Original Article

A quantitative analysis of long-term follow-up computed tomography of idiopathic pulmonary fibrosis: the correlation with the progression and prognosis

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Abstract

Background: Quantitative analyses of computed tomography (CT) images using computer-aided detection (CAD) are correlated with visual assessments and pulmonary function test findings and might be useful for predicting the prognosis of patients with idiopathic pulmonary fibrosis (IPF).

Purpose: To evaluate the association between the quantitative analysis of long-term follow-up CT of IPF and the progression and prognosis.

Material and Methods: A total of 48 patients with IPF who received over one year of follow-up CT were included in this study. The results of quantitative analyses (emphysema, ground-glass attenuation [GGA], consolidation, reticulation, and honeycombing) using a CAD software program of initial and follow-up CT findings were evaluated, and the association with the progression of the total lesion of IPF and prognosis using Spearman's rank correlation and Cox regression analyses was considered.

Results: Results of quantitative analyses of consolidation, reticulation, honeycombing, and the total lesion on initial CT were correlated with progressive changes in the total lesion of IPF per year ($r = 0.4375$, 0.4128, 0.4649, and 0.4095, respectively). The results of quantitative analyses of honeycombing (hazard ratio [HR] = 1.40, 95% confidence interval [CI] = 1.03–1.89, $P = 0.0314$) and GGA (HR = 0.85, 95% CI = 0.72–0.99, $P = 0.0384$) at initial CT were prognostic factors according to a multivariate Cox regression analysis.

Conclusion: The quantitative analysis of honeycombing using a CAD software program of CT findings may be useful for predicting the progression and prognosis of patients with IPF.

Keywords
Computed tomography, X-ray, pulmonary fibrosis, quantitative evaluation

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrosing interstitial pneumonia of unknown cause, associated with a histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP), and has a poor prognosis (1). Computed tomography (CT) findings correlate well with pulmonary fibrosis on pathological findings, and high-resolution CT (HRCT) is essential for the diagnosis of IPF (1–3). In addition, the severity of IPF can be evaluated by a quantitative analysis of CT images.

Quantitative analyses involve radiologists' visual assessments and computer-aided detection (CAD) software

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programs. Previous studies have reported that quantitative analyses using CAD were correlated with visual assessments and pulmonary function test findings and might be useful for predicting the prognosis of patients with IPF (4–7).

CAD-based quantitative analyses of emphysema, ground-glass attenuation (GGA), consolidation, reticulation, and honeycombing are possible with the Gaussian histogram normalized correlation (GHNC) system developed by Iwasawa et al. (4,8). Results of quantitative analyses using CAD can also be useful for evaluating interval changes in IPF. However, the risk factors for progression of IPF in patients with long-term follow-up are unclear.

The aim of the present study was to evaluate the results of quantitative analyses of long-term follow-up CT using the GHNC system and determine significant indicators for progression of IPF and a poor prognosis.

Material and Methods

The institutional review board of our institution approved this study. The requirement for informed consent was waived for this study owing to the retrospective design.

Patients

We retrospectively reviewed the CT images of patients with IPF between January 2009 and December 2017. At first, we identified a total of 300 cases clinically diagnosed with interstitial pneumonia. Among these, 176 cases were excluded due to diagnoses of non-IPF based on previously established criteria (1). Next, 43 cases were excluded because the patients had not received over one year of follow-up CT. A further 14 cases were excluded because the patients had undergone thoracic surgery or therapies for IPF or lung cancer before the initial CT examinations. In addition, 17 cases were excluded because the patients had undergone chemotherapy or radiation therapy for lung cancer during follow-up. Finally, two cases were excluded because they involved pulmonary infections, and the CT findings of IPF had not been evaluated correctly. Thus, 48 cases (40 men, 8 women; mean age = 68.8 ± 6.5 years; age range = 53 − 80 years) were ultimately included in the study. All cases were diagnosed as IPF based on previously established criteria (1). Among these, 29 cases were diagnosed based on pathologic findings in which surgical resection was performed, and 19 cases without pathological confirmation were diagnosed based on HRCT findings. All CT images were assessed by two chest radiologists with 17 and >30 years of experience, and all pathological findings were diagnosed by one pathologist.

