

# Usefulness of quantitative computed tomography analysis using a commercially available software program through its simple and automatic procedures in evaluation of emphysema and pulmonary fibrosis

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## Research article

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# **Abstract**

## Background

The aim of this study was to investigate the usefulness of quantitative computed tomography (CT) analysis using a commercially available software program through its simple and automatic procedures. The software program, which was developed with the density mask technique using two thresholds, was used for simultaneously assessing both the low attenuation volume (LAV) and high attenuation volume (HAV) to detect emphysema and pulmonary fibrosis.

## Methods

In this prospective cohort study of stable patients with chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), we investigated the correlations between quantitative assessments performed using the software program and visual assessments, and between pulmonary function parameters and quantitative assessment parameters. We also investigated whether the utility of quantitative assessments could improve by assessing the destroyed lung volume (DLV), defined as the LAV+HAV.

## Results

Strong significant correlations were detected between the percentage of LAV (LAV%) and the visual assessment of emphysema and between the percentage of HAV (HAV%) and the visual assessment of pulmonary fibrosis. A receiver operating characteristic curve analysis revealed 86.8% sensitivity and 84.2% specificity for the LAV% to detect emphysema, using 1.5% as the cut-off value, and 87.5% sensitivity and 96.1% specificity for the HAV% to detect pulmonary fibrosis, using 12% as the cut-off value. The percentage of DLV (DLV%) significantly correlated with the diffusion capacity of lung for carbon monoxide (DLco) and delta N2 in patients with COPD. Meanwhile, the DLV% significantly correlated with DLco and the composite physiologic index in patients with IPF. Moreover, the DLV% significantly also correlated with DLco in total patients with COPD and IPF.

## Conclusions

The quantitative CT analysis using a commercially available software program could be useful in clinical practice by the advantage of the simple and automatic procedures. The utility of the quantitative CT analysis could improve by assessing the DLV%.

# **Background**

A software-based quantification of the extent of emphysema and airway wall thickness on chest computed tomography (CT), known as quantitative CT, has been increasingly utilized in patients with chronic obstructive pulmonary disease (COPD) [1–3]. The quantification of emphysema based on the lung density threshold in CT images dates back three decades [4].

In addition to COPD/emphysema, the use of computer-based CT image analysis methods has been previously reported for idiopathic pulmonary fibrosis (IPF), some of which are already utilized in clinical practice at specialist centers [5]. Furthermore, it has been reported that emphysema complicates IPF in approximately 30% of patients [6–7]. Recently, this disease state has been termed combined pulmonary fibrosis and emphysema (CPFE). Emphysema and pulmonary fibrosis can sometimes be superimposed on chest CT, making it difficult to visually assess the extent of emphysema and pulmonary fibrosis. Therefore, the software-based quantitative CT analysis simultaneously detecting emphysema and pulmonary fibrosis may be important.

Several software-based CT image analysis methods have been developed for assessing emphysema and interstitial lung disease (ILD), such as the density histogram analysis, the density mask technique, and the texture classification method. Among these, the density mask technique is the most widely used method with a threshold on the order of -950 Hounsfield units (HU), for the quantification of emphysema in patients with COPD [4–5, 8–11]. The density mask technique is also convenient for evaluating the disease status in patients with ILD [12–13]. The threshold value of -950HU distinguishes emphysema from normal lungs, whereas the threshold value of -700 or -750 HU distinguishes normal lungs from ground-glass opacity [5]. Thus, the density mask technique has universal applicability as a method based on CT values, and exhibits high consistency with visual assessment because the CT values provide clear cut-off points [5]. The previous study revealed that the percentage of low attenuation area (%LAA) and the percentage of high attenuation area (%HAA), which were simultaneously evaluated using semi-automatic software program for four CT slices selected from the CT images, were independent contributors to the diffusion capacity of lung for carbon monoxide (DLco) in patients with CPFE [14]. It also clarified the usefulness of the percentage of destroyed lung area, defined as the %LAA+%HAA, in the longitudinal study [15].

In this study, a commercially available software program, which was developed with the density mask technique using these two thresholds, was used for automatically and simultaneously assessing both the low attenuation volume (LAV) and high attenuation volume (HAV) based on volumetric image data of whole lungs in patients with COPD and IPF. In the first part, we assessed the validity of the quantitative assessment performed by the software program as compared with a visual assessment using an established method, and determined cut-off values of the LAV and HAV for detecting emphysema and pulmonary fibrosis on chest CT. In the second part, we investigated the usefulness of the quantitative CT analysis as compared with pulmonary function in patients with COPD and IPF, and investigated whether the utility of the quantitative CT analysis could improve by assessing the destroyed lung volume (DLV), defined as the LAV + HAV.

