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**ORIGINAL PAPER**

# A comparative study on the utility of biomarkers – serum interleukin-13 against serum immunoglobulin E in assessing the severity of asthma

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**ABSTRACT**

**Introduction and aim.** Asthma is a complex respiratory condition with fluctuating symptoms, airflow obstruction, bronchial hyperresponsiveness, and inflammation. Interleukin (IL)-13 induces various biological responses, including B-cell immunoglobulin E (IgE), eosinophil chemo-attractants, and mucus-secreting goblet cell maturation. B-cell immunoglobulin E antibodies are essential for the onset and propagation of the inflammatory cascade, triggering the allergic response. The aim was to compare the utility of biomarkers – serum IL-13 against serum IgE in assessing the severity of asthma.

**Material and methods.** A cross-sectional observational study was conducted involving 68 asthmatic children aged 6–12 years and 68 age- and sex-matched healthy controls. Asthma severity was assessed using spirometry and categorized as mild, moderate, or severe based on GINA guidelines. Serum IL-13 and IgE levels were measured using validated using enzyme-linked immunosorbent assay.

**Results.** The study confirmed elevated levels of serum IL-13 and IgE in children with asthma compared to the control group, suggesting their involvement in the development of asthma ($p<0.001$). The threshold values for identifying the existence of asthma were 1.86 pg/mL for IL-13 and 314 ng/ml for IgE. The IL-13 level could accurately classify asthmatic children as having either moderate or severe asthma, using a cut-off value of ≥2.66 pg/mL, with a statistically significant $p=0.001$. However, no such results were observed with IgE.

**Conclusion.** Bronchial asthma patients had markedly higher levels of total IgE and IL-13 compared to the healthy controls included in the study. Furthermore, it has been shown that IL-13 plays a role in discerning the extent of asthma severity.

**Keywords.** serum IgE, serum IL-13, severity of asthma

## Introduction

Asthma is a widespread and complex long-term respiratory condition marked by fluctuating and recurrent symptoms, obstruction of airflow, hyperresponsiveness of the bronchi, and underlying inflammation.[1] Asthma, according to the Global Initiative for Asthma (GINA),

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is a diverse disorder characterized by fluctuating expiratory airflow limitation and respiratory symptoms, including dyspnea, chest tightness, and wheezing, which vary over time and in severity.[2] Asthma is commonly diagnosed in childhood, although it may develop at any stage in life.[3] Typically, 50% to 80% of asthma ailments are evident by age 5.[4]

Although it is most challenging during early childhood years, as many as 50% of children with relatively modest severity have a remission of symptoms by late adolescence; in contrast, 80% of those with more severe symptoms will continue to experience symptoms well into adulthood.[4]

Serum periostin, fractional exhaled nitric oxide (FeNO), serum immunoglobins E (IgE), and interleukin (IL)-13 are among the biomarkers of type 2 disorders that are being studied concerning asthma.

The development of mucus-secreting goblet cells, the generation of protein molecules from the extracellular matrix and myofibroblast differentiation, the eosinophil chemo-attractants, the generation of B-cell immunoglobulin E, and the increased contractility of airway cells of smooth muscle in reaction to cholinergic agonists are just a few of the numerous biological responses that IL-13 induces in relation to asthma.[5]

Allergy-induced asthma also involves a hypersensitivity reaction that is triggered by immunologic processes mediated by IgE antibodies. IgE is essential for the onset and propagation of the inflammatory cascade, which in turn triggers the allergic response.[6] IgE is considered the primary molecular target for the treatment of asthma and allergic disorders, prompting extensive research aimed at disrupting its synthesis or function within the immune system. The efficacy of anti-IgE monoclonal antibodies (mAbs) in asthma treatment substantiates this claim.[7]

