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Titrated oxygen requirement and prognostication in idiopathic pulmonary fibrosis

J.L. Hook*,#, S.M. Arcasoy*,#, D. Zemmel#, M.N. Bartels#,¶, S.M. Kawut+,§,ƒ and D.J. Lederer*,#,**

ABSTRACT: The supplemental oxygen flow rate is a common bedside measure of gas exchange impairment. We aimed to determine whether a titrated oxygen requirement (TOR) predicted mortality in idiopathic pulmonary fibrosis (IPF).

We examined 104 adults with IPF enrolled in a prospective cohort study and a validation cohort of 151 adults with a variety of interstitial lung diseases (ILDs). The TOR was defined as the lowest oxygen flow rate required to maintain an oxyhaemoglobin saturation of 96% while standing. Cox proportional hazards models and time-dependent receiver operating characteristic curves were used to examine survival time.

A higher TOR was associated with a greater mortality rate independent of forced vital capacity and 6-min walk test results in IPF (adjusted hazard ratio (per 1 L·min^{-1}) 1.16, 95% CI 1.06–1.27). The TOR was at least as accurate as pulmonary function and 6-min walk testing at predicting 1-yr mortality. Findings were similar in other ILDs.

The TOR is a simple, inexpensive bedside measurement that aids prognostication in IPF.

KEYWORDS: Idiopathic pulmonary fibrosis, interstitial lung diseases, outcome prediction, pulmonary fibrosis, pulmonary gas exchange

The interstitial lung diseases (ILDs) are a heterogeneous group of diseases characterised by inflammation and fibrosis of the lung parenchyma [1]. Idiopathic pulmonary fibrosis (IPF), a common ILD that affects older adults, carries a median survival time of ~3 yrs [2, 3]. However, a significant fraction of affected individuals survive for >10 yrs [4, 5]. Accurate tools to improve prognostication in IPF would aid clinicians and researchers by informing guidelines for the referral and prioritisation of patients for lung transplantation, facilitating discussions of end-of-life planning and identifying appropriate candidates for experimental therapies.

A number of studies have identified associations between reduced exercise test performance and higher mortality rates in IPF [4–11]. For example, both reduced maximal exercise capacity during cycle ergometry [5, 7, 11] and a shorter distance walked during hallway walk testing are associated with higher mortality rates [8–10]. Well-designed studies have indicated that exertional desaturation during 6-min walk testing may explain the association between decreased exercise capacity and mortality in IPF [4, 6].

Exercise capacity and exertional desaturation, however, are strongly influenced by the fraction of inspired oxygen administered during testing [12, 13]. Current guidelines suggest that 6-min walk testing be performed using the patient's ''standard rate'' of oxygen flow [14]. Previous studies have excluded those with low resting oxyhaemoglobin saturation (arterial oxygen saturation measured by pulse oximetry (S_{P,O_2})) and have administered supplemental oxygen in a nonstandardised fashion during 6-min walk testing [4, 6, 8–10], limiting the widespread application and interpretation of submaximal exercise test results in this population.

The amount of supplemental oxygen required to maintain S_{P,O_2} at physiological levels is a common bedside measure of disease severity across a wide spectrum of lung diseases, and the degree of gas exchange impairment at rest is linked to higher mortality rates in IPF [4, 5, 15–17]. However, there are no data examining the reliability and predictive validity of a standardised measure of

AFFILIATIONS
Depts of *Medicine, and ¶Rehabilitation and Regenerative Medicine, College of Physicians and Surgeons,
**Dept of Epidemiology, Mailman School of Public Health, Columbia University,
#New York Presbyterian Lung Transplant and Interstitial Lung Disease Programs, New York Presbyterian Hospital/Columbia, New York, NY,
+Penn Cardiovascular Institute,
§Dept of Medicine, and
ƒCenter for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA.

