Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Increased Serum EphA2 is Associated with Disease Severity in Pediatric Patients with Asthma

Suli Ma, Weiguang Qu

Department of Pediatrics, Pudong New Area People's Hospital, Shanghai, 201299, People's Republic of China

Correspondence: Weiguang Qu, Department of Pediatrics, Pudong New Area People's Hospital, 490 Chuanhuan South Road, Chuansha Town, Pudong New Area, Shanghai, 201299, People's Republic of China, Tel +86-15000586588, Email 15000586588@163.com



**Background:** Asthma is the most prevalent chronic inflammatory airway disease in children, with increasing incidence and prevalence. Ephrin type-A receptor 2 (EphA2) belongs to the Ephrin (Eph) family. It is predominantly found in bronchial epithelial cells and may play a potential role in mediating airway inflammation in asthma. However, this study aimed to evaluate the association between a novel biomarker, EphA2, in two distinct pediatric asthma populations stratified by disease severity.

**Materials and Methods:** Serum levels of interleukins (IL-1β, IL-4, IL-6, IL-8, IL-13), tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), matrix metalloproteinase (MMP-2 and MMP-9), and EphA2 were measured by ELISA in all participants. In addition, blood eosinophil counts, Total IgE levels and exhaled nitric oxide (FeNO) levels were evaluated.

**Results:** Serum EphA2 levels in patients with asthma (n=195) were significantly higher than those in healthy controls (n=120), and the levels were notably elevated in patients with severe asthma (n=82) than in those with mild-moderate asthma (n=113). Receiver Operating Characteristic (ROC) curve analysis revealed that the ideal threshold for serum EphA2 was 324.76 pg/mL. This cutoff point demonstrated a sensitivity of 88.7% and a specificity of 92.5%, yielding an Area Under the Curve (AUC) of 0.959. Further correlative analysis indicated that serum EphA2 level was negatively correlated with forced expiratory volume in 1 second (FEV1) ($r=-0.376$, $P<0.001$), the ratio of FEV1 to forced vital capacity (FVC) ($r=-0.476$, $P<0.001$), and peak expiratory flow (PEF) ($r=-0.699$, $P<0.001$). Furthermore, we observed that serum EphA2 positively correlated with Eosinophil count ($r=0.227$, $P=0.001$), Total IgE ($r=0.715$, $P<0.001$), FeNO ($r=0.560$, $P<0.001$), IL-1β ($r=0.423$, $P<0.001$), IL-4 ($r=0.314$, $P<0.001$), IL-6 ($r=0.625$, $P<0.001$), IL-8 ($r=0.628$, $P<0.001$), IL-13 ($r=0.569$, $P<0.001$), TNF-α ($r=0.562$, $P<0.001$), TGF-β1 ($r=0.535$, $P<0.001$), MMP-2 ($r=0.273$, $P<0.001$), and MMP-9 ($r=0.266$, $P<0.001$) in all asthma patients.

**Conclusion:** Our research suggests that EphA2 might be a valuable marker for assessing the risk of exacerbation, inflammation of the airways, and airway remodelling in asthma patients.

**Keywords:** asthma, chronic airway disease, mild-moderate asthma, severe asthma, EphA2

## Introduction

Asthma is a complex condition that presents with a variety of respiratory symptoms, including coughing, chest tightness, wheezing, and shortness of breath (dyspnea). A significant feature of asthma is airway remodeling.[1] This condition has become a major global public health concern, affecting approximately 300 million people worldwide and resulting in substantial medical and financial burdens.[2] Additionally, asthma is primarily caused by an allergic response that is closely related to the differentiation of T lymphocytes and production of cytokines.[3,4] The causes of asthma are complex, and airway remodeling is a vital aspect of the disease.[5] However, among the various treatment options available, glucocorticoids (GCs) are essential for managing asthma because of their strong anti-inflammatory effects. However, some patients may develop resistance to GCs, and long-term use of these medications can lead to serious side effects.[6] Therefore, it is crucial to investigate the underlying mechanisms of asthma, particularly focusing on airway inflammation and remodeling, to develop more effective treatment strategies.[7]

Ephrin (Eph) receptors represent the most significant family of tyrosine kinase receptors, and play a crucial role in cellular communication in conjunction with ephrin ligands. The interactions between Eph receptors and ephrin ligands

Received: 23 January 2025
Accepted: 27 March 2025
Published: 8 April 2025

influence the pathogenesis of various conditions, including wound healing, ischemia-reperfusion injury, nerve damage, endothelial impairment, and epithelial damage.[8–11] Furthermore, Eph receptors and ephrin ligands regulate critical processes during embryonic neuronal development, angiogenesis, and oncogenesis.[8,11] Recently, numerous investigations have focused on the intricate roles of Eph and ephrin in cancerous conditions.[12,13] According to various studies, EphA2 receptor and ephrinA1 ligand also modulate inflammatory responses through the mechanism of vascular endothelial injury. In an in vivo investigation conducted in rats, ephrin A1 induced histological disruption of the endothelium in the pulmonary tissue. Simultaneously, the inhibition of EphA2 signaling significantly diminished the albumin leakage.[8,11,14] An additional study revealed that activation of EphA2 prompted the expression of vascular cell adhesion molecule-1 and E-selectin.[15] The EphA2 receptor may be implicated in sepsis owing to its pivotal role that endothelial injury plays in the pathophysiology of sepsis.[16] In this study, we hypothesized that EphA2 protein might be significantly linked to the severity of asthma in children, potentially making it a crucial area of research. Therefore, the present study explored the clinical relevance of serum EphA2 levels in differentiating between children patients with asthma and healthy controls.

