85. What is new in the approach to pulmonary fibrosis?

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Preliminary results of the French national prospective cohort on IPF

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Introduction: Owing the absence of published prospective cohorts, the epidemiology and natural history of IPF remains unclear.

Aims: To determine the factors associated with the occurrence of pre-defined evolutive events: slow progression of IPF, acute exacerbation (AE), subacute exacerbation (subAE), pulmonary hypertension (PH) and death.

Methods: Prospective cohort involving all the 24 French University Hospitals. The diagnosis of IPF was based on 2000 ATS/ERS criteria and centrally reviewed.

Results: From 12/2007 to 12/2010, 240 incident cases of IPF (diagnosis <9 months) were included. Data are available for 210 patients (men: 80%; age: 69±10 years; non-smokers: 29%). At inclusion, a history of neoplasia was reported in 13% and at least one cardiovascular disease in 29% (coronaropathy: 18%). BMI was 27.5±4.3 and it was >25 in 68%. A familial form of IPF was noted in 8%. A combined pulmonary fibrosis and emphysema syndrome was seen in 18% and asymetrical IPF in 7%. Baseline FVC was 76±21% and DLCO was 47±17%. On BAL, lymphocytes were ≥30% in 4.1% and eosinophils ≥20% in 2.1%. Surgical lung biopsy was performed in 31%. After a follow-up of 14±9 months (range: 1-36 months) following events were observed: 34 slow progressions, 19 AE, 10 subAE, 9 PH and 46 deaths. Eight patients were transplanted. The incidence of AE was 12% at 1 year. Survival was 80% and 63% at 1 and 2 years. Mortality

was related to respiratory causes in 78% (AE: 37% and end-stage respiratory insufficiency: 26%).
Conclusion: Our results confirm the high frequency of overweight and severe co-morbidities in IPF. Despite a relatively low incidence of evolutive events, mortality is already high, with AE being the major cause of death.

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Arterial stiffness and endothelial dysfunction in idiopathic pulmonary fibrosis (IPF)
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Background: Fibrotic lung diseases are associated with an increased prevalence of coronary artery disease and cardiovascular complications [Kizer et al., 2004]. Arterial stiffness and endothelial dysfunction are widely accepted as markers of cardiovascular risk.
Objectives: The aim of the present study was to assess aortic stiffness and endothelial dysfunction in patients with IPF and to determine the association of these markers with other clinical and functional parameters.
Methods: We enrolled 25 IPF patients (age 57±8 yrs; FVC 80±18%; DL_{CO} 38±15%) and 30 normal control subjects (age 52±5 yrs). Assessment of arterial stiffness was performed by use of digital photoplethysmography (Pulse Trace PCA 2, Micro Medical). Change in reflection index of the digital volume pulse in response to salbutamol (ΔRI_{SALB}) was used to assess endothelial function.
Results: In IPF patients stiffness index (SI) was significantly higher than in normal control subjects: 9.8±3.1 vs 6.9±1.0 m/s ($p<0.001$). The correlations between SI and sleep time spent with SpO_2 < 88% ($r=-0.67$, $p<0.05$) and total serum cholesterol level ($r=-0.77$, $p<0.05$) were highly significant in IPF patients. ΔRI_{SALB} was significantly lower in IPF patients than in control subjects: 2.2±1.2% vs 15.8±9.3% ($p=0.01$). ΔRI_{SALB} was significantly associated with FEV_1 ($r=-0.57$, $p<0.05$), mean nocturnal SpO_2 ($r=-0.83$, $p<0.05$) and total cholesterol level ($r=-0.71$, $p<0.05$).
Conclusions: Arterial stiffness and endothelial dysfunction are significantly impaired in IPF patients. Decreased FEV_1 was associated with endothelial dysfunction. Nocturnal hypoxemia and total cholesterol level have an association with both arterial stiffness and endothelial function.

