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IPF: New insight in diagnosis and prognosis

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Summary
Idiopathic pulmonary fibrosis (IPF) is a progressive parenchymal lung disease of unknown etiology and poor prognosis; effective therapy has remained elusive and the pathogenesis enigmatic. It has become clearer that a marked heterogeneity in disease progression exists in IPF patients. The factors affecting the prognosis of patients with IPF are poorly understood. Poor prognosis has been associated with older age, male gender, lower FVC, lower diffusing capacity of the lung for carbon monoxide (DLCO), desaturation during exercise, and the extent of fibrosis seen on imaging studies. Data from placebo-controlled trials have demonstrated that deterioration in the conditions of IPF patients over time may not be linear. These data have highlighted the concept and importance of acute exacerbations. Rapid respiratory decompensation may be more important than previously appreciated. The development of pulmonary arterial hypertension (PAH) in patients with pulmonary fibrosis is well recognized. The six-minute-walk test has emerged as an important addition to prognostic evaluation, with significant oxygen desaturation identifying a subgroup of patients with a much higher mortality. It is not yet known whether this observation denotes incipient pulmonary hypertension, itself a malignant prognostic determinant. It appears that the six-minute-walk test might have particular utility as a basis for prioritizing lung transplantation.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease associated with a poor prognosis and a median survival of 2.5 to 5 years from the time of diagnosis.[1,2] There is no effective treatment and many patients, if eligible, are referred for lung transplantation. IPF appears to be substantially more prevalent than previously reported; it is not clear whether these findings primarily represent changes in clinician diagnostic thresholds or whether there has been a real increase in disease prevalence. However, this uncertainty should not obscure the fact that IPF appears to be approximately as prevalent as a number of the more common malignancies, all of which attract a much larger share of community and research resources.[3] Although IPF is likely to be more common than previously thought, with an estimated prevalence ranging from 14 to 43 per 100,000 persons in the United States,[4] it still is a rare disease. However, rare does not mean unimportant.

The diagnosis is confirmed by the identification of usual interstitial pneumonia (UIP) either by surgical lung biopsy

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(SLB) or through integrated clinical evaluation including high-resolution CT (HRCT).[1,5] While ongoing research continues to investigate multiple hypotheses of UIP pathogenesis, neither the natural history nor the pathogenesis of UIP is currently well understood. The traditional view of IPF progression holds that a slow and steady decline in respiratory function ultimately leads to respiratory failure and death. Emerging evidence, however, has suggested that multiple injuries, or *hits*, to the lung occur over a period of time, and these hits lead to acute exacerbations that result in periods of more rapid decline in lung function, which can ultimately result in death.[6–8] The disease course in IPF is variable, with many patients remaining stable for long periods of time while a significant proportion experience exacerbations leading to respiratory failure and death.[7] This variability leads to a need for the early and accurate diagnosis and early referral for lung transplantation.[9] The unpredictable nature of UIP/IPF highlights the importance of identifying factors that can help refine the prognosis for patients at the time of initial diagnosis. Identification of surrogate short-term measures of mortality is critical to the management and study of patients with IPF. Several factors have been identified that predict poor survival in patients with IPF, including age, sex, smoking history, diffusion capacity for carbon monoxide (DLCO), FVC, degree of fibrosis on HRCT of the chest, and number of fibroblastic foci on histopathology.[10–14] To date, the tools available to predict prognosis have been imprecise and have complicated clinical decision making regarding the use of potentially toxic therapies and the timing of referral for lung transplantation.

