



Clinical impact of forced vital capacity on exercise performance in patients with chronic obstructive pulmonary disease

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Background: Forced vital capacity (FVC) has been suggested to be a good biomarker for decreased exercise performance in patients with chronic obstructive pulmonary disease (COPD). However, as FVC is highly correlated with forced expiratory volume in 1 second (FEV₁), the relationship between FVC and exercise capacity should be assessed within the category of FEV₁, i.e., COPD severity. However, this was not considered in previous studies. Thus, limited data are available on the association between reduced FVC and exercise capacity measured by 6-min walk distance (6MWD) based on COPD severity.

Methods: We performed a cross-sectional study using data from the Korean COPD Subgroup Study (KOCOSS) cohort. We evaluated 1,386 patients with moderate (n=895) and severe-to-very severe (n=491) COPD. Reduced FVC was defined as FVC <80% predicted and short 6MWD as <350 m. Multivariable logistic regression was used to evaluate the association between reduced FVC and short 6MWD.

Results: There were no significant differences in respiratory symptoms and quality of life between the patients with reduced FVC and those with preserved FVC. However, patients with reduced FVC had shorter 6MWD (30.5 cm in moderate and 34.5 cm in severe-to-very severe COPD) and higher BODE index scores than those with preserved FVC. The cubic spline model revealed 6MWD peaked around 93% predicted of FVC in moderate COPD, whereas FVC showed a positive association with 6MWD in severe-to-very severe

COPD. Multivariable analyses showed that reduced FVC was significantly associated with short 6MWD in both moderate [adjusted odds ratio (aOR) =1.44, 95% confidence interval (CI): 1.03–2.02] and severe-to-very severe (adjusted OR =1.55, 95% CI: 1.01–2.40) COPD.

Conclusions: Reduced FVC was significantly associated with shorter 6MWD in moderate-to-very severe COPD patients, suggesting that reduced FVC might be reflective of 6MWD-measured exercise capacity in moderate-to-very severe COPD.

Keywords: Chronic obstructive pulmonary disease (COPD); 6-min-walk test (6MWT); forced vital capacity (FVC)

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Introduction

Physical inactivity is an important predictor of chronic obstructive pulmonary disease (COPD) outcomes. COPD patients with physical inactivity have reduced health-related quality of life, increased hospitalization, and higher mortality than those with good exercise capacity (1-5). Physical activity can be assessed using various methods, such as questionnaire surveys, self-reported diaries, and objective measurements (6,7). The 6-min walk test (6MWT) is a well-known exercise test that is useful for stratifying the degree of exercise performance in COPD patients (3,8-10). A short 6-min walk distance (6MWD) is strongly associated with reduced daily activity (8).

Spirometry is an essential and useful tool for diagnosing COPD, as well as for classifying its severity and prognosis (11). Although the forced expiratory volume in 1 second (FEV₁) has been widely used as a biomarker, recent studies have shown that forced vital capacity (FVC) could provide valuable information for both non-COPD and COPD patients. Accumulating evidence shows that reduced FVC is associated with multiple comorbid conditions (e.g., aging, cardiovascular disease, and obesity) and reduced exercise capacity in the general population (12-15). Several other studies on the COPD population revealed that FVC and FEV₁ are correlated with exercise capacity based on measures such as 6MWD, shuttle walk test distance, and peak maximum rate of oxygen consumption (VO₂ max) (16-20), and that reduced FVC is associated with behavior restriction, especially in those with moderate airflow limitations (21).

The above studies suggested that reduced FVC might be a good biomarker for predicting decreased 6MWD and behavior restriction. However, the relationship between reduced FVC and 6MWD in the COPD population is still

inconclusive because previous studies evaluated a small number of patients and analyzed FVC as a continuous variable (18,19). In addition, as FEV₁ is one of the most significant factors affecting exercise capacity and 6MWD, the severity of COPD needs to be considered for the evaluation of the relationship between FVC and 6MWD. However, this was not considered in previous studies (18,19). Thus, in this study, we aimed to investigate the relationship between FVC and exercise capacity measured using 6MWD, with stratification of the severity of airflow limitations, in a prospective observational COPD cohort.

