Pulmonary Function in Idiopathic Pulmonary Fibrosis and Referral for Lung Transplantation

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Of patients awaiting lung transplantation, the death rates are highest in those with idiopathic pulmonary fibrosis (IPF), suggesting that many IPF patients are referred late for transplantation. Therefore this study was undertaken to evaluate baseline pulmonary function test (PFT) and high-resolution computed tomography (HRCT) fibrosis scores, and the relationship to survival in IPF patients younger than 65 yr of age. A total of 115 patients with usual interstitial pneumonia (UIP) were studied. At presentation to a tertiary referral center, PFT and HRCT data were collected and analyzed for prognostic significance: the primary outcome measure was patient death. Based on the length of the waiting list for transplantation, prediction of 2-yr survival was examined. D_{LCO} percent predicted and HRCT–fibrosis score were found to be independent predictors of survival and in combination gave the best prognostic prediction. The optimal points on the receiver operating characteristic (ROC) curves for discriminating between survivors and nonsurvivors corresponded to 39% D_{LCO} percent predicted, and to a HRCT–fibrosis score of 2.25. The combination of these parameters yielded an optimal point with a specificity and a sensitivity of 84% and 82%, respectively. A model based on a combination of D_{LCO} percent predicted and HRCT–fibrosis score may optimize the timing of referral for transplantation.

Keywords: high-resolution computed tomography; idiopathic pulmonary fibrosis; lung transplantation; pulmonary function testing

Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal, and increasingly common disease (1). Usual interstitial pneumonia (UIP)–pattern IPF is the commonest histologic subtype and is generally unresponsive to steroid therapy. In a recent study, it was shown that incident cases of IPF have an extremely limited prognosis with a median survival of 2.8 yr (2). After the failure of medical treatment, single-lung transplantation results in an actuarial survival of 73% at 1 yr and 57% at 3 yr (3). In the United States, lung transplantation for IPF has been shown to confer an improved survival compared with patients remaining on the waiting list (4).

A limited window of opportunity exists to refer IPF patients for lung transplantation. The short transplant window is reflected in the high mortality rate in IPF patients awaiting lung transplantation (4). Currently, the median waiting period for single-lung transplantation in the United Kingdom is 351 d (confidence interval [CI] 293 to 427 d) (5). Given an expected median survival of 34 mo after the diagnosis of IPF and a mean waiting list for transplantation of 12 mo, there is a window of just 22 mo for referral for transplantation. It is because of the limited transplant window and the difficulty predicting survival that IPF patients in the United States are given a 3-mo waiting advantage compared with patients with emphysema (6). Despite this, IPF patients still have the highest death rate while awaiting lung transplantation (4).

The timing of referral for transplantation is therefore dependent on predicting survival. In previous studies, poor survival was associated with male sex (7), older age (7, 8), nonresponse to steroids (9), and reduced pulmonary function at presentation (10–12). However, current estimates of survival are based upon studies in which patients are of a wide age range, whereas lung transplantation is limited to patients younger than 65 yr of age. Pulmonary function test (PFT), as a noninvasive quantitative measurement, is the cornerstone of current practice in the assessment of the disease severity and progression. It has been recommended that symptomatic patients with IPF younger than 65 yr of age should be discussed with the transplant center after a failed trial of corticosteroid therapy and referred in any of the following circumstances: diffusing capacity of the lungs for carbon monoxide (D_{LCO}) less than 50 to 60%, FVC less than 60 to 70%, resting hypoxia, or pulmonary hypertension (3, 13). However, these are class C recommendations, i.e., based on expert opinion only.

Since these international recommendations, two developments have occurred. First, Katzenstein's histologic classification of IPF (14) has been shown by Bjoraker and coworkers (2) to be of importance in estimating the natural history of the disease and, second, high-resolution computed tomography (HRCT) has increasingly become accepted as the key noninvasive investigation for the diagnosis of IPF (15). Therefore this study was undertaken to evaluate baseline PFT and HRCT fibrosis scores and the relationship to survival in IPF patients younger than 65 yr of age. The aim was to provide a noninvasive estimate of survival, to facilitate the timing of referral of IPF patients for transplantation.

METHODS

Patient Selection Criteria

Patients with UIP-pattern IPF were studied. The diagnosis of UIP was based on either HRCT or an open lung biopsy (OLB). All patients had been treated with corticosteroids and various chemotherapeutic regimes before and after referral to our institution.