P648
Clinical course of idiopathic pulmonary fibrosis (IPF): Prediction and outcome
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Background: IPF is a progressive disease for which a median survival time of 2.8 years was reported. However the clinical course of IPF is variable. Acute exacerbation (AE) is a major cause of death in IPF, but only a minority of patients develop AE.
Objectives: The aim of this study was to examine different clinical courses of IPF and to evaluate associated risk factors and predictors.
Methods: We retrospectively studied 85 consecutive patients diagnosed with IPF based on the criteria of the ATS/ERS consensus statement. Clinical data and serial pulmonary function tests were obtained. In accordance to King et al. (King, TE et al. AJRCCM 2011; 183:431-40) patients were grouped to four clinical phenotypes: stable disease, slowly progressive, rapid progressive to death or mixed course. Furthermore, AEs as defined by the criteria of Collard et al. (Collard, HD et al. AJRCCM 2007; 176:636-643) were reported. Serial serum CCL18 concentrations were measured by ELISA.
Results: AE occurred in 34 (40%) patients, with multiple episodes in 6 (7%) patients. The 5-yr survival rate of IPF patients with and without AE was 15% and 41%. Baseline CCL18 serum concentrations differed significantly between the four clinical phenotypes ($p<0.0001$). IPF patients with a rapid progressive or mixed course showed higher CCL18 serum concentrations ($p<0.0001$), lower FVC predicted (FVC<60%; $p=0.0156$) and lower TLC predicted ($p=0.002$). Stepwise multivariate regression analysis of all patients revealed that CCL18 serum concentration ($p=0.016$) was independently associated with AE.
Conclusions: We demonstrate that baseline serum CCL18 levels are elevated in IPF patients prone to AE and predict a rapid progressive or mixed course of IPF.

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Risk factors of acute exacerbation of idiopathic pulmonary fibrosis-extended analysis of the pirfenidone trial in Japan
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Background: Although acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is a well known clinical condition, predicting risk factors remain unknown. Recent studies reported that various baseline factors, and at least 10% decline in FVC at six months were reported as risk factor for AE (Sarcoidosis Vasc Diffuse Lung Dis 2010;27:103-110). We sought to evaluate the risk factors of AE by analyzing our phase III clinical trial of pirfenidone for patients with IPF (n=275) (Eur Respir J 2010; 35: 821-9).
Methods: Baseline characteristics including age, sex, smoking, BMI, dyspnoea grade (Hugh-Jones classification), AaDO2, PaO2,%VC,%DLco, KL-6, SP-A, SP-D were evaluated as possible risk factors for AE. Decline of VC≥10% within 6 months was also evaluated. In addition, effect of pirfenidone therapy was also evaluated.
Results: During 52 weeks, 14 patients experienced AE-IPF. Univariate analysis by Cox proportion hazards model were as follows: age (HR, 0.982, p=0.642), sex (HR, 1.505, p=0.489) smoking (HR, 0.464, p=0.168), BMI (HR, 0.935, p=0.460), dyspnea grade (HR, 1.763, p=0.168), AaDO2 (HR, 1.047, p=0.069), PaO2 (HR, 0.955, p=0.110),%VC (HR, 0.971, p=0.078),%DLco (HR, 0.994, p=0.714), KL-6 (HR, 1.000, p=0.698), SP-A (HR, 0.998, p=0.776), SP-D (HR, 1.000, p=0.875), pirfenidone treatment (HR, 1.211, p=0.732). Decline of VC was a significant risk factor for AE-IPF (HR, 3.780, p=0.014). Stepwised multivariate analysis revealed that initial AaDO2 (HR, 1.055, p=0.045) and decline in VC within 6 months (HR, 3.951, p=0.012) were significant risk factors for AE-IPF.
Conclusions: Baseline higher AaDO2 and decline of VC≥10% within 6 months are significant risk factors of AE-IPF.

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Clinical profile of idiopathic pulmonary fibrosis with lung cancer
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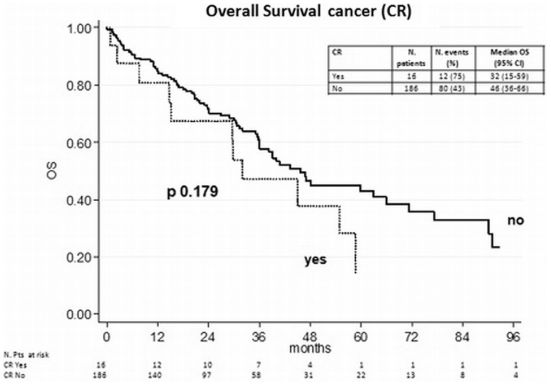
Background: The association of lung cancer (LC) and idiopathic pulmonary fibrosis (IPF) is well recognized. The poor prognosis of both conditions and the risk of serious complications related to LC treatment make the clinical management particularly difficult.
Aims: To describe the clinical profile and survival of IPF associated or not with LC
Methods: Retrospective cohort study from data collected in a prospective manner and retrieved from the IPF registry of Pulmonology Unit (Morgagni Hospital, Forlì, Italy). Study period from January 2000 to December 2010.
Results: 208 patients diagnosed with IPF according to ATS/ERS criteria and followed in our IPF Clinic. Nineteen (9.1%) patients developed LC (cancer group, CG). Compared to patients without LC (non-cancer group, NCG), CG were older (68.5±7.9 vs 63.9±8.9 years), more frequently smokers (79.5% vs 67.8%) and heavier smokers (pky 44.3±32.1 vs 30.6±21.9), they had better baseline functional respiratory tests and similar number of familial IPF cases. There was not a statistically significant difference in median survival in the two groups (32 months in CG and 46 months in NCG, p=0.179).



