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Title: Physiological predictors of hypoxic challenge testing (HCT) outcomes in Interstitial Lung Disease (ILD).

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Abstract: Background: Pre-flight risk assessments are currently recommended for all Interstitial Lung Disease (ILD) patients. Hypoxic challenge testing (HCT) can inform regarding the need for supplemental in-flight oxygen but variables which might predict the outcome of HCT and thus guide referral for assessment, are unknown.

Methods: A retrospective analysis of ILD patients attending for HCT at three tertiary care ILD referral centres was undertaken to investigate physiological variables that might predict a hypoxaemic response to HCT. Concordance between HCT and existing predictive equations for prediction of in-flight hypoxia was also explored.

Results: A total of 106 ILD patients (69 of whom (65%) had Idiopathic Pulmonary Fibrosis (IPF)) underwent HCT. Of these, 54 (51%) patients (of whom 37 (69%) had IPF) failed HCT and were recommended supplemental in-flight oxygen. Existing predictive equations were unable to accurately predict the outcome of HCT. ILD patients who failed HCT had significantly lower resting SpO2, baseline PaO2, reduced walking distance, FEV1, FVC and TLCO, but higher GAP index than those who passed HCT.

Conclusions: TLCO >50% predicted and PaO2 >9.42kPa were independent predictors for passing HCT. Using these discriminators, a novel, practical pre-flight algorithm for evaluation of ILD patients is proposed.

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October 2017

Dear Editing team,

Re: Physiological predictors of hypoxic challenge testing (HCT) outcomes in Interstitial Lung Disease (ILD)

Thank you for taking the time to consider the manuscript detailed above. The manuscript reports the results of a multi-centre study analysing the use of physiological variables to predict a hypoxaemic response to hypoxic challenge testing (HCT) in patients with Interstitial Lung Disease (ILD). We present an algorithm using physiological variables to assist clinicians in their pre-flight assessment of ILD patients to decide when supplemental in-flight is or not required, and when further assessment with HCT should be used.

We think this will be of interest to your readership due to its relevance to clinical practice. As the largest study of its kind, we believe it will highly cited in the future as an important article in this field.

This manuscript is not in consideration in any other journal. All authors have read and agreed to the final manuscript submitted.

Kind regards

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***Conflict of Interest Statement**

None declared.

Title: Physiological predictors of hypoxic challenge testing (HCT) outcomes in Interstitial Lung Disease (ILD).

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Conflicts of interest: None declared.

Take home message: A novel algorithm is proposed to guide pre-flight assessment of patients with interstitial lung disease.

Abstract

Background: Pre-flight risk assessments are currently recommended for all Interstitial Lung Disease (ILD) patients. Hypoxic challenge testing (HCT) can inform regarding the need for supplemental in-flight oxygen but variables which might predict the outcome of HCT and thus guide referral for assessment, are unknown.

Methods: A retrospective analysis of ILD patients attending for HCT at three tertiary care ILD referral centres was undertaken to investigate physiological variables that might predict a hypoxaemic response to HCT. Concordance between HCT and existing predictive equations for prediction of in-flight hypoxia was also explored.

Results: A total of 106 ILD patients (69 of whom (65%) had Idiopathic Pulmonary Fibrosis (IPF)) underwent HCT. Of these, 54 (51%) patients (of whom 37 (69%) had IPF) failed HCT and were recommended supplemental in-flight oxygen. Existing predictive equations were unable to accurately predict the outcome of HCT. ILD patients who failed HCT had significantly lower resting SpO_2, baseline PaO_2, reduced walking distance, FEV1, FVC and TLCO, but higher GAP index than those who passed HCT.

Conclusions: TLCO >50% predicted and PaO_2 >9.42kPa were independent predictors for passing HCT. Using these discriminators, a novel, practical pre-flight algorithm for evaluation of ILD patients is proposed.

Keywords

Interstitial lung disease, hypoxic challenge test, Idiopathic Pulmonary Fibrosis

Introduction

Hypobaric hypoxia arises during air travel because of the inverse relationship between the partial pressure of oxygen and altitude, observed as a fall in total ambient pressure during ascent. Commercial airlines commonly cruise at 38000 feet to improve fuel economy, typically pressurizing air cabins to a maximum of altitude of 8000 feet (2438m), reducing the effective altitude to which passengers are exposed[1]. This pressurisation is equivalent to breathing approximately 15% oxygen at sea level,

but the precise cabin altitude can vary according to the aircraft design and exact aircraft altitude, which may be exceeded to avoid adverse weather conditions[2].

In healthy individuals, increased minute ventilation, heart rate and cardiac output compensate, such that little physiological impact is experienced by most individuals at typical cabin altitudes[3,4]. Clinical manifestations of hypobaric hypoxia include headache, euphoria, impairment of judgement or memory and in more severe cases peripheral visual field defects, unconsciousness and death[5,6].

