

Longitudinal change of FEV₁ and inspiratory capacity: clinical implication and relevance to exacerbation risk in patients with COPD

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Yong Suk Jo,¹ Sung Kyoung Kim,² Seoung Ju Park,³ Soo-Jung Um,⁴ Yong-Bum Park,⁵ Ki Suck Jung,⁶ Deog Kyeom Kim,⁷ Kwang Ha Yoo⁸

¹Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Kyung Hee University Hospital, Seoul, Republic of Korea;

²Department of Internal Medicine, Division of Pulmonology, St Vincent's Hospital, The Catholic University of Korea, Seoul, Republic of Korea;

³Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Republic of Korea;

⁴Department of Internal Medicine, Division of Pulmonology, Dong-A University Hospital, Busan, Republic of Korea;

⁵Department of Internal Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea;

⁶Department of Internal Medicine, Division of Pulmonary Medicine, Hallym University Sacred Heart Hospital, Hallym University Medical School, Anyang, Republic of Korea;

⁷Department of Internal Medicine, Seoul Metropolitan Government, Seoul National University Boramae Medical Center, Seoul, Republic of Korea;

⁸Department of Internal Medicine, Division of Pulmonary and Allergy Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

Correspondence: Kwang Ha Yoo
Department of Internal Medicine,
Division of Pulmonary and Allergy
Medicine, Konkuk University School
of Medicine, 120-1, Neungdong-ro,
Gwangjin-gu, Seoul, Republic of Korea
Tel +82 22 030 7522
Fax +82 22 030 7748
Email khyou@kuh.ac.kr

Background and objective: FEV₁ is the gold standard for assessment of COPD. We compared efficacy of FEV₁, inspiratory capacity (IC), and IC to total lung capacity (TLC) ratio in the evaluation of COPD and their association with exacerbation.

Methods: We analyzed the association of dyspnea severity, quality of life status, and lung function with lung function measurements and exacerbation risk in 982 patients enrolled in the Korea COPD Subgroup Registry and Subtype Research study. Exacerbation and longitudinal lung function change were evaluated in 3 years' follow-up.

Results: The FEV₁, IC, and IC to TLC ratio showed comparable negative correlations with dyspnea severity and quality of life status, and positive correlation with exercise capacity. In patients with >2 events/year, annual rate of change in FEV₁ and IC tended to decline more rapidly in those with FEV₁ <50% than in those with FEV₁ >50% (−14.46±19.40 mL/year vs 12.29±9.24 mL/year, *P*=0.213; −4.75±17.28 mL/year vs −78.05±34.16 mL/year, *P*=0.056 for FEV₁ and IC, respectively), without significance.

Conclusion: Longitudinal changes in IC and FEV₁ were not significantly associated with exacerbation risk.

Keywords: COPD, exacerbation, FEV₁, inspiratory capacity

Introduction

COPD, characterized by persistent and progressive airflow limitation, is a leading cause of morbidity and mortality worldwide and its prevalence is increasing. Currently, COPD is ranked the fourth most common cause of mortality in the USA, and is expected to be the third most common in 2020.¹ The prevalence of COPD in Korea has recently been reported as 13.1%–14.6%, which is more than the worldwide prevalence; moreover, COPD is reported as one of the major causes of death in Korea.^{2,3}

The goals of COPD assessment are to determine not only the severity of airflow limitation but also the patients' disease-specific self-perceived health status and the risk of future adverse events, including exacerbations.⁴ Traditionally, both COPD diagnosis and severity assessment have been based on severity of airflow limitation, represented by FEV₁.⁵ The level of airflow limitation has been regarded as an important index in the prediction of clinical outcomes including exacerbation and mortality, and change in FEV₁ over time is still the most widely used index of disease progression.^{6,7} However, there is a limitation in that FEV₁ reflects only one aspect of the disease and does not actually predict the degree of the disease, especially in the early stage.^{8,9} In addition, correlations of FEV₁ with symptoms and impairment of a patient's health status have been noted as weak.^{10,11}

Lung hyperinflation which is caused by destructive lung parenchymal emphysema and expiratory flow limitation,¹² is an important feature of COPD and is known to contribute to symptoms, exercise capacity, exacerbation, and even mortality.^{13–15} Prognostic impact of an altered inspiratory capacity (IC) and the IC in relation to total lung capacity (TLC) at rest are proven predictors of all-cause and respiratory mortality.^{14,16} Hence, several studies analyzing the efficacy of inhaler treatment have used IC as an outcome measure.^{17–20}

In the present study, we compared IC, IC to TLC ratio, and FEV₁ as clinical measurements in patients with COPD, and analyzed the risk of exacerbation according to the longitudinal change in values through Korean COPD cohort.

