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ORIGINAL

Analysis of Smokers With Normal Spirometry on the athletic performance of Athletes.

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ABSTRACT

Objective: To determine the heterogeneity in smokes with normal spirometry on the athletic performance of Athletes.
Methods: By Chest CT reconstruction, we assess airway structure and emphysema index of the 87 athlete smokers with normal spirometry. Five parameters related to lung function were selected as objects. Firstly, the five parameters were reduced into several principal components by principal component analysis method. Then, using these principal components as variables, the 87 high-risk people were grouped into several subtypes by k-means dynamic clustering method, and the imaging and lung function characteristics of these subtypes were analysed. 70 cases were followed up one year later to analyse the differences in lung function and imaging changes of various subtypes.
Results: Principal component analysis reduced five variables to 2 principal components, of which the first principal component mainly reflected emphysema index and the second principal component mainly reflected primary bronchial structure. Using these two principal components as variables, we divided 87 athlete patients into two subtypes by K-means cluster

analysis. The first subtype: relatively severe airflow limitation, large wall area, and lumen area, and high emphysema index; The second subtype: relatively light airflow limitation, small wall area, and lumen area, and low emphysema index. A year later, a total of 70 athletic patients were followed up. As a result, compared with a year ago, the two subtypes maintained the previous heterogeneity in imaging, while FEV1/FVC decreased in lung function, and the decrease in the first subtype was more prominent (statistically significant). However, the changes in FEV1 and FEV1% Pred in these two subtypes were not statistically significant. After one year, 5 cases of the first subtype had FEV1/FVC less than 0.7, which became COPD athletic patients meeting GOLD diagnostic criteria, while no athletic patients of the second subtype had FEV1/FVC less than 0.7.
Conclusion: Athlete smokers with normal spirometry has heterogeneity in chest CT. Using imaging data and cluster analysis, the high-risk population of COPD can be divided into two subtypes, of which one subtype has a rapid decline in lung function and early occurrence of airflow restriction, requiring early intervention. However, the other subtype's lung function decreases slowly, and the urgency of intervention is not strong. The degree of airway remodeling may be the basis of heterogeneity in smokes with normal spirometry.

KEY WORDS: COPD, heterogeneity, cluster analysis, Athlete smokers, subtypes

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common chronic airway disease. It is characterized by persistent respiratory symptoms and limited airflow due to airway and/or alveolar abnormalities usually caused by extensive exposure to toxic particles or gases. COPD is the third leading cause of death in the world(Burney, Patel, Newson, Minelli, & Naghavi, 2015) and early diagnosis may possibly prevent the progression of COPD (Aaron, 2014; Drummond, Buist, Crapo, Wise, & Rennard, 2014). COPD is defined by airflow obstruction on spirometry traditionally. The primary cause of COPD is smoking. According to the studies, only a subset of Athlete smokers with normal spirometry which was classified as GOLD 0 grade will develop to COPD. We should identify this subset urgently to prevent progression to COPD. How can we discover this subset?

The typical symptoms such as cough, sputum, and dyspnea are not common in smokers with normal spirometry which we labelled as GOLD 0 athletic patients in this study. It is inadequate to judge the subset that will rapidly develop to COPD by symptoms. However, COPD is heterogeneous, not all smokers with normal spirometry will progress to COPD(Qaseem et al., 2011), we should find heterogeneity of these people. According to previous studies,

quantitative chest CT (QCT) is an essential means to diagnose and evaluate early COPD (Drummond et al., 2014; Hersh et al., 2013; Wan et al., 2011) . Tools for evaluating air attenuation have been developed to identify emphysema.(Grydeland et al., 2010; Grydeland et al., 2011; Lynch & Al-Qaisi, 2013) Chest CT scans can also evaluate airway structure, and some studies have evaluated the correlation between airway remodelling and emphysema.(Grydeland et al., 2010; Grydeland et al., 2011) So physicians can also detect respiratory impairments in smokers with normal spirometry by quantitative chest CT.

COPD is a heterogeneous disease with pulmonary pathologies including airway remodeling and emphysema which can have been detected by quantitative chest CT.The heterogeneity exists in every stage of COPD. CT can measure the heterogeneity of airway obstruction and emphysema present in an individual of COPD.So we can assess the heterogeneity of smokers with normal spirometry using chest CT. Cluster analysis will be done to devide these smokers into some subtypes. One subtype maybe the subset that rapidly progresses to COPD .