# Patients and Method

## Study Population

A total of 315 subjects (195 patients with asthma and 120 healthy controls) from the Department of Pediatrics in our Hospital were enrolled between January 2022 and June 2024. The diagnosis of asthma was based on the following criteria: typical symptoms and confirmed variable expiratory airflow limitations that were proposed by "Global Initiative for Asthma".[17] Asthma severity status was assessed according to the measured lung function results, and all asthmatic children were further divided into mild-moderate (n=113) and severe (n=82) subgroups. (1) Mild-moderate subgroup: Pulmonary function test showed that the forced expiratory volume in one second (FEV1) or maximum expiratory flow (PEF) was greater than 60% of the normal expected value (2) Severe subgroup: FEV1 or PEF was less than 60% of the normal expected value. The exclusion criteria were as follows: (1) children who experienced upper respiratory tract infection; (2) children who received systemic corticosteroid treatment within 8 weeks; (3) children with critically ill graded asthma; (4) shortness of breath, wheezing, and coughing caused by other reasons; and (5) rheumatoid arthritis or allergic rhinitis. The control group included children who underwent routine physical examinations with matched age and genders. The research procedure complied with the Helsinki Declaration and was approved by the Medical Ethics Committee of the Pudong New Area People's Hospital.

## Clinical Data Collection

Complete clinical and laboratory data of the enrolled patients after admission were collected, including age, gender, body mass index (BMI), and duration of asthma. Portable spirometry was used to monitor lung function parameters, such as forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and peak expiratory flow rate (PEF). The FEV1/FVC ratio was calculated.

## Enzyme-Linked Immunosorbent Assay

Fasting venous blood samples (5 mL) were collected from all the participants. Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of interleukin (IL)-1β (DLB50, R&D Systems), IL-4 (D4050, R&D Systems), IL-6 (D6050B, R&D Systems), IL-8 (SEKH-0016, Solarbio), IL-13 (SEKH-0022, Solarbio), TNF-α (DTA00D, R&D Systems), TGF-β1 (ml022522, Shanghai Enzyme-linked Biotechnology), MMP-2 (MMP200, R&D Systems), MMP-9 (DMP900, R&D Systems), and EphA2 (ml038095, Shanghai Enzyme-linked Biotechnology) in the serum of all study participants.

## Statistical Analysis

All statistical analyses were performed using SPSS software 20.0. Data are displayed as mean ± standard deviation (SD) for continuous variables and as frequency (percentage) for categorical variables. Normality tests were performed using the Shapiro–Wilk test for all the continuous variables of interest. The comparison between two groups was analyzed

using the Student's *t*-test or Mann–Whitney *U*-test when the normal distribution was not satisfied. The comparison between three groups was analyzed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test, or by Kruskal–Wallis tests when the normal distribution is not satisfied. Pearson's correlation analysis was conducted to assess the association between EphA2 and other continuous variables. ROC curve analysis was performed to evaluate the diagnostic value of serum EphA2 levels in children with asthma and healthy controls. P<0.05 was considered statistically significant.

# Results

## Baseline Characteristics of the Investigation

The investigation used a comprehensive method to compare patients with mild-moderate and severe asthma to healthy controls. The results from the Student's *t*-test indicated that mild-moderate and severe asthma patients exhibited significantly higher levels of various health indicators, including the duration of asthma (years), eosinophil count, total immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO), Interleukin-1 beta (IL-1β), IL-4, IL-6, IL-8, IL-13, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta 1 (TGF-β1), matrix metalloproteinase 2 (MMP-2), MMP-9, and EphA2 compared to healthy controls. In contrast, levels of forced expiratory volume in 1 second (FEV1), the ratio of FEV1 to forced vital capacity (FVC), and peak expiratory flow (PEF) were significantly lower (P<0.05), as shown in Table 1. However, there were no significant differences between the mild-moderate and severe asthma patients to healthy controls in terms of age, gender, and body mass index (BMI) (P<0.05).

ELISA testing was used to measure the serum levels of EphA2 in patients with asthma (n=195) and healthy controls (n=120). We further divided all asthmatic children into mild-moderate (n=113) and severe (n=82) subgroups. We compared serum EphA2 levels among the healthy controls (n=120), mild-moderate (n=113), and severe (n=82). We observed that EphA2 levels were significantly elevated in both the mild-moderate and severe groups compared to the

