

Age-related annual decline of lung function in patients with COPD

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Background: According to the Fletcher–Peto curve, rate of decline in forced expiratory volume in 1-second (FEV_1) accelerates as age increases. However, recent studies have not demonstrated that the rate of FEV_1 decline accelerates with age among COPD patients. The objective of the study is to evaluate annual rate of FEV_1 decline as age increases among COPD patients.

Methods: In this retrospective cohort study, we enrolled COPD patients who were followed up at two tertiary care university hospitals from January 2000 to August 2013. COPD was defined as post-bronchodilator (BD) FEV_1 /forced vital capacity (FVC) of <0.7 . All participants had more than two spirometries, including BD response. Age groups were categorized as follows: below versus above median age or four quartiles.

Results: A total of 518 participants (94.2% male; median age, 67 years; range, 42–90 years) were included. Mean absolute and predictive values of post-BD FEV_1 were 1.57 ± 0.62 L and $52.53\% \pm 18.29\%$, respectively. Distribution of Global initiative for Chronic Obstructive Lung Disease groups did not show statistical differences between age groups categorized by two different criteria. After grouping the population by age quartiles, the rate of FEV_1 decline was faster among older patients than younger ones whether expressed as absolute value (-10.60 ± 5.57 mL/year, -15.84 ± 6.01 mL/year, -18.63 ± 5.53 mL/year, 32.94 ± 6.01 mL/year, respectively; $P=0.048$) or predicted value ($-0.34\% \pm 0.19\%$ /year, $-0.53\% \pm 0.21\%$ /year, $-0.62\% \pm 0.19\%$ /year, $-1.26\% \pm 0.21\%$ /year, respectively, $P=0.010$).

Conclusion: As suggested conceptually by the Fletcher–Peto curve, annual FEV_1 decline among COPD patients is accelerated among older patients than younger ones.

Keywords: age, chronic obstructive lung disease, respiratory function tests

Introduction

Since the 1970s, the idea that forced expiratory volume in 1-second (FEV_1) decline accelerates with age has been generally accepted. Fletcher and Peto¹ suggested a model of lung function decline across the lifespan of an individual – the Fletcher–Peto curve. The Fletcher–Peto curve, which was obtained by extrapolating data from 792 men aged 30–59 years working in West London, showed that the rate of FEV_1 decline accelerates slightly with age. Another cohort study, including participants from six eastern and midwestern cities in the United States, reported that the annual rate of FEV_1 decline increased more rapidly with age in never smokers.²

Based on the Fletcher–Peto curve, FEV_1 decline among COPD patients typically occurs more quickly than FEV_1 decline among smoking non-COPD patients. At the same time, recent studies have showed the rate of FEV_1 decline is highly variable among COPD patients.^{3,4} The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study reported a wide range of annual change in FEV_1 , from a decrease of more than 40 mL to an increase of more than 20 mL, among COPD patients.⁴

Many factors contributing to rapid FEV₁ decline have been suggested among COPD patients. Previous studies reported that rates of decline were associated with smoking status,^{4,6} exposure to biomass,⁷ experience of acute exacerbation,^{4,5} bronchodilator (BD) reversibility,⁴ presence of emphysema,⁴ and body mass index (BMI).³ However, there is controversy about whether lung function decline accelerates with age among COPD patients, although age has been recognized as a factor contributing to rapid decline of FEV₁.

The ECLIPSE observational study did not demonstrate an increasing rate of FEV₁ decline with an increase in age among COPD patients.⁴ Another study reported that “rapid” decliners were significantly younger than “slow” decliners.³ More recent data showed a decline of lung function among younger patients with COPD was similar to that of older patients.^{8,9} However, these studies did not include patients with Global initiative for Chronic Obstructive Lung Disease (GOLD) stage I for FEV₁ decline analysis,^{3,4} nor did they include all ages of COPD patients. Moreover, previous studies compared “rapid” with “slow” decliners, defined by extremes of distribution among individual rates of decline.

Therefore, it is still unclear whether age is a real factor influencing the rate of FEV₁ decline among COPD patients. The objective of this study is to evaluate the differences of annual FEV₁ decline among COPD patients of different ages.

