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ORIGINAL RESEARCH

Emphysema extent on computed tomography is a highly specific index in diagnosing persistent airflow limitation: a real-world study in China

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Objective: The diagnostic value of emphysema extent in consistent air flow limitation remains controversial. Therefore, we aimed to assess the value of emphysema extent on computed tomography (CT) on the diagnosis of persistent airflow limitation. Furthermore, we developed a diagnostic criterion for further verification.

Materials and methods: We retrospectively enrolled patients who underwent chest CT and lung function test. To be specific, 671 patients were enrolled in the derivation group (Group 1.1), while 479 patients were in the internal validation group (Group 1.2). The percentage of lung volume occupied by low attenuation areas (LAA%) and the percentile of the histogram of attenuation values were calculated.

Results: In patients with persistent airflow limitation, the LAA% was higher and the percentile of the histogram of attenuation values was lower, compared with patients without persistent airflow limitation. Using LAA% with a threshold of −950 HU >1.4% as the criterion, the sensitivity was 44.3% and 47.2%, and the specificity was 95.2% and 95.7%, in Group 1.1 and Group 1.2, respectively. The specificity was influenced by the coexistence of interstitial lung disease, pneumothorax, and post-surgery, rather than the coexistence of pneumonia, nodule, or mass. Multivariable models were also developed.

Conclusion: The emphysema extent on CT is a highly specific marker in the diagnosis of persistent airflow limitation.

Keywords: computed tomography, lung function test, emphysema, persistent airflow limitation

Introduction

COPD is characterized by persistent airflow limitation, which is usually progressive and associated with an enhanced chronic inflammatory response to noxious particles or gases.[1] In the US, COPD is the fourth leading cause of morbidity and mortality, while its burden is estimated to be the fifth in 2020 worldwide.[1,2] COPD is a preventable and treatable disease, and the effective treatment of COPD relies on accurate diagnosis and assessment. Thus, using different methods to facilitate the diagnosis of COPD and evaluate the severity of the disease accurately is of great significance.

According to the current diagnostic criteria of COPD, persistent airflow limitation in spirometry is indispensable. The ratio of post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) <0.70 confirms persistent airflow limitation.[1] However, in clinical practice, some patients are not able to take the spirometry examination. Patients with dysaudia or other hearing disorders tend to get unsatisfactory spirometry results.[3,4] Furthermore, patients with severe emphysema

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are not recommended to do spirometry for the high risk of pneumothorax.[5] In addition, spirometry could detect and monitor the fluctuation of airflow limitation such as COPD exacerbation sensitively.[6,7] Therefore, spirometry during COPD exacerbation may not reflect the baseline lung function accurately.

Computed tomography (CT) is widely used in the diagnosis of lung disease. It is sensitive and accurate enough to help with the diagnosis of lung infections, pneumonia, bronchiectasis, interstitial lung disease, and pleural effusion. The airflow limitation is due to several pathological structural changes in the lung, such as lung parenchyma destruction (or emphysema) and small airway disease.[8] Chest CT can be used to assess the severity of emphysema correctly.[9] The main index of emphysema extent on CT includes the percentage of the lung volume occupied by low attenuation areas (LAA%) and percentile of the histogram of attenuation values (Perc n).[10] Mohamed Hoesein et al[11] had suggested that the emphysema extents on CT in patients with airflow limitation was significantly higher than in those without airflow limitation. Moreover, the change of emphysema extent on CT can predict mortality in COPD patients.[12] In addition, Mets et al had successfully identified airflow limitation using CT images in participants in a lung cancer screening trial.[13] A meta-analysis systemically analyzed the diagnostic value of CT for COPD and concluded that CT might be useful in identifying the potential suspected patients with COPD.[14] However, in previous studies, the sample sizes of these studies were relatively small. Besides, in the biggest study of Mets et al, bronchial dilation test was not performed and subjects were not from Asia.[15]

In the present study, we evaluated the efficacy of emphysema extent on CT in diagnosing persistent airflow limitation in China and tried to develop diagnostic criteria for further verification.

Materials and methods

Study population

This was a retrospective cross sectional study, which was performed in Shanghai Ruijin Hospital in China. Patients who underwent chest CT and lung function test from January 2010 to June 2014 were retrospectively enrolled in the study and divided to four groups (groups 1–4). The results of chest CT and lung function tests were recorded. The inclusion criteria of each group were as follows.

The inclusion criteria for Group 1 were 1) patients who underwent lung function test together with a bronchodilation test and 2) CT images reconstructed using a standard (or B26, B30, B31, B41, I30, I31, I41) algorithm, a section thickness of 5 mm, and an interval of 5 mm. Patients who had interstitial lung disease, pneumothorax, and/or post-thoracic surgery were excluded. The patients in Group 1 were further randomly divided into two groups, including a derivation group (Group 1.1) with 60% of the patients and an internal validation group (Group 1.2) with the remaining 40%.

The inclusion criteria for Group 2 were 1) patients who underwent lung function test without a bronchodilation test and 2) CT images reconstructed using a standard (or B26, B30, B31, B41, I30, I31, I41) algorithm, a section thickness of 5 mm, and an interval of 5 mm. Patients who had interstitial lung disease, pneumothorax, and/or post-thoracic surgery were excluded.

The inclusion criteria for Group 3 were 1) patients who underwent lung function test with a bronchodilation test and 2) CT images reconstructed using other parameters (mostly a standard algorithm and a section thickness of 7.5 mm). Patients who had interstitial lung disease, pneumothorax, and/or post-thoracic surgery were excluded.

The inclusion criteria for Group 4 were 1) patients who underwent lung function test with a bronchodilation test; 2) CT images reconstructed using a standard (or B26, B30, B31, B41, I30, I31, I41) algorithm, a section thickness of 5 mm, and an interval of 5 mm and 3) patients who had CT manifestation of other diseases. Group 4 was further divided into seven subgroups. Group 4.1 included patients with lung infiltration on chest CT. Group 4.2 included patients with CT manifestation of bronchiectasis. Group 4.3 included patients with a lung mass on chest CT. Group 4.4 included patients with a lung nodule on chest CT. Group 4.5 included patients with interstitial lung disease reflected on CT. Group 4.6 included patients with pneumothorax, while Group 4.7 included patients who had undergone thoracic surgeries.

The present study was approved by the Ruijin North Hospital Ethics Committee.

CT scanning and analysis

Chest CT was performed according to the standardization protocols by using one of the five following CT scanners: Discovery CT750 HD (GE Medical Systems, Milwaukee, WI, USA), LightSpeed VCT (GE Medical Systems), LightSpeed16 (GE Medical Systems), Perspective (Siemens Medical Solutions, Forchheim, Germany), and SOMATOM Definition Flash (Siemens Medical Solutions). The following technical parameters were used: tube voltage, 100–140 kVp; tube current, 100–250 mA; tube rotation time, 0.8 seconds; single collimation width, 1.25 mm; total collimation width, 20 mm; table speed, 23 or 34 mm per rotation; table feed

per rotation, 18.75 or 27.5; and spiral pitch factor, 0.9375 or 1.375. Images were reconstructed using a standard, bone, boneplus, lung, or B26, B30, B31, B41, B50, B70, B75, B80, I30, I31, I41, I50, I80 algorithm, a section thickness of 1.25–10 mm, an interval similar to the section thickness, and a 512×512 matrix.

