



# Objective Quantitative CT Evaluation using Different Attenuation Ranges in Patients with Pulmonary Fibrosis: Correlations with Visual Scores

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## Abstract

**Introduction:** Objective quantitative evaluation for the extent of fibrosis has been introduced using CT densitometry in patients with interstitial lung diseases, however, there have been no definitive attenuation cut-off values to evaluate the extent of ground-glass opacity and fibrosis separately. This study was conducted to investigate the relationships between quantitative CT measurements using different attenuation ranges and visual CT scores, and to determine whether the different attenuation ranges can estimate the extent of ground-glass opacity and fibrosis separately in patients with pulmonary fibrosis.

**Methods:** This study included 40 pulmonary fibrosis patients. The extent of an interstitial lesion was defined as a high attenuation area (HAA) using thresholds with pixels between 0 and -700 HU, and the extent of fibrosis was obtained by calculating the mean percentage HAA for the whole lung (%HAA<sub>0/-700</sub>). Likewise, the mean percentage HAA of different attenuation ranges, between -500 and -700 HU and between 0 and -500 HU, were obtained (%HAA<sub>-500/-700</sub> and %HAA<sub>0/-500</sub>, respectively). The extents of ground-glass opacity and lung fibrosis were evaluated visually. The correlations of the %HAAs and visual scores were evaluated using Spearman rank correlation coefficients.

**Results:** There were significant correlations between the mean %HAA<sub>0/-700</sub> and the overall extent of interstitial lung lesions ( $\rho = 0.911$ ,  $p < 0.0001$ ). The mean %HAA<sub>0/-500</sub> had a high correlation coefficient with fibrosis ( $\rho = 0.751$ ,  $p < 0.0001$ ). The mean %HAA<sub>-500/-700</sub> had a high correlation coefficient with ground-glass opacity ( $\rho = 0.739$ ,  $p < 0.0001$ ).

**Conclusion:** Different attenuation ranges can be used to estimate the extent of ground-glass opacity and fibrosis separately.

## Keywords

Pulmonary fibrosis, Computed tomography, Densitometry, CT quantification

## Introduction

In patients with pulmonary fibrosis, the extent of fibrosis on computed tomography (CT) correlates with pulmonary function

[1,2], and it has been reported to be an important factor for predicting its prognosis [3,4]. The extent of fibrosis that can be evaluated by quantitative visual scoring systems is limited due to interobserver variation [5,6]. Therefore, objective quantitative evaluations are essential for reproducibility and for a multicenter study.

Recently, objective quantitative evaluation for the extent of fibrosis has been introduced using CT densitometry in patients with interstitial lung diseases [1,2,7-15]. Shin et al. adopted the threshold attenuation range between -500 HU and -700 HU for the evaluation of the extent of interstitial lung disease, and they found that it had an excellent correlation with the decrease of diffusing capacity of the lungs for carbon monoxide (DLco) [2]. Severzellati et al. evaluated the relationship between several different attenuation ranges and pulmonary function tests (PFTs), and they found that the attenuation range between -400 HU and -700 HU provided a good correlation with DLco in patients with a predominant pattern of ground-glass and reticular opacities without honeycombing [7]. More recently, in patients with combined pulmonary fibrosis and emphysema (CPFE), the extent of interstitial lung lesions was evaluated using an attenuation range between 0 HU and -700 HU [12,13], and significant correlations were found between the quantitative extent of fibrosis and the results of PFTs including DLco. These previous studies showed good correlations between CT densitometry and PFTs, but there have been no definitive attenuation cut-off values to evaluate the extent of interstitial lung lesions.

Although some studies showed good correlations in the extent of interstitial lung lesions between CT densitometry and visual CT scores, these studies evaluated only the total score of interstitial lung lesions [2,12,13]. In patients with interstitial lung diseases, in contrast to patients with emphysema, there are different pathological lesions with different attenuation values. In fact, in the previous study [11], lung attenuation between -750 and -450 HU was considered as the range of ground-glass opacity, lung attenuation between -450 and -150 HU was considered the range of reticular opacity, and lung attenuation between -150 and 100 HU was considered the range of consolidation and fibrosis, but, to the best of our knowledge, there has been no study evaluating the relationships between different

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attenuation ranges and each CT finding in patients with interstitial lung diseases. In particular, separate evaluations of the extent of ground-glass opacity and fibrosis would be important to assess the progression or acute exacerbation of interstitial lung diseases. We hypothesized that quantitative CT measurements with different lung attenuation ranges could evaluate the extent of ground-glass opacity and fibrosis separately.

