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Long-term Course and Prognosis of Idiopathic Pulmonary Fibrosis in the New Millennium

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The American Thoracic Society and European Respiratory Society guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis (IPF) have been published recently. However, the influence, practical application, and utility of the prior consensus statement for IPF have never been evaluated. Demographics, diagnostic criteria, pulmonary function data, and disposition of patients with IPF evaluated at an interstitial lung disease center between 2000 and 2009 were analyzed. Enrollment in clinical drug trials, lung transplantation, and mortality also were assessed. A total of 521 patients with IPF were evaluated, with pulmonary function testing available in 446. In the 64% of patients without surgical lung biopsy, the most common major criterion not fulfilled was bronchoscopy. Lung transplantation was performed in 16.1% of patients, whereas 27.4% of prescreened patients were enrolled in a prospective drug study. Patients with mild, moderate, and severe disease categorized by FVC % predicted had median survivals of 55.6, 38.7, and 27.4 months, respectively. The attrition rate of patients who survived beyond 5 years was attenuated in subsequent years. IPF remains a deadly disease with a poor prognosis. Bronchoscopy does not appear to be required for an accurate diagnosis. A minority of patients were accommodated within a clinical trial or with transplantation. Categorization by baseline FVC % predicted effectively discriminates groups with different long-term outcomes. Our analysis supports the view that the value of statements also can be realized in the subsequent demonstration of their impact on patient management, which might enable further refinements in a continuous, iterative rediscovery process.

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Abbreviations: ATS = American Thoracic Society; DLCO = diffusing capacity of lung for carbon monoxide; ERS = European Respiratory Society; HRCT = high-resolution CT; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test

Idiopathic pulmonary fibrosis (IPF) is a deadly disease that carries a poor prognosis for which therapeutic options are limited.¹⁻⁵ As the understanding of the disease has grown, similar but distinct entities have been differentiated from IPF,⁶ but the disease

remains heterogeneous in many respects, with ongoing uncertainty of the diagnosis in many cases.⁷ In 2000, a committee of experts in the field, under the auspices of the American Thoracic Society (ATS) and the European Respiratory Society (ERS), published a consensus statement for the diagnosis and treatment

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of IPF.⁸ The goal of this statement was to homogenize the diagnosis and management of the disease and to provide a foundation for the characterization of the disease. This statement has been updated in a recently published guideline.⁹ However, to our knowledge, the impact of the 2000 statement has never been evaluated in a busy clinical practice. Given the publication of the guideline, it is incumbent on the

community to evaluate the usefulness of the previous statement to determine whether there are lessons to be learned that might be applicable to the way in which the new guideline should be viewed and interpreted.

The long-term prognosis of patients with IPF has been derived mostly from studies performed prior to the publication of the 2000 statement.^{2-4,10,11} More recent information about prognosis has emanated from large, multicenter clinical trials, but these have only provided relatively short follow-up periods of 2 years or less.¹²⁻¹⁶ In addition, these studies often only included highly selected patients because many were excluded by virtue of their age, disease severity, or comorbid conditions. Therefore, we sought to characterize the nature and outcomes of all patients with IPF who were seen and evaluated at a tertiary-care interstitial lung disease program over the 10-year period since the publication of the ATS/ERS statement in 2000.

Specifically, there were three major aims of this study. First, we sought to determine how readily the ATS/ERS statement could be applied in a busy interstitial lung disease clinic (ie, how “user friendly” it was) and to assess whether any variation in the application of the statement had an impact on the accuracy of the diagnostic process. Second, we sought to assess how commonly patients were recruited into clinical trials of novel therapies and how many received lung transplantations as recommended by the statement. Third, we sought to determine long-term IPF outcomes in a well-categorized, all-inclusive patient cohort in which the suggestions of the 2000 statement were followed prospectively.

MATERIALS AND METHODS

We performed a review of all patients with IPF who were seen at the Inova Fairfax Hospital Interstitial Lung Disease Clinic between January 2000 and November 2009. The clinic maintains a database of all patients evaluated, with data entered prospectively at the time of their initial evaluation. This database was used as the source in identifying the cohort. When available, chart reviews were performed for missing data to provide as complete a data set as possible. Patients were given a diagnosis of IPF based on their clinical presentation, high-resolution CT (HRCT) scan appearance, and, where there was any element of doubt, surgical lung biopsy. Patient demographics and pulmonary function test (PFT) data at or near the time of presentation were collated and analyzed. The prediction equations of Knudson et al¹⁷ were used in patients whose PFTs were obtained at the Inova Fairfax pulmonary laboratory. If the patients presented with PFTs performed at another laboratory, these data were entered based on that laboratory's prediction equation standard. Records of the number of patients considered for entry into clinical trials of therapy and for lung transplantation evaluation were interrogated.

