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Lack of Association between Inhaled Corticosteroid Use Based on the Exhaled Nitric Oxide and Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) is known to useful biomarker for detecting eosinophilic airway inflammation. However, there is a lack of evidence regarding the role of FeNO in chronic obstructive pulmonary disease (COPD). We aimed to assess whether elevated FeNO and its impact on treatment change into an inhaled corticosteroid (ICS)-containing regimen and association with acute exacerbation (AE) in patients with COPD.

Methods: We retrospectively analyzed 107 COPD patients without a history of asthma from March 2016 to December 2019. The patients whose FeNO value was more than 50 parts per billion (ppb) were defined into the high FeNO group. Multivariable analysis with logistic regression was used to identify factors associated with AE in COPD.

Results: The median FeNO value was 32 ppb (interquartile range, 19 to 45) and 34 (20.0%) patients were classified as high FeNO group (median 74 ppb). In the high FeNO group, changes in inhaler treatment into an ICS-containing regimen occurred in 23 of 34 patients after the measurement of FeNO. In multivariate analysis, high FeNO was not a contributing factor for AE, but only the high blood eosinophil count (≥300 cells/μL) was associated with AE (adjusted odds ratio, 2.63; 95% confidence interval, 1.01 to 6.91; p=0.049).

Conclusion: High FeNO value had a significant impact on the prescription of ICSs in COPD patients, but it did not show a significant association with AE either on its own or with changes in treatment.

Keywords: Chronic Obstructive Pulmonary Disease; Fractional Exhaled Nitric Oxide; Inhaled Corticosteroid; Exacerbation

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a combination of small airway disease and parenchymal destruction due to airway inflammation and remodeling[1]. Airway inflammation in COPD is generally thought to be primarily characterized by neutrophils and CD8+ lymphocytes. However, some

COPD patients exhibit a component of Th2-mediated airway inflammation[2] with increased numbers of eosinophils in lung tissue and sputum compared to healthy controls[3,4]. When these COPD patients experience frequent exacerbations, inhaled corticosteroids (ICS) are recommended in addition to long-acting bronchodilators[5]. Notably, higher blood eosinophil counts predict a greater response to ICS in several COPD randomized controlled trials[6-10].

Fractional exhaled nitric oxide (FeNO) serves as another useful biomarker for detecting eosinophilic airway inflammation because it is modestly associated with both sputum and blood eosinophils[11], and its measurement is simple and non-invasive. While FeNO measurement has not yet been officially endorsed as a diagnostic tool for asthma, it is widely utilized as a significant biomarker for eosinophilic inflammation in asthma due to its usefulness and value as a predictor of ICS initiation and response evaluation in numerous research[12-14].

Regarding COPD, several studies have reported that FeNO might predict the ICS response in COPD as well, but the role of FeNO in COPD remains controversial[15]. In addition, the utility of FeNO has been highlighted in asthma and partly in COPD with exacerbation. Therefore, our study aimed to assess whether elevated FeNO and its impact on treatment change into an ICS-containing regimen, and its association with acute exacerbation (AE) in COPD patients without a history of asthma in real-world clinics.

Materials and Methods

1. Study population

This study included only patients diagnosed with COPD who were measured for FeNO from March 2016 to December 2019 at two referral hospitals: Samsung Medical Center and Kangdong Sacred Heart Hospital. The definition of COPD was based on compatible medical history and fixed airflow limitation on spirometry (post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity ratio <70%)[5]. Patients previously diagnosed with asthma by a physician and those with lung cancer who underwent lung resection surgery were excluded. Patients without a recorded blood eosinophil value at the time of FeNO measurement were also excluded. All patients were followed up for at least 6 months after the FeNO measurement.

This study obtained approval from the Samsung Medical Center Institutional Review Board (IRB no. 2020-11-158). Informed consent was waived because patient information was de-identified and anonymized before the analysis.

