Hamod *et. al.,* Babcock Univ. Med. J.2026 9(1):26-34
https://doi.org/10.38029/babcockuniv.med.j..v9i1.1165
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Influence of clinical biomarkers and demographic characteristics on predicted FEF25–75 in Iraqi patients with Asthma

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Submitted: 10th July 2025
Accepted: 23rd September 2025
Published: 31st March 2026
ID: Orcid ID

Abstract

Objective: This study aimed to investigate the associations between predicted Forced Expiratory Flow at 25–75% of pulmonary volume (FEF25–75) and selected clinical biomarkers, namely serum periostin, peripheral blood eosinophil count, and immunoglobulin E (IgE) levels, in a cohort of Iraqi patients diagnosed with bronchial asthma. Given that FEF25–75 reflects small airway function and is considered a sensitive marker of early airway obstruction, this study sought to explore its potential correlation with established indicators of airway inflammation and allergic response.

Methods: A cross-sectional analytical design was employed to assess the relationship between mid-expiratory lung function and inflammatory biomarkers among adult asthmatic patients. The study was conducted at a private respiratory clinic in Hillah, Iraq, and spanned a duration of one year. Patients were enrolled based on a clinical diagnosis of asthma according to Global Initiative for Asthma (GINA) guidelines, and spirometric measurements were obtained to assess lung function. Blood samples were collected for biomarker analysis using standard laboratory techniques.

Results: The mean age of patients is 38.1, and the percentage of female patients is 54.8%. Patients with low predicted FEF25–75 (≤65%) had significantly higher levels of serum periostin (p=0.035), blood eosinophil counts (p=0.03), and IgE (p=0.05) compared to those with normal FEF25–75. There are no significant associations found with age, sex, or BMI. However, family history was associated.

Conclusion: This supports the use of FEF25–75 alongside biomarker profiling for improved asthma phenotyping.

Keywords: Asthma, FEF25–75, Serum Periostin, Eosinophil Count, Immunoglobulin E (IgE), Small airway inflammation, Biomarkers, Iraq

Plain English Summary

Asthma is a common disease that causes inflammation and narrowing of the airways, making it difficult to breathe. Doctors often use lung tests, such as measuring how much air a person can blow out in one second (FEV_1), to monitor asthma. However, another test called FEF25–75 looks at how well the smaller airways work and may detect early problems that the usual tests can miss.

This study examined how small airway function (measured by FEF25–75) relates to certain blood markers of inflammation in Iraqi adults with asthma. These markers were serum periostin, eosinophil count, and immunoglobulin E (IgE), substances in the blood that reflect allergic and inflammatory activity in the lungs. Eighty-four patients with asthma were tested at a clinic in Hillah, Iraq. Each person completed lung function tests and gave a blood sample for laboratory analysis. The researchers found that patients with poorer

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small airway function (low FEF25–75) had higher levels of periostin, eosinophils, and IgE. This means that inflammation linked to allergic asthma was strongly associated with small airway problems.
Age, sex, and body weight did not seem to affect the results, but people with a family history of asthma were more likely to have reduced small airway function.
These findings suggest that combining lung function tests with blood biomarkers can help doctors better understand and monitor asthma, especially in patients who may have hidden small airway damage. Detecting these changes early may allow for more personalised treatment, including newer "biologic" medicines that target inflammation.

Background

Asthma is a chronic, heterogeneous respiratory disease characterised by airway inflammation, hyperresponsiveness, and variable airflow obstruction (1).

Globally, it is estimated that more than 300 million people suffer from asthma, and the prevalence is steadily rising, particularly in low and middle-income countries. Not only does the disease harm quality of life, but it also places a considerable economic burden on society as a result of frequent hospitalisations, absenteeism from work or school, and the requirement for long-term utilisation of pharmaceutical treatment.

In the Middle East, including Iraq, asthma represents a growing public health concern, yet its clinical characteristics and underlying pathophysiological mechanisms remain incompletely described (2, 3). In Iraq, asthma prevalence is rising, but data on biomarkers are still underrepresented, with limited studies addressing their role in small airway dysfunction and disease phenotyping (4).