Conclusions: Cigarette smoke was the only clinical variable associated with increased risk of developing LC in IPF patients. We did not observe any difference in incidence of LC when comparing familial and sporadic forms of IPF. Survival did not differ despite better functional tests at baseline in the CG.

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Effects of nitric oxide synthase up-regulation in early remodeling of usual interstitial pneumonia has impact on long term outcome of patients

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Recently, impaired endothelial-dependent vascular tone suggest that NOS enzymatic activity, as well as vascular NO synthesis and release, may decrease or increase dependent on early or late pulmonary remodeling process. In this study, we validated the importance of the expression of NOS isoforms (neuronal [nNOS], inducible [iNOS], and endothelial [eNOS]) protein and studied the relationships between NOS isoforms in early and late remodeling of usual interstitial pneumonia (UIP).

Material and methods: We determined density of endothelial, muscular, myofibroblasts and alveolar cells expressing NOS in surgical lung biopsies from 25 patients with UIP. We used immunohistochemistry and histomorphometry to evaluate the amount of endothelial, muscular, myofibroblasts and alveolar cell staining for NOS.

Results: Unaffected areas of UIP had increased eNOS and iNOS expression, whereas a significant increase of nNos expression was found in unaffected and vascular areas. Kaplan–Meier analysis for nNOS and eNOS dichotomized percentages revealed respectively a statistically significant prolonged disease specific survival for patients in the low risk group (estimated median survival 51.73 vs. 33.36 and 55.56 vs. 9.87 months for the high risk group, log rank $p<0.01$).

Conclussions: We conclude that these differences in the frequency and distribution of lung cells expressing NOS isoforms in early remodeling may represent adaptive changes that contribute both to the vasodilation of distal segments as new muscle develops in the UIP lung and consequence of alveolar surface stress from the effects of oxidant injury.

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Imbalance between circulating endothelial cells and endothelial progenitors in idiopathic pulmonary fibrosis

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Background: Fibrogenesis during idiopathic pulmonary fibrosis (IPF) is associated with abnormal vascular remodeling. Respective abundance of circulating endothelial cells (CEC) and endothelial progenitor cells (EPC) might reflect the balance between vascular injury and repair and potentially serve as a biomarker of the disease.

Objectives: We postulated that CEC and all EPC subtypes might be differently modulated in IPF. We aimed at 1) assessing them in early stages of IPF and 2) searching for correlations with disease severity.

Methods: 64 consecutive patients with newly diagnosed IPF and 10 healthy age-matched volunteers were studied. CEC were isolated with CD146-coated beads. CD34, CD133 and KDR antigens, characterizing EPC, were assessed through flow cytometry. EPC (early CFU-Hill and late endothelial cells forming colonies (ECFC)) were also counted using cell culture.

Results: CEC numbers were significantly increased in IPF ($p=0.004$) whereas EPC assessed using both flow cytometry (CD34+KDR+) and cell culture were decreased vs controls ($p<0.05$). CEC did not differ according to disease severity (DLCO > or < 40%) nor did CD34+KDR+ cells. In contrast, progenitors obtained in culture were markedly increased in the most severe vs the least severe IPF subgroup ($p=0.04$ and $p=0.01$ for CFU-Hill and ECFC, respectively, for DLCO<40% vs >40%). ECFC was the only cell type found to be correlated to DLCO (Spearman correlation test, $p=0.04$).

