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Risk Factors for Progression to Frequent Exacerbators in Stable Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Background: Little is known about the transition to frequent exacerbators in stabilized patients with chronic obstructive pulmonary disease (COPD).

Methods: This study utilized data obtained from the Korean COPD Subgroup Study cohort (KOCOSS), including 511 infrequent exacerbators. The outcome for these groups was progression to frequent exacerbators. Multivariable logistic regression analysis was used to investigate the risk factors for progression.

Results: Within 1 year, 40 patients (7.8%) progressed to frequent exacerbators. Among patients with severe airflow limitation and those who used inhaled corticosteroids (ICS), the incidence of progression was significantly higher. The risk factors for this progression were older age (adjusted odds ratio [aOR], 2.01; 95% confidence interval [CI], 1.19 to 3.39 per 10-year increase), decreased percent-predicted post-bronchodilator forced expiratory volume in 1 second (FEV_1 %predicted, aOR, 1.32; 95% CI, 1.05 to 1.66 per 10% predicted decrease), increased blood eosinophil count (aOR, 1.20; 95% CI, 1.07 to 1.35 per 100 cells/μL increase), and use of ICS-containing inhalers (aOR, 3.30; 95% CI, 1.59 to 6.85). In stratified analysis, decreased percent-predicted post-bronchodilator FEV_1 (aOR, 1.39; 95% CI, 1.05 to 1.85 per 10%pred decrease) and ICS-containg inhalers (aOR, 4.01; 95% CI, 1.61 to 9.95) predicted progression among patients with eosinophils <300/μL, while higher eosinophils ≥300/μL showed a nonsignificant trend (aOR, 1.16; 95% CI, 1.00 to 1.36; p=0.058).

Conclusion: Among stable COPD patients, older age, decreased lung function, an increased eosinophil count, and use of ICS-containing inhalers were associated with progression to frequent exacerbators.

Keywords: Chronic Obstructive Pulmonary Disease; Disease Progression; Prediction; Exacerbation; Eosinophil

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) plays a critical role in the management of chronic obstructive pulmonary disease (COPD)[1]. While AECOPD is life-threatening, it also contributes to the economic burden, lung function decline, physical deconditioning, and increased risk of future events[2,3]. Preventing AECOPD is essential to stabilize COPD. While bronchodilator inhalers are commonly used to maintain disease stability[4], a substantial number of patients experience recurrent exacerbations, despite periods of stabilization[5].

While a history of frequent exacerbations is the strongest predictor of future events, patients without recent exacerbations remain at risk[6]. Soriano et al.[7] found that only 70 % of patients in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) group A maintained their severity status over 5 years, and 4% even progressed to GOLD group D, based on GOLD 2017 severity stage. These instabilities in infrequent exacerbators were also found in randomized controlled trials (RCTs). A *post hoc* analysis of large, long-term RCTs found that 45% of patients without exacerbations in the previous year experienced exacerbations during treatment[8]. Furthermore, Flynn et al.[9] reported that approximately 5% of patients with low risk of exacerbation transitioned to a high-risk group within about 1 year, with these patients exhibiting higher risk of hospitalization and mortality. These findings highlight the need to identify how many patients, and which ones with infrequent exacerbations, are likely to exacerbate frequently in the future.

The latest GOLD guidelines have suggested initial pharmacologic treatment based on A/B/E classification and follow-up pharmacological treatment according to the dyspnea or exacerbation[10]. Unfortunately, for stabilized patients after initial treatment, there are no specific recommendations to maintain stable status. Given the current lack of understanding regarding the stability of COPD, it would be highly informative to investigate the transition from stable COPD patients to frequent exacerbators. Therefore, we evaluated the incidence and risk factors for becoming frequent exacerbators among COPD patients with infrequent exacerbations.

