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Original article

Study of Some Blood Biomarkers during Bronchial Asthma Flare-ups

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Abstract

Background: Bronchial asthma is one of the most common chronic pediatric diseases. It is a heterogeneous disease with multiple overlapping phenotypes. Biomarkers have been investigated for better phenotype characterization and to identify the response to targeted therapies. **Purpose**: The study aimed to assess serum periostin level and mean platelet volume in children with asthma flare-ups compared to age and sex-matched healthy controls. **Methods**: This case-control study included one hundred asthmatic children and fifty healthy children as controls. Both groups were aged 6-12 years. Bronchial asthma was diagnosed according to the Global Initiative for Asthma (1). Blood mean platelet volume and serum periostin levels were assessed for both groups. **Results**: The mean platelet volume was significantly lower in the patients group (9±1 fL) than in the controls (11±1 fL) (P < 0.001). Serum periostin was significantly higher in the patients group (78.85±26.33 ng/ml) than in the controls (42.72±3.4 ng/ml) (P <0.001). ROC analysis revealed a significant-excellent AUC of 0.930 with a 95% confidence interval of 0.885–0.974. Serum periostin showed a significant positive correlation with the degree of severity of asthma flare-ups (r = 0.477, P <0.001). **Conclusion**: Serum periostin and mean platelet volume help detect bronchial asthma flare-ups. Serum periostin is useful in severity assessment of asthma exacerbations.

Keywords: Asthma; Biomarker; Flare-ups; Periostin

Introduction

Bronchial Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation **(1).**

A biomarker is a quantifiable biological indicator that provides an objective measure of health status or disease. The ideal biomarker should be ‘‘measured in an analytical test system with established performance characteristics and should have a scientific body of evidence that elucidates the physiologic, pharmacologic, or clinical significance of the test results. Furthermore, a valid biomarker should have practical availability and reliability **(2).**

The rapid increase and application of molecular techniques to the field of asthma and allergic airway diseases- have resulted in the emergence of new “biomarkers” for disease presence, susceptibility, and even differential response to treatment. These biomarkers are laying the foundation for “personalized” medicine whereby medical treatments can be tailored to individual characteristics as opposed to the “one-size-fits-all” paradigm of existing clinical management guidelines **(3).**

Biomarkers have great potential use in the clinic as a noninvasive means to make more accurate diagnoses, monitor disease progression, and create personalized treatment regimens **(4)**.

With the increasing prevalence of asthma, the continuous lack of novel therapies, and inefficient disease prevention- the demand for predictive biomarkers for allergic rhinitis and asthma is steadily increasing **(5).**

Studies in animal models showed that platelet activation plays an important role in the transmigration of circulating lymphocytes and eosinophils to the airways of patients with allergic asthma **(6).**

Activated platelets play a critical role in atherogenesis, inflammation, and atherothrombosis. The mean platelet volume (MPV) is an early marker of platelet activation **(7).**

Although periostin has been the target of many scientific publications since its first identification in 1993, almost all of the research has been conducted in narrowly

defined areas. Considerable in-depth molecular knowledge on periostin is evolving in selected fields. As a matricellular protein, periostin has defined functions in osteology, tissue repair, oncology, cardiovascular and respiratory systems and in various inflammatory settings and diseases. Extensive research has helped elucidate its mechanism of action or role in many diseases. Emerging data associates periostin with Th2-associated inflammatory diseases, sparking research on several atopic conditions, including bronchial asthma **(8)**.

Aim of study

The study aimed to assess serum periostin level and mean platelet volume in children with asthma flare-ups compared to age and sex-matched healthy controls.

Materials and methods

This case-control study included 100 patients diagnosed with bronchial asthma according to the Global Strategy for Asthma Management and Prevention **(1)** and 50 age and gender-matched healthy children as controls. All children were recruited from the pulmonology and allergy clinic in Benha University Hospital, during the period from September 2019 to September 2020. The study was approved by the Research and Ethics Committee of the Faculty of Medicine, Benha University. A consent was obtained from all caregivers before inclusion in the study.

Inclusion criteria

1) Children older than 6 years and younger than 12 years.

2) Children with:

- Asthma symptom pattern, according to ***GINA guidelines*** **(1)**
- Pulmonary function tests (spirometry) showing obstructive lung disease.
- Good response to short-acting β2-agonists according to ***GINA guidelines*** **(1).**
- Chest X-rays showing hyperinflation and increased broncho-vascular markings.
- Free stool and urine analysis.
- Caregivers gave consent to be included in the study.