Conclusion: IPF is associated with markers of vascular injury and with a global decrease in EPC. Disease severity is associated with an EPC mobilization whose mechanisms and clinical impact need to be explored.

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Leptin and adiponectin levels in idiopathic pulmonary fibrosis

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Background: Studies in the literature suggest a regulatory role of adipokines in the development of fibrosis in various organs. Leptin is a critical factor for the development of fibrosis in the liver. In contrast, adiponectin inhibits liver fibrogenesis both *in vivo* and *in vitro*. However, their role in pulmonary fibrosis has not been examined in the past.

Objectives: We hypothesized that leptin and adiponectin may be involved in the development of pulmonary fibrosis and therefore we measured levels of leptin and adiponectin (RIA) in the serum of 37 Idiopathic Pulmonary Fibrosis (IPF) patients (mean±SD: 68.8±8.8 years) and 22 controls (65±7.5 years). Clinical and radiological data were collected from all subjects. Pulmonary function tests, arterial blood gas analysis and transthoracic echocardiography were performed.

Results: The levels of leptin and adiponectin did not differ between patients and controls. However, leptin levels when divided by BMI in male patients with PaO2<65 were significantly reduced as compared to male patients with PaO2 ≥65mmHg (0.21 vs 0.38, $p=0.031$, respectively). Additionally, leptin to adiponectin ratio in male IPF patients with <65 mmHg was significantly reduced versus male patients with PaO2 ≥65 mmHg (1.07 vs 1.45, $p=0.045$, respectively).

Conclusions: Leptin levels when adjusted for BMI and leptin to adiponectin ratio are reduced in male IPF patients with hypoxia. Our findings suggest a possible role of leptin in the severity and/or pathogenesis of IPF. Further studies are required in order to clarify the association of leptin and adiponectin with the disease.

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HRCT score to control and evaluate the prognosis in idiopathic pulmonary fibrosis

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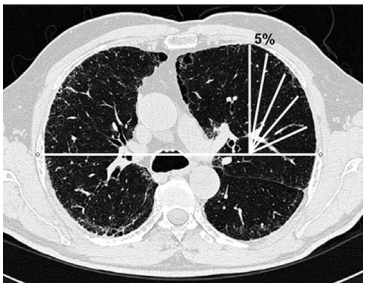
Introduction: HRCT is not commonly used to assess the severity of idiopathic pulmonary fibrosis (IPF).

To assess: We sought to evaluate the usefulness of a semiquantitative HRCT score and its relation with respiratory function tests normally used to ascertain IPF severity and to monitor the evolution and progression of the fibrotic process.

Patients and methods: A prospective 4 years study including 36 consecutive IPF patients. A semiquantitative score was used to score every predefined IPF 4 patterns on HRCT. As a result of summing up all of them we had the Total Score of Fibrosis for each patient.



We studied its relation with functional respiratory tests, bronchoalveolar lavage (BAL) cellularity and analyzed the differences found among the death patients.

Results: We found a significant correlation between the honeycomb score and% DLCO (r= -0.48, p=0.004), total score of fibrosis with% FEV1 (r= -0.41, p=0.01),% DLCO (r= -0.41, p=0.01) and% TLC (r= -0.36, p=0.03). The 6-minutes walking test (6MWT): the final SaO2 correlated with the total score (r= -0.48, p=0.04). A-aO2grad also correlated with the honeycomb score (r=0.43, p= 0.01) and the total score (r=0.48, p=0,005). Dead patients had a higher total score and a tendency of higher neutrophilia in BAL (p=0.059).

Conclusions: A semiquantitative score of HRCT is useful in assessing the initial severity of IPF and should be able to predict its development.

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Daily hand-held spirometry for the monitoring of patients with idiopathic pulmonary fibrosis

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Introduction: Idiopathic pulmonary fibrosis (IPF) is an invariably fatal condition characterised by a variable course; prolonged periods of apparent disease stability are often interspersed by dramatic and often cryptogenic acute deteriorations. These acute exacerbation are a significant cause of morbidity and mortality in IPF. For lung transplant recipients, daily hand held spirometery has been shown to be an effective means of detecting acute rejection episodes. This exploratory study aims to determine the utility of daily hand held spirometry in IPF.

Methods: Patients with IPF were recruited from amongst new referrals to our unit. Baseline severity was assessed by FVC, DLco and 6 minute walk. Patients were given a hand held spirometer (Carefusion, UK) and provided with instruction on how to self-administer spirometry. Patients were asked to record daily FEV1 and FVC values.

