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Incidence and prognostic significance of hypoxemia in fibrotic interstitial lung disease: an international cohort study

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Summary conflict of interest statements

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NAH declares no competing interests.

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ABBREVIATIONS LIST

6MWT	6-minute walk test
ABG	Arterial blood gas
AIC	Akaike information criterion
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CTD-ILD	Connective tissue disease-associated interstitial lung disease
DLCO	Diffusion capacity of the lung for carbon monoxide
FEV_1	Forced expiratory volume in 1s
FVC	Forced vital capacity
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
PaO2	Partial arterial oxygen tension
SpO_2	Oxyhemoglobin saturation

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ABSTRACTS

Background: Hypoxemia is a cardinal feature of fibrotic interstitial lung disease (ILD). The incidence, progression, and prognostic significance of hypoxemia in patients with fibrotic ILD is currently unknown.

Research Question: What are the epidemiology of hypoxemia and its additive prognostic value in current risk prediction model in fibrotic ILD?

Methods: We identified 848 patients with fibrotic ILD (258 with idiopathic pulmonary fibrosis (IPF)) in five prospective ILD registries from Australia, Canada, and Switzerland. Cumulative incidence of exertional and resting hypoxemia from the time of diagnosis was estimated at 1-year intervals in patients with baseline 6-minute walk tests, adjusted for competing risks of death and lung transplantation. Likelihood ratio tests were used to determine the prognostic significance of exertional and resting hypoxemia for 1-year mortality/transplantation when added to the ILD-GAP model. The cohort was divided into derivation and validation subsets to evaluate performance characteristics of the extended model (the "ILD-GAP-O_2" model), which included oxygenation status as a predictor.

Results: The 1-, 2-, and 5-year overall cumulative incidence was 6.1%, 17.3%, and 40.1% for exertional hypoxemia, and 2.4%, 5.6%, and 16.5% for resting hypoxemia, which were significantly higher in IPF patients compared to non-IPF patients ($p<0.001$ for both). Addition of exertional or resting hypoxemia to the ILD-GAP model improved 1-year mortality/transplantation prediction ($p<0.001$ for both). The ILD-GAP-O_2 model had improved discrimination (C-index of 0.80 vs 0.75) and model fit (Akaike information criteria of 400 vs 422) in the validation cohort, with comparable calibration.

Interpretation: IPF patients have higher cumulative incidence of exertional and resting hypoxemia than non-IPF patients. The extended ILD-GAP-O_2 model provides additional risk stratification for 1-year prognosis in fibrotic ILD.

Fibrotic interstitial lung diseases (ILDs) comprise a heterogeneous group of chronic pulmonary diseases characterized by diffuse parenchymal fibrosis, leading to irreversible lung function decline and impaired gas exchange. Hypoxemia is a key feature among patients with ILD, although its incidence is unclear.[1] Exertional hypoxemia is an independent predictor of dyspnea and reduced physical activity.[2,3], and is associated with increased mortality.[4,5] Exertional hypoxemia is more severe in patients with ILD than those with chronic obstructive pulmonary disease (COPD),[6] and can occur in patients with ILD who have relatively preserved lung function.[1] As ILD deteriorates, some patients develop resting hypoxemia. Recent studies suggest ambulatory oxygen may improve symptoms and health-related quality of life in patients with ILD.[7-10]

The incidence, progression, and prognostic significance of hypoxemia in patients with fibrotic ILD is unknown. A better understanding of the natural course of hypoxemia in fibrotic ILD is needed to aid discussion regarding patient expectations and guide management decisions. In this study, we aimed to determine the cumulative incidence for the progression of normoxemia to exertional and resting hypoxemia from the time of diagnosis, as well as the survival and prognostic significance of hypoxemia in patients with fibrotic ILD. We hypothesized that the incidence of both exertional and resting hypoxemia would be higher in patients with idiopathic pulmonary fibrosis (IPF) than in those with other fibrotic ILDs, and that the presence of either exertional or resting hypoxemia would be associated with increased 1-year mortality in patients with fibrotic ILD, independent of the ILD-GAP model. [11]

METHODS

Study design and population

This international retrospective cohort study included prospective registries from five ILD centers in three countries [Australia: Alfred Health (2010-2019), Austin Health (2015-2019); Canada: Providence Health Care (2015-2019), South Health Campus (2015-2019); Switzerland: University Hospital Inselspital Bern (2014-2019)] (**e-Table 1**). Consecutive patients aged ≥18 years with a multidisciplinary diagnosis of fibrotic ILD were included if they had baseline 6-minute walk tests (6MWT) at the initial ILD visit. Multidisciplinary discussion was conducted according to international guidelines at each site.[12-14] This study

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was approved by the Austin Health Human Research Ethics Committee (LNR/18/Austin/388).