The assessment of lung function through spirometry is fundamental in diagnosing and monitoring asthma (5). While Forced Expiratory Volume in one second (FEV_1) is commonly used, mid-expiratory flow rate FEF25–75 is gaining attention as a more sensitive marker of small airway dysfunction, which may be impaired even when FEV_1 remains within normal limits. Those airways that extend to the periphery of the lung and have an interior diameter of less than two millimetres are referred to as the small airways (6). Thus, investigating determinants of FEF25–75 can provide valuable insights into the pathophysiology and management of asthma (7). Furthermore, a reduced FEF25–75 correlates with bronchial reversibility and responsiveness to pharmacological and biological therapies (8).

Inflammatory biomarkers play a crucial role in characterising asthma phenotypes and guiding targeted therapies. Among these, serum periostin has emerged as a biomarker associated with type 2 (T2) inflammation (9). Periostin is a matricellular protein that plays a critical role in maintaining the structural integrity of tissues by stimulating type I collagen synthesis and promoting collagen cross-linking (9). excessive periostin production contributes to pathological tissue remodelling, most notably through the development of abnormal subepithelial fibrosis. This fibrinogenic remodelling can impair organ function by stiffening tissues and altering their physiological elasticity (10).

Eosinophils play a pivotal role in the pathogenesis of asthma, particularly in allergic and eosinophilic phenotypes of the disease. These cells are recruited into the airways under the influence of Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, where they release toxic granule proteins, including major basic protein and eosinophil peroxidase, leading to epithelial damage and sustained airway inflammation (11). Their mediators also enhance airway smooth muscle contractility, contributing to bronchial hyperresponsiveness, while growth factors like transforming growth factor-β promote airway remodelling through fibrosis, mucus hypersecretion, and thickening of the airway wall. Elevated eosinophil counts in blood and sputum are associated with more severe disease, frequent exacerbations, and poorer lung function. (12, 13). Clinically, eosinophils serve as important biomarkers for asthma severity and corticosteroid responsiveness, and they are therapeutic targets in severe asthma, as demonstrated by the efficacy of anti-IL-5 biologics such as mepolizumab, reslizumab, and benralizumab in reducing exacerbation rates and improving disease control (14).

Similarly, high IgE levels reflect atopic status and are linked to heightened bronchial hyperresponsiveness. Together, these biomarkers may influence or reflect small airway dysfunction as measured by FEF25–75, although evidence remains limited and sometimes conflicting across populations (15).

In Iraq, asthma prevalence is rising, but data on biomarker associations with small airway dysfunction are lacking (16). The process of establishing the relationship between lung function indices, such as FEF25–75, and biomarkers may provide deeper insight into subclinical inflammation and early airway involvement (17).

In addition to immunological factors, demographic characteristics play an important role in shaping asthma expression and lung function outcomes. Age can modify airway remodelling processes, with younger patients often demonstrating reversible airway narrowing, while older patients exhibit more fixed obstruction. Sex differences have also been documented, with hormonal influences affecting airway reactivity and immune responses (18). Moreover, body mass index (BMI) is increasingly recognised as a modifier of asthma severity, where obesity has been associated with reduced lung volumes, systemic inflammation, and a more difficult-to-control asthma phenotype (19). Understanding how these demographic factors interact with clinical biomarkers to influence small airway function is particularly relevant in diverse populations such as Iraqi patients, who may differ in genetic, environmental, and lifestyle exposures compared to Western cohorts (20).
Therefore, this study was designed to explore the influence of clinical biomarkers, specifically serum periostin, blood eosinophil counts, and IgE concentrations, as well as demographic variables including age, sex, and BMI, on predicted FEF25–75 in Iraqi patients with asthma. By integrating physiological, immunological, and demographic perspectives, the present research seeks to provide a more comprehensive understanding of small airway dysfunction (21) and its clinical correlates in this understudied population (4).

Materials and Methods

This is a cross-sectional study of 84 adult Iraqi asthmatic patients recruited from Alhillah Pulmonology Outpatient Clinic from January 2024 until January 2025.

Inclusion criteria

Individuals diagnosed with asthma, according to GINA criteria, include a history of respiratory symptoms, such as wheeze, breathlessness, cough, and chest tightness that vary over time and in intensity (22).

