World Journal of Respirology

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DOI: 10.5320/wjr.v6.i1.14

World J Respirol 2016 March 28; 6(1): 14-23
ISSN 2218-6255 (online)

MINIREVIEWS

Prognostic scoring systems for clinical course and survival in idiopathic pulmonary fibrosis

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Author contributions: Both Puxeddu E and Rogliani P performed literature review and wrote the paper.

Conflict-of-interest statement: Rogliani P and Puxeddu E have no conflict of interest to declare.

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Received: September 23, 2015
Peer-review started: October 3, 2015
First decision: November 24, 2015
Revised: December 22, 2015
Accepted: January 29, 2016
Article in press: January 31, 2016
Published online: March 28, 2016

Abstract

Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly fatal among idiopathic interstitial pneumonias. Its clinical course is variable. A significant fraction of the population of patients display a slow disease course and can remain stable for years, while other patients show a rapid progressive course and may die within few months from diagnosis. For these reasons estimating prognosis of IPF patients is extremely difficult and has important clinical repercussions on optimal patients management including patients referral for lung transplantation. Several studies have tried to address this key point in the course of the two last decades analyzing different clinical, functional, radiological and biological variables. The purpose of this review is to assess relevant studies published on this subject and to examine the variety of prognostic predictors proposed along with staging systems.

Key words: Idiopathic pulmonary fibrosis; Prognosis; Survival; Scoring systems

Core tip: Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly lethal among interstitial lung disease. Its clinical course is highly variable and estimating prognosis of patients with IPF is extremely difficult with important impacts on the best clinical management of patients, including the referral of patients for lung transplantation. In this review article we evaluate relevant studies published on this subject and examine the variety of proposed prognostic predictors along with staging systems.

Puxeddu E, Rogliani P. Prognostic scoring systems for clinical course and survival in idiopathic pulmonary fibrosis. *World J Respirol* 2016; 6(1): 14-23 Available from: URL: http://www.wjgnet.com/2218-6255/full/v6/i1/14.htm DOI: http://dx.doi.org/10.5320/wjr.v6.i1.14

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common and rapidly fatal among idiopathic interstitial pneumonias (IIP), a group of interstitial disorders of

unknown origin limited to the lung[1]. IPF is characterized by the pattern of usual interstitial pneumonia (UIP) defined by the presence of areas of reticular opacities and honeycomb cysts alternating with areas of apparently unaffected parenchyma at high resolution computerized tomography (HRCT) of the chest and of focal fibroblast proliferation resulting from microscopic foci of acute lung injury at histological evaluation of lung biopsy specimens[2].

Although the pathogenesis of IPF remains largely unknown, recent works has shed light on the molecular mechanism involved in the disease shifting the current pathogenic concept from a traditional inflammatory paradigm to a model centered on alveolar epithelia cell (AEC) dysfunction. In this view a number of potential risk factors, including environmental factors and among them tobacco smoke[3], would lead to repetitive (AEC) injury with subsequent abnormal wound healing in genetically predisposed subjects[4]. According to this concept, the alveolar epithelium is subject to clinically silent microinjuries over a prolonged period of time with activation of pro-fibrotic signaling pathways that lead to interstitial matrix remodeling through the up regulation of specific molecules, such as metalloproteinases[5], and migration, proliferation and activation of mesenchymal cells with aberrant extracellular matrix deposition[4]. It is believed that abnormal release of oxidants and various cytokines and growth factors by alternatively activated alveolar macrophages (AM) is also involved in the constitution of the alveolar mileu that characterize this fibro-proliferative disorder[6-8].

Epidemiological studies conducted in different geographical areas estimate IPF prevalence and incidence in the range of 20 to 40 cases per 100000 inhabitants and of 6.8 to 16 new cases per 100000 per year inhabitants respectively, although, given the complexity of IPF diagnosis, those data might underestimate the real burden of this disease[9,10]. In fact, the diagnosis of IPF is difficult and requires the recognition on HRCT scans or on lung biopsy specimen of the typical UIP pattern in the absence of clinical feature suggesting alternative diagnosis that may be associated to the UIP pattern, *i.e.,* connective tissue diseases or exposure to known environmental agents like asbestos. For this reason current guidelines[2] recommend that the diagnosis is performed in centers experienced in the field of interstitial lung diseases in a process defined multidisciplinary discussion that should take place with the participation of different specialists, the pulmonologist, the radiologist, the rheumatologist and, in those cases where biopsy is performed, of the thoracic surgeon and the pathologist. Albeit recent data enforce the role of HRCT in the diagnosis of IPF, that in the appropriate setting allows the diagnosis combined with a detailed clinical picture in the large majority of IPF patients[11], biopsy is still required in a fraction of patients with non typical UIP radiological presentation. Given the significant morbidity and mortality associated with traditional surgical lung biopsy approach, less invasive approaches have been recently proposed with success[12,13].

