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Prediction of Treatment Response in Patients with Chronic Obstructive Pulmonary Disease by Determination of Airway Dimensions with Baseline Computed Tomography

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Objective: To determine the predictive factors for treatment responsiveness in patients with chronic obstructive pulmonary disease (COPD) at 1-year follow-up by performing quantitative analyses of baseline CT scans.
Materials and Methods: COPD patients (n = 226; 212 men, 14 women) were recruited from the Korean Obstructive Lung Disease cohort. Patients received a combination of inhaled long-acting beta-agonists and corticosteroids twice daily for 3 months and subsequently received medications according to the practicing clinician's decision. The emphysema index, air-trapping indices, and airway parameter (Pi10), calculated using both full-width-half-maximum and integral-based half-band (IBHB) methods, were obtained with baseline CT scans. Clinically meaningful treatment response was defined as an absolute increase of $\geq$ 0.225 L in the forced expiratory volume in 1 second (FEV_1) at the one-year follow-up. Multivariate logistic regression analysis was performed to investigate the predictors of an increase in FEV_1, and receiver operating characteristic (ROC) analysis was performed to evaluate the performance of the suggested models.
Results: Treatment response was noted in 47 patients (20.8%). The mean FEV_1 increase in responders was 0.36 ± 0.10 L. On univariate analysis, the air-trapping index (ATI) obtained by the subtraction method, ATI of the emphysematous area, and IBHB-measured Pi10 parameter differed significantly between treatment responders and non-responders (p = 0.048, 0.042, and 0.002, respectively). Multivariate analysis revealed that the IBHB-measured Pi10 was the only independent variable predictive of an FEV_1 increase (p = 0.003). The adjusted odds ratio was 1.787 (95% confidence interval: 1.220–2.619). The area under the ROC curve was 0.641.
Conclusion: Measurement of standardized airway dimensions on baseline CT by using a recently validated quantification method can predict treatment responsiveness in COPD patients.
Keywords: *Chronic obstructive pulmonary disease; Computed tomography; Quantification; Forced expiratory volume in 1 s; Treatment response; Airway*

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by the presence of airflow limitation that is not fully reversible (1). It is a heterogeneous disease with a long clinical course associated with pulmonary structural changes, including parenchymal destruction and reduction in the caliber of the small airways (2).

Due to the heterogeneity in the composition and progression of emphysema and airway inflammation, evaluation of treatment response remains a challenge. Several methods have been developed to predict the outcome of COPD; the pulmonary function test (PFT), particularly the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) values, is undoubtedly the most widely used outcome variable thus far. However, these tests are highly effort-dependent, cannot distinguish if the airflow limitation is due to emphysema or airway inflammation, and are inadequate as the sole procedure for risk assessment of some adverse events, such as acute exacerbation (3). Quality of life indices have been validated to be sensitive to changes resulting from events such as acute exacerbation of COPD, but these assessments are time-consuming, subjective, and measure merely some aspects of health status (4). CT can separately quantify emphysema, airway dimensions, and air trapping (5-7) in a single breath hold, with the potential to aid in the process of identifying their relative contribution to the disease process. According to Han et al. (8), the results of a quantitative CT assessment significantly correlate with the COPD exacerbation frequency independent of the severity of airflow limitation. However, to date, few studies have used this approach to assess clinical response after treatment. Since the treatment targets airway disease rather than emphysema, the recently introduced "square root of airway wall area of the theoretical airway with an internal perimeter of 10 mm (Pi10)," a standardized measure of airway wall thickness (9, 10), and air-trapping measurement using the co-registration method, may possibly provide an accurate assessment of the status of small-airway disease.

We hypothesized that quantitative CT methods, including the aforementioned, recently emerging techniques, have the potential to predict clinical improvement in patients with COPD, which would be important for planning adequate personalized management strategies. Therefore, we aimed to determine the predictive factors for treatment responsiveness in patients with COPD after a 1-year follow-up using quantitative analytic techniques at baseline CT.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of our center, which waived the requirement for patients' informed consent (approval number: 2015-1164).

