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Evaluating the Role of Fractional Exhaled Nitric Oxide (FeNO) and Inflammatory Biomarkers in Diagnosing Non-Chronic Cough in Pediatric Patients: A Cross-Sectional Study

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ABSTRACT

Fractional exhaled nitric oxide (FeNO) has emerged as a potential biomarker for differentiating between various causes of non-chronic cough, particularly in conditions associated with airway inflammation, such as asthma. This study aimed to evaluate the diagnostic efficacy of FeNO in pediatric patients with non-chronic cough and its ability to differentiate between asthma exacerbations and respiratory tract infections.

Seventy-five pediatric patients aged 10-18 years with non-chronic cough were categorized into three groups: good control asthma (GCA, n=28), acute asthma exacerbation (AAE, n=26), and respiratory tract infection (RTI, n=21). Clinical assessments included FeNO measurement, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, hemoglobin (HB), platelet count (PLT), and immunoglobulin E (IgE) levels. Univariate and multivariate multinomial logistic regression models were applied to assess the predictive value of these variables.

FeNO levels were significantly higher in the AAE group (46.58±22.66 ppb) compared to the GCA and RTI groups, indicating elevated eosinophilic airway inflammation in asthma exacerbations. CRP was a significant predictor of both AAE and RTI, with a one-unit increase in CRP increasing the odds of exacerbation or infection by 2.6-fold. Body max index (BMI) was inversely associated with the risk of RTI. Hemoglobin, platelet count, and IgE levels were significantly higher in the AAE group compared to the other groups, while WBC counts, though elevated, were not statistically significant.

FeNO associated with other inflammatory markers, including CRP and BMI, could enhance diagnostic accuracy and inform clinical decision-making in managing pediatric respiratory conditions. To confirm these results, future studies with larger sample sizes should be performed.

Keywords: Asthma exacerbation; Biomarkers; FeNO test; Non-chronic coughs; Pediatrics; Respiratory tract infection

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INTRODUCTION

Cough is one of the most common reasons for medical consultations worldwide and is classified into 3 types based on its duration: acute (lasting less than 3 weeks), subacute (3 to 8 weeks), and chronic (more than 8 weeks).[1] While chronic cough has well-established diagnostic pathways, non-chronic cough remains diagnostically challenging due to its diverse etiologies, ranging from respiratory tract infections (RTIs) to asthma exacerbations and post-infectious inflammation. Accurate differentiation between these causes is crucial for effective treatment, especially in pediatric populations where misdiagnosis can lead to unnecessary treatments or delayed intervention.

Recent advances in the field of respiratory diagnostics have suggested the potential use of biomarkers, such as fractional exhaled nitric oxide (FeNO), to improve diagnostic accuracy in cases of non-chronic cough.[2-4] FeNO is a non-invasive marker of eosinophilic airway inflammation and has been extensively studied in asthma, where elevated levels correlate with airway inflammation due to T_H2-mediated responses.[5-7] FeNO has been extensively studied in asthma patients and chronic cough. The existing literature does not adequately address how FeNO levels correlate with non-chronic cough specifically, leading to uncertainty about its diagnostic value in this context. While FeNO levels are generally elevated in asthma, they may not show the same pattern in infections or other non-inflammatory causes of cough.[8]

In addition to FeNO, other inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and immunoglobulin E (IgE) levels have been associated with various respiratory conditions.[9,10] CRP, in particular, is widely used to assess systemic inflammation, often elevated in both infections and inflammatory diseases like asthma.[11-14] Similarly, IgE is a key marker of allergic inflammation, frequently elevated in asthmatic patients, especially during exacerbations.[15,16] However, the integration of these markers alongside FeNO for diagnosing non-chronic cough in pediatric patients has not been fully explored.

Given the complexity of non-chronic cough and the need for more precise diagnostic tools, this study aims to evaluate the diagnostic efficacy of FeNO and other inflammatory markers in differentiating between asthma exacerbations and respiratory infections in pediatric patients with non-chronic cough. The pediatric population often requires tailored diagnostic approaches due to physiological differences compared to adults. By examining the levels of FeNO, CRP, ESR, IgE, and other relevant clinical parameters, this study seeks to identify reliable diagnostic markers that can aid clinicians in the accurate and timely treatment of pediatric patients presenting with non-chronic cough.

This research is particularly relevant in pediatric settings, where misclassification of asthma exacerbations or infections can lead to suboptimal treatment strategies. Understanding the diagnostic potential of FeNO, especially when used in conjunction with other biomarkers, could significantly enhance the management of non-chronic cough in children.