Histopathologic pattern and survival

The ATS/ERS consensus panel revised the classification schema and emphasised the importance of an integrated clinical, radiological and pathological approach to the diagnosis of idiopathic interstitial pneumonia (IIP). In addition, they concluded that the IIPs comprised a number of clinical-pathological entities which were sufficiently different from one another to be designated as separate diseases.[1] The published IIP classification is by no means the final word but rather the basis for future refinement of definition.[15]

The examination of SLB specimens allows identification of histopathological subsets of IIP with different prognoses.[1,16,17] Of these disorders, the two entities that have provoked most discussion and debate are IPF (as currently defined with a UIP pattern of pathology) and non-specific interstitial pneumonia (NSIP).[15] UIP is the most common pattern of IIP, being seen in 47 to 62% of recent series compared with 14 to 36% for NSIP.[1,18–20] Previous studies have identified the histopathologic pattern as the most important baseline factor in determining prognosis.[19,21–24] However, the disease course for individual patients with either UIP or NSIP can vary greatly and the relationship of NSIP to IPF remains harder to integrate.[18,19,21] NSIP is often difficult to distinguish from UIP in the setting of IPF.[18,19,21,23,25,26] Growing data suggested this is not simply an academic or semantic argument, because UIP/IPF is shown to carry a far worse prognosis than idiopathic NSIP in studies where this distinction is attempted.[18,19,22,23] Consequently, this differentiation carried important clinical implications regarding patient outcome and choice of therapy. As the name implies, there are many ''nonspecific'' features from a clinical, radiologic, and pathologic view in NSIP. In particular, the histopathologic pattern of NSIP could be found in a wide variety of clinical contexts, including diseases of known cause (e.g., hypersensitivity pneumonitis) as well as in the setting of an IIP.[27] Thus, it has been argued that when a histopathologic diagnosis of NSIP has been made, the work of the clinician has only just begun.[28] An HRCT showing a typical pattern of UIP (in particular, honeycomb changes) leads to a diagnosis of IPF, even when a SLB shows histologic features of NSIP.[22,29] The histologic findings of NSIP and UIP are frequently noted in multiple lobes (and even in the same lobe) of patients undergoing SLB.[22,29,30] Most importantly, the presence of UIP in any lobe from a patient with IIP is associated with impaired survival.[22,29] The diagnosis of idiopathic NSIP requires a dynamic integrated approach with input from clinicians, radiologists, and pathologists. The survival of patients with idiopathic NSIP is very good; however, additional studies are required to define the proper approach to treatment and long-term follow-up. If disease is well advanced, the outcome appears to be no different between UIP and NSIP. In this regard, Latsi et al.[14] showed that if the DLCO was $<35\%$ predicted, there was a similarity in survival between these two populations. The role of SLB needs to be considered critically in the context of functionally severe disease, in with fibrosis appears to be established; in this case biopsy evaluation provided no prognostically useful information.

A high profusion of fibroblastic foci in UIP has been associated with higher mortality in patients with IPF in several reports.[10,31–33] Until recently, fibroblastic foci were considered to be discrete sites of lung injury or repair (Fig. 1). However, on the basis of morphometric analysis with three-dimensional reconstruction, fibroblastic foci appear to be highly interconnected and may represent the edge of a complex reticulum extending from the pleura into the underlying parenchyma.[34] However, a potential sources of bias of these studies is that the current pathologic criteria for diagnosis of UIP requires presence of

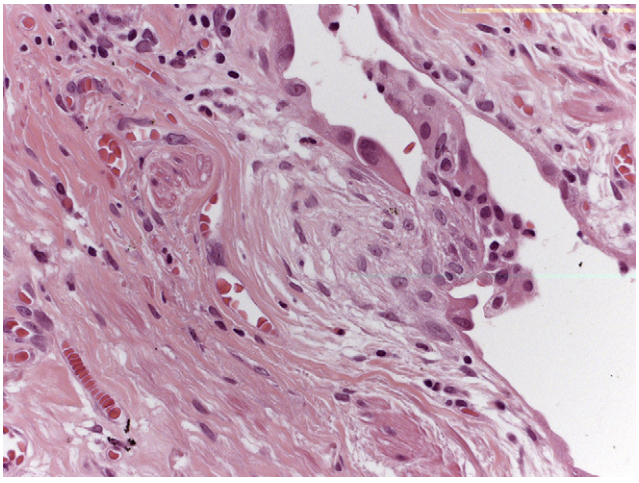

Figure 1 The frequency of fibroblastic foci in lung biopsy from IPF patients correlates with poor prognosis.

