# Prognostic Importance of Th1:Th2 (IL-1β/IL-10) Cytokine Ratio in Adult Onset-Bronchial Asthma

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**Abstract.** Bronchial asthma is a complex respiratory disorder, exhibits several endotypes and phenotypes due to different underlying cellular and molecular mechanisms. Globally it affects 300 million individuals, with the prevalence of 2–3% in India, contributing to morbidity and mortality. Over 50 cytokines have been identified in asthma. The dysregulation in Th1 and Th2 cytokines is implicated in the patho-mechanism of pulmonary inflammation and airway remodeling. The aim of the current study was to access the circulating levels of IL-1β (pro-inflammatory) and IL-10 (anti-inflammatory) cytokines using sandwich enzyme-linked immunosorbent assay (ELISA). In this case-control study we recruited a total of 164 subjects (104 adult onset asthma patients and 60 non-asthmatic healthy controls) from south India. Data exhibited increased levels of IL-1β and decreased levels of IL-10 in asthma patients compared to the healthy controls. Subgroup analysis revealed significant elevation in the circulating levels of IL-1β and Th1:Th2 (IL-1β/IL-10) ratio in patients with uncontrolled and long-standing disease (>10 years). Receiver operating curve analysis of individual cytokines and ratios showed good and excellent discriminating capacity respectively for health vs disease and controlled vs uncontrolled. However, IL-1β showed better incisive capacity for disease duration. Based on our observation it appears that rather than individual cytokine(s), the balance between pro and anti-inflammatory cytokines are crucial in the patho-mechanism of asthma. However, developing a signature profile of multiple cytokines using cut-off values may prove to be more promising for diagnostic, prognostic and therapeutic purposes of bronchial asthma.

**Keywords:** Inflammation · uncontrolled asthma · Th1 and Th2 cytokine balance · ROC

## 1 Introduction

Bronchial asthma is a common, complex respiratory disorder that exhibits clinical variability both acute and chronic due to several underlying cellular and molecular mechanisms [1]. Globally it affects 300 million individuals [2], with the prevalence of 2–3% in India, contributing to morbidity, mortality and economic burden [3]. Over 50 cytokines are reported to be involved in the initiation and progression of inflammation in asthma


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[4–7]. Based on the current understanding, the panel of cytokines are classified into Th1 (pro-inflammatory) and Th2 (anti-inflammatory). These cytokines are tightly regulated by cross-inhibition mechanism [8], the dysregulation in Th1 and Th2 cytokines is implicated in the patho-mechanism of various diseases including pulmonary inflammation, emphysema and airway remodeling [9–15]. IL-1β (Th1) cytokine generally meant for stimulation of local, systemic responses and the recruitment of inflammatory cells at the site of inflammation. Interestingly, this cytokine is shown to linked with both eosinophilic and neutrophilic inflammatory phenotype of asthma and also associated with repair, remodelling and fibrosis of the lung [16, 17]. On other hand IL-10 cytokine (Th2) is shown to minimize the inflammation and is implicated in the reduced severity of various diseases such as Intestinal Bowel Disease, Systemic Lupus Erythematosus and allergic asthma [14, 15]. In the present study, we assayed a pair of pro and anti-inflammatory serum immune mediators IL-1β and IL-10 and its ratio in adult onset asthma patients and non-asthmatic healthy individuals (age and sex matched). We tried to establish the link between circulating levels of the above cytokines with asthma, severity and disease duration. Further, Receiver Operating Characteristic (ROC) curve was constructed to assess their potentiality as diagnostic and prognostic marker for severity.

Tributing to morbidity, mortality and economic burden [3]. Over 50 cytokines are reported to be involved in the initiation and progression of inflammation in asthma [4–7]. Based on the current understanding, the panel of cytokines are classified into Th1 (pro-inflammatory) and Th2 (anti-inflammatory). These cytokines are tightly regulated by cross-inhibition mechanism [8], the dysregulation in Th1 and Th2 cytokines is implicated in the patho-mechanism of various diseases including pulmonary inflammation, emphysema and airway remodeling [9–15]. IL-1β (Th1) cytokine generally meant for stimulation of local, systemic responses and the recruitment of inflammatory cells at the site of inflammation. Interestingly, this cytokine is shown to linked with both eosinophilic and neutrophilic inflammatory phenotype of asthma and also associated with repair, remodeling and fibrosis of the lung [16, 17]. On other hand IL-10 cytokine (Th2) is shown to minimize the inflammation and is implicated in the reduced severity of various diseases such as Intestinal Bowel Disease, Systemic Lupus Erythematosus and allergic asthma [14, 15]. In the present study, we assayed a pair of pro and anti-inflammatory serum immune mediators IL-1β and IL-10 and its ratio in adult onset asthma patients and non-asthmatic healthy individuals (age and sex matched). We tried to establish the link between circulating levels of the above cytokines with asthma, severity and disease duration. Further, Receiver Operating Characteristic (ROC) curve was constructed to assess their potentiality as diagnostic and prognostic marker for severity.