MATERIALS AND METHODS

Participants

In this study, we included 88 children with non-chronic coughs aged 10 to 18 years who visited Imam Reza Medical Clinic in 2023. Of these, 9 patients were excluded based on inclusion and exclusion criteria, and 4 patients declined to participate. Finally, 75 children were included in this study. The inclusion criteria specified that participants must have a non-chronic cough lasting 3 to 8 weeks that could not be diagnosed through physical examination. Significant exclusion criteria included a history of psychiatric disorders, use of ACE inhibitors, and explicit abnormalities in chest X-rays, as well as a history of chronic obstructive pulmonary disease, gastroesophageal reflux disease, or psychogenic cough.

To determine the appropriate sample size for this study, we conducted a power analysis based on preliminary data from similar studies assessing the diagnostic efficacy of FeNO in respiratory conditions. Using an alpha level of 5% and a power of 80%, and an effect size of 0.418 from a similar study,[3] we estimated that a minimum sample size of 60 participants would be necessary to detect significant differences in FeNO levels among the 3 groups (good control asthma (GCA), acute asthma exacerbation (AAE), and respiratory tract infection (RTI)). Given the expected dropout rate and to enhance the robustness of our findings, we aimed to recruit a total of 88 participants.

Participants were categorized into 3 distinct groups: GCA (n=28), AAE (n=26), and RTI (n=21). Informed consent was obtained from patients before recruiting to the study. To assess the patients, several crucial tests and examinations were conducted, including chest X-ray, blood sampling, cell blood count differential, pulmonary function tests, FeNO measurement, postnasal discharge examination, otitis media examination, sinus tenderness examination, IgE level measurement, CRP test, ESR, white blood cell (WBC) count, hemoglobin (Hb), and platelet tests (PLT). Additionally, a physical examination was performed to check for abnormal lung sounds such as crackles and wheezes. Each participant also completed a questionnaire that provided crucial information regarding age, medical history, body mass index (BMI), sex, history of allergic rhinitis, acute or chronic sinusitis, drug use, and use of asthma spray. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.383).

Diagnosis of Cough-Predominant Asthma, Cough Variant Asthma, and Infectious Cough

Patients were categorized into 3 distinct groups based on their clinical presentation and diagnostic criteria:

The GCA group included patients who had a confirmed diagnosis of asthma and demonstrated good control of their symptoms, as defined by having no recent exacerbations and maintaining normal pulmonary function test results. Additionally, these patients were required to undergo maintenance therapy with ICS+LABA.

The AAE patients presented with an acute worsening of asthma symptoms, characterized by increased dyspnea, wheezing, and/or cough. These individuals had a history of exacerbations requiring medical intervention, such as increased use of rescue inhalers or oral corticosteroids. The diagnosis was confirmed through clinical evaluation and pulmonary function tests showing reduced lung function.

The RTI group comprised patients diagnosed with RTIs based on clinical assessment and physical exams and relevant laboratory tests. Symptoms included cough, fever, and other signs indicative of infection without significant signs of asthma symptom.

The grouping criteria were developed in accordance with the Japanese Guideline for Cough, 2nd edition, which outlines diagnostic approaches for asthma and RTIs in pediatric populations.[17] Following this categorization, participants exhaled into the FeNO measurement instrument (NObreath) (NObreath® FeNO Device by Bedfont® Scientific Ltd.) during their initial visit. To perform this test, participants were instructed to refrain from using short-acting bronchodilators for at least 6 hours before testing to avoid any influence on FeNO levels. They were then asked to perform a slow, steady exhalation into the NObreath device through a mouthpiece. The exhalation was maintained at a specified flow rate (typically around 50 mL/s) to ensure optimal measurement conditions. The device captures the exhaled air and analyzes the concentration of nitric oxide present, providing an immediate reading of FeNO levels.

Statistical Analysis

Quantitative data are presented as mean ± standard deviation, while qualitative data are shown as numbers (percentage). Distributions were compared using Pearson chi-square tests or one-way analysis of variance (ANOVA). Additionally, univariate and multivariate multinomial logistic regression models were applied to investigate associations with exacerbation and infection compared to well-controlled asthma. Analyses were performed using IBM SPSS version 24, with *p* values less than 0.05 considered statistically significant.