A number of survival analyses were performed, including a survival analysis of all patients with IPF, a similar analysis with transplantation recipients excluded, an analysis by early and late eras, and an analysis based on severity of PFT indices at presentation. For the latter analysis, patients were divided (at the closest

5% cut point) into approximate terciles based on their FVC % predicted. A similar analysis based on approximate terciles was performed for diffusing capacity of lung for carbon monoxide (DLCO) % predicted. A survival analysis incorporating both the FVC and the DLCO % predicted also was performed. In this regard, within the three FVC groups, serial decile cut points in DLCO % predicted were tested, and the best discriminator of survival based on the smallest *P* value was chosen for report. Patient mortality was ascertained through the hospital's advanced lung disease program database and the Social Security Death Index. The study was approved by the Inova Fairfax Institutional Review Board (IRB #10.059).

Statistics

All demographic and pulmonary function data are presented as means with ranges if continuous or as frequencies if categorical. Kaplan-Meier survival curves were calculated using GraphPad, version 5.0 software (GraphPad Software, Inc; La Jolla, California). Differences in the 3-year survival are reported where median survival was not achieved in the duration of follow-up. Differences in survival curves were evaluated using the log-rank test. Cox proportional hazards modeling was used to account for the influence of the following factors on mortality: age, sex, FVC % predicted, and DLCO % predicted. Hazard modeling was performed using SAS, version 9.2 software (SAS Institute; Cary, North Carolina).

RESULTS

Baseline Data and Demographics

There were 521 patients with IPF who were seen and evaluated in the clinic during the 10-year period. The demographics of the cohort and PFT data at the time of initial evaluation, which were available in 446 of the patients, are shown in Table 1. The date of the PFT was in many cases different from the date of the patient's initial evaluation. Most of the PFTs (273 of 446, 61.2%) were within 90 days of the initial evaluation, with a median time difference of 45.7 days. In most cases (337 of 446, 75.6%), the PFTs were obtained prior to patients' initial evaluation, whereas in 93 of 446 (20.8%), they were obtained after the patient was evaluated, and in 16 of 446 (3.6%), they were obtained on the same day. A histogram distribution of the initial FVC % predicted is shown in Figure 1.

How Closely Was the ATS/ERS Statement Followed?

In the 2000 statement, there were three major criteria required for a diagnosis of IPF to be made if the patient had undergone a surgical lung biopsy to confirm the diagnosis: the exclusion of other known causes of interstitial lung disease, abnormal pulmonary function studies, and bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scan.⁸ The same three major criteria plus a bronchoscopic evaluation that suggested no alternative diagnosis on transbronchial biopsy specimen or BAL were required if there had been no surgical biopsy.

Table 1—Demographics of the IPF Cohort

Demographic	Value
Age, y	65 (30-90)
Sex, %	
Male	71.7
Female	28.3
Ethnicity, %	
White	77.7
Black	13.8
Hispanic	4.6
Asian	2.7
Native American	1.2
FVC, % predicted	61.01 (16-108)
FEV ₁ , % predicted	66.40 (15-133)
DLCO, % predicted	40.96 (9-102)

Data are presented as mean (range) unless otherwise indicated. DLCO = diffusing capacity of lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis.

In our series, all patients had other known causes of interstitial lung disease excluded through a thorough history, physical examination, and connective tissue disease serologies. Baseline pulmonary function data were consistent with IPF in the majority of instances. There were only 61 of 446 (13.7%) patients with a “normal” FVC (defined as > 80% predicted). Of the 394 patients with both FVC and DLCO data available, only 10 (2.5%) had a DLCO \geq 80% predicted, and five (1.3%) had both a normal FVC % predicted and DLCO % predicted. In these subgroups, 18 of 61 (29.5%), 4 of 10 (40%), and 2 of 5 (40%) had surgical biopsy specimens that confirmed the diagnosis of IPF. Of the 61 patients with normal FVC % predicted, there was follow-up spirometry performed in 32 patients at a mean of 20.1 months. In this subgroup, the FVC decreased from a mean of 90.2% to 84.5%, with 13 of 32 (40.6%) below the 80% threshold of normality on follow-up.