IPF clinical course is variable. A significant fraction of the population of patients display a slower and less aggressive disease course, with longer survivals[14] and these patients can remain stable for years even without any medical intervention. On the other hand, other patients show a rapid progressive course and may die within few months from diagnosis. Furthermore, the course of disease can change, with patients who originally displayed a slow and stable disease course progressing to a rapid decline in lung function[14].

For these reasons, predicting the clinical course of the disease is crucial for the optimal management of IPF patients, especially for a prompt referral to lung transplantation of those patients with worst prognosis. Albeit the extensive research in the field, predicting IPF clinical course remains a challenging task. To this end, several biological and functional variables have been evaluated as predictors of outcome. Furthermore a number of multi-dimensional scoring systems, based on the combination of different variables have been recently proposed and validated in cohorts of IPF patients. The purpose of this review is to assess relevant studies published on this subject and to examine the variety of prognostic predictors proposed along with staging systems.

BIOMARKERS

The term "biomarker" stands for an objectively quantifiable biological measurement, *i.e.,* the level of a serum protein or a specific genetic mutation or polymorphism, that gives clinical meaningful information about the disease state of an individual patient[15]. Biomarkers can be divided into several classes based on the type of the information they offer. Diagnostic biomarkers allow the distinction of affected subjects from healthy individuals and to distinguish one disease from the other, and therefore can be used in disease diagnosis and classification. Disease susceptibility markers, that are often included with diagnostic markers, are those markers that in the healthy individual indicate an increased risk to develop the disease and therefore their diagnostic value in complex disease like IPF is not fully accepted. Prognostic biomarkers are markers that allow the prediction of outcome, usually at the time of presentation[16]. Several molecular signature belonging to this last group has been evaluated for their prediction ability in cohorts of IPF patients.

Krebs van den Lungen-6 (KL-6) is a mucin-like glycoprotein expressed into alveolar and bronchiolar lumen by activated alveolar type Ⅱ alveolar epithelial cells (AEC-Ⅱ) and bronchiolar epithelial cells where it acts as a chemotactic factor favoring circulating mesenchymal cell migration in the lungs and resident lung fibroblasts proliferation[17-20]. When the integrity of alveolar capillary barrier is compromised, KL-6 can leak into the circulation and can therefore be detected. Serum KL-6 levels

are significantly elevated in patients with IPF. Similar results are described in other ILDs such as non-specific interstitial pneumonia and systemic sclerosis-related ILD and as a result this marker does not show high specificity for IPF[21,22]. Nevertheless, KL-6 has been evaluated as a prognostic marker in multiple forms of ILD, including IPF. A prospective study by Satoh *et al*[21] conducted in a cohort of 152 patients with idiopathic interstitial pneumonias and 67 patients with ILD associated to connective tissue disease, demonstrated that patients with high KL-6 levels had a worst survival compared with those with lower levels. However, this results were not replicated in one of the largest study involving IPF patients where baseline KL-6 did not improve the prediction ability of traditional clinical variables[23].

Matrix metalloproteinase (MMP) are a structurally and functionally related superfamily of 23 zinc-dependent proteases that are thought to play an important role in the tissue fibrogenic process promoting interstitial matrix remodeling, cell migration and activation of profibrotic pathways[24,25]. MMP7, the smallest member of the MMP family, is thought to degrade multiple components of the extra cellular matrix playing a pivotal role in the fibrogenic process[24]. Elevated serum MMP7 levels have been reported in studies comparing IPF patients with patients affected by sarcoidosis and COPD, but MMP7 concentrations in IPF patients do not differ from those observed in other forms of ILD[26,27]. Nevertheless, Rosas *et al*[28] evaluating serum levels of both MMP7 and MMP1 were able to distinguish IPF from hypersensitivity pneumonitis, that represent one of the more complex differential diagnosis of IPF, with high sensitivity and specificity. The same study demonstrated that serum MMP7 concentrations were inversely correlated with lung function measurements proposing MMP7 as a possible prognostic biomarker. Coherently, in a subsequent study Richardson and al. demonstrated that levels of MMP7, analyzed together with other variables in a multidimensional index, were significantly associated with patients' outcome[29].