Objects and Methods

Inclusion criteria:

1) The age is between 45 and 80 years old;2) History of smoking;3) Lung function: FEV1/FVC> 0.7,after bronchodilator inhalation(S. Chen et al., 2017) ;4)Willing to accept chest CT examination.

Exclusion criteria:

1)Asthma patients;2) Patients with structural lung diseases such as bronchiectasis;3) Cognitive impairment;4) Athletic Patients with malignant tumors;5) Patients with severe chronic diseases (patients with advanced liver and kidney failure), etc.

According to the above criteria, 87 athletics were enrolled. All athletic patients in the group signed informed consent.

Detection method:

1) Collect demographic data including sex, age, height, weight, smoking history, chronic disease history, and hereditary disease history;

2) Lung function examination: Jaeger Master screen lung function instrument is selected, and all lung function examinations meet the instrument quality control standards recommended by ATS (American Thoracic Society) and ERS (European Respiratory Association). Examination contents: the first second forced expiratory volume (FEV1), the first second forced expiratory

volume as a percentage of predicted value (FEV1% Pred), one-second rate (FEV1/FVC), residual volume (RV), residual volume as a percentage of predicted value (RV% Pred), total lung volume (TLC), carbon monoxide diffusivity as a percentage of predicted value (DLCO% Pred), total lung volume as a percentage of predicted value (TLC% Pred) and total residual ratio (RV/TLC), etc.

4) Chest CT scan: All selected people were scanned by chest CT, and breathing training was carried out before scanning to ensure that all athletic patients were scanned at the end of deep inhalation and when the inflation condition of lung tissue reached the best. CT scanning uses GE's VCT 16-slice spiral CT machine. The athletic patient holds his head in both hands and takes the supine position. According to the technician's instructions, he scans at the end of deep inhalation.

Parameters of CT scan:

Scope: Whole lung: from lung tip to lung floor;

Tube voltage: 120Kv, tube current: 20-40mAs, matrix: 512 x 512; Acquisition layer thickness: 1mm;; The thickness of reconstruction layer is 0.5 mm;; Reconstruction interval: 0.5 mm.

Evaluation of air attenuation (emphysema index):

The original data of CT scans of people are saved in DICOM format and imported into IntelliSpacePortal software of Philips Company. The software automatically reconstructs and calculate the parameters used to evaluate the severity of emphysema include median lung density (MLD), the low-density attenuation area(LAA-950)in inspiratory, the volume of voxels less than-950HU in inspiratory low-density attenuation area as a percentage of total lung volume (LAA-950%), the volume of voxels less than-856HU in inspiratory low-density attenuation area (LAA-856) and total lung volume (LV).

Evaluation of airway structure

IntelliSpacePortal software of Philips Company is still used for airway analysis. DICOM files of CT scanning are imported into the software. The software reconstructs the bronchial tree through the algorithm and then selects the target airway and measurement point. The software can automatically output the following airway parameters: the average thickness of the bronchial wall (T), bronchial lumen area (LA), bronchial wall area (WA), and percentage of bronchial wall area (WA%). This study mainly analyzes the first to third-grade bronchus, among which the first-grade bronchus measures the parameters of the left and right main bronchus and takes its average value; The second-grade bronchus mainly measured the right upper lobe,

middle lobe, lower lobe, and left upper lobe and lower lobe bronchus, and took their average values. The third-grade bronchus mainly measured the right upper lobe tip segment, the middle lobe lateral segment, the lower lobe posterior basal segment, the left upper lobe tip posterior segment, and the lower lobe posterior basal segment bronchus and took their average values. These parameters were expressed as T1, T2, T3, LA1, LA2, LA3, WA1, WA2, WA3, WA1%, WA2%, and WA3%. Considered the differences in height and weight among individuals, these parameters were corrected by body surface area (BSA).

Follow-up:

One year later, 70 athletic patients were followed up, and the related indexes of chest CT and lung function were reexamined, and the changes of lung function and imaging of each subtype were analyzed.

Statistical analysis:

If the measurement data obey normal distribution, it is expressed by mean ± standard deviation; If it does not obey the normal distribution, it is expressed by the median (value range); Counting data is expressed by frequency.

