Quantitative texture-based analysis of pulmonary parenchymal features on chest CT: comparison with densitometric indices and short-term effect of changes in smoking habit

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https://bit.ly/3tiIF9a

Cite this article as: Romei C, Castellana R, Conti B, *et al*. Quantitative texture-based analysis of pulmonary parenchymal features on chest CT: comparison with densitometric indices and short-term effect of changes in smoking habit. *Eur Respir J* 2022; 60: 2102618 [DOI: 10.1183/13993003.02618-2021].

Received: 3 Oct 2021
Accepted: 24 Feb 2022

Abstract

Purpose To investigate the correlations between densitometric and Computer Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)-derived indices of pulmonary emphysema and their change in the short-term period for groups of patients with different smoking habits.

Method This retrospective study included 284 subjects from the ITALUNG trial (198 men and 86 women; mean±SD age 60±4 years) who underwent low-dose chest computed tomography at baseline and 2-year follow-up. Subjects were divided into four groups (persistent smokers, restarters, quitters and former smokers) according to their smoking habit at baseline and follow-up. Densitometric and texture analyses were performed, using CALIPER software. A correlation analysis was conducted between CALIPER-derived low-attenuation areas (LAAs) and densitometric indices, including the 15th percentile of the whole-lung attenuation histogram ($Perc_{15}$) and the relative areas with density $\leqslant$−950 HU (RA_{950}). Densitometric indices and LAAs were evaluated at baseline and variation assessed longitudinally with comparisons between groups with different smoking habit. Further analysis of parenchymal changes per pulmonary zone was performed.

Results LAAs were strongly correlated with $Perc_{15}$ (r_s=0.81; p<0.001) and RA_{950} (r_s=0.905; p<0.001). At baseline, the group of smokers showed higher $Perc_{15}$, lower RA_{950}, lower LAAs (particularly mild subclass of LAAs) than the group of ex-smokers (p<0.001). At 2-year follow-up, densitometric indices and LAAs increased in persistent smokers, former smokers and quitters (p<0.05). The progression was larger and statistically more significant in quitters (p<0.001).

Conclusion CALIPER texture analysis provides an objective measure comparable to traditional density/histogram features to assess the lung parenchymal changes in relation to different smoking habits.

Introduction

Cigarette smoking is the leading cause of COPD. One of the primary pathological findings associated with cigarette smoking is the lung parenchymal destruction caused by emphysema, defined as a permanent, abnormal enlargement of pulmonary air spaces distal to the terminal bronchiole, accompanied by the destruction of alveolar walls [1], in addition to airway obstruction, pulmonary hyperinflation, airway and parenchymal inflammatory/fibrotic changes [2]. Complex mechanisms are thought to be responsible for the development and progression of emphysema in response to cigarette smoking, including the protease–

antiprotease imbalance, inflammation, oxidative stress and matrix remodelling [3]. The progression of emphysema leads to loss of pulmonary function, which can result in respiratory insufficiency and ultimately death [4].

Although emphysema is a pathological diagnosis, chest computed tomography (CT) is a well-established tool for assessment of extent and distribution of disease *in vivo*. At imaging, emphysema appears as areas of lung parenchyma with reduced attenuation of X-rays and vascular loss in symptomatic and asymptomatic subjects [5, 6]. Visual assessment of emphysema on CT is a subjective evaluation and depends on radiologist experience and opinion [7]. Historically, computer-aided quantitative assessment of emphysema has been based on software performing densitometric analysis of lung parenchyma, through the use of threshold values or whole-lung histogram features [8]. It has been shown that quantitative densitometry analysis of CT can show that short-term emphysema variations depend on smoking habit [9, 10].

Texture analysis is a different approach to CT analysis that can assess both density and morphological features. For example, the spatial ratios of the density values detected in adjacent voxels may provide an alternative method of emphysema quantification. This may be less susceptible to the effects of noise and other artefacts from low-dose or thinner-slice imaging, which typically requires different thresholds for densitometric pixel-counting metrics [11, 12].

Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) is a texture-analysis software developed by Mayo Clinic Biomedical Imaging Resource. The detection and quantification of lung parenchymal patterns by CALIPER depends on histogram signature mapping and texture/morphology detection techniques that classify each pixel based on the characteristics of a regional volume. CALIPER was trained using a supervised machine-learning approach through expert radiologist consensus evaluation of volumetric images from pathologically confirmed datasets [13, 14]. CALIPER analysis characterises and quantifies lung parenchymal patterns on CT as follows: low-attenuation areas (LAAs) with mild, moderate and severe subtypes, normal lung, reticular densities, honeycombing and ground-glass opacities [13, 15, 16].

The purpose of this study was three-fold: 1) to assess correlations between standard densitometric indices of emphysema and CALIPER texture features; 2) to compare both indices of emphysema between smokers and ex-smokers at baseline; 3) to evaluate changes in densitometric indices of emphysema and CALIPER texture features in relation to the variations of smoking habit over follow-up.

Materials and methods

Institutional review board approval and subjects' consents were obtained.

Subjects

The study subjects were the participants in the active group of the ITALUNG CT trial who were enrolled at the Pisa centre. The ITALUNG CT trial was a randomised controlled lung cancer screening trial conducted from 2004 to 2009 in three screening centres in Tuscany, Italy: Florence, Pistoia and Pisa. The aim of the study was to assess the efficacy of lung cancer screening with chest low-dose CT (LDCT) in reducing nonsmall cell lung cancer mortality in adult smokers and former smokers [17]. Eligible for the study were subjects aged 55–69 years with a smoking history of ⩾20 pack-years in the past 10 years (former smokers who had quit for >10 years were excluded). Subjects with a previous cancer other than nonmelanoma skin cancer or with general conditions precluding thoracic surgery were excluded from the trial. The design of the study included annual LDCT for the active group *versus* usual care for control. The CTs were performed at baseline (T1) and at three annual repeats (T2–T4). Lung function tests were performed following the American Thoracic Society/European Respiratory Society protocol [18]. The following parameters were measured: forced expiratory volume in 1 s (FEV_1), FEV_1/forced vital capacity (FVC) and total lung capacity (TLC). Smoking habit information was obtained through a standardised administered questionnaire at each visit.

