

# Lung function decline rates according to GOLD group in patients with chronic obstructive pulmonary disease

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**Background:** Since the Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups A–D were introduced, the lung function changes according to group have been evaluated rarely.

**Objective:** We investigated the rate of decline in annual lung function in patients categorized according to the 2014 GOLD guidelines.

**Methods:** Patients with COPD included in the Korean Obstructive Lung Disease (KOLD) prospective study, who underwent yearly postbronchodilator spirometry at least three times, were included. The main outcome was the annual decline in postbronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>), which was analyzed by random-slope and random-intercept mixed linear regression.

**Results:** A total 175 participants were included. No significant postbronchodilator FEV<sub>1</sub> decline was observed between the groups (–34.4±7.9 [group A]; –26.2±9.4 [group B]; –22.7±16.0 [group C]; and –24.0±8.7 mL/year [group D]) ( $P=0.79$ ). The group with less symptoms (–32.3±7.2 vs –25.0±6.5 mL/year) ( $P=0.44$ ) and the low risk group (–31.0±6.1 vs –23.6±7.7 mL/year) ( $P=0.44$ ) at baseline showed a more rapid decline in the postbronchodilator FEV<sub>1</sub>, but the trends were not statistically significant. However, GOLD stages classified by FEV<sub>1</sub> were significantly related to the annual lung function decline.

**Conclusion:** There was no significant difference in lung function decline rates according to the GOLD groups. Prior classification using postbronchodilator FEV<sub>1</sub> predicts decline in lung function better than does the new classification.

**Keywords:** annual lung function decline, chronic obstructive pulmonary disease, GOLD 2014

## Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed a new classification system that grouped patients with COPD into four categories, groups A–D, based on symptom and risk categories.<sup>1</sup> Several studies have since evaluated clinical outcomes in COPD patients, including exacerbation and mortality, according to the GOLD groups.<sup>2–4</sup> However, the decline in lung function, which is another critical therapeutic target,<sup>5</sup> has been investigated in only two studies.<sup>2,6</sup> Furthermore, in these studies, the lung function decline rates were analyzed with no adjustment<sup>2</sup> or with adjustment by using only disease severity as the sole covariate.<sup>6</sup> Finally, the impact of specific details related to the GOLD classification (ie, “more symptoms” group vs “less symptoms” group or GOLD high risk group vs low risk group), which could provide information on the use of the GOLD classification system, was not fully investigated.<sup>2,6</sup> In the present study, we evaluated the annual lung function decline

according to the GOLD guidelines, by using data from the Korean Obstructive Lung Disease (KOLD) cohort study, a multicenter prospective longitudinal study of patients with COPD in South Korea.<sup>7</sup>

## Methods

### Participant eligibility and study protocol

The KOLD cohort included patients diagnosed with COPD or asthma who were recruited from pulmonary clinics at eleven referral hospitals in Korea from June 2005 to October 2012. The inclusion criteria were: (1) age  $\geq 40$  years; (2) postbronchodilator forced expiratory volume in 1 second ( $FEV_1$ )/forced vital capacity (FVC)  $< 0.7$ ; (3) current or ex-smoker with a smoking history  $\geq 10$  pack-years; and (4) greater than three annual pulmonary function tests (PFTs). Patients with “pure” asthma were excluded based on the judgement of physicians. As there was a 2-week period to wash out therapeutic drugs just before enrollment in the KOLD cohort study, it was expected that lung functions would increase in the early period of study, which is commonly observed in large clinical trials. Therefore, the 12th month from the initial enrollment was set as a baseline of the study, and analysis of lung function changes started from the baseline and continued to the last follow-up at 1-year intervals. The study was approved by the ethics committees of the Seoul National University Hospital Institutional Review Board and by the institutional review boards of the other 16 hospitals; and all patients provided written, informed consent. We adhered to the Declaration of Helsinki.

