

## Typing of chronic obstructive pulmonary disease using high-resolution computed tomography and the association with smoking, airway inflammation, and common comorbidities

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**Background/aim:** This study performed typing of chronic obstructive pulmonary disease (COPD) using high-resolution computed tomography (HRCT) to determine the association with smoking, matrix metalloproteinases, and common comorbidities.

**Materials and methods:** The study enrolled 94 hospitalized patients. Participants were divided into a group of 69 current and former smokers (group A) and a group of 25 that had never smoked (group B). Patients were also divided into 3 categories according to the degree of emphysema and bronchial wall thickness using HRCT to determine the association with levels of matrix metalloproteinase 9 (MMP-9) and TIMP-1, as well as associated comorbidities. These three categories were: type A - no or mild emphysema, with or without bronchial wall thickening; type E - emphysema without bronchial wall thickening; and type M - both emphysema and bronchial wall thickening.

**Results:** The low attenuation area (LAA) scores in group A patients were higher than those in group B ( $t = 2.86$ ,  $P < 0.01$ ); correlation analysis showed that smoking was associated with a decline of the forced expiratory volume in 1 s and forced vital capacity ratio (FEV1/FVC%) and higher LAA scores in patients with COPD ( $F = 4.46$ ,  $F = 8.20$ ,  $P < 0.05$ ). The levels of MMP-9 in group A were higher than those in group B ( $t = 3.65$ ,  $P < 0.01$ ). Among COPD patients with more than 3 comorbidities, there were statistically significant differences in both the smoking group and the nonsmoking group ( $\chi^2 = 12.08$ ,  $P < 0.01$ ). When compared to type A patients, who had coincident cardiovascular diseases in the smoking group, patients of type M and E showed statistically significant differences ( $F = 2.42$  and  $2.12$ ,  $P < 0.05$ ).

**Conclusion:** Emphysema was more severe in smokers. Metalloproteinase levels in smokers were higher than those in nonsmokers. Moreover, comorbidities were more severe in smokers.

**Key words:** Smoking, COPD, high-resolution computed tomography, emphysema, chronic bronchitis, metalloproteinase, comorbidities

### 1. Introduction

Pulmonary function testing plays an important role in the diagnosis and evaluation of chronic obstructive pulmonary disease (COPD). However, as the severity of COPD cannot be assessed using pulmonary function alone, it is also necessary to evaluate airway inflammation, the time of onset, the extent of lung destruction, pathological changes, and associated comorbidities (1,2). Neutrophils, macrophages, lymphocytes, and inflammatory mediators are involved in airway inflammation and structural damage. Metalloproteinases also play a key role in airway and parenchymal structural damage and airflow limitation in COPD (3–5). High-resolution computed tomography (HRCT) can be used to assess the destruction of lung structure in COPD (6) and the findings are associated with pathological changes in COPD (7,8). In

addition, a variety of comorbidities affect the quality of life in patients with COPD. Smoking and other factors, such as biofuel exposure, are important causes of COPD (9,10). This study examined the use of CT to classify airway inflammation and the association with matrix metalloproteinases and their inhibitors, as well as common comorbidities in COPD patients with and without a smoking history. The clinical features of COPD patients were comprehensively assessed to establish a theoretical basis for individualized treatment of COPD.

### 2. Materials and methods

#### 2.1. Subjects

The study was conducted in the Petroleum Clinical Medical College of Hebei Medical University and enrolled

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94 patients hospitalized between January 2016 and December 2016. There were 56 males and 38 females, with ages ranging from 48 to 87 years old. The average age was  $71 \pm 9$  years old. Participants were divided into a group of 69 (73.4%) current and former smokers (group A) and a group of 25 that had never smoked (26.6%) (group B). The diagnosis of COPD was based on criteria in the literature (7–9). The Petroleum Clinical Medical College of Hebei Medical University approved the study, and all patients provided signed informed consent. All patients had pulmonary function testing and chest HRCT. Routine blood testing was performed on the day after admission, and levels of matrix metalloproteinases and their inhibitors were determined.

