SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2013; 30; Suppl 1; 13-20

Classification, natural history and staging of idiopathic pulmonary fibrosis

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Abstract. Idiopathic pulmonary fibrosis (IPF) is defined as a fibrosing disease limited to the lungs of unknown aetiology characterised radiologically and/or morphologically by the usual interstitial pneumonitis pattern. It is a disease with an ominous prognosis. There is currently no consensus regarding the staging and classification of IPF. As highlighted in the revised ATS/ERS guidelines, proposed stages may be based on resting pulmonary function test measurements and/or the extent of radiologic abnormalities, but it is unknown if these staging approaches are relevant to clinical decision-making. Thus, the unmet needs in IPF include a complete knowledge of the pathogenetic mechanisms leading to lung destruction, an improved understanding of different clinico-radiological subtypes of this disorder and finally, the identification of staging systems of clinical value. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30 Suppl 1: 13-20)*

Key words: IPF, staging, mild-to-moderate, advanced disease, mortality

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, debilitating, progressive, and fibrosing proliferative interstitial lung disease (ILD) of unknown cause, occurring primarily in older adults (1). Recent genetic studies have suggested that it is not limited to the lung, at least in cases in which a genetic background is identified. Involvement of other organs including bone marrow, liver, skin, and hair, is present in familial cases and these are now included in the telomeropathies (2). IPF is associated with a significantly poor prognosis (3) and carries an estimated median survival ranging from approximately 2 to 5 years from diagnosis (1, 4-6), worse than several types of cancer (6). Furthermore, the incidence of lung cancer is markedly increased among patients with IPF (7, 8).

Potential risk factors for the development of IPF include cigarette smoking, wood, mineral and metal dust exposure, past viral infection, and chronic gastro-oesophageal reflux with micro-aspiration (1, 9). Patients with IPF may have subclinical or overt comorbid conditions including pulmonary hypertension, gastro-oesophageal reflux, obstructive sleep apnoea, obesity, and emphysema, but the impact of these conditions on the outcome of patients with IPF is unclear (1).

Large gaps also remain in the understanding of how quality of life (QoL) is affected in patients with IPF. Clinicians need to appreciate how this disease and its progression affect the various aspects of patients' lives (10, 11). The classification and staging of IPF patients may allow a better follow-up of this disease and is also critical for adequate lung transplantation indication and the development of new treatment protocols (12, 13).

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Definition and classification of IPF

IPF is defined by the main thoracic and respiratory professional societies as 'a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathological and/or radiological pattern of 'usual interstitial pneumonia' (UIP) (1, 14-16). Collectively termed interstitial lung disease (ILD), IPF is classified as one of the idiopathic interstitial pneumonias. Thus, the diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, systemic connective tissue disease, and drug toxicity), and the presence of a UIP pattern on high-resolution computed tomography (HRCT), as well as specific combinations of HRCT and histopathological patterns in patients subjected to surgical lung biopsy (SLB) (1, 17).

New paradigms have been recently proposed in the pathogenesis of IPF. There is growing evidence supporting a 'double hit' pathogenic model where the cumulative action of an accelerated senescence of pulmonary parenchyma (determined by either telomere dysfunction and/or a variety of genetic predisposing factors), and the noxious activity of cigarette smoke-induced oxidative damage are able to severely compromise the regenerative potential of precursor cell compartment of the alveolar epithelium (18, 19).

Over the last few decades, some classification systems have been proposed in an attempt to standardise the use of HRCT in the assessment of disease severity progression in IPF, e.g. by categorised HRCT according to the predominant type of lesion (20), or intensity of reticular pattern (21). However, such classification proposals were suggested prior to the currently accepted definition of IPF based on standard histological UIP (1). On the basis of current international guidelines, there are three degrees of 'certainty': 'definite', 'probable', or 'possible' IPF (1). However, this classification still leaves ill-defined questions. For instance, should patients with an atypical HRCT scan and a UIP pattern on histology be categorised within the same group of patients with a similar typical HRCT scan and histology, and what are the therapeutic options of patients with 'probable' or 'possible' IPF? Furthermore, the definition of an UIP pattern is uncertain and it is unclear whether or not HRCT data add valid information about disease progression (22). It is unknown if these differences represent distinct phenotypes of IPF or are influenced by geographic, ethnic, cultural, racial, or other factors (1).