Hypoxemia assessments and definitions

Baseline and serial data of 6MWTs and arterial blood gases (ABGs) were extracted from clinical records (**e-Table2 and e-Figure 1**). 6MWTs were performed according to guideline recommendations, with continuous monitoring of oxyhemoglobin saturation (SpO_2) using a pulse oximeter.[15,16] Exertional hypoxemia was defined as a nadir SpO_2 <88% during 6MWTs on room air. Resting hypoxemia was defined as either a SpO_2 <88% at the beginning of 6WMTs on room air, or partial arterial oxygen tension (PaO_2) ≤55mmHg in isolation or 56–59mmHg on resting ABG measurement on room air with evidence of hypoxemic organ damage (right heart failure, pulmonary hypertension, or polycythemia).[17] ABG results were prioritized if both ABG and 6MWT were available. New-onset exertional or resting hypoxemia was defined as the date of first assessment at which patients met the abovementioned criteria. Clinical stability was not a requirement for inclusion. Given the eligibility criteria for domiciliary oxygen at each study site are consistent with the study definitions of hypoxemia, patients using long-term oxygen and ambulatory oxygen were considered to have resting and exertional hypoxemia, respectively.

Additional data collection

The date of ILD diagnosis was defined as the date of surgical lung biopsy, when available, or the first date of HRCT evidence of pulmonary fibrosis if a biopsy was not performed. Patient demographics, smoking history, body mass index, cardiopulmonary comorbidities, medications (anti-fibrotic and immunosuppressive agents), and survival or lung transplantation status and dates were extracted. A high likelihood of pulmonary hypertension was defined as pulmonary artery systolic pressure ≥35mmHg on echocardiogram, mean pulmonary artery pressure ≥25mmHg on right heart catheterization, documented pulmonary hypertension as comorbidity, or documented therapies for pulmonary hypertension. Serial pulmonary function test parameters extracted were the forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and diffusion capacity of the lung for carbon monoxide (DLCO).

Statistical analysis

Statistical analyses were performed using Stata (v15.1 StataCorp, USA). Data are presented as mean ± standard deviation, median (interquartile range), or frequency (%).

Progression of hypoxemia: The cumulative incidence of exertional and resting hypoxemia from the date of diagnosis was estimated at 1-year intervals for the first 5 years after diagnosis. Death and lung transplantation were considered as competing risks by the method of Fine and Gray.[18] Time to exertional and resting hypoxemia were calculated as the time from the date of diagnosis to the date of hypoxemia occurrence. The outcome was censored if a patient had not developed hypoxemia by the date of last follow-up. Cumulative incidence of exertional and resting hypoxemia stratified by ILD diagnosis (IPF vs non-IPF) were performed, adjusting for age, sex, lung function (FVC and DLCO % predicted), and study site. This was supplemented by subgroup analyses of patients without a high likelihood of pulmonary hypertension. The progression from exertional to resting hypoxemia was evaluated in the subgroup of patients with new-onset exertional hypoxemia during follow-up, with logistic regression analyses used to assess potential predictor variables associated with the progression. The a priori potential predictors included age, sex, lung function (FVC and DLCO % predicted), diagnosis of IPF, and time since diagnosis.

Survival and prognostic significance of hypoxemia: Time to death or lung transplantation following the development of exertional hypoxemia was evaluated using the Kaplan-Meier method, adjusting for age and lung function (FVC and DLCO % predicted) at the date of hypoxemia assessment, sex, diagnosis of IPF, and study site. A similar analysis was undertaken for resting hypoxemia. For both analyses, follow-up began at the dates of exertional and resting hypoxemia (time zero), respectively. Transplant-free survival stratified by ILD diagnosis (IPF vs non-IPF) was performed, with subgroup analyses excluding patients with a high likelihood of pulmonary hypertension. To decrease risk from immortal time bias, landmark analyses were performed in patients surviving beyond two years, with the hypoxemia status being determined at the landmark time. Time-varying Cox regression methods were used to examine the association between hypoxemia (both baseline and incident events) and 1-year mortality or transplantation, using age and concurrent lung function values at each oxygen assessment that change over time. The incremental value of

adding exertional and resting hypoxemia to the ILD-GAP model for 1-year mortality or transplantation in patients with fibrotic ILD was determined using likelihood ratio tests.