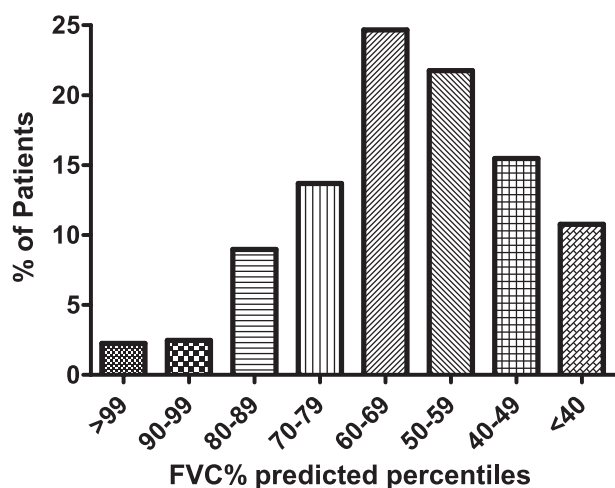


FIGURE 1. Histogram distribution of the initial FVC % predicted at the time of presentation.

In the majority of cases, HRCT scanning was consistent with IPF. In the absence of an HRCT scan study consistent with IPF, surgical lung biopsy was performed in 187 of 521 (35.9%) of the cases (Fig 2). Bronchoscopy with transbronchial biopsy or BAL was not performed in any of the patients after evaluation. Of the 334 patients who were given a diagnosis without a surgical lung biopsy or bronchoscopy, 49 subsequently underwent lung transplantation. The explanted specimens showed changes consistent with usual interstitial pneumonia in 45 cases and indiscernible end-stage fibrosis in three. The one remaining patient, a 42-year-old white man, had advanced fibrosis with evidence of noncaseating granulomas.

The 2000 ATS/ERS statement required the presence of three of four minor criteria to be present in addition to the four major features if no surgical biopsy had been performed. These minor criteria included age > 50 years, insidious onset of otherwise unexplained dyspnea on exertion, duration of illness > 3 months, and bibasilar inspiratory crackles (dry or “Velcro type” in quality).

In our series, there were 40 patients who were aged < 50 years, of whom 22 had a confirmatory surgical lung biopsy procedure. Lung transplantation was performed in 12 of these patients (six of whom did not have a prior surgical lung biopsy), with histologic confirmation of the diagnosis in all 12 explant specimens. Thus, 28 of the 40 patients aged < 50 years had biopsy-proven IPF. Most patients presented with insidious onset of unexplained exertional dyspnea, but 16.8% had no dyspnea on presentation. Of these, approximately 12% of patients presented with cough alone, whereas 5% of the patients were asymptomatic at the time of diagnosis. Ninety-nine percent of the symptomatic patients had their symptoms for > 3 months. The presence of inspiratory crackles was noted in 96.8% of the patients. Of the patients who did not have a surgical lung biopsy, 94.3% did not fulfill all the major criteria (primarily due to the lack of a bronchoscopy), whereas only 2.9% failed to fulfill three of the four minor diagnostic criteria as recommended.⁸

Role of Lung Transplantation and Clinical Trials of Therapy

Patients were evaluated and deemed appropriate candidates for lung transplantation on the basis of the standard accepted eligibility criteria.¹⁸ There were 93 of 521 (17.9%) patients who were deemed appropriate and listed for lung transplantation, 84 (16.1%) of whom subsequently survived to have the procedure (Fig 2). Of these patients, 35 (41.6%) had undergone a prior surgical lung biopsy. Therefore, there

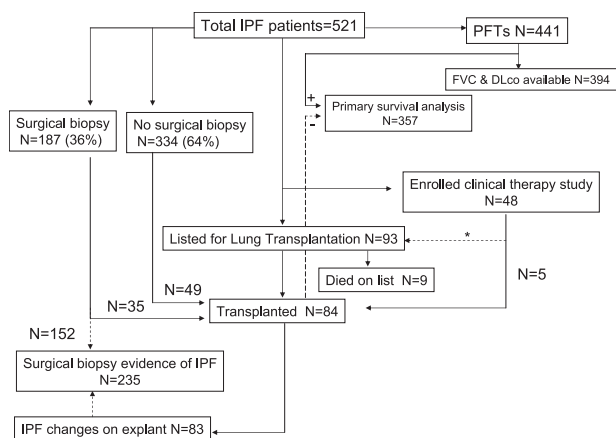


FIGURE 2. Flowchart of disposition of patients with IPF in relation to surgical lung biopsy, enrollment in clinical trials, and lung transplantation. * = five study patients listed for and received lung transplants; DLco = diffusing capacity of lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; PFT = pulmonary function test.

was histopathologic evidence of IPF in 45.1% (235 of 521) of the cases (48 explantation samples plus 187 surgical biopsy samples) (Fig 2). All but one of the 84 patients receiving transplantations at our institution received a single lung transplantation.

