

# Risk factors for FEV<sub>1</sub> decline in mild COPD and high-risk populations

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**Background:** Early diagnosis of COPD is often not achieved due to limited recognition and limited access to the pulmonary function test. Our hypothesis was that lung function decline may be different between populations with mild COPD and those who are at high risk and do not receive treatment.

**Patients and methods:** Subjects with mild COPD and those from a high-risk COPD population were recruited from a community-based COPD epidemiological study after obtaining consent. Baseline clinical characteristics, symptom questionnaire, spirometry, low-dose computed tomography (LDCT) chest scan, and blood plasma biomarker data were collected initially and then 1 year later.

**Results:** A total of 617 participants were recruited, and 438 eventually completed the first-year follow-up visit; 72 participants (46 males) were in the mild COPD group, and 225 participants (165 males) were in the high-risk group. The mean forced expiratory volume in the first second of expiration (FEV<sub>1</sub>) decline in the mild COPD group was 129 mL, which was significantly higher than the 30 mL decline in the high-risk population group ( $P=0.005$ ). Group category (odds ratio [OR] =0.230) and COPD Assessment Test (CAT) score (OR =9.912) were independent risk factors for an FEV<sub>1</sub>% predicted decline of >15% for all participants. In the mild COPD group, patients with a higher CAT (OR =5.310) and Emphysema Index (OR =5.681) were associated with a FEV<sub>1</sub>% predicted decline of >15% at the first-year follow-up. No factor showed a significantly predictive effect on FEV<sub>1</sub> decline in the high-risk COPD group.

**Conclusion:** Group category was an independent influential factor associated with FEV<sub>1</sub> decline.

**Keywords:** COPD, biomarker, lung function decline, Emphysema Index, spirometry

## Introduction

COPD is a leading cause of morbidity and mortality worldwide.<sup>1</sup> The prevalence of physiologically defined COPD in adults older than 40 years is ~9%–10%, with variation due to differences in survey methods, diagnostic criteria, and statistical methods.<sup>2</sup> In a study from China, the overall prevalence of COPD (males, 12.4%; females, 5.1%) among 20,245 participants aged 40 years or older from seven provinces/cities was 8.2%.<sup>3</sup> Among the participants, 35.5% were asymptomatic and only 6.5% had been tested with spirometry. Most of the underdiagnosed COPD patients had no clinical symptoms and no awareness of the lung function test as a medical examination. Owing to the lack of awareness about the high prevalence of COPD among both doctors and patients, underdiagnosis is a severe problem.<sup>3–6</sup> Many patients are diagnosed in the moderate-to-severe stage and even in the very severe stage, when they come to the hospital for help with respiratory symptoms. Patients with high-grade COPD impose a high economic burden on the health care system. The severity of COPD is positively correlated with total direct costs, including costs of medications, ventilation therapy,

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beds, and nursing care during hospitalization, as well as with the cost and duration of ICU care.<sup>7,8</sup> Early detection may allow for appropriate medical intervention to slow down lung function decline in patients.<sup>9</sup> The value of spirometry screening is still being debated to date, and it is not supported by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>10</sup>

As being reported, mean forced expiratory volume in the first second of expiration (FEV<sub>1</sub>) loss is higher in moderate than that in severe–very severe COPD patients,<sup>11,12</sup> but there is very limited information on FEV<sub>1</sub> decline in patients with mild COPD and high-risk population. Our hypothesis was that lung function decline may be different between patients with mild COPD and those in the high-risk COPD population who do not receive treatment. The annual FEV<sub>1</sub> changes in patients with mild COPD and high-risk population in the real world are to be investigated. Identifying the clinical profile of lung function decline together with laboratory examinations may provide a new screening approach for rapid FEV<sub>1</sub> decline.

## Patients and methods

### Trial organization

Five tertiary hospitals in Shanghai participated in this study from September 20, 2013, to May 20, 2014. Participants were either individuals from a community-based COPD epidemiological study or patients with a high-risk of COPD seeking medical services at a participating institution.