Results: To date, 19 subjects have been recruited; 17 male, age 66.5±7.6 years (mean ± SD). Overall the subjects have moderate to severe disease with FVC 74.2±21.8% predicted, DLco 40.6±13.5% predicted and 6 minute walk distance 325±120m. For subjects thus far completing over 4 weeks of diary monitoring (n=9), mean hand held FVC correlates well with formal clinic spirometry (r^2

0.902). Reproducibility of daily FVC has been good with mean variance 6.9% (range 3.0-12.1%).
Discussion: This pilot study suggests that daily spirometery can be reliably and reproducibly performed by patients with IPF. By recording daily FVC it is to be hoped that it will be possible to gain a clearer insight in to the true natural history of IPF and detect, and thus treat, acute exacerbations at an early stage in their evolution.

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Slow *versus* rapid progressors in idiopathic pulmonary fibrosis
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Background: Idiopathic pulmonary fibrosis (IPF) is usually characterized by the insidious onset of dyspnea or cough, but there is a subgroup of patients who display a rapid progression to an end-stage disease. These two phenotypes, slow progressors (SP) and rapid progressors (RP) have not yet been fully characterized.
Aim: To characterize SP and RP and identify baseline factors predicting each progression.
Methods: A retrospective study with 81 IPF patients was performed. They were classified as SP and RP. Patients with acute exacerbations were excluded. Baseline differences in progression covariates or factors were assessed through U Mann-Whitney, Chi square or Fisher exact test. Median survival was estimated using Kaplan-Meier survival curves.
Results: Patients were classified as SP in 55 (67.9%) and as RP in 10 (12.3%). Median survival time was 41 months in SP and 9 months in RP (Log Rank test $p<0.001$). The comparison between two groups showed lower median values of FVC (60 *versus* 73) and TLC (57.8 *versus* 72) and a higher percentage of non-smokers in RP group at time of diagnosis.
Conclusion: The analysis of this group of IPF patients confirms two clearly separated phenotypes, SP and RP, that must be discriminated, since they seem to have different presentations and a remarkably different evolution. These results could mean distinct physiopathological pathways, which could implicate different therapeutic approaches.

P657
Clinical picture analysis of idiopathic pulmonary fibrosis (IPF) and lung cancer (LC) concomitance in the population of patients hospitalized in Ist Clinic of Lung Diseases Institute for Tuberculosis and Lung Diseases in Warsaw, Poland in the years 1994-2009
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It is commonly considered that idiopathic pulmonary fibrosis (IPF) predisposes to the occurrence of lung cancer (LC). The frequency of IPF and LC coexistence is assessed at 4,8% to 48,2% depending on the country of origin and type of the report. Based on the medical records in years 1994 – 2009 in the 1st Clinic of Lung Diseases were hospitalized 1701 patients with pulmonary fibrosis of different aetiology including 668 patients with IPF. Between them 21 patients (15 men and 6 women, median age 66 years) with concomitant lung tumor were found (3,1437%). In 62% of these patients histopathological diagnosis of LC was obtained. It constituted 1,946% of deadly coincidence.
We have characterized the group in terms of demographic data, histopathological diagnosis, moment of recognizing LC in relation to duration and treatment of IPF, clinical symptoms, images of computed tomography, clinical status and treatment of LC. Low percentage of LC and IPF coexistence is probably caused by underdiagnosis and genetic differences of populations.
Unlike most studies, tumors in study population were often localized in the upper lobes (60%). Predilection to lower lobes is explained by more severe fibrosis in this location.
Other data characterizing the group are consistent with literature. In the group of interest is men domination (71,4%), cigarette smokers (76%), the median exposure to tobacco smoke 31,5 pack-years, the most frequently asked histopathological diagnosis is squamous cell carcinoma (38%), the predominant location is peripheral.