Exclusion criteria

These are respiratory diseases other than asthma, malignancy, and heavy smokers.

Spirometry

Predicted values of forced expiratory flow between 25% and 75% of forced vital capacity FEF25-75 were used in this study, as implied by the study title. Spirometric measurements were obtained according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards. Predicted values for FEF25-75 were calculated using the Global Lung Function Initiative (GLI) reference equations (2012), which adjust for age, sex, height, and ethnicity. The patients were analysed and stratified based on predicted FEF25-75 into two groups: Low FEF25-75: ≤ 65% and Normal FEF25-75: > 65%. The following parameters were examined: Serum Periostin (ng/mL), Eosinophil Count (10^3 cells/μL), Serum IgE (kU/L) in addition to Age, Sex, Weight, Height, and BMI. Anthropometric measurements: calculation of body mass index (BMI), the weight in kilograms (kg) divided by the height (m) squared (23). Mean body mass index was (28.61 ± 5.38) Kg/m^2, with a maximum value of 46.87 Kg/m^2 and a minimum value of 15.21 Kg/m^2.

Spirometry

Skilled operators performed pulmonary function tests using a MIR Portable, Desktop and PC-Based Spirometer, with Oximetry Spirolab Version 4.4. A bronchodilator reversibility test was done to confirm the diagnosis (defined as an increase in FEV1 of >12% and >200 mL from baseline after inhalation of 200-400 μg albuterol for 10 minutes). Peripheral blood eosinophil counts: Eosinophil number and percentage were determined as part of a complete blood count (CBC) with five-part differential using the Sysmex XN-1000 automated haematology analyser.

IgE Measurement

Serum IgE concentrations are measured using the VIDAS total IgE kit by BioMérieux. According to the manufacturer, the IgE normal range is from 0-150 kU/L

Serum periostin

Serum periostin levels were quantified using a human periostin (POSTN) enzyme-linked immunosorbent assay (ELISA) kit, supplied by Bioassay Technology Laboratory, Shanghai, China (Catalogue No. E3226Hu). This is a quantitative sandwich ELISA designed for the detection of human periostin in serum, plasma, or other biological fluids.

Statistical Analysis

Data were analysed using SPSS version 27. Continuous variables are expressed as means ± standard deviations, while categorical variables are clarified as frequencies and percentages. The t-test was used to compare means between groups, and the Chi-square test assessed associations for categorical variables. Statistical results have been considered significant when the p-value < 0.05.

Results

The study has been done on 84 patients. The mean age of patients in this study is 38.1 years, 45.2% male and 54.8% are female. Based on FEF25–75% values, patients were categorised into two groups: 56 patients (66.7%) had low Predicted FEF25-75% (<65%), 28 patients (33.3%) had normal Predicted FEF25-75% (≥65%). Table 1.

Table 1: Demographic characteristics

Characteristic	Total (n=84)	Low FEF25-75 (n=56)	Normal FEF25-75 (n=28)	p-value
Age, years (Mean Â± SD)	38.1 Â± 17.87	36.5 Â± 17.60	41.4 Â± 18.30	0.25
BMI, kg/mÂ² (Mean Â± SD)	29.84 Â± 18.97	27.44 Â± 5.18	34.91 Â± 32.43	0.24
Sex, Male n (%)	38 (45.2%)	26 (45.6%)	12 (44.4%)	1
Sex, Female n (%)	46 (54.8%)	31 (54.4%)	15 (55.6%)	1
Family Hx, Positive n (%)	53 (63.1%)	41 (71.9%)	12 (44.4%)	0.03

The relation between Age, BMI and FEF25-75

Using the Mann-Whitney U Test (due to parametric distribution), Age vs FEF25-75 Group. Both Age and BMI show no significant difference between normal (>65) and reduced (<65) FEF25-75 groups ($p > 0.05$).

Age versus FEF25-75 Group: Median Age, Normal = 42.0, Reduced = 32.0, U = 888.5, p = 0.26

BMI versus FEF25-75 Group: Median BMI, Normal = 29.76, Reduced = 26.67, U = 881.5, p = 0.29. Figures 1 and 2.