The LAA% was calculated automatically using the commercial software Myrian® (Intrasense, Montpellier, France) under every threshold from −1,020 to −201 HU with an interval of 1 HU. Every Perc n was further calculated (Perc 1–Perc 99 with an interval of 1%).

Lung function test

The lung function test (spirometry and single-breath determination of carbon monoxide uptake), including reversibility tests, was performed using Jaeger® MasterScreen Body/Diff system (CareFusion Corporation, San Diego, CA, USA) according to the American Thoracic Society/European Respiratory guidelines. The single-breath determination of carbon monoxide uptake in the lung was used to calculate the diffusing capacity and lung volume. A post-bronchodilator FEV_1 to FVC ratio <70% was defined as the persistent airflow limitation.

Statistical analysis

Descriptive statistics included frequency tables, median and interquartile range (for the data without normal distribution), and mean and SD (for the data with normal distribution).

The emphysema extents (LAA% of every threshold and every percentile [Perc] of the histogram) were compared in Group 1 between patients with and without persistent airflow limitation using Mann–Whitney *U* test.

The LAA% using thresholds ranging from −1,000 to −850 HU with an interval of 5 HU and Perc 1, Perc 3, Perc 5, Perc 6, Perc 9, Perc 12, Perc 15, Perc 18, and Perc 21 were included for the diagnostic efficiency evaluation. The areas under the receiver-operating characteristic (ROC) curve (AUCs) for LAA% and Perc n were calculated in diagnosing persistent airflow limitation in Group 1.1 (derivation group). The cut points were chosen where the highest Youden index was observed, and where the specificity equaled to 90%, 95%, and 99% in Group 1.1. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) were calculated for every cut point mentioned above using data from Group 1.1 (derivation group), Group 1.2 (internal validation group), and Groups 2, respectively. The AUC was also measured in diagnosing persistent airflow limitation in Group 1.2. The cut points were chosen as mentioned above.

Binary logistic regressions were performed to examine the factors for predicting persistent airflow limitation. Common index of emphysema extent (LAA% [−950 HU]) and demographic characteristics of the patients (age, sex, height, and weight) were included in Model 1. Model 2 included LAA% (−950 HU), Perc 15, and the demographic characteristics. Model 3 included LAA% (−950 HU), LAA% under the threshold where the AUC was the highest, Perc 15, the percentile where the AUC was the highest, and the demographic characteristics. LAA% under every threshold, every percentile (Perc 1–Perc 99), and the demographic characteristics were included in Model 4. The AUCs for different models were calculated and the cut points were chosen as above. The sensitivity, specificity, PPV, and NPV were calculated for every cut point in Group 1.1 and Group 1.2. The ROC curve of different models and emphysema extent index were compared using *Z* test. All statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Informed consent

The present study was approved by the Ruijin North Hospital Ethics Committee, and the requirement to obtain informed written consent was waived. The reasons are as follows: 1) no foreseeable harm is expected to result from this study and less than minimal risk; 2) the waiver of informed consent will not affect the health and rights of the subjects; and 3) patient data confidentiality was protected. Statement: Informed consent was waived by the Ruijin North Hospital Ethics Committee.

Results

Population characteristics

A total of 2,976 patients who underwent chest CT and lung function test from January 2010 to June 2014 were enrolled. After excluding 435 patients with interstitial lung disease, pneumothorax, or post-thoracic surgery and 141 patients whose CT images were reconstructed using other parameters, 2,400 patients (CT images were reconstructed using a standard algorithm and a section thickness of 5 mm) were included in Group 1 and Group 2. Among these 2,400 patients, 1,250 patients did not undergo bronchodilation tests (Group 2, the external validation group), while 1,150 patients did (Group 1). Therefore, 671 patients were randomly assigned to Group 1.1 (the derivation group) and 479 to Group 1.2 (the internal validation group). The flow chart is illustrated in Figure 1. The demographic features

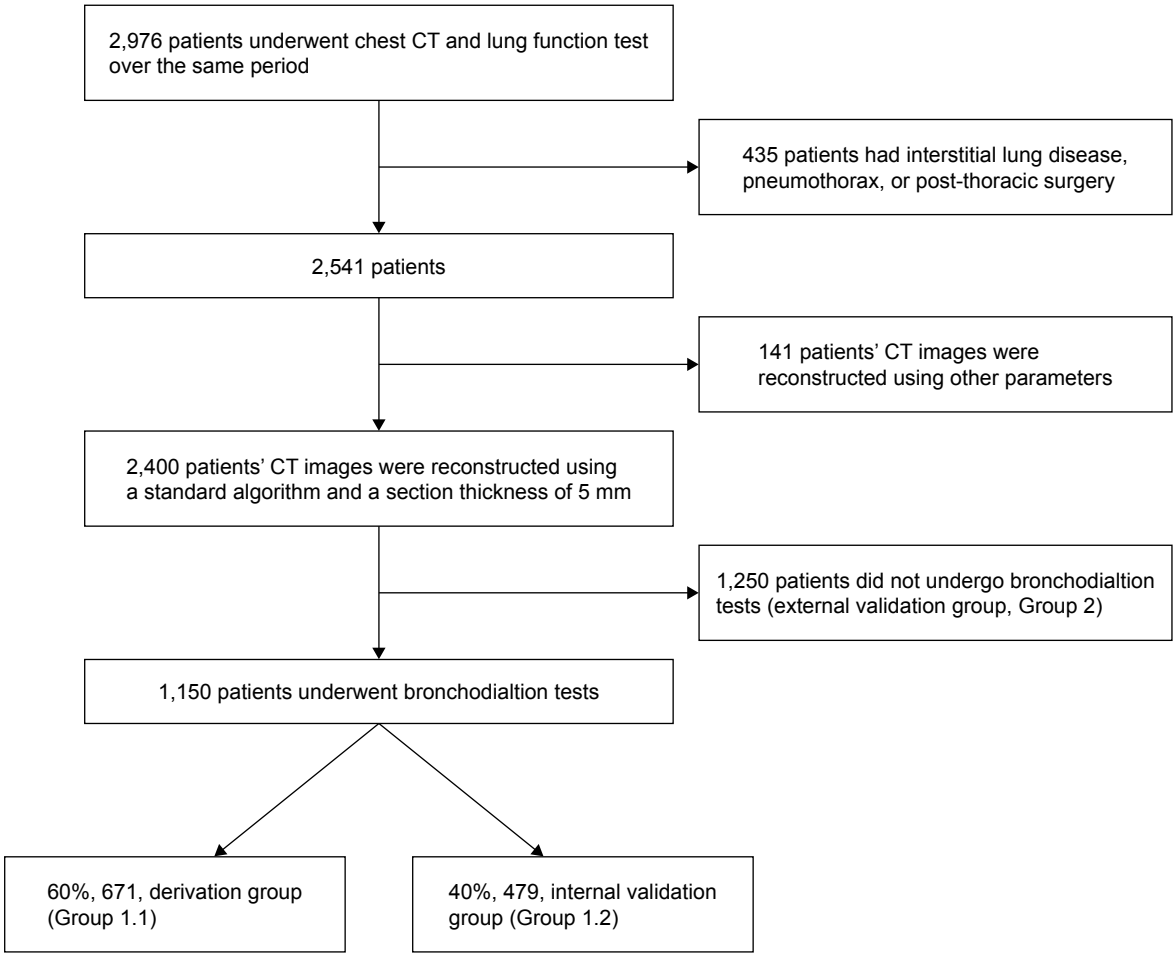

Figure 1 The flow chart of patient selection.
Abbreviation: CT, computed tomography.

of Group 1.1, Group 1.2, and Group 2 are summarized in Table 1. The demographic features for Group 3 and Group 4 are available in Table S1.