The British Thoracic Society (BTS) currently recommends risk assessment of all interstitial lung disease (ILD) patients prior to air travel to predict the likelihood of respiratory problems and to identify those requiring supplemental in-flight oxygen[3].

Hypoxic challenge testing (HCT)[7] is the method of choice to identify patients who might require supplemental in-flight oxygen, based on its ability to reliably identify patients requiring supplemental oxygen when compared to hypobaric chamber, its widespread availability and relative low cost[8,9]. Arbitrary cut-offs of PaO_2 of <6.6kPa or SpO_2 <85% are positive indicators of the need for supplemental in-flight oxygen[10]. The evidence surrounding which ILD patients to refer for HCT is currently lacking.

Predictive equations are alternatives that have been developed for use in clinical practice, to predict PaO_2 at altitude[7, 11-15], but have been developed almost exclusively using patients with COPD and their role in patients with ILD has not been fully defined.

The aim of this study was to explore the correlation and concordance between HCT and predictive equations for prediction of in-flight hypoxia in ILD patients and secondly to identify physiological variables that might be used to predict the outcome of HCT in patients with ILD.

Methods

This study was approved by the Health Research Authority, United Kingdom (UK) (Reference 17/HRA/0007). The clinical records of 106 consecutive ILD patients presenting to three UK secondary care ILD centres for routine HCT (between January 2010 and March 2017), were retrospectively analysed. All patients had an

ILD multidisciplinary team (MDT) consensus diagnosis. Baseline demographic data, oxygen saturations (SpO_2) using pulse oximetry and capillary ear lobe partial pressure of oxygen (PaO_2) were collected. Spirometry, transfer factor for carbon monoxide (TLCO) and 6-minute walk tests (6MWT), performed according to BTS guidelines[16] and within 6 months of the HCT, were also evaluated. The GAP index[17] (gender, age and lung physiology index) was calculated from the collated information.

HCT was undertaken using the Ventimask method, whereby 100% nitrogen was delivered through a 40% Ventimask at a designated flow rate of 10.0 l/min, resulting in an equivalent inspired fraction of oxygen (FiO_2) of 15% O_2[18]. A fall of PaO_2 to <6.6kPa during the test indicated that the individual should be recommended supplemental in-flight oxygen (Failed HCT), according to BTS guidelines[3].

The predicted partial pressure of oxygen at altitude (PaO_2 Alt) was calculated by applying the collated data to four published predictive equations (Supplemental Table 1). Supplemental in-flight oxygen requirement predictions were compared to the actual HCT results.

Physiological variables were compared between patients requiring supplemental in-flight oxygen, as determined by the HCT, compared to those who did not. Patients were either compared as a single group of ILD patients or stratified into Idiopathic Pulmonary Fibrosis (IPF) versus non-IPF.

Statistical analyses were performed using Graphpad Prism 7.0 software (CA, USA), with multivariable analysis using STATA data analysis and statistical software (Texas, USA). The sensitivity and specificity of existing published predictive equations as compared to actual HCT results were calculated using a cut-off of PaO_2 of <6.6kPa.

Categorical variables were presented as counts, whilst continuous variables were presented as means +/- standard deviation (S.D.). Univariable logistic regression analysis was used to compare physiological variables in a) ILD patients and b) IPF patients referred for hypoxic challenge testing (HCT) and the outcome of HCT in a priori statistical analysis plan. Results were presented as Odds Ratios (OR) with 95% confidence intervals (CI).

Receiver operating characteristics (ROC) curve analyses were performed on correlating variables with the identification of optimum cut-off points (decision point) for each variable, identified using the maximum Youden's index (J), where J max = Sensitivity + Specificity-1. Multivariable logistic regression analysis was performed to identify factors independently predicting the outcome of HCT, with results presented as ORs with 95% CI. A P value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 106 ILD patients underwent HCT in 3 UK centres. Table 1 demonstrates baseline demographic data and diagnostic subgroups of ILD patients. The majority of patients were male (70%, n=74), with a mean age of 69.25 years. Mean baseline FVC % predicted (76.40 ± 20.73), TLCO (46.89 ± 13.96) and GAP Index of (3.87 ± 1.47) suggests that the population had at least moderate ILD. Approximately two-thirds of the group had a MDT consensus diagnosis of IPF (65%, n=69).

Fifty-four (51%) patients failed HCT, of whom 37 (69%) had IPF, and were recommended supplemental in-flight oxygen.

