

# FEF<sub>25-75%</sub> Values in Patients with Normal Lung Function Can Predict the Development of Chronic Obstructive Pulmonary Disease

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**Purpose:** The forced mid-expiratory flow (FEF<sub>25-75%</sub>) value is a potentially sensitive marker of obstructive peripheral airflow. We aimed to assess whether FEF<sub>25-75%</sub> can be an early predictor of chronic obstructive pulmonary disease (COPD).

**Patients and Methods:** Between July 1, 2007 and June 31, 2009, we identified 3624 patients who underwent a pulmonary function test (PFT) in Gangnam Severance Hospital. We selected 307 patients aged over 40 years without COPD who had normal PFT results at baseline and who had follow-up PFT records more than 1 year later. A FEF<sub>25-75%</sub> z-score less than -0.8435 was considered low. We defined COPD as a forced expiratory volume in one second/forced vital capacity value of less than 0.7 before July 31, 2019.

**Results:** Among 307 patients, 91 (29.6%) had low FEF<sub>25-75%</sub> at baseline. After 10 years, the incidence rate of COPD in the low FEF<sub>25-75%</sub> group was significantly higher than that in the normal FEF<sub>25-75%</sub> group (41.8% vs 7.4%; *P*-value<0.001). The Cox proportional hazard model showed that age (hazard ratio [HR] 1.09; *P*-value<0.001), smoking status (occasional smoker HR, 4.59; *P*-value<0.001 and long-term smoker HR, 2.18; *P*-value=0.023), and low FEF<sub>25-75%</sub> (HR, 3.31; *P*-value<0.001) were predictive factors for the development of COPD.

**Conclusion:** The FEF<sub>25-75%</sub> value in patients with normal lung function is a useful predictor for the development of COPD. We should carefully monitor patients who present with low FEF<sub>25-75%</sub> values, even if they have normal lung function.

**Keywords:** COPD, respiratory function tests, tobacco

## Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable chronic airway disease;<sup>1</sup> however, the economic burden of terminal COPD is enormous, with COPD being a leading cause of death worldwide. Accurate prediction and early detection of COPD may encourage patients to stop smoking and allow for appropriately timed treatments.<sup>2</sup> Ultimately, the ability to predict COPD may prevent airway remodeling, improve prognosis, and diminish its medical and economic burden.<sup>3,4</sup> Many researchers have attempted to identify early predictors for COPD development. The pulmonary function test (PFT) is a safe and practical procedure that is widely performed to detect COPD. Recently, a decrease in the forced expiratory volume in one second (FEV<sub>1</sub>)<sup>5</sup> or diffusing capacity of the lungs for carbon monoxide (DLCO)<sup>6</sup> in PFT has been suggested as a marker to predict COPD development (FEV<sub>1</sub>/forced vital capacity [FVC] <0.7). In the clinic, we frequently encounter patients who smoke, have respiratory symptoms, and have normal PFT results. We hypothesized that among some patients with normal lung

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function, including normal FEV<sub>1</sub> and DLCO values, forced mid-expiratory flow (FEF<sub>25-75%</sub>) may be an early predictive marker for the development of COPD among high-risk individuals.

FEF<sub>25-75%</sub> is the most sensitive measure of airflow in peripheral airways where primary airflow obstruction originates,<sup>7</sup> and it is reduced in early bronchial impairment, which is associated with small airway disease.<sup>8-11</sup> Airway remodeling, mucus plugging, and immune cell infiltration induced by cigarette smoking ultimately result in small airway disease, which is a cardinal feature of COPD.<sup>12</sup> Some researchers have found that decreased FEF<sub>25-75%</sub> is frequently observed in patients with COPD.<sup>13</sup> We can therefore assume that FEF<sub>25-75%</sub> might be an earlier marker for COPD than other markers, such as FEV<sub>1</sub>, DLCO, and FVC. However, no prospective study has examined FEF<sub>25-75%</sub> as a predictor of COPD.

Thus, in this observational cohort study, we aimed to determine whether the FEF<sub>25-75%</sub> value measured at baseline can predict COPD development over 10 years.

