

Performance of quantitative CT parameters in assessment of disease severity in COPD: A prospective study

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Abstract

Background: Both emphysematous destruction of lung parenchyma and airway remodeling is thought to contribute to airflow limitation in cases of chronic obstructive pulmonary disease (COPD). **Objective:** To evaluate the value of quantitative computed tomography (QCT) parameters of emphysema and airway disease with disease severity in patients with COPD. **Materials and Methods:** We prospectively studied 50 patients with COPD, which included nonsmokers and patients with different degrees of cumulative smoking exposure. Three QCT parameters namely LAA% (low attenuation area percentage), WA% (Wall area percentage), and pi10 were calculated as per the standard technique. Forced expiratory volume in 1 s (FEV1), BODE score, and MMRC dyspnea scale were used as measures of disease severity. **Results:** FEV1 was inversely and significantly associated with all three QCT parameters. Receiver operated characteristic curves in prediction of GOLD class 3 COPD yielded cut-off values of 12.2, 61.45, and 3.5 for LAA%, WA%, and pi10, respectively, with high sensitivities and specificities. In multiple linear regression model, however, only LAA% proved to be significantly associated with FEV1, BODE, and dyspnea. **Conclusion:** QCT indices of both emphysema and airway disease influence FEV1, dyspnea, and BODE score in patients with COPD. Emphysema, however, appears to be more closely related to disease severity.

Key words: Chronic obstructive pulmonary disease; LAA%; pi10; quantitative CT; WA%

Introduction

Chronic obstructive pulmonary disease (COPD) is a gradually progressive disorder characterized by irreversible or partially reversible airway obstruction.^[1] It is predicted to be the fifth leading cause of disability in the world by the year 2020.^[2] The accompanying histopathological changes that lead to air flow limitations appear to be a combination of varying degree of parenchymal destruction (emphysema), small and large airway changes (bronchiolitis and bronchitis), air

trapping on expiration, vascular alterations, and chest wall and diaphragmatic changes.^[3,4] High-resolution computed tomography (HRCT) allows detailed anatomical analysis of pulmonary structure, and hence, is currently widely used for the detection and characterization of COPD. HRCT has been used to define and categorize these patients into two predominant groups – those with emphysema-predominant disease and those with airway-predominant disease. The former group can be further subclassified based on the type

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Cite this article as: Kumar I, Verma A, Jain A, Agarwal SK. Performance of quantitative CT parameters in assessment of disease severity in COPD: A prospective study. Indian J Radiol Imaging 2018;28:99-106.

Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/ijri.IJRI_296_17

of emphysematous disease into centrilobular, panlobular, paraseptal, and bullous emphysema.^[5] Various researchers have shown that CT is of considerable value in quantifying the severity of the disease in COPD, either using visual or, more preferably, using quantitative CT techniques (QCT). The aim of this prospective study was to assess the relationship between the commonly used QCT parameters and commonly utilized clinical and spirometric measures of disease severity in patients with COPD.

Materials and Methods

Patients

This was a prospective observational study carried out at a tertiary-level, university-based teaching hospital over a period of two years. The study was approved by the institutional review board (IRB) at the outset and was carried out between 2013 and 2015. During this period, a total of 62 patients with a diagnosis of COPD [post-bronchodilator forced expiratory volume in 1 s to forced expiratory vital capacity ratio (FEV1/FVC) <0.7] were referred for CT scan of thorax for clinical assessment of disease pattern, disease severity, and to rule out malignancy. Out of these, 12 patients having giant emphysematous bulla, coexisting lung carcinoma, pulmonary nodule suspicious of malignancy, interstitial pneumonitis, pneumonia, and low attenuation lesions such as cavities or bronchiectasis on CT scan were excluded from the study. Fifty patients were included in this study and informed consent was obtained from all the patients.