Concordance of predictive equations with outcome of actual Hypoxic Challenge Testing

Table 2 demonstrates the sensitivity, specificity, positive and negative predictive values of existing predictive equations compared to actual HCT outcomes. Based on the availability of complete data required for these equations in 101 patients (n= 51 Failed HCT, n=50 Passed) and using the previously defined cut-off of PaO_2 <6.6kPa, predictive equations 2 and 3 were shown to be highly specific (100%); no patient who passed HCT was predicted to require supplemental in-flight oxygen using these equations. The sensitivity of both equations was poor however, leading to a failure of supplemental in-flight oxygen provision to 41 and 47 patients respectively who were deemed to need it by HCT. Predictive equation 1 was the most sensitive of the models resulting in a failure to provide supplemental in-flight oxygen to only 5

patients who required it, but resulting in the supply of supplemental in-flight oxygen erroneously to an additional 30 patients who passed their HCT.

Comparison of physiological variables and outcome of HCT

Univariable logistic regression of physiological variables in the cohort of 106 ILD patients, revealed that patients who failed HCT (n=54/106) had significantly lower resting SpO_2, baseline PaO_2, reduced walking distance, FEV1, FVC and TLCO, but higher GAP index than those who passed HCT (Supplementary Table 2). Interestingly, 27.8% of patients with $SpO_2 \geq$ 96% failed HCT.

Similarly, in the IPF subgroup, patients who failed HCT (n=30/61) had significantly lower baseline PaO_2, FEV1, FVC and TLCO % predicted, but higher GAP index than those who passed HCT. Additionally, the IPF subgroup demonstrated lower minimum SpO_2 on 6MWT compared to the overall ILD group (Supplementary Table 3).

Multivariable logistic regression analysis was applied to the results of 86 patients with ILD and 49 IPF patients who had complete data sets. Baseline PaO_2 was also found to be an independent predictor of failing HCT in both ILD patients (n=86) and IPF for both groups (Tables 3 and 4).

ROC curve analysis suggested that TLCO % predicted and baseline PaO_2 gave the highest area under the curve (AUC) values for all variables studied, 0.7343 and 0.8206 respectively (Figure 1). Using the maximum Youden's index for each variable, FEV1 >85.0% predicted, FVC % predicted >81.50% predicted, TLCO % predicted >50% predicted, resting SpO_2 >95.5%, GAP index <0.45 and 6MWT >333.0m were identified as the optimum cut-offs for predicting a 'Passed HCT' (Supplementary Table 4).

Multivariable logistic regression for passed HCT in ILD patients (n=86 with complete data sets) using significant variables from univariable logistic regression and optimum cut-offs as determined from ROC curve analysis identified that TLCO >50% predicted and baseline $Pa0_2$ >9.42 kPa were independently related to the outcome of

HCT (Table 5). GAP index was excluded from the analysis as 84/86 of the ILD patients in this data set had a GAP index of >0.45.

ILD pre-flight algorithm

Based on these analyses a pre-flight algorithm was developed using baseline PaO_2 and TLCO % predicted as key determinants to evaluate whether supplemental in-flight oxygen was recommended, whether the patient could fly without oxygen or whether advice was given for further pre-flight assessment with HCT (Figure 2). This algorithm had a sensitivity of 86% and specificity 84% when all patients with complete datasets for this information (n=88) were individually tested. Thirty-five patients (40%) would have been advised to have pre-flight HCT. Four patients were misclassified as not requiring supplemental in-flight oxygen (mean PaO_2 10.41kPa $\pm$ 0.64) and mean TLCO 58.25% predicted $\pm$ 5.32) and 4 patients would have received supplemental in-flight oxygen inappropriately (mean PaO_2 8.94kPa $\pm$ 0.18 and mean TLCO 36.00% predicted $\pm$ 3.56).

Discussion

Large numbers of patients with respiratory disease use commercial air-travel every year without adverse effect[19], but the potential serious manifestations of hypobaric hypoxia are well described[5,6] and as such, the BTS recommends risk assessment of all ILD patients prior to travel to assess the likelihood of complications and to identify those requiring supplemental in-flight oxygen[3]. Whilst HCT is the method of choice to identify those patients in need of supplemental in-flight oxygen[8,9], it is not always readily available, particularly in primary care. The use of a predictive equation or algorithm that may help identify which ILD patients require supplemental in-flight oxygen or those that require referral for HCT would be of considerable value in this population.

Several predictive equations are available in the published literature but they have been developed almost exclusively from patients with COPD and their role in ILD has not been fully defined. Our results suggest that although the predictive equations

tested[7,14] would provide a relatively cheap and easily accessible method of determining the estimated PaO_2 at altitude, they cannot be used in isolation to accurately predict the need for supplemental in-flight oxygen in ILD patients. Equations 1 and 4, using baseline sea-level PaO_2 as the main discriminator, overestimated the need for supplemental in-flight oxygen in 30 and 11 patients in our cohort respectively. Inclusion of FEV1 measurements (predictive equations 2 and 3), as a second discriminator, improved specificity at the expense of sensitivity, failing to predict the need for supplemental in-flight oxygen in 41 and 47 patients respectively. These findings are consistent with those from small cohorts of ILD patients[12,20].