Comparison of parameters in each subtype: If it obeys normal distribution and the variance is homogeneous, use variance analysis; otherwise, use a nonparametric test.

Principal component analysis:

The parameters related to emphysema index in imaging: Median lung density (MLD), The volume of voxels in the low-density attenuation region of inspiratory phase is less than-950HU (LAA-950), The volume of voxels less than-950HU in inspiratory phase low-density attenuation area accounts for the percentage of total lung volume (LAA-950%), Volume of voxels less than-856HU (LAA-856) in the low-density attenuation area of inspiratory phase and parameters of total lung volume (LV) and airway structure: T1/BSA, T2/BSA, T3/BSA, LA1/BSA, LA2/BSA, LA3/BSA, WA1/BSA, WA2/BSA, WA3/BSA and WA1%, WA2%, and WA3%, In the first part of the study, We found that there are six variables: LAA-950, LAA-950%, LAA-856, MLD, WA1/BSA, and LA1/BSA had significant correlation with lung function. However, 0 in LAA-950% data is more prone to bias, so the remaining five variables are discarded for the following analysis, but these variables are not independent of each other. In order to avoid data redundancy, this study first uses principal component analysis to reduce the dimension of these five variables and selects the components with cumulative eigenvalues greater than 80% for the following analysis.

Cluster analysis:

The COPD athletic patients were divided into several subtypes by the k-means dynamic clustering method. Firstly, the best classification number K is obtained by evaluation. K patients are randomly selected as the center, clustered into K categories according to distance measurement. Then K patients are re-selected as the center in this K category to cluster again, to circulate until the categories to which all populations belong no longer change.

Comparison of subtypes:

T-test, chi-square test, and non-parametric test were used to analyze and compare the epidemiological, pulmonary function, and imaging characteristics of each subtype and define each subtype.

Comparison of prognosis of subtypes:

The pulmonary function and imaging changes of each subtype were analyzed with the follow-up data after one year.

Statistical analysis uses R language version 3.5. 3, using "psych" **and** "factoextra" and "cluster" **software packages.**

Research results

The basic situation of athletic patients is shown in Table 1.

A total of 87 high-risk groups of COPD were included.

Table 1 Basic situation of patients

Variable	Value
Age (year-old)	56.82±7.81
Bmi (kg/m2)	24.71±2.61
FEV1 (L)	2.36±0.52
FEV1% pred	86.05±5.96
FEV1/FVC%	81.74±9.38
RV/TLC	40.26±6.50
DLCO% Pred	77.05±11.03
LV (ml)	3621.96±1022.75
LAA-950	7.00(584.40)
LAA-950%	0.20(10.20)
LAA-856	963.50(4143.90)
MLD (HU)	-777.55±52.33
T1/BSA (cm/m2)	0.97±0.13
WA1/BSA (mm2/m2)	44.15±7.90
LA1/BSA (mm2/m2)	78.95±20.33

WA1%	36.91±4.18
T2/BSA (cm/m2)	0.83±0.12
WA2/BSA (mm2/m2)	27.51±4.85
LA2/BSA (mm2/m2)	36.34±9.22
WA2%	44.19±5.09
T3/BSA (cm/m2)	0.78±0.13
WA3/BSA (mm2/m2)	17.48±3.31
LA3/BSA (mm2/m2)	13.59±3.81
WA3%	56.80±6.22

The correlation analysis between the selected variables is shown in Table 2. As can be seen from this table, There is a correlation between these five variables; if cluster analysis is carried out directly without processing, The results will be biased. To reduce the correlation between variables, While reducing the dimension of analysis data, In this study, principal component analysis is used to reduce the dimension at first. The results of the principal component analysis are shown in Figure 1 and Table 3. The results show that after linear transformation, the cumulative variance variation of the first two components reaches 81%, so these two components contain most of the differences of five variables, so these five variables can be reduced into two principal components for the subsequent cluster analysis. The first principal component is the emphysema index, and the second principal component mainly reflects the primary bronchial structure.

Cluster analysis:

The principal components above were taken as objects. Eighty-seven objects were clustered by the k-means clustering method. Firstly, determine the best cluster number (see Figure 1), which shows that two categories are the most suitable classification number. K-means cluster diagram is shown in Figure 2. That is, 87 subjects are divided into two subtypes.

