INTRODUCTION

Emphysema and small-airway disease are the two major components of chronic obstructive pulmonary disease (COPD) [1-3]. Varying combinations and severities of emphysema and small-airway disease can manifest...
differently among individual patients with COPD, leading to varying degrees of lung function impairment.

Many studies have focused on quantifying these two components using computed tomography (CT). Quantification of emphysema on CT by determining the relative area of the lungs below -950 Hounsfield units (HU) on inspiration CT is an established method that shows significant correlations with airflow obstruction parameters on pulmonary function tests (PFTs) [4-10]. Small-airway disease is quantified indirectly by determining the air-trapping area on CT because of the limited resolution of CT in visualizing small airways. Air trapping is an indicator of small-airway obstruction [11,12]. Several methods for evaluating air trapping, such as quantifying the area below -856 HU on expiration CT (Exp-856), have been reported [7,10,13-15]. The air trapping index (ATI) is a novel method for quantifying air trapping by comparing the densities between inspiration and expiration CT scans using the co-registration method [16]. The ATI defines air trapping as an area with a density increase of less than 60 HU between inspiration and expiration CT scans [17], considering that air trapping is defined as no or less density increase during respiration compared to normal lungs [18]. However, the optimal method for evaluating small-airway disease on CT is still under debate.

Parametric response mapping (PRM) has been introduced to assess each COPD component by performing inspiration and expiration CTs [19]. It allows for differentiation between emphysematous and non-emphysematous air trapping. In PRM, small-airway disease is defined simply as lung areas with densities greater than or equal to -950 HU on inspiration CT and less than -856 HU on expiration CT. However, this method considers only slight dynamic density changes in each voxel and excludes the contribution of emphysema to air trapping in assessing small-airway disease.

Hence, in this study, we proposed a novel method of CT analysis of two major disease components of COPD: emphysema air-trapping composite (EAtC) mapping, using quantitative CT analysis of emphysema and ATI in the co-registration of inspiration and expiration CT scans. We analyzed the potential use of this method as an imaging biomarker for assessing lung function in patients with COPD and compared this method with PRM.

MATERIALS AND METHODS

Patients
This retrospective study was approved by the Institutional Review Board of our medical center (IRB No. 2012-0226 and 2013-1032), and written informed consent was obtained from all patients. All patients were selected from the Korean Obstructive Lung Disease (KOLD) [20] and KOLD 2 Cohorts (Supplementary Materials 1). From these two cohorts, 584 patients with COPD who were available for baseline inspiration and expiration CT and PFT results were included in this study between June 2005 and June 2015 (Fig. 1).

All patients underwent volumetric inspiration and expiration CT scans, as well as PFTs with spirometry, lung volumes, and diffusion capacity measurements. PFTs were performed on the same day or within 2 weeks of CT scans, according to the guidelines [21-23]. The St. George’s Respiratory Questionnaire (SGRQ) questionnaire was used to assess the degree of dyspnea [24]. Other clinical variables were also assessed, such as the exercise capacity of a six-minute walk distance, the degree of dyspnea according to the modified Medical Research Council dyspnea scale, and body mass index. The Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index was calculated [25]. Of the 584 patients, 174 were included in the study population of a previous report [17]. A previous study assessed the optimal ATI threshold for quantifying air trapping; in this study, we used the modified ATI method.

CT Examination
Volumetric CT scans were obtained in the supine position at both full inspiration and expiration using one of the following scanners: Somatom Sensation 16, Definition AS+ or Definition Flash (Siemens Healthineers) (n = 463) at 140

Fig. 1. Flow diagram of patient inclusion. KOLD = Korean Obstructive Lung Disease, PFT = pulmonary function test
kVp and 100 effective mAs or Brilliance 40 or 64 (Philips Medical Systems) (n = 121) at 140 kVp and 100–135 effective mAs with a pitch of 1.0, and collimation of 0.75 or 0.625 mm. The CT data were reconstructed at a 0.75-mm slice thickness and 0.7-mm increment using a B30f kernel (Siemens Healthineers) or at a 0.8-mm slice thickness and 0.8-mm increment or a 0.67-mm slice thickness and 0.67-mm increment using a standard reconstruction algorithm (B or C kernel) (Philips Medical System). All CT scanners were calibrated weekly using an American Association of Physicists in Medicine standard phantom.