Study Population

All participants were selected from the Korean Obstructive Lung Disease cohort (11); this cohort included patients with COPD prospectively recruited from 17 hospitals in South Korea between June 2005 and October 2013. The inclusion criteria in this study were as follows: 1) diagnosis of COPD in accordance with the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria (1); 2) availability of baseline CT scans; and 3) availability of PFT results at baseline and after 1 year of follow-up. The exclusion criteria were as follows: 1) any current diagnosis of other respiratory conditions, including asthma; 2) insufficient washout period for the prescribed COPD medication with a possible risk of carryover; and 3) suboptimal image quality or severe post-infectious sequelae or large bullae. On the basis of these criteria, 226 patients (212 men and 14 women; mean age, 65.0 ± 7.4 years) were included (Fig. 1). Baseline characteristics of the study population are presented in Table 1.

With regard to the treatment interval, patients were treated twice daily for 3 months with a combination of long-acting beta-agonists and corticosteroids (long-acting beta-agonists, salmeterol [50 μg] or formoterol [9 μg]; corticosteroids, fluticasone propionate [500 μg] or budesonide [320 μg]). Baseline clinical data were obtained after discontinuation of inhaled corticosteroids for 2 weeks, inhaled long-acting beta-agonists for 2 days, and
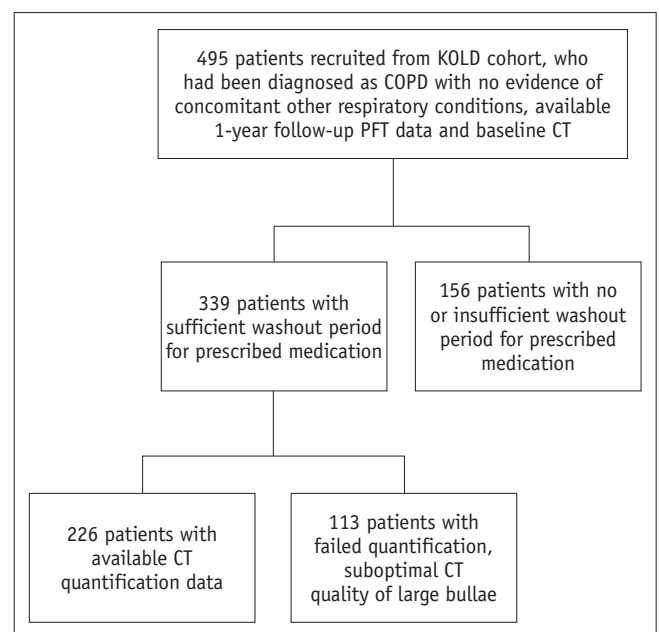
Fig. 1. Flowchart of study population. COPD = chronic obstructive pulmonary disease, KOLD = Korean Obstructive Lung Disease, PFT = pulmonary function test

inhaled short-acting beta-agonists for 12 hours. Patients were treated with a salmeterol/fluticasone propionate powder inhaler twice per day for 3 months, and during this period, only salbutamol was allowed additionally as needed. Subsequently, all patients continued to receive their prescribed medications according to the practicing clinician's decision.

Table 1. Baseline Characteristics of 226 Patients with COPD

Variables	Mean ± SD
Age (years)	
All patients	65.0 ± 7.4 (44–82)
Male patients	65.0 ± 7.4 (44–82)
Female patients	63.9 ± 7.2 (49–73)
Male:female	212:14
BMI (kg/m^2)	23.7 ± 3.2 (14.0–33.7)
Smoking history (PY)	45.0 ± 29.1 (0.8–177)
GOLD stage (n)	
I	25
II	121
III	66
IV	14

Unless otherwise noted, data are means ± SD, with ranges in parentheses. BMI = body mass index, COPD = chronic obstructive pulmonary disease, GOLD = Global initiative for chronic Obstructive Lung Disease, PY = pack-years, SD = standard deviation

Physiologic Data

All baseline PFTs were performed within 1 month before or after CT scanning. Follow-up PFTs were performed 12 months after the baseline PFTs. Spirometry was conducted using a Vmax 22 system (SensorMedics, Yorba Linda, CA, USA) or a PFDX machine (MedGraphics, St. Paul, MN, USA) and according to the guidelines of the American Thoracic Society and European Respiratory Society (12). Values were obtained for FEV_1, FVC, FEV_1/FVC, mean forced expiratory flow between 25% and 75% of FVC, diffusing capacity of the lung for carbon monoxide, and 6-minute walk distance (6MWD, measured in meters). Results (apart from FEV_1/FVC and 6MWD) were expressed as percentages of normal predicted values. Clinically significant improvement in lung function (treatment response) was defined as an increase of > 0.225 L in FEV_1 from baseline to follow-up PFTs (13, 14).