Comparison of the emphysema extent between patients with and without persistent airflow limitation

The emphysema extent of patients in Group 1 (including groups 1.1 and 1.2) is shown in Figure 2. The emphysema index of patients with persistent airflow limitation was significantly higher than that of those without persistent airflow limitation ($P<0.01$). LAA% (–950 HU) was significantly different between patients with and without persistent airflow limitation for patients in different genders and different age groups between 40 and 90 years.

The correlation between post-bronchodilator FEV_1/FVC and emphysema extent is shown in Figure 3. Post-bronchodilator FEV_1/FVC was negatively correlated with LAA% with the threshold of –950 HU (group 1.1: $r=-0.355$; group 1.2: $r=-0.320$) and positively correlated with Perc 15 (group 1.1: $r=0.306$; group 1.2: $r=0.377$).

The diagnostic value of emphysema extent in diagnosing persistent airflow limitation

The AUCs of different emphysema indexes in diagnosing persistent airflow limitation are shown in Figure 4. The max AUC of LAA% was 0.83 (SD 0.02) with the threshold of –930 HU, while the AUC with the threshold of –950 HU was 0.79 (SD 0.02). The max AUC of Perc n was 0.83 (SD 0.02) in Perc 3, while the AUC of Perc 15 was 0.78 (SD 0.02). However, no significant difference was observed in AUC between LAA% (–930 HU) and LAA% (–950 HU), as well as between Perc 15 and Perc 3.

The diagnostic value of emphysema extent in diagnosing persistent airflow limitation using different cut points is summarized in Part A in Table 2. Using LAA% (–950 HU) >1.4% as the criterion, the sensitivity was 44.3%

Table 1 Demographic features of the derivation, internal validation, and external validation groups

	Group 1.1 (derivation)	Group 1.2 (internal validation)	Group 2 (external validation)
Number	671	479	1,250
Male	347 (51.7)	255 (53.2)	644 (51.5)
Age (years)	59 (50–65)	59 (51–65)	61 (53–69)
Height (cm)	165 (160–171)	165 (160–171)	165 (158–171)
Weight (kg)	63 (55–71)	65 (58–72)	62 (55–70)
BMI (kg/m^2)	23.4±3.4	23.6±3.6	23.2±3.4
FVC (L)	2.71 (2.19–3.32)	2.70 (2.23–3.35)	2.49 (1.98–3.14)
FEV_1 (L)	2.18 (1.63–2.70)	2.11 (1.61–2.69)	2.04 (1.62–2.60)
FEV_1/FVC (%)	82.1 (72.2–89.5)	81.1 (69.6–89.7)	84.3 (76.5–91.3)
RV/TLC (%)	46.7±9.2	47.2±9.1	46.5±8.4
TLC-SB	4.60±0.99	4.63±1.02	4.46±0.99
DLCO SB	5.44±1.88	5.46±1.89	5.12±1.77
DLCO/VA	1.29 (1.08–1.46)	1.28 (1.06–1.48)	1.21 (1.01–1.40)
FEV_1% pred	85.1 (66.4–97.5)	84.7 (65.0–96.3)	83.4 (67.9–95.7)
FVC% pred	83.4±17.5	83.0±17.3	80.3±17.5
TLC-SB% pred	79.9±12.1	79.9±12.3	79.1±12.2
DLCO SB% pred	67.3±17.3	66.4±18.7	63.0±17.5
DLCO/VA% pred	87.8 (76.2–99.2)	88.7 (75.1–99.5)	82.0 (70.7–93.4)
FEV_1 (L) post-bronchodilation	2.31±0.86	2.27±0.81	NA
FEV_1/FVC (%) post-bronchodilation	84.1 (73.9–91.0)	83.2 (72.0–90.2)	NA
FEV_1%pred post-bronchodilation	89.1 (72.2–100.5)	87.5 (70.8–99.2)	NA
FEV_1/FVC <70% post-bronchodilation	131 (19.5)	106 (22.1)	NA
FEV_1/FVC <70%	147 (21.9)	117 (24.4)	180 (14.4)
Positive in bronchodilation test	87 (13)	63 (13.2)	NA
LAA% (–950 HU)	0.30 (0.07–0.69)	0.30 (0.05–0.73)	0.24 (0.06–0.55)
Perc 15 (HU)	–889 (–906 to –868)	–889 (–906 to –867)	–875 (–896 to –849)

Abbreviations: BMI, body mass index; DLCO, diffusion capacity for carbon monoxide of the lung; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAA%, percentage of the lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values; RV, residual volume; TLC, total lung capacity; TLC-SB, the single-breath diffusing capacity of the lung for CO; DLCO SB, diffusion capacity for carbon monoxide of the lung, using single-breath method; DLCO/VA, diffusion capacity for carbon monoxide of the lung per liters of alveolar.

and 47.2%, while the specificity was 95.2% and 95.7% in Group 1.1 and Group 1.2, respectively.

In patients who did not undergo the bronchodilation test, the emphysema extent was also a highly specific index in diagnosing airflow limitation (Table 2 Part B). Using LAA% (threshold of –950 HU) >1.4% as the criterion, the sensitivity in Group 2 was 38.3%, while the specificity was 94.9%.

On CT reconstructed by a section thickness of 7.5 mm, the emphysema extent using the same cut point showed similar specificity and a slightly lower sensitivity in diagnosing persistent airflow limitation in Group 3 (Table 2 Part C).

The diagnostic value of emphysema extent in diagnosing persistent airflow limitation in patients with other lung diseases

The diagnostic value of emphysema extent in diagnosing persistent airflow limitation in patients with other lung diseases in Group 4 is shown in Part D in Table 2. Using LAA% (threshold of –950 HU) >1.4% as the criterion, the specificity was still above 95% in patients with lung infiltration, as well as mass and nodule in lungs, 92.9% in patients with bronchiectasis, and lower than 90% in patients with interstitial lung disease, pneumothorax, or post-thoracic surgery.

Multivariable model based on emphysema extent for diagnosing persistent airflow limitation

Four models were established by logistic regressions. The independent predictors of persistent airflow limitation are summarized in Table S2. The models are as follows.