**Table 1** Characteristics of the Healthy Controls and Subjects with Mild-Moderate and Severe Asthma

| Variables | Controls (n=120) | Asthma (n = 195) | | P-Value |
|---|---|---|---|---|
| | | Mild-Moderate (n = 113) | Severe (n = 82) | |
| Age (years) | 6.94±2.13 | 7.27±1.91 | 7.37±1.82 | 0.264 |
| Gender (male, %) | 65 (54.2%) | 68 (60.2%) | 48 (58.5%) | 0.634 |
| BMI (kg/m$^2$) | 19.19±2.07 | 19.03±1.91 | 19.36±1.65 | 0.606 |
| Duration (years) | 0 | 2.45±0.69 | 2.74±0.69 | <0.001 |
| FEV1 (L) | 2.11±0.36 | 1.82±0.30 | 1.59±0.18 | <0.001 |
| FEV1/FVC (%) | 84.00±4.66 | 76.95±4.10 | 72.80±3.29 | <0.001 |
| PEF (L/min) | 85.15±2.60 | 70.11±2.86 | 62.77±3.51 | <0.001 |
| Eosinophil count (per/μL) | 152.29±27.92 | 479.07±83.70 | 527.82±82.63 | <0.001 |
| Total IgE (IU/mL) | 134.05±22.30 | 191.34±22.05 | 282.90±43.62 | <0.001 |
| FeNO (ppb) | 21.91±3.25 | 32.43±3.59 | 40.50±5.22 | <0.001 |
| IL-1β (pg/mL) | 56.29±7.18 | 104.94±13.07 | 125.35±18.82 | <0.001 |
| IL-4 (pg/mL) | 45.71±6.44 | 74.26±8.34 | 78.70±8.77 | <0.001 |
| IL-6 (pg/mL) | 6.84±0.86 | 17.31±2.18 | 21.58±2.07 | <0.001 |
| IL-8 (pg/mL) | 11.61±1.56 | 16.74±1.78 | 22.09±2.31 | <0.001 |
| IL-13 (pg/mL) | 9.28±1.11 | 15.65±1.74 | 20.20±2.40 | <0.001 |
| TNF-α (pg/mL) | 21.50±3.17 | 27.98±3.21 | 35.52±6.22 | <0.001 |
| TGF-β1 (pg/mL) | 27.01±3.58 | 39.00±5.17 | 46.21±6.29 | <0.001 |
| MMP-2 (ng/mL) | 118.05±20.84 | 158.77±25.91 | 179.45±36.58 | <0.001 |
| MMP-9 (ng/mL) | 82.70±13.65 | 120.21±15.80 | 133.89±21.58 | <0.001 |
| EphA2 (pg/mL) | 275.65±40.10 | 359.07±42.87 | 521.08±60.34 | <0.001 |

**Notes**: Continuous variables are expressed as mean ± SD, and analyzed by ANOVA followed by Tukey's post hoc test. Categorical variables are expressed as frequency (percentage), and analyzed using the chi-square test.


https://doi.org/10.2147/JAA.S515475

healthy controls (Figure 1A). Additionally, the Receiver Operating Characteristic (ROC) curve analysis indicated that the optimal cutoff value for serum EphA2 is 324.76 pg/mL, with a sensitivity of 88.7% and a specificity of 92.5%, resulting in an Area Under the Curve (AUC) of 0.959 (Figure 1B).

## Correlation Between Serum EphA2 Levels and Lung Function in Children with Asthma

Pearson correlation analysis was used to investigate the relationship between serum EphA2 levels and lung function in asthma patients. We observed that Serum EphA2 level is negatively correlated with FEV1 (r=−0.376, P<0.001), FEV1/FVC (r=−0.476, P<0.001), and PEF (r=−0.699, P<0.001) (Figure 2A–C).

## Correlation of Serum EphA2 Levels with Inflammatory Indicators of T2 Inflammation, Cytokines, and Serum Markers of Airway Remodeling in Children with Asthma

Pearson correlation analysis was used to investigate the relationship between serum EphA2 levels with inflammatory indicators of T2 inflammation, cytokines, and serum markers of airway remodeling in children with asthma. We found that serum EphA2 positively correlates with Eosinophil count (r=0.227, P=0.001), Total IgE (r=0.715, P<0.001), and FeNO (r=0.560, P<0.001) (Figure 3A–C). Additionally, we observed that serum EphA2 is positively associated with inflammatory cytokines, including IL-1β (r=0.423, P<0.001), IL-4 (r=0.314, P<0.001), IL-6 (r=0.625, P<0.001), IL-8 (r=0.628, P<0.001),

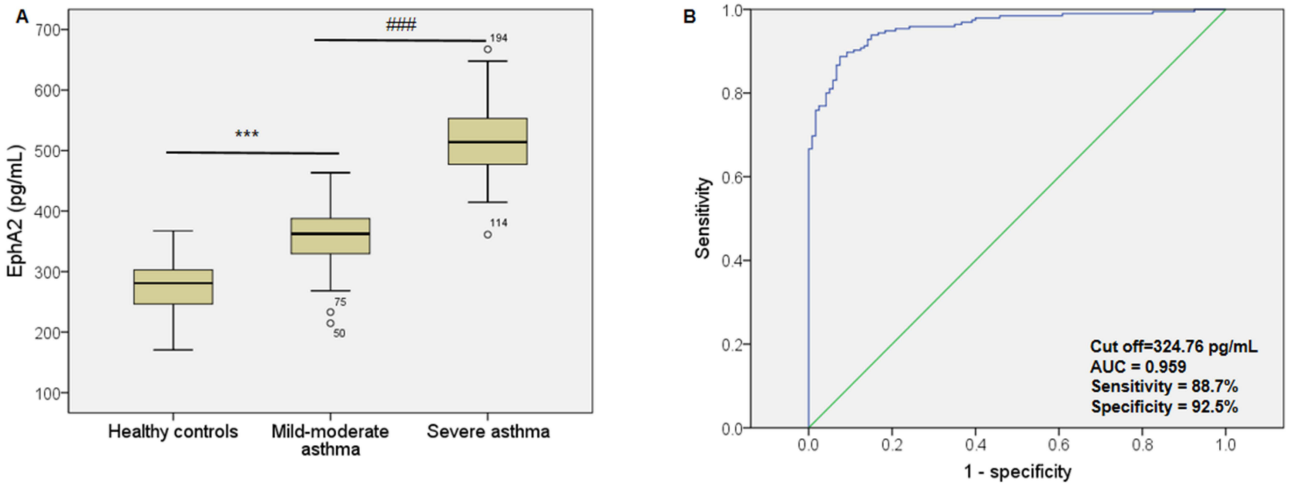


**Figure 1** Comparison of serum EphA2 in children with asthma. (**A**) Serum EphA2 levels in control subjects (n=120), Mild-moderate (n=113) and severe (n=82) ELISA detected asthmatic patients. (**B**) The ROC curve is used to obtain the critical point of serum EphA2 levels that distinguish between healthy controls and asthma. ANOVA will be used to compare the differences between the three groups. The optimal critical point is 324.76 pg/mL. The area under the curve is 0.959. ***P<0.001; ###P<0.001.