## 2.2. Measures of emphysema by using HRCT

Subjective, semiquantitative measurement of emphysema was made by visual assessment of HRCT images, using Syngo CT SOMATOM Definition Flash Pulmo 3D image-processing software (Siemens AG, Germany), with a low attenuation area (LAA) defined as less than  $-960$  HU. The following three anatomical layers were evaluated: 1) close to the upper margin for 1 cm of the aortic arch; 2) horizontal margin for 1 cm of carina; 3) upper margin for 3 cm of the right diaphragm, as shown in Figure 1. The LAA was determined for three lung fields, based on the percentage of each layer in each lung field. The LAA score was calculated for each layer as previously described (11): 0 points for LAA of  $<5\%$ , 1 point for  $5\% \leq \text{LAA} < 25\%$ , 2 points for  $25\% \leq \text{LAA} < 50\%$ , 3 points for  $50\% \leq \text{LAA} < 75\%$ , and 4 points for LAA of  $>75\%$ . The grade was determined by the total score for the three layers: grade 0 for 0 points, grade 1 for 1–3 points, grade 2 for 4–6 points, grade 3 for 7–9 points, and grade 4 for 10–12 points.

## 2.3. Measurement of bronchial wall

Enlarged targeted scanning images of the right upper lobe were used to rebuild the apical segmental bronchus with multiplanar reformation, after determining the cross-section perpendicular to the fifth bronchial lumen, as confirmed by two experienced radiologists. Bronchial wall

thickness (T) and pulmonary artery (PA) diameter in the same layer were measured using image magnification, and the ratio of the airway wall thickness to the pulmonary artery diameter (T/PA) was calculated. Classification of bronchial wall thickness in 3 layers was performed as previously described (12): grade 0 for T/PA of  $<30\%$ , grade 1 for  $30\% \leq \text{T/PA} < 50\%$ , and grade 2 for T/PA of  $\geq 50\%$ .

## 2.4. HRCT classification

The modified Kitaguchi method (11) was used for evaluation of emphysema and bronchial wall thickness, and three imaging types were defined, as follows: 1) type A: no or mild emphysema (LAA  $\leq$  Grade 1), with or without bronchial wall thickening; 2) type E: emphysema (LAA  $\geq$  Grade 2) without bronchial wall thickening; and 3) type M: both emphysema (LAA  $\geq$  Grade 2) and bronchial wall thickening (LAA  $\geq$  Grade 1).

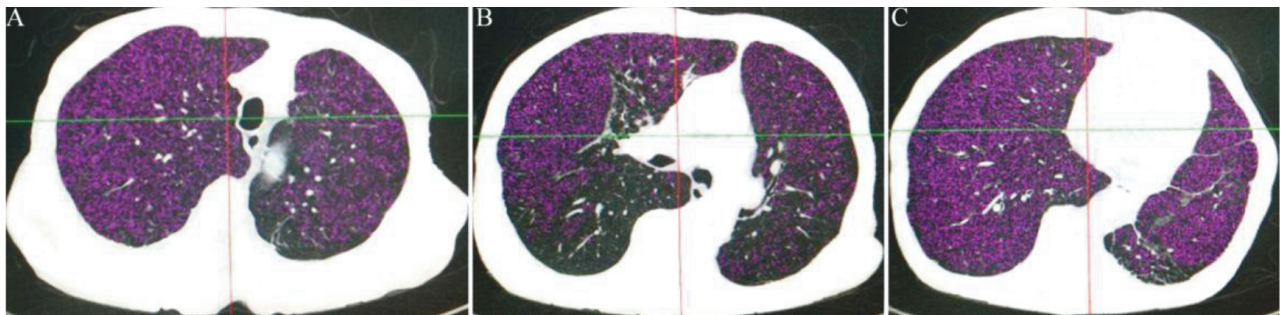
## 2.5. Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM Corp., Armonk, NY, USA) and data were analyzed using the t-test for comparisons between two groups. Analysis of variance (ANOVA) was used for comparisons among multiple groups. Enumeration data were analyzed using the chi-square test. Correlation analysis was performed using Pearson's chi-square, and  $P < 0.05$  was considered a statistically significant difference.