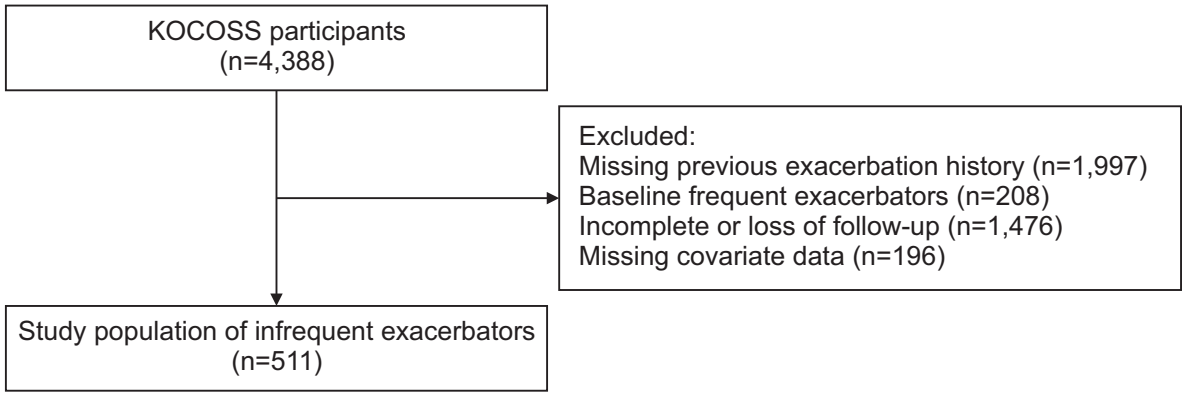
Materials and Methods

1. Study population

This study used data obtained from the Korean COPD Subgroup Study (KOCOSS) cohort, which is a multicenter, ongoing, registered prospective study (NCT02800499)[11]. More than 50 hospitals have participated since 2011, and participant recruitment is still in progress. In brief, the inclusion criteria for the KOCOSS study were patient aged 40 years or older with a COPD diagnosis confirmed by pulmonologist and spirometry, with fixed airflow obstruction, defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.7[12]. A trained nurse or doctor collected patient information using a complete case report form. At the baseline, detailed information was obtained, which included smoking status, frequency and severity of exacerbation within the previous year, and current COPD medications. Comprehensive assessments of the condition information since the last visit were performed every 6 months. This included a thorough history of exacerbations involving the use of antibiotics or steroids, outpatient department (OPD) visits, emergency room (ER) visits, or hospitalization. Studies have been published using KOCOSS data, and have described additional details[13-16].

Of 4,388 enrolled patients, 1,997 patients with frequent exacerbations at enrollment were excluded.

Figure 1. Flow chart of the study population. KOCOSS: Korean COPD Subgroup Study.



In addition, 1,597 patients with incomplete or no follow-up, and 283 patients with missing covariate data, were excluded. Finally, a total of 511 patients were included in the analytic cohort (Figure 1).

2. Frequent exacerbators

Patients were categorized as frequent exacerbators or infrequent exacerbators at the time of enrollment in the KOCOSS. Frequent exacerbators were defined as having experienced either ≥2 moderate exacerbations, or ≥1 severe exacerbation within the prior year[10]. A moderate exacerbation was defined as an event that necessitated the administration of steroids or antibiotics in the OPD. A severe exacerbation was defined as an ER visit or hospitalization due to worsening respiratory symptoms[17].

3. Outcome

The primary outcome was being classified as frequent exacerbator over a 1-year follow-up period. Physicians evaluated exacerbation events twice, at 6 and 12 months, respectively.

4. Covariates

Chronic bronchitis was defined as the presence of cough and phlegm for at least 3 months in each of 2 consecutive years[18]. Cardiovascular disease included heart failure and myocardial infarction. GOLD group B were defined as the modified Medical Research Council (mMRC) scale ≥2 points, or the COPD Assessment Test (CAT) score ≥10 points. Comorbidities were assessed using self-reported questionnaires. The Charlson comorbidity index (CCI) was used to determine the overall burden of comorbidities[19]. COPD was excluded from the CCI calculation.

