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PHYSIOLOGICAL PREDICTORS OF EXERTIONAL OXYGEN DESATURATION IN PATIENTS WITH FIBROTIC INTERSTITIAL LUNG DISEASE

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Contents

Abbreviations

ILD	Interstitial lung disease
IIP	Idiopathic interstitial pneumonia
SGRQ	Saint George's Respiratory Questionnaire
SF-36	Medical Outcomes Study Short Form
WHOQOL-100	WHO Quality of Life 100 Item Instruments
UCSD SOBQ	University of California San Diego Shortness of Breath Questionnaire
PROMs	patient-reported outcome measures
K-BILD	King's Brief Interstitial Lung Disease
HADS	Hospital Anxiety and Depression Scale
BMI	Body mass index
LFTs	Lung function tests
FVC	Forced Vital Capacity
FEV1	Forced Expiratory Volume at 1st second
DLCO	Diffusing capacity of the lung for carbon monoxide
KCO	Transfer coefficient of the lung for carbon monoxide
CPI	Composite physiologic index
SpO2	Oxygen saturation
6MWT	6-minute walk test
6MWD	6-minute-walk distance
CPET	Cardiopulmonary exercise test

Abstract

Introduction: In patients with fibrotic interstitial lung disease, hypoxaemia on exertion is frequent, and contributes to exercise intolerance, exertional dyspnoea and reduce quality of life. The recent AmbOx trial shown that ambulatory oxygen is associated with improved quality of life in ILD patients with isolated exertional hypoxia. However, few data are available on the predictors of desaturation in ILD and no physiological parameter thresholds have been identified.

Methods: We analysed predictors of oxygen desaturation (SpO2 ≤88%) on a 6MWT in patients with ILD without severe resting hypoxia (SpO2 at rest ≥92%), in a derivation cohort (N=146) and a validation cohort (n=154) presenting at a single institution. Univariable logistic regression analyses was used to identify variables predictive of oxygen desaturation (SpO2 ≤88%) on a 6MWT. Any factors potentially associated on univariable analysis ($p < 0.10$) were added to the multivariable model. Finally, a backward stepwise selection (p-in <0.05, p-out >0.10) was used to determine the factors independently associated with SpO2 ≤88%. Receiver operator curve (ROC) analyses were performed on significant variables derived from the final logistic regression models, and optimal cut-off points for each variable were identified by using the Youden's index.

Results: A total of 300 ILD patients were included in the analysis. Patients from the validation cohort had less severe disease (mean CPI: 44.4 (SD 13) vs 52.9 (SD 10.6), $p=0.0001$) and were less likely to desaturate on 6MWT (26% vs 63%, $p < 0.001$). On univariable analysis, SpO2 at rest, DLCO%, FVC%, FEV1% and CPI were associated with desaturation on 6MWT in the derivation cohort, and were confirmed in the validation cohort. On multivariable analysis, only DLCO and SpO2 remained independently predictive of oxygen desaturation on 6MWT in both cohorts. The

optimal predictive threshold of DLCO ≤40% and SpO2 ≤95%, respectively, was identified in the derivation cohort and confirmed in the validation cohort. Integrating the two variables into a "DeOX" score (0-2), we have created a prediction model of desaturation on 6MWT where the presence of one or both variables (DLCO ≤40% and/or SpO2 ≤95%) strongly increased the risk of desaturation in both cohorts separately and in all patients (for both cohort: OR: 8.1 (95%CI: 4.14-15.88) for score 1; OR: 24.8 (95%CI 11.78-57.04) for score 2).

Conclusions: We propose a novel scoring system for the risk of oxygen desaturation during 6MWT in patients with ILD, using a combination of two physiological variables, widely available in clinical practice.

Introduction

Interstitial lung disease (ILD) encompasses a heterogeneous group of pathologies characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium. In the last two decades, ILDs have been reclassified in comprehensive international consensus statements [1-4].

A practical classification distinguishes ILDs of known cause from those of unknown aetiology. ILD of known aetiology include pneumoconiosis, diseases associated with systemic disease (e.g. connective tissue disease), hypersensitivity pneumonitis, iatrogenic (e.g drug-related) and post-infectious ILD. Forms of unknown causes comprise idiopathic interstitial pneumonias (IIPs), granulomatous ILD (e.g. sarcoidosis) and miscellaneous (e.g. lymphangioleiomyomatosis, pulmonary langerhans cell histiocytosis) (Table 1).

Establishing an accurate diagnosis of ILD can be challenging for clinicians as there are more than 200 different subtypes of pathologies, and they frequently share similar clinical, radiographic, physiologic, and pathologic features.

Patients with ILD often report progressive shortness of breath, exercise intolerance and a persistent dry cough. Breathlessness is the hallmark symptom of fibrotic ILD, first on exertion then at rest [5]. As pulmonary fibrosis advances, exertional breathlessness is triggered by simple activities of daily life, progressively limits the independence of patients and importantly contributes to perceived poor health status [6].

