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Original Article

Diagnostic value of IgE, fractional of exhaled nitric oxide, and peripheral blood eosinophils in adult bronchial asthma and their relationship with disease severity

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Abstract: Objective: To investigate the diagnostic value of immunoglobulin E (IgE), fractional of exhaled nitric oxide (FeNO), and peripheral blood eosinophils (EOS) in adult bronchial asthma and to analyze their relationship with asthma severity. Methods: A retrospective analysis was conducted on 336 patients diagnosed with bronchial asthma and admitted to Xi'an Fourth Hospital from January 2022 to January 2024, forming the asthma group. Additionally, another 127 healthy subjects were selected as the non-asthmatic control group. The patients in the asthma group were categorized into a mild asthma group (n=138), a moderate asthma group (n=115), and a severe asthma group (n=83) according to the severity of the disease. Clinical data, lung function indices, and IgE, FeNO, and EOS levels were compared across groups. ROC curves were used to assess the diagnostic value of IgE, FeNO, and EOS levels for bronchial asthma. Spearman's rank correlation analysis was used to analyze the correlation between IgE, FeNO, EOS and other indicators and asthma severity. Results: The levels of IgE, FeNO, and EOS were significantly higher in the asthma group than those in the non-asthma group, while lung function indices, peak expiratory flow rate (PEF) and forced expiratory volume in 1 s (FEV1), were significantly lower (all $P < 0.05$). The areas under curve (AUCs) of IgE, FeNO, and EOS for the diagnosis of asthma were 0.79, 0.93, and 0.88, respectively. Significant differences were observed in smoking history, family history of asthma, co-existing allergic rhinitis, and combined atopic eczema across different severity groups (all $P < 0.05$). Spearman's rank correlation analysis showed that IgE, FeNO, and EOS were positively correlated with asthma severity (all $P < 0.05$), with r_s values of 0.718, 0.679, and 0.540, respectively. Conclusion: IgE, FeNO, and EOS are valuable in diagnosing bronchial asthma in adults. Higher levels of IgE, FeNO, and EOS correspond to increased asthma severity, making these biomarkers useful for assessing asthma severity.

Keywords: IgE, FeNO, EOS, adult bronchial asthma, diagnostic value

Introduction

Bronchial asthma is a prevalent chronic respiratory disease, typically characterized by wheezing, shortness of breath, chest tightness, and coughing with reversible airflow limitation. Individual heterogeneity further complicates the diagnosis and treatment of asthma, presenting significant challenges for clinicians [1]. Over the past decade, approximately 260 million people worldwide have been affected by bronchial asthma, resulting in 455,000 deaths. In recent years, the incidence of bronchial asthma has been increasing annually [2]. Although pulmonary function tests are routinely used for diagnosis, there is an urgent need for alternative diagnostic tools for patients who cannot complete these tests or those who have yet to show significant pulmonary function abnormalities in the early stages of the disease. The discovery of biomarkers provides new possibilities for early detection and treatment of asthma.

Bronchial asthma can result from many factors, including exposure to allergens or irritants, respiratory infections, climate change, stress, smoking habits, or genetics, with its mechanisms involving multiple inflammatory pathways [2]. The pathologic process of bronchial asthma

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is closely related to type I hypersensitivity, with the Th2 inflammatory response being the primary factor in mild to moderate asthma and in most cases of severe asthma, characterized by the accumulation of eosinophils (EOS) in the airways and the production of large amounts of specific immunoglobulin E (IgE) antibodies [2-4]. Fractional exhaled nitric oxide (FeNO), primarily produced by inducible nitric oxide synthase (iNOS) in bronchial epithelial cells, plays an important role in regulating airway function and serves as a biomarker for the Th2-type inflammatory response in bronchial asthma [5]. Some studies suggest that measuring FeNO can help identify asthma phenotypes and control disease progression [6-8]. Modern research has shifted from treating asthma as a single disease to a heterogeneous disease influenced by genetic and environmental factors. A deep understanding of the pathophysiology and biomarkers of asthma is crucial for achieving more accurate diagnosis and treatment.