## 3. Results

### 3.1. Chest CT types

The chest CT types of smokers belonging to group A are shown in Table 1 and Figure 1. In this study, we found that the sample size of group B was significantly less than that of group A. Thus, we verified that each parameter between the two groups was not a statistically significant difference ( $F = 0.283, 0.660, 0.247, 0.714, 0.422, 0.686, 0.140; P > 0.05$ ) by using the homogeneity of variance test. The sample size of the two groups was found to be appropriate. The LAA score ( $9.38 \pm 4.62$ ) in group A showed a statistically significant difference ( $t = 2.86, P < 0.01$ ) compared with



**Figure 1.** A) The layer close to the upper margin for 1 cm of arcus aortae; B) horizontal margin for 1 cm of carina; C) upper margin for 3 cm of the right diaphragm, pink-purple part is the low attenuation area (LAA).

**Table 1.** The comparison of LAA score and T/PA of subtypes between the smoking patients and nonsmoking patients (mean  $\pm$  SD).

Group	Subtype	Case	LAA score	T/PA	F	P
A	A	11	4.73 $\pm$ 4.61	0.35 $\pm$ 0.07		
	E	13	9.92 $\pm$ 4.57 <sup>a</sup>	0.25 $\pm$ 0.04	121.27	<0.05
	M	45	10.36 $\pm$ 3.99 <sup>a</sup>	0.41 $\pm$ 0.08 <sup>a</sup>	66.34	<0.05
B	A	9	2.56 $\pm$ 0.53	0.32 $\pm$ 0.06		
	E	6	9.83 $\pm$ 4.26 <sup>b</sup>	0.26 $\pm$ 0.03	193.73	<0.05
	M	10	7.60 $\pm$ 4.27 <sup>b</sup>	0.40 $\pm$ 0.06 <sup>b</sup>	24.96	<0.05

<sup>a</sup> Compared with type A,  $t = 2.42\text{--}4.07$ ,  $P < 0.05$ ; <sup>b</sup> compared with type A,  $t = 2.82\text{--}5.16$ ,  $P < 0.05$ .

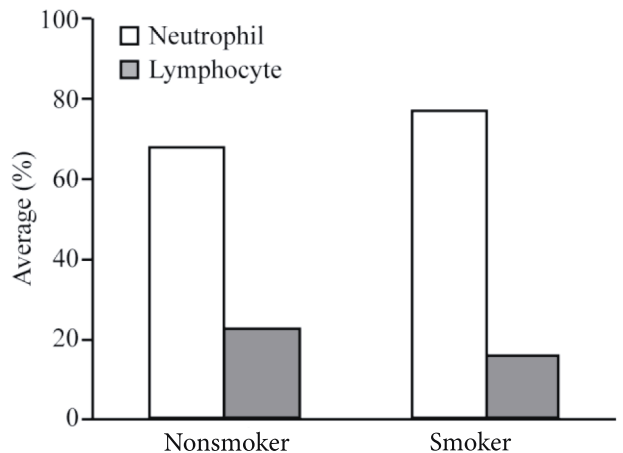
that in group B (6.32  $\pm$  4.45). One-way ANOVA showed that the LAA score in COPD patients was correlated with smoking, and it was considered to indicate a statistically significant difference ( $F = 8.20$ ,  $P < 0.01$ ).

