Respiration

Clinical Investigations

Respiration 2022;101:1078–1087
DOI: 10.1159/000525871

Received: February 23, 2022
Accepted: June 27, 2022
Published online: November 4, 2022

Risk Factors of Rapid FEV_1 Decline in a Real-World Chronic Obstructive Pulmonary Disease Cohort

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Keywords

Forced expiratory volume · Respiratory function tests · Risk factors · Chronic obstructive pulmonary disease · Cohort studies

Abstract

Background: Rapid forced expiratory volume in 1 s (FEV_1) decliners have been considered a unique subgroup of patients with chronic obstructive pulmonary disease (COPD). Rapid FEV_1 decline manifests early and is associated with poor prognosis. This necessitates the pre-emptive identification of risk factors for rapid FEV_1 decline. ***Objectives:*** We aimed to determine the risk factors and clinical outcomes in patients with COPD. ***Methods:*** This longitudinal, observational study was based on the Korea COPD Subgroup Study cohort (NCT02800499) from January 2012 to December 2019 across 54 medical centers in South Korea. Eligible patients were followed up for 3 years with serial spirometric tests. We calculated the annualized percentage change in FEV_1 from baseline. Rapid decliners were defined as the quartile of patients with the highest annualized percentage FEV_1 decline. ***Results:*** Of the 518 patients, 130 were rapid decliners who lost 6.2%/year and 100 mL/year of FEV_1. The multivariable logistic regression identified male sex, current smoking, blood eosinophil count <150/μL, and high forced vital capacity as the independent risk factors for rapid FEV_1 decline. Among rapid decliners, the lung function deteriorated more rapidly in current smokers and patients with severe dyspnea, while triple combination therapy attenuated lung function decline in comparison with mono-bronchodilator therapy. Rapid decliners had a higher rate of severe exacerbation than nonrapid decliners (0.2/year vs. 0.1/year, p value = 0.032). ***Conclusions:*** We identified the independent risk fac-

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tors for rapid FEV_1 decline. This information may assist physicians in the early detection and pertinent management of rapid decline among patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airway inflammation that induces mucus hypersecretion and alveolar wall destruction and contributes to small airway narrowing and deformity [1–3]. Airflow limitation is a hallmark of COPD. High levels of airway inflammatory mediators are significantly associated with a faster decline in forced expiratory volume in 1 s (FEV_1), which leads to progression of airflow limitation [4, 5]. The severity of airflow limitation has been graded by using the FEV_1 as a percentage of the predicted value and is positively related with symptomatic burden, exacerbation risk, hospitalization, and mortality [6–8]. Recently, inhaled pharmacotherapy for patients with COPD has played an important role in reducing the rate of decline in lung function and improving the clinical prognosis [9, 10].

The natural course of lung function change in COPD patients is heterogeneous and should be evaluated in consideration of individual clinical factors. Half of the patients with COPD exhibit an accelerated decline in lung function than healthy smokers or nonsmokers without COPD, while the other half exhibit impairment during lung development with normal rates of lung function decline [11]. Among patients with COPD, "rapid FEV_1 decliners" have been considered a unique subgroup, and a rapid FEV_1 decline was related with high rates of hospitalization and mortality [12]. As the rate of FEV_1 decline is reportedly at its peak in mild or early stage COPD [13, 14], early interventional strategies should be considered for rapid FEV_1 decliners.

Previous studies have identified risk factors for a rapid lung function decline in patients with COPD. Demographic risk factors included a higher age, a lower body mass index (BMI), a current smoker, and more severe dyspnea [12, 15]. Frequent exacerbation was an important risk factor for the rapid decline in lung function [16–18], especially in the COPD patients with high blood eosinophil counts [19]. However, most of these risk factors were derived without considering the relative change in lung function at each individual level. Few studies reported the relative decline of lung function (percentage change from baseline FEV_1 per year [%/year]) rather than reporting the absolute decline of lung function (FEV_1 milliliter per year [mL/year]). In addition, the real-world risk factors of rapid FEV_1 decliner in Asian patients with COPD have not been sufficiently elucidated. Our multicenter, longitudinal study was conducted to investigate the risk factors related to a rapid FEV_1 decline in Korean patients with COPD who underwent spirometric tests for 3 consecutive years.

Materials and Methods

Our study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement [20].

