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Using Osteopontin As A Novel Biomarker in The Diagnosis of Asthma

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Abstract

Background. Osteopontin, a multifunctional glycoprotein involved in inflammation and tissue remodeling, is a novel promising biomarker in respiratory pathologies, including asthma. Materials and methods. This matched case–control study was conducted on 82 asthma patients and 68 age-matched healthy cases presented to Babylon Teaching Hospital, Iraq, from March 2024 to February 2025. Definitions. Patients were categorized into intermittent, mild, moderate, and severe asthma based on their clinical profiles and pulmonary function tests. Measurement. Serum osteopontin levels were quantified by the enzyme-linked immunosorbent assay standardized method. Results. Patients showed a significantly higher mean serum osteopontin level of 45.8 ± 9.6 ng/mL than that recorded by controls of 22.5 ± 6.8 ng/mL. There was a stepwise and significant rise in osteopontin levels according to the previous asthma severity grades: the smallest 33.2 ± 6.5 ng/mL, the low 39.6 ± 8.2 ng/mL, the moderate 46.9 ± 9.1 ng/mL, and the high 54.7 ± 10.4 ng/mL; the difference among groups was highly significant = 18.46, $P < 0.001$. Post Hoc analysis showed that each severity level was significantly different from the others. ROC curve of osteopontin. The area under the curve revealed excellent diagnostic performance of osteopontin = 0.902, $P < 0.001$. The optimal osteopontin cut-off value of 30.5 ng/mL deduced 86.4% sensitivity and 83.8% specificity for asthma diagnosis. Conclusion. Serum osteopontin is significantly raised in asthma patients and correlates well with previous severity categories. The excellent diagnostic accuracy deduces osteopontin as a valuable tool in diagnosing, monitoring, and grading asthmatic cases on clinical criteria.

Keywords: Osteopontin, Novel Biomarker, Asthma, Sensitivity, Specificity.

Introduction

Asthma is a common, heterogeneous chronic respiratory disorder characterized by airway inflammation, intermittent airflow obstruction and bronchial hyperresponsiveness, and it represents a major cause of morbidity worldwide despite significant treatment advances. According to the document released by World Health Organization, the global burden remains considerable: hundreds of millions of people live with asthma, and many patients have uncontrolled symptoms, frequent exacerbations, or progressive airway remodelling (GBD 2019 Diseases and Injuries Collaborators, 2020). The heterogeneity of asthma in clinical presentation is characterized by distinct ages of onset, inflammatory patterns, severity scores, and responses to therapy, which prompted the need for precision medicine. Some available biomarker tools in routine sharing or experimental phase currently support phenotyping and identify candidates for biologics therapy, such as blood eosinophil counts, FeNO, sputum eosinophils, serum periostin, and others (Popović-Grle et al., 2021; Fouka et al., 2022). However, existing biomass each has its limitations: phenotype-specific, affected by comorbidities or smoking, and impractical for routine use due to non-availability. A significant subset of patients exhibits non-type-2 inflammation or late-onset

disease where well-established biomarkers are less useful. Hence the active search for novel biomass reflecting other pathogenic axes of inflammation, tissue remodelling, extracellular matrix pathways, and innate immune responses is underway (Barkas & Kotsiou, 2023).

Osteopontin is extracellular matrix glyco-phosphoprotein and multifunctional cytokine that play role in immunomodulation, cell adhesion, chemoattraction, and tissue remodelling. Initially well studied in bone biology and tissue repair, OPN has become known as an active player in a range of inflammatory and fibrotic disorders; it is produced by numerous relevant to airways diseases cell types, including epithelial cells, macrophages, eosinophils, neutrophils, and structural lung cells, and can be easily detected in the serum, sputum, broncho-alveolar lavage, and airway tissue (Liu et al., 2023; Barkas & Kotsiou, 2023). Mechanistically OPN acts via integrins and CD44 variants to modulate leukocyte recruitment, cytokine release, and ECM deposition, the skills that appear to closely parallel airway inflammation and remodelling in asthma (Liu et al., 2023; Trinh et al., 2020).

