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Pulmonary rehabilitation in idiopathic pulmonary fibrosis and COPD: a propensity matched real-world study

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Key words: Idiopathic pulmonary fibrosis, pulmonary rehabilitation, prognosis, COPD

Ideas or topics central to the study:

- Completion rates and response to PR in a matched group of people with IPF and COPD
- The association between PR completion and response with mortality in people with IPF

Abbreviations:

- ABOT: Ambulatory Oxygen Therapy
- ANOVA: Analysis of variance
- BMI: Body mass index
- CI: Confidence interval

- COPD: Chronic obstructive pulmonary disease
- CRQ: Chronic respiratory questionnaire
- CRQ-T: Chronic respiratory questionnaire – total score
- FEV_1: Forced Expiratory Volume in One Second;
- FVC: Forced vital capacity
- GRCQ: Global rating of change questionnaire
- HR: Hazard ratio
- ILD: Interstitial lung disease
- IPF: Idiopathic pulmonary fibrosis
- ISW: Incremental shuttle walk test
- MID: Minimal Important Difference
- MRC: Medical Research Council
- PR: Pulmonary rehabilitation
- SMD: Standardized Mean Difference
- SpO_2: Peripheral Capillary Oxygen Saturation
- T0: Timepoint zero
- T1: Timepoint one
- T2: Timepoint two

ABSTRACT

Background: The adherence to and clinical efficacy of pulmonary rehabilitation in idiopathic pulmonary fibrosis (IPF), particularly in comparison to people with chronic obstructive pulmonary disease (COPD), remains uncertain. The objectives of this real-world study were to compare the responses of patients with IPF with a matched group of patients with COPD undergoing the same supervised, outpatient pulmonary rehabilitation program, and to determine whether pulmonary rehabilitation is associated with survival in IPF.

Research question: Do people with IPF improve to the same extent with pulmonary rehabilitation as a matched group of individuals with COPD, and are non-completion of and/or non-response to pulmonary rehabilitation associated with one-year all-cause mortality in IPF?

Study design and methods: Using propensity score matching, 163 patients with IPF were matched 1:1 with a control group of 163 patients with COPD referred to pulmonary rehabilitation. We compared between-group pulmonary rehabilitation completion rates and response. Survival status in the IPF cohort was recorded over one-year following pulmonary rehabilitation discharge. Cox proportional-hazards regression explored the association between pulmonary rehabilitation status and all-cause mortality.

Results: Similar pulmonary rehabilitation completion rates (IPF: 69%; COPD: 63%; p=0.24) and improvements in exercise response were observed in both groups with no significant mean (95% confidence interval (CI)) between-group differences in incremental shuttle walk (ISW) change (2 (-18 to 22) meters). Pulmonary rehabilitation non-completion (hazard ratio (HR) (95%CI) 5.62 (2.24 to 14.08)) and non-response (HR (95%CI) 3.91 (1.54 to 9.93)) were independently associated with increased one-year all-cause mortality in IPF.

Interpretation: Compared with a matched group of patients with COPD, this real-word study demonstrates that patients with IPF have similar completion rates and magnitude of response to pulmonary rehabilitation. In IPF,

non-completion of and non-response to pulmonary rehabilitation were associated with increased all-cause mortality. These data reinforce the benefits of pulmonary rehabilitation in patients with IPF.

Idiopathic pulmonary fibrosis (IPF) is characterised by a progressive decline in respiratory and physical function with a median survival of three to five years from diagnosis.[1,2] Although pharmacological therapies may slow lung function decline, their effect upon symptom burden and quality of life are modest.[3,4] Pulmonary rehabilitation, a multi-disciplinary individualized exercise and education program, originally developed for and validated in people with COPD, improves exercise capacity, dyspnea and health-related quality of life in this population,[5] and has been postulated as having a role in the management of IPF.

