Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9508-17
Intern Med 57: 929-937, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

A Volumetric Computed Tomography Analysis of the Normal Lung in Idiopathic Pulmonary Fibrosis: The Relationship with the Survival

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Abstract:

Objective An image analysis of high-resolution computed tomography (HRCT) can provide objective quantitation of the disease status in idiopathic pulmonary fibrosis (IPF). However, to our knowledge, no reports have investigated the utility of the normal lung volume for evaluating mortality from IPF. This study aimed to evaluate the relationship between the normally attenuated lung volume on HRCT as a percentage of whole-lung volume (NL%) and IPF mortality.

Methods The NL% was determined by HRCT (between -950 and -701 Hounsfield units) using a density mask technique and volumetric software. The NL%, visual assessments of the normal lung by two radiologists, pulmonary function variables, and the gender, age, and physiology (GAP) index were retrospectively evaluated for 175 patients with IPF. Uni- and multivariate Cox proportional hazards analyses and C statistics for mortality were performed.

Results The univariate Cox proportional hazards analysis identified the NL% as a prognostic factor [hazard ratio, 0.949; 95% confidence interval (CI), 0.936-0.964; $p<0.0001$]. In the multivariate analysis, the NL% was a prognostic factor, but the radiologists' visual assessment scores of normal lung were not. The C index increased when the NL% was included in the models of the pulmonary function variables. Furthermore, the C index for a combined model of GAP stage and categorized NL% (0.758; 95% CI, 0.751-0.762) was higher than for the model with the GAP stage alone (0.689; 95% CI, 0.672-0.709).

Conclusion The NL% was a prognostic factor in our study population. Quantification of the normal lung using our method may help improve the IPF staging systems.

Key words: idiopathic pulmonary fibrosis, computed tomography, computer-aided diagnosis, mortality

(Intern Med 57: 929-937, 2018)
(DOI: 10.2169/internalmedicine.9508-17)

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia in adults. The prognosis is poor, with the survival estimated at three to five years (1-3). Prognostic factors for this disease include the level of dyspnea, pulmonary function, oxygen desaturation during exercise, and fibrotic findings from high-resolution computed tomography (HRCT). Further prognostic factors that have been reported include pathological findings (4, 5), serum biomarkers (6, 7), and the St. George's Respiratory Questionnaire score (8). In addition, the gender, age, and physiology (GAP) staging system has been widely accepted as useful for predicting the survival in patients with IPF (2).

Many reports have been published on the association be-

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Received: May 14, 2017; Accepted: August 19, 2017; Advance Publication by J-STAGE: December 21, 2017
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tween scores given by radiologists based on a visual examination of HRCT images and the prognosis of IPF (9-12). In addition, objective methods for predicting mortality due to IPF based on image analyses of chest computed tomography (CT) have been reported (13-15). However, to our knowledge, no reports have assessed the utility of the normal lung volume for evaluating the mortality from IPF.

We previously reported a simple method that used a volumetric CT analysis and a density mask technique to quantify the volume of normally attenuated lung as a percentage of the whole-lung volume (NL%), defining normal attenuation as between −950 and −701 Hounsfield units (HU) (16). We showed that this offered a good reflection of physiological variables and was a useful tool for assessing disease severity in 27 patients with IPF who exhibited the radiological usual interstitial pneumonia pattern on HRCT.

In the present study, we hypothesized that the NL% computed by our method was a prognostic factor for patients with IPF. To confirm this, we evaluated the relationship between the NL% and mortality in patients with IPF who had received multidisciplinary diagnoses according to the 2011 guidelines (1).

Materials and Methods

Patients

The ethics review board at Tosei General Hospital, which contributed cases for this study, provided study approval (approval number 536). This study was conducted in accordance with the guidelines of the Declaration of Helsinki. The requirement to obtain informed consent was waived because the data were analyzed anonymously. Patients were excluded from the study if they had experienced acute exacerbations or showed other comorbidities, including lung cancer, infectious diseases, or cardiac failure, at the initial presentation.