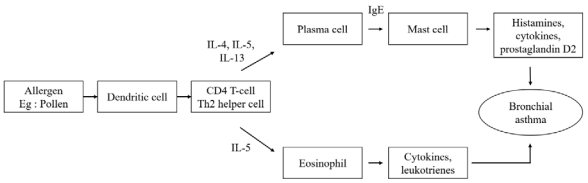


**Fig. 1.** Schematic illustration of the role of IL-13 and IgE in the pathogenesis of asthma

Biomarkers – serum periostin, fractional exhaled nitric oxide (FeNO), serum IgE, and IL-13 were analyzed in a cohort of asthmatics, and the findings demonstrated that the biomarkers were continually distributed and correlated with one another (Fig. 1).[8]

The correlation between IgE concentrations, skin tests, and pulmonary function in individuals with asthma has been demonstrated. According to clinical investigations, asthmatics exhibit an inverse correlation between IgE concentrations and $FEV_1$/FVC ratios.[9] In vitro studies indicate that IgE formation in allergic asthma patients is more reliant on IL-13 compared to non-atopic children, due to increased IL-13 levels and IgE synthesis in response to IL-13.[10]

FEV1 has established itself as the definitive tool for lung function assessment in asthma, due to its ease and speed of measurement, requiring a piece of relatively straightforward equipment. The existing asthma guidelines use $FEV_1$ in addition to daytime and nocturnal symptoms to gauge severity of asthma.[11,12]

As stated by some, children with severe chronic asthma do not experience a substantial reduction in FEV1 during asthma free periods, which is attributed to the slowly progressive nature of the disease.[13]

In light of the substantial contribution of serum IgE and IL-13 to the development of pediatric asthma, The intent of this research is to compare the efficiency of these two variables in assessing the severity of asthma in the population of pediatric asthmatics.

## Aim

To compare the utility of biomarkers – serum IL-13 against serum IgE in assessing the asthma severity.

## Material and methods

The present observational study was conducted at a tertiary hospital in Tamil Nadu after receiving ethical approval from the Institutional Ethics Committee (SRMIEC-ST0922-797). The research was initiated in September 2022 and executed over one year. Based on statistical calculations, considering effect size, a significance level of 0.05, and a study power of 80%, the analysis determined that at least a minimum of 30 participants was necessary to achieve statistical significance.[14] The trial included a cohort of 68 children, aged 6 to 12, recently diagnosed with asthma and initiated on treatment in accordance with GINA recommendations and sex and age-matched controls.[2] An informed consent form was procured from the parents.

The following categories of children were excluded from the study: children younger than the age of six, those already receiving asthma treatment, those who experienced acute exacerbations of asthma requiring systemic steroids in the preceding three months or during the study period, and those who were unwilling to give consent.

The parents provided a thorough medical history that included information about the child's age of onset of wheezing, any history of allergic rhinitis or atopic dermatitis, food allergies, prior use of inhalational corticosteroids, hospital admissions related to the wheezing, and a family history of wheezing and asthma that may have genetic implications.

Children were advised to abstain from physical activity on the morning of the procedure. Trained profes-

sionals performed spirometry, and asthma diagnosis was ascertained by bronchodilator reversibility tests (≥12%).

The patients were clothed in light clothing, with their legs uncrossed, and in an upright position when the procedure was performed. Any dentures that interfered with the process were removed. Air leakage via the nasal passages was minimized by manually blocking the nares using nose clamps. On the day of the test, the spirometer's calibration was verified. The patients were instructed to place the mouthpiece into their mouths. Following confirmation of no air leaks, the following is how the procedure was carried out:

1. The patients were instructed to take a deep breath, draw in as much air as possible, and hold their breath for less than a second at the highest capacity of their lungs.
2. Immediately after taking a deep breath, the mouthpiece was placed within the oral cavity, precisely in the space between the teeth. Tightly sealing the lips surrounding the mouthpiece was crucial to preventing any air leaks. The instructor's recommended time, or a minimum of six seconds, was used for the exhale. To measure only the forced expiratory volume, the patient was instructed to place the mouthpiece after completing step 1 and avoid breathing through the tube.
3. If any of the procedures were performed incorrectly, the technician stopped the procedure and provided the patient with a fresh description of the procedure.
4. Until two matching and good results were achieved, the process was repeated at regular intervals of one minute.
5. After the aforementioned process, the study subjects received 400 micrograms of bronchodilator (salbutamol) to evaluate reversibility.
6. After administering bronchodilators for 15 minutes, the very same procedure was carried out again. The diagnosis of asthma was established when the baseline $FEV_1$ changed by more than 12%, suggesting a positive response and reversibility.