The purpose of this study was to investigate the relationships between the quantitative CT measurements using different lung attenuation ranges and visual CT scores for the different CT findings or the results of PFTs in patients with pulmonary fibrosis, and to determine whether the different attenuation ranges can be used to estimate the extent of ground-glass opacity and fibrosis separately.

## Methods

### Subjects

This retrospective study was approved by our institutional review board, which waived the need for informed consent. One radiologist reviewed medical records and CT images obtained between January 2011 and December 2014, and patients who underwent non-contrast enhanced CT for the evaluation of pulmonary fibrosis were selected. In these patients, patients who underwent PFTs including DLCO within one week of obtaining CT scans were selected.

The pattern of interstitial pneumonia was examined in accordance with IPF guidelines [16], and was categorized as usual interstitial pneumonia (UIP) pattern; possible UIP pattern; and inconsistent UIP pattern. Two chest radiologists reviewed all CT images retrospectively, and the final assessment was achieved by consensus.

Exclusion criteria included prior cardiopulmonary disease; parenchymal lesions other than interstitial change; pneumothorax or pleural effusions; and image noise that prevented image analysis. Subjects with acute exacerbation of interstitial pneumonia were also excluded. We also excluded patients as noted in the IPF guidelines [16]. Additionally, the presence of connective tissue disease or any other interstitial lung disease such as drug-induced interstitial lung disease, pneumoconiosis, hypersensitivity pneumonitis, and sarcoidosis were excluded.

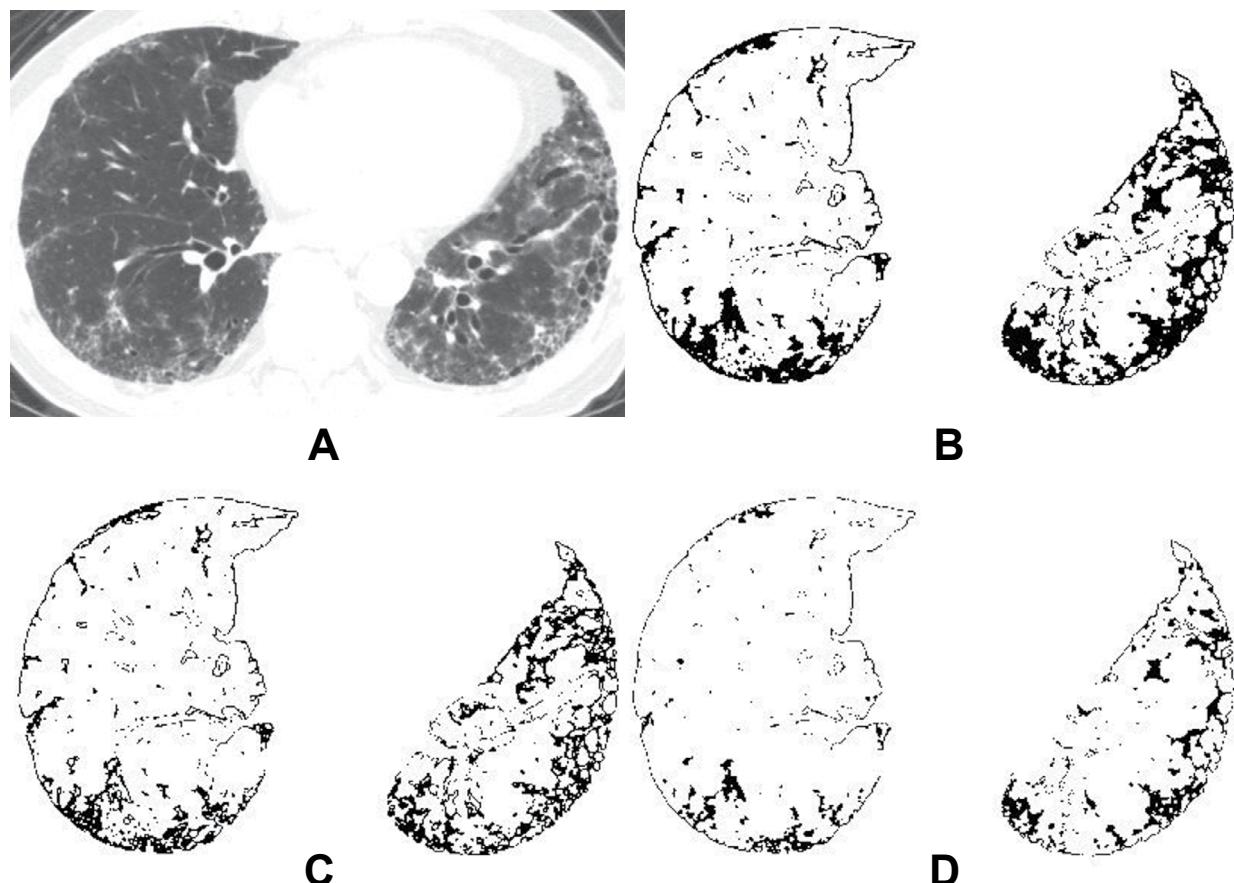
Fifty-seven patients underwent both CT and PFT within one week. According to the CT criteria in this study, 11 patients were excluded because of prior cardiopulmonary disease ( $n = 1$ ), parenchymal lesions other than interstitial change ( $n = 3$ ), pneumothorax or pleural effusions ( $n = 1$ ), and image noise ( $n = 1$ ). In addition, acute exacerbation of interstitial pneumonia ( $n = 1$ ), non-typical IPF ( $n = 5$ ), and the presence of connective tissue disease or any other interstitial lung disease ( $n = 5$ ) were also excluded. Thus, 40 patients were selected for this study.