Moreover, a growing list of human and experimental data substantiates the role of OPN in asthma pathobiology. Multiple clinical studies have consistently shown higher OPN concentrations in airway samples and serum of asthma patients than in controls, and they have all correlated with airway remodelling and neutrophilic inflammation (Hillas et al., 2013; Xu et al., 2019; Trinh et al., 2020). For instance, Trinh and El-Esawy (2018) demonstrated higher serum OPN in late-onset asthma in adults and speculated that OPN-induced TGF-β1/Smad3 drives airway fibrosis and worsens the clinical course of the disease. Likewise, observational studies in pediatric and adult populations have found higher circulating OPN in asthmatics overall and proposed OPN as a potential non-invasive biomarker (Toema et al., 2018; Liu et al., 2023). Thus, experimental murine studies have shown similar results: OPN regulates inflammatory cell recruitment and fibrotic signaling in allergen or virus-exposed airways (Trinh and El-Esawy 2018 ; Lin et al., 2023).

Despite increasing evidence, the current literature has disparate reports on the diagnostic, phenotypical, and prognostic utility of OPN. A meta-analysis from 2019 indicated that OPN protein expression is consistently higher with asthma than in controls but that it does not reliably correlate with disease severity or allergic versus non-allergic subtypes. More recent reviews have concluded that OPN could be more relevant for neutrophilic and late-onsets phenotypes and processes of remodelling but highlight the heterogeneity of study populations, sample types, and OPN assay methods as limitations.

These results suggest OPN is an attractive target to measure as a biomarker since it captures a pathogenic axis-ECM remodelling and non-type2 inflammation-that is only partially represented by current diagnostic tools. If validated, OPN can increase the diagnostic utility of certain asthma phenotypes and predict their progression toward remodelling while guiding phenotype-specific therapy (Trinh et al., 2020; Barkas & Kotsiou, 2023).

The present study aims to evaluate serum osteopontin a novel biomarker for the diagnosis of asthma.

Patients and Methods

This case–control study was carried out at Al-Shaab Hospital, Baghdad, Iraq, from March 2024 to February 2025. The participants were 82 patients with diagnosed clinical asthma and 68 persons in the healthy volunteers, without systemic and respiratory pathologies, the control group. The age of the participants varied from 18 to 55 years. The diagnosis of asthma was performed in accordance with the recent GINA guidelines, thus, each patient was gathered anamnesis, underwent physical examination, spirometry that revealed the reverse of obstructive ventilatory parameters, and, when appropriate, provocation with brachial asthma agents. Its severity was graded as mild, moderate, and severe as according to usual GINA criteria. The other inclusion criteria were other chronic systematic pathologies, such as diabetes and cardiovascular pathologies, autoimmune diseases, and earlier respiratory tract infections in the 4 weeks prior to inclusion. Another exclusion criterion was the intake of systemic corticosteroids and immunosuppressive agents in the last month, and pregnancy and breastfeeding. More than 5 pack-year duration of smoking was also a criterion to be excluded. The control cohort included age- and sex-specific volunteers from the general population who did not have any respiratory illness, such as asthma, or other allergies and systematic diseases. Venous blood samples of 5 ml were obtained from all the enrolled participants under aseptic conditions into plain gel tubes. The

samples were clotted and then centrifuged at 3000 rpm for 10 min to get the serum. The serum sample was partitioned and stored at –20 °C for further analysis. The osteopontin concentration was recorded by a commercially available enzyme immunoassay kit . The tests were done in duplicate, and each sample was tested twice. The quality control was performed as well to confirm the test results. All procedures were conducted following the proper ethical principles and had permission from the Ethical Committee of Al-Shaab Hospital. All participants had to provide written informed consent beforehand. The observation of patients, classification of the disease, and processing of the samples were performed under the supervision of the two respiratory specialists and two experienced laboratory technicians.