Model 1: y1 = 0.792 × LAA% (–950 HU) + 0.026 × age (years) + 0.608 × sex (male = 1, female = 0) – 3.503

Model 2: y2 = 0.68 × LAA% (–950 HU) – 0.017 × Perc 15 + 0.029 × age (years) + 0.023 × wt (kg) – 20.132

Model 3: y3 = 0.168 × LAA% (–930 HU) – 0.064 × Perc 3 + 0.039 × Perc 15 + 0.026 × age (years) – 27.515

Model 4: y4 = 0.218 × Perc 4 – 0.554 × Perc 8 + 0.614 × Perc 33 – 0.321 × Perc 43 + 0.042 × Perc 97 – 0.304 × LAA% (–973 HU) + 0.187 × LAA% (–927 HU) + 1.633 × LAA% (–292 HU) – 190.496

P (persistent airflow limitation) = e^y/(1 + e^y)

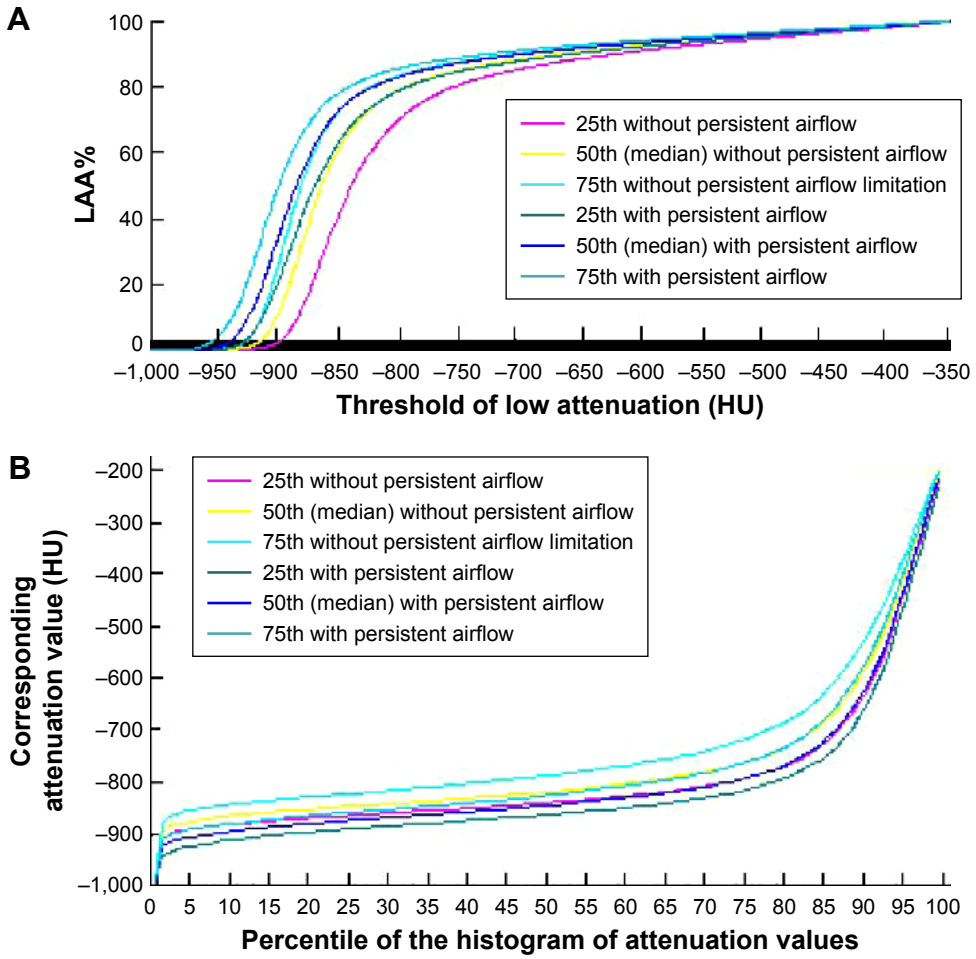

Figure 2 The emphysema extent of patients in Group 1 (including derivation group and internal validation group).
Notes: (**A**) LAA%; (**B**) Perc n.
Abbreviations: LAA%, percentage of the lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values.

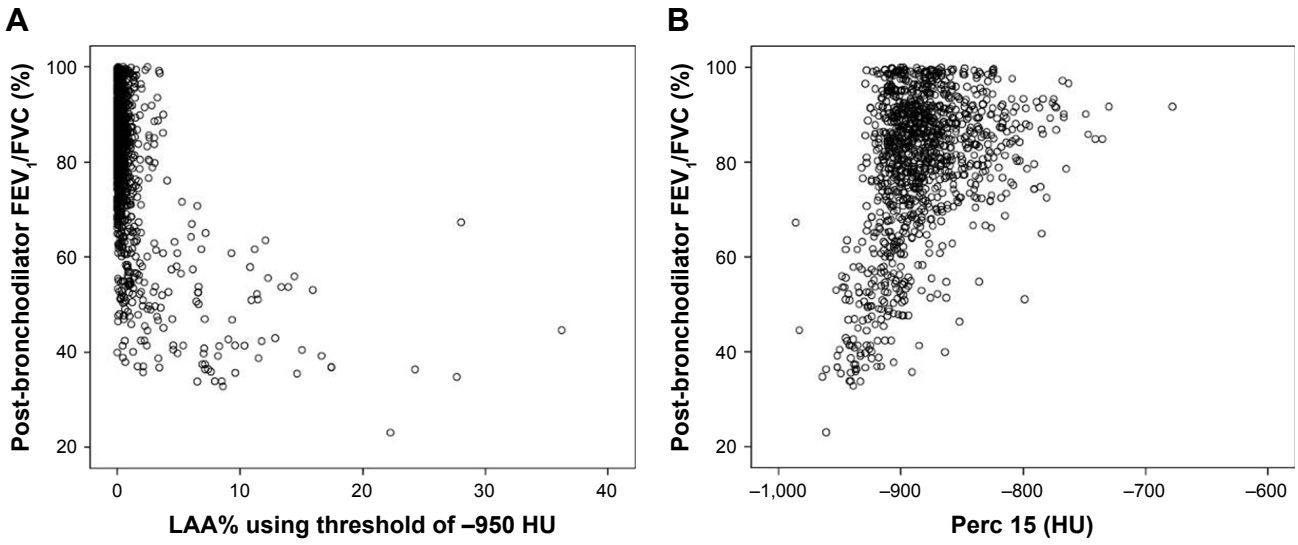

Figure 3 The correlation between post-bronchodilator FEV_1/FVC and emphysema extent.
Notes: (**A**) LAA% using the threshold of –950 HU; (**B**) Perc 15 (HU).
Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LAA%, percentage of the lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values.

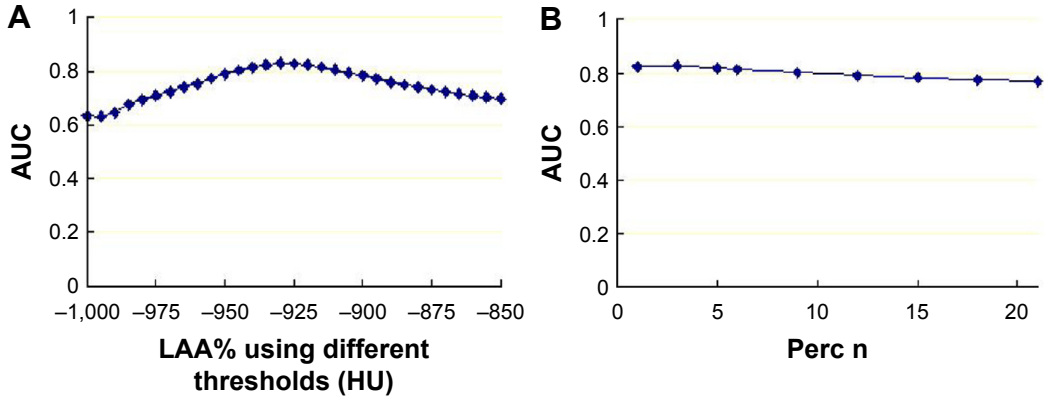

Figure 4 The AUCs of different emphysema indexes in diagnosing persistent airflow limitation.
Notes: (**A**) LAA% using different thresholds (HU); (**B**) Perc n.
Abbreviations: AUC, area under the ROC curve; LAA%, percentage of the lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values; ROC, receiver-operating characteristic.

