Pulmonary Rehabilitation in Idiopathic Pulmonary Fibrosis and COPD
A Propensity-Matched Real-World Study

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BACKGROUND: The adherence to and clinical efficacy of pulmonary rehabilitation in idiopathic pulmonary fibrosis (IPF), particularly in comparison with 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 noncompletion of or nonresponse to pulmonary rehabilitation, or both, associated with 1-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 for pulmonary rehabilitation. We compared between-group pulmonary rehabilitation completion rates and response. Survival status in the IPF cohort was recorded over 1 year after 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%; \( P = .24 \)) and improvements in exercise response were observed in both groups with no significant mean between-group differences in incremental shuttle walk test (ISWT) change (mean, 2 m [95% CI, –18 to 22 m]). Pulmonary rehabilitation noncompletion (hazard ratio [HR], 5.62 [95% CI, 2.24-14.08]) and nonresponse (HR, 3.91 [95% CI, 1.54-9.93]) were associated independently with increased 1-year all-cause mortality in IPF.

INTERPRETATION: This real-world study demonstrated that patients with IPF have similar completion rates and magnitude of response to pulmonary rehabilitation compared with a matched group of patients with COPD. In IPF, noncompletion of and nonresponse 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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KEY WORDS: COPD; idiopathic pulmonary fibrosis; prognosis; pulmonary rehabilitation

ABBREVIATIONS: CRQ = Chronic Respiratory Questionnaire; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; ISWT = incremental shuttle walk test; MRC = Medical Research Council

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Take-home Points

**Study Question:** Do people with idiopathic pulmonary fibrosis (IPF) improve to the same extent with pulmonary rehabilitation as a matched group of individuals with COPD, and are noncompletion of or nonresponse to pulmonary rehabilitation, or both, associated with 1-year all-cause mortality in IPF?

**Results:** This real-world study demonstrated that people with IPF show similar completion rates and response to pulmonary rehabilitation as matched individuals with COPD. In IPF, noncompletion and nonresponse to pulmonary rehabilitation were associated with increased all-cause mortality.

**Interpretation:** This real-word study demonstrated that patients with IPF have similar completion rates and magnitude of response to pulmonary rehabilitation compared with a matched group of patients with COPD. In IPF, noncompletion of and nonresponse 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 characterized by a progressive decline in respiratory and physical function with a median survival of 3 to 5 years from diagnosis. Although pharmacologic therapies may slow lung function decline, their effect on symptom burden and quality of life are modest. Pulmonary rehabilitation, a multidisciplinary 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 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) (n = 182 with IPF 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 because of methodologic concerns. Furthermore, the magnitude of benefit from pulmonary rehabilitation in IPF, compared with COPD, is uncertain because of the more rapidly progressive nature of IPF and the greater prevalence of exercise-induced desaturation. Previous small studies comparing pulmonary rehabilitation response between IPF and COPD have shown a reduced magnitude of benefit in IPF.

Recent data also have shown an association between pulmonary rehabilitation completion and response with survival in COPD. However, limited survival data exist 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. Although a trend toward reduced mortality with pulmonary rehabilitation was found, only a small number of deaths were observed (three with pulmonary rehabilitation intervention, and eight with control treatment).

Given the limited evidence base, clinical guidelines have provided conflicting recommendations. Although 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, the joint American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines on the diagnosis and treatment of IPF published in 2011 made a weak recommendation for pulmonary rehabilitation in IPF, and the updated guidelines did not discuss the...
role of pulmonary rehabilitation. The British Thoracic Society Guidelines and the Australia and New Zealand Guidelines 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 and that the quality of evidence is low. Similarly, the American Thoracic Society and European Respiratory Society Statement on pulmonary rehabilitation did not make a recommendation for pulmonary rehabilitation in IPF. 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 patients with IPF compared with those with 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 or response to pulmonary rehabilitation, or both, are associated with survival in people with IPF. We hypothesized that people with IPF would show a blunted response to pulmonary rehabilitation with reduced completion rates compared with matched people with COPD. We also hypothesized that noncompletion or nonresponse to pulmonary rehabilitation would be associated with increased mortality in IPF.

Study Design and 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 and referral to pulmonary rehabilitation in line with national guidelines. 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. Because national clinical guidance in the United Kingdom recommends the offer of pulmonary rehabilitation to people with IPF, 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 and 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, using the nearest neighbor method, 1:1 accounting for baseline age, sex, BMI, Medical Research Council dyspnea scale grade, self-reported Chronic Respiratory Questionnaire (CRQ) total score (e-Appendix 1), and incremental shuttle walk test (ISWT) distance. Balance between the groups was assessed using standardized mean difference. For both groups, those with contraindications to exercise and comorbidities that would limit exercise performance (eg, unstable cardiovascular disease) were excluded before recruitment.

