



# Analysis of Airway Thickening and Serum Cytokines in COPD Patients with Frequent Exacerbations: A Heart of the Matter

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**Background:** Differences in lung function for Chronic Obstructive Pulmonary Disease (COPD) cause bias in the findings when identifying frequent exacerbator phenotype-related causes. The aim of this study was to determine whether computed tomographic (CT) biomarkers and circulating inflammatory biomarkers were associated with the COPD frequent exacerbator phenotype after eliminating the differences in lung function between a frequent exacerbator (FE) group and a non-frequent exacerbator (NFE) group.

**Methods:** A total of 212 patients with stable COPD were divided into a FE group (n=106) and a NFE group (n=106) according to their exacerbation history. These patients were assessed by spirometry, quantitative CT measurements and blood sample measurements during their stable phase. Univariate and multivariate logistic regression were used to assess the association between airway thickening or serum cytokines and the COPD frequent exacerbator phenotype. Receiver operating characteristic (ROC) curves were calculated for Pi10, WA%, IL-1 $\beta$  and IL-4 to identify frequent exacerbators.

**Results:** Compared with NFE group, FE group had a greater inner perimeter wall thickness of a 10 mm diameter bronchiole (Pi10), a greater airway wall area percentage (WA%) and higher concentrations of IL-1 $\beta$  and IL-4 ( $p < 0.001$ ). After adjusting for sex, age, BMI, FEV1%pred and smoking pack-years, Pi10, WA%, IL-1 $\beta$  and IL-4 were independently associated with a frequent exacerbator phenotype ( $p < 0.001$ ). Additionally, there was an increase in the odds ratio of the frequent exacerbator phenotype with increasing Pi10, WA%, IL-4, and IL-1 $\beta$  ( $p$  for trend  $< 0.001$ ). The ROC curve demonstrated that IL-1 $\beta$  had a significantly larger calculated area under the curve ( $p < 0.05$ ) than Pi10, WA% and IL-4.

**Conclusion:** Pi10, WA%, IL-4, and IL-1 $\beta$  were independently associated with the frequent exacerbator phenotype among patients with stable COPD, suggesting that chronic airway and systemic inflammation contribute to the frequent exacerbator phenotype.

**Trial Registration:** This trial was registered in Chinese Clinical Trial Registry (<https://www.chictr.org.cn>). Its registration number is ChiCTR2000038700, and date of registration is September 29, 2020.

**Keywords:** COPD, frequent exacerbator phenotype, airway thickening, inflammation

## Introduction

Several patients with chronic obstructive pulmonary disease (COPD) may suffer frequent exacerbation events, a distinct clinical subgroup called the frequent exacerbator phenotype.<sup>1,2</sup> Frequent exacerbation of COPD can deteriorate chronic lung function and cause irreparable damage to the airways.<sup>3</sup> Unfortunately, both COPD patients and society incur a severe burden due to the frequent worsening and comorbidities, especially given the significant usage of medical resources.<sup>4</sup> Considering that great financial burden and progressive symptoms are related to acute exacerbations,<sup>5,6</sup> it is

essential to understand the nature of the frequent exacerbator phenotype to inform clinical management and to determine more accurate and accessible biomarkers to identify frequent exacerbators.

The association between COPD exacerbation frequency and quantitative CT metrics has been increasingly explored.<sup>7–9</sup> Several studies<sup>8,10–12</sup> concluded that some factors, such as airway thickening, emphysema severity, airway diseases, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, were related to the frequency of COPD exacerbation. Frequent exacerbation was independently associated with a higher emphysema index or emphysema severity.<sup>8,11</sup> However, airway thickening, instead of emphysema, was associated with the frequency of COPD exacerbation.<sup>7</sup> In addition, patients with airway thickening and emphysema experienced more exacerbation events than emphysema-dominant or airway thickening-dominant types.<sup>9</sup> There was no difference in airway inflammation or exacerbation frequency between patients with emphysema alone and those with bronchiectasis and/or airway thickening.<sup>13</sup> Consequently, the key feature of the frequent exacerbation phenotype of COPD on quantitative CT has been inconsistent and unclear. As disease severity (GOLD stage) increases, exacerbations of COPD become more frequent.<sup>12</sup> Emphysema is associated with COPD disease severity,<sup>14</sup> and airway thickening is associated with lung function in subjects with severe emphysema.<sup>15</sup> In summary, differences in disease severity, especially differences in spirometry between FE group and NFE group, should be considered when identifying frequent exacerbator phenotype-related causes.

Existing airway and systemic inflammation further exacerbate COPD.<sup>16–19</sup> In contrast to non-frequent exacerbators, frequent exacerbators have greater concentrations of interleukin-6 (IL-6), IL-8 and IL- $\beta$  in sputum.<sup>20,21</sup> Moreover, greater serum concentrations of inflammatory mediators, such as C-reactive protein (CRP), IL-6 and serum amyloid A (SAA), are associated with greater frequency of exacerbation.<sup>16,21,22</sup> In summary, COPD frequent exacerbators have greater airway inflammation and systemic inflammation.<sup>21</sup> However, few previous studies have investigated the association between structural changes identified on CT and systemic inflammation among patients with COPD. In addition, this study provides more evidence to determine whether airway and systemic inflammation are associated with the frequent exacerbation phenotype of COPD using more CT biomarkers and serum inflammatory cytokines.