In group A, the number of type M patients (45, 47.95%) was significantly higher than that of type A (11, 11.7%) and type E (13, 13.8%) patients. Compared with type A, the LAA score of type E and type M patients showed a statistically significant difference ( $F = 4.07$ ,  $F = 2.76$ ,  $P < 0.01$ ); however, the LAA score showed no significant difference between type E and type M ( $t = 0.33$ ,  $P > 0.05$ ). In group B, compared with type A (9 cases, 9%), the LAA score of type E and type M patients showed a statistically significant difference ( $F = 3.51$ ,  $F = 5.16$ ,  $P < 0.01$ ), and the LAA score showed no significant difference between type E and type M patients ( $t = 1.01$ ,  $P > 0.05$ ).

A comparison of T/PA in group A (0.37  $\pm$  0.10) with that in group B showed no statistically significant difference ( $t = 1.51$ ,  $P > 0.05$ ), but a comparison of T/PA in type M and type A showed a statistically significant difference ( $t = 2.42$ ,  $t = 2.82$ ,  $P < 0.05$ ) both in group A and group B.

### 3.2. Association of inflammatory markers with lung function

The neutrophil percentage (76.78  $\pm$  10.80%) and lymphocyte percentage (15.73  $\pm$  9.18%) in group A compared with that in group B (N%: 67.41  $\pm$  12.65%, T%: 22.51  $\pm$  12.08%) showed a statistically significant difference ( $t = 3.55$  and  $2.90$ ,  $P < 0.01$ ), as shown in Figure 2. There were no differences ( $P > 0.05$ ) in the level of procalcitonin, neutrophil percentage (N%), and lymphocyte percentage (T%) among types A, E, and M, both in group A and group B. There were no differences ( $P > 0.05$ ) in the forced expiratory volume in 1 s/forced vital capacity ratio (FEV1/FVC%), percent of forced vital capacity (FEV1%), mean maximal midexpiratory flow (MMEF) 25%–75%, and the residual volume to total lung capacity ratio (RV/TLC%) among types A, E, and M. However, the FEV1/FVC% in

**Figure 2.** The neutrophil percentage and the lymphocyte percentage in two groups.

group B (59.80  $\pm$  9.37%) was higher than that in group A (55.07  $\pm$  9.67%), showing a statistically significant difference ( $t = 2.11$ ,  $P < 0.05$ ). ANOVA revealed that the decline of FEV1/FVC% was correlated with smoking, showing a statistically significant difference ( $F = 4.46$ ,  $P < 0.05$ ). There were no differences ( $P > 0.05$ ) in the FEV1/FVC%, FEV1%, MMEF 25%–75%, and RV/TLC% among types A, E, and M, both in group A and group B.

### 3.3. Levels of matrix metalloproteinase 9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1), and the ratio of MMP-9/TIMP-1

The levels of MMP-9 and TIMP-1 and the ratio of MMP-9/TIMP-1 are shown in Table 2. The levels of MMP-9 in the three CT subtypes in group A and B were higher than those in healthy subjects ( $P < 0.05$ ). The differences in TIMP-1 and MMP-9/TIMP-1 between group A and the healthy subjects were statistically significant ( $P < 0.05$ ). The ratio of MMP-9/TIMP-1 in the M and E subtypes of group B

**Table 2.** Comparison of MMP-9 and TIMP-1 in subtypes (mean  $\pm$  SD).

Group		MMP-9 (ng/L)	TIMP-1 (ng/L)	MMP-9/TIMP-1	P
A	Type A (11)	135.62 $\pm$ 9.94 <sup>a</sup>	128.55 $\pm$ 25.78	0.84 $\pm$ 0.18	<0.05
	Type E (13)	133.69 $\pm$ 10.17 <sup>a</sup>	120.25 $\pm$ 10.18	0.91 $\pm$ 0.17	<0.05
	Type M (45)	128.31 $\pm$ 7.78	120.07 $\pm$ 17.76	0.86 $\pm$ 0.10	>0.05
B	Type A (9)	122.93 $\pm$ 8.01	150.03 $\pm$ 87.80	0.84 $\pm$ 0.11	>0.05
	Type E (6)	123.31 $\pm$ 8.15	114.21 $\pm$ 10.63	0.86 $\pm$ 0.05	>0.05
	Type M (10)	123.44 $\pm$ 5.94	123.01 $\pm$ 22.93	0.86 $\pm$ 0.11	>0.05

