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A score for estimating survival in idiopathic pulmonary fibrosis with rest SpO_2>88%

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Abstract. *Background:* Prediction models for survival at baseline evaluation have been proposed in IPF but some are difficult to use. The aim of present study was to develop a new mortality risk scoring system for patients with IPF at initial evaluation. *Methods:* One hundred twenty with definitive IPF were selected through a review of standardized medical records for interstitial lung diseases. Patients with resting SpO_2<89% were excluded. Significant individual predictors we derived by a Cox proportional hazards model and transformed in categorical data according to cut-off points. Beta coefficients for each predictor were similar, so a score was created considering the sum of dichotomic (0 or 1) transformed variables. *Findings:* Median follow-up time was 37.5 months. At the end of follow-up, 80 patients had died. Independent predictors of mortality by multivariate analysis included dyspnea (at rest or to light or moderate activities), FVC<70%,FEV_1/FVC>0.89 and DL_{CO} ≤ 40%. Resting SpO_2 and $ExSpO_2$ were excluded in final analysis. The hazard ratios ranged from 1.95 for dyspnoea to 2.30 for DL_{CO}. When the total score was 0 (Stage I, n=28), median survival time was 68 months; when 1 or 2 (Stage II, n=69), it was 45 months; and when 3 or 4 (Stage III, n=23), it was 19 months (log rank= 60.44, p<0.001). *Interpretation:* The score can separate IPF patients with high, intermediate and low survival.
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Key words: idiopathic pulmonary fibrosis, pulmonary function, interstitial lung diseases

Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) (1). As in other lung diseases, the development of a simple staging system for IPF is necessary to estimate prognosis for clinical decision making, such as the timing of lung transplantation, and to simplify clinical trial designs (2).

The median survival of IPF is between 2 and 4 years after the diagnosis (3).

There appear to be several possible natural histories for patients with IPF; however, the majority of patients demonstrate a slow, gradual progression over many years (3).

Predictors of mortality in patients with IPF can be obtained at a single point in time (baseline predictors) or over time (longitudinal predictors). Many individual clinical variables have been shown to predict survival in IPF. Dyspnoea and baseline forced vital capacity (FVC) are significant predictors of survival (4-10). Diffusion capacity of the lung for car-

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bon monoxide (DL_{CO}) appears to be the most reliable predictor of survival at baseline, and a threshold of approximately 40% has been associated with an increased risk of mortality (1, 2). Oxygen desaturation during exercise has been shown to be an independent predictor of survival in IPF (11, 12). In fibrotic lung diseases, an increase in elastic recoil pressure/ airway resistance ratio can result in an elevated forced expiratory volume in one second and forced vital capacity ratio (FEV_1/FVC); this could also be a prognostic parameter, as shown in a previous study (7).

Clinical prediction models that combine individual variables have been proposed for IPF, but different variables are included 4, (8-10, 13). Recently, a score including age, sex, FVC and DL_{CO} (GAP) was derived and validated (9).

The aim of the present study was to develop a simple score to estimate patient survival using a well-defined retrospective cohort of patients with IPF and a long follow-up time.

Methods

Study Population

The study included retrospectively identified patients with IPF from three reference centers for interstitial lung diseases (ILD) in São Paulo. The patients were identified through a review of medical records obtained between Ja. 1, 1996 and Dec. 31, 2011.

The diagnosis of IPF was based on the following: the presence of a definitive high-resolution computed tomography (HRCT) pattern and age >50 years (n=83); a definitive UIP pattern in surgical lung biopsy (SLB) in those with a possible IPF pattern on HRCT (n=19); or a UIP pattern both on HRCT and in SLB (n=18) (1). All cases were reviewed by experienced pulmonologists and radiologists, and all biopsies were reviewed by lung pathologists with extensive experience in ILD. Patients were excluded from the study if there was any evidence of diseases that could result in UIP (1). Patients with an airflow obstruction (FEV_1/FVC ratio <0.70), oxygen saturation <89% at rest, and those using home oxygen therapy were excluded. Local institutional review boards approved the study.