**Quantitative CT EAtC Mapping**

Quantitative CT EAtC mapping was performed using an automatic segmentation software (Aview, Coreline Soft). Lung segmentation was performed for EAtC mapping, and the airways, vessels, and background were segmented and removed from the lung parenchyma using several specific thresholds [16]. Inspiration and expiration CT images were registered using a non-rigid method. A detailed description of the registration of inspiration and expiration CT images has been documented in a previous study [16].

In EAtC mapping, the lung parenchyma is classified into three lung areas: 1) areas with functional air trapping (fAT), 2) areas with emphysema (Emph), and 3) areas with normal lung parenchyma (Normal) (Fig. 2). Emph was defined as the volume fraction of voxels exhibiting a density lower than -950 HU on inspiration CT; fAT was defined as the volume fraction of voxels exhibiting a change in density of less than 60 HU between inspiration and co-registered expiration CT scans [17] in the lung parenchyma sufficiently inflated on inspiration CT with a lung density less than -856 HU. The remaining volume fraction was defined as Normal. The value of -856 HU was chosen because it is the mean attenuation of a normally inflated lung on inspiration (Supplementary Materials 2, Supplementary Table 1) [26]. Each lung area was presented as its volume relative to the total lung volume.

**Parametric Response Mapping**

We also performed a PRM analysis of the CT scans of our study population [19]. After segmentation of the lungs and registration of inspiration and expiration CT images, the lung parenchyma was classified into three lung areas as documented in a previous study [19]: functional small-airway disease (PRM\(_{\text{fSAD}}\)), emphysema (PRM\(_{\text{Emph}}\)), and normal lung (PRM\(_{\text{Normal}}\)).

**Statistical Analysis**

Each class of EAtC mapping was compared according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [27] using a one-way analysis of variance test. The relationships of each EAtC class with PFTs and clinical findings, including the BODE index and SGRQ score, were assessed using Pearson’s correlation or Spearman’s correlation. Multiple linear regression analysis with stepwise selection was performed to determine the predictors of PFT parameters and BODE index. EAtC classes and clinical variables, such as age and smoking history (pack-years), were used as independent variables. The relative volumes of each EAtC and PRM classes were compared using paired t tests. The relationships of each PRM class with the PFTs, BODE index, and SGRQ score were also assessed. Correlation coefficients were interpreted according to the following categories: \( r < 0.3 \), weak correlation; \( 0.3 < r < 0.7 \), moderate correlation; and \( r > 0.7 \), strong correlation. Correlation statistics of EAtC mapping and PRM analysis were compared using the...
Hittner’s test [28]. Statistical significance was set at $p < 0.05$. All statistical analyses, except for Hittner’s test, were performed using SPSS Statistics for Windows, version 21 (IBM Corp.). Hittner’s test was performed using R software version 3.6.1 (R Project for Statistical Computing).

**RESULTS**

Patient characteristics are summarized in Table 1. The relative volumes of the EAtC classes showed significant differences according to GOLD stage ($p < 0.001$) (Table 2, Figs. 3, 4). With an increase in GOLD stage, fAT and Emph increased, while Normal significantly decreased. Post-hoc analysis showed significant intergroup differences in EAtC classes between GOLD stages ($p < 0.05$), except between Emph of GOLD I and GOLD II.