Table 2 Diagnostic values of the emphysema extent in diagnosing persistent airflow limitation using different cut point in groups 1–4

Rule	A	B	C	D	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
A: Group 1									
LAA% (–950 HU) >0.84%									
Group 1.1	77	63	54	477	58.8	88.3	55.0	89.8	0.83
Group 1.2	65	45	41	328	61.3	87.9	59.1	88.9	0.82
LAA% (–950 HU) >0.90%									
Group 1.1	73	53	58	487	55.7	90.2	57.9	89.4	0.83
Group 1.2	62	39	44	334	58.5	89.5	61.4	88.4	0.83
LAA% (–950 HU) >1.4%									
Group 1.1	58	26	73	514	44.3	95.2	69.0	87.6	0.85
Group 1.2	50	16	56	357	47.2	95.7	75.8	86.4	0.85
LAA% (–950 HU) >3.0%									
Group 1.1	43	5	88	535	32.8	99.1	89.6	85.9	0.86
Group 1.2	33	4	73	369	31.1	98.9	89.2	83.5	0.84
Perc 15 <–907 HU									
Group 1.1	73	76	58	464	55.7	85.9	49.0	88.9	0.8
Group 1.2	63	52	43	321	59.4	86.1	54.8	88.2	0.8
Perc 15 <–910 HU									
Group 1.1	63	53	68	487	48.1	90.2	54.3	87.7	0.82
Group 1.2	60	32	46	341	56.6	91.4	65.2	88.1	0.84
Perc 15 <–915 HU									
Group 1.1	54	23	77	517	41.2	95.7	70.1	87.0	0.85
Group 1.2	49	19	57	354	46.2	94.9	72.1	86.1	0.84
Perc 15 <–928 HU									
Group 1.1	33	4	98	536	25.2	99.3	89.2	84.5	0.85
Group 1.2	24	0	82	373	22.6	100.0	100.0	82.0	0.83
LAA% (–930 HU) >1.4%									
Group 1.1	103	142	28	398	78.6	73.7	42.0	93.4	0.75
Group 1.2	86	97	20	276	81.1	74.0	47.0	93.2	0.76
LAA% (–930 HU) >3.4%									
Group 1.1	76	53	55	487	58.0	90.2	58.9	89.9	0.84
Group 1.2	72	34	34	339	67.9	90.9	67.9	90.9	0.86
LAA% (–930 HU) >5.2%									
Group 1.1	65	26	66	514	49.6	95.2	71.4	88.6	0.86
Group 1.2	56	20	50	353	52.8	94.6	73.7	87.6	0.85
LAA% (–930 HU) >13%									
Group 1.1	38	5	93	535	29.0	99.1	88.4	85.2	0.85
Group 1.2	25	1	81	372	23.6	99.7	96.2	82.1	0.83

(*Continued*)

Table 2 (*Continued*)

Rule	A	B	C	D	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Perc 3 <–922 HU									
Group 1.1	96	124	35	416	73.3	77.0	43.6	92.2	0.76
Group 1.2	85	78	21	295	80.2	79.1	52.1	93.4	0.79
Perc 3 <–931 HU									
Group 1.1	75	52	56	488	57.3	90.4	59.1	89.7	0.84
Group 1.2	70	32	36	341	66.0	91.4	68.6	90.5	0.86
Perc 3 <–937 HU									
Group 1.1	64	24	67	516	48.9	95.6	72.7	88.5	0.86
Group 1.2	54	16	52	357	50.9	95.7	77.1	87.3	0.86
Perc 3 <–951 HU									
Group 1.1	39	4	92	536	29.8	99.3	90.7	85.4	0.86
Group 1.2	28	4	78	369	26.4	98.9	87.5	82.6	0.83
B: Group 2									
LAA% (–950 HU) >0.84%	86	113	94	957	47.8	89.4	43.2	91.1	0.83
LAA% (–950 HU) >0.90%	83	99	97	971	46.1	90.7	45.6	90.9	0.84
LAA% (–950 HU) >1.4%	69	55	111	1,015	38.3	94.9	55.6	90.1	0.87
LAA% (–950 HU) >3.0%	44	11	136	1,059	24.4	99.0	80.0	88.6	0.88
Perc 15 <–907 HU	77	84	103	986	42.8	92.1	47.8	90.5	0.85
Perc 15 <–910 HU	73	61	107	1,009	40.6	94.3	54.5	90.4	0.87
Perc 15 <–915 HU	64	37	116	1,033	35.6	96.5	63.4	89.9	0.88
Perc 15 <–928 HU	35	4	145	1,066	19.4	99.6	89.7	88.0	0.88
LAA% (–930 HU) >1.4%	112	215	68	855	62.2	79.9	34.3	92.6	0.77
LAA% (–930 HU) >3.4%	86	77	94	993	47.8	92.8	52.8	91.4	0.86
LAA% (–930 HU) >5.2%	75	40	105	1,030	41.7	96.3	65.2	90.7	0.88
LAA% (–930 HU) >13%	39	5	141	1,065	21.7	99.5	88.6	88.3	0.88
Perc 3 <–922 HU	108	165	72	905	60.0	84.6	39.6	92.6	0.81
Perc 3 <–931 HU	85	72	95	998	47.2	93.3	54.1	91.3	0.87
Perc 3 <–937 HU	70	38	110	1,032	38.9	96.4	64.8	90.4	0.88
Perc 3 <–951 HU	44	10	136	1,060	24.4	99.1	81.5	88.6	0.88
C: Group 3									
LAA% (–950 HU) >0.84%	2	3	3	32	40.0	91.4	40.0	91.4	0.85
LAA% (–950 HU) >0.90%	2	3	3	32	40.0	91.4	40.0	91.4	0.85
LAA% (–950 HU) >1.4%	2	2	3	33	40.0	94.3	50.0	91.7	0.88
LAA% (–950 HU) >3.0%	1	0	4	35	20.0	100.0	100.0	89.7	0.90
Perc 15 <–907 HU	2	1	3	34	40.0	97.1	66.7	91.9	0.90
Perc 15 <–910 HU	2	1	3	34	40.0	97.1	66.7	91.9	0.90
Perc 15 <–915 HU	2	0	3	35	40.0	100.0	100.0	92.1	0.93
Perc 15 <–928 HU	0	0	5	35	0.0	100.0	NA	87.5	0.88
LAA% (–930 HU) >1.4%	2	6	3	29	40.0	82.9	25.0	90.6	0.78
LAA% (–930 HU) >3.4%	2	2	3	33	40.0	94.3	50.0	91.7	0.88
LAA% (–930 HU) >5.2%	2	1	3	34	40.0	97.1	66.7	91.9	0.90
LAA% (–930 HU) >13%	0	0	5	35	0.0	100.0	NA	87.5	0.88
Perc 3 <–922 HU	2	4	3	31	40.0	88.6	33.3	91.2	0.83
Perc 3 <–931 HU	2	2	3	33	40.0	94.3	50.0	91.7	0.88
Perc 3 <–937 HU	2	1	3	34	40.0	97.1	66.7	91.9	0.90
Perc 3 <–951 HU	1	0	4	35	20.0	100.0	100.0	89.7	0.90
D: Group 4									
LAA% (–950 HU) >0.84%									
With lung infiltration	48	38	40	233	54.5	86.0	55.8	85.3	0.78
With bronchiectasis	19	8	7	34	73.1	81.0	70.4	82.9	0.78
With mass in lung	11	10	4	52	73.3	83.9	52.4	92.9	0.82
With nodule in lung	78	56	55	470	58.6	89.4	58.2	89.5	0.83
With interstitial lung disease	18	14	4	49	81.8	77.8	56.3	92.5	0.79
With pneumothorax	1	1	0	5	100	83.3	50.0	100	0.86
Post-thoracic surgery	1	7	5	21	16.7	75.0	12.5	80.8	0.65

