiclone and zolpidem effectively raised the respiratory arousal threshold, improved AHI, and prolonged slow-wave sleep time, with increasing sleep efficiency in patients with OSA and low AT.[28,29] Based on the theory that disrupted sleep architecture is an important feature of low AT, we separately discuss the relationships between low AT, COPD and asthma as follows:

Low AT and COPD

Many existing evidence suggest that low AT is attributed to COPD in patients with OSA.[7] The possible mechanisms are as follows: 1) hypercapnia episodes activate chemoreceptors stimulating autonomic reflex responses; 2) lung hyperinflation leads to stimulation of chest wall and lower airways mechanoreceptors; and 3) increased nocturnal symptoms and decreased sleep quality.[26–28] Nevertheless, the dose–response relationship between COPD severity and AT values remain unclear. Some studies have shown that hypoxia increases AT, and patients with OVS and high residual volume have greater AT than do those with normal residual volume.[29] Conversely, others have indicated that a low AT might be a consequence of worsened COPD severity, with lower respiratory effort tolerance, greater hyperinflation and a tendency to increase blood CO_2 levels.[13] The loop gain is greater in patients with COPD, and the destabilization of respiratory drive can further worsen the AT.[13] Despite COPD severity, our study revealed that a lower AT was independently associated with increased odds of COPD in patients with OSA, but only in males and in those of younger age (age < 60 years) and less obese (BMI < 27 kg/m^2), most of which are common characteristics of COPD. The AT score is a better indicator of the coexistence of OVS than the AHI. For each score increase in AT, the risk of comorbid COPD increased by 3.2% ($P = 0.007$). Upper airway obstruction can result in carbon dioxide retention, hypercapnia and increased hypoxic burden, thereby exacerbating COPD in OVS. We propose a hypothesis that whether low AT and repeated arousals, with

subsequent excessive ventilation and oxygen recovery, are a protective mechanisms for OVS to counteract the adverse consequences of OSA. Further studies on this issue could help to elucidate the pathophysiological mechanism of OVS.

Low AT and Asthma

The coexistence of asthma and OSA is a common OVS associated with multiple shared risk factors such as obesity, rhinitis and GERD.[30] A bidirectional relationship between the two disorders and a mutual impact on disease severity have been found in many studies.[30] OSA is related to more severe or difficult-to-control asthma with impaired lung function, while asthma contributes to the development of OSA, due to increased airway and systemic inflammation and more frequent use of inhaled glucocorticoids.[23,31] Moreover, the nocturnal asthmatic symptoms can aggravate sleep fragmentation, increasing daytime sleepiness, especially in those with OSA and uncontrolled asthma.[23,30] Antonaglia et al first indicated that patients with OVS were more than twice as likely to have low AT than those with OSA alone, but the sample size was small.[15] Similarly, our study suggested a greater frequency of asthma in patients with OSA and low AT after adjusting for numerous confounding factors. When we stratified the patients based on AT score, the odds of asthma exhibited a stepwise increase with increasing AT score, which was significantly different from that of the AHI. The relationship between low AT and asthma was significantly stronger than that between low AT and chronic cough or COPD. Surprisingly, asthma was more frequently observed in females (OR = 12.24) and elderly patients (age ≥ 60 years, OR = 16.99) with dramatically increasing ORs in the low AT score group. Although male sex is associated with higher predicted AT score, females with low AT score exhibited elevated asthma risk. This may reflect sex-specific airway physiology, hormonal factors, or immune responses not captured by the AT scoring model. Otherwise, the logistic regression showed that advanced age was a smaller influencing factor (OR = 1.62, $P < 0.001$) compared with low AT score, while sex did not affect the association ($P = 0.486$). Taken together, these findings suggest that there is an interaction effect between low AT and female sex (or advanced age) in patients with OSA and asthma, which requires additional investigation. In addition, bronchial hyperresponsiveness was found to be another factor involved in the potential interaction.[14] Both OSA and asthma are highly heterogeneous diseases, and an increase in the arousal threshold and improvement in sleep quality may be the effective methods to benefit patients with the subtype of OVS.