The study was approved by the institutional review board of Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China, and the study was registered in the Chinese Clinical Trials Registry (<http://www.chictr.org.cn/index.aspx>; ChiCTR-OCS-13003610). All the subjects signed written informed consent for participating in this study. And the informed consent was approved by the institution review board.

### Inclusion criteria

The subjects were required to meet the following inclusion criteria: 1) 45–80 years old; 2) history of cigarette smoking or a history of exposure to second-hand smoke for >10 years; 3) post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) ratio <0.70 and FEV<sub>1</sub>% predicted value >80% in the absence of a bronchodilator or an inhaled corticosteroid treatment, defined as the mild COPD group, or an FEV<sub>1</sub>/FVC ratio >0.70 and FEV<sub>1</sub>% predicted value <95%, defined as the high-risk group; 4) predicted to finish the 2-year follow-up; and 5) ability and willingness to undergo low-dose computed tomography (LDCT) at the end of the expiration period.

### Exclusion criteria

The exclusion criteria included asthma, bronchiectasis, psychiatric disease, cognitive disorders, malignancies, severe kidney or liver dysfunction, and life expectancy of <2 years. Participants who could not undergo the spirometry test and/or LDCT, as well as those with restrictive ventilation dysfunction, were also excluded from the study.

### Measurements

After enrollment, participants completed the chest LDCT scan and blood was collected for the biomarker test. Socio-demographic characteristics, such as age, gender, body mass index (BMI), smoking history, allergy history, family history, occupational/bioaerosol exposure, and comorbidities, were recorded. All participants completed the COPD Assessment Test (CAT) and the modified British Medical Research Council (mMRC) questionnaire.

Spirometry was used as the GOLD criteria for COPD diagnosis according to the American Thoracic Society (ATS) operation standard,<sup>13</sup> which was performed by the Jaeger machine (Master Screen PFT, Hoechberg, Germany). All chest LDCT scans were acquired using a 16-slice scanner (Siemens, Erlangen, Germany and GE, Milwaukee, WI, USA) at end expiration with the participants in the supine position. Before the scan began, the technologist let the participants perform breathing exercises. The standard scan parameters used for all examinations were as follows: slice thickness of 1 mm, increment of 0.5 mm, tube current of ~20–40 mAs, tube voltage of 120 kV, and lung window algorithm of “Lung” for the GE machine and “kernel” for the Siemens machine. All images were evaluated at a digital reading workstation using the “Lung Emphysema” application (Myrian Series Software, Paris, France). For each participant, the following parameters were calculated: total lung volume (TLV, liters) and emphysema volume (EV, liters) of both lungs. The EV/TLV ratio (%) was calculated as the Emphysema Index (EI). For the diagnosis of emphysema, a threshold of –950 Hounsfield units (HU) was used. Participants did the spirometry test (pre- and post-bronchodilators) first and then LDCT scan on the same day.

The concentrations of blood biomarkers such as leptin, matrix metalloproteinase-10 (MMP-10), carbon tetrachloride-4 (CCL-4), carbon tetrachloride-2 (CCL-2), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), interleukin-8 (IL-8), and insulin-like growth factor 1 (IGF-1) screened by protein chip technique in the preliminary test were detected in triplicate by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, MN, USA) in 40 patients. The demographics of the patients in the slow-decline group were matched with those of the

patients in the fast-decline group for blood biomarker detection. No intervention was given to the participants during the observation periods.

