Risk Factors of Rapid Lung Function Decline in COPD Patients of Real World

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Research

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Abstract

Background: Rapid lung function decliners have been considered a unique subgroup of patients with chronic obstructive pulmonary disease (COPD). A rapid decline manifests early and is related with a poor prognosis. Therefore, pre-emptive identification of risk factors for rapid decliner is necessary. We aimed to determine those risk factors in Korean patients.

Methods: A longitudinal, observational study was conducted on the KOCOSS cohort (NCT02800499), consisting of patients assessed from January 2012 to December 2019 at 54 medical centers in South Korea. Eligible patients were adults followed up for 3 years with serial spirometric tests. We calculated the annualized percentage change in lung function from baseline. Rapid decliners were defined as the quartile of patients with the highest annualized percentage decline in lung function.

Results: Among the 518 included patients, 130 were rapid decliners. Rapid decliners lost 6.2%/year and 100 ml/year of forced expiratory volume in 1 second from baseline. Rapid decliners had a higher rate of severe exacerbations than non-rapid decliners (0.2/year vs. 0.1/year, P=0.032). Upon multivariable logistic regression, male sex, being a current smoker, a blood eosinophil count <150/μl, and a high forced vital capacity were independent risk factors for a rapid decline. In rapid decliners, lung function deteriorated more rapidly in current smokers and patients with more severe dyspnea, while triple combination therapy attenuated lung function decline compared to mono-bronchodilator therapy.

Conclusions: Identification of risk and aggravating factors for rapid lung function decline may assist physicians in providing earlier intervention for high-risk patients with COPD.

Background

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). Higher levels of airway inflammatory mediators are significantly associated with a faster decline in forced expiratory volume in 1 second (FEV_1) than lower levels, which means a more severe airflow limitation (4, 5). Airflow limitation is a hallmark of COPD. 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, 7). 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 (8, 9).

However, the natural course of decline in lung function in COPD patients is heterogeneous and should be evaluated in consideration of individual clinical factors. Half of patients with COPD exhibit a more rapid decline in lung function than healthy smokers or non-smokers without COPD, while the other half exhibit impairment during lung development with normal rates of decline in lung function (10). Among patients with COPD, “rapid FEV_1 decliners” have been considered a unique subgroup, and a rapid FEV_1 decline is

related with high rates of hospitalization and mortality (11). As the rate of lung function decline is reportedly at its peak in mild or early-stage COPD (12, 13), early interventional strategies should be considered for rapid FEV_1 decliners.

Therefore, it is necessary to identify risk factors for a rapid lung function decline in patients with COPD. Besides demographic risk factors, including a higher age, a lower body mass index (BMI), being a current smoker, and more severe dyspnea (11, 14), frequent or acute exacerbation events are important risk factors for the rapid decline in lung function (15–17). Recent studies indicate that acute exacerbation and a rapid decline in FEV_1 are related with high counts of blood eosinophils (18). However, few researchers report the relative decline of lung function (percentage change from baseline FEV_1 per year [%/year]), rather reporting the absolute decline in lung function (FEV_1 ml per year [ml/year]). In addition, the real-world risk factors of being a 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.

Methods

Our study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (19).

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 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 (20). Diagnosis of COPD was established based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, using the spirometric criterion of a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio < 0.7 (7). The inclusion criteria were patients who 1) were ≥ 40 years old, 2) underwent spirometry at baseline examination, and 3) were followed up with spirometry for 3 years.

Baseline medical information and clinical outcomes

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). We evaluated baseline symptoms and quality of life with the COPD assessment test (CAT) score, St George's Respiratory Questionnaire for COPD Patients (SGRQ-C) score, and the 6-minute walking distance. We also recorded patients' 1-year history of total and acute exacerbations.

The study participants underwent baseline spirometric, laboratory, and radiologic tests. In terms of spirometry, post-bronchodilator FEV_1 and FVC (ml and % of the predicted value), diffusing capacity for carbon monoxide (DLCO) (%), DLCO/alveolar volume (VA) (%), and total lung capacity (ml 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 [ICS]/LABA), phosphodiesterase-4 inhibitor, and methylxanthine.

