Patient-reported distress can aid clinical decision-making in idiopathic pulmonary fibrosis: analysis of the PROFILE cohort

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Responses to a palliative care survey from a clinical cohort of over 240 IPF patients were used to create a concise 11-item distress measure that can help predict disease prognosis with similar reliability to lung function recordings http://ow.ly/QCCt30nMEWU

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ABSTRACT Idiopathic pulmonary fibrosis is a progressive and fatal interstitial lung disease. We aimed to determine if patient response to a palliative assessment survey could predict disease progression or death.

We undertook a cross-sectional study in a UK clinical cohort of incident cases. Rasch-based methodology provided a disease distress value from an abridged 11-item model of the original 45-item survey. Distress values were compared with measures of lung function. Disease progression or mortality alone was predicted at 12 months from survey completion, with risk of death assessed at 3, 6 and 12 months.

Disease distress values were negatively correlated with lung function (r=−0.275 for the percentage predicted diffusing capacity of the lung for carbon monoxide). Expected survey scores computed from distress values could distinguish disease progression (n=8.8, p=0.004) and death (n=10.2, p=0.002) from no disease progression (n=6.9). Actual survey scores predicted disease progression and death with an area under the curve of 0.60 and 0.64, respectively. Each point increment in actual score increased risk of 12-month mortality by 10%; almost 43% of people scoring above 18 did not survive beyond 105 days.

We define a short questionnaire that can score disease distress and predict prognosis, thus assisting clinical decision-making in progressive fibrosis.

This article has supplementary material available from erj.ersjournals.com

This study is a clinical trial with registration number NCT01134822. Individual participant data that underlie the results reported will be available after deidentification, along with study protocol, to investigators whose proposed use of data has been approved by the study steering committee. Proposals related to NCT01134822 should be directed to Gisli.jenkins@nottingham.ac.uk. Requestors will need to sign a data access agreement in order to gain access.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown aetiology, causing scarring of the lung, shortness of breath, cough and reduced lung function. A UK study demonstrated a 35% increase in incidence of IPF between 2000 and 2008, with a higher incidence in men and older age groups [1]. Incidence and mortality continue to rise and are also increasing globally [2]. IPF is fatal, with no current cure, though disease-modifying treatments are being introduced. In many cases, earlier palliative intervention could reduce the burden on the individual, as recommended in cancer care [3, 4], yet the variable natural history of IPF makes it difficult to predict care needs.

The Sheffield Profile for Assessment and Referral to Care (SPARC) is a holistic needs tool, comprising 45 items across nine domains, that can aid health professionals in identifying need for palliative care [5]. Respondents find the questions easy to understand [6] and the tool has been adapted to international settings [7]. Such systematic assessment provides a useful indication of symptom distress [8]. Yet those who have chronic disease may not achieve the SPARC criteria for immediate clinical assessment, defined as a score of 3 in a single question, because habituation or affective comorbidity can affect symptom perception [5, 9, 10]. Regular completion of 45 items can be burdensome for those who suffer most [8], whilst self-assessment may result in inter-patient differences despite the same underlying distress.

Rasch-based methodology generates a scaled value for a set of responses as an interaction between question difficulty and the individuals' likelihood of scoring. Initially used to standardise scholastic tests, extension of the item response theory (IRT) class of models to allow multiple choice or graded options has found increased recognition in the development of healthcare metrics and patient-reported outcomes [11–15]. Further advantages of the method are that it enables question refinement, banking and assessment of the impact of demographics on item response [16–18].

We aimed to determine whether the SPARC could be used with IRT methodology to generate a tool that could appropriately distinguish disease progression in a UK clinical cohort of IPF patients [19, 20], helping to predict short-term prognosis.

Methods

The Prospective Observation of Fibrosis in Lung Clinical Endpoints (PROFILE) Central England (NCT01134822) study is a longitudinal observational clinical trial that has been described previously [19, 20]. Patients were grouped by age as ⩽65, 66–79 or ⩾80 years; comorbidities were grouped as 0, 1–2 or ⩾3. People were asked to complete the SPARC questionnaire, comprising dichotomous items in two domains, as well as polytomous items in six domains (supplementary file 1). 243 people from the PROFILE Central England study completed the SPARC and were subsequently included in the analysis.

