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Association of serum Interleukin-13 and arginase-1 with disease severity and control in patients with asthma: A biomarker-based study

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ABSTRACT

Background: Asthma is a heterogeneous chronic inflammatory airway disease characterized by variable clinical severity and control status. Among these, Interleukin-13 (IL-13) and arginase-1 have emerged as potential biomarkers reflecting immune dysregulation and airway remodeling.

Objectives: This study was designed to examine the correlation between serum Interleukin-13 and arginase-1 levels with asthma severity and control status in Iraqi patients, as well as to assess their viability as biomarker-based indicators of disease activity.

Materials and methods: A case-control study was conducted involving 180 participants, comprising 90 individuals with asthma and 90 healthy controls, from April 2025 to January 2026. According to GINA standards, asthma severity and control were divided into groups. We employed an enzyme-linked immunosorbent assay (ELISA) to quantify the concentrations of arginase-1 and IL-13 in serum and analyzed the data using nonparametric statistical methods to evaluate the findings.

Results: The levels of serum arginase-1 and IL-13 were significantly higher in asthmatic patients than in healthy controls (p<0.001). IL-13 was strongly associated with the severity of the disease, with levels being much higher in severe asthma than in moderate asthma (p<0.0001) and rising steadily as control status got worse (p=0.0009). On the other hand, arginase-1 levels were much higher in people with severe asthma (p=0.0384), but they didn't differ much across asthma control groups (p=0.6079). Correlation analysis demonstrated a weak but statistically significant positive association between IL-13 and arginase-1 levels (r=0.251, p=0.017). Binary logistic regression showed that the overall model was highly significant (χ^2=212.18, p<0.0001) and had excellent explanatory power (Nagelkerke R^2=0.923).

Conclusion: Serum IL-13 is strongly associated with both asthma severity and loss of disease control, reflecting active type-2 inflammation, whereas arginase-1 appears to be primarily linked to disease presence and severity rather than control status. The combined assessment of arginase-1 and IL-13 provides valuable biomarker-based insight into asthma phenotyping and may improve clinical evaluation of disease activity in Iraqi patients.

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Introduction

Asthma is a heterogeneous chronic inflammatory disorder of the airways characterized by episodic wheeze, airflow limitation, mucus hypersecretion, and bronchial hyperresponsiveness.[1-3] It also includes a combination of natural and genetic variables.[4] Globally,

asthma impacts over 300 million people and was responsible for approximately 500,000 deaths in 2019, according to the World Health Organization (WHO).[5] Although asthma is traditionally viewed as an allergic eosinophilic disease, it is now recognized as a spectrum of phenotypes and biological endotypes linked to distinct molecular pathways, treatment responses, and prognoses.[6]

Type-2 (T2)-high asthma represents the most investigated endotype and is driven by the activity of key cytokines, including Interleukin-4 (IL-4), Interleukin-5 (IL-5), and IL-13, which orchestrate IgE synthesis, eosinophil maturation and survival, and recruitment of inflammatory cells into the airway mucosa.[7,8] Among these cytokines, IL-13 has emerged as a dominant effector molecule, inducing structural alterations such as goblet cell metaplasia and subepithelial fibrosis.[9,10]

IL-13 is a central T2 cytokine implicated in mucus hypersecretion, airway hyperresponsiveness, epithelial changes, and amplification of allergic inflammation; it is also associated with downstream remodeling-associated mediators.[11-13]

Arginase is the last enzyme in the urea cycle that's responsible for detoxifying ammonia in mammals by hydrolyzing arginine to ornithine and urea.[14] Arginase is present in two isoforms (Arginase type one and two), each with its tissue distribution and physiological function. Both isoforms are expressed in bronchial epithelial cells, endothelial cells, fibroblasts, and alveolar macrophages.[15,16] Increased arginase-mediated consumption of L-arginine contributes to the development of allergen-induced airway hyperresponsiveness (AHR) in acute allergic asthma by limiting the bioavailability of L-arginine to nitric oxide synthase (NOS) isozymes.[17] This leads to a deficiency of broncho-dilating nitric oxide and increased formation of the highly reactive pro-inflammatory and bronchoconstrictive nitric oxide metabolite peroxynitrite.[18] Reduced nitric oxide synthesis due to increased arginase activity could also contribute to airway remodeling in chronic asthma. This L-arginine/NO imbalance has been linked to airway hyperreactivity and structural changes, suggesting arginase-1 as a plausible biomarker of chronic asthma burden.[19]

Therefore, this study aimed to investigate the association between serum arginase-1 and IL-13 levels and asthma severity and control status in Iraqi patients, and to evaluate their potential as biomarker-based indicators of disease activity.

