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Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study

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Abstract (200 words)

The natural history of idiopathic pulmonary fibrosis (IPF) is not well defined and its clinical course is variable. We sought to investigate the survival and incidence of acute exacerbations (AEs) and their significant predictors in newly diagnosed patients.

Seventy patients newly diagnosed with IPF were prospectively followed for at least 3 years. Baseline evaluation included MRC dyspnoea score (MRCDS), 6-min walk test, pulmonary function tests, which were all repeated at 6 months, and HRCT. A retrospective cohort of 68 patients was used for confirmation.

Mean survival from the time of diagnosis was 30 months, with a 3-year mortality of 46%. A Risk StratificatiOn ScorE (ROSE) based on MRCDS>3, 6-min walking distance≤72% pred and composite physiologic index >41 predicted 3-year mortality with high specificity. 6-month progression of ROSE predicted rapid progression. 3-year incidence of AE was 18.6%, mostly occurring in the first 18 months; risk factors for AE were concomitant emphysema and low DLCO. Results were confirmed in an independent cohort of patients.

In newly diagnosed IPF, advanced disease at presentation, rapid progression and AEs are the determinants of 3-year survival. The purpose of the multifactorial ROSE is to risk-stratify patients in order to predict survival and detect rapid disease progression.

Key words: idiopathic pulmonary fibrosis, usual interstitial pneumonia, survival, prognosis, acute exacerbation.

INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is the most aggressive form of idiopathic interstitial pneumonia (IIP). The natural history of IPF is not well defined. The clinical course is highly variable, with many patients remaining stable for a prolonged period of time, even in the absence of effective medical treatment, while others experience a rapid and relentless progression (1-3). In addition, in some cases, the clinical course consists rather than of a gradual decline, of a stepwise process, with period of stability alternating with acute respiratory worsening (4,5). Some of these events meet the criteria of acute exacerbations (AEs) and carry a high mortality.

Currently, there is no standard approach to stage IPF and studies on the survival of newly diagnosed IPF date back to the 90s (6-8), when the diagnostic criteria of IPF were not well defined. The estimation of survival depends on which time point is used as the starting point: onset of symptoms, time of diagnosis or later time points. Patients are likely to consult a physician when the extent of the disease reaches a threshold that is sufficient to provoke symptoms (3,5). As this can occur more or less rapidly, delays in the diagnosis do occur. Consequently, mean survival rates reported in different studies are highly variable, being estimated between 2 and 4 years from the time of diagnosis (1,3,9,10).

The heterogeneity of the clinical course in IPF makes it difficult to predict the disease outcome, hence the timing of lung transplantation (LTx) and patients with IPF present the highest waiting list mortality among LTx candidates (11). Reliable predictors of outcome are needed to optimise the timing for LTx (11). There is not a single indicator that can correctly stage the disease (12). Most of the studies on the prognostic factors in IPF are retrospective, which limits the strength of their conclusions. The prospective studies recently published have been generated from clinical trial data, and enrollement criteria do usually exclude advanced patients, irrelevant of the symptom starting point, while they include patients with variable timelags from diagnosis (1,10,13-17).

In IPF, the prognostic power of demographic, functional and radiographic factors collected at time of diagnosis remains unclear. The aim of this study was to determine whether 3-year

survival could be predicted on the basis of clinical indicators collected at the time of diagnosis and re-evaluated at 6 months, in a homogenous cohort of patients with a rigorous diagnosis of IPF. The incidence and predictors of AEs were also studied. The results were confirmed in a separate, retrospective cohort of IPF patients from another center.

MATERIAL AND METHODS

Design of the study and subjects

The design of the study is shown in Figure 1. Between October 1st, 2005 and December 31st, 2007, among the 126 subjects diagnosed with IIP at the Pulmonary Unit, University of Rome "Tor Vergata", 23 patients had the pathological diagnosis of usual interstitial pneumonia (UIP) confirmed by surgical biopsy; 81 patients met the 2000 ATS/ERS criteria (18); 22 subjects did not meet them (due to the presence of collagen vascular diseases, drug toxicities, domestic or professional environmental exposures) and were excluded.

HRCT scans of the 81 subjects without histologic confirmation were independently reviewed by 3 radiologists (GS,MZ,NS). In 60 cases, at least 2 radiologists agreed on a pattern consistent with UIP or possible UIP (19,20).

The 23 subjects with biopsy-confirmed UIP and the 60 patients with confirmed radiographic diagnosis were included in the study and followed for at least 3 years; 12 were excluded due to lost follow-up or death for causes other than IPF.

Patients' characteristics are shown in Table 1. Twenty-four subjects (34%) had concomitant emphysema (CE). Survival was defined as time to death or LTx. Time to diagnosis was defined as the time occurring between the onset of symptoms and diagnosis. AEs were defined according to the HRCT criteria described by Akira (21), after excluding infective causes and cardiogenic edema.

Subjects with mild-to-moderate disease were investigated for rapid progression of IPF. The cut-offs for each variable to define "mild-to-moderate disease" at the time of diagnosis were derived from the receiver operating characteristic (ROC) analysis against 3-year survival.

Survival predictors were tested in an independent, retrospective cohort of 68 subjects diagnosed with IPF (18) at the Pulmonary Unit, University of Siena. Twenty-two subjects (32%) had biopsy-confirmed UIP; 13 (19%) had CE.

This study was approved by local Ethical Committees. Further details and treatment regimens are provided in the online depository.

Pulmonary Function Tests

Pulmonary function tests (PFTs) and 6-min walking test (6MWT) were performed according to the ATS guidelines (22,23). 6MWD values were also expressed as % pred (24). The CPI was calculated according to Wells et al. (12). The severity of chronic dyspnoea was rated according to the modified MRC dyspnoea score (MRCDS)(25)(Suppl.Table 1).

High-resolution CT scanning

The inter-observer variability among the 3 core radiologists fell into the limits established by large reports (Suppl.Table 2)(14,26). The total extent of fibrosis was evaluated with a visual score (17,20,27-29). The mean of the fibrosis scores established by each radiologist was calculated for each patient.