Methods

Baseline measures included BMI, spirometry, MRC grade, ISWT distance, CRQ score, and proxy for frailty status (4-m gait speed < 1.0 m/s). MRC grade, ISWT distance, CRQ score, and Global Rating of Change Questionnaire score were measured after pulmonary rehabilitation completion (time point 1). For the Global Rating of Change Questionnaire, patients rated their response to the question, “How do you feel your overall condition has changed after rehabilitation?” on a five-point Likert scale ranging from 1 indicates “I feel much better” to 5 indicates “I feel much worse.” Adherence was defined as the number of supervised sessions that patients attended. Completion was defined as attendance at the assessment after pulmonary rehabilitation and attendance at a minimum of eight supervised sessions. All-cause mortality and, where relevant, time to death were recorded 1 year after the assessment subsequent to pulmonary rehabilitation or the planned completion date for completers and noncompleters, respectively (time point 2), with data obtained from hospital and primary care medical records. Apart from this, patients were not monitored after discharge from pulmonary rehabilitation.

Patients underwent an 8-week outpatient program that comprised two supervised exercise and education sessions as well as additional unsupervised home-based exercise each week. The program is described in e-Appendix 1 and elsewhere. Baseline characteristics were summarized using descriptive statistics. Because of a lack of consensus on the independence of the propensity score-matched pairs, both unmatched and matched analyses were performed. First, the data were analyzed using the Pearson χ² test and independent t test (assuming independence), and second, the data were analyzed using the paired t test and McNemar test. The results were the same for both types of analysis; therefore, only the unmatched analysis is presented. The matched analysis is presented in e-Table 1. Within-group differences were analyzed using the paired samples t test for continuous data.

Evaluation of the association between pulmonary rehabilitation status and all-cause mortality at 1 year was performed in the IPF group only. Because the patients with COPD were selected through propensity score matching, they may not be representative of a typical COPD cohort. Between-group differences in pulmonary rehabilitation status were analyzed using the χ² test for trend and one-way analysis of variance (nonparametric data: Kruskal-Wallis test) for categorical and continuous data, respectively. Pulmonary rehabilitation status was defined as follows. A responder was one who completed pulmonary rehabilitation (defined as attendance at the assessment after pulmonary rehabilitation and a minimum of 8 supervised sessions) and achieved minimal important difference of ISWT
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) (Fig 1). In total, we included 163 people with IPF who 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 grade, ISWT distance, and CRQ total score (standardized mean difference, < 0.1) (Table 1). As expected, spirometry data were significantly different between the groups, and a higher proportion of participants with IPF used supplemental oxygen. Pulmonary rehabilitation completion was similar in both groups (IPF, 69%; COPD, 63%; P = .24); reasons for noncompletion are outlined in Figure 1. No between-group difference was found in the number of sessions attended (mean ± SD: IPF, 10 ± 6; COPD, 10 ± 6; P = .39).

After pulmonary rehabilitation, both groups showed significantly improved MRC grade, ISWT distance, and CRQ score (Table 2), and no significant between-group differences were found (Table 2, Fig 2). Eighty-eight percent of the patients with IPF reported feeling “much...
better” or “a little better” after pulmonary rehabilitation compared with 91% of the patients with COPD (P = .45).

**Association Between Pulmonary Rehabilitation Completion and Response Status With All-Cause Mortality at 1 Year After Pulmonary Rehabilitation in IPF**

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

Of 163 participants with IPF, six died before completing pulmonary rehabilitation. Of the remaining 157, 42 (27%) died in the 1-year follow-up period (from time