heterogeneity in lung, including inflammation and mature fibrosis, as well as fibroblastic foci interspersed with areas of completely normal lung. Biopsy specimens cannot represent the extent of fibroblastic activity of the entire lungs, as it is unclear what part of the lung is represented by the biopsy. Thus, one cannot make prognostic implications based on biopsy samples. It seems that although SLB is required for the diagnosis in atypical IPF cases, it cannot be accurate for comparison of disease activity in different patients due to heterogeneous nature of pathology.[24,35]

The value of HRCT in defining prognosis in IPF

When assessed by expert clinicians and radiologists, the presence of typical clinical and HRCT features is sufficient to allow a confident diagnosis of IPF in more than 50% of suspected cases and may eliminate the need for SLB in these patients.[5,36,37] Thus, HRCT has become an integral part of evaluation of patients with IIP.[1,38]

The characteristic HRCT findings of UIP include the following: honeycombing, reticular opacities, ground-glass attenuation, and both basal and peripheral predominance, which is often associated with traction bronchiectasis and architectural distortion.[39–41] One of the key findings that suggests the diagnosis of UIP on HRCT imaging is the presence of honeycomb cysts in a basilar sub-pleural distribution. Honeycomb changes appear on the HRCT scan as variably-sized cystic spaces that share walls and frequently stack upon one another in several layers (Fig. 2). The presence of centrilobular emphysema can sometimes make the diagnosis of honeycombing more difficult.[38]

It has been reported that initial HRCT findings have prognostic significance in IPF, in that the patients with an atypical pattern for IPF on HRCT had better prognosis than those with typical HRCT pattern for IPF.[42–44] One of the most striking findings of a recent study is the variable HRCT appearance of UIP despite very rigid histopathologic criteria. Interestingly, only approximately one-third of HRCTs showed definite IPF and approximately one-third suggested an alternative diagnosis, such as NSIP, or were unclassifiable[45,46] (Fig. 3). Another study found a high prevalence of histopathologic UIP in patients with an HRCT appearance of indeterminate or NSIP.[42]

HRCT appearance and quantification of features, particularly fibrosis, can be useful to stratify the risk of subsequent mortality for patients with IPF/UIP. The extent and pattern of fibrosis on HRCT scans carry prognostic implications. For example, a multivariate analysis of a large multicenter trial[47] suggested that a higher extent of fibrosis on HRCT scans was an independent predictor of mortality. When using a visual scoring method, IPF exhibits a progressive deterioration both in the extent of disease seen on HRCT scans and in lung function impairment over time, although the changes were subtle and evolved gradually. In clinical practice, the HRCT scan visual score of disease extent can be used in association with function tests to monitor IPF evolution, and to evaluate prognosis and therapy.[9] On the other hand, when compared to physiologic measures, longitudinal changes in HRCT scans during short-term follow-up are less predictive of survival during intermediate follow-up.[12] Use of computerized methods to quantify the amount of fibrosis and ground glass infiltrate[48,49] may be more sensitive to serial changes in HRCT findings but require additional study. Additional studies are required to better define the role of serial HRCT in the follow-up of patients with UIP.

Pulmonary function test (PFT)s: implication for survival

Most published studies in predicting survival time in patients with IPF have looked at the predictive value of baseline variables.[10,11,50–54] A number of baseline predictors of survival in IPF have been proposed; however, there has been little consistency across studies. A retrospective study analyzed mortality according to baseline functional parameters among 168 IPF patients in the placebo arm of a randomized phase III clinical trial. In this analysis, a low

