Body mass index—percent forced vital capacity—respiratory hospitalization: new staging for idiopathic pulmonary fibrosis patients

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Background: Idiopathic pulmonary fibrosis (IPF) is relentless progressive interstitial lung disease. Evaluating predictor of mortality for IPF patients is crucial. The aim of this study was to evaluate the serial trend of important indicators of prognosis and create a useful staging method for IPF patients.

Methods: We retrospectively searched medical records, pulmonary function tests (PFTs), and chest high resolution computed tomography (HRCT) scans from January 1, 2008 through June 30, 2015 at our hospital. We also evaluated the same parameters 1-year later.

Results: We identified 65 IPF patients. The mean age was 71.9±1.8 years (range, 22–85 years). In terms of PFTs, mean percent predicted forced vital capacity (%FVC) was 69.8±2.7. Baseline mean body mass index (BMI) was 24.3±0.6 kg/mm². Mean survival was 39.2 months (range, 0.9–158.9 months). Cox proportional hazard ratios (HRs) showed the following to be predictors of mortality in IPF patients: 1-year BMI (HR: 0.899; 95% CI: 0.825–0.979; P=0.021); 1-year %FVC (HR: 0.932; 95% CI: 0.887–0.979; P=0.005) and 1-year respiratory hospitalization (HR: 3.307; 95% CI: 2.149–5.090; P<0.001). On the basis of these date, we created a new staging method for predicting mortality for IPF patients, consisting of delta BMI, delta %FVC and respiratory hospitalization within a year following diagnosis of IPF (BFR staging). We stratified patients into one of three groups according to the composite points. Mean survival of stages 1, 2, and 3 was 77.9 (30.8–158.9), 43.9 (0.9–145.2) and 14.8 (3.5–32) months (P<0.001), respectively.

Conclusions: In our cohort of IPF patients, this new staging method, including delta BMI and delta %FVC and respiratory hospitalization within 1-year showed a clear survival difference.

Keywords: Idiopathic pulmonary fibrosis (IPF); staging; body mass index (BMI); percent predicted forced vital capacity (%FVC); respiratory hospitalization

Submitted Aug 14, 2016. Accepted for publication Nov 18, 2016. doi: 10.21037/jtd.2016.12.49 View this article at: http://dx.doi.org/10.21037/jtd.2016.12.49

Introduction

Idiopathic pulmonary fibrosis (IPF) is relentless progressive interstitial lung disease (ILD). In the diagnosis of IPF, integration of clinical information, pulmonary function test (PFT) results, chest imaging and pathology are required (1,2). In particular, chest high-resolution computed tomography (HRCT) is considered to be of great importance in diagnosis (3,4). Once IPF is diagnosed, both follow-up of the trend of clinical symptoms and prediction of prognosis are crucial for management of these patients (5). From the clinical point of view, an easy, reproducible, less invasive indicator for staging is useful in

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daily practice (6-8). Recently, meaningful staging such as the composite physiological index (CPI) (9) or the gender, age and physiology (GAP) index (10) have been reported to provide useful information for prediction of mortality in IPF patients (11,12). However, these indices include diffusing capacity for carbon dioxide (DLco). DLco often cannot be performed in patients with more severe disease and may be affected by factors such as anemia and smoking status (13,14). Additionally, du Bois et al. reported that hospitalization predicted mortality of IPF patients (15). Among simple clinical examinations, body mass index (BMI) is easy to measure accurately and repeatedly without stress to the patient (16). Both obesity and body weight loss have a positive relationship with poor prognosis in IPF patients (17). In addition, body weight loss is often associated with dyspnea grade or disease progression in IPF patients, but there are few the clinical studies evaluating body weight change in patients with IPF. We hypothesized that delta BMI, change in the percentage of predicted forced vital capacity (%FVC), and respiratory hospitalization are crucial predictors of mortality in patients with IPF. The aim of this study was to evaluate the serial trend of important indicators of prognosis and create a useful staging method for IPF patients.

Methods

We retrospectively searched medical records, PFT results, and chest HRCT scans from January 1, 2008 through June 30, 2015 at our hospital. The same parameters were evaluated for each patient 1-year later. IPF was diagnosed based on the 2011 International IPF guidelines (1).