Dyspnoea in ILD

In a recent review of the literature, respiratory symptoms are very common in ILD with the highest prevalence for breathlessness (54-98%) and cough (59-100%) [7].

In ILD patients, dyspnoea is an independent predictor of morbidity and mortality and it is associated with impairment in health-related quality of life and reduction in functional capacity [8, 9].

In patients with IPF it has been demonstrated that the severity of dyspnoea was significantly correlated with health-related quality of life assessed with the Saint George's Respiratory Questionnaire (SGRQ) [5], the Medical Outcomes Study Short Form (SF-36) and the WHO Quality of Life 100 Item Instruments (WHOQOL-100) [9].

Despite prevalence and determinants of depression and anxiety may vary across the spectrum of ILD, it seems reasonable that they might be affected by respiratory symptoms in this group of patients. Even if studies are not conclusive, dyspnoea has in fact been reported as an independent predictor of both depression and anxiety [10].

Furthermore, dyspnoea has been associated with frailty in patients with ILD, as the strongest predictor on unadjusted analysis, and the only predictor on adjusted analysis, independently of disease severity. It is probable that the Frailty index and the dyspnoea score (quantified with the University of California San Diego Shortness of Breath Questionnaire - UCSD SOBQ) are not simply associated because surrogates of functional capacity, but they measure distinct aspects of health status [11].

It is therefore clear that dyspnoea has a great impact on quality of life in patients with ILD. When treating those patients, the main focus is usually the impairment in physiological variables such as FVC or DLCO. However, what matters most to patients are measures to improve survival and quality of life: patient-reported outcome measures (PROMs), such as the King's Brief Interstitial Lung Disease (K-BILD) questionnaire, a validated tool to assess health status in patients with ILD, should be used more frequently in routine clinical practice [12].

Given the limited treatment options, it is therefore important to identify and promptly manage all coexisting conditions and the management of dyspnoea should be given greater emphasis in clinical practice.

Hypoxemia in ILD

Breathlessness on exertion is often associated with a drop in oxygen saturation (SpO2) and desaturation. Despite the feeling in clinical practice that hypoxemia is a common feature in fibrotic ILD, the prevalence of this condition among patients remains unclear. Part of the problem is related with the lack of standardized definitions and uniformity of the test for the study of the different types of hypoxemia.

Resting hypoxemia is a marker of advanced disease stages of ILD. It is commonly defined as resting arterial oxygen tension (PaO2) ≤55 mmHg or 56-59 mmHg with evidence of organ damage. Few data are available on the prevalence of resting hypoxemia. Recent large studies on pirfenidone in IPF, reported a prevalence of 21-28% among the participants [13, 14].

The definition of hypoxemia on exercise vary widely. The most used criteria include a nadir arterial oxygen saturation (SpO2) ≤88% [15-18] and a decrease in SpO2 ≥4% with or without a nadir SpO2<90% [19, 23]. In unselected groups of patients with ILD, 49–54% experience exertional hypoxaemia [24, 25].

Pathophysiological alterations of dyspnoea and hypoxemia in ILD

The mechanisms that cause exertional desaturation in ILD are complex with multiple factors contributing in different degrees. Fibrotic interstitial lung diseases progressively alter the architecture and the physiology of the lungs. All the compartments from the conducting airways to the alveoli, to the lung vasculature, might be affected, causing

profound alterations of the mechanical properties (e.g. reduction in lung compliance), of the lung vasculature (e.g. reduction of the diffusing capacity of the lung for carbon monoxide - DLCO) with ventilation/perfusion (V'/Q') mismatch [26]. Ventilation/ perfusion mismatch seems to be the predominant factor, but pulmonary diffusion limitation with decreased pulmonary capillary transit time during exertion also contributes to a significant degree [27, 28]. The presence of pulmonary hypertension in some patients with ILD can further add to the burden of gas exchange and circulatory impairment during exertion [29, 30].

Progressively, all those changes lead to an increase in the alveolar-arterial oxygen gradient (PA-aO2) and arterial hypoxemia, initially on exertion and progressively at rest.

Lung function tests (LFTs) in ILD normally show a restrictive pattern with reduced forced vital capacity (FVC) and total lung capacity (TLC), associated with a reduction in the diffusing lung capacity for carbon monoxide (DLCO).

Detailed evaluation of exercise capacity at rest and under stress with LFTs, 6MWT and cardiopulmonary exercise test (CPET), helps to provide insights into the physiological impairments. These measurements may suggest the best intervention, including supplemental oxygen or exercise training, and assess prognosis more accurately.

Desaturation on exercise in ILD

The importance of desaturation during exercise in ILD is well known and strongly contribute to exercise intolerance, exertional dyspnoea and consequently reduced quality of life [5, 9]. Clinically significant exertional hypoxemia is typically defined as a drop in transcutaneous arterial oxygen saturation (SpO2) to ≤88% on a six-minute walk test (6MWT) [2], and is associated with reduced survival in ILD patients [15].