**Association of EAtC Classes with PFTs and Other Clinical Parameters**

The associations of each EAtC class with the PFTs, BODE

![Fig. 3. Distribution of EAtC classes according to GOLD stages.](https://example.com/fig3.png)

**Table 1. Patients Characteristics**

| Variables       | Data          |
|-----------------|---------------|
| Age, year       | 65.7 ± 11.7   |
| Sex, male:female| 542:42        |
| Pack-years      | 44.5 ± 26.7   |
| GOLD stage      |               |
| I               | 85            |
| II              | 333           |
| III             | 144           |
| IV              | 22            |
| BODE index      | 2.70 ± 1.95   |
| Pulmonary function tests | |
| FEV1, liter     | 1.6 ± 0.6     |
| FEV1, % predicted| 52.2 ± 16.5   |
| FVC, liter      | 3.3 ± 0.9     |
| FVC, % predicted| 79.8 ± 16.4   |
| FEV1/FVC, %     | 46.7 ± 11.1   |
| FEF25–75%, % predicted | 20.9 ± 10.7 |
| DLCO, % predicted| 75.7 ± 22.9   |
| RV, % predicted  | 114.6 ± 57.8  |
| TLC, % predicted | 103.6 ± 22.9  |
| RV/TLC, %       | 41.3 ± 14.2   |
| 6MWD, meter     | 417.9 ± 88.4  |
| SGRQ score      | 30.5 ± 18.6   |

Data are presented as mean ± standard deviation except sex and GOLD stages of which the data are number of patients. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DLco = carbon monoxide diffusing capacity corrected for hemoglobin concentration, FEF25–75% = mean forced expiratory flow between 25% and 75% of FVC, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Obstructive Lung Disease, RV = residual volume, SGRQ = St. George’s Respiratory Questionnaire, TLC = total lung capacity, 6MWD = six-minute walk distance.

**Table 2. Characteristics of CT-Quantitative EAtC Mapping of Lung Parenchyma According to GOLD Stages**

| EAtC Mapping | GOLD Stage             | $p*$  |
|--------------|------------------------|-------|
|              | I (n = 85)             |       |
| Normal       | 62.4 ± 19.8            |       |
| fAT          | 32.9 ± 20.0            |       |
| Emph         | 10.5 ± 11.6            |       |
|              | II (n = 333)           |       |
| Normal       | 53.5 ± 17.6            |       |
| fAT          | 42.0 ± 18.1            |       |
| Emph         | 14.2 ± 11.3            |       |
|              | III (n = 144)          |       |
| Normal       | 37.7 ± 14.5            |       |
| fAT          | 58.8 ± 15.0            |       |
| Emph         | 23.7 ± 15.0            |       |
|              | IV (n = 22)            |       |
| Normal       | 24.8 ± 7.3             |       |
| fAT          | 72.8 ± 7.8             |       |
| Emph         | 38.6 ± 12.2            |       |

Data are presented as means ± standard deviations of the relative volume (%) of each class. *EAtC classes were compared according to GOLD stages using one-way analysis of variance. Post-hoc analysis with Tukey’s test showed the significant inter-group differences between all GOLD stages ($p < 0.05$) except among Emph in GOLD stages I and II. EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, GOLD = Global Initiative for Obstructive Lung Disease, Normal = normal lung parenchyma by EAtC.
index, and SGRQ score are presented in Table 3. fAT and Emph showed significant and moderate negative correlations with forced expiratory volume in 1 second (FEV₁) and FEV₁/forced vital capacity (FVC) (fAT: \( r = -0.567 \) and \( -0.659 \), Emph: \( r = -0.430 \) and \( -0.605 \), respectively, all \( p < 0.001 \)), which are measures of airflow limitation. fAT showed the highest correlation with mean forced expiratory flow between 25% and 75% of FVC (\( \text{FEF}_{25-75}\% \)), residual volume (RV), and RV/total lung capacity (TLC) (\( r = -0.502 \) to \( -0.491 \), \( p < 0.001 \)), which are measures of pulmonary air trapping or small-airway dysfunction, while Emph showed the highest correlation with the carbon monoxide diffusing capacity corrected for hemoglobin concentration (\( \text{DLCO} \)) (\( r = -0.516 \), \( p < 0.001 \)), which is a measure of parenchymal destruction. Each class also showed moderate correlations with the BODE index and SGRQ score, which are integrative prognostic factors of COPD and measures of health impairment, respectively. Table 4 shows results of the multiple linear
regression analysis of EAtC classes and clinical parameters for predicting the PFTs and BODE index results. Among the EAtC classes, considerable multicollinearity (variance inflation factor > 10) between fAT and Normal were found. Hence, fAT and Emph were included as independent variables. Both fAT and Emph were identified as predictors of FEV1 and FEV1/FVC (R² = 0.352 and 0.488, respectively; \( p < 0.001 \)). For FEF25–75% and RV/TLC, fAT was the only significant predictor (R² = 0.264 and 0.233, both \( p < 0.001 \)), while Emph and patient age were significant predictors of DLCO (R² = 0.303, \( p < 0.001 \)).