## Methods

### *Subjects and protocol*

This was a prospective cohort study of consecutive patients with COPD and IPF. A total of 80 subjects (40 patients with COPD and 40 patients with IPF) were enrolled via the outpatient clinic of Shinshu University Hospital from April 2016 to October 2019. The diagnosis of COPD was based on the GOLD Report [16]. The diagnosis of IPF was based on the ATS/ERS/JRS/ALAT guidelines [17-18]. Patients with chronic hypersensitivity pneumonitis, ILD due to autoimmune disease, drug-induced ILD, sarcoidosis, pneumoconiosis, lung cancer, cardiovascular diseases or late sequelae of pulmonary tuberculosis were excluded from the study. Patients who had suffered from a respiratory tract infection or exacerbation of COPD or IPF in the previous six months were also excluded. All patients underwent chest CT and pulmonary function tests within a 1-month interval. Eleven non-smoking healthy control subjects without any respiratory diseases or cardiovascular diseases also participated in the study and underwent spirometry and chest CT.

We investigated correlations between the quantitative assessment performed by the software program and the visual assessment based on the previous reports [19-24] in patients with COPD and IPF. We determined sensitivity and specificity of LAV and HAV to detect emphysema and pulmonary fibrosis, respectively, which were detected in the visual assessment. We also investigated the correlations between the pulmonary function parameters and quantitative assessment parameters.

The study protocol was approved by the institutional review board of Shinshu University School of Medicine (Matsumoto, Japan). Each subject provided written informed consent to be included in the study (approval number: 3294, date of approval: December 9, 2015).

### ***Quantitative CT assessment by the software program and visual CT assessment***

All patients underwent chest CT at inspiratory breath-hold in supine position using a 64-row multi-detector CT scanner (LightSpeed VCT, GE Healthcare, Little Chalfont, Buckinghamshire, UK). The settings of CT scanner were as follows: 120 kV tube voltage, variable tube current, collimation of 64 x 0.625 mm and rotation time of 0.4 second. Image reconstruction was performed using the Standard algorithm with a slice thickness of 0.625 mm. We obtained the Digital Imaging and Communications in Medicine (DICOM)-formatted volumetric image data of whole lungs after scanning. The CT images were automatically analyzed by our Windows® computer using an image-analyzing software program (INTAGE Station LungVision® version 3.0; Cybernet, Inc., Tokyo, Japan). Through automatic procedures, it was possible to isolate the lung parenchyma from the mediastinum and thoracic wall, and then determine the percentage of the LAV (LAV%) and HAV (HAV%) in a few minutes. The LAV% was defined as the percent of lung tissue  $\leq -950$  HU based on previous studies [4, 8-11]. The HAV% was defined as the percent of lung tissue  $\geq -700$  HU based on previous studies [12-13]. The percentage of destroyed lung volume (DLV%) was defined as LAV%+HAV%.

In order to investigate whether the LAV% and HAV% could reflect the extent of emphysema and pulmonary fibrosis, respectively, we assessed the validity of the quantitative assessment performed by the software program as compared with a visual assessment using an established method. The visual

assessment was performed based on the method of previous reports [19-24]. Emphysema was scored visually in the bilateral upper, middle and lower lung fields according to the methods of Goddard et al [25]. The visual score of low attenuation area (LAA) was calculated as the sum of the scores of the six lung fields (possible scores range, 0-24). The detection of pulmonary fibrosis on chest CT was performed visually as previously described [17-18]. The extent of IPF was scored visually to grade the severity as previously described [26].

### **Pulmonary function tests**

All patients underwent spirometry and measurements of the diffusion capacity of lung for carbon monoxide (DLco), DLco corrected for alveolar volume (DLco/VA), a global measure of ventilation heterogeneity (the slope of phase III of the single breath nitrogen washout test [ $\Delta N_2$ ]), the functional residual capacity (FRC), the total lung capacity (TLC) and the residual volume (RV) by using a pulmonary function testing system (Chestac-8900<sup>®</sup>; CHEST Co., Ltd., Tokyo, Japan), as previously described [19-24]. We also evaluated the composite physiologic index (CPI) which was calculated based on pulmonary function parameters [24]. The formula for calculating the CPI was as follows:  $91.0 - [0.65 \times \text{percent predicted DLco}] - [0.53 \times \text{percent predicted forced vital capacity (FVC)}] + [0.34 \times \text{percent predicted forced expiratory volume in 1 second (FEV}_1\text{)}]$  [27].