Methods

Study design and participants

The Korea COPD Subgroup Registry and Subtype Research study (registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) with identifier CT02800499) is an ongoing multicenter, prospective observational study at 48 centers in Korea from December 2011 to-date with details previously described.²¹ Patients with COPD aged ≥ 40 years and whose bronchodilator response (BDR) FEV₁/FVC was $< 70\%$ were included in this cohort. Among patients diagnosed with COPD, only patients with lung volume measurements were included in the analysis. All study procedures were performed in accordance with the Declaration of Helsinki and relevant guidelines and written informed consent was obtained from all participants before enrollment. The study protocol was approved by the institutional review boards of Kyung Hee University Hospital (IRB no KHUH 2018-04-037).

Clinical measurements

At initial evaluation, demographic data including age and sex, smoking status and pack-years, spirometry results including lung volume, 6MWD, mMRC dyspnea scale, and self-perceived quality of life status assessed by COPD assessment test (CAT) and St George's Respiratory Disease Questionnaire (SGRQ) were collected by physicians or trained nurses using electronic case-report forms.

Treatment of individual patients depended on their attending pulmonologist; patients were followed-up at least every 6 months, and exacerbation data (ie, sputum, cough, or dyspnea) beyond changes within normal daytime range were collected on every visit. Moderate exacerbation was defined as a response “yes” from the patient to the question “Have you had an aggravation of respiratory symptoms that led to a visit to the outpatient clinic earlier

than scheduled?”, and severe exacerbation was defined as “yes” to the question “Have you been hospitalized or visited the emergency department due to deterioration of respiratory symptoms?”.

Pulmonary function tests

Spirometry with a bronchodilator (BD) test was performed according to the recommendations of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines.²² Lung volume measurement was carried out according to the ATS and ERS guidelines and was conducted before inhalation of a BD. Body plethysmography was used for lung volume measurements.²³ The predicted percentage values for the results of spirometry were calculated from the equation developed with Korean populations.²⁴

For assessment of longitudinal changes in the lung volume measurements, spirometry including lung volume follow-up was conducted at least once a year.

Statistical analyses

Baseline characteristics variables were expressed as mean \pm SD and absolute number with percentages. Pearson correlation tests were applied to assess the relationships of FEV₁, IC, and IC to TLC ratio with other clinical measurements including mMRC, CAT, SGRQ, and 6MWD. All tests were two-sided and a *P*-value of < 0.05 was considered statistically significant.

To eliminate the short-term improvement effects after the start of treatment, we analyzed up to 3 years' changes in pulmonary function and exacerbation. For longitudinal change of FEV₁, IC and IC to TLC ratio were analyzed by mixed-effect linear regressions. The mean annual rates of change in FEV₁, IC, and IC to TLC ratio were estimated with a random intercept and a random slope model, with multiple covariates: age, sex, smoking pack-years, body mass index (BMI), previous exacerbation history in the past year and inhaled BD use. To determine the effect of covariates on the annual rates of change in lung function, the interaction of each covariate with time was assessed.

The risk of exacerbation was analyzed by Cox proportional hazards model based on the degree of lung function decline using widely accepted minimal clinically important difference (MCID) of 100 mL and 150 mL for FEV₁ and IC, respectively.^{25–27} Covariates including age, sex, BMI, smoking pack-years, and previous history of exacerbation were adjusted for the multivariate analysis.

Statistical analyses were carried out using STATA software version 14.2 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of patients

A total of 982 COPD patients with lung volume measurement were included in the analysis (Figure 1). Table 1 shows baseline characteristics of patients. Most of the patients were male individuals with mean age of 72.7 years and 21.6% (210 of 982) experienced exacerbation in the past year before enrollment. Mean post-BD FEV_1 was $62.7\% \pm 19.3\%$ of the predicted value and mean post-BD FEV_1 to FVC ratio was $49.8\% \pm 11.7\%$ of the predicted value. More than half of the patients were in GOLD stage II. Summary of lung volume measurements are described in Table 2. Mean values of IC and IC to TLC ratio were 1.9 ± 0.6 L ($74.6\% \pm 22.9\%$ of the predicted value) and $31.3\% \pm 9.9\%$, respectively, and each showed moderate positive correlation with post-BD FEV_1 ($r=0.44$ and 0.51 for IC and IC to TLC ratio; $P<0.001$ in both) (Figure S1).

