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Predicting prognosis in idiopathic pulmonary fibrosis

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a parenchymal lung disease characterized by progressive interstitial fibrosis. In 2002, the ATS/ERS published new criteria that significantly changed the definition of IPF, resulting in a more homogeneous group of patients. IPF has a poor prognosis with a median of 2.5-3.5 years, but varying from a few months to a decade. In order to predict survival at diagnosis or during follow-up, a considerable number of studies were conducted identifying promising prognostic biomarkers. However, many had been performed before the new ATS/ERS consensus and included patients who would not meet current IPF criteria. This review provides an overview of prognostic markers of survival in IPF after the ATS/ERS consensus statement in 2002. Molecular biomarkers in serum, especially so-called pneumoproteins are relatively easy to obtain and have been independently replicated as predictors of prognosis. Cellular constituents of bronchoalveolar lavage (BAL) have been investigated as predictors of survival, but results remain contradictory. Further, a robust marker of prognosis is the change in lung function over time. However, calculating change in lung function is usually only possible over a 6-12 months period, and is therefore not useful at first presentation. The extent of fibrosis on HRCT scan and the number of fibroblast foci on lung biopsy can be measured at presentation and correlate with prognosis, but the applicability of these markers is being hampered by the lack of user- and patient friendliness. In conclusion, a number of biomarkers are potential candidates for an individualised prognosis of IPF, of which so-called pneumoproteins appear most promising and should be a major focus of future research. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 85-95)*

Key words: idiopathic pulmonary fibrosis, biomarker, prognosis, survival

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology. It is the most common of seven entities of interstitial pneumonia, as described by the American Thoracic Society/ European Respiratory Society consensus statement in 2002 (1). Clinically, IPF is characterized by dyspnea and worsening of lung function. The disease course of IPF is unpredictable, but in general mean life expectancy varies between 2.4 and 4.2 years (2-5). However, survival from an individual patient may vary from a few months to almost a decade. Despite extensive basic research and several clinical trials, no therapy has yet been proven to prolong survival (6). Therefore, optimal timing of referral for lung transplantation is crucial and dependent on accurately predicting survival for an individual patient.

The clinical history of IPF has been studied in detail in the placebo arm of a clinical trial. The investigators noted frequent hospitalizations for respiratory disorders and although pulmonary function parameters such as FVC changed little during 72

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weeks of follow-up, acute clinical deterioration preceded death in half of the patients who died of IPF (7). This indicated that the incidence of acute exacerbations, which are defined as subjective worsening over 1 month, new radiographic infiltrates, the absence of an identifiable etiology, and acute alveolar injury on biopsy, (8) form a substantial part of the IPF-related deaths.

The natural history of IPF is difficult to predict. Patients with apparently similar stages of disease severity may come to a pulmonary physician, but one may demonstrate rapidly progressive disease with a survival of only one or two years, while another may show a survival time of more than 6 years. Hypothetically it appears as if there are at least three different patterns of disease behaviour and survival (7, 9), which are depicted in figure 1. Pattern A is characterized by a slowly progressive decline in lung function; pattern B is characterized by one or more episodes of rapid deterioration, the last one with fatal outcome; and pattern C is characterized by a devastating rate of deterioration from the first presentation of disease with survival of less than 1 to 2 years. Ideally, pulmonary physicians caring for these patients would have the availability of biomarkers for an early differentiation between these patterns.

A great number of studies have focused on the identification of determinants of prognosis in IPF. However, many of these studies have been conducted before the ATS/ ERS consensus statement, which highlighted the importance of distinguishing usual interstitial pneumonia (UIP) from non-specific interstitial pneumonia (NSIP), and other types of interstitial pneumonia (1). Especially NSIP and UIP appear to be different entities in terms of treatment and prognosis. Before 2002, patients with idiopathic interstitial pneumonias that would now be categorised as NSIP, were often lumped together with IPF/UIP patients, and this would certainly have influenced the results of these studies.