In our cohort, 27.8% patients fulfilled criteria for supplemental in-flight oxygen despite SpO_2 > 95%. Taken together with the findings from above, our results are consistent with previous studies of small cohorts of ILD patients and mixed respiratory disease, suggesting that neither resting SpO_2 or FEV1 reliably predict HCT hypoxaemia[3,18,21-25].

According to our results, PaO_2 and TLCO (% predicted) independently correlated with outcome of HCT in patients with ILD. To the current authors' knowledge this is the largest retrospective multi-centre observational study of ILD patients and the physiological parameters that might predict the requirement for supplemental in-flight oxygen, as determined by HCT. The present study is also unique in that a well-defined cohort of 69 IPF patients was examined as part of this study.

It has previously been suggested that a pre-flight $Pa0_2$ >9.3kPa is sufficient for air travel without the need for supplemental in-flight oxygen[26] but several studies have subsequently refuted its usefulness in predicting in flight hypoxaemia in COPD patients[2,27]. According to our own results, ILD patients with PaO_2 >9.42kPa in conjunction with TLCO >50% predicted, can travel safely without supplemental in-flight oxygen. Conversely, we suggest that patients with PaO_2 ≤9.42kPa in conjunction with TLCO ≤50% predicted, require supplemental in-flight oxygen. Patients with equivocal results should be referred for HCT prior to travel. Further assessment of this algorithm is required in a prospective validation cohort.

An algorithm incorporating pulse oximetry at rest and during 6MWT, was found to be a useful tool for discerning COPD patients who can travel without supplemental in-flight oxygen, those who need supplemental in-flight oxygen and those who require further assessment with HCT[28]. Furthermore, PaO_2 during maximal exercise has also been strongly correlated with the PaO_2 during hypoxic challenge test in cystic fibrosis[29] and COPD patients[21,27]. Our results demonstrate that in this ILD cohort desaturation during exercise is non-discriminatory, in that 8 (20%) patients who passed HCT and 10 (30%) of those who failed HCT desaturated to ≤84% SaO_2 on 6MWT. This supports the findings of others suggesting that light exercise may aggravate hypoxaemia under hypoxic conditions[22,28]. It is our opinion therefore, that further work is required to identify a potential role for exercise testing as part of the HCT in patients with ILD.

There are several limitations to the current study, including those inherent to retrospective analyses and potential bias related to missing data. The HCT has advantages over predictive equations or algorithms in that it also allows determination of the flow rate of supplemental in-flight oxygen required. HCT is not however an absolute gold standard as it only simulates one aspect of altitude exposure, namely the inhalation of a low inspired fraction of oxygen (FiO_2) and disregards the potential effect of decreased barometric pressure[9]. Indeed, discrepancies between SpO_2 obtained during HCT and actual in-flight SpO_2 have been reported[30]. Furthermore, the present authors accept further validation is required in a larger prospective cohort of ILD patients.

In summary, the present authors have undertaken the largest retrospective multi-centre analysis of ILD patients to study the relationship between the development of hypoxia during HCT and physiological variables. The correlation between existing predictive equations and the actual outcome of HCT was also explored. Existing predictive equations are not sufficiently accurate to predict individual hypoxic responses during HCT in ILD patients when used in isolation. This is perhaps unsurprising given the numerous biological and cellular variables that control oxygen homeostasis and the physiological response to hypoxia.

Our findings suggest a correlation between resting PaO_2 and TLCO % predicted and the outcome of HCT. We propose a novel clinically relevant and practical algorithm for assessment of the requirement of supplemental in-flight oxygen in ILD patients (Figure 2). This algorithm stratifies ILD patients into those that do /do not require supplemental in-flight oxygen and those that require HCT for further assessment. This algorithm will require further validation in large prospective ILD cohorts.

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We would also like to thank Paul White, University West of England, Bristol, UK for his advice on statistical analysis for this manuscript. RJ, JS, NM, IC collated the data. SLB, NC, HA, HS all contributed to the study conception. AB and SB undertook data analysis. All authors contributed to the writing of the manuscript.

References

1. Code of Federal Regulations. *Title 14, part 25.841*. Washington: US Government Printing Office, 1986.
2. Seccombe LM, Peters MJ. Oxygen supplementation for chronic obstructive pulmonary disease patients during air travel. Curr Opin Pulm Med 2006;12:140e4.
3. Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, Cummin AR, Gradwell DP, Howard L, Innes JA, Johnson AOC, Lim E, et al. Managing passengers with stable respiratory disease planning air travel: British Thoracic Society recommendations. Thorax 2011;66:Suppl 1.
4. Hultgren HN, Grover RF. Circulatory adaptation to high altitude. Annu Rev Med 1968;19:119-152.
5. Federal Aviation Administration. Chapter 8: Medical facts for pilots, 2014. Available from http://www.faa.gov.
6. Asmaro D, Mayall J, Ferguson S. Cognition at altitude:impairment in executive and memory processes under hypoxic conditions. Aviat Space Environ Med 2013;84:1159-1165.
7. Gong H, Tashkin DP, Lee EY, Simmons MS. Hypoxia-altitude simulation test. Am Rev Respir Dis 1984;130:980e6.

