Prognostic Implications of Physiologic and Radiographic Changes in Idiopathic Interstitial Pneumonia

Kevin R. Flaherty, Jeanette A. Mumford, Susan Murray, Ella A. Kazerooni, Barry H. Gross, Thomas V. Colby, William D. Travis, Andrew Flint, Galen B. Toews, Joseph P. Lynch III, and Fernando J. Martinez

Departments of Radiology and Pathology, Division of Pulmonary and Critical Care Medicine, University of Michigan Health System; Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan; Armed Forces Institute of Pathology, Washington, District of Columbia; and Mayo Clinic, Scottsdale, Arizona

Idiopathic interstitial pneumonias are a diverse group of lung diseases with varied prognoses. We hypothesized that changes in physiologic and radiographic parameters would predict survival. We retrospectively examined 80 patients with usual interstitial pneumonia and 29 patients with nonspecific interstitial pneumonia. Baseline characteristics were examined together with 6-month change in forced vital capacity, diffusing capacity for carbon monoxide, and ground glass infiltrate and fibrosis on high resolution computed tomography. Patients with usual interstitial pneumonia were more likely to have a statistically significant or marginally significant decline in lung volume, diffusing capacity for carbon monoxide, and an increase in ground glass infiltrates ($p \leq 0.08$) compared with patients with nonspecific interstitial pneumonia. For patients with usual interstitial pneumonia, change in forced vital capacity was the best physiologic predictor of mortality ($p = 0.05$). In a multivariate Cox proportional hazards model controlling for histopathologic diagnosis, gender, smoking history, baseline forced vital capacity, and 6-month change in forced vital capacity, a decrease in forced vital capacity remained an independent risk factor for mortality (decrease $> 10\%$; hazard ratio 2.47; 95% confidence interval 1.29, 4.73; $p = 0.006$). We conclude that a 6-month change in forced vital capacity gives additional prognostic information to baseline features for patients with idiopathic interstitial pneumonia.

Keywords: idiopathic pulmonary fibrosis, usual interstitial pneumonia, nonspecific interstitial pneumonia, pulmonary function, serial testing

Idiopathic interstitial pneumonias are a group a diffuse parenchymal diseases. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) comprise the majority of idiopathic interstitial pneumonia cases; UIP is associated with the worst prognosis (1–5).

Recent efforts to predict prognosis for individuals with idiopathic interstitial pneumonia have centered on baseline physiologic (1, 6, 7), radiographic (7–9), and pathologic testing (1–6, 10). Little information has been published regarding the association of serial changes in pulmonary function (11) or radiographic features (12) and prognosis. We hypothesized that short-term serial changes in pulmonary function and high-resolution computed tomography (HRCT) would predict long-term survival in patients with histologically defined UIP and NSIP.

(*Received in original form September 27, 2002; accepted in final form May 16, 2003*)

Supported by National Institutes of Health NHLBI grants P50HL46487, NIH/NCRR 3 MO1 RR00042-33S3, NIH/NIA P60 AG08808-06, NHLBI, 1 K24 HL04212, and 1 K23 HL68713.

Correspondence and requests for reprints should be addressed to Fernando J. Martinez, M.D., M.S., Taubman Center 3916, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0360. E-mail: fmartine@umich.edu

Am J Respir Crit Care Med Vol 168. pp 543–548, 2003
Originally Published in Press as DOI: 10.1164/rccm.200209-1112OC on May 28, 2003
Internet address: www.atsjournals.org

METHODS

Patient Selection

Patients with a surgical lung biopsy and serial physiologic and/or HRCT data referred by participants in the University of Michigan Fibrotic Lung Disease Network between October, 1989, and February, 2000, were eligible for the current study. Patients were referred due to a suspicion of idiopathic interstitial pneumonia. Two pathologists (T.V.C., W.D.T.), blinded to the clinical features, assigned a histologic diagnosis using defined criteria (1, 13, 14). Only patients with UIP and NSIP formed the study group. These patients represent a subset of previously reported patients (1). The study was approved by the Institutional Review Board at the University of Michigan.

Physiologic Testing and HRCT

Pulmonary function tests (PFT), including spirometry, lung volumes, and diffusion capacity for carbon monoxide ($D_{L_{CO}}$), were performed as previously described (9). HRCT examinations were performed with 1.0- or 1.5-mm-thick sections and scored on a scale of 0–5 for ground glass opacity (CT-alv) and interstitial opacity (CT-fib) as previously described (15).

Therapy

Patients were treated with varied treatment regimens (Table 1). The lack of a standardized, prospective treatment regimen in the majority of patients limited our ability to evaluate if a clear treatment effect on survival or serial change in PFT and HRCT was present.