Materials and methods

Study design and population

A case-control study was conducted at Al-Imamain Al-Kadhimain Medical City and in the laboratories of the Department of Chemistry and Biochemistry at the College of Medicine, University of Al-Nahrain in Baghdad from 2025 to December 1, 2025. The study included 180 participants, comprising 90 adults with clinically diagnosed asthma and 90 healthy controls without respiratory disease, matched for age, sex, BMI, and socio-economic status. Asthma patients were diagnosed and classified under the supervision of a specialist physician according to GINA guidelines. Asthma severity (moderate and severe) was defined according to the GINA treatment steps, reflecting the level of treatment required to achieve and maintain disease control. In addition, patients were categorized by control status (controlled, partly controlled, or uncontrolled) based on symptom assessment and treatment response, as outlined by GINA. The control group participants were confirmed not to have asthma based on the same criteria.

Inclusion and exclusion criteria

Participants were aged ≥18 and 70 years and had a physician diagnosis of asthma. Exclusion criteria included age <18 years; patients with other chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) or lung fibrosis, pregnant or lactating women; patients with a history of advanced liver or chronic kidney diseases, advanced malignant tumors, Arthritis or Psoriasis can influence IL-13 level, [20] coronary heart disease,[21] Diabetic Mellitus' effect on arginase-1 level,[22] and active smoking.

Sample size calculation

A priori sample size calculation was performed using G*Power software (version 3.1.9.4). Based on previous studies reporting correlations ranging from 0.25 to 0.35 between IL-13 and asthma-related inflammatory markers, an effect size of r=0.30 was selected as a conservative and clinically meaningful estimate, consistent with Cohen's criteria for a moderate correlation. Using a two-tailed α level of 0.05 and 80% power, the minimum required sample size was calculated to be 84 asthmatic patients. To compensate for potential incomplete data, 90 patients were ultimately enrolled.

Sample collection and biomarker measurement

Venous blood samples (5 mL) were collected under aseptic conditions. Samples were allowed to coagulate and were then centrifuged at 3000 rpm for ten minutes. The serum was isolated and preserved at -80 °C until analysis. Serum IL-13 was quantified using a sandwich enzyme-linked immunosorbent assay ELISA kit (BT-Laboratory, Cat. No. E0098Hu; standard range 0.5-100 ng/L; sensitivity 0.2 ng/L; intra-assay CV<8%, inter-assay CV<10%). Serum arginase-1 was quantified using a sandwich ELISA kit (BT-Laboratory, Cat. No. E4984Hu; standard range: 0.5-200 ng/mL; sensitivity: 0.35 ng/mL; intra-assay CV<8%; inter-assay CV <10%). Absorbance was read at 450 nm, and concentrations were calculated from standard curves according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed using JASP (version 0.95.4) and MedCalc (version 23.4.0) for data processing, tabulation, and inferential testing, whereas GraphPad Prism (version 10.6.0) was used for graphical presentation. As most variables were non-normally distributed, continuous data were reported as median, interquartile range (Q1-Q3), and mean±SD. To compare the groups, the Mann-Whitney U test, the Kruskal-Wallis's test, and Dunn's post hoc multiple comparisons test were used. The relationship between continuous variables was evaluated using Spearman's rank correlation coefficient. In addition, binary logistic regression analysis was performed to identify independent predictors of asthma diagnosis and to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Model performance was evaluated using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). A two-tailed $p<0.05$ was considered statistically significant.