RESULTS

Demographic and Clinical Features of Patients

The study included 75 pediatric patients, with a mean age of 13.40 years (±2.58), among which 54.7% were male. The GCA group had a mean age of 12.77±2.48 years, while the AAE (13.65±2.76 years) and RTI (13.92±2.45 years) groups were slightly older. No significant differences were observed in the age and sex distributions between the groups.

BMI significantly differed between the groups, with the GCA group showing the highest BMI (18.57±3.14 kg/m2), followed by the AAE group (16.37±4.23 kg/m2), and the RTI group (15.18±2.22 kg/m^2). This difference was statistically significant (p=0.002).

ESR was also significantly different, being the highest in the AAE group (28.12±15.43 mm/hr), followed by the RTI group (24.76±15.23 mm/hr), and lowest in the GCA group (10.68±2.78 mm/hr) (p<0.001). Hb levels were significantly higher in the RTI group (13.82±1.83 g/dL), while the AAE group

showed intermediate levels (13.43±1.57 g/dl), and the GCA group had the lowest Hb levels (12.51±1.31 g/dL) (p=0.013).

PLT count was significantly higher in the AAE group (411,615.38±158,393.20 cell/µL), while the GCA group had the lowest count (290,892.86±95,564.34 cell/µL) (p=0.002). FeNO levels were also highest in the AAE group (46.58±22.66 ppb), and lowest in the RTI group (16.86±7.72 ppb) (p<0.001). Additionally, IgE levels were highest in the AAE group (139.27±157.79 IU/mL) and significantly different from the other groups (p=0.003).

CRP levels were significantly elevated in the AAE group (25.58±20.07 mg/L) and RTI group (23.71±14.34 mg/L) compared to the GCA group (4.25±2.40 mg/L) (p<0.001). The eosinophil count was significantly higher in the GCA and AAE groups (4.74±1.34 and 4.42±1.92 cells/µL, respectively) than in the RTI group (3.10±1.70 %) (p=0.003).

The medical history revealed that 66.7% of the total patients had relevant medical conditions, with the GCA group having the highest percentage (50.0%) and the RTI group the lowest (12.0%) (p<0.001). Drug history, particularly regarding asthma spray use, was also significantly different, with the GCA group showing the highest usage (55.8%) and the RTI group the lowest (2.3%) (p<0.001). All data are shown in Table 1.

Table 1. Demographic and clinical features of patients

Factors		Total N=75	GCA n=28	AAE n=26	RTI n=21	*p
Age, y		13.40±2.58	12.77±2.48	13.65±2.76	13.92±2.45	[A]0.253
Men, n (%)		41 (54.7)	17 (41.5)	14 (34.1)	10 (24.4)	[C]0.657
BMI, kg/m^2		16.86±3.60	18.57±3.14	16.37±4.23	15.18±2.22	0.002
ESR, mm/hr		20.67±14.42	10.68±2.78	28.12±15.43	24.76±15.23	[A]<0.001
WBC, cells/µL		17553±48319	7266±1870	31873±80946	13540±3421	[A]0.158
Hb, g/dL		13.20±1.64	12.51±1.31	13.43±1.57	13.82±1.83	[A]0.013
PLT, cells/µL		351987±127910	290893±95564	411615±158393	359619±83286	[A]0.002
FeNO, ppb		27.36±20.53	17.39±9.58	46.58±22.66	16.86±7.72	[A]<0.001
IgE level, IU/mL		83.17±111.27	66.59±73.72	139.27±157.79	35.81±22.73	[A]0.003
CRP, mg/L		17.09±17.15	4.25±2.40	25.58±20.07	23.71±14.34	[A]<0.001
Eosinophil, cells/µL		4.17±1.78	4.74±1.34	4.42±1.92	3.10±1.70	[A]0.003
Medical history, n (%)		50 (66.7)	25 (50.0)	19 (38.0)	6 (12.0)	[C]<0.001
Drug history, n(%)	**Positive**	43 (57.3)	24 (55.8)	18 (41.9)	1 (2.3)	
	Negative	32 (42.7)	4 (12.5)	8 (25.0)	20 (62.5)	[C]<0.001
Severity, n(%)	**Mild**	34 (45.3)	9 (26.5)	8 (23.5)	17 (50.0)	[C]0.001
	Moderate	21 (28.0)	11 (52.4)	6 (28.6)	4 (19.0)	
	Severe	20 (26.7)	8 (40.0)	12 (60.0)	0 (0)	
PND		33 (44.0)	8 (24.2)	14 (42.4)	11 (33.3)	[C]0.115
Family history		19 (25.3)	7 (36.8)	8 (42.1)	4 (21.1)	[C]0.655
Passive smoker		30 (40.0)	10 (33.3)	11 (36.7)	9 (30.0)	[C]0.842
Allergic rhinitis and eczema		19 (25.3)	4 (21.1)	9 (47.4)	6 (31.6)	[C]0.211