## 2 Material and Methodology

The present study recruited a total of 164 subjects of which 104 adult onset asthma patients from the Government and General Chest Hospital, Hyderabad, India and 60 non-asthmatic healthy controls from the same ethnic origin. Approval for the study was obtained from the Ethical Committee, Osmania Medical college, Hyderabad, India. All the subjects enrolled were consented adults, noted their demographic, clinical, and family history of Asthma in a predesigned proforma. Based on the reversibility and clinical symptoms, Pulmonologist diagnosed the asthma patients.

All the asthmatics were clinically evaluated for phenotypes, disease control, allergic status, neutrophil dominance, disease onset (only patients with adult-onset were included), No asthmatics were hospitalized at the time of sample collection. Five millilitres (mL) of blood sample was collected from each of participant and subjected it for serum separation at 2000–2500 rpm for 10 min and stored it at −20 °C till the further use.

### 2.1 Estimation of Circulating Concentration of IL-1β and IL-10 Cytokines

Estimation of circulating concentrations of serum cytokines IL-1β and IL-10 was performed using sandwich ELISA kit (BT LAB, China). In short, the plates were precoated with Human (IL-1β and IL-10) antibodies, each serum sample of asthmatic and Non-asthmatic individuals were to the plates added that binds to antibodies coated on the wells. Biotinylated Human (IL-1β and IL-10) antibodies were added which binds to the cytokines (IL-1β and IL-10) in the present in the sample, Streptavidin-HRP was added which binds to the biotinylated antibodies. Incubation was followed by washing off the unbound Streptavidin. Color development was observed after adding substrate solutions. Finally, the reaction was terminated by the addition of stop solution, OD values were noted at 450 nm to calculate the concentration of cytokines from the standard graph ranging from 5–1500 pg/mL (IL-1β) and 20–6000 pg/mL (IL-10). The sensitivity of IL-1β and IL-10 were 10.07 and 2.59 pg/mL respectively. The ratio between the two cytokines was calculated by taking the quotient of IL-1β and IL-10 (ratio = IL-1β ÷ IL-10).

### 2.2 Statistical Analysis

Clinical variables, measured serum cytokine levels and ratio were analyzed using mean ± standard deviation. Student t test was performed to evaluate the mean difference between the various group. Receiver operating characteristic (ROC) curves were constructed for the IL-1β and IL-10 and IL-1β/IL-10 ratio, the areas under the ROC curve values with 95% CI, Optimal cut-off values sensitivity, and specificity were determined. P value $< 0.05$ was considered statistically significant for each ROC in a GraphPad prism software.

In brief, ROC evaluates the Sensitivity, specificity and accuracy of a test. Sensitivity refers to ability of a test to truly identify an individual with disease as positive (TP), more the sensitivity lesser the false negative results (FN) [Sensitivity = TP/(TP + FN)]. Specificity signifies to correctly identify an individual without disease (TN), highly specific test represents few false positive results (FP) [specificity = TN/(TN + FP)]. In addition, Accuracy refers to the total correct assessment a test could perform [Accuracy = (TN + TP)/(TN + TP + FN + FP)]. The test is more feasible, if it has good sensitivity, specificity and accuracy. Bonferroni correction (α/n) was employed to adjust probability (p) values to reduce the risk of a type I error.

## 3 Results

Perusal of Table 1 reveal a total of 104 asthmatics and 60 non-asthmatic healthy volunteers with mean age of 40.27 ± 9.89 and 40.53 ± 9.83 ($p > 0.05$) respectively. The percentages of males and female were 42.3 vs 57.7 in the patient group and 60 vs 40 in the control. There was no significant difference the BMI between the study groups. 69.2% of the patients had the diseases of ≤ 10 years, 44.2% of the patients had the positive family history of asthma. Clinically, 78.9% vs 21.7% were non-Neutrophilic and Neutrophilic respectively. 52% of the asthmatics had the controlled disease whereas 48% were uncontrolled.

