Automated Computed Tomography Lung Densitometry in Bronchiectasis Patients

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Research Article

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Abstract

Rationale: Bronchiectasis is a complex and heterogeneous disease. Visual computed tomography (CT) scoring systems are used to assess disease severity, disease progression and predict outcomes in bronchiectasis although they have some limitations such as subjectivity, requirement of previous training and are time-consuming.

Objective: To correlate quantitative CT lung densitometry measurements with pulmonary function test (PFT) and multidimensional prognostic scores in patients with bronchiectasis.

Materials and methods: From 2014 to 2017, 100 consecutive adult patients with non-cystic fibrosis bronchiectasis underwent inspiratory and expiratory volumetric chest CT and PFT (spirometry, plethysmograph, diffusing capacity of carbon monoxide measurement [DLCO]). Visual CT score (CF-CT score), CT lung densitometry parameters (kurtosis, skewness and expiratory/inspiratory mean lung density [E/I MLD]) and multidimensional prognostic scores (BSI and FACED) were calculated in all patients and correlated to PFT.

Results: CT lung densitometry parameters (kurtosis and skewness), correlated with forced expiratory volume in 1 second (FEV1) (R=0.32; p=0.001 and R=0.34; p<0.001) and DLCO (R=0.41 and R=0.43; p<0.001). Automated CT air trapping quantification (E/I MLD) showed correlation with residual volume (RV), multidimensional score FACED (R=0.63 and R=0.53; p<0.001) and performed better than the CF-CT score in the diagnosis of high-risk patients and severe air trapping.

Conclusion: CT lung densitometry parameters showed correlations with PFT in non-cystic fibrosis bronchiectasis patients. Automated CT air trapping quantification performed better than visual CT score in the identification of high-risk patients and severe air trapping, suggesting it could be a useful tool in the evaluation of these patients, although further studies are needed to confirm these findings.

Introduction

Bronchiectasis is defined as irreversible bronchial dilation (1). It is usually a progressive disease and patients present with productive cough, shortness of breath, repeated respiratory infections and occasional hemoptysis. Although cystic fibrosis (CF) is the most studied etiology, a great number of diseases and conditions can lead to bronchiectasis, such as infections, congenital malformations, primary ciliary dyskinesia, autoimmune and genetic disorders (2).

Computed tomography of the chest (CT) is the gold standard for the diagnosis of bronchiectasis and it can characterize disease severity, progression and complications (3). Several visual CT score systems were developed to quantify structural lung abnormalities in bronchiectasis patients, particularly in those with CF. These visual CT score systems have a higher sensitivity than lung function to detect early abnormalities in the lung (4, 5) and can be used as an outcome measurement in clinical practice and for research purposes (6). One of the most recent of them, named CF-CT score (7), is derived from the Brody

score (8) and is a visual evaluation of severity and extent of central and peripheral bronchiectasis, airway wall thickening, mucus plugging, pulmonary opacities, cysts and bullae on inspiratory CT images and the pattern and extent of trapped air on expiratory CT images. The drawbacks of these visual CT score systems are the subjective visual analysis, the need for previous training, and they are time-consuming, preventing use in clinical practice.

CT lung densitometry is an automated quantitative method, based on the variable attenuation of X-rays in pulmonary tissue (9). Software automatic segments the lung from the mediastinum and chest wall and thus the density value of each pulmonary voxel is automated measured in Hounsfield units (HU). This automated method reduces the subjective evaluation of visual CT score systems, is fast and reproductible. Studies have shown a good correlation with emphysema quantification by CT lung densitometry and histopathology in resected specimens (10, 11) and with pulmonary function tests (PFT) in chronic obstructive pulmonary disease (COPD)(12–14) and interstitial lung disease (15–19). However, few studies have investigated the role of CT lung densitometry in bronchiectasis patients, most of them in CF (20–22).

The aim of this study was to use CT lung densitometry in the evaluation of non-CF bronchiectasis patients and to investigate the relationship of this automated CT quantification system with PFT and visual CT score system.

Material And Methods

Study Patients

In this cross-sectional study, all consecutive adult patients from May 2014 to October 2017, with non-CF bronchiectasis confirmed by previous CT and clinical investigation were enrolled. Exclusion criteria included diagnosis of cystic fibrosis, asthma, COPD, pregnancy, recent treatment of pulmonary exacerbation (< 30 days), active smokers or previous smokers (> 10 pack-year), previous pulmonary surgery and patients unable to perform PFT (23).