### CT scanning

CT scans were performed using multi-detector spiral CT scanners (Aquilion, Toshiba Medical) within one breath hold at deep inspiration. CT images were obtained with 120 kV, 200 mA, and all images were reconstructed using a standard reconstruction algorithm with a slice thickness of 2 mm.

### Quantitative CT measurements

For the quantitative CT evaluation, four CT slices were selected from CT images. The first upper lung slice was taken ~1 cm above the upper margin of the aortic arch, the second upper lung slice was



**Figure 1:** (a) Axial CT section of the lung shows segmented area using; (b) Pixels with attenuation range between 0 and -700 HU are highlighted in black on the CT scan. The mean percentage of high attenuation area ( $\%HAA_{0/-700}$ ) is calculated as the percentage of the lung attenuation area between 0 and -700 HU for the total lung area; (c) Pixels with attenuation values between -500 and -700 HU are highlighted in black on the CT scan. The mean percentage of high attenuation area ( $\%HAA_{-500/-700}$ ) is calculated as the percentage of the lung attenuation area between -500 and -700 HU for the total lung area; (d) Pixels with attenuation values between 0 and -500 HU are highlighted in black on the CT scan. The mean percentage of high attenuation area ( $\%HAA_{0/-500}$ ) is calculated as the percentage of the lung attenuation area between 0 and -500 HU for the total lung area.

taken at the carina, the first lower slice was taken ~1 cm below the right inferior pulmonary vein, and the second lower lung slice was taken 2 cm above the lung base. These CT images were analyzed using a semiautomatic image-processing software (Image J Version 1.48 f).

For the evaluation of the extent of interstitial fibrotic change, the lung field was segmented using a threshold technique with all pixels between -200 and -1024 HU [12,13]. When auto segmentation was difficult due to the presence of the sub pleural fibrosis, the boundary of the lung field was traced manually. In reference to previous studies, total interstitial lesion was defined as high attenuation area (HAA) using a threshold with all pixels between 0 and -700 HU [2,11-13]. Also areas with different lung attenuation ranges of -500 and -700 HU, and 0 and -500 HU were calculated. The mean percentage of each HAA in different attenuation ranges was obtained by calculating the mean percentage of each HAA ( $\%HAA_{0/-700}$ ,  $\%HAA_{-500/-700}$ , and  $\%HAA_{0/-500}$ , respectively) (Figure 1).

### Quantitative CT visual scoring

Two radiologists performed quantitative visual scoring, and the extent of pulmonary abnormality was recorded. The mean extent of ground-glass opacity, reticular abnormality, and honeycombing was scored to the nearest 5% in each slice that was used for quantitative measurements of the extent of fibrosis [1]. The mean extent of fibrosis was calculated as the mean of the extent of reticular abnormality and honeycombing [1], and the overall extent of interstitial lesion was calculated as the sum of the mean extent of ground-glass opacity and fibrosis. Observers received training sessions prior to the study, and interobserver variability was evaluated and determined to be satisfactory for consistency in visual CT scoring.