Patient clinical characteristics at diagnosis included age, sex, smoking history, BMI. BMI was re-evaluated 1-year later. In laboratory findings, we reviewed white blood cell (WBC), lactate dehydrogenase (LDH) and Krebs von den Lungen-6 (KL-6) values at diagnosis. In terms of physiological findings, we evaluated forced vital capacity (FVC), %FVC, %DLco, total lung capacity (TLC), %TLC, and forced expiratory volume in 1 s (FEV₁) and %FEV₁. We re-evaluated pulmonary function 1-year later when possible or survive. If patient died within 1-year, only baseline PFT results were analyzed. These values were calculated based on Japanese standardized reference. In addition, we calculated the GAP staging system using %FVC and %DLco values (10). We also calculated CPI according to the following formula (9):

 $CPI = 91 - (0.65 \times \% DLco) - (0.53 \times \% FVC) + (0.34 \times \% FEV_1)$

On radiological findings, chest CT was obtained with 1mm-thick axial sections at 1-cm intervals throughout the entire thorax in the inspiratory phase (18). No oral or intravenous contrast material was administered. We chose three levels for imaging scoring; aortic arch, carina, and 1 cm above the right diaphragm (19,20). Reticulation, traction bronchiectasis, honeycombing, and ground glass opacity (GGO) were evaluated. Reticulation was defined as interlacing lines in secondary lobules (21). Fibrosis scores consisted in the combined reticulation, traction bronchiectasis, and honeycombing, and was defined as the 0, none; 1, involvement >25% of each zone; 2, 25–50% of each zone; and 3, >50% of each zone (22). GGO scores were calculated in the same manner.

For our new staging method, we chose three crucial parameters that proved significant predictors of mortality in our cohort; delta BMI, delta %FVC, and respiratory hospitalization within a year (BFR staging). First, delta BMI was defined as baseline BMI minus BMI at 1-year. Delta BMI was scored on a four-point scale (0-3) based on delta value; 0, $\Delta < 0.5$; 1, $0.5 \le \Delta \le 1$, 2, $1 < \Delta \le 2$, 3, $2 < \Delta$. Optimum cut-off levels were determined from receiver operating characteristics (ROC) curves. Second, delta %FVC was defined as baseline %FVC minus %FVC at 1-year. Delta %FVC was scored on a three-point scale (0-2) based on delta value; 0, $\Delta < 5$, 1, $5 \le \Delta < 10$, 2, $10 \le \Delta$. These cut-off value are based on a previous study for evaluation of %FVC in IPF patients (23,24). Third, respiratory hospitalization was defined as admission related to bronchitis, pneumonia, pneumothorax and pulmonary embolism, or acute cor pulmonale within 1-year from IPF diagnosis; hospitalization for heart failure and other causes were excluded. These parameters were summed. Finally, patients were grouped as follows: stage I, consisting of 0-2 points; stage II, consisting in 3–5 points; and stage III, consisting in ≥ 6 points. In making staging, discrimination was measured using the C-statistic Index which ranges from 0 to 1.0. The study was approved by Okinawa Chubu Hospital ethics committee (No. H28-20). They waived informed consent because of the retrospective nature of the medical record review.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation. Linear regression was used to study univariate and multivariable associations between potential predictors and mortality based on previous studies of IPF (25,26). The threshold for the candidates of predictor of mortality

Table 1	Clinical	characteristics	(n=65)

Characteristic	Mean ± SD
Age (years)	71.9±1.8
Sex (male/female)	41/24
Smoking history (ever/never)	19.6±4.4 (38/27)
BMI (kg/mm²)	24.6±0.6
WBC (mm ³)	9,058±504
LDH (IU/L)	256±10
KL-6 (IU/L)	1,237±122
Fibrosis score	1.9±0.1
GGO score	1.5±0.1
Survival (months)	39.2±5.3

BMI, body mass index; WBC, white blood cell; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; GGO, ground glass opacity.

Table 2 Physiological findings (n=65)

Characteristic	Mean ± SD
FVC (L)	1.93±0.1
%FVC	69.8±2.7
%DLco	50.8±3.1
TLC (L)	3.66±0.2
%TLC	78.3±3.0
FEV ₁ (L)	1.58±0.1
%FEV ₁	85.7±3.8
CPI	51.0±3.0
GAP	4.3±1.8

FVC, forced vital capacity; DLco, diffusing capacity for carbon dioxide; TLC, total lung capacity; FEV₁, forced expiratory volume in 1 s; CPI, composite physiologic index; GAP, gender, age, and physiology.

was P<0.1. Next, Cox proportional hazards regression models were used to evaluate hazard ratios (HRs), 95% confidence intervals (CIs) and P values for each factor, adjusted for confounders such as prednisolone (PSL) and immunosuppressants. Analysis of variance (ANOVA) was conducted in the three patient groups.