CT exams

Volumetric inspiratory and expiratory supine chest CT without intravenous contrast administration was performed in a 160-detector multislice CT (Aquillion Prime, Canon Medical Systems Corporation, Japan). Patients were trained to hold maximal inspiration and maximal expiration before CT exam. The following image protocol was used, depending on body weight: patients ≤80 kg – 120 kV and 60 mA on inspiratory scans; 100 kV and 40 mA on expiratory scans; patients > 80 kg – 135 kV and 60 mA on inspiratory scans and 120 kV and 40 mA on expiratory scans. Dose modulation was disabled, and images were reconstructed with adaptative iterative software (AIDR 3D – Canon Medical Systems Corporation, Japan) using a standard kernel (FC 01) at 1 mm slice thickness and 0.8 mm intervals. Total median dose length product (DLP) was 177 mGy.cm (±16 mGy.cm) for the first protocol and 251 mGy.cm (±42 mGy.cm) for the second protocol.

Visual CT score

CF-CT score was calculated by two radiologists with 5 and 7 years of experience (M.S.T. and M.V.Y.S.) who had previously received specific training in a reference center (Lung Analysis, Erasmus Medical Center, Rotterdam, The Netherlands). The exams were deidentified and scored in random order by both readers. The total score (CF-CT score) and the air trapping component score (AT score) were recorded in absolute values, and the mean value of both readers was used in the analysis. CF-CT score can range from 0 to 243 and AT score from 0 to 27. Interobserver variability was accessed in all patients and intraobserver variability was evaluated by one reader in a random sample of 15 cases stratified by disease severity as suggested by Szczesniak et al (24).

CT lung densitometry

Automated CT quantification was performed with a free, open-source software (3D Slicer, version 4.7; National Institutes of Health funded; https://www.slicer.org) with a lung-specific module (Chest Imaging Platform - Applied Chest Imaging Laboratory, Brigham and Women's Hospital, Boston, MA, USA). The lung segmentations were completely automated without user interference, and thus, repeatability was not assessed. Trachea and main bronchi were automated excluded in the segmentations. Quantitative CT parameters recorded included percentage (%) of low attenuation areas (LAA910% = % voxels < -910 Hounsfield units (HU) on inspiratory CT), % of high attenuation areas (HAA700% = % voxels > -700 HU on inspiratory CT), skewness and kurtosis (parameters of the lung density histogram) and expiratory to inspiratory ratio of mean lung density (E/I MLD), a previously described method of automated air trapping quantification (25–27).

Pulmonary functional tests

Patients underwent spirometry and plethysmography (Elite Dx, Elite SeriesTM Plethysmograph - MedGraphics Cardiorespiratory Diagnostic Systems - Medical Graphics Corporation, INC., 2005, St Paul, MN, USA) on the same day as the CT exam, following reference technical parameters (28) and predictive values were calculated using local reference values (29, 30). The forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), residual volume (RV), total lung capacity (TLC), RV/TLC ratio, and diffusing capacity of carbon monoxide (DLCO) were recorded and expressed as percentage of predicted values. Severe air trapping was considered in patients with RV/TLC > 60, as previously described in COPD patients (31).

Multidimensional prognostic scores

Two multidimensional scores that include clinical, functional, microbiological and imaging data, the bronchial severity index (BSI) and FACED (acronym for FEV1, age, chronic colonization, extension and dyspnea), were also calculated. These scores were developed for prognostic evaluation of non-cystic fibrosis bronchiectasis patients and correlate with disease severity, exacerbations and mortality. Both scores classify bronchiectasis patients into three severity classes: mild, moderate and severe disease (32,

33). Patients classified as moderate and severe disease were grouped as high-risk patients since they are related to increased mortality risk.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) and frequency (percentage). Normality assumption was graphically checked using quantile-quantile (QQ) plots and tested with Shapiro-Wilk test. Accordingly, comparisons were made with Student t test (or Mann-Whitney U test), and between three severity classes and etiologies were performed using one-way analysis of variance or Kruskal-Wallis test. Correlations were determined using Pearson's and Spearman's correlation coefficient and no corrections were made for multi comparisons. For the identification of severe air trapping and high-risk patients, sensitivity and specificity were defined from the calculated receiver operator characteristic (ROC) curves. ROC curves were compared using the DeLong method and best cutoff point was chosen using Youden index. CF-CT score interobserver and intraobserver agreement were estimated using Bland-Altman analysis (mean difference, 95% Limits of Agreement [LOA]) and intraclass correlation coefficient (ICC). All statistical analyses were performed using the R statistical software (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) and a p-value < 0.05 was considered to be statically significant.

Results

Patient characteristics

From 167 patients, 100 were included in this study (Fig. 1). The majority were women (57%) with a mean age of 42 ± 15 years. Idiopathic bronchiectasis (34%) was the most prevalent etiology, followed by primary ciliary dyskinesia (20%). Mean FEV1 was 49% ± 20, with most patients presenting air trapping according to RV/TLC rate (Table 1).

The majority of the participants were classified as high-risk patients (moderate and severe groups of multidimensional scores): 63% according to FACED and 54% according to BSI. Worse lung function and increased air trapping (measured by both plethysmograph and quantitative CT) were found as bronchiectasis severity increased (Table 2).