2. Data collection

Baseline demographic data, smoking status, comorbidities, modified Medical Research Council (mMRC) dyspnea dyspnea scale, subjective wheezing, and patient-reported disease-related quality of life (QoL) status assessed by COPD assessment test score were collected by physicians using electronic case-report forms. Blood eosinophil count and FeNO were measured and baseline pulmonary function test results and the previous AE history within the last year were also recorded.

Prescribed inhaler regimens were reviewed before and after FeNO measurement. Moderate AE was defined as an acute worsening of respiratory symptoms that resulted in additional treatment with systemic steroids and/or antibiotics, while severe AE was defined as an AE leading to hospitalization[16].

3. Spirometry and FeNO measurement

Spirometry was performed using standardized equipment following the guidelines established by the American Thoracic Society (ATS) and the European Respiratory Society[17]. Predicted percentage values for the spirometry results were calculated using equation developed for Korean populations[18].

FeNO levels were measured according to ATS guideline recommendation[19]. Patients were instructed to inhale a maximum amount of air outside the valve, then exhale into the valve, which was connected to a chemiluminescent NO analyzer (NIOX MINO, Aerocrine AB, Solna, Sweden). Patients with FeNO values greater than 50 parts per billion (ppb) were classified as the high FeNO group in this study[20,21].

4. Statistical analysis

Data are presented as numbers (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. Continuous data between groups were compared using the Mann-Whitney test, and categorical data were compared using a chi-square test or Fisher's exact test. Multivariable analysis with logistic regression was conducted to identify independent factors associated with AE in COPD, fully adjusted for age, sex, smoking history, mMRC, FEV_1, history of AE, high FeNO, high blood eosinophil, and initiation of ICS-containing inhalers after FeNO measurement. Statistical differences were considered significant at $p<0.05$. All statistical analyses were performed using SPSS version 27 (IBM Co., Armonk, NY, USA).

Table 1. Baseline characteristics (n=170)

Variable	Total (n=170)	High FeNO (n=34)	Low FeNO (n=136)	p-value
Age, yr	69 (62–75)	70 (65–75)	69 (62–75)	0.419
Male sex	151 (88.8)	31 (91.2)	120 (88.2)	0.768
Body mass index, kg/m^2	23.5 (21.5–25.7)	23.3 (21.8–25.2)	23.7 (21.1–26.0)	0.649
Smoking history (n=167)				0.337
Never-smoker	23 (13.8)	3 (8.8)	20 (15.0)	
Ex-smoker	108 (64.7)	26 (76.5)	82 (61.7)	
Current smoker	36 (21.6)	5 (14.7)	31 (23.3)	
Pack-year (n=142)*	40 (27–50)	40 (22–50)	40 (30–50)	0.558
Comorbidity				
Previous history of TB/NTM	25 (14.7)	7 (20.6)	18 (13.2)	0.279
AR/Atopy/Drug allergy	26 (15.3)	11 (32.4)	15 (11.0)	0.002
Hypertension	64 (37.6)	13 (38.2)	51 (37.5)	0.937
Diabetes mellitus	34 (20.0)	8 (23.5)	26 (19.1)	0.565
Cardiovascular disease	23 (13.5)	4 (11.8)	19 (14.0)	1.000
Congestive heart failure	15 (8.8)	1 (2.9)	14 (10.3)	0.309
Cerebrovascular disease	10 (5.9)	2 (5.9)	8 (5.9)	1.000
Lung cancer	5 (2.9)	0	5 (3.7)	0.584
Other malignancy†	33 (19.4)	7 (20.6)	26 (19.1)	0.846
mMRC (n=141)				
≥Grade 2	34 (24.1)	5 (16.1)	29 (26.4)	0.239
Baseline CAT score (n=148)	16 (9–22)	13 (10–18)	17 (9–23)	0.199
Subjective wheezing	25 (14.7)	8 (23.5)	17 (12.5)	0.104
Baseline lung function				
Post-BD FVC, L	3.30 (2.84–3.95)	3.64 (2.98–4.12)	3.24 (2.78–3.80)	0.052
Post-BD FVC, %	81 (71–90)	85 (76–95)	79 (70–89)	0.074
Post-BD FEV_1, L	1.86 (1.46–2.27)	2.08 (1.60–2.41)	1.80 (1.42–2.17)	0.030
Post-BD FEV_1, %	65 (56–74)	69 (56–81)	64 (53–73)	0.033
FEV_1 <50%	31 (18.2)	4 (11.8)	27 (19.9)	0.275
Post-BD FEV_1/FVC	57 (49–62)	59 (54–62)	56 (48–63)	0.333
BDR positivity	32 (18.8)	5 (14.7)	27 (19.9)	0.492
DLco, % (n=68)	86 (72–96)	88 (78–96)	85 (68–97)	0.538
History of AE in previous 1 year				0.645
Yes	84 (49.4)	18 (52.9)	66 (48.5)	
Severe AE‡	16 (9.4)	2 (5.9)	14 (10.3)	0.742
Blood eosinophil count, cells/μL				
≥300 cells/μL	28 (16.5)	7 (20.6)	21 (15.4)	0.469
FeNO, ppb	32 (19–45)	74 (58–101)	25 (17–37)	<0.001