Results

The present study reports a case-control analytical evaluation of 180 participants, comprising 90 asthmatic patients and 90 healthy controls. The asthmatic cohort included both moderate and severe disease phenotypes: 56 (62.2%) had moderate disease severity, and 34 (37.8%) had severe disease severity. Based on asthma control, 31 (34.4%) were controlled, 34 (37.8%) were partially controlled, and 25 (27.8%) were uncontrolled, according to the GINA 2025 criteria. The percentage distribution of asthmatic patients according to disease severity and level of asthma control is shown in Figure 1.

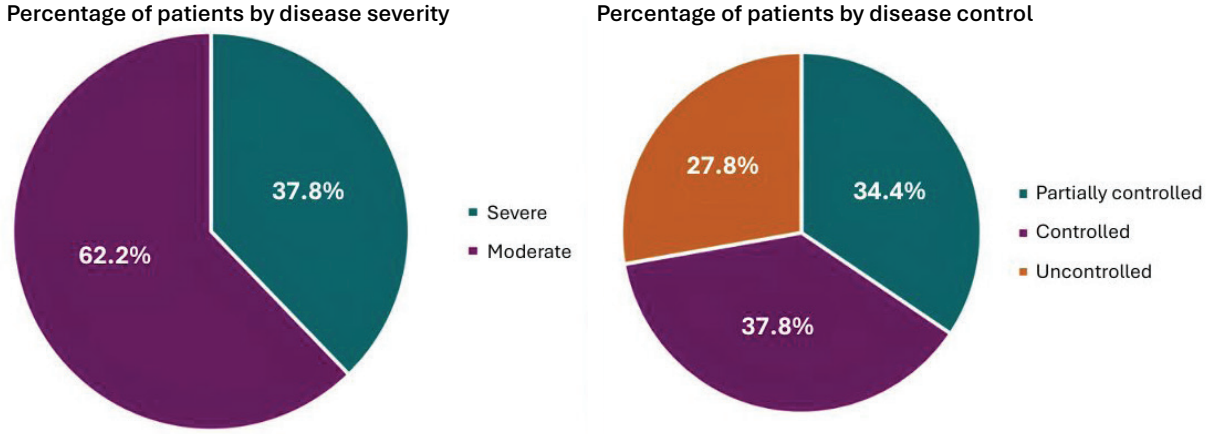


Figure 1. *Pie charts showing the percentage distribution of asthmatic patients according to disease severity and level of asthma control.*

The baseline characteristics of the study population are briefly outlined in Table 1. There were no significant differences between patients and controls regarding gender (χ^2=0.023, p=0.879), indicating that sex-matching is appropriate, and no differences in the number of subjects of each sex in the comparison groups. Likewise, no significant age difference was observed between cohorts (p=0.265), indicating comparable age groups. Body mass index was also similar between the two groups (p=0.242), with average body mass index in both populations being overweight or obese. Overall, these results indicate that the two cohorts were well balanced across most demographic characteristics, which should help minimize potential confounders in downstream biomarker analyses.

Table 1. Baseline demographic and anthropometric characteristics of the study population according to gender, age, and body mass index (BMI).

Subject	**Control** (N=90)	**Patient** (N=90)	**Statistical value**
Gender			
Male (N, %)	35 (38.9%)	37 (41.1%)	p=0.879
Female (N, %)	55 (61.1%)	53 (58.9%)	χ^2=0.023
Age (years) Mean±SD	48.30±12.69	46.00±14.87	p=0.265 t=1.116
BMI (kg/m^2) Mean±SD	29.36±3.43	30.16±5.55	p=0.242 t=1.173

Note: *Data are presented as frequency (N), percentage (%), and mean±SD. BMI: body mass index, χ^2: Chi-Square, t: T test*

Comparison of serum IL-13 and arginase-1 concentrations between asthmatic patients and healthy control subjects. As demonstrated in Table 2 and Figure 2, the asthma group exhibited significantly elevated levels of both biomarkers. The median serum IL-13 concentrations were significantly higher in patients [14.0 (9.9-16.6) ng/L] than in controls [10.05 (7.2-13.1) ng/L] (p<0.001). Similarly, arginase-1 levels were substantially higher in people with asthma, with a median concentration of [64.05 (54.7-72.1) ng/mL] compared to [26.50 (21.7-32.1) ng/mL] in healthy controls. All descriptive measures showed highly significant differences (p<0.001).