This study focuses on the relationship between IgE, FENO, and EOS in the diagnosis of adult bronchial asthma and their association with asthma severity. It elucidates the diagnostic significance of IgE, FENO, and EOS by comparing biomarker levels in asthma patients and exploring their potential as tools for assessing disease severity. These findings may provide a scientific basis for the personalized treatment of asthma.

Materials and methods

General information

This study included 336 adult patients admitted to Xi'an People's Hospital (Xi'an Fourth Hospital) from January 2022 to January 2024 with confirmed diagnosis of bronchial asthma and complete data, selected as the asthma group. Among them, 138 cases were classified as mild asthma, 115 as moderate asthma, and 83 as severe asthma. Another 127 cases of healthy adult medical examiners in the same period were selected as the non-asthmatic control group.

Based on prior literature [9, 10], asthma is the second most prevalent chronic airway disease in the world, affecting more than 10% of the population, with a higher prevalence in developing countries. For this study, a prevalence rate of 12% was used. The sample size calculation followed the formula: $n = \frac{(Z_{\alpha/2}+Z_{\beta})^2 \times p(1-p)}{\delta^2}$ (n is the required sample size; $Z_{\alpha/2}$ is the Z-score at the 5% significance level, which is approximately 1.96; Z_{β} is the Z-score at 90% statistical efficacy, which is approximately 1.28; p is the prevalence of bronchial asthma, 0.10; δ is the minimum clinically important difference, 0.05). After calculation, the minimum sample size of this study was determined to be 444 cases. Considering a practical situation, the exact sample size included in this study was 463 cases. This study was approved by the Ethics Committee of Xi'an People's Hospital (Xi'an Fourth Hospital).

Asthma diagnosis and severity grading

Bronchial asthma was diagnosed according to the Global Initiative for Asthma Strategy (GINA 2021) [1]. Diagnostic confirmation required a positive bronchial provocation test, indicated by a 20% reduction in FEV from baseline following a standardized dose of acetylmethacholine. According to the GINA 2021 grading criteria, patients in the asthma group were categorized into mild, moderate, and severe categories according to disease severity. Mild asthma: intermittent symptoms, nocturnal symptoms less than twice a month, peak expiratory flow rate (PEF) or forced expiratory volume in 1 s (FEV1) greater than 80% of predicted value; Moderate asthma: symptoms occurring more than three times per week and nocturnal symptoms occurring more than three times per month, with PEF or FEV1 between 60%-80% of predicted values; Severe asthma: persistent symptoms, frequent nocturnal symptoms, and PEF or FEV1 below 60% of the predicted value. Based on these criteria, patients in this study were categorized into mild (n=138), moderate (n=115), and severe (n=83) asthma groups.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age ≥ 18 years; (2) Presence of respiratory symptoms such as wheezing, shortness of breath, chronic cough, and chest tightness with recurrent episodes; (3) Ability to undergo IgE, FeNO, EOS, pulmonary function tests, and bronchial provocation tests; (4) No use of glucocorticosteroids in the past month.

Exclusion criteria: (1) Combination of other respiratory diseases, such as chronic obstructive pulmonary disease, lung infection disease, and lung cancer; (2) Conditions causing eosinophilia, including parasitic infections, rheumatoid immunity, and other diseases that cause eosinophilia; (3) Pregnant and lactating females; and (4) Incomplete clinical data.

Access to indicators

Observation indicator acquisition: Relevant patient data were collected from electronic medical records in the hospital's pathology management system, including information on gender, age, body mass index (BMI), pulse pressure, emergency admission time, lifestyle habits, and concomitant underlying diseases.