### Definition of groups and stages

The recent GOLD guidelines categorize patients with COPD into groups A–D according to symptoms based on either the modified Medical Research Council (mMRC) grade or the COPD assessment test (CAT) score. Risk is based on either the  $FEV_1$  or the exacerbation history. As CAT scores were not measured in the KOLD study before 2011, we used the St George’s Respiratory Questionnaire (SGRQ) score as a surrogate for the CAT score.<sup>3</sup> According to the most recent GOLD guidelines, a symptom score equivalent to an SGRQ score  $\geq 25$  should be used as the cutoff for considering regular treatment of COPD symptoms.<sup>5</sup> Patients with an mMRC  $\geq 2$  or a SGRQ score  $\geq 25$  were placed in the more symptoms group. Those with a postbronchodilator  $FEV_1 < 50\%$  of the predicted value or who experienced  $\geq$  two exacerbations (hospitalization  $\geq$  one time) in the previous year were placed in the high risk group.

GOLD stages were classified based on the percentage of predicted  $FEV_1$ :<sup>5</sup> stage I was defined as predicted  $FEV_1 \geq 80\%$ ;

stage II was defined as predicted  $FEV_1 50\%–79\%$ ; stage III was defined as predicted  $FEV_1 30\%–49\%$ ; and stage IV was defined as predicted  $FEV_1 < 30\%$ .

### Pulmonary function test

PFT was performed according to American Thoracic Society guidelines<sup>8</sup> using the Vmax 22 (Sensor Medics, Yorba Linda, CA, USA) and PFDX (Medgraphics, St Paul, MN, USA). The spirometry reference values were based on the Korean equation.<sup>9</sup> Postbronchodilator spirometry values were measured 15 minutes after administering 400  $\mu$ g of salbutamol. Lung volume, including the total lung capacity (TLC) and residual volume (RV), was measured using body plethysmography which were V6200 (CareFusion, San Diego, CA, USA), PFDX, or Vmax 22.<sup>10</sup> The diffusing capacity of carbon monoxide (DLCO) was measured by assessing the single-breath carbon monoxide uptake (Vmax 22 or PFDX).<sup>11</sup> The postbronchodilator  $FEV_1$  and FVC, TLC, RV, and DLCO were measured at baseline and at each annual visit.

### Statistical analysis

Baseline characteristics between groups were compared using the  $\chi^2$  and Fisher’s exact tests for categorical variables and the *t*-test and Mann–Whitney *U*-test for continuous variables. The main outcome was the annual rate of change in the postbronchodilator  $FEV_1$ . Assuming an annual rate of decline in the  $FEV_1$  between groups A and D of 30 mL/year with a 45 mL/year standard deviation, the estimated sample size was calculated as 192 (48 patients per group) with a 5% type 1 error and 90% power.

The annual  $FEV_1$  decline rates were subjected to random-slope and random-intercept mixed linear regression analyses. Covariates in the models included time (year), time by group (or category) interaction, age, sex, height, weight, smoking status,<sup>12,13</sup> and the medication possession ratio of respiratory medications. Respiratory medications included combined inhaled corticosteroids and long-acting  $\beta$ -agonists (ICS/LABA), and inhaled long-acting muscarinic antagonists (LAMA), as these drugs may affect the decline in lung function according to recent large random controlled trials.<sup>13,14</sup> Akaike information criterion (AIC) was used to select a better statistical model. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, USA). A *P*-value  $< 0.05$  indicated a significant difference.