Correlation between the lung function and other clinical measurements

Figure 2 shows the correlation between IC, IC to TLC ratio and dyspnea scale, disease specific quality of life status, and exercise capacity. The IC and IC to TLC ratio had slightly negative correlations with mMRC ($r=-0.24$ and -0.29 , respectively; $P<0.001$ in both), SGRQ ($r=-0.19$ and -0.24 , respectively; $P<0.001$ in both), and CAT ($r=-0.22$ and -0.24 , respectively; $P<0.001$ in both), and a positive correlation with 6MWD ($r=0.11$ and 0.14 , respectively; $P=0.001$ and <0.001 for IC and IC/TLC, respectively). FEV_1 showed similar correlation results with IC and IC to TLC ratio; $r=-0.36$, -0.24 , 0.31 , and 0.16 for mMRC, SGRQ, CAT, and 6MWD, respectively, and $P<0.001$ for all.

Longitudinal changes in lung function

Mean change of FEV_1 and IC from enrollment are presented in Figure 3. In patients who had mild to moderate

airflow obstruction ($FEV_1 \geq 50\%$ of predicted value), FEV_1 decreased significantly compared with baseline at 3-year follow-up (-20.35 ± 21.82 mL, $P<0.001$) and in those with more than severe airflow obstruction ($FEV_1 < 50\%$ of predicted value), FEV_1 was significantly increased during the first 2 years of treatment, and IC decreased significantly at 3 years (-76.86 ± 71.69 mL, $P=0.040$). During the 3 years' follow-up period, mean ratio of IC to TLC decreased gradually from 32.5% to 31.5%, without significance considering the basal IC to TLC ratio of 31.3%.

Baseline demographic characteristics, smoking status, and pulmonary function had no significant effect on the annual rates of change in FEV_1 , IC, and IC to TLC ratio. Both dyspnea severity and quality of life status did not significantly affect lung function change. The occurrence of exacerbation seemed to affect the decline in IC but not FEV_1 over time (Figure S2). However, the exacerbation did not significantly affect the annual decline of FEV_1 , IC, and IC to TLC ratio after adjusting for multiple covariates even after dividing patients according to the severity of airflow limitation (mild to moderate, $FEV_1 \geq 50\%$ of predicted value; and more than severe, $FEV_1 < 50\%$ of predicted value) (Table 3). Even in patients with frequent exacerbation, no significant reductions in FEV_1 , IC, and IC to TLC ratios were observed compared with patients who did not.

Risk of exacerbation depending on lung function decline

Whether the exacerbation occurred was identified in 194 out of 544 subjects (35.7%) in the first, 144 out of 386 (37.3%) in the second, and 114 out of 248 (46.0%) in the third year, with 0.42 ± 1.17 , 0.29 ± 0.89 , and 0.24 ± 0.10 events/year incidence rate, respectively. On adjusting for multiple covariates, for the 3 years' follow-up, clinically important difference defined as FEV_1 change more than 100 mL and IC change more than

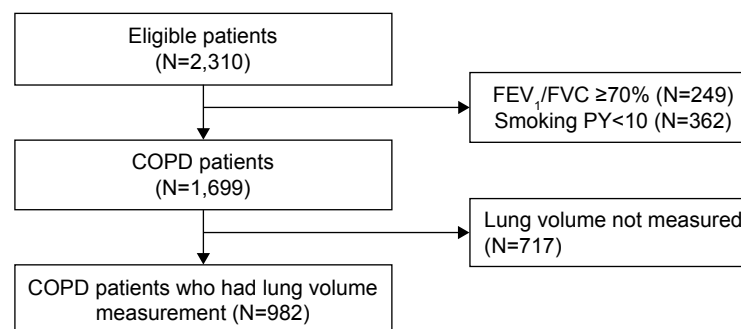


Figure 1 Study population.
Abbreviation: PY, pack-years.