Statistical Analysis

Changes in PFT and HRCT scores were determined by estimating percent change for absolute value of HRCT and PFT measurements over a 6-month period. Measurements over a 6-month period related to the biopsy time were used to fit a linear regression for each patient. The fitted line from the linear regression was then used to estimate a 6-month measurement, which, together with the baseline measurement, allowed the calculation of percent change. Percent change values over 12 months were similarly created for patients with additional data over a 12-month period.

The date of surgical lung biopsy was used to mark the beginning of the survival time period for each individual. Death and follow-up times were supplemented by the use of the Social Security Death Master File (16). Patients who had not been seen within 3 months and who did not appear in the Social Security Death Master File were called to confirm their vitality. Event times 3 months before the date of analysis were censored. Three patients underwent a lung transplant; physiologic, radiographic, and survival information was censored at the time of transplant. Cox proportional hazards models were used to examine the influence on survival of percent change for HRCT and PFT measurements while adjusting for histopathologic diagnosis, onset of symptoms, gender, and smoking status. The levels of more than 10% increase, between 10% decrease and 10% increase, and more than 10% decrease were used to study percent changes of the PFT and HRCT scores. These cutoff points were chosen *a priori* as they were believed to be clinically reasonable. Survival proportions were estimated and displayed using Cox proportional hazards models evaluated for average covariate profiles in the study population. Characteristics for UIP versus NSIP were compared using *t* tests for continuous measures and chi-square statistics and Fisher's

TABLE 1. TREATMENT ADMINISTERED TO 109 PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA OR NONSPECIFIC INTERSTITIAL PNEUMONIA

Treatment Regimen	UIP n (%)	NSIP n (%)
None	3 (4)	2 (7)
Prednisone alone*	25 (31)	15 (52)
Prednisone + azathioprine or cyclophosphamide	27 (34)	4 (14)
Zileuton†	20 (25)	4 (14)
Azathioprine alone	5 (6)	4 (14)

Definition of abbreviations: NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

* Thirty-one of these patients received prednisone as part of a prospective study of high-dose steroids in idiopathic pulmonary fibrosis.

† A subset of patients were treated in a phase I/II trial comparing zileuton with azathioprine at our institution.

exact (17) statistics for categoric measures. The potential interaction of variables that were significantly different at baseline (UIP compared with NSIP) and histologic diagnosis were also evaluated in multivariate survival models. Significance of individual risk factors were tested using Wald tests, whereas grouped risk factors were tested using likelihood ratio tests. The proportionality assumptions were tested using Schoenfeld residuals.

RESULTS

Baseline Characteristics

One hundred and nine patients with UIP (n = 80) and NSIP (n = 29) were identified. Patients with UIP were older, had a longer duration of symptoms, had a lower percent-predicted total lung capacity (TLC), and more fibrosis on HRCT (Table 2). Gender distribution, CT-alv scores, and other measures of pulmonary physiology were similar between groups.

Change in Serial Measurements over Time

Histologic diagnosis was significantly or marginally associated with changes in pulmonary function and radiographic characteristics over time (Table 3). In general, more patients with UIP had a decline in $D_{L_{CO}}$ compared with patients with NSIP, who were more likely to show an improvement in $D_{L_{CO}}$ over 6 or 12 months of follow-up (6-month p = 0.03; 12-month p = 0.05). Similarly, there was a trend for more patients with UIP to have a decline in FVC or TLC compared with patients with NSIP (6-month p = 0.08, 0.07, respectively). Over 6 months of follow-up, a higher percentage of patients with UIP had an increase in CT-alv compared with patients with NSIP, who were more likely to show a decrease in CT-alv (p = 0.07). Observed associations between histologic diagnosis and CT-fib percent changes over time were not statistically significant.

Survival

The median follow-up time was 4.86 years (95% confidence interval [CI], 4.46, 5.84); median survival was 5.81 years (95% CI, 5.22, 7.31). Initially, models studying percent change of the PFT and HRCT measurements over time adjusted for baseline values were investigated for patients with UIP (Table 4). Decreased FVC over 6 months was associated with increased mortality when adjusted for baseline FVC values. Patients with a decrease in FVC greater than 10% had a higher risk of mortality than those with a percent change between a 10% decrease and a 10% increase (hazard ratio 2.06; 95% CI 1.09, 3.89; p = 0.03; six month change). Patients with an improved FVC of greater than 10% were not observed to have a significantly different hazard of mortality than those with a moderate change in either direction. This may reflect a lack of power as there were fewer patients with an improvement in FVC (n = 14) compared with patients with a decline in FVC (n = 24). Furthermore, patients with a greater than 10% increase in ground glass opacity on HRCT also had a higher risk of subsequent death (relative risk 2.88; 95% CI 1.26, 6.57; p = 0.01) compared with patients with

TABLE 2. BASELINE DEMOGRAPHIC, PHYSIOLOGIC, AND RADIOLOGIC FEATURES FROM PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA AND NONSPECIFIC INTERSTITIAL PNEUMONIA