(*Continued*)

Table 2 (*Continued*)

Rule	A	B	C	D	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
LAA% (–950 HU) >0.90%									
With lung infiltration	45	32	43	239	51.1	88.2	58.4	84.8	0.79
With bronchiectasis	19	8	7	34	73.1	81.0	70.4	82.9	0.78
With mass in lung	10	7	5	55	66.7	88.7	58.8	91.7	0.84
With nodule in lung	76	47	57	479	57.1	91.1	61.8	89.4	0.84
With interstitial lung disease	17	12	5	51	77.3	81.0	58.6	91.1	0.80
With pneumothorax	1	1	0	5	100	83.3	50.0	100	0.86
Post-thoracic surgery	1	6	5	22	16.7	78.6	14.3	81.5	0.68
LAA% (–950 HU) >1.4%									
With lung infiltration	33	9	55	262	37.5	96.7	78.6	82.6	0.82
With bronchiectasis	14	3	12	39	53.8	92.9	82.4	76.5	0.78
With mass in lung	8	2	7	60	53.3	96.8	80.0	89.6	0.88
With nodule in lung	65	24	68	502	48.9	95.4	73.0	88.1	0.86
With interstitial lung disease	17	9	5	54	77.3	85.7	65.4	91.5	0.84
With pneumothorax	1	1	0	5	100	83.3	50.0	100	0.86
Post-thoracic surgery	0	4	6	24	0.0	85.7	0.0	80.0	0.71
LAA% (–950 HU) >3.0%									
With lung infiltration	22	2	66	269	25.0	99.3	91.7	80.3	0.81
With bronchiectasis	10	1	16	41	38.5	97.6	90.9	71.9	0.75
With mass in lung	5	0	10	62	33.3	100	100	86.1	0.87
With nodule in lung	40	5	93	521	30.1	99.0	88.9	84.9	0.85
With interstitial lung disease	16	4	6	59	72.7	93.7	80.0	90.8	0.88
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74
Perc 15 <–907 HU									
With lung infiltration	43	40	45	231	48.9	85.2	51.8	83.7	0.76
With bronchiectasis	17	9	9	33	65.4	78.6	65.4	78.6	0.74
With mass in lung	7	5	8	57	46.7	91.9	58.3	87.7	0.83
With nodule in lung	79	68	54	458	59.4	87.1	53.7	89.5	0.81
With interstitial lung disease	14	5	8	58	63.6	92.1	73.7	87.9	0.85
With pneumothorax	0	2	1	4	0.0	66.7	0.0	80.0	0.57
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74
Perc 15 <–910 HU									
With lung infiltration	37	25	51	246	42.0	90.8	59.7	82.8	0.79
With bronchiectasis	15	4	11	38	57.7	90.5	78.9	77.6	0.78
With mass in lung	6	1	9	61	40.0	98.4	85.7	87.1	0.87
With nodule in lung	71	49	62	477	53.4	90.7	59.2	88.5	0.83
With interstitial lung disease	14	4	8	59	63.6	93.7	77.8	88.1	0.86
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74
Perc 15 <–915 HU									
With lung infiltration	28	16	60	255	31.8	94.1	63.6	81.0	0.79
With bronchiectasis	12	2	14	40	46.2	95.2	85.7	74.1	0.76
With mass in lung	6	1	9	61	40.0	98.4	85.7	87.1	0.87
With nodule in lung	55	22	78	504	41.4	95.8	71.4	86.6	0.85
With interstitial lung disease	14	2	8	61	63.6	96.8	87.5	88.4	0.88
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	2	6	26	0.0	92.9	0.0	81.3	0.76
Perc 15 <–928 HU									
With lung infiltration	19	1	69	270	21.6	99.6	95.0	79.6	0.81
With bronchiectasis	8	1	18	41	30.8	97.6	88.9	69.5	0.72
With mass in lung	5	0	10	62	33.3	100	100	86.1	0.87
With nodule in lung	34	5	99	521	25.6	99.0	87.2	84.0	0.84
With interstitial lung disease	15	4	7	59	68.2	93.7	78.9	89.4	0.87
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74

(*Continued*)

Table 2 (*Continued*)