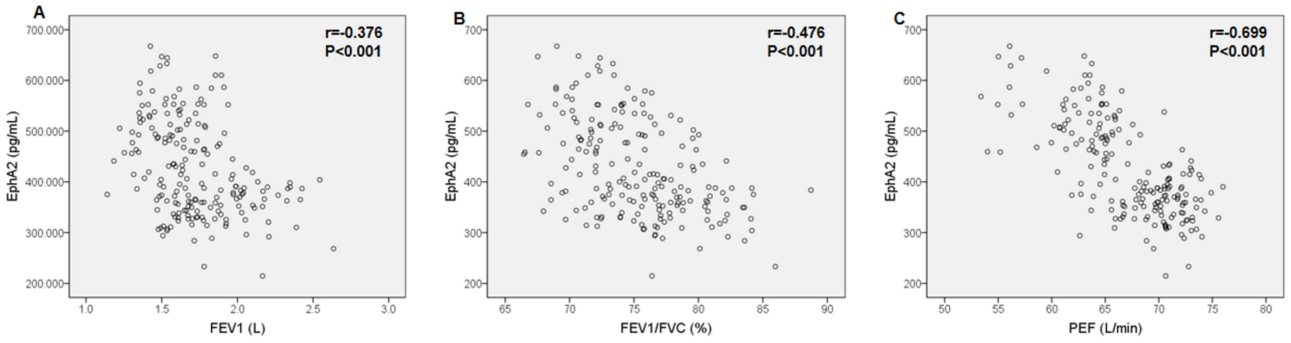


**Figure 2** Correlation between serum EphA2 levels and lung function in children with asthma. Serum EphA2 is negatively correlated with (**A**) forced expiratory volume in one second (FEV1), (**B**) FEV1/forced vital capacity (FEV1/FVC), and (**C**) peak expiratory flow rate (PEF). Pearson correlation analysis was performed.

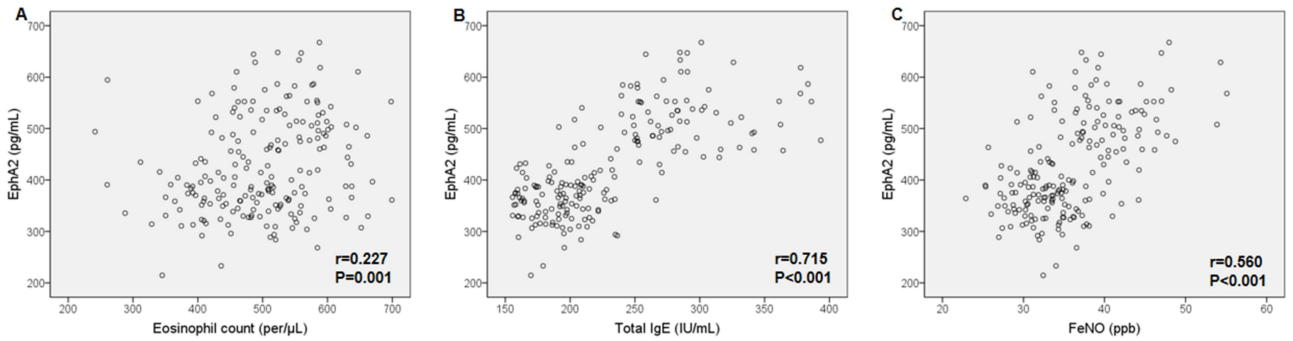


**Figure 3** Correlation between serum EphA2 levels and inflammatory indicators of T2 inflammation in children with asthma. Serum EphA2 is positively correlated with (**A**) Eosinophil count, (**B**) Total IgE, and (**C**) FeNO.

