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Predictive value of exhaled nitric oxide in assessing the therapeutic efficacy of corticosteroid treatment for acute exacerbation of chronic obstructive pulmonary disease

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Abstract: Fractional exhaled nitric oxide (FeNO) is a promising biomarker of airway inflammation. Its predictive value for corticosteroid responsiveness during acute exacerbations of chronic obstructive pulmonary disease (AECOPD) remains unclear. To evaluate whether baseline FeNO levels predict corticosteroid treatment efficacy in hospitalized AECOPD patients. A total of 116 AECOPD patients were enrolled and stratified into high-FeNO (>25 ppb, n=45) and low-FeNO (≤25 ppb, n=71) groups. All received standard treatment including bronchodilators, anti-infectives, oxygen and 7-day intravenous corticosteroids. Biomarkers (CRP, eosinophils), arterial blood gases and COPD Assessment Test (CAT) scores were measured before and after treatment. The high-FeNO group showed significant reductions in CRP and $PaCO_2$ post-treatment ($p<0.001$), with a greater decline in CAT scores compared to the low-FeNO group ($p<0.001$). Eosinophil counts differed significantly between groups at baseline and post-treatment. Baseline FeNO >25 ppb predicts better corticosteroid responsiveness in AECOPD, supporting its utility as a practical biomarker for guiding steroid therapy and reducing overtreatment risks.

Keywords: Acute exacerbations; Chronic obstructive pulmonary disease; Corticosteroids; Efficacy; Fractional exhaled nitric oxide; Prediction

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD), a chronic respiratory condition characterized by persistent airflow limitation, represents a major global health burden due to its elevated prevalence and recurrent hospitalization rates (Christenson *et al*., 2022). The clinical trajectory of COPD is punctuated by acute exacerbations (AECOPD), critical events associated with accelerated pulmonary function decline and systemic complications that collectively heighten long-term mortality risks (Machado *et al*., 2023). While current management guidelines emphasize corticosteroid therapy as a cornerstone intervention for AECOPD mitigation, emerging evidence reveals significant heterogeneity in therapeutic responses (Lea *et al*., 2023). Clinical trials demonstrate that systemic corticosteroids (e.g., 40 $mg \cdot d^{-1}$ methylprednisolone for 5-7 days) can enhance FEV1 recovery and reduce hospitalization duration in moderate-to-severe cases (Koarai *et al*., 2024). However, indiscriminate administration may paradoxically increase risks of gastrointestinal symptoms (Hu *et al*., 2022), hyperglycemia(Golubic *et al*., 2025) and all-cause mortality (Rastoder *et al*., 2021), underscoring the urgent need for predictive biomarkers to optimize corticosteroid stewardship.

Fractional exhaled nitric oxide (FeNO), a non-invasive marker of eosinophilic airway inflammation, has garnered attention for its potential role in COPD phenotyping (Ragnoli *et al*., 2023; Rupani & Kent, 2022). The Chinese Expert Consensus on FeNO Applications in Airway Diseases highlights its diagnostic and therapeutic relevance in COPD management(Rutkowski *et al*., 2020). Recent investigations suggest FeNO levels may predict poor clinical outcomes in stable COPD cohorts (Keeratichananont *et al*., 2024; Liu *et al*., 2020), though current clinical practice predominantly prioritizes its established utility in asthma management(Bacharier *et al*., 2024). This critical knowledge gap regarding FeNO's prognostic value during AECOPD episodes remains unaddressed in contemporary literature.

This prospective cohort study aims to investigate the predictive capacity of baseline FeNO levels for corticosteroid treatment efficacy in hospitalized AECOPD patients. Through rigorous longitudinal assessment of clinical outcomes and inflammatory biomarkers, we seek to establish evidence-based thresholds for FeNO-guided corticosteroid therapy. Our findings may inform precision treatment algorithms to balance therapeutic efficacy against adverse effect risks, ultimately advancing personalized care paradigms in COPD exacerbation management.