Rule	A	B	C	D	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
LAA% (–930 HU) >1.4%									
With lung infiltration	64	78	24	193	72.7	71.2	45.1	88.9	0.72
With bronchiectasis	23	17	3	25	88.5	59.5	57.5	89.3	0.71
With mass in lung	11	15	4	47	73.3	75.8	42.3	92.2	0.75
With nodule in lung	109	132	24	394	82.0	74.9	45.2	94.3	0.76
With interstitial lung disease	18	18	4	45	81.8	71.4	50.0	91.8	0.74
With pneumothorax	1	2	0	4	100	66.7	33.3	100	0.71
Post-thoracic surgery	2	7	4	21	33.3	75.0	22.2	84.0	0.68
LAA% (–930 HU) >3.4%									
With lung infiltration	49	28	39	243	55.7	89.7	63.6	86.2	0.81
With bronchiectasis	17	8	9	34	65.4	81.0	68.0	79.1	0.75
With mass in lung	10	4	5	58	66.7	93.5	71.4	92.1	0.88
With nodule in lung	85	53	48	473	63.9	89.9	61.6	90.8	0.85
With interstitial lung disease	17	11	5	52	77.3	82.5	60.7	91.2	0.81
With pneumothorax	1	1	0	5	100	83.3	50.0	100	0.86
Post-thoracic surgery	1	6	5	22	16.7	78.6	14.3	81.5	0.68
LAA% (–930 HU) >5.2%									
With lung infiltration	38	17	50	254	43.2	93.7	69.1	83.6	0.81
With bronchiectasis	16	4	10	38	61.5	90.5	80.0	79.2	0.79
With mass in lung	6	1	9	61	40.0	98.4	85.7	87.1	0.87
With nodule in lung	71	24	62	502	53.4	95.4	74.7	89.0	0.87
With interstitial lung disease	16	5	6	58	72.7	92.1	76.2	90.6	0.87
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74
LAA% (–930 HU) >13%									
With lung infiltration	19	1	69	270	21.6	99.6	95.0	79.6	0.81
With bronchiectasis	9	0	17	42	34.6	100	100	71.2	0.75
With mass in lung	5	1	10	61	33.3	98.4	83.3	85.9	0.86
With nodule in lung	35	3	98	523	26.3	99.4	92.1	84.2	0.85
With interstitial lung disease	10	1	12	62	45.5	98.4	90.9	83.8	0.85
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	1	6	27	0.0	96.4	0.0	81.8	0.79
Perc 3 <–922 HU									
With lung infiltration	60	59	28	212	68.2	78.2	50.4	88.3	0.76
With bronchiectasis	21	15	5	27	80.8	64.3	58.3	84.4	0.71
With mass in lung	11	12	4	50	73.3	80.6	47.8	92.6	0.79
With nodule in lung	103	114	30	412	77.4	78.3	47.5	93.2	0.78
With interstitial lung disease	17	16	5	47	77.3	74.6	51.5	90.4	0.75
With pneumothorax	1	2	0	4	100	66.7	33.3	100	0.71
Post-thoracic surgery	1	8	5	20	16.7	71.4	11.1	80.0	0.62
Perc 3 <–931 HU									
With lung infiltration	47	28	41	243	53.4	89.7	62.7	85.6	0.81
With bronchiectasis	17	8	9	34	65.4	81.0	68.0	79.1	0.75
With mass in lung	10	3	5	59	66.7	95.2	76.9	92.2	0.90
With nodule in lung	82	51	51	475	61.7	90.3	61.7	90.3	0.85
With interstitial lung disease	17	10	5	53	77.3	84.1	63.0	91.4	0.82
With pneumothorax	1	1	0	5	100	83.3	50.0	100	0.86
Post-thoracic surgery	1	5	5	23	16.7	82.1	16.7	82.1	0.71
Perc 3 <–937 HU									
With lung infiltration	18	0	70	271	20.5	100	100	79.5	0.81
With bronchiectasis	9	0	17	42	34.6	100	100	71.2	0.75
With mass in lung	4	0	11	62	26.7	100	100	84.9	0.86
With nodule in lung	32	2	101	524	24.1	99.6	94.1	83.8	0.84
With interstitial lung disease	10	1	12	62	45.5	98.4	90.9	83.8	0.85
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	1	6	27	0.0	96.4	0.0	81.8	0.79

(*Continued*)

Table 2 (*Continued*)

Rule	A	B	C	D	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Kappa
Perc 3 <–951 HU									
With lung infiltration	38	15	50	256	43.2	94.5	71.7	83.7	0.82
With bronchiectasis	16	4	10	38	61.5	90.5	80.0	79.2	0.79
With mass in lung	7	1	8	61	46.7	98.4	87.5	88.4	0.88
With nodule in lung	72	25	61	501	54.1	95.2	74.2	89.1	0.87
With interstitial lung disease	17	5	5	58	77.3	92.1	77.3	92.1	0.88
With pneumothorax	0	0	1	6	0.0	100	NA	85.7	0.86
Post-thoracic surgery	0	3	6	25	0.0	89.3	0.0	80.6	0.74

Notes: A, true positives (with obvious emphysema and persistent airflow limitation); B, false positives (with obvious emphysema, but without persistent airflow limitation); C, false negatives (without obvious emphysema, but with persistent airflow limitation); D, true negatives (without obvious emphysema and persistent airflow limitation).
Abbreviations: LAA%, percentage of the lung volume occupied by low attenuation areas; NPV, negative predictive value; Perc n, percentile of the histogram of attenuation values; PPV, positive predictive value.

Model 4 showed the best discrimination in both Group 1.1 and Group 1.2. The discrimination in Group 1.1 was Model 4>Model 3>LAA% (–930 HU)>Perc 3>Model 2>Model 1>LAA% (–950 HU)>Perc 15. In Group 1.2, it was Model 4>Model 3>Model 2>Perc 3>LAA% (–930 HU)>Model 1>Perc 15>LAA% (–950 HU), as shown in Figure 5 and Table S3.

There was a significant difference between Model 4 and LAA% (–950 HU) both in Group 1.1 and Group 1.2. The diagnostic value of the multivariable model in diagnosing persistent airflow limitation using different cut points is shown in Table S4. Using y4>–0.7 as the criterion, the sensitivity was 63% and 61%, and the specificity was 95% and 97% in Group 1.1 and Group 1.2, respectively.

Discussion

In this study, we analyzed patients' emphysema extent on CT scans and found its diagnostic value in identifying persistent airflow limitation. We also developed a diagnostic criterion for further verification.

Our results showed that almost all patients with high FEV_1/FVC had low LAA% and high Perc 15. These findings