8. Akerø A, Edvardsen A, Christensen CC, Owe JO, Ryg M, Skjønsberg OH. COPD and air travel: oxygen equipment and pre-flight titration of supplemental oxygen. Chest. 2011 Jul;140(1):84-90.
9. Dillard TA, Moores LK, Bilello KL, Phillips YY. The preflight evaluation. A comparison of the hypoxia inhalation test with hypobaric exposure. Chest 1995;107:352e7.
10. Cramer D, Ward S, Geddes D. Assessment of oxygen supplementation during air travel. Thorax 1996;51:202–3.
11. Apte NM, Karnad DR. Altitude hypoxaemia and the arterial-to-alveolar oxygen ratio. Ann Intern Med 1990;112:547e8.
12. Billings CG, Wei HL, Thomas P, Linnane SJ, Hope-Gill BDM. The prediction of in-flight hypoxaemia using non-linear equations. Resp Med 2013;107:841-847.
13. Dillard TA, Rosenberg AP, Berg BW. Hypoxaemia during altitude exposure. A meta-analysis of chronic obstructive pulmonary disease. Chest 1993;103:422e5.
14. Dillard TA, Berg BW, Rajagopal KR, et al. Hypoxaemia during air travel in patients with COPD. Ann Intern Med 1989;111:362e7.
15. Henry JN, Krenis LJ, Cutting RT. Hypoxaemia during aeromedical evacuation. Surg Gynecol Obstet 1973;136:49e53.
16. Guidelines for measurement of respiratory function. recommendations of the British thoracic society and the association of respiratory technicians and physiologists. Respir Med 1994;38:165-194.
17. Ley B, Ryerson CJ, Vittinghof E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE, Collard HR. et al. A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis. Ann Intern Med 2012;156:684.
18. Vohra KP, Klocke RA. Detection and correction of hypoxemia associated with air travel. Am Rev Respir Dis 1993;**148**:1215–19.
19. Coker RK, Shiner RJ, Partridge MR. Is air travel safe for those with lung disease? Eur Respir J 2007;30:1057e63.
20. Martin SE, Bradley JM, Buick JB, et al. Flight assessment in patients with respiratory disease: hypoxic challenge testing vs. predictive equations. QJM 2007;100:361e7.

21. Akerø A, Edvardsen A, Ryg M, Skjønsberg OH. PaO_2 during exercise as a predictor for in-flight hypoxaemia in COPD patients (abstr). ERS Annual Congress; 2008.
22. Christensen CC, Ryg M, Refvem OK, Skjønsberg OH. Development of severe hypoxaemia in chronic obstructive pulmonary disease patients at 2,438m (8,000 ft) altitude. Eur Respir J. 2000;15:635e9.
23. Schwartz JS, Bencowitz HZ, Moser KM. Air travel hypoxemia with chronic obstructive pulmonary disease. Ann Intern Med 1984;100:473e7.
24. Robson AG, Hartung TK, Innes JA. Laboratory assessment of fitness to fly in patients with lung disease: a practical approach. Eur Respir J 2000;16:214e19.
25. Seccombe LM, Kelly PT, Wong CK, et al. Effect of simulated commercial flight on oxygenation in patients with interstitial lung disease and chronic obstructive pulmonary disease. Thorax 2004;59:966e70.
26. Medical guidelines for air travel. Aerospace Medical association , Air transport Medicine Committee, Alexandria, Va. Aviat Space Environ Med. 1996;67:B1-16.
27. Akerø A, Christensen CC, Edvardsen A. Hypoxaemia in chronic obstructive pulmonary disease during commercial flight. Eur Respir J. 2005;25:725-30.
28. Edvardsen A, Akerø A, Christensen CC, Ryg M, Skjønsberg OH. Air travel and chronic obstructive pulmonary disease: a new algorithm for pre-flight evaluation. 2012 Thorax. 2012;67(11):964-9.
29. Edvardsen A, Akerø A, Skjønsberg OH Skrede B. Pre-flight evaluation of adult patients with cystic fibrosis: a cross-sectional study. BMC Res Notes. 2017;10:84.
30. Buchdahl RM, Babiker A, Bush A, Cramer D. Predicting hypoxaemia during flights in children with cystic fibrosis. Thorax. 2001;56:877-9.

