Allergol Immunopathol (Madr). 2026;54(1):96–104 eISSN:1578-1267, pISSN:0301-0546

SEICAAP

Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
www.all-imm.com

CODON PUBLICATIONS

ORIGINAL ARTICLE

Predictors of obstructive sleep apnea syndrome in bronchial asthma patients: investigating the obesity-inflammation interplay through LEP, IL-6, and NLR

Lili Miao

Department of Respiratory and Critical Care Medicine, General Hospital of Ningxia Medical University, Yinchuan, China

Received 15 July 2025; Accepted 19 October 2025
Available online 1 January 2026

KEYWORDS
bronchial asthma;
interleukin-6;
leptin;
neutrophil-to-lymphocyte ratio;
obstructive sleep apnea syndrome;
predictors

Abstract

Background: Bronchial asthma (BA) frequently coexists with obstructive sleep apnea syndrome (OSAS). The obesity-inflammation axis may underlie this overlap, but pragmatic predictors and biomarker utility remain incompletely defined.

Objective: To identify clinical predictors of OSAS in BA and evaluate the diagnostic performance of leptin (LEP), interleukin-6 (IL-6), and neutrophil-to-lymphocyte ratio (NLR), individually and in combination.

Materials and Methods: In a prospective study, 263 adults with BA were enrolled and classified into OSAS (n=124) and non-OSAS (n=139) groups by polysomnography. The OSAS group was stratified by apnea-hypopnea index (AHI) into mild (n=59), moderate (n=42), and severe (n=23). Clinical variables were compared with univariate tests. Independent predictors were identified using binary logistic regression. Serum LEP and IL-6 (immunoassays) and NLR (hematology) were measured. Biomarker-AHI relationships were assessed by Spearman's correlation. Diagnostic performance was evaluated using receiver operating characteristic (ROC) curves and DeLong's test.

Results: On univariate analysis, OSAS cases were older and more often male, with higher rates of obesity, severe BA, neck circumference >40 cm, rhinitis, and gastroesophageal reflux disease (GERD). Logistic regression confirmed obesity, severe BA, neck circumference >40 cm, rhinitis, and GERD as independent predictors. LEP, IL-6, and NLR were significantly higher in OSAS than non-OSAS and increased progressively across AHI strata. LEP correlated strongly with IL-6, IL-6 with NLR, and LEP with NLR to a lesser extent (all $P<0.001$). For diagnosing BA-OSAS, AUCs were 0.746 (LEP), 0.771 (IL-6), 0.742 (NLR), and 0.826 for their combination, which outperformed individual markers (DeLong, $P<0.05$).

Conclusion: Obesity, neck circumference >40 cm, severe BA, rhinitis, and GERD independently predict OSAS in BA. LEP, IL-6, and NLR correlate with OSAS severity, and their combined use

***Corresponding author:** Lili Miao, Department of Respiratory and Critical Care Medicine, General Hospital of Ningxia Medical University, No. 804, Shengli South Street, Yinchuan 750004, Ningxia Hui Autonomous Region, China. *Email address*: Hellen424@163.com

https://doi.org/10.15586/aei.v54i1.1473

provides superior diagnostic value for identifying BA–OSAS comorbidity and may aid targeted screening and referral. (≈240 words)

Introduction

Bronchial asthma (BA) is a chronic inflammatory airway disease characterized by variable airflow obstruction, airflow limitation, and airway hyperresponsiveness.[1,2] Driven by lifestyle changes and escalating environmental pollution, the prevalence of BA has been rising annually, establishing it as a major chronic disease of global public health concern. According to World Health Organization (WHO) statistics, approximately 300 million people currently suffer from asthma globally, with the number exceeding 45 million in China, posing a significant threat to patient's quality of life and the efficient allocation of societal healthcare resources.[3] Clinical practice increasingly reveals a frequent comorbidity between BA and obstructive sleep apnea syndrome (OSAS),[4–6] OSAS is characterized by recurrent episodes of upper airway collapse and obstruction during sleep, manifesting primarily as snoring, apneas, nocturnal hypoxemia, and excessive daytime sleepiness. Literature reports indicate a complex pathophysiological interplay between BA and OSAS. BA patients comorbid with OSAS exhibit poorer asthma control, higher frequency of acute exacerbations, and diminished quality of life.[7–9] BA may contribute to the development of OSAS through heightened airway hyperresponsiveness and increased mucus secretion, while nocturnal hypoxemia and sympathetic activation associated with OSAS can exacerbate airway inflammation and asthma symptoms. This comorbid relationship may establish a vicious cycle, increasing disease burden and complicating its management.

Obesity, recognized as a common risk factor for both BA and OSAS, has garnered significant attention in recent years.[10–12] Adipose tissue functions not only as an energy reservoir but also as an endocrine organ, secreting various pro-inflammatory cytokines, such as leptin (LEP) and interleukin-6 (IL-6). LEP, beyond its role in regulating energy metabolism, can activate immune cells and promote airway inflammatory responses.[13] IL-6 serves as a pivotal cytokine bridging acute and chronic inflammation.[14] Furthermore, the neutrophil-to-lymphocyte ratio (NLR), an easily accessible peripheral blood inflammatory marker, has recently been proposed as a potential biomarker for various chronic inflammatory diseases and may reflect an individual's systemic inflammatory status.[15] The current research on BA comorbid with OSAS predominantly focuses on clinical manifestations and assessment of quality of life, lacking systematic investigation into the underlying mechanisms and influencing factors from the perspective of obesity–inflammation interactions.

