Serum interleukin 38 (IL-38) as a new potential biomarker of pediatric asthma

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Abstract
Background: Bronchial asthma is considered the most prevalent chronic respiratory disease worldwide and is one of the main causes of hospitalization in the pediatric population. Serum interleukin 38 (IL-38) levels are elevated in several inflammatory and autoimmune diseases. However, its exact role in the pathogenesis of these diseases is unclear.

Objectives: To investigate the role of IL-38 as a potential biomarker in pediatric patients with bronchial asthma.

Methods: Serum IL-38 levels were measured in 73 pediatric patients with bronchial asthma (34 atopic and 39 non-atopic) and 30 age- and sex-matched healthy control subjects using enzyme-linked immunosorbent assay.

Results: Serum IL-38 levels were significantly higher in patients with bronchial asthma compared to the control group ($p < 0.001$). A significant negative correlation was found between serum IL-38 levels and both relative and absolute eosinophilic counts in the atopic group ($R = -0.575, p < 0.001$ and $R = -0.474, p = 0.005$, respectively).

Conclusion: IL-38 could be a useful prognostic and therapeutic biomarker of atopic asthma in pediatric patients.

Keywords: Bronchial asthma, IL-38, Biomarker, Inflammatory diseases, Eosinophilic asthma

Introduction
Bronchial asthma is a chronic airway inflammatory disease characterized by recurrent episodes of chest tightness, wheezing, cough, and dyspnea [1].

Bronchial asthma is estimated to be the most prevalent chronic respiratory disease worldwide [2] affecting about 339 million people and is ranked 16 among the leading causes of years lived with disability (YLDs) [3]. In children, the incidence of bronchial asthma has increased in the last two decades, particularly in low-middle-income countries [4].

The global asthma-related costs, whether direct, indirect, or intangible, are high. Direct costs include clinic visits, investigations, medications, and hospital admission [5, 6]. In fact, bronchial asthma is considered one of the main causes of hospitalization in the pediatric population [7] and is reported to be responsible for about 30% of all the causes of pediatric hospitalization [8, 9]. Indirect costs include work- and school-related losses [10]. Intangible costs are related to impaired quality of life, decrease in physical activities, and low study performance, which are associated with various psychological effects, such as depression and anxiety [11].

Globally, bronchial asthma is a disease of high prevalence and morbidity, particularly in children with impaired quality of life in both children and their parents [4]. Understanding the pathogenicity of the disease could improve therapeutic modalities and provide better control of disease outcomes, ultimately improving the overall quality of life of the patients and their relatives. Recent studies in the field of asthma are focused on discovering novel noninvasive biomarkers that could be used for evaluating asthmatic patients, monitoring disease progression, and predict asthmatic attacks [12, 13].

Interleukin 38 (IL-38), previously called IL1HY2, is a relatively new biomarker discovered about 20 years ago. It is a member of the IL-1 family and consists of 152...
amino acids. IL-38 is normally expressed in the thymus, spleen, skin, tonsils, fetal liver, skin, and salivary glands [14–16].

Most of the IL-1 family members are considered pro-inflammatory cytokines as they regulate the expression of genes that are involved in inflammatory diseases [17]. However, recent studies have reported an anti-inflammatory role of IL-38 via inhibition of inflammatory cytokines release from macrophages and by its antagonist action on the inflammatory cytokine IL-36 [17, 18].

Serum IL-38 levels are elevated in several inflammatory and autoimmune diseases. However, its exact role in the pathogenesis of these diseases is still poorly understood [17].

Chu and his colleagues [19] have reported a significant increase of IL-38 serum levels in patients with childhood asthma. Moreover, they found a significant negative correlation between IL-38 serum levels and the percentage of Treg lymphocytes in the patients with high level of periostin which is considered a new serum biomarker of airway eosinophilia.

In the same context, a recent review conducted by Tsang et al. [20] on the importance of IL-1 family cytokines in the development and pathogenesis of allergic diseases revealed that IL-38 could be a promising cytokine in the control of allergic diseases.

In this study, we tried to shed more light on the potential role of IL-38 in bronchial asthma in pediatric patients.