### **Statistical analyses**

Statistical analyses were conducted using the software program (StatFlex<sup>®</sup> version 6.0; Artech, Osaka, Japan). Simple correlations were examined by calculating Pearson's correlation coefficients. A receiver operating characteristic curve (ROC) analysis was performed to determine sensitivity and specificity of LAV% and HAV% to detect emphysema and pulmonary fibrosis, respectively, which were detected in the visual assessment. The ROC analysis was also performed to determine cut-off values of the LAV% and HAV% for detecting emphysema and pulmonary fibrosis, respectively, because these parameters must include normal anatomical structures, such as pulmonary arteries in the HAV%. Continuous variables between two groups were compared using the Student's t-test. Continuous variables among three groups were compared using one-way analysis of variance followed by the Tukey-Kramer multiple comparisons. P-values of less than 0.05 were considered to indicate statistical significance in all of the statistical analyses.

## **Results**

**Table 1** shows the clinical characteristics and chest CT findings in the healthy control, COPD and IPF groups. **Table 2** shows the details of the pulmonary function in these groups. The FEV<sub>1</sub>/FVC was significantly lower and the VC, FVC, FRC, RV and TLC significantly higher in the COPD group than in the IPF group. The DLco was significantly lower in the IPF group than in the COPD group.

**Figure 1a** shows the correlation between the LAV% and the visual score of LAA ( $r=0.865$ ,  $p<0.001$ ). The ROC analysis revealed 86.8% sensitivity and 84.2% specificity for LAV% to detect emphysema on a visual assessment, using 1.5% as the cut-off value (**Figure 1b**). **Figure 2a** shows the correlation between HAV% and the pulmonary fibrosis severity of the visual assessment ( $r=0.840$ ,  $p<0.001$ ). The ROC analysis revealed 87.5% sensitivity and 96.1% specificity for HAV% to detect pulmonary fibrosis on a visual assessment, using 12% as the cut-off value (**Figure 2b**).

**Tables 3** and **4** show the correlations between the pulmonary function parameters and quantitative assessment parameters in the COPD and IPF groups, respectively. There were significant correlations between the LAV% and the parameters of diffusion capacity of the lung (DLco, DLco/VA), between the LAV% and delta N<sub>2</sub>, between the DLV% and the parameters of diffusion capacity of the lung (DLco, DLco/VA), and between the DLV% and delta N<sub>2</sub> in the COPD group. There were also significant correlations between the DLV% and DLco, between the LAV% and DLco/VA, and between the DLV% and the CPI in the IPF group. **Figure 3a** and **3b** show the correlation between the DLV% and DLco in patients with COPD and IPF, respectively ( $r=-0.792$ ,  $p<0.001$  and  $r=-0.726$ ,  $p<0.001$ , respectively). **Figure 3c** shows the correlation between the DLV% and DLco in total patients with COPD and IPF ( $r=-0.757$ ,  $p<0.001$ ). **Figure 4** shows the correlation between the DLV% and the CPI in patients with IPF ( $r=0.825$ ,  $p<0.001$ ).

**Figures S1, S2, S3** and **S4** are box-and-whisker diagrams of the total lung volume, LAV%, HAV% and DLV% in the healthy control, COPD and IPF groups [see Additional file 1, 2, 3 and 4]. The total lung volume was significantly lower in the IPF group than in the other groups. The LAV% was significantly higher in the COPD group than in the other groups. The HAV% was significantly higher in the IPF group than in the other groups. The DLV% was significantly lower in the healthy control group than in the other groups. There was no significant difference in the DLV% between the COPD and IPF groups.

## Discussion

The aim of this study was to investigate the usefulness of quantitative CT analysis using a commercially available software program through its simple and automatic procedures. The software program, which was developed with the density mask technique using the two thresholds, was used for simultaneously assessing both the LAV and HAV to detect emphysema and pulmonary fibrosis. The ROC analysis revealed a high sensitivity and high specificity for LAV% and HAV% to detect emphysema and pulmonary fibrosis, respectively, which were detected on a visual assessment. The parameters of the software-based quantification were able to predict some pulmonary function parameters. In particular, the DLV% was found to be significantly correlated with the diffusion lung capacity in patients with COPD as well as in those with IPF. The DLV% was also significantly correlated with the DLco in total patients with COPD and IPF.

Imaging software programs can provide highly accurate and reproducible measurements [28]. There is evidence to suggest that quantitative emphysema is better correlated with the morphological measure of emphysema than visual scoring [29–30]. Although fully automated quantitative CT eliminates inter- and

intra-observer variation, it is important to note that high-quality quantitative CT requires verification by an expert analyst, particularly in clinical applications where quantitative CT may be used to make a diagnosis or where the findings may influence treatment decisions [28]. Thus, the present study confirmed a good correlation between the results of the quantitative assessment performed by the software program and the visual assessment using an established method [19–24].