Pulmonary surfactants proteins are lipoprotein complexes synthesized by AEC-Ⅱ that play in the alveoli the essential function of decreasing the surface tension at the air-liquid interface. The reduction in surface tension allows lung expansion during inspiration with lower transpulmonary pressures and prevents alveoli from collapsing during expiration[30]. Surfactant proteins A (SP-A) and D (SP-D) have shown interesting potentiality both as diagnostic and prognostic markers in IPF and other forms of ILD. Abnormal surfactant proteins synthesis is thought to play a role in AEC-Ⅱ cell dysfunction activating endoplasmic reticulum stress and the unfolded protein response[31]. Interestingly, defects in the genes encoding SP-A1 and SP-A2 have been associated with familial forms of pulmonary fibrosis, suggesting that these proteins may be involved in IPF pathogenesis. However only a minority of sporadic forms of IPF carry these mutations[32-40]. Levels of SP-A and SP-D have been found to be elevated in IPF patients due to increased permeability of the alveolar-capillary barrier or for increased secretion by AEC-Ⅱ[41]. Increased serum levels of either surfactant protein at the time of diagnosis has been demonstrated to be independent predictor of survival and has been proposed as a tool for patients referral to lung transplantation[41-43]. However, similarly to KL-6, ancillary studies conducted during recent clinical trials showed no difference in serum surfactant protein levels between treatment and placebo groups[44]. For this reason further evidences are required for their implementation into routine clinical practice.

CC chemokine ligand 18 (CCL18) is a chemokine protein that stimulates collagen production and fibroblasts differentiation[45]. It is produced by alternative activated AM and it has been reported to be elevated in a variety of fibrotic lung diseases, including IPF, sarcoidosis and systemic sclerosis-related ILD limiting its role as diagnostic biomarker for IPF[46,47]. However, Prasse *et al*[48] in a prospective cohort of 72 IPF patients were able to demonstrate correlation between serum CCL18 levels and physiological variables. In fact, in this cohort of patients baseline serum CCL18 levels were able to predict subsequent functional decline, and CCL18 serum levels > 150 ng/mL were independently associated with death in the follow up period.

In 2011 Seibold *et al*[49] by means of a genome wide linkage approach detected linkage between idiopathic interstitial pneumonia and a 3.4-Mb region of chromosome 11p15 in 82 families. Further analysis revealed that common polymorphism in the promoter region of the Mucin 5B (MUC5B) is associated with both familial interstitial pneumonia and IPF, being the minor-allele of the single-nucleotide polymorphism rs35705950 present at a frequency of 34% among subjects with familial interstitial pneumonia, 38% among subjects with IPF and 9% among controls. The association between the MUC5B promoter variant and IPF is the most consistently reproduced in the literature since studies conducted in other cohorts have independently confirmed these results[50]. Interestingly no association has been found with systemic sclerosis related ILD or sarcoidosis[51]. The MUC5B promoter variant appears to have prognostic value, as it is associated with decreased mortality when compared with the wild-type allele in IPF patients[52]. This observation seems to be independent of clinical factors and stratification of patients based on the presence of this polymorphism significantly improves the accuracy of previously validated prediction index[52].

PHYSIOLOGIC VARIABLES

Baseline pulmonary function test values poorly predict survival in IPF. Baseline forced vital capacity (FVC) shows an unclear predictive value[53,54] probably due to the confounding effect of comorbid conditions such as emphysema, pulmonary vascular disease and obesity[2].

Baseline diffusing capacity for carbon monoxide (DLCO) appears to be a better survival predictor compared to FVC, and a threshold of approximately 40 percent of predicted values has been associated with an increased risk of mortality[54-57]. Studies conducted in small IPF patients cohorts suggest that baseline total lung capacity (TLC) and alveolar-arterial oxygen difference in partial pressures [P(A-a)O_2] may predict outcome in IPF. In particular change in P(A-a)O_2 greater than 15 mmHg after 12 mo has been shown to correlate with patients survival[55]. However, these results were not replicated in large cohorts of IPF patients.