In November 2002, we instituted a log for all patients considered for enrollment in a clinical trial. During the period from November 2002 to November 2009, 418 patients were evaluated, of whom 243 were deemed unsuitable for prescreening because of readily apparent reasons. The remaining 175 were prescreened 259 times for potential enrollment in one of seven phase 2 or 3 prospective trials of a therapeutic agent for IPF. Included among the 259 screening episodes were 58 patients who were rescreened for the same study. Therefore, 26 patients were prescreened for two different studies. Signed consent for enrollment was obtained in 81 patients, 33 of whom were subsequently disqualified from randomization and were regarded as study “screen failures.” Of the patients who were prescreened, therefore, 48 (27.4%) qualified and were randomized into a prospective clinical drug study, representing only 11.5% of all the patients with IPF evaluated during this time period. In addition, two of these patients were enrolled in a subsequent study after completion of the initial trial. The exclusionary factors and the stage that patients were eliminated from further consideration for study enrollment are shown in Figure 3. Of the 48 study patients, five subsequently went on to receive lung transplantations.

IPF Outcomes

For the whole cohort (N = 521), the median survival from the time of evaluation was 41.2 months.

Our primary survival analysis excluded patients who underwent lung transplantation and included only those in whom PFTs were available. This group (n = 357) demonstrated a median survival of 45.87 months from the time of their initial PFTs (Fig 4). Examination of the survival curve demonstrates a biphasic curve with an initial attrition rate characterized by a constant linear slope over the first 48 to 60 months. Thereafter, the curve appears flatter, attesting to a better subsequent outcome for those patients with IPF who survived the first 5 years. Survival by era also was evaluated with patients divided into two periods: 2000-2004 (n = 247) and 2005-2009 (n = 274). No difference was demonstrated. The median survival of the 43 study patients enrolled in a clinical trial was 52.13 months compared with the 34.33 months for the nonstudy patients (P = .03). Cox proportional hazards modeling revealed age, male sex, FVC % predicted, and DLCO % predicted to all be significant predictors of mortality, with hazard ratios of 1.02, 1.88, 0.98, and 0.90, respectively.

Inclusion of the 84 IPF transplantation recipients resulted in a median survival for all patients with PFT data (n = 441) of 47.8 months, with the transplantation cohort having a median survival of 63.3 months from their initial PFT data set. Survival of all lung transplantation recipients from the time of transplantation was 83.1% at 1 year, 60.6% at 3 years, and 41% at 5 years, with a median survival of 55.5 months for this group.

Lastly, we stratified the nontransplantation patients with available pulmonary function data and long-term follow-up (n = 359) into approximate terciles as follows: mild (FVC ≥ 70% predicted) (n = 110), moderate (FVC 55% to 69% predicted) (n = 129), and severe (FVC < 55% predicted) (n = 120) disease. The median survival of the three groups was 55.6 months, 38.7 months, and 27.4 months, respectively (P = .008) (Fig 5). A similar analysis based on approximate DLCO terciles also was performed in those with available data (n = 317). The DLCO % predicted also appeared to discern groups with distinct survival differences; specifically, those with a DLCO ≥ 50% predicted (n = 101) had a median survival of 67.3 months compared to those with a DLCO of 35% to 49% (n = 112) and a DLCO < 35% (n = 104), whose median survivals were 47.8 months and 31.3 months, respectively (P = .0003) (Fig 6). We also assessed various cut points of the DLCO % predicted to see whether this allowed further discrimination of survival in the three FVC severity groups (Fig 7). For the mild patients, a DLCO < 60% appeared to discern the subgroup with a worse outcome (3-year survival of 61% vs 80%; P = .002), whereas in those with moderate disease, a DLCO ≤ 40% identified the subgroup with worse outcomes; specifically, these