Study Design and Eligibility Criteria

In this longitudinal, observational study, we made use of the Korea COPD Subgroup Study (KOCOSS) cohort (NCT02800499), a prospective database consisting of patients diagnosed with COPD who were ≥40 years old and registered from January 2012 to December 2019 at 54 medical centers in South Korea. The methodologic information of the KOCOSS cohort was described in a previous study [21]. Diagnosis of COPD was established based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, using the spirometric criterion of a post-bronchodilator (BDR) FEV_1/forced vital capacity (FVC) ratio <0.7 [7]. The inclusion criteria were patients who (1) underwent spirometry at baseline examination and (2) were followed up with spirometry for 3 years.

Variables

All baseline variables were identified when patients were enrolled in KOCOSS cohort. At the initial assessment, we obtained the baseline information of the included patients. Detailed medical information included age, sex, BMI, years of education, area of residence, smoking status, Charlson comorbidity index (CCI), and history of lung disease (asthma and tuberculosis). CCI was generated by examining all baseline comorbidities and previous history of diseases at the time patients were enrolled. We evaluated baseline symptoms and quality of life with the COPD assessment test (CAT) score, St George's Respiratory Questionnaire for COPD Patients score, and the 6-min walking distance. We also recorded previous history of total and severe exacerbations.

The study participants underwent baseline spirometric, laboratory, and radiologic examination. In terms of spirometry, post-BDR FEV_1 and FVC (milliliter and % of the predicted value), bronchodilator reversibility (defined as an FEV_1 improvement from the predose value by 12% and >200 mL), diffusing capacity for carbon monoxide (DLCO) (%), DLCO/alveolar volume (%), and total lung capacity (milliliter and % of the predicted value) were obtained. In terms of laboratory tests, complete and differential counts were evaluated. In terms of radiology, structural abnormalities such as emphysema, bronchiectasis, and tuberculous-destroyed lung were evaluated. We investigated current medication use for COPD management, including inhaled pharmacologic therapy (e.g., long-acting beta-agonist [LABA], long-acting muscarinic antagonist [LAMA], LABA/LAMA, inhaled corticosteroids [ICSs]/LABA), phosphodiesterase-4 inhibitor, and methylxanthine.

Definition of Rapid Decliners

We divided the study participants into four quartiles of change in FEV_1. We determined the change of FEV_1 as an annualized percentage change from the baseline FEV_1 in each individual (online suppl. Information 1; for all online supplementary material, see www.karger.com/doi/10.1159/000525871) [12]. The group with the most negative change in FEV_1 (1st quartile) was defined as rapid decliners. The other quartiles (2nd, 3rd, and 4th quartiles) were defined as nonrapid decliners. For a sensitivity analysis, we used a different definition of rapid decliners as annual FEV_1 change < −60 mL/year [22].

Outcomes

As primary outcome, we evaluated risk factors of rapid FEV_1 decline. As secondary outcome, we compared clinical outcomes between rapid and nonrapid decliners including moderate or severe acute exacerbation and mortality over a 3-year follow-up.

In addition, sensitivity analyses evaluated the risk factors of rapid FEV_1 decline and clinical outcomes in two different conditions: (1) with a different definition of rapid decliner (annual FEV_1 change < −60 mL/year) and (2) after propensity score matching on sex and smoking status.

Statistical Analyses

Student's *t* test or the Wilcoxon rank-sum test was used to compare continuous variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. Univariable logistic regression analyses were conducted to find the variables related with rapid FEV_1 decline. Multivariable logistic regression analyses were performed with clinically important variables related to rapid FEV_1 decline. Clinically important variables included the variables with statistical significance in univariable analysis, and the clinical factors that have been reported to be related with lung function decline. A variance inflation factor >4.0 was determined as a significant multicollinearity. We obtained a slope estimate of the annualized percentage change of FEV_1 from baseline (%/year) for each clinically important confounder in rapid decliner using a multivariable linear mixed model. *p* values <0.05 were considered statistically significant. For statistical analyses, R statistical software, version 3.6.3 (R Core Team (2020), Vienna, Austria) was used.

Ethics

This study followed the principles of the Declaration of Helsinki. All included patients submitted their written informed consent at study enrolment. Ethical approval was obtained from the Institutional Review Board Committee of each participating medical center (Seoul National University Seoul Metropolitan Government [SNU-SMG] Boramae Medical Center IRB No. 06-2012-36).