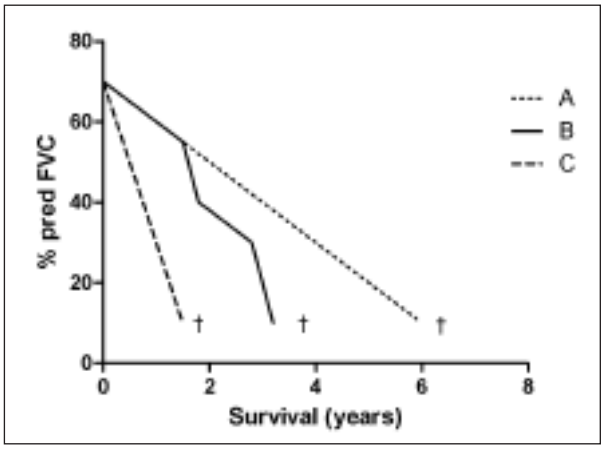

Fig. 1. Hypothetical clinical courses of IPF. A: slowly progressive IPF; B: slowly progressive with two episodes of rapid deterioration; C: rapidly progressive IPF.

In an attempt to provide an up to date overview of molecular and non-molecular markers that can predict prognosis in IPF, one needs to consider the studies that only included IPF patients according to the new definition. The aim of this review is to provide such an overview of determinants of prognosis in definite IPF patients. A table which summarizes all relevant studies evaluating prognostic biomarkers is available in the online appendix.

Baseline characteristics that influence survival

The incidence of IPF is lower in females (10) and it is has been found that the female sex is associated with a better survival (4). Recently, Han et al.(11) demonstrated that males indeed showed a greater rate of disease progression. The survival benefit for the female sex persisted after adjustment for relative change in desaturation and percentage predicted FVC. The influence of age at the time of diagnosis on survival has also been described but is less convincing. Some studies reported an unfavourable prognosis in case of an age older than 50 years, but these studies were all from before the ATS/ERS consensus statement (12-14), In recent studies, however, age did not turn out to be a significant factor in multivariate analysis (15, 16). In fact, as NSIP patients are generally younger than IPF patients (17, 18), misdiagnosis could possibly account for the survival differences in former studies.

A relationship between body mass index (BMI) and mortality has recently been demonstrated by Alakhas and colleagues (19). They studied 197 patients with IPF that were categorized into three groups according to BMI: < 25, 25-30, and > 30. Median survival was 3.6, 3.8 and 5.8 years respectively. Although the exact underlying mechanism remains to be elucidated, it is an interesting finding

that higher BMI is associated with better survival. Unfortunately, BMI > 30 is regarded as a contraindication for lung transplantation(20) .

Predictive markers in blood

In 1999, Hermans and Bernard extensively described lung epithelium-specific proteins and their applications as biomarkers in serum (21). These so-called pneumoproteins, are thought to occur in the bloodstream due to increased permeability of the alveolar-capillary membrane and increased secretion by regenerating alveolar type II cells. Krebs von den Lungen 6 (KL-6) is a lung specific antigen on mucin (MUC)1 that also displays chemotactic activity for human fibroblasts (22). High concentrations of KL-6 are present in bronchoalveolar lavage fluid (BALf) and serum of IPF patients. A Japanese group found that initial serum KL-6 levels could predict long-term survival in IPF patients. A total of 27 IPF patients were followed up during at least 3 years. At the optimal cut-off level of 1000 U/ml, patients were categorized as having low or high serum levels of KL-6. Although the study involved only a small cohort of IPF patients, a significant difference in survival was observed between patients with low and high serum levels of KL-6 levels(23).

Surfactant proteins are produced by type II pneumocytes and contribute to surfactant homeostasis and local immune defence. Surfactant proteins A (SP-A) and D (SP-D) can be detected in serum and are elevated in patients with IPF, pulmonary alveolar proteinosis (PAP) and interstitial pneumonia associated with collagen diseases (24-26). The prognostic value of SP-A and SP-D was first described by Takahashi et al. in 2000 (27). Kinder et al. independently confirmed these results in a large and well-characterised cohort of IPF patients (15). They found an association between serum levels of SP-A and SP-D and mortality in 82 patients with biopsy-proven IPF. In the first year after the diagnosis, each increase of 49 ng/ml in concentration of serum SP-A was associated with a 3.3 fold increase of mortality risk, after controlling for age, gender, smoking, lung function parameters and BALf neutrophil percentage. The association of serum SP-D with survival was less obvious, but showed a trend towards significance. Adding serum SP-A and SP-D levels to a statistical model for IPF prediction demonstrated a significant improvement compared to clinical characteristics only.