**Patients and methods**

**Study participants**

This case-control study was conducted on 103 subjects (73 pediatric patients with bronchial asthma and 30 age- and sex-matched healthy control subjects). The patients were recruited from the allergy outpatients’ clinic of the Department of Pediatrics at Cairo University Hospitals.

The study was approved by the Institutional Research of Faculty of Medicine, Cairo University, Egypt. Informed consents were obtained from the parents of all study participants.

The patients underwent thorough clinical examinations, detailed history taking, and proper routine investigations, including pulmonary function tests and complete blood count (CBC). All subjects were subjected to stool analysis to exclude the presence of parasitic infestations.

The patients were divided into two groups, atopic and non-atopic. The atopic patients had a history of allergic sensitization, which was confirmed by a positive specific immunoglobulin E (IgE) test. The non-atopic patients had a negative history of allergic sensitization, and their specific IgE test was negative.

The asthma control test (ACT), a five-question assessment tool with a score range of 5–25, was performed for all patients. Based on the results, the patients were subdivided into two groups: good asthma control (ACT score > 19) and poor asthma control (ACT score ≤ 19) [21].

The patients were further subdivided according to their peripheral blood eosinophilic counts into two groups: eosinophilic asthma (peripheral eosinophilic count ≥ 150 cells/μL) and no eosinophilic asthma (peripheral eosinophilic count < 150 cells/μL) [22–25].

**Inclusion and exclusion criteria**

All subjects were 6–14 years old, only patients fulfilled the criteria of the Global Initiative for Asthma (GINA) [1] were included in the study. Patients with malignant, other chronic allergic, or inflammatory diseases were excluded from our study. In addition, all patients stopped any antihistamine drug treatment a week before involvement in our study. The control subjects were free from any allergic diseases.

**Pulmonary function**

Pulmonary function tests were performed for each patient using Spirometry. Jager Master Screen spirometry was done. This system was calibrated for room temperature and pressure of saturated gas and volumes. Calibration was performed on site before each testing session and according to the manufacturer’s instructions. Spirometric indices included forced expiratory volume in the 1st second (FEV1), forced vital capacity (FVC), and FEV1/FVC were measured and were expressed as percentage to predict values based on age, height, sex, and ethnicity.

**Laboratory investigations**

**Sample collection**

Briefly, 5 ml of the venous blood was collected from all subjects and divided into two vacutainer tubes: one containing ethylenediaminetetraacetic acid (EDTA) for the CBC and one empty vacutainer tube. The sera were separated and divided into three Eppendorff tubes and stored at −20°C until the time of total IgE, specific IgE, and IL-38 assays.

**Total IgE assay**

Human IgE enzyme-linked immunosorbent assay (ELISA) kit (BioCheck, USA) was used for measurement of total IgE serum levels. The minimum detectable concentration was 5.0 IU/ml.

**Specific IgE assay**

Specific IgE serum levels were measured for the patients using the commercially available Euroline Test kit.
(Euroimmune, Germany) using the immunoblot technique. The kit includes test strips coated with various allergens. First, the strips were incubated with the patients’ sera to allow the reaction between IgE-specific antibodies with the allergens coated on the strips. Then, a second incubation with an enzyme conjugate (enzyme-labeled anti-human IgE) was carried out for the detection of the bound antibodies using a catalyzing color reaction.

The test was considered positive if the specific IgE serum levels were more than 0.35 kU/L. The patient was considered atopic in the presence of at least one positive specific IgE against common allergens, such as house dust mites, animal dander, German cockroaches, and fungi.

**Serum interleukin 38**

Serum IL-38 levels were measured using the human IL-38 ELISA kit (SinoGeneClon Biotech Co., China). The assay range was 30–2500 pg/ml. The minimum detectable concentration was 6 pg/ml.

**Statistical analysis**

Statistical package for social science version 21 was used for the statistical analysis. The mean and standard deviation were used to represent normally distributed data, while the median and percentiles were used for non-normally distributed data. For categorical variables, the frequency and percentages were used for data presentation, while the chi-square test and Fisher’s exact test were performed for comparison between groups. For quantitative data, Student’s t test and the nonparametric Mann–Whitney U test were performed for comparison between two groups. The analysis of variance and the Kruskal–Wallis test were performed for comparison between multiple groups. A p-value of <0.05 was considered statistically significant.