Results

Of the 1,324 patients with baseline spirometric results, 518 (39.1%) were followed up with serial spirometric tests for 3 years. They included a higher proportion of patients with age ≥75, CCI ≥3, previous history of asthma, St George's Respiratory Questionnaire for COPD Patients ≥25, lower FVC or FEV_1, higher DLCO or blood eosinophil count compared to the patients who did not receive follow-up spirometric examination (online suppl. Information 2 and 3). During the follow-up for 3 years, median annualized percent change from baseline FEV_1 was −0.3%/year, and the median absolute change in FEV_1 was −4.2 mL/year. Among them, 130 patients met the definition of rapid decliners and the other 388 were classified as nonrapid decliners. Rapid decliners lost 6.2% and 100 mL of FEV_1 every year from their baseline lung function (Fig. 1). The annual lung function changes according to a blood eosinophil count in each quartile of change in FEV_1 were summarized in online supplementary Information 4.

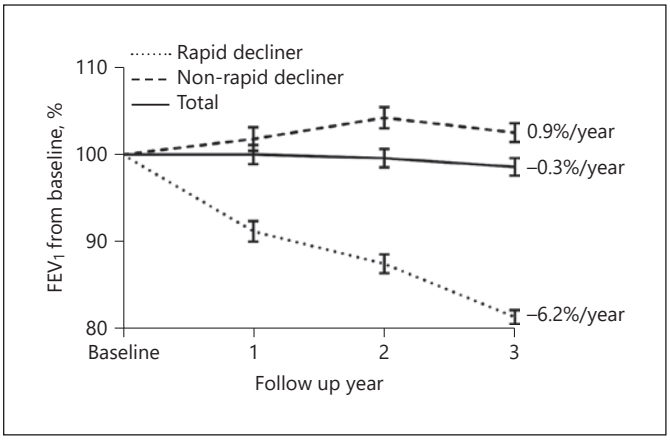

Fig. 1. Natural course of FEV_1 changes in rapid and nonrapid decliner. FEV_1, forced expiratory volume in 1 s. The annualized percent change of FEV1 from baseline (%/year) was estimated in total patients (solid line), rapid decliner (dotted line), and nonrapid decliner (dashed line) with linear regression model.

Baseline Characteristics and Clinical Features of Rapid and Nonrapid Decliners

At baseline, a higher proportion of men and current or ex-smokers were found in rapid decliners (Table 1). There were no significant differences in symptomatic burden or exacerbation history between rapid and nonrapid decliners.

In spirometric examination, we detected no significant differences in post-BDR FEV_1 or GOLD grade between rapid and nonrapid decliners (Table 2). However, a higher FVC and lower FEV_1/FVC, DLCO, and DLCO/alveolar volume values were detected in rapid decliners. In blood tests, there were no differences in white blood cell or differential count. Neither the blood neutrophil/lymphocyte ratio nor the proportion of

Table 1. Baseline demographic characteristics of rapid and nonrapid FEV_1 decliner in COPD patients

	Rapid decliner (n = 130)	Nonrapid decliner (n = 388)	p value
Age, years, mean (SD)	68.3 (7.4)	68.4 (7.1)	0.895
Age category, years, *n* (%)			
40–64	35 (26.9)	115 (29.6)	0.632
65–69	31 (23.8)	95 (24.5)	0.977
70–74	40 (30.8)	99 (25.5)	0.291
≥75	24 (18.5)	79 (20.4)	0.732
Male, *n* (%)	126 (96.9)	351 (90.5)	0.030
BMI, kg/m^2, mean (SD)	22.3 (3.1)	23.2 (3.3)	0.009
Smoking status, *n* (%)			
Never smoker	8 (6.2)	34 (8.8)	0.457
Ex-smoker	78 (60.5)	278 (71.8)	0.021
Current smoker	43 (33.3)	75 (19.4)	0.002
CCI, category, *n* (%)			
0	52 (40.0)	136 (35.1)	0.363
1–2 (mild)	45 (34.6)	134 (34.5)	1.000
≥3 (moderate to severe)	33 (25.4)	118 (30.4)	0.327
Previous history of asthma, *n* (%)	51 (39.2)	142 (36.6)	0.593
Symptoms and quality of life			
CAT score, mean (SD)	14.5 (7.6)	14.6 (7.51)	0.906
≥10, *n* (%)	96 (74.4)	273 (70.5)	0.464
SGRQ-C, mean (SD)	34.7 (21.4)	33.7 (20.3)	0.649
≥25, *n* (%)	78 (60.5)	232 (59.9)	1.000
6MWD, mean (SD)	384 (123)	384 (116)	0.982
Previous exacerbation history, *n* (%)			
Total	24 (18.8)	87 (22.5)	0.436
Severe	12 (9.4)	29 (7.5)	0.627