Computed tomography scan and image analysis

CT scan was performed on 64-slice scanner (Lightspeed, GE medical systems, Milwaukee, Wisconsin) in a craniocaudal direction with breath-hold from the lung apices to lateral costophrenic sulci, with 1 mm slice thickness, 120 kVp, and 80–100 mAs. Patients having difficulty in breathing were coached and counselled prior to the scan and the scan was done after breath-hold practice.

Images were analyzed by two radiologists (IK and AV) in tandem. Three CT parameters, i.e. low attenuation area

percentage (LAA%), wall area percentage (WA%), and pi10 were calculated for each patient. For calculation of LAA%, density mask (−950 to −1024 HU) was applied using the MDCT workstation (Advantage Windows 4.4 software, GE Healthcare Medical Systems, Milwaukee, WI) [Figure 1].

Airway morphology of segmental airways were manually assessed at six areas (right upper, middle, and lower lobes, left upper, lower lobes, and lingular segments). Airways with maximal visually perceivable luminal narrowing were chosen by two radiologists in agreement. Multiplanar reconstruction was utilized to obtain true cross-sectional view of the bronchus in consideration and to ensure that measurements were taken perpendicular to the slide of scan. WA% ($100 \times \text{wall area}/\text{total bronchial area}$) was calculated for each of the chosen six segmental airways, and an average of the three lowest values of WA% was calculated [Figure 2].^[6,7]

The internal perimeter (Pi) of all six measured airway (with at least 6mm perimeter) was plotted along the x-axis against the square root of the wall area on y-axis. A straight-line relationship between these two indices was used to obtain a value (Pi10) of the square root of the wall area corresponding to an inner perimeter of 10 mm to predict the square root of the wall area for a hypothetical airway with Pi of 10 mm.^[8,9]

Spirometry and clinical parameters

Pulmonary function test was performed according to the American Thoracic Society (ATS) guidelines^[10] to evaluate FEV1, and percentage predicted FEV1 (here after referred to as FEV1%). Information about clinical outcome parameters was collected and documented. Dyspnea of each patient was categorized with the help of the modified medical research council (MMRC) dyspnea scale, which is a five-point scale ranging from grade 0 (dyspnea on strenuous exercise) to grade 4 (too dyspnic to leave the house).^[11] BMI obstruction dyspnea exercise (BODE) index was calculated for each patients using six-min walk distance, FEV1, BMI, and MMRC dyspnea scale.^[12]

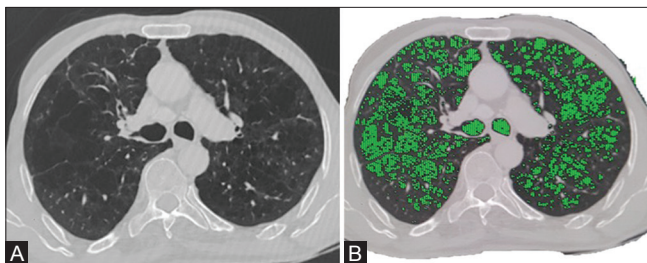


Figure 1 (A and B): (A) Axial CT image of a 65-year-old male with COPD shows multiple low attenuation areas with imperceptible wall in bilateral lung fields. (B) Axial CT image with application of density mask technique in the same lung fields as in (A). Total area with CT attenuation <950 HU are depicted in green. To quantify the LAA%, percentage of total lung field occupied by voxel with CT attenuation −950 HU or lower were calculated from CT data

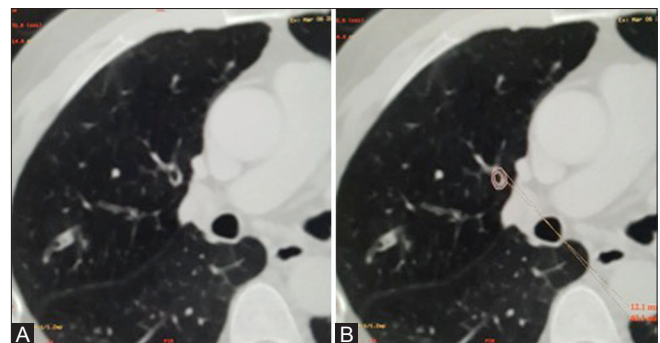


Figure 2 (A and B): (A) Axial CT image of the right middle lobe of a 65-year-old nonsmoker (GOLD stage 3) residing in the vicinity of coal mines. CT shows significant decrease of lumen area. (B) Axial oblique reformatted image showing calculation of WA% which is significantly decreased