Predictor Variables

Duration of symptoms, sex, age at symptom onset, smoking status, symptoms of gastroesophageal reflux disease (heartburn, regurgitation), dyspnoea, cough, crackles, finger clubbing, and presence of honeycombing or emphysema on HRCT were recorded using a systematic protocol. The patients were categorised as non-smokers or smokers (current or former smokers).

Dyspnoea was assessed by Magnitude of Task of Basal Dyspnea Index (BDI) (14). Total BDI score was not considered because functional impairment and magnitude of effort do not involve the same activities in different patients. Spirometry, DL_{CO} and peripheral oxygen saturation (SpO_2) measured by digital oximetry (*Nonin®*) at rest and at the end of exercise ($ExSpO_2$), were evaluated at initial visits. No supplemental oxygen was used during exercise. Pulmonary function tests were conducted according to standard criteria (15, 16). SpO_2 was measured before and at the end of a 4-minute step test (4MST) (12) or at the end of a 6-minute walk test (6MWT) (17). SpO2 in these two tests have similar prognostic value in IPF (11, 12). The predicted values for spirometry were those derived from Brazilian population (18). The values for predicted DL_{CO} were those derived by Crapo (19). The decision of whether to provide specific treatment was made by individual clinicians.

Statistical Analysis

To estimate the sample size for the Cox models, a minimum of 10 outcome events should be present per predictor variable (20). Possible categorical predictors were dyspnoea (4-6), FVC (4-10), FEV_1/FVC (7), DL_{CO} (1), and $ExSpO_2$ ≤88% (11, 12). Based on the analysis of a previous study conducted in our centre (12), approximately 120 cases should be included to obtain 50 deaths in a study with similar duration.

Analyses were completed using IBM SPSS version 19. The values were expressed as the count, percentage, mean, median, and standard deviation. Group comparisons were made using unpaired t-tests (for normally distributed, continuous variables). Correlations were calculated using Pearson's coefficient.

Survival time was calculated from the date of diagnosis to death or lung transplantation (n=2) or loss to follow-up. Survival status was obtained from telephone interviews and/or medical records in June 2013.

The effect of each potential explanatory variable, expressed in continuous values, on the hazard function was calculated by univariate analysis using a Cox proportional hazards regression. To avoid multicollinearity, only one of the highly correlated variables (Pearson's correlation coefficient ≥0.6) was entered in the multivariate model. Candidate variables with p-values of <0.10 in a univariate analysis were then transformed into categorical variables. Thresholds for physiological variables were based on previously published values (1, 2, 8-12, 21), ROC points with greater sums of sensitivity and specificity, and the greatest log-rank in Kaplan-Meier analysis. The categorical variables to be included in the final model were selected by Cox multivariate analysis. Outliers were identified by SPSS and excluded (22). The results were summarised as the hazard ratios (HRs), which represent the relative risk of death as a result of a specific characteristic during the observation period. Each predictor variable was categorised as zero or one, and survival curves were compared between the summed final scores using Kaplan-Meier curves.

The overall performance of the risk scoring system was quantified by the C-statistic (23).

Results

A total of 125 patients were evaluated. Five outliers were identified and excluded from the subsequent analyses, two with FVC>120% predicted, two with SpO_2 at exercise <70%, and one with DL_{CO}<15%. Coincidently with the calculated sample, a total of 120 patients with IPF were included in the final analysis; their baseline characteristics and clinical and physiological data are summarised in Table 1. Most patients were male, smokers or former smokers, and had honeycombing in HRCT; the mean age was approximately 70 years. All patients who had no honeycombing in HRCT were diagnosed with UIP by SLB. Based on FVC%, the restriction was typically mild. DL_{CO} was moderately reduced and ranged from 20-75%. A total of 72 patients (60.0%) had an $ExSpO_2$ ≤88%. Thirty-eight patients (31.7%) completed the 6MWT, and the remaining 82 completed the 4MST. The $ExSpO_2$ was 87.4±5.1% in the 6MWT and 85.6±6.1% in the 4MST (p=0.12).