Data are expressed as mean (± standard deviation) or number (percentage). CAT, COPD assessment test; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; SD, standard deviation; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients; 6MWD, 6-min walking distance.

blood eosinophil counts ≥300/μL were significantly related with a rapid decline. Additionally, we discovered no association of radiologic abnormalities such as emphysema, bronchiectasis, and tuberculous-destroyed lung with a rapid decline.

Risk Factors Related to Rapid FEV_1 Decline

In the univariable logistic regression model, male sex, low BMI, being a current smoker, a blood eosinophil count <150/μL, a high FVC (%), a low DLCO (%), and use of LABA/LAMA were significant risk factors for rapid FEV_1 decline (Table 3). Multivariable logistic regression analysis showed that male sex (odds ratio [OR] = 3.25; 95% confidence interval [CI] = 1.10–9.65), being a current smoker (OR = 1.91; 95% CI = 1.17–3.10), a blood eosinophil count <150/μL (OR = 1.96, 95% CI = 1.05–3.57; compared to ≥300/μL), and a high FVC (%) (OR = 1.88, 95% CI = 1.37–3.13) were independent risk factors for rapid FEV_1 decline. Sensitivity analysis with a different definition of rapid decliners (annual FEV_1 change < −60 mL/year) showed similar results (online suppl. Information 5). After matching on sex and smoking status, a blood eosinophil count <150/μL (compared to ≥300/μL) and a high FVC (%) were independent risk factors for rapid FEV_1 decline (online suppl. Information 6).

Contributing Factors Affecting the Change of FEV_1 in Rapid Decliners

The factors contributing to an accelerated decline of FEV_1 in rapid decliners were current smoking (slope estimate = −2.98, p value = 0.039) and a high CAT score (slope estimate = −0.23, p value = 0.025) (Table 4). Conversely, taking a combination of inhaled treatments contributed to a rapid annual percentage improvement in FEV_1 from baseline. ICS/LABA/LAMA treatment yielded a statistically significantly favorable effect on the annualized percentage change in FEV_1 from baseline (slope estimate = 3.85, p value = 0.030).

Table 2. Baseline clinical features of rapid and nonrapid FEV_1 decliner in COPD patients

	Rapid decliner (n = 130)	Nonrapid decliner (n = 388)	p value
Baseline lung function			
Post-BDR FEV_1, L	1.6 (0.5)	1.6 (0.6)	0.511
Post-BDR FEV_1, % of predicted value	55.8 (17.2)	55.5 (17.4)	0.855
GOLD grade 1, *n* (%)	10 (7.7)	37 (9.5)	0.648
GOLD grade 2, *n* (%)	72 (55.4)	204 (52.6)	0.650
GOLD grade 3, *n* (%)	41 (31.5)	123 (31.7)	1.000
GOLD grade 4, *n* (%)	7 (5.4)	24 (6.2)	0.905
Bronchodilator reversibility,*n* (%)	17 (13.1)	55 (14.2)	0.868
Post-BDR FVC, L	3.3 (0.8)	3.1 (0.8)	0.001
Post-BDR FVC, % of predicted value	80.7 (16.5)	75.3 (15.3)	0.001
<80%, *n* (%)	61 (46.9)	243 (62.8)	0.002
Post-BDR FEV_1/FVC, *n* (%)	48.1 (11.2)	51.0 (11.8)	0.014
DLCO, % of predicted value	62.1 (20.6)	67.1 (20.4)	0.029
DLCO/VA, % of predicted value	72.4 (23.7)	80.5 (22.2)	0.002
TLC, L	5.7 (0.8)	5.5 (1.0)	0.248
TLC, % of predicted value	95.3 (12.7)	94.6 (14.6)	0.730
Laboratory test			
WBC, /μL, mean (SD)	7,351 (2,167)	7,524 (2,196)	0.474
Neutrophil, *n* (%), mean (SD)	60.6 (10.7)	60.1 (28.1)	0.868
Lymphocyte, *n* (%), mean (SD)	27.0 (8.9)	28.2 (9.4)	0.248
Neutrophil-lymphocyte ratio, mean (SD)	2.7 (1.9)	2.9 (4.9)	0.627
Eosinophil, *n* (%), mean (SD)	2.9 (2.7)	3.5 (3.8)	0.128
Eosinophil, /μL, mean (SD)	205 (196)	263 (332)	0.086
<150/μL, *n* (%)	54 (41.5)	135 (34.8)	0.201
150–199/μL, *n* (%)	13 (10.0)	41 (10.6)	0.986
200–299/μL, *n* (%)	43 (33.1)	122 (31.4)	0.812
≥300/μL, *n* (%)	20 (15.4)	90 (23.2)	0.078
Radiologic structural abnormality, *n* (%)			
Emphysema	45 (34.6)	128 (33.0)	0.690
Bronchiectasis	9 (6.9)	26 (6.7)	1.000
Tuberculous-destroyed lung	13 (10.0)	33 (8.5)	0.621
Treatment, *n* (%)			
No treatment	18 (13.8)	60 (15.5)	0.761
LABA monotherapy	5 (3.8)	19 (4.9)	0.801
LAMA monotherapy	36 (27.7)	128 (33.0)	0.310
LABA/LAMA combination	13 (10.0)	17 (4.4)	0.031
ICS/LABA combination	16 (12.3)	54 (13.9)	0.752
ICS/LABA/LAMA combination	42 (32.3)	110 (28.4)	0.456
PDE4 inhibitor	9 (7.3)	20 (5.4)	0.567