Values are presented as median (interquartile range) or number (%).
*Pack-year information of two ever smoker is unknown. †Prostate cancer (n=8), esophagus cancer (n=5), gastric cancer (n=5), bladder cancer (n=3), larynx cancer (n=3), rectal cancer (n=3), breast cancer (n=1), lymphoma (n=1), thymic carcinoma (n=1), thyroid cancer (n=1), renal cell carcinoma (n=1). ‡≥1 hospitalization.
FeNO: fractional exhaled nitric oxide; TB: tuberculosis; NTM: nontuberculous mycobacteria; AR: allergic rhinitis; mMRC: modified Medical Research Council; CAT: COPD assessment test; BD: bronchodilator; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; BDR: bronchodilator response; DLco: diffusing capacity for carbon monoxide; AE: acute exacerbation; ppb: parts per billion.

Results

1. Baseline characteristics

A total of 170 COPD patients were included in this study, with a median age of 69 (IQR, 62 to 75), and males accounting for 88.8%. Most of the patients (86.3%) were ex- or current smokers and had a mean smoking history of 40 pack-years. The mean FeNO value for all patients was 32 ppb (IQR, 19 to 45), and they were classified into the high FeNO group (n=34, 20%) and low FeNO group (n=136, 80%).

A comparison of baseline clinical features between the two FeNO groups is shown in Table 1. There were no significant differences in age, sex, body mass index, and proportion of ex- or current smokers and smoking pack-years between the two groups. Comorbidities such as allergic rhinitis, atopy, and drug allergy history were more prevalent in the high FeNO group than in the low FeNO group (32.4% vs. 11.0%, p=0.002). The severity of dyspnea and disease-related QoL status were similar, but post-bronchodilator FEV_1 was significantly higher in the high FeNO group. Previous exacerbation history did not differ between the groups, and the proportion of patients with blood eosinophil counts over 300 cells/μL also did not differ significantly (p=0.469).

2. Changes in treatment after FeNO measurement

The use of inhalers before and after FeNO measurement is presented in Table 2. In the high FeNO group, a higher proportion of patients did not use inhalers as maintenance treatment before the FeNO measurement (32.4% vs. 15.4%, p=0.024). Among those who received inhaler treatment before the FeNO measurement, there was no significant difference in the type of inhaler use between the two groups based on FeNO value. However, after FeNO measurement, long-acting muscarinic antagonist (LAMA)/long-acting beta-agonist (LABA) combined inhalers were more commonly prescribed to the low FeNO group (11.8% vs. 47.1%), and ICS-containing inhalers were used more frequently in the high FeNO group (88.2% vs. 44.8%).