Table 1. General findings in 120 patients with idiopathic pulmonary fibrosis

Findings	
Age ($\bar{x}$±SD), years	68.6±7.9
Sex, male/female (%)	84 (70%)/36 (30%)
Smokers or former smokers, %	74 (61.2)
Cough, n (%)	68 (56.7%)
Dyspnoea, n, grades 1/2/3/4	17/34/54/15
GERD symptoms, n (%)	46 (38.3%)
Velcro crackles, n (%)	118 (98.3%)
Clubbing, n (%)	23 (19.2%)
Biopsy proven, %	37 (30.8)
FVC ($\bar{x}$±SD), % predicted	75.2±15.3
FEV1 ($\bar{x}$±SD), % predicted	79.1±15.1
FEV1/FVC ($\bar{x}$±D)	0.83±0.07
DLCO ($\bar{x}$±SD), % predicted	47.1±13.5
Rest SpO_2 ($\bar{x}$±SD), %	94.4±2.2
$ExSpO_2$ ($\bar{x}$±SD), %	86.2±5.9
Emphysema in HRCT, n (%)	22 (18.3%)
Honeycombing, n (%)	101 (84.2%)
Treatment (0=none; 1=corticosteroids or immunosuppressants or both)	34 /86

The median of follow-up time was 37.5 months (range 4-120 months). The median survival was 44 (95% CI=38-50) months. At the end of follow-up period, 80 patients were deceased. All patients, except two, died from IPF or related complications (four died from lung cancer). Two were censored due to lung transplantation.

Based on the univariate Cox proportional hazards model, dyspnoea was the only clinical finding significantly related to survival (Table 2). In BDI greater scores indicate less dyspnoea. Due to similar median survival times among patients with scores of 3 and 4 and among patients with scores of 0, 1 and 2, these grades were grouped and the patients were dichotomised into scores of 0 and 1, respectively.

Based on the univariate Cox proportional hazards model, FVC%,FEV_1%, the FEV_1/FVC ratio, DL_{CO}, and resting SpO_2 and $ExSpO_2$, expressed as continuous or categorical variables, were significant

Table 2. Univariate analysis – clinical and functional variables

Variables	HR	95% CI	p
Age (years)	1.02	(0.99-1.04)	0.27
Sex (male=1)	1.08	(0.68-1.72)	0.75
Surgical lung biopsy	1.12	(0.70-1.80)	0.62
Smoking status (1=smokers/ex or non-smokers)	1.24	(0.78-1.97)	0.32
Time of symptoms (months)	1.00	(1.00-1.01)	0.84
Dyspnoea (Mahler*, magnitude of task, grade 4 or 3/2 or 1 or 0)	1.66	(1.28-2.15)	0.001
Cough (yes/no)	1.34	(0.85–2.10)	0.20
Emphysema (yes/no)	1.23	(0.70-2.16)	0.48
Honeycombing (yes/no)	1.30	(0.74-2.28	0.36
Clubbing (yes/no)	1.11	(0.65-1.90)	0.70
GERD symptoms (yes/no)	1.31	(0.83-2.07)	0.25
Treatment (0=none; 1=corticosteroids or immunosuppressants or both)	1.32	(0.75-2.32)	0.33
FVC, % predicted (↓)	1.05	1.03-1.06	<0.001
FEV1, % predicted (↓)	1.04	1.02-1.05	<0.001
FEV_1/ FVC (↑)	1,04	1.01-1.08	0.017
DL_{CO}, % predicted (↓)	1.04	1.02-1.06	<0.001
Rest SpO_2, % (↓)	1.19	1.08-1.31	0.001
$ExSpO_2$, % (↓)	1.07	1.03-1.10	<0.001