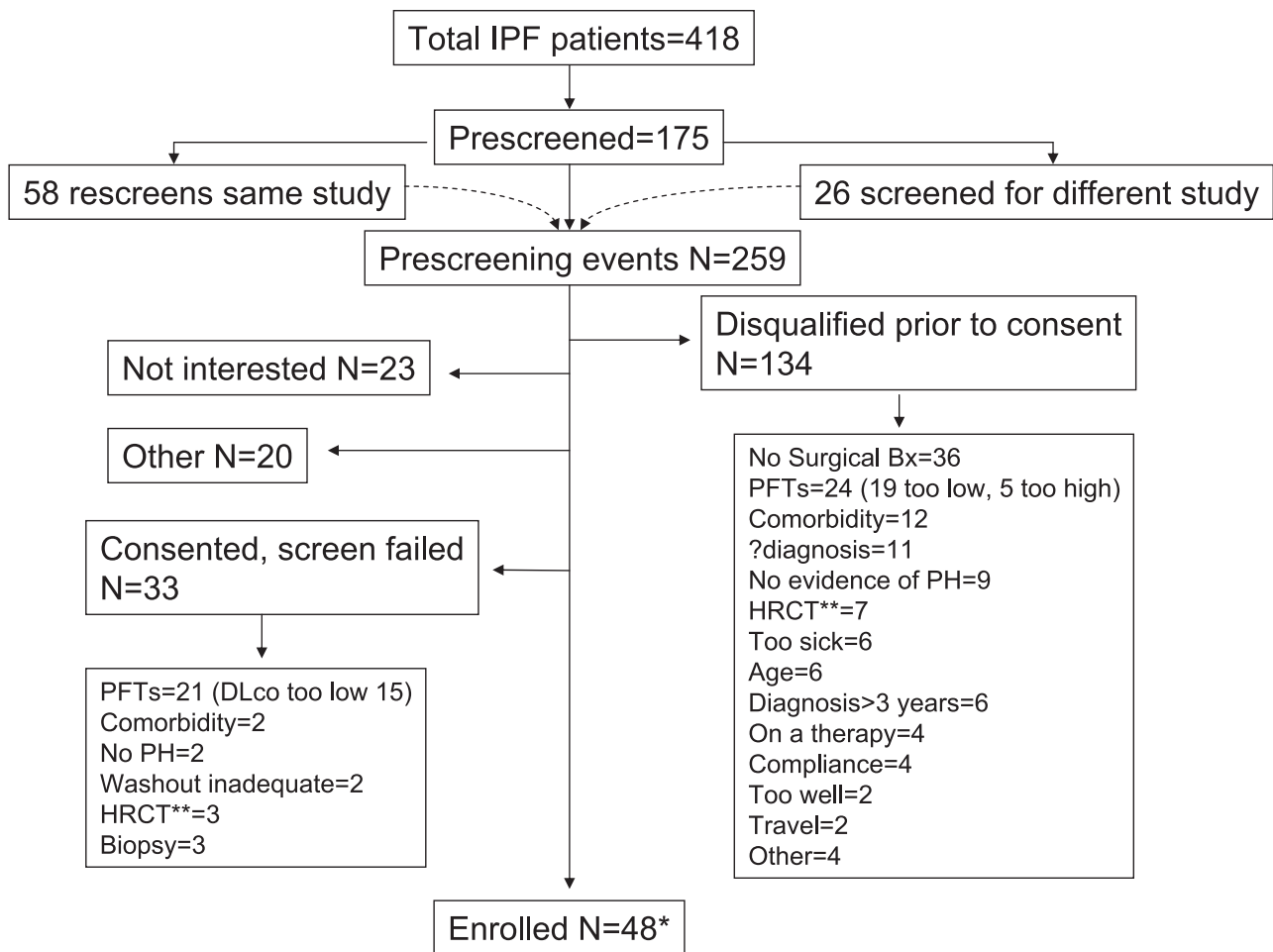


FIGURE 3. Flowchart demonstrating exclusionary factors and the stage that patients were eliminated from study enrollment into clinical trials of novel therapies. * = two patients enrolled twice in sequential studies; ** = usually too much honeycombing; Bx = biopsy; HRCT = high-resolution CT; PH = pulmonary hypertension; ?diagnosis = sponsor uncertainty regarding diagnosis. See Figure 2 legend for expansion of other abbreviations.

patients had a median survival of 27.8 months compared with 59.9 months for those with a DLCO > 40% ($P = .0005$). For the severe group, the small subgroup of patients ($n = 15$) with a DLCO $\leq 20\%$ predicted had a median survival of 11.47 months compared with the remaining patients ($n = 77$) in the severe category whose median survival was 35.2 months ($P = .026$).