Statistical analysis

Values are expressed as mean±SD. Weighted k coefficients were used to assess the level of interobserver agreement among radiologists. Comparisons were made with the Student's t unpaired test or with the Mann-Whitney test, where appropriate. The optimal cut-off value for different variables to detect mortality or AE was assessed using ROC analysis. Survival was evaluated using

Kaplan-Meier curves and the log-rank test. Cox proportional hazards regression analysis was used to identify significant variables predicting survival status. Variables selected via univariate analysis were evaluated in the multivariate Cox regression analysis. p values <0.05 were regarded as significant.

RESULTS

Survival in newly diagnosed patients

In the prospective cohort, the time to diagnosis was variable (Table 1). Mean survival after diagnosis was 30±21 months. During the 3-year follow-up after diagnosis, 32 subjects (46%) died and 1 underwent a LTx (Figure 2)(survival rate 53%). Mortality in the first year after diagnosis was 26%, and 34% at 2 years from diagnosis. In biopsy-confirmed patients, mean survival after diagnosis was 28±12 months, with a 3-year survival rate of 57%.

Prediction of 3-year survival and 6-month disease progression

The comparison of characteristics at the time of diagnosis (Table 2) showed that non-survivors had significantly higher BMI, MRCDS, alveolar-arterial gradient in O_2 (A-aO_2), CPI, HRCT disease extent and BAL total cell count (BAL-TCC), and significantly lower 6MWD (m and % pred), FVC and DLCO compared to survivors. This probably reflects more advanced disease. There was no significant difference in BAL-TCC between smokers and non-smokers (608,750±572,897 vs. 577,772±403,062 cells/ml, respectively). BAL-TCC did not show any significant correlation with any other variable, including pack-years (*data not shown*).

Non-survivors were more often affected by CE and more frequently had a significant desaturation ($SaO_2 \leq 88\%$) during the 6MWT compared with survivors (Table 2). The correlation between HRCT disease extent and CPI at the time of diagnosis was significant (Suppl.Figure 1).

Kaplan-Meier survival curves were grouped according to ROC cut-off values (Figure 3, Suppl.Table 3). Univariate analysis and Kaplan-Meier curves confirmed that several variables at the time of diagnosis were significant predictors of 3-year survival (Table 3A, Suppl.Figure 2A-L). 6MWD (% pred) showed a higher predictive value than 6MWD (m) (Suppl.Figure 2C-D), while the CPI was superior to the HRCT disease extent (Suppl.Figure 2J-K).

Multivariate analysis showed that MRCDS>3, 6MWD≤72% pred and CPI>41 at diagnosis were significant and independent predictors of 3-year survival (Table 3B). Therefore, for the purpose of 3-year survival prediction, risk groups were defined as follows (Risk stratificatiOn ScorE - ROSE): low risk (n=16): MRCDS≤3, 6MWD>72% pred and CPI≤41; intermediate risk (n=41): MRCDS>3, 6MWD≤72% or CPI>41; high risk (n=13): MRCDS>3, 6MWD≤72% and CPI>41. 3-year mortality was 19% in the low risk group, 42% in the intermediate risk group and 100% in the high risk group ($p<0.0001$)(Figure 4A). The ROSE predicted 3-year survival with a 39% sensitivity and a 100% specificity (Figure 4B, Suppl.Table 3).

Subjects with mild-to-moderate disease (low/intermediate ROSE) based on the baseline evaluation were investigated for rapid disease progression. At 6 months after diagnosis, changes of MRCDS, 6MWD % pred and CPI were evaluated. Mortality was 100% in the group of patients upgraded to high ROSE and 27% in those who remained in the intermediate ROSE (Figure 4C). Among the 3 deaths observed among the patients with low ROSE at baseline, 2 subjects had advanced to intermediate ROSE at 6 months follow-up. Among the 17 deaths observed among the subjects with intermediate ROSE at baseline, 6 patients had advanced to high ROSE at 6 months follow-up. Among the patients who advanced to high ROSE, no one survived. Three more patients in the intermediate risk group, who died before 3 years and did not advance, had an AE. Two more patients in this group died before the 6-month re-evaluation. An advancement of the ROSE predicted 3-year mortality with 94% sensitivity and 40% specificity (Figure 4D).

6-month changes of single parameters are shown in the online depository.

Acute exacerbations: incidence and prediction

During the follow-up period, 13 AEs were observed (incidence 18.6%), mostly (11 out of 13) within the first 18 months after diagnosis (Figure 2B). Three AE were immediately fatal and in 6 more cases exitus occurred within 3 months from the occurrence of AE. Although univariate analysis showed a number of significant predictors of AE at the time of diagnosis (Table 4A), multivariate analysis showed that the only independent, significant predictors of AE were DLCO and the presence of CE (Table 4B). ROC analysis showed that a DLCO≤47% was the optimal cutoff to detect AE (Suppl.Figure 4). The incidence of AEs was indeed significantly higher in patients with CE than in those without CE (24% vs. 11%, p=0.022).

Comparative analysis in the retrospective cohort

The retrospective cohort consisted of relatively younger patients, with more severe exercise impairment (Table 1). A lower prevalence of smoking and CE could explain the higher DLCO and, consequently, lower CPI values. During the 3-year follow-up period after diagnosis, 19 patients died (28%) and 7 had a LTx. Therefore, compared with the prospective cohort, 3-year survival was better (62% vs. 53%), although not significantly (Suppl.Figure 5A). According to the univariate analysis, 6MWD (% pred), A-aO_2, FVC, DLCO and CPI at the time of diagnosis were significant predictors of 3-year survival (Suppl.Table 4). In the multivariate analysis, 6MWD ≤72% pred and CPI>41 were independent, significant predictors of survival (Table 5C). In this cohort, ROSE at baseline predicted 3-year mortality with a 67% sensitivity and 91% specificity (Suppl.Figure 5B).

The incidence of AE in this cohort was 22% (Suppl.Figure 5C). In 86% of the cases, death occurred within 3 months from AE. DLCO predicted the occurrence of AE (Hazard ratio 0.91, C.I. 0.83-0.98, p=0.013) while CE was only close to significance (p=0.063).

