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Quantitative CT analysis of honeycombing area in idiopathic pulmonary fibrosis: Correlations with pulmonary function tests

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ABSTRACT

Objectives: The 2011 official statement of idiopathic pulmonary fibrosis (IPF) mentions that the extent of honeycombing and the worsening of fibrosis on high-resolution computed tomography (HRCT) in IPF are associated with the increased risk of mortality. However, there are few reports about the quantitative computed tomography (CT) analysis of honeycombing area. In this study, we first proposed a computer-aided method for quantitative CT analysis of honeycombing area in patients with IPF. We then evaluated the correlations between honeycombing area measured by the proposed method with that estimated by radiologists or with parameters of PFTs.

Materials and methods: Chest HRCTs and pulmonary function tests (PFTs) of 36 IPF patients, who were diagnosed using HRCT alone, were retrospectively evaluated. Two thoracic radiologists independently estimated the honeycombing area as Identified Area (IA) and the percentage of honeycombing area to total lung area as Percent Area (PA) on 3 axial CT slices for each patient. We also developed a computer-aided method to measure the honeycombing area on CT images of those patients. The total honeycombing area as CT honeycombing area (HA) and the percentage of honeycombing area to total lung area as CT %honeycombing area (%HA) were derived from the computer-aided method for each patient.

Results: HA derived from three CT slices was significantly correlated with IA ($\rho = 0.65$ for Radiologist 1 and $\rho = 0.68$ for Radiologist 2). %HA derived from three CT slices was also significantly correlated with PA ($\rho = 0.68$ for Radiologist 1 and $\rho = 0.70$ for Radiologist 2). HA and %HA derived from all CT slices were significantly correlated with FVC (%pred.), DL_{CO} (%pred.), and the composite physiologic index (CPI) (HA: $\rho = -0.43$, $\rho = -0.56$, $\rho = 0.63$ and %HA: $\rho = -0.60$, $\rho = -0.49$, $\rho = 0.69$, respectively).

Conclusions: The honeycombing area measured by the proposed computer-aided method was correlated with that estimated by expert radiologists and with parameters of PFTs. This quantitative CT analysis of honeycombing area may be useful and reliable in patients with IPF.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. Honeycombing is one of the key findings on high-resolution computed tomography (HRCT) in IPF. The 2011 American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) statement mentions that the extent of honeycombing on HRCT independently predicts mortality in IPF patients [1–3]. Therefore, quantifying the extent of honeycombing on HRCT helps doctors manage patients with IPF better. The extent of honeycombing has been evaluated as CT visual scores by experts [4–6]. However, the evaluation process is uncertain; the agreements of honeycombing area among expert radiologists and pulmonologists are only from fair to moderate [7].

Pulmonary function tests (PFTs) are considered to be a standard approach to objectively monitoring patients with IPF. Both FVC and DL_{CO} are strongly correlated with extent of the disease, measured histologically or estimated visually on CT images [2]. However, the interpretation of PFTs in IPF patients is confounded by coexistent emphysema [8,9]. The composite physiologic index

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(CPI) was developed to improve on previous prognostic measures in IPF by adjusting for emphysema [8]. The CPI, which is calculated from values of FEV_1, FVC and DL_{CO}, is a more accurate prognostic determinant than any individual parameters of PFTs [8].

A few computer-aided methods have been developed to automatically evaluate the extent of the disease. These methods have been used to classify patterns of fibrotic features on HRCT. The extent of certain fibrotic patterns has been shown to be correlated with PFTs [10,11]. However, there is no report about the agreement of the disease extent measured automatically and estimated visually. To the best of our knowledge, there is no commercially available computer-aided method to automatically evaluate the disease extent.

In this study, we first proposed a computer-aided method for quantitative CT analysis of honeycombing area in IPF patients. We then evaluated the correlations between honeycombing area measured by the method with that identified by radiologists or with parameters of PFTs.