Based on their history and pulmonary function test results, the children were categorized as having intermittent, mild persistent, moderate persistent, or severe persistent asthma, and therapy with inhalational corticosteroids was started in accordance with established guidelines.[2]

Following spirometry, blood samples for serum IL-13 and serum IgE levels were collected from the children in EDTA, endotoxin/pyrogen-free collection tubes and centrifuged at 1000 rotations/min for 10 minutes. Blood samples for the same were collected from 68 age and sex-matched controls. The generated supernatant serum (250–500 µL) was preserved at -70°C in deep freezers at the Molecular Biology Laboratory, SRM Institute of Science and Technology. The samples were subsequently examined by enzyme-linked immunosorbent assay (ELISA) upon thawing at room temperature. The assay analysis was conducted using the Human IL-13 ELISA Kit (Diaclone SAS, Besançon Cedex, France; Cat. No: 850.080.096, Batch: 1013-45T), which exhibited an intra-assay coefficient of variability of 5% and an inter-assay coefficient of 8%. Additionally, the Total IgE EIA Kit (XEMA, Moscow, Russia; Cat. No: 9398-200-18619450-2010) was utilized, with intra-assay and inter-assay coefficients of variability recorded at 5% and 10%, respectively. Absorbance measurements were recorded using the Merilyzer EIA Quant. By plotting the average absorbance of each standard against the corresponding concentrations of human IL-13 and IgE standards along the horizontal axis, a linear standard curve was generated. Using the standard curve and extrapolating optical density values against standard concentrations, the IL-13 and IgE concentrations in each sample were determined.

**Table 1.** Baseline characteristics of the subjects

| Baseline characteristics | Asthmatics | Controls | p |
|---|---|---|---|
| Age in months | | | |
| Mean (SD) | 101.4±25.2 | 102±24.9 | 0.010 |
| Gender, n (%) | | | |
| Male | 54 (79%) | 54 (79%) | 0.999 |
| Female | 14 (21%) | 14 (21%) | |
| Height (cm) | 127.8±16.9 | 129.2±16.3 | 0.768 |
| Weight (kg) | 27.8±10.9 | 16.3±9.8 | 0.338 |
| BMI (kg/m$^2$) | 16.3±3.8 | 17.2±4.2 | 0.414 |
| Family history, n (%) | | | |
| Yes | 59% | – | |
| No | 41% | | |
| History of atopic dermatitis, n (%) | 29% | – | |
| Yes | 71% | | |
| No | | | |
| History of allergic rhinitis, n (%) | | | |
| Yes | 44% | – | |
| No | 56% | | |
| Previous hospital admission, n (%) | 33% | – | |
| Yes | 67% | | |
| No | | | |
| $FEV_1$ | 74.72% | – | |
| Severity based on spirometry | | | |
| Mild asthma | 85% | – | |
| Moderate asthma | 6% | | |
| Severe asthma | 9% | | |

*Statistical analysis*

The comparison of the control versus cases group was analyzed using the students T-test. All statistical analysis was performed using SPSS version 26.0 (IBM, Armonk, NY, USA) and Medcalc version 22.030. A significant p-value was defined as one less than 0.05 for a 95% confidence interval (CI). The receiver operating characteristic (ROC) was employed to assess the ability of the

diagnostic test, specifically IL-13 in our case, to reliably differentiate between two patient conditions – mild versus moderate and severe asthma.

## Results

A total of 68 asthmatic children and 68 non-asthmatics (control group) were recruited in the study (as per inclusion and exclusion criteria). Table 1 lists the baseline characteristics of the study subjects.