Exclusion criteria

1) Children below 6 years and above 12 years of age.

2) Children who had:

- Diseases other than bronchial asthma.
- Normal Pulmonary function tests (spirometry) or showing extra-thoracic obstructive lung disease or restrictive lung disease.
- X-rays showing other findings such as collapse, pneumonia, pleural disease…etc.
- Stool and urine analysis revealing parasitism.
- Caregivers refused to take part in the study.

Serum periostin and complete blood count, including mean platelet volume, were performed for all the patients and the control group.

All children will be subjected to the following

- Full history taking with special onset to the age of onset of asthma, sex, residence, frequency of exacerbations, nocturnal symptoms, drug therapy, family history of atopy, and history of other atopy.
- Full clinical examination that included temperature, heart rate, respiratory rate, blood pressure, clinical features of respiratory distress, and other system examination.
- Work-up investigation included serum periostin and complete blood count, including mean platelet volume (MPV), and other laboratory or radiological investigations were performed when appropriate.

A venous blood sample (5 cc) was withdrawn from all recruited subjects using aseptic technique from the antecubital vein. Two ml of which were collected in EDTA tubes for complete blood picture assessment, and the rest was collected into sterile serum separating plastic tubes, centrifuged, and serum was collected and frozen for assessment of periostin level.

CBC was done, including mean platelet volume (MPV) in both asthmatic patients and controls. Whole blood count (WBC) was performed via Beckman Coulter LH 780, and blood samples, which were anticoagulated with K3EDTA, were used. The Coulter principle is volumetric analysis. The cells in suspension pass through a small

aperture between two chambers, between which there is an electrical current. As each cell passes, it creates an impulse that is proportional to the volume of the cell detected between the two electrodes. In the LH780 analyzers, particles between two and 20 fl are counted as platelets, with possible extrapolation up to 60.00 fl. A log-normal curve is fitted to these points. The curves have a range of 0–70 fl, and the platelet count and parameters are derived from this curve. The hemoglobin level, WBC, platelet count, and MPV values were recorded for each patient. The reference range for MPV was between 7.0 and 11 fl.

Sample size calculation

The sample size was calculated using G*power software version 3.1.9.2 based on an expected medium effect size of periostin between asthma exacerbation cases and controls. The total sample size calculated was 150 (100 cases and 50 controls). Alpha and power were adjusted at 0.05 and 0.8, respectively.

Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using Kolmogorov–Smirnov test and direct data visualization methods. Numerical data were summarized as means and standard deviations. Categorical data were summarized as numbers and percentages. Quantitative data were compared between the study groups using independent t-test. Categorical data were compared using the Chi-square test. Receiver-operating characteristic (ROC) analysis was done for using periostin and mean platelet volume for predicting asthma exacerbation. Area Under Curve (AUC) with 95% confidence interval, best cut-off point, and diagnostic indices were calculated. Correlations were done using Pearson’s or Spearman’s correlation. Serum periostin was compared according to different parameters using independent t-test. Multivariate logistic regression analysis was done for predicting asthma exacerbation. The odds ratios and the 95% confidence intervals were calculated. All statistical tests were two-sided. P values less than 0.05 were considered significant.

Results

The current study enrolled 100 patients with bronchial asthma during their flare-ups as a

patients group compared to 50 healthy children as a control group. Serum periostin and complete blood count, including mean platelet volume, were estimated for each child.

No significant differences were noted between the studied groups regarding age (P = 0.691) and gender (P = 0.906). Passive smoking was significantly more frequent in the patients (59%) than controls (28%) (P < 0.001) ***(Table 1 & Figure 1)***.

The most common clinical manifestation was shortness of breath (90%), followed by wheeze (87%), chest tightness (81%), and cough (80%) ***(Table 2).***

The mean platelet volume was significantly lower in the patients (9 ±1 fL) than in the controls (11±1 fL) (P < 0.001). Serum periostin was significantly higher in the patients (78.85±26.33 ng/ml) than in controls (42.72±3.4 ng/ml) (P < 0.001) ***(Table 3 & Figures 2, 3)***. Also, serum periostin showed a significant positive correlation with the degree of severity of the flare-up (r = 0.477, P < 0.001). However, it showed no significant correlations with age (P = 0.216), asthma duration (P = 0.604), or mean platelet volume (P = 0.214) ***(Table 4 & Figure 4)***.