## Statistical analysis

Mean and standard deviation for normally distributed differences were calculated. Differences in the baseline characteristics of patients in the mild COPD group and in the high-risk group were evaluated using the independent *t*-test or chi-square test as appropriate. Univariate and multivariate logistic regressions were performed for the mild COPD and high-risk groups, respectively, to evaluate the effects of baseline characteristics and serum biomarkers on the FEV<sub>1</sub> decline. Age, gender, BMI, occupational exposure, bioaerosol exposure, family history, CAT score, mMRC score, and EI were evaluated as covariates. A stepwise backward procedure was used to derive a final model of the variables that had a significant effect on rapid FEV<sub>1</sub> decline. The Youden Index was calculated to identify the cutoff point of the CAT score and EI. A *P*-value <0.05 was considered as statistically

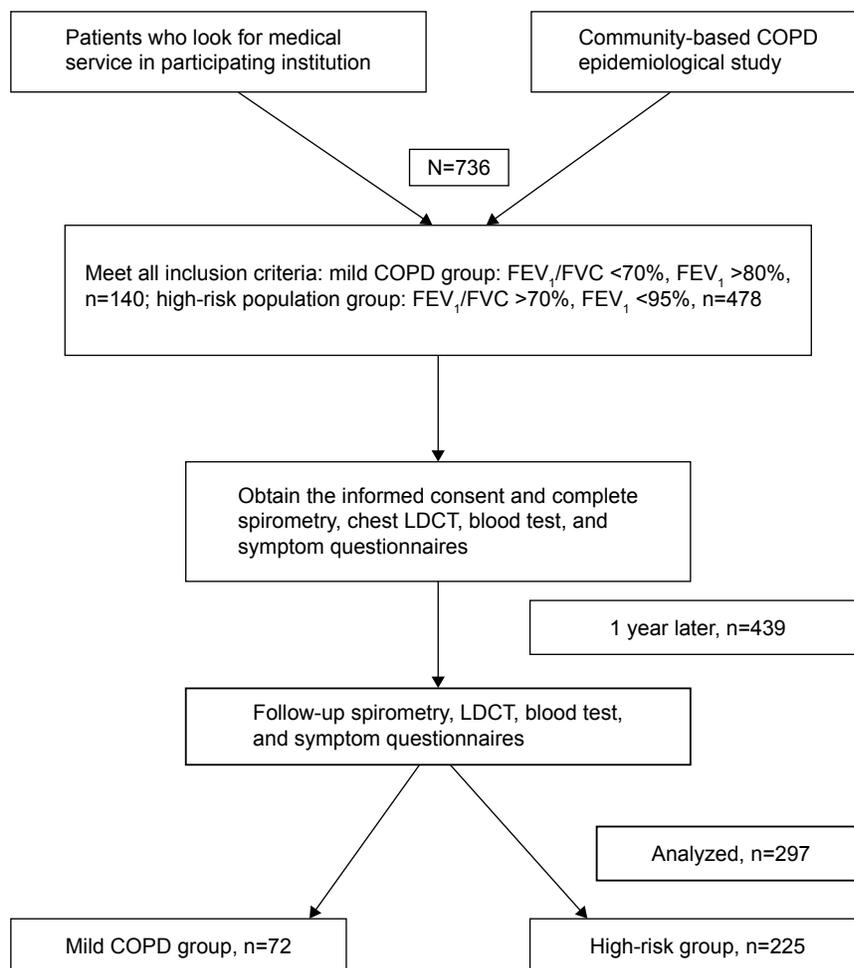
significant. Statistical analysis was performed using the SAS9.4 software (SAS Institute Inc., Cary, NC, USA).

## Results

In total, 617 participants were screened and enrolled in the study for investigation at baseline. After 1 year, 438 (71%) participants returned for the first follow-up visit. Based on the completed data collection in both visits, 297 participants (72 in the mild COPD group and 225 in the high-risk group) were ultimately analyzed in this study. All of them had no medical intervention and smoking status change due to COPD. The flow chart of the study is presented in Figure 1. All participants with restrictive lung function were excluded after the follow-up spirometry.