### Pulmonary function tests

PFTs included spirometry and measurement of DLco was performed. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured according to standard techniques. Values for each pulmonary function test were expressed as percentages of predicted values. DLco was measured by the single-breath method, and the predicted value for DLco was determined.

### Statistical analysis

The correlations between each  $\%HAA_{0/-700}$ ,  $\%HAA_{-500/-700}$ , and  $\%HAA_{0/-500}$  and visual CT scores including ground-glass opacity, fibrosis, and overall extent of interstitial lesion, and also the correlations with the results of PFT were evaluated using Spearman rank correlation coefficients. Multiple linear regression analysis using the ground-glass opacity and fibrosis as dependent variables was also performed to evaluate the impact of measured  $\%HAA_{-500/-700}$  and  $\%HAA_{0/-500}$ . For all statistical analyses, the null hypothesis was rejected at the 5% level. All statistical analyses were performed using JMP 8.0 software (SAS Institute, Cary, NC).

### Results

Patient's characteristics, the results of PFTs and quantitative CT measurement are shown in table 1. The mean  $\%HAA_{0/-700}$  was  $22.9\% \pm 8.6$ , and the mean  $\%HAA_{-500/-700}$  and  $\%HAA_{0/-500}$  was  $11.4\% \pm 6.4$ , and  $11.4\% \pm 4.1$ , respectively. In regard to the pattern of interstitial pneumonia, 10 patients (25%) were classified into UIP, 17 patients (42.5%) were classified into possible UIP pattern, and 13 patients (32.5%) were classified into inconsistent UIP pattern.

The mean total extent of interstitial lung lesion, ground-glass opacity, and fibrosis were  $25.2\% \pm 9.3$ ,  $9.3\% \pm 5.0$ , and  $15.9\% \pm 7.1$ , respectively. Mean visual score of fibrosis was relatively higher than  $\%HAA_{0/-500}$ . The correlations between the %HAA and visual CT score are shown in table 2. There were significant correlations between the mean  $\%HAA_{0/-700}$  and ground-glass opacity ( $\rho = 0.596$ ,  $p < 0.0001$ ), fibrosis ( $\rho = 0.765$ ,  $p < 0.0001$ ), and overall extent of interstitial lesion ( $\rho = 0.911$ ,  $p < 0.0001$ ) (Figure 2). The mean  $\%HAA_{-500/-700}$  had a high correlation coefficient with ground-glass opacity ( $\rho = 0.739$ ,  $p < 0.0001$ ) (Figure 3). The mean  $\%HAA_{0/-500}$  had a high correlation

**Table 1:** Patients characteristics, pulmonary function and CT measurements.

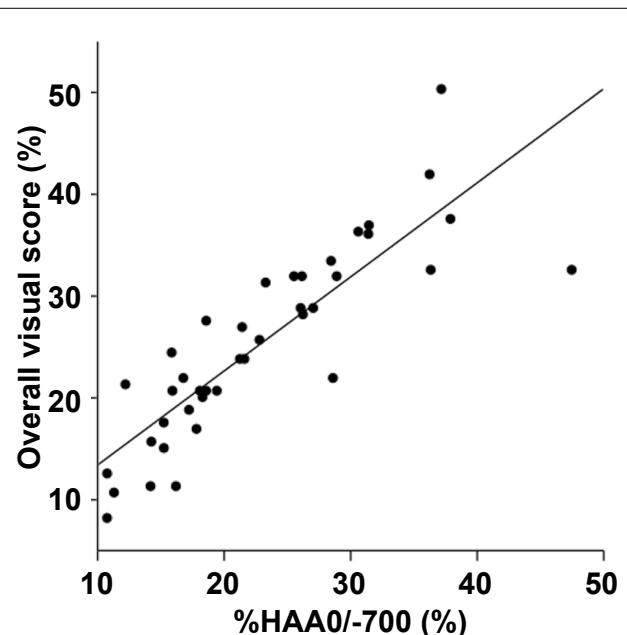
Age (year)	71 ± 7
Male/female	37/6
BMI	$23.8 \pm 2.6$
Pack-years	$43.9 \pm 27.9$
FVC %predicted (%)	$81.9 \pm 17.5$
FEV1 %predicted (%)	$85.5 \pm 16.7$
DLco %predicted (%)	$51.5 \pm 20.1$
$\%HAA_{0/-700}$ (%)	$22.9 \pm 8.6$
$\%HAA_{-500/-700}$ (%)	$11.4 \pm 6.4$
$\%HAA_{0/-500}$ (%)	$11.4 \pm 4.1$
Visual score - GGO (%)	$9.3 \pm 5.0$
Visual score - Fibrosis (%)	$15.9 \pm 7.1$
Overall interstitial lesion (%)	$25.2 \pm 9.3$