Despite the strong clinical impact, the prevalence of exertion desaturation in ILD is still unclear. A recent retrospective study on 400 subjects shown an overall prevalence of 54% at baseline. In the group of patients with exertional desaturation, the mean DLCO was 41% and the mean SpO2 at rest was 94%, significantly lower than the values of patients that did not show desaturation on 6MWT [24].

Few data are available on the severity of exertional hypoxemia, predictors of desaturation and utility of ambulatory oxygen in ILD. In a group of 134 ILD and 274 COPD (chronic obstructive pulmonary disease), patients with ILD shown greater desaturation on 6MWT (6 minute walk test) compared to COPD, and a low DLCO was the strongest predictor of desaturation [25].

Although exertional desaturation has been correlated with gas transfer measurements [25, 31], few data are available on the predictors of a drop of SpO2 to ≤88% in ILD, and no physiological parameter thresholds have been identified to help select ILD patients who would most benefit from performing a 6MWT.

The AmbOX trial

Effective management of exertional dyspnoea and desaturation in fibrotic ILD is challenging and treatment options to reduce dyspnoea are limited.

Although ambulatory oxygen is commonly prescribed for ILD patients with exertional desaturation, with the aims of relieving symptoms and improving activity levels and quality of life, little is known about the real benefits in clinical practice.

The first randomized prospective clinical trial in patients with ILD, evaluating the effect of ambulatory oxygen is the AmbOx trial (Ambulatory Oxygen in Fibrotic Lung Disease). This study was a multicentre randomized controlled crossover trial performed in three centres in the UK with the aim to assess the effects of ambulatory

oxygen on health-related quality of life, symptoms and activity in patients with fibrotic ILD, not hypoxic at rest but with oxygen desaturation on 6MWT (defined as SpO2 ≤88%). 84 patients were enrolled and randomly assigned to the two arms of the study (ambulatory oxygen versus placebo air) and 76 completed the study. To assess effects of the ambulatory oxygen on health-related quality of life, primary and secondary outcomes included the scores on K-BILD (primary outcome), UCSD-SOBQ, SGRQ, and Hospital Anxiety and Depression Scale (HADS). Compared to no oxygen, ambulatory oxygen was significantly associated with improvement in both the "Breathlessness and activity" and "Chest symptoms" domains of the K-BILD, but not the "Psychological" domain. Although total K-BILD score was improved with ambulatory oxygen (difference 3.7 points; $p<0.0001$), the minimal clinically important difference (MCID) of 5 points was not met [32]. However, the MCID was met for the "Breathlessness and activity" domain (difference 8.6 points; MCID of 7 points), the domain most likely to be affected by an intervention used only during activity. The majority of patients (n=51, 67%) in this study chose to continue using the oxygen at study end [33, 34].

Material and Methods

Study design and study population

We performed a retrospective observational study and analysed predictors of oxygen desaturation (SpO2≤88%) on 6MWT in ILD patients without severe resting hypoxia (SpO2 at rest≥92%), in a two cohorts (derivation and validation cohort) screened at the Royal Brompton Hospital (RBH) between September 2014 and May 2018. Approval for this study was obtained from the RBH Institutional Ethics Committee.

The study was performed in accordance with the Good Clinical Practice guidelines recommended by the International Conference on Harmonization of Technical Requirements.

Subjects should have to fulfill the following criteria:

- aged ≥18 years;
- diagnosis of fibrotic interstitial lung disease reached by multidisciplinary team (MDT) consensus;
- stable symptoms and treatment, with no history of exacerbation, chest infections or changes in treatment, during the period of 4 weeks prior to lung function tests and 6MWT;
- patients whose oxygen saturation at rest on room air was ≥92%;
- lung function tests and chest computed tomography (CT) scan carried out within six months from the 6MWT.

Patients requiring oxygen at rest and/or with clinical signs of right heart failure, and/or symptomatic ischemic heart disease were excluded. Patients with fibrotic sarcoidosis or CTD-ILD and significant musculoskeletal involvement were also excluded because of the possible impairment during the 6-minute walk test.

Procedures

Information collected for each patients included:

- demographic details (gender, age, body mass index - BMI, ethnicity),
- smoking history,
- working and personal exposures,
- date of symptom onset, date of diagnosis, type of diagnosis,
- medication,
- presence of comorbidities,
- physical examination,
- lung function tests,
- 6-minutes walk test,
- CT scan of the chest.

Clinical information were documented based on referral letters, medical records or clinical history.

Lung function tests

Lung function tests (LFTs) were performed according to international recommendations [35, 36]. Lung diffusion capacity for carbon monoxide (DLCO) was measured by the single breath method using a mixture of carbon monoxide and methane. Predicted values of lung volumes and expiratory flows as well as DLCO were obtained from regression equations by Quanjer et al and Cotes et al, respectively [37, 38].

LFTs were carried out in all patients within six months from the 6MWT. The composite physiological index (CPI) was used as a functional index of lung fibrosis severity [39].

6-minute walk test

All subjects performed 6-minute walk test (6MWT) according to a standard protocol [40] and as previously described [34].