A few devised methods of density histogram, density mask technique, and texture classification method have been reported to be potentially useful in clinical practice due to their convenience despite scarce evidence in large cohorts [5]. The texture classification method can be used for the differentiation of the parenchymal pathology associated with both emphysema and interstitial lung diseases [31]; however, this method is significantly more expensive computationally [5]. The density histogram can evaluate the extent of emphysema or pulmonary fibrosis using kurtosis and skewness scores; however, these parameters are not “user friendly” in routine practice [12]. Thus, the density mask technique is more often used because of its convenience and universal applicability as a method based on CT values [5, 32]. The texture classification method appears to be more successful than the density mask analysis [5]; however, our findings suggest that simultaneously assessing both the LAV and HAV based on volumetric image data of whole lungs may improve the utility of the density mask technique due to the software program’s simple and automatic procedures. Thus, the density mask technique may be useful in clinical practice as well as the texture classification method.

In the previous study, a semi-automatic software program was used for simultaneously assessing both the %LAA and %HAA in four CT slices selected from the CT images in patients with CPFE [14]. The study revealed that the %HAA and %AA, defined as %LAA+%HAA, were significantly correlated with DLco. In this study, a commercially available software program was used for automatically and simultaneously assessing both the LAV% and HAV% based on volumetric data of whole lungs in patients with COPD and IPF. The results of these studies seem to be consistent, although their patient populations were different. We found that the DLV% was significantly correlated with the DLco without disease-specificity in patients with COPD and IPF. Our methodology is easy to apply in clinical practice by the advantage of the simple and automatic procedures, which can be performed in a few minutes.

We found that the DLV% was slightly better correlated with the DLco and DLco/VA, which reflected the diffusion lung capacity, than the LAV% in patients with COPD. The LAV% has been shown to be negatively correlated with the DLco and DLco/VA in patients with COPD in previous studies [33]. In addition, the high attenuation areas (HAA), which was defined as regions with an attenuation between – 600 and – 250 HU, have been shown to be associated with cigarette smoking [34]. The HAA has also been shown to be associated with biomarkers of inflammation, extracellular matrix remodeling, a reduced lung function and an increased risk of death among community-dwelling adults [35]. This may explain why the DLV%, which is defined as the LAV%+HAV%, seems to be better correlated with the diffusion capacity than the LAV%, as all patients with COPD had a smoking history of > 10 pack-years in the present study, and the pathological changes observed in COPD include chronic inflammation [16].

The DLV% was strongly correlated with parameters of diffusion lung capacity in Fig. 3a, 3b and 3c, suggesting that the DLV%, which is easily obtained by chest CT, may be useful for predicting the diffusion lung capacity when patients with COPD or IPF cannot undergo pulmonary function tests for some reason. In addition, the DLV% was also strongly correlated with the CPI in patients with IPF. The mortality rate in IPF was predicted more accurately by the CPI than by each pulmonary function parameter, and a subanalysis demonstrated that the better fit of the CPI was ascribable to a correction of the confounding effects of emphysema [27]. These findings suggest that the DLV% can predict mortality in patients with IPF.

There was no significant difference in the HAV% between the healthy control and COPD groups. This finding seems to be inconsistent with decreases in alveolar and capillary surface area in patients with COPD who have apparent emphysema on chest CT. In the present study, some patients with COPD had bronchial wall thickness and little emphysema, which may have resulted in an increase of the HAV%. In addition, the previous study revealed that more than half of lobectomy specimens excised from smokers with lung cancer had interstitial fibrosis pathologically; however, these patients did not have CT findings of interstitial lung disease visually, and some of them had emphysema [36], which might result in an increase of HAV% in a software-based quantitative CT analysis in patients with COPD. For these reasons, we speculated that the HAV% became equivalent between the healthy control and COPD groups.

Several limitations associated with the present study warrant mention. First, this was a single-center, uncontrolled-design prospective study with a lack of statistical power, as the sample size was small. Additional studies with large populations are required to confirm our results. Second, the IPF in some patients with IPF was not pathologically–proven IPF in this study, because patients who underwent surgery for lung cancer resection or a lung biopsy before undergoing chest CT and pulmonary function tests were excluded from the study, since the procedure influences the results of the pulmonary function and quantitative CT analysis. However, the role of CT has been expanded to involve making a diagnosis of IPF without a surgical lung biopsy. Third, there may be differences in image acquisition and analysis protocols between this study and previous studies using quantitative CT. Therefore, an international consensus concerning the methodology of quantitative CT should be obtained and applied to future studies. Forth, there is a fundamental problem in software-based quantification by the density mask technique when analyzing the LAV% to detect emphysema in patients with IPF. Honeycombing areas can be extracted by the density mask technique based on the presence of LAA surrounded by thick walls [37]. Thus, we assumed that the LAV% would differ between pulmonary fibrosis with and without honeycombing, which may affect the results. Fifth, although the diagnosis of IPF was based on the ATS/ERS/JRS/ALAT guidelines [17–18], IPF cases were identified using two different definitions according to the time of diagnosis, which might have affected the results.