Data from 180 patients with IPF who underwent systemic initial evaluation between June 2008 and July 2013 were retrospectively reviewed. Starting in 2011, the diagnosis of IPF was made according to the 2011 international guidelines (1), and the accuracy of the diagnosis was confirmed by multidisciplinary discussion (MDD). Patients who initially presented before 2011 were diagnosed based on different guidelines, but these diagnoses were confirmed by MDD as being in accordance with the 2011 guidelines before May 2015. Chest HRCT images obtained at the initial evaluation were re-examined by a thoracic radiologist with 27 years' experience who was blinded to the clinical course and examination data for each patient. Two patients were excluded because of a lack of 0.5-mm slice HRCT data, and 3 were excluded because they underwent lung transplantation. Ultimately, 175 patients were enrolled in the study. The duration from the initial evaluation to the last attendance or death was recorded. We analyzed the censored cases and confirmed their life-or-death status by telephone; this survival assessment was performed as of March 2016.

Computed tomography

All patients underwent CT using a commercially available CT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan) with a high-frequency algorithm. HRCT images were obtained, without intravenous contrast, with the patient in the supine position at full inspiration. Spirometric gating was not performed during CT. Whole-lung HRCT images of 0.5-mm-thick slices over 0.5-mm intervals were used for the analysis. The pixel sizes were as follows: X and Y axes, 0.66±0.05 mm; and Z axis, 0.5 mm.

Visual scoring of normal lung on HRCT

Two chest radiologists (with 25 and 27 years' experience) who were blinded to the clinical data of the patients performed independent evaluations of the data. The visual estimation was done at the lung parenchymal window setting (window level, -600 HU; window width, 1,600 HU). The observers made subjective assessments about the extent of the normal lung, excluding emphysema and fibrotic findings. The overall percentage of normal lung was calculated by averaging the values for six lung zones (upper, middle, and lower on both sides) according to previously published methods (9).

Derivation of NL% using an imaging analysis software

Image analyses were performed using a specialized software program (SYNAPSE VINCENT; Fujifilm Medical Systems, Tokyo, Japan). The HRCT data were made uniform by applying a Gaussian filter (σ=1.0) to the images to remove noise. After whole-lung extraction was performed, areas of lung with normal attenuation, defined as -950 HU to -701 HU, and the resultant NL% were computed according to previously published methods (16). Fig. 1 shows sample HRCT images for a patient with IPF, alongside the same images with the normally attenuated areas colored yellow.

The GAP index and stage, and GAP-NL% stage

The GAP index and stage were determined according to previously published methods (2). For this study, we defined an additional index, the GAP-NL% stage, which combined the GAP stage and NL% using a points system. To do this, NL% was categorized (and points assigned) according to its tertile values as >71% (2 points), 63-71% (1 point), or <63% (0 points). These points were added to the original GAP index. Patients with a total of 0-3, 4-5, and 6-10 points were classified as GAP-NL% stages I, II, and III, respectively.

Pulmonary function tests

Pulmonary function tests were performed using a Chestac-55 V instrument (Chest M.I., Tokyo, Japan) according to the American Thoracic Society/European Respiratory Society criteria (17). The values for forced vital capacity