CT examinations and CAD analyses

The CT scans at the initial and follow-up examinations were acquired using a 64-row detector CT scanner (Aquilion 64; Toshiba Medical Systems Otawara, Japan) with a slice thickness of 2 mm and were obtained at suspended end inspiration effort in the supine position without intravenous contrast medium injection. The scanning parameters were 120 kVp and automated mAs. Monitors were used to view the lung image (window width = 1600 HU; window level = −600 HU).

The CAD analysis using the GHNC system (Mebius, Yokohama, Japan) (4,8) (Fig. 1) was performed by a chest radiologist and a radiological technologist. A total of 96 CT examinations, including initial and follow-up CT (two CT examinations per case), were analyzed in this study. The pixels of the lung were classified into six categories based on the predesigned samples using the CT attenuation values and their local histograms, as follows: normal; emphysema; GGA; consolidation; reticulation; and honeycombing. The extent rate of each category within the entire lung field was automatically calculated. For the cases that underwent surgical resection during follow-up, CT images for the opposite lung were evaluated at both the initial and follow-up examinations. For cases with lung cancer, the extent of the tumor was omitted manually on the GHNC system. For cases with multiple follow-up CT examinations, the most recent CT images were evaluated as follow-up CT.

Statistical analyses

The extent rate of each lesion (emphysema, GGA, consolidation, reticulation, and honeycombing) and progression rate per year for IPF lesions were compared using Spearman's correlation analysis. The age, sex, presence of therapies for IPF, thoracic surgery history, lung cancer presence, serum KL-6 levels, %VC values at the timing of initial CT examinations, and GHNC scores were investigated with a Cox regression analysis to identify survival prognostic factors. All of these variables were included in the multivariate analysis.

The receiver operating characteristics (ROC) curve was calculated for the GHNC score based on the progression of IPF (> median progression rate per year). The survival curves were constructed using the Kaplan–Meier method with the log-rank test.

A P value <0.05 was considered indicative of a significant difference. All statistical analyses were performed using the JMP® Pro 15 software program (SAS Institute Inc., Cary, NC, USA).

Results

The patients' characteristics and GNHC scores are shown in Tables 1 and 2, respectively. The median rates according to the GHNC analysis were as follows: emphysema = 2.3% (interquartile range [IQR] = 5.9); total lesion of IPF = 23.4% (IQR = 11.7); GGA = 8.2% (IQR = 4.6); consolidation = 0.1% (IQR = 0.2); reticulation = 5.8% (IQR = 6.3);