Statistical methods

Data analysis was performed using SPSS software (IBM Corp 2013. Version 22.0. Armonk, NY). Scatter plots were drawn between FEV1 and QCT parameters, and fitted linear correlation lines were calculated for each CT parameter. Correlations between FEV1 and individual CT parameters were determined and quantified using Pearson’s correlation coefficients. $P < 0.05$ was considered as statistically significant correlation. Receiver-operated characteristic (ROC) curves were plotted for each CT parameters in the prediction of FEV1 <50% as well as MMRC dyspnea grade >2, and cut-off values were calculated for these outcomes. Multiple linear regression analysis was performed to examine the relationship between the clinical outcomes such as FEV1, MMRC dyspnea score, and BODE index as response variables, and the quantitative CT parameters such as LAA%, WA%, and pi10 as explanatory variables.

Results

Out of the total 50 patients, 27 were classified as moderate-to-heavy smokers (>20 pack years), 8 patients were mild or light smokers (0.1 to 20 pack years), and 15 were classified as never-smokers (0 pack years) based on the history of cigarette smoking. Out of 15 patients with no history of cigarette smoking, 7 patients had been exposed to biomass fuel and 8 had absolutely no history of any kind of smoking.

We found good overall correlation between FEV1 and QCT parameters, i.e. LAA [Figure 3A], WA% [Figure 3B], and

pi10 [Figure 3C]. Table 1 lists the Pearson’s correlation coefficient of individual groups with different degrees of smoking exposures, comparing the three QCT parameters to FEV1. All the parameters showed an inverse relationship with the FEV1. Of the three, LAA% showed the best correlation with FEV1 ($r = -0.58$) for the whole sample. WA% and pi10 also showed statistically significant correlation with r values of -0.38 and -0.35 , respectively. Among individual groups, statistically significant correlation was obtained between FEV1 with LAA% and pi10 in the never-smokers. Correlation with WA% was, however, not significant in this group. Table 2 summarizes the mean values of LAA%, WA%, and pi10 in individual groups. One-way analysis of variance showed that there was significant difference in the means of all the three parameters between the individual groups with different smoking exposure.

Figure 4 shows ROC curve of three quantitative CT parameters in the prediction of FEV1 <50% (GOLD stage 3). Of the three imaging parameters, LAA showed the highest area under the curve of 0.75. LAA of 12.2 had 76.5% sensitivity and 72.7% specificity in the prediction of FEV1 <50%. Table 3 shows the area under the ROC curve of the three parameters in predicting FEV1 <50%, their cut-off values, and corresponding sensitivities and specificities.

Figure 5 depicts ROC curve of three quantitative CT parameters in the prediction of MMRC dyspnea score of 3 or more. Of the three imaging parameters, LAA showed the highest area under the curve of 0.88. LAA of 14.4 had

Table 1: Respective correlation of LAA%, WA%, pi10 with FEV1 in individual groups of patients with different cumulative smoking exposures

Smoking	Pearson correlation LAA	P	Pearson correlation WA%	P	Pearson correlation Pi10	P
Absent (n=8)	-0.862	0.006	-0.444	0.27	-0.766	0.027
Biomass (n=7)	-0.218	0.639	0.061	0.89	-0.317	0.488
Mild (n=8)	-0.232	0.581	-0.037	0.93	-0.147	0.72
Heavy (n=27)	-0.159	0.43	-0.133	0.51	0.096	0.63
Total (n=50)	-0.58	<.01	-0.382	0.006	-0.354	0.012

