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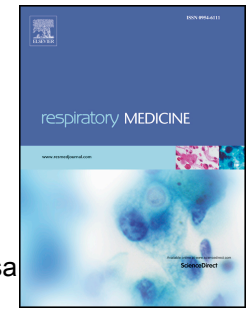

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Familial pulmonary fibrosis: clinical and radiological characteristics and progression analysis in different high resolution-CT patterns.

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Short Title: Clinical and radiological characterisation of familial pulmonary fibrosis.

Abbreviations: Familial pulmonary fibrosis (FPF), High Resolution Computed Tomography (HRCT), Pulmonary function test (PFT), Bronchoalveolar lavage (BAL).

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Abstract

BACKGROUND. Familial pulmonary fibrosis (FPF) is defined as an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family. The aim of the present study was to contribute to the clinical, functional and radiological characterisation of FPF with particular regards to disease progression and survival.

METHODS. Baseline clinical, functional and radiological data of a FPF population (n=46 patients) were retrospectively collected and analysed according to the 2011 IPF guidelines HRCT classification. A PFT follow-up after 1-year and survival analysis was conducted among to different HRCT patterns.

RESULTS. 22 female and 24 male patients (age at diagnosis 58.5±9.7 years-old), belonging to 30 families, were included in this study. Radiological analysis demonstrated the presence of a UIP pattern at HRCT in 54.3% of patients, Poss-UIP in 21.8% and Incon-UIP in 23.9%. Incon-UIP patients were younger and more frequently female. Pulmonary function test showed a restrictive ventilatory defect in patients with UIP and Incon-UIP patterns, while Poss-UIP patients had normal volumes with only a mild reduction of DLCO. BAL composition revealed increased lymphocytes in Incon-UIP patients. Respiratory functional 1-year follow-up showed a significant worsening in UIP patients only. HRCT pattern progression was only demonstrated from Poss-UIP to UIP (18% of patients). Median survival was not statistically different among the 3 HRCT groups, although Poss-UIP patients presented a better outcome.

CONCLUSIONS. FPF has been confirmed to be a complex condition with poor prognosis. The present study firstly analysed functional and radiological follow-up data of patients with FPF, showing that it may manifests with several HRCT patterns with different rates of progression, in which Possible UIP and UIP could be considered phases of the same disease and Inconsistent UIP patients may represent a different clinical and radiological condition.

Introduction.

Familial pulmonary fibrosis (FPF) is defined as an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family (1). Since the 1950-60s when the first cases were described (28, 29), interest in FPF has increased and in 2013 FPF was also reported in the ATS/ERS Idiopathic Interstitial Pneumonias Statement (2). Pulmonary fibrotic involvement is present in numerous genetic disorders, such as Hermansky-Pudlak Syndrome (3), neurofibromatosis (4), tuberos sclerosis (5, 6), Niemann-Pick Syndrome (7), Gaucher's Diseases (8), familial hypercalcemia hypocalciuric (9). Some common genetic variations have been documented in FPF as well as idiopathic pulmonary fibrosis (IPF), suggesting a similar genetic background of the two conditions (2, 10-12). In particular, TERT and TERC genes for the telomerase complex (12, 13), the surfactant proteins C and A genes (SFTPC and SFTPA) (14), the ABCA3 gene that encodes for an intracellular SFTPC carrier (15) and the MUC5B polymorphism (rs35705950) (16) are responsible for about 20% of all FPF cases; the majority of genetic alterations are still unknown (12).

Clinical observational studies have suggested the presence of some differences between FPF clinical behaviour and IPF. Major points that emerged were the younger age of presentation in FPF, the more equal gender distribution and the common predisposing role of smoke habit (17-21). Exact epidemiology of FPF is unknown; a wide range of prevalence has been reported, varying from 0.05 to 19% (17, 22-25). FPF can be associated to different pathological and radiological features, not only with UIP pattern. Non-specific Interstitial Pneumonia (NSIP), Cryptogenetic Organizing Pneumonia (COP), centrolobular nodules and non-classifiable pulmonary fibrosis have been reported (19, 20).

The aim of the present study was to contribute to the clinical, functional and radiological characterisation and phenotype definition of patients with FPF, with particular regard to the evaluation of the disease progression and survival according to different chest high resolution computed tomography (HRCT) patterns.

Methods.

A cohort of 46 patients, belonging to 30 families, was included in this retrospective study. All patients were followed at the Regional Referral Centre for Sarcoidosis and other Interstitial Lung Diseases of the Respiratory Diseases and Lung Transplant Unit of the Siena University Hospital (AOUS), Italy.
The analysis focused on demographic, clinical, functional and radiological data according to different HRCT patterns. In particular, familial history of fibrosis, age at diagnosis, smoking history, BMI, symptoms at onset, comorbidities and acute exacerbation (AE) episodes were analysed. Respiratory physiological variables included pulmonary functional tests (PFT), 6-minute walking test (6MWT) and arterial blood gas analysis (ABGA). All data was collected at the time of chest HRCT and at 1-year follow-up. Bronchoalveolar lavage (BAL) cellular composition at diagnosis was included together with lymphocyte phenotype. All participants gave their written informed consent to the study.
The earliest (the closest to the onset of symptoms) available HRCT scan of all patients was included in the study. According to the 2011 ATS/ERS/JRS/ALAT IPF guidelines (26), an expert thoracic radiologist classified all patients into three different groups: UIP, possible UIP (poss-UIP) and inconsistent with UIP (incon-UIP). A radiological CT follow-up analysis was conducted in a subgroup of patients to evaluate evolution and pattern modification. Data collection from patients with FPF started in 2007 and many of our functional and radiological data date before the introduction of specific antifibrotic therapies for IPF in our Country. Only two patients started Pirfenidone during the 1-year follow-up period of observation: one was classified at HRCT as Incon-UIP (but pathology was a mixed pattern UIP/NSIP), another showed a UIP pattern.

Statistical analysis.
Statistical analysis was performed by GraphPad Prism v 6.0 and SPSS v 16.0, differences with $p<0.05$ were considered significant. Non-parametric tests were applied because data failed normality tests; differences between two groups were studied by the Mann-Whitney's test, while analysis of the variance was made by Kruskal-Wallis' test. Differences of prevalence on contingency tables were analysed by Fisher's test or Chi-square. Survival analysis was performed by Kaplan-Meyer's curves, comparison of survival curves was made by log rank test (Mantel-Cox's test); lung transplantation was considered a fatal event. Data was expressed as mean ± standard deviation; survival was reported as median.

Results.