CORRESPONDENCE
D.J. Lederer
Division of Pulmonary, Allergy and Critical Care Medicine
College of Physicians and Surgeons
Columbia University
622 W 168th Street
PH-14
Room 104
New York
NY 10032
USA
E-mail: davidlederer@columbia.edu

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oxygen requirement in IPF, limiting the ability to examine oxygen requirement in epidemiological studies and clinical trials. At our centre, we implemented an oxygen titration protocol to standardise the use of supplemental oxygen during 6-min walk testing in 2007. In the current study, we hypothesised that the oxygen flow rate required to maintain S_{P,O_2} at $\geqslant$96% would predict short-term outcomes in IPF.

METHODS

Study subjects and study design

We examined 104 adults with IPF who enrolled in a prospective cohort study of ILD patients at the New York Presbyterian Lung Transplant and Interstitial Lung Disease Programs (New York Presbyterian Hospital/Columbia, New York, NY, USA) between February 2007 and June 2010. We screened 505 adults seen by a pulmonologist at our centre with suspected or known ILD (fig. 1). Of these, 418 consented and 151 met American Thoracic Society/European Respiratory Society criteria for IPF [18]. We excluded 262 who met criteria for an ILD other than IPF, such as those with evidence of connective tissue disease, a history of occupational or environmental exposures known to cause pneumoconioses and those with suspected drug-induced lung disease. We excluded 47 who did not undergo oxygen titration testing at our centre. The most common reasons for not undergoing testing at our centre were: patient preference (n=17), testing not ordered (n=12) and testing performed according to a clinical trial protocol (n=7). The study cohort consisted of 104 participants with IPF who underwent an oxygen titration study at our centre (fig. 1). The Columbia University Medical Center Institutional Review Board (New York, NY) approved the prospective study. All participants gave written informed consent.

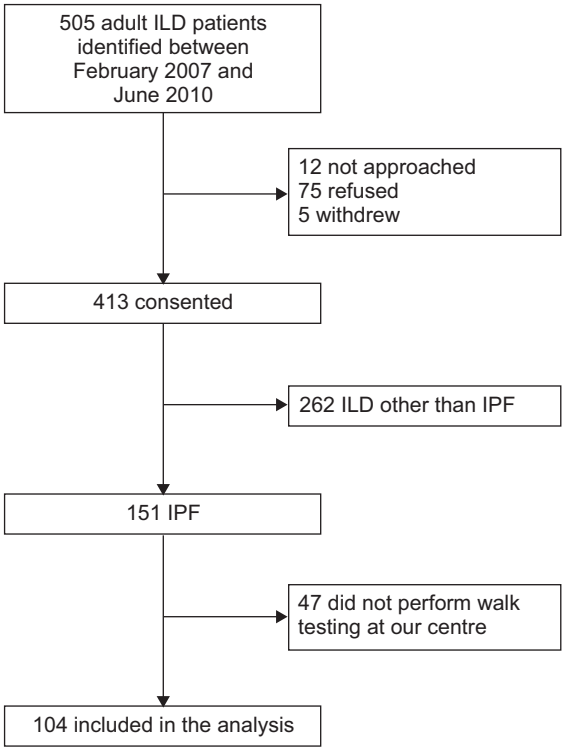

FIGURE 1. Study participant flow. ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

To validate our findings, we subsequently assembled a cohort of 152 ILD patients not enrolled in the prospective study by searching the Clinical Data Warehouse at Columbia University (New York, NY) for all 6-min walk tests performed for adults with ILD between February 2007 and April 15, 2010. We excluded one patient who did not have available spirometry data. The Columbia University Medical Center Institutional Review Board approved this retrospective study and waived informed consent.