| Variable                                  | IPF (n = 163) | COPD (n = 163) | SMD   | P Value |
|-------------------------------------------|---------------|----------------|-------|---------|
| Propensity-matched analysis                |               |                |       |         |
| Age, y                                     | 73 ± 9        | 73 ± 8         | 0.00  | ...     |
| Male sex                                  | 110 (67)      | 111 (68)       | 0.00  | ...     |
| BMI, kg/m²                                 | 27.4 ± 6.0    | 27.9 ± 6.5     | 0.07  | ...     |
| MRC dyspnea scale grade                   | 3.3 ± 1.2     | 3.2 ± 1.1      | 0.00  | ...     |
| ISWT distance, m                          | 196 ± 158     | 197 ± 149      | 0.04  | ...     |
| CRQ total score                           | 77.6 ± 23.0   | 78.8 ± 22.4    | 0.01  | ...     |
| Other                                     |               |                |       |         |
| FEV₁ to FVC ratio                         | 0.81 ± 0.08   | 0.47 ± 0.13    | ...   | < .001  |
| FEV₁, %                                   | 70.0 ± 20.8   | 47.3 ± 17.3    | ...   | < .001  |
| FVC, %                                    | 66.7 ± 23.2   | 74.8 ± 19.8    | ...   | < .01   |
| Prescribed supplemental oxygen            | 49 (30)       | 7 (20)         | ...   | < .001  |
| Prescribed ABOT                           | 41 (25)       | 11 (7)         | ...   | < .001  |
| Resting SpO₂                              | 96 ± 4        | 96 ± 4         | ...   | .20     |
| Smoking history                           |               |                |       | < .001  |
| Current                                   | 0 (0)         | 17 (11)        | ...   |         |
| Former                                    | 85 (52)       | 121 (74)       | ...   |         |
| Never                                     | 78 (48)       | 25 (15)        | ...   |         |
| Hospitalized in past year                 | 41 (25)       | 60 (37)        | ...   | .01     |
| Antibiotics for respiratory tract infection in past year | 87 (53) | 117 (73) | ... | < .001 |
| Prescribed antifibrotic therapy           | 15 (9)        | NA             | ...   | NA      |
| Cardiovascular disease                    | 93 (57)       | 93 (57)        | ...   | .55     |
| Pulmonary hypertension                    | 15 (9)        | 3 (2)          | ...   | < .01   |
| Diabetes                                  | 26 (16)       | 23 (14)        | ...   | .64     |
| Frail                                     | 122 (75)      | 117 (72)       | ...   | .60     |
| CRQ domain                                |               |                |       |         |
| Dyspnea                                   | 14.9 ± 6.1    | 14.9 ± 6.3     | ...   | .96     |
| Fatigue                                   | 13.9 ± 5.8    | 14.0 ± 5.3     | ...   | .89     |
| Emotional function                        | 31.2 ± 9.1    | 31.6 ± 9.2     | ...   | .70     |
| Mastery                                   | 17.7 ± 5.9    | 18.4 ± 5.7     | ...   | .26     |
| No. of supervised sessions attended       | 10 ± 6        | 10 ± 6         | ...   | .39     |
| Completed PR                              | 113 (69)      | 103 (63)       | ...   | .24     |

Data are presented as No. (%) or mean ± SD, unless otherwise indicated. ABOT = ambulatory oxygen therapy (supplemental oxygen prescribed for exercise-induced desaturation); CRQ = Chronic Respiratory Questionnaire; IPF = idiopathic pulmonary fibrosis; ISWT = incremental shuttle walk test; MRC = Medical Research Council; NA = not applicable; PR = pulmonary rehabilitation; SMD = Standardized Mean Difference; SpO₂ = peripheral capillary oxygen saturation.

*Prescribed long-term oxygen therapy (for resting hypoxemia), ambulatory oxygen therapy (for exercise-induced desaturation), or both.
point 1 to time point 2). A significant association was demonstrated between pulmonary rehabilitation status and mortality in the univariate analysis (Table 3). Two multivariate analyses were performed because of collinearity between MRC grade and ISWT distance. Both confirmed that pulmonary rehabilitation status remained associated independently with all-cause mortality at 1 year (Table 3). That is, noncompletion and nonresponse were associated with a significantly higher risk of all-cause mortality at 1 year (Table 3).

When stratified according to pulmonary rehabilitation status, a greater proportion of noncompleters and nonresponders died in the 1-year period compared with responders (40%, 24%, and 10%, respectively; \( P < .01 \)). The Kaplan-Meier curve demonstrated a shorter time to all-cause mortality for noncompleters and nonresponders compared with completers (\( P < .001 \), log-rank test for trend) (Fig 3).