Characteristic	UIP (*median, range*)	NSIP (*median, range*)	*t* Test p Value	Wilcoxon Test p Value
Sex, female/male	40/40	17/12	0.56*	0.52†
Age, yr	62 (26, 78)	53 (29, 62)	0.001	0.0004
Onset, yr	2 (0.1, 20)	0.7 (0.08, 2.5)	0.43	0.04
Weight, kg	86 (47, 125)	90 (51, 120)	0.81	0.65
Smokers, %	65 ± 5	66 ± 9	0.86*	1
Pack years	10 (0, 100)	20 (0, 90)	0.42	0.46
Physiologic				
FVC, L	2.44 (0.97, 5.57)	2.48 (1.49, 5.27)	0.21	0.31
FVC, % predicted	67 (22, 114)	71 (44, 109)	0.26	0.22
TLC, L	4.12 (2.34, 7.68)	4.32 (2.61, 7.61)	0.14	0.21
TLC, % predicted	72 (42, 121)	82 (51, 120)	0.05	0.04
$D_{L_{CO}}$, ml/min/mm Hg	12.45 (3.42, 30.51)	12.52 (7.58, 23.6)	0.71	0.90
$D_{L_{CO}}$, % predicted	50 (17, 98)	48 (26, 80)	0.97	0.76
HRCT				
Alveolar, CT-alv	1.8 (0.2, 4.2)	2.0 (0, 5)	0.78	0.60
Interstitial, CT-fib	1.9 (0.6, 3.6)	0.9 (0, 2.6)	< 0.0001	< 0.0001

Definition of abbreviations: CT-alv = high-resolution computed tomography score for ground glass; CT-fib = high-resolution computed tomography score for interstitial infiltrates (*see* text for details); $D_{L_{CO}}$ = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography; NSIP = nonspecific interstitial pneumonia; TLC = total lung capacity; UIP = usual interstitial pneumonia.

* p Values calculated by chi-squared test.

† p Values calculated by Fisher's exact test.

TABLE 3. PERCENT CHANGE OF PULMONARY FUNCTION TEST AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCORES OVER TIME BY HISTOLOGIC DIAGNOSIS

	6 Months			12 Months		
	UIP n (%)	NSIP n (%)	p Value*	UIP n (%)	NSIP n (%)	p Value*
FVC change, %			0.08			0.10
> 10% increase	14 (19)	10 (34)		6 (10)	5 (24)	
10% decrease/10% increase	37 (49)	15 (52)		21 (21)	10 (48)	
> 10% decrease	24 (32)	4 (14)		32 (54)	6 (29)	
TLC change, %			0.07			0.14
> 10% increase	9 (14)	8 (35)		9 (29)	2 (22)	
10% decrease/10% increase	39 (59)	12 (52)		6 (19)	5 (56)	
> 10% decrease	18 (27)	3 (13)		16 (52)	2 (22)	
D_{LCO} change, %			0.03			0.05
> 10% increase	15 (23)	13 (50)		5 (14)	7 (47)	
10% decrease/10% increase	24 (36)	4 (15)		6 (17)	2 (13)	
> 10% decrease	27 (41)	9 (35)		24 (69)	6 (40)	
CT-alv change, %			0.07			
> 10% increase	25 (42)	4 (22)		NA	NA	
10% decrease/10% increase	22 (37)	5 (28)		NA	NA	
> 10% decrease	13 (22)	9 (50)		NA	NA	
CT-fib change, %			0.94			
> 10% increase	17 (28)	6 (33)		NA	NA	
10% decrease/10% increase	24 (40)	7 (39)		NA	NA	
> 10% decrease	19 (32)	5 (28)		NA	NA	

Definition of abbreviations: CT-alv = HRCT score for ground glass; CT-fib = HRCT score for interstitial infiltrates (*see* text for details); D_{LCO} = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography; NA = not available; NSIP = nonspecific interstitial pneumonia; PFT = pulmonary function test; TLC = total lung capacity; UIP = usual interstitial pneumonia.

* p Value represents a comparison of UIP and NSIP and was calculated using Fisher's exact test.

a less than 10% change. Changes in CT-fib or TLC were not significant predictors of long-term survival when adjusted for the corresponding baseline values.

Multivariate models of PFT and HRCT changes over time, adjusting for baseline value, histologic diagnosis, onset of symptoms before biopsy, smoking history, and gender were examined. A 6-month decrease in FVC of over 10% and a UIP diagnosis were significant predictors for reduced survival compared with patients with NSIP or moderate increases or decreases in FVC over time (Table 5, Figure 1). The magnitude and direction of the hazard for the levels of FVC percent change are similar to the unadjusted model. No significant interaction between histologic diagnosis and demographic, physiologic, or radiographic variables was noted. Changes in TLC, D_{LCO}, CT-alv, and CT-fib did not contribute further information once these factors were included in the multivariate model. Baseline A–a gradient was not a significant predictor of survival in univariate (hazard ratio 1.0; 95% CI 0.98, 1.03; p = 0.79) or multivariate analysis (hazard ratio 1.0; 95% CI 0.97, 1.04; p = 0.65). Similar results were seen in a multivariable 12-month model, although change in FVC was no longer statistically significant.