Clinical significance of each subtype:

The clinical characteristics of each subtype are shown in Table 2.4. In lung function, the FEV1/FVC of the first subtype is smaller than that of the second subtype, and there is no difference in FEV1% PRED, FEV1, DLCO% PRED, and RV/TLC among the two subtypes. Airway structure: The LA/BSA of the first three grades of the first subtype was higher than that of the second subtype, and the WA/BSA of the first two grades of the bronchus was higher than that of the second subtype, but there was no statistical difference between the two types of the bronchus: WA3/BSA; In addition, the WA% of the first subtype was less than that of the second subtype, and there was no statistical difference in the transverse diameter (T/BSA) of the two subtypes. The absolute values of LAA-950, LAA-950%, LAA-856, and MLD in the first

subtype were higher than those in the second subtype. The first subtype: the airflow restriction is relatively heavy, the tube wall area and lumen area are large, and the emphysema index is high; The second subtype: the airflow restriction is relatively light, the tube wall area and lumen area are small, and the emphysema index is low.

Table 2 Correlation analysis among variables

	LAA-950	LAA-856	MLD	WA1/BSA	LA1/BSA
LAA-950	1	0.68	-0.66	0.50	0.62
LAA-856	0.68	1	-0.70	0.41	0.54
MLD	-0.66	-0.70	1	-0.43	-0.47
WA1/BSA	0.50	0.41	-0.43	1	0.67
LA1/BSA	0.62	0.54	-0.47	0.67	1