5. Statistical analysis

As appropriate, data for continuous variables were expressed as the mean with standard deviation, or the median with interquartile range (IQR). Categorical variables were expressed as the number with percentage. Pearson's chi-square test was used to assess differences in progression incidence among subgroups. Multivariable logistic regression analysis was used to investigate the progression risk of becoming frequent exacerbator after a 1-year follow-up. To explore the effect of eosinophil on progression to frequent exacerbtor status, stratified analysis based on blood eosinophil count (300 cells/μL) was performed. Our study included demographic variables (age, sex, and body mass index [BMI]), smoking amount, known exacerbation risk factors (GOLD group B, previous history of one moderate exacerbation, lung function [FEV_1%predicted], and blood eosinophil count), inhaler medication, and the CCI in the multivariable model[20,21]. All analyses were performed using R version 4.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

6. Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. All hospitals involved in the KOCOSS cohort obtained approval from the Institutional Review Board (IRB), and obtained informed consent from their patients. Ethics approval for the study protocol was obtained from the IRB of Konkuk University Medical Center (IRB No. KHH1010338). All participants signed a written informed consent form to participate, and all data were completely anonymized prior to being accessed.

Results

1. Baseline characteristics

Table 1 describes the baseline characteristics. Among the 511 study patients, the median age was 69 years (IQR, 64 to 74). The proportion of males was 97.7%, and all patients were current or past smokers. Patients who progressed to frequent exacerbators had more dyspnea episodes at (55.0% vs. 22.7%, p<0.001) for mMRC ≥2, and lower FEV_1 at (51%pred vs. 65%pred, p=0.001) and FEV_1/FVC at (44% vs. 54%, p<0.001), whereas proportion of GOLD group B did not differ significantly (p=0.181). In addition, the pattern of medication use in these patients was significantly different (p<0.001). Most comorbidities were similar between the two groups. However, asthma was more prevalent in patients who progressed to frequent exacerbators (30.0% vs. 11.7%, p=0.002). No other significant differences were observed between the two groups in terms of age, sex, BMI, smoking status, chronic bronchitis, a previous history of one moderate exacerbation, blood eosinophil counts, or CCI.

2. Incidence of becoming frequent exacerbators

Figure 2 shows that after a 1-year follow-up, 40 patients (7.8%) in the entire cohort progressed to frequent exacerbators. Across FEV_1 strata (≥80%pred, 50%–79%pred, and <50%pred), the incidence was 4.7%, 6.1%, 14.2% (p=0.007). Regarding strata based on inhalers, the incidence was 2.8%, 5.0%, 12.9%, 17.0% for long-acting beta-2-agonist (LABA) or long-acting muscarinic antagonist (LAMA), LABA/LAMA, inhaled corticosteroid (ICS)/LABA, and ICS/LABA/LAMA, respectively (p<0.001). There was a tendency toward