Laboratory indicator acquisition: (1) Eosinophil test: 2 mL of peripheral venous blood was drawn from all patients on the first day of admission. A fully automatic blood cell analyzer was used to perform routine blood tests and record the EOS content in peripheral blood. Patients on anti-asthma medications were required to discontinue them two weeks prior to testing. (2) FeNO test: FeNO was measured using a nitric oxide detector. Patients exhaled deeply to empty their lungs, and used a disposable filter to cover their mouth, inhaled fully, and exhaled immediately. The detector reading was recorded. Patients were instructed to abstain from eating nitrogen-rich foods, strenuous exercise, and smoking for at least one hour before the test. (3) IgE assay: The IgE levels were determined using a human immunoglobulin E (IgE) enzyme-linked immunosorbent assay kit (E-EL-H6104 Wuhan Eli Ritter).

Lung function test: A lung function detector was used to measure PEF and FEV1 in all patients. Patients inhaled deeply, pressed their lips against the mouthpiece, and forcefully exhaled to record PEF and FEV1.

Statistical methods

Graphpad prism 9 software was used to process the data. Measured data were expressed as ($\overline{x} \pm s$) and analyzed using a t-test. Counted data were expressed as the number of cases and percentage [case (%)] and analyzed using the chi-square test. Receiver Operating Characteristic curve (ROC) was used to analyze the diagnostic value of indicators for bronchial asthma. Spearman rank correlation was used to analyze the relationship between clinical indicators and asthma severity. A *P*-value of less than 0.05 was considered significant.

Results

Comparison of baseline information between non-asthmatic and asthmatic groups

A comparison of general data between the non-asthmatic and asthmatic groups showed no statistical difference in age, gender, BMI, systolic blood pressure, diastolic blood pressure, or emergency room admission time (all $P > 0.05$), as shown in **Table 1**.

Comparison of IgE, FeNO, and EOS levels between non-asthmatic and asthmatic groups

Comparison of the IgE, FeNO, and EOS levels between the non-asthmatic and asthmatic groups demonstrated that these markers in the asthmatic group were significantly higher than those of the non-asthmatic group (all $P < 0.05$) (**Figure 1**).

Comparison of lung function between non-asthmatic and asthmatic groups

By comparing the lung function of the two groups of patients, it was found that the PEF and FEV1 in the non-asthma group were significantly higher than those in the asthma group (all $P < 0.05$) (**Figure 2**).

ROC curve analysis

ROC curve analysis was used to identify critical values for each biomarker. IgE demonstrated an area under the ROC curve (AUC) of 0.79 in predicting asthma at a cutoff value of 87.975 ng/mL, with the specificity and sensitivity of 74.02% and 86.61%, respectively. FeNO demonstrated an AUC of 0.93 in predicting asthma at a cutoff value of 19.735 ppb, with the specificity and sensitivity of 91.34% and 96.73%, respectively. EOS reached an AUC of 0.88 in predicting asthma at a cutoff value of 0.145×10^9/L, with the specificity and sensitivity of 83.46% and 93.75%, respectively (**Table 2** and **Figure 3**).

Table 1. Comparison of baseline information between the non-asthmatic and asthmatic groups

		Non-asthma group (n=127)	Asthma group (n=336)	t/χ^2	P
Age (years, $\bar{x} \pm s$)		43.69±10.23	44.03±12.49	0.275	0.783
Gender [cases (%)]	Male	69 (0.54)	179 (0.53)	0.041	0.839
	Female	58 (0.46)	157 (0.47)		
BMI (kg/m^2)		23.72±2.96	24.07±2.89	1.165	0.245
Pulse pressure (mmHg)	Systolic pressure	130.40±10.86	129.10±11.43	1.148	0.252
	Diastolic pressure	74.61±7.57	74.01±8.06	0.725	0.469
Emergency admission time (h)		7.64±1.09	7.49±1.06	1.349	0.178
Exercise habits [cases (%)]		-	119 (0.35)		
Marriage history [cases (%)]		-	162 (0.48)		
History of alcohol abuse [cases (%)]		-	83 (0.25)		
History of smoking [cases (%)]		-	125 (0.37)		
Family history of asthma [cases (%)]		-	75 (0.22)		
Combined allergic rhinitis [cases (%)]		-	55 (0.16)		
Combined allergic eczema [cases (%)]		-	97 (0.29)		
Combined diabetes mellitus [cases (%)]		-	49 (0.15)		
Combined hypertension [cases (%)]		-	31 (0.09)		

Note: BMI: Body mass index.