## Results

A total 175 patients were included, with 58 (33.1%) categorized as group A, 45 (25.7%) as group B, 15 (8.6%) as group C, and

**Table 1** Baseline patient characteristics and long-term outcomes

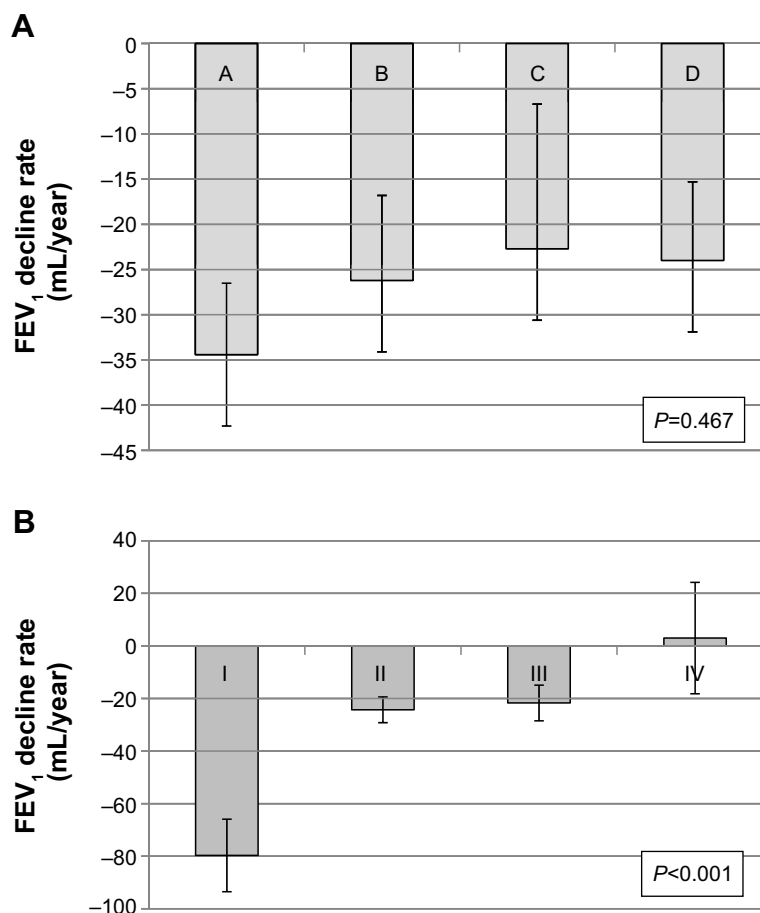
	Total (n=175)	GOLD group			
		A (n=58)	B (n=45)	C (n=15)	D (n=57)
Age (years)	66.4±7.1	66.1±7.6	64.9±6.6	68.8±6.4	67.2±7.0
Males (%)	169 (96.6%)	57 (98.3%)	42 (93.3%)	15 (100%)	55 (96.5%)
Height (cm)	165.5±6.4	165.9±5.9	165.2±6.1	168.2±6.1	164.4±6.9
Weight (kg)	64.1±10.3	67.1±11.3	65.2±7.9	63.1±7.0	60.4±10.7
Body mass index	23.3±3.2	24.2±3.2	23.9±2.7	22.3±2.6	22.3±3.4
Smoking status					
Current smoker	54 (30.9%)	22 (37.9%)	12 (26.7%)	2 (13.3%)	18 (31.6%)
Pack-year	48.5±26.7	50.1±28.6	52.9±28.2	37.6±18.2	46.4±24.9
SGRQ score	29.9±17.7	14.9±7.2	36.5±14.3	18.8±4.8	43.4±16.4
mMRC grade					
0	35 (20.0%)	27 (46.6%)	4 (8.9%)	4 (26.7%)	0
1	72 (41.1%)	31 (53.5%)	13 (28.9%)	11 (73.3%)	17 (29.8%)
2	52 (29.7%)	0	23 (51.1%)	0	29 (50.9%)
3	12 (6.9%)	0	4 (8.9%)	0	8 (14.0%)
4	4 (2.3%)	0	1 (2.2%)	0	3 (5.3%)
Spirometry					
Prebronchodilator					
FEV <sub>1</sub> (L)	1.59±0.54	1.96±0.45	1.80±0.43	1.38±0.41	1.11±0.30
FEV <sub>1</sub> (% predicted)	52.3±15.7	63.6±11.6	58.4±10.7	44.6±12.7	38.0±10.5
FVC (L)	3.35±0.77	3.65±0.68	3.63±0.73	3.10±0.66	2.88±0.67
FVC (% predicted)	79.6±15.8	85.5±14.2	86.2±12.8	71.5±14.0	70.4±14.6