Table 1. Baseline characteristics of the study population

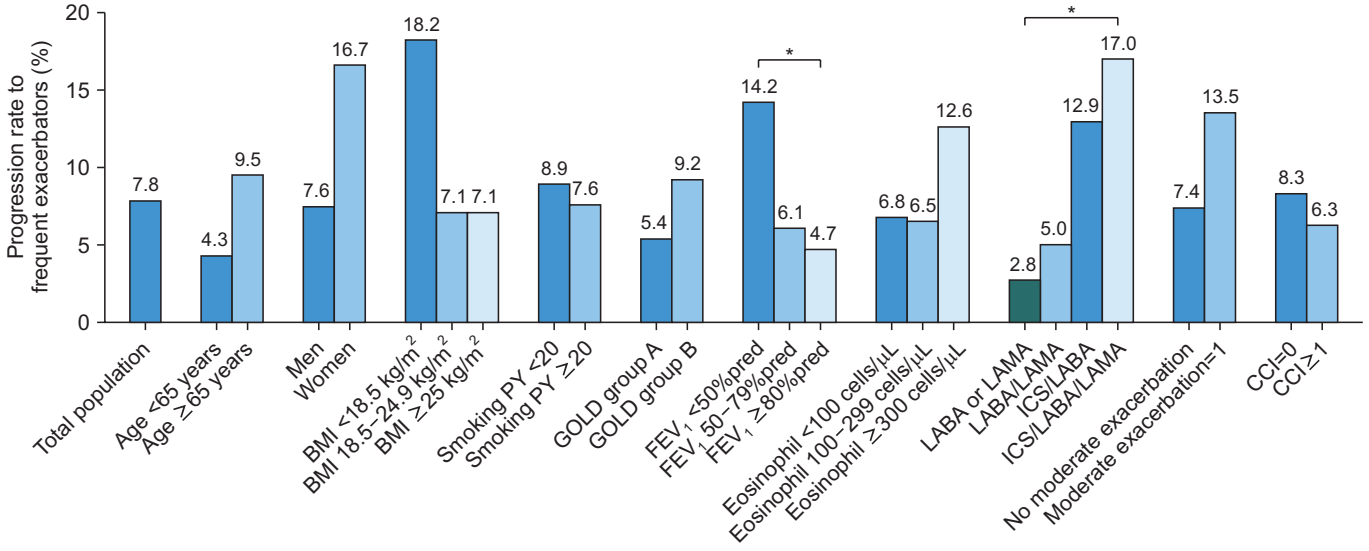
Characteristic	Total population (n=511)	Progression to frequent exacerbators		p-value
		No (n=471)	Yes (n=40)	
Age, yr	69 (64–74)	69 (63–74)	72 (67–74)	0.065
≥65	164 (32.1)	157 (33.3)	7 (17.5)	0.060
<65	347 (67.9)	314 (66.7)	33 (82.5)	
Male sex	499 (97.7)	461 (97.9)	38 (95.0)	0.542
BMI, kg/m^2	23.4 (21.2–25.6)	23.6 (21.3–25.7)	22.7 (20.3–25.1)	0.142
<18.5	33 (6.5)	27 (5.7)	6 (15.0)	0.073
18.5–24.9	322 (63.0)	299 (63.5)	23 (57.5)	
≥25	156 (30.5)	145 (30.8)	11 (27.5)	
Smoking status				
Ever smoker	511 (100)	471 (100)	40 (100)	
Amount, PY	38 (23–50)	38 (23–50)	36 (20–46)	0.699
<20	90 (17.6)	82 (17.4)	8 (20.0)	0.844
≥20	421 (82.4)	389 (82.6)	32 (80.0)	
Chronic bronchitis	45 (8.8)	40 (8.5)	5 (12.5)	0.570
Cough	61 (11.9)	55 (11.7)	6 (15.0)	0.713
Sputum	83 (16.2)	76 (16.1)	7 (17.5)	0.999
GOLD group B	327 (64.0)	297 (63.1)	30 (75.0)	0.181
Total CAT score ≥10	306 (59.9)	278 (59.0)	28 (70.0)	0.233
mMRC ≥2	129 (25.2)	107 (22.7)	22 (55.0)	<0.001
A previous history of one moderate exacerbation	37 (7.2)	32 (6.8)	5 (12.5)	0.308
Blood eosinophil count, cells/μL	154 (91–263)	153 (91–259)	168 (101–426)	0.099
<100	147 (28.8)	137 (29.1)	10 (25.0)	0.127
100–299	261 (51.1)	244 (51.8)	17 (42.5)	
≥300	103 (20.2)	90 (19.1)	13 (32.5)	
Lung function measurements				
Post-BD FVC, L	3.5 (3.0–4.1)	3.5 (3.0–4.1)	3.4 (2.8–3.8)	0.045
Post-BD FVC, %pred	84 (73–95)	84 (74–96)	83 (71–92)	0.207
Post-BD FEV_1, L	1.9 (1.4–2.4)	1.9 (1.4–2.4)	1.4 (1.0–2.0)	<0.001
Post-BD FEV_1, %pred	64 (50–77)	65 (51–78)	51 (36–65)	0.001
Post-BD FEV_1/FVC, %	53 (44–63)	54 (44–64)	44 (35–55)	<0.001
Medication				<0.001
LABA or LAMA	71 (13.9)	69 (14.6)	2 (5.0)	
ICS+LABA	70 (13.7)	61 (13.0)	9 (22.5)	
LABA+LAMA	282 (55.2)	268 (56.9)	14 (35.0)	
ICS+LABA+LAMA	88 (17.2)	73 (15.5)	15 (37.5)	