**Results**

This study included 73 pediatric patients with bronchial asthma (34 atopic and 39 non-atopic) and 30 age and sex-matched healthy control children. The demographic, clinical, and laboratory features of the studied groups are summarized in Table 1.

**Serum IL-38 levels in asthmatic patients and healthy controls**

The median serum levels of IL-38 were significantly higher in patients with bronchial asthma compared with the healthy control subjects (482 (412–632) vs 404 (306–493) pg/ml, \( p < 0.001 \), Fig. 1). There was no statistically

| Table 1  | Descriptive characteristics of the studied groups |
|----------|--------------------------------------------------|
|          | HC (n=30) | Asthmatic patients (n=73) | p-value\(^a\) | Atopic patients (n=34) | Non-atopic patients (n=39) | p-value\(^b\) |
| Age, years | 8.6 ± 2.9 | 8.4 ± 2.5 | 0.739 | 8.7 ± 2.2 | 8.1 ± 2.7 | 0.311 |
| Male sex, n (%) | 11 (36.7) | 40 (54.8) | 0.095 | 18 (52.9) | 22 (56.4) | 0.766 |
| Laboratory | | | | | | |
| Total IgE, (IU/mL) | 7.7 (5.4–20.9) | 31.6 (14.3–209.8) | <0.001 | 62.5 (17.9–292.3) | 27.6 (9.1–165.4) | 0.034 |
| Eosinophils % in PB | 4.0 (2.0–7.0) | 4.0 (2.0–7.0) | 4.0 (2.0–7.0) | 4.0 (2.0–7.0) | 4.0 (2.0–7.0) | 0.327 |
| Absolute eosinophils count (cells/ul) | 294 (135–522) | 334 (144–566) | 255 (122–485) | 255 (122–485) | 255 (122–485) | 0.197 |
| Exacerbation, n (%) | | | | | | |
| Seasonal | 50 (68.5) | 24 (70.6) | 26 (66.7) | 26 (66.7) | 26 (66.7) | 0.719 |
| Perennial | 23 (31.5) | 10 (29.4) | 13 (33.3) | 13 (33.3) | 13 (33.3) | 0.719 |
| Pulmonary functions | | | | | | |
| FEV1 | 86.4 ± 17.2 | 87.7 ± 13.7 | 85.3 ± 19.8 | 85.3 ± 19.8 | 85.3 ± 19.8 | 0.609 |
| FVC | 86.8 ± 15.4 | 89.3 ± 11.0 | 84.8 ± 18.3 | 84.8 ± 18.3 | 84.8 ± 18.3 | 0.277 |
| FEV1/FVC | 98.5 ± 11.1 | 96.2 ± 11.0 | 100.5 ± 11.0 | 100.5 ± 11.0 | 100.5 ± 11.0 | 0.139 |
| ACT | 18.6 ± 4.6 | 17.7 ± 5.1 | 19.4 ± 4.1 | 19.4 ± 4.1 | 19.4 ± 4.1 | 0.121 |
| Asthma control, n (%) | | | | | | |
| Poor | 41 (56.2) | 23 (67.6) | 18 (46.2) | 18 (46.2) | 18 (46.2) | 0.065 |
| Good | 32 (43.8) | 11 (32.4) | 21 (53.8) | 21 (53.8) | 21 (53.8) | 0.121 |
| Eosinophilic asthma, n (%) | 50 (68.5) | 24 (70.6) | 26 (66.7) | 26 (66.7) | 26 (66.7) | 0.719 |

Variables with normal distribution are presented as mean ± standard deviation. Skewed variables are presented as median (interquartile range)

HC healthy controls; IgE immunoglobulin E; PB peripheral blood; FEV1 forced expiratory volume in 1st second; FVC forced vital capacity; ACT asthma control test

\(^a\) p value of asthmatic patients vs healthy control

\(^b\) p value of atopic vs non-atopic asthmatic patients
significant difference in the median serum levels of IL-38 between atopic and non-atopic groups (475 (400–618) vs 510 (432–646) pg/ml, \( p = 0.259 \), Fig. 2).