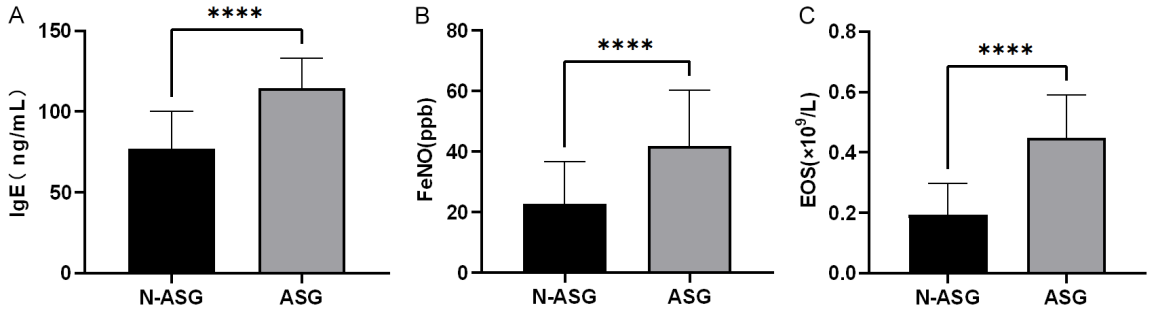

Figure 1. Comparison of IgE, FeNO, and EOS levels between non-asthma and asthma groups. A: Comparison of IgE between asthma and non-asthma groups; B: Comparison of FeNO between asthma and non-asthma groups; C: Comparison of EOS between asthma and non-asthma groups. Note: IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide; EOS: eosinophils. ****P < 0.0001.

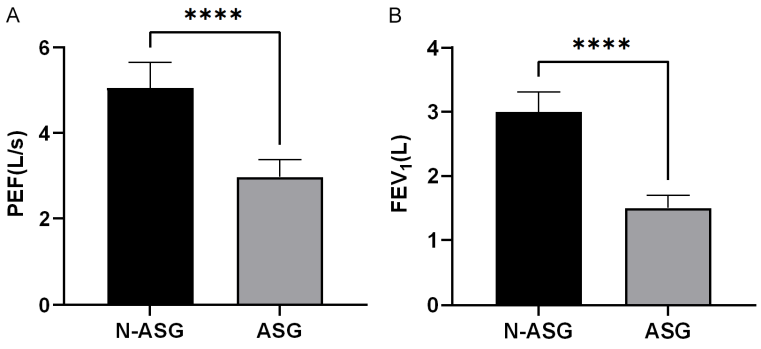

Figure 2. Comparison of pulmonary function indicators between the non-asthma group and asthma group. A: Comparison of PEF between asthma and non-asthma groups; B: Comparison of FEV1 between asthma and non-asthma groups. Note: PEF: peak expiratory flow rate; FEV1: forced expiratory volume in 1 s. ****P < 0.0001.

Comparison of general information in asthma patients across different severity groups

Comparison of general information across mild, moderate and severe asthma groups revealed no statistical difference in age, gender, BMI, systolic blood pressure, diastolic blood pressure, emergency admission time, exercise habits, marital history, history of alcoholism, combined diabetes mellitus, or combined hy-

Table 2. Diagnostic value of IgE, FeNO, and EOS levels for bronchial asthma

Marker	AUC	Cutoff	95% CI	Specificity	Sensitivity	Youden index
IgE	0.79	87.975	0.737-0.843	74.02%	86.61%	60.62%
FeNO	0.93	19.735	0.897-0.964	91.34%	96.73%	88.06%
EOS	0.88	0.145	0.842-0.925	83.46%	93.75%	77.21%

Note: IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide; EOS: eosinophils; AUC: area under curve.