It was observed that the mean concentrations of both IL-13 and IgE were higher than in controls (p<0.001). Table 2 provides details of the analysis.

**Table 2.** Comparison of IL-13 and IgE concentration in asthmatics and healthy controls

| Parameter | Asthmatics, mean±SD | Controls, mean±SD | p |
|---|---|---|---|
| IL-13 (pg/mL) | 2.12±0.82 | 1.49±0.27 | <0.001 |
| IgE (IU/mL) | 553.01±371.81 | 385.55±346.07 | <0.001 |

Given below are the ROC curves for IL-13 and IgE, which illustrate the cut-off value of IL-13 (1.86 pg/mL) and serum IgE (314 IU/mL) in evaluating the presence of asthma among cases as compared to controls (Fig. 2).

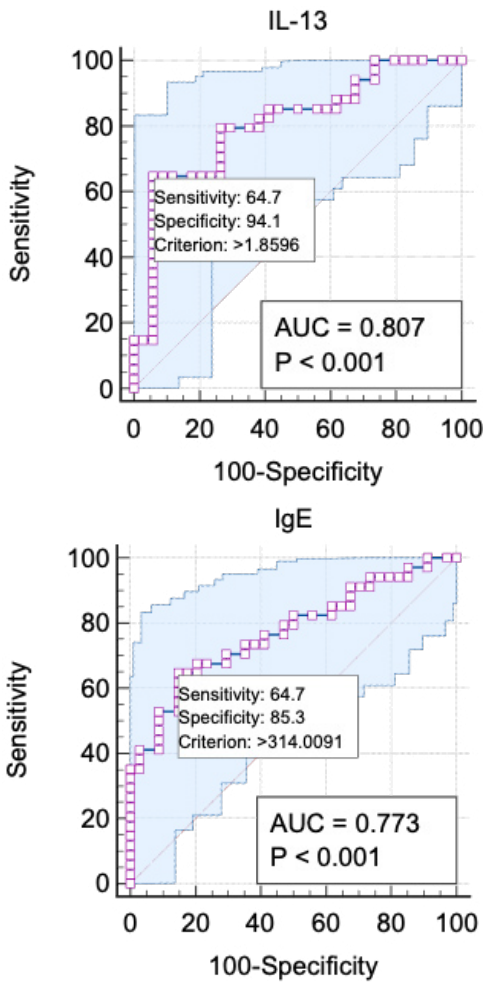


**Fig. 2.** ROC curve for IL-13 and IgE in detecting the presence of asthma in cases

The mean $FEV_1$ of those enrolled in the study was 74.72±10.18%. Serum IL-13 and total IgE levels were determined using conventional ELISA kits. The mean circulating IL-13 level in asthmatic children was 2.12±0.82 pg/mL, whilst the mean serum IgE concentration was 553.01±371.8 IU/mL (Table 3).

**Table 3.** Descriptive statistics of the study subjects

| Parameter | Mean | SD | Min–max. | Median |
|---|---|---|---|---|
| $FEV_1$ | 74.72 | 10.18 | 44–102 | 77 |
| IL-13 (pg/mL) | 2.1268 | 0.82 | 0.8–4.03 | 2.4 |
| IgE (IU/mL) | 553.01 | 371.8 | 39.10–1092.61 | 498.2 |

The study participants were categorized into mild asthmatics (85%), moderate asthmatics (6%), and severe asthmatics (9%) based on the results of the pulmonary function test.

A one-way analysis of variance demonstrated that mild asthmatics exhibited significantly lower levels of IL-13 compared to moderate asthmatics, who, in turn, had lower levels than severe asthmatics. Conversely, there was no discernible variation in IgE levels (Fig. 3).