CC chemokine ligand 18 (CCL-18) is a chemokine that is expressed at high levels in the lung. It is produced by macrophages and attracts lymphocytes to the lung. CCL-18 also stimulates fibroblast proliferation and collagen production (28). Baseline serum CCL18 concentrations in IPF patients are associated with the change in TLC and FVC at 6 month follow up, and a significant higher mortality was observed in the group who had serum CCL-18 levels > 150 ng/ml. Thus, serum CCL-18 levels were found to be highly predictive for the change in lung function parameters and survival (16).

Recently, another interesting finding was the occurrence of fibrocytes in blood as indicators of prognosis. Fibrocytes are circulating mesenchymal progenitor cells which are involved in tissue repair and fibrosis. Fibrocytes were significantly elevated in IPF patients compared to healthy controls and ARDS patients, with a further elevation in patients with an acute exacerbation. Fibrocyte numbers were not correlated with lung function impairment or radiological extent of disease, but they were an independent predictor of mortality within 2 years of follow-up (29).

Interestingly, changes of markers of oxidative stress in exhaled breath condensate, sputum and serum have been found in IPF patients. IPF patients seem to have lower anti-oxidant capacity and higher levels of reactive oxygen species than healthy controls. The role of anti-oxidants and reactive oxygen species seems promising, both in the pathophysiology of the disease, as well as markers reflecting disease severity. This has extensively been reviewed (30-34) and seems to be a promising direction for new diagnostic and prognostic markers, however associations with mortality have not been described yet. Future studies are necessary to determine the prognostic value of these markers.

Predictive markers in BALf

The relationship between cell types in bronchoalveolar lavage fluid (BALf) and the clinical course of patients with IPF has been the subject of several studies. The first studies showed that in-

creased numbers of eosinophils were associated with increased mortality and that lymphocytosis was associated with a better prognosis (35-37). However, these studies were all conducted before the new ATS/ ERS classification of IIPs in 2002 (1). After the new classification, three studies on this subject with a considerable number of patients were conducted. Ryu et al. included 87 pathologically confirmed UIP and 35 NSIP patients in their study (17). They found that UIP patients had a higher number of neutrophils (7%) compared to NSIP (3%) and that lymphocyte count was higher in NSIP patients (29%) compared to UIP (5.5%). The pathologic diagnosis of NSIP seemed to be the best predictor of longer survival. When only UIP patients were included in the analysis, lymphocytosis was the only predictor of longer survival. Of note, Ohshimo and colleagues recently described that increased lymphocytes in BALf in patients with suspected IPF are indicative of an alternative diagnosis, i.e. chronic extrinsic allergic alveolitis and idiopathic NSIP, which underlines the importance of disease homogeneity in the search for predictive markers for IPF in BALf (38). The predictive value of lymphocytosis could not be confirmed by Kinder et al. who included 156 biopsy-proven IPF patients and did not find an association between lymphocytosis or eosinophils and survival (39). Interestingly, they found that BALf neutrophil percentage was the only independent predictor of death and that this relation was most prominent in the first years of follow-up and attenuated over time. Another study, from Veeraghaven et al. did not find any association between cellular profiles in BALf and prognosis at all (40).

Next to cellular components of BALf, other proteins in BALf can also be informative in the context of estimating prognosis. Matrix metalloproteinases (MMPs) degrade all of the extracellular matrix components of the interstitium and may play a role in abnormal alveolar permeability. MMP-8 and MMP-9 levels in BALf were significantly elevated in those patients who showed rapid lung function decline compared to patients who showed slow deterioration. Patients who died during 3-year follow-up showed higher MMP-8 and MMP-9 levels compared to those who did not die, but BALf levels did not predict survival time (41). MMPs are also detectable in serum, but have not been described to predict survival yet (42, 43).