Exclusion criteria were: (*1*) the presence of known histories of collagen vascular disease, allergic alveolitis, or exposure to organic dusts; (*2*) patients with a tissue diagnosis of nonspecific interstitial pneumonia (NSIP)/fibrosis, desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated with interstitial lung disease (RB-ILD), or bronchiolitis obliterans organizing pneumonia (BOOP); (*3*) patients with a predominantly ground-glass attenuation on HRCT scan (16, 17); (*4*) patients who demonstrated an objective response to corticosteroids alone; (*5*) patients who subsequently underwent lung transplantation; (*6*) patients older than 65 yr were excluded (on the grounds that they are not eligible for transplantation).

The date of the PFT was taken as the baseline from which survival was measured. Follow-up concluded with patient's death or last pre-

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sentation. Deaths were confirmed from either the hospital notes or by contacting the patient's general practitioner (primary care physician).

Surgical Lung Biopsies

Surgical lung biopsies were completed either through a thoracotomy incision or by video-assisted thoracoscopic surgery. The site of the biopsy was directed by HRCT.

Definition of UIP–Pattern IPF by histologic criteria. The diagnosis of UIP was based on the following histopathologic criteria (14): (*1*) a variegate picture of interstitial fibrosis, inflammation, and normal tissue; (*2*) tendency for fibrosis to subpleural and peripheral distribution; (*3*) the absence of the uniform fibrotic changes characteristic of NSIP and of features indicating other causes (e.g., asbestos bodies, granulomata).

HRCT Scanning

All patients underwent HRCT scan of the chest. All HRCT scans were obtained at Wythenshawe Hospital immediately after referral, using a Picker PQ scanner (Picker International, Cleveland, OH). The HRCT scans consisted of 1.5-mm-thick slices acquired at 10-mm increments through the thorax, reconstructed with a high-spatial-frequency algorithm. Scans were performed at end-inspiration with the patients in the supine position; no intravenous contrast was given. The HRCT scans were reviewed independently by two pulmonary radiologists (SMG and AWH) who were unaware of the clinical and functional findings.

Definition of UIP–Pattern IPF by HRCT criteria. HRCT criteria for diagnosing UIP were as follows (16, 18): (*1*) a reticular pattern of intralobular interstitial thickening demonstrating a peripheral, subpleural, and basal predominance with irregular pleuroparenchymal interfaces; (*2*) may show areas of honeycombing and traction bronchiectasis; (*3*) ground-glass opacification may be present but the reticular pattern predominates; (*4*) consolidation and nodules must be absent.

Each lobe of the lung was scored (SMG, AWH) for the extent of ground-glass opacity (HRCT–ground glass) and reticular opacities and honeycombing (HRCT–fibrosis) on a scale of 0–5 based on the method used by Kazerooni and coworkers (19). The mean value for all lobes was incorporated into a fibrotic (HRCT–fibrosis) and ground-glass (HRCT–ground glass) score for each patient and scores were then averaged for the two readers.

Lung Physiology

Spirometry (Vmax 22; Sensormedics Yorba Linda, CA), plethysmographic lung volumes (6200 Plethysmograph; Sensormedics) and D_{LCO} (P.K. Morgan, Rainham, England) were measured. All lung function measurements were performed in the same laboratory at the North West Lung Centre. D_{LCO} values were corrected to hemoglobin. Alveolar volume (V_A) was measured by a single-breath helium dilution method, and diffusing capacity per unit volume (K_{CO}) was calculated by dividing D_{LCO} by V_A. Values were expressed as absolute values and, where appropriate, as percentages of the predicted values calculated according to sex, weight, and age. The definitions and methods for performing lung volumes and diffusing capacity followed the recommendation of the European Coal and Steel Community (20, 21). All lung function measurements used in this study were obtained immediately after the referral of the patients to the North West Lung Centre.

Statistical Analysis

Statistical analysis was performed on the patients as follows. All patients fulfilling the criteria for UIP–pattern IPF were subjected to statistical analysis as a single group. A subgroup analysis was completed on those patients in whom histologic material from OLB was available. To specifically examine 2-yr survival, only those patients who died or had at least 2-yr follow-up were analyzed. A two-tailed *t* test was used to compare those patients who had undergone OLB with those who had not. Univariate Cox proportional-hazards regression analysis was completed to identify significant variables predicting survival status. Variables that were significant by univariate Cox regression analysis were taken as potential predictors of survival, and were then used as covariates in the stepwise multivariate Cox regression analysis to identify independent predictors of survival. The results were summarized as hazard ratios, representing the relative risk of dying as a result of a specific characteristic during the entire period of observation.