This study aims to analyze the independent risk factors for OSAS comorbidity in BA patients based on obesity- and inflammation-related indicators, including LEP, IL-6, and NLR. It further seeks to explore the correlations between these indicators and severity of OSAS as well as their combined diagnostic value. By constructing an accessible and accurate biomarker system, this research provides theoretical support and a practical basis for early clinical identification and personalized intervention.

Materials and Methods

Patient grouping

A total of 263 patients with BA, admitted to the Department of Respiratory Medicine at the General Hospital of Ningxia Medical University between January 2023 and April 2025, were enrolled prospectively. The cohort comprised 140 males and 123 females, aged 28–77 years (mean: 52.27 ± 10.06 years). Based on the occurrence of OSAS during hospitalization, patients were categorized into an OSAS group (n = 124) and a non-OSAS group (n = 139). Patients in the OSAS group were subsequently stratified into three subgroups according to the apnea-hypopnea index (AHI):[16] a mild subgroup (AHI 5–14 events/h, n = 59), a moderate subgroup (AHI 15–29 events/h, n = 42), and a severe subgroup (AHI ≥ 30 events/h, n = 23).

Inclusion criteria

Patients were included based on the following criteria: (1) meeting the diagnostic criteria for BA as defined by the Global Initiative for Asthma (GINA);[17] (2) patients assigned to the OSAS group meeting the diagnostic criteria for OSAS established by the American Academy of Sleep Medicine (AASM);[16] (3) completion of a full polysomnography (PSG) study with interpretable data during hospitalization; (4) a body mass index (BMI) ≥ 18.5 kg/m^2 (to exclude potential confounding by malnutrition); (5) no prior treatment with continuous positive airway pressure (CPAP) therapy or oral appliances before hospital admission; (6) absence of acute respiratory infections or asthma exacerbations within the 4 weeks preceding enrollment; (7) age between 18 and 80 years; and (8) a written informed consent from patient.

Exclusion criteria

Patients were excluded from the study based on the following criteria: (1) concomitant chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, or other significant structural lung diseases; (2) presence of severe cardiac, hepatic, or renal failure; (3) a history of prior pharyngeal/laryngeal surgery or craniofacial deformities known to affect upper airway anatomy; (4) long-term use of systemic corticosteroids (prednisone-equivalent dosage of >10 mg/day for ≥4 weeks); (5) active autoimmune disorders, malignancy, or hematological diseases; (6) thyroid dysfunction; (7) use of biologics within the 3 months preceding the enrollment; or (8) incomplete clinical data (including pulmonary function tests, neck circumference measurements, comorbid conditions, etc.) or missing samples required for the assay of key inflammatory markers (LEP, IIL-6, and NLR).

Clinical data collection

Clinical data were systematically collected for all enrolled patients, encompassing the following domains: (1) *demographic characteristics*: age, gender, and BMI, with obesity defined as BMI ≥ 28.0 kg/m^2 according to Chinese criteria;[18] (2) *asthma-related parameters*: duration of BA, BA severity classification, and daily inhaled corticosteroid (ICS) dosage, categorized as low, medium, or high based on the GINA recommended ICS equipotency dosing standards;[19] (3) *upper airway and metabolic indicators*: neck circumference (measured at the level of the prominentia laryngea in the upright position; >40 cm considered abnormal), smoking history (defined as cumulative consumption of >100 cigarettes), and history of alcohol consumption (defined as >30 g of alcohol per day for ≥1 year); and (4) *comorbidities and medical history*: hypertension, diabetes mellitus, coronary heart disease, and a family history of asthma, rhinitis, and gastroesophageal reflux disease (GERD).[20]

Sleep data monitoring

The primary sleep parameter monitored was AHI. Full-night PSG was performed using the Philips Alice 6 LDxS system (Philips Respironics, 1001 Murry Ridge Lane, Murrysville, Pennsylvania 15668, USA) under constant ambient temperature and humidity conditions, with continuous monitoring lasting for ≥7 h. Respiratory events were scored according to the AASM criteria: apnea was defined as a ≥90% reduction in airflow lasting for ≥10 s, and hypopnea was defined as a ≥30% reduction in airflow accompanied by a ≥3% decrease in oxygen saturation (SpO_2) or an associated microarousal. The AHI was calculated using the following formula:

$$\text{AHI} = \frac{\text{total number of apneas} + \text{total number of hypopneas}}{\text{total sleep time (h)}}.^{21}$$

Serological marker assays

Venous blood samples (4 mL) were collected from patients after an overnight fasting (≥8 h) on the morning following hospital admission. Each blood sample was aliquoted into one plain serum separator tube (with a red top, 2 mL) and two ethylenediaminetetraacetic acid (EDTA) anticoagulant tubes (with a lavender top, 3 mL). The plain tube was allowed to clot at room temperature for 30 min and subsequently centrifuged at 3000 rpm for 10 min. The separated serum was then aliquoted in 0.5-mL eppendorf/microcentrifuge tubes (EP tubes) and stored at -80°C for subsequent LEP and IL-6 quantification. EDTA–anticoagulated blood samples were also stored at room temperature for 30 min and centrifuged at 3000 rpm for 10 min (centrifugation radius: 15 cm). The resulting plasma was used for NLR determination, which was completed within 2 h of collection. LEP and IL-6 levels were measured using enzyme-linked immunosorbent serological assay (ELISA) kits (CUSABIO Technology LLC, China). NLR was calculated based on complete blood count results obtained using an automated hematology analyzer (Sysmex XN-9000, Japan), followed by manual computation of the ratio. All procedures were strictly performed in accordance with the manufacturers' protocols and established quality control requirements for biological specimens.