Materials and methods

Subjects

We enrolled the COPD patients who were followed up at two tertiary care university hospitals—the Seoul National University Hospital and Seoul National University Bundang Hospital—during the period from January 2000 to August 2013.

All COPD diagnoses were confirmed with spirometry, defined by post-BD FEV₁/FVC less than 0.7. The COPD patients above 40 years of age were included if they had performed more than two spirometries, including BD response, during follow-up. Patients with lung cancer or a history of lung resection surgery were excluded.

Study design

A retrospective cohort study was performed. The study was reviewed and approved by the Institutional Review Board of both institutions and was performed in accordance with Good Clinical Practice guidelines (IRB number: H-1309-107-523, B-1406/212-105). The IRB granted a waiver of informed consent for our retrospective study.

Demographic and clinical data were collected from medical records. Serial measurements of spirometric values were collected during follow-up period. Both absolute and

predicted values of spirometry were collected. The predicted values of FVC and FEV₁ were calculated by published formula for Korean people, because when compared with predicted values for Caucasian populations, the predicted values were comparable or higher.¹⁰ Positive BD responsiveness was defined as more than 12% increase in FEV₁, and more than 200 mL increase in FEV₁.¹¹

The participants were categorized according to age as follow: below versus above the median age or four quartiles. Primary outcome was annual decline rate of post-BD FEV₁ according to age, and secondary outcome was pre-BD FEV₁.

Additionally, we analyzed the annual decline rate of post-BD FEV₁ in subgroup of individuals who satisfied a post-BD FEV₁/FVC ratio below the lower limit of normal (LLN) due to concerns that some normal participants may be included in the older groups of this study when using fixed FEV₁/FVC ratio.¹²

Statistical analysis

Continuous variables are presented as means (\pm standard deviation [SD]), and categorical variables are expressed as relative frequencies and percentages. Age groups were compared using the chi-square test for continuous variables, or Student's *t*-test for categorical variables. A two-tailed *P*-value less than 0.05 indicated statistical significance. Annual changes in pre- and post-BD FEV₁ for each age group were assessed using a multilevel mixed-effects linear regression model. It was adjusted for sex, body mass index, smoking status (current smokers, former smokers, or never smokers), bronchodilator response, experience of acute exacerbation, and initial FEV₁.

Results

Study subjects

Five hundred and eighteen patients with COPD were enrolled. Baseline characteristics and lung function are shown in Table 1. Among 518 participants, 94.2% of patients were male, and their median age was 67 years (range, 42–90 years). Mean absolute and predicted values of post-BD FEV₁ were 1.57 \pm 0.62 L and 52.53% \pm 18.29%, respectively. On the basis of FEV₁ severity using GOLD grade,¹³ 8.7%, 44.8%, 37.3%, and 9.3% of patients distributed GOLD I, II, III, and IV, respectively. Mean duration of observation was 55.08 \pm 28.00 months. Mean frequency of pulmonary function test was 0.57 \pm 0.29/year.

Annual rate of FEV₁ decline in patients above versus below median age

To evaluate whether FEV₁ decline is accelerated among older COPD patients, we first categorized patients into two groups above and below the median age of 67 years. COPD patients