2. Materials and methods

2.1. Patients

All IPF patients who visited the outpatient clinic of our hospital from April 2012 to March 2013 were enrolled in this study. All patients who were diagnosed with IPF based on HRCT criteria alone according to the 2011 IPF guidelines were included. All the four following features of usual interstitial pneumonia (UIP) pattern must be observed on HRCT of each enrolled patient: subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis, and absence of features listed as inconsistent with UIP pattern [1]. Patients with secondary interstitial pneumonitis (such as collagen vascular disease, occupational or environmental exposure, chronic hypersensitivity pneumonitis, and drug-induced pneumonia) were excluded. Thus, 36 patients with IPF were enrolled in this study. The study protocol was approved by our institutional review board (approval number 24-182, May 1, 2013), with a waiver of informed consent due to the retrospective study design.

2.2. CT scans and pulmonary function tests

HRCT scans of the chest were obtained by using Toshiba Aquillion ONE (Toshiba Medical Systems Corp., Otawara, Tochigi, Japan). The CT scanning protocol was spiral mode, 120 kVp, 80 mA, 0.5-s rotation time, 0.5-mm collimation. CT scanning was performed from the lung apices to the lung bases with the patient in the supine position at full inspiration. CT images were reconstructed with 1-mm slice thickness, 10-mm interval, and FC52 kernel.

Among 36 patients enrolled, 27 patients had corresponding PFTs obtained within 30 days of the selected CT scans. The CPI was calculated from the following formula: $91 - (0.65 \times \%\text{predicted } DL_{CO}) - (0.53 \times \%\text{predicted FVC}) + (0.34 \times \%\text{predicted } FEV_1)$ [8]. PFTs were performed in accordance with JRS guidelines [12].

2.3. Evaluation of honeycombing area by radiologists

HRCT images were independently reviewed by two thoracic radiologists who were blinded to the clinical data and lung function of the patients. Both radiologists are board certified diagnostic radiologists, with experience in chest diagnosis of 30 and 15 years. The radiologists made a subjective evaluation of the honeycombing area after reviewing the criteria of honeycombing according to the Fleischner Society's guidelines [13]. The radiologists evaluated three axial CT slices (6 images in bilateral lungs) for each patient: slice 1, at the level of the tracheal carina; slice 2, midway between slices 1 and 3; and slice 3, at the level of the right inferior pulmonary vein. The three CT slices were printed on film papers with a window width of 1500HU and a window level of −650HU. First, the radiologists identified and marked the honeycombing areas on each image (Fig. 1). One analyst used a public domain computer program, ImageJ (Version 1.46. National Institutes of Health, Bethesda, MD, USA), to measure the corresponding honeycombing areas marked on film papers. All the honeycombing areas from the 6 images were summed to get the total honeycombing area as Identified Area (IA) for each patient. The percentage of IA to total lung area was defined as %Identified Area (%IA). Second, the radiologists visually estimated the honeycombing areas on each image as a percentage (to the nearest 5%) of the total lung area; they averaged the percentages from the six images to get the mean percentage of honeycombing area as Percent Area (PA) for each patient. %IA and PA were also scored using the following 5-grade scale: 0, absent; 1, 1 to 25%; 2, 26 to 50%; 3, 51 to 75%; and 4, 76 to 100%. The area of traction bronchiectasis that could not be distinguished from honeycombing area was counted as honeycombing area.

2.4. Quantitative CT analysis of honeycombing area

A computer-aided method for quantitative CT analysis of honeycombing area was developed to automatically measure the honeycombing areas on HRCT images by using ImageJ. Minimal user intervention by one analyst was required to exclude non-lung structures such as the trachea, large blood vessels, and large bronchi near the hilum.

To develop the method, the following procedures were performed: (1) We randomly chose three IPF patients. (2) We extracted the pixels that had CT attenuation value under a certain threshold (Fig. 2B). To decide the best cut-off value, we compared 11 different thresholds of CT attenuation value ranging from −650Hounsfield