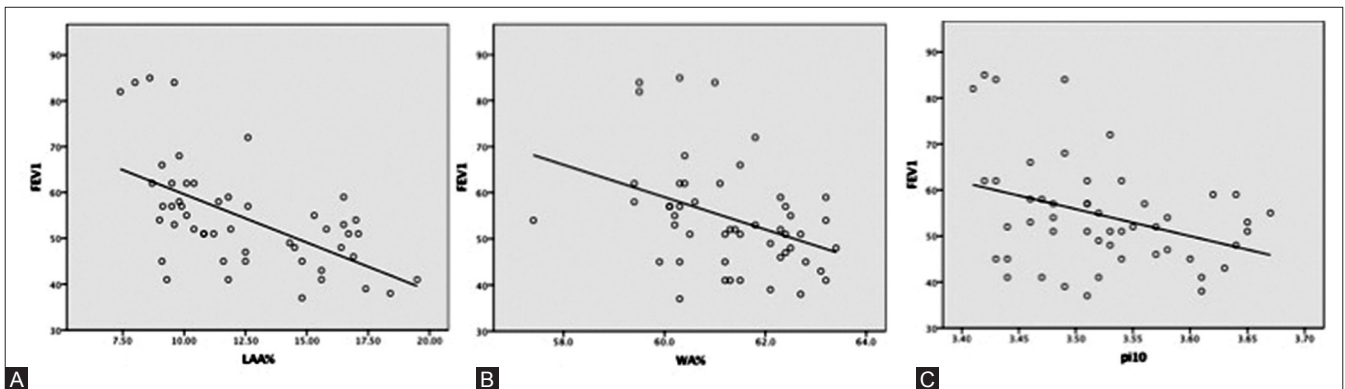


Figure 3 (A-C): Scatter plot of FEV1 to COPD assessed by CT, defined as percentage of LAA% (A), wall area % (B), and pi10 (C) in 50 patients with COPD

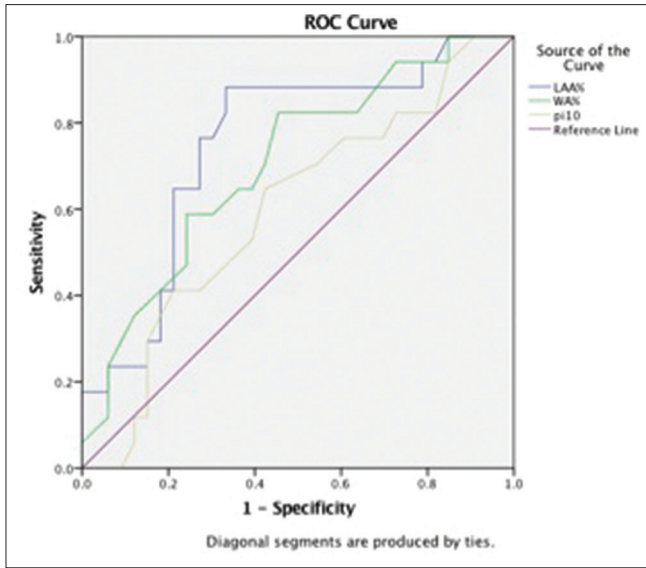


Figure 4: ROC curve of three quantitative CT parameters in prediction of FEV1 <50%

87.55% sensitivity and 91.2% specificity in prediction of the same. Table 4 shows the area under ROC curve of the three parameters in predicting MMRC dyspnea score of 3 or more, their cut-off values, and corresponding sensitivities and specificities.

Further analysis of the relationship between QCT parameters and clinical outcomes was done by multiple linear regression analysis which showed that LAA% was constantly and negatively associated with FEV1 in patients with COPD [Table 5]. Changes in LAA% could explain 32.3% change in FEV1, 80.5% change in BODE, and 61.5% changes in MMRC dyspnea score. Addition of airway variables (WA% and pi10) to low attenuation area measures in multiple regression model did not account for greater proportion of variation in FEV1, BODE, and MMRC dyspnea score [Table 5].