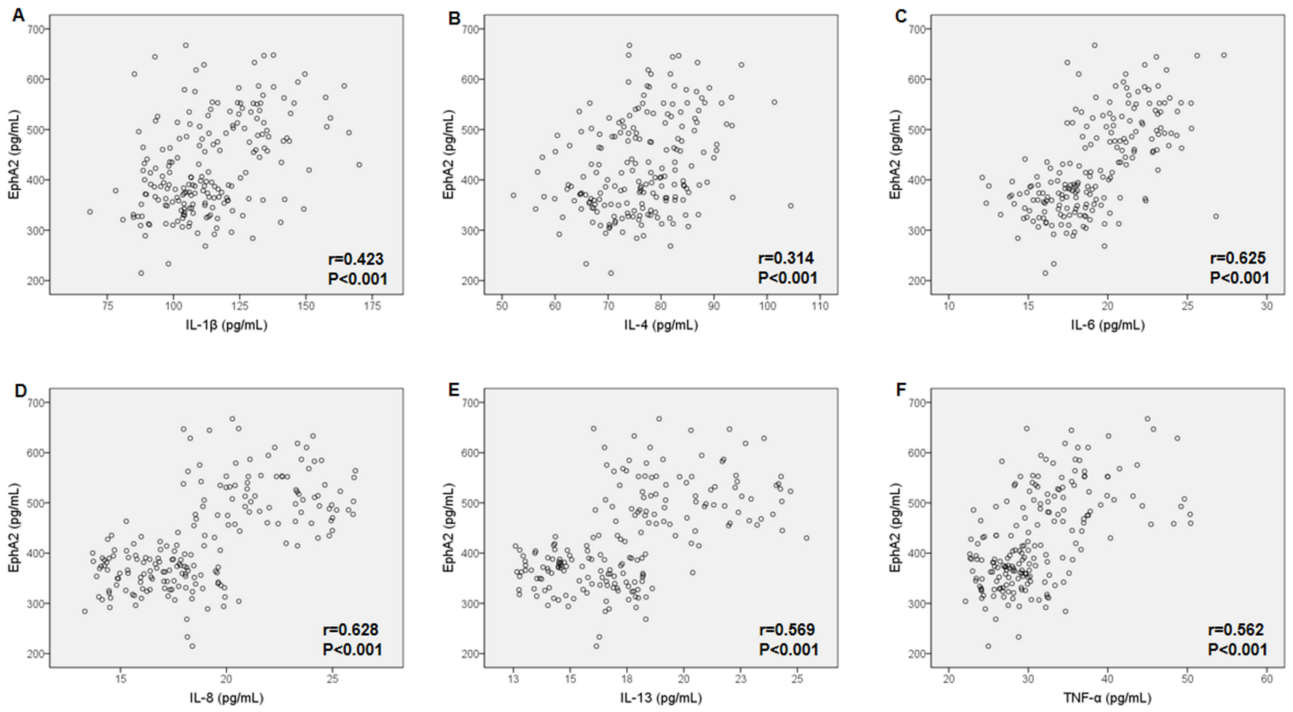


**Figure 4** Correlation between serum EphA2 levels and inflammatory cytokines in children with asthma. Serum EphA2 is positively correlated with (**A**) IL-1β, (**B**) IL-4, (**C**) IL-6, (**D**) IL-8, (**E**) IL-13, and (**F**) TNF-α.

IL-13 (r=0.569, P<0.001), and TNF-α (r=0.562, P<0.001) (Figure 4A–F). Furthermore, the results showed that Serum EphA2 is positively related to TGF-β1 (r=0.535, P<0.001), MMP-2 (r=0.273, P<0.001), and MMP-9 (r=0.266, P<0.001) (Figure 5A–C).

## The Molecular Mechanism of How EphA2 Regulates the Development of Asthma

To conclude, we provide a diagram that illustrates the molecular mechanism by which EphA2, an important factor in the development of asthma, regulates the development of asthma (Figure 6). Elevated levels of EphA2 in children with asthma promote the release of inflammatory cytokines from the airway epithelium, leading to increased airway inflammation and hyper responsiveness (AHR). Additionally, EphA2 contributes to airway remodeling and sub epithelial fibrosis by stimulating the release of fibrotic cytokines such as TGF-β1, MMP-2, and MMP-9. Consequently, the rise in EphA2 levels exacerbates the damage to the airway epithelium caused by allergens.


https://doi.org/10.2147/JAA.S515475

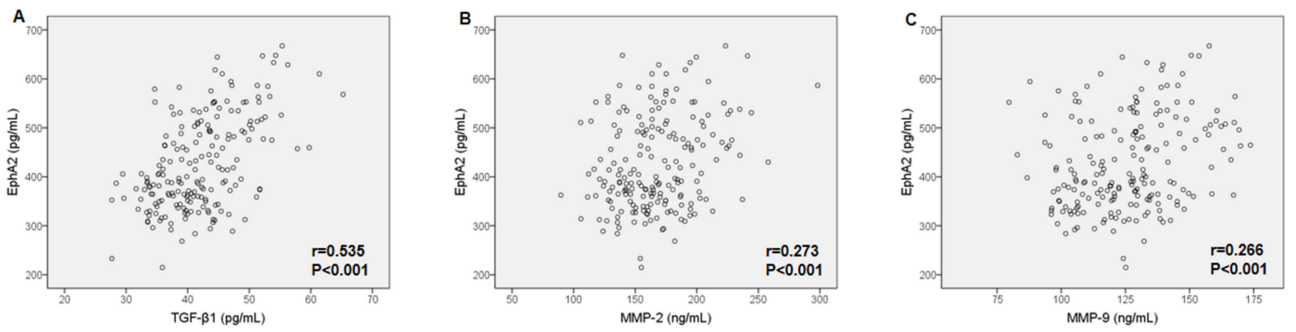


**Figure 5** Correlation between serum EphA2 levels and serum airway remodeling markers in children with asthma. Serum EphA2 is positively correlated with (**A**) TGF-β1, (**B**) MMP-2, and (**C**) MMP-9.

