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# Predictors of mortality of idiopathic pulmonary fibrosis

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**Abstract. – Idiopathic pulmonary fibrosis (IPF), a disease with histological features corresponding to usual interstitial pneumonia (UIP), is a disorder of unknown cause. Not only it is the most common subtype of idiopathic interstitial pneumonias but it is also associated with the highest mortality rate. Despite a good number of studies investigating the mortality of-patients with UIP the prognostic factors that have been studied have several limitations. To date it is unclear when in the course of the disease and with what modality these patients should be treated. According to the literature we subcategorized predictors of mortality into (a) baseline predictors; (b) dynamic predictors. IPF perspectives in therapy have been also analyzed. Moreover, the principal aims of this review were: (1) to analyze and to clarify the clinical utility of different prognostic factors for IPF; (2) to enable clinicians to better evaluate the eligibility criteria for lung transplantation in the clinical practice.**

*Key Words:*

Idiopathic pulmonary fibrosis, Survival, Mortality, Prognostic factors, Outcome.

## Introduction

Idiopathic pulmonary fibrosis (IPF), which has histological features corresponding to usual interstitial pneumonia (UIP), is a disorder of unknown cause. This disease is the most common among different subtypes of idiopathic interstitial pneumonia (IIP), and is associated with the highest mortality rate. Current therapies have little effect on IPF[1]. In the UK, i.e. patients with IPF have a poor prognosis with a median survival rate from diagnosis of 3-5 years, and an average loss of 7 years of life expectancy[2].

Studies on mortality in-patients with UIP and non-specific interstitial pneumonia (NSIP) have addressed a variety of possible prognostic factors. All these studies were limited because retrospective and with a short median observation time (Jegal et al. = 23, 7 months)[3].

The histopathologic pattern remains the most important prognostic factor for IPF, but other non-invasive markers may also be relevant[4]. Survival may be lower in UIP patients than in those affected by NSIP[5].

Walter et al[6] addressed the therapeutical problems that clinicians face in the management of patients with IPF. To date it is unclear when in the course of the disease and with what modality these patients should be treated. Most IPF patients do not improve with conventional therapy (corticosteroids and cytotoxic agents) and suffer the associated side effects.

Clinical trials investigated potential new strategies such as off-label use of investigational agents and lung transplantation. Only the latter has been proven effective in prolonging survival, but given the variable course of IPF and the lack of validated prognostic measures, the right timing for this procedure has not yet been defined. Validation of several new prognostic factors that have emerged in the literature could help to determine the right moment for lung transplantation, or to better stratify patients' in future trials.

Predictors of mortality could be divided into (i) baseline predictors; and (ii) dynamic predictors. IPF perspectives in therapy have been also analysed.

The aims of the review were: (1) to analyse and to clarify the clinical utility of different prognostic factors for IPF; (2) to enable clinicians to better evaluate the eligibility criteria for lung transplantation in the clinical practice.

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### *Baseline Predictors of Mortality*

Bjoraker et al[7] reviewed 104 patients diagnosed with IPF by open lung biopsy, and divided them into the pathologic subsets currently used. He observed that NSIP patients had a better prognosis than those affected with UIP. In a retrospective study Flaherty et al[8] examined different prognostic factors among 80 patients with UIP and 29 patients with NSIP. He concluded that baseline pulmonary function tests and high-resolution computer tomography (HRCT) were useful in assessing the prognosis of these patients. In addition forced vital capacity at 6-month intervals was also useful for assessing the prognosis of idiopathic interstitial pneumonia (IIP) patients. The same authors[9] in a recent article highlighted the importance of stratifying patients by the degree of desaturation during a 6-minutes walk test (6-MWT) as a mean to estimate the mortality risk before different interventions such as transplantation. Furthermore, the 6-MWT was shown to be of prognostic importance when evaluating patients with UIP (n = 83) and NSIP (n = 22)[10].

Jegal et al[3] applied a multivariate analysis to evaluate the survival of 131 patients with UIP and 48 with NSIP (41 fibrotic and 7 cellular). While the pathologic pattern, age and diffusion capacity of lung for carbon monoxide (DLco) were important prognostically at baseline, the parameters that remained significant after 6 months of follow-up were forced vital capacity (FVC) and DLco[11]. Nevertheless, pulmonary functional tests (PFTs) may be normal in the presence of histologic and radiographic evidence of IPF. Therefore, normal PFTs cannot exclude IPF in the presence of suggestive clinical or radiographic abnormalities[12].