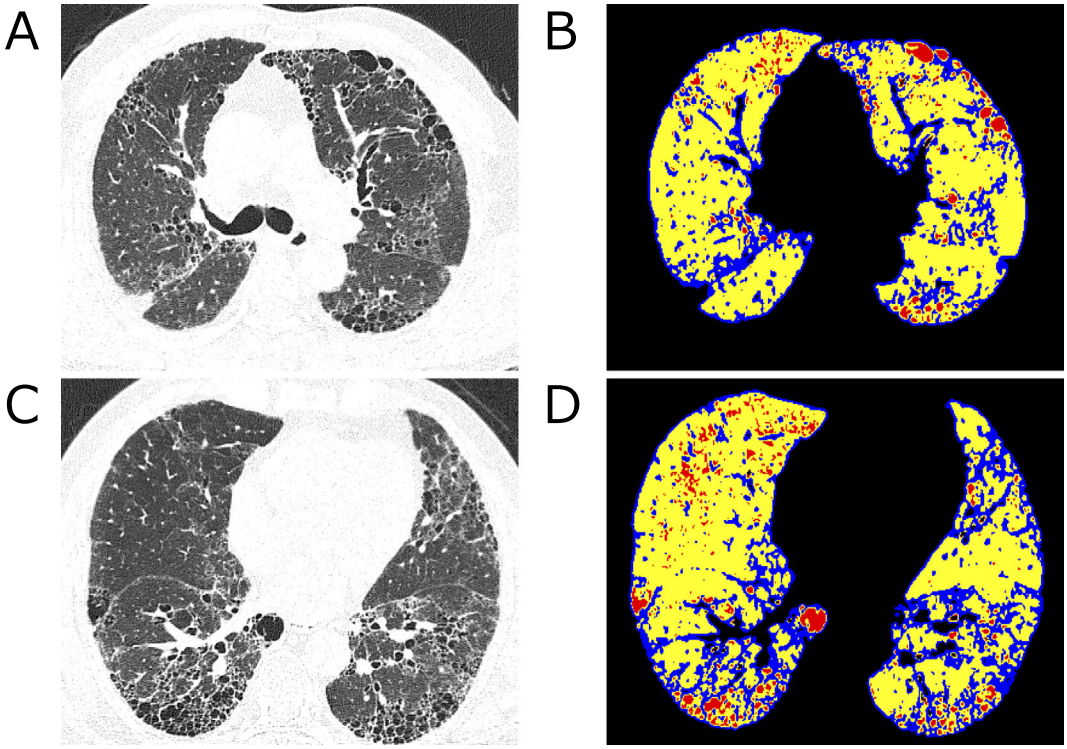

Figure 1. **High-resolution computed tomography images with the normally attenuated areas identified (A and C). High-resolution computed tomography (HRCT) chest images of a 72-year-old man with idiopathic pulmonary fibrosis (B and D). The same images, colored as follows: yellow, normally attenuated lung [defined as -950 to -701 Hounsfield units (HU)]; red, areas of low attenuation (lower than -950 HU); blue, areas of ground-glass attenuation and consolidation (higher than -701 HU). This patient's whole-lung volume by volumetric HRCT analysis was 3,323 mL, and the volume of normally attenuated lung was 2,170 mL. Thus, the normally attenuated lung volume as a percentage of the whole-lung volume (NL%) was 65.3%.**

(FVC), forced expiratory volume in 1 second (FEV_1), and diffusing capacity of the lungs for carbon monoxide (DLco) were measured according to the American Thoracic Society/European Respiratory Society recommendations (18).

Statistical analyses

Continuous variables are presented as the means ± standard deviation (SD), and categorical variables are presented as counts and percentages. Pearson product-moment correlation coefficients were used to test correlations between the NL% and clinical parameters. Uni- and multivariate Cox proportional hazards analyses were performed to evaluate the relationships between parameters and mortality. The goodness of fit for survival models was calculated using Harrell's C index (19). The survival was analyzed using Kaplan-Meier survival plots and log rank testing. Analyses of variance were used to compare the NL% among the different causes of death. Values of $p<0.05$ were considered statistically significant. All statistical analyses were conducted using the IBM SPSS software program, version 24 (IBM Japan, Tokyo, Japan).

Results

Patient characteristics

The baseline patient characteristics for the study population are shown in Table 1. The mean duration of follow-up was 39.5±22.9 months, and 94 patients (54%) died during the study period. The treatment comprised pirfenidone in 107 patients (61%), with a mean duration of 78.0±62.7 weeks. Twelve patients (6.8%) received nintedanib after the discontinuation of pirfenidone; the duration of nintedanib treatment for these patients was 94.0±68.0 weeks. Ten patients (6%) received nintedanib without preceding pirfenidone; the duration of nintedanib treatment among these patients was 18.5±20.9 weeks.