Discussion

Various techniques such as spirometry, diffusing capacity for carbon monoxide (DLCO), and CT scan are currently used to diagnose and assess disease severity of COPD. Of these techniques, spirometry and DLCO cannot distinguish between the relevant anatomical and pathological changes in these patients.^[13] Studies have shown that QCT can be used as a reliable and reproducible technique to interrogate various underlying pathological processes in COPD. Based on the predominant changes identified on CT, COPD has been categorized between emphysema-predominant and airway-predominant subtype.^[3,4] This distinction is therapeutically important because COPD with predominant airway disease is more likely to respond to medical treatment whereas those with emphysema-prominence should undergo volume reduction surgery.^[14]

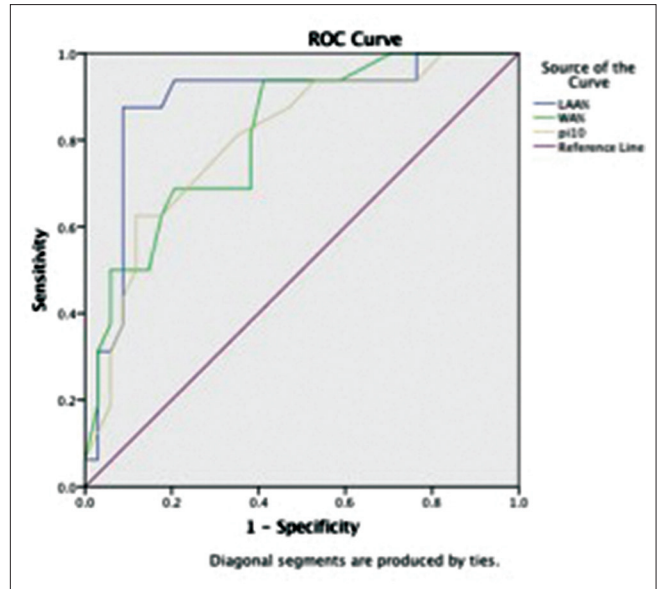


Figure 5: ROC curve of three quantitative CT parameters in prediction of MMRC dyspnea score of 3 or more

Table 2: Mean values of QCT parameters in patients with different cumulative smoking exposures

Smoking exposure	LAA%	WA%	Pi10
Absent (n=8)	9.26	60.31	3.47
Biomass (n=7)	10.40	61.08	3.49
Mild (n=8)	10.31	60.67	3.52
Heavy (n=27)	14.52	61.81	3.54
Total (n=50)	12.43	61.29	3.52
P	<0.001	0.007	0.06

Table 3: Area under ROC curve of the three parameters in predicting FEV1 <50% (GOLD stage 3), their cut-off values, and corresponding sensitivities and specificities

CT parameter	AUC	Cut-off value	Sensitivity	Specificity
LAA%	0.750	12.20	76.5	72.7
WA%	0.705	61.45	64.5	63.6
pi10	0.597	3.5	64.7	57.6

Table 4: Area under ROC curve of the three parameters in predicting MMRC dyspnea score of 3 or more, their cut-off values, and corresponding sensitivities and specificities

CT parameter	AUC	Cut-off value	Sensitivity	Specificity
LAA%	0.884	14.4	87.5	91.2
WA%	0.814	61.2	81.3	61.8
pi10	0.801	3.52	75	70.6

Emphysema is defined by the American thoracic society as permanent, abnormal enlargement of the airspaces distal to the terminal bronchioles along with destruction of the alveolar walls.^[15] The airflow limitation in patients with emphysema can be attributed to decrease in elastic recoil, airway collapse during expiration, and air trapping.^[16,17] However, according to some studies,

Table 5: Multiple linear regression models for QCT parameters in predicting forced expiratory volume in 1 second (FEV1), BODE, score and MMRC dyspnea scale