DISCUSSION

Previous studies have identified the histopathologic pattern as the most important baseline factor in determining prognosis (1–5). However, the disease course for individual patients with either UIP or NSIP can vary greatly. We hypothesized that short-term changes in physiologic and radiographic criteria would give additional prognostic information to the baseline features of patients with UIP and NSIP.

In this report of a well-characterized group of patients with UIP or NSIP, we identify (*1*) that a decrease in FVC during the initial 6 months of follow-up is the best physiologic predictor of mortality, (*2*) a decrease in FVC during the initial 6 months after surgical lung biopsy gives additional information to other previously described predictive factors such as gender, smoking history, and histologic subtype (UIP or NSIP), and (*3*) patients with UIP are more likely to experience a decline in FVC or an increase in ground glass on HRCT over the first 6 months after surgical lung biopsy compared with patients with NSIP. These data aid in defining the optimal format of follow-up for patients with UIP or NSIP and identify the change in FVC over the first 6 months of follow-up as an important additional prognostic factor.

Our data demonstrate that change in FVC during follow-up is the strongest physiologic predictor of survival for patients with UIP and NSIP. The proportion of patients with a greater than 10% decrease in FVC during follow-up was greater in patients with UIP compared with patients with NSIP. Previous investigators have suggested that decreased FVC at baseline may identify patients at subsequent risk of mortality (18–23). In addition, some have suggested that a decrease in FVC of 10% or more after 1 year can predict mortality in patients with idiopathic pulmonary fibrosis (11). Spirometric assessment is particularly valuable as its measurement is standardized (24) and the variability in FVC has been well defined among normal subjects and patients with pulmonary disease (24). Despite these standards, previous investigators have noted variability in the physiology of patients with idiopathic interstitial pneumonia over time (25, 26). As a result, a wide variety of thresholds for change in FVC have been used by investigators, including changes ranging from 10 to 15% in FVC (11, 22, 27–30). Our analyses document that a 10% decrease in FVC over a 6-month period from the time of the surgical lung biopsy exhibited strong predictive ability in defining long-term survival. Additional data have suggested that an increased profusion of fibroblastic foci is associated with a greater rate of decline in pulmonary function (10) and poorer survival (10, 31). Our data expand these findings by demonstrating that change in FVC over a short duration of follow-up (6 months) is predictive of long-term survival and that this short-term change in FVC gives additional prognostic information to the histopathologic classification. Our data are strengthened by

TABLE 4. PROGNOSTIC EFFECT OF PREDICTOR WHEN IN COX MODEL ADJUSTED FOR INITIAL VALUE OF PREDICTOR IN UNIVARIATE ANALYSES OF DATA FOR PATIENTS WITH USUAL INTERSTITIAL PNEUMONIA

Predictor	n	Hazard Ratio	95% CI	p Value	LR p Value*
6-Month change					
FVC change, %	75				0.05
> 10% increase		0.89	(0.36, 2.24)	0.81	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		2.06	(1.09, 3.89)	0.03	
TLC change, %	66				0.33
> 10% increase		1.51	(0.63, 3.65)	0.36	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.68	(0.82, 3.44)	0.16	
D_{LCO} change, %	66				0.03
> 10% increase		2.49	(1.15, 5.39)	0.02	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.95	(0.44, 2.05)	0.89	
CT-alv change, %	60				0.01
> 10% increase		2.88	(1.26, 6.57)	0.01	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.81	(0.30, 2.21)	0.68	
CT-fib change, %	60				0.18
> 10% increase		1.09	(0.48, 2.47)	0.84	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.46	(0.18, 1.16)	0.13	
12-Month change					
FVC change, %	59				0.15
> 10% increase		0.66	(0.15, 2.86)	0.58	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.70	(0.76, 3.81)	0.20	
TLC change, %	31				0.29
> 10% increase		0.59	(0.09, 3.67)	0.57	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		1.50	(0.31, 7.13)	0.61	
D_{LCO} change, %	35				0.82
> 10% increase		0.62	(0.09, 4.24)	0.63	
10% decrease/10% increase		1.00	REF	REF	
> 10% decrease		0.65	(0.18, 2.43)	0.53	

Definition of abbreviations: CI, confidence interval; CT-alv = high-resolution computed tomography score for ground glass; CT-fib = high-resolution computed tomography score for interstitial infiltrates (*see* text for details); D_{LCO} = diffusing capacity for carbon monoxide; LR = likelihood ratio; REF = reference group; TLC = total lung capacity.