Methods

Study population

The study population comprised patients from the Korean COPD Subgroup Study (KOCOSS) cohort (registered on ClinicalTrials.gov with identifier NCT02800499), which is an ongoing multicenter, prospective observational cohort of COPD that has included participants from 53 centers in South Korea since December 2011. The inclusion criteria were as follows: age ≥40 years and post-bronchodilator FEV₁/FVC ratio of <0.7. At the first visit, medical history information was collected, such as smoking status, patient-reported education level, medications including those already prescribed for COPD, and self-reported comorbidities taken from questionnaires. The modified Medical Research Council (mMRC) scores for dyspnea severity (22), COPD assessment test (CAT) scores (23), and scores from the COPD-specific version of St George's Respiratory Questionnaire (SGRQ-C) were assessed (24). Spirometry and 6MWT were performed at the time of enrolment. "History of asthma" was defined as patients' self-report of physician-diagnosis of asthma. All data were

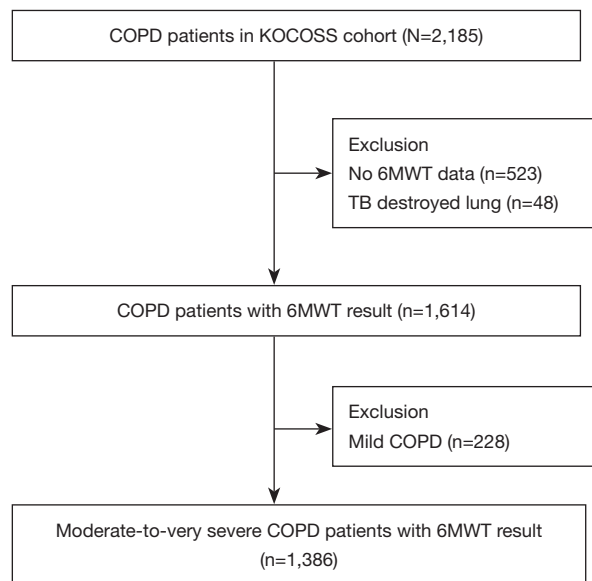


Figure 1 Study population. COPD, chronic obstructive pulmonary disease; KOCOSS, Korea COPD Subgroup Study; 6MWT, 6-min walk test; TB, tuberculosis.

documented in case report forms completed by physicians or trained nurses. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all study patients. Ethics approval for this study was obtained from the institutional review boards of each center (Samsung Medical Center, IRB No. 2014-06-132). All methods were performed in accordance with the relevant guidelines and regulations.

Initially, 2,185 patients recruited from the KOCOSS cohort were eligible for this study. Patients who had no 6MWD data ($n=523$), those with tuberculosis-destroyed lungs, defined as lung destruction of one lobe or more due to tuberculosis infection (25) ($n=48$), and those with a mild degree of airflow limitation ($n=228$) were excluded. Patients who had only history of tuberculosis infection without lung destruction were not excluded in this study. Finally, 1,386 patients were included our analysis (Figure 1).

Pulmonary function tests and disease severity

Spirometry was performed according to the recommendations of the American Thoracic Society/European Respiratory Society (26). All of the spirometric measures used included post-bronchodilator values for FEV_1 and FVC. COPD severity was categorized according to Global Initiative for Chronic Obstructive Lung Disease

grading system, as follows: moderate [50% predicted (pred) $\leq FEV_1 < 80\%$ pred], or severe-to-very severe ($FEV_1 < 50\%$ pred) (11). Patients were further classified into the preserved FVC group ($FVC \geq 80\%$ pred) and reduced FVC group ($FVC < 80\%$ pred) (21). We performed 6MWT according to the American Thoracic Society guidelines (27). Short 6MWD was defined as < 350 m in 6MWT (8,28).

Statistical analyses

For continuous variables, descriptive statistics were reported as mean \pm standard deviation, whereas categorical variables were reported as a number of patients (%) per category and the frequency of response. Continuous variables were compared using two-sample *t*-tests, whereas categorical variables were compared using chi-square or Fisher's exact tests, as appropriate. Cubic spline models were used to demonstrate an association between FVC (% pred) and 6MWD in patients with moderate and severe-to-very severe COPD, separately. We used multivariable logistic regression to evaluate the association between FVC and 6MWD, and patients with $FVC \geq 80\%$ pred were the reference group. We calculated the adjusted odds ratios (aOR) with progressive degrees of adjustment in patients with moderate and severe-to-very severe COPD, separately: Model 1 was adjusted for age, sex (male *vs.* female), and smoking status (ever smoker *vs.* never smoker); Model 2

included all variables in model 1 plus body mass index (BMI) (≥ 25 vs. < 25 kg/m²); and Model 3 included all variables in model 2 plus history of asthma. We considered a value of $P < 0.050$ as statistically significant. All statistical analyses were performed using STATA 15.1 version (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