To predict the likelihood of death, a predictive model (using the two independent predictors of survival) was derived from a formula given by Collett (22) (*see* Model 1 in APPENDIX E1, ONLINE DATA SUPPLEMENT, for details). From this, a look-up table has been derived, summarizing the probability of survival for various time periods. Survival curves were also plotted by Cox survival analysis for patients according to the availability of tissue to confirm the diagnosis (OLB versus no OLB). Univariate logistic regression analysis was performed on those patients who died, or survived at least 2 yr, to identify significant variables predicting 2-yr survival. Variables that were significant by the univariate logistic regression analysis were taken as potential predictors of survival, and were used as covariates in the stepwise multivariate logistic regression analysis to identify independent predictors of 2-yr survival. A predictive model (using the two independent predictors of survival) was derived (*see* Model 2 in APPENDIX E2, ONLINE DATA SUPPLEMENT, for details of the formula). Receiver operating characteristic (ROC) analyses were performed on those patients included in the logistic regression for a mathematical expression combining those variables identified as independent predictors of survival (D_{LCO} percent predicted and HRCT–fibrosis score). For comparison, the ROC curves were also plotted for FVC percent predicted, D_{LCO} percent predicted, and HRCT–fibrosis score. The areas under the curves were compared. The statistical analyses were performed using the SPSS/PC software package (version 9.0, SPSS Inc., Chicago, IL). Values are expressed as means ± SD and a statistical significance level of 0.05 was used; 95% CI are quoted throughout.

RESULTS

Patient Selection

Of 379 patients with diffuse parenchymal lung disease attending the North West Lung Centre, Manchester, 321 with the clinical syndrome of UIP were evaluated. Forty-three patients with a diagnosis of NSIP, DIP, and BOOP were excluded. Sixty-two patients without HRCT scoring (HRCT completed in another hospital) and 71 patients with an age over 65 yr were excluded from the analysis. During the follow-up, 30 patients underwent lung transplantation and were excluded (Figure 1).

Patient details are given in Table 1. A cohort of 115 patients formed the total study group, consisting of 81 men and 34 women, mean age 56 ± 8 yr (range 17 to 65). The diagnosis of UIP-pattern IPF was established by surgical (open or thoracoscopic) lung biopsy in 44 (38%). For the remaining patients (62%), the diagnosis of UIP was based on HRCT appearance: for six of these patients, the diagnosis was verified by necropsy. Median follow-up was 26.2 mo (range 1 to 97 mo). As of December 14, 1999, 46 (40%) of the 115 patients have died. The median survival was 55 mo. The major cause of death was respiratory failure due to progression of the IPF. Bronchogenic carcinoma accounted for 7% of deaths. By the *t* test (two-tailed), there were no significant differences in any of the pulmonary function and HRCT variables between those patients who had had an OLB and those who had not.

Factors Associated with Survival by Univariate and Multivariate Cox Regression Analysis

For the entire study group of 115 patients, a total of 12 variables were significant on univariate regression analysis, as shown in Table 2. By multivariate stepwise regression analysis, only D_{LCO} percent predicted ($p = 0.005$) and HRCT–fibrosis score ($p = 0.026$) were independent predictors of survival. The multivariate regression analysis yielded the hazard ratios shown in Table 3. For the whole patient group, the hazard of death increases by 4% (CI 1 to 7%) for every 1% decrease in D_{LCO} percent predicted and increases by 106% (CI 9 to 291%) for each unit increase in HRCT–fibrosis score.

Equation to predict the probability of survival for a specified time from the significant variables. A model (Model 1) was completed for D_{LCO} percent predicted and HRCT–fibrosis score. The probability of survival for various time points after diagnosis and a worked example of the calculation of the probability of survival are given in APPENDIX E1, ONLINE DATA SUPPLEMENT. From this model, the look-up table (Table 4) has been derived. By subgroup analysis of patients with OLB by univariate analysis, only TLC, TLC percent predicted, and HRCT–fibrosis score were significant. On multivariate analysis, only HRCT–fibrosis score ($p = 0.048$) was an independent predictor of survival (Table 3). For those patients who underwent OLB, the hazard of death increases by 375% (CI 2 to 2,114%) for each unit increase in HRCT–fibrosis score.