Visual CT score

Mean visual CF-CT score was 54 ± 18 (ranging from 14 to 99) and mean AT score was 11 ± 5. The average time required to obtain the visual CT score was 14 ± 4 minutes. CF-CT score had a negative correlation with FEV1 ($R = -0.42$; $p < 0.001$) and a positive correlation with DLCO ($R = 0.43$; $p < 0.001$) and FACED ($R = 0.32$; $p = 0.001$). AT score had a positive correlation with RV ($R = 0.44$; $p < 0.001$) and with RV/TLC ($R = 0.30$; $p = 0.002$) (Figs. 1–4). We found good agreement for both interobserver (mean difference of 7.1, LOA 1.4 to 12.8) and intraobserver analysis (mean difference of 4.0, LOA − 6.9 to 14.9) and excellent reliability (ICC of 0.96 and 0.95 respectively).

CT lung densitometry

Regarding automated CT quantification, mean skewness, kurtosis and E/I MLD values were 3.2 ± 0.5, 7.1 ± 2.9 and 0.91 ± 0.05, respectively. The average time required to obtain the lung density measures for each series was 2.5 ± 0.5 minutes.

Kurtosis and skewness had a positive correlation with FEV1 (R = 0.32 and R = 0.34; p < 0.001, respectively) and DLCO (R = 0.43 and 0.41; p < 0.001).

Automated air trapping measure (E/I MLD) had a positive correlation with RV (R = 0.63; p < 0.001) and RV/TLC (R = 0.68; p < 0.001) and also with DLCO (R = 0.42; p < 0.001). There was also correlation of E/I MLD with FACED (R = 0.53; p < 0.001) and CF-CT score (R = 0.38; p < 0.001). Results are shown on Table 3 and 4.

E/I MLD performed better than CF-CT in the identification of high-risk patients (AUC = 0.81; CI 95% 0,72 – 0,91versus AUC = 0.71; CI 95% 0.60–0.81). Using a threshold of E/I MLD > 0.91 we achieved 85% of sensibility and 72% of specificity for the diagnosis of high-risk patients in the ROC curve (Fig. 3). E/I MLD also performed better than CF-CT in the identification of severe air-trapping (AUC = 0.83 CI 95% 0.74–0.92 versus 0.67 CI 95% 0.56–0.79). Using a threshold of E/I MLD > 0.93 we achieved 83% of sensibility and 75% of specificity for the diagnosis of severe air-trapping in the ROC curve (Fig. 4).

Discussion

In this study we were able to demonstrate that CT lung densitometry parameters show correlation with PFT in non-cystic fibrosis bronchiectasis patients. Automated CT air trapping quantification performed better than visual CT score in the identification of high-risk patients and severe air trapping. Visual CT scoring systems are currently used to quantify lung disease in bronchiectasis patients. Although studies suggest that these scores can be used as a surrogate outcome measure (6) and have a higher sensitivity than lung function to detect early abnormalities in the lung (4, 5), they are subjective, require previous training and are time-consuming.

Previous automated CT quantification studies in bronchiectasis patients have focused on analysis of the airways, including its size, geometry, and bronchial wall thickening (34–36). Although this is the most straightforward approach to quantification of bronchiectasis, it is very difficult to automatically identify the airways in these patients, especially because of its irregular dilation and distortion, association with parenchymal abnormalities and great variability of disease extension in these individuals. Considering these challenges, recent studies have used CT lung densitometry to quantify disease in CF (20, 21) and primary ciliary dyskinesia (22), with a good correlation with PFT.

In our cohort of 100 non-CF bronchiectasis patients, automated CT lung densitometry correlated with PFT, and the results are comparable to the correlation of visual CT scores with PFT. From all CT densitometry parameters in inspiratory scans, skewness and kurtosis had the better correlation with PFT. These parameters are histogram characteristics of lung densitometry values, related to the degree of distribution asymmetry and sharpness of the distribution peak. They presented a better correlation with PFT than the

percentage of high attenuation areas (HAA700%) and percentage of low attenuation areas (LAA910%) in pulmonary parenchyma. CT high attenuation areas correspond to structural changes such as consolidations, ground glass opacities, atelectasis, airway wall thickening and mucus plugging. On the other hand, CT low attenuation areas correspond to bronchiectasis, cysts and bullae, and air trapping. Bronchiectasis patients usually have a complex variability of structural changes of both high and low attenuation on CT images. We believe that this heterogeneity compromises the use of mean lung density and the percentage of high and low attenuation areas in the cross-section evaluation of these patients, although there might be a role for these markers in longitudinal studies. On the other hand, skewness and kurtosis are parameters that account for both high and low attenuation areas, and are more suitable in the evaluation of bronchiectasis patients (20–22). Also, the average time required to obtain the automatic CT measures was substantially shorter than visual CT scoring, enabling its use in daily practice.