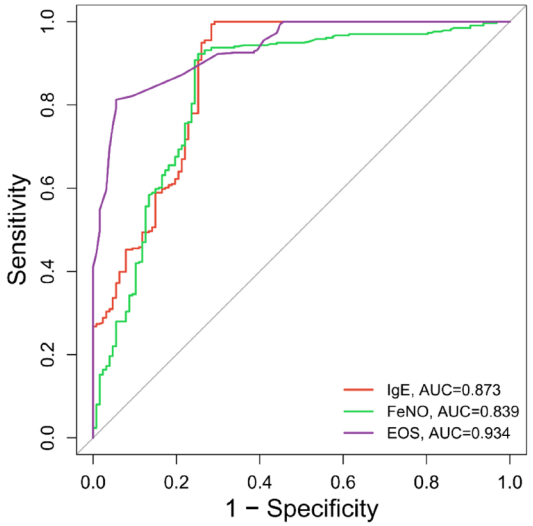

Figure 3. ROC curves for IgE, FeNO, and EOS in diagnosing adult asthma. Note: IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide; EOS: eosinophils; ROC: receiver operating characteristic curve.

pertension (all P > 0.05). However, significant differences were found in smoking history, family history of asthma, co-existing allergic rhinitis, and combined allergic eczema (all P < 0.05) (**Table 3**).

Comparison of IgE, FeNO, EOS levels in asthma patients across different severity groups

Comparing IgE, FeNO, and EOS levels among asthma patients of different severities showed that IgE, FeNO, and EOS levels in the moderate and severe asthma groups were significantly higher than those in the mild asthma group (all P < 0.05). Furthermore, levels of these markers in the severe asthma group were also significantly higher than those in the moderate asthma group (all P < 0.05) (**Figure 4**).

Correlation analysis of IgE, FeNO, EOS with bronchial asthma severity

Spearman's rank correlation analysis indicated that smoking history, family history of asthma, co-existing allergic rhinitis, co-existing allergic eczema, IgE, FeNO, and EOS were all positively correlated with the severity of bronchial asthma in adults (all P < 0.05), with correlation coefficients (r_s values) of 0.148, 0.154, 0.170, 0.157, 0.718, 0.679, and 0.540, respectively. Among these, IgE, FeNO, and EOS showed particularly strong correlations (r_s > 0.3) (**Table 4**).

Discussion

Bronchial asthma is a prevalent chronic respiratory disease, with significant regional variations, affecting more than 10% of the global population [9-11]. Despite advancements in healthcare that have improved asthma control, some patients remain poorly controlled and incurable. Therefore, early and accurate diagnosis of asthma is crucial for effective disease control. Due to age-related changes and associated conditions in adults, the diagnosis of adult asthma can be more challenging than in children [12]. While airway inflammation is the underlying pathology of asthma, conventional tests often fail to assess it accurately [13]. In clinical practice, lung capacity measurements like FEV1 and PEF are commonly used to diagnose asthma, evaluating airflow limitation and response to bronchodilators [14]. However, these measurements cannot reliably estimate airway inflammation or its type. Therefore, relying solely on spirometry to assess the presence and type of airway inflammation is insufficient. Therefore, seeking a more reliable diagnostic method for bronchial asthma is of great significance.

The results of this study showed that IgE, FeNO, and EOS levels in the asthma group were higher than those in the non-asthma group, while PEF and FEV1 were lower. The pathogenesis of asthma involves factors such as excessive mucus secretion, activation of inflammatory cells, airway remodeling, and airway obstruction, all resulting from interactions between epithelial cells and immune cells [10,