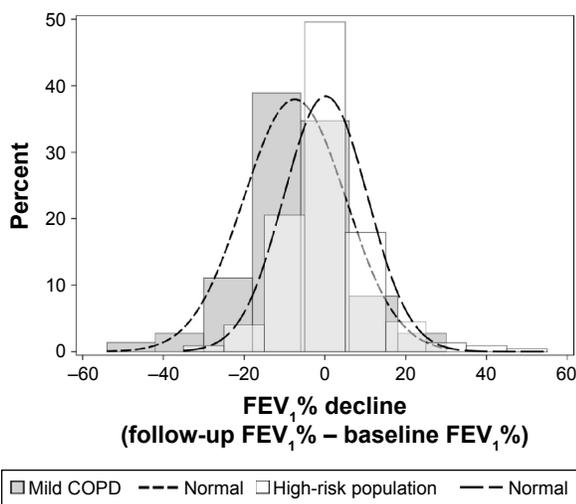
### Fast-decline group definition

A larger proportion of patients in the mild COPD group presented with a reduced FEV<sub>1</sub>% predicted at follow-up than that in the high-risk group. In addition, the FEV<sub>1</sub>% predicted for the mild COPD group of patients was significantly lower than



**Figure 1** Flow diagram of the study.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; LDCT, low-dose computed tomography.



**Figure 2** The change in FEV<sub>1</sub> between baseline and the first-year follow-up.  
**Abbreviation:** FEV<sub>1</sub>, forced expiratory volume in the first second of expiration.

that for the high-risk group (Figure 2). Based on the histogram of FEV<sub>1</sub>% predicted decline, 15% was chosen as the cutoff value to define the fast-decline group, ie, an individual with an FEV<sub>1</sub>% predicted decline >15% at the follow-up was included in the fast-decline group (n=34), while individuals with a <15% decline were included in the slow-decline group (n=263).

**Table 1** Patient demographics and baseline characteristics

Demographic parameter	Mild COPD group (n=72)	High-risk group (n=225)	P-value
Mean age, years (SD)	57.23±7.56	61.74±8.52	<0.0001
Range	(48.00, 80.00)	(47.00, 77.00)	
Male, n (%)	46 (63.89)	165 (73.33)	0.124
BMI, kg/m <sup>2</sup> (SD)	24.58±2.82	24.64±3.15	0.882
Mean cigarette smoking years (SD)	19.43 (20.95)	18.63 (19.10)	0.762
Occupational exposure, n (%) – including dust and harmful gas	2 (2.78)	16 (7.11)	0.180
Bioaerosol exposure, n (%)	0	1 (0.44)	0.571
Allergic rhinitis, n (%)	5 (6.94)	9 (4.00)	0.305
Family disease history, n (%)	12 (16.67)	25 (11.11)	0.214
Chronic bronchitis	6 (8.33)	11 (4.89)	0.274
Emphysema	0 (0.00)	11 (4.89)	0.056
COPD	0 (0.00)	6 (2.67)	0.162
Asthma	1 (1.39)	1 (0.44)	0.430
Bronchiectasis	0 (0.00)	0 (0.00)	–
Lung cancer	5 (6.94)	5 (2.22)	0.053
CAT score (SD)	5.21 (4.62)	4.2 (3.73)	0.118
>6	20 (27.78)	43 (19.11)	0.117
≤6	52 (72.22)	182 (80.89)	
mMRC score (SD)	0.43 (0.67)	0.25 (0.50)	0.014
0	48 (66.67)	176 (78.22)	0.035
1	17 (23.61)	42 (18.67)	
2–3	7 (9.72)	7 (3.11)	
EI (%)	11.44±8.18 (n=47)	9.18±8.39 (n=59)	0.167
Lung function (SD)			
FEV <sub>1</sub> (L)	2.37 (0.53)	2.62 (0.55)	0.001
FEV <sub>1</sub> % predicted	91.41 (8.67)	87.48 (6.21)	<0.0001
FVC (L)	3.62 (0.80)	3.32 (0.64)	0.002
FVC% predicted	111.68 (11.12)	91.32 (7.6)	0.001
FEV <sub>1</sub> /FVC%	65.59 (3.64)	78.91 (7.12)	<0.0001

**Abbreviations:** BMI, body mass index; CAT, COPD Assessment Test; mMRC, modified British Medical Research Council; EI, Emphysema Index; FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; SD, standard deviation.