Lettieri et al[13] demonstrated that only Pulmonary Arterial Hypertension (PAH) correlated with mortality. Baseline measurements of pulmonary function tests, FVC and total lung capacity (TLC) did not correlate with the presence of PAH, neither were accurate predictors of mortality**.** The results of this study differed from data reported before, that showed that age, function tests and a decreased DLco were associated with higher mortality rates.

Conversely, Hamada et al recently demonstrated that DLco was an accurate critical prognostic factor compared with pulmonary-artery pressure (PAP)[11].

Carbone et al[14] in a recent study showed that the New York Heart Association (NYHA) class could be used as an effective substitute of PAH in the assessment and prognosis of IPF. He demonstrated that systolic pulmonary-artery pressure (sPAP) predicted a negative outcome in UIP and NSIP while the NYHA score could be used as a simple prognostic factor to assess mortality in IIP. A preliminary study investigating 78 patients with IIP diagnosed by open pulmonary biopsy showed a good correlation between NYHA score and IIP, UIP, NSIP (Figures 1 A-C) (Carbone, unpublished data). Interestingly also Figures 2 A-C shows a significant relationship between the survival rate, age and the histological diagnoses.

Greene et al[15] showed that baseline serum surfactant protein-A (SP-A) and surfactant protein-D (SP-D) distinguished between IPF and other interstitial lung disease (ILD), and that the serum levels of both proteins were highly predictive of survival in-patients with IPF. Surprisingly survival among smokers was better than in non-smokers. The hypothesis advanced by the authors to explain this finding was that smokers might have had an underlying obstructive lung disease, which could have produced symptoms earlier, thereby permitting an identification of the disease earlier. Conversely, in a Japanese study[16] the increase in the BALF CD4/CD8 ratio was identified as a favourable predictor in the non-current smoker group, whereas it was difficult to identify a definite prognosticator in current smokers.

Enomoto et al[17] showed that quantifying the presence of limited areas of proliferating fibroblasts so called "fibroblast foci" could reflect that fibrosis associated with UIP. This scoring method of fibroblast foci was more objective than the semi quantitative scoring methods in use.

The number of such foci present in a lung biopsy had a good correlation with median survival and in predicting prognosis of IPF/UIP patients, but not with acute exacerbations of IPF/UIP[18]. By contrast, using a different histological scoring system, Flaherty et al[19], don't found relationship between fibroblastic foci and survival (hazard ratio 1.33, 95% CI 0.86 to 2.05, $p = 0.20$).

Lebtahi et al[20] showed an increased Octreoscan uptake index (U.I.) in patients with systemic scleroderma (SSc) associated IPF and confirmed the diagnostic accuracy of the procedure, which was found to be better than radiological imaging. The data was supported by the observation that lung Octreoscan U.I. correlated with the degree of fibrosis assessed by the HRCT score ($p = 0.007$), but not with the ground glass score present in IPF. This difference could be explained by two differ-