An extension of the ILD-GAP model for predicting mortality or transplantation was created by including oxygenation status as a predictor variable. To develop the extended ILD-GAP-O_2 model, the study population was divided according to the study sites into derivation and validation cohorts to achieve a 3:1 ratio. The derivation and validation of GAP and ILD-GAP models have been described previously.[11,19] The "connective tissue disease-associated ILD (CTD-ILD) / idiopathic non-specific interstitial pneumonia / chronic hypersensitivity pneumonitis" category for the ILD-GAP model was re-termed as "other ILD" to include other ILD subtypes, including pneumonoconiosis, sarcoidosis, and other idiopathic interstitial pneumonia. Point assignments for exertional and resting hypoxemia were weighted based on the existing ILD-GAP model. Regression coefficient values for variables of the ILD-GAP model and the oxygenation status derived from the derivation cohort were compared. Points for exertional and resting hypoxemia were then determined in proportion to that for the variables with the closest coefficient values. The Akaike information criterion (AIC) was used to compare the goodness-of-fit between the existing and extended models. Predictive performance of the two models was further evaluated using Harrell's C-index for discrimination and a Goodness-of-fit likelihood ratio test for calibration in both derivation and validation cohorts. A staging system was then devised by grouping the point scores into three clinically meaningful risk categories: low, intermediate, and high.

RESULTS

Study population and characteristics

The study flow and patient characteristics of the excluded cohort are presented in **Figure 1** and **e-Table 3**, respectively. Of the 1272 who were excluded from the analysis, the majority (n=1063) did not have baseline hypoxemia assessments. A total of 848 eligible patients were included (Australia: Alfred Health: n=146, Austin Health: n=131; Canada: Providence Health Care: n=352, South Health Campus: n=171; Switzerland: University Hospital Inselspital Bern: n=48; **Table 1**). The study population had approximately equal numbers of males and females, with a median age of 63 years at diagnosis. The most common diagnoses were CTD-ILD (39%) and IPF (30%). Most patients (74%) had been treated with either anti-fibrotic

therapies or immunosuppressive agents during their disease course. The median follow-up duration was 3.8 (2.4-6.1) years. Three hundred and one patients (35%) had a high likelihood of pulmonary hypertension during the observation period.

Cumulative incidence and hypoxemia progression

At baseline, 490 patients (57.8%) were normoxemic, 336 (39.6%) had isolated exertional hypoxemia, and 22 (2.6%) had resting hypoxemia. Of 490 patients who were normoxemic at baseline, 186 (38%) developed exertional hypoxemia during follow-up, with 1-, 2-, and 5-year cumulative incidence of 6.1% (95% CI: 4.1-8.5%), 17.3% (95% CI: 13.9-21.0%), and 40.1% (95% CI: 34.7-45.5%), respectively. Of 826 who were either normoxemic or had isolated exertional hypoxemia at baseline, 139 (17%) patients developed resting hypoxemia, with 1-, 2-, and 5-year cumulative incidence of 2.4% (95% CI: 1.5-3.7%), 5.6% (95% CI: 4.1-7.4%), and 16.5% (95% CI: 13.6-19.7%), respectively. Patients with IPF had significantly higher cumulative incidence of exertional and resting hypoxemia than patients with non-IPF fibrotic ILD ($p<0.001$; **Figure 2a** and **2b**). Results were similar after adjusting for the presence of a high likelihood of pulmonary hypertension, cardiac disease, or COPD.

In the 186 patients with new-onset exertional hypoxemia, 34 subsequently developed resting hypoxemia during the median follow-up of 28 (14-44) months. The median time for progression from incidence exertional to resting hypoxemia was 19 (5-29) months. Of the demographics and disease severity measurements, DLCO % predicted was the only independent predictor of hypoxemia progression on both unadjusted and adjusted analyses (**e-Table 4**).