Figure legends

Table 1: Demographic data (ILD: Interstitial lung disease, CTD-ILD: Connective tissue disease related ILD, CPFE: Combined Pulmonary Fibrosis and Emphysema, COP: Cryptogenic Organising Pneumonia).

Table 2: Sensitivity and specificity of predictive equations in determining the need for supplemental in-flight oxygen compared to actual HCT results with calculated positive (PPV) and negative predictive values (NPV) in a) ILD patients b) IPF subgroup.

Figure 1: Receiver operating characteristics (ROC) curve analysis of physiological variables for the outcome of HCT. A) FEV1 % predicted, B) FVC % predicted, C) TLCO % predicted, D) baseline PaO_2 (kPa), E) Resting SaO_2 (%) and F) GAP index. AUC = area under the curve.

Table 3: Multivariable logistic regression for failed HCT test in ILD (only patients with complete data sets used n=86). 6MWT variables not included as large number of patients had missing data for this variable. P value = significance level, CI = confidence interval.

Table 4: Multivariable logistic regression for failed HCT in IPF (n=49 patients with complete data). 6MWT variables not included as large number of patients had missing data for this variable. P value = significance level, CI = confidence interval.

Table 5: Multivariable logistic regression for passed HCT in ILD patients (n=86 with complete data sets) using significant variables from univariable logistic regression and optimum cut-offs as determined from ROC curve analysis.

Figure 2: ILD pre-flight algorithm. ILD patients with PaO_2 >9.42kPa in conjunction with TLCO >50% predicted can travel safely without supplemental in-flight oxygen. Patients with PaO_2 ≤9.42kPa in conjunction with TLCO ≤50% predicted require supplemental in-flight oxygen. Patients with equivocal results should be referred for further assessment with HCT prior to travel. ILD- Interstitial lung disease, PaO_2 – partial pressure of oxygen, TLCO – transfer factor for carbon monoxide, kPa – kilo pascals.

Table 1

	Mean ± S.D.	n
Age (years)	69.25 ± 8.85	106
Gender	74M: 32F	-
FEV1 (litres)	2.05 ± 0.62	105
FEV1 % predicted	78.22 ± 19.47	105
FVC (litres)	2.52 ± 0.79	106
FVC % predicted	76.40 ± 20.73	106
FEV1/FVC	81.21 ± 6.96	105
TLCO	3.78 ± 1.31	93
TLCO % predicted	46.89 ± 13.96	93
KCO	1.10 ± 0.33	92
KCO % predicted	83.02 ± 23.03	92
Baseline PaO_2 (kPa)	9.34 ± 1.41	101
Resting SpO_2 (%)	94.79 ± 2.85	105
GAP index	3.87 ± 1.47	101
6MWT **-actual distance (m)** **-%theoretical distance (%)** **-minimum SpO_2 (%)** **-maximum heart rate (bpm)**	 339.51 ± 103.77 70.56 ± 2.32 86.80 ± 5.44 111.71 ± 15.24	 73 71 73 47
Diagnoses **-Idiopathic Pulmonary Fibrosis** **-Non-specific interstitial pneumonia** **-CTD-ILD** **-Sarcoidosis** **-Hypersensitivity pneumonitis** **-CPFE** **-Asbestosis** **-Drug induced ILD** **-COP** **-Smoking related ILD** **-Unclassifiable ILD**	 - - - - - - - - - - -	 69 9 9 3 6 3 1 1 1 1 3

Table 1: Demographic data (ILD: Interstitial lung disease, CTD-ILD: Connective tissue disease related ILD, CPFE: Combined Pulmonary Fibrosis and Emphysema, COP: Cryptogenic Organising Pneumonia).

Table 2

a) ILD Patients				
Predictive equation	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
Equation 1	90	60	70	86
Equation 2	20	100	100	55
Equation 3	8	100	100	52
Equation 4	75	78	78	75

b) IPF Patients				
Predictive equation	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
Equation 1	92	59	63	81
Equation 2	19	100	100	52
Equation 3	8	100	100	49
Equation 4	78	78	80	76

Table 2: Sensitivity and specificity of predictive equations in determining the need for supplemental in-flight oxygen compared to actual HCT results with calculated positive (PPV) and negative predictive values (NPV) in a) ILD patients b) IPF subgroup.

Table 3

	Odds ratio	p value	95% CI
FEV1 % predicted	0.937	0.151	0.857 to 1.024
FVC % predicted	1.044	0.291	0.964 to 1.132
TLCO % predicted	0.915	0.130	0.816 to 1.299
KCO predicted	0.987	0.671	1.048 to 2.074
Baseline PaO_2 (kPa)	0.205	**<0.001**	0.090 to 0.471
Resting SpO_2 (%)	0.866	0.299	0.880 to 1.513
GAP Index	0.974	0.958	0.387 to 2.718

Table 3: Multivariable logistic regression for failed HCT test in ILD (only patients with complete data sets used n=86). 6MWT variables not included as large number of patients had missing data for this variable. P value = significance level, CI = confidence interval.