Postbronchodilator					
FEV <sub>1</sub> (L)	1.70±0.55	2.07±0.45	1.92±0.42	1.53±0.37	1.20±0.32
FEV <sub>1</sub> (% predicted)	55.8±15.6	67.1±11.1	62.4±9.6	49.3±11.3	40.8±10.9
FVC (L)	3.48±0.77	3.78±0.66	3.81±0.76	3.23±0.63	2.99±0.62
FVC (% predicted)	82.7±15.6	88.5±13.8	90.4±13.6	74.4±12.6	73.0±13.4
DLCO (% predicted)	81.5±25.0	90.2±24.4	75.8±20.7	85.4±19.9	76.2±27.7
TLC (L)	6.34±1.08	6.11±0.88	6.29±1.04	6.51±1.47	6.57±1.16
TLC (% predicted)	114.3±18.0	108.9±16.7	113.3±16.1	112.3±17.4	121.2±19.2
RV (L)	2.89±0.99	2.35±0.73	2.59±0.78	3.31±1.08	3.59±0.91
RV (% predicted)	134.6±46.1	109.2±33.8	123.0±39.4	144.7±41.5	167.6±43.6
RV/TLC (%)	45.1±11.1	38.0±9.1	40.8±8.8	50.2±6.92	54.4±8.0
GOLD stage					
I	13 (7.4%)	10 (17.2%)	2 (4.4%)	1 (6.7%)	0
II	98 (56.0%)	48 (82.8%)	43 (95.6%)	2 (13.3%)	5 (8.8%)
III	56 (32.0%)	0	0	12 (80.0%)	44 (77.2%)
IV	8 (4.6%)	0	0	0	8 (14.0%)
Drugs					
ICS/LABA use	157 (89.7%)	45 (77.6%)	43 (95.6%)	15 (100%)	54 (94.7%)
ICS/LABA MPR	0.73±0.39	0.53±0.45	0.80±0.32	0.71±0.38	0.87±0.29
LAMA use	146 (83.4%)	44 (75.9%)	38 (84.4%)	12 (80%)	52 (91.2%)
LAMA MPR	0.67±0.41	0.63±0.43	0.57±0.42	0.70±0.44	0.80±0.35
ICS/LABA and LAMA combination	130 (74.3%)	32 (55.2%)	37 (82.2%)	12 (80.0%)	49 (85.9%)
Exacerbation in previous year	0.57±2.23	0.07±0.26	0.18±0.39	0.93±2.13	1.28±3.61
Severe exacerbation in previous year <sup>a</sup>	0.11±0.50	0	0	0.27±0.59	0.28±0.80