Table 3 Principal component analysis of QCT parameters

	PC1	PC2
LAA-950	0.476	0.170
LAA-856	0.459	0.402
MLD	-0.448	-0.437
WA1/BSA	0.403	-0.643
LA1/BSA	0.447	-0.453

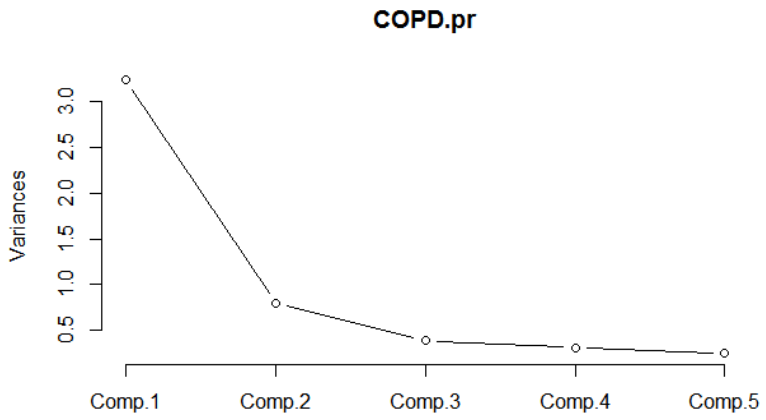

Fig. 1 Principal component analysis diagram

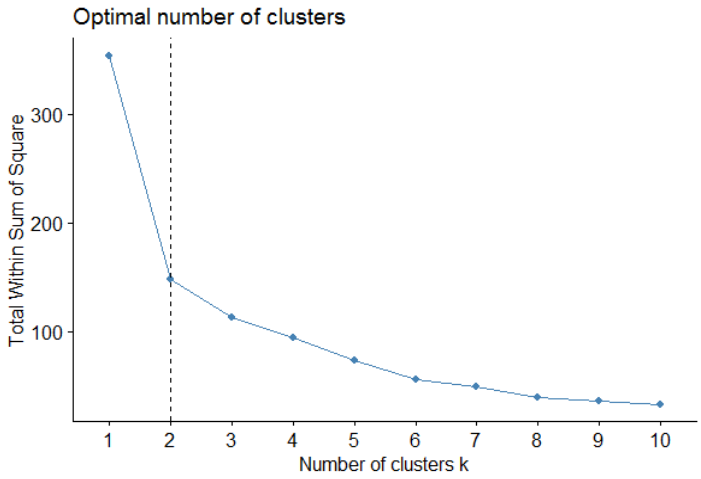

Fig. 2 Determination of the best cluster number

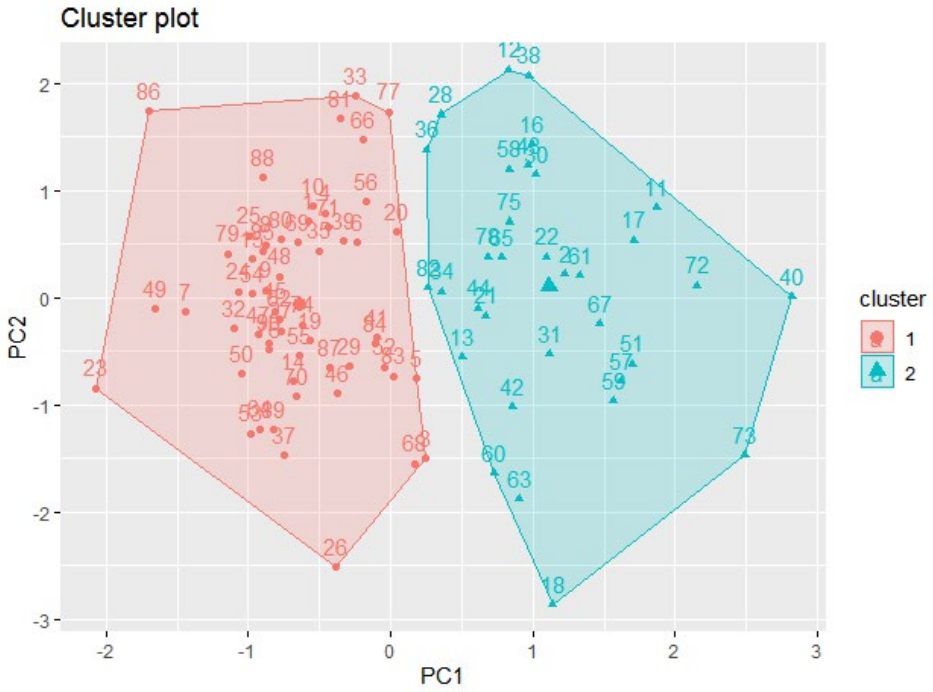

Fig. 3 k-means dynamic clustering analysis diagram

Table 4 Pulmonary function and imaging characteristics of each subtype

	Subtype 1	Subtype 2	P
Number	32	55	-
FEV1 (L)	2.54±0.51	2.30±0.46	0.11
FEV1% pred	86.72±6.31	86.80±5.16	0.78
FEV1/FVC	81.31±5.18	84.04±5.16	0.01*
RV/TLC	39.36±6.09	40.53±6.90	0.81
DLCO% Pred	76.88±8.25	78.86±10.83	0.68
T1/BSA (cm/m^2)	1.01±0.21	0.95±0.11	0.1
WA1/BSA (mm^2/m^2)	49.94±7.72	40.32±5.01	0.00**

WA1%	35.72±3.85	38.23±3.62	0.00**
LA1/BSA (mm^2/m^2)	92.47±16.35	67.97±1271	0.00**
T2/BSA (cm/m^2)	0.84±0.12	0.82±0.13	0.96
WA2/BSA (mm^2/m^2)	29.86±4.93	25.70±4.04	0.00**
WA2%	42.23±4.61	45.70±4.96	0.00**
LA2/BSA (mm^2/m^2)	42.34±8.51	31.58±6.12	0.00**
T3/BSA (cm/m^2)	0.76±0.14	0.80±0.13	0.12
WA3/BSA (mm^2/m^2)	18.21±4.14	17.10±2.82	0.22
WA3%	54.69±5.84	58.64±5.82	0.00**
LA3/BSA (mm^2/m^2)	15.29±4.08	12.28±3.13	0.00**
LAA-950	26.85±12.38	3.79±4.16	0.00**
LAA-950%	0.64±0.30	0.10±12	0.00**
LAA-856	2108.31±823.08	650.85±616.11	0.00**
MLD	-817.83±33.82	-749.22±42.34	0.00**
Age	57.18±7.01	54.78±7.08	0.13
BMI	24.60±2.58	25.28±2.41	0.22

*: P < 0.05; **: P < 0.01

Follow-up of each subtype:

The follow-up results of chest CT one year later are shown in Table 2.5. A total of 70 athletic patients were followed up. Through CT scan reconstruction, the parameters of emphysema index and airway structure were measured again. The results showed that these two subtypes maintained the heterogeneity of imaging one year ago after one year. The first subtype had a large wall area and lumen area and high emphysema index; the second subtype's wall area and lumen area are small, and the emphysema index is low. The follow-up results of lung function one year later are shown in Table 2.5. Compared with the results one year ago, FEV1/FVC of these two subtypes decreased, and the decline of the first subtype was more prominent (with statistical significance). However, the changes of FEV1 and FEV1% Pred in these two subtypes were not statistically significant. After one year, the FEV1/FVC of 5 patients in the first subtype was less than 0.7, which became COPD athletic patients meeting the diagnostic criteria of GOLD, while there were no patients in the second subtype who were less than 0.7. Fisher's accurate test showed that the P value was 0.01, which was statistically significant.