Table 2. Comparative serum levels of interleukin-13 and arginase-1 between patients with asthma and healthy controls.

Biomarker	**Patient** (N=90)	**Control** (N=90)	***p* value**
Interleukin-13 (ng/L)			
Median (Q1-Q3)	14.00 (9.9-16.6)	10.05 (7.2-13.1)	**<0.001**
Mean±SD	15.96±9.57	11.05±6.26	
Arginase-1 (ng/mL)			
Median (Q1-Q3)	64.05 (54.7-72.1)	26.50 (21.7-32.1)	**<0.001**
Mean±SD	65.63±18.08	27.33±8.14	

Note: *Statistical comparisons between groups were performed using the Mann-Whitney U test, based on data distributions and central tendencies, with results summarized as Median (Q1-Q3). Mean values are presented for descriptive purposes only. (Q1-Q3) represent the 25th and 75th percentiles.*

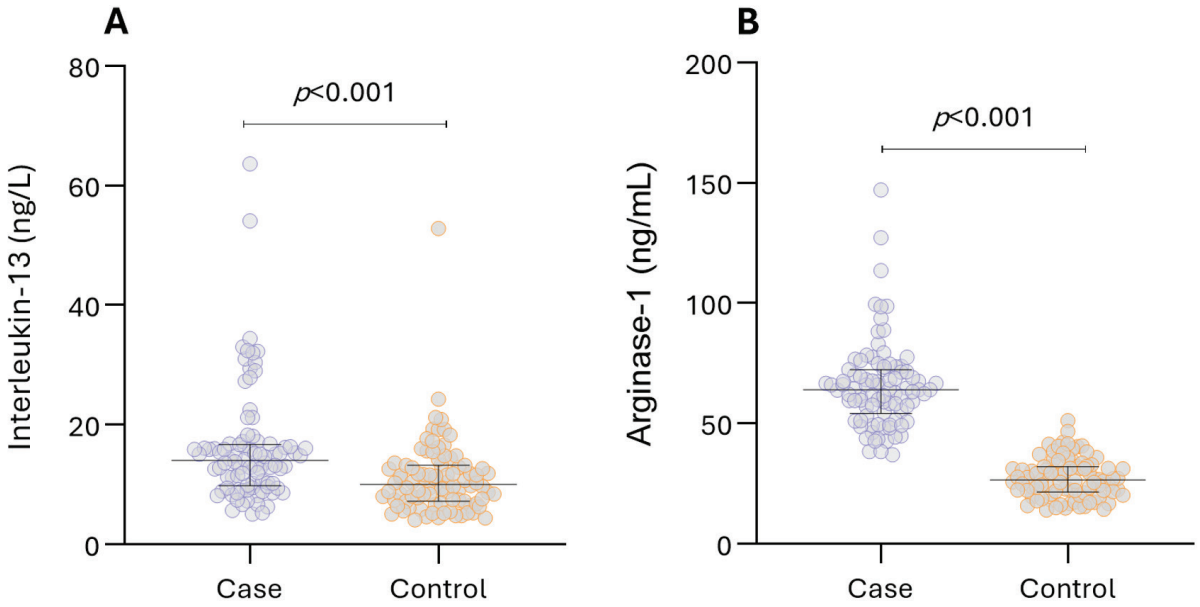


Figure 2*. Comparison of serum biomarker levels between patients with asthma (cases) and healthy controls. Data are presented as individual column scatter plots. A: serum concentration of IL-13 in ng/L, B: serum concentration of Arginase-1 in ng/mL. Statistical significance was determined using the Mann-Whitney U test, and the exact p values are indicated on the plots, with a value of p<0.001 indicating highly significant differences.*

Biomarker levels from moderate and severe asthma groups were compared to determine association with disease severity. As shown in Table 3, the median serum IL-13 level was significantly higher in patients with severe asthma [16.8 (14.9-28.7) ng/L] than in those with moderate asthma [12.3 (8.9-15.1) ng/L] (p<0.0001). A statistically significant difference in arginase-1 levels was also observed between patients with severe [65.4 (59.5-73.8) ng/mL] and moderate disease [62.95 (49.3-67.9) ng/mL] (p=0.0384) (Table 3).