6-min walk testing and titrated oxygen requirement

6-min walk testing was performed in a ~30-m (100-ft), straight indoor hallway by a single physiotherapist in accordance with American Thoracic Society guidelines [14]. Supplemental oxygen was administered according to the results of the oxygen titration study described below using a commercially available integrated E-cylinder, valve and regulator device (Linde Integrated Valve; Linde North America, Murray Hill, NJ, USA). Pulse oximetry was performed prior to the 6-min walk test and during patient-initiated rests using a single Nellcor OmiMax N-65 pulse oximeter (Covidien-Nellcor, Boulder, CO, USA). A single pulse oximeter was selected in order to minimise measurement variability. Pulse oximetry was not monitored during ambulation. Distance walked during testing (6-min walk distance (6MWD)), oxyhaemoglobin saturation at the end of the test (end-walk S_{P,O_2}) and modified Borg dyspnoea score were measured after each walk. Testing was not terminated for desaturation <80%.

Immediately prior to 6-min walk testing, an oxygen titration study was performed to determine the lowest oxygen flow rate required to maintain an S_{P,O_2} of $\geqslant$96% in the standing position (titrated oxygen requirement (TOR)). Titration began with the patient breathing room air. S_{P,O_2} was monitored for 1 min. If the S_{P,O_2} was $\geqslant$96%, the study ended. If the S_{P,O_2} was <96%, the oxygen flow rate was increased each minute to achieve a target S_{P,O_2} of $\geqslant$96% using the following titration steps: 1, 2, 3, 4, 5, 6, 8, 12 and 15 L·min^{-1}. A nasal cannula was used to administer 1–6 L·min^{-1} and a non-rebreather mask was used for 8–15 L·min^{-1}. To examine the interobserver reliability (precision) of the TOR, two investigators measured the TOR of 10 study participants with IPF in a blinded fashion <7 days apart. The results were identical for nine out of 10 participants and disagreed by only 1 L·min^{-1} in the remaining participant. The weighted kappa (a test of agreement between groups for ordinal variables, such as TOR) was 0.90, suggesting that the TOR is a reliable measure. 6-min walk testing was performed using the TOR; no further changes were made to oxygen flow during 6-min walk testing. We have performed 6-min walk testing using the titrated oxygen flow rate in >300 patients with ILD with no adverse events other than dyspnoea.

Analysis

The cohort was divided into rough quartiles of TOR. We examined associations between TOR and the rate of death using Cox proportional hazards models censored at the time of transplantation. Stratified Cox models with strata for diagnostic category were used in the validation cohort in order to account for variation by diagnosis. We included purposefully selected covariates known to be important prognostic factors in IPF: age, 6MWD, end-walk S_{P,O_2} and forced vital capacity (FVC). We

examined the ability of TOR and other established prognostic factors to predict the risk of death and transplantation using time-dependent receiver operating characteristic (ROC) curves (survivalROC package in *R*) [19]. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA), and *R* version 2.8.1 (R Foundation, Vienna, Austria). p-values <0.05 were considered statistically significant.

RESULTS

IPF participant characteristics

The mean±SD age of the study participants was 62±7 yrs and 79% were male. 45% had diagnoses confirmed by surgical lung biopsy. FVC was 54±21% predicted and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) was 37±13% pred. 6MWD was 394±133 m and 56% had an end-walk S_{p,O_2} of ⩽88% (interquartile range (IQR) 82–92%). Compared with those who performed an oxygen titration study, excluded participants were older (mean age 68 *versus* 62 yrs; p<0.001), more frequently female (38 *versus* 21%; p=0.03) and had lower FVC (mean 46 *versus* 54% pred; p=0.046).

The median TOR was 2 L·min^{-1} (IQR 0–4 L·min^{-1}) and the mean±SD TOR was 3.3±4.6 L·min^{-1}. Other than shortness of breath, no adverse events occurred during 6-min walk testing or oxygen titration. Those with higher TOR values were more likely to be male, and tended to have lower FVC, lower total lung capacity, lower $D_{L,CO}$, higher pulmonary artery pressure and lower 6MWD (table 1).