Survival Plots

Survival curves are shown in Figure 2, for patients who underwent an OLB and for patients whose diagnosis was based on HRCT scan alone. There is no significant difference between the two curves ($p = 0.472$).

Logistic Regression Analysis

Ninety-five patients were subjected to this analysis, consisting of 29 patients who died within 2 yr and 66 who survived more than 2 yr. Univariate logistic analysis showed 12 variables to be significant predictors of survival (Table 2). On multivariate analysis only D_{LCO} percent predicted ($p = 0.021$) and HRCT–fibrosis score ($p = 0.021$) were significant independent predictors. The multivariate logistic regression analysis yielded the hazard ratios show in Table 3. The hazard of death increases by 8% (CI 1 to 14%) for every 1% decrease in D_{LCO} percent predicted and increases by 527% (CI 32 to 2,890%) for each unit increase in HRCT–fibrosis score.

Equation to derive the probability of 2-yr survival from the significant variables. A model (Model 2) was completed for D_{LCO} percent predicted and HRCT–fibrosis score; *see* APPENDIX E2, ONLINE DATA SUPPLEMENT, for details.

ROC Analysis to Define the Ability of Evaluated Tests to Predict Survival at 2 Yr

ROC analysis was performed on the logistic regression model. FVC percent predicted gave an area under the curve of 0.693 (CI 0.567 to 0.819); D_{LCO} percent predicted gave an area of 0.802 (CI 0.706 to 0.898); HRCT–fibrosis score gave an area of 0.863 (CI 0.772 to 0.953); and the prediction model (combining D_{LCO} with HRCT–fibrosis score) gave an area of 0.907 (CI 0.831 to 0.983) (Figure 3).

DISCUSSION

This study was conducted to assess the ability of pulmonary function and HRCT scores to predict survival in a group of IPF patients younger than 65 yr of age with UIP-pattern IPF who are potentially eligible for lung transplantation. The data presented confirm that D_{LCO} percent predicted and HRCT–fibrosis score are significant independent predictors for survival. Model 1, combining these two variables, gives the best prediction of survival (Table 4) and may contribute to optimizing the timing of referral of IPF patients for lung transplantation.

This report excluded other histologic subtypes of IPF, such as NSIP and DIP, on the grounds that they pursue a more benign course compared with UIP. Only patients with a secure

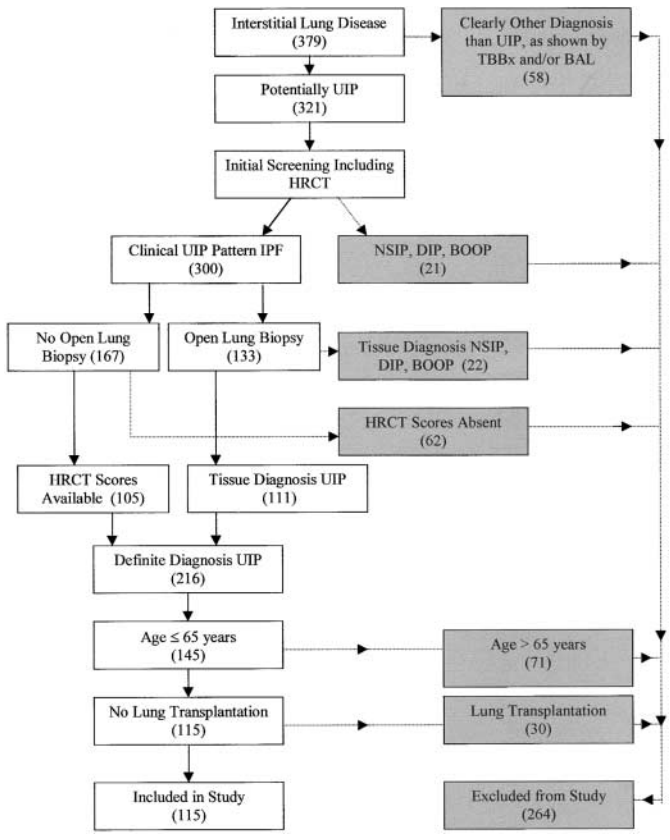

Figure 1. Patient flow through the enrolment to make up the study group.