## Baseline characteristics

Participant demographic information is presented in Table 1. The mean age of the mild COPD group was 57.23 years, which was less than that of the high-risk group (61.74 years). Males comprised 63.89% of the mild COPD group and 73.33% of the high-risk group. There was no statistically significant difference between these two groups with respect to BMI, mean cigarette smoking years, exposure frequency, or family disease history. The symptom evaluation showed that the CAT and mMRC scores of the mild COPD group were higher than those of the high-risk group. The FEV<sub>1</sub>/FVC% ratio in the mild COPD group was significantly lower than that in the high-risk group ( $P<0.001$ ).

## Follow-up analysis

The results showed that group category (odds ratio [OR]=0.230) and CAT score (OR=9.912, with 6 defined as the cutoff value) were the independent risk factors for an FEV<sub>1</sub>% predicted decline of >15% (fast decline) for all participants at the follow-up. The mean FEV<sub>1</sub>% predicted decline was 7.46% (95% confidence interval [CI]: 4.49–10.43) in the mild COPD group and 0.19% (95% CI: 1.18–1.56) in the high-risk group. The difference in the declines in FEV<sub>1</sub>%

**Table 2** The factors influencing FEV<sub>1</sub>% predicted decline in the mild COPD group

Variables	P (univariate)	OR (95% CI; univariate)	P-value*	OR (95% CI)*
Age group 3-1	0.342	0.306 (0.029, 3.169)		
Age group 3-2	0.619	0.802 (0.211, 3.043)		
Gender 2-1	0.134	0.375 (0.104, 1.352)		
BMI	0.130	1.196 (0.949, 1.508)		
Exposure 2-1	0.536	1.594 (0.364, 6.979)		
Family history 2-1	0.462	0.431 (0.046, 4.069)		
CAT 2-1	0.055	3.714 (0.973, 14.177)	0.033	5.310 (1.141, 24.718)
mMRC 2-0	0.929	0.842 (0.128, 5.561)		
mMRC 2-1	0.857	0.800 (0.102, 6.249)		
Smoking years 2	0.318	0.983 (0.951, 1.016)		
EI 2-1	0.035	4.140 (1.104, 15.521)	0.023	5.681 (1.274, 25.325)

**Note:** \*Multivariate logistic regression.

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; OR, odds ratio; CI, confidence interval; BMI, body mass index; CAT, COPD Assessment Test; mMRC, modified British Medical Research Council; EI, Emphysema Index.

predicted between these two groups was statistically significant ( $P < 0.0001$ ). Meanwhile, the mean absolute value of FEV<sub>1</sub> decline in the mild COPD group was 129 mL (95% CI: 73–186), which was significantly greater than the 30 mL decline in the high-risk group (95% CI: 5–65;  $P = 0.005$ ). Furthermore, in the fast-decline group, the mean absolute value of FEV<sub>1</sub> decline was 380 mL (95% CI: 290–460) and the mean predicted decline of FEV<sub>1</sub>% was 21.54% (95% CI: 18.95–24.13). In contrast, in the slow-decline group, the mean predicted declines of FEV<sub>1</sub> and FEV<sub>1</sub>% were 10 mL (95% CI: –20–40) and –0.82% (95% CI: –1.94–0.3), respectively. The differences in the FEV<sub>1</sub> absolute and FEV<sub>1</sub>% predicted declines between the fast- and slow-decline groups were statistically significant ( $P < 0.0001$ ). Other factors, including age, gender, BMI, exposure frequency, family disease history, mMRC score, smoking, and EI, were not risk factors for fast FEV<sub>1</sub> decline at the first-year follow-up.