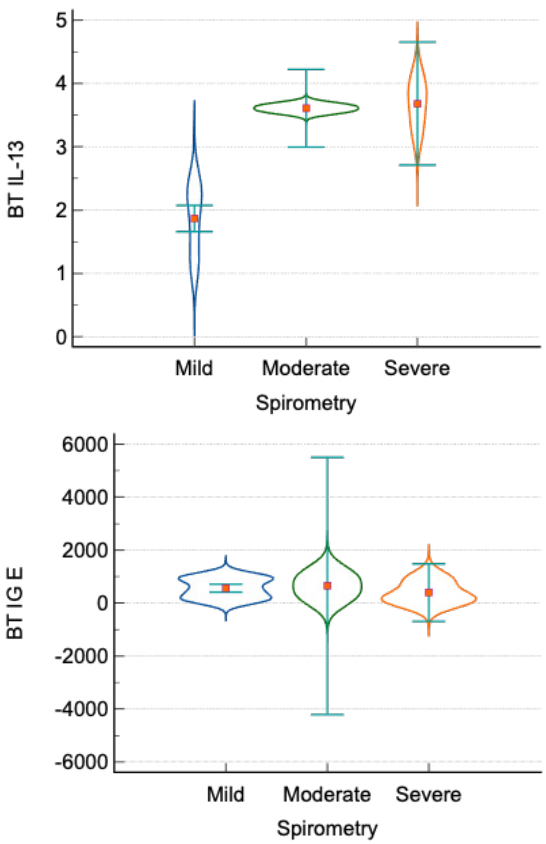


**Fig. 3.** Violin plot of IL-13 and IgE levels among mild, moderate and severe asthmatics

The results of our study indicate that IL-13 may effectively discern between individuals with mild asthma and those with moderate to severe asthma, with a sensitivity and specificity of 100%. The determined threshold

value for distinguishing between the groups was 2.6 pg/mL (p=0.001), as depicted in Figure 4.

However, a comparable degree of statistical significance was not observed concerning IgE.

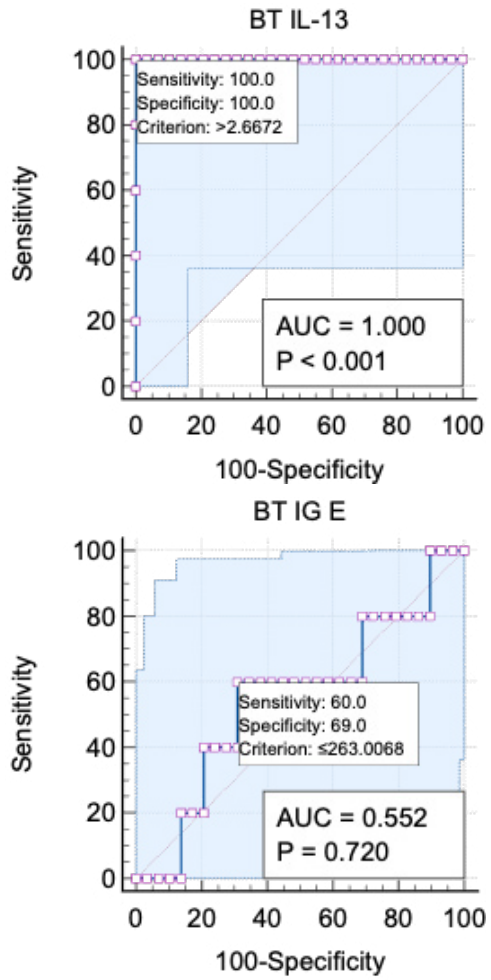


**Fig. 4.** ROC curve for IL-13 and IgE in differentiating mild, moderate and severe asthma

The closer the ROC curve is to the upper left corner of the graph, the higher the efficacy of the test because in the upper left corner, the sensitivity=1 and the false positive rate=0. The graph below illustrates the greater value of IL-13 as a marker in indicating the severity of asthma in comparison to IgE (Fig. 5).

## Discussion

The role of the Th2 cytokine interleukin IL-13 as a fundamental regulator of allergic diathesis has been convincingly demonstrated by a multitude of studies. The emerging paradigm is that, rather than eosinophils and IgE-mediated processes, which are the classic effector routes, IL-13 initiates aspects of the allergic response by acting on smooth muscle and epithelial cells.[15]

In light of these recent advances, this study explores our current comprehension of the function of IL-13 in the etiology of asthma, with a particular emphasis on determining the utility of IL-13 in distinguishing the severity of asthma and its comparison against IgE.