Associations of TOR with survival time in IPF

During a median follow-up time of 11 months (IQR 5–21 months), 17 study participants died without undergoing lung transplantation and 35 underwent lung transplantation. Figure 2a shows unadjusted survival by TOR group. After adjustment for age, 6MWD, end-walk S_{p,O_2}, and FVC, greater TOR was associated with a higher mortality rate (table 2). For example, after adjustment for potential confounders, a TOR of ⩾8 L·min^{-1} was associated with a 6.7-fold increased mortality rate (95% CI 1.7–25; p=0.005) compared with a TOR of 0 L·min^{-1}. Examination of TOR as a quasicontinuous variable showed a similar finding, with an adjusted hazard ratio (HR) for death of 1.16 (95% CI 1.06–1.27; p=0.001) per 1-L·min^{-1} increase in TOR. Survival time was shorter for those with a TOR of ⩾1 L·min^{-1} compared with those with a TOR of 0 L·min^{-1} (multivariable-adjusted HR 3.2, 95% CI 1.11–9.3; p=0.003) (online supplementary fig. E1).

After adjusting for age, TOR and FVC (model 2 in table 2), each 100-m decrement in 6MWD was associated with a two-fold higher mortality rate (HR 2.1, 95% CI 1.4–3.0; p<0.001), but end-walk S_{p,O_2} was not associated with the risk of death (p=0.32). Similarly, an end-walk S_{p,O_2} <88% was associated with a nonsignificant 80% increase in mortality rate (adjusted HR 1.8, 95% CI 0.6–5.4; p=0.31).

Prediction of death at 1 yr in IPF

Time-dependent ROC curves for the prediction of death at 1 yr using TOR and other established prognostic factors are shown in figure 3a. The areas under the curves (AUCs) for TOR were 0.75 for death; this was similar to or greater than the AUCs for FVC, $D_{L,CO}$, 6MWD and end-walk S_{p,O_2}, which ranged from 0.60 to 0.70. A TOR of ⩾1 L·min^{-1} was 89% sensitive and 62% specific for death within 1 yr, yielding positive- and negative-likelihood ratios of 2.34 and 0.18, respectively (table 3). Table 3 shows the positive and negative predictive values for three TOR thresholds calculated using hypothetical low (10%), intermediate (50%) and high (90%) pre-test event probabilities. A TOR of 0 L·min^{-1}

TABLE 1 Participant characteristics in the derivation cohort

	Participants n	TOR L·min^{-1}			
		0	1–2	3–6	8–15
Participants n	104	42	20	28	14
Age yrs	104	62±12	62±6	62±7	64±4
Males %	104	79	70	79	93
Body mass index kg·m^{-2}	104	28±5	30±6	28±4	30±5
Ever-smokers %	104	71	70	61	64
FVC % pred	104	65±21	45±17	44±16	50±16
Total lung capacity % pred	103	67±18	48±11	49±9	53±10
$D_{L,CO}$ % pred	101	45±13	37±8	33±11	27±10
Resting supplemental oxygen prescription					
L·min^{-1}	104	0 (0–0)	2 (0–2.5)	3 (2–4)	3.5 (0–4)
Room air#	104	79	40	18	43
$\bar{P}_{pa}$¶ mmHg	83	19±4	22±4	23±7	27±11
PVR Wood units	76	2.3±0.7	2.5±0.7	3.2±1.3	3.0±1.4
6MWD m	104	456±134	372±133	335±101	357±119
End-walk S_{p,O_2} %	104	89±7	84±7	83±7	92±6

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. End-walk arterial oxygen saturation measured by pulse oximetry (S_{p,O_2}) represents oxyhaemoglobin saturation at the end of 6-min walk testing. TOR: titrated oxygen requirement; FVC: forced vital capacity; % pred: % predicted; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; $\bar{P}_{pa}$: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; 6MWD: 6-min walk distance. #: 0 L·min^{-1}; ¶: missing for 14 participants in the 0 L·min^{-1} group, three in the 1–2 L·min^{-1} group, two in the 3–6 L·min^{-1} group and two in the 8–15 L·min^{-1} group.