**Association and correlation of IL-38 with demographic, clinical, and laboratory features of bronchial asthma**

The association and correlation between serum IL-38 levels with different demographic, clinical, and laboratory features of the patients are summarized in Tables 2 and 3.

There was no significant association between serum IL-38 levels with any of the demographic, clinical outcomes of bronchial asthma (sex, pattern of asthma exacerbation, asthma control level) neither in all patients nor in any of the asthma subgroups (Table 2). Also, no significant correlation could be found between serum IL-38 levels and any of the demographic, clinical outcomes of bronchial asthma (age, pulmonary function indices, and ACT score) neither in all patients nor in any of the asthma subgroups (Table 3).

Regarding the laboratory features of bronchial asthma, no significant correlation was found between the serum levels of IL-38 and the total IgE (Table 3). However, a significant negative correlation was found between serum IL-38 levels and both relative and absolute eosinophilic counts of the asthmatic patients (\( R = -0.345, p = 0.003; \) \( R = -0.287, p = 0.014 \), respectively). This correlation was evident in the atopic group (\( R = -0.575, p < 0.001; \) \( R = -0.474, p = 0.005 \), respectively, Figs. 3 and 4), while it was absent in the non-atopic group (\( R = -0.134, p = 0.386; \) \( R = -0.102, p = 0.535 \), respectively).

**Serum IL-38 levels according to the presence or absence of eosinophilic asthma**

The median serum levels of IL-38 were significantly higher in patients with both eosinophilic asthma and non-eosinophilic asthma as compared to the healthy control subjects (\( p = 0.012; <0.001 \), respectively, Fig. 5). In harmony to the previous results of our study, IL-38 serum levels were significantly lower in patients with eosinophilic asthma compared with those without eosinophilic asthma (468 (401–584) vs 616 (477–715) pg/ml, \( p = 0.011 \), Table 2 and Fig. 5). Again, this effect was evident in the atopic group only (425 (370–525) vs 620 (526–778) pg/ml, \( p = 0.012 \), Table 2 and Fig. 6), while the difference was statistically not significant in the non-atopic group (495 (410–606) vs 615 (454–749) pg/ml, \( p = 0.290 \), Table 2).

**Discussion**

In this study, we analyzed the role of IL-38 as a biomarker of pediatric asthma in order to better understand the pathogenicity of the disease, therefore provided better monitoring and management of asthma.
In the present study, we found that the serum IL-38 levels were significantly higher in the asthmatic children than that in the healthy control subjects. Moreover, the serum levels of IL-38 were inversely correlated with the degree of eosinophilia in the atopic group only which suggests that IL-38 serum level could be a biomarker of atopic asthma in the pediatric patients.

Interleukin 38 is a relatively new member of the IL-1 family, which is a major player in inflammatory and allergic diseases [20]. The IL-38 gene is located in the IL-1F cluster on chromosome 2 beside the IL-1Ra and IL-36Ra genetic loci [26], sharing 41% and 43% structural homology with IL-1Ra and IL-36Ra, respectively [15]. IL-38 binds to IL-36 receptors, representing a new member of

Table 2 Association of IL-38 serum levels (pg/ml) with the demographic and clinical outcomes of the asthmatic groups

|                         | Asthmatic patients (n=73) | p-value | Atopic patients (n=34) | p-value | Non-atopic patients (n=39) | p-value |
|-------------------------|---------------------------|---------|------------------------|---------|---------------------------|---------|
| Sex                     |                           |         |                        |         |                           |         |
| Males                   | 481 (418–660)             | 0.855   | 456 (416–714)          | 0.408   | 509 (425–638)             | 0.461   |
| Females                 | 516 (407–614)             |         | 493 (363–552)          |         | 557 (421–733)             |         |
| Exacerbation            |                           |         |                        |         |                           |         |
| Seasonal                | 505 (415–651)             | 0.316   | 505 (370–623)          | 0.705   | 528 (435–706)             | 0.356   |
| Perennial               | 472 (404–598)             |         | 434 (412–546)          |         | 510 (367–601)             |         |
| Asthma control          |                           |         |                        |         |                           |         |
| Poor                    | 477 (409–629)             | 0.530   | 436 (364–607)          | 0.408   | 527 (435–660)             | 0.933   |
| Good                    | 512 (412–635)             |         | 514 (420–625)          |         | 509 (410–703)             |         |
| Eosinophilic asthma     |                           |         |                        |         |                           |         |
| Present                 | 468 (401–584)             | 0.011   | 425 (370–525)          | 0.012   | 495 (410–606)             | 0.290   |
| Absent                  | 616 (477–715)             |         | 620 (526–778)          |         | 615 (454–749)             |         |