Table 3. Comparison of baseline information across different severity groups

		Mild asthma group (n=138)	Moderate asthma group (n=115)	Severe asthma group (n=83)	t/χ^2	P
Age (years, $\bar{x} \pm s$)		44.03±12.49	44.66±11.91	42.95±11.68	0.327	0.722
Sex [cases (%)]	Male	74 (0.54)	60 (0.52)	45 (0.54)	0.092	0.955
	Female	64 (0.46)	55 (0.48)	38 (0.46)		
BMI (kg/m^2)		24.07±2.89	24.03±2.84	23.91±3.14	1.178	0.309
Emergency admission time		7.49±1.06	7.57±0.99	7.37±1.11	1.458	0.234
Pulse pressure	Systolic pressure	129.10±11.43	130.20±11.10	129.60±11.27	0.829	0.437
	Diastolic pressure	74.01±8.06	73.67±7.72	74.32±8.58	1.464	0.233
Marital history		73 (0.53)	49 (0.43)	40 (0.48)	2.660	0.264
Smoking history		42 (0.30)	42 (0.37)	41 (0.49)	8.012	0.018
History of alcohol abuse		31 (0.22)	28 (0.24)	24 (0.29)	1.172	0.557
Exercise habit		49 (0.36)	41 (0.36)	29 (0.35)	0.012	0.994
Family history of asthma		22 (0.16)	26 (0.23)	27 (0.33)	8.233	0.016
Co-existing allergic rhinitis		14 (0.10)	19 (0.17)	22 (0.27)	10.137	0.006
Co-existing allergic eczema		29 (0.21)	36 (0.31)	32 (0.39)	8.270	0.016
Combined diabetes		22 (0.16)	15 (0.13)	12 (0.14)	0.424	0.809
Combined high blood pressure		13 (0.09)	10 (0.09)	8 (0.10)	0.062	0.970

Note: BMI: Body mass index.

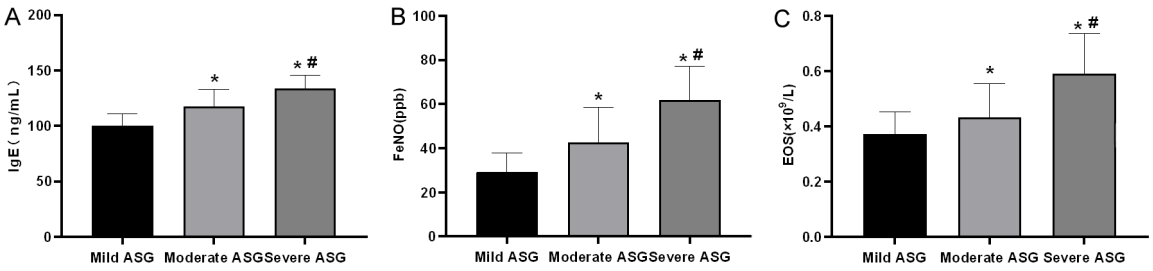

Figure 4. Comparison of IgE, FeNO, and EOS levels across different severity groups. A: Comparison of IgE levels among patients with mild asthma, moderate asthma, and severe asthma; B: Comparison of FeNO among patients with mild asthma, moderate asthma, and severe asthma; C: Comparison of EOS among patients with mild asthma, moderate asthma, and severe asthma. Note: IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide; EOS: eosinophils. Compared with mild asthma group, *P < 0.05; compared with moderate asthma group, #P < 0.05.

Table 4. Correlation analysis between IgE, FeNO, EOS, and other indicators with severity of bronchial asthma

Item	r_s	P
Smoking history	0.148	0.007
Family history of asthma	0.154	0.005
Combined allergic rhinitis	0.170	0.002
Combined allergic eczema	0.157	0.004
IgE	0.718	< 0.001
FeNO	0.679	< 0.001
EOS	0.540	< 0.001

Note: IgE: immunoglobulin E; FeNO: fractional exhaled nitric oxide; EOS: eosinophils; AUC: area under curve.