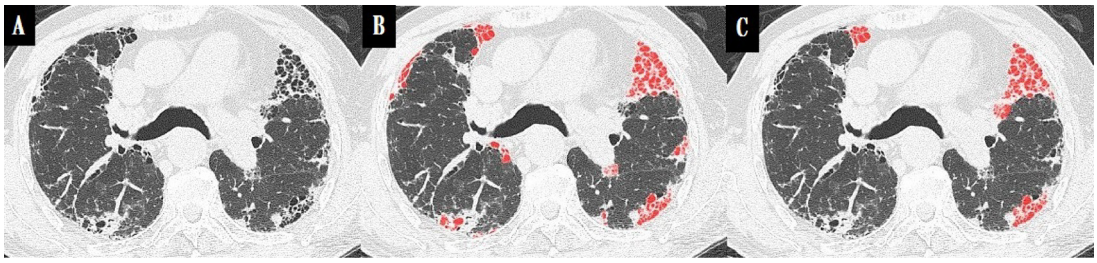

Fig. 1. Honeycombing area estimated by two radiologists. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
Seventy eight years old man with IPF. (A) Original CT image at the level of the tracheal carina in lung window setting. (B) The red areas are honeycombing lesions identified manually by Radiologist 1; the total honeycombing area for this CT slice was 849 mm^2. (C) The red areas are honeycombing lesions identified manually by Radiologist 2; the total honeycombing area for this CT slice was 646 mm^2.

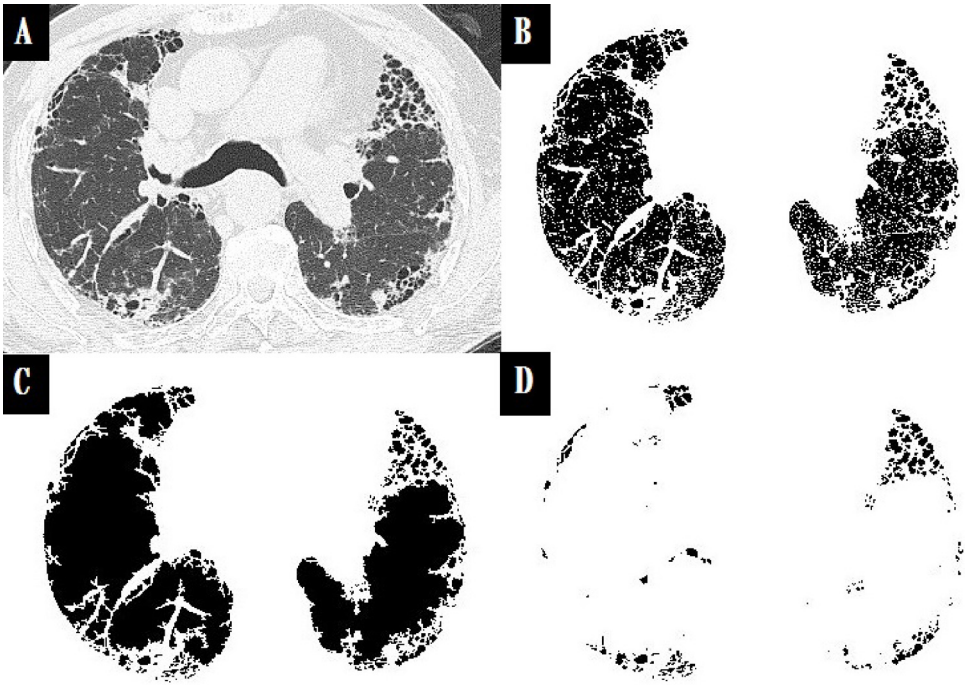

Fig. 2. Quantitative CT analysis method.
(A) Original CT image at the level of the tracheal carina of the same patient as in Fig. 1. (B) At the threshold of −720 HU, all the pixels with CT attenuation value under −720 HU are extracted and displayed in black. (C) The small white pixels that four directions were surrounded by the black pixels extracted by the previous process (2B) are changed to the black pixels. (D) At the cut-off value of 150 mm^2, areas smaller than 150 mm^2 are classified as honeycombing areas. By adding all honeycombing areas together, the CT honeycombing area for this slice is 900 mm^2.

units (HU) to −750HU at every 10HU. (3) We automatically selected the small white pixels surrounded by the black pixels extracted by the previous process, and changed the color from the white to the black (Fig 2C). (4) We extracted the area that had their each size smaller than a certain cut-off value as honeycombing areas (Fig 2D). To decide the best cut-off value, we compared 10 different size ranging from 50 mm^2 to 500 mm^2 at every 50 mm^2. (5) The total honeycombing area was derived by adding all the honeycombing areas from all chosen CT slices together. The total honeycombing area was defined as CT honeycombing area (HA) for each patient. The percentage of HA to total lung area was defined as CT %honeycombing area (%HA).