## Conclusions

The quantitative CT analysis using the commercially available software program could be useful in clinical practice by the advantage of the simple and automatic procedures. The utility of the quantitative

CT analysis could improve by assessing the DLV%.

## Declarations

### Abbreviations

COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; LAV, low attenuation volume; HAV, high attenuation volume; DLV, destroyed lung volume; LAV%, percentage of low attenuation volume; HAV%, percentage of high attenuation volume; DLV%, percentage of destroyed lung volume; VC, vital capacity; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of lung for carbon monoxide; DLco/VA, diffusing capacity of lung for carbon monoxide corrected for alveolar volume; delta N<sub>2</sub>, slope of phase III of the single-breath nitrogen washout test; CPI, composite physiologic index; ROC, receiver operating characteristic; N/A, not applicable

### Ethics approval and consent to participate

The study protocol was approved by the institutional review board of Shinshu University School of Medicine (Matsumoto, Japan). Each subject provided written informed consent to be included in the study (approval number: 3294, date of approval: December 9, 2015).

### Consent for publications

Not applicable

### Availability of data and materials

The datasets used and/or analyzed are available from corresponding author upon reasonable request after the study design is approved by the appropriate ethics review boards

### Competing interests

The authors declare that they have no competing interests.

### Funding

There is no funding source to declare.

### Author's contributions

YK and KF conceived and designed the study; YK, KF, MY, YW, FU, TK, KF and MH acquired the clinical data; YK and KF conducted the statistical analyses; SK and KF were involved radiologic support. YK wrote the paper; KF and MH reviewed and edited the manuscript; All authors read and approved the manuscript.

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Not applicable

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## Supplementary Files Legend

Supplementary information

Additional file 1: Figure S1. The box-and-whisker diagrams of the total lung volume in the healthy control ( $n = 11$ ), COPD ( $n = 40$ ) and IPF ( $n = 40$ ) groups.

Additional file 2: Figure S2. The box-and-whisker diagrams of the LAV% in the healthy control ( $n = 11$ ), COPD ( $n = 40$ ) and IPF ( $n = 40$ ) groups.

Additional file 3: Figure S3. The box-and-whisker diagrams of the HAV% in the healthy control ( $n = 11$ ), COPD ( $n = 40$ ) and IPF ( $n = 40$ ) groups.

Additional file 4: Figure S4. The box-and-whisker diagrams of the DLV% in the healthy control ( $n = 11$ ), COPD ( $n = 40$ ) and IPF ( $n = 40$ ) groups.

## Tables

Due to technical limitations, all tables are only available for download from the Supplementary Files section.