**Notes:** Data are presented as n (%) or the mean ± standard deviation (range). <sup>a</sup>Exacerbations requiring hospitalization or an emergency department visit.

**Abbreviations:** DLCO, diffusing capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Round Council; MPR, medication possession ratio; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity.

57 (32.6%) as group D. Table 1 summarizes the baseline characteristics, including the demographic, symptomatic, and spirometry values, and exacerbation history. The subjects underwent a mean 4.7±1.2 annual PFTs over the follow-up period (mean 48.2 months). A total 59.4% underwent annual PFTs

more than five times, and 78.3% underwent PFT more than four times. The proportion of patients who had ever used LAMA during the follow-up period was similar among the four groups ( $P=0.17$ ), meanwhile patients who had more severe symptoms or lower FEV<sub>1</sub> were likely to use ICS/LABA ( $P=0.003$ ).



**Figure 1** Annual rate of decline in postbronchodilator FEV<sub>1</sub> adjusted by age, sex, height, weight, smoking status, and medication possession ratio of respiratory medications (ICS-LABA and LAMA).

**Notes:** (A) Among GOLD groups (A–D). (B) Among GOLD stages (I–IV).

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS-LABA, inhaled corticosteroid/long-acting  $\beta$ -agonist; LAMA, long-acting muscarinic antagonist.

The adjusted annual rates of decline in the postbronchodilator FEV<sub>1</sub>, postbronchodilator FVC, DLCO, and RV/TLC were  $-28.3 \pm 4.9$  mL/year,  $-26.8 \pm 8.6$  mL/year,  $-1.02\% \pm 0.38\%$ , and  $-0.40\% \pm 0.23\%$ , respectively (Figure 1). The decline in postbronchodilator FEV<sub>1</sub> was highest in the GOLD group A, although no significant differences were observed according to group (Table 2). The group with the fewest symptoms at baseline based on the mMRC and SGRQ criteria showed the fastest decline in postbronchodilator FEV<sub>1</sub>, although this trend was not statistically significant ( $P=0.44$ ). The risk group at baseline was not associated with the decline in postbronchodilator FEV<sub>1</sub>. However, GOLD stage was significantly related with the annual FEV<sub>1</sub> decline rates. Stage I COPD patients showed the fastest lung function decline, while stage IV patients the slowest ( $P<0.001$ ). The GOLD stage was a better predictor than was the GOLD group (AIC =423.75 vs 622.08). The decline rates in postbronchodilator FVC were more prominent in groups A and C, which included patients

with the least severe symptoms ( $P=0.13$ ). When data were examined according to the percent change per year, the trends were similar (Table 3). The GOLD stage was also a better predictor than the GOLD group in the annual decline rates of FEV<sub>1</sub>%. (AIC =5,384.6 vs 5,497.9) There were no significant differences in the annual rates of decline in the postbronchodilator FEV<sub>1</sub>/FVC, DLCO, and RV/TLC. The severity of decline in RV/TLC decreased from group A to group D (Table 4).

## Discussion

Our findings show that the rate of lung function decline did not differ significantly among the GOLD 2014 groups, which is similar to results in the ECLIPSE cohort study.<sup>2</sup>

The new GOLD guidelines emphasize that the goals of COPD assessment are to determine the disease severity and its impact on the patient's current health and risk of future events; to this end, four patient categories were introduced,

**Table 2** Annual rate of decline in postbronchodilator FEV<sub>1</sub> and FVC (mL/year)

Patient categories	Patients (n)	Unadjusted		Adjusted <sup>a</sup>	
		Rate (mL/year)	P-value	Rate (mL/year)	P-value
<b>FEV<sub>1</sub></b>					
Total patients	175	-25.8±3.8		-28.3±4.9	
GOLD group			0.474		0.467
A	58	-32.9±6.3		-34.4±7.9	
B	45	-27.4±7.4		-26.2±9.4	
C	15	-22.8±12.9		-22.7±16.0	
D	57	-18.3±6.9		-24.0±8.7	
Symptom group			0.255		0.444
Less	73	-30.9±5.7		-32.3±7.2	
More	102	-22.2±5.1		-25.0±6.5	
Risk group			0.145		0.443
Low	103	-30.6±4.8		-31.0±6.1	
High	72	-19.2±6.1		-23.6±7.7	
GOLD stage			<0.001		<0.001
I	13	-78.3±13.5		-79.7±13.8	
II	98	-24.5±4.8		-24.3±4.9	
III	56	-21.4±6.6		-21.7±6.8	
IV	8	3.9±20.9		3.0±21.2	
<b>FVC</b>					
Total patients	175	-27.9±7.3		-26.8±8.6	
GOLD group			0.463		0.477
A	58	-42.7±12.0		-41.9±13.8	
B	45	-21.4±14.2		-11.2±16.3	
C	15	-32.9±24.7		-34.1±27.8	
D	57	-16.1±13.2		-19.3±15.1	
Symptom group			0.118		0.129
Less	73	-40.8±10.8		-40.4±12.4	
More	102	-18.0±9.7		-15.6±11.2	
Risk group			0.345		0.699
Low	103	-33.8±9.2		-29.2±10.7	
High	72	-19.7±11.7		-22.7±13.4	
GOLD stage			0.195		0.191
I	13	-81.3±26.3		-81.2±26.3	
II	98	-25.1±9.4		-25.3±9.4	
III	56	-24.5±12.9		-24.8±12.9	
IV	8	-2.1±40.2		0.8±40.2	