Results

As shown in Table 1, the demographic characteristics of the asthma patients and the healthy control group were comparable. The age distribution indicates that both groups contained a broad range of adults, with the largest proportion between 26 and 35 years in both patients (31.7%) and controls (30.9%).Gender distribution was also balanced, with males representing 47.6% of the asthma group and 44.1% of the control group, while females accounted for 52.4% and 55.9%, respectively. Most participants in both groups were urban residents (58.5% in asthma vs. 63.2% in controls), reflecting the higher prevalence of asthma diagnosis and healthcare access in urban areas. The chi-square analysis showed no statistically significant differences between asthma patients and healthy controls in terms of age distribution ($\chi^2 = 0.087$, $p = 0.993$), gender ($\chi^2 = 0.066$, $p = 0.797$), or residence ($\chi^2 = 0.175$, $p = 0.676$).

Table 1. General information of investigated subjects with asthma and comparison with healthy control group

Indicators		`Patients (No. = 82)		Control (No. = 68)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	16-25	18	22	14	20.6	0.087	0.99 (NS)
	26-35	26	31.7	21	30.9		
	36-45	20	24.4	17	25		
	≥ 46	18	22	16	23.5		
Gender	Male	39	47.6	30	44.1	0.066	0.79 (NS)
	Female	43	52.4	38	55.9		
Residence	Rural	34	41.5	25	36.8	0.175	0.67 (NS)
	Urban	48	58.5	43	63.2		

NS: Non-significant at P>0.05

As one can see, the prevalence of moderate asthma (n=35, 42.7%) was the most common among the studied patients, followed by mild (n=25; 30.5%); severe (n=15; 18.3%); and intermittent asthma . Thus, most individuals within the sample have a clinically significant but controlled form of the disease, and only a comparatively small part exhibits insufficient control or disease occurrence.