Statistical methods

Statistical analyses were performed using the SPSS software (version 27.0), while data visualization was conducted with Prism (version 8.0.2). Categorical data were presented as (n (%)) and compared using the Chi-square (x^2) test. The normality of continuous variables was assessed using the Shapiro–Wilk test, and homogeneity of variances was verified with Levene's test. Normally distributed data with homogeneous variances were expressed as mean ± standard deviation ($\bar{x} \pm S$). Comparisons among three groups were performed using one-way analysis of variance (ANOVA). If a significant difference was detected ($P < 0.05$), *post hoc* pairwise comparisons were conducted using Tukey's honestly significant difference (HSD) test for equal variances, or the Games–Howell test when variances were unequal. Comparisons between two independent groups employed independent samples *t*-test for equal variances or Welch's *t*-test for unequal variances. Non-normally distributed continuous data were described using median and interquartile range (M (P_{25}, P_{75})). Comparisons between three groups used the Kruskal–Wallis H test; if significant ($P < 0.05$), *post hoc* pair-wise comparisons were performed using the Dunn–Bonferroni method. The Mann-Whitney U test was used for comparisons between two independent groups, And Spearman's correlation analysis was done between LEP, IL-6, NLR, and their respective correlations with AHI. Receiver operating characteristic (ROC) curve analysis, complemented by the DeLong test, was used to evaluate the diagnostic value of LEP, IL-6, NLR, and their combination for identifying BA comorbid with OSAS. Youden's index was calculated as sensitivity + specificity − 1. The level of statistical significance was set at $P < 0.05$ for all tests.

Results

Univariate analysis of BA with OSAS comorbidity

Univariate analysis demonstrated that patients in the OSAS group were significantly older than those in the non-OSAS

Table 1 Univariate analysis of BA complicated by OSAS.

Indicator	OSAS group (n = 124)	Non-OSAS group (n = 139)	t/x2	P
Age (years)	53.94 ± 9.38	50.77 ± 10.44	2.581	0.010
Gender (n)			6.120	0.013
Male	76 (61.29)	64 (46.04)	-	-
Female	48 (38.71)	75 (53.96)	-	-
Obesity (n)			28.224	<0.001
No	57 (45.97)	108 (77.70)	-	-
Yes	67 (54.03)	31 (22.30)	-	-
Duration of BA (n)			1.780	0.182
≤10 years	47 (37.90)	64 (46.04)	-	-
>10 years	77 (62.10)	75 (53.96)	-	-
BA severity (n)			8.390	0.015
Mild	20 (16.13)	36 (25.90)	-	-
Moderate	41 (33.06)	56 (40.29)	-	-
Severe	63 (50.81)	47 (33.81)	-	-
Daily ICS dose (n)			5.264	0.072
Low	36 (29.03)	54 (38.85)	-	-
Medium	51 (41.13)	59 (42.45)	-	-
High	37 (29.84)	26 (18.71)	-	-
Neck circumference (n)			26.721	<0.001
≤40 cm	54 (43.55)	104 (74.82)	-	-
>40 cm	70 (56.45)	35 (25.18)	-	-
Smoking history (n)	52 (41.94)	53 (38.13)	0.396	0.529
Alcohol history (n)	28 (22.58)	32 (23.02)	0.007	0.932
Hypertension (n)	45 (36.29)	38 (27.34)	2.432	0.119
Diabetes mellitus (n)	22 (17.74)	18 (12.95)	1.167	0.280
Coronary heart disease (n)	16 (12.90)	17 (12.23)	0.027	0.869
Family history of asthma (n)	30 (24.19)	28 (20.14)	0.625	0.429
Rhinitis (n)	68 (54.84)	43 (30.94)	15.351	<0.001
GERD (n)	50 (40.32)	26 (18.71)	14.906	<0.001

BA: bronchial asthma; OSAS: obstructive sleep apnea syndrome; ICS: inhaled corticosteroid; GERD: gastroesophageal reflux disease.

group. Furthermore, the OSAS group exhibited significantly higher proportions of males, patients with obesity, severe BA, neck circumference > 40 cm, rhinitis, and GERD, compared to the non-OSAS group (all $P < 0.05$) (Table 1).

Binary logistic regression analysis for BA with OSAS comorbidity

Binary logistic regression analysis identified obesity, severe BA, neck circumference > 40 cm, rhinitis, and GERD as significant independent risks influencing OSAS comorbidity in BA patients (all $P < 0.05$) (Tables 2 and 3).

Comparison of serum LEP, IL-6, and NLR levels across groups

Serum levels of LEP, IL-6, and NLR were significantly elevated in the OSAS group, compared to the non-OSAS group ($P < 0.05$). Furthermore, within the OSAS group stratified by severity, the severe subgroup demonstrated significantly higher levels of all three markers, compared to both moderate and mild subgroups, while the moderate subgroup also exhibited significantly higher levels than the mild subgroup ($P < 0.05$ for all comparisons) (Table 4).

Table 2 Assignment table.