Comparison of EAtC Mapping and PRM Analysis

The results of the EAtC mapping and PRM analysis are summarized in Supplementary Table 2. The mean relative volumes of Normal vs. PRMNormal, fAT vs. PRMfSAD, and Emph vs. PRMEmph were compared, and they differed significantly between the two methods (\( p < 0.05 \)). The mean relative volume of fAT was significantly higher than that of PRMfSAD, and that of Emph was higher than that of PRMEmph. Each PRM class also showed a significant correlation with the PFT results, BODE index, and SGRQ score (Table 3). When the correlation statistics were compared between EAtC mapping and PRM, fAT showed significantly stronger correlations with PFT results, including FEF25–75%, RV, and RV/TLC than PRMfSAD (all, \( p < 0.001 \)) (Fig. 5). PRMEmph showed slightly stronger correlations with most of the PFT results than Emph of EAtC mapping (\( p < 0.001 \)); however, Emph showed a slightly stronger correlation with DLco than PRMEmph, although this trend was not statistically significant (\( p = \).

Table 3. Correlation of CT-Quantitative EAtC Mapping and PRM Classes with PFTs, BODE Index, and SGRQ Score

| Method  | FEV1  | FEV1/FVC | FEF25−75% | RV   | TLC  | RV/TLC | DLco | BODE Index | SGRQ |
|---------|-------|----------|------------|------|------|--------|------|------------|------|
| EAtC Normal | 0.559 | 0.674 | 0.500 | -0.475 | -0.471 | -0.452 | 0.361 | -0.561 | -0.349 |
| fAT | -0.567 | -0.659 | -0.502 | 0.491 | 0.469 | 0.474 | -0.333 | 0.584 | 0.354 |
| Emph | -0.430 | -0.605 | -0.423 | 0.327 | 0.384 | 0.280 | -0.516 | 0.425 | 0.256 |
| PRM Normal | 0.547 | 0.661 | 0.463 | -0.454 | -0.454 | -0.426 | 0.349 | -0.533 | -0.324 |
| PRMfSAD | -0.383 | -0.411 | -0.337 | 0.331 | 0.279 | 0.345 | -0.041* | 0.319 | 0.191 |
| PRMEmph | -0.488 | -0.647 | -0.471 | 0.366 | 0.407 | 0.326 | -0.502 | 0.475 | 0.275 |

Table 4. Multiple Linear Regression Analysis for CT-Quantitative EAtC Mapping and Clinical Variables (Age, Pack-Years) for PFTs and BODE Index

| Variables | Coefficients | \( P \) | \( R^2 \) |
|-----------|--------------|--------|---------|
| FEV1      | -0.409       | < 0.001 | 0.352   |
| Emph      | -0.188       | < 0.001 |         |
| FEV1/FVC  | -0.277       | < 0.001 | 0.488   |
| Emph      | -0.224       | < 0.001 |         |
| FEF25−75% | -0.281       | < 0.001 | 0.264   |
| fAT       | 0.344        | < 0.001 |         |
| RV/TLC    | -0.891       | < 0.001 |         |
| DLco      | -0.153       | 0.038   |         |
| BODE index| 0.087        | 0.022   |         |