Survival time was analyzed using the Kaplan-Meier method and the log-rank test with the end points being

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death or the last contact. P<0.05 was considered statistically significant.

All analyses were performed using Stata Data Analysis and Statistical Software STATA version 11.0 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics

Our cohort of IPF patients consisted in 65 consecutive patients; patient clinical characteristics are shown in *Table 1*. Mean age was 71.9 ± 1.8 years, and there were 41 men and 24 women. In terms of smoking status, 38 were active or ex-smokers (mean 19.6 pack-years). Mean follow-up period was 32.4 months. Baseline BMI was 24.6 kg/m². In major comorbidities, diabetes mellitus (DM) and hypertension were 18% and 43%.

In laboratory findings, mean WBC, LDH and KL-6 were 9,058 mm³, 256 IU/L, and 1,237 IU/L, respectively. Mean survival was 39.2 months (*Table 1*).

PFTs

Mean FVC, %FVC, %DLco, TLC and %TLC were 1.93 L, 69.8%, 50.8%, 3.66 L, and 78.3%, respectively. Mean FEV₁, and %FEV₁ were 1.58 L and 85.7%. In addition, mean CPI and GAP were 51.0 and 4.3, respectively (*Table 2*). In diagnostic method, 11 patients (17%) were pathologically proven IPF.

Management

Of the 65 patients, 29 patients received PSL alone and 19 patients took both PSL and cyclosporine A. Three patients received pirfenidone (PFD) and five took both PSL and PFD. One patient received nintedanib. Eight patients were followed up without active medication (*Figure 1*). We had no transplanted patient.

Cause of death

During the follow up period, 39 patients died. The leading cause of death was bacterial pneumonia (n=13). Other causes included acute exacerbation (n=10) and progression of respiratory failure (n=8), lung cancer (n=4), alveolar hemorrhage (n=2), and extra-pulmonary diseases (n=2) (*Figure 2*).

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Figure 1 Treatment content. PSL, prednisolone; CSA, cyclosporine A.



Figure 2 Cause of death. DAH, diffuse alveolar hemorrhage.

Predictors of mortality

Among the clinical parameters including demographic, laboratory, physiological, radiological and admission history, univariable analysis revealed 16 items as statistically significant predictors of mortality. After adjustment for age, sex, and treatment, multivariate analysis showed LDH, KL-6, %DLco, 1-year %FVC, BMI, 1-year BMI, and 1-year respiratory hospitalization were significant predictors of mortality (*Table 3*).

Among these predictor candidates, delta BMI, delta

Factor	Hazard ratio	95% CI	P value
WBC	0.416	0.436-1.530	0.300
LDH	0.623	0.103–2.150	0.008
KL-6	0.601	0.663–0.784	0.007
Fibrosis score	0.408	0.157–0.974	0.135
GGO score	0.042	0.085–0.094	0.917
TLC	0.666	0.140-0.732	0.071
%TLC	0.410	0.699–1.510	0.422
%DLco	4.084	3.556-4.374	0.022
FEV ₁	0.328	0.133–0.677	0.474
%FEV ₁	0.267	0.591–0.593	0.960
FVC	0.303	0.109–0.487	0.402
%FVC	0.948	0.741–26.381	0.232
1-year %FVC	0.932	0.887–0.979	0.005
Delta %FVC	1.075	0.972–1.189	0.016
BMI	7.708	2.669–12.748	0.008
1-year BMI	9.058	2.925–15.192	0.009
Delta BMI	1.028	0.891–1.187	0.007
1-year hospitalization	3.307	2.149–5.089	<0.001

Table 3 Univariate Cox proportional hazards for predictors of

CI, confidence interval; WBC, white blood cell; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; GGO, ground glass opacity; TLC, total lung capacity; DLco, diffusing capacity for carbon dioxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index.

%FVC and respiratory hospitalization within 1-year were strong predictors of mortality in patients with IPF (*Table 4*).