HRCT evaluation

Our FPF population (n=46, 52.1% male, age at diagnosis 58.5±9.7 years-old) presented different HRCT pictures. According to the ATS/ERS/JRS/ALAT IPF guidelines (26), the majority of patients were classified as UIP (25/46, 54.3%), while the others as Poss-UIP (10/46, 21.8%) and Incon-UIP (11/46, 23.9%).

HRCT scans were performed 781.5±885.3 days after symptoms onset; patients with the Poss-UIP pattern performed chest HRCT closer to the clinical onset, although the difference did not reach significance (p=0.21, table 1).

Patients with a UIP pattern at HRCT typically showed reticular abnormalities and honeycomb changes with basal, bilateral and subpleural predominance. Poss-UIP patients showed bibasal and subpleural parenchymal reticular alterations without honeycombing. Patients with Incon-UIP pattern had some atypical features or localisations inconsistent with the UIP pattern (26). Among patients of this group, three different subgroups could be recognised: NSIP was observed in 6/11 (54.5%) cases, Respiratory Bronchiolitis-associated to Interstitial Lung Disease (RB-ILD) in 1 patient (9%) and unclassifiable pulmonary fibrosis in 4/11 patients (36.5%). In table 2 HRCT findings of Incon-UIP patients were reported. Moreover, unclassifiable fibrosis patients revealed 2 different pictures: 1 with prevalent fibrotic ground-glass combined with multiple areas of air-trapping and zones of fibrotic sparing; and the other with multiple low-density centrilobular nodules associated with subpleural fibrotic consolidations in the upper-lobes and/or in the dorsal region of apical segments of the lower lobes and irregular interfaces along the bronchovascular walls (Fig. 1 a-f).

Bilateral calcified and sometimes merged micronodules with random distribution resulted as a common feature in the majority of Incon-UIP patients, particularly in unclassifiable fibrosis patients (66.6%). Pulmonary emphysema was present in a minority of patients with FPF (3/46 patients, 6.5%). A combination of paraseptal and centrilobular emphysema was evident in 1 patient with UIP and in another with an Incon-UIP pattern; centrilobular emphysema alone was present in 1 patient with Poss-UIP. In all cases emphysema was prevalent in the upper lobes and not prevailing the extent of fibrosis; all these patients were former smokers.

Of 15 families we have the possibility to enrol in the study two or more members (32 patients totally). The same HRCT pattern was observed among different members of the same family in 9 cases (6 families with UIP and 3 with Incon-UIP). In 6 of the 15 families different HRCT patterns were observed among relatives: in 5 families the contemporary presence of UIP and Poss-UIP patterns was recorded; in only one family a member with Poss-UIP and another with Incon-UIP pattern were present. The contemporary presence of UIP and Incon-UIP patterns was not observed in any of the families.

Pathology was available in 9/46 patients: in all HRCT UIP patients (n=3), histology was conclusive for UIP; in Poss-UIP patients (n=2), it showed UIP in one and unclassifiable pulmonary fibrosis in another; in Incon-UIP patients (n=4), in 3 cases diagnosis was NSIP and a mixed pattern NSIP/UIP in the last.

Clinical, functional and BAL data

The age at diagnosis was not statistically different among the 3 HRCT groups, however the Incon-UIP patients were the youngest (with a mean age lower of seven years) and were significantly more frequently female (p=0.003). No patient was current smoker at the time of analysis and the percentage of former smokers was not statistically different among the 3 groups. The amount of tobacco exposure (pack/year) was not statistically different (p=0.75) and no significant difference in body mass index (BMI) was found (p=0.21) (table 1). We had access to complete data of 12 pairs of brothers, 2 pairs of cousins and 3 mother/father and daughter/son. Among brothers or cousins, age at presentation differed of 4.8 ± 2.6 years from one to another family member; daughters/sons were 18 ± 2 years younger with respect their relative mother/father. Among brothers or cousins, in all cases in which we observed the presence of one member with UIP pattern and one with Poss-UIP, the patient with the Poss-UIP pattern was younger at clinical presentation than the other. All enrolled patients showed a direct consanguinity (being from the same kinship) with at least one other member with pulmonary fibrosis. In particular, in 19 families affected members were at the 2nd degree of kinship (brothers/sisters), 4 families were at the 1st (parents), two families were at the 1st, 2nd, 3rd and 4th (parents, brothers/sisters, aunts/uncles, first cousins), one family were at the 1st and 2nd (parents, brothers/sisters), one family were at the 1st and 3rd (parents, aunts/uncles), one family were at the 1st, 2nd and 3rd (parents, brothers/sisters, aunts/uncles), one family were at the 2nd and 3rd (brothers/sisters, aunts/uncles) and one family were at the 2nd, 3rd and 4th (brother/sisters, aunts/uncles and first cousins).

PFT showed a restrictive defect in UIP and Incon-UIP patients, while in patients with Poss-UIP pattern, forced and static volumes were in the normal range with only a mild reduction of DLCO (see table 1). DLCO was significantly reduced in UIP than Poss-UIP patients ($p<0.05$). Interestingly, no reduction of residual volume (RV) was observed in patients with Incon-UIP pattern at HRCT ($p<0.05$), although these patients had a similar restrictive functional defect than the UIP patients with which had comparable FVC and TLC (table 1, fig. 2). ABGA and 6MWT parameters were not statistically different among the 3 groups (data not shown).

BAL cellular composition revealed a significant increase of lymphocyte percentages in Incon-UIP ~~and~~ than in UIP patients ($p<0.05$); Poss-UIP patients had high, but not statistically significant, lymphocyte % in BAL. Moreover, Poss-UIP patients showed a significant lower percentage of neutrophils than the other patient groups ($p<0.05$). BAL CD4+/CD8+ lymphocytes ratio was not significantly different, however in Poss-UIP and Incon-UIP increased values were found (see table 1).

Analysis of comorbidities revealed a higher prevalence of thyropathies in patients with Incon-UIP pattern than the other groups (p=0.04). Table 3 lists the principal comorbidities of our FPF population.

Follow-up analysis

1-year PFT follow-up demonstrated a significant worsening of the PFT parameters (FEV1, FVC, DLCO and KCO, $p<0.05$) among UIP patients. In the Incon-UIP group a decrement at the limit of significance of FEV1, FVC and TLC (p=0.06) was found. Poss-UIP patients did not show a significant worsening of any functional parameters (Tab. 4, fig. 3).