Table 3. Comparison of serum levels of interleukin-13 and arginase-1 between moderate and severe asthma groups.

Biomarker	**Severe** (N=34)	**Moderate** (N=56)	***p* value**
Interleukin-13 (ng/L)			
Median (Q1-Q3)	16.8 (14.9-28.7)	12.3 (8.9-15.1)	**<0.0001**
Mean±SD	21.7±12.1	12.5±5.3	
Arginase-1 (ng/mL)			
Median (Q1-Q3)	65.4 (59.5-73.8)	62.9 (49.3-67.9)	**0.0384**
Mean±SD	69.9±17.1	61.5±14.4	

Note: *Statistical comparisons between groups were performed using the Mann-Whitney U test, based on data distributions and central tendencies, with results summarized as Median (Q1-Q3). Mean values are presented for descriptive purposes only. (Q1-Q3) represent the 25th and 75th percentiles.*

Additionally, patients were classified according to the GINA guideline control status into controlled, partially controlled, and uncontrolled groups. Serum IL-13 levels increased progressively with worsening control status (p=0.0009; Table 4). The median IL-13 level was [9.9 (8.5 -14.9) ng/L] in the controlled group, [15.5 (12.9-17.2) ng/L] in the partially controlled group, and [15.1 (12.6-27.9) ng/L] in the uncontrolled group. Post hoc analysis indicated significant differences between the uncontrolled and controlled groups (U>C) and between the partially controlled and controlled groups (P>C). In contrast, no statistically significant difference in median serum arginase-1 levels was seen between the three asthma control groups (p=0.6079, Table 4)

Table 4. Comparison of serum levels of interleukin-13 and arginase-1 among asthmatic patients grouped by GINA guideline control status (controlled, partially controlled, and uncontrolled).

Biomarker	**Controlled** (N=31)	**Partially controlled** (N=34)	**Uncontrolled** (N=25)	***p* value**	**Post-hoc analysis**
Interleukin-13 (ng/L)					
Median (Q1-Q3)	9.9 (8.5 -14.9)	15.5 (12.9-17.2)	15.1 (12.6-27.9)	**0.0009**	U>C U=P P>C
Mean±SD	11.6±5.4	17.6±10.1	19.0±11.06		
Arginase-1 (ng/mL)					
Median (Q1-Q3)	64.6 (59.5-69.3)	63.8 (51.9-72.1)	61.5 (49.2-71.4)	**0.6079**	U=C U=P P=C
Mean±SD	66.0±12.6	64.1±16.7	63.8±18.5		

Note: *Statistical comparisons among the three asthma control groups (controlled (C), partially controlled (P), uncontrolled (U)) were performed using the Kruskal-Wallis test based on data distributions and central tendencies, summarized as Median (Q1-Q3), followed by Dunn's post-hoc analysis for pairwise comparisons. Mean±SD values are presented for descriptive purposes only and are not implied in the p value calculations. The symbols in the "Post-hoc analysis" column indicate the direction of significant differences between groups.*

A weak but statistically significant positive correlation was observed between serum IL-13 and arginase-1 levels (r=0.251, *p*=0.017). This relationship suggests partial interaction between Type-2 inflammatory cytokine activity and arginine metabolic pathways in asthma (Figure 3).