One major difference in our study was the acquisition of volumetric expiratory images, enabling automated quantitative measurement of air trapping (E/I MLD). Of all automated quantitative measures, E/I MLD had the best correlation with FEV1, RV and RV/TLC and was superior to visual analysis of air trapping compared with functional data, suggesting that air trapping could be underestimated in visual CT analysis. This could be explained because visual evaluation of air trapping is very subjective (6). We believe that small areas of air trapping generate higher contrast with adjacent normal lung, are easier to see, and could be more valued than larger areas, like air trapping in a whole pulmonary lobe. Also, E/I MLD had better performance than the visual CF-CT score in the diagnosis of high-risk patients and severe air trapping. Recent studies have highlighted the importance of bronchiolitis and small airway disease in bronchiectasis patients (37–39) and an increased mortality in bronchiectasis patients with a high RV/TLC ratio and low DLCO (40). With that in mind, we believe that automated CT quantification of air trapping could be a useful tool in the prognostic evaluation of these patients.

Multidimensional scores (BSI and FACED) also correlated with E/I MLD. These scores include pulmonary function data but also clinical, microbiological and imaging data and have good prognostic capacity for exacerbations and mortality in bronchiectasis patients. These results also support the possible role of E/I MLD in the evaluation of bronchiectasis patients.

CT lung density is known to be influenced by several factors, such as lung volumes, CT scanner models, CT scanner calibration, X-ray dose and reconstruction kernel (41). In our study, all the CT exams were acquired in one calibrated scanner, and images were reconstructed with the same reconstruction algorithm and kernel. We optimized radiation dose, especially on expiratory scans, to comply with CT radiation reference levels (42). Because our goal was to evaluate a simple and reproductible quantitative method, we did not use correction methods or adapted thresholds in the quantitative CT density measures. COPD and pulmonary emphysema are known to influence CT densitometric measures. To avoid this bias, we excluded smokers and previous smokers with more than 10 year/pack history of smoking.

Limitations of our study include the unicentric and cross-sectional design. A larger cohort with longitudinal evaluation could further validate these results. Also, we did not use spirometry control for lung volumes in the CT scan, although all patients were trained to hold maximal inspiration and maximal expiration before the exam. Another limitation was the use of the CF-CT score. Although visual CT scores were firstly designed to evaluate CF patients, they have been used in the quantification of non-CF bronchiectasis patients in previous studies (3, 43).

Conclusion

We describe a fast, objective and reproductible method of automatic quantification of lung disease in a non-CF bronchiectasis population. CT lung densitometry parameters correlated with PFT parameters. Also, E/I MLD was superior to CF-CT in the diagnosis of high-risk patients and patients with severe air trapping.

Since air trapping seen to have a role in the prognostic of bronchiectasis patients, we believe that an objective quantification of air trapping on CT scans could be a useful tool in the evaluation these patients. Further studies are needed to confirm our findings.

Abbreviations

AUC: area under the curve

BSI: bronchiectasis severity index

CF: cystic fibrosis

CI: confidence interval

COPD: chronic obstructive pulmonary disease

CT: computed tomography

DLCO: diffusing capacity of carbon monoxide

E/I MLD: expiratory/inspiratory mean lung density ratio

FACED: bronchiectasis score (acronym for FEV1, age, chronic colonization, extension and dyspnea)

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

HU: Hounsfield units

PFT: pulmonary function test

ROC: receiver operating characteristic

RV: residual volume

TLC: total lung capacity

LAA910%: percentage of low attenuation areas of lung (<-910UH) in inspiratory CT

HAA700%: percentage of high attenuation areas of lung (>-700UH) in inspiratory CT

Declarations

Ethics approval and consent to participate

This research was approved by the Institutional Ethics Committee of the University of São Paulo – Hospital das Clínicas da Faculdade de Medicina, on 06-07-2018 under the number 2.697.966.2.

Written informed consent was obtained from all participants and all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this section.

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Authors' contributions

MVYS and RAA had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MCNTMN, SZR, AC, RS, ANAJ, MST and CHN contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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Tables

Table 1
Patient characteristics and lung function.