All analyses were performed in Stata (SE15.1; StataCorp, College Station, TX, USA). Lung function measures recorded at the initial SPARC assessment (±30 days) were used as baseline, with an outcome of disease progression within 12 months of SPARC completion defined as a 10% relative decline in forced vital capacity (FVC) or death. Percentage predicted diffusing capacity of the lung for carbon monoxide (*D*LCO % pred) and FVC (FVC % pred) were calculated using the suite of Global Lung Function Initiative tools available from the European Respiratory Society [21]. Where FVC % pred (n=21) or *D*LCO % pred (n=75) could not be confirmed owing to missing data, people were excluded from the relevant statistical analyses.

A two-parameter graded response model was ultimately constructed, with items showing good discrimination, and model assumptions were verified [11, 22]. Parameters of discrimination and difficulty were assigned to each item (survey question) according to how well it could differentiate people across the scale of the underlying distress trait (θ), as well as the probability of a particular answer. Detailed information on the construct of the IRT model is provided as supplementary information; a final model of 11 items was built, in which larger θ values indicate more distress (supplementary file 2; supplementary table S1; supplementary figure S1).

Pearson's correlation determined whether distress (θ) values correlated with *D*LCO % pred or FVC % pred measures. *D*LCO % pred was log transformed to meet normality assumptions. IRT test characteristic curves estimated expected questionnaire scores according to distress values calculated from the concise 11-item model, hereafter termed IPF Prognostic Assessment and Referral to Care (IPARC). One-way ANOVA assessed differences in mean distress between categories of *D*LCO % pred (<40%, 40–60%, >60%). Two-way t-test assessed mean distress between those with disease progression and those without, whilst one-way ANOVA additionally assessed categories of disease progression (no disease progression, lung function decline only, death only). Tukey's *post hoc* analysis between categories was applied.

We calculated the area under the receiver operating characteristic (ROC) curve for the ability of the cumulative IPARC score to predict disease progression within 12 months, as well as overall mortality,

compared with FVC % pred or *D*LCO % pred. The sensitivity and the specificity were compared using the Chi-squared test [23].

Kaplan–Meier curves were plotted to show time to disease progression and overall mortality against days since completing the questionnaire according to categories of IPARC score. Cox regression was used to estimate the hazard ratio (HR) of disease progression or death at 12 months (365 days), 6 months (180 days) and 3 months (90 days) according to increment or categories of IPARC scores, with the lowest scorers as reference. The risk in comparison groups is contingent upon the proportion of the reference group that fails during the specified timescale. Analyses were initially univariate, and then adjusted for age, comorbidity, sex and a significant interaction between age and comorbidity. Proportional hazard assumptions were checked using Schoenfeld residuals.

Results

Demographics

From 243 people within the cohort, 103 (42.4%) had evidence of disease progression within 12 months, whilst 140 (57.6%) did not (table 1). Of those with disease progression, 49 died within 12 months (47.6%). Within the disease progression subgroup, 80.6% were male but no significant sex interaction was observed; similarly comorbidity count was not associated with progression. Disease progression was more common in those aged ⩾80 years. We identified no significant relationships between communication and progression status. Lower proportions of people with disease progression wanted information about personal finances. No relationship reached significance following Bonferroni correction.

Disease distress is associated with lung function and disease progression

A mild negative correlation was observed between distress values and baseline FVC % pred or *D*LCO % pred, indicating that higher distress correlated with worse lung function performance (figure 1). The Pearson correlation coefficient for distress and FVC % pred was −0.267 (p=0.0001), and for distress and *D*LCO % pred was −0.275 (p=0.0003).