Chest CTs at baseline (T1) and 2-year follow-up (T3) were assessed by a radiologist with 10 years of experience in thoracic imaging (C. Romei) and calculation of the lung volume was performed with Syngo software (version 2009B VE36A; Siemens Medical Solutions, Forcheim, Germany).

The exclusion criteria were: 1) impossibility of retrieving the CT data; 2) inadequate quality of baseline or 2-year follow-up CT for the presence of motion artefacts; and 3) variation in lung volume >20% between baseline and follow-up CT.

The study subjects were first divided into smokers and ex-smokers, according to their smoking habit at T1.

The study subjects were also separated into four longitudinal categories of smoking habit, accordingly to self-reported information assessed by a standardised questionnaire, without biochemical verification. Persistent smokers were smokers at both T1 and T3; quitters were smokers at T1 and abstinent at T3; restarters were abstinent at T1 and smokers at T3; and former smokers were abstinent at both T1 and T3.

Chest CT protocol

All CTs were obtained on a multidetector Somatom Volume Zoom CT system (Siemens, Erlangen, Germany) with four detector rows. The following scanning parameters were used: tube voltage 140 kVp, tube current 70–80 mA, gantry rotation time 500 ms, pitch 1.75, matrix 512×512, reconstructed slice thickness 1.5 mm, reconstructed slice interval 1 mm, kernel: intermediate sharp (B50f; Siemens). The scan was performed from the apex to the base during a single breath-hold obtained at maximal inspiration with the subject in supine position. The acquisition time ranged between 20 and 24 s according to the length of the spiral acquisition. No intravenous contrast material was administered.

Densitometric analysis

The LDCT scans of the subjects were sent to a post-processing workstation and analysed with an integrated Syngo software tool for pulmonary densitometry (Inspace).

A preliminary smoothing procedure with a three-dimensional Gaussian filter was performed to reduce the image noise due to the sharp reconstruction kernel and thin collimation, parameters that may affect the quantification of emphysema [11].

Then, the algorithm included the computation of densitometric parameters.

Parameters recorded for this study were: the 15th percentile point ($Perc_{15}$) of the whole-lung density, which is defined as the threshold value in Hounsfield units below which 15% of all voxels are distributed, and the percentage of relative areas with density $\leqslant -950$ HU (RA_{950}).

We selected $Perc_{15}$ as a measurement for lung density, because it was previously adopted in longitudinal quantitative studies of emphysema [19, 20].

The RA_{950} threshold was chosen, since this value was reported as a valid index of macroscopic and microscopic emphysema [21, 22]. This threshold has been employed in previous studies for emphysema quantification with LDCT [23, 24]. LDCT has a minimal effect on CT quantification of emphysema [25].

The quantity of emphysema, evaluated by both methods, correlates with the pulmonary function tests [19, 26–29].

CALIPER software

Additionally, all LDCTs were analysed by CALIPER, which calculated total lung volume, percentage of different lung patterns including mild, moderate and severe LAAs, and the percentage of vascular-related structures (VRS).

CALIPER processing starts with an automated lung parenchyma, vascular and airway extraction based on density, region-growing and morphology. The trachea is extracted using an iterative region-growing process using increasingly aggressive threshold-based techniques and analysis of connected components to prevent extraction of nontracheal structures. VRS are segmented using an optimised multiscale tubular structure enhancement filter based on the eigenvalues of the Hessian matrix [30]. In addition to trachea and vascular structures, six regions/zones are defined in each lung: the central and the peripheral parenchyma of the upper, middle and lower zones. These zones are based on the position of the carina, the craniocaudal extent of the lungs and peripheral stepwise erosion of the segmented lung to provide roughly 50%/50% central and peripheral regional volumes. All CT segmentations were verified and, if necessary, corrected by a thoracic radiologist.

CALIPER detects and classifies parenchymal abnormalities by matching parenchymal histogram features within 15×15×15-pixel volumes of interest to signatures of characteristic voxels corresponding to seven parenchymal patterns with a combination of supervised and unsupervised learning [31]. These patterns are as follows: normal, mild LAA, moderate LAA, severe LAA, reticular densities, ground-glass opacities and honeycombing. Then, each pixel in the dataset is labelled with one of the patterns as shown in figure 1. The extent of interstitial lung disease (ILD) is represented by the sum of percentage of areas of ground glass, reticular pattern and honeycombing.

Statistical analysis

For the first purpose of the study, correlations between densitometric indices and CALIPER texture features (LAA subclasses and VRS), and between LAA subclasses and VRS were tested using Spearman correlations.

Secondly, Wilcoxon–Mann–Whitney testing was performed in order to cross-sectionally compare densitometric indices of emphysema and CALIPER texture features between the group of smokers and ex-smokers at baseline. In addition, the Wilcoxon–Mann–Whitney test, along with the Chi-squared test, was used to compare continuous and categorical demographic variables between these two groups of subjects. Binomial logistic regression analysis was performed to identify factors that predict the inclusion of a subject in one of the two smoking groups at baseline.