**Notes:** Data are the mean ± standard deviation (range). <sup>a</sup>Adjusted by age, sex, height, weight, smoking status, and the medication possession ratio of respiratory medications (inhaled corticosteroid/long acting β-agonist and long-acting muscarinic antagonist).

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

groups A–D.<sup>5</sup> However, it remains unclear whether the GOLD category can accurately predict future risk, including mortality, exacerbations, and the rate of lung function decline. The ECLIPSE cohort study, which included 2,101 COPD patients, showed that group D had the highest mortality and group A the lowest, but surprisingly, group C showed a lower mortality rate than did group B.<sup>2</sup> Similar results were reported in a Danish study, which also observed higher mortality in group B than in group C.<sup>15</sup> In a Norwegian study (HUNT2 study), the mortality increased in order from group A to D in men with COPD, but this trend was not observed in the female patients.<sup>16</sup> A similar trend was observed for

severe exacerbation requiring hospitalization and the GOLD group – the risk of severe exacerbation in groups B and C were similar in the Danish study,<sup>15</sup> ECLIPSE study,<sup>2</sup> and the COPDGen study.<sup>3</sup>

The association between the rate of annual lung function decline, another important outcome, and the GOLD groups has rarely been investigated. Although a post hoc analysis of the UPLIFT trial showed group C had lower annual FEV<sub>1</sub> decline rates compared with group B (38 vs 48 mL) ( $P=0.01$ ), various covariates were not adjusted in that analysis.<sup>6</sup> Only one cohort study has examined the relationship,<sup>2</sup> and this report found that the annual FEV<sub>1</sub>

**Table 3** Annual rate of percentage decline in postbronchodilator FEV<sub>1</sub> and FVC (%/year)

Patient categories	Patients (n)	Unadjusted		Adjusted <sup>a</sup>	
		Rate (%/year)	P-value	Rate (%/year)	P-value
<b>FEV<sub>1</sub></b>					
Total patients	175	-0.40±0.25		-0.52±0.33	
GOLD group			0.981		0.941
A	58	-0.27±0.21		-0.34±0.26	
B	45	-0.16±0.25		-0.12±0.31	
C	15	-0.16±0.44		-0.19±0.53	
D	57	-0.17±0.23		-0.34±0.29	
Symptom group			0.708		
Less	73	-0.25±0.19		-0.21±0.24	0.798
More	102	-0.16±0.17		-0.23±0.22	
Risk group			0.813		0.858
Low	103	-0.23±0.16		-0.25±0.20	
High	72	-0.16±0.21		-0.31±0.26	
GOLD stage			0.021		0.022
I	13	-1.54±0.47		-1.53±0.47	
II	98	-0.06±0.17		-0.06±0.17	
III	56	-0.26±0.23		-0.26±0.23	
IV	8	0.49±0.73		0.48±0.73	
<b>FVC</b>					
Total patients	175	-0.66±0.34		-0.64±0.41	
GOLD group			0.436		0.463
A	58	-0.68±0.28		-0.67±0.33	
B	45	-0.15±0.33		0.08±0.39	
C	15	-0.55±0.58		-0.57±0.66	
D	57	-0.05±0.31		-0.18±0.36	
Symptom group			0.102		0.127
Less	73	-0.65±0.26		-0.65±0.29	
More	102	-0.08±0.23		-0.06±0.27	
Risk group			0.401		0.828
Low	103	-0.46±0.22		-0.36±0.25	
High	72	-0.16±0.28		-0.27±0.32	
GOLD stage			0.213		0.215
I	13	-1.55±0.63		-1.54±0.62	
II	98	-0.24±0.22		-0.24±0.22	
III	56	-0.32±0.31		-0.32±0.31	
IV	8	0.37±0.96		0.38±0.96	

**Notes:** Data are the mean ± standard deviation (range). <sup>a</sup>Adjusted by age, sex, height, weight, smoking status, and medication possession ratio of respiratory medications (inhaled corticosteroid-long acting β-agonist and long-acting muscarinic antagonist).