The supporting evidence for the benefits of pulmonary rehabilitation in IPF are more modest than in COPD. A Cochrane review that evaluated the efficacy of pulmonary rehabilitation in interstitial lung disease (ILD) (IPF n=182 allocated to intervention arm) concluded that although pulmonary rehabilitation was associated with improvement in people with IPF the quality of evidence was low to moderate due to methodological concerns.[6] Furthermore, the magnitude of benefit from pulmonary rehabilitation in IPF, compared to COPD, is uncertain due to the more rapidly progressive nature of IPF and the greater prevalence of exercise-induced desaturation.[6] Previous small studies comparing pulmonary rehabilitation response between IPF and COPD have shown a reduced magnitude of benefit in IPF.[7,8]

Recent data have also shown an association between pulmonary rehabilitation completion and response with survival in COPD.[9-11] However limited survival data exists in people with IPF. In a recent Cochrane systematic review of pulmonary rehabilitation for ILD, the authors identified only three trials in people with IPF (n=127 participants, with 67 receiving pulmonary rehabilitation) that reported on survival.[6] Although there was a trend towards reduced mortality with pulmonary rehabilitation, there were only a small number of deaths observed (three with pulmonary rehabilitation intervention, eight with control).

Given the limited evidence base, clinical guidelines have provided conflicting recommendations. Whilst the United Kingdom National Institute for Health and Care Excellence (which largely bases its recommendations on

cost-effectiveness) recommends regular assessment for and offering pulmonary rehabilitation to people with IPF,[12] the joint American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines on the diagnosis and treatment of IPF published in 2011 made a weak recommendation for pulmonary rehabilitation in IPF,[13] and the updated guidelines did not discuss the role of pulmonary rehabilitation.[14] the British Thoracic Society Guidelines[15] and the Australia and New Zealand Guidelines[16] for pulmonary rehabilitation provide weak recommendation for the provision of pulmonary rehabilitation in individuals with ILD with the recognition that benefits are unlikely to be sustained[15] and that the quality of evidence is low.[16] Similarly, the American Thoracic Society/European Respiratory Society Statement on pulmonary rehabilitation did not make a recommendation for pulmonary rehabilitation in IPF.[17] Given the uncertainty over the role of pulmonary rehabilitation in IPF management, the overall study aims were to provide real-world data on the effects of pulmonary rehabilitation in IPF compared to COPD, a population in whom the benefit and magnitude of improvement with pulmonary rehabilitation are well-established, and to understand the magnitude of those effects and their clinical consequences. Specifically, the primary objective was to compare the responses of people with IPF with a matched group of people with COPD undergoing the same supervised outpatient pulmonary rehabilitation program. A secondary objective was to determine whether completion of and/or response to pulmonary rehabilitation are associated with survival in people with IPF. We hypothesized that people with IPF would have a blunted response to pulmonary rehabilitation with reduced completion rates compared with matched people with COPD. We also hypothesized that non-completion or non-response to pulmonary rehabilitation would be associated with increased mortality in IPF.

METHODS

Study participants and propensity score matching

We prospectively recruited patients with IPF consecutively referred to the Harefield Pulmonary Rehabilitation Unit between June 2013 and July 2018. Inclusion criteria were a primary diagnosis of IPF determined by a specialist ILD multidisciplinary team according to international guidelines[14] and referral to pulmonary rehabilitation in line with national guidelines.[18] Exclusion criteria included a coexisting diagnosis of COPD. Patients provided informed consent and the study was approved by the London Riverside and London Central Research Ethics Committee. As national clinical guidance in the United Kingdom recommends the offer of pulmonary rehabilitation to people with IPF,[12] it was not considered ethical to recruit a control group of patients with IPF denied the opportunity of referral to pulmonary rehabilitation.

The control group comprised patients with COPD, diagnosed according to international guidelines[19] referred over the same period. An exclusion criterion for this group was a diagnosis of coexisting IPF. Recruitment was conducted by retrospective propensity score matching,[20] using the nearest neighbour method,[21] 1:1 accounting for baseline age, sex, body mass index (BMI), Medical Research Council (MRC), self-reported Chronic Respiratory Questionnaire-total score (CRQ-T) (supplementary file) and incremental shuttle walk test (ISW) distance. Balance between the groups was assessed using standardised mean difference.[22] For both groups, those with contraindications to exercise and co-morbidities that would limit exercise performance (e.g. unstable cardiovascular disease) were excluded prior to recruitment.