Visual scoring of the normal lung

The mean estimates of the extent of normal lung for all patients made by the two radiologists by visual scoring were 65.4%±13.2% (visual score 1) and 60.4%±15.1% (visual score 2).

Table 1. Patient Characteristics.

Characteristics	
Total (n)	175
Gender, male/female (n) (%)	142 (81.1%) / 33 (18.9%)
Age (years)	66.1±7.9
Never smoked (n) (%)	40 (22.9%)
Ex-smoker (n) (%)	115 (65.7%)
(pack-year)	50.0±20.3
Current smoker (n) (%)	20 (11.4%)
(pack-year)	51.4±77.1
Body mass index (kg/m^2)	23.7±3.4
Biopsy-proven IPF (n) (%)	90 (51.4%)
PaO_2(Torr)	81.4±11.6
FVC (mL)	2,511±765
FVC, percent predicted (%)	80.1±19.9
FEV_1/ FVC	93.3±21.1
DLco (mL/min/mmHg) *	10.1±3.9
DLco, percent predicted (%)*	59.8±20.6
Walk distance during a 6-min walk test (m) †	571±142
Lowest SpO_2during a 6-min walk test (%) †	83.1±8.1
GAP index	3.3±1.4
GAP stage I (n) (%)/ II (n)(%) / III (n)(%)	100 (57.1%) / 69 (39.4%) / 6 (3.4%)

Values are presented as means and standard deviations or counts and percentages. IPF: idiopathic pulmonary fibrosis, PaO_2: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, FEV_1: forced expiratory volume in 1 second, DLco: diffusing capacity of the lungs for carbon monoxide, SpO_2: percutaneous oxygen saturation, GAP index: the Gender, Age, and Physiology index. * n=174 (one patient was unable to perform the DLco test). † n=171 (data were missing for four patients.)

Table 2. Correlations between NL% and Clinical Parameters.

Parameters	PaO_2 at rest	FVC, percent predicted	DLco, percent predicted *	GAP index	Visual score 1	Visual score 2
NL%	r=0.381	r=0.537	r=0.539	r=−0.596	r=0.622	r=0.422
	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001

PaO_2: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, DLco: diffusing capacity of the lungs for carbon monoxide, SpO_2: percutaneous oxygen saturation, GAP index: the Gender, Age, and Physiology index, NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis. * n=174 (one patient was unable to perform the DLco test.)

Calculation of the NL% by the imaging analysis software program

The mean NL% value for all of the patients calculated by the software program was 66.8%±9.4%. The first and second tertiles were 62.9% and 70.7%, respectively. Correlations between the NL% and other parameters are shown in Table 2. There were statistically significant correlations between the NL% and partial pressure of arterial oxygen (PaO_2) at rest, percent predicted FVC, percent predicted DLco, GAP index, and the visual scores for the normal lung by the two radiologists.

Prognostic factors

The hazard ratio (HR) and 95% confidence interval (CI) for each baseline parameter by a univariate Cox proportional hazards analysis are shown in Table 3. Gender and age were not significant prognostic factors in this cohort, whereas the percent predicted FVC, percent predicted DLco, visual score 1, visual score 2, GAP index, NL%, and the lung volume of ground-glass attenuation and consolidation (higher than −701 HU) were significant prognostic factors. In a multivariate Cox proportional hazards analysis, the NL% was a prognostic factor when the lung volume of ground-glass attenuation and consolidation was included (Table 4). The NL% was also a prognostic factor when the radiologists' visual scores of normal lung were included in the model (Table 5). The results of the uni- and multivariate Cox proportional hazards analyses and C index with adjustments for age and gender are shown in Table 6. The percent predicted FVC and NL% were identified as independent prognostic factors. The C index was wholly elevated when the NL%

Table 3. Predictors of Mortality, by Univariate Cox Proportional Hazards Analyses.