CT Acquisition and Analysis

All CT scans were acquired at full inspiration or expiration with patients in the supine position. Several different scanners were used (Sensation 16; Somatom Definition, Definition AS+, and Somatom Definition flash; all from Siemens Medical Solutions, Erlangen, Germany). Scan parameters were as follows: tube voltage, 140 kVp; effective tube current, 100 mAs; collimation, 0.75 mm; slice

Fig. 2. Measurement of standardized small-airway dimensions. Commercial software (Aview, Coreline Soft) automatically segments airways and detects airway level, lumens, and inner and outer boundaries of airway walls. After selecting most properly measured airways, software shows Pi10 with two different measurement algorithms (full-width-half-maximum and IBHB algorithms). IBHB = integral-based half-band, Pi10 = square root of airway wall area of theoretical airway with internal perimeter of 10 mm

thickness, 0.75 mm; and pitch, 1.0. The acquired data were reconstructed using the B30f kernel.

Whole-lung images were evaluated using commercial software (Aview; Coreline Soft, Seoul, Korea) to automatically reduce inconsistencies and accurately determine disease progression. From the CT data, the emphysema index (EI, defined as the lung volume fraction of < -950 Hounsfield unit [HU] on inspiratory CT scans) (5-7) was calculated. Airway measurements were conducted in a semi-automated fashion on a workstation (Fig. 2). A standardized measure for airway wall thickness was derived for each patient by obtaining the Pi10, the square root of the wall area of the theoretical airway with an internal perimeter of 10 mm (9). To obtain the Pi10, after plotting the square root of the wall area of the internal perimeters of multiple airways at different locations, the resulting regression line was used to calculate the square root of the wall area for a theoretical airway with an internal perimeter of 10 mm. We obtained the Pi10 value by plotting the obtainable values of the internal perimeter and the square root of the wall area of the 5th–8th branch of the segmental bronchi in all segments of both lungs (Fig. 3). The software automatically detected airway lumens, magnified the images 10-fold, and detected the inner and outer boundaries of airway walls by using two different measurement algorithms: full-width-half-maximum (FWHM) and integral-based half-band (IBHB). In the FWHM method, the inner and outer edges of the airway wall were defined as being halfway to the maximum HU from the lumen toward the airway wall and halfway to the minimum HU from the airway wall toward the outer parenchyma in the attenuation
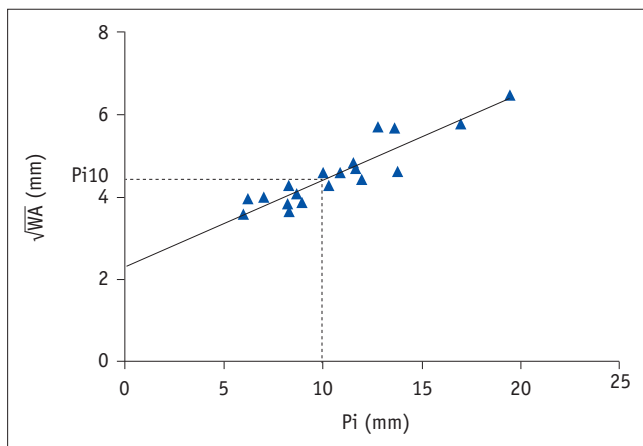
profile, respectively, from the radiating linear rays starting from the luminal center-point through the airway wall. The airway wall thicknesses were then calculated. In the IBHB method, after the initial circular rays (initial bands) were identified along lumen boundaries with a 50-HU threshold, larger circular rays were generated one after another through the airway wall. The circular rays showing the maximum HU were identified as the peak band, and half-wall thicknesses were measured using the integration of the initial and peak bands. The half-wall thickness was then doubled for the final measurement of airway wall thickness. Details of the airway measurement algorithms for the IBHB method have been described previously (15).