At 1-year, 6MWT and ABGA did not show a significant deterioration, although the number of patients requiring oxygen supplementation to complete the walking test increased in all groups: in the UIP patients from 5.8% to 29.4%, in the Poss-UIP from 10% to 20% and in the Incon-UIP from 14.3% to 28.6%. The walked distance worsened in all groups, but it did not reach significance (p=0.91); Poss-UIP patients worsening was inferior than other groups (UIP basal metres 367.2 ± 82.3, at 1-y 323.3 ± 98.0, delta -43.9 ± 125.4; Poss-UIP basal 346.7 ± 157.3, at 1-y 330.0 ± 75.6, delta -16.7 ± 205.3; Incon-UIP basal 331.0 ± 194.7, at 1-y 290.0 ± 133.5, delta -41.0 ± 196.3).

Radiological follow-up was available in 28/46 patients (median interval between basal and follow-up HRCT was 1049 days). A modification of the basal pattern was demonstrated in only 5 patients (17.8%); in all cases this was from a possible UIP to a consistent UIP pattern (Fig. 4 a-b). All these patients were belonging to families which members showed UIP or Poss-UIP patterns. Table 5 reports demographic, functional radiological data of such patients. In all cases we observed a PFT worsening at 1-year follow-up.

Survival analysis

Median survival from the clinical onset in our cohort of patients was 2670 days (7.31 years). Although Poss-UIP patients showed a better survival than the other FPF patients, a comparison of the survival curves did not reach any significance: median survival in UIP and Incon-UIP patients was 2040 and 2226 days, respectively, and 3060 days in Poss-UIP (p=0.51) (1020 days more than the UIP group and 834 days more than the Incon-UIP group) (Fig. 5). One UIP patient and 3 Incon-UIP patients underwent lung transplantation.

Considering the whole FPF group, female gender was associated with a longer, albeit not significant, survival (median male survival 1609 days vs. 3060 days for females, p=0.43). Males with a UIP pattern showed the worst survival (median 1950 days). The age at diagnosis, smoking history and BMI did not impact on survival.

FPF patients with FVC<50% of predicted showed a significantly reduced survival (1350 vs. 3060 days, p=0.005). According to HRCT groups, UIP patients with FVC < 50% of predicted had a significantly reduced survival (840 vs. 2670 days, p=0.02), while only a trend was present in the Incon-UIP group (1921 vs. 2226 days, p=0.29) (the analysis could not be performed on Poss-UIP patients because none of them had FVC<50% predicted at the time of analysis). Multiple FVC% cut-off values analysis (<50%, 51-65%, 66-79%, >80%) showed a significantly progressive worsening survival (p=0.02) according to FVC categorical aggregation. FPF patients with DLCO <40% predicted demonstrated a significantly reduced survival (1609 vs. 3060 days, p=0.02). According to the groups, UIP patients with DLCO <40% predicted had a significantly poorer survival (1424 vs. 3959 days, p=0.01), but only a trend in the same direction was present in the other 2 groups. 1-year PFT follow-up showed that a FVC worsening greater than 10% was associated with a significant reduction of survival (median 3210 vs. 1860 days, p=0.03). We also tested the so-called “FVC minimal clinically important difference” (25) categorising FVC worsening in <5%, 5-10% and >10% at 12 months. FPF patients who worsened less than 5% at 1-year follow-up showed a significant better survival than those who reached 10% of worsening (3210, 2040, 1860 days, p=0.04). DLCO worsening cut-off of 10% or 15% at 1-year follow-

up failed to predict survival.

The 6MWT analysis demonstrated that patients belonging to the UIP group, which at baseline walked more than 250 metres, had a statistically significant better survival (2670 vs. 840 days, p=0.05).

Incidence of AE episodes was not statistically different among the 3 groups (UIP 32%, Poss-UIP 10%, Incon-UIP 27.2%). Patients with a UIP pattern who presented an episode of AE showed a significantly reduced survival time (p=0.001).

Discussion.

HRCT evaluation

The present study confirms that FPF is associated with different HRCT features. In our population the UIP pattern was present in the majority of patients (54.3%), while the others patients were equally divided into Poss-UIP and Incon-UIP. HRCT patterns prevalence in FPF is not clear; there is not yet agreement on pattern distribution, probably depending on the interpretation criteria and the variability of the studied cohorts. After the IPF guidelines publication (1), Ravaglia et al. reported a cohort of FPF in which the prevalent pattern was inconsistent UIP (50%) (21). In 2005, Steele et al. performed the biggest multicentre analysis on 309 patients with FPF classifying their patients as IPF (80.2%), NSIP (6.4%), COP (0.6%), centrilobular nodules (0.3%) and non-classifiable pulmonary fibrosis (12.3%) (19).

In the present study, the prevailing HRCT pictures in patients with Incon-UIP were NSIP and unclassifiable pulmonary fibrosis. Incon-UIP patients presented diffuse micronodules as a frequent feature (more than half of patients). In unclassifiable fibrosis patients, the prevalent finding was the association of low-density peribronchial micronodules with bilateral subpleural fibrotic consolidations in the upper lobes, resembling HRCT alterations reported in pleuroparenchimal fibroelastosis (26). Pulmonary emphysema was present in a minority of our patients and was strongly associated ~~to~~ with tobacco exposure (100%). Radiological imaging of this subgroup was consistent with combined pulmonary fibrosis and emphysema syndrome (CPFE), which has previously been reported in FPF (27). Pathology was available in a small number of enrolled patients, but showed a robust concordance with HRCT findings.

Clinical, functional and BAL data.

Our results on patients' age at clinical onset and gender prevalence are in line with the literature (17-21) confirming that FPF is associated with a young age at presentation (men age 58.5 years in our study) and equal prevalence in females and males. We also observed the presence of the anticipation phenomenon of clinical presentation in FPF: daughters/sons were 18 ± 2 years younger with respect their mother/father; among brothers age at onset was similar. Moreover, in our population, female gender and younger age were more frequently associated with an Incon-UIP pattern at HRCT. Intriguingly, Incon-UIP patients also had a higher prevalence of thyreopathy that, when associated to gender and age characteristics, recalls autoimmune disorders. A link with autoimmunity has also been proposed for idiopathic NSIP (28) and a new entity called interstitial pneumonia with autoimmune features (IPAF) has recently been recognised. This condition identifies patients with an idiopathic interstitial pneumonia and the presence of some clinical features indicative of an autoimmune process without meeting established criteria for a particular connective tissue disease diagnosis (29). Autoimmunity role in FPF is intriguing, a genome-wide significant association with two HLA alleles (DRB1*15:01 and DQB1*06:02) has recently been demonstrated (30) and some pathogenic pathways in common with autoimmune disorders have been found in BAL by proteomics in a study from our group (31).