Parameters	HR	95%CI	p
Male	1.283	0.760-2.319	0.417
Age	1.013	0.987-1.039	0.320
FVC, percent predicted	0.955	0.943-0.967	<0.0001
DLco, percent predicted *	0.975	0.963-0.987	<0.0001
Visual score 1	0.966	0.952-0.980	<0.0001
Visual score 2	0.974	0.963-0.997	<0.0001
GAP index	1.751	1.474-2.085	<0.0001
GAP stage	3.082	2.119-4.488	<0.0001
NL%	0.949	0.936-0.964	<0.0001
Volume (<-950 HU)	0.998	0.968-1.026	0.9191
Volume (>-701 HU)	1.043	1.029-1.057	<0.0001

HR: hazard ratio, CI: confidence interval, FVC: forced vital capacity, DLco: diffusing capacity of the lungs for carbon monoxide, GAP: the Gender: Age, and Physiology index and stage, NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis. * n=174 (one patient was unable to perform the DLco test.)

was included as a physiological variable. The results of the univariate Cox proportional hazards analysis and C index for the GAP index and the multivariate Cox proportional hazards analysis and C index for the model of the GAP index combined with the NL% are shown in Table 7. The C index for the model of the GAP index combined with the NL% (0.775; 95% CI, 0.767-0.785) was higher than that for the GAP index alone (0.727; 95% CI, 0.719-0.738). The GAP index and NL% were confirmed as independent prognostic factors. The results of the multivariate Cox proportional hazards analysis and C index for the GAP stage and GAP-NL% stage are shown in Table 8. Interestingly, the C index for the GAP-NL% stage (0.758; 95% CI, 0.751-0.762) was higher than that for the GAP stage alone (0.689; 95% CI, 0.672-0.709).

Kaplan-Meier plots, log rank tests, and number at risk

Kaplan-Meier curves for NL% categorized into its three tertiles (>71%, 63-71%, and <63%) and for GAP-NL% stage are shown in Fig. 2, along with the results of the associated log rank tests. The mean survival times were as follows: NL% >71%, 63.0 months; NL% 63-71%, 36.2 months; and NL% <63%, 17.2 months. The distribution of patients by GAP-NL% stage was as follows: stage I, n=63; stage II, n=58; and stage III, n=54. The mean survival times by GAP-NL% stage were as follows: stage I, 58.2 months; stage II, 41.9 months; and stage III, 29.9 months. The mortality rates associated with GAP-NL% stages I, II, and III were as follows: 1-year mortality rates, 1.6%, 13.8%, and 24.5%, respectively; 2-year mortality rates, 7.9%, 37.5%, and 54.8%, respectively; and 3-year mortality rates, 11.1%, 44.6%, and 67.9%, respectively.

Causes of death

A total of 94 patients died, with 48 (51%) dying from chronic respiratory failure during palliative care. Acute exacerbation of IPF was the cause of death in 27 patients (29%). Seven patients (7%) died from lung cancer, and 6 (6%) suffered from sudden death. Other comorbidities caused death in 6 patients (6%) as follows: cardiovascular diseases (n=1), hematological malignancies (n=2), sepsis (n=1), colon cancer (n=1), and aspergillosis (n=1). For the analysis, the causes of death were classified as 1) chronic respiratory failure, 2) acute exacerbation, 3) lung cancer, 4) sudden death, and 5) others. There were no significant differences in the NL% among these cause of death categories (p=0.54).

Discussion

This report is the first to show that a volumetric analysis of the normal lung from HRCT is a useful prognostic factor in patients with IPF. Univariate Cox proportional hazards analyses revealed the percent predicted FVC, percent predicted DLco, visual score of normal lung by radiologists, GAP index, GAP stage, and NL% to be significant prognostic factors. A multivariate Cox proportional hazards analysis also showed the NL% to be a prognostic factor when the radiologists' visual scores for the extent of normal lung were included in the model. The C index offers a useful statistical approach for predicting mortality (19). Ley et al. reported that adding the visual fibrosis HRCT score made by radiologists to the GAP model did not increase the C index (20). However, in the present study, the C index increased when the NL% was included in some models using pulmonary function tests and the GAP model. The NL% is thus a useful measure that represents a prognostic factor in patients with IPF, along with the percent predicted FVC, GAP index, and GAP stage.