MATERIALS AND METHODS

Subjects

The study involved a cohort of 116 AECOPD patients who

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were admitted to our hospital's Department of Respiratory Medicine from January 2022 to July 2023 and who met the specified inclusion and exclusion criteria. This group consisted of 70 males and 46 females, with ages ranging from 43 to 78 years and an average age of (62.48 ± 4.27) years. Prior to participation, all subjects were thoroughly briefed about the study and each provided written informed consent.

The inclusion criteria were as follows: (1) A confirmed COPD diagnosis, in accordance with the "2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD)"; AECOPD criteria were chiefly based on an acute onset pattern, characterized by the aggravation of respiratory symptoms beyond daily fluctuations, requiring additional treatment; (2) Absence of recent steroid or antibiotic therapies; (3) Stability of vital signs and normal liver and kidney functions; (4) Clear mental status and full consciousness, ensuring the smooth conduct of the study.

The exclusion criteria encompassed: (1) Patients unable to undergo FeNO testing; (2) Patients with contraindications to steroid treatment; (3) Presence of coexistent bronchial asthma, bronchiectasis, obstructive bronchiolitis, or other pulmonary disorders; (4) Individuals with infectious diseases, malignant tumors, or systemic infections; (5) A history of corticosteroid use within the 28 days preceding the study.

Treatments

Upon admission, all patients were assessed on the first day for fractional exhaled nitric oxide (FeNO) levels, complete blood count, C-reactive protein (CRP), arterial blood gases and COPD Assessment Test (CAT) scores. FeNO cutoff level of ≥ 25 parts per billion (ppb) has been suggested as a useful biomarker for predicting a response to anti-inflammatory treatment in patients with chronic respiratory symptoms (Castro *et al*., 2025; Lee *et al*., 2024). Based on their FeNO levels, patients were divided into two categories: a high FeNO group (FeNO > 25 ppb), including 45 cases and a low FeNO group (FeNO ≤ 25 ppb), comprising 71 cases. A standard regimen of treatment was applied to all patients, incorporating strategies such as bronchodilation, antispasmodic therapy, anti-infection measures and oxygen inhalation. This was supplemented with a 7-day intravenous corticosteroid therapy. Following the completion of the corticosteroid treatment, a thorough reevaluation was conducted, encompassing the FeNO levels, complete blood count, CRP, arterial blood gases and CAT scores. Statistical analyses were then carried out to explore the differences in CAT scores and other pertinent parameters before and after the treatment within the two distinct groups.

Observation indicators

(1) FeNO Measurement: On the day of testing, subjects were instructed to abstain from consuming alcoholic beverages, smoking and participating in strenuous exercise. For the measurement, they were guided to inhale deeply into the abdominal cavity, then align their mouths with the filter, followed by a gradual exhalation of lung gas until fully exhaled. Approximately one minute later, the corresponding reading was obtained using the FeNO measuring device.

(2) CAT Scoring: Subjects were assessed using the detailed criteria of the COPD Assessment Test (CAT) scale, allowing for a self-evaluation of their health status and quality of life in congruence with their personal experiences. The scale consists of 8 specific items, covering symptoms such as coughing, sputum production, chest tightness and sleep disturbances. Each item is rated on a scale of 0 to 5 points, culminating in a total possible score ranging from 0 to 40 points. The impact of COPD is categorized based on this score, with a mild impact corresponding to 0-10 points, moderate impact to 11-20 points, severe impact to 21-30 points and very severe impact to 31-40 points. Completion of the scale was conducted independently by each subject, ensuring an individualized and genuine assessment.