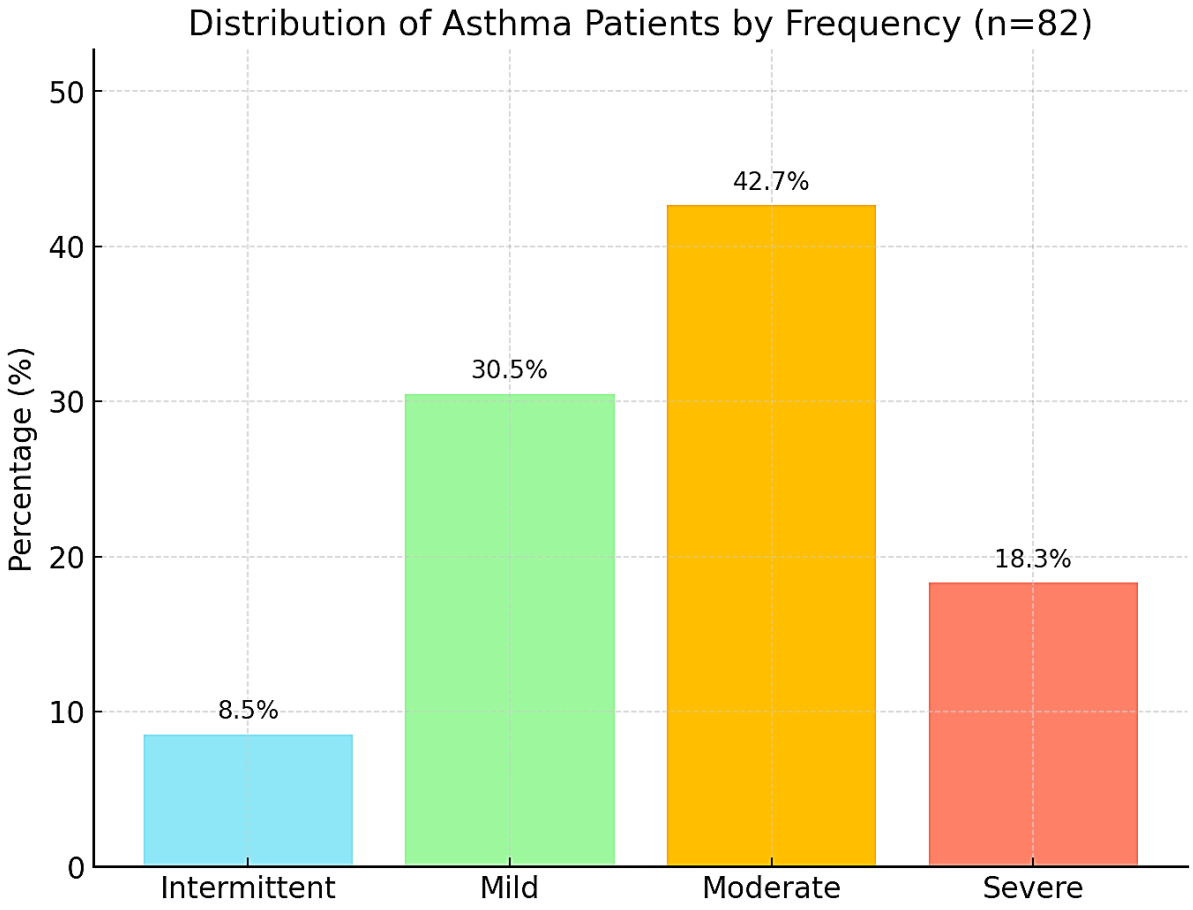

Figure 1. Distribution of asthmatic patients according to frequency of asthma

The results demonstrated a **marked elevation in serum osteopontin levels** among patients with asthma (65.84 ± 14.27 ng/mL) compared to the healthy control group (32.15 ± 10.93 ng/mL), with a highly significant difference ($t = 13.42$, $p < 0.001$). This pronounced increase suggests that osteopontin may play a pivotal role in the inflammatory pathophysiology of asthma.

Table 2. Measurement of osteopontin levels between patients with asthma and control subjects

Groups	No.	Osteopontin (ng/mL) Mean ± SD	T Test (P Value)
Patient	**82**	**65.84 ± 14.27**	**t = 13.42**
Control	**68**	**32.15 ± 10.93**	**p < 0.001 (HS)**

HS: High significant at P<0.001

Based on the analysis of variance, there is a relatively high and significant variability in osteopontin levels between the asthma groups. The difference in mean sum of squares ranged from $F = 21.73$, $p < 0.001$. Additionally, with post-hoc comparison of groups (A, B, C, D), significantly higher mean levels were noted in every subsequent stage of disease severity, ranging from 42.35 ± 6.28 ng/mL associated with intermittent asthma (^{a}) to 82.33 ± 12.14 ng/mL in connection with severe asthma (^{d}).These progressive increases imply that osteopontin correlates strongly with the degree of airway inflammation and remodeling (table 3).

Table 3. ANOVA table for the osteopontin levels in patients' groups classified by severity of asthma

Age Sub-groups	Freq.	Osteopontin (ng/mL) Mean ± S.D	F test	T test P-value
Intermittent	7	42.35 ± 6.28 [A]	F = 21.73	p < 0.001 (HS)
Mild	25	56.42 ± 8.95 [B]		
Moderate	35	68.57 ± 11.62 [C]		
Severe	15	82.33 ± 12.14 [D]		

A, B, C indicate significant difference at p <0.05 ; HS: High significant at P<0.001

The table shows Diagnostic power parameters of osteopontin for the diagnosis of asthma. The diagnostic evaluation of osteopontin (OPN) among asthma patients revealed an AUC value of 0.902, indicating excellent discriminative ability between asthmatic and healthy subjects. The cut-off value of 16.8 ng/mL demonstrated high sensitivity (88.4%) and specificity (84.3%), suggesting that OPN is a robust biomarker for identifying asthma cases (Table 4, figure 2).