The baseline characteristics of the study population are summarized according to COPD severity and FVC category in *Table 1*. Among moderate COPD patients, those with reduced FVC were more likely to be older ($P < 0.001$), have higher BMI ($P < 0.001$), and include fewer smokers ($P < 0.001$) than those with preserved FVC. However, in patients with severe-to-very severe COPD, there were no statistically significant differences in terms of age, BMI, and smoking status according to the FVC category.

With respect to pulmonary comorbidities, asthma was more common in patients with reduced FVC than in those with preserved FVC ($P = 0.044$ for moderate COPD, $P = 0.004$ for severe-to-very severe COPD). However, the prevalence of a history of previous tuberculosis infection was not different between the two groups.

With respect to extrapulmonary comorbidities, patients with reduced FVC in the moderate COPD group were more likely to have peripheral vascular disease ($P = 0.002$), diabetes mellitus ($P = 0.002$), hypertension ($P < 0.001$), and dyslipidemia ($P = 0.017$) than those with preserved FVC.

Among moderate and severe-to-very severe COPD patients, those with reduced FVC were more likely to have a higher BODE index score ($P < 0.001$) than those with preserved FVC. In contrast, patients with reduced FVC were more likely to have lower FEV₁ (L) (%pred) ($P < 0.001$) and higher FEV₁/FVC ratio ($P < 0.001$) than those with preserved FVC. In addition, patients with reduced FVC were more likely to have shorter 6MWD ($P < 0.001$ for moderate COPD, $P = 0.003$ for severe-to-very severe COPD) than those with preserved FVC. However, there were no statistically significant differences in the mMRC score, CAT score, and SGRQ-C total score between patients with reduced FVC and those with preserved FVC.

Relationship between FVC and 6MWD in COPD patients

Figure 2 shows the relationship between FVC (%pred)

and 6MWD evaluated using a cubic spline model. In moderate COPD patients, 6MWD steadily increased up to approximately 93% pred of FVC and plateaued (*Figure 2A*). While, in severe-to-very severe COPD patients, 6MWD steadily increased as FVC (%pred) increased (*Figure 2B*). The performance of FVC was comparable with that of FEV₁ as a predictor for short 6MWD (area under the receiver operating characteristic curve: 0.682 for FVC, 0.694 for FEV₁, $P = 0.301$) (*Figure S1*). Similarly, as analyzed using multivariable logistic regression, the performance of FVC was comparable with that of FEV₁ (Akaike's Information Criterion: 1,500.322 for FVC, 1,491.202 for FEV₁).

Impact of reduced FVC on 6MWD in moderate and severe-to-very severe COPD patients

As shown in *Table 2*, patients with reduced FVC were more likely to have a shorter 6MWD than those with preserved FVC in the moderate COPD group (22.4% vs. 32.7%; $P = 0.001$) and in the severe-to-very severe COPD group (36.9% vs. 46.0%; $P = 0.065$).

In moderate COPD patients, reduced FVC was significantly associated with short 6MWD [unadjusted OR = 1.68, 95% confidence interval (CI): 1.25–2.27], which was persistent even after adjusting for confounders including age, sex, smoking status, BMI, and asthma (aOR in model 3 = 1.44, 95% CI: 1.03–2.02).

In severe-to-very severe COPD, reduced FVC was significantly associated with short 6MWD in the final model, which was adjusted for age, sex, smoking status, BMI, and asthma (aOR = 1.55, 95% CI: 1.01–2.40).

Discussion

By using data from the KOCOSS cohort, we evaluated the association between FVC and exercise capacity measured using 6MWT in COPD patients. We observed that reduced FVC was significantly associated with short 6MWD in COPD patients with moderate (aOR = 1.44, 95% CI: 1.03–2.02) and severe-to-very severe (aOR = 1.55, 95% CI: 1.01–2.40) airflow limitations. 6MWD steadily increased in severe-to-very severe COPD patients, whereas the highest 6MWD value was observed at around 93% pred of FVC in moderate COPD patients.