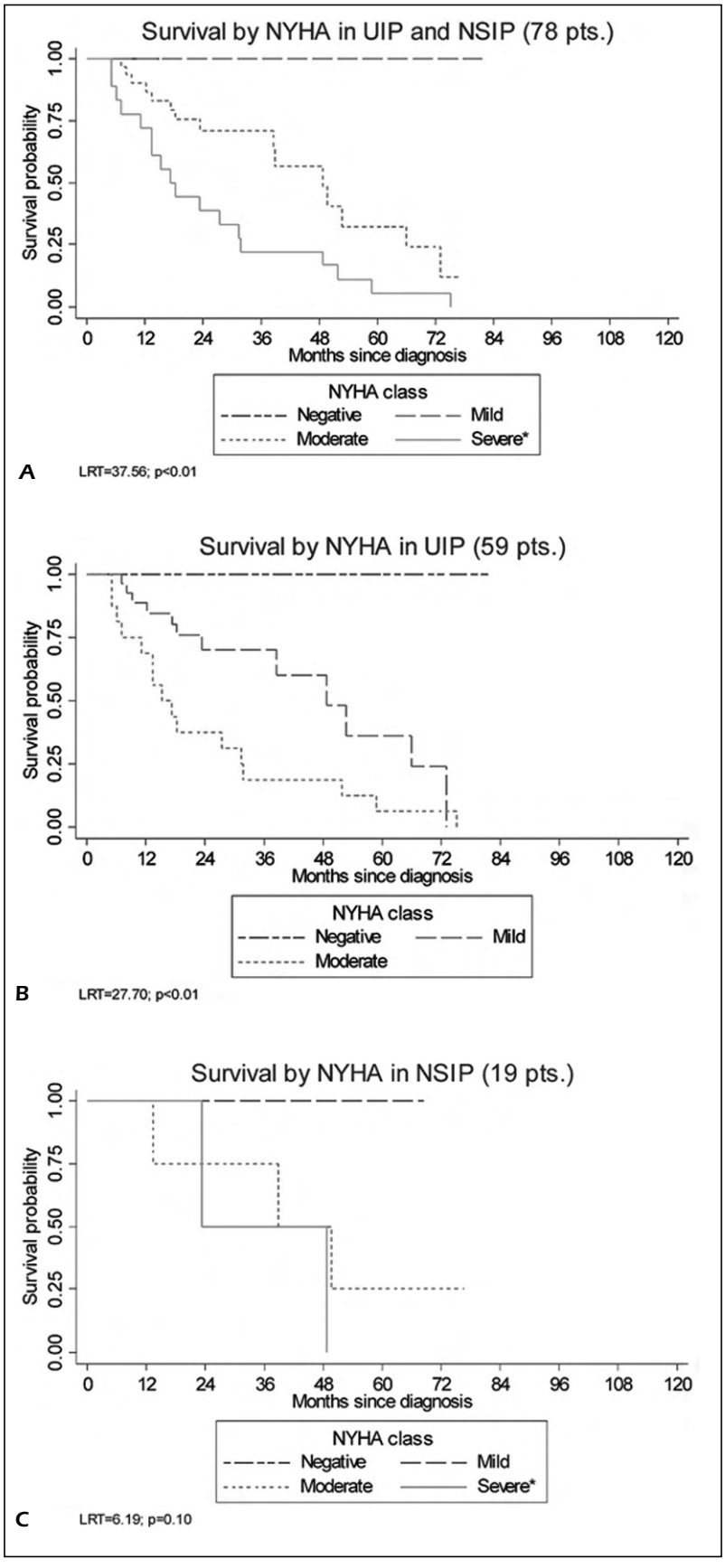


**Figure 1.** ***A-C,*** The graphics (Panel A) confirmed a good correlation between survival with NYHA class in IIP group ($p < 0.01$) in Panel B and C a same strongly correlation was found between UIP and NSIP respectively