Table 1 Baseline characteristics: below versus above the median age of 67 years

	Total patients (n=518)	Younger patients (n=235)	Older patients (n=283)	P-value
Sex, male	488 (94.2)	225 (95.7)	263 (92.9)	0.173
BMI, kg/m ²	22.52±3.30	23.21±3.04	21.95±3.39	<0.001
Smoking status				
Current smoker	219 (42.3)	117 (49.8)	102 (36.0)	0.008
Former smoker	224 (43.2)	87 (37.0)	137 (48.4)	
Never smoker	33 (6.4)	14 (6.0)	19 (6.7)	
Unknown	42 (8.1)	17 (7.2)	25 (8.9)	
Pack-year	43.48±22.43	40.57±19.37	45.90±24.45	0.006
GOLD				0.848
I	45 (8.7)	24 (10.2)	21 (7.4)	
II	232 (44.8)	102 (43.4)	130 (45.9)	
III	193 (37.3)	85 (32.6)	108 (38.2)	
IV	48 (9.3)	24 (10.2)	24 (8.5)	
Post-bronchodilator				
FVC, L	3.32±0.84	3.59±0.85	3.10±0.77	<0.001
FVC, %	80.35±16.72	83.28±16.97	77.92±16.14	<0.001
FEV ₁ , L	1.57±0.62	1.74±0.67	1.43±0.53	<0.001
FEV ₁ , %	52.53±18.29	53.22±18.79	52.13±17.88	0.501
FEV ₁ /FVC, %	46.83±11.58	47.80±12.08	46.02±11.10	0.082
Pre-bronchodilator				
FVC, L	3.16±0.88	3.41±0.90	2.95±0.80	<0.001
FVC, %	76.53±17.83	79.06±18.45	74.43±17.05	0.003
FEV ₁ , L	1.46±0.62	1.62±0.69	1.33±0.52	<0.001
FEV ₁ , %	48.94±18.69	49.54±19.44	48.45±18.06	0.514
FEV ₁ /FVC, %	45.59±11.56	46.58±12.22	44.77±10.94	0.079
Positive BDR	24 (4.6)	10 (4.3)	14 (4.9)	0.709
History of acute exacerbation	174 (33.6)	63 (26.8)	111 (39.2)	0.003
Follow-up months	55.08±28.00	60.57±28.80	50.53±26.52	<0.001

Note: Data presented as mean ± SD or n (%).

Abbreviations: BDR, bronchodilator response; BMI, body mass index; FEV₁, forced expiratory volume in 1-second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease.

below the median age had lower BMI, more significant smoking history, and less experience of acute exacerbation than those above median age (Table 1). The distribution of FEV₁ severity by GOLD stage was not significantly different between two groups ($P=0.848$). Therefore, the annual rate of FEV₁ decline among the two groups was compared after adjustment of the following covariates: sex, height, BMI, smoking status, experience of acute exacerbation, presence of BD response, and initial FEV₁. Post-BD FEV₁ declined more rapidly among older patients (-13.01 ± 4.10 mL/year versus -25.04 ± 4.01 mL/year, respectively, $P=0.036$), even when expressed as the predictive value in FEV₁ ($-0.40\%\pm 0.12\%/year$ versus $-0.90\%\pm 0.12\%/year$, respectively, $P=0.003$). The rate of pre-BD FEV₁ decline was also faster among older patients, but less steep than that of post-BD FEV₁ (Table 2).

Annual rate of FEV₁ decline in quartiles of age

Next, participants were divided into quartiles based on age. The numbers and ages of patients within each quartile group

were as follows: Q1 (n=128, below 63 years), Q2 (n=107, 63–67 years), Q3 (n=141, 67–72 years), and Q4 (n=142, above 72 years). The distribution of FEV₁ severity by GOLD was not different between age groups ($P=0.490$) (Table S1). The annual rate of FEV₁ decline was also compared after adjustment of covariates. Annual decline in post-BD FEV₁ increased with increasing age, whether expressed as absolute value (-10.60 ± 5.57 mL/year, -15.84 ± 6.01 mL/year, -18.63 ± 5.53 mL/year, -32.94 ± 6.01 mL/year, respectively, $P=0.048$) or predicted value ($-0.34\%\pm 0.19\%/year$, $-0.53\%\pm 0.21\%/year$, $-0.62\%\pm 0.19\%/year$, $-1.26\%\pm 0.21\%/year$, respectively, $P=0.010$) (Table 3).

Annual rate of FEV₁ decline in subjects meeting the LLN criterion

Among 518 patients, 481 patients had post-BD FEV₁/FVC ratio below the LLN. When patients were categorized according to median age, there was a trend toward greater FEV₁ decline with age (-13.17 ± 4.19 mL/year versus -23.15 ± 4.13 mL/year, $P=0.062$) (Table 4). When

Table 2 Lung function decline: below versus above the median age of 67 years

	Unadjusted		Adjusted	
	Mean ± SE	P-value	Mean ± SE	P-value
FEV ₁ , mL/year				
Post-bronchodilator				
Younger	-12.60±3.56	0.021	-13.01±4.10	0.036 ^a
Older	-24.24±3.57		-25.04±4.01	
Pre-bronchodilator				
Younger	-6.45±3.53	0.009	-6.97±3.79	0.022 ^a
Older	-19.55±3.57		-19.22±3.79	
FEV ₁ , %/year				
Post-bronchodilator				
Younger	-0.42±0.11	0.004	-0.40±0.12	0.003 ^b
Older	-0.90±0.12		-0.90±0.12	
Pre-bronchodilator				
Younger	-0.22±0.12	0.001	-0.21±0.14	0.008 ^b
Older	-0.76±0.12		-0.74±0.14	

Notes: ^aAdjusted for sex, body mass index, smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁. ^bAdjusted for smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁.
Abbreviations: FEV₁, forced expiratory volume in 1-second; SE, standard error.