Statistical analysis

Statistical analysis was conducted using Statistic Package for Social Science (SPSS) 25.0 software (IBM, Armonk, NY, USA). Categorical data were summarized by frequency (n) and proportion (%), while continuous data that followed a normal distribution were presented as mean ($\bar{X}$) ± standard deviation (S). Comparisons between groups were performed using the t-test for normally distributed data. For data not adhering to a normal distribution, the median (M) and interquartile range ([P25, P75]) were utilized to represent the data and differences between the groups were analyzed employing the independent Mann-Whitney U rank-sum test. Comparisons within groups at two separate time points were examined through the Wilcoxon signed-rank test, while differences in categorical data between groups were evaluated using the chi-squared test. Correlation analysis involving two continuous variables that did not follow a normal distribution was achieved with Spearman's rank correlation and rank data were examined through Kendall's tau-b correlation. All tests were two-sided and a p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Comparison of baseline characteristics and FENO, FEV1 indicators between the two groups

No significant differences were detected between the two groups in terms of gender, age, disease duration, GOLD classification, hypertension and diabetes (P > 0.05).

However, notable differences were found in the eosinophil count, FeNO values and FEV1 between the two groups ($p < 0.001$). A subsequent Spearman correlation analysis focusing on the eosinophil count and FeNO values revealed

a positive correlation between these two parameters (r = 0.563, $p < 0.001$), as detailed in tables 1 and 2.

Analysis of antibiotic and bronchodilator utilization in both patient groups during treatment

A comparative examination of antibiotic and bronchodilator utilization during the treatment phase was conducted across both groups and the analysis revealed no significant differences ($p > 0.05$). Further details are provided in table 3.

Analysis of clinically relevant indicators before and after treatment within and among both patient groups

No marked differences were discerned in CRP, arterial blood carbon dioxide pressure (PaCO2) and CAT scores between the two patient groups prior to treatment ($p > 0.05$). Following treatment, neither group displayed statistically significant variations in CRP ($p > 0.05$). A within-group analysis in the high FeNO group uncovered a significant reduction in CRP post-treatment compared to pre-treatment levels ($p < 0.001$), while no meaningful change in CRP was observed in the low FeNO group ($p > 0.05$).

Both groups demonstrated a statistically notable difference in eosinophil counts pre and post-treatment ($p < 0.001$), but within-group comparisons revealed no substantial variations ($p > 0.05$). Furthermore, the differential in eosinophil counts between the groups pre and post-treatment remained statistically inconsequential ($p > 0.05$). After treatment, the high FeNO value group experienced a significant reduction in PaCO2 compared to before ($p < 0.001$), whereas the low FeNO value group showed no significant difference in PaCO2 post-treatment ($p > 0.05$). Post-treatment CAT scores did not diverge appreciably between the two groups ($p > 0.05$), though within the groups, both the high FeNO value group and the low FeNO value group exhibited a substantial decrease in CAT scores, a change that was statistically significant ($p < 0.001$). The variation in CAT scores before and after treatment between the two groups was likewise statistically meaningful ($p < 0.001$). Comprehensive details are presented in table 4.

DISCUSSION

COPD characterized by heterogeneous inflammatory endotypes, demonstrates divergent therapeutic responses depending on airway immune polarization(Choi, 2025). Current evidence indicates that COPD pathogenesis is predominantly driven by type 1 immunity (Th1/Tc1 axis), manifesting as neutrophilic inflammation in approximately 70-80% of cases (Barnes, 2016). However, 20-30% of patients exhibit concurrent type 2 inflammatory signatures, marked by eosinophil infiltration and upregulation of characteristic cytokines (Polverino & Sin, 2024). In this subtype, corticosteroid therapy demonstrates clinically meaningful benefits, reducing acute exacerbation frequency and attenuating FEV1 decline in longitudinal cohorts (David *et al*., 2021).