## Materials and Methods

### Patients and Study Flow

From July 1, 2007 to June 31, 2009, we identified 6624 patients who underwent PFT at Gangnam Severance Hospital. We excluded 4458 patients with abnormal PFT results, defined as at least one of the following three criteria: the FEV<sub>1</sub>/FVC [ $<0.7$ ], FVC [ $<80\%$  of predicted value], and FEV<sub>1</sub> [ $<80\%$  of predicted value]. An additional 1859 patients were excluded for the following reasons: no records of PFT performed more than 1 year after the baseline ( $n=1297$ ), under 40 years of age ( $n=156$ ), restrictive lung disease history ( $n=137$ ), and history of asthma ( $n=125$ ) and COPD ( $n=144$ ). Finally, we reviewed the electronic medical records of the remaining 307 patients with normal PFT results at baseline and grouped them according to the FEF<sub>25-75%</sub> values (Figure 1).

### Parameters

We collected clinical information on sex, age, body mass index (BMI), smoking history, and the following comorbidities: arterial hypertension, diabetes mellitus, coronary heart disease (CHD), old cerebrovascular accident (CVA), alcoholics, reflux esophagitis (RE), peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), depression, and history of pulmonary tuberculosis. These co-morbidities were checked through electronic medical records. BMI was calculated by dividing the weight in kilograms by the square of height in

meters ( $\text{kg}/\text{m}^2$ ) when the first spirometry was performed. Smoking status was classified as never smoked, occasional smoker ( $<20$  pack-years), or long-term smoker ( $\geq 20$  pack-years), in accordance with a previous study.<sup>14</sup> We calculated pack-years by multiplying the number of packs of cigarettes smoked per day by the number of years the person smoked. This retrospective study was approved by the Institutional Review Board (IRB) of Gangnam Severance Hospital (number: 2019-0556-001). The requirement of informed consent was waived because of the retrospective nature of the study.

### PFT

Baseline spirometry tests were performed during the cohort period using Vmax229 and Vmax22 spirometers (SensorMedics Corp., Italia). The procedures were performed following the American Thoracic Society and European Respiratory Society criteria, 2005,<sup>15</sup> with all patients seated and wearing nose clips. The procedure was repeated three times, which is an acceptable and reproducible method of effort. When a suitable spirometry test was performed, the FEV<sub>1</sub> and FVC values were determined to be the most significant values on the FEV curves, and the two values could be determined on different curves. Baseline FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, FVC, and FEF<sub>25-75%</sub> values were obtained for the study. All of the reference values were based on the Global Lung Function Initiative 2012.<sup>16</sup>