Perusal of Fig. 1 revealed the mean ± standard deviation of IL-1β was significantly higher in asthmatics than non-asthmatic healthy volunteers (656.70 ± 356.30 vs 332.01 ± 211.82; $p = 0.0001$), uncontrolled asthmatics had elevated levels than controlled asthmatics (723.35 ± 388.17 vs 587.58 ± 298.89; $p = 0.05$), non-neutrophilic phenotype have higher levels than Neutrophilic phenotype (674.28 ± 371.36 vs 591.17 ± 291.57, $p = 0.04$) and the disease duration more than ten years had the elevated values (824.72 ± 393.694 vs 609.80 ± 420.45; $p = 0.0001$). Additionally, sub categories of allergic status, gender and family history didn't show any significant difference ($p > 0.05$) (Fig. 1).

**Table 1.** Charecteristic features of Asthma patients and Healthy controls

| Features | | Asthma Patients | Healthy Controls |
|---|---|---|---|
| | | N = 104(%) | N = 60(%) |
| Age | Mean ± SD | 40.27 ± 9.89 | 40.53 ± 9.83 |
| Age at onset | | 29.93 ± 14.70 | – |
| Gender | Male | 44 (42.3) | 36 (60) |
| | Female | 60 (57.7) | 24 (40) |
| BMI ($kg/m^2$) | | 24.79 ± 3.46 | 24.93 ± 2.67 |
| Allergic Status | Allergic | 84 (80.8) | – |
| | Non-Allergic | 20 (19.2) | |
| Family History of Asthma | Yes | 46 (44.2) | |
| | No | 58 (55.8) | |
| Disease Duration | ≤ 10 years | 72 (69.2) | – |
| | > 10 years | 32(30.7) | |
| Phenotype | Non-Neutrophilic | 82 (78.9) | |
| | Neutrophilic | 22 (21.1) | |
| Disease Status | Controlled | 54 (52) | |
| | Uncontrolled | 48) | |

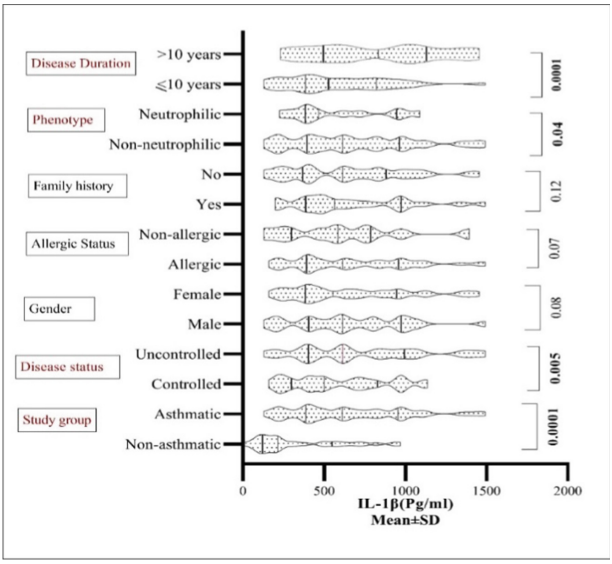


**Fig. 1.** Circulating levels of IL-1β in various categories of asthma patients

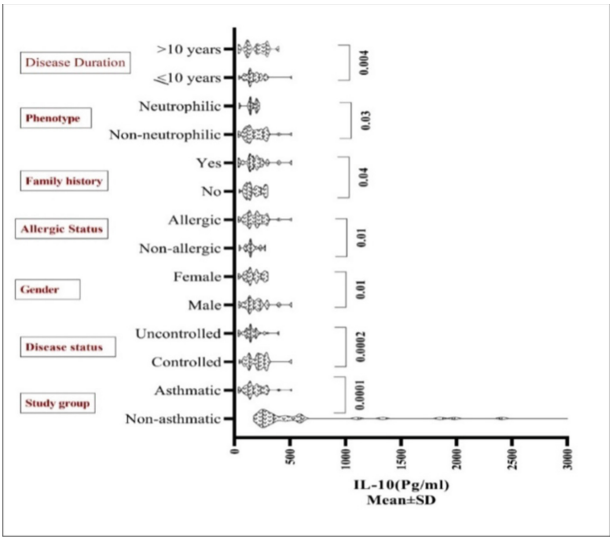


**Fig. 2.** Circulating levels of IL-10 in various categories of asthma patients

Table 2 showed cytokines cut-off points based on comparison between non-asthmatic healthy controls vs asthma patients, Controlled vs uncontrolled and disease duration $\leq$ 10 vs $>$ 10 years. The ROC characteristic of IL-1β, IL-10 and IL-1β/IL-10 in non-asthmatic healthy controls vs asthma patients were (AUC = 0.78, 0.90, 0.93, cut-off

