Combined obstructive airflow limitation associated with interstitial lung diseases (O-ILD): the bad phenotype?

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Abstract

Background: Patients suffering from combined obstructive and interstitial lung disease (O-ILD) represent a pathological entity which still has to be well clinically described. The aim of this descriptive and explorative study was to describe the phenotype and functional characteristics of a cohort of patients suffering from functional obstruction in a population of ILD patients in order to raise the need of dedicated prospective observational studies and the evaluation of the impact of anti-fibrotic therapies.

Methods: The current authors conducted a retrospective study including 557 ILD patients, with either obstructive (O-ILD, n=82) or non-obstructive (non O-ILD, n=475) pattern. Patients included were mainly males (54%) with a mean age of 62 years.

Results: Patients with O-ILD exhibited a characteristic functional profile with reduced percent predicted forced expired volume in 1 s (FEV₁) [65% (53–77) vs 83% (71–96), p < 0.00001], small airway involvement assessed by maximum expiratory flow (MEF) 25/75 [29% (20–41) vs 81% (64–108), p < 0.00001], reduced sGaw [60% (42–75) vs 87% (59–119), p < 0.01] and sub-normal functional residual capacity (FRC) [113% (93–134) vs 92% (75–109), p < 0.00001] with no impaired of carbon monoxide diffusing capacity of the lung (DLCO) compared to those without obstruction. Total lung capacity (TLC) was increased in O-ILD patients [93% (82–107) vs 79% (69–91), p < 0.00001]. Of interest, DLCO sharply dropped in O-ILD patients over a 5-year follow-up. We did not identify a significant increase in mortality in patients with O-ILD. Interestingly, the global mortality was increased in the specific sub-group of patients with O-ILD and no progressive fibrosing ILD phenotype and in those with connective tissue disease associated ILD especially in case of rheumatoid arthritis.

Conclusions: The authors individualized a specific functional-based pattern of ILD patients with obstructive lung disease, who are at risk of increased mortality and rapid DLCO decline over time. As classically those patients are excluded from clinical trials, a dedicated prospective study would be of interest in order to define more precisely treatment response of those patients.

Keywords: Interstitial lung disease, Progressive fibrosing ILD, Idiopathic pulmonary fibrosis, Obstructive lung disease

Background

Interstitial lung disease (ILD) is known to be a heterogeneous group of diseases characterized by irreversible fibrotic changes in the lung parenchyma [1–3]. The archetypal disease of ILD is idiopathic pulmonary fibrosis...
fibrosis (IPF) which is known to be progressive over the time despite specific anti-fibrotic therapies [4, 5]. In IPF, even though specific association with genetic susceptibility have been described, it is widely admitted that smoking status is a risk factor for developing IPF [6]. However, other subtypes can also exhibit progressive phenotypes including connective tissue disease-associated ILD (CTD-ILD) [7–9], fibrotic hypersensitivity pneumonitis (HP) [10], idiopathic non specific interstitial pneumonia (iNSIP) [11, 12], organizing pneumonia [13], unclassifiable ILD, rarely sarcoidosis [14, 15], and ILD associated with occupational exposures [16, 17].

Although ILDs display a phenotype characterized by fibrotic lesions in lung leading to a reduction in lung capacity, some of them can also be associated with a specific bronchial disease. Moreover, a subset of IPF patients presenting extended emphysematous lesions, named combined pulmonary fibrosis and emphysema (CPFE), are associated with more severe outcome [18–21]. Both IPF and CPFE patients may develop acute exacerbations that have important implications for the treatment and prognosis of the disease [20]. In addition, Kitaguchi et al. have evaluated differences in pulmonary function test between CPFE patients with and without airflow obstruction [22]. They found that the proportions of emphysema and pulmonary fibrosis on chest High-resolution computed tomography (HRCT) were different between CPFE patients with and without airflow obstruction.