Pulmonary function parameters

Lung function impairment at diagnosis is indicative of the severity of the disease, but does not necessarily reflect the progressiveness of the underlying pathological process. It requires at least two measurements with a substantial time interval, usually 6-12 months, to collect this information. Change in lung function parameters over time has therefore been proven to be a better predictor of survival than baseline values at the time of diagnosis. Collard et al. evaluated the predictive value of changes in clinical and physiologic variables over time for survival in 81 patients with biopsy-proven IPF (44). Six and 12- month changes in dyspnea score, total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), diffusing capacity of carbon monoxide (DL_{CO}), partial pressure of arterial oxygen (p_aO_2) and oxygen saturation (s_aO_2) were predictive of survival time even after adjustment for baseline values. That changes in these variables predict survival, suggests that the rate of progression is independent of the initial degree of severity (44, 45). Interestingly, the change in FVC over time appeared to be superior in predicting prognosis compared to the histological pattern. After 12 months of follow-up, the distinction between biopsy-proven IPF and another idiopathic interstitial pneumonia, namely NSIP, provided no additional prognostic information, once serial pulmonary function trends had been taken into account (46, 47).

Cardiopulmonary exercise testing (CPET), especially V_{O2max}, integrates pulmonary function with cardiovascular and neuromuscular function (48) and has been shown to be significantly related to mortality in IPF. In a retrospective analysis of 117 IPF patients, V_{O2max} did not predict survival when examined as a continuous variable, but a threshold of 8.3 ml/min/kg was associated with an increased risk of mortality (49). The importance of reduced oxygen uptake as a predictor of prognosis also follows from the clinical radiographic and physiologic (CRP) score. A decrease in p_aO_2 during CPET is one of the constituents of the CRP score and contributes for 10.5% to this CRP score that estimates survival. The CRP score is derived from a cohort of 238 biopsy-proven IPF patients and integrates smoking status, clubbing, extent of radiographic profusion, pul-

monary hypertension, TLC (% pred) and p_aO_2 at maximal exercise (50).

The six minute walk test (6MWT) is relatively easy to perform: the patient is instructed to walk as fast and as far as possible in 6 minutes. Desaturation < 88% during the test has been shown to be a strong predictor of mortality. Biopsy-proven IPF patients who desaturate during a 6MWT had an increased risk of dying during a median follow-up time of 3 years (51, 52). Further, the 6 minute walk distance (6MWD) also showed to be highly predictive of mortality. Lederer et al. investigated waiting list mortality in IPF patients listed for transplantation. They found that a lower 6MWD was associated with increased mortality. A cut-off value of 207 m was used to identify patients at a high risk of mortality and showed to be a better predictor than the change in percent predicted FVC at 6 months (53).

The composite physiology index (CPI) is a score that consists of different pulmonary function tests (54). It combines the values of FVC, FEV_1 and DL_{CO} and as it includes FEV_1, the confounding effect of emphysema is hereby of minimal value. The CPI was derived in one group of 106 IPF patients by fitting pulmonary function tests against disease extent on HRCT and tested in a second group of 106 IPF patients. The CPI correlated more strongly with disease extent on HRCT and survival than individual pulmonary function variables. However, the score has to be calculated from other parameters, and is therefore not easy applicable in everyday clinical practice.

Imaging

HRCT

Flaherty and colleagues have evaluated the influence of HRCT appearance on survival in patients with idiopathic interstitial pneumonia (18). They divided HRCT scans from patients with histological UIP (n=73) or histological NSIP (n=23) into 5 categories: definite UIP, probable UIP, indeterminate, probable NSIP, or definite NSIP. Patients with an HRCT that was diagnosed as definite or probable UIP had a shorter survival than those with an indeterminate HRCT or definite or probable NSIP. Patients with histological UIP but without the corresponding HRCT diagnosis of probable or definite UIP showed a better survival than patients with the corresponding UIP pattern on HRCT. Thus, patients with a typical UIP pattern on HRCT scan have the highest risk of mortality. A subsequent study from Lynch et al. described 315 IPF patients, who were included in a randomized controlled study evaluating interferon (IFN) -γ (55). Lung function parameters and HRCT features were studied in relation to mortality. A higher extent of fibrosis on HRCT was found to be an independent predictor of mortality in the multivariate analysis. A recent study by Best and colleagues confirmed this finding (56). They included 167 IPF patients who underwent HRCT scanning at enrolment and in 95 cases also at 12 months follow-up. A greater extent of fibrosis at baseline as well as an increase of fibrosis during one year were both significant predictors of survival. Not only disease extent, but also disease pattern was identified as a predictor of prognosis. Akira and colleagues studied HRCT data of 58 IPF patients before and at the time of an acute exacerbation (57). New areas of parenchymal ground glass opacification that spread rapidly throughout the lung were pathologically correlated with diffuse alveolar damage (DAD). This diffuse pattern was associated with worse survival compared to patients with a multifocal and peripheral pattern.