Prognostic significance of hypoxemia

Within the period of observation, 169 patients died and 30 underwent lung transplantation. The median transplant-free survival was 26 months after the onset of exertional hypoxemia (13.0-41.1 months), with 1-, 2-, and 3-year transplant-free survival rates of 96%, 92%, and 84%, respectively. After the development of resting hypoxemia, the median transplant-free survival was 8.2 months (3.2-17.8 months), and the transplant-free survival rates at 1, 2, and 3 years were 58%, 44%, and 28%, respectively. The landmark analyses showed worse

transplant-free survival in patients who developed exertional and resting hypoxemia, compared to those who did not (e-Figure 1). Compared to patients with non-IPF fibrotic ILD, patients with IPF had worse transplant-free survival after the occurrence of exertional hypoxemia (p=0.004; **Figure 3a**), but not after the occurrence of resting hypoxemia (p=0.77; **Figure 3b**). Adding either exertional or resting hypoxemia to the ILD-GAP model significantly improved the prognostic value for 1-year mortality or transplantation in patients with fibrotic ILD (exertional hypoxemia: p<0.001; resting hypoxemia: p<0.001).

The study population was divided into a derivation set (n=669) and a validation set (n=179) in order to create and validate the ILD-GAP-O_2 model (**e-Table 5)**. Compared to the derivation cohort, the validation cohort was older, was more often male, had lower baseline DLCO % predicted, and was more often diagnosed with IPF. The new predictor (oxygenation status) was categorized into normoxemia, isolated exertional hypoxemia, and resting hypoxemia, with point assignment based on the existing weighting of DLCO for the ILD-GAP model (**e-Table 6**). The extended ILD-GAP-O_2 model is presented in **Table 2**. By incorporating exertional or resting hypoxemia as a predictor, the extended model had lower AIC scores compared to those for the ILD-GAP model in the derivation cohort (exertional hypoxemia: 969 vs 993; resting hypoxemia: 732 vs 767), indicating a better goodness-of-fit (**Table 3**). The extended ILD-GAP-O_2 model also had improved discrimination (exertional hypoxemia: C-index 0.83 vs 0.81; resting hypoxemia: 0.86 vs 0.83) and comparable calibration in the derivation cohort. When both models were applied to the validation cohort, their performance characteristics remained unchanged, with the extended model showing superior goodness-of-fit (AIC 400 vs 422) and discrimination (C-index 0.80 vs 0.75). The mortality and lung transplant rates according to the ILD-GAP and ILD-GAP-O_2 models are presented in **e-Table 7**.

DISCUSSION

Our study established that the development of exertional and resting hypoxemia in patients with fibrotic ILD is both common and has prognostic importance. We show that patients with IPF are at higher risks of developing exertional and resting hypoxemia compared to patients with non-IPF fibrotic ILD. Furthermore, we derived and externally validated an

extension of the well-validated ILD-GAP model by incorporating oxygenation status, with this new model improving prognostic risk stratification in fibrotic ILD.

To our knowledge, this is the first longitudinal study of a large international cohort of patients with well-defined fibrotic ILD to evaluate the cumulative incidence and prognosis of exertional and resting hypoxemia. We show that exertional hypoxemia is a common early feature in fibrotic ILD, with 17.3% of patients developing it within two years of the first objective evidence of lung fibrosis. Conversely, resting hypoxemia is a late feature that signifies end-stage disease with similar poor prognosis in both IPF and non-IPF patients, with 42% of patients having died or received lung transplantation within a year of developing resting hypoxemia. Qualitative studies have identified that patients with ILD want general information on their prognosis, including what they should expect regarding the need for oxygen over their disease course.[20,21] There is substantial patient and carer anxiety associated with the initiation of oxygen therapy, including ambulatory oxygen for exertional hypoxemia.[8,22] Our population estimate on the expected prognosis after the development of exertional and resting hypoxemia in ILD will aid clinicians in discussions concerning advanced care planning, although individual patients may differ. Our real-world study design that captures patients with different ILD subtypes, disease severities, follow-up intervals, and comorbidities allows the application of our study findings to day-to-day clinical practice.