DISCUSSION

This study demonstrates that in a homogenous cohort of patients newly diagnosed with IPF the mean survival from the time of diagnosis was 30 months, and 3-year survival could be predicted with high specificity based on a risk stratification score (ROSE) defined by MRCDS, 6MWD (% pred) and CPI. Furthermore, a 6-month deterioration with risk group advancement predicted mortality risk even in patients with only mild-to-moderate disease at presentation. Finally, AE mostly occurred in the first 18 months after diagnosis, more frequently in patients with CE and low DLCO.

In this prospective study patients newly diagnosed with IPF were followed from the time of diagnosis for at least 3 years. The mean survival after diagnosis was lower than what reported by previous prospective reports (7,8), although retrospective studies reported a range between 2 and 3 years (30-32). The importance of studying survival prospectively is relevant, as in retrospective studies some patients who died quickly from aggressive disease might be excluded (8).

Although many studies on the prognostic factors in IPF have been published, there is a surprising lack of prospective studies conducted from the time of diagnosis. The disease extent and the severity of functional impairment of patients with IPF at the time of diagnosis are variable (2). In this study, MRCDS >3, 6MWD ≤72% pred and CPI >41 were the independent predictors of 3-year survival. A risk stratification score (ROSE) based on these 3 parameters predicted 3-year survival with a 100% specificity, but with a sensitivity of only 39%. This can be explained by both the rapid progression of initially mild disease at presentation in some patients, and by the occurrence of AEs in some others. Therefore, identifying a rapidly progressing disease in patients with only mild-to-moderate impairment at diagnosis is also of pivotal importance. 6-month changes of ROSE were considered, and an advancement to high ROSE predicted mortality with a 94% sensitivity and a 41% specificity. If validated, our results suggest that these indicators are able to detect a clinically significant disease progression.

The use of dyspnoea scores in the evaluation of IPF is controversial. Retrospective reports pointed to a significant role for the MRCDS (33,34), although concern has been raised due to the

potential confounding factors in the determination of dyspnoea and its subjective perception (35). Our study with longitudinal evaluation strongly support the use of the MRCDS, which was in fact the most significant single predictor of survival. We also showed, for the first time, that a 6-month increase of the score from 0-3 to 4-5 predicted a poor prognosis, suggesting that the MRCDS is a sensitive tool in detecting IPF progression. Although this score is an objective evaluation based on precise questions, the patient's perception of dyspnoea remains subjective, implying that the concomitant use of other validated tools is recommended.

The use of 6MWT has been validated in IPF (13) and it strongly correlated with VO_2 max results (36). Our study provides further support to the use of this simple test in IPF, as 6MWD at the time of diagnosis was a significant predictor of survival (cut-offs=350 m or 72% pred) and added independent prognostic information to the multivariate analysis. Another novel finding of this study is that 6MWD (% pred) based on the reference equations of Enright (24) was a more reliable predictor of survival and disease progression than 6MWD (m). This observation supports the development of new reference equations on a larger number of normal subjects. As a limiting factor, several patients with IPF are elderly, have mobility issues and may not perform an accurate 6MWT. This further underlines the importance of using a panel of different prognostic factors in IPF.

HRCT represents an integral part of the evaluation of patients with IIP (14,17). The importance of accurate assessment of HRCT images has been highlighted by a recent study reporting a relevant quote of misdiagnosis (20). When biopsy was not available, we relied on a panel of 3 experienced radiologists to establish a confident diagnosis of IPF. The fibrosis score that we used provides an overall estimate of the disease extent (27,28), which significantly correlated with the CPI. Interestingly, the CPI was a more significant prognostic factor (cutoff=41) that HRCT disease extent. By taking into account the confounding factor of CE, CPI provides an estimate of disease extent (12) and added independent prognostic power to the multivariate model. A low DLCO, which is part of CPI, may also reflect the presence of associated pulmonary hypertension

(PH), which is highly prevalent in IPF and has a negative impact of survival (37). However, the presence and severity of PH in IPF can be reliably assessed only with right heart catheterisation (38), which was not part of this study.

The use of FVC as a predictor of survival in IPF is also controversial. After initial supportive reports (39-42) based on retrospective data, enthusiasm was dampened by the data collected from clinical trials, which showed significant mortality in patients with stable FVC (43). In our cohort, both baseline FVC at the time of diagnosis (cut-off 70%) and 6-month FVC deterioration predicted survival. While we considered only newly diagnosed cases, patients were enrolled in clinical trials at various time points of the natural history of IPF, and this may explain the discrepancy. Patients with advanced disease may not be able to perform an accurate DLCO, and therefore FVC and also A-aO_2 (cutoff=35 mmHg) may still have a prognostic role.

A relevant quote of IPF patients has CE (44). Studies from Cottin et al. identified combined pulmonary fibrosis and emphysema (CPFE) as a relevant clinical entity, as mean survival is shorter than in other forms of IIP, the incidence of PH is higher and PFTs are potentially confounding (44-46). Although CE was not an independent prognostic factor, our study showed that, in the long term, patients with CE have a worse prognosis than those without CE. This finding fits with the previous observation that CE significantly contributes to the functional impairment in patients with IPF (27,44), and with the retrospective study from Mejia et al. (47).

BAL-TCC at the time of diagnosis was significantly increased in non-survivors compared with survivors. Probably due to the limited amount of BAL-TCC data available, this was not an independent predictor of survival. While routine performance of BAL in the work-up of IPF is now being questioned (2), this and other reports (48) should encourage larger studies with systematic bronchoscopy to explore the hypothesis that BAL cellularity carries a prognostic value. This is most relevant since BAL-TCC did not correlate with any other parameter considered or smoking history and might therefore capture a different phenomenon of the disease, such as active inflammation.