*See footnote Table 4

Table 3. COX multivariate analysis for categorical dyspnoea, functional variables and SPO_2

Variables, n, (%)	HR	95% CI	p
Dyspnoea (Mahler*, magnitude of task, grade 2/3 /4	1.95	1.22-3.11	0.005
FVC <70% (predicted)	2.02	1.27-3.22	0.003
FEV_1/FVC >0.89	2.42	1.37-4.27	0.002
DL_{CO} ≤40% (predicted)	2.30	1.42-3.71	0.001
RestSpO_2 ≤ 93%	1.36	0.70-2.32	0.266
$ExSpO_2$ ≤88%	1.10	0.65-1.86	0.716

*See footnote Table 4.

predictors of survival (Tables 2). FEV_1% was correlated with FVC% (r=0.90, p<0.001) and was excluded from the multivariate analysis. The correlation between DL_{CO} and $ExSpO_2$ was significant but poor (r=0.41, p<0.001). The correlation between resting SpO_2 and $ExSpO_2$ was 0.56 (p<0.001);

The presence of emphysema (any degree) on HRCT did not influence survival; the median survival time was 50 months in those with emphysema compared to 41 months in those without emphysema (log-rank=0.52, p=0.47). The median for dyspnoea was the same for patients with and without emphysema, 3 for both groups. Those with emphysema had non-significantly higher mean values for FVC% (80.2±17.0 *vs.* 74.0±15.2, p=0.09) and significantly lower values for FEV_1/FVC (0.79±0.06 *vs.* 0.84±0.07, p=0.001) and DL_{CO}% (40.0±10.3 *vs.* 48.7±13.7, p=0.006). Exercise SpO_2 was similar between the groups: 84.6±5.5% in those with emphysema and 86.5±5.9% in those without emphysema (p=0.18). FEV_1% was also similar in the two groups.

A multivariate Cox analysis including the following categorical variables was performed: dyspnoea, FVC<70%, DL_{CO}≤40% (predicted), FEV_1/ FVC >0.89, SpO2 at rest ≤93%, $ExSpO_2$≤88%. SpO_2 at rest and in exercise did not remain significant. The results are shown in Table 3.

A multivariate Cox analysis including the four

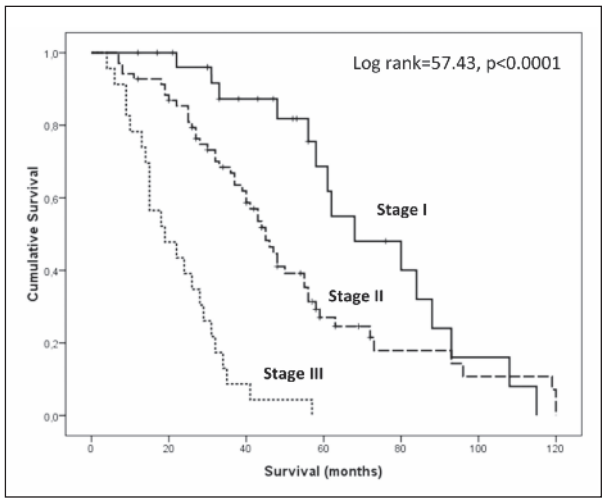

Fig. 1. Survival in patients with IPF, separated according stages (see Table 4)

significant variables shown in Table 3 demonstrated similar HRs (and *beta).* Therefore, a point score was developed that assigned the same weight (zero or one) to these categorical variables and summed the results. A total score (0 to 4 points) was derived, and survival curves were estimated by the Kaplan-Meier method. Only six patients had a score of 4 (median survival=14 months, 95% CI=8.0-21.0 months). These six patients were merged with patients with a score of 3 (median survival=24 months, 95% CI=13.0-35.0 months). The median survival times were also similar between patients with scores of 1 and 2 (44 [95% CI=29-59] months and 45 [95% CI=36-54] months, respectively), and they were therefore also merged.