Data are expressed as mean (± standard deviation) or number (percentage). COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; PDE-4, phosphodiesterase-4; post-BDR, post-bronchodilator; SD, standard deviation; TLC, total lung capacity; VA, alveolar volume.

Clinical Outcomes

Rapid decliners exhibited a higher rate of severe exacerbations than nonrapid decliners (0.2/year vs. 0.1/year, p = 0.032, Table 5). Overall mortality did not differ between the groups. After matching on sex and smoking status, no significant difference in severe COPD exacerbation rate was found between the groups (online suppl. Information 7). In addition, there was no difference in

Table 3. Logistic regression model to evaluate the risk factors of rapid FEV_1 decline in COPD

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.00 (0.97–1.03)	0.930	1.00 (0.97–1.04)	0.869
Male	3.30 (1.15–9.45)	0.026	3.25 (1.10–9.65)	0.033
BMI	0.92 (0.86–0.98)	0.009	0.95 (0.88–1.03)	0.211
Current smoker	2.08 (1.33–3.24)	0.001	1.91 (1.17–3.10)	0.009
CCI (ref: 0)				
1–2	0.89 (0.56–1.42)	0.621	0.95 (0.57–1.57)	0.829
≥3	0.74 (0.45–1.22)	0.241	0.91 (0.53–1.59)	0.751
CAT score ≥10	1.21 (0.77–1.91)	0.399	1.18 (0.69–2.03)	0.545
SGRQ-C score ≥25	1.02 (0.68–1.54)	0.917	0.94 (0.57–1.57)	0.827
Any previous exacerbation history	0.79 (0.48–1.30)	0.354	0.60 (0.29–1.22)	0.155
Previous severe exacerbation history	1.27 (0.63–2.56)	0.511	1.91 (0.73–5.03)	0.188
Blood eosinophil (ref: <150/μL)				
150–200/μL	0.79 (0.39–1.59)	0.515	0.93 (0.44–1.96)	0.841
200–300/μL	0.87 (0.54–1.39)	0.556	0.94 (0.56–1.55)	0.800
≥300/μL	0.56 (0.31–0.99)	0.046	0.51 (0.28–0.95)	0.034
Baseline post-BDR FEV_1, % of predicted value (ref: ≥80%)				
≥50% and <80%	1.29 (0.61–2.74)	0.500	1.15 (0.50–2.65)	0.747
≥30% and <50%	1.23 (0.56–2.70)	0.600	1.18 (0.45–3.11)	0.739
<30%	1.08 (0.36–3.22)	0.891	0.92 (0.23–3.64)	0.906
Bronchodilator reversibility, positive	0.92 (0.51–1.64)	0.769	0.80 (0.43–1.48)	0.471
Baseline FVC, % of predicted value				
<80%	0.53 (0.35–0.79)	0.002	0.53 (0.32–0.88)	0.015
Baseline DLCO, % of predicted value	0.99 (0.98–1.00)	0.025	0.99 (0.98–1.00)	0.200
Inhaled therapy (ref: no treatment)				
LABA monotherapy	0.93 (0.30–2.85)	0.897	0.85 (0.26–2.79)	0.790
LAMA monotherapy	1.00 (0.52–1.92)	0.999	1.10 (0.55–2.22)	0.789
LABA/LAMA combination	2.70 (1.10–6.64)	0.031	2.61 (0.99–6.87)	0.052
ICS/LABA combination	1.05 (0.48–2.27)	0.910	1.13 (0.50–2.56)	0.775
ICS/LABA/LAMA combination	1.36 (0.71–2.59)	0.351	1.46 (0.71–3.02)	0.304