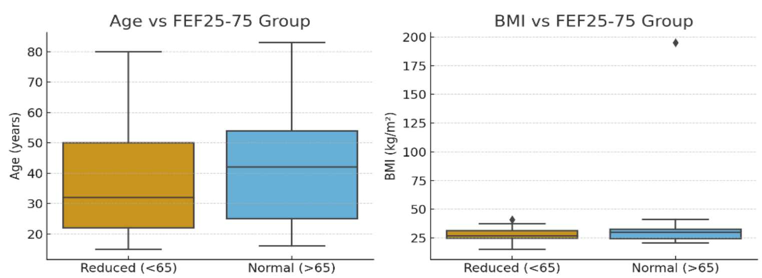

Figure 1 and 2: Boxplots for Age(left) and BMI (right) across the normal vs reduced FEF25-75 group

Family History effect on predicted FEF25-75 Predicted FEF25-75 Group

Chi-square analysis (Table 2 and Figure 3).

There is a significant association between family history and predicted FEF25-75 status. Patients with a positive family history are more likely to have reduced FEF25-75 (<65%). $\chi^2 = 4.82$, df = 1, p-value = 0.028 $p < 0.05$.

Table 2: The relation between family History and predicted FEF25-75 Predicted FEF25-75

FEF25-75 Group	Negative Family History	Positive Family History
Normal (>65)	15	12
Reduced (<65)	16	41

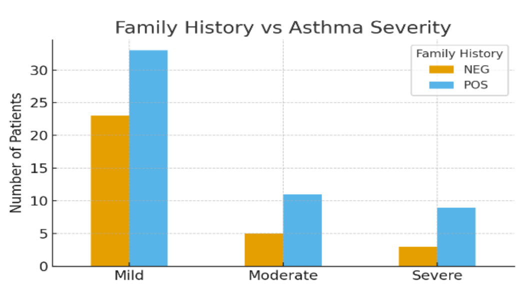

Figure 3: stacked bar chart showing the relation between family history and predicted FEF25-75 groups

Effect of Sex on Predicted FEF25-75

Chi-square analysis (Table 3 and Figure 4) There is no association between sex and predicted FEF25-75 status. Both males and females show nearly identical distribution across normal and reduced groups.: $\chi^2 = 0.00$, df = 1, p-value = 1.00.

Table 3: The relation between sex and FEF25-75:

FEF25-75 Group	Female	Male
Normal (>65)	15	12
Reduced (<65)	31	26

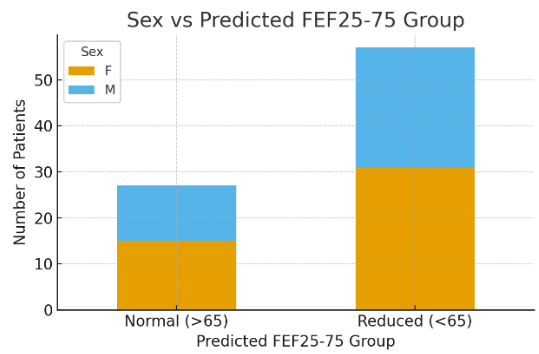

Figure 4: Stacked bar chart for the Chi-square analysis of sex versus predicted FEF25-75 groups.

Biomarker Results

According to the t-test, the mean serum periostin level was significantly higher in the reduced FEF_{25-75} group (63.47 ± 9.31 ng/mL) compared to the normal group (59.33 ± 7.41 ng/mL), P=0.035. Serum IgE was significantly higher in the reduced group, 294.32 ± 345.72 Ku/L, compared to serum IgE level in the normal group, 121.60 ± 198.09, P=0.05. Blood eosinophil count is much higher in the reduced group, 369.82 ± 347.63 cells/μL, in comparison to the normal group, 187.41 ± 202.19, P=0.003. Table 4 and Figures 5 to 7.

Table 4: The relation between blood biomarkers and Predicted FEF25-75%.