In the fast-decline group, 19 of 34 patients were in the mild COPD group and 15 of 34 patients were in the high-risk group. The mild COPD group presented a higher proportion of individuals with fast FEV<sub>1</sub> decline at the follow-up ( $P < 0.01$ ). Considering that the prognostic characteristics of patients with a low FEV<sub>1</sub>/FVC ratio at baseline may be different from those of patients with a normal FEV<sub>1</sub>/FVC ratio, the participants were stratified into the mild COPD group and high-risk group according to their baseline FEV<sub>1</sub>/FVC ratio, and prognostic effect analysis was performed separately for these two groups. In the analysis of the mild COPD group, CAT score (OR = 5.310, with 6 defined as the cutoff value) and EI (OR = 5.681, with 12.3 defined as the cutoff value) were predictive factors for FEV<sub>1</sub>% predicted decline  $> 15\%$  (Table 2). Combining the CAT score with the EI, the model Akaike information criterion was 53.6 and its consistency rate was 63.3%, which was significantly better than those for the CAT score or EI alone. However, in the analysis of

the high-risk group, there were no factors, including CAT score and EI, that showed a significant effect on rapid FEV<sub>1</sub>% decline, both in the univariate and multivariate analyses (Table 3). This finding indicates that as soon as the patients met the criteria for early COPD diagnosis, they were more likely to undergo rapid FEV<sub>1</sub> decline. For these patients, the risk of developing rapid FEV<sub>1</sub>% decline was associated with an increased CAT score and/or EI.

### Blood biomarker measurement

The results showed that the levels of MMP-10, CCL-4, CCL-2, and IL-1 were all higher in the fast-decline group than in the slow-decline group (Table 4), although there were no significant differences between the groups in the levels of the eight cytokines that were detected at baseline.

### Discussion

It has been reported that age, smoking, and exposure to inhaled particles are the main recognized COPD risk factors.<sup>14–16</sup>

**Table 3** The factors influencing FEV<sub>1</sub>% predicted decline in the high-risk group

Variables	P (univariate)	OR (95% CI; univariate)
Age group 3-1	0.621	0.241 (0.022, 2.583)
Age group 3-2	0.420	0.188 (0.018, 2.002)
Gender 2-1	0.838	1.268 (0.13, 12.378)
BMI	0.999	1.000 (0.770, 1.299)
Exposure 2-1	0.157	0.256 (0.039, 1.69)
Family history 2-1	0.975	–
CAT 2-1	0.772	0.714 (0.074, 6.944)
mMRC 2-0	0.958	–
mMRC 2-1	0.984	–
Smoking years 2	0.261	1.024 (0.983, 1.066)
EI 2-1	0.710	0.65 (0.067, 6.296)

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in the first second of expiration; OR, odds ratio; CI, confidence interval; BMI, body mass index; CAT, COPD Assessment Test; mMRC, modified British Medical Research Council; EI, Emphysema Index.

**Table 4** Cytokine levels in the fast-decline and slow-decline groups

Cytokines (pg/mL)	Fast-decline group	Slow-decline group	F-value	P-value
Leptin	2.37 (0.53)	2.62 (0.55)	1.305	0.261
MMP-10	91.41 (8.67)	87.48 (6.21)	0.735	0.397
CCL-4	3.62 (0.80)	3.32 (0.64)	0.365	0.550
CCL-2	111.68 (11.12)	94.85 (46.50)	0.295	0.590
VEGF	65.59 (3.64)	78.91 (7.12)	0.450	0.507
IL-1	109.24 (24.98)	96.74 (21.59)	0.523	0.474
IL-8	67.89 (13.06)	88.26 (16.93)	1.402	0.793
IGF-1	145.61 (33.81)	114.32 (25.77)	0.070	0.793

**Abbreviations:** MMP-10, matrix metalloproteinase-10; CCL-4, carbon tetrachloride-4; CCL-2, carbon tetrachloride-2; VEGF, vascular endothelial growth factor; IL-1, interleukin-1; IL-8, interleukin-8; IGF-1, insulin-like growth factor 1.