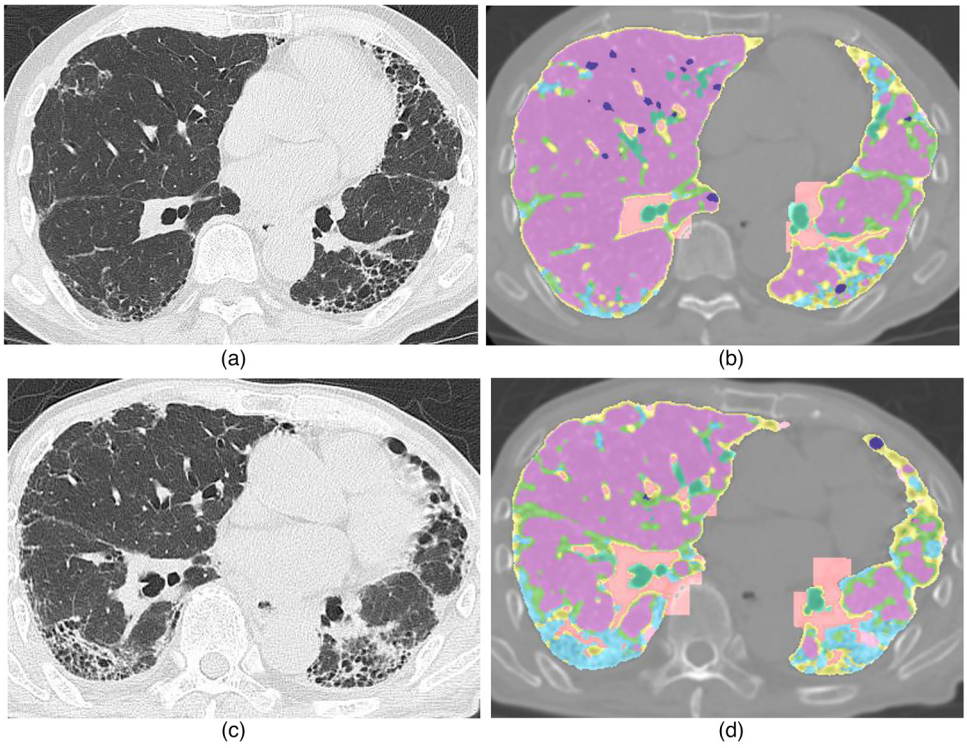

Fig. 1. The GHNC results. (a) An initial HRCT image of an 80-year-old man with IPF. (b) A GHNC image of panel (a). The patterns of emphysema, GGA, consolidation, reticulation, and honeycombing were 6.7%, 6.6%, 0.4%, 7.4%, and 12.7%, respectively. (c) A follow-up HRCT image obtained 524 days after panel (a). (d) A GHNC image of panel (c). The patterns of emphysema, GGA, consolidation, reticulation, and honeycombing were 0.7%, 8.8%, 1.4%, 14.6%, and 16.6%, respectively. The median progression rates per year were as follows: emphysema −4.2%, a total lesion of IPF 9.9%, GGA 1.5%, consolidation 0.7%, reticulation 5.0%, and honeycombing 2.7%. For GHNC images: pink = normal, dark blue = emphysema, light green = GGA, dark pink = consolidation, light blue = reticulation, yellow = honeycombing, dark green = bronchi, orange = vessels. GGA, ground-glass attenuation; GHNC, Gaussian histogram normalized correlation; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis.

Table 1. The characteristics of patients with IPF.

	IPF (n = 48)
Age (years)	68.8 ± 6.5
Male	40 (83.3)
SLB	29 (60.4)
Treatment	27 (56.3)
Lung cancer	15 (31.3)
KL-6 > 1000 U/mL	17 (35.4)
%VC < 80	23 (47.9)

Values are given as n (%) or mean ± SD.
IPF, idiopathic pulmonary fibrosis; SD, standard deviation; SLB, surgical lung biopsy; VC, vital capacity.

and honeycomb lung = 9.0% (IQR = 3.6). The median progression rates per year were as follows: emphysema = 0.6% (IQR = 1.9); total lesion of IPF = 3.0% (6.6); GGA = 0.3% (IQR = 1.8); consolidation = 0.01% (IQR = 0.1); reticulation = 0.8% (IQR = 3.5); and honeycomb lung = 0.9% (IQR = 2.0). The median duration between initial CT and follow-up CT date was 1190 days (range = 377–3122 days; IQR = 1178.5).

Table 2. Results of the quantitative analysis of CT images using the GHNC system in patients with IPF.

	IPF (n = 48)	
	Initial CT examination	Progression per year
Emphysema (%)	2.3 (5.9)	0.6 (1.9)
A total lesion of IPF (%)	23.4 (11.7)	3.0 (6.6)
GGA (%)	8.2 (4.6)	0.3 (1.8)
Consolidation (%)	0.1 (0.2)	0.01 (0.1)
Reticulation (%)	5.8 (6.3)	0.8 (3.5)
Honeycombing (%)	9.0 (3.6)	0.9 (2.0)

Values are given as median (IQR).
CT, computed tomography; GGA, ground-glass attenuation; GHNC, Gaussian histogram normalized correlation; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range.