No significant correlations were detected between the mean platelet volume and age (P = 0.895), asthma duration (P = 0.703), or degree of severity of asthma exacerbation (P = 0.263) ***(Table 5)***.

ROC analysis was done for serum periostin in predicting asthma exacerbation. It revealed a significant-excellent AUC of 0.930 with a 95% confidence interval of 0.885 – 0.974. The best cut-off point was > 49.06 ng/ml, at which sensitivity and specificity were 88% and 98%, respectively ***(Figure 5)***.

In addition, ROC analysis was done for the mean platelet volume in predicting asthma exacerbation. It revealed a significant-excellent AUC of 0.879 with a 95% confidence interval of 0.815 – 0.942. The best cut-off point was ≤ 9 fL, at which sensitivity and specificity were 80% and 82%, respectively ***(Figure 6)***.

The Multivariate logistic regression analysis was done for predicting asthma exacerbation. The predictors were the mean platelet volume (OR = 0.213, 95% CI = 0.127 – 0.356, P < 0.001), serum periostin (OR = 1.235, 95% CI = 1.132 – 1.345, P < 0.001), controlling for the effect of age and gender ***(Table 6)***.

Table (1) General characteristics of the studied patients

		Cases (n = 100)	Controls (n = 50)	P-value
Age (years)	Mean ±SD	9 ±2	9 ±2	0.691
Gender	Males n (%)	59 (59.0)	30 (60.0)	0.906
	Females n (%)	41 (41.0)	20 (40.0)	
Passive smoking	n (%)	59 (59.0)	14 (28.0)	< 0.001

Independent t-test was used for age. Chi-square test was used for gender and passive smoking

Table (2) Clinical manifestations in the studied patients

	n (%)
Cough	80 (80.0)
Wheeze	87 (87.0)
Shortness of breath	90 (90.0)
Chest tightness	81 (81.0)

N:number, (%): percent.

Table (3) Asthma exacerbation markers in the studied groups

		Cases (n = 100)	Controls (n = 50)	P-value
Mean platelet volume	Mean ±SD	9 ±1	11 ±1	< 0.001*
Serum periostin (ng/mL)	Mean ±SD	78.85 ±26.33	42.72 ±3.4	< 0.001*

Independent t-test was used for MPV and periostin. *: significant

Table (4) Correlation between serum periostin and other parameters

	Serum periostin (ng/ml)	
	r	**P**
Age (years)	-0.125	0.216
Duration of asthma (months)	-0.053	0.604
Degree of severity	0.477	< 0.001*
Mean platelet volume	-0.125	0.214

Pearson's or Spearman correlation was used
r: Correlation coefficient
* Significant

Table (5) Correlation between mean platelet volume and other parameters

	Mean platelet volume	
	r	**P**
Age (years)	0.013	0.895
Duration of asthma (months)	0.039	0.703
Degree of severity	0.113	0.263

Pearson's or Spearman correlation was used
r: Correlation coefficient

Table (6) Multivariate logistic regression analysis for predicting asthma exacerbation

	OR (95% CI)**	**P-value**
Passive smoking	3.689 (1.768 - 7.698)	< 0.001*
Mean platelet volume	0.213 (0.127 - 0.356)	<0.001*
Serum periostin (ng /ml)	1.235 (1.132 - 1.346)	< 0.001*

* Significant **Adjusted for age and gender OR: Odds ratio CI: confidence interval

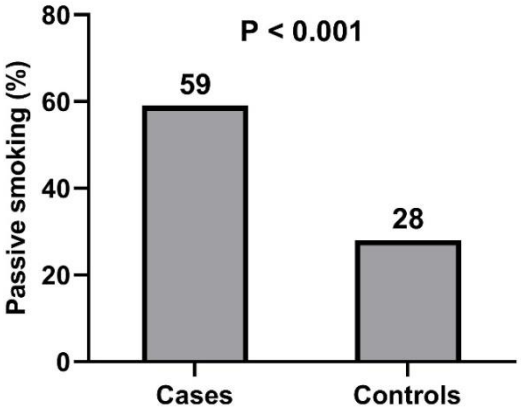

Figure (1): Passive smoking in the studied patients.