For the third purpose of the study, the Wilcoxon test for paired samples was used to assess, in a longitudinal analysis, changes of densitometric indices of emphysema and CALIPER texture features in

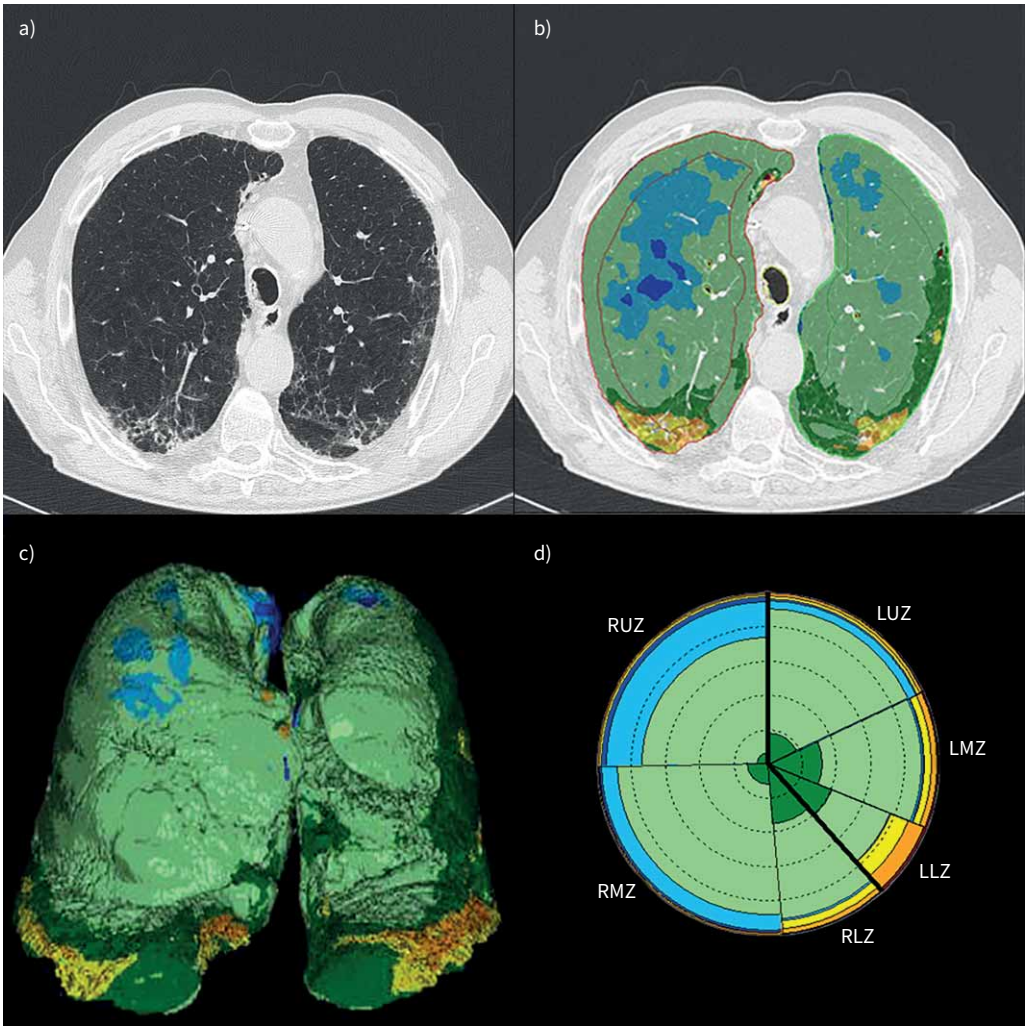

FIGURE 1 a) Axial computed tomography (CT) slice; b) axial Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER)-derived colour image overlays, c) three-dimensional CALIPER anterior view rendering of the lungs displaying different parenchymal patterns (colour-coded), and d) a glyph that provides summary of distribution for CT patterns as various colours. Dark green: normal lung (in this subject, 18.1% of the total lung volume); light green: mild LAAs (63.4%); light blue: moderate low-attenuation areas (LAAs) (8.6%); dark blue: severe LAAs (1.2%); yellow: ground-glass opacity (2.5%); orange: reticular pattern (2.3%); red: honeycombing (0.3%). LLZ: left lower zone; LMZ: left middle zone; LUZ: left upper zone; RLZ: right lower zone; RMZ: right middle zone; RUZ: right upper zone.

each of the four groups of subjects with different smoking habit (persistent smokers, quitters, restarters and former smokers). Moreover, changes of densitometric and CALIPER indices were compared among the four groups using the Kruskal–Wallis test. The Kruskal–Wallis test was also used, along with the Chi-squared test, to compare continuous and categorical demographic variables between the four groups of subjects with different smoking habits. A further analysis to evaluate all LAAs changes per pulmonary zone (upper, middle lower) in each of the four groups was performed using the Wilcoxon test for paired samples.

A p-value <0.05 was considered statistically significant.

Statistical analysis was performed using SPSS Statistics for Windows (version 24; IBM, Armonk, NY, USA).

Results

Correlations between standard densitometric indices of emphysema and CALIPER texture features

The inclusion and exclusion criteria of the 284 subjects enrolled in the study are summarised in figure 2.

The extent of CALIPER mild, moderate, and severe LAAs, singularly and together, was correlated with standard densitometric indices of emphysema ($Perc_{15}$ and RA_{950}) at baseline, as shown in table 1. Since pulmonary emphysema is associated with pulmonary vascular destruction, CALIPER VRS was also included in this analysis.

The sum of all LAAs had the strongest association with $Perc_{15}$ and RA_{950} (r_s=−0.810 and 0.905, respectively; p<0.001) (figure 3). $Perc_{15}$ and RA_{950} had stronger correlations with mild LAAs than with moderate or severe LAAs or VRS. Moreover, VRS was also correlated with all, mild, moderate and severe LAAs (p<0.001 for all tests), and the strongest association was with all LAAs (r_s=−0.759).

Characteristics of subjects at baseline and CT features comparison according to smoking habit

The final cohort of 284 subjects was divided into two groups (smokers and ex-smokers) based on smoking habit at baseline. The baseline characteristics of the subjects by smoking habit are shown in table 2. In order to cross-sectionally assess the difference of indices of emphysema according to the smoking habit, densitometric and CALIPER-derived indices of emphysema were compared between the group of smokers and ex-smokers at T1.