Spearman's correlation analysis showed that the correlation between the GHNC scores at the initial CT examination and the progression rate of total IPF lesions per year

was as follows: emphysema (r = –0.1465); total lesion of IPF (r = 0.4095); GGA (r = 0.2030); consolidation (r = 0.4375); reticulation (r = 0.4128); and honeycombing (r = 0.4649) (Fig. 2).

Table 3 shows the results of the Cox regression analysis. The univariate analysis showed that the presence of surgical resection (hazard ratio [HR] = 0.24, 95% confidence interval [CI] = 0.07−0.82, $P = 0.0194$), presence of lung cancer (HR = 0.18, 95% CI = 0.02−1.38, $P = 0.0372$), %VC (HR = 8.20, 95% CI = 1.78−37.78, $P = 0.0013$), and honeycombing by GHNC (HR = 1.32, 95% CI = 1.06−1.61, $P = 0.0129$) were significant indicators. The other parameters were not significant indicators ($P > 0.05$). A multivariate analysis showed that GGA (HR = 0.85, 95% CI = 0.72 −0.99, $P = 0.0384$) and honeycombing (HR = 1.40, 95% CI = 1.03−1.89, $P = 0.0314$) by GHNC were significant

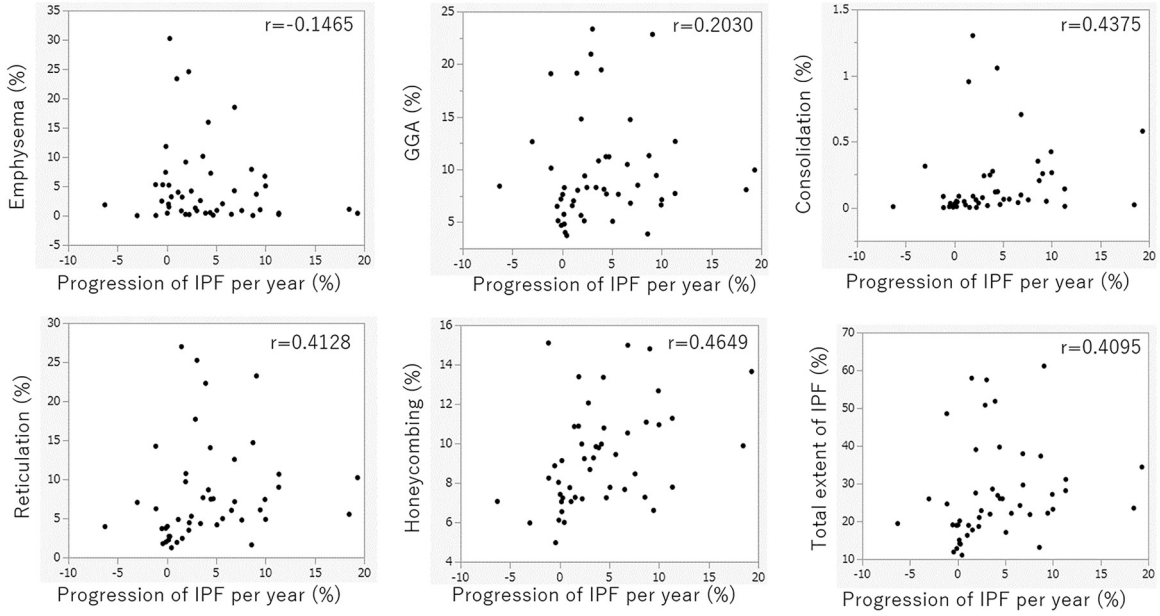

Fig. 2. The correlation between the GHNC scores at the initial CT examination and the progression rate of total IPF lesions per year. The correlation coefficient of each score was as follows: emphysema (r = –0.1465), total lesion of IPF (r = 0.4095), GGA (r = 0.2030), consolidation (r = 0.4375), reticulation (r = 0.4128), and honeycombing (r = 0.4649). CT, computed tomography; GGA, ground-glass attenuation; GHNC, Gaussian histogram normalized correlation; IPF, idiopathic pulmonary fibrosis.