Table 3 Lung function decline according to age quartile

	Unadjusted		Adjusted	
	Mean ± SE	P-value	Mean ± SE	P-value
FEV ₁ , mL/year				
Post-bronchodilator				
Q1	-10.62±4.84	0.048	-10.60±5.57	0.048 ^a
Q2	-14.82±5.24		-15.84±6.01	
Q3	-19.71±4.71		-18.63±5.53	
Q4	-30.34±5.46		-32.94±6.01	
Pre-bronchodilator				
Q1	-4.99±4.78	0.029	-4.91±5.66	0.044 ^a
Q2	-8.17±5.21		-8.09±6.10	
Q3	-15.26±4.69		-13.78±5.45	
Q4	-25.45±5.50		-27.35±6.18	
FEV ₁ , %/year				
Post-bronchodilator				
Q1	-0.33±0.16	0.005	-0.34±0.19	0.010 ^b
Q2	-0.50±0.17		-0.53±0.21	
Q3	-0.68±0.16		-0.62±0.19	
Q4	-1.17±0.18		-1.26±0.21	
Pre-bronchodilator				
Q1	-0.18±0.16	0.002	-0.17±0.19	0.007 ^b
Q2	-0.28±0.17		-0.27±0.21	
Q3	-0.54±0.15		-0.47±0.18	
Q4	-1.04±0.18		-1.08±0.21	

Notes: The numbers and ages of patients within each quartile group were as follows: Q1 (n=128, below 63 years), Q2 (n=107, 63–67 years), Q3 (n=141, 67–72 years), and Q4 (n=142, above 72 years). ^aAdjusted for sex, body mass index, smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁. ^bAdjusted for smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁.
Abbreviations: FEV₁, forced expiratory volume in 1-second; SE, standard error.

Table 4 Annual rate of post-bronchodilator FEV₁ decline in subjects meeting the lower limit of normal criterion

	Unadjusted		Adjusted	
	Mean ± SE	P-value	Mean ± SE	P-value
According to median age				
FEV ₁ , mL/year				
Younger	-11.79±3.64	0.053	-13.17±4.19	0.062 ^a
Older	-21.83±3.68		-23.15±4.13	
FEV ₁ , %/year				
Younger	-0.39±0.12	0.017	-0.40±0.15	0.039 ^b
Older	-0.80±0.12		-0.83±0.14	
According to age quartile				
FEV ₁ , mL/year				
Q1	-10.62±5.22	0.113	-11.11±6.03	0.085 ^a
Q2	-12.87±5.05		-13.17±5.79	
Q3	-17.40±4.80		-16.67±5.47	
Q4	-28.12±5.70		-31.43±6.28	
FEV ₁ , %/year				
Q1	-0.33±0.17	0.021	-0.34±0.21	0.023 ^b
Q2	-0.50±0.17		-0.46±0.20	
Q3	-0.60±0.16		-0.55±0.19	
Q4	-1.08±0.19		-1.20±0.22	

Notes: The numbers and ages of patients within each quartile group were as follows: Q1 (n=107, below 62 years), Q2 (n=115, 62–67 years), Q3 (n=133, 67–72 years), and Q4 (n=126, above 72 years). ^aAdjusted for sex, body mass index, smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁. ^bAdjusted for smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁.
Abbreviations: FEV₁, forced expiratory volume in 1-second; SE, standard error.

FEV₁ was expressed as a percentage of the predictive value, post-BD FEV₁ declined more rapidly in older patients (-0.40%±0.15%/year versus -0.83%±0.14%/year, respectively, *P*=0.039). Dividing participants into quartile groups based on age demonstrated consistent results whether expressed as absolute value (-11.11±6.03 mL/year, -13.17±5.79 mL/year, -16.67±5.47 mL/year, -31.43±6.28 mL/year, respectively, *P*=0.085), or predicted value (-0.34%±0.21%/year, -0.46%±0.20%/year, -0.55%±0.19%/year, -1.20%±0.22%/year, respectively, *P*=0.023).