Based on the thresholds of CT attenuation value and the cut-off values of area size, we had 110 ways to calculate the HA for each patient. The best threshold of CT attenuation value and the best cut-off value of area size were determined by the mean Jaccard index from the three patients. Jaccard index (X, Y) was defined as $|X \cap Y| / |X \cup Y|$, where X was the HA and Y was the IA by one analyst [14].

After the best threshold and the best cut-off value were determined, we applied the program to all enrolled patients. The quantitative CT analysis of honeycombing area was divided into two steps. First, the low attenuation areas surrounded by thick walls were extracted as honeycombing areas. Second, the total of the honeycombing areas of each slice was calculated. For each patient, HA was derived from three CT slices to compare with IA and from all CT slices (23 to 40 slices) to compare with PFTs.

2.5. Statistical analysis

The interobserver agreement in either %IA scores or PA scores between the two radiologists was evaluated using the weighted kappa statistic [15]. The interobserver agreement was categorized as previously described [16].

The correlations of the honeycombing area measured by quantitative CT analysis with that estimated by the radiologists or with PFTs were evaluated using the Spearman's correlation coefficient.

All statistical analyses were performed using JMP, version 9.0.2 (SAS Institute, Cary, NC, USA). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

The demographic, clinical and physiologic characteristics of the 36 patients are summarized in Table 1. The mean age of patients were 72.2 ± 8.3 years, and most of them (86.1%) were men.

Table 1
Demographic, clinical and physiologic characteristics of 36 IPF patients.

Characteristics	Value
Age (years)	72.2 ± 8.3
Male/female	31/5
BMI (kg/m^2)	23.3 ± 4.5
Smoking history (current/past/never)	6/27/3
Pack-years	44.9 ± 31.2
FVC%pred. (%)*	81.4 ± 18.8
FEV_1 %pred. (%)*	81.9 ± 18.7
FEV_1/FVC (%)*	80.5 ± 8.3
DL_{CO} %pred. (%)**	63.5 ± 18.6
DL_{CO}/V_A %pred. (%)**	71.9 ± 23.9
CPI**	39.3 ± 21.9
KL-6 (U/ml)***	1235.4 ± 858.2
Receiving corticosteroid therapy	3
Receiving immunosuppressive therapy	2

Data are number or mean ± SD. *n = 27, **n = 19 and ***n = 25.
BMI = body mass index, FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, DL_{CO} = diffusing capacity of the lung for carbon monoxide, V_A = alveolar volume, CPI = composite physiologic index, KL-6 = Krebs von de Lungen-6.

Table 2
Correlations of honeycombing area derived from three CT slices between quantitative CT analysis and radiologists.

	Radiologist 1		Radiologist 2	
	ρ	p Value	ρ	p Value
Identified area/CT honeycombing area (mm^2)	0.65	<0.0001	0.68	<0.0001
Percent area/CT%honeycombing area (%)	0.68	<0.0001	0.70	<0.0001

Data are the Spearman's correlation coefficient.

Table 3
Correlations between honeycombing area derived from all CT slices by quantitative CT analysis and PFTs.

	CT honeycombing area		CT %honeycombing area	
	ρ	p Value	ρ	p Value
FVC%pred. (%)	−0.43	0.023	−0.60	0.001
FEV_1 %pred. (%)	−0.55	0.003	−0.66	<0.001
FEV_1/FVC (%)	0.19	0.339	0.20	0.322
DL_{CO} %pred. (%)	−0.56	0.012	−0.49	0.032
DL_{CO}/V_A %pred. (%)	−0.55	0.015	−0.41	0.085

Data are the Spearman's correlation coefficient.
Abbreviations used are the same as those in Table 1.

Current or past smoking history was found in 33 patients (91.7%). Only three patients were treated with corticosteroids (prednisolone) and two of the three patients with immunosuppressant (cyclosporine or azathioprine) at the time of enrollment.

3.2. Interobserver agreement

The median (25th, 75th percentiles) IA was 1675 (398, 4353) mm^2 for Radiologist 1 and 888 (96, 2510) mm^2 for Radiologist 2. The median (25th, 75th percentiles) PA was 4.5% (1.8%, 11.4%) for Radiologist 1 and 4.3% (0.8%, 7.0%) for Radiologist 2. The agreement between the two radiologists was almost perfect for %IA and PA (weighted kappa = 0.91 and 0.93, respectively).