Dependent variable	Predictors	Adjusted R ²	ANOVA		Coefficients					
			F	Sig (P)	LAA%		WA%		Pi10	
					B	Sig	B	Sig	B	Sig
FEV1	LAA, WA%, pi10	0.301	8.05	0.000	-2.398	0.001	-0.198	0.904	21.870	0.479
FEV1	LAA%	0.323	24.34	0.000	-2.109	0.000	-	-	-	-
BODE	LAA, WA%, pi10	0.798	65.555	0.000	0.293	0.000	0.044	0.590	-0.188	0.902
BODE	LAA%	0.805	203.555	0.000	0.302	0.000	-	-	-	-
MMRC	LAA, WA%, pi10	0.601	25.551	0.000	0.168	0.000	0.025	0.744	0.222	0.878
MMRC	LAA%	0.615	79.435	0.000	0.178	0.000	-	-	-	-

owing to other contributory factors, the severity of airflow limitation does not always correlate with the extent of emphysema.^[18,19]

Quantification of emphysema on CT scan has been done following three common approaches. Most common among these techniques is “density mask technique” which uses a threshold value below which emphysema is said to be present. The second commonly used method is the analysis of frequency distribution or histogram of lung densities in a given slice. In this technique, a preselected range of densities is described as emphysematous (currently, the lowest 15th percentile is recommended as the optimal threshold for emphysematous tissue).^[20,21] Another less commonly used approach described in the literature is calculation of “mean lung density (MLD)” obtained through computer-assisted volumetric technique.^[5] Of these three techniques, density mask technique has been most commonly used by investigators. Various investigators have used different thresholds for characterization of a tissue as emphysematous. Muller *et al.* were the first to describe this technique with pathological validation using a threshold value of -910 HU.^[22] Various researchers have used this method advocating different threshold, however, a value of -950 has been most commonly recommended for quantitative CT evaluation of emphysema.^[23,24] Some investigators have suggested that D-value (slope of log-log plot of representative cumulative frequency of LAA%) is a more sensitive method for detecting early emphysema.^[25] It is imperative to note that, besides the threshold HU value, a number of technical factors also influence the quantitative assessment such as slice thickness, tube current, reconstruction algorithm, use of contrast media, window setting, and type of scanner used.^[5,26,27]

In addition to emphysematous changes in lung parenchyma, airway remodeling is another extremely important contributor in COPD. The mechanism of airflow limitation include increased mucus secretion, epithelial hyperplasia, and smooth muscle hypertrophy which in combination cause luminal stenosis.^[14,28] Studies have shown that airways with a diameter of 2 mm or less are the usual site of air flow resistance in these patients.^[13] CT has been used to quantify

airway changes in COPD, however, reliable measurements of airway parameters have been difficult to obtain compared to the quantitative parameters for emphysematous changes. The present literature suggests two approaches for quantification of airway changes in COPD. The first approach uses paired inspiratory and expiratory CT calculations allowing indirect estimate of obstructive air trapping.^[29-31] A study by Eda *et al.* showed a statistically significant correlation between expiratory-inspiratory attenuation ratio and FEV1.^[32] However, an important criticism of this approach is the presence of coexisting emphysema in these patients which might act as a confounding factor.^[14,33] The second approach for airway changes is the direct measurement of lumen and airway wall visualized on CT. The advent of state of the art modern scanners have enabled us to obtain increasingly thinner sections, and a more accurate calculation of distal airway (up to 3rd to 5th generation airway). Studies have shown that calculations of 3rd to 5th generation airway might act as a surrogate for changes further distally.^[9,34] Nakano *et al.* first showed that WA% calculated as wall area/(lumen area + wall area) ×100, correlated with FEV1 and FVC.^[35] Subsequent study by Nakano *et al.* showed a correlation between CT measured WA% and histologically measured wall area.^[9] Hasegawa *et al.* compared WA% and luminal area (LA) values of proximal and distal airway in the prediction of FEV1 and obtained a closer correlation for distal airway values.^[36] Another commonly used QCT measurement that has been suggested for airway measurement is pi10 which represents square root of wall area of a hypothetical airway with an internal perimeter of 10 mm (Pi10).^[7] Pi10 has been suggested as a more standard measure of airway remodeling as it adjusted for lumen area, which can be an important confounding factor in determining airflow resistance.^[37]