Imaging methods and respiratory function tests are the most commonly used examinations in IPF cases. However, there is currently no consensus regarding classification proposals for IPF based on radiologic and pulmonary function assessments. Concerning lung function, the most widely used severity classification for restrictive disturbance is based on the percentage values of either total lung capacity (TLC) or forced vital capacity (FVC) (23). However, such measurements do not consider other important symptoms or disease characteristics commonly observed in clinical practice, or take into account the underlying restrictive disease, used for both intrapulmonary and extra-pulmonary restriction causes.

Thus, the definition of IPF should be revised and new classifications of IPF based on pathophysiologic considerations proposed (24). For example, new immunohistochemical data suggest the use of molecular biology parameters as an addition and/or alternative to histological morphology (25, 26).

IPF natural history and disease progression

The natural history of IPF has been described as a progressive decline in subjective and objective pulmonary function until eventual death from respiratory failure or complicating comorbidity (27-29). Disease progression is manifested by increasing respiratory symptoms, worsening pulmonary function test results, progressive fibrosis on HRCT, acute respiratory decline, or death. Available retrospective longitudinal studies suggest a median survival time from 2 to 5 years from the time of diagnosis (1, 3-5, 30-33). However, recent data from clinical trials of IPF patients with preserved pulmonary function suggest this may be an underestimate (1, 34-36).

For any given patient, the natural history is unpredictable at the time of the diagnosis. (1) IPF disease progression is not well defined and its clinical course is variable and unpredictable with heterogeneous disease progression (1, 37, 38). The clinical course of individual patients varies considerably,

from slow progression over many years to acute exacerbation, rapid loss of lung function and early death (39). The majority of patients demonstrate a slow, gradual progression with an inexorable decline in lung function occurring over a period of years (Figure 1) (1, 27, 37, 40). However, approximately 10-15% of individuals have a much more rapid disease course progressing from first symptoms to death from respiratory failure over a period of months. The third pattern of disease progression is that of periods of relatively slow decline punctuated by episodes of rapid and acute exacerbations (1). These episodes often prove to be fatal, but if survived, invariably lead to a permanent decline in pulmonary function (41). It is unknown if these different natural histories represent distinct phenotypes of IPF or if the natural history is influenced by geographic, ethnic, cultural, racial, or other factors. Other comorbid conditions such as emphysema and pulmonary hypertension may impact the disease course (1, 42-44). It has been suggested that earlier diagnosis and treatment of IPF may influence the course of the disease and outcomes, and may improve the long-term clinical outcomes of this fatal disease (45).