The incidence of COPD is associated with age,<sup>17</sup> and COPD is less frequently diagnosed in adults younger than 45 years.<sup>18</sup> Most studies target populations older than 40 or 45 years.<sup>4,5,19,20</sup> Pulmonary function progressively deteriorates and inflammation increases with airway/parenchyma structural changes, which are characteristics of senile emphysema.<sup>16</sup> Emphysema in computed tomography (CT) imaging is more frequently seen in elderly participants with a history of smoking. Chest CT has been recognized as the most sensitive method to show pulmonary lesions. Several studies used  $-900$  HU,  $-910$  HU, and  $-950$  HU as the cutoff points for distinguishing normal lung inflation and emphysema.<sup>21–24</sup> Although it is still debated whether an end-inspiration or end-expiration scan is better at reflecting air trapping and lung overinflation, more studies supported the use of the end-expiration scan.<sup>25–27</sup> In a previous study, it was found that the EI derived from CT 3D reconstruction was significantly and negatively correlated with FEV<sub>1</sub>, FEV<sub>1</sub>% predicted, FEV<sub>1</sub>/FVC, and TLC% predicted when an end-expiration scan was performed with a  $-950$  HU threshold setting.<sup>28</sup> From lung function testing, it has been interpreted that year-to-year changes in FEV<sub>1</sub> exceeding 15% over 1 year could be considered a clinically meaningful change.<sup>29</sup> According to the histogram of FEV<sub>1</sub>% predicted decline in our study, the cutoff values of 10%, 15%, 20%, and 25% were all analyzed for their possibility in defining the fast-decline group. As a result, a 15% FEV<sub>1</sub>% predicted decline was chosen as the best cut-off point based on clinical significance. In addition, COPD is a systemic inflammatory disease causing persistent airflow limitation. Symptom assessments and serum inflammatory biomarker evaluations are considered very important for disease evaluation and exacerbation prediction.<sup>30–32</sup> These parameters may help to determine what type of population requires immediate intervention to slow down the lung function decline process.

There were several interesting findings in our study. First, the lung function variation between the mild COPD patients

and the high-risk population was observed at the first-year follow-up. The results demonstrated that the group category was an independent influential factor for a FEV<sub>1</sub>% predicted decline  $>15\%$ . A previous study showed that FEV<sub>1</sub> declined faster in current smokers and in moderate or severe COPD patients with a lower BMI.<sup>33</sup> FEV<sub>1</sub> mean loss was higher in moderate COPD (stage II) patients than in stage III and stage IV patients.<sup>11,12</sup> With treatment, the mean decline in FEV<sub>1</sub> in the moderate COPD patients was reported to be 35 mL per year<sup>12</sup> or 112 mL per year.<sup>11</sup> Obviously, the data for FEV<sub>1</sub> decline in mild COPD patients were limited. In our study, the stage of disease itself had an effect on lung function decline in mild COPD, without the influences of age, gender, BMI, exposure frequency, family disease history, and smoking. Without any intervention, the FEV<sub>1</sub> of mild COPD patients may decline rapidly. The mean annual decline of 129 mL in mild COPD patients is far greater than the 30 mL decline in the high-risk group under the natural state. Therefore, when patients are diagnosed with mild COPD, medical intervention should be recommended immediately to slow down lung function decline. Second, a new cutoff value of the CAT score for predicting FEV<sub>1</sub> decline in the mild COPD group was defined. The CAT score consists of eight items covering common COPD symptoms ranging from 0 to 40 and is broadly used for assessing COPD symptoms with a cutoff point of 10. A CAT score  $<10$  indicates fewer symptoms, whereas a CAT score  $\geq 10$  indicates a greater number of symptoms.<sup>34</sup> Additionally, a recent review noted that the CAT may be used as a complementary tool for predicting COPD exacerbation, depression, acute deterioration of health status, and mortality.<sup>35</sup> A CAT score  $\geq 13.5$  is a significant risk factor for a composite event (new ambulatory or emergency exacerbation, hospitalization, or death).<sup>36</sup> The probability cutoffs for a CAT score to identify a mild COPD exacerbation and moderate–severe exacerbation were 11 and 17, respectively.<sup>37</sup> It is clear that the cutoff value may differ according to different diagnostic goals. In our study, the target population had mild COPD and a high risk for rapid FEV<sub>1</sub> decline, so they had fewer symptoms than patients with more severe COPD. The results verified that 6 was the best cutoff point; it was an independent influential factor for FEV<sub>1</sub>% predicted decline  $>15\%$  for all participants and also had a good predictive effect on rapid FEV<sub>1</sub> decline in the mild COPD group. Third, imaging examination and reconstruction are useful for detecting emphysema and predicting rapid lung function decline. Previous studies have shown that worsened lung function, airflow obstruction, and larger increases in residual lung volume existed in patients with emphysema based on CT scanning compared with patients with radiological evidence of bronchiectasis or bronchial wall