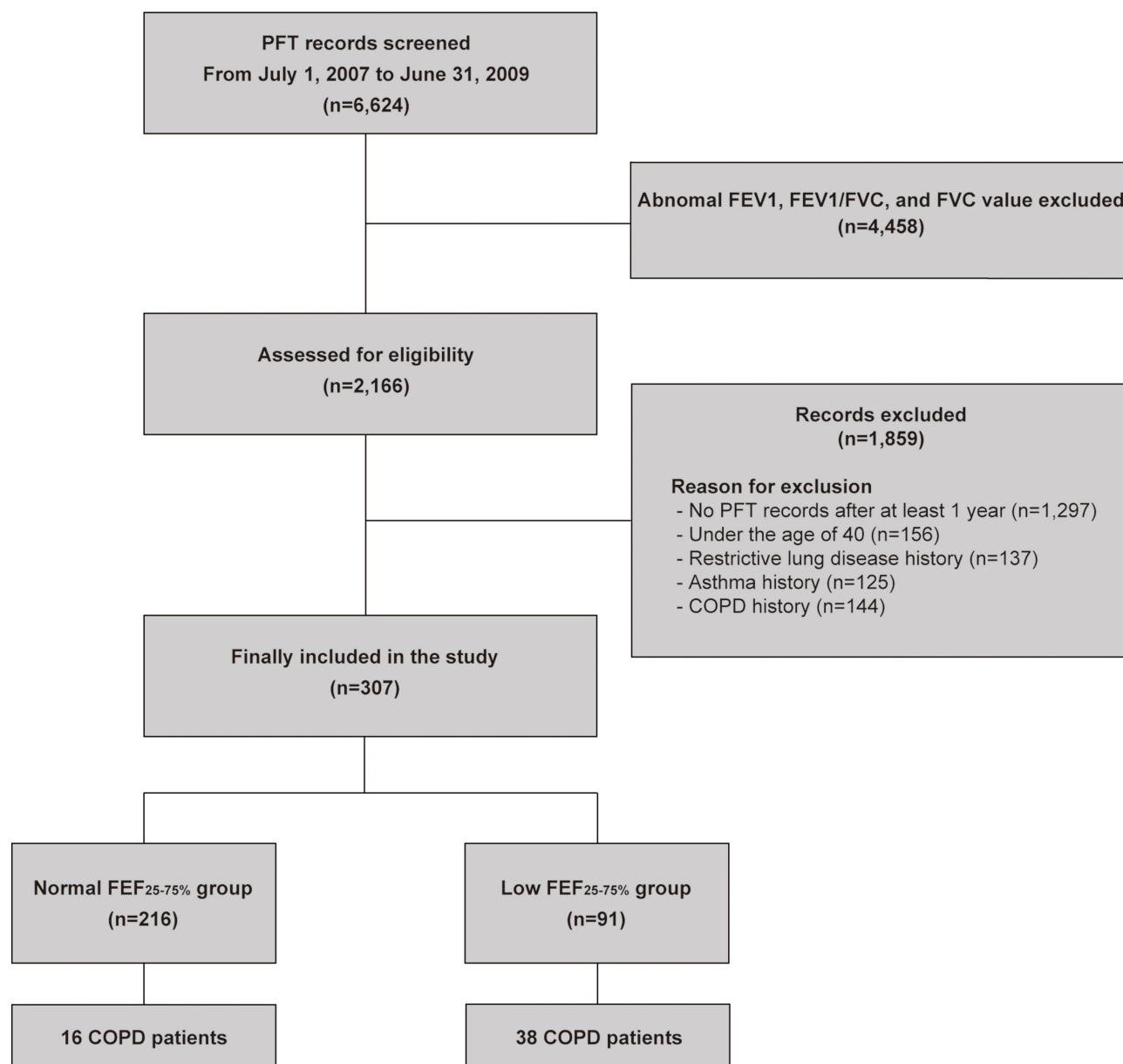
### COPD Development

Patients underwent follow-up PFTs at intervals between 6 months and 1 year. While not on a standard schedule, most patients in this study underwent PFTs frequently. Reasons for follow-up PFTs differed among patients and were as follows: routine follow-up, respiratory symptoms, abnormal lesion in chest images, patient's request, and doctor's recommendation. If an obstructive pattern was shown in the PFT, a bronchodilator test was performed to evaluate the reversibility of bronchial obstruction.

We reviewed all PFT results, which were conducted before July 13, 2019. We defined the development of COPD when post-bronchodilation FEV<sub>1</sub>/FVC was less than 0.7.

### Statistical Analysis

All analyses were performed using R Statistical Package (version 4.0.2; Institute for Statistics and Mathematics, Vienna, Austria). The values are expressed as means  $\pm$  standard deviations for continuous variables and as numbers and percentages for categorical variables. FEF<sub>25-75%</sub> z-score was treated as both a continuous and categorical dependent variable in the



**Figure 1** Flow chart of this study.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEF, forced mid-expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PFT, pulmonary function test.

analyses. We used t-tests for continuous variables and chi-square tests for categorical variables to evaluate the relationship between the outcome and independent variables. Univariate and multivariate Cox proportional hazards models were used to analyze factors associated with COPD development. In the univariate analysis, independent variables with a *P*-value <0.05 were statistically significant and were included in the multivariate model. Cox proportional hazard analysis was used to identify differences in the cumulative development of COPD (%) between the normal FEF<sub>25-75%</sub> and low FEF<sub>25-75%</sub> groups.

## Results

### Baseline Clinical Characteristics of Enrolled Patients According to the Groups and the Optimal Cut-off Value for Low FEF<sub>25-75%</sub>

To classify patients with normal PFT results into low and normal FEF<sub>25-75%</sub> groups, we initially estimated the optimal cut-off value of FEF<sub>25-75%</sub> z-score for predicting COPD development using the Youden index method.<sup>17</sup> The optimal cut-off value for FEF<sub>25-75%</sub> z-score was -0.8435

(sensitivity 0.7037 and specificity 0.7905). Among 307 patients, 216 (70.4%) and 91 (29.6%) patients were included in the normal FEF<sub>25-75%</sub> and low FEF<sub>25-75%</sub> groups, respectively (Table 1). The baseline clinical characteristics, including BMI, presence of co-morbidity, history of pulmonary tuberculosis, and smoking status were not significantly different between the two groups. However, males were more predominant in the low FEF<sub>25-75%</sub> group than in the normal FEF<sub>25-75%</sub> group (73.6% vs 36.1%,  $P<0.001$ ). In addition, mean patient age was lower in the low FEF<sub>25-75%</sub> group than in the normal FEF<sub>25-75%</sub> group ( $58.9\pm10.1$  vs  $62.5\pm10.5$ ,  $P=0.006$ ). Regarding co-morbidities, depression was more prevalent in the low FEF<sub>25-75%</sub> group than in the normal FEF<sub>25-75%</sub> group (12.1% vs 1.9%,  $P<0.001$ ) (Table 1).