Molecular imaging

On HRCT scan, one can not differentiate between established fibrosis or lesions that exist of actively proliferating fibroblasts. HRCT pictures give information on lung density, but can not visualize the actual activity of the fibrotic process, *i.e.* fibrogenesis. Imaging of fibrogenesis could be very useful in the prediction of disease progression in IPF and other fibrotic interstitial lung diseases. Molecular imaging techniques, using radio-labelled markers to detect disease activity are relatively novel and promising techniques in this respect. Umeda and colleagues have described the use of dual-time-point ^{18}F-FDG PET to asses disease progression in IIP patients (58). Fifty IIP patients (of whom 21 IPF, 18 NSIP and 11 COP) underwent one scan at 60 minutes and a second scan at 180 minutes after ^{18}F-FDG injection. The retention index (percent difference between the first and second scan) in IPF and NSIP

patients was significantly greater in patients who showed lung function deterioration after one year, compared to patients without deterioration. Further, ^{18}F-proline PET has been shown to be a reliable marker for fibrosis formation in animal studies. This technique was recently also tested in IPF patients, but the results showed only low uptake in the lungs. Therefore ^{18}F-proline PET does not seem to be a promising biomarker for the imaging of fibrogenesis in IPF, but better radioligands may appear on the horizon in the near future (59).

Another imaging technique to visualize fibroblast activity may be the ^{111}In-ocreotide-scintigraphy. Ocreotide is a somatostatin-analog with strong affinity for the somatostatin receptor subtype 2, and inhibits fibroblast activity. Lebtahi and colleagues evaluated the expression of somatostatin receptors in patients with IPF and pulmonary fibrosis associated with systemic sclerosis, and healthy controls (60). They found an increased uptake in both patient groups. Furthermore the degree of uptake correlated with deterioration of lung function parameters over time, and BALf cellularity.

Histology

The relevance of distinguishing UIP from other interstitial pneumonias was first pointed out by Bjoraker and colleagues (61). They reviewed the lung biopsy material of 104 patients with a diagnosis of IPF before the ATS/ERS consensus paper on the classification of IIPs in 2002, and related pathologic diagnosis to survival. Patients with a UIP pattern on lung biopsy had a median survival of 2.8 years, which was significantly worse than those with NSIP, DIP, BOOP and other interstitial pneumonias. In 2004, Monaghan and colleagues investigated 64 patients in whom multiple biopsies at different locations were performed that showed either a pattern of UIP or NSIP (62). Patients were categorized in three groups: concordant UIP-UIP (n = 25), discordant UIP-NSIP (n = 8) and concordant NSIP-NSIP (n = 31). Patients with discordant UIP-NSIP showed clinical behaviour similar to those with concordant UIP-UIP and should thus be regarded as having UIP, in the context of prognosis and therapeutic management.

A typical finding in the histopathology of UIP is a fibroblast focus. The presence of these aggregates of actively proliferating myofibroblasts indicates that fibrosis is actively ongoing rather than representing the residuum of a process that occurred in the past. King et al. studied 87 patients with UIP confirmed on lung biopsy (63). The extent and degree of histological features such as fibroblast foci, alveolar space cellularity and alveolar wall fibrosis were graded by independent pathologists and related to survival. The number of fibroblast foci present in a UIP biopsy predicted survival. Thus, the ongoing process of damage and aberrant epithelial repair is more important in the pathway to end-stage fibrosis than alveolitis. Moreover, the number of fibroblast foci correlated with the decline in FVC and DL_{CO} (64). Enomoto et al. confirmed this and added to these findings by using a more objective method to score the extent of fibroblast foci (65). Instead of counting fibroblast foci in a selected area by 2 or more independent pathologists, they used a camera and image analysis software. This quantitative scoring method was less observer-dependent and still showed a significant relation of the degree of fibroblast foci with survival. However, Hanak et al. were unable to find any association between the number of fibroblast foci and survival (66). In their study, patients with accelerating IPF were excluded in order to investigate if the number of fibroblast foci was informative in the stable IPF patient. Additionally, they randomly selected the areas to count the number of fibroblast foci, including areas with normal lung tissue or honeycombing.