All subjects received standard instructions before the walk and were encouraged by the investigator who repeated set phrases every 30 seconds during the walk. Each subject underwent the 6MWT in an undisturbed 30-m indoor hospital corridor. The oxygen saturation (SpO2, %) and the heart rate (bpm) were continuously monitored from 2 min before the walk until test completion, and 2 min after completion, or until recovery of the baseline value by using a lightweight portable pulse oximeter (WristOx2™ model 3150) with a finger probe on non-dominant hand. For each subject, the resting SpO2 values (resting SpO2, %), such as the average of the SpO2 readings taken before the walk, and the mean saturation recorded during the walk (walking SpO2, %) were noted. A significant oxygen desaturation was considered both as a difference between resting and walking SpO2 greater than 4% and as a walking SpO2 ≤88%.

Computed tomography scan of the chest

Emphysema extent was quantified on the inspiratory CT scan by an expert radiologist and classified as:

- absent (emphysema score=0);
- limited if visible in the upper areas of the lung but not reaching the carina (emphysema score=1);
- extensive if reaching the carina or further caudally (emphysema score=2).

Statistical analysis

Categorical variables were reported as numbers and percentages and continuous variables as means ± standard deviations or as medians (1st quartile; 3rd quartile) for normal and non-normal distributions, respectively. Categorical variables were compared using the Chi-squared test or the Fisher exact test, continuous variables with t-test or non-parametric Mann-Whitney test, as appropriate.

Univariable logistic regression analysis was used to identify variables predictive of 6MWT oxygen desaturation [41]. Any factors potentially associated on univariable analysis with SpO2 ≤88% on 6MWT ($p<0.10$) were added to the multivariable model. If two variables were highly correlated (r coefficient > $|\pm 0.30|$), the one with the largest variance was excluded from the multivariable analysis [42]. Finally, a backward stepwise selection (p-in <0.05, p-out >0.10) was used to determine the factors independently associated with SpO2≤88% on 6MWT. Receiver operator curve (ROC) analyses were performed on significant variables derived from the final logistic regression models, and optimal cut-off points for each variable were identified by using the Youden's index [43]. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the final models. All statistical analyses were performed using IBM SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

Results

We analysed predictors of oxygen desaturation (SpO2≤88%) on 6MWT in ILD patients without severe resting hypoxia (SpO2 at rest≥92%), in a derivation cohort (patients screened at the Royal Brompton Hospital (RBH) for the AmbOx study between September 2014 and July 2016) [33] and a validation cohort (consecutive ILD referrals to RBH seen between August 2016 and May 2018).

A total of 300 ILD patients (derivation cohort: N=146; validation cohort: N=154) were included in the analysis. Overall, 112 patients (37.3%) had an MDT diagnosis of IPF, 65 (21.6%) of cHP, 35 (11.7%) of CTD-ILD, 14 (4.7%) of NSIP, 8 (2.7%) of sarcoidosis and 66 (22%) of other ILDs (Table 2).

The two cohorts of patients were well matched for demographic characteristics as age, sex, BMI and smoking history did not significantly differ between them (derivation cohort: age: 66.5±10.4; male sex: 65%, BMI: 28±5.4; ever smokers: 55.5% - validation cohort: age: 65.2±10.7; male sex: 61%; BMI: 29.5 ± 5.4; ever smokers: 55.8%) (Table 3). Patients from the validation cohort had less severe disease (mean CPI: 44.4 (SD 13) vs 52.9 (SD 10.6), p=0.0001) and were less likely to desaturate on 6MWT (26% vs 63%, p<0.001).

For the 297 patients with available CTs (144 in the derivation cohort and 153 in the validation cohort), emphysema was scored as absent (emphysema score=0), limited (emphysema score=1), and extensive (emphysema score=2). Limited emphysema was present in 23 (16%) and 12 (7.8%) patients in the derivation and validation cohort, respectively, while extensive emphysema was present in 5 (3.5%) and 6 (3.9%) patients, respectively (Table 4).

On univariable analysis, variables associated with desaturation on 6MWT in the derivation cohort included SpO2 at rest (OR: 0.57; 95%CI: 0.45-0.73), DLCO% (OR: 0.94; 95%CI: 0.91-0.97), FVC% (OR: 0.97; 95%CI: 0.96-0.99), FEV1% (OR: 0.98; 95%CI: 0.96-0.99), and CPI (OR: 1.06; 95%CI: 1.02-1.09), and were confirmed in the validation cohort, while diagnosis of IPF, age, sex, BMI and smoking history were not associated in either cohort (Table 5 and 6).

On multivariable analysis, only DLCO and SpO2 remained independently predictive of oxygen desaturation on 6MWT ≤88% in each cohort, with adjustment for age, sex, smoking history and either SpO2 or DLCO as appropriate (adjusted OR for DLCO in derivation cohort: OR: 0.94; 95%CI: 0.90-0.98; p=0.002; in validation cohort: OR: 0.91; 95%CI: 0.87-0.95; p<0.0001 - adjusted OR for resting SpO2 in derivation cohort: OR: 0.56; 95%CI: 0.43-0.73; p<0.0001; in validation cohort: OR: 0.57; 95%CI: 0.43-0.74, p<0.0001) (Table 5 and 6).