The group of current smokers included a significantly higher number of males, who had a heavier smoking history (higher number of pack-years) and a greater ILD extent as compared to the group of ex-smokers. Moreover, the group of smokers had significantly lower RA_{950}, all LAAs and mild LAAs, and higher

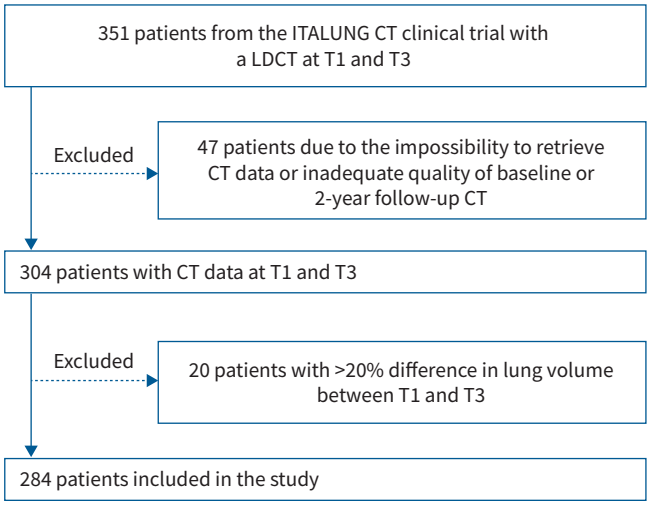

FIGURE 2 Flowchart of the inclusion and exclusion decision tree at the Pisa screening centre. LDCT: low-dose computed tomography; T1: baseline; T3: 2 years after baseline.

TABLE 1 Correlations between Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) texture analysis and densitometric indices at baseline

	$Perc_{15}$, HU		RA_{950}, %	
	ρ correlation coefficient	p-value	ρ correlation coefficient	p-value
Mild LAAs	−0.776	**<0.001**	0.863	**<0.001**
Moderate LAAs	−0.531	**<0.001**	0.616	**<0.001**
Severe LAAs	−0.500	**<0.001**	0.608	**<0.001**
All LAAs	−0.810	**<0.001**	0.905	**<0.001**
VRS	0.480	**<0.001**	−0.570	**<0.001**

Data are presented as %, unless otherwise stated. Bold type represents statistical significance. $Perc_{15}$: 15th percentile of the attenuation curve; RA_{950}: relative areas ⩽−950 HU; LAAs: low-attenuation areas; VRS: vascular-related structure.

$Perc_{15}$ than the group of ex-smokers (p<0.001). The two groups were not significantly different according to age, FEV_1, FEV_1/FVC ratio and TLC.

A binomial logistic regression was performed to ascertain the effects of sex, age, pack-years, all subclasses of LAAs, ILD and VRS on the likelihood that subjects belonged to the group of smokers or ex-smokers. In order to avoid multicollinearity, only all subtypes of LAAs, among the emphysema indices, were considered in the analysis. The logistic regression model was statistically significant (Chi-squared (6 degrees of freedom) 20.263, p=0.002). Of the six variables, both sex (p=0.009) and all subtypes of LAAs (p=0.002) were statistically significant. Increased all subtypes of LAAs was associated with a higher likelihood of belonging to the group of ex-smokers at baseline. Moreover, men had 2.21 times higher odds of belonging to the group of smokers than to the group of ex-smokers.

Characteristics of subjects and CT features in the longitudinal analysis based on different smoking habit

The 284 subjects were additionally divided into four longitudinal categories of smoking habit (persistent smokers, restarters, quitters and former smokers). The characteristics of the subjects are shown in table 3.

The four groups were not significantly different according to age, sex, pack-years, FEV_1, FEV_1/FVC and TLC (p>0.05). Densitometric and CALIPER texture features at baseline were not significantly different among persistent smokers, restarters and quitters (p>0.05). Former smokers had significantly lower $Perc_{15}$, ILD and higher RA_{950}, all LAAs and mild LAAs than persistent smokers and quitters (p<0.001). Furthermore, former smokers had significantly lower $Perc_{15}$ and higher RA_{950} than restarters (p<0.05).

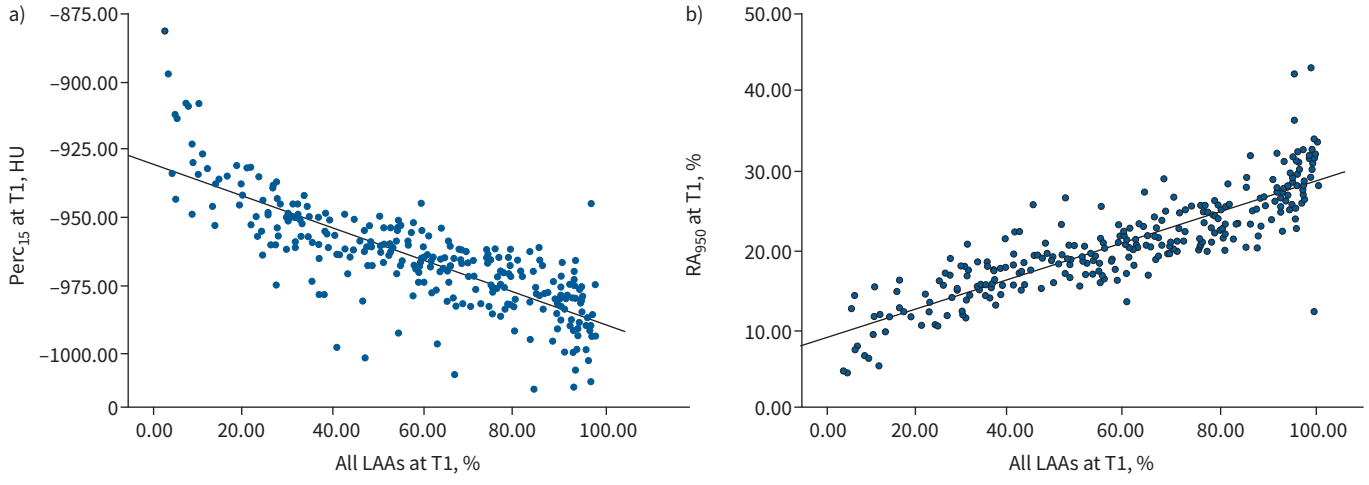

FIGURE 3 Correlations of a) the 15th percentile of the attenuation curve ($Perc_{15}$) and b) the relative areas ⩽−950 HU (RA_{950}) with all low-attenuation areas (LAAs) measured by Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER).