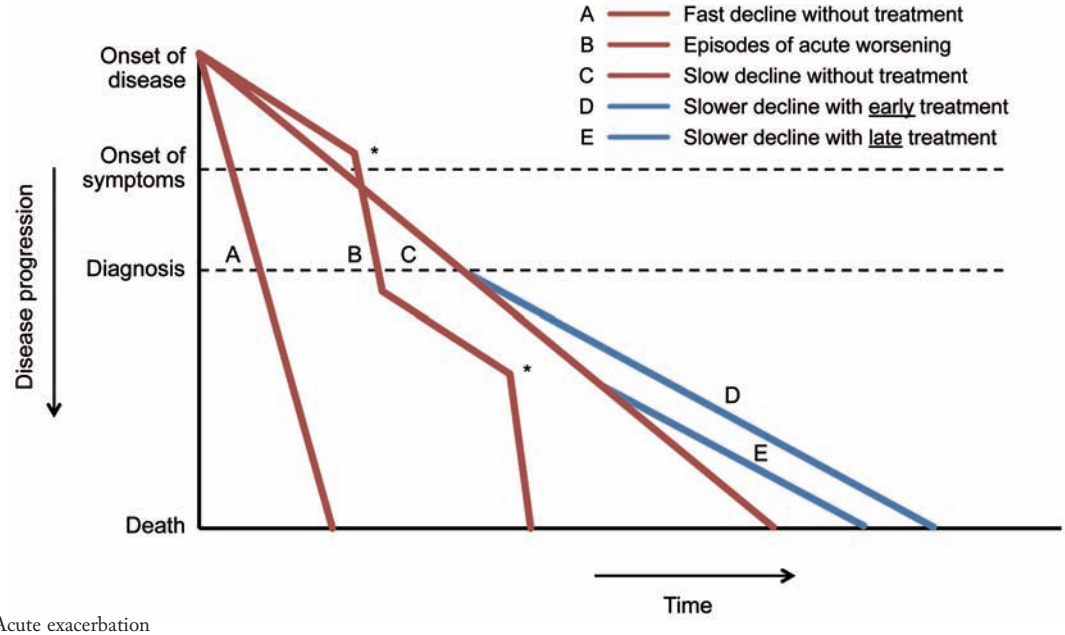
Acute exacerbation of IPF

Recent observations suggest that acute respiratory worsening occurs, despite previous stability, in a small minority of patients with IPF annually (approximately 5-10%) (Table 1) (1, 46, 47). Acute exacerbation can occur at any point in the course of IPF and occasionally can be its presenting manifestation (41, 47-50). Worsened cough, fever, and/or increased sputum are common observed symptoms (47, 48, 51). Bronchoalveolar lavage (BAL) may document atypical type II pneumocytes and a significant increase of neutrophils (52).

Table 1. Incidence of acute exacerbation (AE) and rapid deterioration (RD) (41)

Incidence[#]	AE[¶]	RD
1-yr	58 (14.2)	97 (23.0)
2-yr	71 (18.8)	124 (31.2)
3-yr	75 (20.7)	134 (35.4)

Data are presented as n (%). The cumulative incidences of AE, excluding patients first presented at the time of AE, are 11.6% (1-yr), 16.3% (2-yr) and 18.2% (3-yr). #: first event; ¶: 14 patients first presented at the time of AE



*Acute exacerbation
Illustration courtesy of Prof. V. Cottin, University of Lyon, France. Adapted from Kim et al. 2006 (40)

Fig. 1. Schematic representation of potential clinical courses of IPF (40). Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Kim DS, Collard HR, King, Jr TE. Classification and natural history of the idiopathic interstitial pneumonias. Proc Am Thorac Soc 2006; 3: 285-92.

It is presently unclear whether acute exacerbation of IPF is simply a manifestation of secondary unidentified but common respiratory complications such as pneumonia, pulmonary embolism, pneumothorax, or cardiac failure contributing to an acute worsening in a patient with IPF, or whether it represents an inherent acceleration in the pathobiological processes involved in IPF (53). Recent data from gene expression profiling of patients with acute exacerbation of IPF do not suggest an infectious aetiology (54). There have also been reports of acute respiratory decompensation after thoracic surgery (55-57), transbronchial lung biopsy and bronchoalveolar lavage (49, 58-60). It is unclear whether or not these events represent true acute exacerbations or complications of the respective procedures. When a cause cannot be identified for the acute respiratory decline, the term acute exacerbation of IPF has been used (51, 54, 61-63).

Staging of IPF

A consistent and accurate staging of IPF severity would be useful for both clinicians and patients, as well as for clinical trials (12). Such a system could standardise nomenclature, facilitate counselling of patients and their families, enable an estimate of survival, guide treatment options, or determine eligibility for lung transplantation (64). Terms such as 'mild', 'moderate', 'severe', 'early', and 'advanced' have been suggested for staging IPF. Whilst these different patterns of disease progression are retrospectively recognisable, prospective identification of disease behaviour would enable better recognition of patients with increased risk for mortality within two years, which could be useful for prompt consideration for lung transplantation and for the tailoring of therapeutic regimens, as well as permit the development of strategies to prevent or ameliorate acute exacerbations.