Patients with a Poss-UIP pattern at HRCT were functionally less compromised (at PFT they had pulmonary volumes in the normal range with only a mild DLCO reduction) than UIP and Incon-UIP patients, which showed a restrictive functional impairment with greater DLCO reduction. Interestingly, Incon-UIP patients at the same degree of functional impairment in comparison to UIP patients, showed an unchanged residual volume suggesting a possible different involvement of bronchial and bronchiolar structures in these patients.

BAL cellular composition in FPF according to different HRCT patterns is described for the first time in our study. In Incon-UIP patients, we found a significantly increased percentage of lymphocytes. This finding, together with previously reported age and gender distribution data, reinforces similarities with NSIP and pulmonary fibrosis associated to autoimmune disorders (2). Unexpectedly, we found an increased CD4/CD8 lymphocytes ratio in Poss-UIP and Incon-UIP patients. This data is of interest as none of the fibrotic conditions similar to FPF (IPF, NSIP, DIP, HP or other IIPs) has been associated with a high CD4/CD8 ratio that is instead common in pulmonary sarcoidosis (32).

Comorbidity analysis revealed higher prevalence of thyropathy in Incon-UIP patients, as previously discussed, and GERD in line with previous findings (33).

Follow-up and Survival analysis

Follow-up analysis of PFTs, 6MWT and chest HRCT in FPF are firstly described in the present work. Lung function tests at 1-year showed a significant progression among UIP patients (FEV1, FVC and DLCO) and within limits of significance in Incon-UIP patients. On the contrary, Poss-UIP patients remained stable after 1 year.

Our FPF population, despite presenting with different clinical, functional and radiological characteristics, had a poor prognosis with median survival around 7 years from diagnosis. Median survival was not statistically different among the 3 HRCT groups, although Poss-UIP patients presented a better survival (circa 1000 days more than UIP and Incon-UIP patients) and 3/11 of our Incon-UIP patients underwent lung transplantation resulting in an underestimation of survival in this group.

FVC and DLCO are considered valid indicators to assess disease severity and the risk of death in interstitial lung diseases (1 ~~26~~). Functional prognostic assessment in FPF patients is herein described for the first time. As expected, FPF patients with advanced stage disease (FVC < 50% pred. or DLCO < 40% pred.) had a worse prognosis with a significant reduction of survival. Slow progressive patients (FVC deterioration < 5% per year) demonstrated a significant better survival, while patients with FVC progression >10% at 1-year had a reduced survival.

6-MWT walked distance is also recognised to have a prognostic value in IPF and recently the cut-off of 250 metres walked distance and worsening of 50 metres at 24 week follow-up has been proposed as an independent predictor of mortality (34). In our study, absolute 6-minute walk and the cut-off of 250 metres at baseline were predictive of survival.

Higher rates of acute exacerbation, disease progression and lung cancer prevalence than sporadic IPF has been reported in FPF (21). In our experience, AE incidence was not statistically different among the 3 groups, although it was lesser in the Poss-UIP group; as expected patients with UIP had the worst

outcome with reduced post-AE survival. Lung cancer was observed in only 2 patients (1 with a UIP pattern and 1 with Incon-UIP).

Radiological follow-up in FPF patients is herein reported for the first time. Although it was available in a limited number of patients, it showed clearly that FPF patients with UIP and Incon-UIP patterns strive to maintain their basal HRCT pattern; the only modification we observed was from the Poss-UIP to UIP pattern, with the appearance of honeycombing in the basal subpleural parenchyma (17.8% of our cases). In these patients lung function declined for some but not significantly for all the subjects.

Numerous observations in the present work, due in particular to follow-up data from different HRCT patterns, suggest the hypothesis that FPF patients can be divided in two major scenarios with Poss-UIP and UIP patterns in a sort of *continuum* on one side, and patients with an Incon-UIP pattern on the other: -basal and 1-year follow-up PFT and DLCO analysis indicated that Poss-UIP patients tended to have a less advanced and more stable disease at a functional follow-up with better survival; -the radiological follow-up showed pattern modification only in the direction from Poss-UIP to UIP and all these cases demonstrated a consensual worsening of lung function; -and lastly, members of the same family may present Poss-UIP and UIP patterns, but the contemporary presence of a UIP pattern and Incon-UIP was never found in our cohort. These findings might support the theory of a common genetic background in these two major groups. The hypothesis that in FPF the Poss-UIP pattern could represent the early radiological presentation of UIP is intriguing and need further analysis. Moreover, in support of this speculation, in brothers or cousins in whom one member showed the UIP pattern and another the Poss-UIP, we observed that the latter was always younger at clinical presentation. A debate on the interpretation of the possible UIP pattern in IPF is currently ongoing (35-37); a recent publication reported a positive predictive value of 94% in possible UIP patients at HRCT having histologically confirmed usual interstitial pneumonia (35).

Despite over objectives of our study, our analysis also showed some interesting data about the differential diagnosis of FPF. In particular, FPF patients with Incon-UIP pattern at HRCT demonstrated some similarities with other diseases (i.e. micronodules, BAL lymphocitosis, high CD4/CD8 ratio), which suggest considering FPF in the differential diagnosis of pulmonary sarcoidosis, NSIP and hypersensitivity pneumonitis for example. A specific study with this purpose will be of interest.

The number of enrolled patients represents the principal limit of the present work. However, being single-center study and because of the rarity of FPF, numerosity should not be considered so small and in line with other previous publications. Further multicenter studies could let increase the number of patients in order to correlate phenotype data to genetics analysis that have been herein omitted. In the next future we expect research will address the evaluation of efficacy of new antifibrotic drugs on different FPF phenotypes.

In conclusion, FPF is a complex condition with poor prognosis. Our study firstly analysed functional and radiological follow-up data of patients with FPF, showing that it may manifests with several HRCT patterns with different rates of progression, in which Possible UIP and UIP could be considered phases of the same disease and Inconsistent UIP patients may represent a different clinical and radiological condition. Our results are of particular interest in order to better clarify FPF heterogeneity and prognosis bringing out some unresolved issues, in particular on different potential therapeutic

approaches in FPF.

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Figures and tables captions.

Fig. 1: HRCT scans of 3 of 4 patients with unclassifiable pulmonary fibrosis. Axial (a) and coronal (b) images of fibrotic ground-glass type of presentation combined with multiple areas of air-trapping and zones of fibrotic sparing. Axial image of a female suffering from an unclassifiable pulmonary fibrosis characterized by multiple low-density centrilobular nodules associated with subpleural fibrotic consolidations in the upper-lobes (c) and related magnification demonstrating low-density centrilobular nodules (d) and calcification in the subpleural fibrotic consolidations (e). Axial image of a younger sister of the patient reported above (f) showing the same HRCT pattern of unclassifiable pulmonary fibrosis with multiple low-density centrilobular nodules associated to subpleural fibrotic consolidations in the upper-lobes, even with a modest degree of subpleural fibrotic involvement.