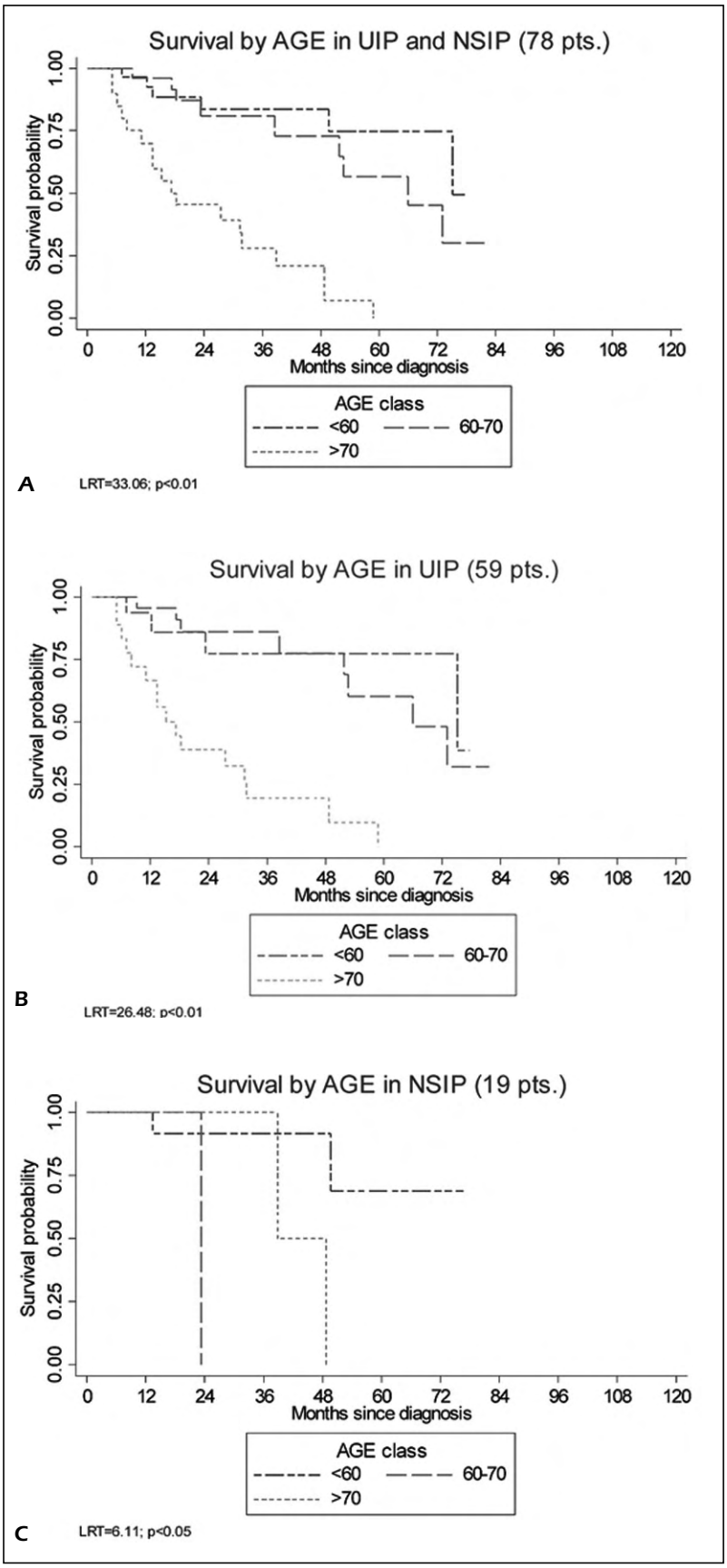


**Figure 2.** ***A-C,*** The graphics showed a strong correlation between survivals compared with age in IIP.

ent histological patterns of IPF, UIP and NSIP, which may both be present in SSc. In addition these data also showed that lung Octreoscan U.I. correlated with the intensity of alveolitis, and may be related to the severity of lung fibrosis.

King et al[21] applied to selected IPF patients a multiple baseline scoring system, which consists of Clinical, Radiological, or Physiological measurements (CRP score). This score was shown to be an accurate predictor of survival in IPF patients. However, it required both a detailed radiographic analysis and exercise physiologic measurements, which may not be readily available to every physician.

A composite physiologic index (CPI) where IPF patients were evaluated by HRCT and pulmonary functional tests (FVC, $FEV_1$, DLco) was developed by Wells et al[22]. The strength of the CPI method lies in the fact that it does not require a complete exercise test or experienced radiologists for the interpretation of HRCT. This index could be used as a clinical guide for staging disease severity and predicting outcome in ILD patients. However the scoring systems currently used may not be easily applicable to the broader community of non-specialist centers, especially when exercise testing and radiographic profusion scores are included.

### Dynamic Predictors of Mortality

Latsi et al[23] compared the survival of 63 UIP patients and 41 NSIP patients, using a combination of parameters which included the histopathologic diagnoses, baseline pulmonary function indices and related serial trends (diffusing capacity, FVC, $FEV_1$, CPI) at 6 and 12 months of follow up. The median survival rate for UIP and NSIP patients was 33 and 56 months, respectively. He found that at 12 months of follow up, serial pulmonary function trends are of considerable prognostic value in UIP and NSIP patients. At this time histology does not change the prognosis in the presence of a clear deterioration of the lung function tests or when the functional impairment is severe. In contrast, the mortality at two years of follow up was correlated to the histopathologic diagnosis.

Furthermore, Collard et al[24], provided important data regarding survival among UIP patients. He observed 81 UIP patients for 6-months and recorded changes in physiologic variables such a dyspnoea score, total lung capacity, thoracic gas volume, FVC, $FEV_1$, diffusing capacity of carbon monoxide, partial pressure of arterial oxygen, oxygen saturation and alveolar (A)-arterial (a) oxygen gradient. Fifty-one patients were evaluated at 12 months, concluding that changes in the dyspnoea score, total lung capacity, FVC, partial pressure of arterial oxygen, oxygen saturation and A-a oxygen gradient, were predictive of survival after adjustment for baseline values.