<sup>a</sup> Compared with type M,  $t = 2.05$ – $2.65$ ,  $P < 0.05$ .

was significantly different from that in healthy subjects ( $P < 0.05$ ). There was a significant difference between group A and group B ( $P < 0.05$ ).

In COPD patients, the level of MMP-9 ( $130.49 \pm 9.01$  ng/L) was significantly higher than that in group B ( $123.21 \pm 6.96$  ng/L), showing a statistically significant difference ( $t = 3.65$ ,  $P < 0.01$ ). However, there was no difference in TIMP-1 and the ratio of MMP-9/TIMP-1.

In group A, the level of MMP-9 ( $128.31 \pm 7.77$  ng/L) in type M patients was significantly lower than that in type A ( $135.62 \pm 9.94$  ng/L) and E ( $133.69 \pm 10.17$  ng/L), showing a statistically significant difference ( $t = 2.05$ ,  $2.65$ ,  $P < 0.05$ ). There was no difference in TIMP-1 and the ratio of MMP-9/TIMP-1 among types A, E, and M. In group B, there was no difference in MMP-9, TIMP-1, and the ratio of MMP-9/TIMP-1 among types A, E, and M. The levels of MMP-9 and TIMP-1 showed a significantly negative correlation with FEV<sub>1</sub>, with statistical significance ( $F = 27.11$  and  $91.62$ ,  $P < 0.05$ ).

### 3.4. Comorbidities

Among the 94 patients, 65 (69.1%) had cardiovascular disease and 29 (30.9%) did not have cardiovascular disease, but there were no differences among types A, E and M ( $P > 0.05$ ). There were no differences in CT subtypes between 25 patients with respiratory failure and 69 without respiratory failure. There were no differences in CT subtypes between 55 patients with fewer than 3 comorbidities and 39 with more than 3 comorbidities.

There were no significant differences between group A and group B in terms of combined respiratory failure and cardiovascular disease ( $P > 0.05$ ). Among patients with combined cardiovascular disease, the differences between types M and E and type A were statistically significant ( $F = 2.42$  and  $2.12$ ,  $P < 0.05$ ). In patients with more than 3 comorbidities, there were statistically significant differences in subtypes between group A and group B (chi-square =  $12.08$ ,  $P < 0.01$ ). In group A, there were statistically significant differences ( $t = 2.59$ ,  $P < 0.05$ )

between type M and type A in patients with more than three comorbidities.

The associations of MMP-9 with comorbidities are shown in Table 3. In group A, MMP-9 levels in those with combined cardiovascular disease and 3 or more comorbidities showed statistically significant differences compared to those without cardiovascular disease and fewer than 3 comorbidities ( $t = 3.07$  and  $5.69$ ,  $P < 0.01$ ). MMP-9 levels in type M patients showed statistically significant differences compared to levels in type A and E ( $F = 2.65$  and  $2.05$ ,  $P < 0.05$ ). In group B, there were statistically significant differences ( $t = 2.54$ ,  $P < 0.05$ ) in MMP-9 levels between patients with and without cardiovascular disease. There were no significant differences in MMP-9, TIMP-1, and the ratio of MMP-9/TIMP-1 according to the three CT types.