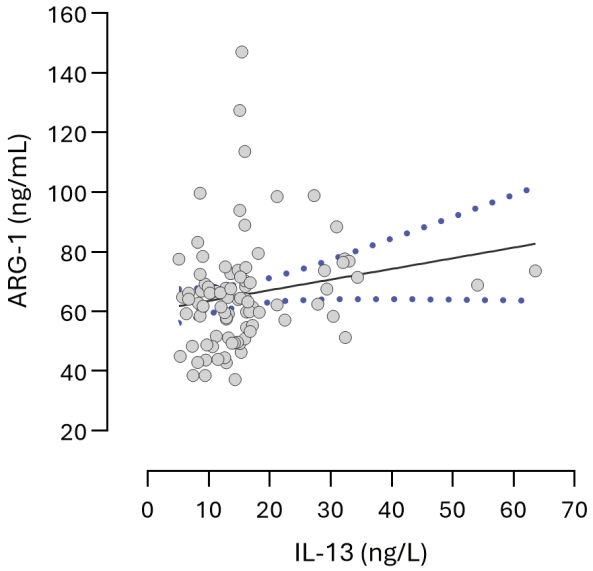


Figure 3. *Scatter plot illustrating the correlation between serum IL-13 and arginase-1 levels in patients with asthma. The solid line represents the fitted linear regression trend, while the dashed lines indicate the 95% confidence interval of the regression estimate.*

In our study, we used binary logistic regression to determine whether IL-13 and arginase-1 could serve as predictors of an asthma diagnosis. The overall model proved to be highly significant (χ^2=212.18, *p*<0.001) and demonstrated exceptional explanatory power (Nagelkerke R^2=0.923). Arginase-1 was identified as a significant independent predictor of asthma (OR=1.48, 95% CI: 1.24-1.77, *p*<0.0001), whereas IL-13 did not show statistical significance after adjustment. The model showed good calibration (Hosmer–Lemeshow *p*=0.738), excellent discrimination (AUC=0.993), and a high overall classification accuracy (97.2%) as shown in Table 5 and Figure 4.

Table 5. Binary logistic regression analysis identifying independent biomarker predictors of asthma (case vs healthy control)

Variable	**β coefficient**	**Odds ratio** (OR)	**95% CI for OR**	***p* value**
Interleukin-13 (ng/L)	-0.111	0.8948	0.73 to 1.08	0.2643
Arginase-1 (ng/mL)	0.398	1.4823	1.24 to 1.77	0.0001

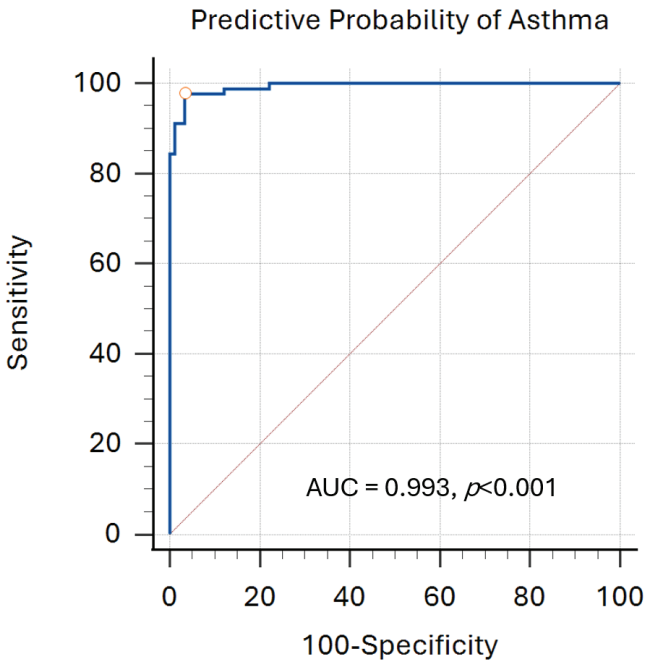


Figure 4. *Receiver Operating Characteristic (ROC) curve analysis assessing the diagnostic accuracy of the combined biomarker model. The curve demonstrates the exceptional discriminative performance of the multivariable logistic regression model incorporating both serum IL-13 and Arginase-1 (AUC=0.993, 95% CI: 0.984-1.000, Overall Accuracy = 97.2%) in differentiating asthmatic patients from healthy controls.*

Discussion

In this study, we examined the correlation between IL-13 and arginase-1 levels and asthma severity and control status in an Iraqi population and assessed their potential as biomarker-based indicators of disease activity. In this context, these findings also contribute to the growing interest in identifying complementary biomarkers. While established biomarkers such as blood eosinophil count (BEC), fractional exhaled nitric oxide (FeNO), and IgE are widely used in clinical practice, there remains a need to further characterize additional biomarkers that may provide complementary insights into disease mechanisms. This is particularly relevant in underrepresented populations, where regional environmental, genetic, and healthcare-related factors may influence disease expression and biomarker profiles.