DISCUSSION

IPF is a disease with a poor prognosis that appears unchanged over the past decade in comparison with the pre-ATS/ERS statement period. The median survival in our nontransplantation IPF cohort of about 3.5 years is very similar to survival rates reported prior to the publication of the statement.²⁴ Of patients who were considered for enrollment in a prospective therapeutic study, only 27% qualified despite the availability and contiguity of multiple clinical trials, whereas only 16% of the patients qualified for and

received a lung transplantation. We demonstrate that an appropriate and accurate diagnosis of IPF can be attained without bronchoscopy. Stratification of patients into mild, moderate, or severe disease on the basis of

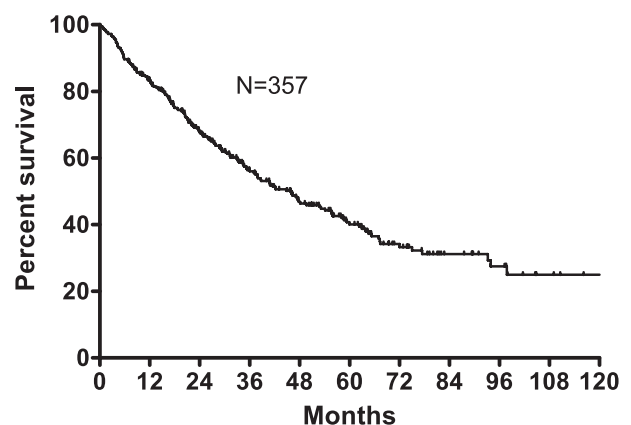


FIGURE 4. Survival of patients with IPF from the time of initial PFT, with transplantation recipients excluded. See Figure 2 legend for expansion of abbreviations.

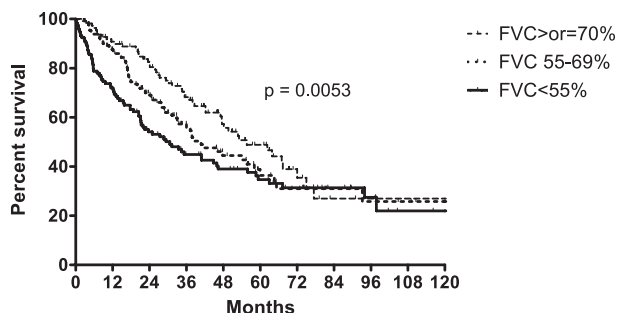


FIGURE 5. IPF survival stratified by the initial FVC % predicted. See Figure 2 legend for expansion of abbreviation.

their initial FVC % predicted allowed discrimination of groups with distinctly different long-term survivals. The DLCO appeared to allow further delineation of survival from among these patients.

IPF is a condition that is heterogeneous in many respects, including its presentation, unpredictable clinical course, histopathologic features, and prognosis. These characteristics have resulted in heterogeneity among physicians in making an accurate diagnosis and in the management of these patients. The goals of the 2000 ATS/ERS statement were to enable a uniform approach to the diagnosis of IPF and management of patients with this condition as well as to identify deficiencies in the knowledge base and thereby provide a foundation and impetus for future research.⁸ Although the guideline has been published recently, to our knowledge, there has been no systematic review of how it was implemented or the lessons learned from the diagnostic and management recommendations of the consensus statement. We sought to evaluate and provide insight into specific aspects of the statement in a broad group of patients with IPF. This included an evaluation of the need for bronchoscopy in the absence of a surgical lung biopsy, insight into the opportunity for transplantation and enrollment in clinical trials, and an assessment of the long-term natural history of IPF as diagnosed under the umbrella of the 10-year-old statement.

Bronchoscopy is one of the four major criteria suggested by the ATS/ERS statement for the diagnosis

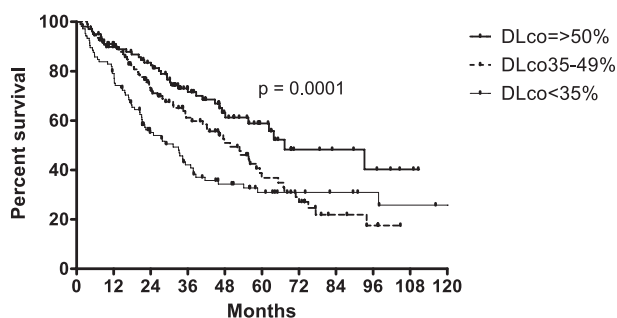


FIGURE 6. IPF survival stratified by the initial DLco % predicted. See Figure 2 legend for expansion of abbreviations.