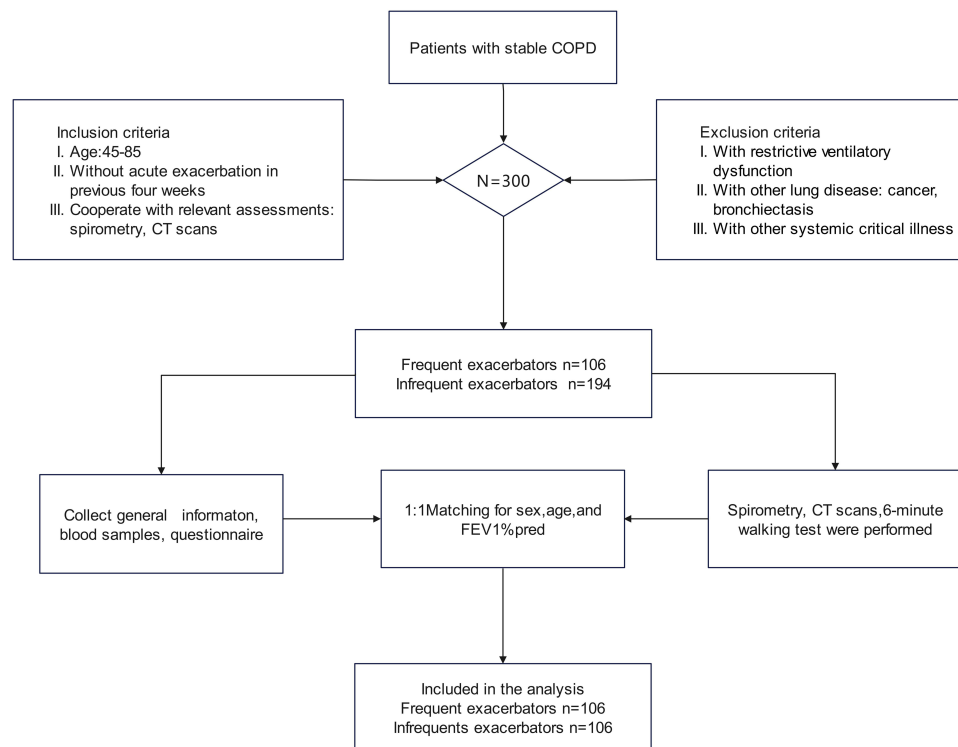
## Patients and Methods

### Sample Estimation

The sample capacity was estimated as follows: airway wall area percentage (WA%) [mean: NFE group ( $\mu_1=16.99$ ) vs FE group ( $\mu_2=17.93$ ), SD: NFE group ( $\sigma_1=3.14$ ) vs FE group ( $\sigma_2=3.44$ ),  $\alpha=0.05$ ,  $1-\beta=0.8$ ]. By using PASS 15, the total sample was estimated to be 218.<sup>8</sup>

### Study Design and Participants

Three hundred participants with stable COPD were selected from treated patients from the Respiratory Department of The First Affiliated Hospital of Guangzhou Medical University. Those who met the inclusion criteria and agreed to participate in the research were invited to the hospital for pre- and post bronchodilator spirometry, CT scans and venipuncture. Eligible patients were (a) aged between 40 and 85 years; (b) had a diagnosis of COPD based on an FEV1/FVC ratio  $< 0.70$ ; (c) had no symptomatic deterioration in the last 4 weeks; and (d) had the capacity to provide signed written informed consent and cooperate with relevant assessments; (e) patients with other lung diseases (asthma, malignancies, bronchiectasis and tuberculosis), heart failure, gastroesophageal reflux and cognitive disorders were excluded; (f) had the restrictive ventilatory dysfunction. A total of 106 frequent exacerbators (2 exacerbations or more in the last year without any exacerbations in the previous 4 weeks) and 106 nonfrequent exacerbators (fewer than 2 exacerbations in the last year without any exacerbations in the previous 4 weeks) were selected and matched for sex, age and FEV1%pred at a 1:1 ratio (Figure 1). All participants gave written informed consent, and this study was approved by the First Affiliated Hospital of Guangzhou Medical University professional ethics committee (reference number for the study: 2016-20).



**Figure 1** Study diagram showing the flowchart of subject recruitment.

## CT Scans and Quantitative Image Analysis

All subjects underwent volumetric CT imaging at full inspiration and expiration.

The scanning parameters consisted of a slice thickness of 1 mm, a slice separation of 1 mm, a reconstructed thickness of 1 mm, a matrix of 512×512, tube voltage of 120 kV and tube current of 30 mAs. Reconstructed three-dimensional tracheobronchial tree images were used for airway quantitative analysis using VIDA Pulmonary Workstation, version 2.0 (Vida Diagnostics, Coralville, Iowa). Each parameter was measured in the following six segmental bronchi: right upper lobe, right middle lobe, right lower lobe, left upper lobe, posterior basal segment, and left lower lobe. The total emphysema percentage was defined as all lung voxels with a CT attenuation value of less than −950 HU (Hounsfield units), and air trapping was defined as all lung voxels with a CT attenuation value of less than −856 HU. Quantitative analysis of emphysema and air trapping was performed on segmented lung images using VIDA version 2.0.

The quantitative CT parameters included the wall area percentage  $WA\% = (\text{total airway area} - \text{airway lumen area}) / (\text{total airway area}) \times 100$ , inner perimeter wall thickness of a 10 mm diameter bronchiole (Pi10), emphysema index [EI, CT automatic calculation of the volume fraction of the lungs below 950 HU at full inspiration (%LAA-950)] and air trapping [CT automatic calculation of the volume fraction of the lungs below 856 HU at full expiration (%LAA-856)]. Emphysema severity was categorized as follows using the Goddard score: 0=emphysema index<5%, 1=5%<emphysema index<25%, 2=25%<emphysema index<50%, 3=50%<emphysema index<75%, and 4=75%≤emphysema index.