## Figures

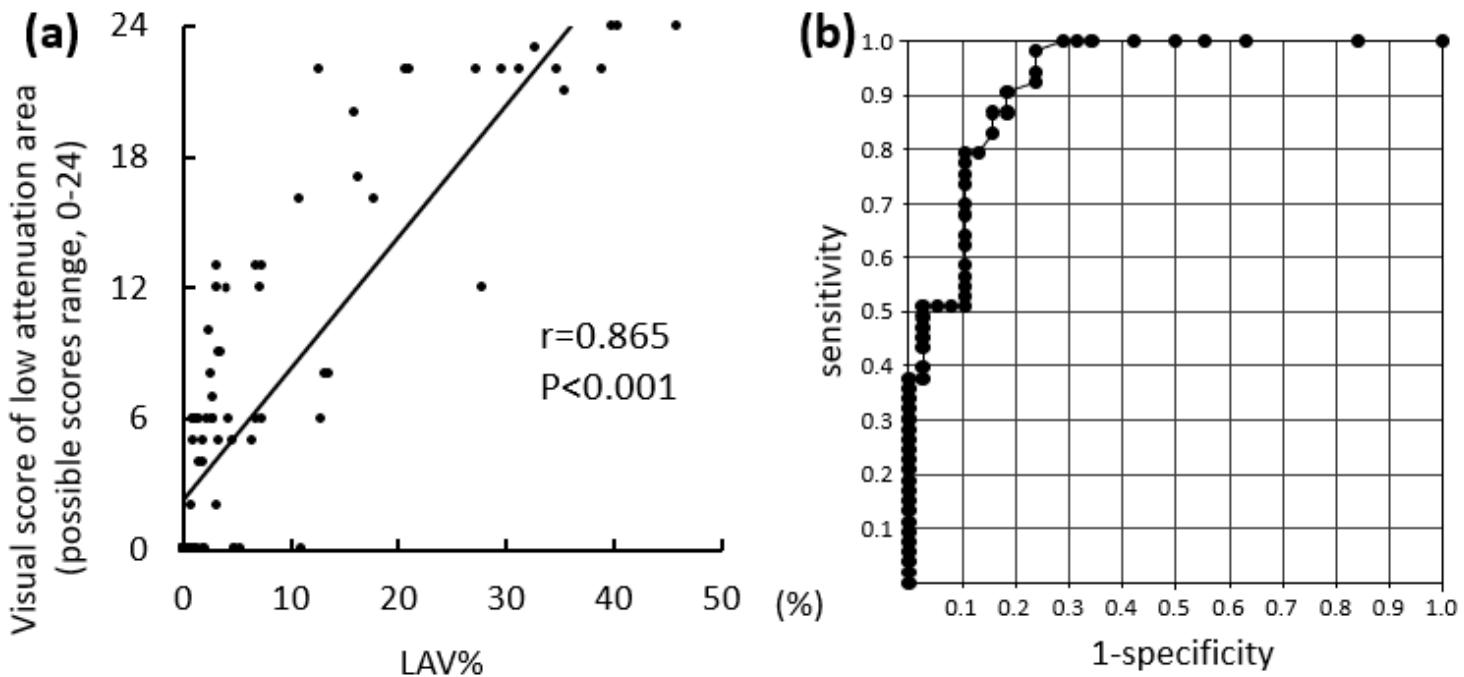
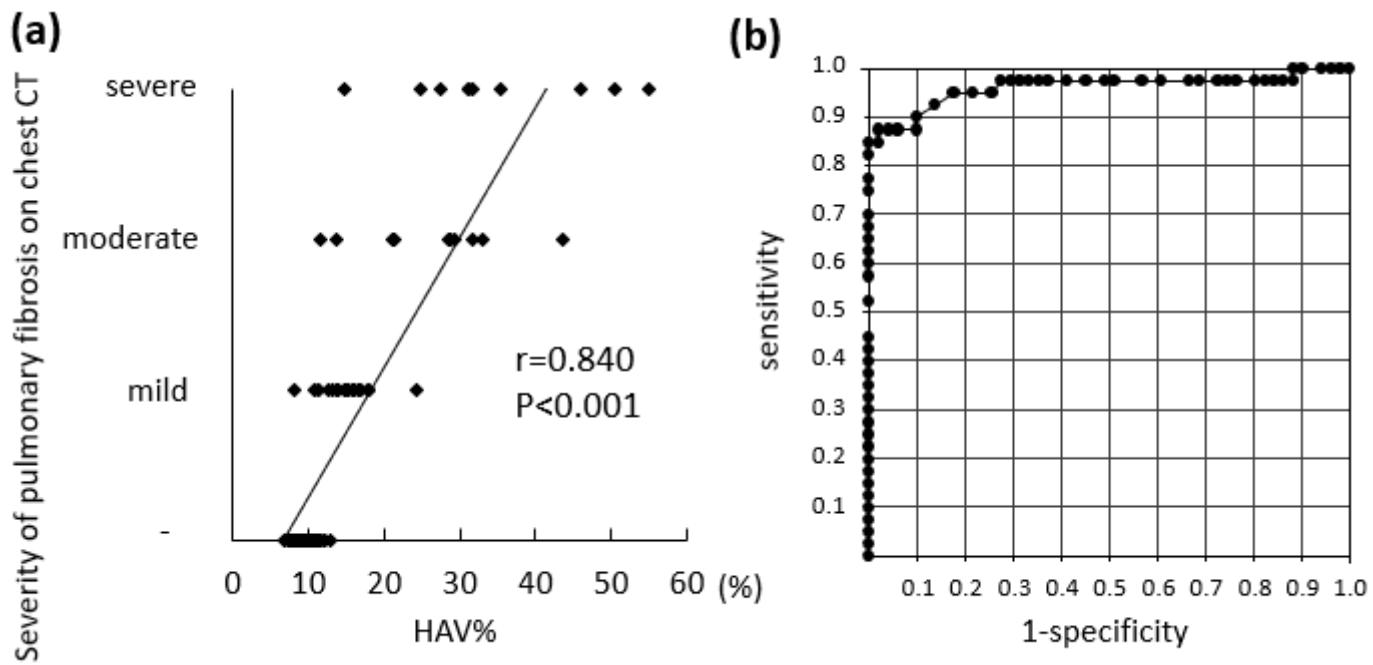