Biomarkers	Normal >65% (Mean ± SD)	Reduced ≤65% (Mean ± SD)	P-value
Serum Periostin ng/ml	59.33 ± 7.41	63.47 ± 9.31	0.035
IgE kU/L	121.60 ± 198.09	294.32 ± 345.72	0.005
Eosinophil Count (cells/μL)	187.41 ± 202.19	369.82 ± 347.63	0.003

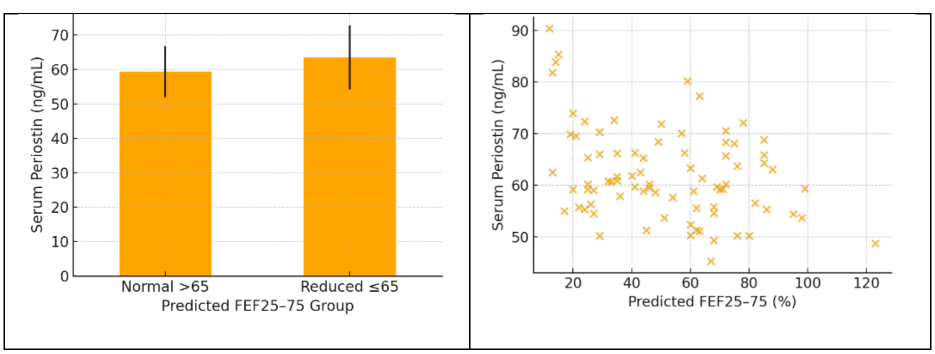

Figure 5: (Left) Bar chart, (Right) Box plot shows the relation between FEF25-75 and serum perostin

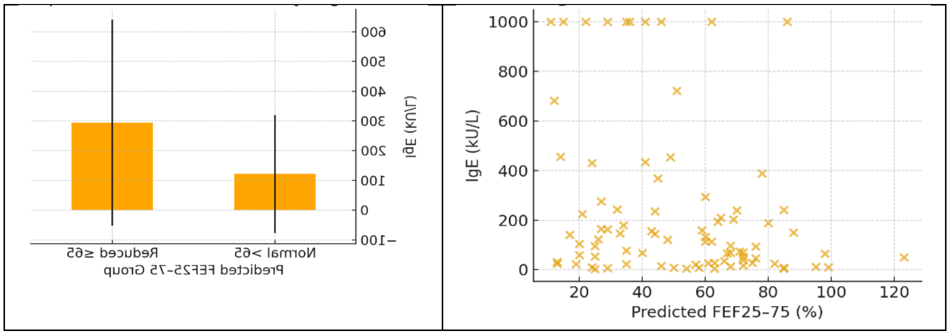

Figure 6: (Left) Bar chart, (Right) Box plot shows the relation between FEF25-75 and total serum IgE.

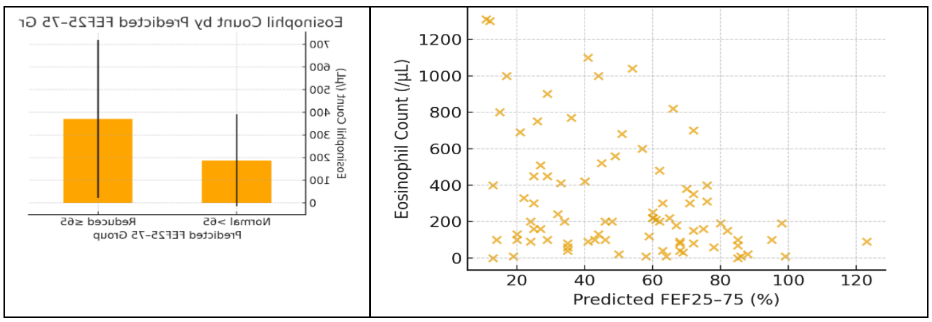

Figure 7: (Left) Bar chart, (Right) Box plot shows the relation between FEF25-75 and blood eosinophil count

Discussion

This study demonstrates that a reduced FEF25–75% predicted is significantly associated with elevated serum periostin levels, blood eosinophil counts, and total IgE levels in Iraqi adults with asthma. The importance of this research lies in its focus on an Iraqi population, where data on small airway function and inflammatory biomarkers remain limited. By integrating spirometric indices with immunological markers, this work provides important insights into the role of Type 2 inflammation in small airway dysfunction within this regional context. FEF25-75 is considered a more reliable indicator of airway function, inflammatory condition, and degree of illness than FEV1 in asthmatic patients, as FEV1% does not always exhibit a strong correlation with other asthma symptoms (24, 25). The research demonstrates that lower FEF25-75 values are significantly associated with elevated serum periostin, higher eosinophil counts, and increased serum IgE levels, all of which are key indicators of Type 2 airway inflammation (26).