Methods

Baseline measures (T0) included BMI; spirometry,[23] MRC,[24] ISW,[25] CRQ[26] and proxy for frailty status (four-meter gait speed <1.0m/s[27,28]). MRC, ISW, CRQ and a Global Rating of Change Questionnaire (GRCQ) were measured following pulmonary rehabilitation completion (T1). For the GRCQ, patients rated their response to *'How do you feel your overall condition has changed after rehabilitation?'* on a five-point Likert scale ranging from *'1: I feel much better'* to *'5: I feel much worse'*. Adherence was defined as the number of supervised sessions patients attended. Completion was defined as attendance at the post- pulmonary rehabilitation assessment[29] and

attendance at a minimum of eight supervised sessions.[30] All-cause mortality, and where relevant, time to death, were recorded one year following the post-pulmonary rehabilitation assessment or planned completion date for completers and non-completers respectively (T2), with data obtained from hospital and primary care medical records. Apart from this, patients were not monitored following discharge from pulmonary rehabilitation.

Patients underwent an eight-week, outpatient program that comprised two supervised exercise and education sessions as well as additional unsupervised home-based exercise each week. The programme is described in the supplementary file and elsewhere.[31-33]

Baseline characteristics were summarised using descriptive statistics. Due to lack of consensus on the independence of the propensity scored matched pairs,[22,34] both unmatched and matched analyses were performed. First, the data were analysed using the Pearson's chi-square test and independent t-test (assuming independence), second the data were analysed using the paired t-test and McNemar's test. The results were the same for both types of analysis, therefore the unmatched analysis only will be presented. The matched analysis is presented in the supplementary file (e-Table 1). Within-group differences were analysed using paired samples t-test for continuous data.

Evaluation of the association between pulmonary rehabilitation status and all-cause mortality at one year were performed in the IPF group only. As the COPD patients were selected through propensity score matching, they may not be representative of a typical COPD cohort. Between group differences in pulmonary rehabilitation status were analysed using chi-square test for trend and one-way ANOVA (non-parametric data: Kruskal-Wallis) for categorical and continuous data respectively. Pulmonary rehabilitation status was defined as follows: Responder: completed pulmonary rehabilitation (defined as attendance at the post-pulmonary rehabilitation assessment and a minimum of eight supervised sessions) and achieved minimal important difference (MID) of ISW change (≥38 meters[25]), Non-responder: completed pulmonary rehabilitation but did not achieve MID of ISW

change (<38 meters); Non-completer: did not complete pulmonary rehabilitation. Cox proportional-hazards regression assessed the association between pulmonary rehabilitation status and all-cause mortality at one year (T1-T2), adjusting for a priori confounders using a justified approach (informed by previous literature or clinical experience)[35]: T0 age, sex, smoking status, MRC, forced vital capacity (FVC) %predicted, ISW, prescription of anti-fibrotic therapy, four meter gait speed. Log-log plots and Schonfeld's residuals tested the proportional-hazard assumption. Kaplan–Meier analysis compared time to all-cause mortality according to pulmonary rehabilitation status, with significance assessed using the log-rank test for trend We also investigated determinants of change in ISW and the association between ISW and pulmonary rehabilitation completion in people with IPF; the methods and results are described in the online supplement (e-Table 2 and e-Table 3). Analyses were performed using SPSS version 26 (IBM, New York, USA). Statistical significance was considered at $p<0.05$.

RESULTS

Baseline characteristics and response to pulmonary rehabilitation

A total of 228 patients with IPF were approached during the study period. Of these, 26 did not consent, and 39 were excluded because of unclassifiable ILD (n=19), coexisting COPD diagnosis (n=7), coexisting cardiac comorbidity that made exercise unsafe (n=6) and other reasons (n=7) (figure 1). In total, we included 163 people with IPF that were matched 1:1 with a control group of people with COPD. Baseline characteristics are described in table 1. Balance diagnostics demonstrated that the groups were well-matched in terms of age, sex, BMI, MRC, ISW and CRQ-T (standardised mean difference <0.1) (table 1). As expected, spirometry data were significantly different between the groups, and a higher proportion of IPF participants used supplemental oxygen. Pulmonary rehabilitation completion was similar in both groups (IPF: 69%; COPD: 63%; p=0.24);reasons for non-completion are outlined in figure 1. There was no between-group difference in the number of sessions attended (mean (standard deviation) IPF 10 (6), COPD 10 (6); p=0.39).

Following PR, both groups significantly improved MRC, ISW and CRQ (table 2) and there were no significant between-group differences (table 2, figure 2). Eighty-eight percent of the IPF group reported feeling '*much better'* or *'a little better'* following pulmonary rehabilitation compared to 91% of the COPD group (p=0.45).