Some ILDs can manifest themselves both at a bronchial and parenchymal level. For instance, sarcoidosis which is recognized to be a granulomatous disease, is frequently associated with airway obstruction, mimicking asthma or COPD symptoms, and more severe cases induces decline of lung function [(reduction of Forced expired Volume in 1s (FEV1)] [23]. Indeed, sarcoidosis can affect airway at any level resulting in a significant airway obstruction in up to 4–63% of cases [24]. Inhalation of tobacco smoke is one of the common risk factor in ILD [6, 25] and COPD [26, 27] that can lead combined pathological situations.

COPD is defined as a preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities associated with a persistent airway obstruction [28–30]. It can be challenging to identify obstructive airflow limitation in patients suffering from ILDs due to the reduction of total lung capacity (TLC). Whereas HRCT is nowadays the major way to explore and diagnose ILDs [31, 32], it is of low interest in order to identify O-ILD patients. Facing a significant vital forced capacity (FVC) reduction in the ILDs, this can, by definition, reduce the capability of clinicians to confirm obstructive airflow limitation. Moreover, emphysematous hyperinflation can lead to an overestimation of the total lung capacity (TLC) than can underestimate ILD severity.

In most clinical trials evaluating anti-fibrotic therapies, ILD patients exhibiting significant airway obstruction are systematically excluded, reducing the validation of anti-fibrotic treatments for this subset of patients. Therefore, there is an unmet clinical need to better define the subset of O-ILD patients and subsequently investigate the use of ILD-targeted therapies (such as antifibrotics) in this group.

The aim of this descriptive and explorative study was to describe the phenotype and functional characteristics of O-ILD patients. For this, we retrospectively analyzed our clinical database from Liège University Hospital in order to define the subgroup of patients with ILD exhibiting airway obstruction.

Methods

Patient cohorts

A retrospective observational cohort study on patients suffering from ILD recruited from our ambulatory care polyclinic at the University Hospital of Liège from April 31st 2004 to January 28th 2021 in our tertiary reference center was performed. We identified patients using electronic hospital records and assessed them for eligibility. We included patients aged from 18 years old and over. All cases were discussed in a multidisciplinary group about ILDs composed of a pulmonologist, a specialist in pulmonary rehabilitation, a rheumatologist, a radiologist, a pathologist and a specialist in occupational medicine [33]. Prior to the analysis, ILDs were classified in five different sub-groups: IPF (n = 68), non IPF-idiopathic interstitial pneumonia (IIP) (n = 91), CTD-ILD (n = 186), sarcoidosis (n = 149) and other-ILDs (n = 63).

Airway obstruction was defined by a Tiffeneau index (FEV1/FVC assessed after having treated patients with bronchodilator salbutamol 400 µg)<70%. The demographic parameters collected are those evaluated on the day of the diagnosis. The protocol was approved by the ethics committee of CHU of Liège (Belgian number: B707201422832; ref: 2014/302).

Collected data

Information was collected on patients’ characteristics (age, gender, smoking status) and clinical characteristics (diagnosis, medical history, radiological patterns, lung function, biomarkers, treatment). Data on medications were collected throughout the study, including immuno-suppressive agents.

Peripheral blood cell count has been studied in order to identify mainly patient with hypereosinophilic status. Moreover, monocyte blood count has been reported to be associated with worse outcome in patients suffering
from ILD justifying the need of evaluating those parameters [34].

Statistical analysis
Statistical analysis were performed using TIBCO Statistica (13.3.1) software. A p-value of less than 0.05 was considered to be statistically significant. Descriptive analyses of patient characteristics were completed using standard summary statistics for distributions. Results are expressed as frequency tables for qualitative variables and as median and interquartile range (IQR) for continuous variables. Contingency tables were analyzed by two-tailed chi-square test, and two-tailed Mann Whitney test was used to compare continuous variable, followed by Bonferroni correction for multiple comparisons. Overall, survival was represented by a Kaplan–Meier curve. Survival between groups was compared by Log Rank test and the Hazard Ratio (Mantel–Haenszel) was reported. For the longitudinal study, the evolution of parameters between two visits was analyzed with a repeated measures using two-tailed ANOVA test followed by the post hoc Tukey’s test.

