Salem *et. al.,* Babcock Univ. Med. J.2026 9(3):262-270
https://doi.org/10.38029/babcockuniv.med.j..v9i3.1459
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Diagnostic utility of 8-isoprostane and serum trace minerals in assessing asthma severity and control

8-Isoprostane and trace minerals in asthma

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Submitted: 24th January 2026
Accepted: 25th April 2026
Published: 30th September 2026
ID: Orcid ID

Abstract
Objective: Oxidative stress and micronutrient deficiencies contribute to asthma pathophysiology, yet their combined diagnostic utility remains underexplored. This study aimed to evaluate serum 8-iso-prostaglandin F2α (8-iso-PGF2α), zinc, and selenium levels in adults with asthma and determine their association with disease severity and control status.
Methods: A case-control study enrolled 90 physician-diagnosed asthmatic patients and 90 age- and sex-matched healthy controls. Patients were stratified by severity (moderate, n=56; severe, n=34) and by GINA-based control status (controlled, n=31; partly controlled, n=34; uncontrolled, n=25). Serum 8-iso-PGF2α was quantified using ELISA, while zinc and selenium were measured by atomic absorption spectroscopy. Non-parametric tests (Mann-Whitney U, Kruskal-Wallis) were used for comparisons.
Results: Serum 8-iso-PGF2α was significantly higher in patients than in controls (median 217.6 vs. 137.3 pg/mL; $p<0.001$) and increased progressively with worsening severity (severe vs. moderate: 272.6 vs. 191.1 pg/mL; $p<0.001$) and poorer control (uncontrolled vs. controlled: 253.7 vs. 186.1 pg/mL; $p=0.032$). Conversely, zinc and selenium were significantly lower in patients than in controls (zinc: 11.68 vs. 13.22 µmol/L; selenium: 1.175 vs. 1.518 µmol/L; both $p<0.001$) and showed stepwise depletion with increasing severity (both $p<0.001$). Selenium also declined significantly with loss of asthma control ($p=0.046$).
Conclusions: Elevated lipid peroxidation coupled with progressive trace mineral depletion reliably reflects inflammatory burden and clinical deterioration in asthma. These findings support the integrated utility of 8-iso-PGF2α and selenium as complementary biomarkers for disease monitoring.

Keywords: Asthma, 8-iso-prostaglandin F2α, Zinc; Selenium, Oxidative stress

Plain English Summary

Asthma is a long-term lung condition that causes coughing, wheezing and difficulty breathing. Researchers believe that an imbalance between harmful molecules called “free radicals” and protective nutrients may make asthma worse. In this study, we measured three substances in the blood of 90 adults with asthma and 90 healthy adults: a marker of free radical damage (8-iso-prostaglandin F2α) and two protective minerals (zinc and selenium). We found that people with asthma had much higher levels of the damage marker and much lower levels of the protective minerals than healthy people. Importantly, these differences became larger as asthma became more severe or less well-controlled. This suggests that measuring these blood markers could help doctors understand how active a person’s asthma is and whether treatments are working. However, more research is needed before these tests can be used routinely in clinics.

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Introduction

Asthma is a chronic inflammatory disorder of the airways that affects people of all ages worldwide. It is characterised by variable respiratory symptoms, airflow limitation, and bronchial hyperresponsiveness, often triggered by environmental or genetic factors (1, 2). The Global Initiative for Asthma (GINA) has shifted the focus of asthma management towards achieving both current symptom control and reducing future risks such as exacerbations and lung function decline (3, 4).

Oxidative stress plays a central role in asthma pathogenesis. Inflammatory cells in the airways release reactive oxygen species (ROS) that damage cellular membranes, a process known as lipid peroxidation (5). Isoprostanes, particularly 8-iso-prostaglandin F2α (8-iso-PGF2α), are stable products of non-enzymatic arachidonic acid oxidation and are considered reliable biomarkers of oxidative stress in vivo. Emerging evidence suggests that elevated 8-iso-PGF2α levels correlate with disease severity and airway remodelling in asthma (6, 7).

Trace elements are essential for maintaining antioxidant defences. Zinc (Zn) serves as a cofactor for over 300 enzymes, including superoxide dismutase, and helps regulate T-helper cell balance. Zinc deficiency has been linked to enhanced eosinophilic inflammation in allergic airway disease (8, 9). Selenium (Se) is a critical component of glutathione peroxidases, which neutralise hydrogen peroxide and lipid hydroperoxides. Low selenium levels may shift T-cell responses toward a pro-inflammatory Th2 phenotype and have been associated with worse asthma outcomes (10, 11, 12).