In the high FeNO group, 11 (32.4%) patients were not on maintenance inhalers and started them after FeNO measurement. All 11 patients initiated treatment with an ICS-containing inhaler (four with triple therapy with ICS, LABA, LAMA; and seven with ICS & LABA or ICS & LAMA). In the low FeNO group, 21 (15.4%) patients were not on maintenance inhalers. After FeNO measurement, 17 patients started treatment and the other

Table 2. Changes in treatment after FeNO measurement (n=170)

Variable	Total (n=170)	High FeNO (n=34)	Low FeNO (n=136)	p-value
Treatment before FeNO measurement				
No treatment	32 (18.8)	11 (32.4)	21 (15.4)	0.024
LAMA or LABA	20 (11.8)	3 (8.8)	17 (12.5)	0.768
LAMA/LABA combined	74 (43.5)	11 (32.4)	63 (46.3)	0.142
ICS & LABA or ICS & LAMA	16 (9.4)	2 (5.9)	14 (10.3)	
Triple (ICS & LABA & LAMA)	28 (16.5)	7 (20.6)	21 (15.4)	
Any ICS use	44 (25.9)	9 (26.5)	35 (25.7)	0.930
Treatment after FeNO measurement				
No treatment	4 (2.4)	0	4 (2.9)	0.585
LAMA or LABA	7 (4.1)	0	7 (5.1)	0.347
LAMA/LABA combined	68 (40.0)	4 (11.8)	64 (47.1)	<0.001
ICS & LABA or ICS & LAMA	35 (20.6)	17 (50.0)	18 (13.2)	
Triple (ICS & LABA & LAMA)	56 (32.9)	13 (38.2)	43 (31.6)	
Any ICS use	91 (53.5)	30 (88.2)	61 (44.8)	<0.001
Changes in treatment after FeNO measurement	76 (44.7)	21 (61.8)	55 (40.4)	0.025
Newly started ICS	62 (36.5)	21 (61.8)	41 (30.1)	<0.001

Values are presented as number (%).
FeNO: fractional exhaled nitric oxide; LAMA: long-acting muscarinic antagonist; LABA: long-acting beta-agonist; ICS: inhaled corticosteroid.

four remained untreated. Among the 17 who started treatment, one was on LAMA, nine on LAMA & LABA, three on ICS & LABA or ICS & LAMA, and four on triple therapy. In the low FeNO group, less than half of those who initiated treatment (7/17, 41%) used an ICS-containing inhaler.

In the high FeNO group, a significant number of changes in inhaler prescriptions occurred. Before the measurement of FeNO, only nine (26.5%) patients used ICS-containing inhalers, but after the measurement, 30 (88.2%) patients used ICS-containing inhalers (Figure 1).

3. Risk factors related to follow-up AE of COPD

During the 6 months of the follow-up period, AE events occurred in 48 (28.2%) patients, and severe AE occurred in nine (5.3%) patients. Total moderate AE events and severe AEs developed in eight (23.5%) and one (2.9%) in the high FeNO group, and 40 (29.4%) and eight (5.9%) in the low FeNO group, respectively, without statistical significance. There were no significant differences in total AE events between ICS-containing inhalers and non-ICS-containing inhalers in both the low FeNO group and the high FeNO group (Figure 2).

The analysis of risk factors related to total AE is de-

Figure 1. Changes in inhaler use before and after fractional exhaled nitric oxide (FeNO) measurement. (A) Low FeNO group. (B) High FeNO group. Data are presented as number (%). ICS: inhaled corticosteroid.