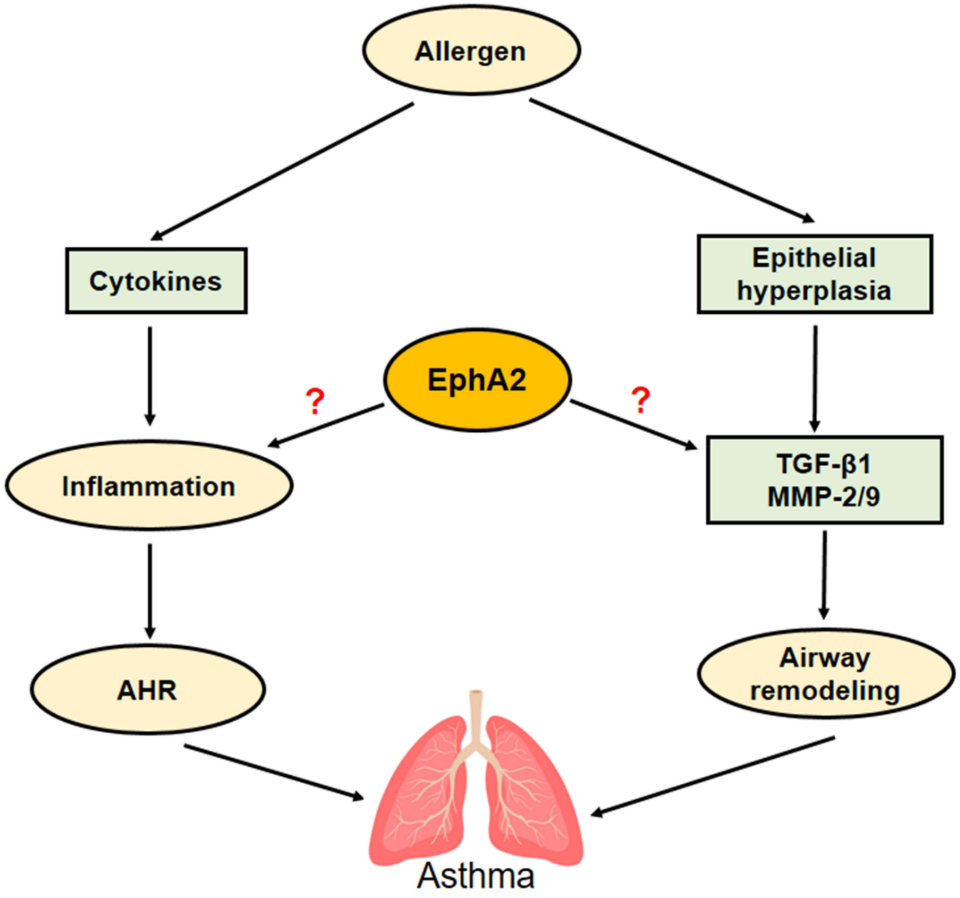


**Figure 6** Schematic diagram of EphA2 in the development of asthma. Increased EphA2 in asthmatic children promotes the release of inflammatory cytokines from airway epithelium, enhancing airway inflammation and hyperresponsiveness (AHR). EphA2 also enhance airway remodeling and subepithelial fibrosis by promoting the release of fibrosis-related cytokines (TGF-β1, MMP-2 and MMP-9). Therefore, the increase in EphA2 levels aggravates the injury of airway epithelium caused by allergens.

## Discussion

This investigation sought to assess the clinical significance of serum EphA2 levels in distinguishing between pediatric asthma patients and healthy controls. The results showed that serum EphA2 levels were significantly higher in patients with asthma than in healthy controls. Our investigation revealed that asthma patients had significantly higher levels of different health indicators, including the duration of asthma (in years), FEV1, ratio of FEV1 to forced vital capacity (FVC), PEF, eosinophil count, IgE, FeNO, IL-1β, IL-4, IL-6, IL-8, IL-13, TNF-α, TGF-β1, MMP-2, MMP-9, and EphA2. In addition, EphA2 levels were significantly elevated in both the mild-moderate and severe groups compared

with healthy controls. Furthermore, patients with asthma with serum EphA2 levels exceeding 324.76 pg/mL were found to have a significantly higher risk of developing asthma. Moreover, serum EphA2 levels are positively associated with inflammatory indicators of T2 inflammation, cytokines, and serum markers of airway remodeling, and are negatively correlated with FEV1, FEV1/FVC, and PEF in children with asthma. These findings suggest that serum EphA2 level may serve as a potential biomarker for the early detection of asthma in children.

EphA2 is a member of the Eph family and is primarily found in epithelial cells.[18] Recent research has highlighted that the EphA-ephrin signaling pathway plays a crucial role in the development of inflammation and inflammatory disorders caused by infections and tissue damage.[19] However, investigations focusing on the relationship between serum levels of EphA2 and the severity of asthma in pediatric patients are lacking. In the present study, EphA2 concentrations were markedly elevated in the mild-moderate and severe patients compared to those in the healthy control group. Furthermore, serum EphA2 concentrations demonstrated a positive correlation with inflammatory markers indicative of T2 inflammation, cytokines, and serum biomarkers associated with airway remodeling, while exhibiting a negative correlation with FEV1, FEV1/FVC, and PEF in pediatric asthma patients.

Numerous studies have explored the complex roles of the Eph receptor and ephrin ligand in cancer development.[20,21] Notably, several reports have identified associations between the EphA2 receptor and various oncogenic signaling pathways, including the MAP/ERK, phosphoinositide 3-kinase, E-cadherin, and integrin/FAK/paxillin pathways.[20,22,23] EphA2 is being investigated as a potential therapeutic target in oncology with ongoing clinical trials involving patients with advanced malignancies.[24–27] Inflammation may influence tumor development, progression, and response to therapy.[12] Interestingly, cancer and infectious diseases exhibit many similarities. Programmed cell death ligand 1 (PD-L1) inhibitors were initially developed for cancer treatment as potential therapeutic agents for chronic infections and sepsis.[13] Furthermore, the EphA2 receptor and ephrin ligand also play a role in inflammation, particularly by causing vascular endothelial injury.[8,12,14] EphA2 and other inflammatory mediators, such as TNF-α and interferon (IFN)-γ, can upregulate NF-κB, leading to an increased expression of intercellular adhesion molecule-1. This process facilitates the migration and attachment of leukocytes.[14,28] Recent studies have established a connection between EphA2 receptor and inflammation.[29–33]