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

decline rates did not differ significantly between groups A, B, C, and D (-33.4, -38.0, -30.2, and -31.9 mL/year, respectively) ( $P=0.157$ ). Similarly, we did not observe any significant rate change according to the GOLD groups. In the present study, the annual FEV<sub>1</sub> decline rates in groups A, B, C, and D in the KOLD cohort were -34.4, -26.2, -22.7, and -24.0 mL/year, respectively ( $P=0.467$ ).

The lack of significant change in the annual lung function decline between GOLD groups A to D may be explained in several ways. First, the exacerbation history and FEV<sub>1</sub> may exert differing effects on the annual lung function decline. The exacerbation history and FEV<sub>1</sub> are the two criteria used

to categorize patients into the low vs high risk GOLD groups.<sup>2</sup> In the ECLIPSE study, the prior exacerbation history did not affect the annual FEV<sub>1</sub> change ( $P=0.57$ ).<sup>12</sup> Interestingly, a lower FEV<sub>1</sub> was associated with a slower rate of lung function decline in the BODE cohort<sup>17</sup> and a pooled analysis of 15 randomized controlled trials.<sup>18</sup> These varying effects of exacerbation history and FEV<sub>1</sub> on long-term lung function decline may eliminate any difference in the rate of declines between groups C and D (high risk group) and groups A and B (low risk group). Consistent with these earlier results, in our study, there was no statistical difference between the high risk and low risk groups.



**Table 4** Annual rate of decline in postbronchodilator FEV<sub>1</sub>/FVC, DLCO, and RV/TLC (%/year)

Patient categories	Patients (n)	Unadjusted		Adjusted <sup>a</sup>	
		Rate (%/year)	P-value	Rate (%/year)	P-value
<b>FEV<sub>1</sub>/FVC (%)</b>					
Total patients	175	-0.07±2.59		-0.41±0.11	
GOLD group			0.561		0.576
A	58	-0.24±0.43		-0.25±0.18	
B	45	-0.48±0.51		-0.53±0.22	
C	15	-0.29±0.88		-0.30±0.37	
D	57	0.44±0.47		-0.60±0.20	
GOLD stage			0.536		0.521
I	13	-0.63±0.93		-0.65±0.94	
II	98	-0.34±0.34		-0.36±0.4	
III	56	0.43±0.46		0.43±0.46	
IV	8	0.11±1.41		0.16±1.42	
<b>DLCO (%)</b>					
Total patients	175	-0.95±0.33		-1.02±0.38	
GOLD group			0.317		0.278
A	58	-0.57±0.54		-0.44±0.62	
B	45	-1.51±0.64		-1.81±0.73	
C	15	0.54±1.09		0.36±1.23	
D	57	-1.34±0.59		-1.49±0.68	
GOLD stage			0.320		0.315
I	13	-1.54±1.18		-1.54±1.18	
II	98	-0.69±0.43		-0.70±0.43	
III	56	-0.99±0.59		-1.00±0.59	
IV	8	-4.14±1.88		-4.16±1.87	
<b>RV/TLC (%)</b>					
Total patients	175	-0.33±0.21		-0.40±0.23	
GOLD group			0.526		0.482
A	58	-0.59±0.35		-0.69±0.37	
B	45	-0.51±0.41		-0.62±0.44	
C	15	0.08±0.71		-0.09±0.74	
D	57	0.09±0.39		0.09±0.42	
GOLD stage			0.436		0.429
I	13	0.14±0.78		0.19±0.78	
II	98	-0.59±0.27		-0.58±0.27	
III	56	0.13±0.38		0.13±0.38	
IV	8	-0.35±1.26		-0.41±1.26	

**Notes:** Data are the mean ± standard deviation (range). <sup>a</sup>Adjusted by age, sex, height, weight, smoking status, and medication possession ratio of respiratory medications (ICS-LABA and LAMA).