Demographics n = 100	
Age (years)	43 ± 15
Male, n (%)	43 (43)
White race, n (%)	63 (63)
BMI, kg/m^2	24 ± 5
Etiology	
Idiopathic, n (%)	34 (34)
Primary Ciliary dyskinesia, n (%)	20 (20)
Post infectious, n (%)	14 (14)
Bronchiolitis, n (%)	12 (12)
Others, n (%)	20 (20)
Lung function	
FEV1 (% predicted)	49 ± 20
FVC (% predicted)	70 ± 17
FEV1/FVC (%)	57 ± 15
TLC (% predicted)	107 ± 17
RV (% predicted)	202 ±59
RV/TLC (%)	53 ± 11
DLCO (% predicted)	71 ± 27

Table 2
Lung function and tomographic measurements according to bronchiectasis severity

BSI	**Mild (n = 46)**	**Moderate (n = 35)**	**Severe (n = 19)**	**p value**
FEV1 (% predicted)	53±22	47±18	41±18	0.052
RV/TLC (%)	48±9	54±9	60±8	< 0.001
DLCO (% predicted)	82±23	64±27	54±25	< 0.001
CF-CT score	51±17	54±18	61±15	0.105
E/I MLD	0.90±0.06	0.91±0.05	0.93±0.04	0.062
LAA910% (%)	29.5±15.4	30.8±15.3	31.7±9.9	0.840
HAA700% (%)	9.8±2.6	11.1±4.2	10.9±2.1	0.173
Skewness	3.2±0.3	3.1±0.5	3.0±0.3	0.073
Kurtosis	13.3±3.4	12.0±4.3	11.0±3.1	0.065
FACED	**Mild (n = 37)**	**Moderate (n = 56)**	**Severe (n = 7)**	**p value**
FEV1 (% predicted)	67±16	38±14	40±11	< 0.001
RV/TLC (%)	43±7	57±8	60±7	< 0.001
DLCO ((% predicted)	87±24	59±24	61±17	< 0.001
CF-CT score	45±16	59±16	56±26	0.001
E/I MLD	0.87±0.06	0.93±0.03	0.94±0.02	< 0.001
LAA910% (%)	25.7±14.6	33.4±14.2	31.5±7.8	0.039
HAA700% (%)	10.4±3.2	10.5±3.3	10.4±3.2	0.971
Skewness	3.2±0.4	3.1±0.4	3.1±0.3	0.114
Kurtosis	13.4±3.8	11.8±3.7	11.8±3.4	0.133

Table 3
Correlations of visual CT scores and lung densitometry parameters with lung function.

	FEV1 (p value)	FVC (p value)	FEV1/FVC (p value)	RV (p value)	TLC (p value)	RV/TLC (p value)	DLco (p value)
CF-CT score	-0.43 (< 0.001)	-0.38 (< 0.001)	-0.29 (0.003)	0.44 (< 0.001)	0.10 (0.25)	0.50 (< 0.001)	-0.43 (< 0.001)
AT score	-0.48 (< 0.001)	-0.32 (0.001)	-0.42 (< 0.001)	0.42 (< 0.001)	0.04 (0.69)	0.30 (0.002)	-0.30 (0.004)
LAA910%	-0.29 (0.003)	0.12 (0.20)	-0.60 (< 0.001)	0.16 (0.097)	0.25 (0.012)	0.05 (0.59)	-0.16 (0.12)
HAA700%	-0.13 (0.17)	-0.43 (< 0.001)	0.21 (0.029)	0.06 (0.54)	0.39 (< 0.001)	0.19 (0.056)	-0.26 (0.012)
Skewness	0.34 (< 0.001)	0.58 (< 0.001)	-0.01 (0.9)	-0.11 (0.27)	0.34 (< 0.001)	-0.38 (< 0.001)	0.43 (< 0.001)
Kurtosis	0.32 (< 0.001)	0.57 (< 0.001)	-0.04 (0.68)	-0.10 (0.34)	0.35 (< 0.001)	-0.36 (< 0.001)	0.41 (< 0.001)
E/I MLD	-0.51 (< 0.001)	-0.35 (< 0.001)	-0.57 (< 0.001)	0.63 (< 0.001)	0.37 (< 0.001)	0.68 (< 0.001)	-0.42 (< 0.001)

Table 4
Correlations of visual CT scores, lung densitometry parameters and multidimensional scores.

	BSI score (p value)	FACED score (p value)	CF-CT score (p value)	AT score (p value)
CF-CT score	0.24 (0.015)	0.32 (0.001)	-	0.50 (< 0.001)
AT score	0.001 (0.98)	0.28 (0.004)	0.50 (< 0.001)	-
Skewness	-0.28 (0.005)	-0.22 (0.03)	-0.50 (< 0.001)	-0.06 (0.58)
Kurtosis	-0.29 (0.003)	-0.21 (0.03)	-0.51 (< 0.001)	-0.03 (0.78)
E/I MLD	0.29 (0.004)	0.53 (< 0.001)	0.38 (< 0.001)	0.34 (< 0.001)