The survival curves for the three groups are shown in Figure 1. When the total score was 0 (n=28), the median survival was 68 months (95% CI =46-90 months), whereas the median survival was 45 months (95% CI=39-51 months) when the total score was 1 or 2 (n=69). By contrast, when the score was 3 or 4 (n=23), the median survival was 19 months (95% CI=8-30 months) (log-rank=57.43, p<0.0001).

The scores were transformed in stages I, II and III. The survival for these stages at 24 and 48 months is shown in Table 4**.**

The C-statistic for the global scoring performance was 0.785 (95% CI=0.705-0.865).

Table 4. The DDS index and staging system

	Predictor	Points
D	Dyspnoea (Mahler, magnitude of task)*	
	3/4	0
	0/1/2	1
D	DL_{CO} % (predicted)	
	>40%	0
	≤40%	1
S	Spirometry	
	FVC % (predicted)	
	≥70%	0
	<70%	1
	FEV_1/FVC	
	≤0.89	0
	>0.89	1

	Survival	
Stage**	24 months	48 months
I	96%	82%
II	85%	40%
III	39%	4%

***Grade 4: Extraordinary.** Becomes short of breath only with extraordinary activity such as carrying very heavy loads on level ground, lighter loads uphill, or running. No shortness of breath with ordinary tasks. **Grade 3: Major.** Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on level ground**. Grade 2: Moderate.** Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing less than three flights of stairs, or carrying a light load on the level**. Grade 1. Light:** Becomes short of breath with light activities such as walking on level ground, washing, or standing. **Grade 0: No task.** Becomes short of breath at rest, while sitting, or while lying down (Mahler et al. *Chest* 1984;85:751-8).
** Stage I = 0 points; Stage II = 1 or 2 points; stage III = 3 or 4 points.

Discussion

In this study, we found that physiological variables commonly measured during the initial evaluation of patients with IPF can be combined with dyspnoea in a score to predict mortality in patients with a resting SpO_2 >88%.

The development of a prognostic scoring system for IPF is important because it may serve as a basis for clinical decision making and simplify clinical trial design (8, 9). Several studies have suggested a median survival of 2 to 4 years from the date of diagnosis in IPF. In our study, the median survival was 4.6 years; however, patients with low resting SpO_2 values were excluded.

Several individual clinical variables have been shown to predict survival in IPF (1, 2). IPF is more

prevalent in older males. In GAP study (9) age and sex had a significant correlation with survival. In our study, age and sex were not associated with survival. Although some studies have found a worse prognosis in older individuals (4, 8, 9), others have found no influence (5-7, 10, 11, 21). Similarly, a worse prognosis has been observed for males in some studies (4, 9) but not in others (5-8, 11, 21). General mortality is considered in almost all studies on survival in IPF, and most deaths (approximately 80%) in IPF result from progression of lung fibrosis rather than other causes (3). In the general population, mortality is greater in older men (24). This finding could explain the significant influence of age on mortality in large series of IPF (8, 9).

In larger studies, several cut-off points have been proposed, with lower FVC% values showing progressive greater HRs for mortality (8, 9). In our study, a cut-off point of 70% for FVC% was found to be the best discriminatory value. This cut-off point has also been described by others (10).

The DL_{CO} is the functional variable that best correlates with disease extent in IPF (13), and it is also the variable that is most reliably predictive of survival at baseline (2, 3). The threshold of 40% suggested by several authors (1-3, 21) was also the cut-off point with the greater discriminatory value in our study.

Previous studies have shown a similar and significant influence of oxygen desaturation on survival (11, 12); however, $ExSpO_2$ was excluded as a predictive factor in our study by multivariate analysis.

In IPF, the interpretation of lung function tests is confounded by coexistent emphysema, which results in spurious preservation of lung volumes, a lower FEV_1/FVC, and worse gas transfer (25). In our study, an FEV_1/FVC >0.89 was associated with worse survival, an expected finding reflecting a higher degree of fibrosis (7, 26). In the present study, emphysema had no significant influence on survival, which has also been described by others (27). However, patients with an FEV_1/FVC <0.70 and those with low resting SpO_2 were excluded from our study.