It is not surprising that patients with fibrotic ILD develop exertional hypoxemia early in their disease course. There are multiple contributing pathophysiological mechanisms for exertional hypoxemia in fibrotic ILD, including ventilation-perfusion mismatch, diffusion limitation with the disruption of alveolar-capillary membrane, and low mixed venous oxygen concentration during exertion with reduced cardiac output and proportionally increased extraction of oxygen by working muscles.[23-26] Using multiple inert gas elimination techniques, studies have shown that ventilation-perfusion mismatch is the predominant factor, with a lesser contribution from diffusion limitation.[23-25] DLCO correlates with exertional hypoxemia in patients with ILD.[27] Consistent with these findings, DLCO was the only predictor of progression from exertional to resting hypoxemia in patients with fibrotic ILD in this study. However, the severity of gas exchange appears to differ across different ILD subtypes, with a greater degree of exertional desaturation in patients with IPF compared to those with sarcoidosis or asbestosis.[28-30] This may be attributed to the underlying

pathophysiological mechanisms with varying degrees of interstitial fibrosis. In addition to varying progression, this could partially explain the differential cumulative incidence of hypoxemia in patients with IPF and non-IPF fibrotic ILD. Given the recently described progressive fibrosing ILD phenotype,[31,32] it is important to further explore the relationship between disease progression and the development of hypoxemia, irrespective of ILD subtype.

Extending beyond previous studies examining the relationships of mortality with hypoxemia in fibrotic ILD,[4,5,33] we provide further evidence that the development and progression of hypoxemia can be used to improve the performance of the ILD-GAP index, a well-validated prediction model in fibrotic ILD.[11] The ILD-GAP-O_2 model demonstrated consistently superior performance in both the derivation and validation cohorts despite differences in patient characteristics in these populations, further supporting the generalizability of this extended model. This finding suggests that resting SpO_2 by pulse oximetry should be routinely checked at clinic visits and that regular 6MWTs have a potential role in the routine clinical care of patients with ILD. A recent study has proposed the use of a scoring system of DLCO and resting SpO_2 for predicting exertional hypoxemia during 6MWTs.[27] Future studies are needed to validate clinical prediction models for the development and progression of hypoxemia, which will help guide appropriate assessment intervals for at-risk patients.

There are some limitations to this study. As a retrospective study, serial 6MWTs were conducted at irregular intervals, typically between three and twelve months. It is possible that hypoxemia could have developed between serial assessments. In this situation, we may have overestimated the time to develop hypoxemia and underestimated the survival duration post-hypoxemia. There was also missing serial 6MWT data during follow-up, ranging from 18.5 to 32.9%, which may result in biased estimates. Nevertheless, the estimated survival after development of resting hypoxemia is consistent with previous studies examining the survival of patients with ILD following initiation of long-term oxygen therapy for resting hypoxemia.[34,35] In addition, the potentially imprecise determination of hypoxemia onset represents real-world clinical practice. We included consecutive patients in order to minimize selection bias. However, a large proportion of patients without baseline hypoxemia assessment were excluded from this study and all study sites are specialized ILD

centers that may have different patient population compared to non-academic centers. We included study sites located at different altitudes (from sea-level up to 1000m above sea-level), which improves generalizability.

There is a lack of standardized definitions and test modalities for exertional hypoxemia. A nadir SpO_2 <88% during 6MWT was chosen for this study, given that it is a common prescribing threshold for ambulatory oxygen across different regions.[17,36,37] We used pulse oximetry measurements for evaluation of resting hypoxemia in this study, which may not be as accurate as arterial blood gas assessments. However, this again increases the clinical applicability of our findings. Furthermore, SpO_2 <88% is an accepted prescribing threshold for long-term oxygen therapy in various countries, which has been recommended in international guidelines.[37-40] The prognostic significance of new-onset hypoxemia observed and validated in our study provides reassurance that this is not a major limitation. We could not account for pulmonary hypertension with accuracy given that it was not routinely assessed in all patients. Incidence of acute exacerbation, a rare event for ILD,[41] and the reversibility of hypoxemia following acute events or hospitalizations were similarly not available for this study population. However, the reason for the development of hypoxemia would not influence the clinical utility of this prognostic model, as it is developed for application irrespective of clinical status. In this study, all tests were performed as part of outpatient care rather than during admission to hospital for respiratory worsening. Due to incomplete data, the potential effects of anti-fibrotic therapies and immunosuppressive agents for the development and progression of hypoxemia in this population could not be determined.