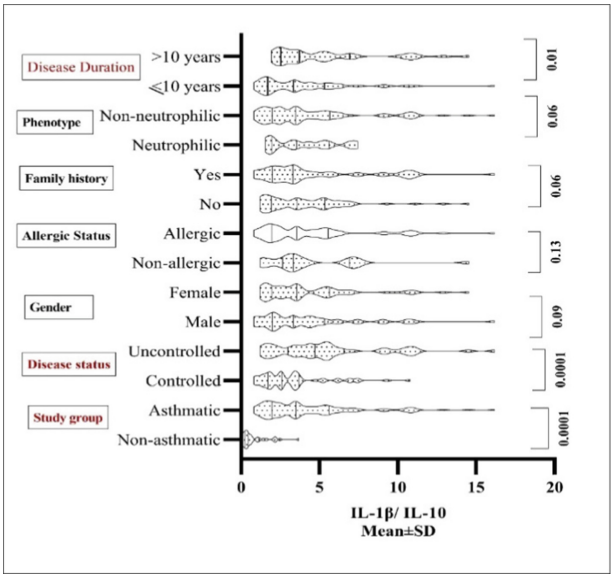


**Fig. 3.** Circulating levels of IL-1 B/IL-10 in various categories of asthma patients

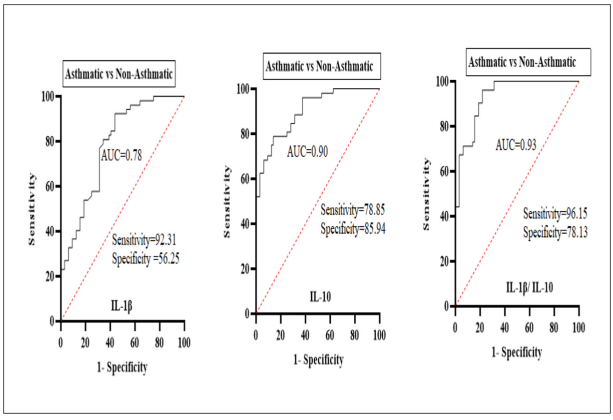


**Fig. 4.** ROC of IL-1β, IL-10 and its ratio between asthmatics and non-asthmatics

= 223.80, 245.80, 1.20, Sensitivity = 92.31, 78.85, 96.15, Specificity = 56.25, 75.00, 78.13, Accuracy = 80, 81 and 89.02) with $p < 0.05$ respectively (Figs. 2 and 3).

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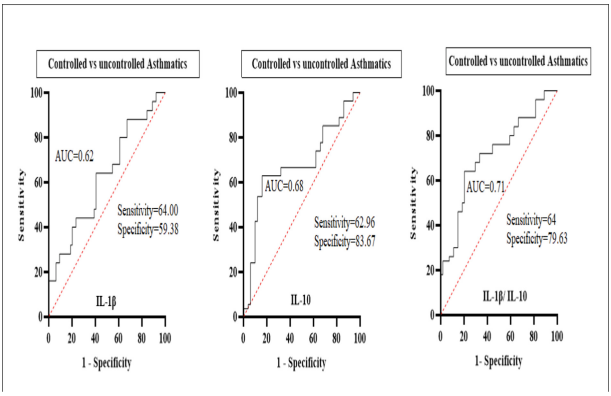