Results
Subject demographic
We retrospectively recruited 557 ILD patients from our ambulatory care policlinic at the University Hospital of Liège (Fig. 1). We identified a proportion of 14.7% (n = 82) of patients suffering from O-ILD whereas 35% of the entire cohort exhibit a progressive fibrosing-ILD (PF-ILD) pattern according to the INBUILD criteria [35]. Demographic characteristics of the subjects are shown in Table 1 and Additional file 1: Table S1. The median age of ILD patients is 62 (50–71) years old with a male predominance (54%). In non O-ILD subgroup, there are 13.3% of IPF, 16.6% of IIP, 34.5% of CTD-PF, 25.3% of sarcoidosis

Table 1 Patient characteristics

| Data are expressed as median (IQR) | Non O-ILD (n = 475 (85.3%)) | O-ILD (n = 82 (14.7%)) | p-value |
|-----------------------------------|-----------------------------|------------------------|---------|
| Demography                        |                             |                        |         |
| Age (years)                       | 62 (50–71)                  | 61 (49–70)             | n.s     |
| Gender (M/F)                      | 252/223                     | 51/31                  | n.s     |
| BMI (Kg/m²)                       | 26 (24–30)                  | 25 (22–28)             | <0.01   |
| Smokers NS/FS/CS(%)               | 44%/44%/13%                 | 31%/57%/12%            | n.s     |
| ILD category                      |                             |                        |         |
| IPF                               | 63 (13.3%)                  | 5 (6.1%)               |         |
| IIP                               | 79 (16.6%)                  | 12 (14.6%)             |         |
| CTD-ILD                           | 164 (34.5%)                 | 22 (26.8%)             |         |
| Sarcoidosis                       | 120 (25.3%)                 | 29 (35.4%)             |         |
| Other ILD                         | 49 (10.3%)                  | 14 (17.1%)             |         |

Bold to indicate statistically significant p values

BMI body mass index, CTD-ILD connective tissue disease-associated ILD, FS former smoker, ILD interstitial lung disease, IPF idiopathic pulmonary fibrosis, n.s. not significant, NS non smoker, non O-ILD non obstructive-interstitial lung disease, O-ILD obstructive-interstitial lung disease, S smoker

![Fig. 1 Flow chart of patient inclusion in our study](image-url)
and 10.3% of other ILDs, whereas in O-ILD subgroup, there are 6.1% of IPF, 14.6% of IIP, 26.8% of CTD-PF, 35.4% of sarcoidosis and 17.1% of other ILDs. In the O-ILD cohort, we did not identify significant differences in comparison to the non O-ILD group for smoking status, age or gender. Of interest, O-ILD patients exhibited a lower BMI compared to patients with non-obstructive pattern.

Blood analysis

The results of blood leukocyte counts are listed in Table 2. Patients with O-ILD presented a higher concentration of blood leucocytes compared to those without obstructive pattern. O-ILD patients exhibited a higher levels of TLC (93% (82–107) vs 79% (69–91), p < 0.00001) and functional residual capacity (FRC) (113% (93–134) vs 92% (75–109), p < 0.00001) compared to those without O-ILD pattern. Of interest, there was no difference with regards to the FVC value but a significant reduction of the FEV1 in the O-ILD group compared to the non O-ILD group (65% (53–77) vs 83% (71–96), p < 0.00001). By definition, all patients in the O-ILD group were exhibiting a Tiffeneau index (FEV1/FVC) under 70%. As commonly identified in other obstructive airway diseases, O-ILD patients presented a significant reduction in their specific conductance as referred by the sGaw value compared to non O-ILD patients (60% (42–75) vs 87% (59–119), p < 0.01), and small airway involvement assessed by maximum expiratory flow (MEF) 25/75 (29% (20–41) vs 81% (64–108), p < 0.00001). DLCO and KCO were similar in both groups.