Despite growing recognition of these individual associations, few studies have simultaneously evaluated 8-iso-PGF2α, zinc, and selenium in relation to both asthma severity and control status. The present study, therefore, aimed to measure serum concentrations of these three biomarkers in adult asthmatic patients and healthy controls, and to investigate their association with disease severity (moderate vs. severe) and level of asthma control (controlled, partly controlled, uncontrolled) as defined by GINA guidelines.

Materials and Methods

Study design and population

This was a case-control study conducted at the Department of Chemistry and Biochemistry, College of Medicine, Al-Nahrain University, Baghdad, Iraq. Adult patients with a physician-confirmed diagnosis of asthma were recruited consecutively from outpatient clinics and the respiratory ward of Al-Imamin Alkadmeen Hospital City between March 2024 and January 2025. Age- and sex-matched apparently healthy individuals accompanying the patients were enrolled as controls. All participants provided written informed consent before any study procedure. The study protocol was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University (decision no. 2024/1023, dated 11 February 2025) and complied with the ethical principles of the Declaration of Helsinki.

Diagnostic criteria and clinical classification

Asthma diagnosis was established according to GINA 2024 criteria, based on a history of typical respiratory symptoms (wheeze, shortness of breath, chest tightness, cough) that varied over time and intensity, together with documented evidence of variable expiratory airflow limitation (spirometry performed at the referring clinic, though raw data were not available for this analysis).

Asthma severity was classified retrospectively based on the level of treatment required to maintain control, in line with GINA recommendations. Patients were categorised as:

Moderate asthma (n = 56): well-controlled with low-to-moderate dose inhaled corticosteroids (ICS) plus a long-acting beta-agonist (LABA); or low-dose ICS/formoterol as maintenance and reliever therapy.

Severe asthma (n = 34): required high-dose ICS plus a second controller (e.g., LABA, leukotriene receptor antagonist, or long-acting muscarinic antagonist) to maintain control, or remained uncontrolled despite optimised high-intensity treatment.

Asthma control was assessed using GINA symptom-based criteria over the preceding four weeks, including daytime symptoms (>2 times/week), nocturnal awakenings, activity limitation, and reliever use (≥2 times/week). Patients were categorised as:

Controlled (n = 31): none of the above features present.

Partly controlled (n = 34): one or two of the features present.

Uncontrolled (n = 25): three or four features present.

The Asthma Control Test (ACT) was used as a supportive tool where available, with scores >19 indicating well-controlled asthma and ≤19 indicating poorly controlled asthma.

Inclusion and exclusion criteria

Eligible patients were adults aged 18–70 years with a confirmed asthma diagnosis. Exclusion criteria were: current or former smoking (active smoking within the past year), diabetes mellitus, chronic kidney or liver disease, chronic obstructive pulmonary disease, acute respiratory

infection within four weeks, autoimmune or systemic inflammatory disorders, pregnancy or lactation, and use of systemic corticosteroids (oral or injectable) within four weeks before enrolment. Healthy controls had no history of asthma, atopy, or chronic respiratory disease.

Blood sampling and laboratory analysis

Venous blood (5 mL) was collected from each participant between 8:00 and 10:00 a.m. after an overnight fast. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3,000 rpm for 10 minutes. Serum was separated, aliquoted into cryovials, and stored at −80°C until analysis.

Serum 8-iso-PGF2α was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Cayman Chemical, Item No. 516351, Ann Arbor, MI, USA). The assay was performed according to the manufacturer's protocol. Optical density was read at 450 nm on a microplate reader (BioTek ELx808, Winooski, VT, USA). The intra-assay coefficient of variation was <8%, and the inter-assay CV was <12%. Concentrations were calculated from a standard curve prepared with known amounts of 8-iso-PGF2α (range 3.9–500 pg/mL).

Serum zinc and selenium were quantified by atomic absorption spectroscopy (AAS). For zinc, a flame AAS instrument (Shimadzu AA-7000, Kyoto, Japan) was used with an air-acetylene flame at 213.9 nm. For selenium, a graphite furnace AAS (PerkinElmer PinAAcle 900Z, Waltham, MA, USA) was used at 196.0 nm with palladium-magnesium nitrate matrix modifier. Calibration curves were prepared using certified reference standards (Merck, Darmstadt, Germany). Quality control samples (ClinChek® control lyophilised serum, Recipe, Munich, Germany) were run with each batch; recovery ranged from 95–105% for both elements. Detection limits were 0.5 µmol/L for zinc and 0.05 µmol/L for selenium.