Discussion

Previous studies showed an accelerated decline in FEV₁ with age among healthy participants. A prospective epidemiological study by Fletcher and Peto,¹ which evaluated 1,136 working men aged 35–59 years over an 8-year follow-up period, demonstrated that FEV₁ falls gradually over a lifetime, and the rate of FEV₁ decline accelerates slightly with age. Ware et al² reported that annual rate of FEV₁ decline was higher among elderly non-smokers: 12.9 mL/year at age 25 years versus 58.2 mL/year at age 75 years. In more recent cross-sectional and longitudinal studies, an accelerated decline in FEV₁ with age was also reported in never-smoker patients.^{14,15}

Sandford et al¹⁶ reported that among smokers, rapid decline was associated with older age compared with non-decline. These results suggest an accelerated decline of FEV₁ with aging among non-COPD patients.

Thus, it can be speculated that decline of FEV₁ among COPD patients is also accelerated with age. However, it has not been clear whether FEV₁ is also accelerated among aged COPD patients compared with young COPD patients. Recent studies have not demonstrated that the rate of FEV₁ decline accelerates with age among COPD patients. Casanova et al³ defined decliners with significant slope as patients showing a statistically significant annual loss of FEV₁ (−86 mL/year; 95% confidence interval, −32 to −278 mL/year) and decliners with nonsignificant slope as those who demonstrated a nonstatistically significant annual FEV₁ decline (−28 mL/year; 95% confidence interval, +9 to −214 mL/year). They demonstrated that rapid decliners with significant slope were younger, compared with nonstatistically significant slope decliners (64±9 years versus 66±9 years, $P=0.018$, respectively). However, unlike our study, they categorized participants according to the rate of FEV₁ decline and not by age, which may have affected the results. In addition, the proportion of decliner with significant slope was small (18%), and the range of annual rate of FEV₁ decline in our study was approximately 10–33 mL/year, which is much lower than that of significant slope decliners in the previous study. These factors may also have influenced the results. Furthermore, Casanova et al³ also reported that rapid decliners had a lower BMI and better lung function at baseline. However, after multivariate logistic regression including age, sex, pack-years, smoking habit, comorbidity, and annual hospital exacerbation rate, higher level of FEV₁ and low BMI at baseline were the only two independent and significant predictors of FEV₁ decline and they failed to show association between age and FEV₁ decline.

In contrast, Nishimura et al⁸ reported that mean age was not significantly different between rapid decliner and slow decliner (69±6 years versus 70±8 years, $P=0.11$, respectively). This trial had limitation and categorized all patients into only three groups by rate of FEV₁ decline. Vestbo et al⁴ reported that age was not associated with the rate of decline of FEV₁ in the ECLIPSE cohort. However, this study did not include COPD patients with GOLD stage I disease. A more recent study evaluated progression of FEV₁ among younger (≤55 years) and older (≥65 years) COPD patients.⁹ They reported that average annual rate of FEV₁ decline was similar among younger and older COPD patients (38.8 mL/year versus 40.6 mL/year, respectively; $P=0.86$). In this study, the proportion of GOLD stage I was higher among younger

COPD patients. It could affect the rate of FEV₁ decline because it appears to be inversely related to the GOLD stage.^{17,18} Moreover, COPD patients between the ages of 55 years and 65 years were not included. Different results in these studies might be due to different inclusion criteria.

When compared with previous trials, our study included all COPD patients between the ages of 42 and 90 years. GOLD stage I COPD patients were also included in our study, and the distribution of GOLD stage and predictive values of FEV₁ were not different between age groups. To minimize the effect of arbitrary categorization of age groups on the rate of FEV₁ decline, participants were categorized according to age by two different criteria: median age and quartiles of age. After categorizing patients into age groups based on median age or quartile, acceleration of FEV₁ decline with aging was observed.