A major strength of this study is the use of real-world data with well-designed external validation using different patient cohorts from different countries to support the accuracy and reproducibility of our model. This study design allows a wide application of the ILD-GAP-O_2 model in clinical practice, compared to an alternative approach of a post-hoc analysis of clinical trials with standardized assessment intervals, which has limited generalizability due to limited number of serial assessments, short follow-up duration, and strict inclusion criteria with highly selected populations of better disease prognosis.[42]

INTERPRETATION

In conclusion, this large international multicenter cohort study demonstrates that exertional and resting hypoxemia are important clinical events that have significant prognostic value in patients with fibrotic ILD. We further show that these events are common and can occur at early stages of the disease, particularly in patients with IPF. Regular monitoring resting pulse oximetry and 6MWT can help stratify patients into different mortality risk groups to facilitate discussions for advanced care planning. Additional studies are needed to evaluate the effects of ambulatory and long-term oxygen therapy in altering the natural history of hypoxemia in patients with fibrotic ILD.

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Take Home Point:

Study Question: What are the epidemiology of hypoxemia and its additive prognostic value in current risk prediction model in fibrotic ILD?

Results: The 2-year cumulative incidence was 17.3% for exertional hypoxemia and 5.6% for resting hypoxemia in patients with fibrotic ILD, which were significantly higher in IPF patients compared to those with non-IPF, and the extended ILD-GAP-O_2 prognostic model improved mortality prediction.

Interpretation: Exertional and resting hypoxemia are key clinical events in patients with fibrotic ILD, particularly in those with IPF, and the oxygenation status provides risk stratification for prognostication in this population.

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Table 1. Patient characteristics.

	Overall (n = 848)	IPF (n = 258)	Non-IPF (n = 590)
Age at diagnosis, years	63 (53-71)	69 (63-74)	59 (49-68)
Male	426 (50)	199 (77)	227 (38)
BMI at diagnosis, kg/m^2	28.4 ± 5.7	29.4 ± 5.2	28.0 ± 5.8
Smoking history at baseline			
• **Ever-smoker**	490 (58)	181 (70)	309 (52)
• **Pack-years**	20 (10-37)	26 (12-40)	20 (6-30)
• **Unknown**	10 (1)	4 (2)	6 (1)
Pulmonary function at diagnosis			
• **FEV_1/FVC ratio**	81 ± 8	81 ± 7	80 ± 8
• **FEV_1, % predicted**	80 ± 19	83 ± 18	79 ± 19
• **FVC, % predicted**	78 ± 19	78 ± 18	78 ± 20
• **DLCO, % predicted**	58 ± 20	55 ± 18	59 ± 20
• **6MWD, m**	420 (350-500)	420 (349-505)	420 (350-499)
• **Resting SpO_2, %**	96 (95-98)	96 (93-97)	97 (95-98)
ILD therapies			
• **Anti-fibrotic therapies**	193 (23)	172 (67)	21 (4)
• **Immunosuppressive agents**	456 (54)	42 (16)[1]	414 (70)[2]
• **N-acetylcysteine**	76 (9)	22 (9)	54 (9)
• **No treatment**	218 (26)	64 (25)	154 (26)
Comorbidities			
• **Cardiac disease**[3]	142 (17)	65 (25)	77 (13)
• **COPD**	113 (13)	40 (16)	73 (12)
• **Pulmonary hypertension**	301 (35)	64 (25)	237 (40)
• **Sleep disordered breathing**	136 (16)	53 (21)	83 (14)
ILD subtypes			
• **IPF**	258 (30.4)		
• **Non-IPF**			
– **CTD-ILD**[4]	327 (39)		
– **Fibrotic HP**	68 (8)		
– **NSIP**	17 (2)		
– **Sarcoidosis**	21 (2.5)		
– **Unclassifiable ILD**	143 (16.5)		
– **Other**[5]	14 (1.6)		

Data are expressed as mean ± standard deviation, median (interquartile range], or n (%).

Abbreviations: 6MWD, 6-minute walk distance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia; SpO_2, oxyhemoglobin saturation.