Table 3. Results of the Cox regression analysis in patients with IPF.

		IPF (n = 48)			
		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age		0.97 (0.89–1.05)	0.4133		
Male		2.70 (0.35–21.09)	0.2764		
SLB		0.24 (0.07–0.82)	0.0194		
Treatment		2.89 (0.78–10.70)	0.0890		
Lung cancer		0.18 (0.02–1.38)	0.0372		
KL-6 > 1000 U/mL		0.60 (0.16–2.25)	0.4376		
%VC < 80		8.20 (1.78–37.78)	0.0013		
GHNC analysis	Emphysema	1.04 (0.97–1.10)	0.2412		
	GGA	1.07 (0.96–1.23)	0.8113	0.85 (0.72–0.99)	0.0384
	Consolidation	1.21 (0.11–5.31)	0.8400		
	Reticulation	1.04 (0.92–1.09)	0.7335		
	Honeycombing	1.32 (1.06–1.61)	0.0129	1.40 (1.03–1.89)	0.0314

CI, confidence interval; GGA, ground-glass attenuation; GHNC, Gaussian histogram normalized correlation; HR, hazard ratio; IPF, idiopathic pulmonary fibrosis; SLB, surgical lung biopsy; VC, vital capacity

indicators. The cutoff value of honeycombing extent at the initial CT examination for predicting the progression of IPF (>3.0% per year) was determined to be 9.3% (sensitivity = 66.7%, specificity = 75.0%, and area under the curve = 0.72) (Fig. 3). Fig. 4 shows the Kaplan–Meier curves comparing the survival times and score of honeycombing (≥9.3% or <9.3%) at the initial CT examination.

Discussion

We investigated CT images by a quantitative analysis using a CAD technique in patients with IPF who underwent long-term follow-up CT.

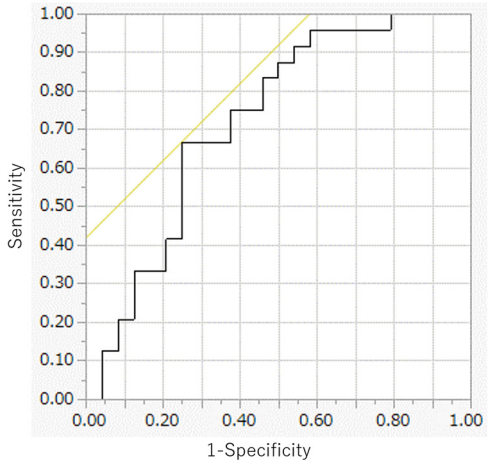

Fig. 3. The AUC of the GHNC honeycombing score based on the progression of IPF. The cutoff value of the honeycombing extent at the initial CT examination for the progression of IPF (>3.0% per year) was determined to be 9.3% (sensitivity = 66.7%, specificity = 75.0%, and AUC = 0.72). AUC, area under the receiver operating characteristic curve; CT, computed tomography; GHNC, Gaussian histogram normalized correlation; IPF, idiopathic pulmonary fibrosis.

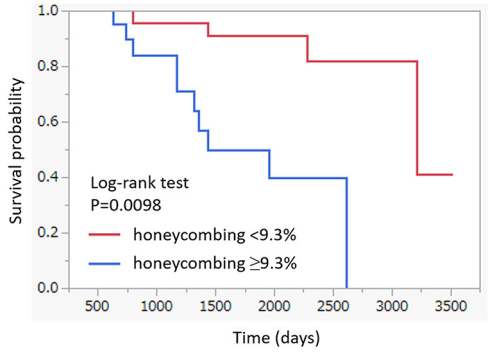

Fig. 4. Kaplan–Meier distribution of survival time. Kaplan–Meier curves comparing survival times and the score of honeycombing (≥9.3% or <9.3%) at the initial computed tomography examination ($P = 0.0098$) are shown.