**Table 1** Baseline Characteristics of Enrolled Patients According to FEF<sub>25-75%</sub> z-Score

Variables	Total (n=307)	Normal FEF <sub>25-75%</sub> (n=216)	Low FEF <sub>25-75%</sub> * (n=91)	P-value
Male	145 (47.2%)	78 (36.1%)	67 (73.6%)	<0.001
Mean age (years)	61.4±10.5	62.5±10.5	58.9±10.1	0.006
Height (cm)	160.7±8.7	161.0±9.0	160.2±8.0	0.486
Weight (kg)	62.2±9.4	62.6±9.7	61.2±8.8	0.231
BMI (kg/m <sup>2</sup> )	24.0±3.0	24.1±3.0	23.8±3.0	0.535
Co-morbidity				
Hypertension	126 (41.0%)	87 (40.3%)	39 (42.9%)	0.770
Diabetes	57 (18.6%)	39 (18.1%)	18 (19.8%)	0.846
CHD	26 (8.5%)	19 (8.8%)	7 (7.7%)	0.926
Previous CVA	11 (3.6%)	8 (3.7%)	3 (3.3%)	1.000
RE, PUD or GERD	18 (5.9%)	11 (5.1%)	7 (7.7%)	0.536
Depression	15 (4.9%)	4 (1.9%)	11 (12.1%)	<0.001
History of tuberculosis	54 (17.6%)	33 (15.3%)	21 (23.1%)	0.140
Smoking status**				0.851
Never smoker	197 (66.8%)	142 (65.7%)	55 (60.4%)	
Occasional smoker	24 (8.1%)	16 (7.4%)	8 (8.8%)	
Long-term smoker	74 (25.1%)	50 (23.1%)	24 (26.4%)	
Unknown	12 (3.9%)	8 (3.7%)	4 (4.4%)	

**Notes:** Data are presented as mean ± standard deviation or number of patients (%). \*Low FEF<sub>25-75%</sub>: FEF<sub>25-75%</sub> z-score below -0.8435 (the optimal cut-off value for predicting COPD development). \*\*Occasional smoker: an adult who has smoked less than 20 pack-years in his or her lifetime; long term smoker: an adult who has smoked over 20 pack-years in his or her lifetime.

**Abbreviations:** BMI, body mass index; CHD, coronary heart disease; CVA, cerebrovascular accident; FEF, forced mid-expiratory flow; GERD, gastroesophageal reflux disease; PUD, peptic ulcer disease; RE, reflux esophagitis.

## Baseline Pulmonary Function According to the Groups

When comparing baseline PFT results between the normal and low groups, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and FVC values in the low FEF<sub>25-75%</sub> group were all significantly lower than those in the normal FEF<sub>25-75%</sub> group (Table 2). However, all PFT results were within the normal range at baseline.

## Significant Predictive Factors for the Development of COPD

Over the 10-year follow-up, 54 patients (17.6%) developed COPD among 307 patients. The incidence of COPD in the low FEF<sub>25-75%</sub> group was significantly higher than that in the normal FEF<sub>25-75%</sub> group (38 patients, 41.8% vs 16 patients, 7.4%;  $P<0.001$ ). We identified significant factors for the development of COPD using Cox proportional hazard analysis. In the univariate analysis, age, depression, smoking status, FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and FEF<sub>25-75%</sub> z-scores were significant factors in COPD development (Table 3). We selected significant factors in the univariate analysis and included them in the multivariate analysis. However, the variance inflation factor of FEV<sub>1</sub> z-scores was 6.390 in the multivariate analysis model, and it was not analyzed owing to multi-collinearity with other variables. The multivariate analysis revealed that the significant factors for COPD development were age (HR, 1.088; 95% confidence interval [CI], 1.050–1.128), smoking status (occasional smoker HR, 4.586; 95% CI, 1.913–10.993 and long-term smoker HR, 2.179; 95% CI, 1.115–4.258), FEV<sub>1</sub>/FVC z-score (HR, 0.452; 95% CI, 0.219–0.936), and FEF<sub>25-75%</sub>