### 4. Discussion

COPD is a chronic disease with high morbidity and mortality rates. Smoking is the most important risk factor for COPD (13,14). Smith et al. (6) showed that smoking patients demonstrated emphysema subtypes on HRCT, and that smoking was correlated with centrilobular emphysema and panlobular emphysema, but had no correlation with paraseptal emphysema. This study aimed to determine whether there were differences in lung structure, airway inflammation, and airflow limitations according to smoking status and other risk factors for COPD, to provide a theoretical basis for individual treatment. The Kitaguchi method was used to evaluate emphysema and small airway thickness. The results showed that the LAA score for emphysema in smokers was significantly higher than that in nonsmokers, and that the LAA score was significantly correlated with smoking. In addition, airflow limitation was an important feature in COPD. The study found that the FEV<sub>1</sub>/FVC% in nonsmoking patients was better than the FEV<sub>1</sub>/FVC% in smoking patients, and that FEV<sub>1</sub>/FVC% was negatively associated with smoking, with restriction being a more severe contributor to COPD



**Table 3.** Comparison of two groups of metalloproteinases and their inhibitors in comorbidities (mean  $\pm$  SD).

Comorbidities	Group A			Group B			P
	MMP-9	TIMP-1	MMP-9/TIMP-1	MMP-9	TIMP-1	MMP-9/TIMP-1	
Respiratory failure							
Yes	128.99 $\pm$ 8.52	121.13 $\pm$ 13.61	0.88 $\pm$ 0.13	123.97 $\pm$ 5.66	119.17 $\pm$ 9.44	0.88 $\pm$ 0.06	>0.05
No	130.41 $\pm$ 9.49	120.64 $\pm$ 19.83	0.86 $\pm$ 0.13	123.09 $\pm$ 7.29	132.81 $\pm$ 9.97	0.85 $\pm$ 0.10	
Cardiovascular disease							
Yes	132.06 $\pm$ 8.93 <sup>a</sup>	120.99 $\pm$ 18.30	0.89 $\pm$ 0.13	125.62 $\pm$ 7.35 <sup>a</sup>	132.70 $\pm$ 63.49	0.85 $\pm$ 0.11	<0.05
No	125.26 $\pm$ 8.02	120.32 $\pm$ 17.94	0.87 $\pm$ 0.14	118.97 $\pm$ 3.52	126.93 $\pm$ 38.99	0.86 $\pm$ 0.07	
Comorbidities							
>3	135.24 $\pm$ 8.17 <sup>b</sup>	120.20 $\pm$ 18.71	0.88 $\pm$ 0.13	128.04 $\pm$ 2.99	199.65 $\pm$ 107.86	0.82 $\pm$ 0.18	>0.05
$\leq$ 3	124.99 $\pm$ 7.09	121.35 $\pm$ 17.68	0.86 $\pm$ 0.13	122.31 $\pm$ 7.16	117.47 $\pm$ 27.59	0.86 $\pm$ 0.08	
Hospitalized							
>1	131.04 $\pm$ 9.11	117.92 $\pm$ 19.19	0.89 $\pm$ 0.13	125.48 $\pm$ 6.10	114.86 $\pm$ 13.55	0.87 $\pm$ 0.06	>0.05
$\leq$ 1	128.97 $\pm$ 9.23	123.50 $\pm$ 16.74	0.86 $\pm$ 0.13	121.73 $\pm$ 7.29	141.14 $\pm$ 69.19	0.84 $\pm$ 0.12	

<sup>a</sup> Compared with group "No",  $t = 2.54-5.69$ ,  $P < 0.05$ ; <sup>b</sup> compared with group  $\leq 3$ ,  $P < 0.05$ .

compared with other causative factors. Based on CT subtypes analysis, LAA scores of types M and E, whose main manifestation was emphysema both in the smoking and nonsmoking groups, were significantly higher than those in group A in the nonsmoking group; moreover, the more severe the degree of emphysema, the more significant the decline in athletic ability and the more significant the clinical symptoms (6,15). The present study showed that patients with type A had a milder condition and better prognosis than those with type M and type E. The pathology in COPD patients was mainly manifested as small airway stenosis and alveolar abnormalities. The results of this study showed that the airway wall thickness in type M was greater than in type A in both the smoking and nonsmoking groups; however, the small airway wall in the smoking group was not more significantly thickened than that in the nonsmoking group, indicating that smoking is not the only reason for small airway wall thickening, but may be correlated with abnormalities in the airway smooth muscle, mucus secretion, airway inflammation, and other factors.