An acute exacerbation was defined using the following criteria proposed by Kondoh et al[25]: (1) acute shortness of breath within 1 month of presentation, (2) new radiographic pulmonary infiltrates, (3) worsening hypoxemia gas exchange or functional measurements (a decrease in $PaO_2 \geq$ 10 mm Hg or $PaO_2/FiO_2 < 300$), and (4) absence of an identifiable cause including infections, pulmonary embolism, PTX or heart failure.

Occasionally, systemic symptoms such as fever, fatigue, and weight loss are present. In fact, rapid progression and hospitalization due to respiratory decompensation were both independent predictors of mortality in the subsequent 3 months. A better understanding and management of these episodes appears critical for reducing the death rate in IPF[26,27].

### Perspectives in the Therapy

While IPF patients respond poorly to therapy, about a third of treated patients survive longer[28]. Current evidence suggests that corticosteroid mono therapy is not indicated in the treatment of IPF. Corticosteroids in association with azathioprine in the IFIGENIA study showed a decline in FVC that was similar to that in the placebo group from the IFN trial and the placebo group from the pirfenidone trial. The comparison suggests that corticosteroid in association with azathioprine is not better than placebo in preserving FVC in IPF patients[6]. A retrospective study comparing IPF patients treated with corticosteroids and cyclophosfamide with untreated patients matched for age and FVC showed no significant difference in mortality[29]. Only double blind clinical trials of corticosteroids and cytotoxic agents versus no treatment may be the correct approach to assess the effect of therapy on survival. IFN-γ1b an endogenous cytokine was applied in a large multi center randomized placebo-controlled trial of IPF patients. No significant benefit were noted in primary outcome of progression-free survival or the secondary outcome based on the monitoring of pulmonary function tests or on the quality of life[6,30]. The results of a second ongoing randomized, double blind, placebo controlled multi centers phase III study are pending.

Pirfenidone, an inhibitor of transforming growth factor-β (TGF-β) provided encouraging data in a recent phase II study where it was compared to placebo. At 6 and 9 month treated patients showed an improvement in exercise-induced hypoxemia. However, the benefit was small (< 3% oxygen saturation). Interestingly, at 9 month the rate of decline of FVC in treated patients was significantly lower and the acute exacerbations were seen in only non-treated patients[31-33].

## Discussion

To date, the only treatment proven effective in prolonging survival is lung transplantation. The post-transplant 5-yr survival for IPF patients is of approximately 40% and median transplant waiting is of approximately 46 mo. As a consequence that > 30% of IPF patients listed die before receiving a transplant. Yet, there are still no valid prognostic factors for scoring patients that are enlisted for transplantation. Therefore, in light of the limited organ donor pool, efforts should be focused on limiting transplantation to subjects with the highest probability of successful outcome[6,34]. Some factors predicting survival have a higher impact compared with others. We have found reference that age, histological diagnoses, DLco < 60%, desaturation on 6-MWT (< 88%), sPAP (> 25 mm Hg), NYHA class, HRCT evidence, elevated A-a oxygen gradient, and acute exacerbations, can lead to precipitous worsening of disease and death. These risk factors are effective and reproducible. According to Barst et al[35] sPAP studied by Doppler echocardiography is a good screening test for early pulmonary hypertension with high sensitivity and specificity[36]. Moreover Doppler echocardiography correlates well with invasive measurements (r = 0.92)[37].

We suggest reference that the risk factors may be grouped in an IPF predictive score (PrP-IPF score) and applied routinely in clinical practice after a validation of the project submitted to ILD network. The score should be calculated using a combination of clinical, physiological, and laboratory tests.

Decision based on a PrP-IPF score should be derived from an evaluation of the different impact of the prognostic factors of severity disease identified and registered in a flow-chart. PrP-IPF score could be an accurate method for evaluating IPF patients by: (i) predicting the progression of disease, considering the different resources available in different parts of the world, (ii) applying it to future large randomized prospective studies (iii) creating guidelines for IPF management.

The utility of Pr-IPF score could be remarkable in the monitoring IPF and in its treatment. In fact, IPF patients with late-stage disease and poor prognostic score are unlikely to respond to therapy, so consideration should be given to forgoing treatment for these patients, especially if the risk of adverse effects to therapy is high. By the same token, it may enable clinicians to better evaluate the eligibility criteria for lung transplantation (Table I).