of IPF in the absence of surgical lung biopsy. This procedure is undertaken primarily to rule out other conditions but is performed inconsistently among different centers and regions of the world. If a surgical lung biopsy is not deemed necessary, the diagnostic approach adopted at our institution has been to forego the performance of bronchoscopy in the context of the appropriate clinical setting and characteristic HRCT scan. Indeed, it appears that this approach does not compromise the accuracy of diagnosis. Specifically, the survival of the nontransplantation patients whose condition was confirmed by surgical lung biopsy specimens was similar to those who did not undergo lung biopsy (data not shown), which supports the notion that the two groups had the same disease. In addition, there were 45 cases in whom there was no diagnostic biopsy and who subsequently underwent lung transplantation. In all but one of these cases, the explanted lung either demonstrated usual interstitial pneumonia-like changes or end-stage fibrosis with no other pathologic pattern suggestive of an alternate diagnosis.

Another of the ATS/ERS major criteria is the presence of abnormal lung function that includes evidence of restriction and impaired gas exchange.⁸ It is noteworthy that, in our cohort with evaluable PFT data, 14% did not have restrictive physiology, whereas 2.5% had a normal diffusing capacity. In a future era that will hopefully include therapies that slow the rate of decline in lung function, the earlier diagnosis of IPF appears crucial. Therefore, we are of the opinion that consideration of the diagnosis should not be precluded by the absence of discernable physiologic abnormalities because the opportunity to have an impact on disease progression at the earliest stage might be lost. The clinical features that constitute the minor criteria were fulfilled in the majority of patients; thus, only a small proportion of patients without a surgical lung biopsy failed to meet three of the four criteria recommended in the ATS/ERS statement.

The most definitive management recommendation from the statement is to refer appropriate patients for a transplantation evaluation and to enroll patients with IPF in clinical trials of therapy.⁸ The proportion of all patients with IPF who can be thus accommodated has never been previously quantified to our knowledge. Despite the availability of sequential studies of novel therapy, in our series, only 46% (81 of 175) consented for enrollment, of whom almost 40% “screen failed.” Qualification for enrollment in a clinical trial appeared to be associated with improved outcomes, perhaps reflecting the bias of the inclusionary criteria, which mostly sought to identify patients with early disease, and the exclusionary criteria, which similarly sought to exclude patients with significant comorbidities. The small subset of