Statistical analysis

Data distribution was assessed using the Shapiro–Wilk test and visual inspection of Q-Q plots. Most continuous variables were not normally distributed; therefore, non-parametric methods were applied throughout. Results are presented as median with interquartile range (IQR) and, for descriptive purposes, as mean ± standard deviation (SD). Comparisons between two independent groups (asthma vs. control; moderate vs. severe asthma; ACT >19 vs. ≤19) were performed using the Mann–Whitney U test. Comparisons among three groups (controlled, partly controlled, uncontrolled) were performed using the Kruskal–Wallis test, followed by Dunn's post-hoc test with Bonferroni correction for multiple comparisons. All tests were two-tailed, and a p-value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9.0 (San Diego, CA, USA).

Results

Participant characteristics

A total of 180 participants (90 asthmatic patients and 90 healthy controls) were enrolled. There were no significant differences between the groups in age (patients: median 45.0 years, IQR 34.0–58.0; controls: median 49.0 years, IQR 39.0–58.0; p = 0.265), sex distribution (61.1% female in patients vs. 58.9% in controls; p = 0.879), or body mass index (BMI: patients median 29.9 kg/m², IQR 26.5–33.8; controls median 29.4 kg/m², IQR 26.8–32.1; p = 0.242). Among patients, 56 (62.2%) had moderate asthma and 34 (37.8%) had severe asthma. Regarding control status, 31 (34.4%) had controlled asthma, 34 (37.8%) partly controlled, and 25 (27.8%) uncontrolled.

Comparison between asthmatic patients and healthy controls

Table 1 summarises serum biomarker levels in patients versus controls. Serum 8-iso-PGF2α was significantly elevated in asthmatic patients (median 217.6 pg/mL, IQR 163.0–274.8) compared to controls (median 137.3 pg/mL, IQR 126.5–151.2; p < 0.001). In contrast, both zinc and selenium were significantly lower in patients. Zinc levels in patients (median 11.68 µmol/L, IQR 9.57–13.16) were reduced relative to controls (median 13.22 µmol/L, IQR 12.01–14.31; p < 0.001). Similarly, selenium levels in patients (median 1.175 µmol/L, IQR 0.94–1.37) were markedly lower than in controls (median 1.518 µmol/L, IQR 1.31–1.76; p < 0.001).

Table 1: Serum 8-iso-PGF2α, zinc, and selenium concentrations in asthmatic patients and healthy controls

Parameter	Patients (n=90)	Controls (n=90)	Mann-Whitney U p-value
8-iso-PGF2α (pg/mL)			
Median (IQR)	217.6 (163.0–274.8)	137.3 (126.5–151.2)	<0.001
Mean ± SD	227.8 ± 74.3	139.7 ± 15.5	
Zinc (µmol/L)			
Median (IQR)	11.68 (9.57–13.16)	13.22 (12.01–14.31)	<0.001

Mean ± SD	11.77 ± 2.76	13.18 ± 1.58	
Selenium (µmol/L)			
Median (IQR)	1.175 (0.94–1.37)	1.518 (1.31–1.76)	<0.001
Mean ± SD	1.156 ± 0.28	1.504 ± 0.30	

Associations with asthma severity

When patients were stratified by disease severity (Table 2), significant differences emerged for all three biomarkers. Serum 8-iso-PGF2α was markedly higher in severe asthma (median 272.6 pg/mL, IQR 220.2–339.1) than in moderate asthma (median 191.1 pg/mL, IQR 151.0–240.2; $p < 0.001$). Conversely, both zinc and selenium were significantly lower in severe disease. Zinc decreased from a median of 12.10 µmol/L (IQR 11.68–13.36) in moderate asthma to 9.50 µmol/L (IQR 8.70–10.50) in severe asthma ($p < 0.001$). Selenium decreased from 1.28 µmol/L (IQR 1.11–1.43) to 0.94 µmol/L (IQR 0.78–1.09; $p < 0.001$). These stepwise changes suggest that greater oxidative stress and deeper trace mineral depletion accompany more severe asthma phenotypes.