Additionally, we performed further analysis categorizing patients into groups with 10-year intervals (Table S2). When the data were expressed as predictive values, the rate of decline of the mean post-BD FEV₁ was significantly faster among older patients, when compared with younger patients (−0.39%±0.80%/year, −0.24%±0.24%/year, −0.61%±0.14%/year, −0.83%±0.19%/year, −2.00%±0.46%/year, respectively; $P=0.015$) (Table S3). Only seven patients were allocated to the youngest age group, and it might explain why the 40- to 49-year-old group showed higher rates of FEV₁ decline.

It could be argued that our results were the effect of regression-to-the-mean phenomenon. Regression-to-the-mean is the phenomenon that if a variable is extreme on its first measurement, it will tend to be closer to the average on its next measurement. In our study, although it did not reach statistical significance, older patients showed slightly higher proportion of GOLD III–IV (Table 1), suggesting the possibility of better FEV₁ in younger group. In fact, the absolute initial value of FEV₁ was higher in the younger group than that in the older group (Tables 1, S1, and S2). Thus, according to regression-to-the-mean, higher initial FEV₁ value in younger patients would be followed by the lower FEV₁ value on next measurement, resulting in more rapid decline of FEV₁ compared with older patients. However, our result is opposite, that is, faster FEV₁ decline in older groups. Therefore, our result of faster FEV₁ decline in younger group seems less likely to be due to regression-to-the-mean phenomenon.

Absolute value of FEV₁ has been conventionally used for analysis of lung function decline in COPD patients.^{3,4,8,9,19} However, the Toward a Revolution in COPD Health (TORCH) study demonstrated that the trend of FEV₁ decline was preserved when FEV₁ decline was expressed as predictive

value.²⁰ In this study, the rate of FEV₁ decline was expressed not only as absolute value, but also as predictive value. Change of absolute value of FEV₁ could be underestimated in older patients, because absolute value of FEV₁ among old patients was lower than among younger patients. Therefore, predictive value of FEV₁ could be a more appropriate measure of the decline of FEV₁ than absolute value. Thomsen et al²¹ reported that relative changes of FEV₁ seem to explain changes in lung function better than absolute measurement among heavy smokers.

We used pre-BD FEV₁, as well as post-BD FEV₁, to evaluate the rate of decline in FEV₁. Interestingly, the rate of decline of the post-BD FEV₁ was higher than that of pre-BD FEV₁ among all age groups. This observation is consistent with findings in previous studies.^{22,23} Tashkin et al²³ reported that the slopes of post-BD FEV₁ were significantly steeper than the slopes calculated from the pre-BD measurements. In addition, post hoc analysis of data from the Long-Term Impacts on Function with Tiotropium (UPLIFT) trial demonstrated that FEV₁ response to bronchodilators declined significantly over time, and the rate of FEV₁ decline was generally more significant among older patients. Development of tolerance to bronchodilator therapy over the course of the disease could be an explanation for the rapid decline in post-BD lung function.²⁴

Our study has some limitations. First of all, as our study design was retrospective, we could not directly evaluate the effect of treatment regimens. Instead, because prescribed medications vary as the years go by, we analyzed the rate of FEV₁ decline in each group by adding “year of diagnosis” as variable for adjustment. When patients were categorized into quartiles, the annual decline in post-BD FEV₁ was still accelerated with age, whether expressed as absolute value or predicted value. Next, over-adjustment for baseline FEV₁ may be of concern. However, this method has already been used in previous studies including a post hoc analysis of the TORCH study.²⁰ Third, patients with spirometries at irregular intervals were excluded, which might have introduced a selection bias. However, excluding irregular spirometries could also decrease bias because it is possible that spirometries were performed irregularly during an acute event.

Despite some of the aforementioned limitations, to our knowledge, this is the first study that includes COPD patients of all ages and all GOLD severity stages to evaluate the annual decline of FEV₁ across age groups. This study demonstrated that the rate of decline among both post-BD and pre-BD FEV₁ groups accelerated with age, conceptually in accordance with the Fletcher–Peto curve.