**Abbreviations:** DLCO, diffusing capacity for carbon monoxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; RV, residual volume; TLC, total lung capacity.

Second, there is no evidence that more severe symptoms are associated with a faster decline in lung function. In a Hokkaido COPD study, the mMRC dyspnea scale score ≥2 did not predict rapid vs slow decline in lung function ( $P=0.60$  [multivariate model excluding emphysema score];  $P=0.75$  [multivariate model excluding transfer factor coefficient of the lung for carbon monoxide]).<sup>19</sup> The ECLIPSE study found that symptoms of chronic bronchitis did not predict a faster decline in lung function.<sup>12</sup> These data suggest that there may not be any difference in the lung function decline between groups A and C (less symptoms) and groups B and D (more symptoms).

Potentially, a lower statistical power may be unable to detect any difference in the rates of lung function decline. In the UPLIFT trial, in which the primary end point was the annual FEV<sub>1</sub> decline rate, the sample size was estimated as 758 patients per group to detect a 15 mL/year difference between groups (5% significance, 90% power, and 4-year standard deviation of 90 mL).<sup>20</sup> The KOLD study included fewer patients per group (15 to 58), which is a weakness of our study. However, the similar estimation of lung function decline rates between the groups (range from -34mL/year to -24mL/year) suggests that there may not be any significant

differences among the groups. Furthermore, we still found no significant difference after adjustment of possible confounders, including ICS/LABA and LAMA. However, the initial GOLD stage was significantly related with the lung function decline rate. Compared with the model using GOLD groups, the statistical model using GOLD stages was the better one in the prediction of the annual lung function declines. Similarly, a study using the data in the UPLIFT trial reported that the GOLD stage showed a better model fitness, although the GOLD group was also significantly associated with lung function decline in the study.<sup>6</sup> Interestingly, in our study, the better the initial FEV<sub>1</sub>% was, the faster annual FEV<sub>1</sub> decline was observed ( $P < 0.001$ ), as reported in previous studies.<sup>17,18</sup>

The strength of our study is that a sufficient number of annual spirometry examinations were performed. The subjects underwent a mean 5.4 annual spirometry tests during the study period, and ~90% of patients underwent more than four annual PFTs. In addition, we adjusted for multiple covariates, including the medication possession ratio of ICS/LABA and LAMA, which can affect lung function decline<sup>13,14</sup> in the random-slope and random-intercept mixed linear regression models.

This study has several limitations. The most notable limitation is that the study may be statistically underpowered due to the relatively small number of participants, as mentioned earlier, although our sample size met the initial sample size estimation. All participants were Korean, and most were male, which may limit any generalization; however, Korean men have a higher prevalence and more severe disease than Korean women (25.8% [men] vs 9.6% [women]).<sup>21</sup> Third, we used the SGRQ score as a surrogate for the CAT score, as suggested by the new GOLD classification. However, the results of both questionnaires are strongly correlated,<sup>22,23</sup> and the SGRQ score was also used to assess COPD classification in the COPDGene study.<sup>3</sup> In addition, the recent GOLD guidelines recommend that a symptom score equivalent to an SGRQ score  $\geq 25$  should be used as the cutoff for considering regular treatment of symptoms.<sup>5</sup>

In conclusion, we found no significant differences in the rate of lung function decline according to the GOLD groups. Compared with the new classification model using GOLD 2014, the older classification model using solely FEV<sub>1</sub> could predict the rate of decline in lung function better.

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## Disclosure

The authors report no conflicts of interest in this work.

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