Serum Periostin and FEF25–75

Serum periostin, a matricellular protein involved in airway remodelling and eosinophilic inflammation, was significantly higher in patients with impaired FEF25–75 ($p = 0.035$). This finding is consistent with prior studies suggesting that periostin correlates with asthma severity, particularly in Type 2-high phenotypes (27). The elevated levels in this group reinforce its role as a biomarker for small airway dysfunction and possibly for predicting therapeutic response to anti-IL-13 or anti-IL-5 therapies (28, 29).

Eosinophilia and FEF25–75

Importantly, eosinophil count was also negatively associated with FEF25–75, with higher eosinophil levels predicting worse lung function. Eosinophilic inflammation is well-recognised in asthma pathophysiology, and our results add further evidence that peripheral eosinophilia may reflect ongoing small airway involvement. These results align with prior research indicating that peripheral eosinophilia reflects the extent of airway inflammation and is associated with poor asthma control and exacerbation risk (30).

Serum IgE and FEF25–75

Similarly, IgE levels showed a significant negative association with FEF25–75, reinforcing the role of allergic sensitisation and IgE-mediated inflammation in airflow limitation. Elevated IgE has been implicated in airway hyperresponsiveness, and our data support its potential contribution to small airway obstruction. Elevated IgE levels are often linked with more severe disease and are a hallmark of allergic asthma, which is highly prevalent in the Iraqi population (31).

Demographic Variables

Consistent with previous reports, traditional demographic factors such as age, sex, and BMI were not significantly associated with reduced FEF25–75. This suggests that the decline in small airway function in our cohort cannot be explained solely by demographic variability and highlights the importance of examining biological pathways. This suggests that immunological biomarkers may offer more precise diagnostic and prognostic information than general demographic features.

Study limitations

Several limitations must be acknowledged. First, the cross-sectional design precludes inference of causality between biomarker levels and reduced FEF25–75%. Longitudinal studies are required to clarify temporal relationships. Second, the sample size was relatively small (n=84), which may limit statistical power and generalizability. Larger multicentre studies are needed to confirm these findings and extend their relevance to broader populations. Despite these limitations, the consistency of associations across periostin, eosinophils, and IgE strengthens the validity of the results.

Conclusion

In Iraqi asthmatics, impaired small airway function, measured by FEF25–75, is strongly associated with elevated biomarkers of Type 2 inflammation but not with demographic factors. This supports the use of FEF25–75 alongside biomarker profiling as a sensitive parameter for evaluating small airway dysfunction for improved asthma phenotyping and proper management.

Early detection of impaired FEF25–75, particularly in the context of elevated periostin, eosinophils, and IgE, could aid in identifying patients with uncontrolled or treatment-resistant asthma who may benefit from targeted biologic therapies (32).

Future research directions include:

1. Longitudinal studies to determine whether these biomarkers can predict accelerated decline in small airway function.
2. Interventional trials testing whether biologic therapies that reduce eosinophils, IgE, or periostin also preserve or improve FEF25–75.
3. Multi-biomarker models that integrate periostin, IgE, and eosinophil counts with imaging or exhaled nitric oxide (FeNO) for better disease stratification.
4. Measure additional small airway indices such as FEV_1/FEV_6 and FEV_3/FEV_6.

Declarations

Ethical approval and consent to participate

This study was approved by the Ethical Approval Committee at Kufa College of Medicine with reference number: MEC-15. Informed consent was obtained from all participants.

Consent for publication

Availability of data and materials

The data and materials associated with this review will be made available by the corresponding author upon reasonable request.

Competing interests

The authors have declared no competing interests.

Funding

Nil.

Author's contributions

HA conceived and designed the study, supervised data collection, performed statistical analysis, interpreted the results, and drafted the initial version of the manuscript. AZA contributed to study design, patient recruitment, laboratory analyses of biomarkers, and interpretation of clinical findings. AZA also critically reviewed and revised the manuscript for important intellectual content. Both authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Al-MZA:

Acknowledgment

Nil.

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