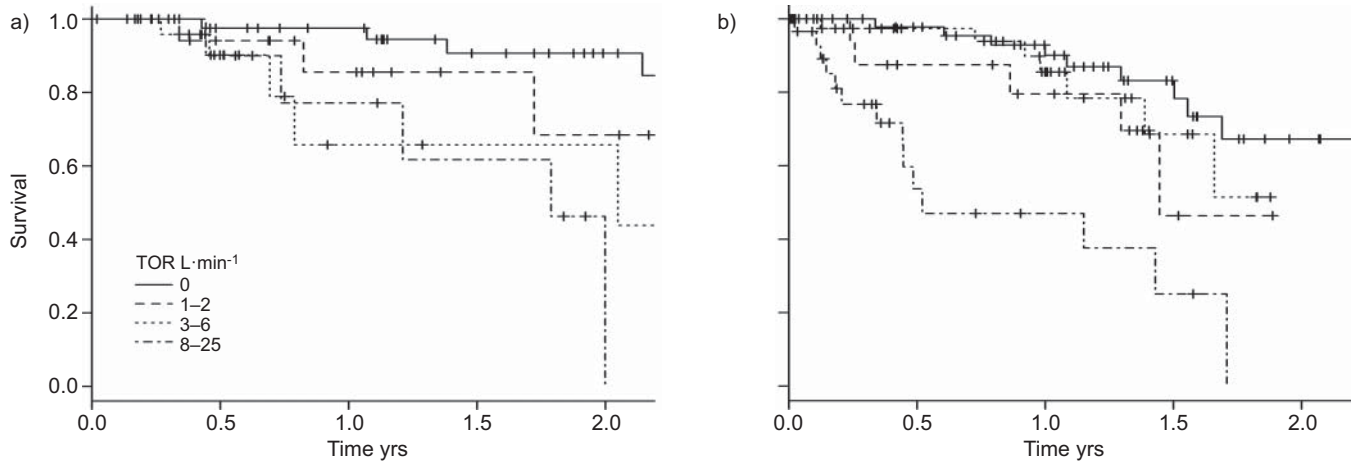

FIGURE 2. Unadjusted survival in the a) derivation (p-value for trend (p_{trend})=0.001) and b) validation (p_{trend}<0.001) cohorts. TOR: titrated oxygen requirement.

combined with a low pre-test probability of death had a 98% negative predictive value at 1 yr.

Validation cohort

The validation cohort consisted of 151 patients: 46 patients with connective tissue disease-associated ILD, 19 with IPF (who were not included in the original cohort), 27 with idiopathic nonspecific interstitial pneumonia and 59 with other forms of ILD (14 with hypersensitivity pneumonitis, 15 with uncharacterised ILD, 11 with pulmonary sarcoidosis, five with lymphangioleiomyomatosis, three with ILD due to prior chemotherapy, three with alveolar proteinosis, two with asbestosis, two with silicosis, and one each with Hermansky–Pudlak syndrome, idiopathic pleuroparenchymal fibroelastosis, pulmonary Langerhans' cell histiocytosis and neurofibromatosis). Associations of TOR with survival time and prediction of survival time in the validation cohort were similar but of smaller magnitude than in the derivation cohort (tables 2 and 3, figs 2b and 3b, and online supplementary fig. E2). For example, the multivariable-adjusted HR for death was 1.10 (95% CI 1.01–1.18; p=0.02) in the validation cohort compared with 1.16 in the derivation cohort.