The association between pulmonary rehabilitation completion and response status with all-cause mortality at one-year post- pulmonary rehabilitation in IPF

Differences in baseline characteristics according to pulmonary rehabilitation status (responders n=63 (38%); non-responders: n=50 (31%), non-completers: n=50 (31%)) are described in the supplementary file (e-Table 4). There was significant and progressive worsening of the following variables measured at T0 across the three respective groups: FVC %predicted, MRC, prescription of supplemental oxygen, resting peripheral oxygen saturation, exercise capacity, health-related quality of life and pulmonary rehabilitation adherence.

Out of 163 participants with IPF, six died before completing PR. Of the remaining 157, 42 (27%) died in the one-year follow-up period (T1-T2). A significant association was demonstrated between pulmonary rehabilitation status and mortality in the univariable analysis (table 3). Two multivariable analyses were performed because of co-linearity between MRC and ISW. Both confirmed that pulmonary rehabilitation status remained independently associated with all-cause mortality at one year (table 3). That is, non-completion and non-response were associated with a significantly higher risk of all-cause mortality at one year (table 3).

When stratified according to pulmonary rehabilitation status, a greater proportion of non-completers and non-responders died in the one-year period compared to responders (40%, 24%, 10% respectively; p<0.01). The Kaplan-Meier curve demonstrated a shorter time to all-cause mortality for non-completers and non-responders compared to completers (log-rank test for trend: p<0.001) (figure 3).

DISCUSSION

This study comprises the largest single cohort of patients with IPF undergoing pulmonary rehabilitation. We demonstrate that a real-world pulmonary rehabilitation program is associated with significant improvements in exercise capacity, dyspnea and health-related quality of life in IPF. These improvements, as well as completion rates, were comparable to those observed in a propensity score matched group of patients with COPD. Compared to pulmonary rehabilitation responders, non-completion of or non-response to pulmonary rehabilitation were independently associated with higher all-cause mortality at one year in IPF. These data provide additional evidence to support the provision of pulmonary rehabilitation in IPF.

To date, only small numbers of patients with IPF have been recruited to randomized controlled trials of pulmonary rehabilitation or exercise training (182 allocated to intervention arms).[6] There remains uncertainty around the benefits of pulmonary rehabilitation in IPF due to methodological concerns including selection bias, lack of assessor blinding, small sample size, inadequate power to detect differences and program duration shorter than international recommendations.[6] Our study adds to the existing literature by providing real-world observational data of patients with IPF undergoing pulmonary rehabilitation. Although many programs are designed for people with COPD, our study demonstrates that people with IPF have similar clinical benefits and completion rates to those with COPD. Indeed, there was a trend for higher completion rates in the IPF compared to the COPD group which may be explained by factors not included in the propensity-matching (for example, a lower number of hospitalizations in the previous 12 months in the IPF group).

Two studies have compared the magnitude of change associated with pulmonary rehabilitation in IPF and COPD.[7,8] An observational study of 22 patients with IPF and a control group of 27 unmatched patients with COPD reported similar effect sizes for functional exercise capacity (IPF: 0.29, COPD: 0.26) following a 10-week programme,[7] but smaller changes in exercise capacity, peak work rate, quadriceps force, dyspnea and quality

of life in IPF. The results are difficult to interpret owing to selection bias (people ≥75 years or prescribed long-term oxygen therapy were excluded), small sample size, unmatched disease groups and no statistical evaluation of between-group differences. Kozu *et al* demonstrated that 45 patients with IPF achieved a smaller magnitude of change in exercise capacity, dyspnea, quadriceps force and quality of life than patients with COPD matched for age and MRC,[8] in contrast to our study. Potential explanations include the larger sample size and multi-variable propensity score matching in our study, as well as the greater intensity of our aerobic exercise prescription (our study: 60-80% $V0_2$max for 30 minutes: Kozu: 50% peak workload for 20 minutes). Although our real-world completion rates were lower than observed in the controlled environment of clinical trials, they were comparable to national audit data.[29]

A novel finding of our study is that pulmonary rehabilitation may confer prognostic benefits in IPF, which deserves further investigation. The authors of a Cochrane review of pulmonary rehabilitation for ILD, identified only three trials in people with IPF that reported on survival (n=127 participants, with 67 receiving pulmonary rehabilitation).[6] Although there was a trend towards reduced mortality in the pulmonary rehabilitation arm, only a small number of deaths observed (pulmonary rehabilitation: n=3, control: n=8; p=0.09).

