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# ASTHMA PHENOTYPE, BIOMARKERS ESSENTIAL FOR THE DIAGNOSIS AND TREATMENT OF SEVERE ASTHMA

By

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## ABSTRACT

**Background:** Asthma is a global health problem that causes reversible airway obstruction. Chronic airflow obstruction shows airway wall remodeling as increased airway wall thickness. Recurrent exacerbations show increased sputum esinophils and reduced response to inhaled corticosteroids (ICS) and/or oral corticosteroids (OCS). Corticosteroid insensitivity shows increased neutrophils in sputum.

**Objective:** Assessment of interleukin 13 (IL-13), IL-4, immunoglobulin E (IgE), and others as biomarkers in cases of severe asthma and their role in the detection of asthma phenotypes and choice of treatment.

**Patients and Methods:** A cross sectional study was conducted on forty patients with severe asthma admitted at ICU Unit at Al-Hussein University Hospital between January 2016 and April 2021. The patients were categorized into atopic and non-atopic asthma, early and late onset asthma, and persistent airflow obstruction and non-persistent airflow obstruction. All patients were subjected to full history taken, full clinical examinations, and laboratory investigations included complete blood count (CBC), blood and sputum esinophils, blood and sputum neutrophils, blood and sputum immunoglobulin E (IgE), blood and sputum IL-13, and IL-4.

**Results:** There were statistically significant negative correlations between IL-13 (pg/ml) and neutrophils, and between IL-4 (pg/ml) and ICs dose (mcg/d) in the studied asthma patients. However, no statistically significant difference between non-atopic and atopic asthma groups regarding total count cell (×106 cells/mL), neutrophils %, and esinophils % was detected. Also, there was no statistically significant difference among the studied asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml).

**Conclusion:** Our study concluded high burden of severe asthma in adults with the existence of clinical possible phenotypes among them.

**Keywords:** Asthma, Phenotype, Interleukin 4 and 13, Esinophils, Atopic, Non-atopic and IgE.

## INTRODUCTION

Asthma is a phenotypically heterogeneous disorder that results from complex interactions between environmental and genetic factors *(Saha et al., 2010)*. Over the years, many different clinical subtypes of asthma have been described in the literature *(Shehata et al., 2010)*.

It is uncertain regarding whether all these different subtypes represent the variable expression of one single disease

or whether some subtypes represent distinct diseases with similar symptomatology *(Jain et al., 2011)*.

The management of patients with severe refractory asthma (SRA) is a difficult task that may benefit from the use of non-invasive assessment by biomarkers interleukin (IL)-13 is a cytokine with a central role in the TH2 response *(Neill et al., 2010)*. Severe asthma may occur in childhood as well as in adulthood, may be associated with different allergic or non-allergic provoking factors, and may exhibit an esinophilic or non-esinophilic type of inflammation *(Trudeau et al., 2010)*.

Clinically, different patterns of severe asthma may be observed, including near-fatal asthma, asthma with fixed airflow obstruction, and corticosteroid-resistant asthma *(Starosta et al., 2011)*.

The expression of asthma may vary according to age and gender, association with atopy or specific provoking factors, type of airway inflammation, or severity of the disease *(De Boever et al., 2014)*.

**The aim of the present study was to** assess IL-13, IL-4, IgE, and others as biomarkers in cases of severe asthma and their role in the detection of asthma phenotype, and the choice of treatment.

## PATIENTS AND METHODS

A cross sectional study was conducted on forty patients with severe asthma admitted at ICU Unit, Al-Hussein University Hospital between January 2016 to April 2021. The patients were categorized into atopic (n=26) and non-atopic asthma (n=14), early onset (n=21) and late onset asthma (n=19), and persistent airflow (n=33) and non-persistent airflow obstruction asthma (n=7).

The patients were adults aged >18 years with the onset of asthma among them were after the age of 18. All patients with dysfunctional breathlessness/vocal cord dysfunction, chronic obstructive pulmonary disease, hyperventilation with panic attacks, bronchiolitis obliterans, congestive heart failure, adverse drug reaction (e.g. angiotensin-converting enzyme inhibitors, ace-i), bronchiectasis/cystic fibrosis, hypersensitivity pneumonitis, hyperesinophilic syndromes, pulmonary embolus, herpetic tracheobronchitis, endobronchial lesion/foreign body (e.g. amyloid, carcinoid, tracheal stricture), allergic bronchopulmonary aspergillosis, acquired tracheobronchomalacia, and Churg-Strauss syndrome were excluded from our study.