The optimal predictive threshold for DLCO (DLCO ≤40%) and SpO2 (SpO2 ≤95%), respectively, were identified in the derivation cohort and confirmed in the validation cohort (Figure 1).

The two variables were then integrated into a predictive "DeOX" score (0-2; 0=SpO2>95% and DLCO>40%; 1=SpO2≤95% or DLCO≤40%; 2=DLCO≤40% and SpO2≤95%). The presence of one or both variables progressively increases the risk of desaturation in both cohorts, separately and combined (Figure 2).

Considering both cohorts together, our data show that with a DeOX score of 1, the OR for 6MWT desaturation was 8.1 (95%CI: 4.14-15.88) with a Likelihood Ratio (LR) of 1.5 (95%CI: 1.1-1.4), and increased markedly with a score of 2 (OR: 24.8; 95%CI: 11.78-57.04) with LR of 4.4 (95%CI: 2.6-3.5) (Table 7). Patients with a DeOX score of 2 have a significant higher risk of desaturate on 6MWT, meaning that they represent

the cohort of ILD patients for whom more efforts should be made to ensure that oxygen desaturation on exercise is promptly tested.

The strength of this association did not change on adjusting for the presence of the emphysema score in the multivariable analysis in each cohort separately, or in both combined (for both cohorts: OR: 8.7; 95%CI: 4.4-17.3 for a DeOX score of 1, and OR: 25.7; 95%CI: 11.1-59.1 for a score of 2).

Discussion

In this study we analyzed physiological predictors of oxygen desaturation (SpO2≤88%) on 6MWT in fibrotic ILD patients without severe resting hypoxia (SpO2 at rest≥92%), in two different cohorts.

We found that resting SpO2 and DLCO (% predicted) are independently correlated with oxygen desaturation on 6MWT. To our knowledge, this is the largest study correlating physiological variables with the likelihood of oxygen desaturation on 6MWT in fibrotic ILD patients.

Furthermore, although DLCO has been correlated with exertional desaturation [31], no physiological parameter thresholds have been identified to predict the oxygen desaturation on 6MWT. In our study, we were able to identify an optimal predictive threshold for both the variables DLCO (DLCO ≤40%) and SpO2 (SpO2 ≤95%) correlated with oxygen desaturation on 6MWT.

Then, we propose a novel predictive score (DeOX score) to assess likelihood of oxygen desaturation on exertion, by combining DLCO and SpO2 at rest, two non-invasive variables readily obtainable in a respiratory service.

In the recent AmbOx trial [33], ambulatory oxygen significantly improved quality of life in patients with SpO2 desaturation to ≤88% on a 6MWT, compared to no intervention. However predicting likelihood of exercise desaturation in clinic can be difficult. While newly referred ILD patients all tend to perform a 6MWT, if feasible, often the limited time and staff available on follow up in the context of busy outpatient services, mean that the 6MWT is not consistently performed and patients may miss out at least in having a discussion about the pros and cons of ambulatory oxygen. The limited time and staff available in busy outpatient services, mean that the

6MWT is not consistently performed on routine follow-up, and the identification of exertional hypoxia may be missed.

Furthermore a significant desaturation on a 6MWT is a prognostic indicator and thereby a useful measure in itself. Our data suggest that when the DeOX score is 1 (either SpO2≤95% at rest or DLCO%≤40%) the OR for 6MWT desaturation is 8.1, and increases markedly with a score of 2 (when both thresholds are met), such that 78.5% of patients with a score of 2 desaturate on a 6MWT, highlighting the cohort of ILD patients for whom more efforts should be made to ensure that oxygen desaturation on exercise is promptly tested.

The finding that DLCO and SpO2 are independent determinants of oxygen desaturation on exercise suggests that two separate phenomena are being captured. While in DLCO we have our best measure of morphologic disease severity, a lower SpO2 for a given DLCO is likely to be linked to an important pulmonary vascular component [44, 45].

Although exertional desaturation has been associated with worse prognosis in ILD patients, the long term effects of this therapy in patients hypoxic at rest and/or on exercise have not been elucidated. The threshold for prescription of ambulatory oxygen therapy is also uncertain. Identify categories of patients with different risk of desaturation on exertion, might allow not only to select patients to screen with a 6MWT but also to identify patients that might benefit more from a treatment.

Despite the various definition of exertional desaturation, the 6MWT is a simple and inexpensive test, non invasive, widely used in both clinical practice and clinical trials. It is normally well tolerated, self-paced and reflective of daily activities.