IL-38 serum levels are presented as median (interquartile range)
the IL-36 subfamily, and acts as a natural antagonist to the inflammatory cytokine IL-36 [27].

Previous studies revealed that Th17 cell immunity are implicated in the pathogenesis of allergic asthma through the production of IL17 and IL22 [28, 29]. In van de Vee-donk et al. study [27], which is performed in order to evaluate the biological functions of IL-38, the authors used heat killed Candida albicans to stimulate cytokine production by the memory T-helper cells invitro through culturing freshly derived human peripheral blood mononuclear cells together with heat killed Candida albicans. The authors found that, the addition of recombinant IL-38 to the culture media resulted in the suppression of T cell cytokines production; IL17 by 39% and IL22 by 37%.

In this study, serum IL-38 levels were significantly higher in pediatric patients with bronchial asthma compared with healthy controls ($p < 0.001$). Additionally, atopic patients had a significant negative correlation between serum IL-38 levels and both relative and

**Table 3** Correlation of IL-38 serum levels with different demographic, clinical, and laboratory outcomes of the asthmatic groups

|                                      | Asthmatic patients ($n=73$) | Atopic patients ($n=34$) | Non-atopic patients ($n=39$) |
|--------------------------------------|-----------------------------|--------------------------|-----------------------------|
|                                      | $R$            | $p$         | $R$            | $p$         | $R$            | $p$         |
| Age (years)                          | $-0.194$       | $0.100$     | $-0.192$       | $0.276$     | $-0.130$       | $0.432$     |
| Total IgE, (IU/mL)                   | $-0.202$       | $0.087$     | $-0.073$       | $0.683$     | $-0.227$       | $0.1640$    |
| Eosinophils % in PB                  | $-0.354$       | $0.003$     | $-0.575$       | $<0.001$    | $-0.143$       | $0.386$     |
| Absolute eosinophils count (cells/ul)| $-0.287$       | $0.014$     | $-0.474$       | $0.005$     | $-0.102$       | $0.535$     |
| FEV1                                 | $0.073$        | $0.588$     | $0.037$        | $0.859$     | $0.092$        | $0.623$     |
| FVC                                  | $0.221$        | $0.098$     | $0.009$        | $0.967$     | $0.346$        | $0.056$     |
| FEV1/FVC                             | $-0.175$       | $0.192$     | $-0.199$       | $0.331$     | $-0.093$       | $0.299$     |
| ACT                                  | $-0.025$       | $0.835$     | $-0.060$       | $0.738$     | $-0.094$       | $0.570$     |

$\text{IgE}$ immunoglobin E; $\text{PB}$ peripheral blood; $\text{FEV1}$ forced expiratory volume in 1st second; $\text{FVC}$ forced vital capacity; $\text{ACT}$ asthma control test

Fig. 3 Correlation between relative blood eosinophilic counts and IL-38 serum levels in atopic asthmatic patients
Fig. 4 Correlation between total blood eosinophilic counts and IL-38 serum levels in atopic asthmatic patients

Fig. 5 IL-38 serum levels in the studied groups
absolute eosinophilic counts ($R = -0.575, p < 0.001$ and $R = -0.474, p = 0.005$, respectively). However, no significant correlation was found in the non-atopic group. In the same context, the serum IL-38 levels were significantly lower in patients with eosinophilic asthma as compared to those without eosinophilic asthma ($p=0.011$). Again, this difference was evident only in the atopic group of patients ($p=0.012$) and was absent in the nonatopic group ($p=0.290$).