The high mortality and the difficult prediction of AEs implies that a completely reliable system of survival prediction is nearly impossible to obtain at baseline. The 3-year incidence of AE was 18.6%. Although the relatively limited number of patients precludes any definitive conclusion, this is the first prospective study to investigate the incidence of AE, which was highest in the first 18 months post-diagnosis, and carried a high mortality (69% within 3 months from the AE occurrence). While AEs are difficult to predict with the same parameters used to predict survival, it is important to note that AEs do not occur in patients with mild disease at presentation, classified as low risk group. In a large retrospective study, the prevalence of AE resulted analogous (49). Risk factors for AE were a low DLCO (cutoff=47%) and the presence of CE, which may not be completely independent from each other, as patients with CPFE generally have a very low DLCO (44). Risk factors were substantially confirmed in the retrospective cohort. This observation is intriguing, as it may identify a particular phenotype of patients. We previously showed a higher expression of metalloproteinases in the lungs of CPFE patients compared with those without CE, hypothesising that this could determine a more aggressive activation of fibroblasts, remodelling and tissue destruction and, consequently, a more precipitous course (50). Whether this phenomenon is reflected by the severely impaired gas exchange commonly observed in CPFE, and whether this is implicated in the occurrence of AE, has to be further elucidated.

The analysis of retrospective cohort confirmed that ROSE predicted 3-year survival with high specificity (91%) and even improved sensitivity (67%). The incidence and the predictors of AE were also similar.

This study has some limitations. First, the independent confirmation cohort was retrospective, which can limit the reliability of the results. However, reassuringly, however, despite some demographic differences, the main findings were confirmed. Second, the assessment of PH, an important determinant of survival, was not available. Third, the diagnostic criteria for AE still lack specificity, which is common to other studies as well. Last, the number of subjects included was relatively small, although the population was homogenous and carefully selected.

In conclusion, the 3 main factors determining high risk of mortality in newly diagnosed IPF are advanced disease at presentation, rapid progression and occurrence of AE. AEs are more frequent during the first 18 months after diagnosis and in patients with CE. Due to their multifactorial nature, MRCDS, 6MWD and CPI are able to capture clinically important domains of IPF, including ventilatory and gas exchange impairment, increased dead space ventilation, peripheral muscle dysfunction and associated PH. Consequently, the multifactorial ROSE could be used to risk-stratify patients at the time of diagnosis, and detect rapid disease progression, providing guidance for the management of this life-threatening condition. Prospective studies on larger populations of newly diagnosed patients are necessary to confirm or refute these findings, and could potentially define a comprehensive, multidimensional prognostic index.

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TABLES

Table 1. Demographic, clinical, functional and radiographic characteristics of the two cohorts at the time of diagnosis. Prospective cohort: Pulmonary Unit, University of Rome "Tor Vergata". Retrospective cohort: Pulmonary Unit, University of Siena.

Variable	**Prospective cohort** (n=70)	**Retrospective cohort** (n=68)	**p value**
M/F (% male)	57/13 (81%)	50/18 (74%)	n.s.
Age (years)	67 ± 8	62 ± 9	0.0011
BMI (m/Kg^2)	28 ± 4	27± 5	n.s.
Time to diagnosis (months)	23 ± 20	N/A	N/A
Biopsy-based diagnosis (yes/no) (%)	23/47 (33%)	22/46 (32%)	n.s.
Smokers/never smokers (%)	44/26 (63%)	34/34 (50%)	n.s.
Pack-years	33 ± 18	24 ± 17	0.028
Concomitant emphysema (Yes/No) (%)	24/46 (34%)	13/55 (19%)	0.044
MRC dyspnoea score	2.5 ± 1.1	N/A	N/A
6MWD (m)*	372 ± 146	350 ± 116	n.s.
6MWD (% pred)*	79 ± 29	68 ± 24	0.049
A-aO_2 (mmHg)	32 ± 14	26 ± 10	n.s.
FVC (% pred)	75 ± 22	75 ± 21	n.s.
DLCO (% pred)**	46 ± 19	55 ± 17	0.013
CPI	48 ± 15	42 ± 12	0.038
HRCT disease extent* ** (% of total lung volume)	36 ± 12	N/A	N/A
BAL total cell count (cells/ml)****	596,130 ± 502,073	N/A	N/A

p value: Chi Square, Student's t test or Mann-Whitney test, where required
CPI: composite physiologic index
* n = 64
** n = 65
*** mean of the scores from each of the 3 core radiologists
**** n = 28

Table 2. Prospective cohort: demographic, clinical, functional and radiographic characteristics at the time of diagnosis of 3-year survivors and non-survivors.

Variable	**Survivors** (n=39)	**Non-survivors** (n=31)	**p value**
Age (years)	66 ± 4	67 ± 9	n.s.
BMI (m/Kg^2)	29 ± 4	27 ± 3	0.0384
Time to diagnosis (months)	20 ± 19	27 ± 22	n.s.
Pack-years	32 ± 16	34 ± 22	n.s.
Concomitant emphysema (Yes/No)(%)	9/30 (23%)	15/15 (50%)	0.0267
MRC dyspnoea score	2.1 ± 0.8	3.3 ± 1.1	<0.0001
6MWD (m)	412 ± 128	319 ± 153	0.0184
6MWD (% pred)	89 ± 27	66 ± 27	0.0018
Desaturation at 6MWT* (yes/no)(%)	19/16 (54%)	25/4 (86%)	0.0061
A-aO_2 (mmHg)	28 ± 13	36 ± 17	0.0392
FVC (% pred)	81 ± 21	68 ±23	0.0027
DLCO (% pred)	53 ± 17	37 ± 17	0.0005
CPI	43 ± 15	55 ± 13	0.0006
HRCT disease extent (% of total lung volume)	33 ± 11	41 ± 11	0.0098
BAL total cell count (cells/ml)	417,972 ± 319,004	952,444 ± 623,505	0.0037

p value: Chi Square, Student's t test of Mann-Whitney test, where required
* SaO_2 ≤88%
CPI: composite physiologic index

Table 3A. Prospective cohort: 3-year survival, univariate analysis of variables at the time of diagnosis.