For evaluation of clinical outcomes, the 3-year total number of moderate or severe exacerbations, annual rate of moderate or severe exacerbations, and number of mortalities were recorded.

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 (Supplementary information 1) (11). The group with the most negative change in FEV_1 (1st quartile) were defined as rapid decliners. The other quartiles (2nd, 3rd, and 4th quartiles) were defined as non-rapid decliners.

Statistical analyses

Student's t-test or the Wilcoxon rank-sum test was used to compare continuous variables. The chi-square test or Fisher's exact test was used to compare categorical variables. Univariable and multivariable logistic regression analyses were performed with clinically important confounders related to rapid decliners. A variance inflation factor < 4.0 was determined as a significant multicollinearity. Sensitivity analysis was conducted in the rapid decliner group to obtain a slope estimate of the annualized percentage change of FEV_1 from baseline (%/year) for each clinically important factor 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. Their 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 non-rapid decliners. Rapid decliners lost 6.2% and 100 ml of FEV_1 every year from their baseline lung function (Figure 1). The annual lung function changes according to a blood eosinophil count in each quartile of change in FEV_1 were summarized in Supplementary information 2.

Baseline characteristics and clinical features of rapid and non-rapid decliners

At baseline, rapid decliners were predominantly men and current or ex-smokers (Table 1). There were no significant differences in symptomatic burden or exacerbation history between rapid and non-rapid decliners.

In terms of spirometric evaluation, we detected no significant differences in post-bronchodilator FEV_1 or GOLD grade between rapid and non-rapid decliners (Table 2). However, a higher FVC and lower FEV_1/FVC, DLCO, and DLCO/VA values were detected in rapid decliners. In terms of blood tests, there were no differences in white blood cell or differential count. Neither the blood neutrophil/lymphocyte ratio nor the proportion of 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. In terms of treatment for COPD, rapid decliners more commonly used LABA/LAMA than non-rapid decliners. Other pharmaceutical treatments did not differ between the groups.

In terms of clinical outcomes, rapid decliners exhibited a higher rate of severe exacerbations than non-rapid decliners (0.2/year *vs.* 0.1/year, P=0.032, Table 3), while overall mortality did not differ between the groups.

Risk factors related to rapid 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 decline (Table 4). Multivariable logistic regression analysis showed that male sex (odds ratio [OR]=3.32; 95% confidence interval [CI]=1.12-9.85), being a current smoker (OR=1.91; 95% CI=1.17-3.13), a blood eosinophil count <150/μl compared to (OR=1.96, 95% CI=1.04-3.57), and a high FVC (%) (OR=1.03, 95% CI=1.01-1.05) were independent risk factors for rapid decline.

Clinical factors affecting annualized percentage change of FEV_1 from baseline in rapid decliners

In rapid decliners, sensitivity analysis with a multivariable linear mixed model revealed a rapid annual percentage decline in FEV_1 from baseline in current smokers (slope estimate=-2.98, P=0.039) and in patients with a high CAT score (slope estimate=-0.23, P=0.025) (Table 5). 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=0.030).

Discussion

In the present observational cohort study, we identified that rapid FEV_1 decliners are a unique COPD subgroup by investigating the change in FEV_1 in Korean patients with COPD over 3 years. In this population, rapid decliners exhibited a higher rate of severe exacerbations of COPD than non-rapid decliners, while 3-year overall mortality did not differ. We revealed that male sex, being a current smoker, a blood eosinophil count < 150/μl, and a high FVC (%) were independent risk factors for a rapid FEV_1 decline. Whereas being a current smoker and being more symptomatic (a higher CAT score) were the most statistically significant negative effectors on the annualized percentage change of FEV_1 from baseline, taking a combination of inhaled medication, including ICS/LABA/LAMA, was associated with attenuation of that change in rapid decliners. We believe that these results give an important message to clinicians what should do for rapid decliners in COPD patients: abstinence from smoking and symptomatic improvement with combined inhaled bronchodilators should be considered the cornerstones in their treatment.