Table 5 Results of chest CT reexamination after one year for each subtype

	Subtype 1	**Subtype 2**	**P**
Number	29	41	-
T1/BSA (cm/m^2)	1.01±0.15	0.96±0.11	0.16
WA1/BSA (mm^2/m^2)	50.24±7.83	40.85±4.57	0.00**
WA1%	35.77±3.94	38.52±3.99	0.012*
LA1/BSA (mm^2/m^2)	92.84±16.84	67.73±12.11	0.00**

T2/BSA (cm/m^2)	0.84±0.12	0.83±0.13	0.97
WA2/BSA (mm^2/m^2)	29.85±5.10	25.97±4.13	0.00**
WA2%	41.93±4.52	46.22±4.99	0.00**
LA2/BSA (mm^2/m^2)	42.80±8.51	31.38±6.67	0.00**
T3/BSA (cm/m^2)	0.77±0.15	0.82±0.13	0.16
WA3/BSA (mm^2/m^2)	18.47±4.15	17.37±2.95	0.34
WA3%	54.39±5.89	59.42±5.00	0.00**
LA3/BSA (mm^2/m^2)	15.94±3.96	12.00±2.77	0.00**
LAA-950	27.96±11.91	4.22±4.43	0.00**
LAA-950%	0.67±0.28	0.12±0.12	0.00**
LAA-856	2073.85±829.86	519.25±504.15	0.00**
MLD (HU)	-821.60±27.28	-753.55±43.33	0.00**

*: P < 0.05; **: P < 0.01

Table 6 Results of pulmonary function follow-up after one year for each subtype

	Subtype 1	**Subtype 2**	**P**
Number	29	41	-
∆FEV1	0.04±0.19	0.08±0.22	0.35
∆FEV1% Pred	0.97±7.35	4.64±9.28	0.07
∆FEV1/FVC%	-3.43±4.32	-0.77±3.60	0.01*
∆RV/TLC	0.45±6.72	-0.44±4.07	0.53
DLCO% Pred	1.69±7.61	2.80±6.16	0.52
FEV1/FVC% < 70% (Yes/N0)	5/24	0/41	0.01*

*: P < 0.05; **: P < 0.01

Discussion

COPD is a complex disease that partially reversible; thus, prevention in early-stage of COPD is crucial. Smoking is an important risk factor for COPD,but not all Athlete smokers will develop COPD. Medical interventions are not necessary for all Athlete smokers with normal Spirometry, while physician should focus on the Athlete smokers who will develop a rapidly decline of their lung function. How can we identify this subset of the Athlete smokers? This involves the heterogeneity of COPD. Previous studies have found that COPD is a disease with substantial heterogeneity. At present, GOLD grades and groups patients according to their lung function, symptoms, and the number of acute exacerbations within one year. However, such grading and grouping cannot fully reflect the heterogeneity of COPD patients, and Some groups have little difference in prognosis, (Arostegui et al., 2014; Lee et al., 2014)so some scholars put forward the concept of COPD phenotype. Burgel, a French scholar, used cluster analysis to divide 322 COPD patients with different GOLD grades into four phenotypes, and the lung function, BODE index, and prognosis of each phenotype were different, which verified the existence of

COPD heterogeneity (Burgel et al., 2010).

Athlete smokers with normal spirometry , the lung function has not yet reached the standard of GOLD in diagnosing COPD, and it is difficult to find its heterogeneity from the results of lung function examination alone. Therefore, this study starts with imaging and analyses the heterogeneity of COPD high-risk population from airway structure and emphysema index. We can measure 12 parameters such as transverse diameter (T), wall area WA, wall area ratio WA%, and lumen area LA of the first tertiary bronchus through airway reconstruction of chest CT.