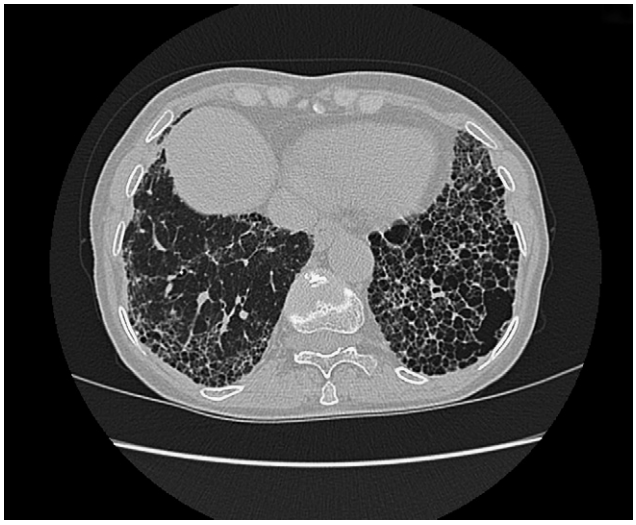

Figure 2 HRCT demonstrates bilateral honeycomb cysts. The honeycombing is more extensive on the left side. A sub-pleural predominance of the honeycomb cysts is particularly evident on the right side.

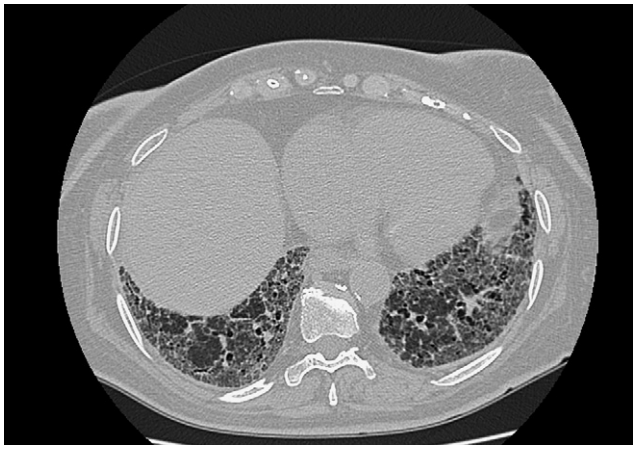

Figure 3 HRCT shows ground-glass opacities, mild reticulation, and marked traction bronchiectasis in a case of NSIP. It should be noted that there is considerable overlap between the HRCT findings seen in NSIP and those present in other interstitial pneumonias.

baseline DLCO appeared to correlate with an elevated risk of death, but the % predicted FVC did not.[55] In another studies, patients with DLCO of less than 35% predicted had a bed prognosis, linked to the severity of pulmonary disfunction (and the severity of pulmonary disease) and not to the histopathologic pattern/diagnosis (UIP or NSIP).[14,56] On the basis of these results one group has proposed a simple stratification system characterizing patients with IPF and patients with NSIP as having advanced disease if the baseline DLCO is less than 39% predicted and limited if the DLCO is greater than 40% predicted.[57,58]

In practice, clinicians generally refine prognostic impressions (and sometimes revisit histologic diagnoses) in individual cases according to longitudinal behavior. Disease progression has historically been monitored through clinical status and lung function tests, although with the advent of HRCT, there is potential for further refinement, with the serial imaging findings providing data relating to disease progression.[59] PFT, as a non-invasive quantitative measurement, is the cornerstone of current practice in the assessment of the disease severity and progression. However, pulmonary function evaluation at presentation is disappointingly imprecise, prognostically[53,60]; the prognostic value of pulmonary function trends over time may prove more useful.[13,14] Furthermore, lung function trends are especially useful when they show unequivocal change (decline or clear-cut stability). However, a large subset of patients exhibits marginal deterioration, with may represent either true decline or the "noise" of measurement. Longitudinal changes in FVC or DLCO have been found to have important prognostic value. A decrease in FVC of at least 10% or DLCO of at least 15% over 6 or 12 months is associated with decreased survival.[12–14,56] FVC is a better predictor than DLCO, which is less reproducible. Although change in FVC is a good surrogate for subsequent mortality, it is imperfect as some patients die without a 10% decline in FVC, whereas others can live for prolonged periods even after a 10% decline in FVC.[7,8,55] Although a lower rate of decrease in lung function does not necessarily translate into longer survival, changes in FVC have been shown to be predictive of survival in at least one large trial.[55] Because serial resting PFTs are the only outcome measures shown to be linked to mortality in IPF, they are increasingly preferred as primary endpoints, with FVC chosen in recent IPF studies.[61–64] However, a number of issues remain to be clarified. The optimal time interval for repetition of PFT in treatment trials has not been established as, in the above studies of pulmonary function trends against mortality, no shorter time interval than 6 months was used to define pulmonary function trends. In most studies, PFTs were repeated every 3–4 months. It is not clear whether PFT trends should be analysed as continuous data (with sub-group comparisons made using t-testing or non-parametric ranked analyses). This approach is usual in treatment studies but an alternative approach is to examine the prevalence of 'significant' decline (categorical analysis). Continuous analysis presupposes that disease progression is likely to be broadly unimodal, whereas categorical analysis, which may be more suited to bimodal patterns of progression, lends itself to 'time to decline' analyses, such as progression-free survival.[65]