Although significant differences were observed between groups, some degree of overlap in biomarker levels suggests that their discriminative utility at the individual level should be interpreted with caution. This consideration motivated the use of multivariable logistic regression analysis, which allows the combined effect of multiple biomarkers to be evaluated to improve discrimination. Overall, our findings demonstrated three principal observations: 1) both IL-13 and arginase-1 levels were significantly elevated in asthmatic patients compared with healthy controls, 2) IL-13 showed a strong association with disease severity and control status, and 3) arginase-1 emerged as a significant independent predictor of asthma in logistic regression analysis with excellent diagnostic performance.

Focusing first on the inflammatory cascade, the significant elevation of serum IL-13 levels observed in asthmatic patients aligns with the well-accepted paradigm that IL-13 is a key Th2 cytokine that mediates T2 airway inflammation and drives IgE class-switching, eosinophilia, mucus hypersecretion, and airway hyper responsiveness. These effects drive airway remodeling and persistent inflammation in asthma. Others have reported increased levels of IL-13 in patients with both allergic and severe asthma phenotypes, establishing its significance as an important mediator of T2-high inflammatory pathways.[11,13,23] In addition, we found that IL-13 levels were significantly higher in severe compared to moderate asthma, supporting a clear relationship between IL-13 and disease severity.

Taken together, this observation is consistent with a role for IL-13 in driving not just inflammatory responses but also remodeling events within the airway epithelium. Experimental and clinical studies have shown that IL-13 induces goblet cell metaplasia, collagen remodeling, and subepithelial fibrosis, which are hallmarks of airway remodeling in severe asthma.[12,24,25]

Beyond simple disease classification, serum IL-13 levels also increased significantly as asthma worsened, representing another key finding of the present study. Both partially controlled and uncontrolled patients showed significantly higher IL-13 levels than controlled subjects. The higher IL-13 levels in patients with recurrent symptoms indicate ongoing inflammatory activity and poor disease suppression, making IL-13 a good candidate as an asthma control molecule. These

data are consistent with previous investigations showing that T2 cytokines are associated with poor asthma control and exacerbations.[13,26-28] Accordingly, elevated serum IL-13 levels have been linked to increased airway inflammation, corticosteroid resistance, and persistent symptoms in severe asthma.

While IL-13 strongly reflects these dynamic fluctuations in inflammation and symptom control, a parallel pathway involving structural modifications is illuminated by altered arginine metabolism. The present study also demonstrated markedly increased serum arginase-1 levels in asthmatic patients compared with healthy individuals. Arginase-1 is an important enzyme in the L-arginine metabolic pathway that competes with nitric oxide synthases (NOS) for the common substrate L-arginine. Elevated arginase-1 activity reduces nitric oxide production and leads to the accumulation of ornithine and downstream metabolites that contribute to airway remodeling.[17,29] Reduced bioavailability of nitric oxide may lead to bronchoconstriction, airway hyperresponsiveness, and oxidative stress in the asthmatic condition. Increased arginase-1 activity has been shown in prior experimental studies to exacerbate allergen-induced airway hyperresponsiveness and promote airway structural remodeling.[17,19,30]

Intriguingly, although arginase-1 concentrations were markedly higher in severe than in moderate disease, this difference was less pronounced than that observed for IL-13, and arginase-1 levels did not differ significantly across asthma control categories. This indicates that arginase-1 might reflect chronic airway remodeling rather than acute inflammatory activity. Arginase-1 levels did not differ significantly in all asthma control categories. This observation suggests that arginase-1 may be more closely associated with structural airway changes and disease burden rather than short-term variations in symptom control.