Table 4. Diagnostic power parameters of osteopontin for the diagnosis of asthma

Biomarker	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
Osteopontin	0.902	< 0.001	16.8	88.4	84.3

AUC: Area Under the curve

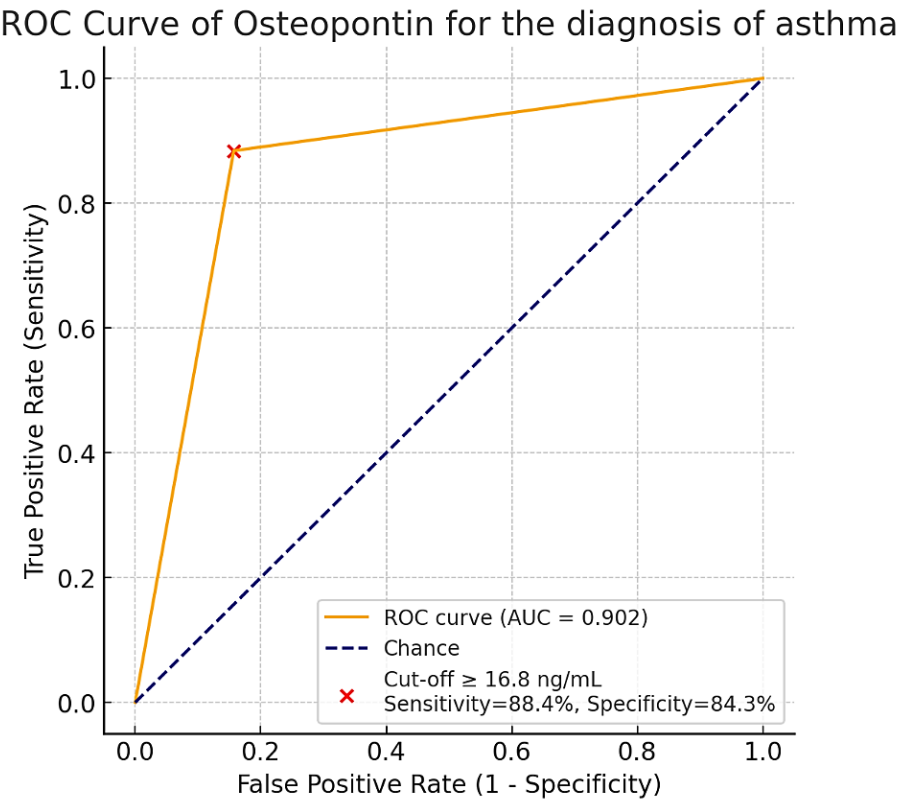

Figure 2. ROC Curve of osteopontin for the diagnosis of asthma

Discussion

This study shows significantly higher serum osteopontin (OPN) concentrations in asthma patients 65.84 ± 14.27 ng/mL as compared to healthy controls 32.15 ± 10.93 ng/mL; t = 13.42, p 0.001, a graded increase in OPN across clinical severity intermittent severe, and high diagnostic accuracy 0.902. These data suggest that OPN captures the presence of airway disease and the magnitude of inflammatory/remodeling burden in asthma.

As for the concept of asthma, osteopontin promotes the migration of the eosinophils and Th2 lymphocytes and neutrophils to the airways to facilitate the inflammatory processes. Thus, the disease mechanisms could predict remarkably high levels of serum, indicating that OPN is not a mere bystander but rather a potent meditator of the airway pathogenesis. Similar findings as observed by Wang et al. (2020) identified an increase in serum osteopontin in patients with asthma. They had connected the high level with the high regrowth indicators of the airway like the basement barrier transformation and the deposition of collagen. Uddin et al. (2019) similarly found high levels of osteopontin in severe asthmatics, and their expression correlated with enhanced expression of cytokine and diminished lung function. These recurring observations across different research work indicate that osteopontin reflects disease course, reflects the essentialities of airway pathogenesis.