Conclusion

Conceptually, in accordance with the Fletcher–Peto curve, annual rates of FEV₁ decline, whether expressed as absolute or predictive values, accelerate with increasing age among patients with COPD.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Baseline characteristics according to age quartile

	Q1 (below 63 years, n=128)	Q2 (63–67 years, n=107)	Q3 (67–72 years, n=141)	Q4 (above 72 years, n=142)	P-value
Sex, male	123 (96.1)	102 (95.3)	132 (93.6)	131 (92.3)	0.145
BMI, kg/m ²	23.49±2.93	22.88±3.16	22.20±3.51	21.71±3.26	<0.001
Smoking status					0.407
Current smoker	76 (59.4)	41 (38.3)	54 (38.3)	48 (33.8)	
Former smoker	35 (27.3)	52 (48.6)	62 (44.0)	75 (58.2)	
Never smoker	9 (7.0)	5 (4.7)	8 (5.7)	11 (7.7)	
Unknown	8 (6.3)	9 (8.4)	17 (12.1)	8 (5.6)	
Pack-year	39.65±20.80	41.66±17.55	45.92±23.13	45.89±25.77	0.051
GOLD					0.490
I	12 (9.4)	12 (11.2)	7 (5.0)	14 (9.9)	
II	58 (45.3)	44 (41.1)	61 (43.3)	69 (48.6)	
III	43 (33.6)	42 (39.3)	56 (39.7)	52 (36.6)	
IV	15 (11.7)	9 (8.4)	17 (12.1)	7 (4.9)	
Post-bronchodilator					
FVC, L	3.68±0.85	3.47±0.83	3.10±0.75	3.10±0.84	<0.001
FVC, %	83.62±16.74	82.88±17.31	76.73±15.78	79.10±16.46	0.002
FEV ₁ , L	1.81±0.69	1.65±0.64	1.41±0.52	1.44±0.53	<0.001
FEV ₁ , %	53.27±18.86	53.16±18.79	48.92±16.79	55.32±18.41	0.027
FEV ₁ /FVC, %	48.52±11.97	46.93±12.21	45.53±11.05	46.51±11.17	0.203
Pre-bronchodilator					
FVC, L	3.49±0.91	3.31±0.88	2.95±0.76	2.97±0.82	<0.001
FVC, %	79.20±18.22	78.91±18.81	73.08±16.33	75.78±17.69	0.016
FEV ₁ , L	1.69±0.72	1.53±0.65	1.31±0.52	1.35±0.53	<0.001
FEV ₁ , %	49.70±19.64	49.34±19.28	45.17±16.82	51.71±18.70	0.027
FEV ₁ /FVC, %	47.45±12.09	45.54±12.37	44.15±10.78	45.39±11.10	0.135
Positive BDR	2 (1.6)	8 (7.5)	7 (5.0)	7 (4.9)	0.335
History of acute exacerbation	26 (20.3)	37 (34.6)	47 (33.3)	64 (45.1)	<0.001
Follow-up months	61.32±30.80	59.66±26.33	56.63±26.10	44.38±25.56	<0.001

Note: Data presented as mean ± SD or n (%).

Abbreviations: BDR, bronchodilator response; BMI, body mass index; FEV₁, forced expiratory volume in 1-second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease.