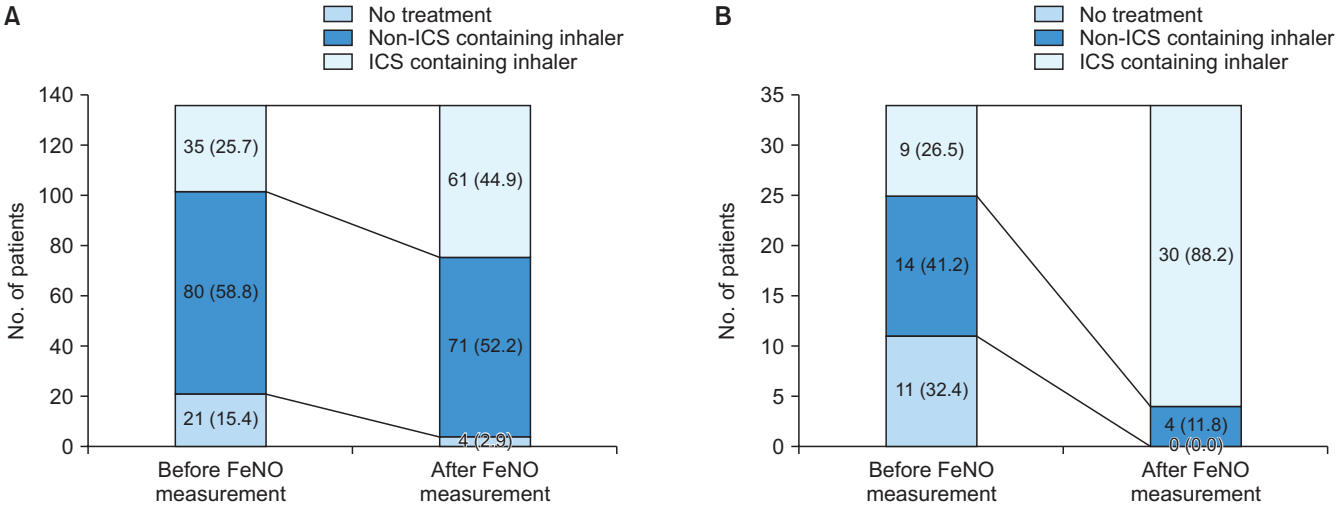
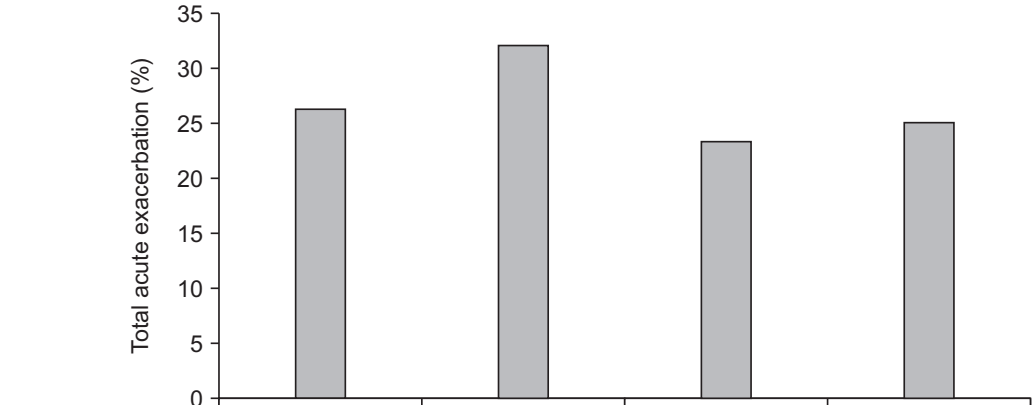


Figure 2. Total acute exacerbation events between inhaled corticosteroid (ICS)-containing inhaler and non-ICS-containing inhaler in both low fractional exhaled nitric oxide (FeNO) group and high FeNO group. Data are presented as percentage.