thickening.<sup>38</sup> In one study, the emphysema group exhibited a faster decline in FVC with a low attenuation areas less than  $-950$  Hounsfield Unit (%LAA<sub>-950</sub>) median of 13.3.<sup>39</sup> Jairam et al<sup>40</sup> reported that emphysema and airway thickening in COPD detected by CT scans were strong independent predictors of severe COPD exacerbation. Emphysema is an important pathophysiological manifestation and is considered a particular phenotype of COPD. In our opinion, patients with mild COPD and emphysema may be more likely to have rapid FEV<sub>1</sub> decline with an EI  $>12.3$  and, therefore, require more clinical attention.

To our knowledge, no recognized blood biomarker can predict the current risk of COPD or the probability of rapid lung function decline in early stage COPD without symptoms. Recent literature showed that a lower plasma leptin/adiponectin ratio was significantly associated with an annual decline in COPD.<sup>41</sup> Inflammatory biomarker detection was mostly based on GOLD stages II–IV COPD patients in the stable or exacerbation phase compared with one another or compared with healthy subjects.<sup>42,43</sup> IL-8, interleukin-6 (IL-6), tumor necrosis factor- $\alpha$ , fibrinogen, and white cell count are generally used to predict the exacerbation and mortality of COPD in clinical trials.<sup>44,45</sup> Our study analyzed the relationships between inflammatory biomarkers and early COPD from a different perspective. According to our findings, there was no significant difference in blood biomarker levels between the baseline and follow-up in either the mild COPD group or high-risk group. In addition, there was an increased trend of inflammatory biomarkers only in the fast-decline group and not in the slow-decline group.

One limitation of this study is that the follow-up period was only 1 year. The process of pathophysiological changes in COPD is long, from normal lung function to emphysema and/or chronic airway inflammation. It would be more meaningful to extend the investigation time to understand the exact magnitude of lung function decline and verify the predictive effect of risk factors on lung function decline in the long term. Inflammatory biomarkers may show significant changes with disease progression. It is assumed that continuous follow-up in these two populations may provide additional insight into the pathophysiological development of COPD in order to explain the reasons of differences in FEV<sub>1</sub> decline between mild COPD patients and high-risk population.

## Conclusion

Airway obstruction was found to be an independent risk factor for FEV<sub>1</sub> decline. The patients with emphysema and a high CAT score were more likely to have rapid FEV<sub>1</sub> decline. Therefore, as soon as patients are diagnosed with

mild COPD, medical intervention must be recommended to slow down lung function decline.

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## Disclosure

The authors report no conflicts of interest in this work.

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