**All patients were subjected in this study for the following:**

1. Full history taken including family and social history.
2. Full clinical examinations including general, chest, heart, and abdominal examinations.
3. Laboratory investigations: Complete blood count (CBC), blood and sputum, blood and sputum neutrophils, blood and sputum IgE, blood and sputum IL-13, IL-4, erthrocyte sedimentation rate (ESR), and C-reactive protein (CRP) test.

For the quantitative determination of human IL-4 and IL-13 concentrations in serum, commercial ELISA kits from R&D Systems, Inc. (Minneapolis, MN) were

used [Catalog Nos.: D4050, D1300, DIF50]. The test procedure as per the manufacturer's instruction was adopted. The minimum detectable dose of IL-4 was less than 10 pg/ml and that of IL-13 was less than 32.0 pg/ml.

Spirometry was performed according to ATS/ERS guidelines *(Miller et al., 2011)*. European coal and steel community (ECSC) prediction equations were used *(Morris, 2010)*.

Prick tests for common aeroallergens (mites, fungi, pollen, and dog and cat fur) were performed. The test was considered positive when at least one antigen-induced reaction was 3 mm in diameter greater than the negative control (saline solution) as measured 15 min after the puncture. Patients with at least one positive prick test were categorized as atopic. Total serum IgE was determined using a fluorescence enzyme immunoassay *(Oppenheimer and Nelson, 2010)*.

**Assessment of the inflammatory markers:**

Sputum induction (SI) was performed as previously described. Esinophil-positive (EOS+) patients were defined as those with induced sputum ≥ 3%, and esinophil-negative (EOS−) patients had esinophil levels < 3% *(Pavord et al., 2010)*.

The study was approved by Institutional Review Board at Al-Hussein Hospital, Al-Azhar University. Patient privacy and confidentiality were maintained throughout the study period.

**Statistical Analysis:**

Data were collected, revised, coded, and entered to the Statistical Package for the Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations (SD) and ranges for parametric variables and presented as median and interquartile range (IQR (upper 75% and lower 25% values)) for non-parametric variables. The comparison between two independent groups with quantitative data and parametric distribution was done by using Independent t-test, while the comparison between two independent groups with quantitative data and non-parametric distribution was done by using Mann-Whitney U test. Pearson correlation coefficient (r) was used to correlate different study variables. P value < 0.05 was considered significant.

## RESULTS

The study included 40 patients with their mean age was 44.54 ± 8.39 years (ranged from 30 to 60 years), 77.5% of them were females, and their mean BMI was 30.3 ± 5.2 Kg/m2. The mean asthma duration of the studied patients was 31.58 ± 10.15 years. Of the studied cases 65% were atopic asthma and 35% were non-atopic asthma. Persistent airflow was found in 82.5% of cases and esinophil positive cases were found in 80% of the studied asthma patients.

The mean total count of cell neutrophils was 0.88×106 cells/mL, the mean neutrophils % was 51.1% and the mean % was 18.55%. The mean distribution of

studied cases according to FVC was 2.67, FEV1 was 1.66, FEV1/FVC was 58.38, TLC was 109.10 and RV/TLC was 159.20. The mean distribution of the studied cases according to IgE was 1042.98 IU/mI, IL-13 was 40.50 pg/ml, and IL-4 was 16.38 pg/ml **(Table 1)**.

**Table (1): Distribution of the studied cases according to total count cell, neutrophils, FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml)**

| Induced sputum | Mean ± SD | Range |
|---|---|---|
| Total count cell (× $10^6$ cells/mL) | 0.88 (0.79-0.9) | 0.6 – 1.96 |
| Neutrophils % | 51.10 ± 14.14 | 30 – 75 |
| % | 18.55 ± 6.22 | 10 – 32 |
| FVC | 2.67 ± 0.51 | 1.95 – 3.4 |
| FEV1 | 1.66 ± 0.41 | 1.06 – 2.5 |
| FEV1/FVC | 58.38 ± 9.03 | 45 – 75 |
| TLC | 109.10 ± 9.21 | 95 – 125 |
| RV/TLC | 159.20 ± 19.16 | 125 – 190 |
| IgE (IU/mI) | 1042.98 ± 93.81 | 898 – 1186 |
| IL-13 (pg/ml) | 40.50 ± 22.38 | 10 – 80 |
| IL-4 (pg/ml) | 16.38 ± 5.24 | 8 – 25 |