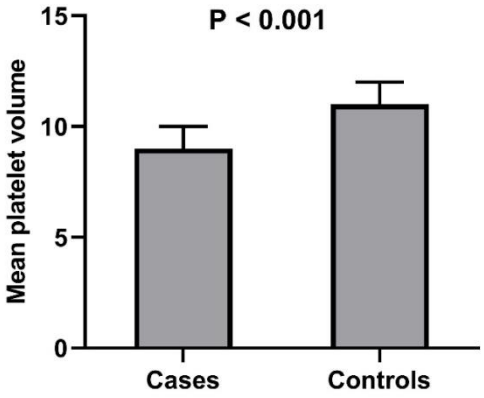

Figure (2): Mean platelet volume in the studied groups.

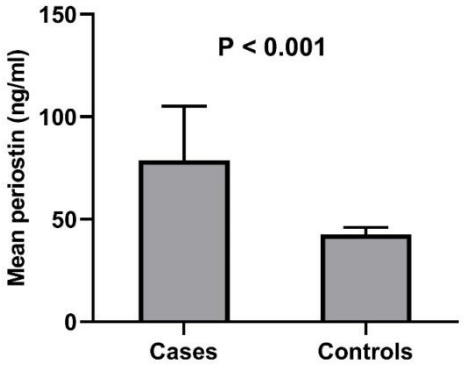

Figure (3): Serum periostin level in the studied groups.

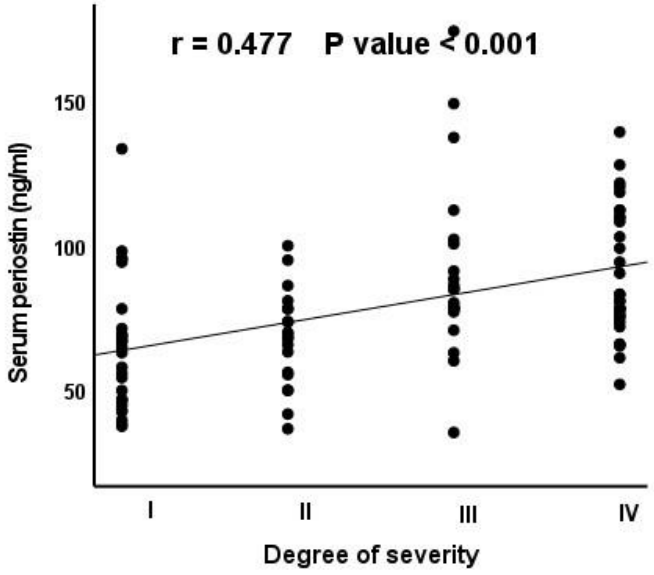

Figure (4): Correlation between serum periostin and degree of asthma severity.

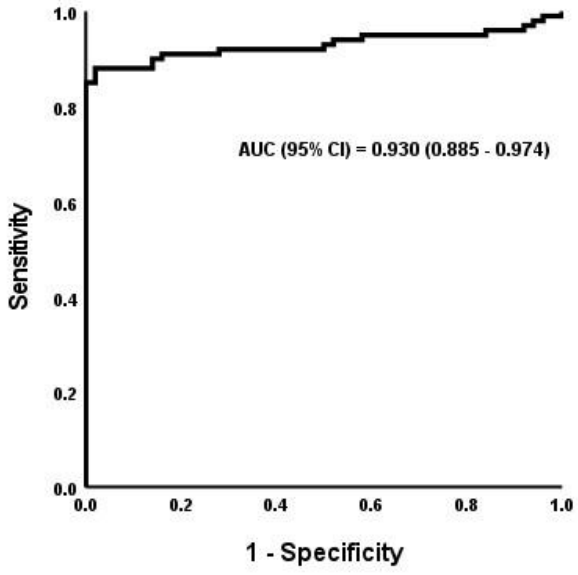

Figure (5): ROC analysis for serum periostin in predicting asthma exacerbation**.**