Another histopathological feature in necroscopic lung tissue of IPF patients is diffuse alveolar damage (DAD). DAD may point to common preterminal events in the critically ill patients, such as shock, intravascular coagulation, sepsis or oxygen toxicity (67). Acute exacerbations of IPF may also be caused by DAD. Tiitto et al investigated whether the number of fibroblast foci was related to DAD at necroscopic lung samples (68). Although the amount of fibroblast foci was indeed increased in the subjects with worst survival, no relation could be demonstrated between fibroblast foci and DAD.

Pulmonary hypertension

The presence of pulmonary hypertension in IPF patients has important prognostic implications.

Nadrous and colleagues investigated 88 IPF patients who underwent transthoracic echocardiography. They found that the systolic pulmonary artery pressure (SPAP) inversely correlated with DL_{CO} and that patients with SPAP > 50 mm Hg had a significantly worse survival compared to patients with SPAP < 50 mm Hg (69). Song et al. added to these findings by including both echocardiography and brain natriuretic peptide (BNP) in their study (70). Using SPAP of 40 mm Hg as a threshold for pulmonary hypertension, patients with pulmonary hypertension had a significantly worse mean survival (10.8 months) compared to patients with SPAP < 40 mm Hg (23.7 months). Further, an elevated level of BNP appeared to be an independent predictor of prognosis on multivariate analysis. Recently, in a cohort of 110 IPF patients, the presence of emphysema, pulmonary hypertension and pulmonary function were evaluated in relation to mortality. Patients with emphysema showed higher mortality rates than patients without emphysema. Further, a Cox regression model showed that FVC < 50 % predicted and SPAP > 75 mm Hg (by echocardiography) were the most important predictors of mortality (71).

However, the golden standard for the measurement of pulmonary hypertension is right heart catheterization. Nathan et al. reported a cohort of 110 IPF who underwent both right heart catheterization and echocardiography (72). In only 40%, echocardiography accurately reflected the SPAP as measured by right heart catheterization. Pulmonary hypertension is common in IPF patients. Shorr et al investigated 2,525 IPF patients who were registered at the lung transplant registry for USA between 1995 and 2004 and had undergone right heart catheterization. Forty-six percent of these patients had a mean pulmonary artery pressure (mPAP) of > 25 mm Hg and 9 percent had severe pulmonary hypertension with a mPAP of > 40 mm Hg (73). Lettieri et al. found that pulmonary hypertension (mPAP > 25 mm Hg) was present in 31.6 % of their cohort of 79 IPF patients undergoing pretransplantation right heart catheterization. Patients with pulmonary hypertension appeared to have a lower $DL_{CO,}$ were more likely to require supplemental oxygen and had a poor 6MWT performance. One-year mortality rates in patients with pulmonary hypertension were significantly higher in patients with pulmonary hypertension (28%) compared to patients without pulmonary hypertension (5.5%) (74). Thus, pulmonary hypertension is common in advanced cases of IPF. These patients may warrant more aggressive management or early referral for lung transplantation.

Conclusions

This review focuses on prognostic factors for IPF that were found after the establishment of international criteria for a clinical diagnosis of this disease, and the reclassification of IIPs in 2002. As such, it summarizes the results of the studies that included patients with IPF according to the newest definition. The key findings are summarized in Table 1, and presented with cut-off values for different parameters. Although far from perfect, these parameters are currently the best tools to help the clinician to distinguish patients who show the rapidly progressive variant of IPF (pattern C, as mentioned in figure 1) from patients who show a slowly progressive clinical course (pattern A). Despite these useful prognostic determinants, it is still impossible to predict whether a patient will develop an acute exacerbation (pattern B).