The correlation between IL-13 (pg/ml) and IL-4 (pg/ml) with their age in yeras, BMI (kg/m2), age of asthma onset, asthma duration, and other study variables was presented in Table (2). There was a statistically significant negative correlation between IL-13 (pg/ml) and neutrophils % while IL-4 (pg/ml) showed a statistically significant negative correlation with ICS dose (mcg/d) **(Table 2)**.

**Table (2): Correlation between IL-13 (pg/ml) and IL-4 (pg/ml) with different study variables**

| Variables | IL-13 (pg/ml) | | IL-4 (pg/ml) | |
|---|---|---|---|---|
| | r | P-value | r | P-value |
| Age (year) | -0.004 | 0.982 | 0.183 | 0.258 |
| BMI (kg/$m^2$) | 0.125 | 0.442 | 0.025 | 0.879 |
| Age of asthma onset (year) | -0.200 | 0.215 | 0.16 | 0.323 |
| Asthma duration (year) | -0.197 | 0.222 | 0.194 | 0.230 |
| Total count cell (× $10^6$ cells/mL) | 0.091 | 0.576 | 0.076 | 0.643 |
| Neutrophils % | **-0.400** | **0.011*** | 0.169 | 0.298 |
| % | 0.050 | 0.760 | -0.299 | 0.061 |
| ICS dose(mcg/d) | 0.067 | 0.682 | **-0.466** | **0.002*** |
| SABA, puff/day | 0.203 | 0.209 | 0.209 | 0.195 |
| ExCO | -0.181 | 0.264 | -0.096 | 0.556 |
| FVC | -0.115 | 0.480 | -0.275 | 0.085 |
| FEV1 | 0.089 | 0.587 | -0.129 | 0.428 |
| FEV1/FVC | -0.069 | 0.674 | 0.100 | 0.541 |
| TLC | 0.148 | 0.363 | -0.161 | 0.320 |
| RV/TLC | 0.079 | 0.630 | 0.177 | 0.274 |
| IgE (IU/mI) | -0.150 | 0.355 | -0.040 | 0.805 |

*Significant

**Table 3** presented the comparison between non-atopic and atopic asthma groups regarding total count cell (×106 cells/mL), neutrophils %, and %. There was no statistically significant difference between non-atopic and atopic asthma groups regarding total count cell (×106 cells/ml), neutrophils %, and %.

**Table (3): Comparison between non-atopic and atopic asthma groups regarding total count cell (× 106 cells/mL), neutrophils %, and %**

| Parameters \ Groups | | Non-atopic (n= 14) | Atopic (n= 26) | P-value |
|---|---|---|---|---|
| Total count cell ($\times 10^6$ cells/mL) | Median (IQR) | 0.89 (0.8 – 1.2) | 0.85 (0.77 – 0.88) | 0.064 |
| | Range | 0.65 – 1.96 | 0.6 – 1.08 | |
| Neutrophils % | Mean ± SD | 56.3 ± 14.49 | 48.29 ± 13.4 | 0.088 |
| | Range | 31 – 75 | 30 – 75 | |
| % | Mean ± SD | 16.64 ± 4.92 | 19.57 ± 6.68 | 0.158 |
| | Range | 10 – 25 | 10 – 32 | |

**Table 4** showed the comparison between non-atopic and atopic asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml). There was no statistically significant difference between non-atopic and atopic asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml).