DISCUSSION

We have shown that the supplemental oxygen flow rate required to maintain an S_{p,O_2} of $\geqslant$96% at rest predicts 1-yr outcomes at least as well as established measures of lung mechanics (FVC), gas exchange ($D_{L,CO}$ and end-walk S_{p,O_2}) and exercise capacity (6MWD) in patients with IPF and other forms of ILD. Death was uncommon among those with a TOR of 0 L·min^{-1} and higher TOR values had greater specificity for the prediction of death. 6-min walk testing using a supplemental oxygen flow rate determined by this novel titration protocol is safe.

The prognostic importance of supplemental oxygen requirements in ILD has previously been examined. EGAN *et al.* [20] used Organ Procurement and Transplantation Network data to examine the association between the ''oxygen requirement at rest'' and the risk of dying while on a waiting list for lung transplantation among 608 ILD patients during the development

TABLE 2 Associations of titrated oxygen requirement (TOR) with survival time

	TOR L·min^{-1}					HR per 1-L·min^{-1} increase in TOR	
	0	1–2	3–6	8–15$^{\#}$	p_{trend}	HR (95% CI)	p-value
Derivation cohort¶							
Unadjusted HR (95% CI)	Ref.	3.7 (1.1–13)	5.3 (1.6–18)	7.5 (2.1–27)	0.003	1.14 (1.06–1.24)	<0.001
Adjusted HR (95% CI)							
Model 1	Ref.	1.8 (0.5–6.9)	3.1 (0.8–11)	6.7 (1.7–26)	0.004	1.16 (1.06–1.27)	0.001
Model 2	Ref.	1.9 (0.5–7.3)	3.0 (0.8–11)	6.7 (1.7–25)	0.005	1.16 (1.06–1.27)	0.001
Validation cohort^{+}							
Unadjusted HR (95% CI)	Ref.	2.2 (0.7–7.2)	1.2 (0.4–3.3)	7.7 (2.7–22)	<0.001	1.13 (1.06–1.20)	<0.001
Adjusted HR (95% CI)							
Model 1	Ref.	1.4 (0.4–5.4)	0.7 (0.2–2.4)	3.8 (1.01–15)	0.01	1.10 (1.01–1.19)	0.02
Model 2	Ref.	1.4 (0.4–5.3)	0.7 (0.2–2.3)	3.9 (1.05–15)	0.01	1.10 (1.01–1.18)	0.02

Model 1 was adjusted for age, 6-min walk distance and oxygen saturation at the end of the 6-min walk test. Model 2 is model 1 plus adjustment for forced vital capacity % predicted. HR: hazard ratio; p_{trend}: p-value for trend; ref.: reference group. $^{\#}$: two participants in the validation cohort who were titrated to 25 L·min^{-1} *via* non-rebreather mask were included in this group; ¶: n=104; $^{+}$: n=151.