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second; DLco = diffusing capacity of lung for carbon monoxide; %HAA = percentage of high attenuation area

**Table 2:** Correlations between CT measurements and visual score.

	Ground-glass opacity		Fibrosis		Overall interstitial lesion	
	$\rho$	$p$	$\rho$	$p$	$\rho$	$p$
$\%HAA_{0/-700}$	0.596	<0.0001	0.765	<0.0001	0.911	<0.0001
$\%HAA_{-500/-700}$	0.739	<0.0001	0.574	0.0001	0.783	<0.0001
$\%HAA_{0/-500}$	0.487	0.0014	0.751	<0.0001	0.850	<0.0001

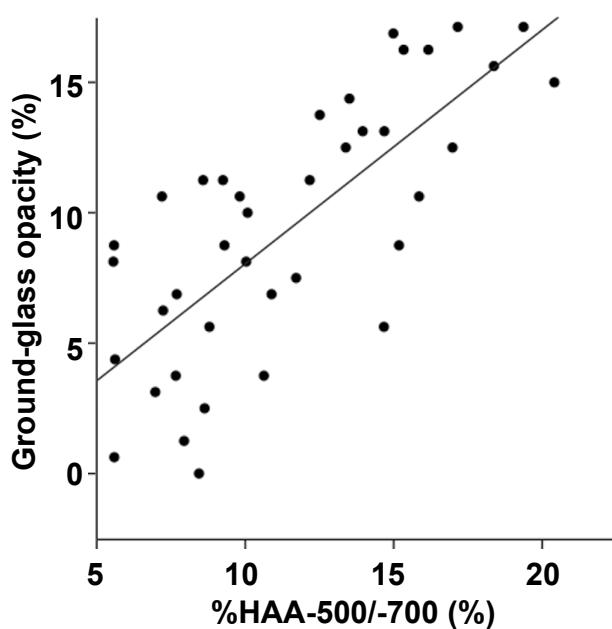
Definition of abbreviations: %HAA = percentage of high attenuation area; GGO = ground glass opacity



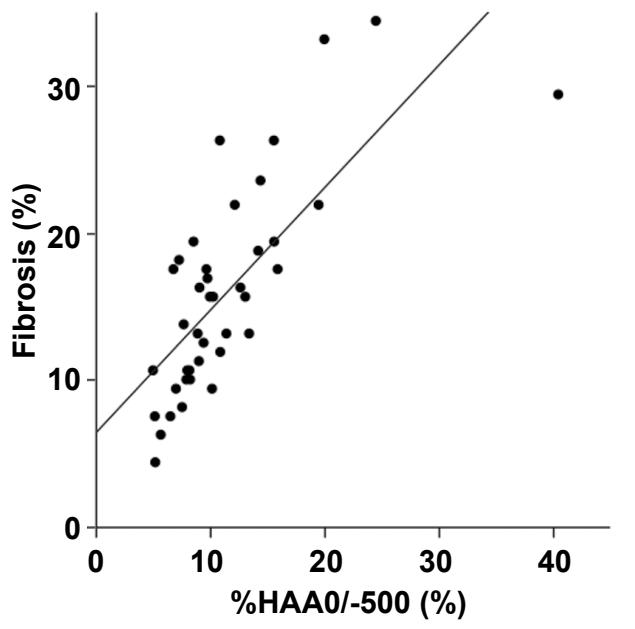
**Figure 2:** The correlations between  $\%HAA_{0/-700}$  and the overall extent of interstitial lesion. There is a significant correlation ( $\rho = 0.911$ ,  $p < 0.0001$ ).

coefficient with fibrosis ( $\rho = 0.751$ ,  $p < 0.0001$ ) (Figure 4), however, there was also had a good correlation coefficient between  $\%HAA_{0/-700}$  and fibrosis ( $\rho = 0.765$ ,  $p < 0.0001$ ). On multiple linear regression analysis with the results of ground-glass opacity and fibrosis as dependent variables,  $\%HAA_{-500/-700}$  was independent contributors to ground-glass opacity ( $r^2 = 0.564$ ,  $p < 0.001$ ). Meanwhile, although both  $\%HAA_{0/-500}$  and  $\%HAA_{-500/-700}$  were independent contributors to fibrosis ( $r^2 = 0.635$ ,  $p < 0.0001$ ), the predictive power of  $\%HAA_{0/-500}$  ( $p < 0.0001$ ) was superior to that of  $\%HAA_{-500/-700}$  ( $p = 0.01$ ) (Table 3).