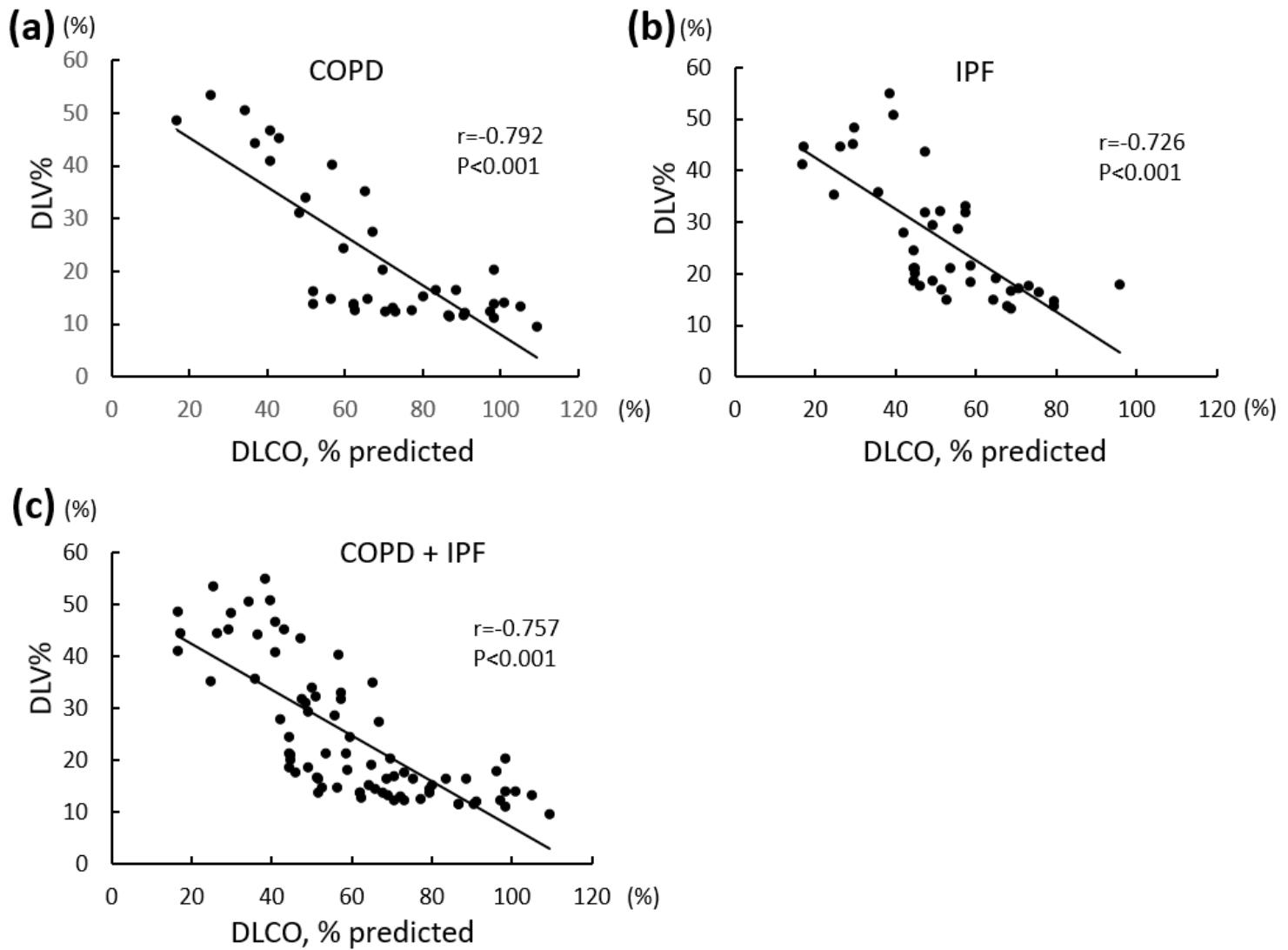
Figure 1

(a) The correlation between the LAV% and the visual score of the LAA in all subjects ( $n=91$ ). (b) The ROC curve of the LAV%. The ROC analysis revealed 86.8% sensitivity and 84.2% specificity for LAV% to detect emphysema on a visual assessment, using 1.5% as the cut-off value (area under the curve=0.926).