Variable	Factor	Assignment
X1	Age	Continuous variable
X2	Gender	Male = 1, female = 2
X3	Obesity	No = 0, yes = 1
X4	BA severity	Mild = 1, moderate = 2, severe = 3
X5	Neck circumference	≤40 cm = 0, >40 cm = 1
X6	Rhinitis	No = 0, yes = 1
X7	GERD	No = 0, yes = 1

BA: bronchial asthma; GERD: gastroesophageal reflux disease.

Correlation analysis of LEP, IL-6, and NLR with AHI

Spearman's correlation analysis showed that LEP was strongly positively correlated with IL-6 ($r = 0.698$, $P < 0.001$)

Table 3 Binary logistic regression analysis of BA complicated by OSAS.

Variable	β	SE	Wald	P	OR (95% CI)
Age	0.026	0.015	3.100	0.078	1.027 (0.997-1.057)
Gender (1)	-0.576	0.293	3.854	0.050	0.562 (0.316-0.999)
Obesity (1)	1.156	0.309	13.979	<0.001	3.178 (1.733-5.826)
BA severity			6.832	0.033	
BA severity (1)	0.589	0.411	2.052	0.152	1.802 (0.805-4.035)
BA severity (2)	1.033	0.400	6.663	0.010	2.808 (1.282-6.151)
Neck circumference (1)	1.026	0.302	11.565	<0.001	2.789 (1.544-5.037)
Rhinitis (1)	0.962	0.296	10.554	0.001	2.616 (1.465-4.674)
GERD (1)	0.951	0.330	8.328	0.004	2.589 (1.357-4.940)

β, regression coefficient (log-odds) from binary logistic regression; SE, standard error of ß; BA: bronchial asthma; OSAS: obstructive sleep apnea syndrome; GERD: gastroesophageal reflux disease.

Table 4 Comparison of serum LEP, IL-6, and NLR levels across groups.

Group		LEP (ng/mL)	IL-6 (pg/mL)	NLR
OSAS	No (n = 139)①	16.48 ± 5.00	5.59 (4.13, 7.07)	2.70 (1.95, 3.47)[a]
	Yes (n = 124)	21.91 ± 6.01[a]	7.74 (5.97, 9.71)[a]	3.66 (2.78, 4.56)
OSAS severity	Mild (n = 59)①	18.01 ± 4.58	5.95 (5.07, 7.26)	2.92 (2.33, 3.48)
	Moderate (n = 42)②	23.46 ± 4.29[a]	8.90 (7.48, 10.06)[a]	3.91 (3.12, 4.97)[a]
	Severe (n = 23)	29.11 ± 3.54[a,b]	10.94 (9.50, 11.31)[a,b]	4.72 (4.53, 5.31)[a,b]

Compared with ①, [a]P < 0.05; compared with ②, [b]P < 0.05.

and weakly positively correlated with NLR ($r = 0.447$, $P < 0.001$), while IL-6 was strongly positively correlated with NLR ($r = 0.603$, $P < 0.001$). Moreover, LEP, IL-6, and NLR were strongly positively correlated with AHI ($r = 0.661$, 0.685, and 0.615, respectively; all $P < 0.001$) (Figures 1A-C).

Diagnostic value of LEP, IL-6, NLR and their combination for BA complicated by OSAS

Receiver operating characteristic curves and DeLong's test demonstrated that LEP, IL-6, NLR, and their combination exhibited significant diagnostic value for BA complicated by OSAS. Areas under the curve (AUC) with 95% confidence intervals (95% CI) were 0.746 (0.687–0.804) for LEP, 0.771 (0.716–0.826) for IL-6, 0.742 (0.683–0.800) for NLR, and 0.826 (0.770–0.882) for their combinations, respectively (all $P < 0.001$). Crucially, the diagnostic efficacy of the combined panel was significantly superior to that of any individual biomarker: LEP ($Z = 3.433$), IL-6 ($Z = 2.250$), and NLR ($Z = 3.060$; all $P = 0.05$), as presented in Tables 5 and 6 and Figure 2.

Discussion

This study, adopting the perspective of the obesity-inflammation interplay, systematically analyzed clinical characteristics, risk factors, and alterations in inflammation-related biomarkers in patients with BA complicated by OSAS, aiming to elucidate the underlying pathological links between these conditions and explore the clinical utility of biomarkers, including LEP, IL-6, and NLR for the early identification of BA-OSAS comorbidity. The findings hold significant clinical and theoretical importance. From an epidemiological viewpoint, the comorbidity rate of BA and OSAS showed a rising trend annually, driven by accelerating lifestyles, increasing obesity proportion, and worsening environmental pollution.[22] Studies indicate that the prevalence of OSAS in asthmatic patients can reach 20–50%, while asthma is also significantly more prevalent among OSAS patients. The two conditions share considerable overlap in pathophysiological mechanisms, including chronic hypoxia, airway inflammation, sympathetic nervous system activation, and oxidative stress.[23-25] Consequently, investigating the influencing factors and inflammatory mechanisms of BA-OSAS comorbidity provides crucial practical guidance.