### Discussion

This study comprised the largest single cohort of patients with IPF undergoing pulmonary rehabilitation. We demonstrated 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 with those observed in a propensity score-matched group of patients with COPD. Compared with pulmonary rehabilitation responders, noncompletion of or nonresponse to pulmonary rehabilitation were associated independently with higher all-cause mortality at 1 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). Uncertainty remains regarding the benefits of pulmonary rehabilitation in IPF because of methodologic concerns including selection bias, lack of assessor blinding, small sample size, and...
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 demonstrated that people with IPF achieve similar clinical benefits and completion rates to those with COPD. Indeed, a trend for higher completion rates in the IPF compared with the COPD group was found that 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) after a 10-week program,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 $\geq$ 75 years of age or prescribed long-term oxygen therapy were excluded), small sample size, unmatched disease groups, and no statistical evaluation of between-group differences. Kozu et al8 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 grade, in contrast to our study. Potential explanations include the larger sample size and multivariate propensity score matching in our study, as well as the greater intensity of our aerobic exercise prescription (our study, 60%-80% maximum oxygen consumption for 30 min; Kozu et al, 50% peak workload for 20 min). Although our real-world completion rates were lower than observed in the controlled environment of clinical trials, they were comparable with 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

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### TABLE 3

Univariate and Multivariate Cox Proportional Hazards Regression Analysis for the Association Between PR Status and Time to All-Cause Mortality at 1 Year From PR Completion in IPF

| Covariate: PR Status | Univariate Analysis | Multivariate Analysis 1$^b$ | Multivariate Analysis 2$^b$ |
|----------------------|---------------------|-----------------------------|-----------------------------|
|                      | HR (95% CI)         | P Value$^c$                 | HR (95% CI)                 | P Value$^c$                 | HR (95% CI)                 | P Value$^c$                 |
| Responder$^d$        | Reference category  | .01                         | Reference category          | .01                         | Reference category          | .01                         |
| Nonresponder$^e$     | 3.91 (1.54-9.93)    | 3.45 (1.24-9.57)            | 3.94 (1.43-10.81)           |
| Noncompleter$^f$     | 5.62 (2.24-14.08)   | 4.70 (1.66-13.34)           | 4.42 (1.53-12.79)           |

HR = hazard ratio; PR = pulmonary rehabilitation.

$^a$Variables included: baseline age, sex, smoking status, FVC % predicted, Medical Research Council dyspnea scale grade, prescription of antifibrotic therapy, frailty status, PR status. (Note that incremental shuttle walk test distance was not included because of collinearity.)

$^b$Variables included: baseline age, sex, smoking status, FVC % predicted, incremental shuttle walk test distance, prescription of antifibrotic therapy, frailty status, PR status. (Note that Medical Research Council dyspnea scale grade was not included because of collinearity.)

$^c$Overall P value for PR status.

$^d$PR completion plus meeting the minimal important difference of incremental shuttle walk test distance.

$^e$PR completion plus not achieving the minimal important difference of incremental shuttle walk test distance.

$^f$Not completing PR.

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![Figure 3](image-url)  
**Figure 3** – Kaplan-Meier curve and at-risk table demonstrating time to all-cause mortality at 1 year according to PR status, with table depicting the numbers at risk. PR = pulmonary rehabilitation.
reported on survival (n = 127 participants, with 67 receiving pulmonary rehabilitation). Although a trend toward reduced mortality in the pulmonary rehabilitation arm was found, only a small number of deaths were observed (pulmonary rehabilitation, n = 3; control, n = 8; P = .09).

Although we found an association between pulmonary rehabilitation status and survival, uncertainty remained about the reliability of the estimate owing to wide CIs. 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 end point in future trials of pulmonary rehabilitation in IPF.

To the best of our knowledge, this study described the largest single cohort of patients with IPF to undergo pulmonary rehabilitation, and therefore adds to the 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 were obtained systematically from hospital and primary care records and therefore are considered accurate. Our data provide novel findings in terms of pulmonary rehabilitation clinical outcomes, completion, and prognosis in a real-world setting.

The study has some limitations. This was a single-center study, and the data should be validated in other settings. We excluded patients with coexisting COPD and IPF and are unable to comment on this population. We did not design a randomized controlled trial because 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 after 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 therefore, we were unable to adjust for lung function measures other than FVC, nor for pulmonary hypertension in the mortality analyses. We could not confirm self-reported adherence to unsupervised home-based exercise objectively, and therefore cannot exclude this as an influencing variable.

**Interpretation**

In conclusion, we 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 be referred for pulmonary rehabilitation. Compared with pulmonary rehabilitation responders, pulmonary rehabilitation noncompletion and nonresponse were associated independently with all-cause mortality at 1 year in the IPF group. Further work is required to corroborate these findings. Nonetheless, these data reinforce the importance of referral to and engagement in pulmonary rehabilitation among the population with IPF.
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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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