Table 2: Biomarker levels according to asthma severity

Parameter	Moderate asthma (n=56)	Severe asthma (n=34)	Mann-Whitney U p-value
8-iso-PGF2α (pg/mL)			
Median (IQR)	191.1 (151.0–240.2)	272.6 (220.2–339.1)	<0.001
Mean ± SD	200.3 ± 55.5	273.0 ± 79.8	
Zinc (µmol/L)			
Median (IQR)	12.10 (11.68–13.36)	9.50 (8.70–10.50)	<0.001
Mean ± SD	12.5 ± 1.5	9.9 ± 2.8	
Selenium (µmol/L)			
Median (IQR)	1.28 (1.11–1.43)	0.94 (0.78–1.09)	<0.001
Mean ± SD	1.26 ± 0.24	0.98 ± 0.25	

Associations with asthma control

Table 3 presents biomarker distributions across the three GINA control categories. Serum 8-iso-PGF2α showed a significant increasing trend with poorer asthma control (Kruskal-Wallis $p = 0.032$). The highest levels were observed in uncontrolled asthma (median 253.7 pg/mL, IQR 192.0–315.6), followed by partly controlled (227.6 pg/mL, IQR 185.8–279.1), and lowest in controlled asthma (186.1 pg/mL, IQR 154.7–232.3). Dunn's post-hoc test (with Bonferroni correction) confirmed a significant difference between uncontrolled and controlled groups (adjusted $p = 0.038$), but not between other pairs. Zinc levels did not differ significantly among control categories (Kruskal-Wallis $p = 0.185$). Although median zinc was numerically higher in controlled (12.26 µmol/L) than in partly controlled (11.43 µmol/L) or uncontrolled (11.58 µmol/L) asthma, the differences were not statistically significant.

Selenium levels showed a significant decline with worsening control (Kruskal-Wallis $p = 0.046$). The controlled group had the highest selenium (median 1.28 µmol/L, IQR 1.03–1.47), followed by partly controlled (1.21 µmol/L, IQR 0.88–1.38), and uncontrolled the lowest (1.10 µmol/L, IQR 0.77–1.25). Post-hoc analysis revealed a significant difference between controlled and uncontrolled groups (adjusted $p = 0.041$), but not between other pairs.

Table 3: Biomarker levels according to GINA asthma control status

Parameter	Controlled (n=31)	Partly controlled (n=34)	Uncontrolled (n=25)	Kruskal-Wallis p	Post-hoc (Dunn's, Bonferroni)
8-iso-PGF2α (pg/mL)				0.032	Uncontrolled > Controlled (adj p=0.038)
Median (IQR)	186.1 (154.7–232.3)	227.6 (185.8–279.1)	253.7 (192.0–315.6)		
Mean ± SD	200.2 ± 58.4	235.3 ± 70.5	251.5 ± 87.8		
Zinc (µmol/L)				0.185	No significant pairwise
Median (IQR)	12.26 (9.71–14.14)	11.43 (10.32–12.02)	11.58 (10.39–12.39)		
Mean ± SD	12.33 ± 3.3	11.35 ± 2.4	11.63 ± 2.2		
Selenium (µmol/L)				0.046	Controlled > Uncontrolled (adj p=0.041)
Median (IQR)	1.28 (1.03–1.47)	1.21 (0.88–1.38)	1.10 (0.77–1.25)		

Mean ± SD	1.24 ± 0.27	1.14 ± 0.28	1.05 ± 0.26

Supplementary analysis using Asthma Control Test (ACT) scores

ACT scores were available for all patients. Using the conventional cut-off of 19, 37 patients had ACT >19 (well-controlled) and 53 had ACT ≤19 (poorly controlled). As shown in Table 4, patients with poorly controlled asthma had significantly higher 8-iso-PGF2α (median 250.9 vs. 186.9 pg/mL; p = 0.002) and significantly lower selenium (median 1.10 vs. 1.33 µmol/L; p = 0.003) compared to well-controlled patients. Zinc levels did not differ significantly between the two ACT groups (p = 0.246). These results reinforce the pattern observed with GINA symptom-based classification.