Table 1. Continued

Characteristic	Total population (n=511)	Progression to frequent exacerbators		p-value
		No (n=471)	Yes (n=40)	
Comorbidities				
Hypertension	200 (39.1)	183 (38.9)	17 (42.5)	0.776
Diabetes	72 (14.1)	66 (14.0)	6 (15.0)	>0.999
Dyslipidemia	82 (16.0)	77 (16.3)	5 (12.5)	0.679
Cardiovascular disease	30 (5.9)	27 (5.7)	3 (7.5)	0.944
Asthma	67 (13.1)	55 (11.7)	12 (30.0)	0.002
A history of TB	92 (18.0)	82 (17.4)	10 (25.0)	0.325
GERD	30 (5.9)	28 (5.9)	2 (5.0)	>0.999
CCI score				
≥1 point	126 (24.7)	118 (25.1)	8 (20.0)	0.603

Values are presented as median (interquartile range) or number (%).
BMI: body mass index; PY: pack-years; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; BD: bronchodilator; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; LABA: long-acting beta-2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; TB: tuberculosis; GERD: gastroesophageal reflux disease; CCI: Charlson comorbidity index.

Figure 2. Incidence of progression to frequent exacerbators. *Statistically significant. BMI: body mass index; PY: pack-year; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 second; LABA: long-acting beta-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; CCI: Charlson comorbidity index.



increased progression incidence among older patients, women, underweight patients (BMI <18.5 kg/m^2), those with GOLD group B, those with a high blood eosinophil count, and those with one moderate exacerbation; however, these trends did not reach statistical significance (p>0.05 for all).

3. Risk factors for becoming frequent exacerbators

Table 2 shows the multivariable logistic regression results for progression to frequent exacerbator. After adjusting for confounders, the following risk factors were identified: older age (adjusted odds ratio [aOR], 2.01; 95% confidence interval [CI], 1.19 to 3.39 per 10-year increase); decreased percent-predicted post-bronchodilator FEV_1 (aOR, 1.32; 95% CI, 1.05 to 1.66 per 10%

Table 2. Risk factors associated with progression to frequent exacerbators

	Total population (n=511)	
	OR (95% CI)	Adjusted OR (95% CI)
Age		
Per 10-year increase	1.52 (0.97–2.38)	2.01 (1.19–3.39)*
Sex		
Male	Ref.	Ref.
Female	2.43 (0.51–11.48)	2.52 (0.42–15.25)
BMI		
Per 1 kg/m^2 increase	0.93 (0.84–1.02)	0.98 (0.87–1.09)
Smoking amount		
Per 10 pack-years increase	1.07 (0.95–1.19)	1.03 (0.92–1.15)
GOLD classification		
A	Ref.	Ref.
B	1.76 (0.84–3.68)	0.80 (0.34–1.88)
A previous history of one moderate exacerbation		
No	Ref.	Ref.
Yes	1.96 (0.72–5.35)	0.96 (0.29–3.20)
Airflow limitation severity		
Per 10%pred decrease in post-BD FEV_1	1.38 (1.16–1.64)*	1.32 (1.05–1.66)*
Blood eosinophil count		
Per 100 cells/μL increase	1.16 (1.04–1.29)*	1.20 (1.07–1.35)*
Medications		
LABA or LAMA or LABA/LAMA	Ref.	Ref.
ICS/LABA or ICS/LABA/LAMA	3.77 (1.94–7.32)*	3.30 (1.59–6.85)*
CCI score		
0 point	Ref.	Ref.
≥1 point	0.75 (0.34–1.67)	0.62 (0.25–1.50)

In the multivariable model, age, sex, BMI, smoking status, GOLD classification, a previous history of one moderate exacerbation, airflow limitation severity, blood eosinophil count, medications, and CCI score were included.
*Statistically significant findings.
OR: odds ratio; CI: confidence interval; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; LABA: long-acting beta-2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; CCI: Charlson comorbidity index.

pred decrease); an increased blood eosinophil count (aOR, 1.20; 95% CI, 1.07 to 1.35 per 100 cells/μL increase); and the use of ICS/LABA or ICS/LABA/LAMA (aOR, 3.30; 95% CI, 1.59 to 6.85).