3.3. Honeycombing areas by the computer-aided program

The mean Jaccard index from the three patients ranged from 46.3% to 61.5%. The concordance rate was highest when the threshold of CT attenuation value was at −720HU and the cut-off value of area size was at 150 mm^2 (e-Table 1). Therefore, HA and %HA for each patients were calculated on the basis of the best threshold and the best cut-off value above. The median (25th, 75th percentiles) HA was 1261 (663, 2685) mm^2 from three CT slices and 12590 (7772, 16465) mm^2 from all CT slices. The median (25th, 75th percentiles) %HA was 2.3% (1.0%, 3.8%) from three CT slices and 3.2% (2.0%, 4.7%) from all CT slices.

3.4. Correlation of honeycombing area between quantitative CT analysis and radiologists

HA was significantly correlated with IA estimated by either Radiologist 1 or Radiologist 2 ($\rho = 0.65$ or $\rho = 0.68$, respectively) (Table 2). Table 2 also shows the significant correlation between %HA and PA estimated by either Radiologist 1 or Radiologist 2 ($\rho = 0.68$ or $\rho = 0.70$, respectively).

3.5. Correlation of honeycombing area by quantitative CT analysis with pulmonary function tests

Table 3 shows the correlations between the honeycombing area measured by quantitative CT analysis from all CT slices and PFTs. HA was significantly correlated with FVC (%pred.) and DL_{CO} (%pred.) ($\rho = -0.43$ and $\rho = -0.56$, respectively). %HA was significantly correlated with FVC (%pred.) and DL_{CO} (%pred.) ($\rho = -0.60$ and $\rho = -0.49$, respectively). HA and %HA were also significantly correlated with the CPI ($\rho = 0.63$, $p = 0.002$ and $\rho = 0.69$, $p < 0.001$, respectively) (Fig. 3) [8].

4. Discussion

We have developed a computer-aided method for quantitative CT analysis of honeycombing area in IPF patients by using public domain computer software. The honeycombing area measured by this method was significantly correlated with that estimated by two expert radiologists (Table 2). It was also correlated with either parameters of PFTs (Table 3) or CPI (Fig. 3). Results of the present study suggest that the proposed quantitative CT analysis of honeycombing area may be a useful and objective method of evaluation of honeycombing in IPF patients.

In the present study, we compared the honeycombing area measured by quantitative CT analysis with that estimated manually by thoracic radiologists. If we compare only the percentage of lesions, we might extract different lesions and the percentages of these lesions agree accidentally. Therefore, we compared the area by our method and the area by radiologists on the pixel-by-pixel to evaluate the concordance rate.

The characteristic of the proposed method is that HA do not include emphysematous lesions. The method that extracts the area with CT attenuation value lower than a certain threshold, for example low attenuation area (LAA) for chronic obstructive pulmonary disease (COPD) patients, is inaccurate for extracting the honeycombing of IPF patients. This is because LAA may include both honeycombing and emphysema in IPF patients with smoking history. Most IPF patients have smoking history and a certain level of emphysematous change on CT images. According to the statement from Fleischner Society, emphysema refers to decreased attenuation areas usually without visible walls, while honeycombing refers to cystic airspaces with thick fibrous walls [13]. We especially focused on the difference in the wall thickness of these cystic lesions in this method. We set the CT attenuation value rather higher than the well-established threshold of −950 HU for LAA. With a window level of −720 HU, normal alveolar structure, emphysema, and thin wall became the large continuous area on the image and only the honeycombing covered with thick walls were distinguished. As the next step, we decided a cut-off level of the size. Our purpose in this stage is to remove the large continuous area including emphysema and to extract only honeycombing area. We succeeded in extracting only honeycombing except emphysema in this way.