Figures

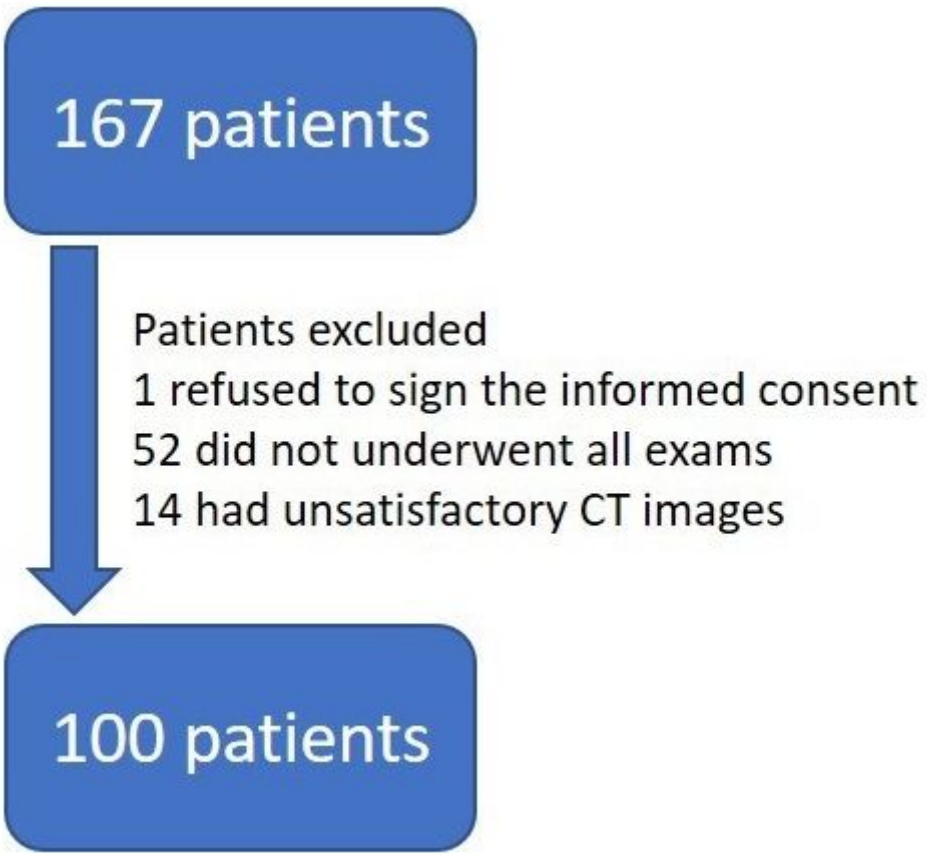

Figure 1

Patient flowchart.