Pulmonary functional tests

Pulmonary functional tests are showed in Table 3. Spirometric values were significantly different between O-ILD patients and those without obstruction. O-ILD patients exhibited a higher levels of TLC (93% (82–107) vs 79% (69–91), p < 0.00001) and functional residual capacity (FRC) (113% (93–134) vs 92% (75–109), p < 0.00001) compared to those without O-ILD pattern. Of interest, we did not identify significant differences for monocyte count and classical inflammatory markers (CRP and fibrinogen).

**Table 2** Blood characteristics

| Blood analysis                  | Non O-ILD (n = 475) | O-ILD (n = 82) | p-value |
|--------------------------------|---------------------|---------------|---------|
| Leucocyte (10⁹/µl)             | 7.99 (6.07–9.86)    | 8.24 (6.68–11.20) | n.s     |
| Neutrophil %                   | 66 (57–74)          | 71 (63–76)    | <0.05   |
| Cell/mm³                       | 4.94 (3.67–6.65)    | 5.48 (4.29–8.33) | <0.05  |
| Lymphocyte %                   | 22 (15–29)          | 19 (12–24)   | <0.05   |
| Monocyte %                     | 7.6 (5.9–9.8)       | 7.5 (5.1–9.8) | n.s     |
| Eosinophil %                   | 0.60 (0.44–0.78)    | 0.60 (0.44–0.80) | n.s     |
| Basophil %                     | 2.3 (1.3–3.75)      | 1.9 (0.6–3.7) | n.s     |
| CRP (mg/L)                     | 4.83 (1.97–17.10)   | 9.35 (2.68–27.47) | n.s     |
| Fibrinogen (g/L)               | 3.84 (3.15–4.93)    | 3.78 (3.33–5.78) | n.s     |

**Table 3** Pulmonary functional tests

| Pulmonary functional test       | Non O-ILD (n = 475) | O-ILD (n = 82) | p-value |
|--------------------------------|---------------------|---------------|---------|
| FEV1 (L)                       | 2.31 (1.76–2.88)    | 1.75 (1.38–2.41) | <0.0001 |
| FEV1 (%pred.)                  | 83 (71–96)          | 65 (53–77)    | <0.0001 |
| FVC (L)                        | 2.81 (2.16–3.64)    | 2.99 (2.32–3.89) | n.s     |
| FVC (%pred.)                   | 83 (69–96)          | 84 (72–98)    | n.s     |
| FEV1/FVCpost-BD                | 81 (77–86)          | 62 (58–67)    | <0.0001 |
| MEF25/75 (L)                   | 2.49 (1.87–3.17)    | 1.02 (0.60–1.36) | <0.0001 |
| MEF25/75 (%)                   | 81 (64–108)         | 29 (20–41)    | <0.0001 |
| RV (L)                         | 1.76 (1.35–2.21)    | 2.43 (1.81–3.26) | <0.0001 |
| RV (%pred.)                    | 83 (63–104)         | 116 (84–152)  | <0.0001 |
| TLC (L)                        | 4.73 (3.82–5.54)    | 5.78 (4.77–6.56) | <0.0001 |
| TLC (%pred.)                   | 79 (69–91)          | 93 (82–107)   | <0.0001 |
| DLco (mmol/kPa min)            | 4.67 (3.3–6.43)     | 4.94 (3.27–6.30) | n.s     |
| KCO (mmol/kPa min/L)           | 1.18 (0.95–1.43)    | 1.09 (0.92–1.38) | n.s     |
| KCO (%pred.)                   | 82 (68–97)          | 77 (65–92)    | n.s     |
| FRC (L)                        | 2.76 (2.33–3.56)    | 3.46 (2.94–4.64) | <0.0001 |
| FRC (%pred.)                   | 92 (75–109)         | 113 (93–134)  | <0.0001 |
| sGaw (L)a                      | 1.15 (0.80–1.54)    | 0.69 (0.51–0.98) | <0.0001 |
| sGaw (%)b                      | 87 (59–119)         | 60 (42–75)    | <0.01    |