## Spirometry

Spirometry was performed using a pulmonary function instrument (MasterScreen Pneumo, Germany) 20 min before and after inhalation of a short-acting bronchodilator and conducted based on pulmonary function test criteria released by the ATS.<sup>23</sup> The severity of airflow limitation was assessed by post bronchodilator spirometry according to GOLD standard grades 1–4 with an FEV1: FVC ratio of <0.7. On the basis of reference values from the European Coal and Steel Community (1993) and the application of conversion factors for Chinese adults (male: 0.95, female: 0.93), we calculated predicted values.<sup>24</sup>

## Blood Sampling and Cytokine Analysis

Venous blood samples were collected from patients with stable COPD, and cell counts were made using a hematological analyzer (DxH 800, Beckman Coulter, California, United States). These blood samples were centrifuged (4°C, 3000 rpm, 10 min) to retain the upper serum sample. The concentration of cytokines in this sample was detected with the human cytokine V-PLEX validated immunoassay kit (Mesoscale Discovery, Gaithersburg, MD), and the average of each variable (IL-1 $\beta$ , IL-4, IL-5, IL-6, IL-13, IL-17 and IFN- $\gamma$ ) is reported.

## Statistical Analysis

SPSS Statistics 26 was used to perform a statistical analysis of data comparison. Normally distributed data are presented as the means  $\pm$  standard deviations ( $x \pm s$ ), nonnormally distributed data are expressed as medians and interquartile ranges, and categorical variables are expressed as absolute frequencies. The associations between airway thickening or systemic inflammation and the frequent exacerbator phenotype of COPD were assessed using univariate and multivariate binary logistic regression. In the linear trend test, associations between quartiles of Pi10, WA%, IL-1 $\beta$ , or IL-4 [Q1-Q4, Q1:  $\leq$ 25th percentile, Q2: 25th percentile-50th percentile, Q3: 50th percentile-75th percentile, Q4:  $\geq$ 75th percentile-100th percentile] and the frequent exacerbator phenotype of COPD were analyzed using multivariate binary logistic regression. Moreover, receiver operating characteristic curves (ROC curves) of Pi10, WA%, IL-1 $\beta$ , or IL-4 were plotted, and  $P < 0.05$  indicated that the difference was statistically significant.

## Results

### Subject Characteristics

In all, 135 males and 77 females with an average age of  $66.2 \pm 7.5$  years were enrolled in this study, comprising 106 nonfrequent exacerbators and 106 frequent exacerbators (Table 1). Participants attended a baseline visit to assess demographics, smoking status, exacerbation history in the past year, medical history, medication use, symptoms (COPD assessment test, CAT, modified Medical Research Council, mMRC, St George's Respiratory Questionnaire, SGRQ) and comorbidities. Frequent exacerbators had more exacerbations, a greater smoking index and worse quality of life, which were consistent with the characteristics of the frequent exacerbator phenotype of COPD. However, it is worth highlighting that there were no differences ( $P > 0.05$ ) in FEV<sub>1</sub>% pred (%), FVC% pred (%), FEV<sub>1</sub> (%) and FVC (%) between the frequent exacerbators and nonfrequent exacerbators. Moreover, in the FE group, fewer patients were in GOLD stage 1 than in other GOLD stages.

### Airway or Systemic Inflammation Between Groups

No significant associations were found between the FE and NFE groups in EI, emphysema grading and air trapping, showing that emphysema severity was hardly associated with the COPD frequent exacerbator phenotype ( $P > 0.05$ ) after excluding the difference in spirometry. This result is inconsistent with the conclusions of other studies.<sup>8,11</sup> However, compared with nonfrequent exacerbators, frequent exacerbators exhibited greater Pi10 [ $2.89 \pm 0.48$  vs  $2.54 \pm 0.54$ ,  $P < 0.001$ ] and WA% [ $57.75 \pm 6.36$  vs  $51.93 \pm 8.23$ , %,  $P < 0.001$ ] values. Moreover, Pi10 and WA% ( $P < 0.001$ ) appeared to be associated with the phenotype (Table 2), implying that frequent exacerbators had further airway thickening. Additionally, we noticed that frequent exacerbators had higher concentrations of IL-1 $\beta$  [ $2.33$  (1.95–2.80) vs  $1.46$  (1.13–1.99) pg/mL,  $P < 0.001$ ], IL-4 [ $4.49$  (3.65–5.11) vs  $3.69$  (3.01–4.37) pg/mL,  $P < 0.001$ ], and IL-6 [ $8.79$  (6.60–10.69) vs  $6.83$  (4.90–13.40) pg/mL,  $P = 0.037$ ] (Table 3).

### Nature of the COPD Frequent Exacerbation Phenotype: Inflammation

There are strong associations between airway thickening or systemic inflammation and the frequent exacerbator phenotype (Table 3). Without adjusting for sex, age, BMI, smoking index and FEV<sub>1</sub>%pred (model 1), the results showed that Pi10 [OR 3.85, (2.14–6.95),  $P < 0.001$ ] and WA% [OR 1.15 (1.00–1.30),  $P < 0.001$ ] were related to the frequent exacerbator phenotype. After adjusting for sex, age, BMI, smoking index and FEV<sub>1</sub>%pred (model 2), an independent relationship between airway thickening based on Pi10 [OR 4.01, (2.05–7.83),  $P < 0.001$ ] and WA% [OR 1.12, (1.06–1.17),