Reduced FVC has been reported to have a relationship with low exercise capacity in COPD. However, most previous studies reported that FVC was simply correlated with 6MWD without considering the severity of COPD

Table 1 Baseline characteristics (N=1,386)

	Moderate COPD (n=895)			Severe-to-very severe COPD (n=491)		
	FVC ≥80%pred (n=513)	FVC <80%pred (n=382)	P value	FVC ≥80%pred (n=141)	FVC <80%pred (n=350)	P value
Male sex, n [%]	473 [92]	347 [91]	0.466	134 [95]	328 [94]	0.574
Age, years	71.6±7.9	75.1±7.2	<0.001	72.2±6.9	73.2±8.0	0.228
BMI, kg/m ²	23.0±2.9	24.3±3.4	<0.001	21.4±2.9	21.8±3.4	0.171
BMI ≥25 kg/m ² , n [%]	123 [24]	159 [42]	<0.001	12 [9]	53 [15]	0.050
Smoking, n [%]			<0.001			0.123
Ex-smoker or current smoker	485 [95]	329 [87]		133 [94]	314 [90]	
Never smoker	27 [5]	51 [13]		8 [6]	35 [10]	
Amount, pack-years	43.3±22.7	41.9±23.0	0.415	44.6±22.7	46.6±28.0	0.481
mMRC score, n [%]						
0–1	343 [71]	239 [67]	0.144	57 [43]	124 [37]	0.255
2–4	137 [29]	119 [33]		75 [57]	207 [63]	
CAT score	13.4±7.1	14.2±7.5	0.124	17.9±8.1	18.6±8.2	0.416
SGRQ score						
Total	29.8±19.0	32.1±19.2	0.155	41.8±19.4	43.8±22.9	0.440
Symptoms	41.1±19.8	41.7±20.0	0.722	50.8±20.8	50.6±20.9	0.921
Activity	41.2±21.0	44.2±20.4	0.089	55.0±21.6	57.1±24.3	0.449
Impact	20.2±17.8	22.1±18.8	0.203	29.4±18.8	31.7±21.7	0.372
SGRQ score, total ≥25, n [%], (n=897)	159 [54]	156 [59]	0.233	77 [79]	186 [77]	0.780
BODE index score	1.3±1.2	1.7±1.3	<0.001	3.9±1.6	4.6±1.7	<0.001
Comorbidities, n [%]						
Asthma	147 [29]	133 [35]	0.049	34 [24]	132 [38]	0.004
History of previous TB	120 [23]	87 [23]	0.829	40 [28]	101 [29]	0.921
Myocardial infarction	22 [4]	23 [6]	0.241	5 [4]	15 [4]	0.708
Heart failure	13 [3]	13 [3]	0.444	6 [4]	12 [3]	0.659
PVD	4 [1]	14 [4]	0.002	2 [1]	8 [2]	0.731
Diabetes mellitus	79 [15]	90 [24]	0.002	21 [15]	60 [17]	0.543
Hypertension	177 [35]	184 [48]	<0.001	50 [35]	128 [37]	0.817
Osteoporosis	22 [4]	24 [6]	0.181	6 [4]	19 [5]	0.593
GERD	50 [10]	41 [11]	0.629	9 [6]	30 [9]	0.417
Dyslipidaemia	53 [10]	60 [16]	0.017	10 [7]	35 [10]	0.312

Table 1 (continued)

Table 1 (continued)