Blood eosinophil count (BEC) remains the most widely adopted biomarker for ICS responsiveness prediction. Meta-analyses of randomized controlled trials confirm that COPD patients with BEC ≥300 cells/μL achieve 20% greater exacerbation risk reduction with ICS-containing regimens compared to those below this threshold (Suissa *et al*., 2018). Nevertheless, substantial intraindividual BEC variability limits its clinical utility (Gibson, 2018). This biological fluctuation, influenced by circadian rhythms, infectious comorbidities and prior corticosteroid exposure undermines reliability in dynamic therapeutic decision-making (Benson *et al*., 2022).

These limitations have catalyzed investigations into next-generation biomarkers with improved phenotypic specificity. Parallel explorations of exhaled breath condensate biomarkers, show promising discriminatory capacity for identifying type 2-high COPD patients (Fuschillo *et al*., 2022; Maniscalco *et al*., 2024). Such advances may enable precision phenotyping to optimize corticosteroid stewardship in heterogeneous COPD populations.

Airway eosinophilic inflammation levels in those affected by chronic obstructive pulmonary disease may act as predictors for treatment outcomes, particularly in relation to steroid therapy. As an indicator of eosinophilic airway inflammation, blood eosinophils have been extensively studied and have demonstrated value in guiding the administration of inhaled corticosteroids during COPD's stable phase. The effectiveness of corticosteroids might be diminished in patients exhibiting lower blood eosinophil concentrations. However, employing blood eosinophils as a predictor of steroid response is not without challenges. A single patient may manifest marked fluctuations in eosinophil counts at various stages throughout the progression of the disease, adding an intricate dimension to the management of treatment.

Our study establishes FeNO as a significant predictor of corticosteroid responsiveness in AECOPD. Post-treatment analysis revealed marked reductions in systemic inflammatory markers (CRP) and respiratory parameters (PaCO2) specifically within the high-FeNO cohort (baseline FeNO ≥25 ppb), suggesting that FENO may become a potential predictive indicator for evaluating treatment responsiveness in AECOPD patients.

The observed biomarker dynamics align with FeNO's pathophysiological role in type 2 airway inflammation. Mechanistically, elevated FeNO levels correlate with eosinophil-mediated corticosteroid sensitivity, as evidenced by the significant CRP reduction reflecting systemic inflammation resolution in high-FeNO patients (Munuswamy *et al*., 2021). Concurrent PaCO2 normalization suggests improved alveolar ventilation, potentially attributable to corticosteroid-induced

Table 1: Comparison of baseline data and FeNO, FEV1 indicators between the two groups

Indicator	Admission FeNO value/ppb		$Z/t/\chi^2$	*P-value*
	≤ 25 (n = 71)	> 25 (n = 45)		
Gender				
Male	42 (59.2 %)	28 (62.2 %)	0.142	0.627
Female	29 (40.8 %)	17 (37.8 %)		
Age (years)	57.51 ± 5.27	55.74 ± 5.16	1.342	0.176
Disease course (years)	6.99 ± 1.67	7.02 ± 1.87	0.122	0.763
Gold classification	3.00 (3.00,4.00)	3.00(3.00,4.00)	-0.137	0.917
Hypertension				
Yes	34(47.9 %)	17(37.8 %)	0.603	0.437
No	37(52.1 %)	28(62.2 %)		
Diabetes				
Yes	19(26.8 %)	13(28.9 %)	0.035	0.853
No	52(73.2 %)	32(71.1 %)		
Eosinophils	0.07 (0.01,0.23)	0.30 (0.07,0.48)	-4.147	<0.001
FENO ($\mu g \cdot L^{-1}$)	21.45 ± 3.84	28.96 ± 4.57	5.431	<0.001
FEV1 (%)	59.71 ± 5.38	50.88 ± 5.16	8.302	<0.001

Table 2: Spearman correlation analysis between eosinophil count and FeNO value

Indicator	Admission FeNO value/ppb	
	r	*p*
Eosinophil Count /$10^9 \cdot L^{-1}$	0.563	< 0.001

Table 3: Analysis of Antibiotic and Bronchodilator Usage during Treatment in Both Groups