BMI, body mass index; CAT, COPD assessment test; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients; post-BDR, post-bronchodilator.

clinical outcomes between COPD patients with annual FEV_1 change < −60 mL/year and ≥ −60 mL/year (online suppl. Information 8).

Discussion

The present observational cohort study evaluated the change of FEV_1 as an annualized percentage change from the baseline FEV_1 in each individual and identified the risk factors of rapid FEV_1 decline in Korean patients with COPD over 3 years. Male sex, being a current smoker, a blood eosinophil count <150/μL, and a high FVC (%) were independent risk factors for rapid decliner. In rapid decliners, current smoking and a higher CAT score were significant negative effectors on the annualized percentage change of FEV_1 from baseline. Meanwhile, treatment with ICS/LABA/LAMA was associated with attenuation of annual decline of FEV_1 in rapid decliners. Rapid decliners exhibited a higher rate of severe exacerbations of COPD than nonrapid decliners, while 3-year overall mortality did not differ. However, after matching on smoking status, there was no difference in severe COPD exacerbation rate between the two groups. These results suggest that smoking may be a major factor influencing exacerbation risk in the rapid decliner. Therefore, the COPD patients at high risk for rapid FEV_1 decline may benefit from more frequent spirometric evaluation by

Table 4. Effect of clinical factors contributing to the annualized percent change of FEV_1 from baseline in rapid decliner

	Annualized percent change of FEV_1 from baseline, %/year	*p* value
Age	−0.05 (0.11)	0.631
Male	5.13 (3.26)	0.117
BMI	−0.29 (0.26)	0.252
Current smoker	−2.98 (1.43)	0.039
CCI ≥3	0.85 (1.68)	0.616
Blood eosinophil, /μL	−0.01 (0.01)	0.279
CAT score	−0.23 (0.10)	0.025
Severe exacerbation history within previous 1 year	−1.07 (2.10)	0.611
Baseline post-bronchodilator FEV_1, % of predicted value	−0.08 (0.06)	0.182
Baseline FVC, % of predicted value	0.11 (0.06)	0.055
Emphysema	0.55 (1.89)	0.772
Inhaled therapy for COPD (reference: LABA or LAMA monotherapy)		
LABA/LAMA	0.92 (2.48)	0.712
ICS/LABA	1.35 (2.69)	0.615
ICS/LABA/LAMA	3.85 (1.76)	0.030

The results of multivariable linear mixed-effect model were summarized as slope estimate %/year (standard error). BMI, body mass index; CAT, COPD assessment test; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

Table 5. Clinical outcomes of rapid and nonrapid FEV_1 decliner during 3-year follow-up period

	Rapid decliner (*n* = 130)	Nonrapid decliner (*n* = 388)	*p* value
Moderate exacerbation, *n* (%)	63 (48.5)	200 (51.5)	0.612
Annual rate of moderate exacerbation, /year	1.1 (1.6)	1.1 (1.6)	0.942
Severe exacerbation, *n* (%)	28 (21.5)	66 (17.0)	0.304
Annual rate of severe exacerbation, /year	0.2 (0.4)	0.1 (0.3)	0.032
Mortality, *n* (%)	1 (0.8)	4 (1.0)	1.000

Data are expressed as mean (± standard deviation) or number (percentage). COPD, chronic obstructive pulmonary disease.

early detection of rapid decliner. Rapid decliners would benefit from abstinence from smoking and symptomatic improvement with inhaled bronchodilators.