P658
Prognostic evaluation in idiopathic pulmonary fibrosis (IPF)
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The clinical course of patients with IPF is variable and can display long periods of stability, a steady gradual decline or periods of acute deterioration.
The aim of the study was to identifying factors that can help refine the prognosis for patients at the time of initial diagnosis.
Methods: Thirty-five patients with IPF according to the ATS/ERS criteria underwent spirometry, O2 saturation, 6-min walking distance (6-MWD) and radiographic evaluation of fibrosis (HRCT score). The independent contributors of dependend variables were selected by using stepwise multiple regression analysis. The Kaplan-Meier method was used to produce estimates and plots for the patient cohort. Survival time was calculated as the number of months from the patients' initial visits until their death or time of censoring. Patients were censored if they: were still alive at the last contact.
Results: From 35 consecutive patients with IPF (18 men and 17 women, mean age 53.5±13.2 yrs) 12 patients (34.3%) died during the study despite standard treatment. The mean survival was 11.7±12.6 months. The subgroup of patients with IPF with resting O2 saturation ≤88%, FVC ≤50%, 6-MWD ≤350 m, fibrosis score ≥10 has a bad prognosis and high death rate.
Conclusions: IPF prognostic markers allow identifying subgroups with different clinical evolution, providing prognostic information to patients and to improve the selection of the most appropriate patients for novel therapeutic interventions.

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The prognostic significance of cardiopulmonary exercise in IPF
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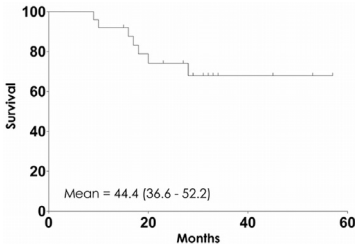
Background: In Idiopathic Pulmonary Fibrosis parenchymal lung damage leads to defects in mechanics and gas exchange, manifesting with progressive dyspnea and exercise limitation. Since IPF carries a poor prognosis, early and reliable prediction of survival is of significant value to the clinician. The role of maximal exercise data in prognostic evaluation of IPF patients is uncertain.
Aims and objectives: The aim of the present study was to evaluate the prognostic significance of cardiopulmonary exercise test (CPET) in this group of patients.
Methods: Twenty five IPF patients were prospectively recruited and underwent functional evaluation through maximal (CPET) and submaximal exercise testing (6 minute walk test- 6MWT) at diagnosis. Patients were followed up regularly; epidemiologic and survival data were gathered. Correlations between survival and parameters of maximal and submaximal exercise were calculated.
Results: Mean survival was 44.4 months.



Statistically significant correlations were found between survival and CPET parameters such as VO2peak (p=0.02, RR=0.99), VO2peak/kg (p=0.01, R=0.78), AT (p=0.01, RR=0.72), SpO2peak (p=0.01, RR=0.8), VE/VCO2slope (p=0.005, RR=1.09), VE/VCO2AT (p=0.008, RR=1.14) and the 6MWT parameters: distance walked (p=0.008, RR=0.99) and desaturation (p=0.01, RR=1.42).
Conclusions: Physiological parameters obtained during maximal and submaximal exercise testing reflect survival in IPF population.

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Proposal for revised clasification of disease severity of idiopathic pulmonary fibrosis in Japan
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Background: PaO_2 at rest and presence of desaturation during a 6-minute walk