Table 4

	Odds Ratio	P value	95% CI
FEV1 % predicted	0.950	0.425	0.837 to 1.078
FVC % predicted	1.000	0.982	0.878 to 1.136
TLCO % predicted	0.897	0.240	0.749 to 1.075
KCO predicted	1.018	0.739	0.916 to 1.131
Baseline PaO_2 (kPa)	0.165	**0.003**	0.749 to 1.075
Resting SpO_2 (%)	0.823	0.484	0.476 to 1.420
GAP index	0.446	0.251	0.112 to 1.771

Table 4: Multivariable logistic regression for failed HCT in IPF (n=49 patients with complete data). 6MWT variables not included as large number of patients had missing data for this variable. P value = significance level, CI = confidence interval.

Table 5

	Odds Ratio	**p value**	**95% CI**
FEV1 % predicted >85.0	1.004	0.995	0.247 to 4.091
FVC % predicted >81.5	2.667	0.175	0.646 to 11.013
TLCO % predicted >50.5	3.481	**0.025**	1.170 to 10.353
Baseline PaO_2 (kPa) >9.42	8.331	**<0.001**	2.547 to 27.253
Resting SpO_2 (%) >95.5	1.040	0.945	0.338 to 3.204

Table 5: Multivariable logistic regression for passed HCT in ILD patients (n=86 with complete data sets) using significant variables from univariable logistic regression and optimum cut-offs as determined from ROC curve analysis.

Figure 1

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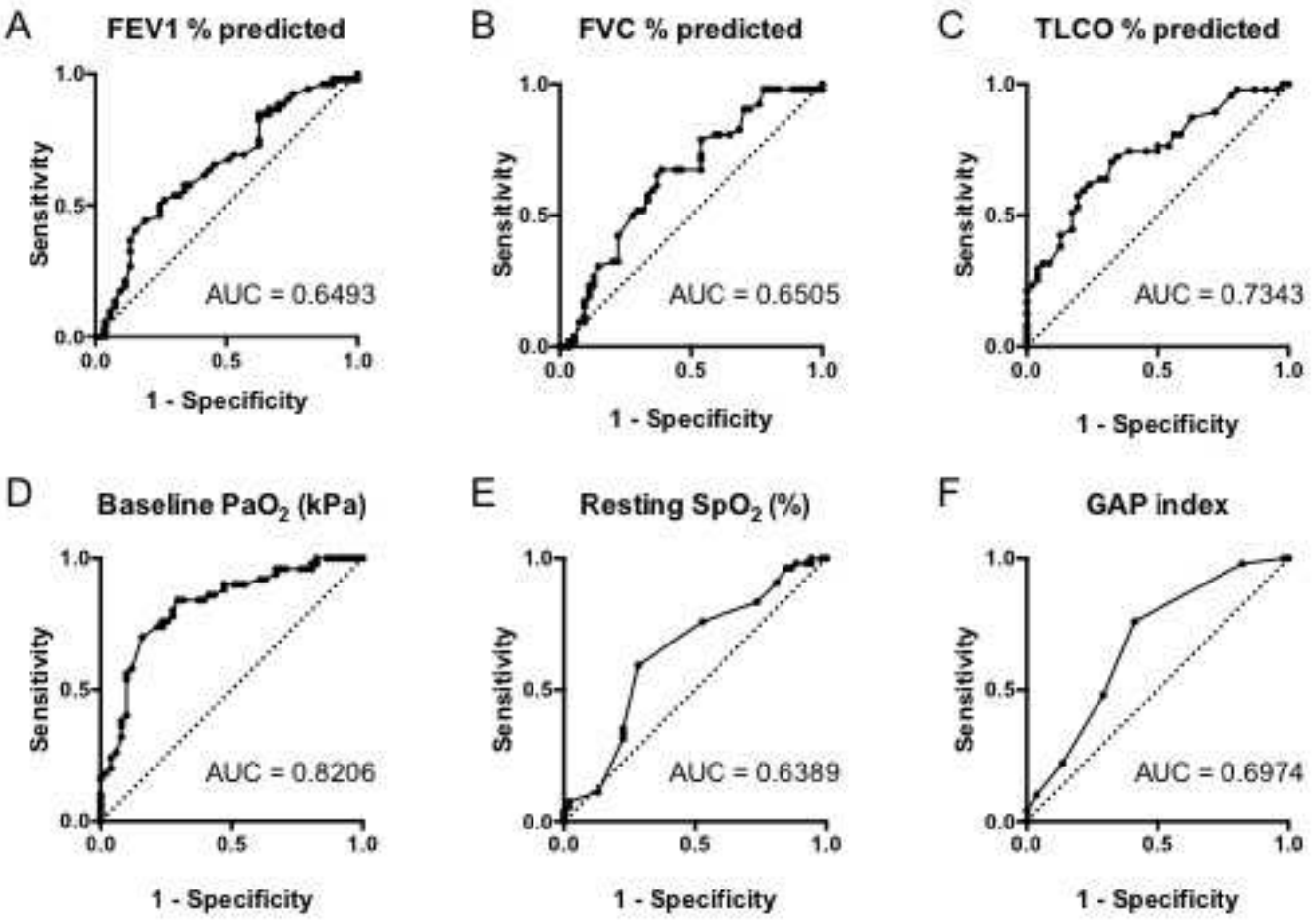