15, 16]. Among them, T help 2 cells (Th2) are recognized as a key pathogenic cell subset in asthma [3, 17]. Interleukin 4 (IL-4), secreted by Th2 cells, promotes B-cell activation and secretes large amounts of IgE antibody [18]. IgE is a key factor in the onset of asthma. Upon re-exposure to an allergen, it binds to IgE and induces mast cells to secrete a large amount of inflammatory mediators, leading to airway epithelial damage, smooth muscle hypertrophy and proliferation, vasodilation, changes in extracellular matrix components, all of which participate in the pathogenic process [10, 19, 20]. In the development of asthma, nitric oxide (NO) mainly promotes type II inflammatory response in asthma and is associated with epithelial cell apoptosis, leukocyte adhesion, as well as recruitment of mast cells, eosinophils, lymphocytes, and eosinophils [6, 21, 22]. EOS,

important inflammatory cells in asthma, are often elevated in asthma patients. EOS contain a many mediators that can induce inflammation, tissue damage, and inflammation cascade reactions, which further contribute to airway remodeling [23]. In addition, ROC curve analysis showed that IgE ≥ 87.975 ng/mL, FeNO ≥ 19.735 ppb, and EOS ≥ 0.145 × 10^9/L were optimal cut-off values for asthma assessment, with AUCs of 0.79, 0.93, and 0.88, respectively. These findings suggest that these biomarkers are valuable indicator for diagnosing asthma, aiding clinicians to take timely control measures and optimizing therapeutic regimens. Niu Mengxi et al. found that tezepelumab (a biopharmaceutical targeting thymic stromal lymphopoietin) significantly reduced the levels of EOS, FeNO, and IgE in patients with severe asthma, significantly improving lung function, quality of life, and asthma control [24]. Multiple studies have shown that IgE, FeNO, and EOS are important biomarkers in bronchial asthma [25-28].

In accordance with GINA 2021 guidelines [1], asthma patients were classified into mild, moderate, and severe categories for analysis. Significant differences were observed among the three groups in terms of smoking history, family history of asthma, co-existing allergic rhinitis and atopic eczema. The may be due to tobacco containing various harmful substances that can damage the airway mucosa, reduce macrophage phagocytic capacity, and induce a series of inflammatory responses, all of which are considered major factors causing asthma [29, 30]. Genetic factors are also one of the important factors causing bronchial asthma. ADAM33 gene, an asthma susceptibility gene, has polymorphisms closely related to airway inflammation and remodeling [23, 31]. Allergic rhinitis, allergic eczema, and bronchial asthma share similarities in their pathogenesis and inflammatory response. Studies have shown that bronchial asthma patients are more susceptible to allergic rhinitis, and its presence can complicate asthma management [32, 33]. Further analysis showed that IgE, FeNO, and EOS levels also differed among the three groups of patients, with the lowest levels in mild asthma patients and highest in severe asthma patients. Spearman rank correlation analysis demonstrated positive correlations between asthma severity and smoking history, family history of asthma, co-existing allergic rhinitis, atopic eczema, and levels of IgE, FeNO, and EOS (r_s=0.148, 0.154, 0.170, 0.157, 0.718, 0.679, 0.540), with IgE, FeNO, and EOS showing particularly strong correlations. This suggests that the more severe the condition of the bronchial asthma patients, the higher the levels of IgE, FeNO, and EOS were, supporting their use as effective indicators for assessing asthma severity.

While this study provides valuable insight, it also has some limitations. This study did not conduct detailed research on different asthma phenotypes or clinical stages. In addition, the small sample size may limit the generalizability of the results, and the lack of long-term follow-up restricts understanding of the role of these biomarkers in the long-term management of asthma. In the future, the practical application value of these biomarkers in the long-term management of bronchial asthma patients can be evaluated by expanding the sample size, including more cases with different clinical stages, and conducting long-term follow-up.

Conclusion

IgE, FeNO, and EOS are useful in the diagnosis and severity assessment of asthma, with FeNO demonstrating the highest diagnostic efficacy. Further research is needed to validate their long-term effects across different asthma phenotypes and treatment responses. A deeper understanding of these biomarkers could support more personalized treatment plans for asthma patients.

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Disclosure of conflict of interest

None.

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