Table 1 Baseline characteristics of study participants

Characteristics	All patients (N=982)
Male sex, n (%)	958 (97.6)
Age, years	72.7±8.4
BMI, kg/m ²	23.0±3.3
Ever smoker ^a	977 (99.8)
Smoking pack-years	45.4±24.0
mMRC dyspnea scale	1.4±0.9
CAT score	15.8±7.7
SGRQ score	35.1±19.0
6MWD, m	394.9±102.4
History of exacerbation in the past year	
Exacerbation (yes, %)	210 (21.6)
Frequency of exacerbation (number/year)	2.2±2.3
Post-bronchodilator FEV ₁	
Value, L	1.7±0.6
% of predicted value	62.7±19.3
Post-bronchodilator FVC	
Value, L	3.4±0.8
% of predicted value	87.8±17.6
Post-bronchodilator FEV ₁ /FVC, %	49.8±11.7
DLCO	
Value, mL/mmHg/min	13.4±5.8
% of predicted value	74.3±23.0
GOLD stage, n (%)	
I	173 (17.6)
II	547 (55.7)
III	230 (23.4)
IV	32 (3.3)

Notes: Data are presented as number (%) or mean ± SD. ^aEver smoker includes current or ex-smoker.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; DLCO, diffusing capacity for carbon monoxide; SGRQ, St George's Respiratory Disease Questionnaire.

150 mL did not relate to increased risk of exacerbation. In addition, based on multivariable analysis, low IC to TLC ratio was not a significant influencing factor for risk of exacerbation (Table 4).

Discussion

The severity of airflow obstruction, represented with FEV₁, is regarded as the most widely acceptable index in assessing patients with COPD. However, IC is also regarded as a potential index of COPD in relation to hyperinflation and exercise capacity. In the present study, FEV₁, IC, and IC to TLC ratio showed similar significant correlation with dyspnea, quality of life status, and exercise capacity. FEV₁ was significantly decreased at 3-year follow-up in patients with mild to moderate airflow limitation, and IC in patients with more than

Table 2 Lung volume measurement

Parameters	Value
VC	
L	3.3±0.8
% of predicted value	92.5±51.9
IC	
L	1.9±0.6
% of predicted value	74.6±22.9
RV	
L	2.8±1.2
% of predicted value	126.6±56.2
FRC	
L	3.8±0.9
% of predicted value	117.2±26.2
TLC	
L	6.1±1.3
% of predicted value	109.6±23.1
RV/TLC ratio, %	44.1±11.7
IC/TLC ratio, %	31.3±9.9
VC/TLC ratio, %	55.3±12.2

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

Abbreviations: FRC, functional residual capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity.

severe airflow limitation, but overall, longitudinal change did not show significant association with exacerbation risk.

The goal of COPD management is to improve symptoms, exercise tolerance, and health status, and to alleviate progression as well as prevent exacerbation. Severity of airflow limitation assessed by FEV₁ is considered as the most powerful biomarker of COPD, which not only reflects disease severity, but is also as a predictor of exacerbation and mortality, and a tool for the evaluation of treatment response.^{28–30} However, FEV₁ could not provide a guideline for treatment. In addition, although the FEV₁ values were the same, the degree of dyspnea and quality of life were different in each patient, and the agreement rate was not high.^{10,11} In the GOLD guideline revised in 2017,⁴ FEV₁ was excluded from the COPD classification due to limitations of disease activity, exacerbation, and mortality prediction. Instead, patients were classified simply by dyspnea severity and exacerbation history. However, there is a debate on the exclusion of FEV₁ in predicting the prognosis of COPD patients, and several studies disprove it.^{28–30} In addition to being a strong predictor of mortality and new hospital admission in COPD patients,³¹ baseline pulmonary function has been reported to be associated with increased exacerbation risk.^{32,33} In contrast, it was reported that the exacerbation incidence measured by patients' self-report was inaccurate.³⁴