Many researchers, including Fletcher et al. (21), evaluated the rate of FEV_1 decline in patients with COPD as absolute values (ml/year). Rapid decliners have previously been defined as patients with a decline in $FEV_1 \geq 40$ (10, 22) or ≥ 60 ml/year (23). In general, the annual rate of FEV_1 decline is larger in patients with early COPD with less pronounced airflow limitation (12, 13). 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, the rate of decline in absolute FEV_1 (ml/year) decreases as the COPD grade increases (13); however, when correcting for the baseline FEV_1, the relative rate of FEV_1 decline (percentage change from baseline/year) actually increases as the COPD grade increases (24). In our study, we 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 higher than in GOLD grade II, III, and IV compared to grade I, although statistical significance was not found. Our findings highlight the need of considering the baseline FEV_1 values 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 than in non-rapid 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. 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 (11). Therefore, it should be elucidated whether rapid decliners are also a unique subtype of COPD in terms of a poorer prognosis.

In our study, 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 (25). 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% (25), 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 (18). Additionally, a low blood eosinophil profile is related with a high bacterial burden (26) and emphysema progression (27). Further, a high risk of mortality was observed in patients with COPD with a low blood eosinophil count (28, 29). One author speculated that a low blood eosinophil count indicates a phenotype of COPD with neutrophilic inflammation (30). Neutrophilic inflammation in COPD is related with rapid lung function decline and a higher exacerbation rate (31, 32). Therefore, patients with COPD with a low blood eosinophil count may constitute a subgroup 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 (33). 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 (11). This discrepancy implies that different factors influence the rate of lung function decline in each sex. In mild to moderate COPD, a higher rate of annual FEV_1 decline was related with smoking and obesity in men, but with more severe airway obstruction in women (34). Interestingly, menopause is related to a more rapid FEV_1 decline in the female population (35). In patients with asthma, inhaled corticosteroid treatment attenuates lung function decline to a lesser extent in women than in men (36). Thus, the characteristics of rapid decliners should be determined separately in each sex by analysing 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 (37). A recent meta-analysis revealed the superiority of ICS/LABA/LMA treatment in improving trough FEV_1 (L) compared to mono-bronchodilator therapy (38). In an expert review, triple therapy was recommended for treatment of patients with COPD with a significant lung function decline (39). However, it remains unclear whether ICS/LAMA/LABA treatment reduces lung function decline more than ICS/LABA or LABA/LAMA treatment (40).

Our study is subject to several limitations. First, a selection bias cannot be excluded in our study because our patients were predominantly from tertiary teaching hospitals. Therefore, patients with COPD at high risk of a rapid decline in lung function were more likely to be included in the present study. Second, 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. In particular, 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. A longer-term observational study is needed to overcome this limitation. Finally, we could not obtain data on longitudinal changes in other important clinical factors affecting lung function change, such as BMI, smoking, exercise, and inhalation therapy. Prospective studies need to be conducted in which longitudinal data of such factors are included.

Conclusions

A rapid FEV_1 decline was related to a higher rate of severe exacerbations. Male sex, being a current smoker, a low blood eosinophil count (<150/μl), and a high FVC % were independent risk factors for a rapid FEV_1 decline. Identification of such risk factors for rapid lung function decline may assist physicians in providing earlier interventions for patients with COPD at high risk.

Abbreviations

BMI, body mass index; CAT, COPD assessment test; CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; 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; OR, odds ratio; SGRQ-C, St George's Respiratory Questionnaire for COPD patients; VA, alveolar volume

Declarations

Ethics approval and consent to participate

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).

Consent for publication

Not applicable

Availability of data and materials

Data can be shared or provided upon reasonable request.

Competing interests

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 within the previous 3 years, and no other relationship or activity that could appear to have influenced the submitted work.