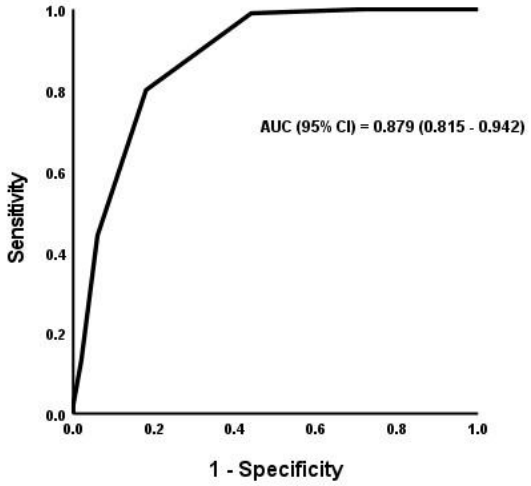

Figure (6) ROC analysis for mean platelet volume in predicting asthma exacerbation

Discussion

Chronic airway inflammation and remodeling are key features of bronchial asthma. Airway inflammation is characterized by infiltration of eosinophils, mast cells, and T-helper type 2 (Th2), cytokines, such as interleukin IL-4, IL-5, and IL-13 **(9).** Evaluation of airway inflammation is important for asthma control. Direct airway sampling through bronchial biopsy or induced sputum is difficult to repeat and often impractical in clinical settings. So, systemic biomarkers of eosinophilic inflammation are desirable for assessing the activity of asthma. Periostin is an extracellular matrix (ECM) protein, and its expression is upregulated by IL-4 and IL-13 in the airway epithelial cells **(10)**. It has been observed in the airway subepithelial layer in patients with asthma **(11)**. Periostin also acts as a matricellular protein that functions in cell activation by binding several integrins on the cell surface to its receptors. The actions of periostin as both an ECM protein and as a matricellular protein are important for the development and remodeling of many tissues, such as bone, heart, and skin **(8,13)**. Also, it has been revealed that periostin plays an important role in allergic inflammations, including asthma **(12)**. Moreover, the level of periostin expression correlates with the thickness of the epithelial basement membrane **(10)**.

Periostin may be a key molecule that links Th2 inflammation and remodeling in asthma which is triggered by uncontrolled inflammation and results in fixed airway narrowing. Airway wall thickening is a prominent feature of remodeling, and it has been evaluated non-invasively in asthma using CT **(14)**.

Activated platelets play a critical role in atherogenesis, inflammation, and atherothrombosis. The mean platelet volume (MPV) is an early marker of platelet activation **(7).**

This case-control study was done on one hundred patients with bronchial asthma (diagnosed according to Global Strategy for Asthma Management and Prevention) **(1)** and fifty age and sex-matched healthy children as controls. The level of serum periostin and the mean platelet volume were assessed for them.

The present study showed that serum periostin levels in the asthmatic group were significantly higher than those in the control group. Similar findings were detected in other studies **(10, 12).** Receiver-operating characteristic (ROC) curve analysis was used to examine the diagnostic value of periostin for discrimination between patients with bronchial asthma and controls. The area under the ROC curve (AUC) was 0.930 with a 95% confidence interval of 0.885 – 0.974. The best cut-off point for periostin was > 49.06 ng/ml with a sensitivity of 88% and a specificity of 98%.

This was in concordance with a study that declared that the best diagnostic cut-off level for periostin was 55ng/mL, with a diagnostic sensitivity of 86.7%, specificity of 100%, and area under the curve (AUC) of 0.960 **(22).**

Also, our study agreed with another study that compared the use of periostin levels to diagnose pediatric asthma by performing AUC calculations, and the sensitivity and specificity were 75.0% and 59.3%, respectively. AUC was 0.70 (which became 0.75 after excluding controls with pectus excavatum) **(23).**

In our study, we found no statistically significant correlations between the mean platelet volume or serum periostin level and the age of the patients. This agreed with other studies where there was an insignificant correlation between serum periostin level and the age of the patients. **(14, 21).** In contrast, other studies declared that serum periostin levels were negatively

correlated with the age of the patients. However, there was no significant difference between the asthmatic and control groups **(23, 24).**

The mean platelet volume (MPV) in the current study was significantly lower in patients with exacerbated asthma compared to the healthy controls. Another study reported that MPV values were lower during periods of asthma flare-ups compared to asymptomatic patients. **(15).** Also, in line with our study, two studies also revealed that MPV decreased significantly during asthmatic attacks compared to after the attacks. **(16, 17).** In addition, other studies reported that MPV was significantly reduced in patients with exacerbated asthma compared to those with stable asthma and healthy controls. **(18, 19)**.