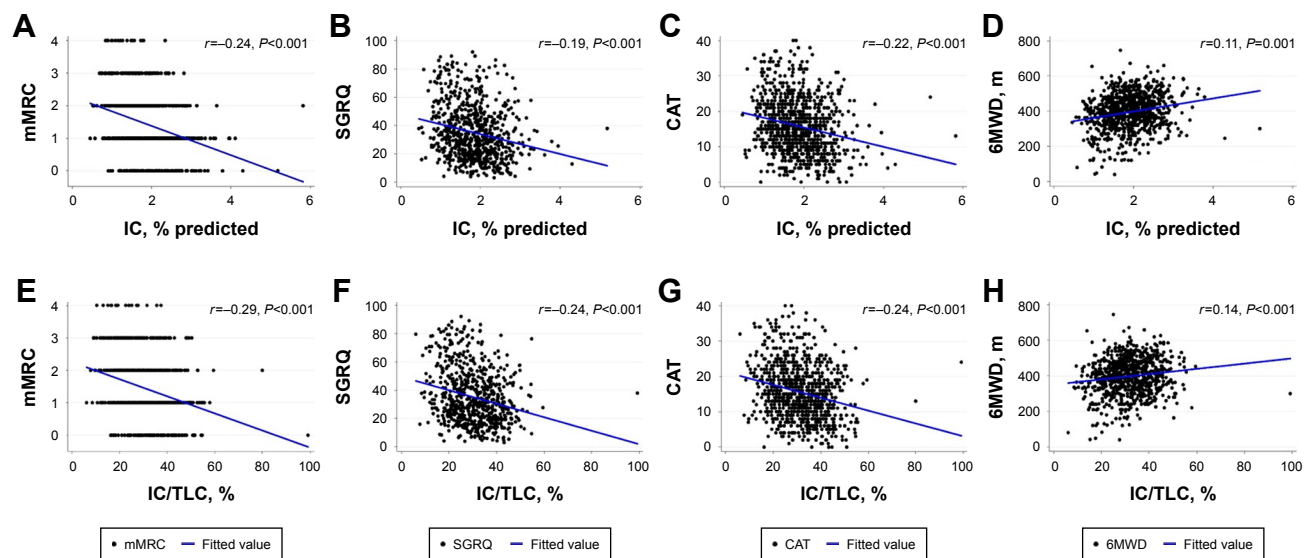
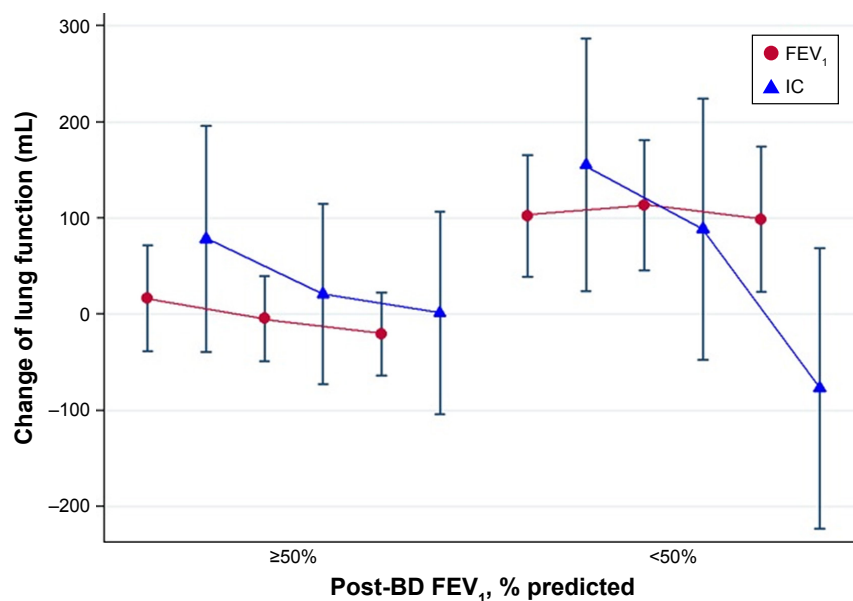


Figure 2 Correlation between IC, IC/TLC and (A, E) mMRC dyspnea scale, (B, F) SGRQ, (C, G) CAT, and (D, H) 6MWD in COPD patients.

Abbreviations: CAT, COPD assessment test; IC, inspiratory capacity; SGRQ, St George's Respiratory Disease Questionnaire; TLC, total lung capacity.



Value (mL)	FEV ₁ ≥50%	P-value	FEV ₁ <50%	P-value
Change of FEV₁				
1 year	16.84±27.80	0.393	102±31.13	<0.001
2 years	-4.47±22.33	0.366	113.43±33.20	0.038
3 years	-20.35±21.82	0.001	98.86±37.20	0.444
Change of IC				
1 year	78.42±59.46	0.491	155.43±64.47	0.089
2 years	20.96±47.30	0.446	88.57±66.85	0.156
3 years	1.40±53.08	0.811	-76.86±71.69	0.040

Figure 3 Mean change of FEV₁ and IC from enrollment.