Our results are consistent with those of Chu et al. [19], who analyzed the serum IL-38 levels in childhood asthma. However, almost all the patients in their study were of the allergic phenotype. The authors did not analyze the IL-38 biomarker in the nonatopic patients. In their study, the authors found that serum levels of IL-38 were significantly higher in the asthmatic patients than those of the control subjects. Additionally, Chu and his colleagues found that IL-38 was negatively correlated with T-reg lymphocyte percentages in the patients with periostin level more than 40 ng/ml, the authors used periostin as an indication for eosinophilic airway inflammation. This goes hand in hand with our findings. However, the authors in Chu et al. study did not classify their patients according to the presence or absence of eosinophilic asthma and they did not evaluate IL-38 cytokine with the degree of eosinophilia.

In children, allergic asthma is considered the main phenotype as about 60% of asthmatic children are allergic, particularly to perennial allergens [30]. Patients with atopic asthma frequently have a high eosinophilic count, and the level of eosinophilia is usually correlated with the degree of asthma severity and are considered as an indication of asthma exacerbation [31, 32].

Patients with eosinophilic asthma have high peripheral blood and airway eosinophilic counts. Eosinophils accumulate in the bronchial tract and lungs, releasing cytotoxic mediators and cytokines. This results in inflammatory reactions and tissue injury, aggravating the severity of asthma [33, 34].

Patients with eosinophilic asthma frequently experience recurrent asthma exacerbation, so they usually need additional lines of biological therapy, in addition to traditional treatments, to control their symptoms [35].

IL-5 is a key cytokine in the maturation and activation process of eosinophils [36, 37]. For a long time, it was a target for scientists to develop additional forms of treatments as an adjuvant therapy for patients with severe eosinophilic asthma [38–44].

Sun et al. [45] conducted a study on animal models to elucidate the anti-inflammatory mechanism of IL-38 in allergic asthma. In their study, the intraperitoneal injection of IL-38 into the allergic asthma mice (house dust...
mite-induced mice) resulted in decreased eosinophilic accumulation in the mice lungs and reduced the expression of the Th2 cytokines IL-4, IL-5, and IL-13 in the lung homogenates and in the bronchoalveolar fluid lavage of the induced-mice models. The authors concluded that IL-38 could act via inhibition of the eosinophilic infiltration of the airway submucosa, almost via downregulation of Th2 inflammatory cytokines, particularly IL-5, which is significant for the differentiation and survival of eosinophils.

The results of our study suggest that IL-38 could be an anti-inflammatory biomarker of atopic asthma. According to our results and that of the previous studies [27, 45], we postulate that IL-38 acts as an anti-inflammatory cytokine in atopic patients almost via the inhibition of inflammatory cytokines production by T-helper cells. IL-38 almost acts through suppression of eosinophil production and accumulation in the airway system via suppression of IL-5 production, the major player in the eosinophil activation and maturation pathway. We hypothesize that in patients with bronchial asthma, the levels of IL-38 production increase to counteract the inflammatory reaction via the anti-inflammatory properties of IL-38. However, in patients with eosinophilic asthma, it seems that the increase in IL-38 production is not high enough to suppress the eosinophilic production. So, we suggest that patients with eosinophilic asthma could benefit from introduction of recombinant IL-38 as a therapeutic option which would decrease the production and accumulation of eosinophils in the bronchial airway leading to relief of the patients’ symptoms. Indeed, further studies are needed to confirm our hypothesis and to validate the efficiency of the use of recombinant IL-38 as a biological treatment in patients with eosinophilic asthma. To our knowledge, our study is the first one to have correlated IL-38 serum levels with the degree of eosinophilia in pediatric patients with bronchial asthma.

**Conclusion**

In conclusion, IL-38 could be a useful new biomarker of atopic asthma, particularly in pediatric patients. It can provide a new line of biological treatments for patients with eosinophilic asthma who might suffering from insufficient increase in their natural production of IL-38 cytokine in order to counteract and suppress the inflammatory reactions and accumulation of eosinophils in the airway system. Further studies, experiments, and clinical trials are needed to elucidate the exact role and mechanism of action of IL-38 and to validate the possibility of its application as a therapeutic option for patients with severe eosinophilic asthma.
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