Our logistic regression analysis identified obesity, neck circumference > 40 cm, severe asthma, rhinitis, and GERD as independent risk factors for BA-OSAS comorbidity. Notably, the odds ratio (OR) for obesity was 3.178, indicating that obese patients face a risk of developing OSAS more than three times greater than non-obese individuals. Obesity not only exacerbates upper airway narrowing through anatomical mechanisms but also activates the T-helper 1 (Th1)-Th17 pathway via pro-inflammatory cytokines such as LEP, triggering chronic airway inflammation.[26] Furthermore, neck circumference, a simple indicator for

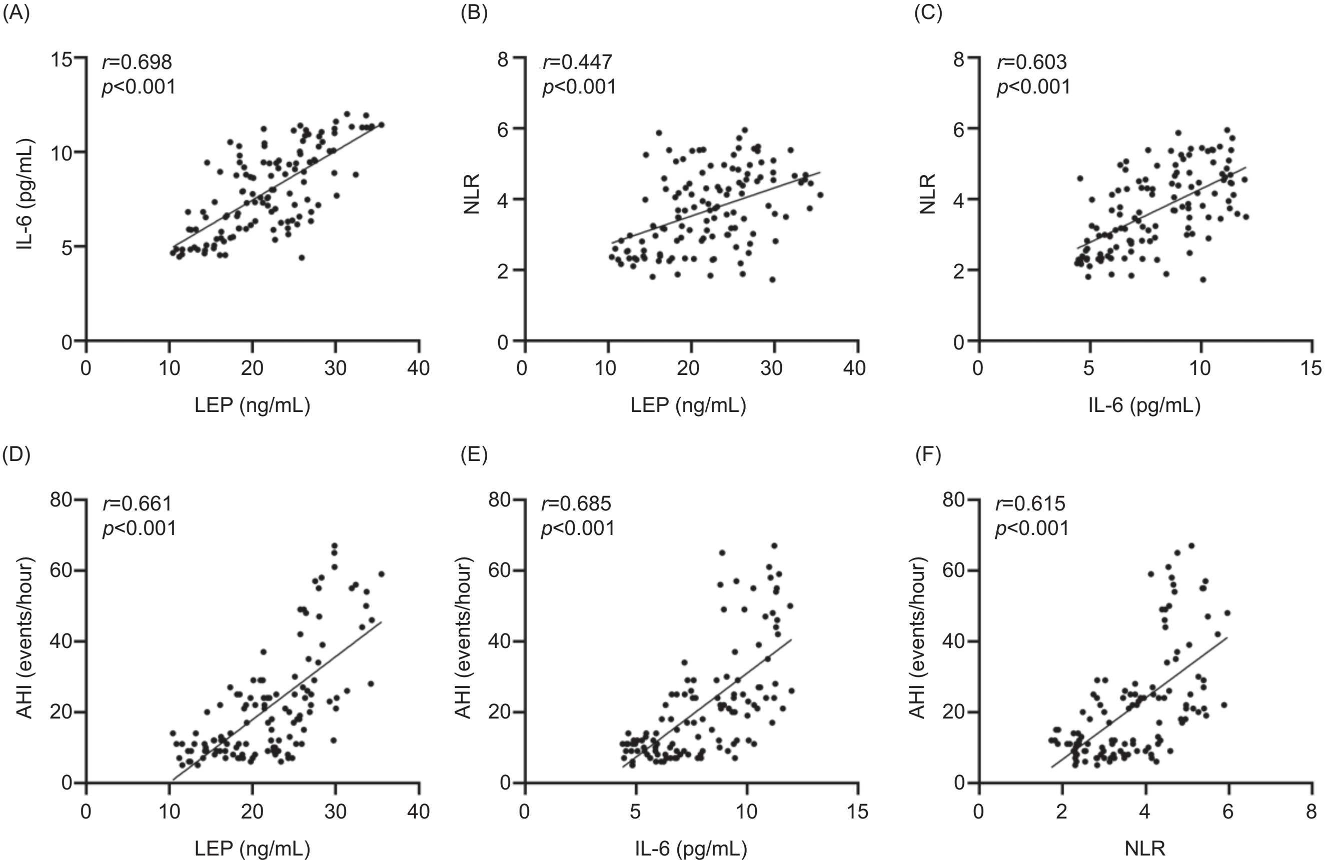

Figure 1 Correlation analysis of LEP, IL-6, and NLR with AHI. (A) Scatter plot of correlation between LEP and IL-6; (B) scatter plot of correlation between LEP and NLR; (C) scatter plot of correlation between IL-6 and NLR; (D) scatter plot of correlation between LEP and AHI; (E) scatter plot of correlation between IL-6 and AHI; and (F) scatter plot of correlation between NLR and AHI.

Table 5 Diagnostic performance of LEP, IL-6, NLR, and their combination for BA complicated by OSAS.

Indicator	AUC (95% CI)	Youden's index	Sensitivity	Specificity	P
LEP	0.746 (0.687-0.804)	0.379	71.60%	66.30%	<0.001
IL-6	0.771 (0.716-0.826)	0.386	70.40%	68.20%	<0.001
NLR	0.742 (0.683-0.800)	0.389	70.30%	68.60%	<0.001
Combination	0.826 (0.770-0.882)	0.649	78.50%	86.40%	<0.001

Table 6 Pairwise comparison of area differences under ROC curves.

Pairwise comparison	**Z**	**P**	**AUC difference**	**95% CI**
Combination-LEP	3.433	0.001	0.080	0.035-0.126
Combination-IL-6	2.250	0.024	0.055	0.007-0.102
Combination-NLR	3.060	0.002	0.084	0.030-0.138

assessing upper airway structural abnormalities, demonstrated high predictive efficacy in this study, reinforcing the association between cervical fat deposition and OSAS pathogenesis. Rhinitis and GERD, common comorbidities in asthma, also emerged as significant risk factors. Rhinitis can alter breathing patterns by increasing upper airway resistance, while GERD induces bronchoconstriction through microaspiration and vagal reflexes, thereby worsening nocturnal asthma and OSAS. Patients with severe asthma, characterized by more pronounced airway remodeling and reduced pulmonary function,[27] exhibited a significantly higher risk of developing OSAS, compared to those with mild-to-moderate disease. This finding suggests that risk assessment for sleep-related breathing disorders warrants particular attention in the management of severe asthma.