In addition to emphysema and airway changes, few researchers have evaluated vascular and diaphragmatic changes to evaluate and quantify changes in COPD. Severe COPD results into luminal narrowing and reduction of small pulmonary artery.^[38] Matsuoka *et al.* have demonstrated a correlation between pulmonary artery cross-sectional area and emphysema.^[33] A study by Jang *et al.* has evaluated

decrease in pulmonary perfusion by dynamic MRI.^[39] Other researchers have evaluated diaphragmatic length and diaphragmatic area to assess disease severity.^[40,41]

Table 6 summarizes the results of prominent studies showing the performance of QCT parameters in the prediction of disease severity in COPD. These studies show that both emphysema measurements (LAA%) and airway parameters (WA% and pi10) significantly correlate with disease severity, however, emphysema appears to be more closely related to various clinical parameters. Martinez *et al.* showed that airway disease is more closely associated with higher SGRQ scores whereas emphysema appears to be more closely associated with BODE.^[7] Grydeland *et al.* reported that pi10 and emphysema were related to dyspnea, but only pi10 was associated with cough and wheeze.^[46] Diaz *et al.* inferred that emphysema, more than airway remodeling of the disease, may be responsible for the effect on the reduction of 6MWD.^[13]

Similar to previous studies we found a better inverse correlation between FEV1 and LAA% compared to airway measures. It was interesting to note that analysis of the individual groups with different level of smoking exposure both emphysema (LAA) and airway measurements (pi10) correlated significantly only in non-smokers. We also noted that while mean LAA and WA% of patients with exposure to biomass fuel was higher than that of patients with history of mild tobacco smoking, whereas pi10 was marginally lower. Pathophysiology in patients with non-smoking COPD patients is complex and poorly understood. Ozbay *et al.* studied 30 patients of COPD with no history of smoking and women exposed to biomass fuel and found that, besides emphysema, other HRCT features such as lung hyperinflation, thickened interlobular septations, and vascular changes were common in these patients.^[47]

Sasaki *et al.* studied 32 patients and concluded that a cut-off value of 1.51 for WA% ratio of 5th to 1st generation airway was able to predict GOLD class 3 or 4 severity in COPD with a sensitivity of 83% and specificity of 89%.^[44] In the present study, ROC curves of airway parameters yielded cut-off value of 61.5 and 3.5 for WA% and pi10, respectively, in the prediction of GOLD class 3 or 4 and similar values for MMRC dyspnea score of 3 or more. The sensitivities and specificities, however, were much higher in predicting dyspnea compared to the spirometric values. On extensive literature search, we could not find clearly defined cut-off values of QCT parameters to predict severity of COPD, which might be a useful value for interpreting radiologists and clinicians. In the present study, LAA% cut-off value of 12.2 and 14.4 were determined by ROC curve for FEV1 and MMRC dyspnea scores, respectively. Multiple linear regression analysis between QCT parameters showed that inclusion of emphysema and airway variables in the model explains on 30.1% variability in FEV1%. QCT performance is significantly better in explaining variations in MMRC dyspnea scale and BODE score ($r^2 = 60.1\%$ and 79.8% , respectively). However, contributions from the airway measurement in this model was nonsignificant and that removal of WA% and pi10 from the model accounted for greater proportion of variation in FEV1, BODE, and MMRC dyspnea score (32.3%, 61.5%, 80.5%, respectively). The adjusted r^2 values in the present study to explain FEV1 variability was significantly lower than that by Schroeder *et al.* who obtained an R^2 value of nearly 72%.^[45] However, Schroeder *et al.* used both LAA-865 and LAA-950 for emphysema calculations, which might lead to higher sensitivity in emphysema detection. He obtained a further accentuation in R^2 value on adding airway measures to the model in contrast to our study. In analyzing clinical outcomes (BODE and MMRC), our study concurred with findings of Diaz *et al.* who concluded that QCT measurements