In terms of emphysema index, LAA-950, LAA-950%, LAA-856, MLD are all higher in subtype one than in subtype 2, which shows that the degree of gas retention in subtype 1 is higher than that in subtype two on imaging, which is related to emphysema index in three parameters used in this cluster analysis. However, through cluster analysis, we can clearly distinguish the COPD high-risk groups with different degrees of gas retention.

In terms of airway structure, although only two parameters, WA1/BSA and LA1/BSA, were included in this study. However, the statistical analysis found apparent differences in airway structure between these two subtypes, among which the lumen area (LA/BSA) of each airway in the first subtype is more significant than that in the second subtype. The wall area (WA/BSA) of the first two bronchi is higher than that in the second subtype, while the wall area of the first subtype is smaller than that of the second subtype, and there is no statistical difference in the transverse diameter (T/BSA) of the two subtypes. Generally speaking, subtype one is characterized by a large wall area, large lumen area, and small wall area, while of subtype 2 is opposite. Athlete smokers in subtype 1 may undergo mild remodelling, which may lead a rapid decrease of FEV1.

Are there any differences in lung function changes among different subtypes of COPD high-risk groups? one year later, we patients were followed up. Among a total of 87 people, 70 cases were followed up. The results showed that these two subtypes maintained the same heterogeneity in terms of imaging one year ago. The first subtype had a large wall area and lumen area and high emphysema index; the second subtype's wall area and lumen area are small, and the emphysema index is low, which shows that it is stable and reliable to divide the subtypes of high-risk groups of COPD by chest CT reconstruction. The lung function follow-up showed that the FEV1/FVC of these two subtypes decreased, and the decline of the first subtype was more evident than the other subtype. However, FEV1 and FEV1% Pred had no statistical significance. FEV1/FVC was less than 0.7 in 5 patients with COPD after one year in subtype 1, which reached GOLD diagnostic criteria of COPD, while no patients with COPD were diagnosed in subtype two,which proved

that FEV1 of subtype one in Athlete smokers with normal spirometry decreases more rapidly.

Some scholars believe that the airway remodeling is an important indicator to evaluate COPD severity in chest CT .(Charbonnier et al., 2019; Lynch & Al-Qaisi, 2013; Nambu et al., 2016) In subtype one, the above analysis has shown that the airway remodeling is mainly in increase of bronchial wall area, which leads to compensatory expansion of bronchus, increasing lumen the decrease of wall area. However, the gas retention of the lung also increases compensatively, which leads the decrease of FEV1.

There have been many kinds of research on the heterogeneity of COPD , most of which use cluster analysis to aggregate patients with similar clinical characteristics and form several phenotypes or subtypes. It is similar to this study, but different studies use different variable parameters. In Burgel's study, eight variables, including age, smoking history, mMRC score, BMI, FEV1% Pred, acute exacerbation times within one year, St. George's score, and hospitalization anxiety and depression score (HAD), were selected to divide 322 patients into four phenotypes by hierarchical clustering method. Compared with the degree of airflow restriction (FEV1% Pred), each phenotype has more significant differences in age, symptoms, complications, and mortality(Burgel et al., 2010). Antenor Rodrigues et al. divided 141 COPD patients into two subtypes by dynamic k-means clustering method with maximum inspiratory pressure (MIF), quadriceps femoris repeat maximum test (IRMQF), and BODE index as variables, and then analyzed the prognosis of the two subtypes with a 2-year survival rate as the endpoint. The results showed that the first subtype had more lung function damage and severe symptoms, and the 2-year survival rate was significantly lower than the second subtype (Rodrigues et al., 2019). Suhyun Kim et al. divided 272 patients into three subtypes by principal component analysis and cluster analysis. And 203 patients were followed up after one year. The results showed that the symptoms and airflow restriction of the first subtype was the lightest, and the number of acute exacerbations was the least within one year of follow-up. The second subtype of symptoms and airflow restriction is the most serious. The number of acute exacerbations is the most within one year of follow-up, and multiple hospitalizations are required; The third subtype is mild airflow restriction, acute exacerbation within one year, and moderate hospitalization frequency (Kim et al., 2017). In addition to the degree of airflow restriction, the heterogeneity of COPD is also reflected in symptoms, exercise ability, and nutritional status, and the degree of airflow restriction alone has little relationship with the prognosis of COPD. For early COPD, the degree of airflow restriction is not severe, so lung function examination alone cannot reflect its heterogeneity, while the symptoms of early COPD are not severe. In this study, all the patients enrolled in the group were scored by mMRC, and the scores of all subtypes were 0-1, so it could not reflect its heterogeneity.