Despite these differing clinical expressions, a biological bridge exists between these two markers, as a weak but statistically significant positive correlation was observed between circulating IL-13 and arginase-1 level. These findings are consistent with type-2 inflammatory cytokines altering arginine metabolic pathways in asthma.[31] Indeed, there is experimental evidence that IL-13 induces arginase-1 expression in airway epithelial and macrophage cells, with a subsequent increase in arginine metabolism and impaired nitric oxide availability. This interaction may serve as a key mediator connecting immune inflammation with airway remodeling processes. [19]

This biological interplay directly informs the diagnostic performance of these markers when evaluated simultaneously. Results of our Binary logistic regression analysis demonstrated that, after adjustment, arginase-1, but not IL-13, was a significant independent predictor of asthma. These results indicate exceptional discriminatory performance, with an area under the receiver operating characteristic curve (AUC) of 0.993, enabling the model to accurately distinguish asthmatic patients from healthy volunteers. The fact that IL-13 loses statistical significance when added into the regression model may be explained by a partial correlation between IL-13 and arginase-1, implying overlapping biological pathways. In this regard, arginase-1 may serve as a more stable biomarker for distinguishing metabolic from structural airway alterations, rather than transient inflammatory signaling.

Taken together, these results suggest that arginase-1 is a highly promising candidate diagnostic biomarker for asthma, which could be assessed alongside inflammatory markers, such as IL-13, to improve characterization of asthma phenotypes.

Limitations

This study has several limitations. The case-control design may have led to an overestimation of discrimination performance, as comparisons were made between clearly distinct groups (asthma vs healthy controls), which may not fully reflect real-world clinical complexity. In everyday clinical practice, diagnostic tools operate in more challenging settings, where they must differentiate asthma from other conditions with overlapping respiratory symptoms. In addition, the relatively small, single-center sample and restriction to an Iraqi population may limit generalizability. Therefore, these findings should be interpreted with caution, and future prospective studies in broader, real-world clinical populations are welcomed to further confirm generalizability. In addition, asthma severity in this study was defined according to GINA guidelines, which reflect treatment intensity rather than intrinsic disease severity and may be influenced by external factors such as treatment adherence and healthcare access. Although this approach has limitations, it remains a widely accepted and practical method for severity classification in clinical research.

Conclusion

In conclusion, the present study demonstrates that serum IL-13 and arginase-1 levels are significantly elevated in asthmatic patients. IL-13 is strongly associated with disease severity and asthma control and may reflect underlying type-2 inflammatory activity, whereas arginase-1 appears to be more closely associated with disease presence and may relate to processes involved in airway remodeling. The combined evaluation of these biomarkers may help clarify aspects of asthma pathophysiology and support the development of biomarker-based approaches for disease phenotyping and clinical assessment.

Ethical approval

The study protocol was approved by the Institutional Review Board (IRB) of the College of Medicine, University of Al-Nahrain on 10-03-2025 under decision number 223/3/2. All participants provided verbal informed consent and were asked to complete a prepared questionnaire. Individual were informed of

their ability to withdraw at any time without any negative impact on their clinical care, and confidentiality was maintained throughout the study. The ethical standards outlined in the Declaration of Helsinki were adhered to by all procedures.

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Conflict of interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Hayder Yaseen Ali: conceptualization, methodology, funding acquisition, writing: original draft, data curation, formal analysis, and investigation; **Haider Abdulhameed Alqaraghuli**: conceptualization, methodology, funding acquisition, writing: original draft, validation, writing: review and edit, supervision; **Raid J. Mohammed AL-TIMIMI**: validation, writing: review and edit, supervision. All authors read and approved the final manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used Gemini (Version 1.5 Pro, Google, USA) and Grammarly (Version 2024, Grammarly Inc., USA) solely to enhance the English language, grammar, and overall readability of the text. These tools were used for linguistic refinement and editorial purposes only, without any involvement in data analysis, interpretation of results, or the generation of original scientific content. The authors assume full responsibility for the integrity and accuracy of the final manuscript and affirm that these AI tools do not qualify for authorship.

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