In summary, the predictor factors of IPF mortality highlighted in this review suggest that age, DLco, 6-MWT, pulmonary hypertension, NYHA class, HRCT, elevated A-a oxygen gradient, and acute exacerbations, can lead to precipitous worsening of quality of life and death. These risk factors showed a potential clinical application because reproducible, simple, widely available, and effective with a higher degree of impact in predicting mortality, and could be incorporated in an IPF disease progression score. The utility of a Pr-IPF score useful in predicting the outcome of IPF and in its treatment. By the same token, it may enable clinicians to better evaluate early the eligibility criteria for lung transplantation. Finally the application of Pr-IPF score could be the first step to meet the urgent need of a large multidisciplinary collaborative controlled trial aimed at evaluating practical and accurate diagnostic strategies in IPF.

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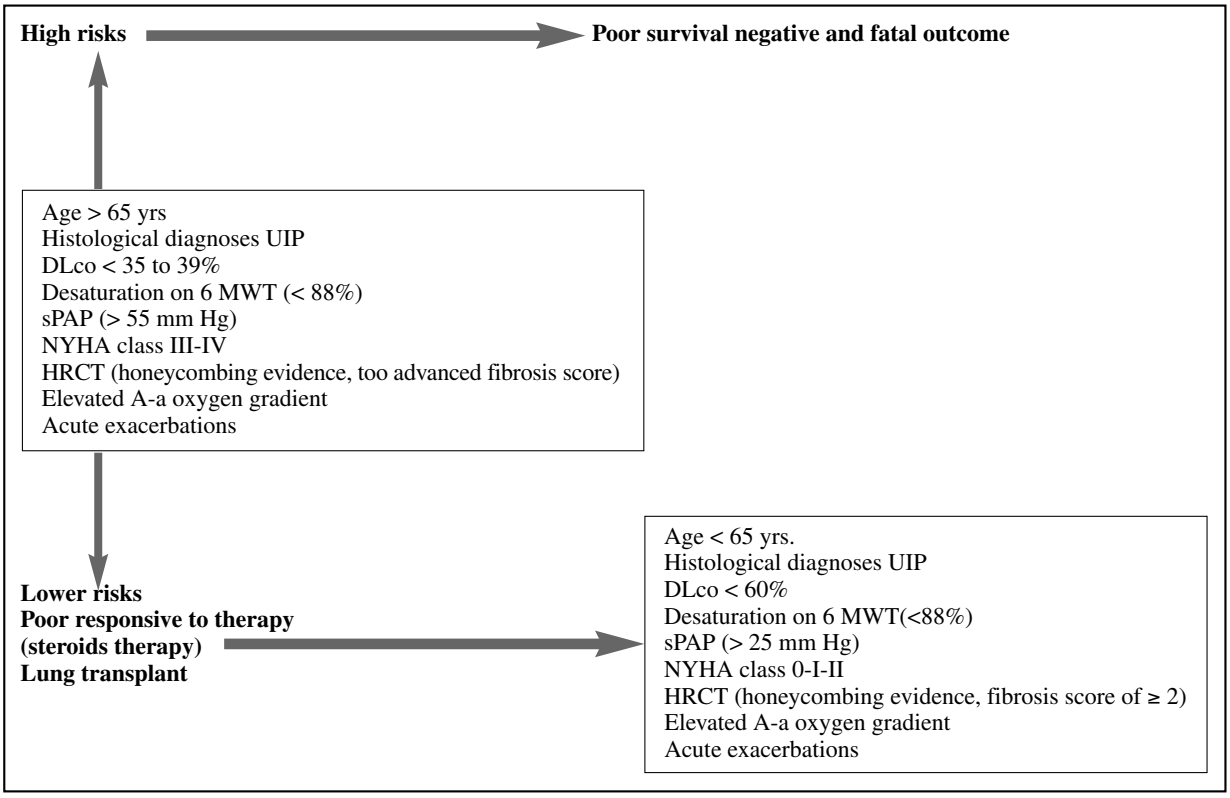
**Table I.** The flow-chart showed the correlation between the predictors of mortality of IPF with survival and therapeutic strategy about lung transplant.





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