**Table 2** Results of Lung Function Test According to the FEF<sub>25-75%</sub> z-Score

Variables	Total (n=307)	Normal FEF <sub>25-75%</sub> (n=216)	Low FEF <sub>25-75%</sub> * (n=91)	P-value
FEV <sub>1</sub> (L)	2.5±0.6	2.6±0.6	2.2±0.6	<0.001
FEV <sub>1</sub> (%) predicted)	105.0 ±16.6	109.8±16.2	93.5±11.2	<0.001
FVC (L)	3.2±0.8	3.3±0.8	3.0±0.8	0.007
FVC (%) predicted)	97.6 ±13.5	99.7±14.3	92.7±10.0	<0.001
FEF <sub>25-75%</sub> (L/sec)	2.2±0.8	2.4±0.8	1.6±0.5	<0.001
FEF <sub>25-75%</sub> (%) predicted)	82.9 ±25.7	93.0±23.4	58.7±10.0	<0.001
FEV <sub>1</sub> /FVC	77.1±4.8	78.6±4.7	73.6±2.9	<0.001

**Notes:** \*Low FEF<sub>25-75%</sub>: FEF<sub>25-75%</sub> z-score below -0.8435 (the optimal cut-off value for predicting COPD development)

**Abbreviations:** FEF, forced mid-expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

z-score (HR, 0.453; 95% CI, 0.267–0.766). However, depression was not a significant factor for the development of COPD in the multivariate analysis (HR, 1.550; 95% CI, 0.674–3.566) (Table 3).

The low FEF<sub>25-75%</sub> group was also a significant risk factor for the development of COPD in the multivariate analysis (HR, 3.308; 95% CI, 1.650–6.632). In the Kaplan-Meier curve, the cumulative development of COPD was significantly higher in the low FEF<sub>25-75%</sub> group than in the normal FEF<sub>25-75%</sub> group (Figure 2;  $P < 0.001$ ).

## Comparison of PFT Parameters for Predicting COPD Development

We obtained and compared the receiver operating characteristic (ROC) curve of each PFT parameter for predicting COPD development (Figure 3). The area under the ROC curve was the highest for FEF<sub>25-75%</sub> z-score (0.779; 95% CI, 0.715–0.843) and FEV<sub>1</sub>/FVC z-score (0.783; 95% CI, 0.716–0.851),

followed by FEV<sub>1</sub> z-score (0.649; 95% CI, 0.578–0.720) and FVC z-score (0.557; 95% CI, 0.480–0.634).

## Discussion

In this 10-year follow-up observational cohort study, we showed that patients with decreased FEF<sub>25-75%</sub> were susceptible to develop COPD, despite the fact that they showed normal lung function, including normal FEV<sub>1</sub> and FVC values. FEF<sub>25-75%</sub> was an independent risk factor for COPD even after adjustment for age, smoking history, and FEV<sub>1</sub>/FVC at baseline. As far as we know, this is the first study to reveal a significant association between FEF<sub>25-75%</sub> and the development of COPD. Small airway obstruction is a fundamental feature of COPD, and FEF<sub>25-75%</sub> reflects small airway disease.<sup>18</sup> However, earlier research studies have described that FEF<sub>25-75%</sub> has high variability, and thus, its normal range is large.<sup>19</sup> Therefore, FEF<sub>25-75%</sub> has not been studied for medical