BMI: body mass index; ESR: erythrocyte sedimentation rate; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; PND: postnasal drip; GCA: good control asthma; AAE: acute asthma exacerbation; RTI: respiratory tract infection; *values are mean ± SD or number (percentage), by chi-square or one-way ANOVA; [a]one-way ANOVA; [b]chi-square test

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Univariate Multinomial Logistic Regression Model

Based on the univariate model, CRP, FeNO, IgE level, ESR, WBC, Hb, PLT count, BMI, medical history, and drug history were significantly associated with either exacerbation or infection (Table 2).

In the univariate logistic regression analysis, several factors were found to significantly influence the odds of experiencing AAE or RTI compared to GCA. A one-unit increase in CRP was associated with a 2.6-fold higher likelihood of both AAE (OR=2.579, 95% CI: 1.335–4.981, p=0.005) and RTI (OR=2.576, 95% CI: 1.334–4.976, p=0.005).

Table 2. Univariate multinomial logistic regression model

Predictor	AAE (n=26)		RTI (n=21)	
	OR (95% CI)	*p*	OR (95% CI)	*p*
CRP	2.579 (1.335, 4.981)	0.005	2.576 (1.334, 4.976)	0.005
Eosinophil	0.848 (0.435, 1.653)	0.628	0.548 (0.268, 1.118)	0.098
FeNO	1.140 (1.064, 1.222)	<0.001	0.993 (0.931, 1.059)	0.834
IgE level	1.006 (1.000, 1.011)	0.049	0.989 (0.974, 1.003)	0.133
ESR	1.462 (1.207, 1.770)	<0.001	1.440 (1.189, 1.743)	<0.001
WBC	1.001 (1.001, 1.001)	<0.001	1.001 (1.000, 1.001)	<0.001
Hb	1.475 (1.023, 2.126)	0.037	1.732 (1.159, 2.588)	0.007
PLT	1.000 (1.000, 1.000)	0.001	1.000 (1.000, 1.000)	0.031
Age	1.151 (0.928, 1.429)	0.202	1.198 (0.953, 1.506)	0.122
BMI	0.833 (0.705, 0.984)	0.032	0.729 (0.594, 0.896)	0.003
Sex (male)	0.755 (0.256, 2.226)	0.610	0.588 (0.187, 1.847)	0.363
Medical history (yes)	0.326 (0.074, 1.428)	0.137	0.048 (0.010, 0.221)	<0.001
Drug history (spray)	0.375 (0.098, 1.442)	0.153	0.008 (0.001, 0.081)	<0.001
Severity (mild)	0.593 (0.160, 2.189)	0.433	NA	NA
Severity (moderate)	0.364 (0.095, 1.386)	0.138	NA	NA
PND	2.917 (0.946, 8.989)	0.062	2.750 (0.840, 9.000)	0.094
Family history	1.333 (0.404, 4.400)	0.637	0.706 (0.177, 2.820)	0.622
Passive smoker	1.320 (0.441, 3.953)	0.620	1.350 (0.423, 4.304)	0.612
Allergic rhinitis and eczema	3.176 (0.839, 12.030)	0.089	2.400 (0.580, 9.930)	0.227

GCA: good control asthma; AAE: acute asthma exacerbation; RTI: respiratory tract infection; BMI: body mass index; ESR: erythrocyte sedimentation rate; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; PND: postnasal drip. Good control asthma was considered as a reference category.

FeNO levels were significantly associated with AAE, with a one-unit increase in FeNO corresponding to 14% higher odds of exacerbation (OR=1.140, 95% CI: 1.064–1.222, p<0.001). However, FeNO was not significantly associated with RTI (P=0.834). Elevated IgE levels were weakly associated with a higher likelihood of AAE (OR=1.006, 95% CI: 1.000–1.011, p=0.049), but no significant relationship was observed with RTI (p=0.133).

ESR, WBC count, and Hb levels were all significantly associated with increased odds of both AAE and RTI. A one-unit increase in ESR increased the odds of both AAE and RTI (OR=1.462 and 1.440, p<0.001). Similarly, WBC count and hemoglobin showed significant associations with both conditions (p<0.001 and p<0.037, respectively).

