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

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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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between 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 25 and 27 years’ experience who was blinded to the clinical data of the patients peripherally 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
(FVC), forced expiratory volume in 1 second (FEV₁), 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. 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%) |
| Current smoker (n) (%)               | 20 (11.4%) |
| (pack-year)                          | 50.0±20.3 |
| Body mass index (kg/m²)              | 23.7±3.4 |
| Biopsy-proven IPF (n) (%)            | 90 (51.4%) |
| PaO₂(Torr)                           | 81.4±11.6 |
| FVC (mL)                             | 2,511±765 |
| FVC, percent predicted (%)           | 80.1±19.9 |
| FEV₁/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 SpO₂ during 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, PaO₂: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, FEV₁: forced expiratory volume in 1 second, DLco: diffusing capacity of the lungs for carbon monoxide, SpO₂: 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                  | PaO₂ 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       | p<0.0001       |

PaO₂: partial pressure of oxygen in arterial blood, FVC: forced vital capacity, DLco: diffusing capacity of the lungs for carbon monoxide, SpO₂: 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 (PaO₂) 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%
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 non-specific 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 (>701 HU)| 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 |
| 95%CI                   |      |                 |                             |       |         |        |
| Model 2B                |      |                 |                             |       |         |        |
| FVC, percent predicted  | 0.989| 0.976-1.000     | 2.463                       | 0.060 |         |        |
| DLco, percent predicted |      |                 |                             |       |         |        |
| Model 2B                |      |                 |                             |       |         |        |
| 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%.

Table 3. The 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...
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

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%.

| Model 1                       | HR  | 95%CI       | Likelihood ratio chi-square | p   | C index | 95%CI        |
|------------------------------|-----|-------------|----------------------------|-----|---------|-------------|
| 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).
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 PaO₂ 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 (27, 28). Some studies have 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.

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**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).

**References**

1. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 183: 788-824, 2011.

2. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 156: 684-691, 2012.

3. Natsuzaka M, Chiba H, Kuronuma K, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med 190: 773-779, 2014.

4. Enomoto N, Suda T, Kono M, et al. Amount of elastic fibers predicts prognosis of idiopathic pulmonary fibrosis. Respir Med 107: 1608-1616, 2013.

5. Harada T, Watanabe K, Nabeshima K, Hamasaki M, Iwasaki H. Prognostic significance of fibroelastic foci in usual interstitial pneumonia and non-specific interstitial pneumonia. Respirology 18: 278-283, 2013.

6. Tajiri M, Okamoto M, Fujimoto K, et al. Serum level of peristin can predict long-term outcome of idiopathic pulmonary fibrosis. Respir Investig 53: 73-81, 2015.

7. Song JW, Do KH, Jung SJ, Colby TV, Han S, Kim DS. Blood biomarkers MMP-7 and SP-A: predictors of outcome in idiopathic pulmonary fibrosis. Chest 143: 1422-1429, 2013.

8. Furukawa T, Taniguchi H, Ando M, et al. The St. George’s Respiratory Questionnaire as a prognostic factor in IPF. Respir Res 18: 10, 2017.

9. Sumikawa H, Jokohk T, Colby TV, et al. Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. Am J Respir Crit Care Med 177: 433-439, 2008.

10. Shin KM, Lee KS, Chung MP, et al. Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. Radiology 249: 328-337, 2008.

11. Oda K, Ishimoto H, Yatera K, et al. High-resolution CT scoring system-based grading scale predicts the clinical outcomes in patients with idiopathic pulmonary fibrosis. Respir Res 15: 10, 2014.

12. Ley B, Elicker BM, Hartman TE, et al. Idiopathic pulmonary fibrosis: CT and risk of death. Radiology 273: 570-579, 2014.

13. Best AC, Meng J, Lynch AM, et al. Idiopathic pulmonary fibrosis: physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology 246: 935-940, 2008.

14. Maldonado F, Moua T, Rajagopalan S, et al. Automated quantification of radiological patterns predicts survival in idiopathic pulmonary fibrosis. Eur Respir J 43: 204-212, 2014.

15. Jacobs J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J 49.
16. Ohkubo H, Kanemitsu Y, Uemura T, et al. Normal lung quantification in usual interstitial pneumonia pattern: the impact of threshold-based volumetric ct analysis for the staging of idiopathic pulmonary fibrosis. PLoS One 11: e0152505, 2016.

17. Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. Thorax 61: 744-746, 2006.

18. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26: 720-735, 2005.

19. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15: 361-387, 1996.

20. Ley B, Elicker BM, Hartman TE, et al. Idiopathic pulmonary fibrosis: CT and risk of death. Radiology 273: 570-579, 2014.

21. Colombi D, Dinkel J, Weinheimer O, et al. Visual vs fully automatic histogram-based assessment of Idiopathic Pulmonary Fibrosis (IPF) progression using sequential Multidetector Computed Tomography (MDCT). PLoS One 10: e0130653, 2015.

22. Park SO, Seo IB, Kim N, Lee YK, Lee J, Kim DS. Comparison of usual interstitial pneumonia and nonspecific interstitial pneumonia: quantification of disease severity and discrimination between two diseases on HRCT using a texture-based automated system. Korean J Radiol 12: 297-307, 2011.

23. Iwasawa T, Ogura T, Sakai F, et al. CT analysis of the effect of pirfenidone in patients with idiopathic pulmonary fibrosis. Eur J Radiol 83: 32-38, 2014.

24. Iwasawa T, Kato S, Ogura T, et al. Low-normal lung volume correlates with pulmonary hypertension in fibrotic idiopathic interstitial pneumonia: computer-aided 3D quantitative analysis of chest CT. AJR Am J Roentgenol 203: W166-W173, 2014.

25. Cotin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 26: 586-593, 2005.

26. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 136: 10-15, 2009.

27. Ryerson CJ, Hartman T, Elicker BM, et al. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest 144: 234-240, 2013.

28. Kurashima K, Takayanagi N, Tsuchiya N, et al. The effect of emphysema on lung function and survival in patients with idiopathic pulmonary fibrosis. Respirology 15: 843-848, 2010.

29. Song JW, Hong SB, Lim CM, Koh Y, Kim DS. Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. Eur Respir J 37: 356-363, 2011.

30. Usui Y, Kaga A, Sakai F, et al. A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia. BMJ Open 3: 2013.

31. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 370: 2083-2092, 2014.

32. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 370: 2071-2082, 2014.

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