A number of studies have shown that selected individual clinical features commonly observed in clinical practice are associated with increased risk of mortality in IPF. These may be subdivided into clinical predictors obtained from the history and physical examination, radiographic, physiologic, pathologic, and biomarker predictors. Proposed stages are commonly based on extent of radiologic abnormalities and/or resting pulmonary function test (PFT) measurements. A number of physiologic variables on PFT at the time of diagnosis have been consistently associated with a prognosis that correlates with disease severity and/or progression. These include longitudinal changes in FVC or in diffusing capacity of carbon monoxide (DLco), and degree of oxyhaemoglobin desaturation or exercise testing, e.g. six-minute walk test (6MWT), or modified 6-MWT (5, 65-75). For example, change in percent-predicted FVC has been identified as an independent predictor of mortality in patients with IPF (Figure 2) (76). However, there is currently no established method of combining these predictors to accurately determine prognosis or define the stage of disease (38). Because of variability in the natural history of IPF, it is unknown whether the presence of one or more of these features identifies subpopulations of patients with 'advanced' or 'end-stage' IPF or relevant to clinical decision making.

Although there is little debate regarding the value of a staging system that can be easily utilised in practice, current proposals based on prospective or retrospective analyses of predictors of mortality are relatively complex and have not achieved widespread use in practice (77). For any staging system to be useful in practice it would need to be simple and reproducible. The criteria used in an ideal staging system should consider the stage of the disease at presentation as well as longitudinal factors.

To better understand the usage of physiologic staging of IPF in current clinical practice, a recent informal survey, including over 150 European IPF expert clinicians attending the AIR Meeting in Berlin, Germany, 4-5, November 2011, was undertaken. Using interactive voting, delegates were asked to review four illustrative cases of IPF patients including infor-

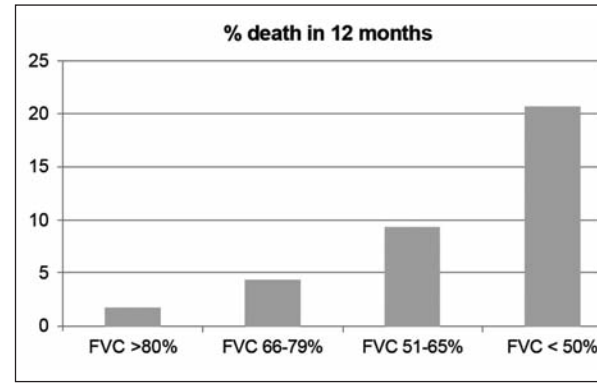


Fig. 2. Baseline FVC as a predictor of mortality (76)

mation on patient gender, age, occupation, and resting lung function (FVC predicted and DLco predicted) (Table 2A). Over 80% of IPF clinicians expressed an interest and relevance in a staging system for IPF with only 4% rejecting such an interest. While there was relatively consistent staging of IPF patients overall, there was less consistency in staging of IPF patients with moderate and advanced disease using a limited set of lung function parameters (e.g. FVC 75% predicted; DLco 35% predicted) (Table 2B). These results suggest that a simplified set of validated multi-parameter PFT criteria may improve discrimination between moderate and advanced disease.

Recent studies have proposed new staging systems to evaluate the risk of progression or increased mortality in IPF. For example, the Risk stratificatiOn ScorE (ROSE) is based on Medical Research Council Dyspnoea Score (MRCDS) >3, 6-MWT ≤72% predicted, composite physiologic index >41 repeated at six months, HRCT, and predicted 3-year mortality with high specificity in patients newly diagnosed with IPF (78). Re-evaluating the ROSE score after six months, it was possible to select a group of patients with advanced disease at increased risk of death over the subsequent time period. Another recent study using data from a large and well-characterised population of patients with IPF found that a clinical model composed of only four predictors (age, history of respiratory hospitalisation, percent-predicted FVC, and change in FVC over six months) predicted the overall risk of 1-year mortality (79). Similarly, a retrospective analysis showed that categorisation by baseline percent FVC effectively predicted IPF patients with mild, moderate, and severe disease and different long-term outcomes (80). Finally, a simple-to-use multidimensional prognostic staging system for IPF using four commonly used clinical and physiologic variables (gen-