BMI showed a protective effect against RTI, with a higher BMI associated with a lower odd of infection

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(OR=0.729, 95% CI: 0.594–0.896, *p*=0.003). A similar trend was observed for AAE, although it was not statistically significant.

In the multivariate logistic regression analysis, CRP remained a significant predictor for both AAE and RTI. A one-unit increase in CRP was associated with a 4.2-fold increase in the odds of AAE (OR=4.211, 95% CI: 1.225–14.477, *p*=0.022) and RTI (OR=4.176, 95% CI: 1.214–14.359, *p*=0.023). Additionally, our analysis revealed that higher BMI was associated with a protective effect against RTI, with a one-unit increase in BMI reducing the odds of infection by 47% (OR=0.530, CI: 0.314–0.892, *p*=0.017). Although this association was not statistically significant for AAE, it suggests that maintaining a healthy weight may play a role in reducing the risk of respiratory infections in children.

FeNO was not a significant predictor in the multivariate model, showing no significant associations with either AAE or RTI (*p*=0.518 and *p*=0.128, respectively). Similarly, gender did not significantly influence the likelihood of either condition, although male patients had lower odds of both AAE and RTI compared to females, with 93% and 98% reductions in odds, respectively (*p*=0.225 and *p*=0.072).

Table 3. Multivariate multinomial logistic regression model

Groups		OR (95% CI)	*p*
AAE	**Gender (Male)**	0.067 (0.001, 5.282)	0.225
	FENO	1.049 (0.908, 1.211)	0.518
	CRP	4.211 (1.225, 14.477)	0.022
	BMI	0.654 (0.396, 1.082)	0.098
RTI	**Gender (Male)**	0.020 (0.000, 1.417)	0.072
	FENO	0.887 (0.760, 1.035)	0.128
	CRP	4.176 (1.214, 14.359)	0.023
	BMI	0.530 (0.314, 0.892)	0.017

BMI: body mass index; CRP: C-reactive protein; FeNO: fractional exhaled nitric oxide; AAE: acute asthma exacerbation; RTI: respiratory tract infection. GCA was considered as a reference category.

DISCUSSION

This study aimed to evaluate the diagnostic efficacy of FeNO in pediatric patients presenting with non-chronic cough and its potential to differentiate between causes of cough such as AAE, RTI, and GCA. The results revealed several key findings regarding the association of FeNO, inflammatory markers, and clinical characteristics in differentiating these groups.

This study revealed significantly elevated FeNO levels in patients with AAE relative to those with RTI or GCA. This is consistent with other research indicating that FeNO serves as a dependable marker of eosinophilic airway inflammation, frequently linked to asthma exacerbations.[18-20] However, the multivariate analysis indicated that FeNO was not a statistically significant independent predictor of AAE or RTI. This indicates that although FeNO may indicate underlying inflammation, its effectiveness as an independent diagnostic marker may be constrained and should be evaluated in conjunction with other clinical indicators.

The research demonstrated the significance of CRP and ESR as critical indicators of inflammation. Increased CRP levels were substantially correlated with both AAE and RTI, indicating systemic inflammation in these diseases. This aligns with research indicating that CRP serves as an effective biomarker for detecting exacerbations in respiratory diseases.[21,22] The multivariate analysis established that CRP is a significant predictor of aggravation or infection, with each one-unit rise in CRP correlating to a 4.2-fold increase in the probabilities of AAE or RTI. This underscores the efficacy of CRP as a more dependable diagnostic marker than FeNO alone, especially in distinguishing various etiologies of non-chronic cough.

BMI was another factor that emerged as a significant predictor in the analysis. Patients in the GCA cohort exhibited the greatest BMI, and an elevated BMI was

determined to confer protection against RTI. This finding aligns with previous studies that underscore the intricate link between obesity, asthma, and respiratory infections.[23-25] Research indicates that obesity can intensify asthma symptoms through mechanical and inflammatory mechanisms, while its impact on respiratory infections is less well-defined.[26,27]

Eosinophil counts were also significantly elevated in the AAE and GCA groups compared to the RTI group, supporting previous findings that link eosinophilia with asthma exacerbations and allergic inflammation.[28,29] Higher eosinophil levels in the AAE group, combined with elevated FeNO levels, suggest the potential of these markers in identifying asthma-related cough.[30] However, as with FeNO, eosinophil count alone may not suffice to differentiate between AAE and RTI, as CRP appeared to be a more robust diagnostic marker in this context.