Recent studies have also identified hematologic biomarkers that may aid in the early identification of OVS, providing complementary value to physiological traits such as the arousal threshold AT. Archontogeorgis et al reported that mean platelet volume and platelet distribution width were significantly elevated in OVS patients compared to those with isolated OSA and healthy controls, suggesting a potential role of platelet activation in the pathophysiology of OVS.[30] Similarly, Akyol Gurses et al demonstrated that red cell distribution width >13.65% independently predicted the presence of OVS among patients with severe OSA, with an AUC of 0.71, sensitivity of 78.3%, and specificity of 60%.[31] In a cohort of exacerbated COPD patients, Ali et al found that an elevated monocyte-to-eosinophil ratio was a strong predictor of OVS and future exacerbation risk (AUC = 0.83).[32] Yang et al further reported that the neutrophil-to-lymphocyte ratio (NLR) was significantly higher in overlap syndrome than in COPD or OSA alone, with a proposed cutoff value of 2.49 for clinical discrimination.[33] These inflammatory and hematologic indices reflect systemic immune activation and hypoxic burden, which are common features of OVS. While the AT score represents a non-anatomical physiological trait related to ventilatory control and sleep stability, integrating it with readily accessible hematologic markers may enhance the accuracy and feasibility of early OVS screening. Future studies should explore whether a multi-marker approach that combines AT score with systemic inflammatory indices can improve diagnostic precision in both clinical and population-level settings.

In patients with OSA, the coexistence of the two diseases can lead to a poorer quality of life, thus early identification of comorbidities and understanding of the special pathophysiological features for individualized treatment are beneficial for determining patient prognosis. This study provides new evidence that low AT is a common characteristic between OSA and COPD or asthma. We also propose that the AT score is a valuable indicator for evaluating the relationship between OSA and OVS compared with the AHI. At present, patients with OSA are inadequately screened for underlying COPD and asthma.[6] If PSG indicates a low AT with concurrent COPD or asthma-related symptoms, physicians should be alert for the presence of a double or even triple overlap syndrome.

This study has several limitations. First, due to its retrospective observational design, causality between AT and OVS cannot be established. Second, while the AT score cutoff of 15 was based on physiological evidence corresponding to −15 cmH_2O epiglottic pressure, the secondary cutoff of 30 was introduced for exploratory stratification and lacks formal physiological

validation. Third, diagnoses of COPD and asthma relied on patient-reported physician diagnoses without objective confirmation (eg, spirometry, GOLD staging, asthma control assessments), potentially introducing misclassification bias. Additionally, key clinical variables such as pulmonary function tests, medication usage, $PaCO_2$ levels, sedative/hypnotic treatments and treatment adherence data were unavailable, preventing control for these possible confounders. Fourth, although the AT score exhibited a physiologically skewed distribution with fewer patients in the very high AT group, this reflects genuine trait distribution rather than sampling bias. Further, multiple subgroup analyses were conducted without adjustments for multiple comparisons, increasing the risk of false-positive findings; thus, these subgroup results must be interpreted cautiously. Finally, although body position was recorded during polysomnography, positional data were not extracted or analyzed, limiting the evaluation of positional OSA effects, which can significantly influence respiratory events and associated arousals.[34] Future prospective studies should validate the clinical utility of the AT score, confirm its physiological thresholds, and comprehensively assess associated respiratory and clinical variables.

Conclusions

Among patients with OSA, low AT is a common pathophysiological feature associated with COPD and asthma. The AT score, measured by PSG and demographic characteristics, is a potentially simple indicator for evaluating the relationship between OSA and OVS. Prospective multicenter cohort study are needed to verify the clinical application of the AT score for quantifying the arousal threshold and the association between low AT and the respiratory disorders.

Abbreviations

AHI, apnea hypopnea index; AT, arousal threshold; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; OVS, overlap syndrome; PSG, polysomnography.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval and Informed Consent

This study complies with the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University with Ethical Approval No. 183, 2022, and all patients gave and signed their informed consent.

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Author Contributions

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All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest.

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