In the stratified analysis based on blood eosinophil count of 300 cells/μL, decreased post-bronchodilator FEV_1 %pred (aOR, 1.39; 95% CI, 1.05 to 1.85) and use of ICS/LABA or ICS/LABA/LAMA (aOR, 4.01; 95% CI, 1.61 to 9.95) were associated with the progression to frequent exacerbators in patients with blood eosinophil count <300 cells/μL (Table 3). On the other hand, blood eosinophil levels tended to increase the risk of progression to frequent exacerbators in patients with blood eosinophil count ≥300 cells/μL (aOR, 1.16; 95% CI, 1.00 to 1.36); however, statistical significance was not reached (p=0.058).

Discussion

The incidence of progression to frequent exacerbators was approximately 8% within 1 year among COPD patients with infrequent exacerbations in the preceding years. Significantly higher incidences were observed among patients with reduced lung function,

Table 3. Stratified analyses according to the blood eosinophil count

Variable	Blood eosinophil count <300 cells/μL (n=408)		Blood eosinophil count ≥300 cells/μL (n=103)	
	OR (95% CI)	Adjusted OR (95% CI)	OR (95% CI)	Adjusted OR (95% CI)
Age				
Per 10-year increase	1.03 (0.98–1.09)	1.05 (0.99–1.12)	1.08 (0.99–1.18)	1.11 (1.00–1.23)
Sex				
Male	Ref.	Ref.	-	-
Female	1.43 (0.18–11.58)	1.39 (0.12–15.77)	-	-
BMI				
Per 1 kg/m^2 increase	0.86 (0.76–0.97)*	0.91 (0.80–1.05)	1.09 (0.92–1.30)	1.11 (0.91–1.34)
Smoking amount				
Per 10 pack-years increase	1.09 (0.96–1.23)	1.01 (0.89–1.15)	0.99 (0.78–1.26)	1.00 (0.78–1.38)
GOLD classification				
Group A	Ref.	Ref.	Ref.	Ref.
Group B	2.56 (0.95–6.90)	0.93 (0.30–2.93)	0.97 (0.29–3.21)	0.53 (0.12–2.29)
A previous history of one moderate exacerbation				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.14 (0.26–5.09)	0.69 (0.14–3.42)	3.56 (0.79–15.99)	2.25 (0.30–16.78)
Airflow limitation severity				
Per 10%pred decrease in post-BD FEV_1	1.63 (1.29–2.04)*	1.39 (1.05–1.85)*	1.02 (0.75–1.38)	1.00 (0.66–1.54)
Blood eosinophil count				
Per 100 cells/μL increase	0.94 (0.54–1.65)	1.04 (0.56–1.90)	1.16 (1.00–1.34)*	1.16 (1.00–1.36)
Medications				
LABA or LAMA or LABA/LAMA	Ref.	Ref.	Ref.	Ref.
ICS/LABA or ICS/LABA/LAMA	5.12 (2.23–11.75)*	4.01 (1.61–9.95)*	2.00 (0.61–6.51)	3.08 (0.70–13.59)
CCI score				
0 point	Ref.	Ref.	-	-
≥1 point	0.90 (0.35–2.29)	1.13 (0.41–3.10)	-	-

In the multivariable model, age, sex, BMI, smoking status, GOLD classification, a previous history of one moderate exacerbation, airflow limitation severity, blood eosinophil count, medications, and CCI score were included for individuals with blood eosinophil count <300 cells/μL, whereas sex and CCI score were excluded for individuals with blood eosinophil count ≥300 cells/μL due to the limited number of patients.
*Statistically significant findings.
OR: odds ratio; CI: confidence interval; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; LABA: long-acting beta-2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; CCI: Charlson comorbidity index.

and among those using ICS-containing inhalers (either ICS/LABA or ICS/LABA/LAMA). Our study found that the increased risk for progression to frequent exacerbators was associated with older age, decreased lung function, an increased blood eosinophil count, and the use of ICS-containing inhalers.