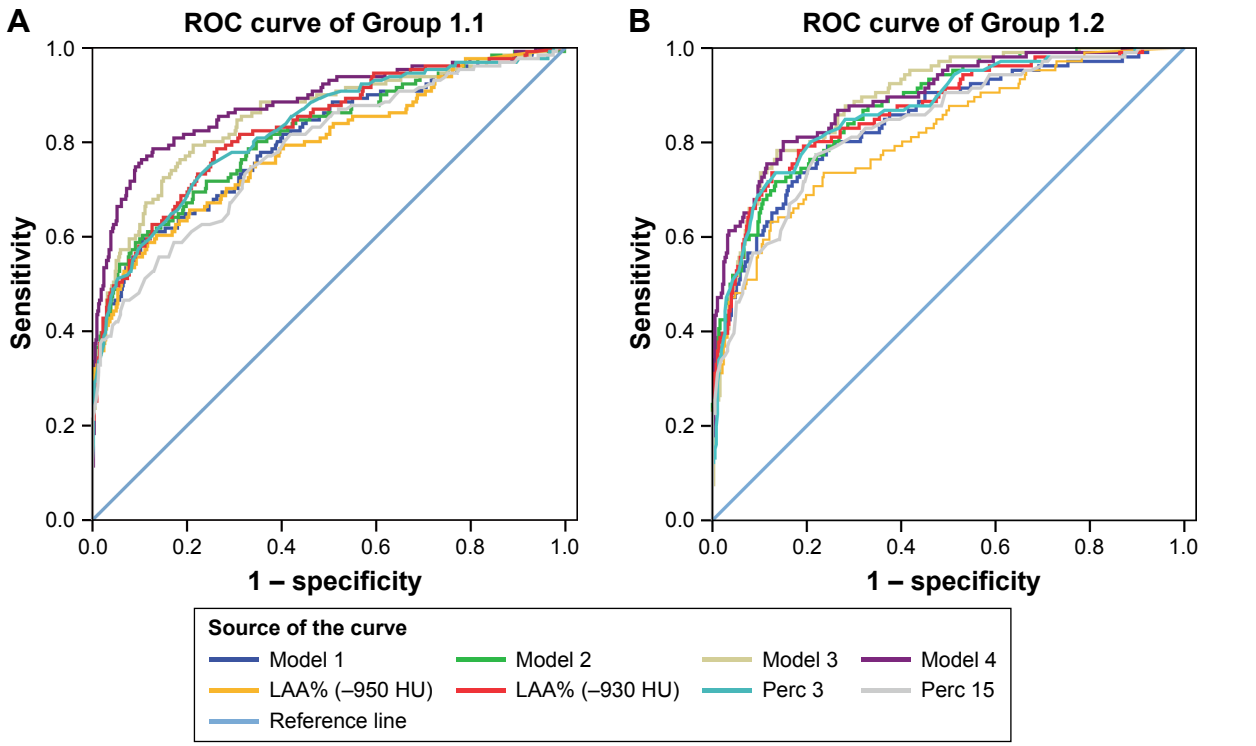

Figure 5 The ROC curve of emphysema indexes and predicting model in diagnosing consistent airflow limitation.
Notes: (**A**) Group 1.1 (derivation group); (**B**) Group 1.2 (internal validation group). LAA% (–950 HU) and LAA% (–930 HU) indicate the percentage of the lung volume occupied by low attenuation areas using the thresholds of –950 and –930 HU; Perc 3 and Perc 15 indicate percentile of the histogram of attenuation values.
Abbreviations: LAA%, percentage of the lung volume occupied by low attenuation areas; Perc n, percentile of the histogram of attenuation values; ROC, receiver-operating characteristic.

indicated that emphysema extent (ie, LAA%, Perc n) on CT can be a highly specific index in diagnosing persistent airflow limitation. Moreover, Table 2 Part A reveals a positive likelihood ratio of 9.3 (Group 1.1) and 11.0 (Group 1.2) of LAA% (–950 HU) >1.4%, 36.4 (Group 1.1) and 28.3 (Group 1.2) of LAA% (–950 HU) >3.0%, and a negative likelihood ratio of 0.58 (Group 1.1) and 0.55 (Group 1.2) of LAA% (–950 HU) >1.4%. It had been reported that a positive likelihood ratio >10 and a negative likelihood ratio <0.1 were regarded as the inclusion and exclusion criteria in most circumstances, respectively.[16] Thus, we could conclude that a patient with an LAA% (–950 HU) >1.4% should be diagnosed with persistent airflow limitation, and the diagnosis was more accurate when LAA% (–950 HU) was >3.0%.

However, when LAA% (–950 HU) was <1.4%, we still could not exclude the possibility of persistent airflow limitation. The sensitivity of the emphysema extent in persistent airflow limitation diagnosis was not as satisfactory as its specificity. In COPD, the narrow peripheral airways, which resulted from inflammation and the loss of alveolar elastic recoil force induced by emphysema (due to parenchymal destruction), could both lead to airflow limitation.[17] Emphysema extent and airway measurements were independent predictive factors of persistent airflow limitation.[18,19] Since COPD was a heterogenetic disease,[20,21] patients with severe emphysema were supposed to suffer from persistent airflow limitation, while the absence of emphysema could not exclude the possibility of persistent airflow limitation.

It had been reported that LAA% (–950 HU) and Perc 15 were widely accepted as the best indexes in CT emphysema evaluation.[22] However, the selection of the optimal threshold was associated with the section thickness and reconstruction algorithm. Previous studies indicated that the LAA% (–910 HU) correlated with the pathology grade of emphysema on CT scan with 1 cm thickness.[23] LAA% (–950 HU) was the best index of macroscopic pathological emphysema extent on a 1 mm thick CT image,[24] and on CT images reconstructed by 1.25, 5.0, and 10.0 mm section thickness and 20 s algorithm, the LAA% (–960 HU), LAA% (–970 HU), and Perc 1 had close correlation with the pathology emphysema extent.[25] In our present study, the LAA% with the threshold of –930 HU and Perc 3 had the highest AUC in identifying persistent airflow limitation. However, there was no significant difference in AUC between LAA% with a threshold of –930 HU and LAA% with a threshold of –950 HU, as well as between Perc 3 and Perc 15.

Patients with COPD often suffered from other lung diseases as well. We found that the coexistence of interstitial lung disease, pneumothorax, post-thoracic surgery, and bronchiectasis decreased the specificity of the emphysema extent. However, the coexistence of lung infiltration, and lung mass and nodule did not affect the specificity. This may be due to the honeycombing in interstitial lung disease, the area without lung texture in pneumothorax, the compensatory emphysema after pulmonary lobectomy, and the dilated airways in bronchiectasis.

In the analysis stratified by sex and age, the difference between the patients with and without persistent airflow limitation was more significant in males and patients aged 50–80 years. This was in line with the previous studies. It was reported that emphysema signs on CT were more common in men than women.[26,27] Furthermore, Grydeland et al indicated that the emphysema extent on CT increased with age in both COPD and control groups.[28] Therefore, the emphysema extent on CT may be affected by age and sex. When LAA% (–950 HU) or Perc 15 was regarded as the only emphysema index, the variables, including age, sex, and weight, were also independent predictors of persistent airflow limitation. However, if all the emphysema indexes were included, these population characteristics were no longer independent predictors.

There were several strengths for this study. First, this was a real-world study in China, with a relatively large sample size. Second, our results could be inferred to the patients coexistent with pneumonia, nodule, or mass. Third, the diagnostic values of emphysema extent and predictor model were validated in both internal validation and external validation groups. However, there were also several limitations in this study. First, some CT characteristics of COPD, including airway remodeling and air trapping, were not included in the present study. Second, the results of the present study were concluded from Chinese patients in a single-center study. Therefore, further researches in other areas and on other populations are still needed to investigate the proper cut points and diagnostic values. Third, COPD is a heterogeneous disease and persistent airflow limitation may be present without obvious emphysema; so, our results cannot reflect COPD patients with such characteristics. Fourth, it had been proved that CT with <1 mm slice thickness was more sensitive[29] and higher-resolution CT provided higher diagnostic value.[30] However, in our study, the emphysema extents were calculated from routing chest CT images (reconstructed by 5 mm thick sections and standard algorithms). Besides, various kernels for CT were used to evaluate the emphysema, which will affect the

results in evaluating emphysema and bring natural limitation to the results. Finally, the medical history including the main symptoms and smoking status was not available, and thus, the diagnosis of COPD was inadequate. However, based on the present study, persistent airflow limitation can be diagnosed based on emphysema extent on CT. Thereafter, COPD can be diagnosed in the context of the medical history in clinics.

Conclusion

The emphysema extent on CT is a specific marker in the diagnosis of persistent airflow limitation, which can help with the diagnosis of COPD.

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Author contributions

Conception and design of the research: Huan Ying Wan, Guo Chao Shi, Qi Jian Cheng, Qing Yun Li, Zi Lai Pan and Shao Guang Huang. Acquisition of data: Ting Cheng and Shuai Pang. Analysis and interpretation of data: Ting Cheng and Zi Lai Pan. Statistical analysis: Ting Cheng and Yong Li. Obtaining funding: Ting Cheng and Huan Ying Wan. Drafting the manuscript: Ting Cheng and Yong Li. Revision of manuscript for important intellectual content: Huan Ying Wan and Qi Jian Cheng. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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