The research revealed notable disparities in HB levels among the patient groups, with the RTI group exhibiting the highest levels and the GCA group the lowest. Increased hemoglobin levels in the RTI group may indicate a compensatory reaction to infection-induced hypoxia, wherein the body elevates hemoglobin to improve oxygen transport.[31] The correlation between infection and hemoglobin levels has been previously documented, indicating that systemic infections and inflammation might alter red blood cell formation and hemoglobin concentration.[32,33] The reduced HB levels in the GCA cohort may indicate a less systemic inflammatory response in well-managed asthma relative to acute infection or exacerbation.

The platelet count was markedly elevated in the AAE group compared to the GCA group. Platelets are becoming more recognized as active contributors to the immune response, especially in inflammatory diseases like asthma.[34] During asthma exacerbations, platelets may become activated, leading to the production of inflammatory mediators that intensify airway inflammation.[34] The substantial increase in platelet counts within the AAE group corresponds with prior research emphasizing the involvement of platelets in the pathogenesis of asthma, especially during exacerbations characterized by heightened inflammation.[35,36] Monitoring platelet counts in asthmatic patients may provide further insights into inflammation intensity and assist in formulating treatment plans.

Increased IgE levels were observed in the AAE group, consistent with the established function of IgE in allergic asthma and atopy. IgE favors allergic reactions by inducing mast cell degranulation and the subsequent release of histamine and other inflammatory mediators.[37] The elevated IgE levels in the AAE group support its involvement in allergic inflammation, especially in asthma exacerbations triggered by allergen exposure. This finding aligns with previous studies that associate elevated serum IgE levels with increased asthma severity and exacerbations.[29,38] Monitoring IgE may assist doctors in identifying individuals at elevated risk for exacerbations and inform the application of medicines such as anti-IgE monoclonal antibodies (e.g., omalizumab) for improved management of allergic asthma.

The ESR was highest in the AAE group, followed by the RTI group, and lowest in the GCA group. ESR is a non-specific inflammatory marker that increases in response to acute-phase proteins generated during inflammatory events.[39,40] The elevation of ESR in the AAE group is attributable to the systemic inflammatory response observed in severe asthma exacerbations, wherein the augmented synthesis of inflammatory cytokines (such as interleukin [IL]-6 and TNF-alpha) results in an enhanced ESR. Likewise, an increased ESR in the RTI cohort indicates the acute inflammatory response elicited by infections. The notable distinction between GCA and both AAE and RTI groups highlights the function of ESR as an indicator of active inflammation, aiding in the differentiation between well-managed asthma and illness exacerbations or infections. The univariate analysis further supported the significance of ESR in distinguishing between the clinical groups. This highlights ESR's role as a strong marker of systemic inflammation in both asthma exacerbations and infections.

The study highlighted a significant difference in drug history, specifically regarding the use of asthma inhalers. The GCA group showed the highest consumption of inhaled drugs, which is expected since these individuals had well-managed asthma. Conversely, a minimal number of patients in the RTI group utilized asthma inhalers, indicating that most of these patients likely lacked a history of asthma. This finding underscores the importance of drug history in understanding the underlying causes of non-chronic cough. Patients with a history of inhaler use are more likely to suffer from asthma-related cough, whereas those without such a history are more likely to have infectious or other non-asthma-related causes.

While FeNO has been suggested as a non-invasive and user-friendly biomarker for inflammation, this study doubts its diagnostic precision in distinguishing the etiology of non-chronic cough. Although higher FeNO levels were noted during asthma exacerbations, the absence of statistical significance in the multivariate model indicates that FeNO should be utilized within a comprehensive diagnostic framework, integrating additional clinical markers such as CRP and BMI, to enhance diagnostic precision. Factors such as patient age, smoking status, and medication use, which may be considered in this study, may have also influenced FeNO levels.

The limitations of this study should be acknowledged. The small sample size and specialized focus of the study may restrict the applicability of the findings to other populations. Moreover, variables like pharmacological interventions, environmental exposures, and dietary influences on FeNO levels were not thoroughly investigated, potentially affecting the outcomes.

This study highlights the potential efficacy of FeNO as a diagnostic tool for non-chronic cough, especially in identifying asthma exacerbations. The findings indicate that FeNO should be used with other clinical indicators, such as CRP and BMI, to enhance diagnostic precision. Additional studies involving larger and more distinct groups are necessary to validate these findings and determine suitable cutoff values for FeNO in distinguishing between different causes of non-chronic cough.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.383).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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