Table 4: Biomarker levels by ACT score

Parameter	ACT >19 (well-controlled, n=37)	ACT ≤19 (poorly controlled, n=53)	Mann-Whitney U p-value
8-iso-PGF2α (pg/mL)			
Median (IQR)	186.9 (155.2–231.8)	250.9 (190.3–308.6)	0.002
Mean ± SD	201.3 ± 56.0	246.3 ± 80.2	
Zinc (µmol/L)			
Median (IQR)	12.11 (9.68–14.15)	11.44 (10.38–12.39)	0.246
Mean ± SD	12.19 ± 3.10	11.47 ± 2.49	
Selenium (µmol/L)			
Median (IQR)	1.33 (1.12–1.49)	1.10 (0.89–1.30)	0.003
Mean ± SD	1.26 ± 0.26	1.08 ± 0.28	

Discussion

This study provides three main findings. First, patients with asthma have significantly higher serum 8-iso-PGF2α and significantly lower zinc and selenium compared to healthy controls. Second, these biomarker abnormalities become more pronounced with increasing asthma severity and, for 8-iso-PGF2α and selenium, with poorer asthma control. Third, while zinc depletion is associated with the presence and severity, it does not discriminate well between different levels of asthma control. Collectively, these results highlight the close relationship between systemic oxidative stress, trace mineral status, and clinically meaningful asthma outcomes.

8-iso-PGF2α as a marker of oxidative burden in asthma

The marked elevation of 8-iso-PGF2α in asthmatic patients (about 1.6-fold higher than controls) aligns with previous reports (13, 14). Isoprostanes are generated by free radical-induced peroxidation of arachidonic acid independent of the cyclooxygenase pathway, and their levels reflect whole-body oxidative stress. In asthma, activated inflammatory cells – particularly eosinophils and neutrophils – release large amounts of ROS, overwhelming endogenous antioxidant defences and damaging airway epithelial cells (15).

Our observation that 8-iso-PGF2α progressively increases from moderate to severe asthma (36% higher in severe disease) and from controlled to uncontrolled asthma (36% higher in uncontrolled vs. controlled) suggests that oxidative stress is not merely a bystander but may actively contribute to disease worsening. Mechanistically, 8-iso-PGF2α itself can induce bronchoconstriction and airway hyperresponsiveness by acting on thromboxane receptors (16). It may also promote airway remodelling by stimulating fibroblast proliferation and collagen deposition (17). Thus, elevated 8-iso-PGF2α could serve as both a biomarker and a potential mediator of asthma progression.

Similar oxidative and micronutrient patterns have been reported in other populations (18, 19, 20), and the GINA framework (21), along with established asthma guidelines (22) support the clinical relevance of our findings. Our results also align with broader literature on trace elements in respiratory disease (23, 24, 25, 26).

Zinc and selenium depletion: two sides of the antioxidant coin

Both zinc and selenium were significantly lower in asthmatic patients than in controls, with reductions of approximately 11–12% for zinc and 23% for selenium. These deficiencies are plausible given the increased consumption of antioxidants during chronic airway inflammation. Zinc is an essential cofactor for superoxide dismutase and helps stabilise cell membranes; its deficiency can shift T-cell polarisation toward a pro-allergic Th2 profile, amplifying eosinophilic inflammation (9, 27). Selenium is incorporated into glutathione peroxidases (GPx), which reduce hydrogen peroxide and lipid hydroperoxides. Low selenium reduces GPx activity, leaving the airways vulnerable to oxidant injury (10).

Notably, both trace elements decreased significantly from moderate to severe asthma

(zinc ~21% lower, selenium ~23% lower). This dose-response relationship reinforces the concept that a greater inflammatory burden consumes more antioxidant reserves. However, only selenium showed a significant association with asthma control status, whereas zinc did not. Several explanations are possible. Selenium has a narrower therapeutic window and may be more susceptible to depletion under sustained oxidative pressure. Alternatively, the control assessment (based on symptoms and reliever use) might be influenced by selenium-dependent mechanisms more directly than by zinc. Indeed, selenium deficiency has been linked to worse lung function and more frequent exacerbations in asthma cohorts (28, 29).

Why does zinc not discriminate against control status?

The lack of significant difference in zinc across control groups (despite clear differences in severity) is intriguing but not without precedent. A recent study found that serum zinc distinguished asthmatics from controls but did not correlate with ACT scores or pulmonary function (30). One possibility is that zinc homeostasis is tightly regulated by metallothioneins and zinc transporters, which may buffer fluctuations in serum zinc once asthma is established. Another possibility is that dietary zinc intake varies widely and may offset inflammatory consumption in some patients. Our study did not collect dietary data, so residual confounding cannot be excluded. Nevertheless, the clear stepwise decline in zinc with severity suggests that when inflammation is intense enough (as in severe asthma), the buffering capacity is overwhelmed.