Especially the research of biomarkers in serum is promising, and might lead to the identification of better markers for a prediction of survival in IPF in the near future. Serologic biomarkers are attractive because they are easily accessible, and may have the ability to reflect change of disease course more accurately than pulmonary function test or HRCT. Ideally, serum biomarkers could even detect disease progression before this becomes clinically apparent. This would be a valuable addition to current determinants of disease progression and prognosis in follow-up. The use of so-called pneumoproteins as prognostic indicators has already been the issue of several studies. A growing body of evidence supports the application of KL-6, SP-A and SP-D as predictors of mortality in IPF. The association between increased levels of pneumoproteins and mortality has now been independently confirmed by different investigators, which adds substantial validity. However, further prospective studies are needed before widespread acceptation will occur.

The identification of new biomarkers is important, and also techniques like microarrays and gene

Table 1. Summary of used determinants and cut-off levels to predict survival.

Determinant	Favourable	Unfavourable	Ref
Sex	Female	Male	(4, 11, 47)
BMI	> 30	< 25	(19)
Serum KL-6	< 1000 U/ml	> 1000 U/ml	(23)
Serum SP-A	<123 ng/ml	> 123 ng/ml	(15)
Serum CCL-18	< 150 ng/ml	> 150 ng/ml	(16)
Serum fibrocytes	< 5%	> 5%	(29)
BAL neutrophils	< 3%	> 3%	(39)
DL_{CO} (% pred)	> 35%	< 35%	(46)
Change dyspnea score (6 mo)	> 2 pt increase	> 2 pt decline	(44)
Change FVC (12 mo)	< 10%	> 10%	(14, 44, 45, 47)
Change A-a gradient (6 mo)	> 5 mm Hg decrease	> 5 mm Hg increase	(44)
V_{O2max}	> 8.3 ml/kg/min	< 8.3 ml/kg/min	(49)
6MWT (desaturation)	> 88%	< 88%	(51, 52)
6MWD (meters)	> 207	< 207	(53)
CPI	Low	High	(54)
Fibrosis score on HRCT	Low	High	(55, 56)
Alveolar opacity pattern on HRCT	Peripheral	Diffuse	(57)
^{18}F-FDG PET Retention index	< 0%	> 0%	(58)
Fibroblast foci score on biopsy	Low	High	(63-65)
Systolic PAP (echocardiography)	< 40 mm Hg < 50 mm Hg < 75 mm Hg	> 40 mm Hg > 50 mm Hg > 75 mm Hg	(70) (69) (71)
Mean PAP (right heart catheterization)	< 25 mm Hg	> 25 mm Hg	(74)

BMI: body mass index; KL-6: Krebs von den Lungen-6; SP: surfactant protein; CC-chemokine ligand 18; BAL: bronchoalveolar lavage; DL_{CO}: diffusion capacity for carbon monoxide; FVC: forced vital capacity; V_{O2max}: maximal O_2 uptake; 6-MWT: 6-minute walking test; 6MWD: 6-minute walking distance; CPI: composite physiology index; HRCT: high-resolution computed tomography; PAP: pulmonary artery pressure

expression profiling may become more and more important. Selman et al. compared gene expression profiles in lung samples from 4 IPF patients with rapid progression and 4 patients with slow progression (75). Rapidly progressing IPF patients strongly expressed genes involved in morphogenesis, cancer, oxidative stress, apoptosis, cell proliferation and genes from fibroblasts and smooth muscle cells. Around 30% of the differentially expressed genes were downregulated in the rapid progressor lungs, including genes related to signal transducer activity, and epithelial receptors. This kind of innovative research is necessary to shed a new light on biomarkers for disease progression and outcome.

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Online Appendix

Table 2. Summary of studies concerning prognostic determinants in IPF, performed after the 2002 consensus statement on IIPs