Previous studies have reported the findings of quantitative analysis using CAD as being correlated with visual assessments and pulmonary function tests in patients with IPF (4–7). Furthermore, automated quantified fibrosis and interval changes in fibrosis on CT were reported to be significant predictors of survival (9). Our study revealed that the progression rate of each GHNC score per year and the median progression rate of total IPF lesions was 3.0%.

IPF is characterized as a progressive worsening disease (1), and its progression can be evaluated visually by radiologists; however, intra- and inter-reader variability in evaluations cannot be discounted (10,11), and the CAD technique would be useful for calculating the progression rate including small values. A recent study reported that a threshold of 4% change by automated texture-based quantitative lung fibrosis at six months corresponded to the mean change that worsened on HRCT visually at 12 months (12).

Spearman's correlation analysis in our study showed the correlation between the GHNC scores other than emphysema and GGA at the initial CT examination and the progression rate of total IPF lesions per year (r = 0.4095 −0.4649) despite the median rate of consolidation by GHNC at the initial CT examination being relatively small (0.1%). The correlation coefficient of honeycombing was the largest among the patterns evaluated (r = 0.4649). Our study also showed that honeycombing by GHNC was a significant indicator for the assessment of a poor prognosis in patients with IPF (HR = 1.40, 95% CI = 1.03−1.89, $P = 0.0314$). Results of quantitative analyses of honeycombing using a CAD software program for CT may be correlated with the progression of IPF and prognosis.

Honeycombing is a distinguishing feature of UIP and must be present for a definite HRCT diagnosis of IPF (1). Inter-observer agreement for honeycombing may be inconsistent (11,13–15), but a computer-based quantitative assessment is free from inter-observer variation and would thus assist in making an accurate diagnosis.

Iwasawa et al. reported that the results of the GHNC analysis correlated significantly with the area and total extent of the lesion in IPF by radiologists, and the extent of fibrosis (reticulation and honeycombing) as determined by GHNC was significantly correlated with the forced vital capacity (4,8). They also reported that the honeycombing pattern according to GHNC was not totally equal to the honeycombing area assessed by radiologists because GHNC included some subpleural irregular lines as honeycombing; however, the presence of subpleural fibrosis would help diagnose IPF versus fibrosing non-specific interstitial pneumonia (8,16).

It is known that a histopathologic and/or radiologic pattern of UIP including honeycombing has a poor prognosis (1). UIP patterns in CT are included as risk factors for developing acute exacerbation of interstitial pneumonia in the postoperative period in patients who undergo pulmonary

resection (17). Outcomes are reported to be poorer in patients with lung cancer with IPF than in those without IPF (18–20). It is also reported that a greater percentage of fibrosis extent according to CAD on preoperative CT independently predicts a poor disease-free survival in patients with lung cancer (21). Results of quantitative analyses of honeycombing may also aid in predicting the progression of IPF after thoracic surgery or with lung cancer.

The present study has some limitations. First, this study was retrospective in nature, and the evaluation was limited to a small number of subjects. Second, patients without a pathologic confirmation of UIP were included; however, a surgical lung biopsy was not recommended in these patients because of the UIP pattern on HRCT (1). Third, patients both with and without treatment for IPF were included, which may have affected the progression of IPF. Quantitative CT using CAD can reportedly be used to assess the slowing of progression of pulmonary fibrosis by anti-fibrotic drugs (22). However, the presence of treatment for IPF was not an indicator of the prognosis in this study. Finally, GHNC categories could not be totally equal to the HRCT findings evaluated visually by the radiologists because the GHNC categories were based on predesigned samples using CT attenuation values and their local histograms.

In conclusion, the quantitative analysis of honeycombing using a CAD software program for CT may be useful for predicting the progression and prognosis in patients with IPF.

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Declaration of conflicting interests

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