Drug Usage	Admission FeNO value/ppb		χ^2	*p-value*
Indicator	≤ 25 (n = 71)	> 25 (n = 45)		
Antibiotics			0.227	0.631
No	37 (52.1 %)	28 (62.2 %)		
Yes	34 (47.9 %)	17 (37.8 %)		
Bronchodilators			0.058	0.814
No	8 (11.3 %)	5 (11.1 %)		
Yes	63 (88.7 %)	40 (88.9 %)		

attenuation of small airway inflammation and mucus hypersecretion. While FeNO serves as a recognized marker for eosinophilic inflammation, its application in COPD management is not without limitations due to its non-exclusive specificity. Elevated FeNO levels can also result from increased nitric oxide production by airway epithelial cells, independent of eosinophilic activity (Escamilla-Gil *et al*., 2022). Given this complexity, it is imperative to consider additional biomarkers such as interleukin-6, which could offer complementary insights into the inflammatory processes at play in COPD (Dawson *et al*., 2021).

Notably, we also found that the high-FeNO cohort displayed lower baseline FEV1% predicted. This is consistent with the findings of Afriyie-Mensah *et al*., who found that the risk of abnormal FEV1% predicted was more than 5-fold increased when FeNO levels were high (< 50 ppb)(Afriyie-Mensah *et al*., 2024). The study of Zeng *et al*. also showed that elevated FENO 200 levels mainly indicated lung function impairment in patients with asthma and COPD, among which FENO 200 in COPD patients was negatively correlated with lung function parameters such as FVC, FEV 1, PEF, MMEF, MEF75 and MEF50 (Zeng *et al*., 2024). The dual role of FeNO in inflammation modulation warrants careful interpretation: while promoting bronchodilation via S-nitrosothiol pathways, excessive nitric oxide generation may exacerbate airway remodeling through protein tyrosine nitration and alveolar phospholipid degradation(Alqarni *et al*., 2023; Bayarri *et al*., 2021). This paradoxical activity underscores the importance of threshold-based FeNO interpretation, as our data indicate differential clinical outcomes below/above 25 ppb. Future studies should investigate whether FeNO-guided corticosteroid titration can simultaneously preserve lung function and mitigate exacerbation risks in this vulnerable population.

Our analysis also revealed differential patterns in patient-reported outcomes following corticosteroid therapy. While intergroup differences in CAT scores between high- and low-FeNO cohorts did not reach statistical significance

Table 4: Analysis of clinical relevant indicators before and after treatment among and within both patient groups.

Indicator	Before and After Treatment	Inpatient FENO value/ppb		*Z value*	*p-value*
		≤ 25 (n = 71)	> 25 (n = 45)		
CRP/mg·L^{-1}	Before	1.31 (1.12,5.87)	2.41 (1.47,5.12)	-1.562	0.137
	After	1.30 (1.34,3.14)	1.87 (0.46,3.12)	-0.427	0.573
	Difference	0.03 (0.01,0.76)	0.37 (0.12,2.89)	-1.364	0.274
	Z value	-2.654	-4.465		
	p value	0.012	< 0.001		
Eosinophils	Before	0.07 (0.01,0.23)	0.30 (0.07,0.48)	-4.147	< 0.001
	After	0.06 (0.03,0.21)	0.24 (0.17,0.48)	-5.726	< 0.001
	Difference	0.01 (0.03,0.02)	0.06 (0.04,0.09)	-2.017	0.029
	Z value	-1.835	-0.876		
	p value	0.076	0.274		
$PaCO_2$/mmHg	Before	43.45 (41.76,55.12)	46.21 (42.31,63.78)	-1.634	0.102
	After	42.87 (40.31,50.11)	45.72 (41.86,62.13)	-1.612	0.127
	Difference	0.87 (-0.67, 2.8)	2.17(0.46,5.13)	-2.012	0.043
	Z value	-2.146	-5.396		
	p value	0.041	< 0.001		
CAT Score	Before	20.00 (18.00,25.00)	23.00 (20.00,27.00)	-1.739	0.072
	After	20.00 (16.00,26.00)	20.00 (16.00,22.00)	-0.121	0.873
	Difference	1.00 (1.00,2.00)	3.00 (2.00,5.00)	-6.512	< 0.001
	Z value	-6.785	-5.376		
	p value	< 0.001	< 0.001		