It was claimed that the levels of MPV values drop due to the consumption of active or large platelets in severe inflammatory conditions and that this can be reversed by anti-inflammatory treatments ***(19).*** Our study supports the theory that MPV can be a marker for acute attacks in patients with asthma. So, platelet indices are sensitive biomarkers for asthma exacerbations.

Another study demonstrated that MPV values in asthmatic children both during an asthmatic attack and during the asymptomatic period had no statistically significant difference compared to the healthy control group **(20).** The mean platelet volume had mean values of 7.8, 7.7, and 7.9 fl in acute attack, attack-free period, and healthy controls, respectively **(20).**

In the current study, using a cut-off value of 9 fl, MPV had sensitivity and specificity of 80 and 82% in predicting asthma. The mean platelet volume during the asthmatic attack was a significant predictor of acute asthma (OR = 0.213, 95% CI = 0.127 – 0.356, P < 0.001).

In another study, the receiver operating characteristic curve showed that the best cut point of the mean platelet volume was 8.2 fL, which is suggested to discriminate between the acute exacerbation phase and the stabilization phase at the time of diagnosis **(17).**

We found no significant correlations between the mean platelet volume and age of the patients (P = 0.895), asthma duration (P = 0.703), and degree of severity (P = 0.263). A study found that the presence of atopy, infection, eosinophilia, elevated IgE,

and severity of asthmatic exacerbation did not influence MPV values **(19).**

Our results denote that the serum periostin levels were increased and that the mean platelet volumes were decreased during the exacerbation phase in the asthmatic children compared to the healthy ones. Therefore, periostin and MPV may be used as biomarkers to determine acute asthma flare-ups.

Furthermore, no statistically significant difference was found between mean MPV values in asthma exacerbation and asymptomatic period. MPV had a mean of 7.8, 7.7, and 7.9 fl in acute attack, attack-free period, and healthy controls, respectively **(19, 20).**

There was no significant difference between acute cases, stable cases, and controls regarding MPV (p = 0.62) in other studies, and the authors did not find any statistical difference between patients with asthma exacerbations, stable asthmatic patients, and healthy subjects in terms of MPV values **(19, 21).**

In the current study, using a cut-off value of 9 fl, MPV had sensitivity and specificity of 80 and 82% in predicting asthma. MPV during the asthmatic attack was a significant predictor of acute asthma (OR = 0.213, 95% CI = 0.127 – 0.356, P < 0.001). In another study, the receiver operating characteristic curve showed that the best cut point of mean platelet volume was (8.2 fL), which is suggested to discriminate between the acute exacerbation phase and the stabilization phase at the time of diagnosis **(17).**

In addition, no significant correlations were reported between mean platelet volume and age (P = 0.895), asthma duration (P = 0.703), and degree of severity (P = 0.263).

A study found that the presence of atopy, infection, eosinophilia, elevated IgE, and severity of asthmatic exacerbation did not influence MPV values **(19).**

The serum periostin levels were increased and MPV was found to be lower during the exacerbation phase in asthmatic children compared to healthy ones. Therefore, periostin and MPV may be used as biomarkers to determine acute asthma flare-ups.

Study limitations

Certainly, larger pediatric studies are needed to confirm our results as this study has limitations. One limitation of this study is

that the authors did not measure serum periostin and mean platelet volume serially to monitor the level change in response to treatment. Also, we need a larger number for better interpretation of data.

Conclusion

The current study concludes that serum periostin increases in patients with asthma flare-ups and can be considered a diagnostic biomarker of bronchial asthma flare-ups and assess severity in asthmatic children. MPV decreases and may also be used as a biomarker during asthma flare-ups.

These findings are particularly useful for diagnosing asthma flare-ups and thus for developing therapeutic approaches. Further studies should evaluate changes in the levels of these blood biomarkers in response to specific therapies.

List of abbreviations

AECs= Airway epithelial cells

AHR=Airway hyperresponsiveness

AS-asthma= aspirin-sensitive asthma

ASOS= Asthma-COPD overlap syndrome

BA= Bronchial asthma

BHR=Bronchial hyperresponsivness

COPD=Chronic obstructive pulmonary disease

Fractional exhaled nitric oxid FeNO=

FEV1= Forced expiratory volume in 1 second

FEV1 %= Forced expiratory volume in 1 second percentage

FVC=Forced vital capacity

GINA=Global initiative for asthma

MPV=Mean Platelet Volume

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