**Bold to indicate statistically significant p values**

Data are expressed as median (IQR). Values not available

DLCO: diffusing lung capacity of CO, FEV1: forced expired volume in 1s, FVC: forced vital capacity, ILD: interstitial lung disease, KCO: DLCO/Alveola ventilation, MEF: maximum expiratory flow, NS/FS: non smokers/former smokers/current smokers, O-ILD: obstructive-ild, RV: residual volume, TLC: total lung capacity, sGaw: specific conductances

**Bold to indicate statistically significant p values**

**Table 2 Blood characteristics**

| Blood analysis                  | Non O-ILD (n = 475) | O-ILD (n = 82) | p-value |
|--------------------------------|---------------------|---------------|---------|
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| Neutrophil %                   | 66 (57–74)          | 71 (63–76)    | <0.05   |
| Cell/mm³                       | 4.94 (3.67–6.65)    | 5.48 (4.29–8.33) | <0.05  |
| Lymphocyte %                   | 22 (15–29)          | 19 (12–24)   | <0.05   |
| Monocyte %                     | 7.6 (5.9–9.8)       | 7.5 (5.1–9.8) | n.s     |
| Eosinophil %                   | 0.60 (0.44–0.78)    | 0.60 (0.44–0.80) | n.s     |
| Basophil %                     | 2.3 (1.3–3.75)      | 1.9 (0.6–3.7) | n.s     |
| CRP (mg/L)                     | 4.83 (1.97–17.10)   | 9.35 (2.68–27.47) | n.s     |
| Fibrinogen (g/L)               | 3.84 (3.15–4.93)    | 3.78 (3.33–5.78) | n.s     |

**Bold to indicate statistically significant p values**

CRP: C-reactive protein, O-ILD: obstructive-interstitial lung disease, O-ILD: obstructive-interstitial lung disease

**Treatment characteristics**

In the O-ILD group, we identified that 43% of patients were treated with bronchodilator therapies with a homogenous repartition between long-acting B2-agonists (LABA) and long-acting muscarinic antagonist (LAMA) (Table 4). Of note, 24% of them were treated
with inhaled corticosteroids (ICS) and 21% of them with immunosuppressive therapies.

### Survival analysis

In the global cohort, we did not identify any significant difference between patients with or without O-ILD (Fig. 2a; Table 5). Nevertheless, after having specifically studied the patients based on the initial ILD diagnosis, we found that patients with stable ILD (no PF-ILD phenotype) exhibiting an O-ILD pattern were displaying a reduced survival rate (111.5 months vs undefined median survival; \( p < 0.01 \)) (Fig. 2b; Table 5). In the IPF cohort, we didn't identify any significant differences between patient with or without the O-ILD phenotype (45 vs 33 months of median survival respectively, \( p > 0.05 \)).

In the CTD cohort, we interestingly found a significant reduced survival rate in patient suffering from the O-ILD pattern, with a median survival rate of 99 versus 146 months (\( p < 0.01 \)) (Fig. 2c; Table 5).

### Pulmonary functional longitudinal follow-up

In both cohorts, we identified a significant decrease in lung volumes as well as in DLCO. We didn't find any significant differences between patients suffering from O-ILD and those without (Additional file 3: Table S3). We then sub-selected ILD patients (n = 96) with a full annual longitudinal follow-up of 5 years (non O-ILD group (n = 76): 37 CTD-PF, 6 IIP, 6 IPF, 25 sarcoidosis and 2 others; O-ILD group (n = 20): 4 CTD-PF, 1 IIP, 2 IPF, 10 sarcoidosis and 3 others) and re-analyzed the lung function decline. Interestingly, we found that DLCO was more severely decreased over the time in the O-ILD group (\( p < 0.05 \)) (Fig. 3).