Note: The bars in this graph represents the mean value and 95% CI.

Abbreviations: BD, bronchodilator; IC, inspiratory capacity.

Table 3 Effect of exacerbation on the change in FEV₁, IC, and IC/TLC ratio

Characteristics	Adjusted annual rate of change in FEV ₁ , mL/year	P-value	Adjusted annual rate of change in IC, mL/year	P-value	Adjusted annual rate of change in IC/TLC, %	P-value
FEV₁ ≥ 50%						
Exacerbation in the past year prior to enrollment		0.189		0.580		0.597
No	-22.28±6.26		-0.04±13.07		0.09±0.22	
Yes	-3.0±12.92		-16.26±26.22		-0.17±0.43	
Exacerbation during follow-up		0.935		0.546		0.520
Infrequent (<2/year)	-18.59±5.87		-5.90±12.14		0.01±0.20	
Frequent (≥2/year)	-16.88±20.29		22.46±45.36		0.50±0.75	
FEV₁ < 50%						
Exacerbation in the past year prior to enrollment		0.900		0.189		0.676
No	8.28±10.82		-2.16±20.34		-0.01±0.34	
Yes	6.12±13.35		-44.78±25.18		-0.23±0.40	
Exacerbation during follow-up		0.213		0.056		0.105
Infrequent (<2/year)	12.29±9.24		-4.75±17.28		0.13±0.29	
Frequent (≥2/year)	-14.46±19.40		-78.05±34.16		-0.95±0.50	

Notes: Data are shown as mean ± standard error. Mixed-effects linear regression analysis was performed, which included the following covariates: age, sex, BMI, exacerbation before and after enrollment, inhaled bronchodilator use, and interaction of each covariate with time.

Abbreviations: BMI, body mass index; IC, inspiratory capacity; TLC, total lung capacity.

This suggests a need for an objective indicator other than FEV₁ in patients' outcome prediction rather than simply self-reporting exacerbation.

The IC and IC to TLC ratio were also taken as an index of inspiratory restraint resulting from hyperinflation of the lung.¹⁴ Moreover, evaluation of IC can be reliably performed by recording flow-volume loop at rest.³⁵ Thus, there is an advantage of immediate measurement without

repeated spirometry for BDR. Hyperinflation of the lung is an important feature that causes exertional dyspnea and reduced exercise capacity in COPD.²⁷ Besides, decrement of lung hyperinflation correlates well with improvement in dyspnea after BD therapy.³⁶ For this reason, several clinical studies have assessed the efficacy of inhaler treatment by change in IC.^{17–20} However, IC has not yet been considered as a standard spirometry index of COPD assessment, and

Table 4 Exacerbation risk during the follow-up period of 3 years according to FEV₁ and IC changes^a and IC/TLC ratio^b

Lung function changes	Crude HR	95% CI	P-value	Adjusted HR ^c	95% CI	P-value
1 year						
IC change ≤ 150 mL	1.00	0.63–1.60	0.988	1.07	0.67–1.72	0.780
FEV ₁ change ≤ 100 mL	0.87	0.56–1.36	0.549	0.89	0.57–1.38	0.597
IC/TLC ≤ 25%	1.11	0.73–1.67	0.632	1.07	0.70–1.62	0.766
2 years						
IC change ≤ 150 mL	0.68	0.51–1.13	0.133	0.77	0.45–1.32	0.345
FEV ₁ change ≤ 100 mL	0.94	0.59–1.50	0.797	1.08	0.67–1.75	0.743
IC/TLC ≤ 25%	1.16	0.73–1.85	0.526	1.04	0.65–1.67	0.870
3 years						
IC change ≤ 150 mL	1.21	0.62–2.34	0.580	1.04	0.53–2.04	0.916
FEV ₁ change ≤ 100 mL	1.01	0.59–1.70	0.980	1.08	0.67–1.75	0.743
IC/TLC ≤ 25%	1.53	0.92–2.54	0.104	1.26	0.74–2.15	0.397

Notes: ^aBased on the minimal clinically important difference, the absolute value of the change was <150 mL for the IC, and 100 mL for the FEV₁, was regarded as reference value. ^bThe IC/TLC ratio was divided into low (IC/TLC ratio ≤ 25%) and high groups (IC/TLC ratio > 25%) ^cadjusted for age, sex, body mass index, smoking pack-years, and previous history of exacerbation in the past year.