On the other hand, HA may include two findings, traction bronchiectasis and emphysema with fibrosis. Confluence of traction bronchiectasis sometimes, especially in basal segments, looks like real honeycombing on CT [17]. It is sometimes difficult to distinguish honeycombing from traction bronchiectasis just with transverse CT images. Emphysema with fibrosis also cause the misdiagnosis of interstitial pneumonia. Sensitivity, specificity, and accuracy for diagnosis of interstitial pneumonia are lower in patients with concurrent emphysema than in patients without concurrent emphysema [18]. Watadani et al. describe that there is greatest disagreement regarding identification of honeycombing consisted of a combination of cystic air spaces and traction bronchiectasis, thin-walled large cysts, and complicated emphysema [7]. In pathological examination, there were significant correlations between airspace enlargement with fibrosis (AEF) and UIP pattern among smoking patients [19]. It is difficult to distinguish these two findings in some cases. On analyzing the honeycombing area quantitatively, we cannot but include traction bronchiectasis or emphysema with fibrosis in honeycombing.

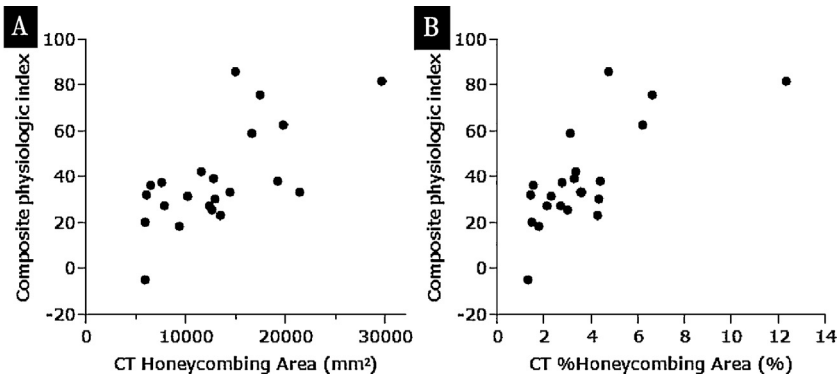

Fig. 3. Scatter plots for correlations between composite physiologic index (CPI) and CT honeycombing area or CT %honeycombing area.
Fig. 3A shows correlation ($\rho = 0.63$, $p = 0.002$) between CPI and CT honeycombing area, and Fig. 3B shows correlation ($\rho = 0.69$, $p < 0.001$) between CPI and CT %honeycombing area.

Therefore, it may be a realistic method to considered the cystic area surrounded by thick wall as honeycombing area.

PFTs, especially FVC and DL_{CO}, are considered to be a standard approach to objectively monitoring patients with IPF. However, it is important to consider that the interpretation of PFTs in IPF patients is confounded by coexistent emphysema [8,9]. In IPF patients with coexistent emphysema, CPI is thought to be a more accurate prognostic determinant than any individual parameters of PFTs [8]. In this study, both HA and%HA were strongly correlated with not only FVC and DL_{CO} (Table 3) but also CPI (Fig. 3). We thus think either HA or %HA reflects the extent of fibrosis exactly.

In clinical practice, it is sometimes difficult to perform PFTs, especially DL_{CO}, due to worsened respiratory status and poor cooperation in patients with severe IPF. On the other hand, HRCT provides useful information about the extent of honeycombing and other reticular abnormalities. Therefore, HRCT is an accurate and useful technique for evaluating IPF. The proposed quantitative CT analysis of honeycombing area may provide an additional useful and objective information and might become a surrogate for PFTs in IPF patients. In the future, we need to evaluate whether this quantitative analysis of honeycombing areas independently predicts mortality in IPF patients [1].

There are several limitations associated with this study. First, this is a retrospective study with small sample size, conducted at a single institution. Second, all IPF patients in the present study were diagnosed using HRCT criteria alone. Therefore, our subjects does not represent the entirety of IPF patients. Third, we randomly chose three patients among the 36 patients to develop the method for quantitative CT analysis of honeycombing area. However, in the sub-analysis with 33 patients, after excluding these three patients, HA was also correlated with FVC (%pred.) ($\rho = -0.43$, $p = 0.03$), DL_{CO} (%pred.) ($\rho = -0.64$, $p = 0.005$), and CPI ($\rho = 0.66$, $p = 0.001$). Finally, the method was based on a 2-dimensional analysis system.

5. Conclusions

We have proposed a computer-aided method for quantitative CT analysis of honeycombing area in patients with IPF. The extent of honeycombing measured by this method was significantly correlated with that estimated by expert radiologists or with PFTs. Quantitative CT analysis presented here may be useful and reliable for the objective evaluation of honeycombing in IPF.

Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejrad.2015.11.011.

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