**Table 1** Baseline Characteristics of Frequent and Nonfrequent Exacerbators

	Total	Nonfrequent Exacerbators (n=106)	Frequent Exacerbators (n=106)	P-value
Age (yrs)	66.18±7.50	67.07±7.54	65.30±7.39	0.085
Male, n (%)	135(63.7)	65(30.7)	70(33.0)	
Female, n (%)	77(36.3)	41(19.3)	36(17.0)	
Height (cm)	160.27±8.63	160.23±8.72	160.31±8.58	0.953
Weight (kg)	63.77±11.45	62.77±11.22	64.77±11.64	0.205
BMI (kg/m <sup>2</sup> )	24.69±3.15	24.32±3.09	25.06±3.18	0.087
6MWT (m)	337.17±116.64	353.54±112.23	320.80±119.17	0.041
Exacerbation frequency	1.50 (0–2.75)	0 (0–0)	2.50 (2–3)	0.001
<b>Smoking condition</b>				0.039
Smoker, n (%)	144(68)	79(37.3)	65(30.7)	
Nonsmoker, n (%)	68(32)	27(12.7)	41(19.3)	
Smoking index	51±25	47±22	55±27	0.001
CAT score,	18 (12–24)	15 (9–20)	22 (16–27)	0.001
mMRC score,	3 (1–3)	2 (1–3)	3 (2–4)	0.004
SGRQ score,	44.72 (27.96–57.51)	38.74 (16.94–50.59)	51.07 (37.56–63.98)	0.001
<b>GOLD stage, n (%)</b>				
1	15(7.1)	8(3.8)	7(3.3)	
2	72(34)	38(18)	34(16)	
3	80(37.7)	34(16)	46(21.7)	
4	45 (21.2)	26 (12.2)	19 (9)	
<b>Inhaled long medicine</b>				
LAMA	20(9.4)	12(5.7)	8(3.8)	
LAMA+ICS	5(2.4)	3(1.4)	2(0.9)	
LAMA+LABA	7(3.3)	3(1.4)	4(1.9)	
LAMA+LABA+ICS	5(2.5)	2(0.9)	3(1.4)	
<b>Spirometry</b>				
FEV <sub>1</sub> (L)	1.30±0.55	1.31±0.56	1.30±0.54	0.979
FEV <sub>1</sub> (% predicted)	47.17±19.97	47.26±21.02	47.09±18.97	0.952
FVC (L)	2.73±0.74	2.71±0.72	2.75±0.77	0.680
FVC (% predicted)	73.50±17.28	72.64±16.88	74.35±17.72	0.472
FEV <sub>1</sub> /FVC (%)	47.35±13.06	47.36±13.43	47.34±12.74	0.992

**Notes:** Values are given as the mean ± SD, number (%), or median (interquartile range).

**Abbreviations:** BMI, body mass index; 6MWT, 6-min walk test; CAT, COPD assessment test; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; LAMA, long-acting antimuscarinic; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroids; FEV<sub>1</sub>, forced expiratory volume in one second; FEV<sub>1</sub>%pred, predicted percentage of FEV<sub>1</sub>; FVC, forced vital capacity; FVC%pred, predicted percentage of FVC.

$P<0.001$ ] and the frequent exacerbator phenotype was revealed. Moreover, in model 1, neutrophils [OR 1.11 (1.07–1.16),  $P=0.044$ ], IL-1 $\beta$  [OR 3.12, (2.02–4.83),  $P<0.001$ ] and IL-4 [OR 2.32, (1.67–3.21),  $P<0.001$ ] were associated with the frequent exacerbator phenotype. However, in model 2, only IL-1 $\beta$  [OR 2.94, (1.87–4.63),  $P<0.001$ ] and IL-4 [OR 2.24, (1.60–3.15),  $P<0.001$ ] were independently related to the frequent exacerbator phenotype. Thus, we determined that there was an independent association between systemic inflammation and the frequent exacerbating phenotype of COPD.

There was a positive association between trend changes in Pi10, WA%, IL-1 $\beta$ , or IL-4 and the frequent exacerbator phenotype (Figure 2). After adjusting for sex, age, BMI, smoking index and FEV<sub>1</sub>%pred, the results showed that the greater the Pi10 [Q2, OR 4.27(1.60–11.37)  $P<0.001$ , Q3, OR 13.18(4.86–35.77)  $P<0.001$ , Q4, OR 12.19(4.20–35.39)  $P<0.001$ ] and WA% [Q2, OR 4.30(1.63–11.34)  $P=0.003$ , Q3, OR 12.70(4.60–35.10)  $P<0.001$ , Q4, OR 13.18(4.53–38.35)  $P<0.001$ ], the greater the risk of being a frequent exacerbator was ( $P$  for trend  $<0.001$ ). Similarly, we found the same linear association between the odds ratio of being a frequent exacerbator and increasing quartiles of IL-1 $\beta$  ( $P<0.001$ ) or IL-4 ( $P$  for trend  $<0.001$ ). Moreover, the odds of being a frequent exacerbator were approximately 31 times greater in the IL-1 $\beta$  quartile ( $\leq 2.57$  pg/mL) than in the lowest IL-1 $\beta$  quartile ( $\leq 1.34$  pg/mL) [OR, 30.84 (9.88–96.26),  $P<0.001$ ].