TABLE 1. CHARACTERISTICS OF THE PATIENTS ACCORDING TO PATIENT GROUP

Evaluated Parameter	All	With OLB	Follow-up 2-yr
No. of subjects	115	44	95
Age, yr	55.5 ± 8.2	54.0 ± 0.6	55.5 ± 8.4
Male/female	81/34	31/13	67/28
Diagnosis (based on tissue), n (%)	52 (45)	44 (100)	50 (52)
OLB	44 (38)	44 (100)	42 (44)
Necropsy	8 (7)	—	8 (8)
Diagnosis (based on HRCT), n (%)	63 (55)	—	45 (48)
Smoking, n (%)			
Never-smokers	39 (34)	4 (9)	36 (38)
Ex-smokers	59 (51)	27 (61)	46 (49)
Current smokers	17 (15)	13 (30)	12 (13)
Follow-up, mo	32.8 ± 24.6	36.0 ± 27.1	36.6 ± 25.3
Lung function, n (%)	111 (97)	41 (93)	93 (98)
FEV_1, L	2.0 ± 0.7	2.1 ± 0.6	2.1 ± 0.7
FEV_1, % pred	70 ± 22	71 ± 21	70 ± 22
FVC, L	2.6 ± 1.0	2.7 ± 0.8	2.6 ± 1.0
FVC, % pred	72 ± 23	72 ± 20	72 ± 25
TLC, L	4.3 ± 1.4	4.3 ± 1.1	4.4 ± 1.5
TLC, % pred	74 ± 23	75 ± 19	75 ± 24
D_{LCO}, ml/min/mm Hg	4.3 ± 1.8	4.5 ± 1.7	4.4 ± 1.7
D_{LCO}, % pred	49 ± 18	50 ± 16	49 ± 17
K_{CO}, mmol · kPa^{-1} · min^{-1}	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4
K_{CO}, % pred	79 ± 25	82 ± 24	79 ± 24
BAL cell differentials, n (%)	73 (63)	30 (69)	59 (62)
Macrophages, %	53 ± 23	51 ± 22	52 ± 23
Neutrophils, %	22 ± 19	21 ± 19	23 ± 20
Lymphocytes, %	9 ± 9	11 ± 12	8 ± 8
Eosinophils, %	6 ± 7	7 ± 8	6 ± 8
Others, %	11 ± 11	11 ± 10	12 ± 12
HRCT score, n (%)	89 (77)	24 (55)	74 (78)
HRCT–fibrosis score	2.1 ± 0.7	1.9 ± 0.7	2.1 ± 0.7
HRCT–ground-glass score	3.0 ± 1.3	3.1 ± 1.0	3.1 ± 1.3

* Values are means ± SD.

TABLE 2. SIGNIFICANT VARIABLES BY UNIVARIATE REGRESSION ANALYSIS ACCORDING TO PATIENT GROUP

Parameter	All* (*n = 115*) p Value	With OLB* (*n = 44*) p Value	Follow-up 2-yr† (*n = 95*) p Value
Lung function			
FEV_1, L	0.0006	NS	0.0063
FEV_1, % pred	0.0014	NS	0.0219
FVC, L	0.0018	NS	0.0031
FVC, % pred	0.0042	NS	0.0094
TLC, L	0.001	0.0425	0.0044
TLC, % pred	0.0014	0.0306	0.0073
D_{LCO}, ml/min/mm Hg	0.0001	NS	0.0002
D_{LCO}, % pred	< 0.0001	NS	0.0001
K_{CO}, mmol · kPa^{-1} · min^{-1}	0.0059	NS	0.0090
K_{CO}, % pred	0.006	NS	0.0101
HRCT score			
HRCT–fibrosis score	< 0.0001		0.0001
HRCT–ground-glass score	0.0504	0.0475	0.0026

* Analysis by Cox regression.
† Analysis by logistic regression.