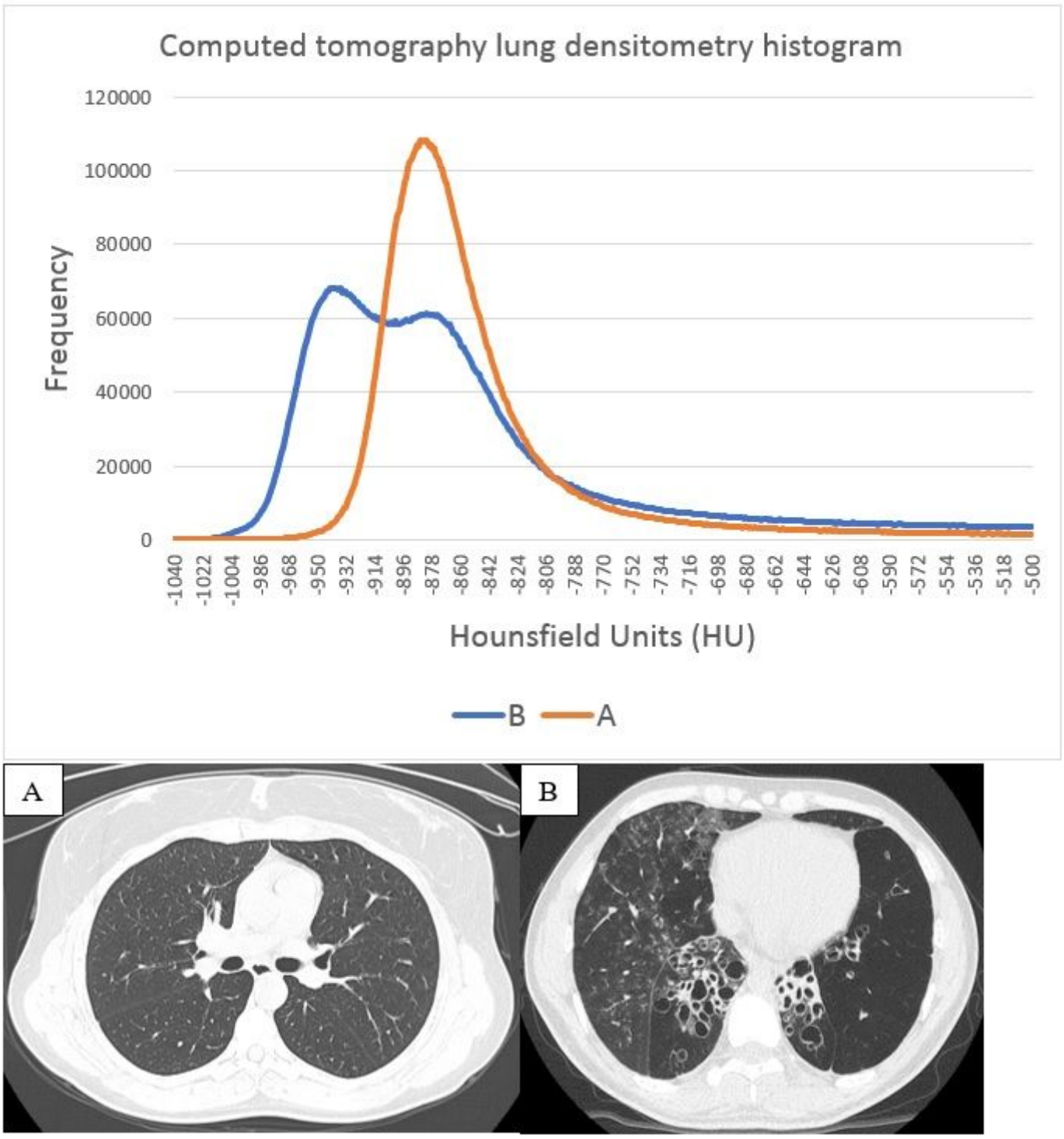

Figure 2

Example of lung densitometry histogram in a patient with normal lung (A) and in a patient with severe bronchiectasis.