**Table 2** Quantitative CT Parameters and Inflammatory Index Between Frequent and Nonfrequent Exacerbators

	Total	Nonfrequent Exacerbators (n=106)	Frequent Exacerbators (n=106)	P-value
<b>Emphysema index (%)</b>	11.54 (3.39–25.42)	12.07 (3.45–30.88)	9.30 (3.42–22.56)	0.369
<b>Emphysema grading (%)</b>				0.222
Emphysema index <5%	66(31.1)	30(14.2)	36(17)	
5%≤emphysema index <25%	92(43.4)	44(20.8)	48(22.6)	
25%≤emphysema index <50%	51(24.1)	29(13.7)	22(10.4)	
50%≤emphysema index <75%	3(1.4)	3(1.4)	0(0)	
<b>Air trapping (%)</b>	44.17 (25.11–62.33)	42.44 (22.91–62.81)	45.83 (26.19–59.63)	0.916
<b>Airway thickness</b>				
Pi10	2.71±0.54	2.54±0.54	2.89±0.48	0.001
WA%	54.80±7.90	51.93±8.23	57.75±6.36	0.001
<b>Inflammatory cells</b>				
Leukocyte ( $\times 10^9/L$ )	7.63±2.59	7.30±2.36	7.97±2.76	0.057
Neutrophil ( $\times 10^9/L$ )	4.82±2.16	4.52±1.84	5.12±2.41	0.041
Neutrophil % (%)	61.54±11.12	60.64±10.51	62.43±11.68	0.242
Leukomonocyte ( $\times 10^9/L$ )	1.95±0.87	1.92±0.91	2.00±0.83	0.547
Leukomonocyte % (%)	26.75±9.73	27.26±9.43	26.24±10.05	0.443
Monocyte ( $\times 10^9/L$ )	0.61±0.23	0.61±0.24	0.60±0.23	0.883
Monocyte % (%)	8.26±2.69	8.59±2.64	7.93±2.72	0.070
Eosinophils ( $\times 10^9/L$ )	0.20±0.18	0.21±0.19	0.20±0.160	0.919
Eosinophils % (%)	2.76±2.11	2.82±2.20	2.70±2.02	0.673
Basophil ( $\times 10^9/L$ )	0.02(0–0.06)	0.03(0–0.06)	0.02(0–0.06)	0.372
Basophil % (%)	1.00(0–1.00)	1.00(0–1.00)	1.00(0–1.00)	0.062
<b>Cytokines</b>				
IL-1 $\beta$ (pg/mL)	1.96(1.34–2.57)	1.46(1.13–1.99)	2.33(1.95–2.80)	0.001
IL-4 (pg/mL)	4.08(3.31–4.77)	3.69(3.01–4.37)	4.49(3.65–5.11)	0.001
IL-5 (pg/mL)	6.75(5.06–9.43)	6.94(5.04–9.48)	6.58(5.23–8.67)	0.602
IL-6 (pg/mL)	8.11(5.60–11.21)	6.83(4.90–13.40)	8.79(6.60–10.69)	0.037
IL-13 (pg/mL)	28.1(26.3–34.9)	27.02(20.37–35.60)	25.18(19.41–34.55)	0.329
IL-17 (pg/mL)	62.1(58.6–71.6)	58.43(44.13–73.49)	58.58(43.19–69.92)	0.996
IFN- $\gamma$ (pg/mL)	93.9(80.3–96.4)	83.73(66.04–102.71)	78.5(58.72–95.40)	0.157

**Notes:** Values are given as the mean  $\pm$  SD, number (%), or median (interquartile range). Emphysema index (EI), CT automatic calculation of the volume fraction of the lungs below 950 HU at full inspiration (%LAA-950), air trapping, CT automatic calculation of the volume fraction of the lungs below 856 HU at full inspiration (%LAA-856). Goddard score: 0=EI < 5%, 1=5%<EI<25%, 2=25%<EI<50%, 3=50%<EI<75%, 4=75%≤ EI.

**Abbreviations:** Pi10, inner perimeter wall thickness of a 10-mm diameter bronchiole airway; WA%, wall area percentage; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-4, interleukin-4; IL-5, interleukin-5; IL-6, interleukin-6; IL-13, interleukin-13; IL-17, interleukin-17; IFN- $\gamma$ , interferon- $\gamma$ .

## Associations Between Airway Thickening and Systemic Inflammation

The quantitative CT parameter Pi10 was independently associated with IL-1 $\beta$  [ $\beta$ , (95% confidence interval, CI, 1.47 (1.11–1.84)),  $P<0.001$ ] and IL-4 [0.41 (0.12–0.69),  $P<0.05$ ] but not the neutrophil count. In addition, as Pi10 increased, the levels of IL-1 $\beta$  ( $P$  for trend  $<0.001$ ) and IL-4 ( $P$  for trend  $<0.05$ ) increased (Table 4). The findings indicated that airway thickening was independently related to systemic inflammation.

## Sensitivity and Specificity of Pi10, WA%, IL-1 $\beta$ and IL-4 to Identify COPD Frequent Exacerbator Phenotypes

For the frequent exacerbator phenotype, the diagnostic values of Pi10, WA%, IL-1 $\beta$  and IL-4 were revealed and compared by drawing ROC curves (Figure 3). For Pi10, WA%, IL-1 $\beta$  or IL-4, the areas under the ROC curves were 0.722, 0.736, 0.807, and 0.706 for the identification of the frequent exacerbator phenotype, and the corresponding optimal cutoffs were 2.51 mm, 54.00%, 1.69 pg/mL and 4.31 pg/mL, respectively. Values above the cutoffs were associated with a significantly increased risk of being a frequent exacerbator.