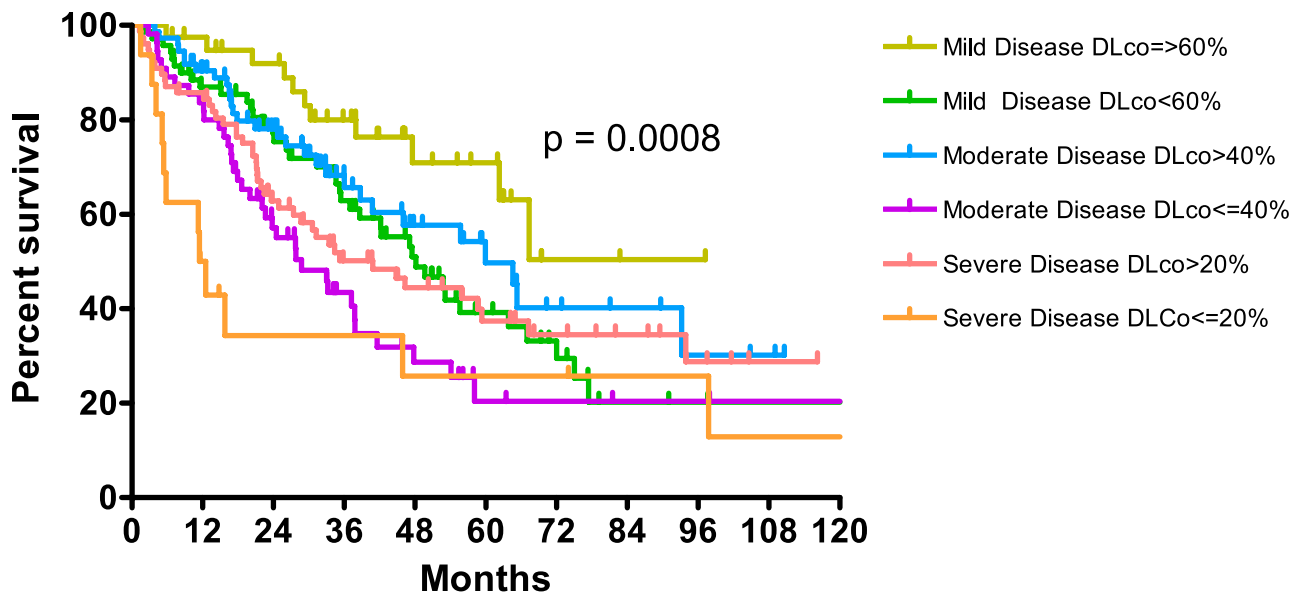


FIGURE 7. IPF survival stratified by the initial FVC % predicted (mild [$\geq 70\%$], moderate [$55\%-69\%$], and severe [$< 55\%$] disease) and DLco % predicted. See Figure 2 legend for expansion of abbreviations.

patients who qualified and were enrolled in a clinical trial also raises a cautionary note about the application of data from such studies to the general IPF population. It is interesting to note that only about one-third of the patients could be accommodated with either enrollment in a clinical trial and/or lung transplantation, underscoring the large, unmet need and current treatment void for most patients with IPF.

We demonstrate in our large cohort of patients with IPF followed prospectively over the course of 10 years that survival has not changed substantively. Our delineation and demonstration of a difference in outcomes among the various groups based on their initial baseline FVC % predicted provides a rational and simple structure to the concept of mild, moderate, and severe disease. We chose to categorize patient severity on the basis of the FVC % predicted because this is the more commonly performed pulmonary function parameter. However, the DLCO % predicted did perform slightly better in discerning survival as indicated by the hazard ratios generated from our Cox proportional hazards modeling. In any event, the DLCO % predicted did appear to have added utility in further discriminating survival from among the three FVC groups.

Another interesting observation is the survival of patients (approximately one-quarter) after the first 4 to 5 years from the time of diagnosis, which appears different from the outcomes of de novo patients. Interestingly, this “survivor” group appears to be equally distributed among disease severity groups. A survival “tail” has been described previously in older publications prior to the recognition of nonspecific interstitial pneumonia as a distinct entity with a more

benign disease course.¹⁹⁻²¹ Indeed, it has been commonly assumed that the attenuated survival demonstrated in these older studies was because of the inclusion of patients with diseases other than IPF. Ours is, therefore, the first description of an apparent survivor group in the most recent era of patients with nonspecific interstitial pneumonia excluded.

There are limitations to our study mostly based on the retrospective nature of its design. Missing data in a few patients resulted from many causes, among them was our inability to perform PFTs on all patients owing to insurance and other constraints encountered in a busy clinical practice, a situation shared by most practicing pulmonologists in the United States and elsewhere. Our analysis of bronchoscopy only included patients with IPF and did not assess the utility of this procedure in ruling out other conditions. For those patients with clinical features consistent with other conditions, bronchoscopy might still be the procedure of choice. We also do not provide an assessment of the treatment aspects of the statement’s suggestion of combined therapy with corticosteroids and either azathioprine or cyclophosphamide.⁸ Additionally, when assessing survival, we did not account for any other therapies implemented. However, it is well recognized that as yet, no commonly available effective medical therapies can alter or modify the course and outcomes of IPF. The survival of our lung transplantation cohort was very similar to that reported by the International Society for Heart and Lung Transplantation,²² but we did not perform a specific survival benefit analysis from among the patient population because this too has been previously

performed and validated.²³⁻²⁶ We could not ascertain the exact cause of death in all patients to know that these were all truly respiratory in nature. However, we believe that all-cause mortality is the best end point because we did account for all patients with IPF, including those who might have had significant contributory comorbidities.²⁷

In conclusion, we have characterized the course and outcomes in a broad group of patients with IPF in the era since the publication of the ATS/ERS statement 10 years ago. In doing so, we have demonstrated that the mortality from IPF remains unchanged and unacceptably high. Our data also support the modification of the original ATS/ERS statement for the diagnosis of IPF. Further, we have shown that only a minority of patients with IPF can be accommodated within clinical therapeutic studies or with lung transplantation. Approximately one-quarter of patients with IPF appear to run an abrogated course with significantly better long-term outcomes. We also have provided a framework and justification for the characterization of disease severity based on the baseline FVC % predicted. Finally, we have demonstrated that the value of statements and guidelines also lies in the lessons learned from their implementation. We suggest that such future documents should provide an inherent framework for the subsequent assessment of their efficacy and impact on patient care.

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