TABLE 2 Characteristics of subjects according to smoking status at baseline

	Smokers	Ex-smokers
Subjects, n	184	100
Sex		
Men	118 (64)	80 (80)
Women	66 (36)	20 (20)
Age, years	59 (56–63)	59 (57–65)
Smoking, pack-years	38.7 (31–51)	36 (29–44)
$Perc_{15}$, HU	−962.5 (−977 to −951)	−979 (−989 to −967)
RA_{950}, %	19.5 (16–24.1)	25.3 (20.9–29.4)
All LAAs, %	56.8 (33.7–77.9)	77.7 (57–93.8)
Mild LAAs	56.1 (33.5–78.7)	75.6 (54.4–91.3)
Moderate LAAs	0.05 (0.01–0.27)	0.06 (0.01–0.43)
Severe LAAs	0.10 (0.03–0.32)	0.12 (0.04–0.37)
ILD, %	0.14 (0.07–0.33)	0.09 (0.05–0.18)
VRS, %	1.81 (1.61–2.08)	1.82 (1.63–2)
FEV_1, L	2.7 (2.2–3.2)	2.8 (2.4–3.3)
FEV_1, % predicted	98 (85–108)	94 (85–109)
FEV_1/FVC	76.9 (71.2–81)	77.2 (70–82.4)
TLC, L	6 (5.1–6.8)	6.2 (5.5–6.9)

Data are presented as n, n (%) or median (interquartile range). $Perc_{15}$: 15th percentile of the attenuation curve; RA_{950}: relative areas ⩽−950 HU; LAAs: low-attenuation areas; ILD: interstitial lung disease; VRS: vascular-related structure; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity.

TABLE 3 Characteristics of subjects divided in four longitudinal categories of smoking habit

	Persistent smokers	Quitters	Restarters	Former smokers
Subjects, n	142	42	7	93
Smoker at T1	Yes	Yes	No	No
Smoker at T3	Yes	No	Yes	No
Sex				
Men	95 (67)	24 (57)	5 (71)	75 (81)
Women	47 (33)	18 (43)	2 (29)	18 (19)
Age at T1, years	59 (56–63)	58 (55–63)	59 (55–59)	61 (57–64)
Smoking at T1, pack-years	37.3 (29.9–48.4)	39.6 (31–52.9)	45.6 (37.5–53)	37.3 (29.1–50.5)
$Perc_{15}$ at T1, HU	−962 (−971– −951)	−963 (−974– −950)	−962 (−980– −954)	−980 (−990– −966)
RA_{950} at T1, %	19.5 (15.9–23.1)	20 (15.8–23.6)	19.3 (16.7–26)	25.4 (21–29.2)
All LAAs at T1, %	54.7 (31–77.2)	60.4 (32.7–77.5)	53.4 (27.4–80.6)	78.5 (59.2–93.4)
Mild LAAs	53.8 (31–76.8)	58.5 (32.7–73.7)	53.2 (27.4–80.4)	75.9 (58.6–90.4)
Moderate LAAs	0.03 (0.01–0.16)	0.05 (<0.01–0.46)	0.03 (0–0.05)	0.06 (0.01–0.37)
Severe LAAs	0.08 (0.03–0.25)	0.12 (0.03–0.66)	0.05 (0.01–0.11)	0.11 (0.04–0.35)
ILD at T1, %	0.14 (0.07–0.34)	0.12 (0.04–0.21)	0.14 (0.08–0.35)	0.09 (0.05–0.17)
VRS at T1, %	1.83 (1.61–2.08)	1.76 (1.60–2.07)	2.01 (1.69–2.07)	1.81 (1.62–1.97)
FEV_1 at T1, L	2.7 (2.3–3.2)[#]	2.6 (2.1–3)	3.2 (2.6–3.5)	2.8 (2.4–3.3)
FEV_1 at T1, % predicted	98 (85–109)[#]	97 (86–108)	100 (87–106)	94 (85–109)[¶]
FEV_1/FVC at T1	76. 2 (71.1–81)[#]	78.1 (71.3–81)	82.7 (77.4–84.2)	76.8 (69.1–82)[¶]
TLC at T1, L	6.2 (5.3–7)[#]	5.5 (4.4–6.6)[+]	6 (5.2–6.4)[§]	6.3 (5.5–6.9)[¶]

Data are presented as n, n (%) or median (interquartile range). T1: baseline; T3: 2-year follow-up; $Perc_{15}$: 15th percentile of the attenuation curve; RA_{950}: relative areas ⩽−950 HU; LAAs: low-attenuation areas; ILD: interstitial lung disease; VRS: vascular-related structure; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity. [#]: data available for 136 out of 142 patients; [¶]: data available for 89 out of 92 patients; [+]: data available for 40 out of 42 patients; [§]: data available for six out of seven patients.