**Fig. 5.** ROC of IL-1β, IL-10 and its ratio between controlled and uncontrolled asthmatics

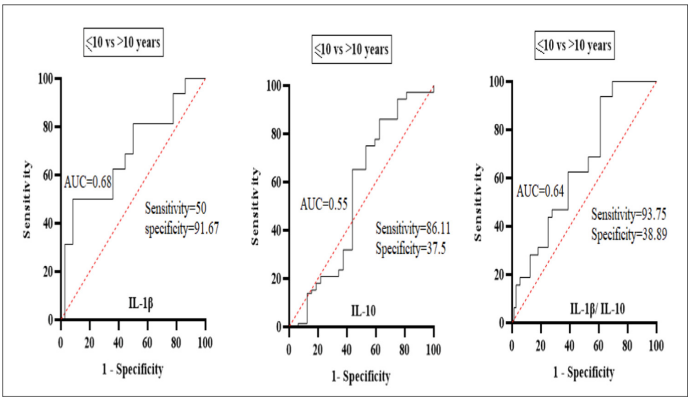


**Fig. 6.** ROC of IL-1β, IL-10 and its ratio between asthmatics with ≤ 10 vs > 10 years of the disease duration

Figure 5 the ROC characteristic of IL-1β, IL-10 and IL-1β/IL-10 in controlled and uncontrolled asthma patients were (AUC = 0.62, 0.68, 0.71, cut-off = 595.00, 197.50, 3.89, Sensitivity = 64.00, 62.96, 64, Specificity = 59.38, 83.67, 79.63, Accuracy = 62.5, 70.19, 76.92) with $p < 0.05$ respectively.

The ROC characteristic of IL-1β, IL-10 and IL-1β/IL-10 in asthma patients with ≤ 10 vs > 10 years of the disease duration were (AUC = 0.68, 0.55, 0.64, cut-off = 974.5, 49.7, 2.22, Sensitivity = 50, 86.1, 93.75, Specificity = 91.67, 37.5, 38.89, Accuracy = 75, 78.8, 53.84) with $p < 0.05$ respectively (Fig. 6).

**Table 2.** ROC characteristics of cytokine in the study groups

| Categories | Cytokines | AUC | Cut-off | Sensitivity (%) | Specificity (%) | Accuracy (%) | P value |
|---|---|---|---|---|---|---|---|
| Asthmatics vs Non-asthmatics | IL-1β | 0.78 | 223.80 | 92.31 | 56.25 | 80 | **0.0001** |
| | IL-10 | 0.90 | 245.80 | 78.85 | 85.94 | 81 | **0.0001** |
| | IL-1β/IL-10 | 0.93 | 1.20 | 96.15 | 78.13 | 89.02 | **0.0001** |
| Controlled Vs Uncontrolled | IL-1β | 0.62 | 595.00 | 64.00 | 59.38 | 62.5 | **0.02** |
| | IL-10 | 0.68 | 197.50 | 62.96 | 83.67 | 70.19 | **0.001** |
| | IL-1β/IL-10 | 0.71 | 3.89 | 64 | 79.63 | 76.92 | **0.0002** |
| Disease Duration $\leq 10$ vs $> 10$ years | IL-1β | 0.68 | 974.5 | 50 | 91.67 | 75 | **0.002** |
| | IL-10 | 0.55 | 249.7 | 86.11 | 37.5 | 78.8 | 0.41 |
| | IL-1β/IL-10 | 0.64 | 2.22 | 93.75 | 38.89 | 53.84 | **0.01** |

## 4 Discussion

Cytokines are the extracellular tiny protein (≤80 kDa) molecules, secreted by a variety of cells that play a crucial role in the initiation, resolution and progression of various inflammatory processes. The shift in the balance of cytokines towards proinflammatory than the anti-inflammatory is heavily implicated in the different aspects of Asthma [4].

### 4.1 IL-1β in Asthma

In the present study we report a significant elevation in the levels of IL-1β in asthma patients than the healthy controls. Further within the patients, sub group analysis showed uncontrolled asthmatics (moderate), non-neutrophilic asthmatics and patients with long-standing asthma with higher circulating concentrations of IL-1β ($p < 0.05$). Slight elevation was noted in allergic patients and patients with positive family history ($P > 0.05$), whereas no difference was seen with respect to gender.

Our observations were consistent with a north Indian study by Thomos et al. (2003) [18] where increased levels of IL-1β in asthmatics as compared to non-asthmatic healthy controls were noted. A report from California by David et al. (1992) [19] showed that symptomatic asthma patients release several pro inflammatory cytokines including IL-1β that makes the condition severe which supports the observation of elevated levels of IL-1β in uncontrolled asthmatics in the current study. The higher levels of this cytokine measured in our patients with non-neutrophilic phenotype is indirectly supported by Esnault et al. (2012) [20] suggesting that eosinophils are the precursor for the production of IL-1β which in turn activate IL-17, a proinflammatory cytokine. Elevated levels of IL-1β observed in patients with long-standing asthma in the current study may be at may have higher risk towards fibrosis or airway remodeling by the induction of Matrix metalloproteinases (MMPs)- fibrogenic agents [21, 22]. Neutralization of IL-1 shown to help in reducing the inflammatory processes and disease severity in the various diseases [23] The above discussion realizes the requirement of IL-1β related studies in various

aspects of asthma in order to exploit the potential of this cytokine in the management of asthma.