To assess the airway-trapping area, the software co-registered inspiration and expiration CT images using a non-rigid method that deformed expiratory images to match inspiratory images at a pixel level. After co-registration, the airway-trapping index (ATI) was calculated by three methods: 1) calculating the volume wherein HU is lower than -856 HU on the expiratory CT scan only (ATI_-856); 2) dividing the lung volume into four sections with two HU thresholds (-950 HU on the inspiratory CT scan and -856 HU on the expiratory CT scan) and then subtracting the volume wherein HU is lower than -950 HU on the inspiratory CT scan from the area in which HU is lower than -856 HU on the expiratory CT scan (ATI_subtraction_1) (16); and 3) measuring the volume wherein the differences for each voxel between inspiratory and expiratory CT scans were less than 60 HU (ATI_subtraction_2) and subsequently dividing it according to the attenuation on the inspiration CT for emphysema (< -950 HU; ATI_emphysema), hyperinflated lung (-950 HU to -900 HU; ATI_hyperinflated), and normal lung (-899 HU to -400 HU; ATI_normal) (17, 18).

Statistical Analysis

To investigate the predictors of an increase in FEV_1, Pearson's chi-squared test and Fisher's exact test were used for categorical variables, and an independent-sample t test was used for continuous variables. Variables associated with a p value of < 0.1 on univariate analysis were used as input variables for multivariate logistic regression analysis with a backward stepwise selection mode and iterative entry of variables based on test results. Removal of variables was based on likelihood-ratio statistics with a probability of 0.1. Receiver operating characteristic (ROC) analysis was performed to evaluate the performance of the multiple logistic regression models.

Fig. 3. Calculation of Pi10. Square root of wall area of each measured airway ($\sqrt{WA}$) was plotted against Pi of that airway. From regression line, standardized measure of airway wall thickness was predicted with Pi of 10 mm. Pi = internal perimeter

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation. A p value < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Comparisons between Treatment Responders and Non-Responders

Compared with baseline, an increase of > 0.225 L in FEV_1 was seen in 47 patients (20.8%). The average FEV_1 changes in the responder and non-responder groups were 0.36 ± 0.10 L (range, 0.23–0.68 L) and -0.02 ± 0.15 L (range, -0.46–

0.22 L), respectively.

Among the demographic measures and initial PFT parameters, no clinical parameter showed a significant difference between the responder and non-responder groups. Body mass index (BMI) showed marginal significance (p = 0.09). As for smoking, the correlation between smoking pack-years and Pi10 values showed no statistical significance ($p \geq 0.29$). In addition, smoking history in pack-years was not significantly different between treatment responders and non-responders (p = 0.186).

With respect to CT quantitative parameters, ATI_ subtraction_1, ATI_emphysema, and Pi10-IBHB were associated with significant intergroup differences (p =

Table 2. Comparisons between Treatment-Response and Non-Response Groups

	Response Group (n = 47)	Non-Response Group (n = 179)	P
Demographics			
Age (years)	64.3 ± 7.1	65.2 ± 7.5	0.509*
Male:female	45:2	167:12	0.375[†]
BMI (kg/m²)	24.37 ± 3.37	23.49 ± 3.09	0.092*
PY	50.04 ± 28.03	43.62 ± 29.27	0.186*
GOLD stage (n)			0.855[†]
I	5	20	
II	26	95	
III	14	52	
IV	2	12	
Initial PFT			
FEV_1 (%)	61.6 ± 16.7	65.6 ± 19.1	0.200*
FVC (%)	91.4 ± 16.8	92.8 ± 19.0	0.632*
FEV_1/FVC	48.9 ± 11.5	50.5 ± 11.8	0.393*
FEF_{25-75} (%)	23.6 ± 12.2	28.7 ± 16.5	0.487*
TLC (%)	110.3 ± 23.0	107.1 ± 23.8	0.425*
VC (%)	89.4 ± 17.0	93.8 ± 23.3	0.229*
RV (%)	134.5 ± 58.3	120.8 ± 63.3	0.194*
DL_{CO} (%)	83.9 ± 21.8	82.9 ± 22.8	0.789*
6MWD (m)	455.8 ± 83.4	439.3 ± 75.5	0.209*
CT indices			
EI	12.1 ± 9.9	15.7 ± 12.4	0.066*
ATI_-856	40.0 ± 19.5	40.8 ± 20.3	0.801*
ATI_subtraction_1	34.5 ± 31.0	28.3 ± 14.6	0.048*
ATI_subtraction_2	59.1 ± 26.0	56.8 ± 26.4	0.599*
ATI_emphysema	8.3 ± 8.6	11.4 ± 11.6	0.042*
ATI_hyperinflated	20.3 ± 10.2	19.6 ± 10.6	0.693*
ATI_normal	27.7 ± 16.8	24.6 ± 17.2	0.267*
Pi10-FWHM (mm)	4.6 ± 0.4	4.5 ± 0.4	0.051*
Pi10-IBHB (mm)	4.6 ± 0.8	4.2 ± 0.8	0.002*