Our study revealed elevated concentrations of serum IL-13 and IgE in children with asthma as compared to the control group, suggesting their involvement in the development of asthma (p<0.001). The threshold values for identifying the existence of asthma were 1.86 pg/mL for IL 13 and 314 IU/mL for IgE.

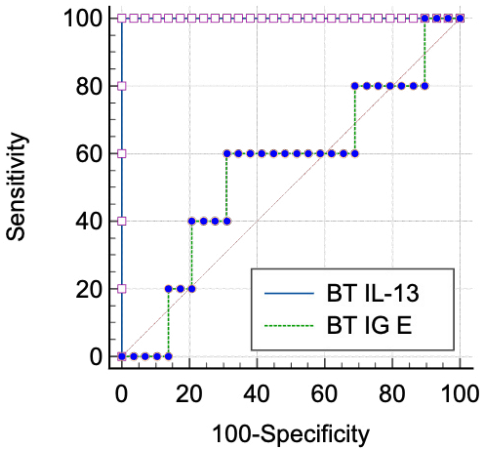


**Fig. 5.** Comparison of ROC curves between IgE and IL-13 in predicting the severity of asthma

Furthermore, it was noted that the IL-13 level could accurately classify asthmatic children as having either moderate or severe asthma, using a cut-off value of ≥2.66 pg/mL, with a statistically significant p=0.001. However, no such results were observed with IgE.

Studies have stated that patients with moderate to severe asthma exhibit elevated IL-13 levels in bronchoalveolar lavage fluid, as well as enhanced gene and protein expression of the same in bronchial tissues.[16] Previous research has shown an association between IL-13 and asthma, as well as IgE and asthma, which aligns with our current study.

Humbert M et al. utilized a semiquantitative reverse transcriptase-polymerase chain reaction approach to quantify the concentrations of IL-13 mRNA in bronchial mucosal specimens obtained from individuals with asthma, as well as control people. The biopsy specimens from the participants with asthma showed substantially higher levels of IL-13 mRNA compared to the control subjects (p≤0.02). Nevertheless, when considering the participants with asthma as a collective, no associations were found between the levels of IL-13 mRNA and measures of disease severity.[17]

Saha et al. conducted a research indicating that the prevalence of detectable IL-13 in sputum was elevated in both the moderate and severe asthma groups relative to the control group(p=0.004). Also, the quantity of IL-13+ cells within the airway smooth muscle bundle was

higher in the severe asthma group compared to the other groups ($p<0.05$).[18]

In 2022, Kursheed et al. aimed to investigate the association between serum IL-13 and IgE in bronchial asthma. The research involved 50 asthmatics aged 18 to 40 in Lahore, Pakistan. Total serum IgE and IL-13 levels were determined using enzyme-linked immunosorbent assay methods. Asthmatics exhibited increased serum IL-13 and IgE levels as opposed to controls (1574±409 pg/mL versus 390±23 ng/ml, respectively). He also concluded a positive correlation between serum IL-13 and IgE levels ($r=0.674$; $p<0.001$).[19]

In 2019, Saleh Jebur et al. conducted a study with 150 individuals with asthma and 50 healthy individuals as controls. The participants' ages ranged from 10 to 65 years. The objective of the study was to determine the levels of serum IL-13 and serum IgE in the blood of patients with allergic asthma. Before initiating inhalational corticosteroids, blood levels of total IgE and IL-13 were assessed in both the patient group and the control group. Consistent with our investigation, a statistically significant increase in serum IL-13 concentrations was noted in asthmatics as compared to controls ($p<0.001$).[20]

In a Spanish study by Davila et al., the researchers intended to assess the link between blood total IgE levels and the extent of disease in adult patients who had persistent allergic asthma. It came to light that, despite elevated serum total IgE levels in adult patients with chronic allergic asthma, a significant correlation between serum total IgE concentrations and the extent of asthma could not be established.[21]