### 4.2 IL-10 in Asthma

We observed drastic decrease in the levels of interleukin-10 in asthma patients as compared to healthy individuals. The sub group analysis of the patients also exhibited significantly decreased levels of IL-10 in each category of uncontrolled asthmatics, female patients, non-allergic patients, patients with negative family history, neutrophilic asthmatics and long-standing asthmatics as compared to opposing categories. The above observation may be explained based on the potential of IL-10 cytokine in the resolution of inflammation by inhibiting the pro-inflammatory cytokines (IL-1β, IL-4, IL-5, IL-6, IL-8 and GM-CSF) [24, 25]. Editors et al. [25] and Iyer et al. [14] showed the increased levels of IL-10 inhibit the production of IgE, shorten Eosinophil survival and induces the allergen specific tolerance there by decreasing the allergic inflammation.

The reduced circulating concentrations of IL-10 noted in uncontrolled and neutrophilic asthma groups of our study is strengthened by others, signifying that this anti-inflammatory cytokine has the potential to inhibit the production of Th2 and Th17-related cytokines to bring down the neutrophilic inflammation in the airway by TLR4/MyD88 and NF-kB pathway [24, 26, 27]. Further, the lower levels of IL-10 in severe cases with longstanding asthma presumed to be a risk factor for airway remodeling and fibrosis. This explanation is reinforced by Hough et al. [28] where they suggested long-standing asthma is a risk factor for airway remodeling and Steen et al. [29] reviewed IL-10 serves as anti-fibrotic agent in the lung by suppressing the pro-fibrotic agent (TGF-β).

### 4.3 Th1/Th2(IL-1β/IL-10) Ratio in Asthma

The Th1/Th2 hypothesis which aroused from 1986 research is with the basis that T-helper cells express different cytokine patterns and serve as important immune regulators of the immune responses [30]. The balance and stability of Th1 and Th2 function is critical for the homeostasis of the immune system. Elevated Th1/Th2 serum cytokine ratio (IL-1β/IL-10) observed in asthma patients, uncontrolled asthmatics and long-standing asthmatics indicate strong systemic inflammation a reflection of pulmonary inflammation. Previously we reported higher Th1/Th2 serum cytokine ratio (IFN-/IL-10) in vitiligo an inflammatory disease [9]. However, there are no studies pertaining to cytokine ratio in asthma, which is warranted.

Though the Receiver Operating Curves of individual cytokines (IL-1β and IL-10) and ratio (IL-1β/IL-10) exhibited excellent characteristics, the ratio was found to be superior in discriminating health vs disease and controlled vs uncontrolled asthma patients. However, IL-1β showed better incisive capacity for disease duration. Thus, our study has emphasized the pro: anti-inflammatory cytokine ratio as a reliable non-invasive marker of inflammation and disease severity, whereas IL-1β alone may serve as an indicative marker for early diagnosis of fibrosis in the lung.

## 5 Conclusion

The study emphasizes the importance of pro/anti-inflammatory cytokineratio for both diagnostic and prognostic purpose in the patient with adult onset asthma. In order to substantiate our observation, signature profile of multiple cytokines using cut-off values may prove to be more promising for diagnostic, prognostic and therapeutic purposes. Add-on, correlation of ratios with immuno-modulatory Treg/Th17 cell populations is required for better understanding the pathophysiology of asthma and to develop cell based or agonist/antagonist cytokines for the management.

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**Authors' Contributions.** Rabia Tahseen performed sampling, literature survey, wet lab experiments, analysed the data and drafted the manuscript, Dr. Mohammad Parvez contributed his efforts to conceptualize the study, reviewed the manuscript, Dr. Sravan Kumar diagnosed the asthma patients helped in patient data acquisition and Prof. Parveen Jahan promoted the concept, designed the study, interpreted the data, edited and reviewed the manuscript. All the authors have read and approved the manuscript.

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