Our study has a number of limitations, including its retrospective nature. However, the predictive ability of the identified thresholds was observed in two independent

cohorts, improving the confidence in our findings. The two cohorts differed in severity, with a significantly higher proportion of patients desaturating on 6MWT in the derivation compared to the validation cohort. The derivation cohort comprised patients screened for the AmbOx trial. Clinicians referring patients for a trial of supplemental oxygen will have been more likely to select those with more extensive ILD and/or reporting significant breathlessness on exertion. There was no selection bias for the validation cohort, where all consecutive patients not requiring oxygen at rest and meeting our exclusion criteria were included. Of interest, the score worked best in this less severe "unselected" validation cohort, more likely to be representative of the ILD population attending respiratory services.

All patients were seen in the same center with a centralized lung function lab. As DLCO measurements can be subject to inter-laboratory variation, the findings should be confirmed in different centres, in order to confirm the robustness of the score across different lung function facilities.

Finally, as the 6MWT was performed at sea level, the validity of the score should also be tested at different altitudes.

In conclusion, our data suggest that resting SpO2 and DLCO% are independently correlated with significant desaturation on a 6MWT. We propose a novel, simple, scoring system to predict the risk of oxygen desaturation during 6MWT in patients with ILD, using a combination of two easily obtainable, non invasive, physiological variables. We suggest that if confirmed by different centres, this score could be useful in clinical practice to screen for ILD patients likely to benefit from a formal 6MWT.

Tables

Table 1 – Practical classification of interstitial lung diseases (ILDs).

Major ILDs of known aetiology
Pneumoconioses (e.g. asbestosis, silicosis)
Hypersensitivity pneumonitis
Iatrogenic ILD caused by drugs and/or radiation
Post-infectious ILD
Major ILDs of unknown aetiology
Idiopathic interstitial pneumonias:
Idiopathic pulmonary fibrosis (IPF)
Nonspecific interstitial pneumonia (NSIP)
Respiratory bronchiolitis-intestitial lung disease (RB-ILD)
Desquamative interstitial pneumonia (DIP)
Cryptogenic organising pneumonia (COP)
Acute interstitial pneumonia (AIP)
Idiopathic lymphoid interstitial pneumonia (LIP)
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias
ILD in connective tissue and in collagen-vascular diseases
Sarcoidosis
Miscellanea (e.g. lymphangioleiomyomatosis, pulmonary langerhans cell histiocytosis)

Table 2 – ILD diagnosis.

	Cohort of patients		
	All patients (N=300)	**Derivation cohort (N=146)**	**Validation cohort (N=154)**
IPF	112 (37.3%)	65 (44.5%)	47 (30.5%)
cHP	65 (21.6%)	29 (19.9%)	36 (23.4%)
CTD-ILD	35 (11.7%)	19 (13%)	16 (10.4%)
NSIP	14 (4.7%)	10 (6.8%)	4 (2.6%)
Sarcoidosis	8 (2.7%)	4 (2.7%)	4 (2.6%)
Other ILD	66 (22%)	19 (13.1%)	47 (30.5%)

IPF, Idiopathic pulmonary fibrosis; cHP, chronic hypersensitivity pneumonitis; CTD-ILD, ILD in connective tissue disease; NSIP, nonspecific interstitial pneumonia.

Table 3 – Demographic and clinical characteristics of patients.

	Cohort of patients			
Variables	**All patients (N=300)**	**Derivation cohort (N=146)**	**Validation cohort (N=154)**	**p-value**
Age, years	65.8 ± 10.6 [31; 91]	66.5 ± 10.4 [33; 91]	65.2 ± 10.7 [31; 85]	0.2797
Male, %	189 (63)	95 (65)	94 (61)	0.4716
Race (c/nc), %	235/63 (78.6/21.1)	113/31 (77.9/21.4)	122/32 (79.2/20.8)	0.8749
BMI, kg/m2	28.5 ± 5.4	28 ± 5.4	29.5 ± 5.4	0.0837
Smoke status (ex or current/n), %	167/133 (55.7/44.3)	81/65 (55.5/44.5)	86/68 (55.8/44.2)	0.9495
FVC, % pred	77.6 ± 21.2	75.3 ± 21.1	79.7 ± 21.2	0.0760
FEV1, % pred	77 ± 21	73.2 ± 20.4	80.5 ± 21	0.0026
DLCO, % pred	43 ± 13.2	38.3 ± 10.9	47.5 ± 13.6	<0.001
KCO, % pred	74 ± 17.6	72.7 ± 17.4	75.3 ± 17.9	0.2045
CPI	48.8 ± 12.6	52.9 ± 10.6	44.4 ± 13.0	<0.001
6MWD, meters	390 [304; 441]	402 [312; 451]	375 [282; 426]	0.1147
SatO2 baseline	96 [95; 98]	96 [95; 97]	96.5 [95; 98]	0.1766
Pts with desat at 6MWT*, %	132 (44)	92 (63)	40 (26)	<0.001

BMI, body mass index, FVC, forced vital capacity; FEV_1, forced expiratory volume at 1 sec; DLCO, diffusion capacity of the lung for carbon monoxide; KCO, transfer coefficient of the lung for carbon monoxide; 6-MWD, 6-min walk distance; 6MWT, 6-min walk test.