post-treatment, both groups demonstrated clinically meaningful improvements from baseline. Notably, the high-FeNO group (≥25 ppb) exceeded the minimal clinically important difference threshold (≥3-point reduction) versus the low-FeNO cohort, suggesting differential therapeutic benefits aligned with baseline FeNO stratification (Kon *et al*., 2014). These findings corroborate earlier observations by Fan *et al*., who reported significant CAT score reductions in elderly AECOPD patients stratified by elevated FeNO levels (FeNO50/FeNO200) post-corticosteroid intervention(Fan *et al*., 2021). Similarly, Yamaji *et al*. demonstrated strong predictive validity of FeNO for CAT improvement (AUC=0.92, p<0.001) in symptomatic COPD cohorts, reinforcing FeNO's potential as a stratification biomarker (Yamaji *et al*., 2020). However, discordant observations by Su *et al*. in treatment-naïve COPD patients found no CAT score divergence between FeNO strata (cutoff 23.5 ppb), potentially attributable to population heterogeneity in corticosteroid-naïve versus pre-treated cohorts (Su *et al*., 2022).

Limitations of this study

This study has several limitations requiring careful interpretation: 1) The modest sample size and exclusion of patients ineligible for FeNO testing may introduce selection bias, potentially affecting result generalizability. 2) Smoking history-a known modifier of FeNO levels-was not systematically documented or adjusted for in analyses, raising concerns about residual confounding. Additional limitations include incomplete adjustment for clinical variables (e.g., concurrent infections, bronchodilator/ antibiotic use) that may modulate inflammatory responses may also introduce residual confounding, obscuring true treatment effect estimates. 3) Our use of literature-derived FeNO cutoffs, while evidence-based, may not fully account for population-specific variations in inflammatory phenotypes. 4) Reliance on subjective CAT scores rather than objective spirometric measures (e.g., FEV1 reversibility) could overestimate treatment effects due to recall bias. 5) Furthermore, the observational design without placebo controls limits causal inferences regarding corticosteroid efficacy. These constraints highlight the necessity for future multi-center randomized controlled trial incorporating standardized FeNO thresholds, smoking status stratification and lung function endpoints to establish clinical utility and optimize predictive algorithms for AECOPD management. At the same time, emphasis should also be placed on the simultaneous assessment of multiple biomarkers to improve the diagnostic accuracy of the inflammatory signature of COPD.

CONCLUSION

Our findings demonstrate that elevated baseline FeNO levels (>25 ppb) in AECOPD patients strongly correlate with eosinophilic airway inflammation and predict superior therapeutic responses to corticosteroids, evidenced by significant reductions in systemic inflammation and respiratory acidosis post-treatment. These results position FeNO as a clinically actionable biomarker for optimizing steroid therapy in AECOPD, enabling phenotype-specific treatment strategies to enhance efficacy while mitigating risks of non-targeted corticosteroid use.

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Authors' contributions
Yunxia Lin and Yuanyuan Liu designed the study. Yunxia Lin collected the data, Yuanyuan Liu analyzed the data. Yunxia Lin prepared the manuscript. All authors read and approved the final manuscript.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval
Ethical clearance for this investigation was granted by the Medical Ethics Committee of Nanjing Brain Hospital affiliated with Nanjing Medical University (approval ID: 2023NL-092-03), with written informed consent systematically acquired from all study participants or their legally authorized guardians.

Conflict of interest
No conflict of interest is associated with this work.

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