### Discussion

The current study provides a comprehensive analysis of a group of 577 patients suffering from ILD and retrospectively analyzed the evolution of patients suffering from ILD exhibiting a specific obstructive functional pattern (O-ILD). Even if ILD patients are typically presenting restrictive lung diseases, we cannot exclude that some of them can experience a mixed obstructive and restrictive disease, combined in the most severe cases with emphysema, known to be of bad prognosis in the particular case of IPF (CPFE) [5, 19].

In our study, we identified that around 15% of them were presenting a functional obstructive lung disease. Those O-ILD patients were displaying higher TLC with globally reduced FEV1, specific conductance (sGaw) and increased FRC. Of interest, the longitudinal follow-up of lung function (FVC, FEV1 and DLCO) over 5 years didn’t show any significant difference between groups. Focusing on the mortality, obstructive patients with non-progressive ILD (based on the INBUILD criteria) were showing an increased mortality rate compared to those without obstruction [35]. Similarly, in CTD and particularly in RA, we identified a significant increase in mortality in patients with obstructive pattern. Conversely in IPF, we didn’t find any significant differences between the two groups.

To the best of our knowledge, this study is the first one exploring obstructive pattern in the particular field of ILD. Indeed, in clinical trial, patients with O-ILD are systematically excluded. As a result, few is known about the evolution of those patients and particularly for the response to new specific anti-fibrotic therapies. Based on our results, we can hypothesize that up to 15% of the patients are potentially considered as not able to participate. Even though the clinical evolution of those patients is generally considered as different, we didn’t show any significant differences between patients with or without obstruction with regards to the evolution of PFT over 3 years of follow-up. If obstruction pattern might have been caused by past smoking history, it worth noting the current smokers were equally distributed among ILD and O-ILD. It may explain why O-ILD did not have an increased FEV1 decline as opposed to ILD. It is also worth noting that O-ILD had greater blood neutrophil count while being less often treated with oral corticosteroids. The reason of this raised neutrophil count is unclear and its possible contribution to airway obstruction needs to be clarified [21, 36]. Of interest, the sub-analysis of the 5-year longitudinal follow-up identified that DLCO was decreasing more severely in the O-ILD cohort. Contrarily to what is seen for PFTs, we identified a significant increase in mortality in the obstructive group for non-PF-ILD patients.
and CTD-PF patients. Moreover, the overall evolution for IPF patients is similar in both groups.

In the particular case of sarcoidosis, several studies indicate that an obstructive pattern is common (4–67% of patients) while a mixed obstructive-restrictive disease is found in around 2–19% of them [24, 37]. The evidence of small airway obstruction originates from pathological studies identifying peribronchial lesions detectable in the HRCT examination by specific bronchial dilatations, mosaic parenchymal attenuation and air trapping [38]. Of note, sarcoidosis associated with airway obstruction is commonly exhibiting a higher morbi-mortality rate [39]. We didn’t find that this observation was specifically true in the particular case of patient with ILD associated to their sarcoidosis, leading us to hypothesize that in this specific case, the ILD is the leading cause of death.

**Table 5** Survival of O-ILD patients

|                      | Non O-ILD | O-ILD | Log rank T test | O-ILD/ILD Hazard ratio (95% CI of ratio) |
|----------------------|-----------|-------|-----------------|-----------------------------------------|
| Figure 2a: Global ILD cohort | Undefined | 156.9 | n.s             | 0.9854 (0.6407–1.516)                    |
| Figure 2b: ILD patient without PF-ILD | Undefined | 111.5 | *p = 0.0036*    | 3.529 (1.511–8.241)                      |
| Figure 2c: CTD cohort | 146.4     | 99.4  | *p = 0.0062*    | 3.362 (1.411–8.011)                      |
| Figure 2d: RA cohort  | Undefined | 99.4  | *p = 0.0148*    | 3.413 (1.272–9.161)                      |