TABLE 4. PROBABILITY OF TWO-YEAR SURVIVAL ACCORDING TO PROPOSED COX REGRESSION MODEL

D_{LCO} % Predicted	HRCT–Fibrosis Score* 1	1.5	2	2.5	3
25	0.79	0.71	0.62	0.50	0.37
30	0.83	0.76	0.68	0.57	0.45
35	0.86	0.80	0.73	0.64	0.52
40	0.89	0.84	0.78	0.70	0.60
45	0.91	0.87	0.82	0.75	0.66
50	0.92	0.89	0.85	0.79	0.72
55	0.94	0.91	0.88	0.83	0.77
60	0.95	0.93	0.90	0.86	0.81
65	0.96	0.94	0.92	0.89	0.84
70	0.97	0.95	0.94	0.91	0.87
75	0.97	0.96	0.95	0.93	0.90

* HRCT score derived by Kazerooni and coworkers (18). For example, a patient with a D_{LCO} of 40% predicted and a HRCT–fibrosis score of 2 has a 78% probability of surviving 2 yr.

diagnosis of UIP were included. Several studies have demonstrated that HRCT findings can accurately predict the histologic pattern of UIP (16, 19, 23, 24). More recently, Raghu and coworkers (25) have shown that clinical assessment combined with HRCT scanning carries a diagnostic specificity of 90% for UIP–pattern IPF. Thirty-eight percent of patients in this study were also subject to histologic confirmation of UIP by OLB. An additional 7% had histologic confirmation of the diagnosis at necropsy. This is higher than the standard practice in the United Kingdom where OLB rates of 15 to 25% are usual (26). Only including patients with histologic confirmation of disease may be ideal. However, such a strategy would result in a selection bias toward patients who are sufficiently well to undergo biopsy. Including those patients in whom the diagnosis has been secured by HRCT should result in a more representative spectrum of cases. Furthermore, the mean HRCT–fibrosis score of 2.1 reported in this study closely mirrors that of Kazerooni and coworkers (19), who demonstrated a significant correlation between HRCT–fibrosis score and the histopathologic fibrosis score.

Our patients receive treatment in the form of corticosteroids, azathioprine and cyclophosphamide, in a manner comparable to other centers. Given the current understanding of treatment and outcome, it is unlikely that these treatment regimes actually influenced survival. Patients who underwent lung transplantation were excluded from the study. Death rates among patients awaiting lung transplantation are the highest in the IPF group. Therefore, to include patients who underwent transplantation, with their enhanced post-transplant survival, would skew the data inappropriately.

Previous studies evaluating lung function and survival have been inconsistent in their findings. Erbes and coworkers (27) identified TLC as the most important predictor of survival, whereas Turner-Warwick and coworkers (8) did not find either TLC or FVC to be significant predictors of survival. Hubbard and coworkers (1) identified FVC and D_{LCO} as independent predictors of survival, whereas Hanson and coworkers (28) found changing, rather than absolute, values for FVC and D_{LCO} to be predictive of prognosis. Schwartz and coworkers (29) suggested that a high FEV_1/FVC ratio was important in determining survival. In contrast to all these studies, Gay and coworkers (9) did not find any measure of pulmonary function to be predictive of survival, but did find both the HRCT–fibrosis score and the pathologic–fibrosis score to be of value in predicting survival. These disparate findings may be explained by small study numbers, studying patients with a broad age range, and including patients who had not undergone HRCT scanning.

Age is recognized as a very important factor in determining survival (7, 8). All previous studies estimating survival in IPF included patients older than 65 yr of age. Therefore, this study

TABLE 3. MULTIPLE STEPWISE REGRESSION ANALYSIS TO IDENTIFY INDEPENDENT PREDICTORS ACCORDING TO PATIENT GROUP

	n	p Value	Hazard and Odds Ratios	95% CI for Hazard and Odds Ratios
For all patients (Model 1)*	85			
D_{LCO}, % pred		0.005	0.957	0.928–0.987
HRCT–fibrosis score		0.026	2.067	1.726–3.914
For OLB*	24			
HRCT–fibrosis score		0.048	4.747	1.017–22.146
For 2-yr follow-up (Model 2)†	70			
D_{LCO}, % pred		0.021	0.923	0.863–0.988
HRCT–fibrosis score		0.021	6.274	1.317–29.897

Definition of abbreviation: n = cases available for the analysis.
* Analysis by Cox regression
† Analysis by logistic regression.