	Low FeNO		High FeNO	
Exacerbation (%)	26.2	32.0	23.3	25.0

Table 3. Risk factors associated with follow-up AE (n=170)

Variable	Univariable		Multivariable	
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
Age, yr	1.01 (0.98–1.05)	0.444	1.02 (0.98–1.07)	0.323
Male sex	2.26 (0.63–8.16)	0.211	3.00 (0.50–18.01)	0.230
Body mass index, kg/m^2	1.02 (0.97–1.07)	0.477	1.02 (0.97–1.08)	0.453
Smoking history, yes	1.48 (0.52–4.25)	0.464	0.93 (0.25–3.41)	0.910
mMRC ≥grade 2	0.71 (0.30–1.68)	0.436	0.59 (0.23–1.52)	0.271
Baseline FEV_1, %				
FEV_1 <50%	Reference		Reference	
FEV_1 ≥50%	0.95 (0.40–2.25)	0.913	0.68 (0.21–2.19)	0.520
History of AE in previous 1 year, yes	2.10 (1.06–4.16)	0.034	1.34 (0.62–2.91)	0.454
High FeNO (≥50 ppb)	0.74 (0.31–1.77)	0.497	0.51 (0.19–1.36)	0.175
High blood eosinophil (≥300 cells/μL)	1.84 (0.79–4.28)	0.159	2.63 (1.01–6.91)	0.049
Newly started ICS-containing inhalers	1.24 (0.63–2.44)	0.532	1.82 (0.81–4.07)	0.146

*Adjusted for age, sex, smoking history, mMRC, FEV_1, history of AE, high FeNO, high blood eosinophil, and newly started ICS-containing inhalers.
AE: acute exacerbation; OR: odds ratio; CI: confidential interval; mMRC: modified Medical Research Council; FEV_1: forced expiratory volume in 1 second; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid.

scribed in Table 3. In multivariable analysis, a high blood eosinophil count (≥300 cells/μL) was associated with an increased risk of total AE (adjusted odds ratio, 2.63; 95% confidence interval, 1.01 to 6.91; p=0.049). However, a high FeNO value was not found to be a significant risk factor for total AE in multivariable analysis. The initiation of ICS-containing inhalers after FeNO measurement did not demonstrate a significant effect on the occurrence of total AE.

Discussion

In our study, more than half of the COPD patients experienced a change in the inhaler prescription after FeNO measurement, particularly notable in the high FeNO group, where more ICS-containing inhalers were prescribed. However, we did not find a significant association between ICS use and the risk of exacerbation at 6 months based on the FeNO group. In addition, we found no significant impact of high FeNO on the risk of exacerbation, while high blood eosinophil count (≥300 cells/μL) was associated to an increased risk of exacerbation.

Although the basis of COPD treatment is inhaled long-acting bronchodilators, a considerable number of patients require ICS treatment concurrently. COPD is a heterogeneous disease, and as many as 30% to 40% of patients exhibit clinical signs of eosinophilic inflammation in either their blood or sputum[22]. Furthermore, the use of ICS-containing inhalers has shown a favorable response in terms of reducing exacerbations when patients have clinical features related to a high Th2-cell signature, including a previous history of asthma and objective parameters indicating eosinophilic airway inflammation[23,24]. Indeed, a blood eosinophil count ≥300 cells/μL has been reported as a significant predictor of a reduced risk of future exacerbation in response to ICS treatment in COPD[25] In this context, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations suggest adding ICS treatment to bronchodilators as initial treatment for patients with a high blood eosinophil (≥300 cells/μL) and an elevated risk of exacerbation[5,26]. However, although eosinophils in sputum or blood are regarded as promising biomarkers for eosinophilic airway inflammation and for predicting the effect of ICS, some limitations exist, including limited accessibility to technicians and potential variations in tests for sputum eosinophil measurement, and concerns about other disease leading to high blood eosinophils and reproducibility of measurements between tests of blood eosinophils[23,27,28]. FeNO is considered an alternative parameter for eosinophilic airway inflammation, but its clinical effectiveness has been highlighted primarily in asthma and partly in COPD, especially in exacerbation status[29,30]. The clinical evidence for the role of FeNO in stable COPD

is lacking because FeNO measurement is not mandatory in COPD assessment. Thus, there are no criteria for measuring FeNO in COPD patients, nor guidelines for prescribing ICS based on FeNO values. In a study of 160 stable COPD patients, FeNO was found to be highly correlated with findings of Th2 inflammation, including a history of asthma and subjective wheezing. However, the role of FeNO was only subsidiary in the use of ICS-containing inhaler treatment[31]. Due to the limited role of FeNO in COPD patients, clinicians may consider using ICS in COPD patients based on other clinical features rather than FeNO values.