Table 2. Baseline patient characteristics and results of AIR Survey 2012

A. Example cases on presentation (confirmed IPF diagnosis).

Patient 1	Patient 2	Patient 3	Patient 4
Female	Male	Male	Male
Age 55	Age 65	Age 61	Age 68
Nurse	Accountant	Shop assistant	Retired teacher
FVC 90% predicted	FVC 90% predicted	FVC 75% predicted	FVC 60% predicted
DLco 67% predicted	DLco 47% predicted	DLco 35% predicted	DLco 30% predicted

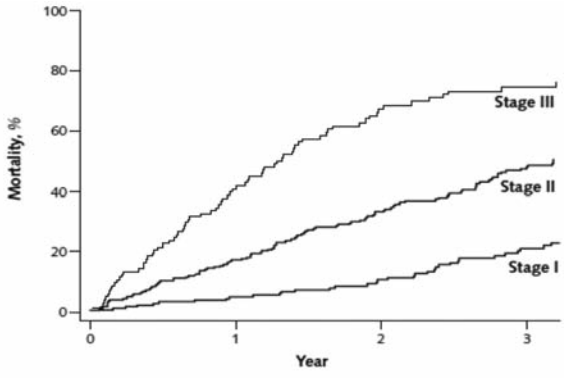
B. Delegate responses regarding estimated survival, staging and treatment options for selected case studies.

	Patient characteristics			
	Patient 1 Female Age 55 Nurse FVC 90% predicted DLco 67% predicted	Patient 2 Male Age 65 Accountant FVC 90% predicted DLco 47% predicted	Patient 3 Male Age 61 Shop assistant FVC 75% predicted DLco 35% predicted	Patient 4 Male Age 68 Retired teacher FVC 60% predicted DLco 30% predicted
Estimated survival				
2 y		11.5%	**50.6%**	**87.7%**
3.5 y	26.9%	**60.3%**	**43.4%**	11.1%
5 y	**57.7%**	25.6%	4.8%	0%
8 y	11.5%	1.3%	0%	0%
10 y	3.8%	1.3%	1.2%	1.2%
Staging				
Mild	**75.3%**	9.2%	1.2%	1.3%
Moderate	24.7%	**88.2%**	**45.2%**	10.1%
Advanced	0%	2.6%	**53.6%**	**88.6%**
Treatment				
Pirfenidone	**93.8%**	**95.9%**	**41%**	20%
Triple therapy	0%	0%	3.8%	3.8%
Oxygen	0%	0%	1.3%	**47.5%**
Transplantation	6.3%	4.1%	**53.8%**	28.8%

der, age, FVC and DLco) and a simple point-scoring system (GAP index) has been developed and validated (Table 3, Figure 3) (81). Three stages (stages I, II, and III) were identified based on the GAP index with 1-year mortality of 6%, 16%, and 39%, respectively (Figure 3). These studies suggest that a combined measure can stage disease, identifying patients with advanced disease at high risk of earlier death from patients with moderate or mild disease with greater precision than tools currently used in clinical practice; in addition, it may improve prognostication, help guide management, and facilitate research.

Table 3. A multidisciplinary index and staging system for IPF (81)

	Predictor	Points
G	**Gender**	
	Female	0
	Male	1
A	**Age**	
	<= 60	0
	61–65	2
	>65	3
P	**Physiology**	
	FVC, % predicted	
	>75	0
	50–75	1
	<50	2
	DLco, % predicted	
	>55	0
	36–55	1
	<=35	2
	Unable to perform	3



GAP = gender, age and two lung physiology variables (FVC and DLco).

Fig. 3. GAP index and staging system (81)

Discussion

In summary, there appears to be a general consensus that it is currently difficult to accurately classify patients based on just a few clinical or functional parameters, and that the development of a simplified staging system for IPF, based on validated multivariate parameters, would be of great benefit for clinicians, patients and their families in every day practice. Finally, there is a requirement for a carefully constructed measurement instrument, sensitive to underlying change in patient-reported QoL for use in clinical trials and longitudinal studies of patients with IPF.

Acknowledgments

The author thanks C. Trenam and M. Smith of IntraMed Europe for editorial assistance in the preparation of the manuscript.

Development of this article was supported by InterMune.

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Disclosures:
Professor Poletti was a member of the Advisory Board for InterMune.
Professor Egan reports no conflict of interests.