Fig 2: Column graph (mean ± standard deviation) of PFT findings of the three HRCT groups (UIP, Poss-UIP and UIP). RV% preservation in Incon-UIP patients; and DLCO% and KCO% in Poss-UIP patients are evident.

Fig. 3: 1-year PFT follow-up column graph according to HRCT groups showing percentage of variation (mean ± standard deviation) from baseline values (*$p<0.05$).

Fig. 4: Axial CT images of the mid-basal zones of the lungs of a man who was diagnosed with FPF at 58 years (patient number 1 of table 5). An older brother and sister were affected by FPF; the brother was also enrolled in the study (age at onset 57 years) showing a Poss-UIP pattern that did not evolved to UIP at follow-up. The images permit to appreciate the modification of HRCT pattern from Poss-UIP (a) to UIP (b), with the appearance of honeycombing in the subpleural parenchyma.

Fig. 5: Median survival of FPF patient according to the three HRCT groups is shown. Poss-UIP patients demonstrated a better survival than other FPF patients.

Tab. 1: Baseline demographic, clinical characteristics, HRCT time from symptoms, Baseline PFT (percentage of predicted) and BAL cellular composition onset according to HRCT patterns. Data expressed as mean ± standard deviation. FEV1= forced expiratory volume in 1 second, FVC= forced vital capacity, ITGV= intrathoracic gas volume, TLC= total lung capacity, RV= residual volumes, DLCO= diffusing capacity of the lungs for carbon monoxide, KCO= carbon monoxide transfer coefficient (DLCO/VA). *= significant, ns= not significant.

Tab. 2: Major HRCT findings of Incon-UIP patients according to the identified three different subgroups: RB-ILD, NSIP and Unclassifiable pulmonary fibrosis.

Tab. 3: Patients comorbidities according to HRCT patterns (number of patients, %).

Tab. 4: 1-year PFT follow-up according to HRCT patterns. Amount of change expressed in specific units of each variables and percentage from baseline are reported (mean ± standard deviation).

Tab. 5: Data collected from patients who showed the modification of HRCT pattern from Poss-UIP to UIP at radiological follow-up. Age at diagnosis, FVC, FEV1, TLC and DLCO basal values are reported (expressed in their own unit of measure and % of predicted), together with their modification from basal (absolute values and % of modification) at 1-year follow-up. HRCT follow-up time is reported in days. In the last column is reported the number of members with FPF (enrolled in the present study too) belonging to the same family of each subject in which the modification of HRCT pattern from Poss-UIP to UIP was observed, together with his/her HRCT pattern.

Tables

Table 1

	UIP	Poss-UIP	Incon-UIP	
N	25	10	11	
Age at diagnosis	60.3 ± 8.6	60.3 ± 6.6	52.9 ± 11.7	ns
Female gender (n, %)	9 (36%)	4 (40%)	10 (91.7%)	* p=0.03
BMI	26.4 ± 4.8	28.9 ± 4.4	25.0 ± 5.2	ns
Smoke history (n, %)	10 (40%)	5 (50%)	3 (27.3%)	
Tobacco amount (pack/year)	21.0 ± 8.8	22.6 ± 13.5	21.3 ± 28.3	ns
HRCT time since onset (days)	977.6 ±1034	351.3 ± 497.8	799.9 ± 750.4	ns
PFT (n)	25	10	11	
• FEV1%	80.6 ± 20.6	87.5 ± 17.9	71.1 ± 21.0	ns
• FVC%	74.8 ± 18.8	86.8 ± 22.5	68.4 ± 22.2	ns
• FEV1/VC	83.2 ± 7.8	80.6 ± 4.7	84.2 ± 8.4	ns
• ITGV%	86.7 ± 25.3	99.4 ± 25.1	92.8 ± 15.3	ns
• TLC%	74.7 ± 16.9	91.4 ± 19.6	78.7 ± 17.4	ns
• RV%	81.8 ± 31.4	106.2 ± 20.0	101.7 ± 25.7	* p=0.03
• DLCO%	44.7 ± 16.6 (n18)	69.0 ± 18.6 (n10)	48.3 ± 19.3 (n7)	* p=0.03
• KCO%	75.8 ± 18.4 (n18)	97.3 ± 17.5 (n10)	74.2 ± 19.1 (n7)	* p=0.01
BAL (n)	13	8	6	
• Cell/ml	127056 ± 73223	123429 ± 41299	196917 ± 248175	ns
• Macrophages%	75.6 ± 15.3	73.0 ± 11.6	61.1 ± 17.7	ns
• Lymphocytes%	12.3 ± 9.8	21.4 ±13.6	24.1 ± 9.0	* p=0.03
• Neutrophils%	8.3 ± 5.9	2.6 ± 1.9	9.8 ± 5.8	* p=0.03
• Eosinophils%	3.5 ± 4.2	2.8 ± 2.2	4.6 ± 4.2	ns
• Ratio CD4+/CD8+	2.4 ± 1.6	5.2 ± 3.4	4.2 ± 3.5	ns

Table 2

INCONSISTENT UIP	HRCT features	Number of patients (total n=11)
NSIP	Ground-glass opacity;	6/11 (54.4%)

	Fibrotic alterations (traction bronchiectasis and bronchiolectasis, intralobular interstitial thickening, irregular interlobular septal thickening); Subpleural sparing in the dorsal regions of the lower lobes; Some calcified micronodules (1 patient); Some cysts.	
UNCLASSIFIABLE PULMONARY FIBROSIS	Diffuse ground-glass opacity + multiple air-trapping areas or relative sparing areas (1 patient) Low-density centrilobular nodules + subpleural fibrotic consolidations in upper lobes + irregular interfaces along bronchovascular wall + calcified micronodules (3 patients)	4/11 (36.4%)
RB-ILD	Centrilobular nodular opacities Patchy ground-glass opacity Associated centrilobular emphysema Upper lobe predominance	1/11 (9%)