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Authors' contributions

Study concept and design: HWL, DKK

Acquisition of data: all authors

Analysis and interpretation of data: HWL, DKK

Drafting the manuscript: HWL

Critical revision of the manuscript and important intellectual content: all authors

Obtained funding: KHY, DKK

Study supervision: DKK

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Not applicable

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Tables

Due to technical limitations, table 1-5 is only available as a download in the Supplemental Files section.

Figures

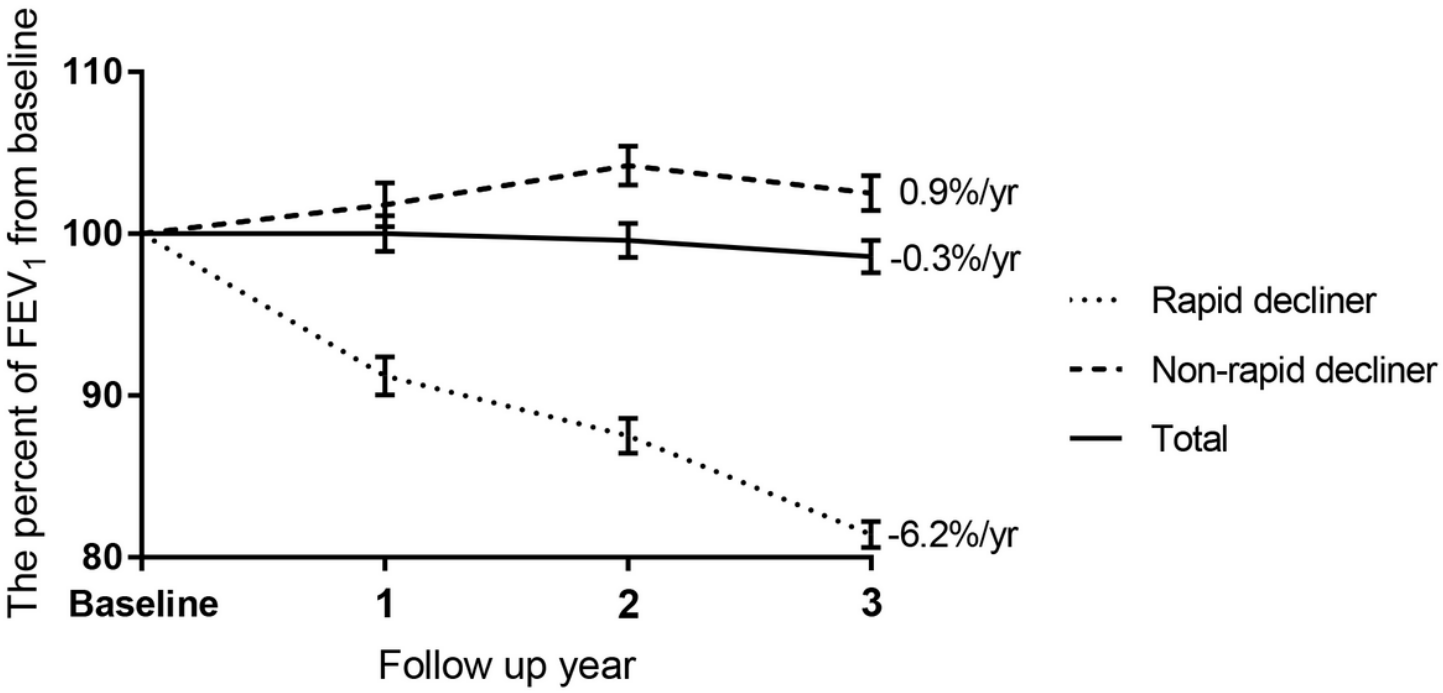

Figure 1

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- Table2RapidDeclinerClinicalfeautre20210608.pdf
- Table3RapidDeclinerClinicalOutcome20210525.pdf
- Table4Regressionanalysis20210525.pdf

- Table5Mixedeffectmodelanalysis20210525.pdf