Abbreviations: IC, inspiratory capacity; TLC, total lung capacity.

there are few studies comparing the usefulness of FEV₁ and IC as an indicator of COPD.

In this study, FEV₁, IC, and IC to TLC ratio showed negative correlation with dyspnea severity and quality of life status but positive correlation with exercise capacity in both. Although all correlations had statistical significance, the degree of association was not high but similar. It might be suggested that based on a single lung function measurement, it would be difficult to accurately assess breathlessness or quality of life status. In the analysis related to exacerbation, annual rate of change in FEV₁ and IC did not significantly differ from patients who experienced exacerbation or those who did not. Although, frequent exacerbators who experience more than two events per year, showed faster annual decline rates of FEV₁ and IC compared to those who did not, but, without statistical significance. During the 3 years' follow-up, IC decreased more rapidly than FEV₁, but until the second year, both values improved compared with those at the time of enrollment. Therefore, it is necessary to pay attention to the interpretation of the lung function decline and its relationship with exacerbation. Severity of airflow limitation is a known predictor of exacerbation,^{31,33} but increased frequency of exacerbation is also a contributing factor to lung function decline.^{6,37} We did not find a significant association between lung function changes and exacerbation. Actually, a 3-year follow-up is a relatively short period considering the course of the disease, and also, the reduction of FEV₁ and IC became clear only in the third year. Thus, further longitudinal analysis for identifying the relationship between change in lung function and exacerbation is needed.

In order to analyze the risk of exacerbation in each year, depending on changes in lung function, the effect of changes in MCID of each lung function index on exacerbation was evaluated. In patients with decreased FEV₁ and IC by more than MCID, the risk of exacerbation increased at 3 years, without statistical significance. In fact, since lung function was reduced after 3 years, analysis over a longer period would be needed. Moreover, a single value estimate may be difficult to use and may not present meaningful results. This is mainly due to heterogeneity of COPD patients. The same MCID estimate cannot be applied in both patients with mild airflow obstruction and with severe airflow obstruction.

Among all enrolled patients, only 4.7% had frequent exacerbation, defined as more than two exacerbations during follow-up period, and >70% of patients were mild to moderate disease status according to FEV₁ criteria, considering this, the overall burden of exacerbations may be underestimated with milder disease. However, in our study, occurrence of

frequent exacerbations was similar in patients with non-severe and severe status according to FEV₁ criteria.

The main strength of this analysis is the use of a large cohort of patients with COPD and lung volume measurement. Although we did not extract a significant relationship between exacerbation risk and lung function decline, we found that the longitudinal decline of FEV₁ and IC were different according to severity of airflow limitation, which reflects that both indices could complement each other in patient assessment. However, there are several limitations concerning interpretation of the findings. First, there were limited patients with annual follow-up of lung volume. Second, longer follow-up duration and prolonged volume measurement were needed for meaningful relevance between lung function change and exacerbation. Third, in our study, exacerbation events occurred only in male subjects, consequently, we could not analyze the sex-based differences in exacerbation risk. In addition, our study did not include a population sample but a sample of symptomatic patients known to respiratory clinicians and only Korean COPD patients were included. Moreover, we assessed exacerbation based on patients' self-reporting but other large cohort studies collected exacerbation data in the same way.^{38,39} Lastly, we could not compare COPD patients by phenotype due to the absence of an integrated radiologic test.

Conclusion

In summary, we showed that the exacerbation risk did not relate to significant change of either FEV₁ or IC over time, although the results of pulmonary function tests showed significant correlation with symptom and exercise performance indicators. This finding supports the hypothesis that assessing and predicting outcome in COPD patients by pulmonary function criteria alone is not appropriate and is consistent with current guidelines. We suggest that variation of FEV₁ and IC should be interpreted differently according to severity of airflow limitation, and follow-up of longer duration is needed to evaluate the relationship between lung function alteration and risk of exacerbation because of marked lung function deterioration from year 3.