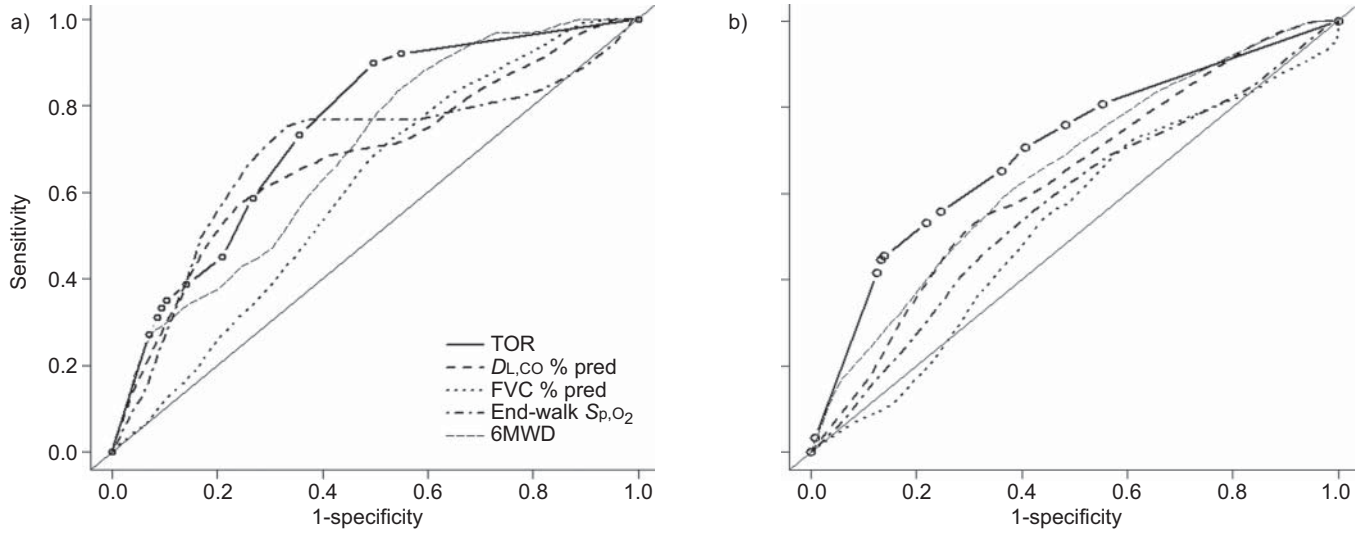

FIGURE 3. Time-dependent receiver operating characteristic curves for the prediction of death within 1 yr in the a) derivation and b) validation cohorts. The area under the curve (AUC) for titrated oxygen requirement (TOR) was 0.75 in the derivation cohort and 0.70 in the validation cohort. The AUC for the other four variables ranged from 0.60 to 0.70 in the derivation cohort and 0.53 to 0.65 in the validation cohort. $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; FVC: forced vital capacity; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; 6MWD: 6-min walk distance.

of the lung allocation score (LAS). Although those investigators ultimately included oxygen use in the waiting list urgency score of the lung allocation score, they reported that the supplemental oxygen flow rate was not significantly associated with a higher mortality rate in ILD in a multivariable-adjusted model [20]. The discrepancy between their results and ours may be due to a number of factors. First, we used a standardised assessment of oxygen requirement, rather than relying on flow rates reported by transplant centre personnel, which could have been prone to misclassification bias. Secondly, since we did not restrict our analysis to those placed on the waiting list, our cohort may have been more heterogeneous with regard to disease severity, easing detection of an association with mortality. Thirdly, the multivariable-adjusted model used in the LAS may have included factors that explain the association between oxygen flow rate and mortality, such as pulmonary hypertension [21]. Only 80% of our study subjects underwent right heart catheterisation, limiting our ability to examine pulmonary hypertension as a confounder. Even if pulmonary hypertension were to explain our findings, TOR would still be a clinically useful test, just as $D_{L,CO}$ [4, 16, 17, 22, 23], end-walk S_{p,O_2} [4, 6] and heart rate recovery [24] remain practical clinical tests that are influenced by pulmonary haemodynamics.

Our results suggest that both TOR and 6MWD are each independently associated a higher risk of death in IPF. In contrast to previous studies [4, 6], however, we did not detect an association between end-walk S_{p,O_2} and the risk of death, possibly due to the administration of higher concentrations of oxygen during walk testing using our protocol. Our approach was to measure and account for supplemental oxygen use, walk distance and desaturation in the same survival models, permitting an

TABLE 3 Sensitivity, specificity, likelihood ratios and predictive values of three titrated oxygen requirements for the prediction of death at 1 yr

	Sensitivity %	Specificity %	LR+	LR-	Pre-test probability 10%		Pre-test probability 50%		Pre-test probability 90%	
					PPV %	NPV %	PPV %	NPV %	PPV %	NPV %
Derivation cohort										
⩾1 L·min^{-1}	89	62	2.34	0.18	21	98	70	85	95	39
⩾6 L·min^{-1}	44	89	4.00	0.63	31	93	80	61	97	15
15 L·min^{-1}	22	94	3.67	0.83	29	92	79	55	97	12
Validation cohort										
⩾1 L·min^{-1}	81	45	1.46	0.43	14	95	59	70	93	20
⩾6 L·min^{-1}	55	86	3.96	0.52	31	95	80	66	97	18
⩾15 L·min^{-1}	3	99.2	3.89	0.98	30	90	80	51	97	10

LR+: positive-likelihood ratio; LR-: negative-likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

independent examination of the impact of each factor. Future studies may help elucidate ideal walk testing practices in order to maximise our ability to predict future events.