Figure 2

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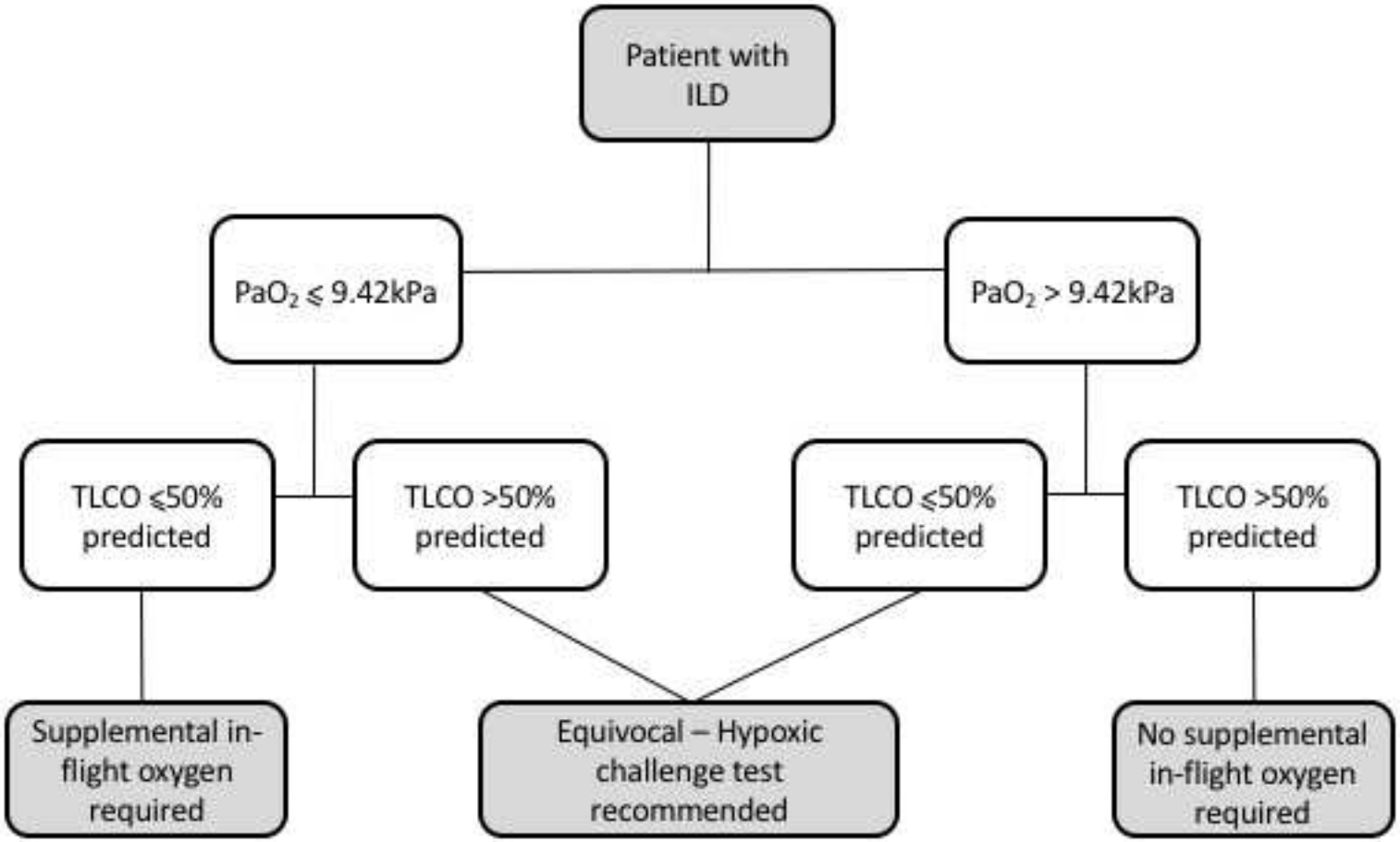

Supplementary Data

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