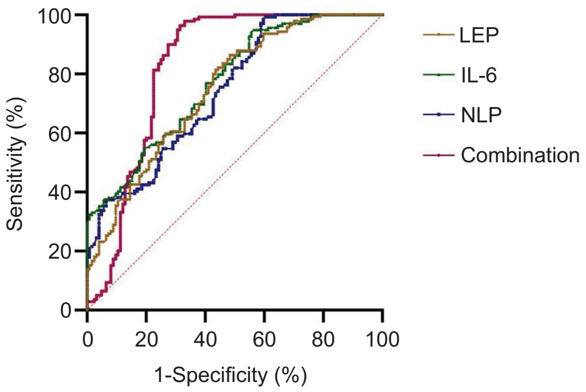

Figure 2 ROC curves illustrating the diagnostic performance of LEP, IL-6, NLR, and their combination for BA complicated by OSAS.

Regarding inflammatory biomarkers, this study provides the first systematic evaluation of the expression changes and correlations of LEP, IL-6, and NLR in BA–OSAS comorbidity. Results revealed significantly elevated levels of LEP, IL-6, and NLR in the OSAS group, compared to the non-OSAS group. Furthermore, these levels exhibited a significant increasing trend across mild, moderate, and severe OSAS subgroups, and Spearman's correlation analysis confirmed positive correlations with AHI. This suggests a progressive elevation in systemic inflammation alongside worsening OSAS severity, a phenomenon potentially driven by recurrent hypoxic stimulation and oxidative stress activating pro-inflammatory pathways. In addition, strong positive correlations were observed between LEP and IL-6 as well as between IL-6 and NLR, while a weaker but significant correlation was observed between LEP and NLR. These inter-marker associations indicate potential synergistic interactions within the obesity–inflammation axis, further supporting their role in the pathophysiology of BA–OSAS comorbidity.[28] To further contextualize our findings, previous international studies also investigated these biomarkers in OSAS populations without asthma, supporting their role as systemic inflammatory indicators. Elevated LEP levels are consistently reported in OSAS patients and are thought to reflect both obesity and intermittent hypoxia, contributing to disease severity.[29] Similarly, circulating IL-6 levels are significantly increased in OSAS and correlate with AHI, indicating their utility as markers of hypoxia-driven inflammation.[30] In addition, a higher NLR was observed in OSAS cohorts, compared to healthy controls, reinforcing its value as a simple marker of systemic inflammation.[31] Taken together, these findings suggest that LEP, IL-6, and NLR are not only relevant in BA–OSAS overlap but are also independently associated with OSAS itself. This external evidence strengthens the generalizability of our results and places them in the broader context of OSAS research, indicating that the observed associations are not confined to asthma-related mechanisms. It highlights the potential of these biomarkers to serve as universal indicators of systemic inflammation in sleep-disordered breathing, and underscores the need for future studies directly comparing asthma–OSAS overlap with isolated OSAS populations to clarify disease-specific versus shared pathways.

Leptin, an adipocyte-derived cytokine, plays a vital role in regulating energy metabolism, respiratory control, and immune responses. It can promote airway inflammatory cell infiltration and exacerbate asthmatic inflammation via the nuclear factor kappa B (NF-κB) signaling pathway.[32] In OSAS, chronic intermittent hypoxia stimulates increased LEP expression, creating a vicious cycle.[33] A significant positive correlation observed between LEP and AHI in this study suggests that LEP can act as a crucial mediator in the mutual aggravation of BA and OSAS.

IL-6, a classic pro-inflammatory cytokine, induces C-reactive protein (CRP) synthesis, activates neutrophils, and promotes inflammatory cascades. Its role in chronic inflammatory diseases is well --established.[34-36] Our data showed markedly elevated IL-6 levels in the OSAS group, positively correlated with AHI, indicating that IL-6 probably plays a central role in the pathogenesis of BA–OSAS comorbidity.

Neutrophil-to-lymphocyte ratio, a simple and cost-effective marker of systemic inflammation, reflects an inflammatory imbalance characterized by neutrophil activation and relative lymphocyte suppression. Its positive correlation with OSAS severity in this study suggests that NLR is not merely a reflection of inflammation but may actively participate in the pathological process. Intermittent hypoxia can promote neutrophil release and inhibits lymphocyte proliferation, thereby elevating NLR levels.[37] Concurrently, neutrophils exacerbate airway inflammation through the release of reactive oxygen species and inflammatory mediators, further promoting the reciprocal worsening of asthma and OSAS. Thus, an elevated NLR may serve as a significant inflammatory marker indicating aggravated BA–OSAS comorbidity.

In terms of diagnostic efficacy, ROC curve analysis demonstrated an AUC of 0.746 for LEP, 0.771 for IL-6, and 0.742 for NLR. Crucially, the combination of all three biomarkers achieved an AUC of 0.826, significantly outperforming any single marker, as confirmed by DeLong's test. This suggests that combined LEP, IL-6, and NLR testing offers a practical, economical, and scalable tool for early screening, potentially enabling OSAS risk stratification and guiding personalized intervention strategies for high-risk BA patients in clinical practice.