Dyspnoea is the most important factor influencing the quality of life in subjects with IPF. As in other studies, we found that dyspnoea has a significant and independent role in predicting survival (6, 10, 26). Exertion dyspnoea and reduced exercise tolerance in IPF are multifactorial, and their correlations with functional variables are poor (28).

Composite scoring systems have been developed that utilise physiological and radiographic variables in an attempt to provide more accurate prognostic information in IPF (3, 21); however, the extent of fibrosis is difficult to measure in HRCT. Other scores have been developed to estimate survival in IPF. The clinical, radiological, and physiological score was a model developed in a large cohort of IPF (4); however, it has not been widely adopted in clinical practice because it uses variables that are not routinely measured. A composite physiologic index (CPI) has been developed that uses FEV_1, FVC, and DL_{CO} to predict the extent of disease on HRCT (13). The CPI was a stronger predictor of mortality than individual measures of lung function such as FEV_1, FVC, and DL_{CO} (13). A CPI >41 was predictive of worse survival (HR=5.36) in a previous study (10). It is unclear whether it is possible to separate patients with high, intermediate, and low mortality with cut-off points derived from the CPI. Moreover, the score has to be calculated from other parameters and is therefore not easy to apply in everyday clinical practice.

A study using data from a large and well-characterised population of patients with IPF found that several parameters were independent predictors of mortality after one year of follow-up (8). An abbreviated clinical model including age, 24-week history of respiratory hospitalisation, baseline % predicted FVC, and 24-week change in % predicted FVC was derived. The strongest independent predictor of mortality was the 24-week change in % predicted FVC. Such a risk-scoring system cannot be applied in the initial evaluation. Moreover, DL_{CO}, the variable with the greatest prognostic predictive value when combined with FVC in IPF (29), was excluded from the model.

More recently, a multidimensional score (GAP), which included gender (G), age (A), and two lung physiology variables (FVC and DL_{CO}) in the final model, was derived and validated. As discussed above, many studies on the prognosis of IPF have reported that age and/or gender are not relevant variables for predicting mortality in IPF (5-8, 11, 21).

When GAP score was applied to our sample, the stages were discriminatory of survival but with lower log rank (14.22, $p<0.001$). The GAP score overestimated the mortality in our patients in stage I

and stage II. In two years, for example, estimated mortality was 11% *vs* 4% for stage I, 30% *vs* 15% for stage II, and 62% *vs* 61% for stage III.

Some limitations of our study are noteworthy. First, the study was retrospective, but all deaths, except two, were related to IPF or its complications. Several patients with IPF develop fatal acute exacerbation of the disease, so a completely reliable system of survival prediction is nearly impossible to obtain at baseline (1).

Additionally, this study did not include patients with SpO2 <89%; however, the poor prognosis of these patients is clear. The use of categorical variables for continuous measurements is less desirable in prediction models, although it allows for simple estimate scoring. Some key factors should be considered when developing risk prediction models (30). The model must be validated in other cohorts; thus, our results must be replicated in other studies. The model should be able to discriminate those with an outcome from those without and should have clinical utility. The discrimination power of our model was calculated by the C statistic, and the value was 0.78. The C statistic ranges from 0.5 (model discrimination is no better than chance) to 1 (model discrimination is perfect). A C statistic between 0.70 and 0.80 is considered acceptable.

The strengths of this study include an adequate sample size, a substantial follow-up duration and a mortality rate sufficient for analysing the roles of the selected predictor variables (20).

In conclusion, we examined a well-characterised population of patients with IPF and found several independent predictors of mortality, including dyspnoea, % predicted FVC, DL_{CO}, and FEV_1/FVC. Categorical values for these variables can be combined to derive a score that is predictive of high, intermediate, and low mortality.

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