* p Value is from the likelihood ratio test of the addition of the levels of percent change to the model that included only the baseline measurements.

the inclusion of a well-characterized cohort with recent confirmation of the histopathologic pattern. The ability to look at a short-term change in FVC gives clinicians an additional tool to help determine prognosis for their patients and may be useful when making therapeutic decisions such as changing therapy or listing patients for lung transplantation. These data also suggest that a short-term change in FVC could be used as a surrogate marker for long-term mortality in therapeutic trials studying patients with UIP and NSIP. Twelve-month data were less predictive of survival; however, this is likely a consequence of a smaller number of patients available with 12-month serial data.

Our data suggest that the change in D_{LCO} over 6 months of follow-up has limited prognostic value. In multivariate analyses, short-term changes in D_{LCO} were not found to add independent predictive value. Although standards have been presented for its measurement (32), the D_{LCO} varies to a greater extent than FVC and clinically significant changes have been believed to be more than 20% (11, 27, 28, 33). As such, a survival advantage was noted by one group in patients with an improved or unchanged D_{LCO} compared with those experiencing a decrease of 20% or more after 1 year of therapy; the concordance between changes in FVC and D_{LCO} was quite good (11). Importantly, our analysis suggests that changes in FVC better predict subsequent survival for patients with UIP and NSIP.

An increase in the semiquantitative HRCT score of CT-alv during the 6 months after biopsy was associated with an increased risk of mortality for patients with UIP in a model adjusting for the baseline CT-alv value. Short-term change in the semiquantitative HRCT score of CT-alv or CT-fib was not an independent predictor of survival when histologic diagnosis, sex, onset of symptoms, and smoking history were included in the models. Our data suggest that only minor changes occur in HRCT over the first 6 months of follow-up and may indicate that a semiquantitative HRCT scoring system lacks sensitivity to detect clinically useful, short-term changes in CT-alv or CT-fib. Previous investigators have suggested that honeycombing on HRCT worsens over intermediate-term follow-up (12, 34–37), whereas improvement has been suggested in limited studies of patients with NSIP (38–40). Use of computerized methods to quantify the amount of fibrosis and ground glass infiltrate (41, 42) may be more sensitive to serial changes in HRCT findings but require additional study. Additional studies are required to better define the role of serial HRCT in the follow-up and treatment for patients with UIP and NSIP.

In summary, we demonstrate that short-term changes in FVC are strongly predictive of long-term survival in patients with well-defined UIP and NSIP. Furthermore, short-term changes in FVC give additional prognostic information to previously

TABLE 5. COX PROPORTIONAL HAZARDS MODEL EVALUATING THE RISK OF MORTALITY FOR PATIENTS WITH UIP AND NSIP ADJUSTING FOR HISTOLOGIC DIAGNOSIS, SEX, SMOKING HISTORY, BASELINE FVC VALUE, AND PERCENT CHANGE OVER TIME IN FVC

Predictor	Hazard Ratio	95% CI	p Value	LR p Value*
6-Month model				
UIP diagnosis	4.94	(1.81, 13.5)	0.002	
Onset	1.05	(0.97, 1.13)	0.23	
Female sex	0.51	(0.25, 1.08)	0.08	
Positive smoking history	0.80	(0.39, 1.65)	0.54	
FVC baseline	0.74	(0.44, 1.24)	0.25	
FVC change (6 mo), %				0.01
> 10% increase	0.88	(0.36, 2.13)	0.77	
10% decrease/10% increase	1.00	REF	REF	
> 10% decrease	2.47	(1.29, 4.73)	0.006	
12-Month model				
UIP diagnosis	3.50	(1.17, 10.5)	0.03	
Onset	1.03	(0.89, 1.18)	0.73	
Female sex	0.47	(0.19, 1.16)	0.10	
Positive smoking history	1.35	(0.58, 3.14)	0.49	
FVC baseline	0.42	(0.21, 0.82)	0.01	
FVC change (12 mo), %				0.02
> 10% increase	0.42	(0.05, 1.39)	0.12	
10% decrease/10% increase	1.00	REF	REF	
> 10% decrease	1.72	(0.78, 3.79)	0.18	

Definition of abbreviations: CI = confidence interval; LR = likelihood ratio; NSIP = nonspecific interstitial pneumonia; REF = reference group; UIP = usual interstitial pneumonia.

* p Value is associated with the likelihood ratio test for the significance of adding the levels of FVC percent change to the Cox survival model with the other predictive factors.

described factors such as smoking history, gender, and histopathologic diagnosis. In contrast, serial changes in D_{LCO} and HRCT are of more limited value.