Clinical (dyspnea scale), radiographic features (chest radiograph), and weighted pulmonary function parameters including exercise testing have been combined to generate a clinical/radiographic/physiologic score (CRP).[66] The correlation of CRP score and histologic severity is good, although clinical validation and use of this staging technique is limited.[66,67] This CRP scoring system was recommended as a quantitative tool for the serial assessment of clinical impairment in patients with IPF.[66,67] A new CRP score was generated to determine whether the risk of death caused by respiratory failure could be predicted based on clinical, radiologic, and physiologic parameters obtained during initial evaluation.[50] This model is an accurate predictor of survival time in IPF but requires radiographic analysis and exercise physiologic measurements not readily available to many physicians: this may limit its practical utility as a predictor of survival time.[50]

Exercise tests: implication for survival

Patients with IPF have impaired ventilatory and cardiovascular responses to exercise[68] due to multiple abnormalities, including low tidal volume, a failure to decrease ventilator dead space, a rapid, shallow breathing pattern, impaired gas exchange due to interstitial fibrosis, pulmonary hypertension, ventilation/perfusion mismatching and low mixed venous O2. Gas exchange worsens with exercise in IPF.[17,69] Several studies have examined this feature using either cardiopulmonary exercise tests (CPET) or the 6-minute-walk test (6MWT). A decrease in PaO2 during CPET in patients with IPF contributes up to 10.5% of the total CRP score[50] used to estimate prognosis in IPF. Desaturation during CPET has been shown to predict mortality in some[69] but not all[52,60] studies. It is now known that in IPF, maximal exercise data and especially the degree of oxygen desaturation are very poorly reproducible, as judged by major inter-test variation at an interval of 1 week,[70] and this makes the definition of significant change highly problematic. VO2max is an integrated measure of cardiovascular, respiratory, and neuromuscular function.[71] In prior studies of patients with interstitial lung disease, VO2max correlated poorly with measures of lung volume, suggesting that it more accurately reflects derangements in hemodynamics as well as ventilation during exercise.[68] VO2max examined as a continuous variable does not predict mortality in IPF. However, baseline threshold VO2max of 8.3 ml/kg/min predicts mortality patients with IPF. This threshold is a robust predictor of survival when compared with desaturation less than 88% during a 6MWT and resting PaO2. Demographic and pulmonary function data can be used to estimate whether VO2max is above or below the 8.3 ml/kg/min threshold.[72] However, not all studies show that CPET measurements of gas exchange predict survival.[52,60] Several authors have examined the prognostic value of the 6MWT or other walk tests in IPF. The 6MWT has emerged as an important addition to prognostic evaluation, with significant oxygen desaturation identifying a subgroup of patients with a much higher mortality.[73,74] Desaturation during 6MWT,[73,74] distance walked,[75,76] and progressive impairment in longitudinal 6MWTs[77] have been found to predict mortality in IPF. In a study of patients listed for transplantation, a walk distance of less than 207 m was associated with a fourfold increase in mortality and was

more prognostically accurate than FVC levels.[75] In our recent study,[76] we demonstrated that distance walked during 6MWT was significantly correlated with pulmonary functional parameters (DLCO, VC, FVC). We also demonstrated that distance walked in 6 min was independently related to mortality in IPF and patients walking less than 212 m had a significantly lower survival rate than those walking farther as assessed by Kaplan-Meier survival curves; 212 m in our study group identified a cut-off distance with a bad prognosis and the use of a change in meters walked as a continuous variable confirms the ability of distance walked to predict a less favorable outcome. Thus, our data confirm recent observation that distance walked during 6-MWT may serve as prognostic indicator in IPF, which may complement other prognostic markers.