**Table 3** Association Between the Frequent Exacerbator Phenotype in COPD and Airway Thickening or Systemic Inflammation

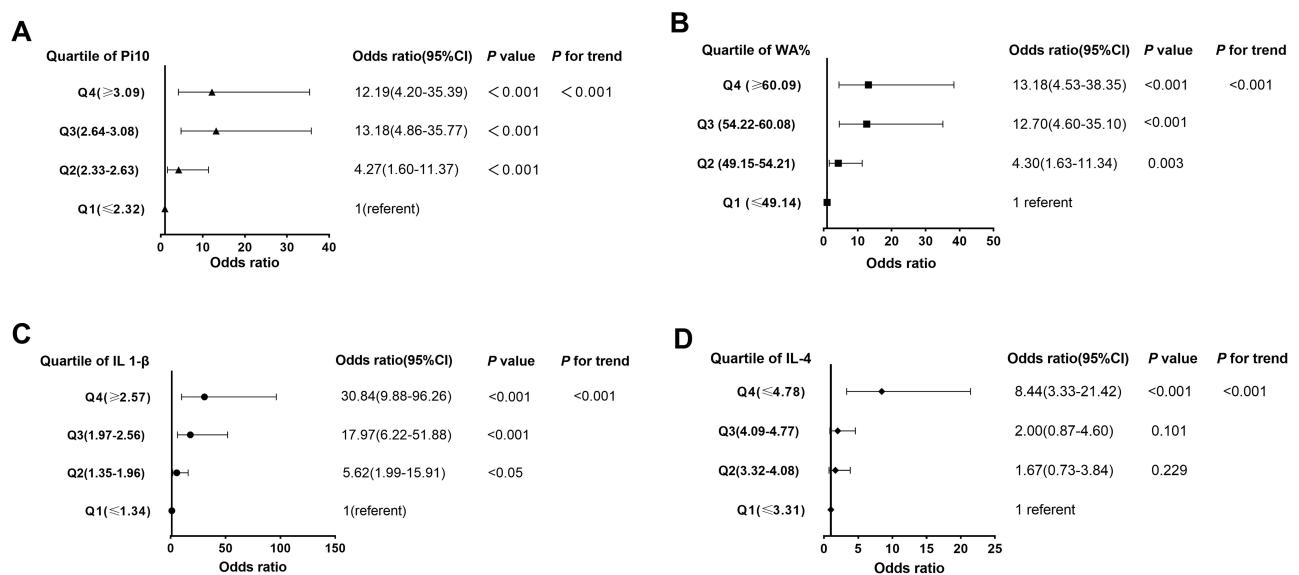
Independent variable	Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
<b>Airway thickening</b>				
Pi10	3.85 (2.14–6.95)	0.001	4.01 (2.05–7.83)	0.001
WA %	1.11 (1.07–1.16)	0.001	1.12 (1.06–1.17)	0.001
<b>Systemic inflammation</b>				
Neutrophil ( $\times 10^9/L$ )	1.15 (1.00–1.30)	0.044	1.14 (0.99–1.31)	0.07
IL-1 $\beta$	3.12 (2.02–4.83)	0.001	2.94 (1.87–4.63)	0.001
IL-4	2.32 (1.67–3.21)	0.001	2.24 (1.60–3.15)	0.001
IL-6	1.00 (0.98–1.03)	0.789	1.00 (0.98–1.03)	0.833

**Notes:** Data are shown as least-square means (95% CI). Model 1: Univariate linear regression model. Model 2: Multivariable linear regression model adjusted for sex, age, BMI, smoking index and FEV1%pred.

**Abbreviations:** Pi10, inner perimeter wall thickness of a 10-mm diameter bronchiole airway; WA%, wall area percentage; IL-1 $\beta$ , interleukin-1 $\beta$ ; IL-4, interleukin-4; IL-6, interleukin-6; OR, odds ratio.

## Discussion

The principal finding of this case-control study was that airway thickening on quantitative CT and systemic inflammation were independently associated with the frequent exacerbator phenotype of COPD after subjects were matched for sex, age and FEV1%pred, suggesting that airway and systemic inflammation contribute to the frequent exacerbation phenotype in COPD. To our knowledge, this study is the first to estimate the association between several metrics of quantitative CT or systemic inflammation and the COPD frequent exacerbation phenotype in consideration of the influence of lung function differences. Compared to other studies,<sup>7–9,11,25,26</sup> this study has an advanced study design and more comprehensive metrics, including quantitative CT, lung function and biochemical tests. Few previous studies have investigated the association between structural changes identified on CT and systemic inflammation in patients with COPD, and quantitative CT parameters did not show any convincing associations with biomarkers.<sup>26</sup> However, this study



**Figure 2** Associations between quartiles of Pi10, WA%, IL-1 $\beta$ , or IL-4 and the frequent exacerbator phenotype. The linear association between the odds ratio (OR) and variables was assessed by P for trend using a logistic regression model. **(A)** OR for quartile of Pi10 associated with the frequent exacerbator phenotype (p for trend <0.001). **(B)** OR for quartile of WA% associated with the frequent exacerbator phenotype (p for trend <0.001). **(C)** OR for quartile of IL-1 $\beta$  associated with the frequent exacerbator phenotype (p for trend <0.001). **(D)** OR for quartile of IL-4 associated with the frequent exacerbator phenotype (p for trend <0.001).