test (6MWT) were shown to be prognostic factor in idiopathic pulmonary fibrosis (IPF). In Japan, classification of disease severity of IPF (stage I-IV) has been used for the decision of medical care subsidies. Stages of severity of IPF are as follows. stage I ($PaO_2 \geq 80$ torr at rest), stage II (70-80 torr), stage III (60-70 torr), stage IV (< 60 torr). For patients with stage II or III, if the SpO_2 during a 6MWT is less than 90%, then the severity should be increased by one stage. We hypothesized that patients whose PaO_2 is ≥ 80 torr with desaturation (classified as stage I in present) might have poor prognosis.
Methods: Two hunred fifteen patients with IPF in 10 centers performing 6MWT routinely were studied by using a questionnaire survey.
Results: The proportion of present stage I was 47.9%, and among them, 51.5% patients showed desaturation during 6MWT. The median survival time (MST) of stage I with and without desaturation were 50.5±1.9 mo. and 99.3±35.0 mo. respectively.(p=0.0033). In revised severity stages of patients with IPF, MST of stage I (n=44), stage II (n=77), stage III (n=50), and stage IV (n=44) were 99.3±35.0 mo., 52.0±2.7 mo., 38.6±8.7 mo., and 22.9±4.3 mo. respectively. New survival curves between the each stage have been adequately separated.
Conclusion: The patients whose PaO_2 is ≥ 80 torr at rest with desaturation during 6MWT should be classified as stage II in revised classification of disease severity in patients with IPF.
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Therapeutic effect of combination of salvia and ligustrazine on bleomycin-induced pulmonary fibrosis
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Background: Current agents for the treatment of idiopathic pulmonary fibrosis (IPF) have not been found to improve the prognosis, thus requiring the development of new types of drugs to treat IPF.
Aims: This study was designed to investigate the effect of combination of Salvia (one kind of traditional Chinese medicine) and Ligustrazine (one kind of traditional Chinese medicine) on the expression of inflammatory mediators, the mRNA expression of type I and III collagen, and hydroxyproline content in lung tissues in bleomycin (BLM)-induced rat pulmonary fibrosis.
Methods: Adult Wistar rats were intratracheally instilled with BLM or normal saline (NS). After intratracheal administration, the animals were intraperitoneally injected with combination of Salvia and Ligustrazine or NS every day. Then they were sacrificed. HE and Masson staining were used to observe alveolitis and fibrosis. Immunohistochemistry analysis was used to examine the expressions of inflammatory mediators in lung tissues, and the mRNA expression of type I and III collagen and hydroxyproline content in lung tissues was also measured.
Results: Combination of Salvia and Ligustrazine could alleviate alveolitis and fibrosis; could attenuate the expression of inflammatory mediators in lung tissues; and could also decrease the mRNA expression of type I and III collagen and hydroxyproline content in lung tissue in rat pulmonary fibrosis.
Conclusions: Combination of Salvia and Ligustrazine had an anti-fibrosis effect, and it might be considered as a clinically viable option to treat pulmonary fibrosis.

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Promising effect of PMX-DHP absorption therapy for acute exacerbation of IPF
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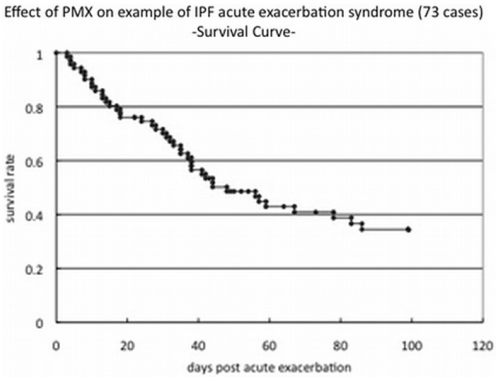
Background: Idiopathic pulmonary fibrosis (IPF)- acute exacerbation (AE) is poorly prognostic and devastating disorder in the IPF management. PMX-DHP (Toraymyxin) is indicated SIRS for endotoxin absorption therapy in Japan, which is widely used with extra cooperative hemo-perfusion and nafamostat mesilate. We tried to use of PMX-DHP for IPF-AE.
Methods: The example of enforcing IPF-AE by PMX-DHP in multicenter experiences (n=73 for IPF in 160, all cases) was retrospectively analyzed. All cases that have P/F data before and after PMX-DHP, and are able to pursue the prognosis until the 90 days, indicated analytical objects.
Results: In comparison of baseline and after PMX-DHP, P/F ratio significantly improved in case of P/F<100 than 100<=P/F<200 at baseline, which was beneficial for survival rate (death rate). P/F ratio actually rose in the survival cases. WBC has decreased in all cases. As for CRP, a significant change was not seen. Survival rate indicates 66.2% (30d), 30.1% (90d) in all cases, and 70.1% (30d), 34.5% (90d) in IPF. These results suggested to improve survival of IPF-AE in comparison with those reported in the past.
Conclusion: PMX-DHP is possibly beneficial for the prognosis of IPF-AE.