The simplicity of the 6MWT and its probable ability to assess complex physiologic interactions and predict prognosis make the 6MWT an important tool for the management of patients with IPF. One criticism of the 6MWT is that it is a patient-driven, symptom and effort-limited test. This may explain the controversy in the literature about whether distance walked or desaturation is a better predictor of mortality.

Specific clinical situations affecting prognosis

Acute exacerbations of IPF

A growing body of evidence suggests that IPF evolves with different clinical phenotypes. IPF usually presents insidiously with symptoms and signs of progressive respiratory insufficiency that slowly progress over a period of months to years. The natural history is invariably one of gradual and progressive deterioration, with median length of survival from the time of diagnosis ranging from 2 to 3 years.[1,17,21] Although chronic in nature, an accelerated phase may occur at any stage in the history of the disease without identifiable cause, leading to death in a period of a few weeks to a few months.[8,78] These episodes are called ''acute exacerbations'' of IPF. Acute exacerbations of IPF are increasingly recognized as common and highly morbid clinical events.[7,79,80] A 2-year frequency of acute exacerbations of approximately 10% has now been reported in a cohort of 147 patients with IPF,[81] underlining the need for a reappraisal of the risk factors and management of this often-lethal disorder. The following criteria have generally been included in most studies[9,82] for the definition of acute exacerbation: (1) acute worsening of dyspnea within 1 month of presentation; (2) new pulmonary infiltrates seen on CXRs or CT scans; (3) deterioration in pulmonary function measurements or gas exchange; and (4) absence of an identifiable cause, including infections or cardiovascular disease. The histologic findings from lung biopsy specimens show variable aspects; the typical UIP pattern is associated with signs of acute lesions, such as diffuse alveolar damage (DAD) with or without hyaline membranes, numerous fibroblastic foci, organizing pneumonia (OP), and hemorrhage with capillaritis.[82–84] Churg and colleagues[85] described that three microscopic patterns of acute lung injury were seen in acute exacerbation of UIP—DAD, OP, and a pattern of numerous very large fibroblastic foci superimposed on underlying fibrosis—and that patients with OP or extensive fibroblastic foci as the acute pattern seem to do better than those with DAD. Martinez and colleagues retrospectively analyzed the course of 168 patients with IPF.[7] Mortality rates may be as high as 60 to 70% over 3 to 6 months.[86]