Table 6: Summary of previous studies showing the performance of Quantitative CT parameters in prediction of disease severity in COPD

Study	Number of patients	Outcome	Significant variable	Insignificant variable	Statistical method	Result
Lee <i>et al.</i> ^[42]	34	6MWD	%LAA-950		Pearson correlation	$R = -0.53$
		MMRC	CT ATI			$R = 0.53$
		BODE	MLD			$R = -.76$
		BMI	WA%			$R = 0.56$
Mair <i>et al.</i> ^[43]	129	FEV1	%LAA-950		Multiple linear regression	$R^2 = 0.33$
Diaz <i>et al.</i> ^[13]	93	6MWD	%LAA	WA%	Multiple linear regression	$R^2 Z = 0.29$
Grydeland <i>et al.</i> ^[34]	288	DLCO	%LAA		Multiple linear regression	$R^2 = 0.65$
		DLCO	Pi10			$R^2 = 0.49$
Martinez <i>et al.</i> ^[7]	1200	BODE	LAA, WA%, Pi10	Segmental Wall thickness (WT)	Univariate association	$P < 0.001$
		SGRQ	LAA, WA%, Pi10, WT		Univariate association	$P < 0.05$
Sasaki <i>et al.</i> ^[44]	32	FEV1 < 50%	Ratios of peripheral-to-central airway Lumen area (Fifth to first)		ROC curve	AUC = 0.821
		FEV1 < 50%	Ratios of peripheral-to-central airway WA%		ROC curve	AUC = 0.885
Schroeder <i>et al.</i> ^[45]	4062	FEV1	LAA ₉₅₀ , LAA ₈₆₅ , inner diameter, airway wall thickness, and Pi10	Outer area, inner area, inner perimeter	Multiple linear regression	$r^2 = 0.72$

SGRQ: St. George's Respiratory Questionnaire

of emphysema and not airway disease correlated with clinical severity (assessed by 6MWD).^[13]

It should be noted that most of the studies in the given literature are retrospective in nature. The strength of our study is its prospective nature aimed to better understand the predictive value of radiologic indices. Moreover, the cohort included in our study consisted of cases with a history of no smoking, mild smoking, heavy smoking, and exposure to biogas. Furthermore, we analyzed the predictive value of radiological parameters with spirometric values as well as composite indices such as the MMRC dyspnea score and BODE. We tried to eliminate the confounding factors by excluding cases with lesions suspicious for malignancy. Another important strength of our study was the utilization of volumetric scanning technique rather than slice gap CT technique used in most previous studies. In this study, we were able to derive cut-off values for various QCT parameters with considerable diagnostic accuracy, an important information for radiologists and clinicians while evaluating these cases.

We realize that there are many limitations of this study. First, the number of patients included in this study was relatively small, especially, non tobacco smokers and those with biomass fuel exposure. Also, we could not quantify the smoking exposure in the group with indoor biomass fuel exposure, which can cause errors in statistical calculations. Second, the two radiologists did not assess the cases separately and we could not assess interobserver agreement. This was more important, especially because subjective selection of airways with maximal visually perceptible luminal stenosis was chosen in six segments. Third, we used manual segmentation for airway measurements owing to nonavailability of automated segmentation and processing softwares in our Institute. However, most centers in the current practice do not have these softwares and a meticulous evaluation of the images, as done in the present study, might obviate the need for these expensive softwares and could be more useful for widespread clinical utilization of QCT.

To conclude, our study demonstrates that the QCT indices of both emphysema (LAA%) and airway disease (WA% and pi10) influence FEV1, MMRC dyspnea scale, and BODE score. Emphysema, however, appears to be more closely related to disease severity in COPD, both in terms of spirometric measures (FEV1) and clinical severity (MMRC dyspnea scale and BODE).

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

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