Radiologists' visual scores of HRCT have been reported to reflect the mortality due to IPF (9-11). Sumikawa et al. reported that traction bronchiectasis and fibrosis scores on HRCT were associated with the mortality in patients with IPF and patients with pathologically confirmed usual interstitial pneumonia (9). Shin et al. reported that high scores for fibrosis on HRCT were associated with a high risk of death in patients with usual interstitial pneumonia or nonspecific interstitial pneumonia (10). Best et al. reported that a visual score of interstitial abnormalities on HRCT was an independent prognostic factor in IPF (13). Oda et al. showed that changes in the HRCT fibrosis scores at 6 and 12 months compared with the baseline scores reflected the mortality in IPF patients (11). In our study, visual assessment scores made by two radiologists for the extent of normal lung, excluding fibrotic findings and emphysema, were found to be prognostic factors.

Several studies have reported on the utility of CT image analyses in patients with IPF (13-16, 21-24). These involved assessments based on density mask or histogram analy-

Table 4. Multivariate Cox Proportional Hazards Analysis for NL% and the Volume>701 HU.

Parameters	HR	95%CI	Likelihood ratio chi-square	p
Volume (>-701HU)	1.008	0.984-1.036	0.419	0.518
NL%	0.958	0.932-0.988	7.230	<0.01

NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis

Table 5. Multivariate Cox Proportional Hazards Analysis for the Visual Scores and NL%.

Parameters	HR	95%CI	Likelihood ratio chi-square	p
Visual score 1	0.997	0.975-1.019	2.474	0.797
Visual score 2	0.986	0.971-1.003	0.066	0.116
NL%	0.958	0.941-0.978	15.208	<0.001

HR: hazard ratio, CI: confidence interval, NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis

Table 6. Uni- and Multivariate Cox Proportional Hazards Analysis and C Index with Adjustments for Age and Gender.

	HR	95%CI	Likelihood ratio chi-square	p	C index	95%CI
Model 1A						
FVC, percent predicted	0.955	0.943-0.967	55.563	<0.001	0.760	0.751-0.771
Model 1B						
FVC, percent predicted	0.963	0.950-0.976	31.473	<0.0001	0.800 *	0.791-0.812
NL%	0.967	0.951-0.986	11.035	<0.001		
Model 2A						
FVC, percent predicted	0.960	0.948-0.974	32.507	<0.001	0.772 †	0.762-0.784
DLco, percent predicted	0.989	0.976-1.000	2.463	0.060		
Model 2B						
FVC, percent predicted	0.964	0.951-0.979	25.074	<0.001	0.794 ‡	0.785-0.805
DLco, percent predicted	0.995	0.981-1.001	0.104	0.549		
NL%	0.968	0.946-0.992	7.545	<0.01		

HR: hazard ratio, CI: confidence interval, FVC: forced vital capacity, DLco: diffusing capacity of the lungs for carbon monoxide, NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis. * C index for the model of percent predicted FVC combined with NL%, †C index for the model of percent predicted FVC combined with percent predicted DLco, ‡C index for the model of percent predicted FVC combined with percent predicted DLco and NL%

ses (13, 16, 21) or texture-based voxel/pixel classification (14, 15, 22-24). Image analyses of CT enable not only the quantification of the extent of disease but also the estimation of disease progression for each specific abnormality, such as ground-glass opacity reticulation and honeycombing. Maldonado et al. reported the efficacy of the Computer-Aided Lung Informatics for Pathology Evaluation and Ratings (CALIPER), a texture-based classification method (14). They showed that short-term changes in the quantified volumes computed by CALIPER of interstitial abnormalities, including reticular opacity and honeycombing, correlated with physiological parameters and reflected the survival in IPF patients. Furthermore, the baseline volumes of pulmonary vessels and honeycombing by CALIPER have been reported as predictors of mortality (15). Iwasawa et al. reported the efficacy of a similar texture-based classification method, the Gaussian Histogram Normalized Correlation (GHNC) system. They reported that the assessment of fibrotic regions using this system was useful for evaluating the treatment efficacy of pirfenidone, an anti-fibrotic drug, in IPF patients (23). They also reported that the normal lung volume, computed by the GHNC system, correlated with the mean pulmonary artery pressure measured by right heart catheterization in fibrotic idiopathic interstitial pneumonia (24).