	Moderate COPD (n=895)			Severe-to-very severe COPD (n=491)		
	FVC \geq 80%pred (n=513)	FVC <80%pred (n=382)	P value	FVC \geq 80%pred (n=141)	FVC <80%pred (n=350)	P value
Pulmonary function test						
FVC, L	3.73 \pm 0.60	2.85 \pm 0.49	<0.001	3.62 \pm 0.54	2.47 \pm 0.57	<0.001
FVC %pred	92.1 \pm 9.3	70.9 \pm 6.6	<0.001	90.7 \pm 8.5	62.4 \pm 11.3	<0.001
FEV ₁ , L	1.86 \pm 0.39	1.65 \pm 0.33	<0.001	1.17 \pm 0.24	1.02 \pm 0.25	<0.001
FEV ₁ %pred	66.1 \pm 8.4	61.8 \pm 7.3	<0.001	42.2 \pm 5.8	37.6 \pm 7.7	<0.001
FEV ₁ /FVC	50.1 \pm 8.5	58.1 \pm 7.0	<0.001	32.5 \pm 5.1	42.2 \pm 10.1	<0.001
DLco	14.2 \pm 4.5	14.3 \pm 4.6	0.820	11.4 \pm 4.5	10.6 \pm 4.0	0.116
Six-minute walk test						
Distance, m	414.5 \pm 100.1	384.0 \pm 106.5	0.001	377.1 \pm 106.1	342.6 \pm 119.5	0.003
SpO ₂ , before test	96.2 \pm 2.4	96.4 \pm 1.9	0.194	95.8 \pm 2.1	95.4 \pm 3.0	0.160
SpO ₂ , after test	94.6 \pm 4.0	94.5 \pm 7.8	0.720	93.0 \pm 4.7	91.7 \pm 7.8	0.080

Two-sample *t*-tests were used for continuous variables, and chi-square or Fisher's exact tests were used for categorical variables. COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; pred, predicted; BMI, body mass index; mMRC, modified Medical Research Council; CAT, COPD assessment test; SGRQ, St George's respiratory questionnaire; BODE, body mass index, airflow obstruction, dyspnoea, and exercise capacity; TB, tuberculosis; PVD, peripheral vascular disease; GERD, gastroesophageal reflux disease; FEV₁, forced expiratory volume in 1 second; DLco, diffusing capacity of the lung for carbon monoxide; SpO₂, peripheral oxygen saturation.

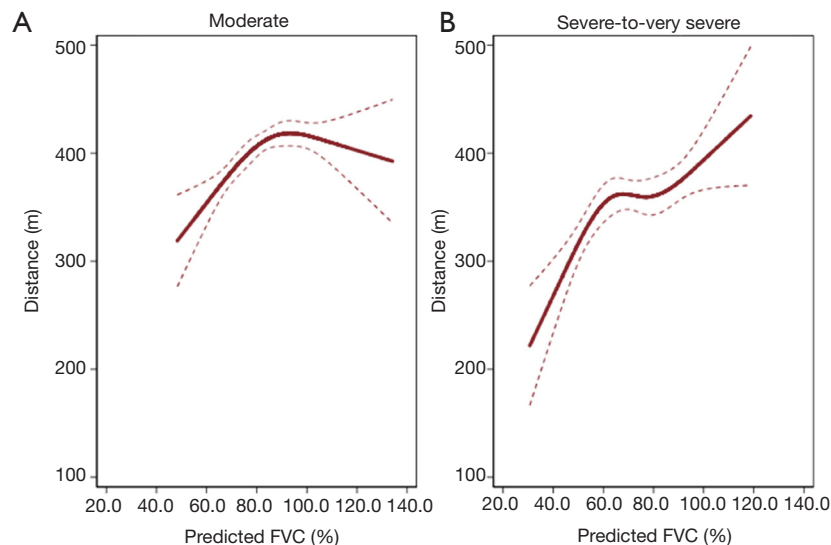


Figure 2 Cubic spline model for the relationship between 6-min walk distance and forced vital capacity, %predicted in patients with moderate and severe-to-very severe COPD. (A) Relationship in patients with moderate COPD. (B) Relationship in patients with severe-to-very severe COPD. COPD, chronic obstructive pulmonary disease.

Table 2 Impact of reduced FVC on short 6MWD in patients with moderate COPD and severe-to-very severe COPD

	Moderate COPD (n=895)		Severe-to-very severe COPD (n=491)	
	FVC \geq 80%pred (n=115/513, 22.4%)	FVC <80%pred (n=125/382, 32.7%)	FVC \geq 80%pred (n=52/141, 36.9%)	FVC <80%pred (n=161/350, 46.0%)
Crude	Reference	1.68 (1.25, 2.27)	Reference	1.46 (0.98, 2.18)
Model 1	Reference	1.43 (1.03, 1.98)	Reference	1.59 (1.04, 2.45)
Model 2	Reference	1.44 (1.03, 2.01)	Reference	1.60 (1.04, 2.46)
Model 3	Reference	1.44 (1.03, 2.02)	Reference	1.55 (1.01, 2.40)