Although we found an association between pulmonary rehabilitation status and survival, there was uncertainty about the reliability of the estimate owing to wide confidence intervals. Furthermore, we are unable to comment on causality, and it is plausible that this relationship could be explained by unmeasured confounding factors such as disease exacerbation, hospitalizations, or worsening of comorbidity. This should be explored in future research. However, we propose that our data support the consideration of mortality as a potential endpoint in future trials of pulmonary rehabilitation in IPF.

To the best of our knowledge, this study describes the largest single cohort of patients with IPF to undergo pulmonary rehabilitation and therefore adds to existing evidence-base. Only patients diagnosed with IPF

according to international guidelines were included and matched to patients with COPD using a validated statistical technique to minimize between-group imbalance. Pulmonary rehabilitation was delivered according to national quality standards. Data on mortality was systematically obtained from hospital and primary care records and is therefore considered accurate. Our data provide novel findings in terms of pulmonary rehabilitation clinical outcomes, completion and prognosis in a real-world setting.

There are some limitations. This was a single center study and the data should be validated in other settings. We excluded patients with co-existing COPD and IPF and are unable to comment on this population. We did not design a randomized controlled trial as it was considered unethical by the local ethics committee to withhold pulmonary rehabilitation based on clinical guidance in the United Kingdom; this limits the interpretation of the data. Although we matched for baseline exercise tolerance and respiratory disability, we did not account for comorbidities in the propensity score matching which may have influenced the results, although the prevalence of cardiovascular disease was similar in both groups. We did not follow up patients after pulmonary rehabilitation and so are unable to comment on disease trajectories, clinical management, exacerbations or hospitalization following pulmonary rehabilitation. Neither assessment of pulmonary artery systolic pressure nor full lung function tests are part of the routine pulmonary rehabilitation assessment in the United Kingdom and we were therefore unable to adjust for lung function measures other than FVC, nor for pulmonary hypertension in our mortality analyses. We could not objectively confirm self-reported adherence to unsupervised home-based exercise, and therefore cannot exclude this as an influencing variable.

INTERPRETATION

In conclusion, we have demonstrated significant real-world improvements in exercise capacity, dyspnea and health-related quality of life in a cohort of patients with IPF undergoing pulmonary rehabilitation. Improvements and completion rates are of similar magnitude to those observed in matched patients with COPD, and support United Kingdom recommendations that patients with IPF are referred for pulmonary rehabilitation. Compared

to pulmonary rehabilitation responders, pulmonary rehabilitation non-completion and non-response were independently associated with all-cause mortality at one year in IPF. Further work is required to corroborate these findings. Nonetheless, these data reinforce the importance of referral to and engagement in pulmonary rehabilitation amongst the IPF population.

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Take Home Point

Study question:

Do people with IPF improve to the same extent with pulmonary rehabilitation as a matched group of individuals with COPD, and are non-completion of and/or non-response to pulmonary rehabilitation associated with one-year all-cause mortality in IPF?

Results:

This real-world study demonstrates that people with IPF have similar completion rates and response to pulmonary rehabilitation as matched individuals with COPD. In IPF, non-completion and non-response to pulmonary rehabilitation were associated with increased all-cause mortality.

Interpretation:

Compared with a matched group of patients with COPD, this real-word study demonstrates that patients with IPF have similar completion rates and magnitude of response to pulmonary rehabilitation. In IPF, non-completion of and non-response to pulmonary rehabilitation were associated with increased all-cause mortality. These data reinforce the benefits of pulmonary rehabilitation in patients with IPF.

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Table 1. Baseline characteristics