Table S2 Baseline characteristics: 40–90 years of age

	40–49 (n=7)	50–59 (n=77)	60–69 (n=241)	70–79 (n=159)	80–90 (n=32)	P-value
Sex, male	7 (100)	77 (97.5)	227 (94.2)	150 (94.3)	27 (84.4)	0.145
BMI, kg/m ²	20.86±3.28	23.57±2.82	22.84±3.37	21.72±3.07	21.94±3.94	<0.001
Smoking						0.253
Current smoker	3 (42.9)	47 (59.5)	105 (43.6)	57 (35.8)	7 (21.9)	
Former smoker	3 (42.9)	22 (27.8)	102 (42.3)	78 (49.1)	19 (59.4)	
Never smoker	1 (14.3)	4 (5.1)	13 (5.4)	10 (6.3)	5 (15.6)	
Unknown	0 (0)	6 (7.6)	21 (8.7)	14 (8.8)	1 (3.1)	
Pack-year	29.80±16.88	41.77±20.46	42.98±20.61	46.51±25.42	39.43±24.15	0.129
GOLD						0.219
I	0 (0)	7 (8.9)	20 (8.3)	16 (10.1)	2 (6.3)	
II	3 (42.9)	34 (43.0)	110 (45.6)	67 (42.1)	18 (56.3)	
III	3 (42.9)	29 (36.7)	85 (35.3)	65 (40.9)	11 (34.4)	
IV	1 (14.3)	9 (11.4)	26 (10.8)	11 (6.9)	1 (3.1)	
Post-bronchodilator						
FVC, L	3.58±0.47	3.72±0.81	3.35±0.85	3.18±0.78	2.75±0.75	<0.001
FVC, %	80.71±11.73	83.43±15.89	80.91±17.35	79.01±16.67	75.09±13.81	0.128
FEV ₁ , L	1.84±0.60	1.81±0.68	1.59±0.63	1.46±0.54	1.25±0.42	<0.001
FEV ₁ , %	50.57±17.06	52.14±18.04	52.17±18.56	53.09±18.65	55.41±15.81	0.890
FEV ₁ /FVC, %	51.57±13.59	44.77±11.04	46.99±12.10	46.01±11.15	46.28±10.71	0.625
Pre-bronchodilator						
FVC, L	3.40±0.53	3.53±0.89	3.19±0.88	3.04±0.80	2.60±0.76	<0.001
FVC, %	76.71±12.69	79.06±17.75	77.01±18.32	75.62±17.63	71.22±15.70	0.285
FEV ₁ , L	1.76±0.61	1.69±0.71	1.47±0.64	1.37±0.54	1.17±0.40	<0.001
FEV ₁ , %	48.14±17.31	48.68±19.10	48.29±18.88	49.58±19.07	51.53±14.92	0.891
FEV ₁ /FVC, %	50.86±13.07	46.80±11.30	46.80±11.30	45.54±12.06	44.86±11.23	0.568
Positive BDR	0 (0)	1 (1.3)	14 (5.8)	9 (5.7)	1 (0)	0.621
History of acute exacerbation	2 (28.6)	16 (20.3)	76 (31.5)	60 (37.7)	20 (62.5)	<0.001
Follow-up months	58.72±24.08	63.38±31.35	57.51±26.95	49.93±26.66	40.75±25.97	<0.001

Note: Data presented as mean ± SD or n (%).

Abbreviations: BDR, bronchodilator response; BMI, body mass index; FEV₁, forced expiratory volume in 1-second; FVC, forced vital capacity; GOLD, Global initiative for Chronic Obstructive Lung Disease.

Table S3 Lung function decline: 40–90 years of age

	Unadjusted		Adjusted	
	Mean ± SE	P-value	Mean ± SE	P-value
FEV ₁ , mL/year				
Post-bronchodilator				
40–49	2.14±20.34	0.123	-10.49±23.06	0.136 ^a
50–59	-7.34±5.97		-7.03±6.96	
60–69	-18.52±3.59		-18.65±4.09	
70–79	-24.51±4.83		-23.93±5.39	
80–90	-31.44±11.89		-42.26±13.32	
Pre-bronchodilator				
40–49	3.79±20.43	0.079	-11.08±23.47	0.152 ^a
50–59	-2.38±5.89		-2.00±7.05	
60–69	-11.49±3.58		-11.12±4.17	
70–79	-21.70±4.85		-20.24±5.52	
80–90	-25.16±11.94		-33.96±13.66	
FEV ₁ , %/year				
Post-bronchodilator				
40–49	-0.01±0.67	0.015	-0.39±0.80	0.015 ^b
50–59	-0.23±0.20		-0.24±0.24	
60–69	-0.62±0.12		-0.61±0.14	
70–79	-0.87±0.16		-0.83±0.19	
80–90	-1.52±0.39		-2.00±0.46	
Pre-bronchodilator				
40–49	0.08±0.67	0.006	-0.33±0.79	0.020 ^b
50–59	-0.08±0.19		-0.07±0.24	
60–69	-0.40±0.12		-0.37±0.14	
70–79	-0.83±0.16		-0.75±0.19	
80–90	-1.28±0.39		-1.62±0.46	

Notes: The numbers of patients within each group were as follows: 40–49 years (n=7), 50–59 years (n=77), 60–69 years (n=241), 70–79 years (n=159) and ≥80 years (n=32).
^aAdjusted for sex, body mass index, smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁.
^bAdjusted for smoking status, bronchodilator response, experience of acute exacerbation, and initial FEV₁.

Abbreviations: FEV₁, forced expiratory volume in 1-second; SE, standard error.

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