Longitudinal functional trends have shown strong prognostic value in IPF. Serial change in FVC is an accepted measure of the disease course and decline in FVC has been used as the primary endpoint in several randomized controlled drug trials[58-63]. A decline in FVC greater than 10% has been consistently correlated with worse survival time in IPF and recent evidence-based guidelines recommend that an absolute decrease in FVC greater than 10% can be used as a surrogate marker of mortality[2]. Recent data indicate that in IPF even declines in FVC of 5% may be predictive of mortality[64] and that using the relative change instead of the absolute change when calculating the decline in FVC allows to identify clinically meaningful information preserving prognostic efficiency[65]. A decline in DLCO and 6-mo change in TLC and P(A-a)O_2 have also been associated with decreased survival[54,55,57,66].

The 6-min walk test (6MWT) is a measure of exercise tolerance, that has been widely used in a variety of cardiac and pulmonary conditions to asses patients performance status and to evaluate the need for oxygen supplementation[67,68]. The 6MWT is a practical, inexpensive and reliable test that requires no special equipment or advanced training and can be performed by all but the most severely impaired IPF patients[69]. A number of studies have evaluated at prognostic utility of the 6MWT in IPF, however, until recently, these studies were limited by the small size of the analyzed cohorts or by the lack of standardization in the procedure[70-72]. However, in a recent study conducted analyzing data from the database of a large randomized controlled study evaluating interferon-gamma 1b in IPF, the 6MWT demonstrated to be a reliable, valid, and responsive clinical measure and to efficiently predict one-year mortality[73]. In a subsequent study, the investigators found that both baseline 6MWT distance (6MWD) and 24-wk change in 6MWD were independent predictors of short-term mortality in an analysis of 748 patients with IPF[74].

MULTI-DIMENSIONAL SCORING SYSTEMS

Published studies on multi-dimensional scoring systems are summarized in Table 1. In 1986 Watters *et al*[75] developed a composite clinical-radiographic-physiologic (CRP) scoring system based on several parameters as dyspnea, radiology, spirometry, lung volume, diffusion capacity, resting alveolar-arterial PO_2, and O_2 saturation corrected for maximal achieved VO_2max in 26 biopsy-proven IPF patients. Scores ranged from 0 to 100 (100 being the most severe disease). The authors looked at the relationship between CRP scores and histopathologic findings, including a cellular pathology score based on abnormalities considered potentially reversible, a fibrotic pathology score based on abnormalities thought to be mainly irreversible, and an overall index defined as "total pathology score". The CRP score determined after 6 mo of corticosteroid treatment correlated with the fibrotic pathology score on open lung biopsy and the change in CRP after 6 mo of corticosteroid therapy correlated with the cellular histopathologic component at biopsy.

In a subsequent study Gay *et al*[76] tested pre-treatment features that could be used to predict short-term improvement in pulmonary function and long term survival in a population of 38 biopsy-proven IPF patients. The CPR, a high-resolution CT scan (HRCT) scores, and histopathologic scores were available in all patients. In a first phase of the study, patients were treated with high-dose steroids for 3 mo and thereafter CRP scoring was repeated. Patients were divided into three groups: Responders with a greater than 10-point drop in CRP, stable with a change in CRP within 10 point, and non-responders with rise in CRP greater than 10 or death. Patients showing improvement continued the steroids treatment for 18 mo tapering the drug dose. In all others patients, steroids therapy was interrupted and oral cyclophosphamide prescribed. Only the HRCT fibrotic score ($P < 0.009$) and the fibrotic pathology score ($P < 0.03$) independently predicted survival in the analyzed population. Addition to the HRCT fibrotic score of physiologic measures, CRP score, or pathologic findings did not improve its predictive value.

King *et al*[77] elaborated an updated of the CRP scoring system in order to predict survival in newly diagnosed cases of IPF. Study population included 238 biopsy-proven IPF patients divided by smoking status into current smokers, former smokers and never smokers.

For each patient, clinical manifestations, chest radiographs, and pulmonary physiology were prospectively assessed by means of Cox proportional hazards models and the effect of these parameters on survival was evaluated. Survival was related to age, smoking status, clubbing, the extent of interstitial opacities on the chest radiograph, presence of pulmonary hypertension, reduced lung volume, and abnormal gas exchange during maximal exercise. Based on these results the authors updated the CRP scoring system elaborated by Watters *et al*[75] and developed an abbreviated model which excluded pulmonary mechanics and exercise variables that was demonstrated to be superior to the original model proposed by Watters *et al*[75].