Conflict of Interest Statement: K.R.F. has no declared conflict of interest; J.A.M. has no declared conflict of interest; S.M. has no declared conflict of interest; E.A.K. received research funding from GE Medical Systems, CT Division, in 2003 totaling $40,000, serves on the G.E. Medical Advisory Board for CT, serves on the Board of the GE Radiology Research Academic Fellowship (receives $2,500 annually), and received $1,500 for a lecture by GE in 2002; B.H.G. has no declared conflict of interest; T.V.C. has no declared conflict of interest; W.D.T. has no declared conflict of interest; A.F. has no declared conflict of interest; G.B.T. has no declared conflict of interest; J.P.L. has no declared conflict of interest; F.J.M. has no declared conflict of interest.

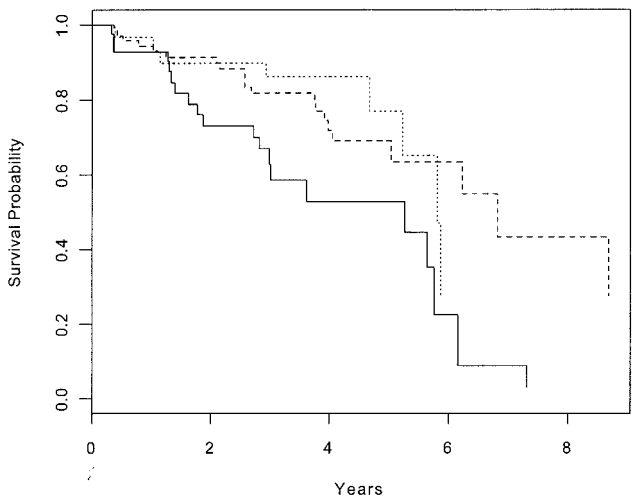

Figure 1. Cox model–based survival estimates for patients across three levels of FVC percent change adjusted for usual interstitial pneumonia (UIP), onset of symptoms, female gender, and positive smoking history. Average patient profiles for UIP, onset of symptoms, sex, and smoking were used in the estimates. *Dotted line* at least 10% increase in FVC, *solid line* at least 10% decrease in FVC, *dashed line* less than 10% increase or decrease in FVC. p = 0.01.

Acknowledgment: The University of Michigan Fibrotic Lung Disease Network includes:
Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI—D. Arenberg, C. Brennan-Martinez, W. Bria, D. Dahlgren, S. Gay, C. Grum, J. Hampton, K. Hariharan, M. Keane, T. Ojo, M. Peters-Golden, R. Simon, T. Sisson, T. Standiford, R. Strieter; Internal Medicine Clinic, Alpena, MI—P. Bachwich, C. Easton, J. Mazur; The Lung Center, Battle Creek, MI—S. Chaparala, G. Harrington, N. Potempa; Bay City, MI—S. Manawar, J. Summer; Clawson, MI—P. Hukku, J. Sung; Clinton Township, MI—R. Babcock; Pulmonary and Critical Care Medicine Consultants, Commerce, MI—J. Belen, M. Dunn, D. Maxwell, R. Reagle, R. Sherman, S. Simecek; Oakwood Hospital, Dearborn, MI—L. Victor; Henry Ford Hospital, Detroit, MI—B. DiGiovine, M. Eichenhorn, R. Hyzy, J. Popovich Jr, D. Spizarny; Botsford General Hospital, Farmington Hills, MI—B. Rabinowitz; Pulmonary and Critical Care Specialists, Farmington Hills, MI—G. Ferguson, P. Kaplan, S. Sklar, W. VanderRoest; Pulmonary Associates, PC, Flint, MI—O. Filos, V. Rao, M. V. Thomas, J. Varghese, J. Vyskocil, F. Wadenstorer; Grand Valley Internal Medicine, Grand Rapids, MI—J. Cantor, W. Katz, R. Johnson Jr, D. Listello, J. Wilt; Michigan Medical Professional Company, Grand Rapids, MI—C. Acharya, W. Couwenhoven, T. Daum, M. Harrison, M. Koets, G. Sandman, G. VanOtteren; Michigan Medical, PC, Holland, MI—S. Kraker; Huntington Woods, MI—M. Greenberger, A. O'Neill, D. Wu; Pulmonary Clinics of Southern Michigan, Jackson, MI—R. C. Albertson III, J. Chauncey, T. Murray, G. Patten; Associated Pulmonary and Critical Care Specialists, PC, Kalamazoo, MI—T. Abraham, J. Dirks, B. Dykstra, G. Grambau, J. Schoell; Pulmonary and Critical Care Associates, PC, Kalamazoo, MI—R. Brush, S. Jefferson, J. Miller, S. Schuldheisz, M. Warlick; Pulmonary and Critical Care Consultants, Lansing, MI—J. Armstrong, A. Atkinson, T. Kantra, L. Rawsthorne, D. Young; Pulmonary Services, Lansing, MI—A. Abbasi, C. M. Gera, G. Kashyap, J. Morlock; Respiratory Medicine, Marquette, MI—S. Danek, A. Saari; Midland, MI—S. Yadam; Central Michigan Healthcare System, Mt. Pleasant, MI—E. Obeid; Muskegon Pulmonary Associates, Muskegon, MI—D. Hoch, A. Kleaveland; Owosso Medical Group, Owosso, MI—A. Allam, M. A. Gad Jr; Lung Associates, Pontiac, MI—A. Desai, U. Dhanjal, A. Sethi. St. Joseph's Hospital, Pontiac, MI - F Ahmad, R Elkus, L Kaiser, L Rosenthal, D Sak. Physician Health Care Network, Port Huron, MI—R. Ailani, M. Basha, A. Hadar, S. Holstine; Pulmonary, Critical Care, and Sleep, PC, Rochester Hills, MI—M. W. Al-Ameri, R. Go, M. Kashlan; Rochester, MI—K. Aggarwal; Roseville, MI—W. Hanna, R. Marchese; William Beaumont Hospital, Royal Oak, MI—R. Begle, D. Erb, K. P. Ravikrishnan, J. Seidman, S. Sherman; Spring Lake, MI—M. Ivey; Lakeside Healthcare Specialists, St. Joseph, MI—S. Deskins, A. Palmer, S. Shastri; Pulmonary and Critical Care Associates, St. Clair Shores, MI, and Troy, MI—R. DiLisio, S. Galens, K. Grady, D. Harrington, R. Herbert, C. Hughes, J. Lee, A. Starrico, K. Stevens, M. Trunsky, W. Ventimiglia; Taylor, MI—D. Mahajan; Pulmonary Medicine Associates, Warren, MI—H. Kaplan, L. Tankanow; Henry Ford Wyandotte Hospital, Wyandotte, MI—M. Pensler; Toledo Pulmonary and Sleep Specialists, Toledo, OH—F. O. Horton III, A. Nathanson, R Wainz.