Many researchers, including Fletcher and Peto [23], evaluated the rate of FEV_1 decline in patients with COPD as absolute values (milliliter/year). Rapid decliners have previously been defined as patients with a decline in FEV_1 ≥40 [11, 24] or ≥60 mL/year [8]. In general, the annual rate of FEV_1 decline is larger in patients with early COPD with less pronounced airflow limitation [13, 14]. Considering that airflow limitation is increased by persistent airway inflammation in patients with COPD [1, 2], it is difficult to explain why the rate of decline in FEV_1 is at its highest in mild COPD. Interestingly, a study provided a clue for this paradoxical phenomenon. Although the rate of decline in absolute FEV_1 (milliliter/year) decreased as the COPD grade increased [14], when correcting for the baseline FEV_1, the relative rate of FEV_1 decline (percentage change from baseline/year) actually increased as the COPD grade increased [25]. In addition, it may not be appropriate to apply the same cut-off for absolute FEV_1 decline rate (milliliter/year) to COPD patients with different baseline lung volumes. In the patients with small lung volumes, even if the rate of decline in absolute FEV_1

is within the normal range, functional status can be significantly decreased with the worsened rate of relative FEV_1 decline [26]. Therefore, our study defined rapid decliners as the quartile of patients with the highest annual percentage of FEV_1 loss from the baseline value. In our multivariable analysis, the risk of rapid decliner was numerically higher in GOLD grade II, III, and IV compared to grade I. Our findings highlight the need of considering the baseline FEV_1 when evaluating the rate of FEV_1 decline in patients with COPD.

In our study, the annual rate of hospitalization due to COPD was higher in rapid decliners than in nonrapid decliners, although the causal relationship is not clear. The rate of FEV_1 decline may have been more rapid due to severe exacerbations, or there may have been more severe exacerbations in the high-risk group defined as rapid decliners. However, it should be noted that a rapid FEV_1 decline was not related with a previous history of exacerbations or symptomatic score, which are well-known predictive factors for exacerbations. Therefore, rapid decliners may be an independent subtype of COPD with poor prognosis. Indeed, in a cohort database compiled to evaluate the atherosclerosis risk, a rapid FEV_1 decline was related to severe exacerbation and mortality over 8 years of follow-up [12].

We demonstrated that the risk of rapid FEV_1 decline was higher in patients with COPD with a low blood eosinophil count (<150/μL) compared to those with a high blood eosinophil count (≥300/μL). In a recent study, patients with COPD with a blood eosinophil count ≥300/μL exhibited an accelerated decline in lung function [27]. This discrepancy may be explained by differences in the proportions of ICS users between that study and ours. In that study, the proportion of patients with a blood eosinophil count ≥300/μL was 24.3% and ICS was used by 14.6% [27], while the proportion with a blood eosinophil count ≥300/μL was 21.2% and ICS was used by 42.9% in our study. Importantly, in patients with COPD with a high blood eosinophil count, the use of ICS was reported to significantly reduce the rate of lung function decline, while FEV_1 decline was more rapid in patients not treated with ICS [19]. Meanwhile, a low blood eosinophil profile is related with a high bacterial burden [28] and emphysema progression [29]. In a recent study, low blood eosinophil counts <100/μL increased risk of pneumonia [30]. Further, a high risk of mortality was observed in COPD patients with a low blood eosinophil count [31, 32]. It was speculated that a low blood eosinophil count indicates a phenotype of COPD with neutrophilic inflammation [33]. Neutrophilic inflammation in COPD is related with a rapid lung function decline and a higher exacerbation rate [34, 35]. Therefore, patients with COPD with a low blood eosinophil count may be related to rapid lung function decline because of a poor response to ICS and susceptibility to neutrophilic inflammation.

In the general population, men have a larger lung volume and exhibit a more rapid FEV_1 decline than women [36]. In our study, men also had a higher risk of rapid decline. However, in another study, a higher proportion of rapid decliners was reported in the female compared to the male population [12]. This discrepancy implies that different factors influence the rate of lung function decline in each sex. In mild to moderate COPD, an accelerated rate of annual FEV_1 decline was related with smoking and obesity in men but with more severe airway obstruction in women [37]. Interestingly, menopause is related to a more rapid FEV_1 decline in the female population [38]. In patients with asthma, ICS treatment attenuates lung function decline to a lesser extent in women than in men [39]. Thus, the risk of rapid decliner should be determined separately in each sex by analyzing a larger COPD cohort.