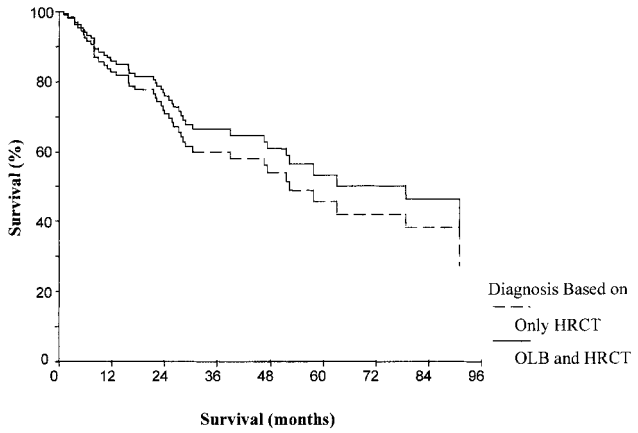

Figure 2. Survival analysis for all patients and patients with OLB. There is no significant difference between the two curves (p = 0.47).

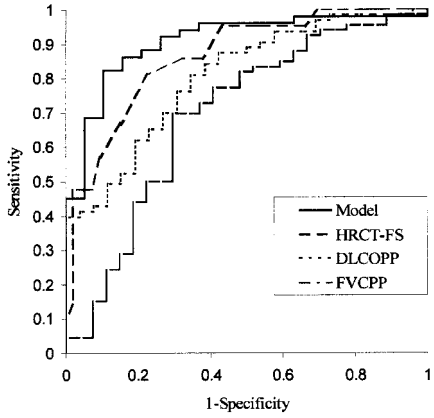

Figure 3. ROC analysis for FVC percent predicted (PP), D_{LCO} PP, HRCT-FS and combined model (HRCT-FS + D_{LCO} PP, using logistic regression, Model 2). The coefficients for the expression were derived from the parameter estimates (β) for the multivariate logistic regression analysis. HRCT-FS denotes high-resolution CT fibrosis score.

is unique in excluding patients older than 65 yr of age on the grounds that they are not eligible for transplantation.

Seventy percent of patients with IPF are current or ex-smokers. Our data indicated that smoking was not a significant factor in predicating survival, as has also been demonstrated by Hubbard and coworkers (1).

The analysis in this group of patients suggests that a model combining D_{LCO} percent predicted and HRCT–fibrosis score may be a more accurate predictor of survival than any previous reported measure. This proposal is strengthened by the application of ROC analysis. ROC provides a useful method of comparing both the sensitivity and specificity of various parameters (or of expressions combining parameters) as predictors of survival. Briefly, the most predictive variable is that which corresponds to the curve that lies to the upper left and has the greatest area under the curve (Figure 3). If the avoidance of false-negative and of false-positive predictions are of equal importance, the optimal point on the curve is that at which the sum of the specificity and sensitivity is maximized. The only previous study to use ROC analysis in the context of IPF was that of Gay and coworkers (9). Their ROC analysis was performed on 38 long-term survivors. In that study ROC analysis failed to reveal a level of pulmonary function that demonstrated clinically acceptable sensitivity and specificity to define survival. ROC analysis for pathologic–fibrosis score demonstrated that a fibrosis score of $\geqslant 16$ predicted death with acceptable sensitivity and specificity (9). The ROC analysis of HRCT–fibrosis score yielded the best curve, with no additional improvement when combined with a CRP (clinical, radiologic, pathologic) score. The area under the ROC curve for HRCT score in this study closely reflects that of Gay and coworkers (Martinez, personal communication).

Our ROC analysis shows progressively superior curves for FVC percent predicted, D_{LCO} percent predicted, and HRCT–fibrosis score. The combined model incorporating both D_{LCO} percent predicted and HRCT–fibrosis score had the best curve (Figure 3). The optimal points on the ROC curves for discriminating between survivors and nonsurvivors corresponded to 39% D_{LCO} percent predicted, and to a HRCT–fibrosis score of 2.25. The curve resulting from the model combining these two parameters yielded a specificity and a sensitivity of 84% and 82% respectively for discriminating between survivors and nonsurvivors.

This study demonstrates that in IPF patients up to 65 yr of age, the best prediction of survival is derived from a combination of D_{LCO} percent predicted/HRCT–fibrosis. This combination has the potential for optimizing the timing of referral for transplantation. It should be stressed, however, that the final decision to proceed toward transplantation is dependent on a comprehensive evaluation of the patient's medical and psychosocial status.

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