References

1. Flaherty K, Toews G, Travis W, Colby T, Kazerooni E, Gross B, Jain A, Strawderman R III, Paine R III, Flint A, *et al.* Clinical significance of histological classification of idiopathic interstitial pneumonia. *Eur Respir J* 2002;19:275–283.

2. Flaherty K, Travis W, Colby T, Toews G, Kazerooni E, Gross B, Jain A, Strawderman R III, Flint A, Lynch J III, *et al.* Histologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;164:1722–1727.
3. Bjoraker J, Ryu J, Edwin M, Myers J, Tazelaar H, Schoreder D, Offord K. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199–203.
4. Daniil Z, Gilchrist F, Nicholson A, Hansell D, Harris J, Colby T, du Bois R. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1999;160:899–905.
5. Nicholson A, Colby T, du Bois R, Hansell D, Wells A. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000;162:2213–2217.
6. King T Jr, Tooze J, Schwarz M, Brown K, Cherniack R. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001;164:1171–1181.
7. Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med* 2001;164: 103–108.
8. Flaherty KR, Thwaite EL, Kazerooni EA, Gross BH, Toews GB, Colby TV, Travis WD, Mumford JA, Murray S, Flint A, *et al.* Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003;58:143–148.
9. Gay S, Kazerooni E, Toews G, Lynch J III, Gross B, Cascade P, Spizarny D, Flint A, Schork M, Whyte R, *et al.* Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med* 1998;157:1063–1072.
10. Nicholson AG, Fulford LG, Colby TV, du Bois RM, Hansell DM, Wells AU. The relationship between individual histologic features and disease progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2002;166:173–177.
11. Hanson D, Winterbauer R, Kirtland S, Wu R. Changes in pulmonary function test results after 1 year of therapy as predictors of survival in patients with idiopathic pulmonary fibrosis. *Chest* 1995;108:305–310.
12. Xaubet A, Agusti C, Luburich P, Roca J, Monton C, Ayuso M, Barbera J, Rodriguez-Roisin R. Pulmonary function tests and CT scan in the management of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;158:431–436.
13. Katzenstein A, Myers J. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med* 1998;157:1301–1315.
14. American Thoracic Society and European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.
15. Kazerooni E, Martinez F, Flint A, Jamadar D, Gross B, Spizarny D, Cascade P, Whyte R, Lynch J III, Toews G. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. *AJR Am J Roentgenol* 1997;169:977–983.
16. Social Security Death Index Interactive Search. Available from: http://ssdi.genealogy.rootsweb.com/cgi-bin/ssdi.cgi
17. Cyrus R, Patel N. Algorithm 643. FEXACT: a Fortran subroutine for Fisher's exact test on unordered r*c contingency tables. *ACM Trans Math Softw* 1986;12:154–161.
18. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis: are they helpful for predicting outcome? *Chest* 1997;111:51–57.
19. Hubbard R, Venn A, Smith C, Cooper M, Johnston I, Britton J. Exposure to commonly prescribed drugs and the etiology of cryptogenic fibrosing alveolitis: a case-control study. *Am J Respir Crit Care Med* 1998;157: 743–747.
20. Jezek V, Fucik J, Michaljanic A, Jeskova L. The prognostic significance of functional tests in kryptogenic fibrosing alveolitis. *Bull Eur Physiopathol Respir* 1980;16:711–720.
21. Schwartz D, Helmers R, Galvin J, van Fossen D, Frees K, Dayton C, Burmeister L, Hunninghake G. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;149:450–454.