The strengths of this study include its prospective design, the biologically plausible selection of biomarkers centered on the obesity–inflammation mechanism, an adequate sample size with clearly defined groups, and rigorous statistical methods. However, several limitations should be noted. Its single-center design may introduce selection bias, and measurements of LEP and IL-6 were performed at a single time point without longitudinal follow-up. Moreover, as an observational study, causality cannot be definitively established. Another limitation is that the present work placed greater emphasis on the relationship between asthma and OSAS. The occurrence or worsening of OSAS can itself be regarded as an adverse complication of asthma, but the precise mechanisms by which LEP, IL-6, and NLR directly influence asthma severity remain unclear. Future studies should therefore explore whether these biomarkers contribute to airway remodeling, immune dysregulation, or corticosteroid resistance in asthma, in order to clarify their role in asthma progression beyond OSAS comorbidity.

Conclusion

This study confirms obesity, neck circumference > 40 cm, severe asthma, rhinitis, and GERD as independent risk factors for BA–OSAS comorbidity. Serum levels of LEP, IL-6, and NLR are closely associated with OSAS severity, and their combined detection exhibits high value for early diagnosis. Moreover, considering that non-T2 inflammation may predominate in asthma patients with OSAS, our findings raise the possibility of developing targeted interventions aimed at the identified inflammatory pathways. In particular, IL-6, together with LEP and NLR, may represent promising therapeutic targets for metabolic–inflammatory modulation. Future prospective and interventional studies are warranted to investigate whether modulation of these non-T2 pathways can improve both OSAS severity and asthma control, thereby reducing the overall disease burden.

Data Availability

The data that supported the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of the General Hospital of Ningxia Medical University (KYLL-2024-1311). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments, or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Author's Contribution

Lili Miao: Conceptualization; project administration; data curation; validation; resources; visualization; investigation; supervision; formal analysis; software; writing–original draft preparation and editing.

Conflict of Interest

The author had no conflict of interest to declare.

Funding

None.

References

1. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell. 2021;184:1469–85. https://doi.org/10.1016/j.cell.2021.02.016
2. Savin IA, Zenkova MA, Sen'kova AV. Bronchial asthma, airway remodeling and lung fibrosis as successive steps of one process. Int J Mol Sci. 2023;24:16042. https://doi.org/10.3390/ijms242216042
3. Reyes-Angel J, Kaviany P, Rastogi D, Forno E. Obesity-related asthma in children and adolescents. Lancet Child Adolesc Health. 2022;6:713–24. https://doi.org/10.1016/S2352-4642(22)00185-7.
4. Prasad B, Nyenhuis SM, Imayama I, Siddiqi A, Teodorescu M. Asthma and obstructive sleep apnea overlap: What has the evidence taught us? Am J Respir Crit Care Med. 2020;201:1345–57. https://doi.org/10.1164/rccm.201810-1838TR
5. Ragnoli B, Pochetti P, Raie A, Malerba M. Interrelationship between obstructive sleep apnea syndrome and severe asthma: From endo-phenotype to clinical aspects. Front Med (Lausanne). 2021;8:640636. https://doi.org/10.3389/fmed.2021.640636
6. Ioachimescu OC. State of the art: Alternative overlap syndrome-asthma and obstructive sleep apnea. J Investig Med. 2024;72:589–619. https://doi.org/10.1177/10815589241249993
7. Tondo P, Hoxhallari A, Lacedonia D, Magaletti P, Sabato R, Foschino Barbaro MP, et al. The CORE syndrome: an overlap of severe asthma, obstructive sleep apnea, rhinosinusitis, and esophageal reflux. Sleep Breath. 2024;28:1761–5. https://doi.org/10.1007/s11325-024-03028-x
8. Li E, Ai F, Liang C. A machine learning model to predict the risk of depression in US adults with obstructive sleep apnea hypopnea syndrome: A cross-sectional study. Front Public Health. 2023;11:1348803. https://doi.org/10.3389/fpubh.2023.1348803
9. Oyama B, Tsuburai T, Tsuruoka H, Nishida K, Usuba A, Hida N, et al. Complicating effects of obstructive sleep apnea syndrome on the severity of adult asthma. J Asthma. 2020;57:1173–8. https://doi.org/10.1080/02770903.2019.1652643
10. Mitra AK, Bhuiyan AR, Jones EA. Association and risk factors for obstructive sleep apnea and cardiovascular diseases: A systematic review. Diseases. 2021;9(4):88. https://doi.org/10.3390/diseases9040088
11. Dixon AE, Que LG. Obesity and asthma. Sem Respir Crit Care Med. 2022;43:662–74. https://doi.org/10.1055/s-0042-1742384
12. Sowho MO, Koehl R, Shade R, Judge E, Woo H, Wu TD, et al. Obstructive sleep apnea screening in children with asthma. Pediatr Pulmonol. 2023;58:1683–90. https://doi.org/10.1002/ppul.26375
13. Wang Y, Hu C. Leptin and asthma: What are the interactive correlations? Biomolecules. 2022;12:1780. https://doi.org/10.3390/biom12121780
14. Lipworth B, Chan R, Kuo C. Systemic IL-6 and severe asthma. Am J Respir Crit Care Med. 2020;202:1324–5. https://doi.org/10.1164/rccm.202006-2354LE
15. Wawryk-Gawda E, Zybowska M, Ostrowicz K. The neutrophil to lymphocyte ratio in children with bronchial asthma. J Clin Med. 2023;12:6869. https://doi.org/10.3390/jcm12216869
16. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine Clinical Practice guideline. J Clin Sleep Med. 2017;13:479–504. https://doi.org/10.5664/jcsm.6506
17. Reddel HK, Bacharier LB, Bateman ED, Brightling CE, Brusselle GG, Buhl R, et al. Global initiative for asthma strategy 2021: Executive summary and rationale for key changes. Eur Respir J. 2022;59(1):2102730. https://doi.org/10.1183/13993003.02730-2021
18. Chinese Nutrition Society Obesity Prevention and Control Section, Chinese Nutrition Society Clinical Nutrition Section, Chinese Preventive Medicine Association Behavioral Health