In an English study by Mogulkoc *et al*[78] a model

Table 1 Summary of characteristics and main results of the studies published on Multidimensional-scoring systems

Ref.	Type of study (number of patients)	Variables included in the model	Summary of results
Gay *et al*[76]	Prospective (38)	HRCT score Pathology fibrotic score	HRCT fibrotic score ⩾ 2: 80% sensitive and 85% specific in predicting death (34 mo average follow-up). The CRP does not add predicting value
King *et al*[77]	Retrospective (91)	Age Smoking status Clubbing HRCT score HRCT score for PH TLC % pred PaO_2 at max exercise	Only prediction results of single variables are reported by the authors. No direct data about performance of the CRP are reported
Mogulkoc *et al*[78]	Retrospective (95)	HRCT score DLCO % pred	HRCT and DLCO% combined model: AUC 0.91; sensitivity 84%, specificity 82% in predicting 2 yr survival
Wells *et al*[79]	Retrospective (212)	DLCO % pred FVC % pred FEV1 % pred	5 yr survival CPI regression coefficient: 0.092 (0.043, 0.141). $P < 0.0005$
du Bois *et al*[80]	Prospective (830)	Age Respiratory hospitalization FVC % pred 24 wk in FVC % pred	Combined scoring system AUC: 0.75. 1 yr survival
Richards *et al*[29]	Prospective (241)	Gender FVC %pred DLCO %pred MMP-7	PCMI ⩾ 330: AUC 0.74-0.84 in predicting survival. Average follow-up 1.8 yr
Mura *et al*[82]	Prospective (138)	MRCDS 6MWD % pred CPI	ROSE > 2:HR 11.4, $P < 0.0001$; AUC 0.76; sensitivity 39%, specificity 100% in predicting survival. 3 yr follow-up
Ley *et al*[83]	Retrospective (558)	Gender Age FVC % pred DLCO % pred	GAP: c-index 69.3. Stages Ⅰ, Ⅱ and Ⅲ 1-yr mortality of 6%, 16%, and 39%, respectively

HRCT: High resolution computerized tomography; CRP: Clinical-radiographic-physiologic; TLC: Total lung capacity; DLCO: Diffusing capacity for carbon monoxide; CPI: Composite physiologic index; PCMI: Personal clinical molecular mortality index; MMP: Matrix metalloproteinase; MRCDS: Medical research council dyspnea score; 6MWD: 6 min walking distance; ROSE: Risk stratificatiOn ScorE; HR: High-resolution; GAP: Gender, age, physiology; PaO_2: Pulmonary arterial oxygen tension; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 s.

based on DLCO percent predicted and HRCT-fibrosis score was developed in order to estimate survival and to optimize the timing of lung transplant referral in IPF patients. Study population was composed of 115 patients under 65 years 38% of which with biopsy proven IPF. The primary endpoint of this study was 2-year survival. Authors found that HRCT-fibrosis score, based on fibrotic and ground glass changes, and DLCO expressed as percent of predicted values were independent predictors of survival and they also determined a cut-off for both measures. The model yielded a specificity and sensitivity of 84% and 82%, respectively.

In 2003 a study by Wells *et al*[79] proposed the Composite Physiologic Index (CPI) as a determinant of prognosis in IPF patients with and without concomitant emphysema. The CPI was derived against a quantitative radiographic score of pulmonary fibrosis and provided an accurate estimate of the disease extent on HRCT. The CPI was calculated in a derivation population of 106 patients, 36 with biopsy-proven IPF, and was eventually tested in a validation population of the same size. Stepwise regression was used to generate a combination of lung function variables reflecting the extent of pulmonary fibrosis on HRCT. Parameters examined included FEV1, FVC, TLC, residual volume, DLCO, carbon monoxide transfer coefficient, PO_2, and A-aO_2. The extent of IPF on HRCT was independently associated to percent predicted DLCO, FVC and FEV1 that were included in the final CPI formula as follows:

Extent of disease on CT = 91.0- (0.65 × percent predicted DLCO)- (0.53 × percent predicted FVC)+ (0.34 × percent predicted FEV1).