	Year	Outcome	N	N_{UIP} design	Follow-up time	Ref
Serum	2006	High KL-6 levels predict shorter survival	27	16 retro	36 mo	(23)
	2009	SP-A is a stronger predictor of mortality than SP-D	82	82 retro	Median 36 mo	(15)
	2009	Higher mortality in patients with high CCL18	72	20 pro	24 mo	(16)
	2009	Circulating fibrocyte numbers predict early mortality	51	17 retro	24 mo	(29)
BAL	2003	No prognostic value of BAL findings	35	35 retro	Median 38 mo	(40)
	2007	Lymphocytosis is associated with better survival	87	87 retro	Median 21 mo	(17)
	2008	Increased BAL neutrophil percentage predicts early mortality	156	156 retro	Median 30 mo	(39)
PFT	2003	12-month changes in dyspnea score, TLC, FVC, p_aO_2, s_aO_2 and A-a gradient were predictive of survival time	81	81 pro	6 mo (n= 81) 12 mo (n = 51)	(44)
	2003	6-month change in FVC predicts mortality	80	80 retro	Median 58 mo	(45)
	2003	Changes in DL_{CO}, CPI, FVC, FEV_1 were more predictive than histological diagnosis	61 (IPF) 43 (NSIP)	61 retro	Median 32 mo	(46)
	2003	Desaturation during 6-MWT was associated with increased mortality	83	83 retro	Median 35 mo	(51)
	2003	CPI is strongly linked to mortality	212	36 retro	Median 28 mo	(54)
	2005	6-month changes in FVC, DL_{CO} and sex were independent prognostic factors	131 (IPF) 48 (NSIP)	131 retro	Median 24 mo	(47)
	2006	Lower 6MWD was associated with an increased mortality	454	NM retro	Median 4 mo	(53)
	2006	Predictive ability of serial changes in PFT varied when patients were stratified by the presence of desaturation < 88%	197	146 retro	NM	(52)
	2009	Patients with baseline maximal oxygen uptake less than 8.3 ml/kg/min had an increased risk of death	117	75 retro	NM	(40)
Imaging	2003	A typical UIP pattern on HRCT predicts high mortality	73 (UIP) 23 (NSIP)	73 retro	Median 37 mo	(18)
	2005	Extent of reticulation and honeycombing is an independent predictor of mortality	315	205 pro	14 mo	(55)
	2008	Disease extent on HRCT predicts mortality and serial imaging can show disease progression	167	NM retro	Median 18 mo	(56)
	2008	Greater disease extent and diffuse opacification pattern on HRCT predict worse survival 58	29	retro	Median 35 mo	(57)
	2009	Dual point ^{18}F-FDG PET predicts deterioration of lung function parameters after 1 year of follow-up 21	9	pro	12 mo	(58)
Histology	2002	Increased numbers of FF were linked to mortality	53	53 retro	Median 24 mo	(64)
	2004	Discordant UIP and NSIP on multiple biopsies should be considered as	UIP 25 8 (UIP & NSIP) 31 (NSIP)	retro	60 mo	(62)
	2006	Quantitative scoring of FF accurately predicts mortality	16	16 retro	NM	(65)
	2006	The number of FF is associated with poor survival but not with DAD. FF can not predict acute exacerbation	64	64 retro	NM	(68)
	2008	A higher number of FF is not associated with survival	43	43 retro	Median 19 mo	(66)
Pulmonary Hypertension	2005	Survival in patients with systolic PAP of > 50 mm Hg (echocardiography) was significantly worse.	88	17 retro	36 mo	(69)
	2006	Mortality rates were higher in patients with mean PAP > 25 mm Hg (right heart catheterization)	79	79 retro	NM	(74)
	2009	Both increased BNP and systolic PAP of > 40 mm Hg (echocardiography) are predictive of poor survival	131	69 retro	Median 10 mo	(70)
	2009	Emphysema, FVC < 50 % and SPAP > 75 mm Hg (echocardiography) were associated with increased mortality.	110	42 retro	NM	(71)

N: number of patients; N_{UIP}: Number of patients with biopsy-proven usual interstitial pneumonia; KL-6: Krebs von den Lungen-6; retro: retrospective; mo: months; SP: surfactant protein; CCL18: CC-chemokine ligand 18; pro: prospective; BAL: bronchoalveolar lavage; PFT: pulmonary function tests; TLC: total lung capacity; FVC: forced vital capacity; p_aO_2: partial pressure of oxygen; s_aO_2: oxygen saturation; IPF: idiopathic pulmonary fibrosis; NSIP: non-specific interstitial pneumonia; 6-MWT: 6-minute walking test; CPI: composite physiology index; DL_{CO}: diffusion capacity for carbon monoxide; 6MWD: 6-minute walking distance; NM: not mentioned; HRCT: high-resolution computed tomography; FF: fibroblast foci; DAD: diffuse alveolar damage; PAP: pulmonary artery pressure; BNP: brain natriuretic peptide