Variable	Hazard ratio	C.I.	p value
Age (years)	1.02	0.98-1.07	n.s.
Pack-years	0.99	0.97-1.02	n.s.
Time to diagnosis (months)	1.01	0.99-1.03	n.s.
BMI (m/Kg^2)	0.89	0.80-0.98	0.0155
MRC dyspnoea score	2.52	1.76-3.62	<0.0001
6MWD (m)	1.00	1.00-1.00	n.s.
6MWD (% pred)	0.98	0.96-0.99	0.0007
Desaturation at 6MWT*	0.54	0.32-0.84	0.0052
A-aO_2 (mmHg)	1.03	1.01-1.05	0.0063
FVC (% pred)	0.97	0.95-0.99	0.0039
DLCO (% pred)	0.94	0.92-0.97	<0.0001
CPI	1.06	1.03-1.10	<0.0001
HRCT Fibrosis Score (% of total lung volume)	1.03	1.00-1.07	0.0497
BAL total cell count (cells/ml)	1.00	1.00-1.00	0.0009
Concomitant emphysema	1.82	0.90-3.66	0.096

* No desaturation (SaO_2 ≤88%) during the 6MWT
CPI: composite physiologic index

Table 3B. Prospective cohort: 3-year survival, cox proportional hazard analysis of variables at the time of diagnosis. p value of the model <0.0001

Variable	**Hazard ratio**	**C.I.**	**p value**
MRC dyspnoea score >3	6.77	2.37-19.41	0.0005
CPI >41	5.36	1.50-34.15	0.0071
6MWD <72% pred	3.27	1.25-8.82	0.0162

Table 3C. Retrospective cohort: 3-year survival, cox proportional hazard analysis of variables at the time of diagnosis. p value of the model 0.0053.

Variable	**Hazard ratio**	**C.I.**	**p value**
6MWD <72% pred	5.43	1.35-36.17	0.016
CPI >41	4.20	1.05-27.93	0.042

Table 4A. Prospective cohort: acute exacerbations, univariate analysis of variables at the time of diagnosis.

Variable	Hazard ratio	C.I.	p value
Age at diagnosis (years)	1.02	0.96-1.10	n.s.
Pack-years	0.99	0.95-1.03	n.s.
Time to diagnosis (months)	1.01	0.98-1.04	n.s.
BMI (m/Kg^2)	0.92	0.79-1.07	n.s.
MRC dyspnoea score	1.96	1.18-3.30	0.0095
6MWD (m)	1.00	1.00-1.00	n.s.
6MWD (% pred)	0.98	0.96-1.00	n.s.
Desaturation at 6MWT*	0.43	0.10-0.97	0.040
A-aO_2 (mmHg)	1.03	1.00-1.07	0.053
FVC (% pred)	0.98	0.95-1.01	n.s.
DLCO (% pred)	0.94	0.90-0.98	0.0007
CPI	1.05	1.01-1.10	0.022
HRCT Fibrosis Score (% of total lung volume)	1.05	1.00-1.10	0.063
BAL total cell count (cells/ml)	1.00	1.00-1.00	n.s.
Concomitant emphysema	3.37	1.12-11.17	0.030

* No desaturation ($SaO_2 \leq 88\%$) during the 6MWT
CPI: composite physiologic index

Table 4B. Prospective cohort: acute exacerbations, cox proportional hazard analysis of variables at the time of diagnosis. Model 1 (cut-off), p value of the model 0.0004.

Model 1(cut-off), p value of the model 0.0004.

Variable	**Hazard ratio**	**C.I.**	**p value**
DLCO (% pred)	0.93	0.89-0.97	0.0008
Concomitant emphysema	3.20	1.06-10.67	0.040

FIGURE LEGENDS

Figure 1. Design of the study.

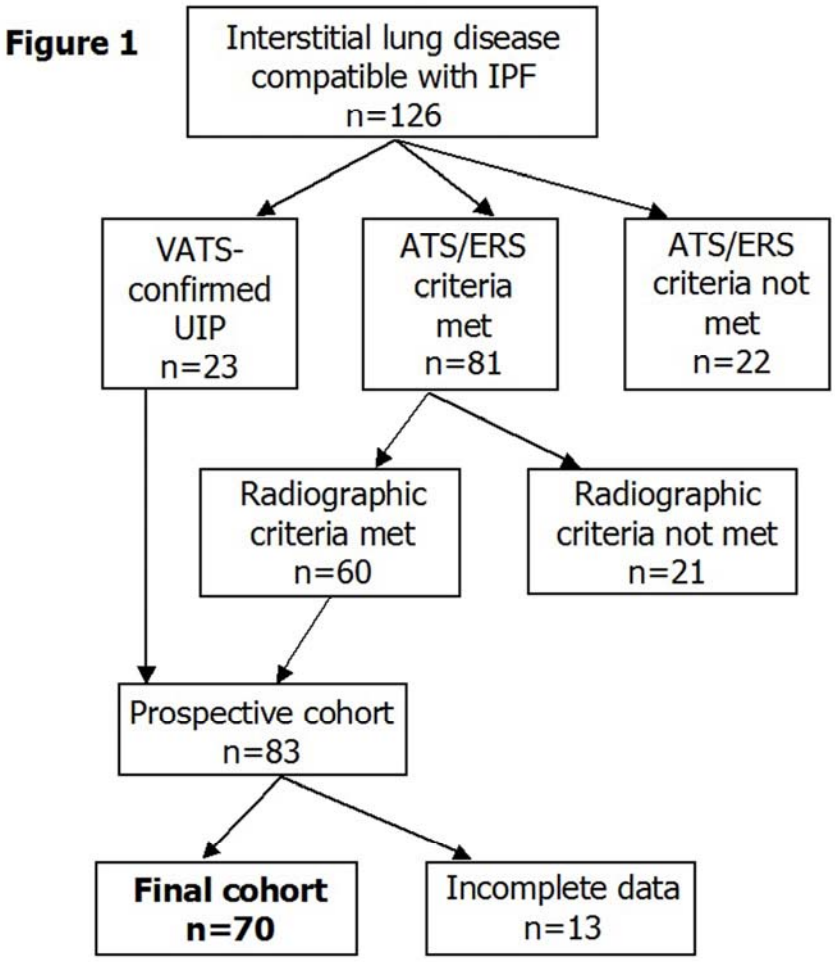


Figure 2. A. Prospective cohort, 3-year survival form the time of diagnosis. B. Prospective cohort, 3-year incidence of acute exacerbations.