Therefore, the above methods do not apply to the study of early COPD heterogeneity. How to study the heterogeneity of early COPD? Philippe Gagnon et al. used primary personal data (gender, age, weight, smoking history, etc.), lung function, symptoms, exercise ability, and physiological function as variables to cluster 85 patients with early COPD by hierarchical clustering method. Results There were three subtypes, among which the first subtype had better lung function, exercise ability, and physiological function, while the second subtype smoked more seriously and had emphysema tendency compared with the first subtype. The third subtype is higher than the first two subtypes in airflow restriction and weaker in physiological function than the other two subtypes(Gagnon et al., 2015). However, the parameters selected in the study are too many and correlated with each other,so the discrimination of these three subtypes is not high, and it is not easy to distinguish them by statistical methods. We should select adequate parameters in our study. The Athlete smokers with normal spirometry have no apparent symptoms. So the symptoms and lung function data were not included in the phenotyping study in our study.We focused on Chest CT.

Many studies have been concerned on Chest CT of COPD. Japanese scholar Masaru Hasegawa performed a three-dimensional reconstruction of chest CT in 52 patients with COPD and found that LA in the airway below grade 3 was strongly correlated with WA% and lung function(Hasegawa et al., 2006). Jean-Paul Char bonnier et al. followed up 2000 Athlete smokers for five years and found that airway wall thickness was negatively correlated with FEV1% Pred, 6-minute walking distance, and St. George score, which could be used as a marker to evaluate the severity of COPD. Joyce D. Schroeder and others studied the emphysema index of 4062 COPD patients. The results showed that LAA-950 in the inspiratory phase and LAA-856 in an expiratory phase were highly correlated with FEV1 and FEV1/FVC. LAA-950 and LAA-856 could predict FEV1 and FEV1/FVC (R^2 was 0.72 and 0.77)in COPD patients, respectively(Schroeder et al., 2013). These studies suggest that airway structure and air retention are correlated with lung function, and CT can assess the severity of COPD patients. Mona Bafadhel et al. used lung function parameters as variables to divided 75 patients into three subtypes. And the chest CT parameters of the three subtypes were distinguished,which indicated that COPD patients had heterogeneity in chest CT. In our study, according to variables of chest CT, we divided smokes of normal spirometry into two subtypes, each of which has distinguished characteristics. Subtype one has relatively serve air retention, and significant airway remodeling, while the other has light airway remodeling and air retention. After one year's follow-up, airflow limitation of the Athlete smokers in subtype one was further aggravated, which required early intervention. So chest is an essential means not only to study the heterogeneity of COPD,but to find the people in risk of COPD.

Which factor causes the heterogeneity of Athlete smokers of normal spirometry? From the current research situation, there is no definitive conclusion. Some scholars think that the phenotype of COPD is different stages in the development of COPD. The specific basis is that patients with different phenotypes are different in age, patients with poor prognoses are often older, and the continuity of symptoms and lung function can be found among different phenotypes(Castaldi et al., 2017). However, it seems complicated to confirm this view because there is no statistical difference in the age of the two subtypes, and no continuity between the two subtypes is found after one year's follow-up. In addition, some scholars believe that the phenotype of COPD may be related to the expression of intrinsic genes, and the level of airway inflammation may be a fundamental reason for the heterogeneity of airway remodeling in COPD.(X. Chen, Tang, Wang, & Zhu, 2019; Perez et al., 2011)

The deficiency of this study is that fewer people are selected, and the results may be biased. In future studies, more patients can be included for further stratification. In addition, this study lacks long-term follow-up and cannot understand the long-term heterogeneity and outcome of each phenotype in smokes with normal spirometry.

Conclusion

The smokes with normal spirometry have heterogeneity in chest CT. Using CT data and cluster analysis, the Athlete smokers are divided into two subtypes, one of which has a rapid decline in lung function and early airflow restriction, which requires early intervention. However, the lung function of the other subtype decreased slowly, and the urgency of intervention was not intense. The degree of airway remodelling may be the basis of heterogeneity in smokes with normal spirometry.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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