Unless otherwise noted, data are means ± SD. *Independent-sample t test, [†]Chi-squared test. ATI = air-trapping index, DL_{CO} = diffusing capacity of lung for carbon monoxide, EI = emphysema index, FEF_{25-75} = forced expiratory flow between 25% and 75% of FVC, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, FWHM = full-width-half-maximum, IBHB = integral-based half-band, PFT = pulmonary function test, Pi10 = square root of airway wall area of theoretical airway with internal perimeter of 10 mm, RV = residual volume, TLC = total lung capacity, VC = vital capacity, 6MWD = 6-minute walk distance

Fig. 4. Representative case of response to treatment in 58-year-old male patient.
(A) Axial and **(B)** sagittal reconstructed images on baseline CT show diffuse bronchial wall thickening in both lungs (arrows). Pi10 by IBHB method was 4.82 mm and baseline FEV_1 was 2.82 L. After receiving treatment, FEV_1 at 1-year follow-up was 3.44 L, indicating increase of 0.62 L. FEV_1 = forced expiratory volume in 1 second

Table 3. Logistic Regression Analysis for Prediction of Increase in FEV_1 in Patients with COPD

| Variable	Odds Ratio	95% Confidence Interval	P
Age			0.677
Sex			0.356
BMI			0.413
ATI_subtraction_1			0.144
ATI_emphysema			0.131
Pi10-FWHM			0.645
Pi10-IBHB	1.787	1.220, 2.619	0.003

0.048, 0.042, and 0.002, respectively). The average ATI_subtraction_1 measurement was 34.5 ± 31.0% in the responder group and 28.3 ± 14.6% in the non-responder group. The average ATI_emphysema values in the responder and non-responder groups were 8.3 ± 8.6% and 11.4 ± 11.6%, respectively. The average Pi10-IBHB measurements in the responder and non-responder groups were 4.6 ± 0.8 and 4.2 ± 0.8, respectively; EI and Pi10-FWHM showed marginally significant intergroup differences, with P values of 0.066 and 0.051, respectively. The average value of Pi10-FWHM was significantly greater than that of Pi10-IBHB in all subjects (4.5 ± 0.4 and 4.2 ± 0.8, respectively, $p < 0.001$, 95% confidence interval [CI]: 0.16–0.44). Luminal diameter, luminal area, luminal perimeter, bronchial wall thickness, and bronchial wall area showed no significant difference between responders and non-responders ($p > 0.82$). Demographic data, initial PFT measurements, and

CT indices of the responder and non-responder groups are summarized in Table 2.

There was a significant correlation between the initial FEV_1 and Pi10 values ($\rho = -0.25$ and $p < 0.001$ for the IBHB method and $\rho = -0.17$ and $p = 0.009$ for the FWHM method). In addition, there was a significant correlation between treatment response and the value of Pi10 obtained by the IBHB method ($\rho = 0.2$, $p = 0.003$).