**Table (4): Comparison between non-atopic and atopic asthma groupsregarding, FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml)**

| Parameters \ Groups | | Non-atopic (n= 14) | Atopic (n= 26) | P-value |
|---|---|---|---|---|
| FVC | Mean ± SD | 2.7 ± 0.44 | 2.66 ± 0.55 | 0.791 |
| | Range | 1.95 – 3.4 | 1.95 – 3.4 | |
| FEV1 | Mean ± SD | 1.7 ± 0.44 | 1.64 ± 0.39 | 0.662 |
| | Range | 1.06 – 2.3 | 1.06 – 2.5 | |
| FEV1/FVC | Mean ± SD | 57.71 ± 9.29 | 58.73 ± 9.04 | 0.739 |
| | Range | 45 – 72 | 45 – 75 | |
| TLC | Mean ± SD | 107.64 ± 10.75 | 109.88 ± 8.4 | 0.470 |
| | Range | 95 – 125 | 97 – 124 | |
| RV/TLC | Mean ± SD | 162.36 ± 16.72 | 157.5 ± 20.47 | 0.452 |
| | Range | 140 – 190 | 125 – 190 | |
| IgE (IU/mI) | Mean ± SD | 1053.43 ± 82.12 | 1037.35 ± 100.64 | 0.611 |
| | Range | 898 – 1186 | 898 – 1186 | |
| IL-13 (pg/ml) | Mean ± SD | 40.57 ± 21.72 | 40.46 ± 23.16 | 0.988 |
| | Range | 10 – 78 | 10 – 80 | |
| IL-4 (pg/ml) | Mean ± SD | 17 ± 5.1 | 16.04 ± 5.38 | 0.586 |
| | Range | 9 – 25 | 8 – 25 | |

**Table 5** showed the comparison between early onset and late onset asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml) and IL-4 (pg/ml). There was no statistically significant difference between early onset and late onset asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml).

**Table (5): Comparison between early onset and late onset asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml) and IL-4 (pg/ml)**

| Parameters \ Groups | | Early onset n= 21 | Late onset n= 19 | P-value |
|---|---|---|---|---|
| FVC | Mean ± SD | 2.64 ± 0.53 | 2.7 ± 0.49 | 0.710 |
| | Range | 1.95 – 3.4 | 1.95 – 3.4 | |
| FEV1 | Mean ± SD | 1.57 ± 0.34 | 1.76 ± 0.46 | 0.134 |
| | Range | 1.06 – 2.3 | 1.06 – 2.5 | |
| FEV1/FVC | Mean ± SD | 58.81 ± 8.98 | 57.89 ± 9.3 | 0.753 |
| | Range | 45 – 75 | 45 – 73 | |
| TLC | Mean ± SD | 108.67 ± 8.6 | 109.58 ± 10.06 | 0.759 |
| | Range | 97 – 124 | 95 – 125 | |
| RV/TLC | Mean ± SD | 156.1 ± 19.63 | 162.63 ± 18.54 | 0.287 |
| | Range | 125 – 190 | 133 – 190 | |
| IgE (IU/mI) | Mean ± SD | 1028.43 ± 98.69 | 1059.05 ± 87.9 | 0.309 |
| | Range | 898 – 1186 | 898 – 1186 | |
| IL-13 (pg/ml) | Mean ± SD | 38.76 ± 23.39 | 42.42 ± 21.69 | 0.612 |
| | Range | 10 – 80 | 10 – 79 | |
| IL-4 (pg/ml) | Mean ± SD | 15.57 ± 5.4 | 17.26 ± 5.04 | 0.314 |
| | Range | 8 – 25 | 9 – 25 | |

**Table 6** presented the comparison between non-persistent airflow and persistent airflow obstruction groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml) and IL-4 (pg/ml). There was no statistically significant difference between non-persistent airflow and persistent airflow obstruction asthma groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml).

**Table (6): Comparison between non-persistent airflow and persistent airflowobstructiongroups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml) and IL-4 (pg/ml)**