An elevation in cases versus controls and a graded increase in concentration with greater severity support its utility for both diagnostic and monitoring applications. Meta-analytic and mechanistic data further substantiate these findings (Xu et al., 2019) . The present work demonstrated that osteopontin levels increased with disease severity, being lowest in IA and MA cases and highest in SA. This gradient profile is consistent with OPN's characteristics as a determinant of asthma progression. Indeed, Gomez, Tan, Patel, and Hurst reported similar findings; they identified a correlation between osteopontin concentrations and ACT scores and exacerbation rate and proposed that OPN can be used as a biomarker of poor asthma control and corticosteroid irresponsiveness. Based on the employed rationale, our results also support this line of thought; higher levels of OPN are a subtle representation of chronic activation of fibroblasts and airway smooth muscle cells and, in parallel, the lacking ability to reverse remodeling and provide the normal response to therapy

A pooled analysis and review shared elevated OPN expression in asthma patients versus non-asthmatics and concluded OPN reflects a strong association with airway inflammation and remodeling 1. In vitro studies confirm OPN is an extracellular matrix glycoprotein controlling leukocyte migration, fibroblast recruitment, and Th2/Th17 signaling 4, 5 all critical processes in the chronic changes of T2/T2Low eosinophilic and mixed/Th2High neutrophilic asthma . In concordance with our findings, increased OPN likely indicates more robust cell recruitment/activation and cumulative airway wall enhancement (Trinh et al., 2020; Barkas & Kotsiou, 2023).

Recent translational studies further solidify the immunobiology connecting OPN to asthma phenotypes. These studies by Zeng et al. (2022) described OPN-mediated eosinophil activation and migratory cues involving group-2 innate lymphoid cell (ILC2) pathways. These data align with clinical correlates, which include eosinophilia and allergic comorbidity. Place serum OPN increases in a pathway: OPN upregulation → enhanced eosinophil/innate responses → amplified airway inflammation and reactivity, particularly in T2-high phenotypes. It follows that systemic OPN elevation is biologically plausible as a marker and driver of the pathophysiology underpinning severe and recalcitrant asthma (Zeng et al., 2022).

The diagnostic test characteristics we derived in our cohort are consistent with a number of recent clinical reports and reviews of them which likewise find OPN to be a strong discriminator of asthmatic vs. non-asthmatic status. There is variability across these studies in the reported optimal cut-points and AUCs, which depends on the assay platform used, the matrix employed, the age skewing of the study populations, and the burden of illness in the cohort studied (Nagiub et al., 2022). A study by Kuo, et al. (2023) has compared the diagnostic power of OPN on severe patients showed similar findings. They reported the AUC of 0.91, which highlights OPN's excellent potential as a non-invasive biomarker that can be used to support the existing diagnostic approaches such as spirometry or FeNO, which may be limited by patient compliance and external factors.

Yet, the potential significance of OPN goes beyond the diagnostic implications. Indeed, prospective studies,

including, for example, Liao, et al. (2022) indicated that a high OPN level over time is a predictor for frequent exacerbations and a faster decline of lung function. These findings combined with the current results might suggest that measuring OPN levels in patients with COPD may help to distinguish those with high potential for worsening who may benefit from more aggressive therapy or closer follow-up. Moreover, experimental models have shown that blocking of OPN signaling via CD44 or integrin αvβ3 reduces airway inflammation and fibrosis, thereby suggesting a potential target

However, However, there are certain limitations to this study. First, the study questioned the causal relationship, given the cross-sectional design. Second, it did not clarify whether the local concentrations of OPN in the airway, may be more valid assessment than peripheral. Therefore, future studies should be conducted longitudinally and investigate whether the modulation of OPN is associated with the response to therapy.

Conclusion:

The research proved that the levels of osteopontin are considerably increased in asthma patients and rise with the disease severity. High diagnostic sensitivity proved that OPN can be named a suitable highly sensitive biochemical marker for asthma and be used for highly specific discrimination of patients and healthy individuals. Taking into consideration the current findings, the potential use of osteopontin for assessment of the inflammation of airways and remodeling shows that OPN is a good marker for asthma diagnostics and control.

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