One of the strong points of our approach is that the evaluation of the proportion of normal lung using a density mask technique is likely to be available at most non-specialist

Table 7. Univariate Cox Proportional Hazards Analysis and C Index for the GAP Index and Multivariate Cox Proportional Hazards Analysis and C Index for the Model of GAP Index Combined with NL%.

	HR	95%CI	Likelihood ratio chi-square	p	C index	95%CI
Model 1						
GAP index	1.751	1.473-2.085	54.942	<0.0001	0.727	0.719-0.738
Model 2						
GAP index	1.492	1.247-1.798	19.816	<0.0001	0.775 *	0.767-0.785
NL%	0.960	0.942-0.980	13.348	<0.001		

HR: hazard ratio, CI: confidence interval, GAP index: the Gender, Age, and Physiology index, NL%: normally attenuated lung volume as a percentage of the whole-lung volume, by volumetric high-resolution computed tomography analysis. * C index for the model combining the GAP index with NL%

Table 8. Multivariate Cox Proportional Hazards Analysis and C Indexes for GAP Stage and GAP-NL% Stage.

	HR	95%CI	Likelihood ratio chi-square	p	C index	95%CI
GAP stage	1.675	0.586-2.148	0.143	0.705	0.689	0.672-0.709
GAP-NL% stage	2.360	1.536-3.697	15.783	<0.001	0.758	0.751-0.762

HR: hazard ratio, CI: confidence interval, NL%: normally attenuated lung volume as a percentage of the whole lung volume: by volumetric high-resolution computed tomography analysis, GAP stage: the Gender, Age, and Physiology index stage, GAP-NL% stage: GAP stage combined with NL% stage

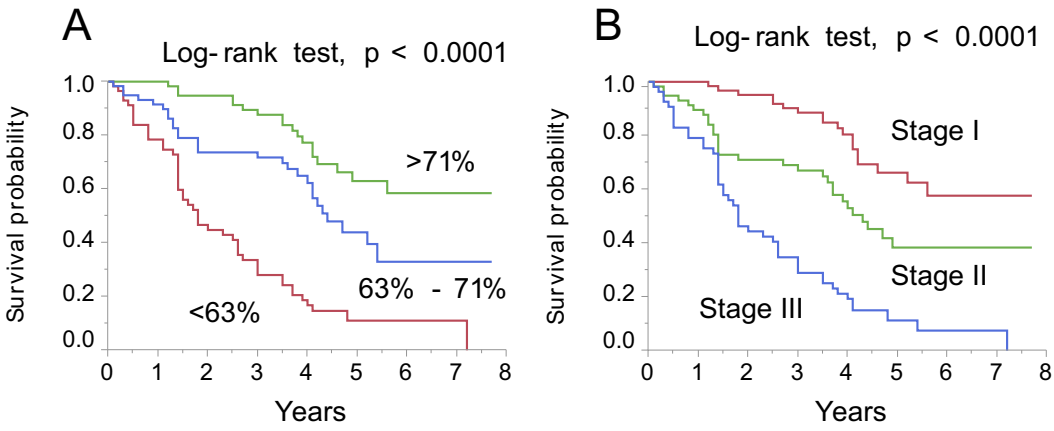

Figure 2. Kaplan-Meier plots. Kaplan-Meier curves (A) categorized by the tertiles of NL% (normally attenuated lung volume as a percentage of the whole-lung volume), and (B) categorized by the GAP-NL% stage (the gender, age, and physiology index stage combined with the NL% stage).

centers. Our method for calculating the NL% using a density mask technique is methodologically simple and convenient compared to the previously published texture analyses (14, 15, 22-24). Determining the NL% only requires quantifying the normally attenuated lung volume, defined as attenuation between −950 and −701 HU, using a traditional density mask technique. The previously published texture analyses based on voxel/pixel classification involved a much more complicated technique. Furthermore, the CALIPER and GHNC systems use different algorithms. Our method of computing the NL% has universality because of its basis in CT values.