Data sharing statement

Data sharing is limited due to the lack of consent from research participants. Thus, no further data will be available.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

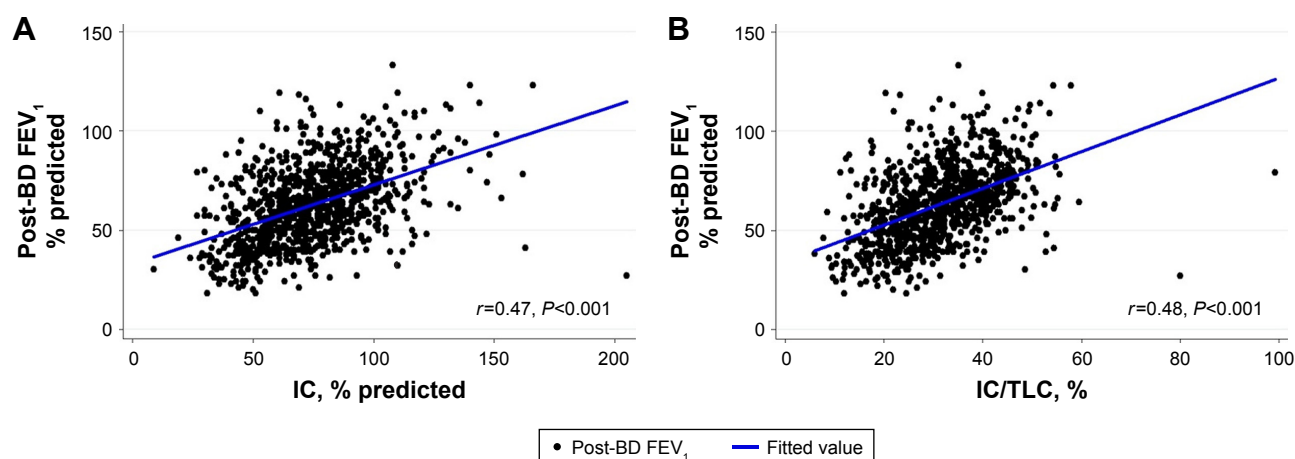


Figure S1 Correlation between (A) IC and (B) IC/TLC ratio with post-bronchodilator FEV_1 .
Abbreviations: BD, bronchodilator; IC, inspiratory capacity; TLC, total lung capacity.

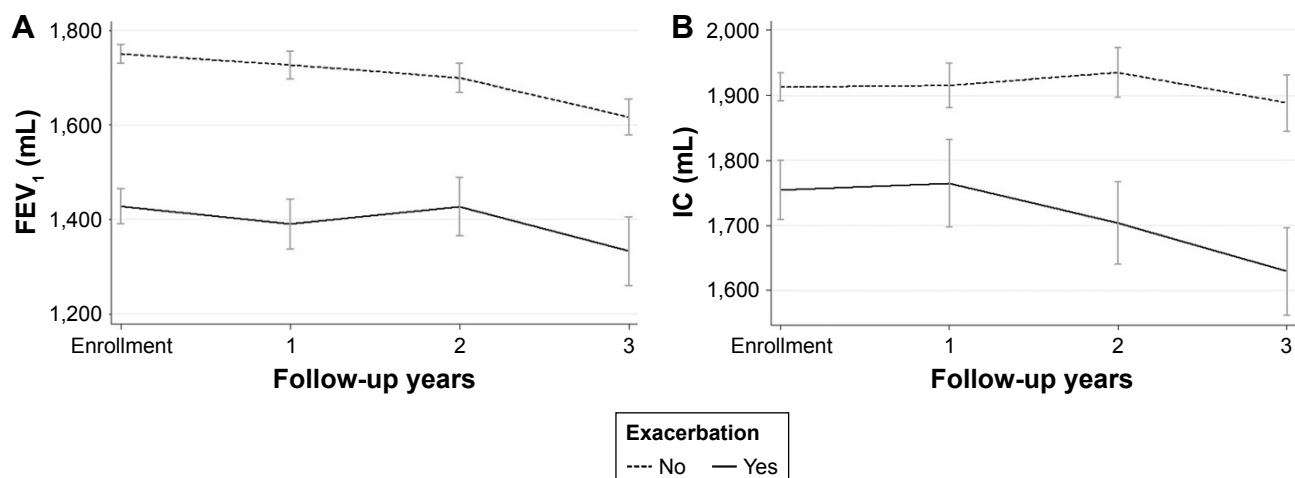


Figure S2 Longitudinal change of annual (A) FEV_1 and (B) IC (mL) in COPD patients during 3-year follow-up according to history of exacerbation.
Abbreviation: IC, inspiratory capacity.

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