Practices of referral, listing and prioritisation for lung transplantation might be improved by standardising the measurement and reporting of supplemental oxygen use. Current guidelines recommend that all patients with IPF be referred for evaluation for lung transplantation at the time of diagnosis. If our findings are validated in future studies, it may be reasonable to incorporate a TOR threshold in referral guidelines. It may also be appropriate to implement our titration protocol at lung transplant centres to standardise reporting of supplemental oxygen use.

It may be that measures of gas exchange (*e.g.* TOR, end-walk S_{P,O_2} and $D_{L,CO}$) are better predictors of outcome than measures of lung mechanics (*e.g.* reduced FVC) [4, 6, 10, 25]. TOR, in particular, may have certain strengths that merit its continued investigation and, perhaps, clinical use. For example, in contrast to pulmonary function testing and 6-min walk testing, TOR is inexpensive (and in many settings cost free) and quick (often $<$3 min). TOR also standardises a widespread clinical practice of gauging disease severity by oxygen requirement. Clinical trialists should consider including TOR as a potential surrogate end-point in studies of novel therapies.

Our findings were somewhat weaker in the validation cohort compared with the derivation cohort. This may be a result of the inclusion of participants with a variety of different ILDs in the validation cohort despite our attempt to control for diagnosis using statistical methods. In addition, the non-IPF diagnoses comprising the validation cohort typically have lower mortality rates than IPF, possibly limiting our ability to detect small differences in mortality rates. Finally, the IPF cohort was prospectively enrolled, while the validation cohort was assembled retrospectively, which may have introduced selection and information bias.

Our study has several limitations. First, we limited our sampling frame to a single tertiary care referral centre with a lung transplant programme, possibly selecting for those with more severe disease. Nevertheless, we were able to identify a subset with low rates of death and lung transplantation. We also excluded those who did not complete an oxygen titration study at our centre, a group characterised by older age and lower lung function. Application of our findings to those with advanced disease should therefore be done cautiously and should be integrated with clinical judgment. Secondly, since priority for lung transplantation in the USA is, in part, based on oxygen requirements, we were careful to avoid treating transplantation as an event of interest, and instead chose to censor upon lung transplantation. However, informative censoring may have limited our ability to examine death as an isolated event. Thirdly, a number of the factors that influence the oxyhaemoglobin desaturation curve, such as arterial pH, 2,3-diphosphoglycerate and body temperature, could have introduced ''noise'' into our study. Since this measurement error is unlikely to be differential to the risk of death, such error would tend to weaken the results. Therefore, the actual relationship may be even stronger than that shown. Lastly, our 6-min walk protocol varies from that suggested by the American Thoracic Society guidelines and from other centres' published experience [4, 6, 10]. Differences in exercise test results between our study and others should, therefore, be interpreted with care. Our oxygen titration protocol may provide a useful means to standardise 6-min walk testing across centres.

In summary, we developed a simple, safe, inexpensive oxygen titration study that standardises the administration of supplemental oxygen during 6-min walk testing. The oxygen flow rate required to reach a resting S_{P,O_2} of $\geqslant$96% may aid in identifying those at high and low risk of death. Our findings support the hypothesis that impaired gas exchange is a clinically useful measure of disease severity in IPF.

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STATEMENT OF INTEREST

Statements of interest for S.M. Kawut and D.J. Lederer can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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