Table 4 – Emphysema extent on CT scan.

	Cohort of patients		
	All patients (N=297)	**Derivation cohort (N=144)**	**Validation cohort (N=153)**
Absent	251 (84.5%)	116 (80.5%)	135 (88.3%)
Limited	35 (11.8%)	23 (16%)	12 (7.8%)
Extensive	11 (3.7%)	5 (3.5%)	6 (3.9%)

Emphysema absent (emphysema score=0), limited (emphysema score=1), and extensive (emphysema score=2).

Table 5 – Univariate and multivariate regression analysis for factors associated with desaturation on 6MWT in the derivation cohort

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Age, years	1 (0.97-1.03)	0.83		
Gender, male	0.58 (0.29-1.18)	0.14		
BMI, kg/m2	1.03 (0.97-1.10)	0.33		
Smoke status (ex or current/n), %	0.79 (0.40-1.55)	0.50		
Diagnosis of IPF	1.29 (0.64-2.6)	0.46		
FVC, % pred	0.97 (0.96-0.99)	0.01		
FEV1, % pred	0.98 (0.96-0.99)	0.02		
DLCO, % pred	0.94 (0.91-0.97)	0.001	0.94 (0.90-0.98)	0.002
KCO, % pred	0.99 (0.98-1.01)	0.8		
CPI	1.06 (1.02-1.09)	0.002		
SatO2 at rest	0.57 (0.45-0.73)	0.0001	0.56 (0.43-0.73)	<0.001

BMI, body mass index, FVC, forced vital capacity; FEV_1, forced expiratory volume at 1 sec; DLCO, diffusion capacity of the lung for carbon monoxide; KCO, transfer coefficient of the lung for carbon monoxide; CPI, composite physiologic index.

Table 6 – Univariate and multivariate regression analysis for factors associated with desaturation on 6MWT in the validation cohort

	Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Age, years	0.99 (0.96-1.02)	0.55		
Gender, male	0.92 (0.44-1.93)	0.83		
BMI, kg/m2	1.01 (0.95-1.08)	0.38		
Smoke status (ex or current/n), %	0.91 (0.44-1.89)	0.81		
Diagnosis of IPF	1.81 (0.83-3.94)	0.14		
FVC, % pred	0.97 (0.95-0.99)	0.01		
FEV1, % pred	0.97 (0.95-0.99)	0.02		
DLCO, % pred	0.91 (0.87-0.95)	0.0001	0.91 (0.87-0.95)	<0.0001
KCO, % pred	0.98 (0.96-1)	0.06		
CPI	1.08 (1.03-1.12)	0.001		
SatO2 at rest	0.56 (0.44-0.71)	0.0001	0.57 (0.43-0.74)	<0.0001

BMI, body mass index, FVC, forced vital capacity; FEV_1, forced expiratory volume at 1 sec; DLCO, diffusion capacity of the lung for carbon monoxide; KCO, transfer coefficient of the lung for carbon monoxide; CPI, composite physiologic index.

Table 7 – Risk of desaturation on 6MWT

	All patients (N=300)		Derivation cohort (N=146)		Validation cohort (N= 154)	
	Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
DeOX score 1	8.1 (4.14-15.88)	<0.0001	4.2 (1.7-5.84)	0.002	14.5 (4.4-47.93)	<0.0001
DeOx score 2	24.8 (11.78-57.04)	<0.0001	21.2 (5.84-77.05)	<0.0001	29.9 (7.93-113.06)	<0.0001