Abstract P662 – Figure 1

P663
Effect of bosentan on MMP-7 levels as add-on therapy in idiopathic pulmonary fibrosis. A prospective study
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Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal lung disease lacking effective treatment. Endothelin receptor antagonists were shown to have possible beneficial effects in early stages of IPF. Recent evidence suggests that increased MMP7 levels may be indicative of disease progression.
Objectives: To determine the effects of bosentan on MMP-7 serum levels in patients with IPF.
Methods: We prospectively studied eleven IPF patients, nine males and two females, aged 68.9±8.8 years. Five were current or ex-smokers (43±23.5 pack/years), the remaining non-smokers. All patients received oral bosentan 62.5 mg twice daily for 4 weeks, increased to 125 mg twice daily thereafter, for 6 months or longer, as add-on therapy to 10mgr prednisolone, acetylcysteine (600 mg tid) and Azathioprine (150 mg/day). Serum MMP-7 levels were measured using commercial ELISA kits. All the patients had routine laboratories, PFTs and radiological (HRCT) tests, 6-minute walking distance (6MWD) and alveolar-arterial gradient of oxygen tension (PA-aO2) measured at baseline, three and six months of treatment.
Results: Serum MMP-7 levels did not show any significant change from baseline (6.4±3.22 pg/ml) to three (7.39±4.77 pg/ml) and 6 months (7.61±4.76 pg/ml). There were no significant alterations in FVC, DLCO, 6MWD and PA-aO2, pre- and post-treatment. No cases of clinically significant infection, leucopenia, elevated liver enzymes or other unexpected adverse events were reported.
Conclusions: The above data suggest that bosentan as an add-on agent to standard therapy is a safe therapeutic modality which results in disease stabilization as assessed by serum MMP-7 and functional status.

P664
Tolerance of pirfenidone in Indian patients with idiopathic pulmonary fibrosis – Usual interstial pneumonitis: An initial experience
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Aim: Pirfenidone has been recently approved for idiopathic pulmonary fibrosis-usual interstitial pneumonitis (IPF-UIP) in Japan & India. To the best of our knowledge, Indian data is not available. Reported side effects include photosensitivity, skin rash & gastrointestinal upset. We present our initial experience with tolerability of Pirfenidone in IPF-UIP.
Methods: 15 patients (mean age 62 yrs, Male: 11) with clinical-radiological diagnosis of IPF-UIP were included. Baseline liver function, Spo2 & 2-D Echo were performed. Lung function tests & six minute walk tests were possible in 10 patients. Follow up oximetry & liver function tests were performed in all patients. Pirfenidone was started at 200 mg three times a day. Dose was increased to 400 mg three times a day after 2 to 4 weeks. Patients also received prednisolone 10 mg/day, n-acetyl cysteine 600 mg three times a day & & PPI.
Results: At baseline mean Spo2 was 92.5%, mean FVC 1.42 Liters. Liver enzyme & bilirubin were normal. 8 patients had pulmonary hypertension on 2-D Echo. There was no significant increase in the liver enzymes at four weeks follow up. 4 patients were initiated on pirfenidone at diagnosis. Rest of patients were diagnosed with IPF-UIP at mean 27.6 months prior to initiating pirfenidone. Mean duration of follow up since starting pirfenidone was 52 days. 2 patients complained of nausea & 1 patient had loose motion. 2 patients skin itching, however, there was no discoloration. These patients were counseled about the adverse event, but preferred to continue the medication.
Conclusion: At short term follow up, pirfenidone appears to be well tolerated in Indian patients with IPF-UIP.

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Correlations of quantitative HRCT score in idiopathic pulmonary fibrosis (IPF)

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The aim of the study was to evaluate the usefulness of visual HRCT-score (fibrosis score, ground-glass score) in the assessment of the disease extent.

Methods: Thin-section (10 mm) images were obtained and scored prospectively in 35 consecutive patients (18 men and 17 women, mean age 53.5±13.2 yrs) with newly diagnosed IPF. Each patient's lobe was scored on a scale of 0-5 for both ground-glass attenuation and fibrosis. The correlations among FVC (% pred.), FEV1 (% pred.), MRC dyspnea score, modified Borg dyspnea score, O2 saturation, 6-MWD and HRCT scores (fibrosis and ground-glass) were studied (Pearson correlation coefficient).

Results: The mean value of the fibrosis score was 11.9±5.2 and of the ground-glass score was 13.8±5.6. Fibrosis score significantly correlated to FVC ($r = -0.33$, $p = 0.04$), MRC ($r = 0.39$, $p = 0.02$), 6-MWD ($r = -0.53$, $p = 0.001$), Borg dyspnea score after 6-MWT ($r = 0.4$, $p = 0.01$), O2 saturation ($r = -0.33$, $p = 0.04$). Ground-glass score didn't corelate to any of analised variables.

Conclusions: In IPF there is a good correlation of functional tests, dyspnea scores, exercise capacity to the HRCT fibrosis score, the best correlation was found with 6-MWD. The correlations of HRCT fibrosis score emphasize the importance of radiographic evaluation in the diagnosis and follow-up of IPF.