Predictive Factors for Treatment Response

BMI, ATI_subtraction_1, ATI_emphysema, Pi10-FWHM, and Pi10-IBHB were used as input variables for multivariate regression analysis. EI was excluded due to the collinearity with ATI_emphysema (variance inflation factor, 10.220). Age and sex were also included in the analysis for adjustment. Pi10-IBHB was the only significant independent predictor of an increase in FEV_1 after treatment in patients with COPD ($p = 0.003$) (Fig. 4). The adjusted odds ratio for Pi10-IBHB was 1.787 (95% CI: 1.220–2.619), which meant that the probability of a response to the treatment was 1.787 times greater if Pi10-IBHB increased by 1. On multivariate regression analysis, BMI, EI, ATI_subtraction_1, ATI_emphysema, Pi10-FWHM, age, and sex were found to show no significant association with treatment response (all $p > 0.05$) (Table 3). In the ROC analysis, the area under the curve for Pi10-IBHB was 0.641 (95% CI: 0.558–0.724) (Fig. 5). The optimal cutoff value to differentiate between
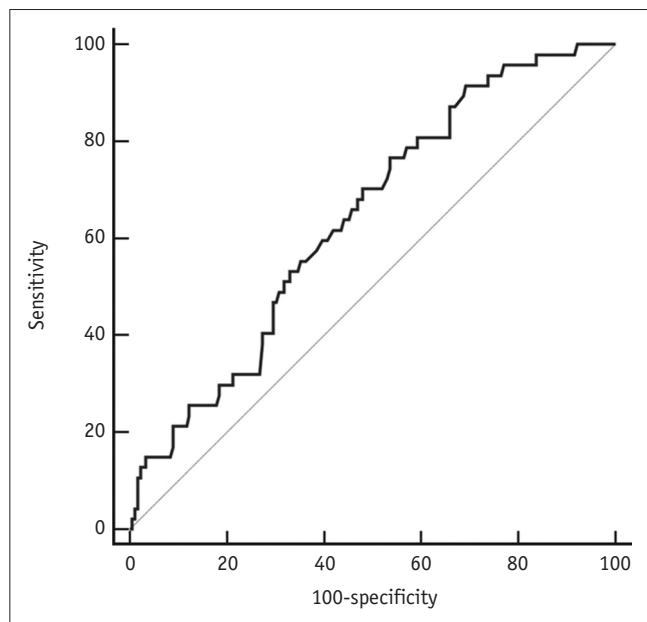
Fig. 5. ROC curve of advanced baseline quantitation of standardized airway dimensions versus treatment response.
Graph shows results of ROC analysis for differentiating between patients with and without treatment response by determining Pi10 obtained by IBHB. Area under curve for Pi10-IBHB was 0.641 (95% confidence interval: 0.558–0.724). Optimal cutoff value of Pi10-IBHB was 4.05 mm. Pi10-IBHB = Pi10 obtained by IBHB, ROC = receiver operating characteristic

patients with and without treatment response was 4.05 mm (sensitivity, 76.6%; specificity, 46.4%; positive predictive value, 27.3%; negative predictive value, 88.3%; overall accuracy, 52.7%).

DISCUSSION

Our study demonstrated that Pi10 measured by the IBHB method was the only independent predictor of treatment response after 1 year of treatment in COPD patients. The performance of this single variable had an area under the curve of 0.641.

Bronchial wall thickening determined by CT in a semi-quantitative manner has previously been shown to be an indicator for prediction of treatment response (19). Our results validate the previous findings and add greater reproducibility and reliability to them because of the absence of interobserver variability with our methodology. Our results indicated that Pi10-IBHB can accurately represent airway dimensions and help predict treatment outcome, unlike all other clinical and pulmonary functional parameters, which were ineffective. However, as the ROC analysis of Pi10-IBHB showed moderate sensitivity (76.6%)

and a high negative predictive value (88.3%), this method may currently be the most useful for identification of non-responders, and additional parameters should be sought to improve its performance. Further validation of these results should be performed in another COPD population.

Unlike the FWHM method, the most widely used methodology for obtaining quantitative airway measurements, the IBHB method is a recent development (15). A known weakness of the FWHM method is that it underestimates luminal dimensions and overestimates wall dimensions, and these deviations magnify as the airways become smaller (20-22). Overestimation of wall dimensions is possibly caused by some outward leakage of radiating rays because of the closely attached non-airway structures showing higher density than the lung parenchyma, such as vessels. Cho et al. (15) reported that the IBHB method using propagating concentric bands and doubling of the inner half-thickness of airway walls can reduce overestimation errors in comparison with the FWHM method and can prevent leakage of rays by using only the inner half-thickness of the airway wall. According to Cho's study (15), the IBHB method showed better agreement between the measured and actual values for small bronchi and showed significantly smaller values than the FWHM method. Similarly, in our cohort, the Pi10-FWHM values were significantly higher than the Pi10-IBHB values ($p < 0.001$). Furthermore, Pi10 measured by the FWHM method was not significantly associated with treatment response. Given that the very small airways are the major targets of measurement in COPD, erroneous measurements of airway wall thickness would be fatal, particularly as the error worsens as the airway becomes smaller. In addition, the overestimation of airway wall thickness by the FWHM method may explain why this variable was not associated with a significant difference between treatment responders and non-responders.