Figures

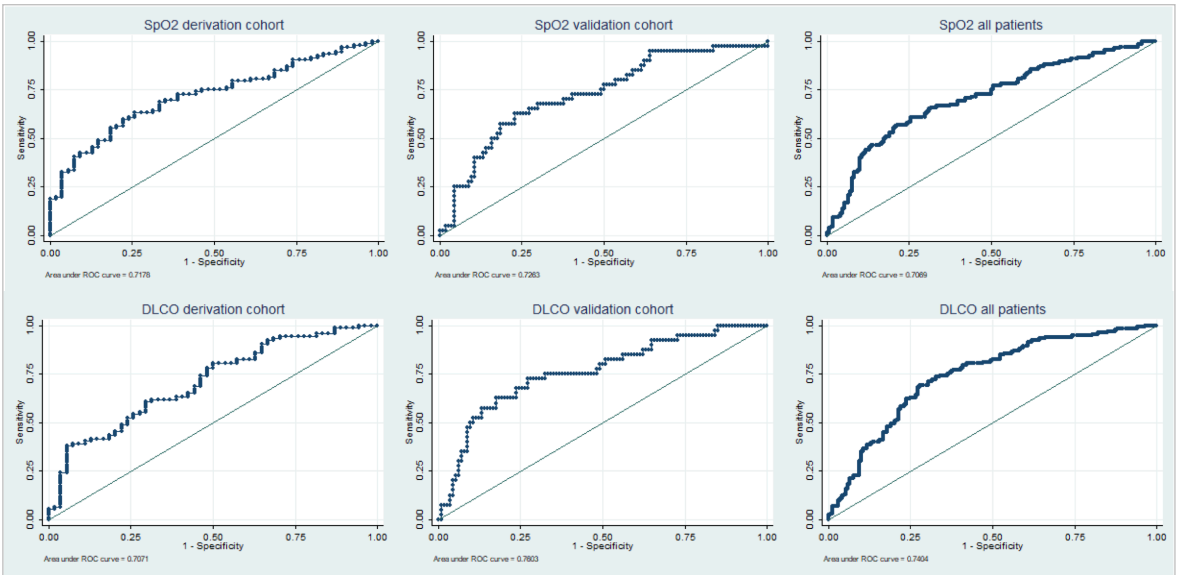

Figure 1 - Receiver-operating curve of discriminative ability power for the threshold of 95% for SpO2 and 40% for DLCO to predict the risk of desaturation on 6MWT.

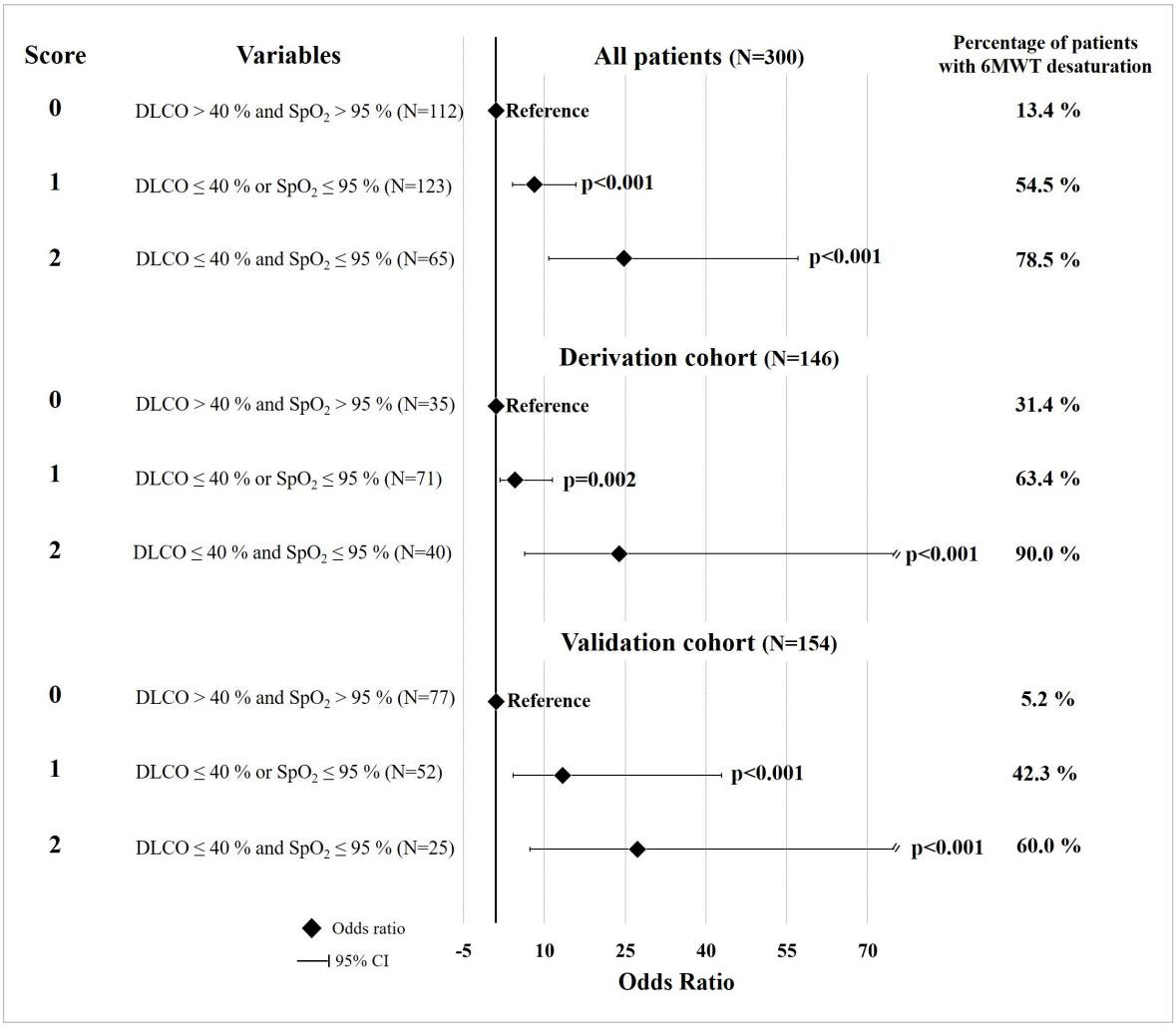

Figure 2 - Multivariate adjusted logistic regression models predicting the probability of oxygen desaturation at 6MWT.

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