Acute exacerbation may repeat in some patients with UIP. In addition, acute exacerbation may be the presenting manifestation in some patients with UIP.[82,87] An accelerated variant of UIP in two previously healthy patients with no known interstitial lung disease is reported.[88] The accelerated variant of UIP is associated with evidence of peripheral ground-glass opacities and consolidation. Subpleural reticulation or honeycombing is not been demonstrable on the initial CT examination. Traction bronchiectasis and cysts were not seen on CT in the two patients until 37 days after presentation. Pathological findings in these two cases were consistent with a diagnosis of UIP.[88] Accelerating variant of UIP had no a chronic course of follow-up and no reticular or honeycomb pattern consistent with IPF on the initial chest HRCT scans, but might have subclinical UIP. Accelerating variant of UIP may be an acute exacerbation in patients with subclinical UIP. Acute exacerbations of IPF have become increasingly important as a target for therapy. For example, one clinical study[79] comparing pirfenidone with placebo was prematurely terminated by the Data Safety Monitoring Board when a higher number of acute exacerbations was noted in the placebo group (placebo group, 5 of 35 patients; pirfenidone group, 0 of 35 patients). Kubo et al.,[80] in studying the utility of anticoagulation as a possible treatment for IPF, noted that the major cause of clinical deterioration was acute exacerbation. In a study of cyclosporine- treated patients vs those treated without cyclosporine, Homma et al.[89] suggested a better prognosis with regard to the acute exacerbation of IPF in the cyclosporine-treated group. These studies indicate that acute exacerbations may be a potential therapeutic target in IPF. Confirmation of these potential therapeutic effects in larger, longer term studies are necessary.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a common accompaniment of IPF, may contribute substantially to morbidity and mortality in IPF[90,91] and has a significant impact on outcomes.[90,92] A possible explanation for the development of PAH is that of progressive fibrosis resulting in destruction of the pulmonary vasculature. If the PAH of IPF is due to progressive fibrosis, then one might expect to see a relationship between measures of fibrosis and the prevalence and severity of PAH. Any authors hypothesized that progressive fibrosis is mostly responsible for the PAH of IPF and assessed the relationship between physiologic measures of fibrosis and PAH. Contrary to initial hypothesis, the authors failed to demonstrate any such correlations. Pathologic vascular findings in IPF consist of changes in the arteries, arterioles, and venules, and destruction of the capillary bed, which are traditionally attributed to hypoxia and fibrosis, respectively. Advential thickening around the pulmonary vessels occurs due to an increase of fibroblasts,

myofibroblasts, and extracellular matrix deposition. Smooth muscle cell hypertrophy and proliferation and collagen and elastin accumulation occur in the media of the small muscular pulmonary arteries, and distal pulmonary arterioles become muscularized. These changes are consistent with those seen in other hypoxia-related lung diseases.[93] PAH is often observed in the clinical course of IPF patients with advanced disease. Lettieri et al.[90] reported a prevalence of 31.6% among IPF patients who underwent the evaluation while waiting for lung transplantation. In this study, there was a significant difference in survival between those with and without PAH ($p < 0.001$). For example, the 1-year mortality rates were 28% and 5.5%, respectively, for those with and without PAH. Despite the documented associations between PAH and the risk of death, the presence of PAH did not adequately discriminate between patients with high and low short term mortality, providing sensitivity and specificity estimates of <80%.[75,90,94] In estimations of PAP by Nadrous et al.[92] using the ultrasonic cardiography method, systolic PAP was >50 mm Hg in 30.7% of patients. In patients with IPF, especially those with more advanced disease, evaluating for the presence of PAH may be useful in determining prognosis and may have a role in monitoring the disease course, triaging for lung transplantation, and deciding on potential therapies. Surrogate markers, such as a reduced DLCO, the need for supplemental oxygen, or a poor performance on the 6MWT, should raise suspicion for the presence of PAH and the need for confirmatory right heart catheterization.[90]

Other predictors under investigation

An area of debate is the utility of bronchoalveolar lavage (BAL) for diagnosis and/or prognostication in IPF. Although the pattern of cells recovered with BAL may narrow the differential diagnosis of interstitial pneumonias, its role in IPF remains controversial.[17] The differential cell count from samples of BAL fluid has been used with limited success to monitor the progression of IPF and to predict the disease prognosis. The presence of BAL lymphocytosis was shown to shift diagnostic probabilities from IPF to hypersensitivity pneumonitis or sarcoidosis. In patients with IPF, as then diagnosed, BAL lymphocytosis denoted a better outcome from treatment.[95] Current noninvasive diagnostic criteria for IPF include the absence of a significant BAL lymphocytosis in the setting of clinical and HRCT findings typical of IPF.[1,17] Although clinical-radiologic-pathologic evaluation is considered to be the "gold standard" for the diagnosis of IIPs, there are certain limitations for the performance of a SLB in elderly patients with IPF, including severely impaired pulmonary function, the risk of acute exacerbation, and potential significant comorbidities. In clinical practice, less than 30% of patients are estimated to have had SLBs.[96] In addition, previous studies have demonstrated interlobar variability and/or interobserver variation, suggesting that the pathologic evaluation alone may result in an incorrect diagnosis.[22,29,42] A previous study have demonstrated that granulocytosis or neutrophilia in BAL is an important diagnostic and prognostic factor in IPF.[97] In this large, well-defined IPF population with long-term follow-up it was showed that baseline BAL fluid neutrophil percentage was a strong predictor of 1-year mortality.[97] To date, studies[53,98,99] evaluating the association of BAL fluid cellular constituents and mortality have yielded conflicting results about the prognostic value of BAL.