The mean Pi10-IBHB value for non-responders was markedly smaller than that for responders, whereas the mean Pi10-IBHB and Pi10-FWHM values were comparable in responders. There may be a possibility that the distribution of the level (i.e., the Nth branch of segmental bronchi) for airway measurements, which we obtained as many as possible in each subject, differed among responders and non-responders. According to Cho's study (15), there is an intersection point of the airway wall thickness estimations obtained by the IBHB and FWHM methods, and the responders' airway wall thickness might have been more

approximate to this point than the non-responders' airway wall thickness.

Among the quantitative parameters derived from CT, ATI_subtraction_1, ATI_emphysema, and Pi10-IBHB, which reflect the severity of small-airway disease, showed significant differences between responders and non-responders. EI showed no significant differences between the two groups. These results correspond well with the current concept that although chronic airway inflammation may respond to medications, airway limitation caused by lung parenchymal destruction is irreversible (19, 23, 24), thus implying that airway disease-predominant COPD may be more treatable than emphysema-predominant COPD. Notably, the Pi10 measured by the IBHB method was the only independent predictive factor that remained in multivariate regression analysis. Although it is difficult to clearly explain why ATI_subtraction_1 and ATI_emphysema could not differentiate responders from non-responders, one possible explanation is that the air-trapping area represents both treatable and untreatable small-airway disease. Conversely, Pi10-IBHB is more closely related to active inflammation in small-airway disease.

In our study, we attempted to evaluate the feasibility of applying Pi10 to COPD patients. If the optimal cutoff values were to be calculated separately according to COPD phenotypes, they would be different from our results. As there are no criteria to determine the dominant COPD phenotype on CT scans, we did not perform further analysis according to COPD phenotypes. Notably, we attempted to divide our subjects according to the criteria recommended by Nakano et al. (6) and identified that our cohorts were mainly of the emphysema-dominant type. Although we used a multicenter cohort, it is also necessary to verify our results in another cohort with different phenotypes.

In our study, treatment response was defined as a > 0.225-L increase in FEV_1 from baseline to follow-up. Current American Thoracic Society/European Respiratory Society guidelines recommend inter-session reproducibility within 0.15 L for FEV_1, as the measurement of FEV_1 is highly effort-dependent (12). However, several studies have demonstrated greater intra- and inter-session variability in patients with COPD than in individuals with normal lung function (25). Herpel et al. (14) defined an absolute change of > 0.225 L to be a clinically significant short-interval inter-session change in FEV_1 in a patient with COPD. Therefore, this definition was used in the present study to provide an accurate and reliable threshold to indicate genuine changes in lung function in patients with COPD.

Our study has some limitations. First, because of its retrospective nature, there may have been selection bias. Second, treatment after the first 3 months was determined individually for each patient and was not homogeneous, which may have affected treatment outcomes. However, all patients were managed according to the GOLD guidelines, and a similar approach has been used previously in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points study, wherein all participants continued to receive the prescribed medication throughout the study (26). Third, the quantification result may have been influenced by the different CT scanners used in this study. If a single CT scanner had been used, the results would have been more homogeneous and the performance of CT quantification for predicting treatment response would have been further enhanced.

In conclusion, measurement of standardized airway dimensions by an advanced CT quantification method can help predict response to treatment in patients with COPD.

Conflicts of Interest

The authors have no financial conflicts of interest.

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REFERENCES

1. Global Strategy for Diagnosis, Management, and Prevention of COPD-2016. Global Initiative for Chronic Obstructive Lung Disease. Available at: http://goldcopd.org/. Accessed October 26, 2017
2. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N Engl J Med* 2011;365:1567-1575
3. Agusti A, Calverley PM, Celli B, Coxson HO, Edwards LD, Lomas DA, et al.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) investigators. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122
4. Daudey L, Peters JB, Molema J, Dekhuijzen PN, Prins JB, Heijdra YF, et al. Health status in COPD cannot be measured by the St George's Respiratory Questionnaire alone: an evaluation of the underlying concepts of this questionnaire.