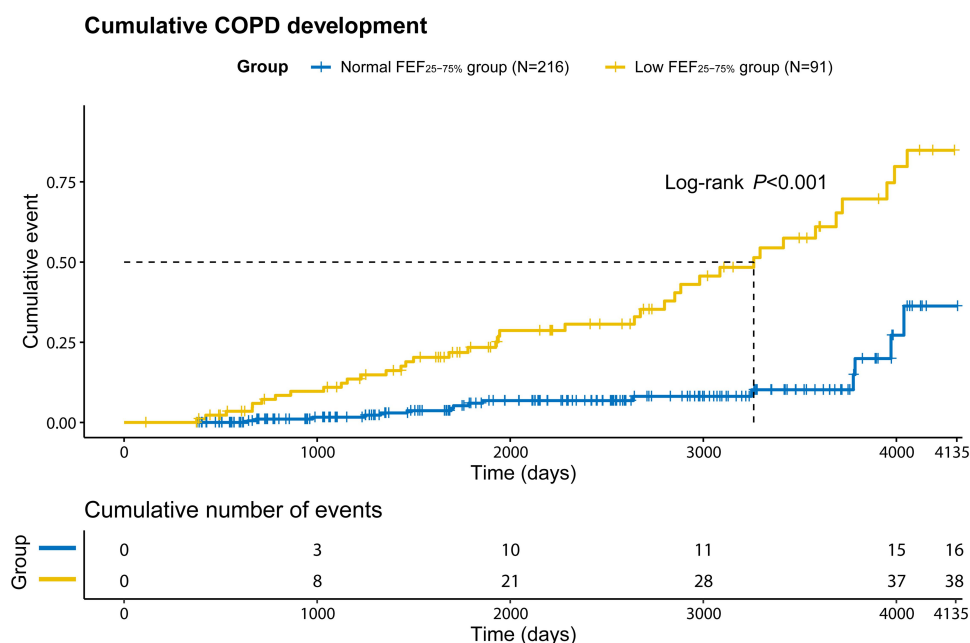
**Table 3** Significant Factors for Development of COPD

	Univariate Analysis			Multivariate Analysis			
	HR	95% CI	P-value	HR	95% CI	P-value	VIF
<b>Low FEF<sub>25-75%</sub>*†</b>	<b>5.665</b>	<b>3.156–10.166</b>	<b>&lt;0.001</b>	<b>3.308</b>	<b>1.650–6.632</b>	<b>&lt;0.001</b>	
Sex (male)	1.616	0.941–2.777	0.082				
Age (years)	1.038	1.009–1.068	0.009	1.088	1.050–1.128	<0.001	1.254
BMI (kg/m <sup>2</sup> )	0.927	0.844–1.017	0.108				
Co-morbidity							
Hypertension	1.668	0.975–2.856	0.062				
Diabetes	1.504	0.817–2.770	0.190				
CHD	1.077	0.387–2.993	0.887				
Previous CVA	1.088	0.264–4.489	0.907				
RE, PUD, or GERD	1.074	0.385–2.993	0.892				
Depression	2.979	1.337–6.639	0.008	1.550	0.674–3.566	0.302	1.057
History of tuberculosis	1.063	0.564–2.001	0.850				
Smoking status**							
(reference: never smoked)							
Occasional smoker	2.242	0.968–5.195	0.060	4.586	1.913–10.993	<0.001	1.166
Long-term smoker	2.003	1.118–3.586	0.020	2.179	1.115–4.258	0.023	1.379
PFT							
FEV <sub>1</sub> z-score	0.743	0.620–0.890	0.001				
FVC z-score	0.875	0.743–1.030	0.109				
FEV <sub>1</sub> /FVC z-score	0.284	0.182–0.444	<0.001	0.452	0.219–0.936	0.033	2.034
FEF <sub>25-75%</sub> z-score	0.366	0.256–0.523	<0.001	0.453	0.267–0.766	0.003	1.882

**Notes:** †Adjusted for age, depression, smoking status, and FEV<sub>1</sub>/FVC z-score. \*Low FEF<sub>25-75%</sub>: FEF<sub>25-75%</sub> z-score below –0.8435 (the optimal cut-off value for predicting COPD development). \*\*Occasional smoker: an adult who has smoked less than 20 pack-years in his or her lifetime; long-term smoker: an adult who has smoked over 20 pack-years in his or her lifetime.

**Abbreviations:** BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular accident; FEF, forced mid-expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; HR, hazard ratio; PFT, pulmonary function test; PUD, peptic ulcer disease; RE, reflux esophagitis; VIF, variance inflation factor.