Section, Chinese Preventive Medicine Association Sports and Health Section. Zhonghua Liu Xing Bing Xue Za Zhi [Expert Consensus on Obesity Prevention and Treatment in China]. 2022;43(5):609-26. https://doi.org/10.3760/cma.j.cn112338-20220402-00253

19. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J. 2008;31:143-78. https://doi.org/10.1183/09031936.00138707
20. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2022;117:27-56. https://doi.org/10.14309/ajg.0000000000001538
21. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF,, et al. AASM scoring manual updates for 2017 (version 2.4). J Clin Sleep Med. 2017;13:665-6. https://doi.org/10.5664/jcsm.6576
22. Wang D, Zhou Y, Chen R, Zeng X, Zhang S, Su X, et al. The relationship between obstructive sleep apnea and asthma severity and *vice versa*: A systematic review and meta-analysis. Eur J Med Res. 2023;28:139. https://doi.org/10.1186/s40001-023-01097-4
23. Cisneros C, Iturricastillo G, Martínez-Besteiro E, Eiros JM, Marcos C, Múgica V, et al. Obstructive sleep apnea: The key for a better asthma control? Sleep Med. 2023;101:135-7. https://doi.org/10.1016/j.sleep.2022.10.015
24. Pardo-Manrique V, Ibarra-Enriquez CD, Serrano CD, Sanabria F, Fernandez-Trujillo L. Asthma and obstructive sleep apnea: Unveiling correlations and treatable traits for comprehensive care. Chron Respir Dis. 2024;21:14799731241251827. https://doi.org/10.1177/14799731241251827
25. Nosetti L, Gozal D. Exploring the bidirectional relationship between asthma and obstructive sleep apnea in Brazilian pediatric patients: One more piece to the puzzle. J Pediatr (Rio J). 2023;99:423-4. https://doi.org/10.1016/j.jped.2023.05.004
26. Wang Y, Wan R, Hu C. Leptin/obR signaling exacerbates obesity-related neutrophilic airway inflammation through inflammatory M1 macrophages. Mol Med. 2023;29:100. https://doi.org/10.1186/s10020-023-00702-w
27. Varricchi G, Ferri S, Pepys J, Poto R, Spadaro G, Nappi E, et al. Biologics and airway remodeling in severe asthma. Allergy. 2022;77:3538-52. https://doi.org/10.1111/all.15473
28. Lv R, Liu X, Zhang Y, Dong N, Wang X, He Y, et al. Pathophysiological mechanisms and therapeutic approaches in obstructive sleep apnea syndrome. Signal Transduct Target Ther. 2023;8:218. https://doi.org/10.1038/s41392-023-01496-3
29. Pamuk AE, Süslü AE, Yalçınkaya A, Öztaş YE, Pamuk G, Özer S, et al. The serum leptin level in non-obese patients with obstructive sleep apnea. Auris Nasus Larynx. 2018;45:796-800. https://doi.org/10.1016/j.anl.2017.11.009
30. Nadeem R, Molnar J, Madbouly EM, Nida M, Aggarwal S, Sajid H, et al. Serum inflammatory markers in obstructive sleep apnea: a meta-analysis. J Clin Sleep Med. 2013;9:1003-12. https://doi.org/10.5664/jcsm.3070
31. Ucar Y, Sahin A. Evaluation of inflammatory markers in obstructive sleep apnea syndrome. Sci Prog. 2025;108:368504251365874. https://doi.org/10.1177/00368504251365874
32. Xu S, Chen Z, Ge L, Ma C, He Q, Liu W, et al. Identification of potential biomarkers and pathogenesis in neutrophil-predominant severe asthma: A comprehensive bioinformatics analysis. Medicine (Baltimore). 2022;101:e30661. https://doi.org/10.1097/MD.0000000000030661
33. Dalesio NM, Lee CKK, Hendrix CW, Kerns N, Hsu A, Clarke W, et al. Effects of obstructive sleep apnea and obesity on morphine pharmacokinetics in children. Anesth Analg. 2020;131:876-84. https://doi.org/10.1213/ANE.0000000000004509
34. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol. 2018;18:773-89. https://doi.org/10.1038/s41577-018-0066-7
35. Ridker PM, Rane M. Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. Circ Res. 2021;128:1728-46. https://doi.org/10.1161/CIRCRESAHA.121.319077
36. Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. Immunity. 2019;50:1007-23. https://doi.org/10.1016/j.immuni.2019.03.026
37. Yang L, Liu S, He Y, Gan L, Ni Q, Dai A, et al. Exosomes regulate SIRT3-related autophagy by delivering miR-421 to regulate macrophage polarization and participate in OSA-related NAFLD. J Transl Med. 2024;22:475. https://doi.org/10.1186/s12967-024-05283-8