**Table 4** Association Between Pi10 and the Inflammatory Index

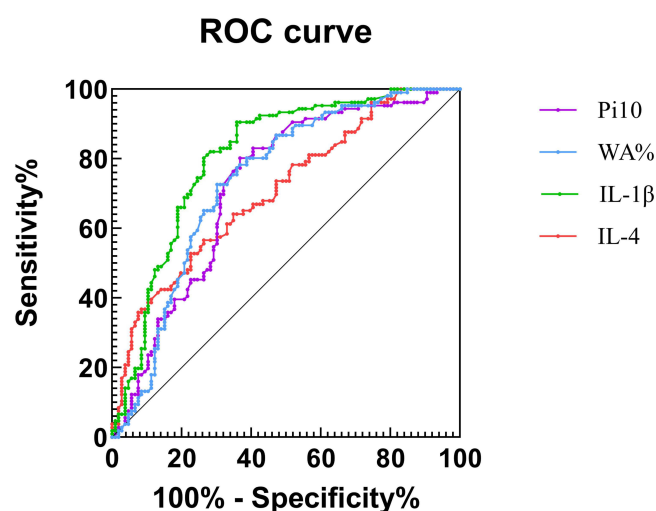
Inflammatory Index	Continuous Variable of Pi10 ( $\beta$ 95% CI)	Quartiles of Pi10 ( $\beta$ 95% CI)				P for trend
		Q1 $\leq$ 2.32 N=52	2.33 $\leq$ Q2 $\leq$ 2.63 N=51	2.64 $\leq$ Q3 $\leq$ 3.08 N=57	3.09 $\leq$ Q4 N=52	
Neutrophil	0.1 (-0.49–0.69)	0 (ref)	0.22 (-0.61–1.06)	0.55 (-0.27–1.37)	0.27 (-0.62–1.16)	0.514
IL-1 $\beta$	1.47 (1.11–1.84) <sup>a</sup>	0 (ref)	0.406 (-0.13–0.94)	0.832 (0.30–1.35) <sup>c</sup>	1.763 (1.19–2.34) <sup>d</sup>	0.001
IL-4	0.41 (0.12–0.69) <sup>b</sup>	0 (ref)	0.336 (-0.06–0.74)	0.298 (-0.09–0.69)	0.55 (0.12–0.98) <sup>e</sup>	0.024

**Notes:** Data are shown as least-square means (95% CI). Q, quartile; Q1,  $\leq$ 25th percentile, Q2, 25th percentile–50th percentile, Q3, 50th percentile–75th percentile, Q4,  $\geq$ 75th percentile–100th percentile, ref, reference,  $\beta$ , regression coefficient. Generalized linear model adjusted for sex, age, BMI, smoking index and FEV1%pred. <sup>a</sup>P <0.001, <sup>b</sup>P <0.05 <sup>c</sup>P<sub>Q1-Q3</sub><0.05, <sup>d</sup>P<sub>Q1-Q4</sub><0.001. <sup>e</sup>P<sub>Q1-Q4</sub><0.05.

demonstrates that airway inflammation is associated with systemic inflammation in COPD from the perspective of airway thickening and inflammatory cytokines.

As reported, airway thickening, severity of pulmonary function and emphysema are associated with the frequent exacerbator phenotype.<sup>7,8,11,12,27</sup> At the same time, a higher Pi10 and worse emphysema are significantly associated with worse FEV1%-predicted COPD.<sup>28,29</sup> In addition, some emphysema phenotypes, such as panlobular emphysema, were associated with greater airflow obstruction.<sup>14</sup> In contrast, there was no significant difference in CT-quantified emphysema between FEs and NFEs in this study, possibly because there was also no difference in spirometry or severity of COPD. Our findings partly support and explain the findings of others in terms of the nonlinear relationship between emphysema percentage and exacerbation frequency.<sup>11</sup> Our data can be used to determine whether emphysema severity is the effect of the difference in spirometry between groups and thus possibly has a causal role. This study suggested that the relationship between emphysema percentage and exacerbation frequency partly mirrored the relationship between disease severity and exacerbation frequency, which explains the difference in factors that drive exacerbations between patients with severe emphysema and patients with severe airway disease.<sup>11</sup> This suggests that while quantitative CT measures of emphysema are useful tools for reflecting pulmonary physiology and functional status, they may not be useful tools for assessing the frequency of COPD exacerbation.

Traditional airway measurements on CT, for example, wall thickness or luminal area, require an accurate set of labeled airway branches.<sup>28</sup> However, Pi10 and WA%, as imaging biomarkers of airway thickening, are easily measured



**Figure 3** Receiver operating characteristic curve for identification of the frequent exacerbator phenotype. ROC analysis yielded areas under the curve (AUCs) of 0.722, 0.736, 0.807 and 0.706, respectively, for the identification of FE. The greatest sum of sensitivity and specificity occurred at Pi10 = 2.51 mm, WA%=54%, IL-1 $\beta$ =1.686 (pg/mL), and IL-4=4.316 (pg/mL).



and associated with chronic airway inflammation in patients with COPD.<sup>30</sup> Moreover, Pi10 is a standardized parameter for a comprehensive assessment of bronchial wall thickness and a clinical biomarker indicating smoking-related injury in smokers' airways.<sup>28,31</sup> Consistent with prior studies,<sup>7,11</sup> airway thickening was associated with the frequency of COPD exacerbation. Nevertheless, our findings between FEs and NFEs provide more quantitative CT parameters and adopt advanced inclusion and exclusion criteria. Moreover, we considered that Pi10 and WA% were independently associated with the frequent exacerbator phenotype among patients with COPD. With increasing Pi10 and WA%, the risk of being a frequent exacerbator increased ( $p$  for trend  $<0.001$ ). For patients with stable COPD, Pi10 and WA% would be useful imaging biomarkers to forecast the frequency of COPD exacerbations because the AUCs of Pi10 and WA% in the ROC analysis were 0.722 and 0.736, respectively, according to our results.