In the present study, we assessed the association between FeNO values and ICS use and further examined the association with six-month exacerbation risk. FeNO values were measured using the same NO analyzers, NIOX MINO, in two hospitals, ensuring the reliability of the measured values according to the test methods. We demonstrated that more ICS was prescribed in the high FeNO group (≥50 ppb), but there were no significant results regarding exacerbation risk after ICS use in both the high FeNO group and low FeNO group. The possible explanations for the non-significant association between ICS use and exacerbation even in the high FeNO group might be a weak biomarker of FeNO representing eosinophilic inflammation in COPD patients because FeNO can be affected by age, gender, smoking, and dietary factors[32]. Another explanation can be the different mechanisms of FeNO elevation in COPD patients. The level of exhaled NO is usually increased and mediated by the inducible nitric oxide synthase enzyme, whose activity is elevated during certain inflammatory processes. Pedoto et al.[33] suggested that acidosis caused systemic hypotension and activated myeloperoxidase activity, which was associated with increased FeNO levels.

A single measurement could affect our results. In one prospective study, patients with COPD who consistently had FeNO values consistently higher than 20 ppb on at least two occasions showed a higher risk of AE[34]. However, in contrast to this study, our findings indicate that when the FeNO value measured once exceeded 20 ppb, there was no significant difference in AE compared to patients who never had a FeNO value exceeding 20 ppb. In our study, baseline FeNO was measured only once to assess its relationship with AE, similar to the results shown in the aforementioned study, and we found no significant association with AE development. Repeating FeNO measurements was not feasible due to the lack of coverage by health insurance and the test is not recommended as an essential diagnostic modality in COPD. Consequently, we were unable to identify patients with consistently elevated FeNO values. Thus, the association between a high FeNO value measured once and the risk of exacerbation may be limited in interpretation. Rouhos et al.[35] suggested that the short-term repeatability of FeNO measurements in COPD patients was comparable to that in healthy subjects. Further analysis of the effect of changes in the FeNO value beyond the minimum measurement changes and persistently elevated FeNO values in serial measurements on exacerbations will be needed.

Our study has several limitations. Firstly, due to its retrospective nature, we included patients with COPD irrespective of their smoking status and current use of ICS. These factors could potentially influence the level of FeNO[36]. Second, the measurement of FeNO in COPD is not deemed essential for diagnosis, assessing severity, or predicting future AE risk. We only included patients with FeNO values recorded during their initial assessment at referral hospitals, which might introduce selection bias. Third, since the FeNO values were measured only once in this study, we were unable to identify individuals with persistently high FeNO levels. Lastly, the small number of patients in each FeNO group may have resulted in insufficient statistical power to obtain clinically significant results.

In conclusion, our findings indicate that a high FeNO value influenced clinicians to prescribe more ICS in real-world clinics. However, we did not identify FeNO as a predictor or risk reduction strategy of exacerbation. Further studies are warranted to evaluate the effect of ICS use in patients with COPD based on FeNO measurement on prognosis, including the risk of AE.

Authors' Contributions

Conceptualization: Jo YS, Park HY. Methodology: Kim BG, Jo YS, Park HY. Formal analysis: Kim BG, Park HY. Data curation: Kim BG, Shin SH, Jo YS, Park HY. Software: Kim BG, Jo YS, Park HY. Validation: all authors. Investigation: Kim BG, Shin SH, Jo YS, Park HY. Writing - original draft preparation: Kim BG. Writing - review and editing: Shin SH, Jo YS, Park HY. Approval of final manuscript: all authors.

Conflicts of Interest

Yong Suk Jo is an editor of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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