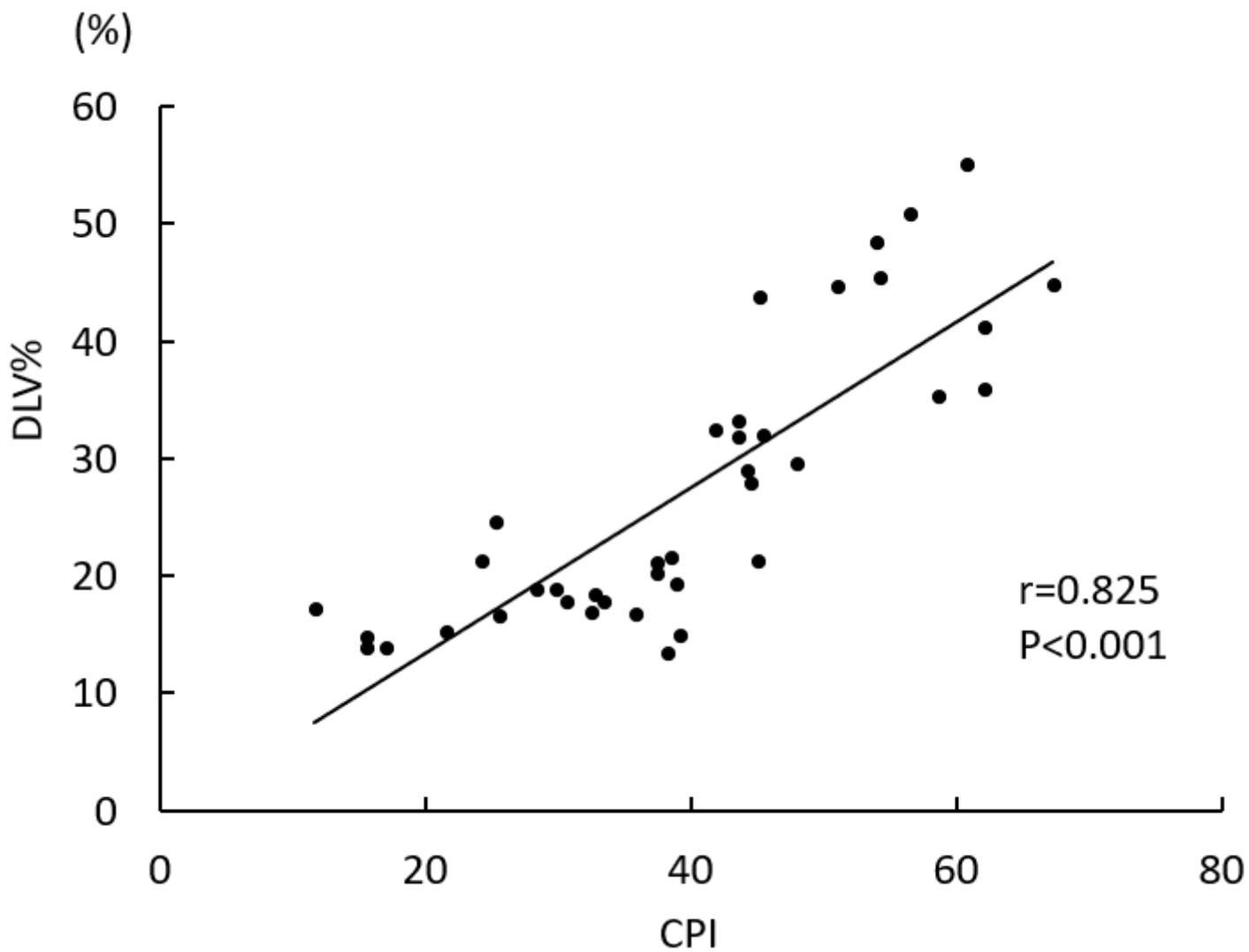
**Figure 2**

(a) The correlation between the HAV% and the severity of pulmonary fibrosis on chest CT in all subjects ( $n=91$ ). (b) The ROC curve of the HAV%. The ROC analysis revealed 87.5% sensitivity and 96.1% specificity of HAV% to detect pulmonary fibrosis on a visual assessment, using 12% as the cut-off value (area under the curve=0.962).



**Figure 3**

(a) The correlation between the DLV% and the DLco in patients with COPD ( $n=40$ ). (b) The correlation between the DLV% and the DLco in patients with IPF ( $n=40$ ). (c) The correlation between the DLV% and the DLco in total patients with COPD and IPF ( $n=80$ ).



**Figure 4**

The correlation between the DLV% and the CPI in patients with IPF (n=40).

## Supplementary Files

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