In our study, ICS/LABA/LAMA treatment yielded a potential benefit in reducing the annualized percent change of FEV_1 from baseline compared to mono-bronchodilator therapy in rapid decliners. This outcome is consistent with the results of the TRINITY trial, in which ICS/LABA/LAMA treatment was superior to LAMA treatment alone in reducing the change in FEV_1 over 52 weeks [40]. A recent meta-analysis revealed the superiority of ICS/LABA/LMA treatment in improving trough FEV_1 (L) compared to mono-bronchodilator therapy [41]. In an expert review, triple therapy can be considered for treatment of COPD patients with a significant lung function decline [42]. However, it remains unclear whether ICS/LAMA/LABA treatment reduces lung function decline more than ICS/LABA or LABA/LAMA treatment in rapid decliner [43].

Our study had several strengths. First, this is a multicenter cohort study including a large number of patients with detailed clinical information in real-world setting. Therefore, the results of our study are generalizable to a broader group of patients or situations. Second, various sensitivity analyses were performed with different indexes for FEV_1 decline or medical conditions.

Our study has some limitations. First, although our study included all available COPD patients, sufficient sample size was not justified considering the proportion of clinical outcomes. Second, selection bias and immortal time bias cannot be excluded. As our patients were predominantly from tertiary teaching hospitals, patients

with COPD at high risk of a rapid FEV_1 decline were more likely to be included in the present study participants compared to general COPD population. In addition, our study did not include the patients who were censored at death during follow-up because their follow-up spirometric examination was not performed. Therefore, the risk of severe exacerbation or mortality might be underestimated in our study participants. Third, the progression of airflow limitation caused by the natural course of COPD is not the only factor that can affect the median rate of FEV_1 decline over 3 years. Although our study revealed that 47.9% of our patients had an annual increase in FEV_1, it would be unreasonable to say that their lung function actually increased every year because COPD is irreversible and progressive. When interpreting our results, one should bear in mind the initial improvement in FEV_1 that a patient exhibits when starting to use inhaled bronchodilators. Therefore, as in most previous studies, lung function needs to be followed up for at least 3 years to evaluate lung function decline [12, 14–19]. A longer term observational study is needed to obtain an approximation of the actual lung function decline rate in nonrapid decliner. Finally, we could not obtain data on longitudinal changes in clinical factors affecting lung function change, such as BMI, smoking, and exercise. In addition, our study could not evaluate other important longitudinal variables including the time since first diagnosis of COPD and the duration of inhaled therapy. Prospective studies need to be conducted in which such important clinical factors are longitudinally controlled.

Conclusion

Rapid FEV_1 decline was independently related with male sex, current smoking, a low blood eosinophil count (<150/μL), and a high FVC in COPD patients. Rapid decliner may benefit from smoking cessation and inhaled therapy for symptomatic improvement. Considering a higher rate of severe exacerbations, earlier detection and management for rapid decliner is necessary.

Statement of Ethics

This study followed the principles of the Declaration of Helsinki. All included patients submitted their written informed consent at study enrolment. Ethical approval was obtained from the Institutional Review Board Committee of each participating medical center (Seoul National University Seoul Metropolitan Government [SNU-SMG] Boramae Medical Center IRB No. 06-2012-36).

Conflict of Interest Statement

The authors declare no support from any organization interested with the submitted work, no financial relationship with any organization that might have an interest in the submitted work, and no other relationship or activity that could appear to have influenced the submitted work.

Funding Sources

This work was supported by the research program funded by the Korea National Institute of Health (Fund CODE 2016ER670100, 2016ER670101, 2016ER670102, 2018ER67100, 2018ER67101, 2018ER67102, and 2021ER120500).

Author Contributions

Hyun Woo Lee contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, and important intellectual content. Jung-Kyu Lee, Myung Goo Lee, Kyung-Chul Shin, Seung Won Ra, Tae-Hyung Kim, Yong-Il Hwang, and Ki-Suck Jung contributed to acquisition of data, critical revision of the manuscript, and important intellectual content. Kwang Ha Yoo contributed to acquisition of data, critical revision of the manuscript, important intellectual content, and acquisition of funding. Deog Kyeom Kim contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, important intellectual content, acquisition of funding, and study supervision.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (Deog Kyeom Kim) upon reasonable request.

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