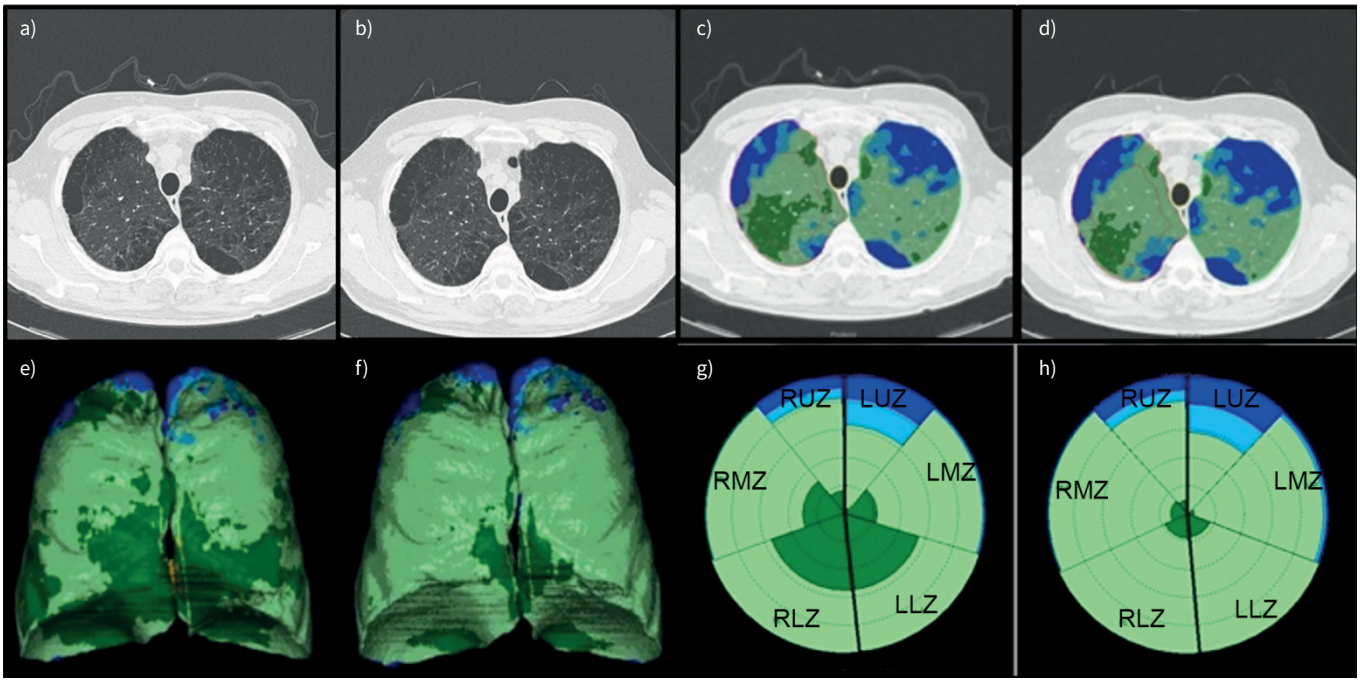

FIGURE 4 Computer-Aided Lung Informatics for Pathology Evaluation and Rating (CALIPER) analysis of computed tomography (CT) scans at baseline (T1) and follow-up (T3). Axial CT images at a) T1 and b) T3 and CALIPER-derived colour image overlays at c) T1 and d) T3. Three-dimensional CALIPER coronal rendering of the lungs at e) T1 and f) T3 displaying different parenchymal patterns (colour-coded). In g) and h) the glyphs provide summary of distribution for CT patterns in lung parenchyma at T1 and T3 in various colours (dark green: normal lung; light green: mild low-attenuation areas (LAAs); light blue: moderate LAAs; dark blue: severe LAAs). All, mild, moderate and severe LAAs increased from 65.2%, 58.4%, 3.4% and 3.4%, respectively, at T1 to 88.5%, 80%, 4.1% and 4.4%, respectively, at T3. LLZ: left lower zone; LMZ: left middle zone; LUZ: left upper zone; RLZ: right lower zone; RMZ: right middle zone; RUZ: right upper zone.

Densitometric and CALIPER texture features were evaluated in each of the four groups during the 2-year follow-up (table 4). Significant reduction of $Perc_{15}$ and increase of RA_{950}, all, mild, moderate and severe LAAs were found in persistent smokers, quitters and former smokers. An illustrative example of CT scans at T1 and T3 analysed using CALIPER is shown in figure 4. $Perc_{15}$, RA_{950}, all and mild LAAs changes were significantly higher in quitters than in persistent smokers or former smokers (for all tests: $p<0.001$). Conversely, in the group of restarters, a nonsignificant increase of $Perc_{15}$ and a reduction of RA_{950}, all, mild, moderate and severe LAAs were observed. VRS did not show significant change between T1 and T3 in all groups.

LAAs variation among pulmonary zones

In the groups of persistent and former smokers, a significant increment of all LAAs was observed in upper lung zones between T1 and T3; conversely in quitters, the progression of all LAAs resulted significant in all lung zones (table 5).

Discussion

CALIPER texture analysis has a well-established application in the assessment of interstitial lung disease [13, 15, 16, 32, 33] and combined pulmonary fibrosis and emphysema [34, 35], while only a few studies have investigated its utility in the evaluation of emphysema. CALIPER can identify and quantify three pulmonary patterns related to emphysema: mild, moderate and severe LAAs.

In a previous study, Jacob *et al.* [16] included the sum of moderate and severe emphysema in the CALIPER emphysema index, while mild LAAs were excluded because they did not correlate with visual emphysema extent score and with carbon monoxide transfer coefficient. Furthermore, at visual assessment, Jacob *et al.* [16] found that mild LAAs appear to encompass areas of centrilobular emphysema and normal lung, while moderate and severe LAAs correspond to discrete and conglomerate foci of emphysema [16].

https://doi.org/10.1183/13993003.02618-2021

TABLE 4 The 15th percentile of the attenuation curve ($Perc_{15}$), the relative areas ⩽−950 HU (RA_{950}), low-attenuation areas (LAAs) and vascular-related structures (VRS) at baseline (T1) and 2 years' follow-up (T3) in relation to subjects' smoking behaviour