Variables used in the propensity matched analysis	**IPF (n=163)**	**COPD (n=163)**	**SMD**
Age (years)	73 (9)	73 (8)	0.00
Gender (male: n (%))	110 (67)	111 (68)	0.00
BMI (kg/m^2)	27.4 (6.0)	27.9 (6.5)	0.07
MRC	3.3 (1.2)	3.2 (1.1)	0.00
ISW (metres)	196 (158)	197 (149)	0.04
CRQ Total score	77.6 (23.0)	78.8 (22.4)	0.01
Other variables	**IPF (n=163)**	**COPD (n=163)**	**p-value**
FEV_1/FVC	0.81 (0.08)	0.47 (0.13)	<0.001
FEV_1 (%)	70.0 (20.8)	47.3 (17.3)	<0.001
FVC (%)	66.7 (23.2)	74.8 (19.8)	<0.01
Prescribed supplemental oxygen (n (%))*	49 (30)	7 (20)	<0.001
Prescribed ABOT (n (%))	41 (25)	11 (7)	<0.001
Resting SpO_2	96 (4)	96 (4)	0.20
Smoking history (n (%))			
Current	0 (0)	17 (11)	<0.001
Former	85 (52)	121 (74)	
Never	78 (48)	25 (15)	
Hospitalised in past year (n (%))	41 (25)	60 (37)	0.01
Antibiotics for respiratory tract infection in past year (n (%))	87 (53)	117 (73)	<0.001
Prescribed anti-fibrotic therapy (n (%))	15 (9)	-	-
Cardiovascular disease (n (%))	93 (57)	93 (57)	0.55
Pulmonary hypertension (n (%))	15 (9)	3 (2)	<0.01
Diabetes (n (%))	26 (16)	23 (14)	0.64
Frail (n (%))	122 (75)	117 (72)	0.60
CRQ Dyspnoea domain	14.9 (6.1)	14.9 (6.3)	0.96
CRQ Fatigue domain	13.9 (5.8)	14.0 (5.3)	0.89
CRQ Emotional Function domain	31.2 (9.1)	31.6 (9.2)	0.70
CRQ Mastery domain	17.7 (5.9)	18.4 (5.7)	0.26
No. of supervised sessions attended	10 (6)	10 (6)	0.39
Completed PR (n (%))	113 (69)	103 (63)	0.24

*Prescribed supplemental oxygen: Prescribed long-term oxygen therapy (for resting hypoxaemia) and/or ambulatory oxygen therapy (for exercise-induced desaturation).

Baseline data are presented as mean (standard deviation) or number (percent).

Abbreviations: ABOT: Ambulatory Oxygen Therapy (supplemental oxygen prescribed for exercise-induced desaturation); BMI: Body Mass Index; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CRQ: Chronic Respiratory Questionnaire; FEV_1: Forced Expiratory Volume in One Second; FVC: Forced Vital Capacity; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk Test; ; MRC: Medical Research Council Dyspnoea Scale; PR: Pulmonary Rehabilitation; SMD: Standardized Mean Difference; SpO_2: Peripheral Capillary Oxygen Saturation.

Table 2. Response to PR

Variables	Within group response to PR				Between group difference in response to PR	
	IPF (n=113)		COPD (n=103)		Between group difference	p
	Mean (95 % CI)	p*	Mean (95 % CI)	p*	Mean (95 % CI)	p
Δ ISW (metres)	53 (37 to 69)	<0.001	55 (44 to 66)	<0.001	2 (-18 to 22)	0.84
Δ MRC	-0.7 (-0.8 to -0.5)	<0.001	-0.7 (-0.9 to -0.6)	<0.001	0.0 (-0.2 to 0.3)	0.36
Δ CRQ Dyspnoea	4.0 (2.9 to 5.1)	<0.001	5.0 (3.7 to 6.2)	<0.001	1.0 (-0.7 to 2.6)	0.25
Δ CRQ Fatigue	1.9 (1.0 to 2.8)	<0.001	2.2 (1.3 to 3.1)	<0.001	0.3 (-0.9 to 1.5)	0.62
Δ CRQ Emotional Function	2.3 (1.0 to 3.5)	<0.01	3.3 (2.0 to 4.7)	<0.001	1.1 (-0.7 to 2.9)	0.24
Δ CRQ Mastery	1.4 (0.6 to 2.2)	<0.001	2.2 (1.3 to 3.1)	<0.001	0.8 (-0.4 to 1.94	0.19
Δ CRQ Total	9.6 (6.5 to 12.6)	<0.001	12.7 (9.2 to 16.2)	<0.001	3.2 (-1.4 to 7.7)	0.18

*p-value is testing the difference between the pre- and post-pulmonary rehabilitation values

Abbreviations: Δ: Change; COPD: Chronic Obstructive Pulmonary Disease; CRQ: Chronic Respiratory Questionnaire; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk Test; MRC: Medical Research Council Dyspnea Scale; PR: Pulmonary Rehabilitation.