The following independent variables were used for the multivariable model: EAtC classes (fAT and Emph), age, and smoking history (pack-years). Normal from the EAtC classes was not considered as an independent variable because considerable multicollinearity (variance inflation factor > 10) between fAT and Normal were found. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DLco = carbon monoxide diffusing capacity corrected for hemoglobin concentration, EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, FEF25−75% = mean forced expiratory flow between 25% and 75% of FVC, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, Normal = normal lung parenchyma by EAtC, PFT = pulmonary function test, PRM = parametric response mapping, PRMEmph = emphysema by PRM, PRMfSAD = functional small airways disease by PRM, PRMNormal = normal lung by PRM, RV = residual volume, SGRQ = St. George’s Respiratory Questionnaire, TLC = total lung capacity.

Data are presented as correlation coefficients determined using the Pearson’s correlation test for Normal, fAT, PRMNormal and PRMfSAD and Spearman’s correlation for Emph and PRMEmph. * \( p \) values > 0.05. Otherwise, \( p \) values < 0.05. BODE = Body mass index, airflow Obstruction, Dyspnea and Exercise capacity, DLco = carbon monoxide diffusing capacity corrected for hemoglobin concentration, EAtC = emphysema air-trapping composite, Emph = emphysema by EAtC, fAT = functional air trapping by EAtC, FEF25−75% = mean forced expiratory flow between 25% and 75% of FVC, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, Normal = normal lung parenchyma by EAtC, PFT = pulmonary function test, PRM = parametric response mapping, PRMEmph = emphysema by PRM, PRMfSAD = functional small airways disease by PRM, PRMNormal = normal lung by PRM, RV = residual volume, SGRQ = St. George’s Respiratory Questionnaire, TLC = total lung capacity.
0.079) (Supplementary Table 3).

**DISCUSSION**

This study showed that each disease component of COPD quantified using EAtC mapping showed progression with increased disease severity according to the GOLD criteria and each component was significantly associated with PFTs and clinical variables. EAtC classes were significant imaging predictors of PFT parameters and the BODE index. When the correlation with lung function was compared between EAtC mapping and PRM, fAT showed significantly stronger correlations with PFT results, including FEF25–75%, RV, and RV/TLC, than PRM. In this respect, EAtC mapping can provide a comprehensive view of each COPD component contributing to the current lung function impairment using the modified ATI. In this study, we focused on the association between EAtC classes and lung function in patients with COPD; thus, the potential use of this method for disease follow-up or assessment of treatment responses should be studied in the future.

PRM analysis may have a unique potential for early identification of disease progression in COPD [29,30] by identifying non-emphysematous air trapping, or early small-airway disease. The focus of EAtC mapping is different from that of PRM analysis. EAtC mapping aims
to evaluate the factors contributing to lung function impairments in individual patients by evaluating the extent and distribution of each COPD component more accurately and comprehensively. It is important to detect the preclinical disease of COPD, which can be a potential target for treatment. However, considering that patients with COPD manifest various lung function declines and treatment plans are devised based on lung function evaluations, accurately evaluating each disease component contributing to various lung function impairments on CT may be helpful in understanding a patient’s current status and planning treatment. EAtC mapping may also be used to evaluate how each disease component that affects lung function impairments changes with the progression of COPD. Moreover, air trapping in the non-emphysematous area within fAT can be assessed separately using the EAtC mapping segmentation software, although this area was not evaluated in this study. In previous studies, air trapping in non-emphysematous and emphysematous areas have been separately evaluated using ATI analysis \[16,17\]. The air trapping in the non-emphysematous area within fAT may correspond with PRM\textsubscript{SAD} or more accurately reflect early small-airway disease using the ATI method.