| Groups / Parameters | | Non-persistent airflow n= 7 | Persistent airflow n= 33 | P-value |
|---|---|---|---|---|
| FVC | Mean ± SD | 2.66 ± 0.57 | 2.67 ± 0.5 | 0.956 |
| | Range | 1.99 – 3.4 | 1.95 – 3.4 | |
| FEV1 | Mean ± SD | 1.42 ± 0.2 | 1.71 ± 0.42 | 0.085 |
| | Range | 1.08 – 1.58 | 1.06 – 2.5 | |
| FEV1/FVC | Mean ± SD | 60.29 ± 10.48 | 57.97 ± 8.82 | 0.544 |
| | Range | 48 – 75 | 45 – 74 | |
| TLC | Mean ± SD | 110.14 ± 8.69 | 108.88 ± 9.44 | 0.746 |
| | Range | 95 – 122 | 96 – 125 | |
| RV/TLC | Mean ± SD | 152.86 ± 21.21 | 160.55 ± 18.77 | 0.741 |
| | Range | 125 – 187 | 125 – 190 | |
| IgE (IU/mI) | Mean ± SD | 1049.71 ± 119.69 | 1041.55 ± 89.6 | 0.837 |
| | Range | 899 – 1186 | 898 – 1186 | |
| IL-13 (pg/ml) | Mean ± SD | 22.71 ± 24.48 | 44.27 ± 20.36 | 0.099 |
| | Range | 10 – 78 | 10 – 80 | |
| IL-4 (pg/ml) | Mean ± SD | 14.29 ± 5.96 | 16.82 ± 5.06 | 0.250 |
| | Range | 8 – 25 | 8 – 25 | |

**Table 7** presented the comparison between non-esinophil+veand esinophil +ve groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml).There was no statistically significant difference between non-EOS+and EOS+ groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml) **(Table 7)**.

**Table (7): Comparison between non-esinophil+veand esinophil+ve groups regarding FVC, FEV1, FEV1/FVC, TLC, RV/TLC, IgE (IU/mI), IL-13 (pg/ml), and IL-4 (pg/ml)**

| Groups / Parameters | | Non-EOS+ n= 8 | EOS+ n= 32 | P-value |
|---|---|---|---|---|
| FVC | Mean ± SD | 2.61 ± 0.51 | 2.69 ± 0.51 | 0.725 |
| | Range | 1.95 – 3.3 | 1.95 – 3.4 | |
| FEV1 | Mean ± SD | 1.58 ± 0.4 | 1.68 ± 0.41 | 0.515 |
| | Range | 1.08 – 2.1 | 1.06 – 2.5 | |
| FEV1/FVC | Mean ± SD | 57.25 ± 10.02 | 58.66 ± 8.91 | 0.699 |
| | Range | 45 – 72 | 45 – 75 | |
| TLC | Mean ± SD | 109.88 ± 11.06 | 108.91 ± 8.89 | 0.794 |
| | Range | 97 – 125 | 95 – 124 | |
| RV/TLC | Mean ± SD | 157.75 ± 27.59 | 159.56 ± 17.01 | 0.814 |
| | Range | 125 – 190 | 125 – 190 | |
| IgE (IU/mI) | Mean ± SD | 1024.75 ± 90.05 | 1047.53 ± 95.57 | 0.546 |
| | Range | 898 – 1186 | 898 – 1186 | |
| IL-13 (pg/ml) | Mean ± SD | 46.13 ± 18.04 | 39.09 ± 23.38 | 0.434 |
| | Range | 17 – 78 | 10 – 80 | |
| IL-4 (pg/ml) | Mean ± SD | 17.13 ± 6.01 | 16.19 ± 5.11 | 0.657 |
| | Range | 8 – 25 | 8 – 24 | |

## DISCUSSION

The patients in the present study displayed elevated sputum despite using high doses of inhaled corticosteroids. Although these patients had been receiving regular treatment for at least four years, they failed to achieve full clinical asthma control and continued to have persistent airflow limitation. Non-adherence to treatment is always a problem to consider, even when patients are followed for an extended period.

Subgroups analyses showed that nonatopic patients had higher levels of sputum than atopics. Patients with early-onset asthma tended to be more atopic and had more ICU admissions than did the late-onset group and based on the subgroups' characteristics, four phenotypes that included 62.2% of well-described patients were identified. In contrast to *ENFUMOSA Study Group (2010)* and *Moore et al. (2010)* on severe asthma, in which patients were recruited from various centers, our severe asthma patients were followed by pulmonary specialists in one tertiary university hospital where they received treatment and medication free of charge based on asthma management guidelines.

The female predominance observed in our patient (77.5 %) was reported by *ENFUMOSA Study Group (2010)* but not by *Moore et al. (2010)* suggesting that severe asthma could be a gender-related disease. However, this observation could result from a selection bias because, on average, women attended medical visits more regularly than men.