Table 3

	UIP (n=25)	Poss-UIP (n=10)	Incon-UIP (n=11)
Arterial Hypertension	11 (44%)	6 (60%)	4 (36.6%)
Coronary artery disease (CAD)	6 (24%)	3 (30%)	-
Pulmonary Hypertension (by echocardiography)	7 (28%)	2 (20%)	5 (45.4%)
Diabetes Mellitus	3 (12%)	-	1 (9%)
Osteoporosis	8 (32%)	3 (30%)	4 (16%)
Hypercholesterolemia	8 (32%)	5 (50%)	2 (12.5%)
Malignancies: • GI • Lung	 1 (4%) 1(4%)	 1 (10%) -	 - 1 (9%)
GERD	10 (40%)	2 (20%)	5 (45.4%)
Hiatal Hernia	2 (8%)	1 (10%)	1 (9%)
Thyropathy	1 (4%)	-	3 (27.2%)
Hepatic Disorders	2 (8%)	1 (10%)	-
Psychiatric Disorders	2 (8%)	1 (10%)	1 (9%)
Psoriasis	-	1 (10%)	-
OSAS	-	2 (20%)	-

Essential Thrombocytopenia	-	1 (10%)	-
Cerebrovascular disease	-	1 (10%)	-

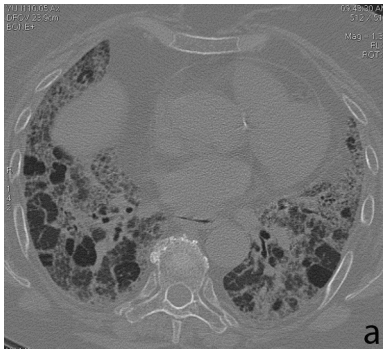
Table 4

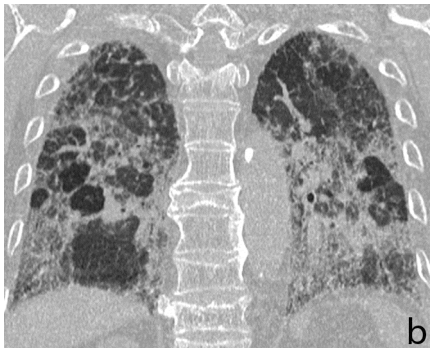
	UIP	Poss-UIP	Incon-UIP
N	17	10	7
FEV1ml (%)	-195.9 ± 251.1 (-7.6 ± 12.9) (*p=0.005)	-39.0 ± 276 (-2.7 ± 9.9) (p=0.31)	-182.9 ± 208.4 (-11.1 ± 13.8) (p=0.06)
FVCml (%)	-211.8 ± 229.7 (-8.8 ± 10.8) (*p=0.002)	-87.0 ± 337.2 (-4.6 ± 10.2) (p=0.30)	-78.5 ± 73.8 (-4,4 ± 4.1) (p=0.06)
TLCml (%)	-94.6 ± 665.8 (0.6 ± 17.8) (p=0.50)	-145.0 ± 492.0 (-3.3 ± 10.3) (p=0.37)	-310 ± 256.9 (-9.2 ± 7.2) (p=0.06)
RVml (%)	4.16 ± 370.5 (4.1 ± 19.4) (p=0.96)	-35 ± 490.4 (-0.07 ± 23.1) (p=0.76)	-168.3 ± 266.1 (-8.3 ± 13.8) (p=0.18)
DLCO mmol/min/kPa (%)	-0.38 ± 0.57 (-8.6 ± 13.5) (*p=0.05), (n10)	-0.32 ± 0.58 (-8.5 ± 13.5) (p=0.20), (n9)	-0.05 ± 0.58 (-5.8 ± 7.8) (p=0.99), (n5)
KCO mmol/min/kPa * VA (%)	-0.09 ± 0.06 (-8.8 ± 5.9) (*p=0.002), (n10)	-0.04 ± 0.07 (-3.2 ± 4.9) (p=0.06), (n9)	0.02 ± 0.15 (2.2 ± 11.2) (p=0.75), (n5)

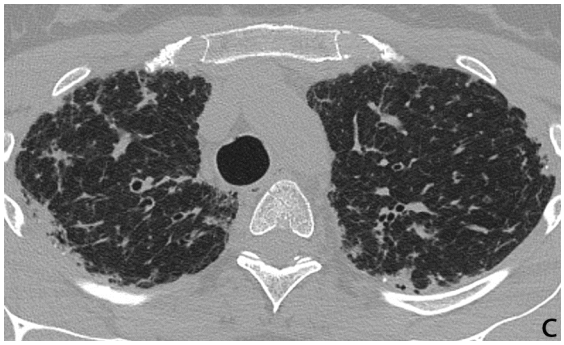
Table 5

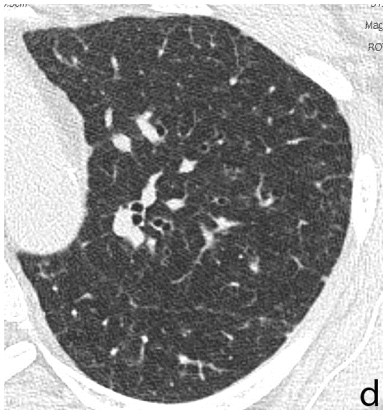
Pt.	Age at diagnosis	FVC		FEV1		TLC		DLCO		HRCT Follow-up (days)	Members with FPF belonging to the same family and enrolled in the study (HRCT pattern)
		Basal (ml, % pred.)	Follow-up	Basal (ml, % pred.)	Follow-up	Basal (ml, % pred.)	Follow-up	Basal (mmol/min/kPa, % pred.)	Follow-up		
1	58	2170 (68%)	-240 (-11%)	1900 (76%)	-210, -11%	4010 (69%)	360, 8.9%	4.74 (63%)	-1.2, -25.3 %	879	Yes (n1) (Poss-UIP)
2	55	3360 (100%)	-310 (-9.2%)	2510 (101%)	-50, -1.9%	5970 (98%)	120, 2.9%	6.86 (98%)	0.2, 2.9%	692	Yes (n1) (UIP)
3	69	2060 (97%)	-50 (-2.4%)	1690 (97%)	-30, -1.8%	4210 (95%)	-480, -11.4 %	3.38 (53%)	0.06, 1.77	1434	Yes (n1) (UIP)
4	67	3540 (102%)	-130 (-3.7)	2840 (106%)	-30, -1.05%	5820 (93%)	-460, -7.9%	6.82 (86%)	-0.98, -14.39	1391	Yes (n1) (UIP)

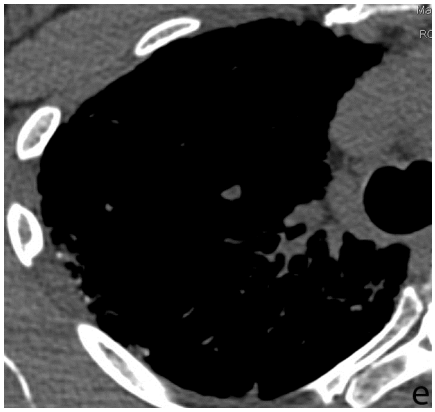
									%		
5	66	1550 (67.3%)	-180 (-11.6)	1200 (64%)	-70, -5.9%	3440 (72%)	200, 5.8%	NA	NA	2787	No