	Persistent smokers				Quitters				Restarters				Former smokers			
	T1	T3	Δ	p-value	T1	T3	Δ	p-value	T1	T3	Δ	p-value	T1	T3	Δ	p-value
Subjects, n	142				42				7				93			
$Perc_{15}$, HU	−962 (−971–−951)	−965 (−974–−952)	−1 (−7–4)	**0.020**	−963 (−974–−950)	−976 (−983–−962)	−10 (−13.3–−5.3)	**<0.001**	−962 (−980–−954)	−951 (−963–−941)	9 (−6–21)	0.200	−980 (−990–−966)	−982 (−990–−973)	−2 (−7–3)	**0.003**
RA_{950}, %	19.5 (15.9–23.1)	20.6 (16.2–23.9)	0.5 (−1–2.9)	**0.006**	20 (15.8–23.6)	24.6 (19.4–27.6)	3.85 (2.57–5.2)	**<0.001**	19.3 (16.7–26)	15.9 (13.2–19.4)	−2 (−8.3–1)	0.237	25.4 (21–29.2)	26.8 (22.6–30)	1.1 (−0.75–3.2)	**0.002**
All LAAs, %	54.7 (31–77.2)	56.2 (33.8–80.2)	1.91 (−5.4–9.7)	**0.027**	60.4 (32.7–77.5)	80.1 (43–92.2)	10.6 (1.5–20.5)	**<0.001**	53.4 (27.4–80.6)	30.4 (18.7–50.1)	−8.2 (−45.1–3)	0.237	78.5 (59.2–93.4)	86.9 (58–95)	1.9 (−3.8–9.2)	**0.033**
Mild LAAs	53.8 (31–76.8)	54 (33.8–75.6)	1.5 (−5.9–9.4)	**0.050**	58.5 (32.7–73.7)	77.2 (43–90.1)	8.8 (0.6–20.1)	**<0.001**	53.2 (27.4–80.4)	30.4 (18.6–50)	−8.1 (−45.4–3)	0.237	75.9 (58.6–90.4)	85.3 (57.2–92.6)	1 (−3.5–10.3)	**0.038**
Moderate LAAs	0.03 (0.01–0.16)	0.05 (0.01–0.27)	0.007 (−0.001–0.08)	**<0.001**	0.05 (<0.01–0.46)	0.08 (0.01–0.88)	0.01 (−0.001–0.39)	**0.004**	0.03 (0–0.05)	0.01 (0–0.02)	−0.007 (−0.03–0)	0.225	0.06 (0.01–0.37)	0.09 (0.01–0.7)	0.01 (0–0.16)	**<0.001**
Severe LAAs	0.08 (0.03–0.25)	0.1 (0.03–0.32)	0.013 (−0.004–0.07)	**<0.001**	0.12 (0.03–0.66)	0.19 (0.13–0.6)	0.02 (−0.01–0.27)	**0.007**	0.05 (0.01–0.11)	0.04 (0.01–0.05)	−0.005 (−0.04–0)	0.063	0.11 (0.04–0.35)	0.15 (0.04–0.49)	0.02 (−0.005–0.12)	**<0.001**
VRS, %	1.83 (1.61–2.08)	1.83 (1.61–2.10)	−0.01 (−0.1–0.07)	0.206	1.76 (1.60–2.07)	1.78 (1.57–2.11)	−0.05 (−0.13–0.12)	0.378	2.01 (1.69–2.07)	1.90 (1.86–2.29)	−0.1 (−0.15–0.24)	0.735	1.81 (1.62–1.97)	1.75 (1.59–1.98)	−0.04 (−0.12–0.08)	0.116

Data are presented as median (interquartile range), unless otherwise stated. Bold type represents statistical significance.

TABLE 5 All low-attenuation areas (LAAs) at baseline (T1) and 2 years' follow-up (T3) per pulmonary zone in relation to subjects' smoking behaviour

	Persistent smokers				Restarters				Quitters				Former smokers			
	T1	T3	Δ	p-value	T1	T3	Δ	p-value	T1	T3	Δ	p-value	T1	T3	Δ	p-value
Subjects, n	142				7				42				93			
Upper zone all LAAs, %	15.1 (6–21.4)	16.2 (7.4–22.6)	**0.6 (−1.1–2.8)**	**0.003**	10 (4.1–27)	7 (3.4–14.4)	−6.4 (−87–0.7)	0.200	15.8 (8.4–22.7)	24.3 (12.6–27.6)	2.6 (0.8–6.9)	**<0.001**	22.9 (16.5–27.2)	24.4 (17.9–27.7)	1 (−0.4–2.9)	**<0.001**
Middle zone all LAAs, %	19.5 (10.2–28.2)	20 (11.4–30)	0.5 (−2.5–3.6)	0.087	18.8 (8.4–35.3)	11.2 (4–14.8)	−4.5 (−21.1–1)	0.128	22.1 (12.8–29)	30.1 (16–33.8)	4.5 (0.6–9.3)	**<0.001**	30.5 (22.3–35)	32.2 (21.6–36.1)	0.6 (−1.6–4.2)	0.070
Lower zone all LAAs, %	20.1 (12.3–27)	20.7 (11.7–29)	0.5 (−2.2–3.4)	0.171	17.7 (8.3–24.6)	12.7 (9.7–19.2)	−0.6 (−10.5–4.3)	0.499	22.6 (13.6–27.8)	25.4 (14.3–28.4)	1 (−0.5–5.8)	**0.009**	25.6 (16.8–30.2)	26.3 (17.7–30.7)	0.3 (−2.4–4.3)	0.251

Data are presented as median (interquartile range), unless otherwise stated. Bold type represents statistical significance.

In our study, we found significant correlations between the well-known densitometric indices of emphysema as $Perc_{15}$ and RA_{950} and mild, moderate, severe and all LAAs. The strongest associations were with all LAAs.

At baseline, CALIPER, like densitometric analysis, found a greater extent of emphysema indices (all LAAs and, in particular, mild LAAs) in the group of ex-smokers in comparison with the group of smokers. This result is consistent with previous studies, in particularly with the study of Zach *et al.* [36], showing that current smokers were characterised by lower quantitative CT measures of emphysema [9, 36, 37]. It has been suggested that cigarette smoking causes accumulation of inflammatory cells in the lung, and this soft tissue material may result in an increase of CT attenuation within individual voxels, resulting in a relative decrease of RA_{950} and all LAAs, and increase of $Perc_{15}$ in smokers [9, 10, 36, 38].

It is of note that mild LAAs, but not moderate and severe LAAs, were significantly higher in ex-smokers than in smokers, probably because this process of material accumulation is more evident in areas of early emphysema and normal lung, while it does not significantly affect the recognition by CALIPER of moderate and severe LAAs, which correspond to areas of discrete foci of emphysema.