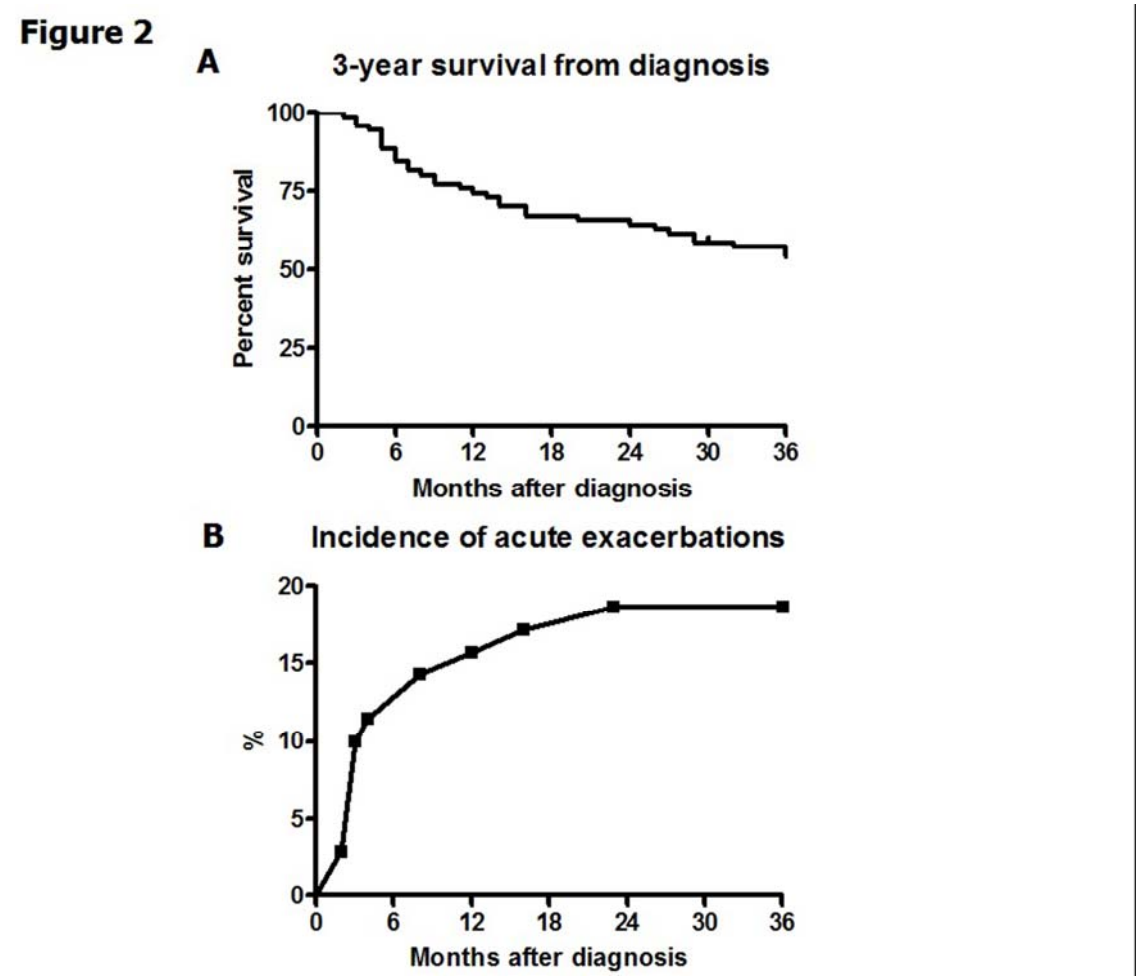
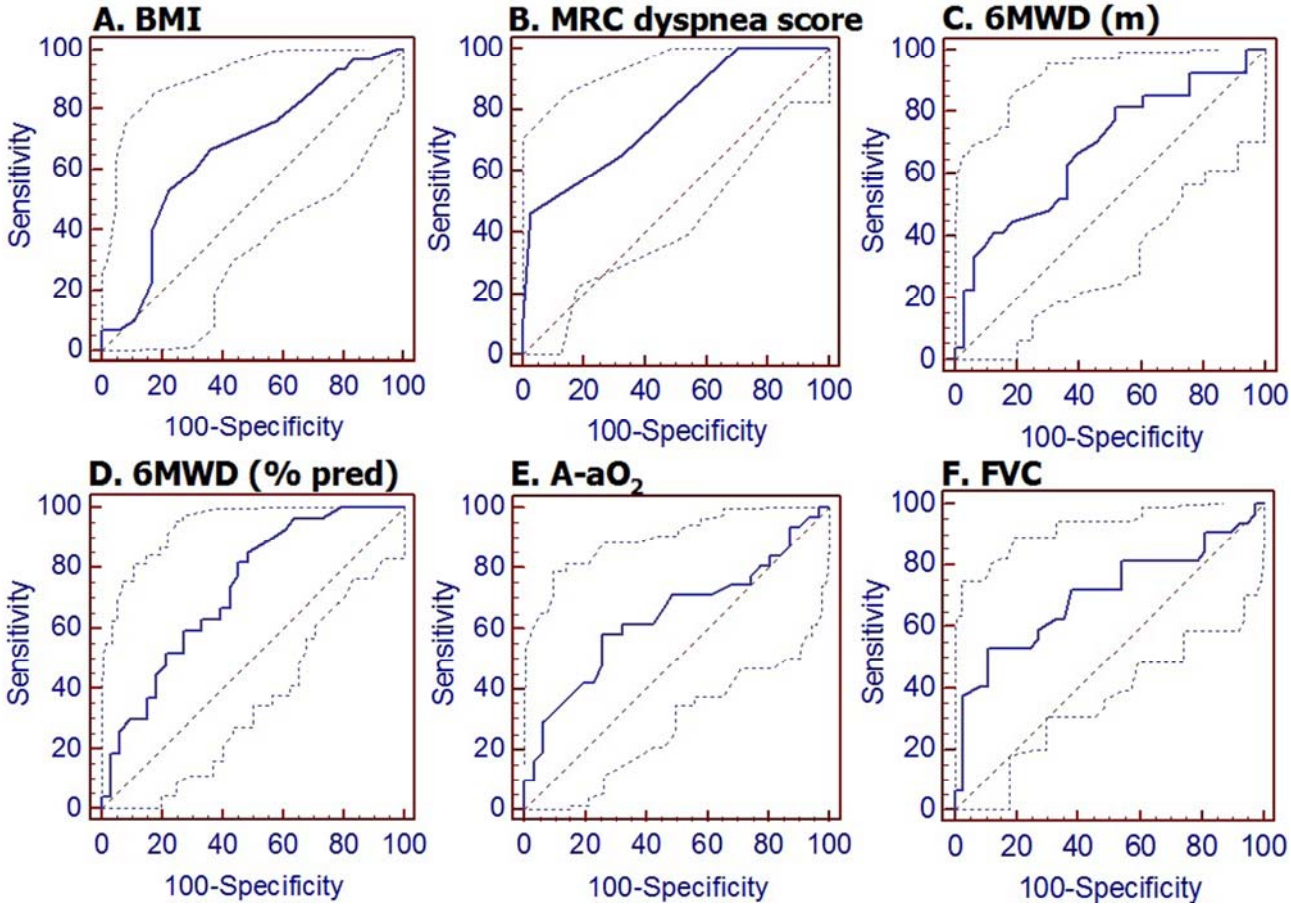