Respir Res 2010;11:98

5. Bergin C, Müller N, Nichols DM, Lillington G, Hogg JC, Mullen B, et al. The diagnosis of emphysema. A computed tomographic-pathologic correlation. *Am Rev Respir Dis* 1986;133:541-546

6. Nakano Y, Sakai H, Muro S, Hirai T, Oku Y, Nishimura K, et al. Comparison of low attenuation areas on computed tomographic scans between inner and outer segments of the lung in patients with chronic obstructive pulmonary disease: incidence and contribution to lung function. *Thorax* 1999;54:384-389

7. Lee YK, Oh YM, Lee JH, Kim EK, Lee JH, Kim N, et al. Quantitative assessment of emphysema, air trapping, and airway thickening on computed tomography. *Lung* 2008;186:157-165

8. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, et al.; COPDGene Investigators. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. *Radiology* 2011;261:274-282

9. Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, et al. Quantitative computed tomography: emphysema and airway wall thickness by sex, age and smoking. *Eur Respir J* 2009;34:858-865

10. Kim SS, Jin GY, Li YZ, Lee JE, Shin HS. CT quantification of lungs and airways in normal Korean subjects. *Korean J Radiol* 2017;18:739-748

11. Park TS, Lee JS, Seo JB, Hong Y, Yoo JW, Kang BJ, et al.; KOLD Study Group. Study design and outcomes of Korean Obstructive Lung Disease (KOLD) cohort study. *Tuberc Respir Dis (Seoul)* 2014;76:169-174

12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al.; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;26:319-338

13. Tweeddale PM, Merchant S, Leslie M, Alexander F, McHardy GJ. Short term variability in FEV1: relation to pretest activity, level of FEV1, and smoking habits. *Thorax* 1984;39:928-932

14. Herpel LB, Kanner RE, Lee SM, Fessler HE, Sciurba FC, Connett JE, et al.; National Emphysema Treatment Trial Research Group. Variability of spirometry in chronic obstructive pulmonary disease: results from two clinical trials. *Am J Respir Crit Care Med* 2006;173:1106-1113

15. Cho YH, Seo JB, Kim N, Lee HJ, Hwang HJ, Kim EY, et al. Comparison of a new integral-based half-band method for CT measurement of peripheral airways in COPD with a conventional full-width half-maximum method using both phantom and clinical CT images. *J Comput Assist Tomogr* 2015;39:428-436

16. Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, et al. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. *Nat Med* 2012;18:1711-1715

17. Kim EY, Seo JB, Lee HJ, Kim N, Lee E, Lee SM, et al. Detailed analysis of the density change on chest CT of COPD using non-rigid registration of inspiration/expiration CT scans. *Eur Radiol* 2015;25:541-549

18. Lee SM, Seo JB, Lee SM, Kim N, Oh SY, Oh YM. Optimal threshold of subtraction method for quantification of air-trapping on coregistered CT in COPD patients. *Eur Radiol* 2016;26:2184-2192

19. Kitaguchi Y, Fujimoto K, Kubo K, Honda T. Characteristics of COPD phenotypes classified according to the findings of HRCT. *Respir Med* 2006;100:1742-1752

20. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, et al. Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. *Am J Respir Crit Care Med* 2000;162(3 Pt 1):1102-1108

21. Nakano Y, Müller NL, King GG, Niimi A, Kalloger SE, Mishima M, et al. Quantitative assessment of airway remodeling using high-resolution CT. *Chest* 2002;122(6 Suppl):271S-275S

22. Kim N, Seo JB, Song KS, Chae EJ, Kang SH. Semi-automatic measurement of the airway dimension by computed tomography using the full-with-half-maximum method: a study of the measurement accuracy according to the orientation of an artificial airway. *Korean J Radiol* 2008;9:236-242

23. Fujimoto K, Kitaguchi Y, Kubo K, Honda T. Clinical analysis of chronic obstructive pulmonary disease phenotypes classified using high-resolution computed tomography. *Respirology* 2006;11:731-740

24. Pistolesi M, Camiciottoli G, Paoletti M, Marmai C, Lavorini F, Meoni E, et al. Identification of a predominant COPD phenotype in clinical practice. *Respir Med* 2008;102:367-376

25. Pennock BE, Rogers RM, McCaffree DR. Changes in measured spirometric indices. What is significant? *Chest* 1981;80:97-99

26. Vestbo J, Anderson W, Coxson HO, Crim C, Dawber F, Edwards L, et al.; ECLIPSE investigators. Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE). *Eur Respir J* 2008;31:869-873