The correlations between the CT measurements and PFTs are shown in table 4. The significant negative correlations were found between all %HAs and DLco% predicted, FVC% predicted, or FEV1% predicted. The correlation coefficients between  $\%HAA_{-500/-700}$  and those results of PFTs were slightly lower than that between  $\%HAA_{0/-700}$  or  $\%HAA_{0/-500}$  and PFTs results.



**Figure 3:** The correlations between %HAA<sub>-500/-700</sub> and the extent of ground-glass opacity. There is a significant correlation ( $\rho = 0.739$ ,  $p < 0.0001$ ).



**Figure 4:** The correlations between %HAA<sub>0/-500</sub> and the extent of fibrosis. There is a significant correlation ( $\rho = 0.751$ ,  $p < 0.0001$ ).

**Table 3:** Independent Contributions of %HAA0/-500 and %HAA-500/-700.

Variable coverable	Partial regression coefficient	p value
Ground-glass opacity		
%HAA <sub>0/-500</sub>	-0.080	0.490
%HAA <sub>-500/-700</sub>	0.772	<0.0001
Fibrosis		
%HAA <sub>0/-500</sub>	0.660	<0.0001
%HAA <sub>-500/-700</sub> %HAA	0.284	0.001

Definition of abbreviations: %HAA = percentage of high attenuation area; GGO = ground glass opacity

## Discussion

In this study, we found that lung attenuation with the range of -500 and -700 HU had a good correlation with the extent of ground-glass opacity, and lung attenuation with the range of 0 and -500 HU had an excellent correlation with the extent of fibrosis. Thus, these different lung attenuation ranges could estimate the extent of each ground-glass opacity and fibrosis separately in some degree. Our current study is a first report evaluating the correlation between objective CT measurements with different lung attenuation ranges and visual CT score in patients with interstitial fibrosis.

For the quantitative CT evaluation, densitometry has been adopted in various lung diseases. Indeed, quantitative CT evaluation of emphysema has been used widely. In contrast, quantitative evaluation of the extent of interstitial lung lesions has not been widespread. The possible main reason may be that there has not been established definition of threshold ranges for the quantitative evaluation of the extent of interstitial change.

Shin et al. demonstrated that there was a positive correlation between the areas with attenuation range of -500 to -700 HU and overall extent of interstitial lung lesion measured using visual score [2]. In our current study, similar to their study, %HAA<sub>-500/-700</sub> also had a good correlation with overall extent of interstitial lung lesion. In addition, the results of the correlation with DLco were also similar. Thus, one might think that the %HAA<sub>-500/-700</sub> could evaluate not only the extent of ground-glass opacity but also overall extent of interstitial lung lesion. However, the mean %HAA<sub>-500/-700</sub> (11%) was different from the mean overall extent of interstitial lung lesion (25%). Thus, the area with attenuation range between -500 HU and -700 HU should be adopted for the evaluation of the extent of ground-glass opacity.

**Table 4:** Correlations between CT measurements and pulmonary functions.

	DLco %P		FVC %P		FEV1 %P	
	p	p	p	p	p	p
%HAA <sub>0/-700</sub>	-0.571	0.0001	-0.785	<0.0001	-0.623	<0.0001
%HAA <sub>-500/-700</sub>	-0.406	0.0094	-0.622	<0.0001	-0.487	0.00014
%HAA <sub>0/-500</sub>	-0.510	0.0008	-0.725	<0.0001	-0.648	<0.0001

Definition of abbreviations: %HAA = percentage of high attenuation area; FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second; DLco = diffusing capacity of lung for carbon monoxide

Although lung attenuation with the range of 0 and -500 HU had an excellent correlation with the extent of fibrosis, interestingly, %HAA<sub>-500/-700</sub> also had an excellent correlation with the extent of fibrosis as with %HAA<sub>0/-500</sub>. So, we did additional evaluation of the relationship between %HAA<sub>-500/-700</sub> and %HAA<sub>0/-500</sub> with Spearman's rank correlation coefficients, and we found high correlation in this relation ( $\rho = 0.936$ ,  $p < 0.0001$ ), which may be able to explain the results. However, as same as %HAA<sub>-500/-700</sub>, the mean %HAA<sub>0/-500</sub> (11%) was different from the mean overall extent of interstitial lung lesion (25%). Thus, the area with attenuation range between 0 and -500 HU should be adopted for the evaluation of the extent of fibrosis.