Data are presented as OR and 95% CI. Model 1: adjusted for age, sex, and smoking status. Model 2: adjusted for age, sex, smoking status, and body mass index \geq 25 kg/m². Model 3: adjusted for age, sex, smoking status, body mass index \geq 25 kg/m², and asthma. Multivariable logistic regression was used and patients with FVC \geq 80%pred were the reference group. FVC, forced vital capacity; pred, predicted; 6MWD, 6-min walk distance; COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

(18,19,29,30). This study revealed the increase patterns were different between moderate COPD group and severe-to-very severe COPD group. In patients with moderate COPD, the exercise capacity did not improved beyond 93% pred of FVC, whereas, in patients with severe-to-very severe COPD, the exercise capacity was positively associated with FVC %pred in all ranges of FVC %pred. In a previous study with analysis based on COPD severity using Korea National Health and Nutritional Examination Survey data, reduced FVC was independently associated with behavior restrictions in the population with moderate COPD (21); however, behavior restrictions were assessed using a self-reported questionnaire. We extended this finding with objective measurement, 6MWT, and our data showed that reduced FVC was closely associated with short 6MWD, defined as a 6MWD of <350 m, in moderate COPD patients. We also showed that FVC %pred was associated with 6MWD in severe-to-very severe COPD patients, which was not captured with the self-reported questionnaire for behavior restriction in the previous study (21). Thus, preserved FVC may indicate better exercise capacity even in patients with severe-to-very severe COPD.

We observed that higher FVC was associated with better exercise performance, indicating that higher FVC is an important predictor of better exercise capacity in COPD patients with severe-to-very severe airflow limitation. In COPD patients with moderate airflow limitation, however, exercise capacity steadily increased up to 93% pred of FVC, and plateaued, suggesting that the role of FVC in estimating exercise capacity would be limited when the FVC reached around 90% pred. It can be speculated by that 6MWT might have a ceiling effect (31) which influenced decreased

discrimination power in moderate COPD patients with greater than 93% pred of FVC. Secondly, the relatively small number of moderate COPD patients with greater than 93% pred of FVC (n=239) may have led to imprecise estimates of 6MWD.

Reduced FVC reflected a mixed pattern with both obstructive and restrictive components or air trapping of obstructive disease (32,33). Given that comorbidities and obesity influence the reduction of FVC in COPD patients (21,34,35), the higher prevalence of comorbidities and BMI in moderate COPD patients could affect reduced FVC, leading to a mixed disorder of lung function. Reduced FVC could also be associated with air-trapping-related pseudo-restriction (33); however, lung volume measurement data were partly (64%, 573/895) of moderate COPD, 55% (268/491) of severe-to-very severe COPD obtained in this study to identify hyperinflation and air trapping (33). Further studies with a measurement of total lung capacity might be helpful for further characterization of the underlying aetiologies of reduced FVC in COPD patients (36).

The relevance of short 6MWD, defined as <350 m, has been emphasized in the previous studies (8,28). Below the threshold of 350 m, 6MWD was associated with increased risks of mortality, hospitalizations, and exacerbations (8,37). Accordingly, patients with reduced FVC showed higher BODE index scores than those with preserved FVC despite the similar mMRC score and higher BMI. Considering that symptoms quantified using mMRC, CAT, and SGRQ were similar between patients with reduced FVC and those with preserved FVC, clinicians need to pay more attention to impairment in FVC in addition to FEV₁ to predict exercise capacity and other outcomes.

This study has several limitations. First, the data were obtained from the cross-sectional KOCOSS cohort; therefore, the directionality of the relationship between reduced FVC and poor exercise capacity is uncertain. Further clinical studies with longitudinal follow-up are needed to confirm our observations. Second, as most of the patients were men with a history of smoking, it is difficult to generalize the results from this study to non-smokers or women with COPD. Last, potential confounding factors which could affect on FVC such as interstitial lung disease and cardiac disease could not be thoroughly investigated in this study due to lack of disease severity-related data such as chest computed tomography and echocardiography in the cohort. Further comprehensive evaluations are warranted.

Conclusions

In conclusion, reduced FVC is significantly associated with short 6MWD in moderate-to-very severe COPD, suggesting that reduced FVC might be reflective of exercise capacity measured by 6MWD. Further studies on the clinical relevance of reduced FVC are warranted.

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Footnote

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obtained from the institutional review boards of each center (Samsung Medical Center, IRB No. 2014-06-132).

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