Table 3. Univariable and multivariable Cox proportional-hazards regression analysis: association between pulmonary rehabilitation status and time to all-cause mortality at one year from pulmonary rehabilitation completion in IPF

Covariates	**Univariable analysis**		**Multivariable analysis 1***		**Multivariable analysis 2#**	
	HR (95% CI)	**p~**	**HR (95% CI)**	**p~**	**HR (95% CI)**	**p~**
PR status^						
PR responder	*Reference category*	0.01	*Reference category*	0.01	*Reference category*	0.01
PR non-responder	3.91 (1.54 to 9.93)		3.45 (1.24 to 9.57)		3.94 (1.43 to 10.81)	
PR non-completer	5.62 (2.24 to 14.08)		4.70 (1.66 to 13.34)		4.42 (1.53 to 12.79)	

*Variables included in the multivariable analysis 1: T0 age, sex, smoking status, FVC% predicted, MRC, prescription of anti-fibrotic therapy, frailty status, PR status. (Note ISW was not included due to co-linearity)

~p-value is the overall p-value for pulmonary rehabilitation status

#Variables included in the multivariable analysis 2: T0 age, sex, smoking status, FVC% predicted, ISW, prescription of anti-fibrotic therapy, frailty status, pulmonary rehabilitation status. (Note MRC was not included due to co-linearity)

^ Pulmonary rehabilitation (PR) status: PR responder was defined as PR completion plus meeting the minimal important difference of ISW, PR non-responder was defined as PR completion plus not achieving the minimal important difference of ISW, PR non-completer was defined as not completing PR.

Abbreviations: CI: Confidence interval; FVC: Forced Vital Capacity; HR: Hazard Ratio; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk Test; MID: Minimal Important Difference; MRC: Medical Research Council Dyspnea Scale; PR: Pulmonary Rehabilitation.

Figure Legends:

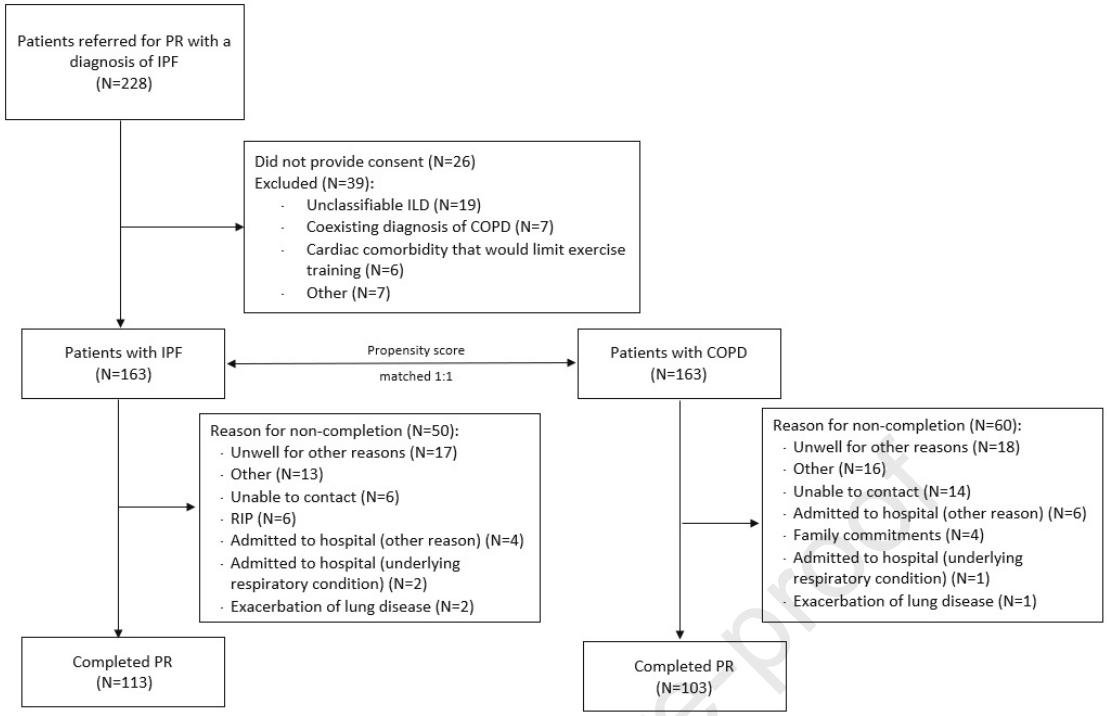
- Figure 1. Flow chart of participant recruitment and reasons for pulmonary rehabilitation non-completion