New staging

mortality

In creating new staging, C-statistic values for univariate survival model of delta BMI, delta %FVC and respiratory hospitalization within 1-year were 0.561, 0.633 and 0.780. And C-statistic values for multivariate survival model of delta BMI + delta %FVC, delta BMI + respiratory hospitalization within 1-year, delta %FVC + respiratory hospitalization within 1-year and delta BMI + delta %FVC + respiratory hospitalization within 1-year were 0.623, 0.692, 0.753 and 0.765. Our new BFR staging system consists in delta BMI, delta %FVC and respiratory hospitalization

 Table 4 Multivariable Cox proportional hazards for predictors of mortality after adjustment of treatment

Factor	Hazard ratio	95% CI	P value
Delta BMI	1.324	1.045–1.676	0.020
Delta %FVC	1.063	0.999–1.131	0.050
1-year hospitalization	5.806	2.265–14.883	<0.001

Cl, confidence interval; BMl, body mass index; FVC, forced vital capacity.

Table 5 Points associated with each parameter

Parameter	0	1	2	3
Delta BMI	<0.5	0.5≤ ∆ ≤1	1<∆≤2	2< Δ
Delta %FVC	<5	5≤ ∆ <10	10≤ ∆	-

BMI, body mass index; FVC, forced vital capacity.

Table 6 BFR staging

Grade	Points
Stage I	0–2
Stage II	3–5
Stage III	≥6

BFR, body mass index, forced vital capacity, and respiratory hospitalization.

within 1-year (*Table 5*). According to these parameters, we divided patients into three stages (*Table 6*). Patient clinical characteristics according to the new staging system are shown in *Table 7*. Stage I patients were light smokers with relatively preserved pulmonary function and fewer respiratory hospitalizations within 1-year. Stage II patients were heavy smokers with high BMI, and showed elevated of KL-6 and decreased %DLco. All stage III patients were never smokers and had low baseline BMI. In addition, this group showed large delta BMI and delta %FVC, and were hospitalized more often for respiratory reasons.

Survival

Finally, we created a survival curve based on the new staging system. Stage III patients showed poor survival compared with that of stage I and II patients (14.8 vs. 77.9

and 43.9 months; P<0.001) (Figure 3).

Discussion

We propose a new staging system for patients with IPF at our hospital. Both age and sex proportions of our cohort were consistent with that of previous studies (27-30). However, smoking history in our patients was rather light compared with classical IPF cohorts. In laboratory findings, mean KL-6 was >1,000 IU/L and stage II patients had the most elevated value. Therefore, these patients may have more active proliferation of type II alveolar cells (31-33).

Regarding physiological findings, mean %FVC and %DLco were consistent with that of IPF patients in a large study (34-37). Mean CPI and GAP scores were approximately 50 and 4, respectively. Therefore, our cohort showed moderate severity of restrictive disorder. Furthermore, mean %FEV₁ was 85.7% in our study; therefore, the obstructive component contributes little.

With respect to medical management, approximately three-quarters of our patients received PSL. This might be associated with the leading cause of death of pneumonia found in this study.

With respect to death in our cohort, both acute exacerbation and progression of respiratory failure were important, consistent with previous studies (38-41). In addition, we sometimes see extra-pulmonary cause including cardiovascular disease. Therefore, we should monitor crucial comorbidity carefully in daily practice (42-45).

On physiological prediction of mortality in IPF patients, both FVC and DLco have been reported as useful parameters (46-50). DLco was a strong predictor of mortality of our cohort on Cox proportional hazard analysis. However, DLco is often variable and is affected by respiratory infection or anemia (51,52). In addition, when the vital capacity of a patient is <1.5 L, it cannot be measured with the single breath method. Therefore, it showed less consistency or reproducibility compared with FVC; accordingly, we omitted DLco from our new staging system, and instead included delta BMI, delta %FVC, and respiratory hospitalization.

For creating new staging system of IPF cohort, we chose delta BMI, delta %FVC and respiratory hospitalization.