Eosinophils are a type of white blood cell that plays a crucial role in the immune system, particularly in allergic reactions and asthma. In eosinophilic asthma, eosinophils accumulate in the airways, releasing mediators and cytokines contributing to severe airway inflammation and tissue damage. Elevated eosinophil counts are associated with increased asthma severity, poor asthma control, and a higher rate of exacerbations.[34] Increased levels of total IgE are often found in patients with allergic asthma and are associated with increased asthma severity.[35] Higher levels of FeNO are associated with increased airway inflammation and asthma severity.[36] Proinflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-13, and TNF-α) play a significant role in the pathogenesis of asthma by promoting and amplifying the inflammatory response in the airways.[19,37] Airway remodeling is a hallmark of chronic asthma and involves structural changes in the airway wall. TGF-β1 promotes the proliferation of airway smooth muscle cells and the production of extracellular matrix proteins, contributing to airway remodeling.[38] MMP-2 and MMP-9 are involved in remodeling the airway wall by breaking down collagen and other matrix proteins. Elevated levels of MMP-9 have been associated with increased airway remodeling in asthma.[39] A recent study reported that EphA2 is highly expressed on bronchial epithelial cells and is activated by allergens such as Dermatophagoides pteronyssinus. Activation of EphA2 leads to the secretion of proinflammatory cytokines like IL-6 and IL-8, which contribute to airway inflammation and hyper responsiveness.[19] However, our results showed that serum EphA2 positively correlates with Eosinophil count, Total IgE, and FeNO. In addition, we observed a positive association of the serum EphA2 levels with inflammatory cytokines, including IL-1β, IL-4, IL-6, IL-8, IL-13, and TNF-α. Furthermore, the results showed that Serum EphA2 is positively related to TGF-β1, MMP-2, and MMP-9.

Our study had several inherent limitations. First, caution should be exercised when interpreting our results because of the relatively small sample size. Second, the study design was not intended to be a prospective longitudinal analysis; rather, it was structured as a cross-sectional study. Therefore, the prognostic significance of serum EphA2 level requires further validation. Finally, this study provides important insights into the irregularities of EphA2 that contribute to the pathophysiology of asthma, particularly in pediatric patients diagnosed with this condition.

## Conclusions

Children diagnosed with asthma have higher serum EphA2 levels than healthy controls. Elevated serum EphA2 levels independently increased the risk of asthma development in these children. A more extensive population-based prospective study is needed to validate the potential role of serum EphA2 as a predictive biomarker for children with asthma.

## Data Sharing Statement

The datasets used/analyzed during the present study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The Ethics Committee of the Pudong New Area People's Hospital approved this study (2025-LW-02). The authors followed all standard protocols in accordance with the 1964 Declaration of Helsinki. Informed consent was obtained from all participated subjects' parents/legal guardians in the study.

## Acknowledgment

We sincerely thank all of the participants in our study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; 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.

## Disclosure

The authors declare that they have no competing interests in this work.

## References

1. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol*. 2019;144(1):1–12. doi:10.1016/j.jaci.2019.05.031
2. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J*. 2014;7(1):12. doi:10.1186/1939-4551-7-12
3. Fahy JV. Type 2 inflammation in asthma is present in most cases but absent in many. *Nat Rev Immunol*. 2015;15(1):57–65. doi:10.1038/nri3786
4. Singhania A, Wallington JC, Smith CG, et al. Multitissue transcriptomics delineates the diversity of airway T-cell functions in asthma. *Am J Respir Cell mol Biol*. 2018;58(2):261–270. doi:10.1165/rcmb.2017-0162OC
5. Banno A, Reddy AT, Lakshmi SP, Reddy RC. Bidirectional interaction of airway epithelial remodeling and inflammation in asthma. *Clin Sci*. 2020;134(9):1063–1079. doi:10.1042/CS20191309
6. Ora J, Calzetta L, Matera MG, Cazzola M, Rogliani P. Advances with glucocorticoids in the treatment of asthma: state of the art. *Expert Opin Pharmacother*. 2020;21(18):2305–2316. doi:10.1080/14656566.2020.1807514
7. Nabe T. Steroid-resistant asthma and neutrophils. *Biol Pharm Bull*. 2020;43(1):31–35. doi:10.1248/bpb.b19-00095
8. Pasquale EB. Eph-ephrin bidirectional signaling in physiology and disease. *Cell*. 2008;133(1):38–52. doi:10.1016/j.cell.2008.03.011
9. Egea J, Klein R. Bidirectional Eph-ephrin signaling during axon guidance. *Trends Cell Biol*. 2007;17(5):230–238. doi:10.1016/j.tcb.2007.03.004
10. Pasquale EB. Eph receptor signalling casts a wide net on cell behaviour. *Nat Rev mol Cell Biol*. 2005;6(6):462–475. doi:10.1038/nrm1662
11. Kullander K, Klein R. Mechanisms and functions of Eph and ephrin signalling. *Nat Rev mol Cell Biol*. 2002;3(7):475–486. doi:10.1038/nrm856
12. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899. doi:10.1016/j.cell.2010.01.025
13. Hotchkiss RS, Moldawer LL. Parallels between Cancer and Infectious Disease. *N Engl J Med*. 2014;371(4):380–383. doi:10.1056/NEJMcibr1404664
14. Coulthard MG, Morgan M, Woodruff TM, et al. Eph/Ephrin signaling in injury and inflammation. *Am J Pathol*. 2012;181(5):1493–1503. doi:10.1016/j.ajpath.2012.06.043
15. Funk SD, Yurdagul JA, Albert P, et al. EphA2 activation promotes the endothelial cell inflammatory response: a potential role in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2012;32(3):686–695. doi:10.1161/ATVBAHA.111.242792
16. Cohen J, Vincent JL, Adhikari NKJ, et al. Sepsis: a roadmap for future research. *Lancet Infect Dis*. 2015;15(5):581–614. doi:10.1016/S1473-3099(15)70112-X
17. Girodet PO, Molimard M. The 2019 Global Initiative for Asthma report: evidence-based or evidence-biased medicine? *Therapie*. 2021;76(1):57–58. doi:10.1016/j.therap.2020.02.021
18. Tuzi NL, Gullick WJ. Eph, the largest known family of putative growth factor receptors. *Br J Cancer*. 1994;69(3):417–421. doi:10.1038/bjc.1994.77