In the validation population, when compared to the single variables, the CPI showed the best correlation to the HRCT disease extent. In terms of survival, five years retrospective mortality analysis demonstrated that the CPI had the greatest prognostic power in both the singles and combined cohorts, including a separate cohort of 36 patients with biopsy proven IPF (CPI, P = 0.0005; FVC, P = 0.002; PO2, P = 0.002).

A risk scoring system for 1-year mortality was proposed by du Bois *et al*[80] in 2011. The authors analyzed clinical data of 830 patients with mild to moderate disease without emphysema included in two large international clinical trials aimed to test the efficacy of IFN-g1b in IPF[58,81].

The endpoint was 1-year survival and the mortality was found to be 9.7% at one year. The following variables were found to be independent predictors of all-cause mortality and were included in a clinical model: Age, history of respiratory hospitalizations, percent

Table 2 Risk stratification Score[82]

Low risk (all of the following conditions)	Intermediate risk (1 or 2 of the following conditions)	High risk (all the following conditions)
MRCDS ⩽ 3	MRCDS > 3	MRCDS > 3
6MWD > 72% predicted	6MWD 72% ⩽ predicted	6MWD 72% ⩽ predicted
CPI ⩽ 41	CPI > 41	CPI > 41

MRCDS: Medical research council dyspnea score; 6MWD: 6 min walking distance; CPI: Composite physiologic index.

predicted FVC, 24-wk change in percent predicted FVC, percent predicted DLCO, 24-wk change in percent predicted DLCO and 24-wk change in health related quality of life questionnaire. A second simplified model was developed based on age, history of respiratory hospitalization, percent predicted FVC and 24-wk change in percent predicted FVC. Both the original and simplified models had comparable discriminatory power. Based on the simplified clinical model a scoring system able to estimate the probability of 1-year mortality in patients with IPF was developed.

A personal clinical molecular mortality index (PCMI) was proposed in a prospective study by Richards *et al*[29]. This multi-dimensional index incorporated for the first time serum biomarkers with pulmonary function test measures. Study population included 241 patients divided into a derivation cohort of 140 patients, 85 with biopsy proved IPF, and a validation cohort of 101, 41 with biopsy. The primary endpoints of the study were mortality, transplant-free survival, and progression-free survival. Sera samples from the 241 patients were tested for the concentrations of more than 90 different proteins. The association of serum biomarkers with primary endpoints were tested in the derivation and validation cohorts using nonparametric methods of survival analysis and the Cox proportional hazards model, and an integrated risk prediction score including FVC and DLCO was derived and tested.

Although concentrations of MMP-7, ICAM-1, IL-8, VCAM-1, and S100A12 were all associated with the primary endpoints in the derivation cohort, the Akaike information criterion (AIC) that was applied for variable selection in the Cox proportional hazards model, included only MMP-7 in the final equation defining PCMI as follows: 114 × I(Male) + 2 (100% - FVC% Predicted) + 3 (100% - DLCO%Predicted) + 111 × I (MMP-7 ⩾ 4.3 ng/mL) where I has to be considered equal to 1 if and only if the condition inside the parentheses is true. With a PCMI cut-off of 330, low-risk patients showed a median survival of 5.13 years while high risk patients had a median survival of 1.56 years.

In an Italian study Mura *et al*[82] elaborated an index, defined as Risk stratificatiOn ScorE (ROSE). This study was conducted on an overall population of 138 newly diagnosed patients, 55 (40%) of those had a biopsy-proven diagnosis, and the rest had a clinical-radiological diagnosis reviewed by three different expert radiologists. The study population comprised a prospective derivation population of 70 patients and a retrospective validation population of 68 patients used for comparative analysis. Minimum follow-up was 3 years and the primary end-point was survival defined as time to death or to lung transplantation. Incidence of acute exacerbation was also addressed in this study. Examination of clinical variables collected at time of diagnosis and at six month from diagnosis by means of ROC curve and multivariate analysis allowed the definition of three independent predictors of 3-year survival: (1) Medical research council dyspnea score (MRCDS) > 3 (HR = 6.77, $P < 0.0005$), (2) 6 min walking distance (6MWD) ⩽ 72% predicted (HR = 3.27, $P < 0.0162$) and (3) CPI > 41 (HR = 5.36, $P < 0.0071$).