First, BMI is a simple and reproducible item, and less invasive for the patient. Among IPF patients, we previously reported that 1-year modified medical research council breathlessness scale is a useful predictor of mortality (53). In IPF patients, severe dyspnea is associated with greater

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Characteristic Stage I (n=15) Stage II (n=34) Stage III (n=14) P value 70±6 77 0.999 Age 68.1±3.3 Pack-year 10.3±6.7 31.5 0 0.366 BMI 26.0 ± 2.0 28.7±3.7 24.9 0.142 1-year BMI 25.8±2.1 27.9±3.1 15.4 0.005 WBC 7.238±764 6.400±300 5.500 0.143 LDH 230±14 264±101 205 0.113 KL-6 990±168 2.564±2.087 625 0.695 74.6±4.4 %FVC 68.3±7.3 88.4 0.451 1-year %FVC 76.0±4.3 57.5±6.4 62.8 0.030 %DLco 68.5±9.2 37.3±4.3 46.8 0.048 %TLC 78.5±2.8 73.0±5.5 83.8 0.985 0.125 0.5 1-year hospitalization 1 < 0.001

Table 7 Clinical characteristics based on new staging system

BMI, body mass index; WBC, white blood cell; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; FVC, forced vital capacity; DLco, diffusing capacity for carbon dioxide; TLC, total lung capacity.



Figure 3 Survival curve of new staging.

consumption of body energy. Therefore, our hypothesis is that body weight loss has a positive relationship with dyspnea severity and mortality.

Second, we chose delta %FVC for the new staging system. %FVC is a classic robust marker of prognosis of IPF patients (23,47). And, more decreased %FVC within six months or 1-year have been reported to predict mortality of IPF patients (23,24,52). We considered the trend of %FVC is more robust than a single measurement of %FVC.

Third, we included respiratory hospitalization within 1-year. du Bois *et al.* reported hospitalization within 1-year

as a crucial predictor of mortality with composite index (15). We considered that respiratory hospitalization such as bronchitis, pneumonia, pneumothorax and pulmonary embolism would contribute more to prognosis of IPF patients. IPF patients often develop respiratory deterioration or pulmonary dysfunction within 1-year of diagnosis (53). Therefore, we set 1-year as the cut-off for evaluating the trend of significant parameters or hospitalization history. Accurate cause of all stage III patients was never smoker remains unknown. According to our previous report, never smoker IPF patients had poor prognosis (53), therefore one possibility is never smoker IPF patients tend to have pure active fibrosis compared to smoker IPF patients. Detailed evaluation of pathological findings is interesting topic.

Finally, we stratified our cohort into three groups according to our new staging. According to our study, stage I patients remained fairly clinically and functionally stable. However, stage II patients had more severe pulmonary dysfunction and elevation of KL-6. Therefore, monitoring IPF activity such as change of pulmonary function or frequent evaluation with chest imaging is required. Stage III patients showed remarkable decreases in BMI and %FVC within 1-year. In addition, stage III patients required respiratory hospitalization more often. Based on these information, we should pay attention to not only physiological trends but also to general medical status, including body weight, nutrition and infection in stage III patients. We require comprehensive management for stage III patients.

There are several limitations. First, this was a retrospective fashion single-center small sample study. A prospective study is required in the future. Second, this study focuses mainly on clinical information. Therefore, we did not evaluate radiological and pathological findings in detail. However, not all patients undergo surgical lung biopsy, owing to advanced age, physical limitations, severe pulmonary dysfunction and patient refusal. Owing to inconsistencies among thoracic radiologists, radiological scoring is often inaccurate compared with body weight or pulmonary function. Our simple staging is easy to use and reproducible. Third, we could not review all clinical parameters 1-year later. However, we could choose important parameters and re-evaluate strong predictors of mortality 1-year later. Fourth, comorbidities such as DM and hypertension may lead to increase of BMI, and steroid therapy may affect BMI change. Last, the majority of these patients were treated with PSL. We can provide two anti-fibrotic agents such as PFD and nintedanib in clinical practice. We should plan a prospective study with modern therapy for IPF patients. Based on these limitations, we could not over-interpret our result. However, our novel findings and staging are easy to apply. And our findings provide important clinical trend of IPF patients.

In conclusion, we propose a simple new staging system for IPF patients. This staging consists in delta BMI, delta %FVC and respiratory hospitalization within 1-year. We showed a clear difference in long-term survival of IPF patients based on this new staging. A multi-center prospective study is warranted in the future.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Okinawa Chubu Hospital ethics committee (No. H28-20). They waived informed consent because of the retrospective nature of the medical record review.

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Cite this article as: Kishaba T, Nagano H, Nei Y, Yamashiro S. Body mass index—percent forced vital capacity—respiratory hospitalization: new staging for idiopathic pulmonary fibrosis patients. J Thorac Dis 2016;8(12):3596-3604. doi: 10.21037/jtd.2016.12.49

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