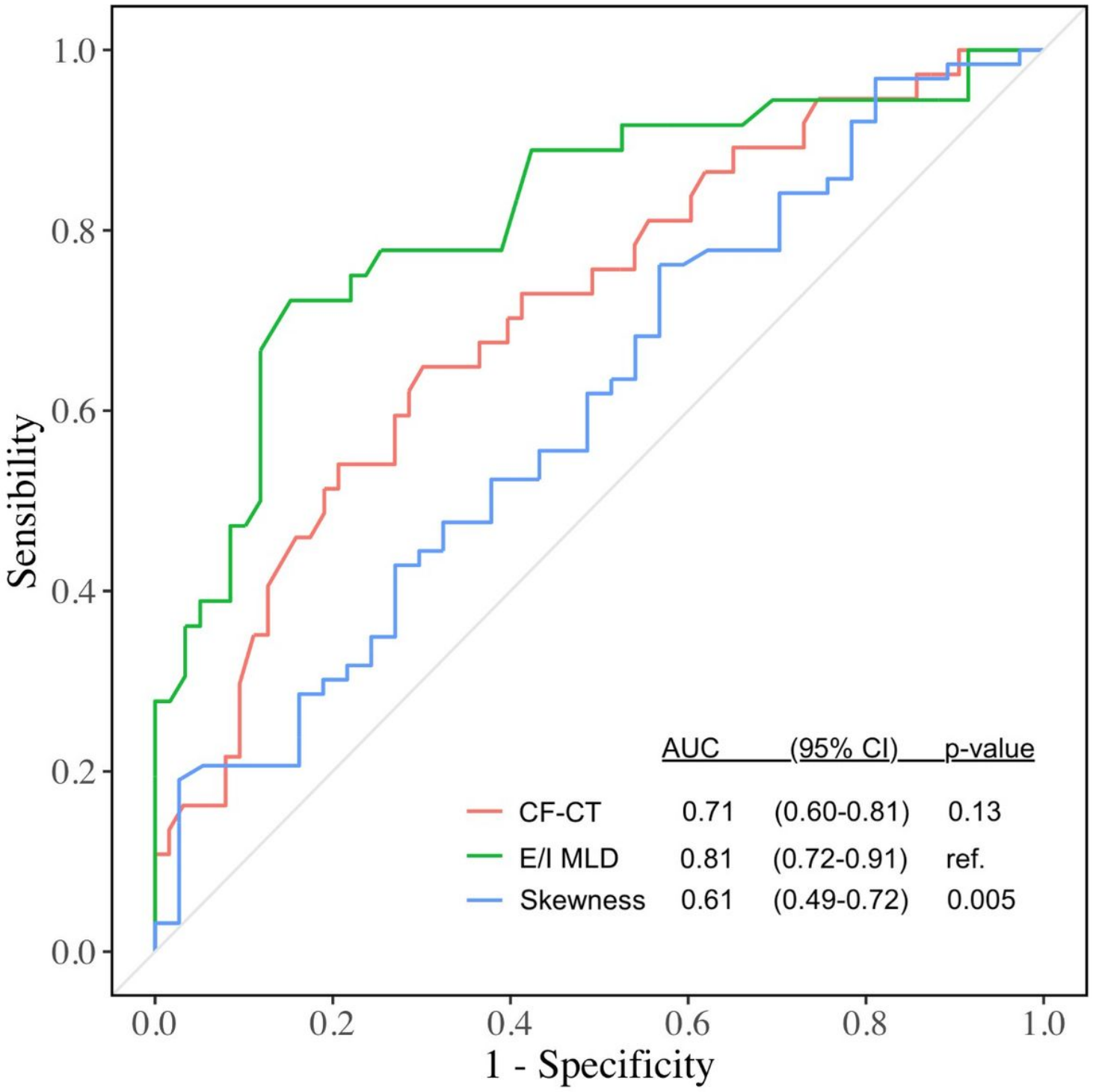

Figure 3

Accuracy of CF-CT score, E/I MLD and skewness in discriminating high-risk patients (moderate and severe FACED score). AUC: area under the ROC curve.

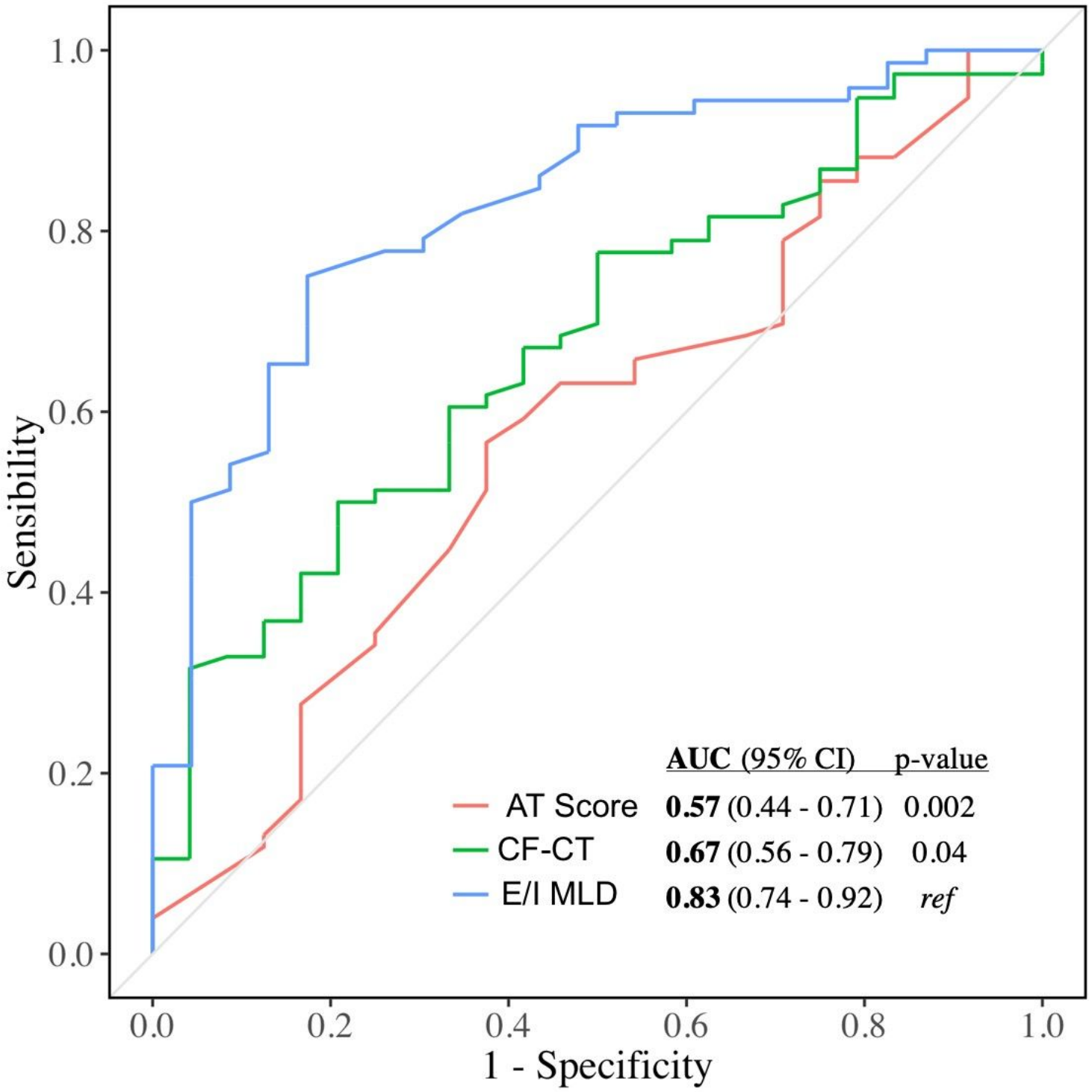

Figure 4

Accuracy of CF-CT score, AT score and E/I MLD in discriminating patients with severe air trapping (RV/TLC > 60). AUC: area under the ROC curve.