The GAP index and stage are widely accepted as useful for predicting the survival in patients with IPF (2). The GAP model is a multidimensional prognostic staging system for IPF that uses commonly measured clinical and physiological variables, including gender, age, and the results of pulmonary function testing. Three stages (I, II, and III) have been identified based on GAP index scores of 0-3, 4-5, and 6-8, respectively. The mortality associated with stages I, II, and III have been estimated as follows: 1-year mortality rates, 6%, 16%, and 39%, respectively; 2-year mortality rates, 11%, 30%, and 62%, respectively; and 3-year mortality rates, 16%, 42%, and 77%, respectively. In the present study, the GAP index and GAP stage were prognostic factors for IPF in the univariate analysis. However, age and gender were not significant predictors of mortality in our cohort. Why this was the case is unclear, but it may be related

to the study population, as the patients in our cohort were all diagnosed by MDD according to the 2011 international guidelines. Furthermore, they exhibited high percent predicted FVC values (80.1%±19.9%), and relatively few patients (3.4%) were classified as GAP stage III. Our results demonstrated that the NL% and the GAP index were independent prognostic factors (Table 6). This result indicated that the GAP index is also a strong prognostic factor in patients with mild to moderate IPF. One important result of our study was that the C index for the combined GAP-NL% stage was higher than for the model with the GAP stage alone (Table 7).

Most areas of emphysema were not included in the evaluation of the NL%. Correctly, some emphysematous areas were included in the NL% when microscopic emphysema coexisted with microscopic lung fibrosis. Some studies have reported emphysema as a determinant of a poor prognosis in IPF (25, 26), while others have disagreed with this observation (27, 28). Some studies reported that the morality caused by acute exacerbation was lower in patients with combined pulmonary fibrosis and emphysema (CPFE) than in patients with interstitial pneumonia who were not diagnosed as CPFE (29, 30). When CPFE was defined according to previously published method (25), 12 patients (6.9%) were diagnosed with CPFE in our IPF population. There were no significant differences in the mortality between patients with CPFE and the others (log rank test: p=0.34). In another cohort of patients with CPFE, the NL% correlated well with the percent predicted DLco. However, no relationship between the NL% and mortality due to CPFE has been demonstrated.

Several limitations associated with the present study warrant mention. First, the results were obtained by a retrospective analysis of a relatively small cohort of all-Japanese patients from a single center. This may have introduced selection bias. Second, the baseline mean values for the percent predicted FVC and PaO_2 in this study population were 80.1%, and 81.4 Torr, respectively, and relatively few patients (3.4%) were classified as GAP stage III. Because most of the patients we examined had mild to moderate IPF at the initial presentation, the results may differ in other cohorts. Third, adjustments of the mortality analysis for treatment were not performed. Pirfenidone (31) and nintedanib (32) may reduce the mortality in IPF patients. Most of the enrolled patients were treated with pirfenidone (61.1% of patients) and/or nintedanib (12.6%). Future studies should consider eliminating this potential confounder. Fourth, our results only demonstrated an association between the NL% and the risk of death. Sequential changes in the NL% were not evaluated. Whether or not NL% is associated with other clinically important outcomes, such as disease progression, is unclear. Fifth, the potential utility of the combined assessment of the NL% and visual score of fibrosis by radiologist was not evaluated. Finally, the study population in this study was not from randomized prospective trials. However, this study can be considered to represent a real-world example of a medical examination and treatment in clinical practice.

Conclusion

We demonstrated that the NL% obtained from baseline routine HRCT can be used as a prognostic factor for IPF, along with the percent predicted FVC and the GAP model. The C index was elevated when the NL% was included in models using pulmonary function testing, the GAP index, and the GAP stage.

The authors state that they have no Conflict of Interest (COI).

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