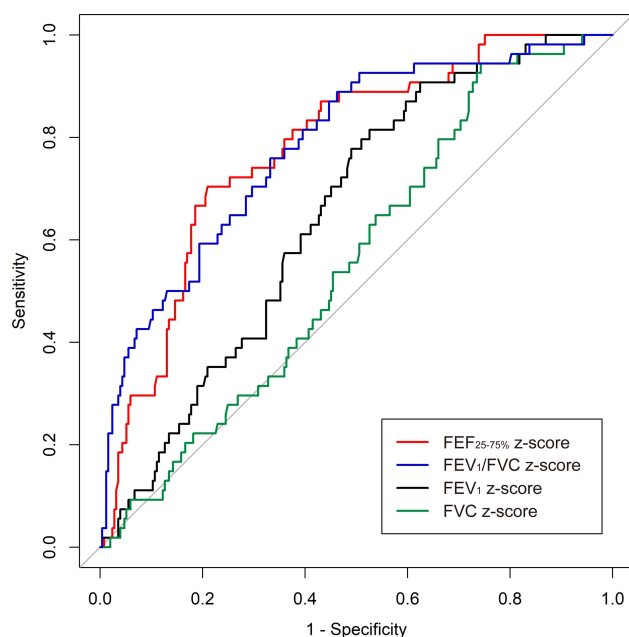




**Figure 2** Differences in cumulative development of COPD (%) between normal FEF<sub>25-75%</sub> and low FEF<sub>25-75%</sub> groups.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEF, forced mid-expiratory flow.

use. Although FEF<sub>25-75%</sub> might have poor repeatability based on earlier studies, the predictive power of FEF<sub>25-75%</sub> for COPD development can cover a large variable range of FEF<sub>25-75%</sub>. In this study, to reduce the variability of FEF<sub>25-75%</sub>, we analyzed the z-score by



**Figure 3** Comparison of AUC of ROC curves.

**Abbreviations:** AUC, area under the curve; FEF, forced mid-expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ROC, receiver operating characteristic.

calibrating the age, sex, height, and race of each patient. The predictability and HR of FEF<sub>25-75%</sub> for COPD development were equivalent to those of FEV<sub>1</sub>/FVC, the parameter used in the diagnostic definition of COPD.

FEF<sub>25-75%</sub> measures airway flow rates on an FVC segment, which describes the flow from medium-to-small airways. The impairment of FEF<sub>25-75%</sub> indicates the impairment of medium-sized and small airways.<sup>20</sup> Compromised FEF<sub>25-75%</sub> is frequently observed in patients with bronchial hyper-responsiveness in asthma or allergic rhinitis.<sup>21</sup> Children with allergic rhinitis/asthma and decreased FEF<sub>25-75%</sub> have elevated values of fractional exhaled nitric oxide.<sup>22</sup> Impairment of FEF<sub>25-75%</sub> is a marker of early bronchial impairment in allergic rhinitis and bronchiolitis obliterans.<sup>8,9</sup> However, the superiority of FEF<sub>25-75%</sub> over FEV<sub>1</sub>/FVC has not been demonstrated in regard to sensitivity.<sup>23</sup> In COPD, FEF<sub>25-75%</sub> is decreased in smokers compared to healthy individuals.<sup>24</sup> Moreover, FEF<sub>25-75%</sub> is decreased in individuals exposed to second-hand smoke<sup>11</sup> or those with air trapping observed on chest computed tomography.<sup>25</sup> However, the role of FEF<sub>25-75%</sub> as a predictor for the development of COPD has not been well studied. Instead, several studies have investigated the parameters associated with FEF<sub>25-75%</sub> and obstructive disease.<sup>20</sup> Although objective criteria for analysis are lacking, the concavity of the flow-volume curve is often used for classifying the obstructive pattern of patients.<sup>20</sup>

Recently, the global concavity index ( $100 \times [\text{reference FEF}_{50\%} - \text{measured FEF}_{50\%}] / \text{reference FEF}_{50\%}$ ) and peripheral concavity index ( $[\text{reference FEF}_{75\%} - \text{measured FEF}_{75\%}] / \text{reference FEF}_{75\%}$ ) were reported to be related to obstructive disease.<sup>26</sup> However, further research is required.

COPD is a chronic airway disease induced by extended exposure to toxic particles, including components of cigarettes. The small airways that are exposed to toxic materials chronically demonstrate marked remodeling with thickened airway wall.<sup>27</sup> This remodeling is caused by wound healing in response to injury by toxic materials, including cigarette smoking, viruses, and bacteria. Airway remodeling includes wall thickness of airway, increased density of inflammatory cells, fibrosis, and smooth muscle hyperplasia. Mucus plugs, which are a significant feature of COPD, also lead to small airway dysfunction.<sup>12</sup> Immune cell infiltration induced by smoking precedes fibrosis of small airways and loss of lung tissue.<sup>28</sup> These above mechanisms might identify subclinical COPD patients with small airway dysfunction before the impairment of lung function and may reveal impairment of  $\text{FEF}_{25-75\%}$  in advance.