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[1] Immunosuppressive agents included prednisolone (15%), azathioprine (5%).
[2] Immunosuppressive agents included prednisolone (49%), mycophenolate (41%), azathioprine (20%), cyclophosphamide (12%), methotrexate (11%), rituximab (7%).
[3] Including ischemic heart disease, heart failure, congenital heart disease
[4] Types of connective tissue diseases included systemic sclerosis (n=174), rheumatoid arthritis (n=46), mixed connective tissue disease (n=31), inflammatory myositis (n=27), undifferentiated connective tissue disease (n=22), systemic lupus erythematosus (n=10), Sjogren's disease (n=9), interstitial pneumonia with autoimmune features (n=8)
[5] Other diagnoses included asbestosis (n=5), drug-related ILD (n=5), organizing pneumonia (n=2), desquamative interstitial pneumonia (n=1), lymphocytic interstitial pneumonia (n=1)

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Table 2. The ILD-GAP-O_2 model

	Predictors	Points
ILD	ILD subtype	
	• IPF/Unclassifiable ILD	0
	• Other ILD	-2
G	Gender	
	• Female	0
	• Male	1
A	Age, years	
	• ≤ 60	0
	• 61-65	1
	• > 65	2
P	FVC, % predicted	
	• > 75%	0
	• 50-75%	1
	• < 50%	2
	DLCO, % predicted	
	• >55%	0
	• 36-55%	1
	• ≤ 35%	2
	• Cannot perform	3
O_2	Oxygenation status	
	• Normoxemia	0
	• Isolated exertional hypoxemia	1
	• Resting hypoxemia	2
	Total possible points	10

Stage	**I**	**II**	**III**
Points	0-3	4-5	>5
Mortality/Lung Transplant			
1-year	1.1	10.1	32.0
2-year	6.6	25.1	52.3
3-year	9.8	33.1	66.1

Abbreviations: CHP, chronic hypersensitivity pneumonitis; CTD-ILD, connective tissue disease-related interstitial lung disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; NSIP, non-specific interstitial pneumonia

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Table 3. Performance statistics for the ILD-GAP and ILD-GAP-O_2 models

a) Derivation Cohort

Performance Statistics	Exertional Hypoxemia		Resting Hypoxemia	
	ILD-GAP	ILD-GAP-Exertional hypoxemia	ILD-GAP	ILD-GAP-Resting hypoxemia
Akaike information criteria	993	969	767	732
Harrell's C-index	0.81	0.83	0.83	0.86
Goodness-of-fit likelihood ratio test	1.00	1.00	0.14	1.00

b) Validation Cohort

Performance Statistics	ILD-GAP	ILD-GAP-O_2
Akaike information criteria	422	400
Harrell's C-index	0.75	0.80
Goodness-of-fit likelihood ratio test	0.95	0.43

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Figure 1. Study flow diagram.

Abbreviation: ILD, interstitial lung disease

[a] Non-fibrotic ILD diagnoses included eosinophilic pneumonia (n = 3), histiocytosis X (n = 4), lymphangioleiomyomatosis (n = 13), sarcoidosis without pulmonary involvement (n = 35), and vasculitis (n = 11).

Figure 2a. Cumulative incidence of exertional hypoxemia from time of diagnosis in patients with IPF and non-IPF fibrotic ILD.

Abbreviation: IPF, idiopathic pulmonary fibrosis

Figure 2b. Cumulative incidence of resting hypoxemia from time of diagnosis in patients with IPF and non-IPF fibrotic ILD.

Abbreviation: IPF, idiopathic pulmonary fibrosis

Figure 3a. Kaplan-Meier survival curve following new-onset exertional hypoxemia.

Abbreviation: IPF, idiopathic pulmonary fibrosis

Figure 3b. Kaplan-Meier survival curve following new-onset resting hypoxemia.

Abbreviation: IPF, idiopathic pulmonary fibrosis

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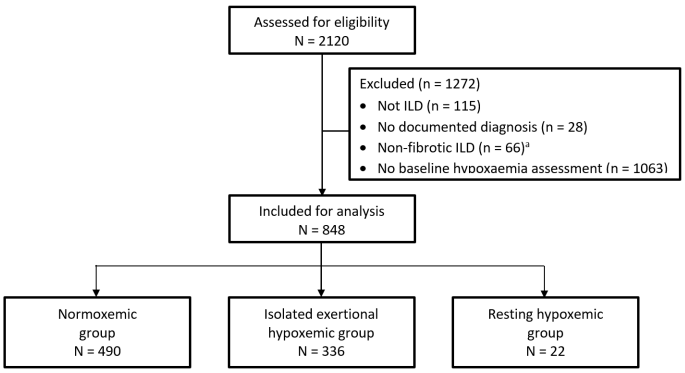