Bold to indicate statistically significant *p* values

Kaplan-Meyer survival analysis of O-ILD patients in each cohort

*non O-ILD* non obstructive-interstitial lung disease, *O-ILD* obstructive-interstitial lung disease
The specific case of RA-ILD is of interest. Indeed, cigarette smoking may play a role in inducing antibody formation and has been linked to occurrence of anti-CCP antibodies induced by the promotion of lung proteins citrullination. Out of the conventional obstruction found similarly to what is seen in COPD, RA patients can suffer from follicular bronchiolitis and obliterative bronchiolitis [40]. Tobacco smoking is associated with an increased risk of RA-ILD (odds ratio of 3.8) for those who smoked > 25 pack-years) [41]. In our cohort, we found that 69% of the O-ILD patients were smokers or former smokers. In this context, we think that obstructive functional pattern in patients suffering from RA needs to be carefully assessed and particularly those with RA associated ILD. We also have to consider that patients suffering from RA-ILD could experience bronchiolitis that can mimic COPD experiencing a different outcome in this context. This point has to be address in further larger clinical trials.

Therapeutic options in O-ILD are limited, considering the lack of well-designed prospective clinical trials in order to confirm the potential benefit of both inhaled and oral anti-fibrotic therapies. Tobacco smoking should be discontinued. It is also surprising that only a small proportion of patients with O-ILD are treated with long-acting bronchodilator therapy (LAMA, LABA or LAMA-LABA) and ICS even though patients are symptomatic with a median FEV1 of 65%. It is therefore important in the follow-up of our patients with ILD to be vigilant to not underdiagnosed and undertreated O-ILD patients while we acknowledge the lack of dedicated clinical trial in order to guide clinicians.

Conclusion
In conclusion, patients with combined obstructive and interstitial lung diseases exhibit a characteristic functional profile with reduced FEV-1, small airway involvement, a reduced sGaw value and sub-normal FRC with similar carbon monoxide diffusing capacity of the lung compared to those without obstruction. O-ILD patients can have normal total lung capacity, which may be responsible for its under recognition compared to the other ILDs. O-ILD patients exhibit a specific evolution over the time that underlies the need of dedicated clinical follow-up.

Our study identified that patients with O-ILD exhibit similar clinical lung function evolution over 5-years in case of IPF. By opposition, we found an increase in mortality in non-progressive ILD raising the hypothesis that
the obstructive airflow limitation due to the bronchial involvement of the lung disease (asthma, COPD) can drive the long-term outcome of those patients. In the particular case of CTD-ILD, we also specifically found a strong increase in mortality associated to the obstructive lung pattern, and particularly in case of RA-ILD. The discrepancy between PFT and survival could be due to the methodology of the study, whereas DLCO progression in the O-ILD subgroup may be due to the fact that those patients survived longer than those in the non O-ILD subgroup, which induces survival bias.

Therefore, patients with O-ILD have to be considered for specific anti-fibrotic therapies in line with the similar clinical outcome found compared to IPF and PF-ILD without obstructive pattern. Patients suffering from CTD-PF require a close follow-up in order to reduce the increase overall mortality in this condition.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12931-022-02006-9.

**Additional file 1: Table S1.** Evaluation of demographic and blood characteristics in each disease.

**Additional file 2: Table S2.** Evaluation of pulmonary functional tests in each disease.

**Additional file 3: Table S3.** Evolution of pulmonary functional test over 3 years.

**Additional file 4: Fig. S1.** Evolution of pulmonary functional test over 3 years from the last visit.

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**Author contributions**

JG designed, supervised and analyzed the experiments, and wrote and revised the manuscript. MH collected and processed blood samples; FG collected clinical characteristics and wrote the manuscript; M‑SN wrote and revised the manuscript. ANF, MT, LG, CD, CM, PM, JLC and RL revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**

The data underlying this article are available in the article and in its online Additional Files. Further inquiries will be shared on reasonable request to the corresponding author.
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