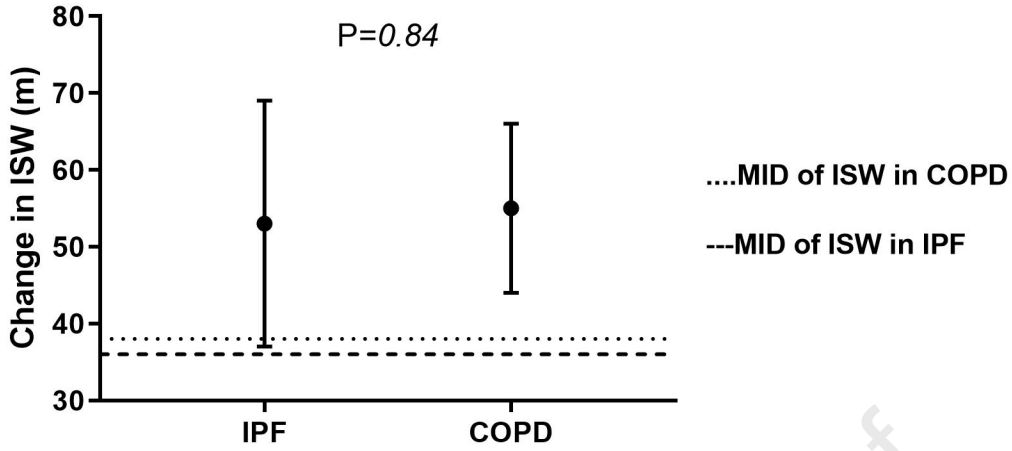
  Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; IPF: Idiopathic Pulmonary Fibrosis

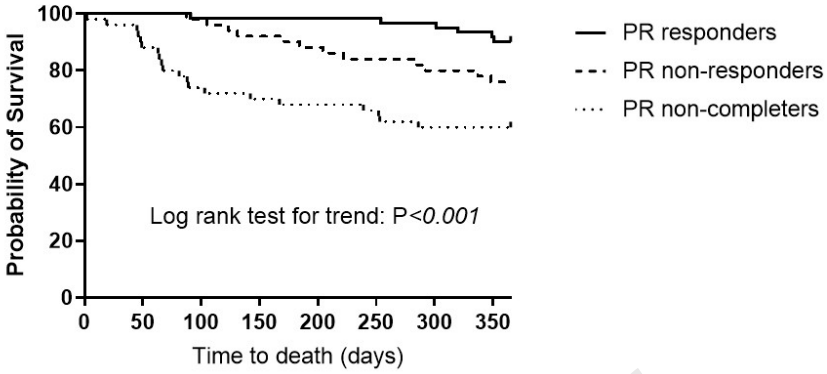
- Figure 2: Mean (95% confidence interval) change in ISW in participants with IPF and COPD (unmatched analysis)

  Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; IPF: Idiopathic Pulmonary Fibrosis; ISW: Incremental Shuttle Walk Test

- Figure 3. Kaplan–Meier curve and at-risk table demonstrating time to all-cause mortality at one year according to pulmonary rehabilitation status with table depicting the numbers at risk







PR responders (N)	61	61	61	61	61	61	58	57
PR non-responders (N)	50	50	50	47	45	43	41	39
PR non-completers (N)	50	45	37	36	35	34	31	31

Abbreviations:

- ABOT: Ambulatory Oxygen Therapy
- ANOVA: Analysis of variance
- BMI: Body mass index
- CI: Confidence interval
- COPD: Chronic obstructive pulmonary disease
- CRQ: Chronic respiratory questionnaire
- CRQ-T: Chronic respiratory questionnaire – total score
- FEV_1: Forced Expiratory Volume in One Second;
- FVC: Forced vital capacity
- GRCQ: Global rating of change questionnaire
- HR: Hazard ratio
- ILD: Interstitial lung disease
- IPF: Idiopathic pulmonary fibrosis
- ISW: Incremental shuttle walk test
- MID: Minimal Important Difference
- MRC: Medical Research Council
- PR: Pulmonary rehabilitation
- SMD: Standardized Mean Difference
- SpO_2: Peripheral Capillary Oxygen Saturation
- T0: Timepoint zero
- T1: Timepoint one
- T2: Timepoint two