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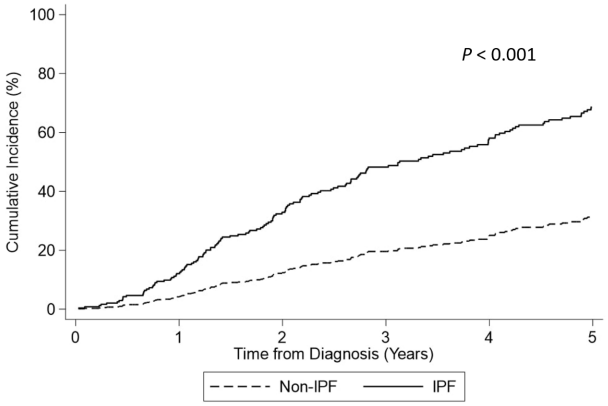

Number at risk

IPF:	120	93	51	33	19	11
Non-IPF:	370	319	252	191	154	120

Cumulative incidence

IPF:	8.0%	24.1%	37.4%	47.0%	58.3%
Non-IPF:	4.1%	13.0%	20.7%	26.9%	35.7%

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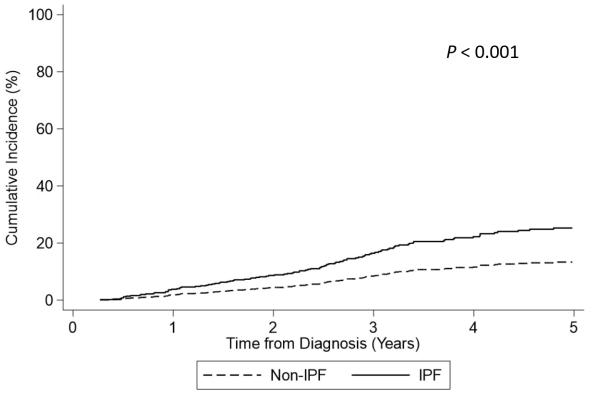

Number at risk

IPF:	234	206	161	107	66	41
Non-IPF:	592	544	469	352	270	211

Cumulative incidence

IPF:	2.7%	7.1%	14.1%	19.1%	22.8%
Non-IPF:	1.2%	3.4%	6.8%	9.4%	11.4%

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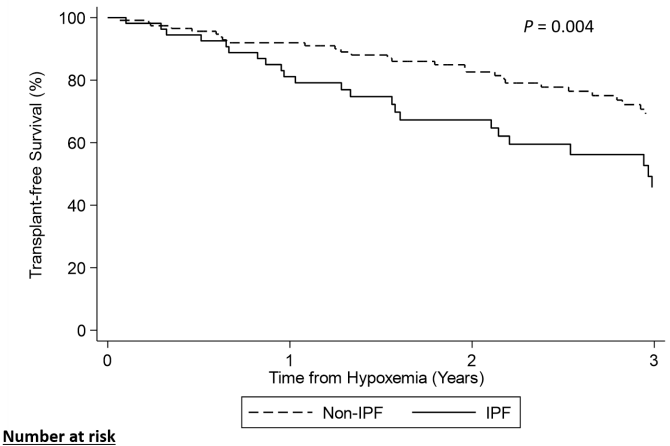

Number at risk

IPF:	63	41	26	13
Non-IPF:	123	96	71	46

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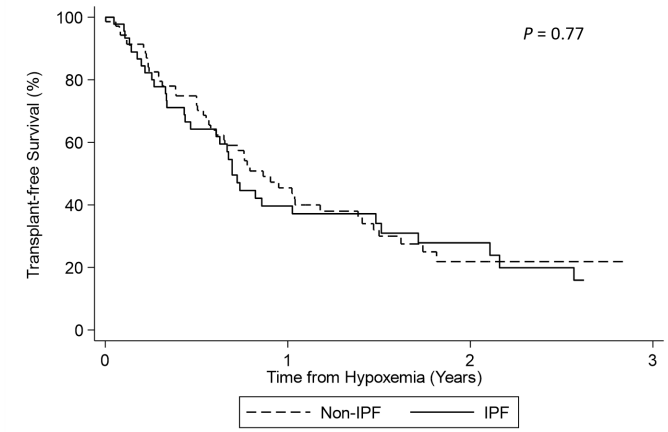

Number at risk

IPF:	55	16	7	3
Non-IPF:	84	25	6	3

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