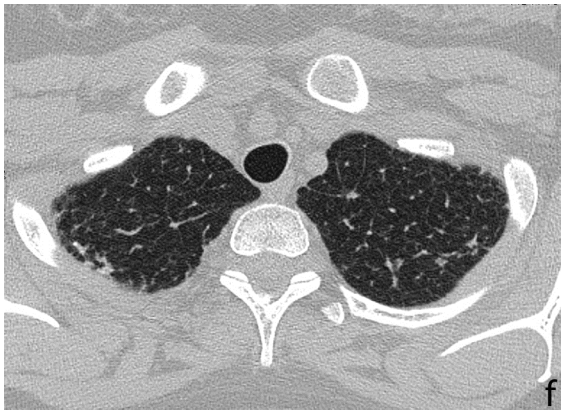


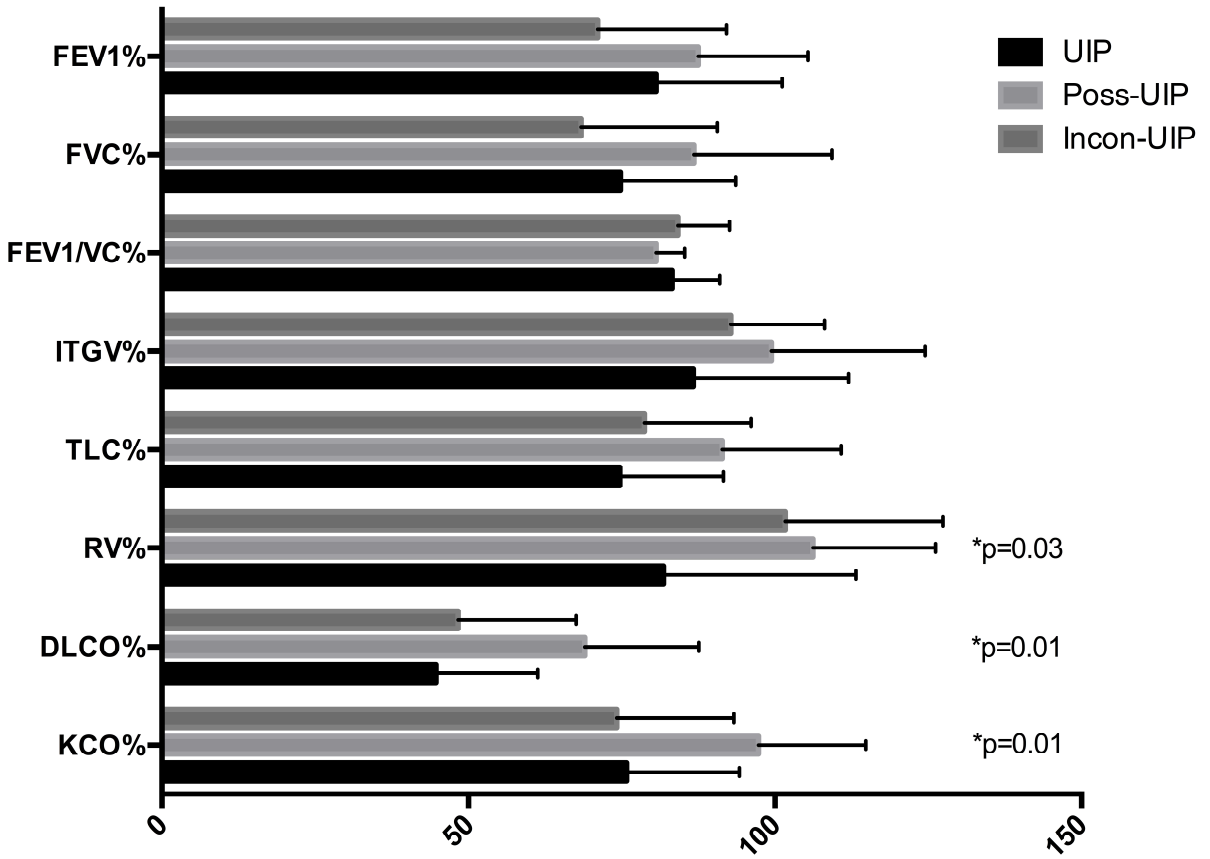


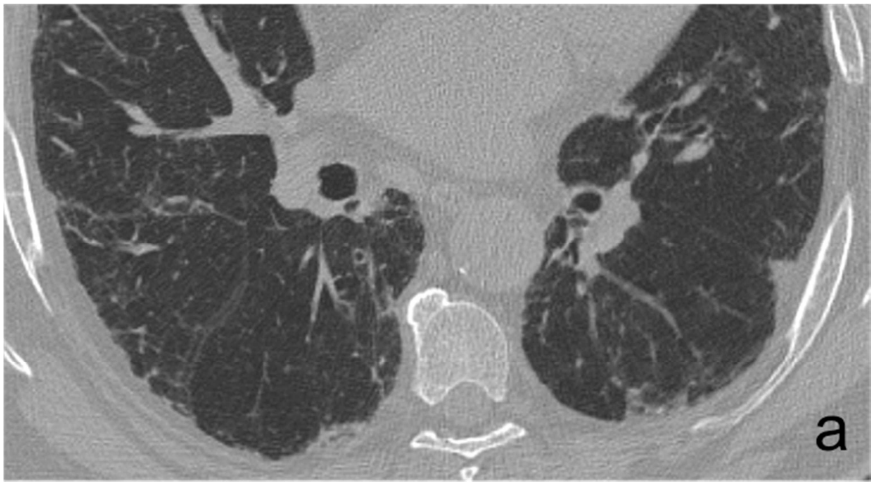


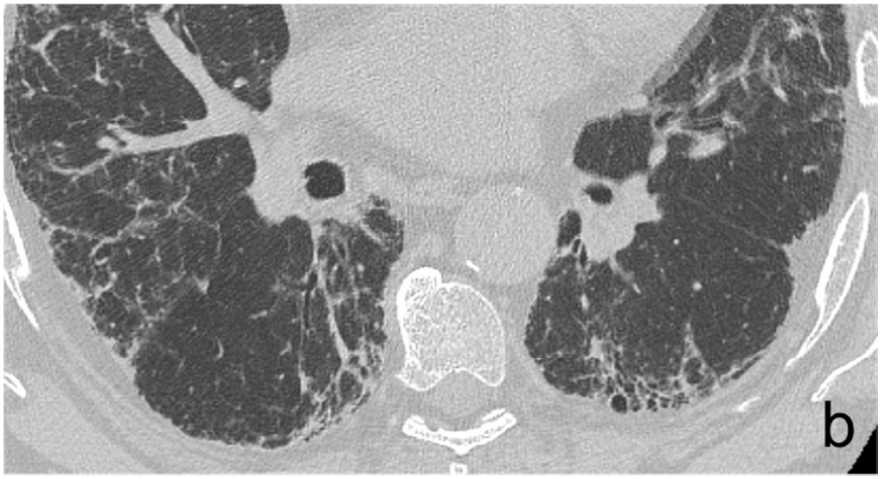


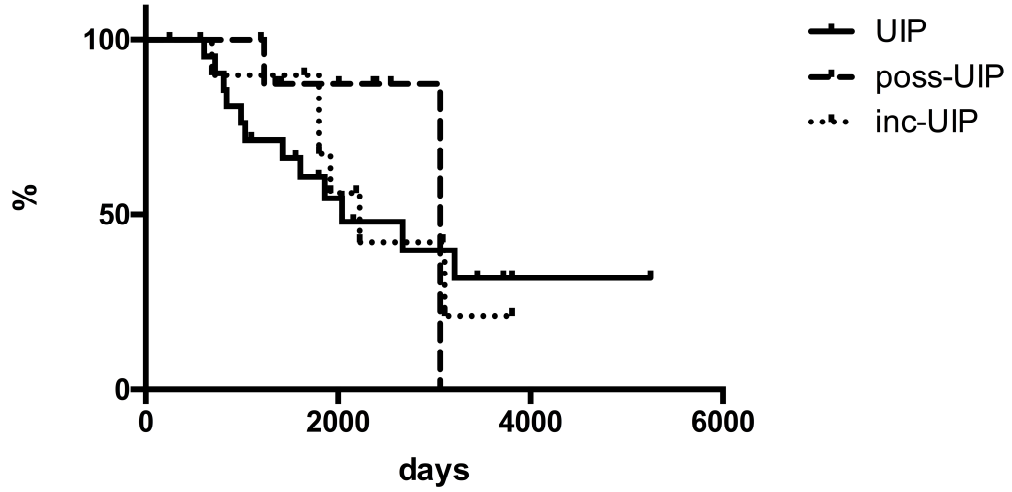


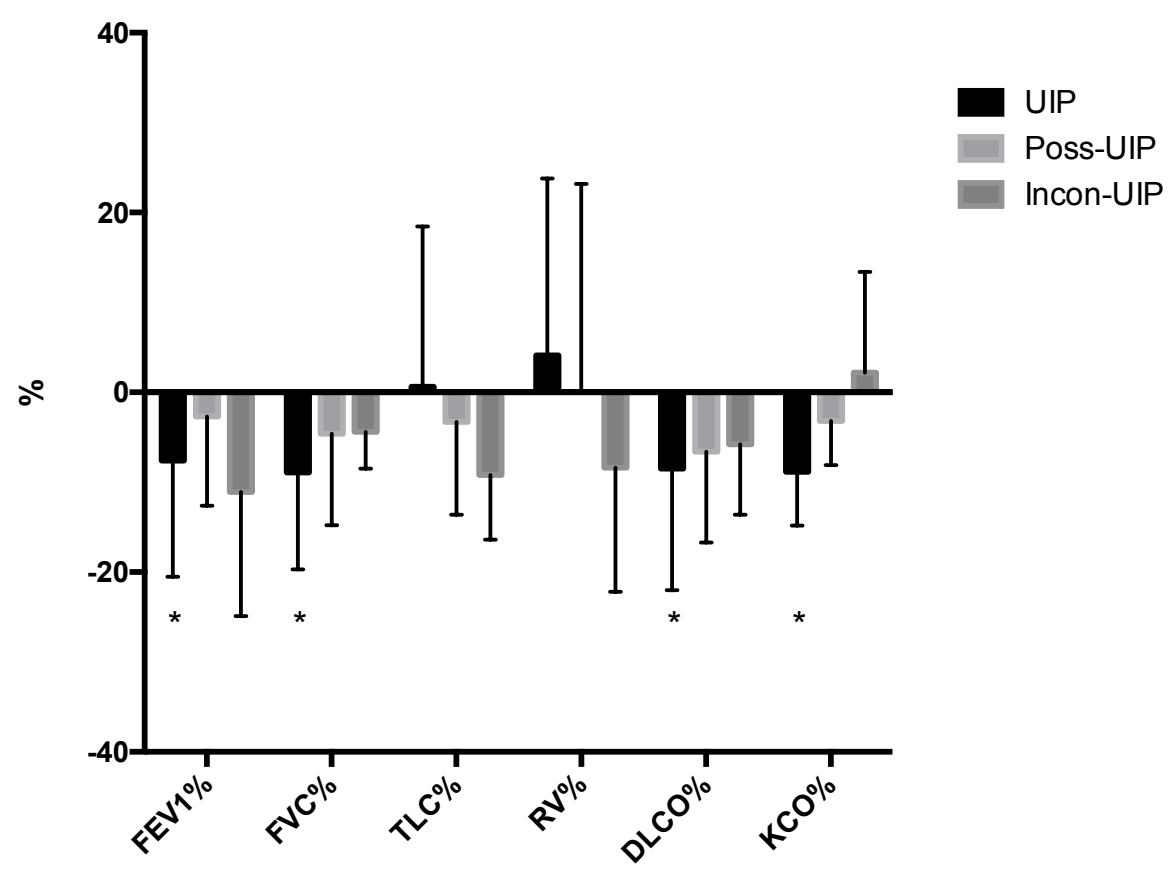








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1. Half of FPF patients may present different HRCT pattern from UIP
2. At PFTs possible UIP patients were less compromised than UIP and inconsistent UIP.
3. BAL showed in incon-UIP patients a significantly increases of lymphocytes.
4. PFTs and HRCT showed progression in UIP and incon-UIP patterns, but not in poss-UIP.
5. Poss-UIP and UIP could be considered phases of the same disease.

Conflict of interest statement

The authors *David Bennett, Maria Antonietta Mazzei, Elena Bargagli, Nevada Cioffi Squitieri, Rosa Metella Refini, Antonella Fossi, Luca Volterrani, Paola Rottoli* of the manuscript titled "Familial pulmonary fibrosis: clinical and radiological characteristics and progression analysis in different high resolution-CT patterns" have no conflict of interest to be declared.