Clinical and research implications

From a clinical perspective, our findings suggest that serial measurement of 8-iso-PGF2α and selenium could complement existing tools for asthma monitoring. Unlike symptom scores or spirometry, these biomarkers reflect systemic oxidative–antioxidant balance, which might provide early warning of worsening control before clinical deterioration becomes apparent. However, we caution that the cross-sectional design prevents us from establishing causality or defining clinically meaningful cut-offs. Large longitudinal studies are needed to determine whether adding these biomarkers to routine care improves outcomes.

For researchers, this study reinforces the value of multi-biomarker panels. Relying on a single marker may miss important aspects of disease pathophysiology. For example, a patient with uncontrolled asthma might have normal 8-iso-PGF2α but low selenium, pointing to a different mechanism (impaired antioxidant capacity rather than excessive ROS production). Future studies should also examine whether supplementation with zinc or selenium can improve asthma control in deficient patients – a question our observational data cannot answer.

Study limitations and future directions

Several limitations warrant consideration. First, this is a cross-sectional study; we cannot determine whether elevated 8-iso-PGF2α and low trace minerals cause worse asthma or result from it. Second, we did not measure dietary intake or supplement use, both of which influence zinc and selenium status. Third, we lacked objective lung function data (spirometry) and inflammatory markers such as fractional exhaled nitric oxide (FeNO), which would have allowed better phenotyping. Fourth, the single-centre design in Baghdad may limit generalisability to other populations with different environmental exposures, diets, and genetic backgrounds. Fifth, our exclusion of active smokers and patients on systemic steroids, while necessary to reduce confounding, means the results may not apply to those common asthma subgroups. Sixth, we did not perform ROC analysis to determine optimal diagnostic cut-offs, so claims of “diagnostic utility” remain preliminary.

Future research should adopt longitudinal designs to assess whether changes in 8-iso-PGF2α and selenium predict future exacerbations or loss of control. Randomised controlled trials of selenium supplementation in deficient asthmatics are also warranted. Additionally, incorporating spirometry and FeNO would help clarify whether these biomarkers reflect airway obstruction or type-2 inflammation specifically.

Conclusion

This study demonstrates that serum 8-iso-prostaglandin F2α is significantly elevated in adult asthma patients and correlates positively with disease severity and poor asthma control, confirming its value as an oxidative stress biomarker. Concurrently, serum zinc and selenium are reduced in asthmatic patients, with selenium showing a significant association with uncontrolled asthma. These findings highlight the role of oxidative imbalance and antioxidant micronutrient depletion in asthma progression. Although zinc depletion accompanies greater severity, it does not discriminate control status. The integrated measurement of 8-iso-PGF2α and selenium may offer complementary information for disease assessment, but further prospective studies are needed to validate their clinical utility.

List of Abbreviations

8-iso-PGF2α: 8-iso-prostaglandin F2α
AAS: Atomic absorption spectroscopy
ACT: Asthma Control Test
BMI: Body mass index
ELISA: Enzyme-linked immunosorbent assay
FeNO: Fractional exhaled nitric oxide
GINA: Global Initiative for Asthma
GPx: glutathione peroxidase
ICS: Inhaled corticosteroids
IQR: Interquartile range
LABA: long-acting beta-agonist
ROC: Receiver Operating Characteristic
ROS: Reactive Oxygen Species
SD: Standard deviation
Th: T helper cell

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of the College of Medicine, Al-Nahrain University (decision no. 2024/1023, dated 11 February 2025). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Consent for Publication

All authors gave consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 license. No person's data is presented, so no additional consent is required.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request, subject to institutional data sharing policies and patient confidentiality protections.

Competing Interests

The authors declare that they have no competing interests. None of the authors has financial or personal relationships that could inappropriately influence or bias the work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was supported by the institutional resources of Al-Nahrain University, College of Medicine.

Author Contributions

SAY worked on the conceptualisation, methodology, validation, formal analysis, investigation, writing of the original draft and visualisation.
AHA did the conceptualisation, methodology, resources, supervision and writing of the review & editing.
ARJ worked on the methodology, validation, formal analysis, investigation, writing of the review & editing and project administration.

Acknowledgements

The authors thank the staff of the Department of Chemistry and Biochemistry, Al-Nahrain University, for their technical support. We are also grateful to the patients and healthy volunteers who participated in this study. The authors acknowledge the use of artificial intelligence-assisted language refinement (ChatGPT) for grammar and readability improvements; all scientific content, data interpretation, and final approval remain the sole responsibility of the authors.

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