fAT includes air trapping in the emphysematous area (small-airway disease with emphysematous destruction) and non-emphysematous areas (small-airway disease with normal alveoli). Indeed, air trapping in the emphysematous area might be controversial in assessing small-airway disease. Although small-airway disease precedes emphysematous destruction \[31,32\], preexisting small-airway disease may co-exist in areas with emphysema, and further narrowing caused by emphysematous destruction of the supporting structures of small airways may also worsen air trapping. Therefore, small-airway disease in both normal alveoli and emphysematous areas may affect air trapping. A previous study revealed that air trapping in emphysematous areas may substantially contribute to small-airway dysfunction \[17\]. Our study also demonstrated similar results and showed that fAT showed significantly better correlations with PFTs than PRM\textsubscript{SAD}, which represents non-emphysematous air trapping only. With respect to functional assessments on chest CT, fAT may characterize small-airway dysfunction better than PRM\textsubscript{SAD}.

The optimal method for quantifying air trapping on CT is still under debate. The ATI analyzes density changes between co-registered inspiration and expiration CT scans \[16,17\], whereas the other CT indices of air trapping such as PRM\textsubscript{SAD}, Exp–856, or expiration/inspiration ratio of the mean lung density use the fixed HU values on expiration or inspiration CT scans. Considering that air trapping is defined as an area that shows no or less density increase during expiration than normal lungs on CT \[18\], the ATI is a logical method that considers dynamic changes. The ATI was significantly correlated with PFTs and was comparable to the other CT indices of air trapping in previous studies \[16,17\]. In EAtC mapping, air trapping was quantified using the modified ATI and presented as fAT, which was significantly correlated with PFTs.

In EAtC mapping, the ATI was modified by excluding the lung areas with densities higher than -856 HU on the inspiration CT from the air trapping area. This value is the attenuation of a normally inflated lung on inspiration CT \[26\], and it is presumed that the lung areas showing density changes less than 60 HU but a density higher than -856 HU on inspiration CT, inflated incompletely or insufficiently, result in small density changes on expiration CT. Therefore, we speculated that these lung areas may be associated with normal lung parenchyma, such as structural components that are not actively involved in gas exchange, and not with air-trapping areas. The modified ATI (fAT) showed stronger correlations with PFTs than the original ATI (of the whole lung area).

The extent of emphysema assessed on chest CT provides information on the degree of lung parenchymal destruction in patients with COPD. In our study, Emph was significantly associated with DL\textsubscript{CO}, which is in accordance with previous studies \[7,33,34\]. Increasing emphysema could cause hypoxemia through impaired diffusion capacity and loss of surface area for gas exchange \[35\]. Therefore, Emph may possibly identify lung areas with destroyed alveoli that can lead to gas exchange impairment. Although Emph and fAT partly overlap in the lung on EAtC mapping, Emph and fAT may provide information on lung parenchymal destruction and small-airway dysfunction, respectively.

Our study has several limitations. First, the retrospective design of the study could have caused selection bias. Second, we modified the ATI using a threshold of -856 HU on inspiration CT. Although it is known that this value reflects the attenuation of a normally inflated lung on inspiration CT, we could not histologically confirm our assumption. Despite this, the modified ATI showed stronger correlations with the PFTs than the original ATI. Third, the optimal threshold for density changes of ATI was determined using a single CT protocol and CT machine in a

---

Hwang et al.