19. Xu Z, Ye Y, Huang G, et al. EphA2 recognizes Dermatophagoidespteronyssinus to mediate airway inflammation in asthma. *Int Immunopharmacol*. 2022;111:109106. doi:10.1016/j.intimp.2022.109106
20. Beauchamp A, Debinski W. Ephs and ephrins in cancer: ephrin-A1 signalling. *Semin Cell Dev Biol*. 2012;23(1):109–115. doi:10.1016/j.semcdb.2011.10.019
21. Tandon M, Vemula SV, Mittal SK. Emerging strategies for EphA2 receptor targeting for cancer therapeutics. *Expert Opin Ther Targets*. 2011;15(1):31–51. doi:10.1517/14728222.2011.538682
22. Wykosky J, Debinski W. The EphA2 receptor and ephrinA1 ligand in solid tumors: function and therapeutic targeting. *mol Cancer Res*. 2008;6(12):1795–1806. doi:10.1158/1541-7786.MCR-08-0244
23. Miao H, Burnett E, Kinch M, Simon E, Wang B. Activation of EphA2 kinase suppresses integrin function and causes focal-adhesion-kinase dephosphorylation. *Nat Cell Biol*. 2000;2(2):62–69. doi:10.1038/35000008
24. Chakar S, Scott A, Gan H. Safety and bio-imaging trial of DS 8895a in patients with advanced EphA2 positive cancers (LUD2014-002). Available from: https://clinicaltrials.gov. Accessed January, 2025.
25. Tao H, Chen J, Niu L. CAR-T cell immunotherapy for EphA2 positive malignant glioma patients. Available from: https://clinicaltrials.gov. Accessed January, 2025.
26. Colrman C. EphA2 gene targeting using neutral liposomal small interfering RNA delivery. Available from: https://clinicaltrials.gov. Accessed January, 2025.
27. Askoxylakis V. A study evaluating MM-310 in patients with solid tumors. Available from: https://clinicaltrials.gov. Accessed January, 2025.
28. Chan B, Sukhatme VP. Receptor tyrosine kinase EphA2 mediates thrombin-induced upregulation of ICAM-1 in endothelial cells in vitro. *Thromb Res*. 2009;123(5):745–752. doi:10.1016/j.thromres.2008.07.010
29. Ivanov AI, Romanovsky AA. Putative dual role of ephrin-Eph receptor interactions in inflammation. *IUBMB Life*. 2006;58(7):389–394. doi:10.1080/15216540600756004
30. Ivanov AI, Steiner AA, Scheck AC, Romanovsky AA. Expression of Eph receptors and their ligands, ephrins, during lipopolysaccharide fever in rats. *Physiol Genomics*. 2005;21(2):152–160. doi:10.1152/physiolgenomics.00043.2004
31. Cheng N, Chen J. Tumor necrosis factor-alpha induction of endothelial ephrin A1 expression is mediated by a p38 MAPK- and SAPK/JNK-dependent but nuclear factor-kappa B-independent mechanism. *J Biol Chem*. 2001;276(17):13771–13777. doi:10.1074/jbc.M009147200
32. Carpenter TC, Schroeder W, Stenmark KR, Schmidt EP. Eph-A2 promotes permeability and inflammatory responses to bleomycin-induced lung injury. *Am J Respir Cell mol Biol*. 2012;46(1):40–47. doi:10.1165/rcmb.2011-0044OC
33. Schruefer R, Sulyok S, Schymeinsky J, Peters T, Scharffetter-Kochanek K, Walzog B. The proangiogenic capacity of polymorphonuclear neutrophils delineated by microarray technique and by measurement of neovascularization in wounded skin of CD18-deficient mice. *J Vasc Res*. 2006;43(1):1–11. doi:10.1159/000088975
34. McBrien CN, Menzies-Gow A. The biology of eosinophils and their role in asthma. *Front Med Lausanne*. 2017;4:93. doi:10.3389/fmed.2017.00093
35. Platts-Mills TA, Souders JE. The role of immunoglobulin E in allergy and asthma. *Am J Respir Crit Care Med*. 2001;164(1):1–5. doi:10.1164/ajrccm.164.1.2104021a
36. Ricciardolo FL, Sorbello V, Ciprandi G. A pathophysiological approach for FeNO: a biomarker for asthma. *Allergol Immunopathol*. 2015;43(6):609–616. doi:10.1016/j.aller.2014.11.004
37. Carlson NG, Wieggel WA, Chen J, Bacchi A, Rogers SW, Gahring LC. Inflammatory cytokines IL-1 alpha, IL-1 beta, IL-6, and TNF-alpha impart neuroprotection to an excitotoxin through distinct pathways. *J Immunol*. 1999;163(7):3963–3968.
38. Chen G, Khalil N. TGF-beta1 increases proliferation of airway smooth muscle cells by phosphorylation of map kinases. *Respir Res*. 2006;7(1):2. doi:10.1186/1465-9921-7-2
39. Lin SC, Chou HC, Chiang BL, Chen CM. CTGF upregulation correlates with MMP-9 level in airway remodeling in a murine model of asthma. *Arch Med Sci*. 2017;13:670–676. doi:10.5114/aoms.2016.60371