In contrast to previous cohorts, *Franco et al. (2011)* and *Santos et al. (2012)*, our study showed a well-characterized severe population treated regularly and sufficiently enough to control their asthma. Those patients had a long disease history with irregular treatment periods with a maximum treatment time of 50% of their asthma lives.

The patients' inability to take physical and emotional control of the disease clearly impacts their lives and probably causes increased levels of anxiety and depression. Low health-related quality of life (HRQoL) was not associated with poor lung function (FEV1 %) but was correlated with poor asthma control and depression symptoms. The evaluation of depression and anxiety symptoms is recommended in asthmatics, as these symptoms heavily influence HRQoL scores *(Coban and Aydemir, 2014)*.

Although the patients had severe asthma, their lung function abnormalities were moderate. However, their high residual volume/total lung capacity ratio values suggest an air-trapping component that is associated with the most severe forms of asthma *(Heckman and O'Connor, 2015)*. Our functional results indicated fixed changes in the peripheral airway and possible airway remodeling. Persistent airflow limitation despite effective asthma treatment has been associated with adult-onset asthma, increased airway hyper-responsiveness, and sputum esinophilia *(Hough et al., 2020)*. These findings highlight the need to evaluate the degree of small airway alterations in severe asthma patients.

Most of the patients in this study of severe asthmatics presented sputum esinophilia despite receiving steroid treatments. Persistent esinophilia is a characteristic of some severe asthma

subgroups *(Walford and Doherty, 2014)*, but, in our study, was not related to any specific clinical characteristic or to the ICS dose used. The higher prevalence of chronic oral corticosteroid use among atopic patients could explain the lower esinophilic inflammation in this group, although both variants of the disease (atopic and nonatopic) may be associated with bronchial mucosal esinophilic inflammation.

The normalization of sputum esinophilia after an intramuscular corticosteroid trial suggests that some severe asthmatics required additional anti-inflammatory treatment to improve airway inflammation *(de Carvalho et al., 2012)*. Our data suggested the need to follow these patients with a maximum anti-inflammatory treatment and objective measures of adherence and response.

A study conducted by *Anto et al. (2010)* in ECRHS also provided epidemiological evidence for distinguishing adult-onset from early-onset asthma. *Moore et al. (2010)* also showed, in their population of adults with more severe asthma, the importance of the age of onset in phenotyping asthma. Asthma phenotypes show age-related variations. Accordingly, *Bush and Menzies-Gow (2010)* identified the age at examination in the EGEA2 study as a major phenotyping criterion. *Moore et al. (2010)* and *Haldar et al. (2011)* also identified groups of subjects composed of older subjects.

Our study is not the first study for phenotypes of adult asthma. *Haldar et al. (2011)* showed four different phenotypes mainly based on distinctions in symptom load and inflammation. Unfortunately, that study did require sputum counts and peak-flow variability, both quite burdensome for the patient. *Ortega et al. (2012)* performed a cluster analysis in primary care data, but they were more focused on describing different asthma exacerbation phenotypes. Another study by *Metting et al. (2016)* produced a diagnostic algorithm for obstructive airway diseases, based on data from 9297 patients, which could be used to distinguish between different obstructive diseases.

*Khusial et al. (2017)* showed five different phenotypes of asthma. They also showed long-term outcomes for each of these. However, some of their phenotypes were small in numbers, which reduces external validity. The key advantages of the recent trial presented by *Kisiel et al. (2020)* compared to other studies are its numbers combined with the use of real-world data. By establishing the different phenotypes in data from over 1200 people and then validating them in another 748, they are firmly rooted and unlikely to be very different when applied to your patients.

*Woodruff et al. (2010)* found elevated bronchial expression of IL-5 and IL-13 had higher blood esinophil count in asthmatic patients compared with non-asthmatic controls. In our study, a statistically significant negative correlation between IL-13 (pg/ml) and Neutrophils %, and between IL-4 (pg/ml) and ICS dose (mcg/d) were found. Similar results were also reported by *Castro et al., (2018)*.

IL-13 and IL-4 appear as the most suitable targets to treat the T helper 2 (TH2)-mediated forms (endotypes) of

asthma. IL-13 and IL-4 partly share the same receptor and signaling pathways, and both are deeply involved in IgE synthesis, esinophil activation, mucus secretion and airways remodeling *(Bagnasco et al., 2016)*. The previous statement was in agreement with our study.