https://doi.org/10.3348/kjr.2021.0033 kjronline.org
previous study [17]. The predetermined threshold can vary according to the CT machines, section thicknesses, and reconstruction algorithms. However, all CT scanners were regularly calibrated, and most CT images were obtained from the same CT machine with the same CT protocol as in the previous study. Nonetheless, further external validation under different conditions is necessary. Fourth, although CT protocols of the KOLD cohort were designed to minimize interpatient differences, CT machines vary between centers. The detailed reconstruction algorithms or voltages of the CT scans also varied slightly by the CT manufacturer. This may have affected the CT parameters in our study. Recently, attempts have been made to develop deep learning-based post-processing techniques that permit interconversion among CT images obtained using different CT protocols [36,37]. This method has the potential to facilitate reliable quantification of CT scans obtained using different protocols and machines. Lastly, as CT was obtained without spirometric control, there was a possibility of variations in the expiration level, which may have influenced the air-trapping quantification. However, we instructed the patients sufficiently regarding the appropriate inspiratory and expiratory levels before CT scanning, although rigorous volume control was difficult.

In conclusion, quantitative CT EATC mapping can provide spatial and quantitative information on the two disease components of COPD, emphysema and small-airway disease, which are associated with COPD severity and lung function status. This method has the potential to serve as an imaging biomarker for assessing lung function in patients with COPD by comprehensively evaluating these components.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2021.0033.

Conflicts of Interest

Joon Beom Seo and Namkug Kim have a patent: method for automatic quantification of air trapping on chest CT data (Patent No. KR-10-0979335). Joon Beom Seo, Sangmin Lee and Namkung Kim are stockholders of Coreline Soft and received royalties for licensing the patent and knowhow of image quantification. Jaeyoun Yi is an employee of Coreline Soft, which is a company that develops software to enable quantitative analysis of medical images. All other authors declare no competing interests. This research did not receive any specific grant from agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to acknowledge Seon Ok Kim, Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, for contributions to statistical analysis in this study.

Author Contributions

Conceptualization: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi. Data curation: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi. Formal analysis: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee. Investigation: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi. Methodology: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi. Project administration: Hye Jeon Hwang, Joon Beom Seo. Resources: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi, Namkug Kim. Software: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi, Namkug Kim. Supervision: Joon Beom Seo, Jae Seung Lee, Sei Won Lee, Yeon-Mok Oh, Sang-Do Lee. Validation: Hye Jeon Hwang, Joon Beom Seo, Sang Min Lee, Jaeyoun Yi. Visualization: Hye Jeon Hwang, Jaeyoun Yi. Writing—original draft: Hye Jeon Hwang, Joon Beom Seo. Writing—review & editing: Hye Jeon Hwang, Joon Beom Seo, Jae Seung Lee, Yeon-Mok Oh.

ORCID iDs

Hye Jeon Hwang https://orcid.org/0000-0003-3508-2870
Joon Beom Seo https://orcid.org/0000-0003-0271-7884
Sang Min Lee https://orcid.org/0000-0002-2173-2193
Namkug Kim https://orcid.org/0000-0002-3438-2217
Jaeyoun Yi https://orcid.org/0000-0002-7664-9493
Jae Seung Lee https://orcid.org/0000-0003-4130-1486
Sei Won Lee https://orcid.org/0000-0003-4814-6730
Yeon-Mok Oh https://orcid.org/0000-0003-0116-4683
Sang-Do Lee https://orcid.org/0000-0001-8189-4509
REFERENCES

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995;152:577-512

2. Agusti A, Vestbo J. Current controversies and future perspectives in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2011;184:507-513

3. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182:598-604

4. 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

5. Gevenois PA, De Vuyst P, de Maertelaer V, Zanen J, Jacobovitz D, Cosio MG, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med 1996;154:187-192

6. Gould GA, Redpath AT, Ryan M, Warren PM, Best JJ, Flenley DC, et al. Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. Eur Respir J 1991;4:141-146

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. Müller NL, Staples CA, Miller RR, Abboud RT. “Density mask”. An objective method to quantitate emphysema using computed tomography. Chest 1988;94:782-787

9. Park YS, Seo JB, Kim N, Chae EJ, Oh YM, Lee SD, et al. Texture-based quantification of pulmonary emphysema on high-resolution computed tomography: comparison with density-based quantification and correlation with pulmonary function test. Invest Radiol 2008;43:395-402

10. Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. AJR Am J Roentgenol 2013;201:W460-W470

11. Lee KW, Chung SY, Yang J, Lee Y, Ko EY, Park MJ. Correlation of aging and smoking with air trapping at thin-section CT of the lung in asymptomatic subjects. Radiology 2000;214:831-836

12. Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N, Ueda K, et al. Air trapping at CT: high prevalence in asymptomatic subjects with normal pulmonary function. Radiology 2003;227:776-785

13. Akira M, Toyokawa K, Inoue Y, Arai T. Quantitative CT in chronic obstructive pulmonary disease: inspiratory and expiratory assessment. AJR Am J Roentgenol 2009;192:267-272

14. Kubo K, Eda S, Yamamoto H, Fujimoto K, Matsuzawa Y, Maruyama Y, et al. Expiratory and inspiratory chest computed tomography and pulmonary function tests in cigarette smokers. Eur Respir J 1999;13:252-256

15. Mets OM, van Hulst RA, Jacobs C, van Ginnenken B, de Jong PA. Normal range of emphysema and air trapping on CT in young men. AJR Am J Roentgenol 2012;199:336-340

16. 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

17. 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

18. Hansell DM, Bankier AA, MacMahon H, McCloud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722

19. 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

20. Park TS, Lee JS, Seo JB, Hong Y, Yoo JW, Kang BJ, et al. Study design and outcomes of Korean obstructive lung disease (KOLD) cohort study. Tuberc Respir Dis (Seoul) 2014;76:169-174

21. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720-735

22. Miller MR, Hankinson J, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-338

23. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511-522

24. Kim YS, Byun MK, Jung WY, Jeong JH, Choi SB, Kang SM, et al. Validation of the Korean version of the St. George’s respiratory questionnaire for patients with chronic respiratory disease. Tuberc Respir Dis 2006;61:121-128

25. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005-1012

26. Lynch DA. Progress in imaging COPD, 2004-2014. Chronic Obstr Pulm Dis 2014;1:73-82

27. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med 2017;195:557-582

28. Hittner JB, May K, Silver NC. A Monte Carlo evaluation of tests for comparing dependent correlations. J Gen Psychol 2003;130:149-168
29. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016;194:178-184

30. Boes JL, Hoff BA, Bule M, Johnson TD, Rehemtulla A, Chamberlain R, et al. Parametric response mapping monitors temporal changes on lung CT scans in the subpopulations and intermediate outcome measures in COPD Study (SPIROMICS). *Acad Radiol* 2015;22:186-194

31. Hogg JC, McDonough JE, Suzuki M. Small airway obstruction in COPD: new insights based on micro-CT imaging and MRI imaging. *Chest* 2013;143:1436-1443

32. 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

33. Mohamed Hoesein FA, de Jong PA, Lammers JW, Mali WP, Mets OM, Schmidt M, et al. Contribution of CT quantified emphysema, air trapping and airway wall thickness on pulmonary function in male smokers with and without COPD. *COPD* 2014;11:503-509

34. 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;162:1102-1108

35. Saure EW, Bakke PS, Lind Eagan TM, Aanerud M, Jensen RL, Grydeland TB, et al. Diffusion capacity and CT measures of emphysema and airway wall thickness - relation to arterial oxygen tension in COPD patients. *Eur Clin Respir J* 2016;3:29141

36. Lee SM, Lee JG, Lee G, Choe J, Do KH, Kim N, et al. CT image conversion among different reconstruction kernels without a sinogram by using a convolutional neural network. *Korean J Radiol* 2019;20:295-303

37. Bak SH, Kim JH, Jin H, Kwon SO, Kim B, Cha YK, et al. Emphysema quantification using low-dose computed tomography with deep learning-based kernel conversion comparison. *Eur Radiol* 2020;30:6779-6787