Neutrophils, especially the aggregation and activation of neutrophils, play a central role in inflammation in COPD.<sup>32</sup> Frequent COPD exacerbators have further neutrophilic inflammation due to strong associations between neutrophilic inflammation and increased small airway resistance and gas trapping.<sup>33</sup> In addition, neutrophilic inflammation disrupts elastic fiber assembly, resulting in a permanent reduction in lung function in a mouse model.<sup>34</sup> As noted above, we found that a greater concentration of neutrophils was associated with a frequent exacerbating phenotype of COPD in this study, which was consistent with high blood neutrophil counts predicting more frequent exacerbations in patients with COPD.<sup>35</sup> IL-1 $\beta$  plays an important role in cytokine-mediated neutrophilic inflammation because IL-1 $\beta$  not only induces bronchial epithelial cells to express the cytokines IL-6 and IL-8 but also increases the number of T lymphocytes and dendritic cells to promote the release of IL-6 and IL-17.<sup>36,37</sup> IL-1 $\beta$  gene expression in sputum was significantly upregulated in frequent exacerbators, and frequent exacerbations in COPD are associated with increased airway IL-1 $\beta$ .<sup>21</sup> The levels of IL-4, IL-17, and IFN- $\gamma$  were significantly higher during the exacerbation of COPD.<sup>38</sup> We previously reported that there is a greater concentration of IL-4 in the serum of frequent exacerbators.<sup>22</sup> In addition, serum IL-6 was significantly higher in frequent exacerbators than in nonfrequent exacerbators in COPD.<sup>21</sup> In this study, frequent exacerbators had greater concentrations of IL-1 $\beta$ , IL-6 and IL-4 in serum. These results suggest that greater concentrations of IL-1 $\beta$ , IL-4 or IL-6 in sputum or serum were associated with the COPD frequent exacerbation phenotype. After adjusting for sex, age, BMI, smoking index and FEV<sub>1</sub>%pred, we found that IL-1 $\beta$  and IL-4 were independently associated with the frequent exacerbator phenotype. In addition, the ROC analysis identified IL-1 $\beta$ =1.686 pg/mL as providing 90.6% sensitivity and IL-4=4.316 pg/mL as providing 56.6% sensitivity for distinguishing nonfrequent from frequent exacerbators, implying that IL-1 $\beta$  may be a better biomarker than IL-4 to forecast the risk of being a COPD frequent exacerbator phenotype.

Abundant evidence has shown significant systemic inflammation in patients with COPD.<sup>39–42</sup> There is supportive evidence that systemic markers may spill over from the lungs into systemic circulation.<sup>42</sup> Systemic inflammation was associated with airway inflammation in COPD and asthma by exploring the link between inflammation biomarkers in the airway and serum.<sup>21,43</sup> In contrast, greater concentrations of IL-1 $\beta$ , IL-6 and IL-4 in serum were associated with the frequent exacerbator phenotype in this study, meaning that the frequency of COPD exacerbation was associated with further systemic inflammation. Airway thickening in COPD can be attributed to airway inflammation and airway remodeling.<sup>28,44</sup> A previous study considered that there were no significant associations between CT parameters, such as Pi10, and blood neutrophils and eosinophils, which was consistent with the results of this study.<sup>26</sup> However, we not only found significantly higher IL-1 $\beta$  or IL-4 concentrations and greater Pi10 in frequent exacerbators, but we also discovered that Pi10 was independently correlated with IL-1 $\beta$  or IL-4, indicating that airway inflammation and airway remodeling may be associated with systemic inflammation in COPD.

As mentioned earlier, we found that frequent exacerbators in COPD always have significantly higher IL-1 $\beta$  or IL-4 concentrations, greater Pi10. In order to further evaluate our findings, the researchers may consider studying relevant data in various freely accessible databases like Spiromics or COPDGene. In order to provide patients with frequent COPD deterioration with a novel kind of therapeutic intervention, we must also apply our findings to clinical practice or to some COPD deterioration prediction algorithms.<sup>45</sup> As global population ages, recognizing and intervening early in patients with frequent acute exacerbations of chronic obstructive pulmonary disease is undoubtedly a great boon.<sup>46</sup>

We recognize that this study has limitations, for instance, the lack of sputum samples, meaning that we were unable to assert whether our findings on CT were consistent with those of cytokines or cells of sputum. However, we found strong

evidence of associations between further inflammation and the frequent exacerbator phenotype in COPD with a small sample size, suggesting that these findings are worth exploring in a larger cohort to validate our findings.

## Conclusion

Our findings indicated that Pi10, WA%, IL-4, and IL-1 $\beta$  were independently associated with the frequent exacerbator phenotype among patients with stable COPD, suggesting that chronic airway and systemic inflammation contribute to the frequent exacerbator phenotype. Additionally, Pi10 was independently related to IL-1 $\beta$  or IL-4 in serum, indicating that there is more supportive evidence to demonstrate an association between the airway and systemic inflammation in patients with COPD. Moreover, based on the results of this study, Pi10, WA%, IL-1 $\beta$  and IL-4 should be used as predictors of future exacerbation risk in COPD. In summary, treatment strategies to attenuate airway and systemic inflammation and reduce COPD exacerbation in stable patients deserve further investigation.

## Abbreviations

CT, Computed tomography; COPD, Chronic obstructive pulmonary disease; FE, Frequent exacerbators; NFE, Non-frequent exacerbators; ROC, Receiver operating characteristic; 6MWT, 6-min walk test; CRP, C-reactive protein; SAA, Serum amyloid A; GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI, body mass index; CAT, COPD assessment test; Mmrc, Modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; LAMA, long-acting antimuscarinic; LABA, long-acting beta2-agonist; ICS, inhaled corticosteroids; FEV1, Forced expiratory volume in 1 s; FEV1%pred, Predicted percentage of forced expiratory volume in 1 s; FVC, Forced vital capacity; FVC% pred, Predicted percentage of forced vital capacity; Pi10, Inner perimeter wall thickness of a 10-mm diameter bronchiole airway; WA%, Wall area percentage; IL-1 $\beta$ , Interleukin-1 $\beta$ ; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-13, Interleukin-13; IL-17, Interleukin-17; IFN- $\gamma$ , Interferon- $\gamma$ ; ref, Reference;  $\beta$ , Regression coefficient; Q, Quartile.

## Data Sharing Statement

All data generated or analysed during this study are included in this published article.

## Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Review Committee of the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. The reference number for the study is 2016-20. Informed consent for this study was obtained from all the subjects. Furthermore, our study complied with the Declaration of Helsinki.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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