IL-4 and IL-13 were among the first identified cytokines orchestrating Th2 inflammation. It is intriguing that IL-13 blockade modulates several aspects of different experimental models of allergic asthma *(Aron and Akbari, 2017)*. The previous study was in agreement with our study.

Approximately 5–10% of asthmatic patients worldwide suffer from severe asthma. Experimental and clinical studies have demonstrated that IL-13 is an important cytokine in chronic airways inflammation. IL-13 is involved in Th2 inflammation and has been identified as a possible therapeutic target in the treatment of asthma *(Alasandagutti et al., 2017)*.

Rapid measurement of biomarkers (serum periostin, FeNo, etc.) would be fundamental in choosing the more appropriate drug for each individual patient *(Chachi et al., 2017)*.

In humans, there seems to be an inverse link between IFN-λ and the severity of allergic asthma and allergic asthma exacerbations *(Koch and Finotto, 2015)*.

## CONCLUSION

Our study concluded the high burden of severe asthma in adults with the existence of clinical possible phenotypes among them.

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# النمط الظاهري و المعملي اللازم لتشخيص وعلاج حالات الربو الشديدة

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**خلفية البحث:** الربو مشكلة عالمية يسبب للمريض انسدادًا في مجرى الهواء قابلاً للانعكاس. أظهر انسداد تدفق الهواء المزمن إعادة تشكيل جدار مجرى الهواء مع زيادة سماكة جدار مجرى الهواء. أظهرت التفاقمات المتكررة زيادة الحمضات في البلغم وانخفاض الاستجابة للكورتيكوستيرويد المستنشق مع الكورتيكوستيرويد المأخوذ بالفم أو مع كلاهما. كماأظهرت الحساسية تجاه الكورتيكوستيرويد زيادة في العدلات في البلغم.

**الهدف من البحث:** تقييم الإنترلوكين 13 و4 والجلوبيولين المناعي هـ وغيرها كمؤشر حيوي في حالات الربو الحاد ودورها في الكشف عن النمط الظاهري للربو واختيار العلاج.

**المرضى وطرق البحث:** كانت هذه دراسة مقطعية أجريت على أربعين مريضاً مصابين بالربو الحاد تم قبولهم في وحدة العناية المركزة في مستشفيات جامعة الأزهر في الفترة بين يناير 2016 حتى إبريل 2021، وقُسّم المرضى إلى مرضى بربو تأتّبي وربو غير تأتّبي، ومرضى بربو متقدّم ومتأخرالظهور، ومرضى بانسداد مجرى الهواء المستمرّ وآخرين بانسدادٍ غير مستمر، وجميع المرضى خضعوا لما يلي: التاريخ المرضى الكامل والفحوصات السريرية الكاملة والفحوصات المخبرية بما في ذلك: تعداد الدم الكامل، الحمضات في الدم والبلغم، انترلوكين 4 و 13، وسرعة ترسّب الدم واختبار البروتين المتفاعل.

**نتائج البحث:** كان هناك ارتباطًا سلبيا ذا دلالة إحصائية بين انترلوكين 13 (بيكوغرام/مل) وبينسبة العدلات، وبين انترلوكين 13 وجرعة الكورتيكوستيرويد المستنشق (ميكروغرام/ديسيلتر). ولم يكن هناك فرق معتد به إحصائيًا بين

مجموعتي الربو المتأتي وغير المتأتي فيما يتعلق بإجمالي خلية العد (× 106 خلية / مل) ونسبة العدلات، ونسبة الحمضات. كما لم يكن هناك فرق معتد به إحصائيًا بين مجموعات المرضى فيما يخصّ السعة الحيوية الزفيرية القسرية، وحجم الزفير القسري في ثانية واحدة، والنسبة بينهما والسعة الإجمالية للرئة ونسبة الحجم المتبقى للسعة الإجمالية للرئة، والجلوبيولين المناعي هـ، والانترلوكين 4 و13.

**الاستنتاج:** هناك عبءٌ مرتفعٌ للربو الحاد عند البالغين مع وجود أنماط ظاهرية سريرية محتملة لديهم.

**الكلمات الدالة:** الربو، النمط الظاهري، انترلوكين 4 و 13، حمضات، تأتبي، غير تأتبي، الجلوبيولين المناعي هـ.