The ROSE predicted 3-yr survival with 39% sensitivity and 100% specificity. A ROSE of 3 (Table 2) carried a hazard ratio of 11.4 towards 3-year mortality. Importantly, advancement to ROSE 3 of patients with an initial score of 1 or 2 six months after diagnosis predicted 3-yr mortality with 94% sensitivity and 41% specificity.

In their retrospective study Ley *et al*[83] developed an index defined as GAP (gender, age, physiology), in order to predict mortality in IPF. United States and Italian patients included in this study were divided in three groups: 228 patients, 44.3% of which with biopsy proven IPF, were included in the derivation cohort and 555, 54.7% of which with biopsy, in two validation cohorts of 330 and 325 patients. Mean follow-up was 1.7 and 2.4 in the derivation and the validation cohorts, respectively. The primary endpoint of the study was time to death or lung transplantation. Overall mortality was 49% in the derivation cohort and 62% in the validation cohorts. A competing-risk regression model was used to screen potential predictors of mortality in the derivation cohort including age, sex, body mass index, smoking status, supplemental oxygen use, FVC, FEV1, TLC and DLCO. Age, sex, FVC% predicted and DLCO% predicted were identified as independent predictors and were used to develop the GAP individual risk calculator towards mortality and staging system. Three stages (stages Ⅰ, Ⅱ, and Ⅲ) were identified based on the GAP index with 1-year mortality of 6%, 16%, and 39%, respectively (Table 3).

CONCLUSION

Predicting clinical course of IPF is extremely difficult and despite the progress in the field reviewed in this article, survival prediction in the single IPF patient remains an unmet clinical need. This task is limited by multiple factors. On one hand diagnostic delays related to

Table 3 Gender, age, physiology index[83]

Stage	I	II	III
Points	0-3	4-5	6-8
	Predictor		Points
	Gender		
G	Female		0
	Male		1
	Age		
A	⩽ 60		0
	61-65		1
	⩾ 65		3
	FVC% predicted		
	> 75		0
	50-75		1
P	< 50		2
	DLCO% predicted		
	> 55		0
	36-55		1
	⩽ 35		2
	Cannot perform		3
	Total possible points		8

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide.

different patients symptoms perception and healthcare operators awareness, but also different biological disease characteristics might cause a high variability of disease presentation at time of diagnosis. Furthermore, largely unknown triggers might dramatically affect disease course, with patients who originally displayed a stable disease progressing to rapid decline in lung function. In this respect, recent data suggest that even medical interventions considered standard therapy until few years ago might have contribute to disease progression in a significant fraction of IPF patients[84,85]. On the other hand, the complex pathophysiology of IPF, that is characterized by a combination of gas exchange, ventilatory and cardiovascular response abnormalities, limits the correlation between single traditional clinical measures such as pulmonary function tests, exercise capability and radiological or histopathological disease extent affecting their clinical utility at time of diagnosis. Observation of trends in clinical variables have shown a better prediction ability compared to baseline measures. However this approach presents the major limitation of the need of follow-up periods ranging from 6 to 12 mo in a disease with a median survival of about 3 years. Recent data suggest that shorter term observations and the validation of clinical meaningful differences in clinical variables of lesser magnitude might improve the clinical utility of this approach[64,74].

Multiple-dimensional scoring systems have significantly improved the prediction of survival in IPF. These scoring systems have the advantage to take into account different aspects of the disease at the same time increasing the amount of information on the status of the single patient. However, to date none of the proposed systems can be considered extent of limitations. In fact, some of the published studies are limited by their retrospective nature or by the relative small numbers of analyzed prospective cohorts. Availability of prospective data from the large database of recent clinical trials has partially overcame these limitations. However, these studies have generally enrolled mild or moderate patients that might not represents the "real life" clinical setting missing advanced and rapidly progressing disease forms and therefore might underestimate the real disease burden of IPF.

In our opinion the search for the optimal survival prediction tool should take into account the increasing information coming from basic studies on the genetics, pathogenetic mechanisms and more in general biology of IPF, some of which have already provided useful hints in form of molecular signature that should be incorporated in old and new clinical models and eventually validated in large prospective cohorts of IPF patients. Such consistent and improved survival tool might be particular useful in the next future to guide the clinicians in patients management with particular regard to the choice of the increasing available effective therapeutic strategies for IPF patients.

ACKNOWLEDGMENTS

The authors thank Maryan Huckvale for having edited this manuscript.

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P- Reviewer: Belliato M, Kawai H
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Jiao XK

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