The worsening of chronic airway inflammation is the basis for COPD pathophysiology. In this study, the percentages of neutrophils and lymphocytes in the peripheral blood of smoking patients were significantly higher than those in nonsmokers; Smith et al. (6) and Saetta et al. (16) showed that centrilobular emphysema in smoking patients was most common, especially in the right upper lung. Compared with panlobular and paraseptal emphysema, the leukocytes in peripheral blood

with centrilobular emphysema were more significantly increased, indicating that smoking was an important factor in the worsening of airway inflammation in centrilobular emphysema. Shin et al. (17) found that melatonin effectively inhibited airway neutrophils induced by smoking and reduced airway mucus secretion in a mouse COPD model; thus, melatonin may become a new drug for treatment of COPD.

Other than chronic inflammation, airway remodeling is also an important pathological change in COPD. MMP-9 is involved in airway and lung reconstruction through the degradation of the extracellular matrix and cell membranes; TIMP-1 is an inhibitor of MMP-9, and imbalance both in MMP-9 and TIMP-1 led to airway and lung reconstruction (18). In COPD patients, MMP-9 levels in the smoking and nonsmoking groups were higher than those in a healthy group, indicating that MMP-9 is involved in the pathogenesis of COPD. MMP-9 levels in the smoking group were higher than in the nonsmoking group, and airway and lung reconstruction and airflow limitation were greater in smoking patients. In smoking patients, analysis showed that MMP-9 and TIMP-1 were negatively correlated with FEV1, consistent with reports by Kwiatkowska et al. and Linder et al. (19,20).

Multiple studies (21-24) reported that patients with cardiovascular disease, diabetes, depression, cancer, and other diseases can show accelerated progression of COPD, and that an increase of C-reactive protein, interleukin-6, interleukin-8, and other markers can also accelerate the process of COPD. The results of this study

indicated that in COPD patients with more than three comorbidities, the status of the smoking group was not more severe than that of the nonsmoking group, and that according to CT types, the status of type M patients with more than three comorbidities was more severe than that of type A patients. There were no differences among the subgroups in the nonsmoking group, indicating that the inflammatory mediators produced by harmful substances in the smoke also aggravate the development of comorbidities in the circulation. Other studies (24,25) showed that in COPD patients with moderate and severe cardiovascular and metabolic diseases, a variety of inflammatory mediators exist in circulating blood. In the type M and type E smoking groups, the status of COPD patients with cardiovascular disease was more serious than that of type A patients; in the nonsmoking group, there were no differences among the three subtypes in COPD patients with cardiovascular disease, indicating that although patients had quit smoking,

chronic inflammatory mediators persisted in the blood of those with COPD and cardiovascular disease. In addition to inflammatory mediators, MMP-9 was strongly linked with cardiovascular diseases and multiple comorbidities in the smoking group. These results suggest that smoking can increase the level of circulating matrix metalloproteinases, thereby aggravating the severity of COPD, cardiovascular diseases, and multiple comorbidities.

In summary, smoking is the main factor that causes significant aggravation of emphysema, as detected on CT in COPD patients. Smoking results in the presence of inflammatory mediators and metalloproteinases in the blood and increases airway inflammation and airway remodeling, thereby aggravating the progress of COPD. Currently, in the COPD patients, classification of CT scan (types A, E, and M) is also a significant tool for assessing the phenotypes in COPD; meanwhile, it can provide the theoretical basis for individualized treatment of COPD patients.

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