We found that old age and smoking status were significant predictors for the development of COPD in this study. Age and smoking history are well-known critical factors for COPD.<sup>1</sup> We demonstrated that well-known factors for the development of COPD are statistically significant in our sample.  $\text{FEV}_1$  is a well-known marker for airway obstruction and is used to measure severity of airway obstruction and can predict mortality.<sup>29</sup> In our univariate analysis,  $\text{FEV}_1$  was significant. However, it showed multi-collinearity with  $\text{FEF}_{25-75\%}$  and  $\text{FEV}_1/\text{FVC}$  and was therefore not included in the multivariate analysis model. We speculated that compared to  $\text{FEV}_1$ ,  $\text{FEF}_{25-75\%}$  is a better predictor for the development of COPD in the comparison of ROC in patients with normal lung function. We can therefore assume that  $\text{FEF}_{25-75\%}$  can be an earlier marker for COPD than  $\text{FEV}_1$ .

Early diagnosis and prediction of COPD are essential for improving the prognosis of COPD patients.<sup>1</sup> We can identify patients susceptible to the development of COPD and provide interventions to prevent COPD. Furthermore, we should recommend patients with decreased  $\text{FEF}_{25-75\%}$  to quit smoking and educate them about lifestyle issues, including avoiding dust, appropriate vaccinations, regular exercise, and nutritional support, even when they do not have symptoms or show reduced lung function.<sup>27</sup> Early intervention, management, and close monitoring will help prevent the progression of COPD. Regular follow-up of

patients can detect COPD in the early stage, leading to improved treatment timing, prevention of airway remodeling, and improvement of severity and prognosis.

This study had some limitations. First, this study was conducted at a single institute with a limited number of patients. In this respect, the optimal cut-off value of  $\text{FEF}_{25-75\%}$  used in this study cannot be generalized. Therefore, further large-scale studies are needed. However, we had sufficient patients to obtain significant results of well-known risk factors, including age and smoking history. Second, the  $\text{FEF}_{25-75\%}$  value is known to have considerable variability, and the normal range was shown to be quite broad in earlier studies. However, previous studies also reported that  $\text{FEF}_{25-75\%}$  is relatively reliable when FVC and  $\text{FEV}_1$  are normal.<sup>29</sup> We included patients with normal FVC and  $\text{FEV}_1$ , specifically to evaluate  $\text{FEF}_{25-75\%}$ . In addition, because all values were calibrated as the z-score, we could reduce the variability of  $\text{FEF}_{25-75\%}$ . Third, we included patients that were assessed with two different types of spirometers, resulting in potential systematic differences between lung function measurements.<sup>30</sup> Finally, the interval between PFTs varied. In Korea, the national health insurance covers almost all Koreans, allowing patients to use medical services frequently and quickly. Thus, frequent PFTs are usually conducted. Most of our study patients underwent PFT at a 6-month to 1-year interval. We think this varied interval of PFT is not a major problem that would weaken the power of the results of the present study.

## Conclusions

This retrospective, observational cohort study revealed that the  $\text{FEF}_{25-75\%}$  value in patients with normal lung function can be useful in predicting the development of COPD. We should thus carefully monitor patients who present with low  $\text{FEF}_{25-75\%}$  values who are susceptible to COPD, even though they may have normal lung function. Early interventions in these patients, including smoking cessation, timed vaccinations, sufficient exercise, and environmental care, may help improve their prognosis.

## Abbreviations

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DLCO, diffusing capacity of the lungs for carbon monoxide;  $\text{FEF}_{25-75\%}$ , forced mid-expiratory flow<sub>25-75%</sub>;  $\text{FEV}_1$ , forced expiratory volume in one second; FVC, forced

vital capacity; GERD, gastroesophageal reflux disease; HR, hazard ratio; PFT, pulmonary function test; PUD, peptic ulcer disease; RE, reflux esophagitis.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval

Institutional Review Board (IRB) of Gangnam Severance Hospital (number: 2019-0556-001).

## Consent for Publication

The requirement of informed consent was waived because of the retrospective nature of the study, and all data were collected in accordance with the amended Declaration of Helsinki.

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## Disclosure

The authors declare that they have no competing interests.

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