Surfactant protein (SP) A and SP-D are members of the collectin family. Secreted primarily by alveolar epithelial type II pneumocytes, plasma SP-A and SP-D levels appear to increase early after breakdown in the alveolar epithelium.[100,101] SP-A has been shown[102,103] to be present in abnormal amounts in the BAL fluid of patients with IPF. A recent study examined the association of serum SP-A and SP-D levels with survival in a relatively large and well-characterized cohort of patients with biopsy-proven IPF through long-term and comprehensive follow-up.[104] This study demonstrated that serum SP-A levels obtained at the time of initial diagnosis among patients with IPF is independently and strongly associated with death or lung transplant within 1 year after presentation.[104] The authors believe that the most likely explanation for the association between serum SP-A levels and mortality in patients with IPF is that serum SP-A levels may be a more sensitive indicator of the extent of lung involvement than any of the conventional functional parameters, such as DLCO or FVC. Some advantages of using this measurement as a prognostic indicator include the ease in obtaining blood samples compared to other more invasive or more expensive measures, the reproducibility and limited interobserver variability of the test, and the relative strength of its association with mortality compared to other conventional measures. Increased serum SP-A concentrations may identify a subset of patients with more "active" disease that increases the risk of death in the following year and was not predicted by other baseline, noninvasive clinical predictors, such as lung function test results.[104]

Conclusions

The non-invasive diagnosis of IIP is sometime uncertain but histologic evaluation is an imperfect gold-standard. In some cases, the biopsy specimen may not be representative of the entire lung. In other cases, there may be differences in interpretation of the histologic findings. In particular, the histologic distinction between fibrotic NSIP and UIP is difficult and is subject to substantial interobserver variation. A previous study showed that the kappa coefficient of agreement between two experienced pathologists for distinguishing UIP from fibrotic NSIP was only 0.26.[19] Pulmonary pathologists are still working to reach consensus on how to draw a distinction between fibrotic NSIP and UIP. In borderline cases, HRCT images may help by showing features more typical of one or the other disease.

IPF remains a devastating parenchymal lung disease, prognosis is poor and death generally occurring as result of slowly progressive respiratory failure.[1,21] More recently, it has been recognized[17,21,53] that some patients without end-stage fibrosis have an acute exacerbation of IPF involving a rapid progression of disease, rendering the clinical course of an individual patient unpredictable.[105] Individual disease course is variable; periods of relative stability are common but acute exacerbation may cause abrupt worsening of symptoms. While clinical predictors are useful in describing

the natural history of IPF, disease progression in individuals remains difficult to predict. Several predictors of survival have been identified that assist in prognosis but nearly half of the deaths in a large prospective randomized trial occurred prior to evidence of disease progression.[61] Staging of disease is controversial. Baseline parameters that are predictive of clinical outcome include dyspnea, DLCO, desaturation on the 6MWT, pulmonary arterial pressure, HRCT pattern (key feature is honeycomb), and pathologic diagnosis of UIP. Dynamic prognostic indicators include dyspnea, FVC, and DLCO. Short-term trends in DLCO or FVC are the most accurate determinants of survival in fibrotic IIP, with FVC trends sometimes easier to interpret, because of lower variability. Serial change in FVC, defined as percentage change from baseline, is the most widely accepted primary end-point for therapeutic studies in pulmonary fibrosis, based upon prognostic evaluation in IPF. It is important to remember that no predictor of survival can ever reliably predict an individual patient's prognosis. Due to the great variability in the natural history of the disease, close monitoring of the patients may be necessary to evaluate the individual course of each patient.

Conflict of interest statement

The authors have no conflict of interest to declare.

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