We know there has been still problem to differentiate ground-glass opacity from fibrosis with CT densitometry technique. Many previous studies showed that there were indispensable overlap of attenuation values between ground-glass opacity and fibrosis [17,18]. In fact, ground-glass opacity can reflect interstitial fibrotic change, and reticular opacity also can be superimposed on ground-glass opacity. These interactions make it difficult to differentiate ground-glass opacity from fibrosis completely. Also those relationships can be related to all %HAs had significant correlation with each visual scores. In addition, quantitative measurement of honeycombing is another problem. Previous study showed that %HAA<sub>-500/-700</sub> had a significant correlation with the extent of honeycombing in small sample subjects [12]. In current study, mean value of visual score of fibrosis was relatively higher than %HAA<sub>0/-500</sub>. Thus, honeycombing cystic air spaces might not be involved in %HAA. Alternative quantitative method should be required to estimate the extent area of honeycombing in a precise manner.

We also found that all %HAA measurements had significant correlations with the results of DLco% predicted. Interestingly, although there was a significant difference between mean %HAA<sub>0/-</sub>

700 (23.1%) and mean %HAA<sub>0/-500</sub> (11.5%), the correlation coefficients between those %HAA and DLco %predicted were very similar. Meanwhile, although there was a significant correlation between %HAA<sub>-500/-700</sub> and DLco, this correlation coefficient was slightly lower than that with %HAA<sub>0/-700</sub> or %HAA<sub>0/-500</sub>. The decline in DLco is likely due to reduced vascular surface area and pulmonary capillary blood volume plus alveolar membrane thickening. Those pathological changes also can be demonstrated as ground-glass opacity on CT findings; therefore, %HAA<sub>-500/-700</sub> may have a significant correlation with the decline in DLco% predicted to some degree. From the results of higher correlation between %HAA<sub>0/-700</sub> or %HAA<sub>0/-500</sub> and DLco% predicted as compared with the relation between %HAA<sub>-500/-700</sub> and DLco% predicted, the decline of DLco may be more related to fibrotic lesion than ground-glass lesion. In fact, additional multiple linear regression analysis using the DLco% predicted as dependent variables for the evaluation of the impact of %HAA<sub>0/-500</sub> and %HAA<sub>-500/-700</sub>, and also the evaluation of the impact of visual score of ground-glass opacity and fibrosis showed that the %HAA<sub>0/-500</sub> and visual score of fibrosis were each independent contributor to DLco% predicted ( $r = -0.397$ ,  $p = 0.01$ , and  $r = -0.629$ ,  $p < 0.0001$ , respectively).

Other objective quantitative CT indexes, such as skewness and kurtosis, have been advocated for the evaluation of the extent of pulmonary fibrosis [1,15,19,20]. These indexes had good correlations with the results of PFTs in patients with interstitial lung diseases [1,15,19,20]. However, skewness and kurtosis cannot be easily obtained. In contrast, densitometry can be conducted with almost all-imaging analysis software. Thus, measurement of %HAA would be practical in both clinical and research field. Furthermore, the densitometry measurement of %HAA is useful not only interstitial fibrosis. Especially, area of different attenuation range can evaluate the extent of ground-glass opacity. Thus, this method can apply many other diseases such as allergic lung diseases or pneumocystis pneumonia, or specific condition of interstitial fibrosis such as acute exacerbation.

This study has some limitations. First, because of the retrospective evaluation, there might be several selection biases in the present subjects. Second, we did not evaluate the relationship between histopathological change and %HAs in pulmonary fibrosis. Third, we did not use spirometric gating during CT acquisition. Lung attenuation can be affected by the phase of respiration.

In conclusion, we found that the objective quantitative evaluation with the area of different attenuation ranges could evaluate ground-glass opacity and fibrosis separately in some degree. In addition, we confirmed that the %HAs could predict the pulmonary functions in patients with pulmonary fibrosis.

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