Figure 3. Prospective cohort, receiver operating characteristics curve of different variables at the time of diagnosis versus 3-year survival. Refer to Supplemental Table 3 for more details. A. BMI; B. MRCDS; C. 6MWD (m); D. 6MWD (% pred); E. A-aO_2; F. FVC; G. DLCO; H. CPI; I. HRCT fibrosis score; J. BAL total cell count.

Figure 3


A. BMI
B. MRC dyspnea score
C. 6MWD (m)
D. 6MWD (% pred)
E. A-aO2
F. FVC
Sensitivity
100-Specificity
0
20
40
60
80
100

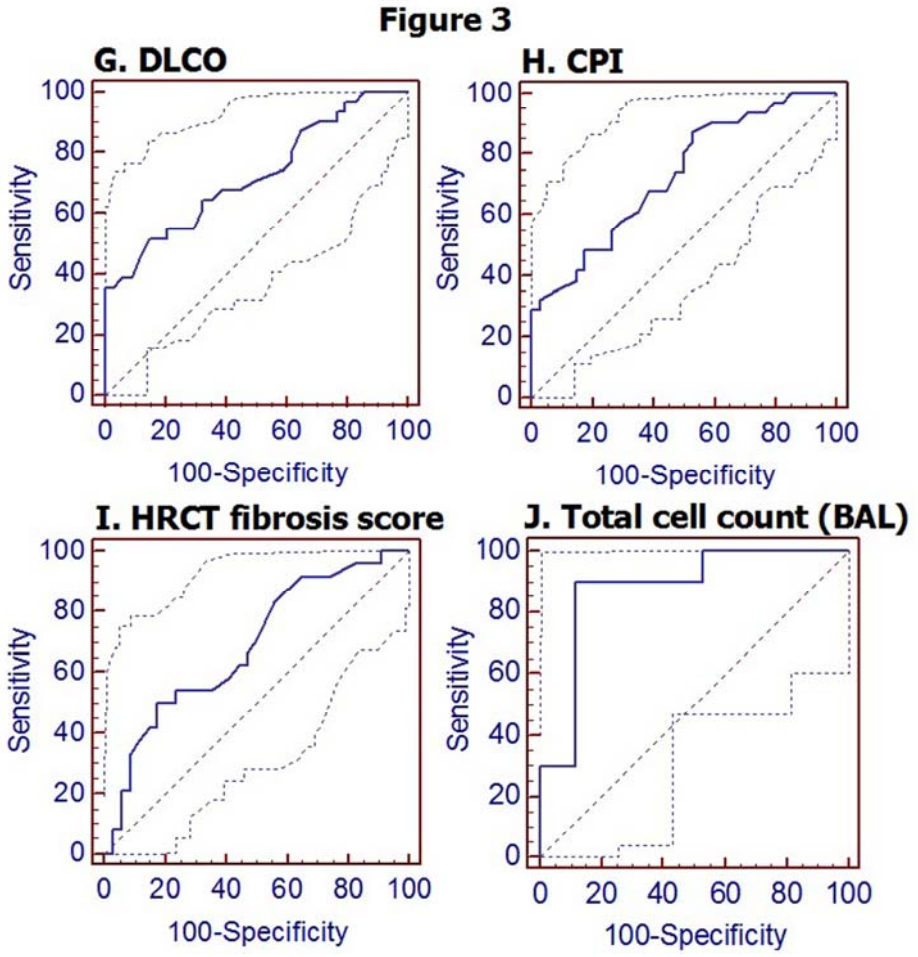
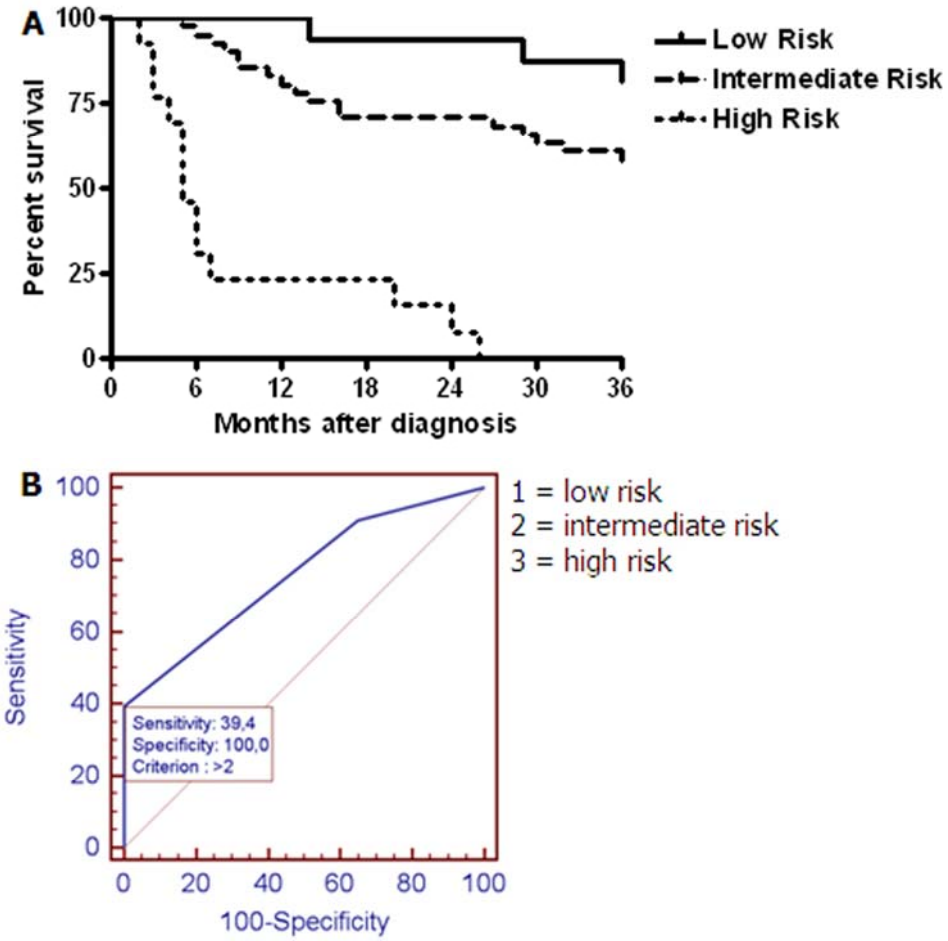
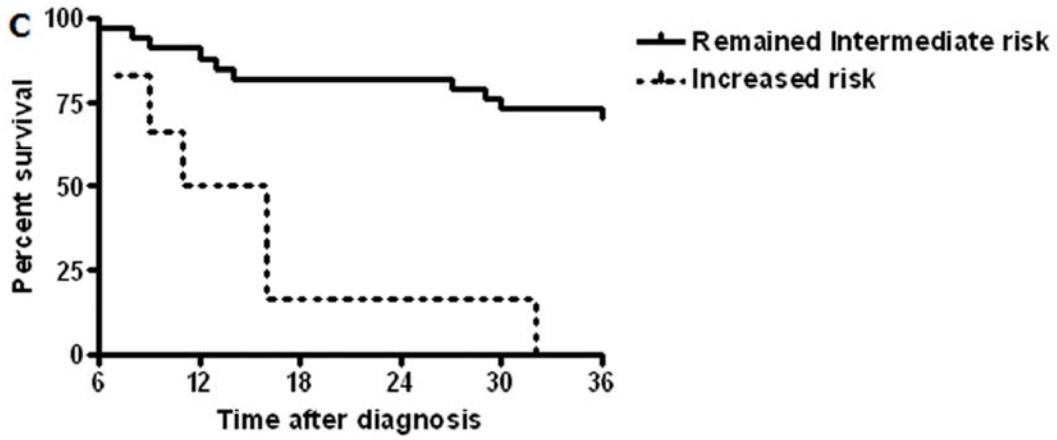
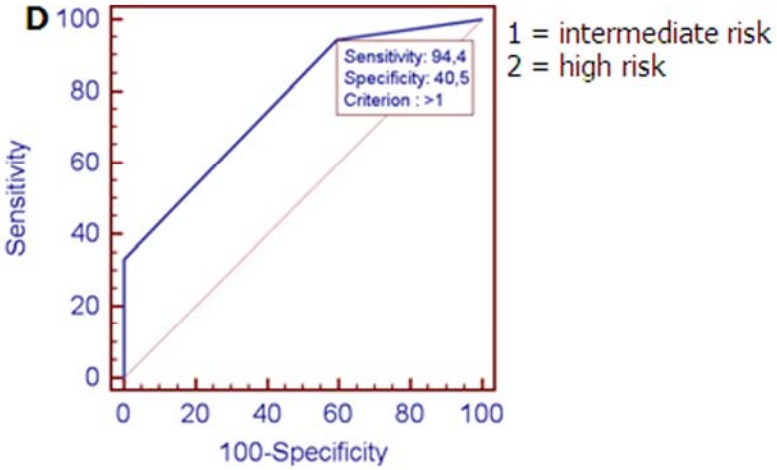


Figure 4. A. Prospective cohort, Kaplan-Meier survival analysis grouped by ROSE (Risk stratificatiOn ScorE). Low risk: MRCDS≤3, 6MWD>72% pred and CPI<41; Intermediate risk: MRCDS>3, 6MWD<72% or CPI>41; High risk: MRCDS>3, 6MWD<72% and CPI>41; p<0.0001. B. Prospective cohort, receiver operating characteristics curve of ROSE at the time of diagnosis versus 3-year survival; Refer to Supplemental Table 3 for more details. C. Prospective cohort, intermediate risk group, Kaplan-Meier survival analysis grouped by 6-month changes of ROSE; p<0.0001. D. Prospective cohort, intermediate risk group, receiver operating characteristics curve of 6-month change of ROSE versus 3-year survival; area under the curve 0.77, standard error 0.055, sensitivity 94% (C.I. 73-100%), specificity 41% (C.I. 25-58%), p value <0.0001.

Figure 4


A
100
75
50
25
0
Percent survival
0
6
12
18
24
30
36
Months after diagnosis
Low Risk
Intermediate Risk
High Risk
B
100
80
60
40
20
0
Sensitivity
Sensitivity: 39,4
Specificity: 100,0
Criterion : >2
0
20
40
60
80
100
100-Specificity
1 = low risk
2 = intermediate risk
3 = high risk


C
100
75
50
25
0
Percent survival
6
12
18
24
30
36
Time after diagnosis
Remained Intermediate risk
Increased risk


D
100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
100-Specificity
Sensitivity: 94,4
Specificity: 40,5
Criterion : >1
1 = intermediate risk
2 = high risk