Furthermore, in the longitudinal analysis, we found large differences in CT lung densitometric indices in relation to different smoking habits and, not surprisingly, large differences in CALIPER-derived LAAs too. In particular, a reduction of $Perc_{15}$ and a progression of RA_{950} and all LAAs were observed in persistent smokers, quitters and former smokers, with the most significant changes occurred in quitters. Conversely, the restarters presented a nonsignificant marginal reduction of emphysema indices. These results could be explained by expected parenchymal density changes related to the smoking habit, as previously proposed by Ashraf and co-workers [9, 10]. Indeed, current smoking habit *per se*, presumably because of soot and tar deposition or inflammation, can result in increased lung density irrespective of the presence or changes in emphysema extent or severity. The cessation of smoking allows for a reduction in anthracosis deposits and inflammation such as respiratory bronchiolitis in lung tissue and thereby a reduction of parenchymal density that is detectable in quitters. It is probable that this cleaning process is mainly detectable in the changes of mild LAAs, since the progression of this only type of LAAs was higher in quitters with respect to the other groups. In former smokers the greater LAAs extent, RA_{950} increase and lower $Perc_{15}$ could be due to progression of emphysema that does not entirely stop with smoking cessation due to the continuing improvement of inflammatory processes and reduction in smoking-related deposits. In addition, it may be that those areas with more severe inflammatory/cellular or debris accumulation in smokers with mild emphysema artefactually transition to “normal” CALIPER CT class in active smokers, and the mild LAA is more correctly classified in quitters or nonsmokers as the inflammation and debris is cleared.

Considering the different zonal changes of RA_{950}, $Perc_{15}$ and CALIPER LAAs, we found that persistent smokers and former smokers had a progression of densitometric indices and all LAAs in the upper zone, while in quitters, an increment of emphysema indices occurred in all zones. These results may be explained speculating that in quitters all lung zones are involved in a recent cleaning process of soot and tar which starts with smoking cessation, while in persistent smokers and former smokers this process does not significantly occur, and the emphysema increases in the upper lobes.

In our study we also found that VRS was moderately correlated with densitometric and CALIPER texture features of pulmonary emphysema. These results may be related to the destruction and remodelling of pulmonary vasculature secondary to emphysema [39] and they are concordant with those of Matsuoka *et al.* [40], who found that the cross-sectional areas of vessels <5 mm and 5–10 mm were negatively correlated to RA_{950}. It is noted that, while in the 2-year follow-up densitometric indices and LAAs suggested a progression of emphysema in persistent smokers, quitters and former smokers, VRS did not change in any group. It may be possible that the reduction of the vascular structure secondary to emphysema requires more time to be significant.

Limitations

The study sample was limited to subjects with a smoking history of ⩾20 pack-years in the past 10 years. Possibly, the inclusion of light-smokers and never-smokers might have allowed more complete assessment of the effect of smoking. Information on smoking habit was obtained by self-completed questionnaires without biochemical verification; however, this is the usual procedure in randomised lung cancer screening trials [41].

There was a small number of subjects in the group of restarters; in particular, we found a decrement of emphysema indices in the 2-year follow-up, but the results were not significant in these seven subjects.

Furthermore, CTs were performed with a low exposure dose which has a minimal effect on densitometric analysis of emphysema [25] and, in our experience, on CALIPER texture analysis, too. However, the LDCT technique was adopted in all the examinations, at both baseline and follow-up, and densitometric and CALIPER texture analyses were both performed on LDCT.

Despite the use of a four-row CT scanner in the study, we may expect concordant results with the CT scanner technology currently available, which is characterised by a better resolution and slice thickness and automatic dose modulation.

Since quantitative analysis of diffuse lung disease may be affected by different reconstruction kernels [42], we performed a preliminary smoothing procedure with a three-dimensional Gaussian filter to reduce the image noise.

Finally, CT measurements of lung volume and emphysema indices are affected by inspiration, which may show a variability between baseline and follow-up for the same subject. In order to limit this bias, subjects with lung volume difference >20% between baseline and follow-up were not included in the study.

Conclusions

CALIPER-detected LAAs have a strong correlation with densitometric indices of emphysema. At cross-sectional analysis at baseline, the extent of mild LAA is significantly lower in current smokers than in ex-smokers, presumably due to soot and tar deposition as well as inflammatory changes, which may result in an increased lung density in current smokers.

In the longitudinal analysis, we found large differences in CT lung densitometric indices and in CALIPER-derived LAAs in relation to change in smoking habits. In particular, a reduction of $Perc_{15}$ and a progression of RA_{950} and all LAAs were observed in persistent smokers, quitters and former smokers, with the most significant changes occurred in quitters.

It is encouraging that a texture-based tool can be used to evaluate features that have been previously proven to be useful analytics in COPD and has the additional ability to characterise other features such as pulmonary fibrosis and vascular-related structures. This suggests that a texture-based tool such as CALIPER might provide a more comprehensive parenchymal assessment and that the different qualitative features of involvement (mild, moderate, severe LAAs) might provide a more nuanced characterisation of both the extent and severity of the parenchymal features of disease.

Author contributions: C. Romei and R. Castellana take responsibility for the content of the manuscript, including the data and analysis. C. Romei and B. Bartholmai made substantial contribution to the study concept and design; R. Castellana was responsible for data analysis; C. Romei, R. Castellana, B. Conti, P. Bemi, A. Taliani, F. Pistelli, L. Carrozzi, R.A. Karwoski, A. De Liperi and B. Bartholmai were responsible for significant manuscript writing and/or critical revisions for important intellectual content. All the authors have read and approved the final version of the manuscript.

Conflict of interest: B. Bartholmai declares personal fees from Promedior, LLC, and from Imbio, LLC, outside the submitted work. Mayo Clinic has received grants from NIH/NHLBI, fees from Imbio, LLC, and Boehringer Ingelheim outside the submitted work. In addition, B. Bartholmai has a patent for Systems and Methods For Analyzing *In Vivo* Tissue Volumes Using Medical Imaging pending to Mayo Clinic. R.A. Karwoski declares personal fees from LLC, and from Imbio, LLC, outside the submitted work. The other authors of this manuscript declare no conflict of interest; the authors received no financial support for the research, authorship, and/or publication of this article.

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