Following the initial assessment, ongoing monitoring of COPD stability facilitates a more comprehensive management approach. This strategy may optimize treatment by evaluating the risk of future exacerbations based on exacerbation frequency and severity[5]. Currently, the GOLD guidelines do not specify criteria for escalating therapy in patients with infrequent exacerbations[10]. Although most patients with infrequent exacerbations remained stable in our study, approximately 8% transitioned to frequent exacerbations within 1

year. This suggest that COPD trajectories may differ based on patient-specific factors, even among patients stabilized with treatment. Despite apparent clinical stability, clinicians should remain vigilant for potential progression to frequent exacerbators in patients presenting with potential risk factors.

ICS use is a critical component in the management of COPD, although despite the existing guidelines, several issues remain open to debate[22,23]. Notably, in our study, both the use of ICS-containing inhaler and increased blood eosinophil count were associated with an increased risk of progression to frequent exacerbator status. However, inconsistent findings have been reported. Previous studies using the same cohort did not demonstrate the association between ICS use and exacerbation risk among patients in GOLD group A[14]. Another retrospective study from Turkey found that frequent exacerbators were more likely to use ICS, while blood eosinophil counts were also lower than for infrequent exacerbators[24].

Although causal relationships cannot be established, there are possible explanations for these discrepancies. First, study settings and populations were different among the studies. Second, the observational nature of the study may have affected the results. Clinicians may prescribe ICS for patients exhibiting worsening clinical manifestations, such as decreased lung function and exacerbated respiratory symptoms[25]. Therefore, ICS users were more likely to experience future exacerbations. Third, patients who became frequent exacerbators may be poor responders to ICS. A *post hoc* analysis of a randomized controlled study evaluating the effect of fluticasone propionate in patients with COPD demonstrated that changes in blood eosinophil counts following ICS use may predict clinical response to ICS therapy[26]. Supporting this interpretation, 25% of patients who became frequent exacerbators exhibited blood eosinophil counts greater than 300 cells/μL, despite the use of ICS. In summary, close monitoring of patients using ICS or increased blood eosinophil count remains essential, even after stabilization.

The limitations of this study to be acknowledged include first, that due to the relatively small sample size, it was not possible to assess various conditions associated with exacerbations, such as adherence to therapy and optimal peak inspiratory flow rate[27,28]. Second, as patients were recurited from referral hospitals, this approach could lead to selection bias. Third, most patients were men who smoked, which might reflect cultural background and the underdiagnosis of COPD in women[29,30]. Future studies on never smokers would be beneficial[31]. Fourth, the heterogeneity of COPD was not fully accounted for in this analysis, which may influence the interpretation of these findings[32]. Although patients with comorbid asthma were more likely to be frequent exacerbators, asthma-related factors were not fully captured to distinguish asthma-related exacerbations from those related to COPD. Fifth, only the Korean population was included in this study; therefore, our findings might not generalize to other populations in different settings[33].

Despite these limitations, our study has several strengths, which include the prospective assessment of exacerbations per protocol at 6 and 12 months following study enrollment, evaluation of variable factors that affected future exacerbations, and meticulous assessment of study participants by chest physicians.

In conclusion, among COPD patients with infrequent exacerbations receiving treatment, older age, decreased lung function, an increased eosinophil count, and use of ICS-containing inhalers were associated with progression to frequent exacerbators. Our findings suggest that when establishing treatment strategies after achieving COPD stability, these factors may be important.

Authors' Contributions

Conceptualization: Kim Y. Methodology: all authors. Formal analysis: Kim SH. Data curation: all authors. Funding acquisition: Yoo KH. Project administration: Yoo KH. Validation: all authors. Investigation: all authors. Writing - original draft preparation: Kim SH. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

Sang Hyuk Kim is an early career editorial board member of the journal, but he 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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