Sandeep T sought to assess and contrast the levels of blood IgE in individuals with mild, moderate, and severe asthma, as well as in those without asthma. Elevated serum IgE levels were seen in individuals with asthma in comparison to those without the condition. Generally, the levels of asthma rose in proportion to the severity of the condition. Nevertheless, due to the substantial diversity observed within each level of asthma, no statistically significant association was found.[22]

In a study by Rathoria et al., it was observed that childhood asthmatics had elevated levels of serum IgE in comparison to individuals without asthma. Although, there was a positive correlation between the severity of asthma and the elevation of serum IgE levels. The degree of heterogeneity within each grade of asthma was substantial, making it unable to identify any statistically significant association.[23] This was a follow-up study by the same lead author.[24]

In 2020, Makieieva et al. sought to assess the clinical and prognostic implications of IL-4 and IL-13 concentrations in children with recurrent wheezing, concluding that the levels of the anti-inflammatory cytokines IL-4 and IL-13 were markedly elevated in these children, with the highest concentrations observed in those developing asthma.[25]

A study conducted by Adel Khattab et al. aimed to examine the association between the IL-13 rs20541 single nucleotide polymorphism and serum IL-13 levels concerning asthma severity in a cohort of asthmatic children. Children with asthma exhibited statistically significant elevations in IL-13 levels compared to controls (median=45 pg/mL versus 4 pg/mL; $p<0.001$). Serum IL-13 had a positive correlation with IgE levels and effectively differentiated between patients with severe asthma and those with mild to moderate asthma at a cutoff value of >83 pg/mL (sensitivity 90%, specificity 90%, positive predictive value 96.4%, and negative predictive value 75%).[26]

It is concluded that IL-13 concentrations are higher in the serum of bronchial asthma patients with allergy history and also help in distinguishing the severity of asthma.

While IgE has been extensively studied, comparative studies evaluating IL-13 alongside IgE in asthma are limited. Many emerging biological therapies (e.g., dupilumab, targeting IL-13 and IL-4 pathways) focus on type 2 inflammation, making IL-13 measurement potentially more relevant for phenotype-targeted therapies. Also, investigating IL-13 as a biomarker for inflammation in non-atopic or low-IgE asthma phenotypes could provide critical insights into the mechanisms underlying non-IgE-driven asthma. This current approach may help address current knowledge gaps, reduce the burden of asthma, and lower treatment costs in the future.

### *Study limitations*

However, conducting a comprehensive multicenter research on a broad scale with a huge sample and adding precision Recall ROC will provide evidence of the effectiveness with optimal cutoff, allowing for its application to the general population.

## Conclusion

Bronchial asthma patients had markedly higher levels of total IgE and IL-13 compared to the healthy control persons included in the study. Furthermore, it has been shown that IL-13 plays a role in discerning the extent of asthma severity. Therefore, serum IL-13 might be a beneficial focus for more research diagnostic applications, as well as for therapy objectives and monitoring.

## Declarations

### *Funding*

The authors received no financial support.

### *Author contributions*

Conceptualization, P.R. and P.S.; Methodology, P.R and P.S.; Software, P.S.; Validation, P.S.; Formal Analysis,

P.R., S.S., P.S., J.T. and P.S.; Investigation, P.R., S.S., P.S., J.T. and P.S., Resources, P.R. and S.S.; Data Curation, P.R. and S.S.; Writing – Original Draft Preparation, P.R. and P.S.; Writing – Review & Editing, P.R. and P.S.; Visualization, P.R.; Supervision, S.S.; Project Administration, P.R.; Funding Acquisition, P.R. and P.S.

***Conflicts of interest***

All authors declare that they have no conflicts of interest.

***Data availability***

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

***Ethics approval***

The current longitudinal study was conducted at the SRM Medical College Hospital and Research Center, a tertiary hospital in Tamil Nadu, with the approval of the Institutional Ethics Committee (SRMIEC-ST0922-797).

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