22. Rudd R, Haslam P, Turner-Warwick M. Cryptogenic fibrosing alveolitis: relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. *Am Rev Respir Dis* 1981;124:1–8.
23. Mapel D, Hunt W, Utton R, Baumgartner KB, Samet J, Coultas D. Idiopathic pulmonary fibrosis: survival in population based and hospital based cohorts. *Thorax* 1998;53:469–476.
24. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202–1218.
25. Tukiainen P, Taskinen E, Holsti P, Korhola O, Valle M. Prognosis of cryptogenic fibrosing alveolitis. *Thorax* 1983;38:349–355.
26. Schwartz D, Van Fossen D, Davis C, Helmers R, Dayton C, Burmeister L, Hunninghake G. Determinants of progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994;149:444–449.
27. Douglas W, Ryu J, Swensen S, Offord K, Shroeder D, Caron G, DeRemee R. Colchicine versus prednisone in the treatment of idiopathic pulmonary fibrosis: a randomized prospective study. *Am J Respir Crit Care Med* 1998;158:220–225.
28. Raghu G, Depaso W, Cain K, Hammar S, Wetzel C, Dreis D, Hutchinson J, Pardee N, Winterbauer R. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991;144:291–296.
29. Raghu G, Johnson W, Lockhart D, Mageto Y. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, Pirfenidone: results of a prospective, open-label Phase II study. *Am J Respir Crit Care Med* 1999;159:1061–1069.
30. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid therapy and its effect on survival. *Thorax* 1980;35:593–599.
31. King T Jr, Schwarz M, Brown K, Tooze J, Colby T, Waldron J Jr, Flint A, Thurlbec W, Cherniack R. Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med* 2001;164:1025–1032.
32. American Thoracic Society. Single-breath carbon monoxide diffusing capacity (transfer factor)—recommendations for a standard technique: 1995 update. *Am J Respir Crit Care Med* 1995;152:2185–2198.
33. O'Donnell D. Physiology of interstitial lung disease. In: Schwarz M, King T Jr, editors. Interstitial lung disease. Hamilton, ON, Canada: B. C. Decker, Inc.; 1998. p. 51–70.
34. Akira M, Sakatani M, Ueda E. Idiopathic pulmonary fibrosis: progression of honeycombing at thin-section CT. *Radiology* 1993;189:687–691.
35. Lee J, Gong G, Song K, Kim D, Lim T. Usual interstitial pneumonia: relationship between disease activity and the progression of honeycombing at thin-section computed tomography. *J Thorac Imaging* 1998;13:199–203.
36. Akira M, Yamamoto S, Hara H, Sakatani M, Ueda E. Serial computed tomographic evaluation in desquamative interstitial pneumonia. *Thorax* 1997;52:333–337.
37. Wells A, Rubens M, du Bois R, Hansell D. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. *AJR Am J Roentgenol* 1993;161:1159–1165.
38. Akira M, Inoue G, Yamamoto S, Sakatani M. Non-specific interstitial pneumonia: findings on sequential CT scans of nine patients. *Thorax* 2000;55:854–859.
39. Kim E, Lee K, Chung M, Kwon O, Kim T, Hwang J. Nonspecific interstitial pneumonia with fibrosis: serial high-resolution CT findings with functional correlation. *AJR Am J Roentgenol* 1999;173:1734–1739.
40. Nishiyama O, Kondoh Y, Taniguchi H, Yamaki K, Suzuki R, Yokoi T, Takagi K. Serial high resolution CT findings in nonspecific interstitial pneumonia/fibrosis. *J Comput Assist Tomogr* 2000;24:41–46.
41. Uppaluri R, Hoffman E, Sonka M, Hartley P, Hunninghake G, McLennan G. Computer recognition of regional lung disease patterns. *Am J Respir Crit Care Med* 1999;160:648–654.
42. Uppaluri R, Hoffman E, Sonka M, Hunninghake G, McLennan G. Interstitial lung disease: a quantitative study using the adaptive multiple feature method. *Am J Respir Crit Care Med* 1999;159:519–525.