TABLE 1 Cohort demographics

Outcome in 12 months	All	No progression	Disease progression	p-value
Subjects n	243	140	103	
Sex				
Male	78.2	76.4	80.6	
Female	21.8	23.6	19.4	0.438
Age group years				
65 and under	15.6	19.3	10.7	
66–79	70.0	70.7	68.9	
80 and over	14.4	10.0	20.4	**0.026**
Comorbidity count				
None	23.9	26.4	20.4	
1–2	47.7	49.3	45.6	
3 or more	28.4	24.3	34.0	0.219
Subjects who were able to talk to:				
Doctor	80.7	80.0	81.6	0.055
Community nurse	14.4	12.1	17.5	0.150
Hospital nurse	53.5	58.6	46.6	0.185
Religious advisor	2.9	2.1	3.9	0.360
Social worker	3.7	4.3	2.9	0.657
Family	65.0	67.1	62.1	0.977
Subjects who wanted more information on their:				
Condition	28.8	32.9	23.3	0.206
Care	13.6	14.3	12.6	0.894
Treatment	18.1	21.4	13.6	0.185
Support	14.0	13.6	14.6	0.653
Finances	9.1	12.9	3.9	**0.025**

Data are presented as percentages, unless otherwise stated, including missing data. Missing values not presented; Chi-squared test p-values based on non-missing data. Significant p-values before Bonferroni correction (p<0.05) in bold. Bonferroni p-value adjustment p=0.0036.

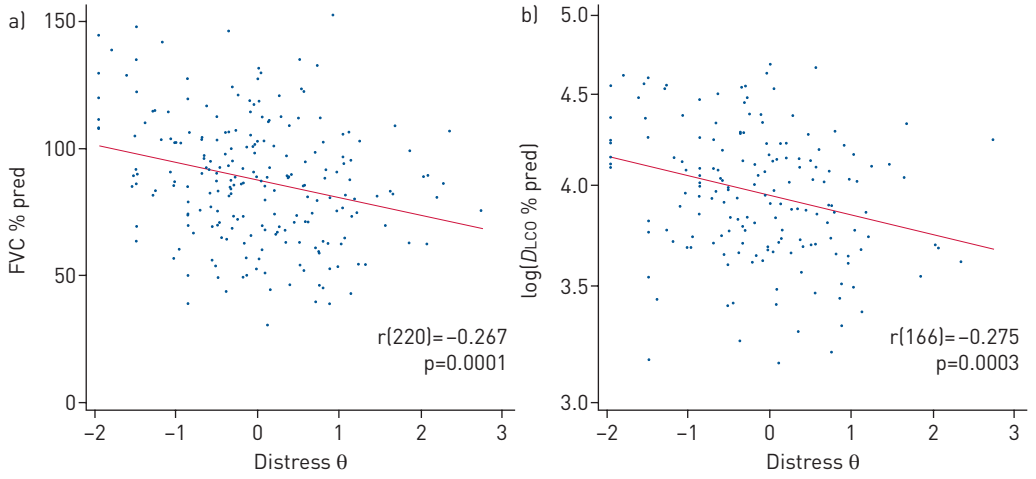

FIGURE 1 Negative correlation of distress with percentage predicted lung function in idiopathic pulmonary fibrosis (IPF). a) Plotted forced vital capacity (FVC) % pred against distress value generated from the IPF Prognostic Assessment and Referral to Care (IPARC) score model resulted in a Pearson correlation coefficient (r) of −0.267 (p=0.0001) from 222 people (220 degrees of freedom); FVC % pred explains 7.1% of variation in disease distress. b) Plotted log transformed diffusing capacity of the lung for carbon monoxide (*D*LCO) % pred against distress value resulted in r=−0.275 (p=0.0003) from 168 people (166 degrees of freedom); *D*LCO % pred explains 7.6% of variation in disease distress.

The mean distress value according to category of *D*LCO % pred was calculated and the IRT test characteristic curve estimated the expected score from the continuum of the distress values, calculated from the IPARC score model. Mean distress values were significantly different according to the category of *D*LCO % pred (p=0.006). People with *D*LCO % pred <40% were significantly more distressed than those with a *D*LCO % pred >60% (p=0.004), leading to expected scores of 9.1 (θ=0.22) and 5.6 (θ=−0.38), respectively (figure 2a).

Mean distress values were also significantly different according to disease progression (p=0.0085), with those with disease progression having an expected score of 8.8 (θ=0.18) compared to an expected score of 6.9 for those with no disease progression (θ=−0.14) (figure 2b). Separately plotting mean distress of

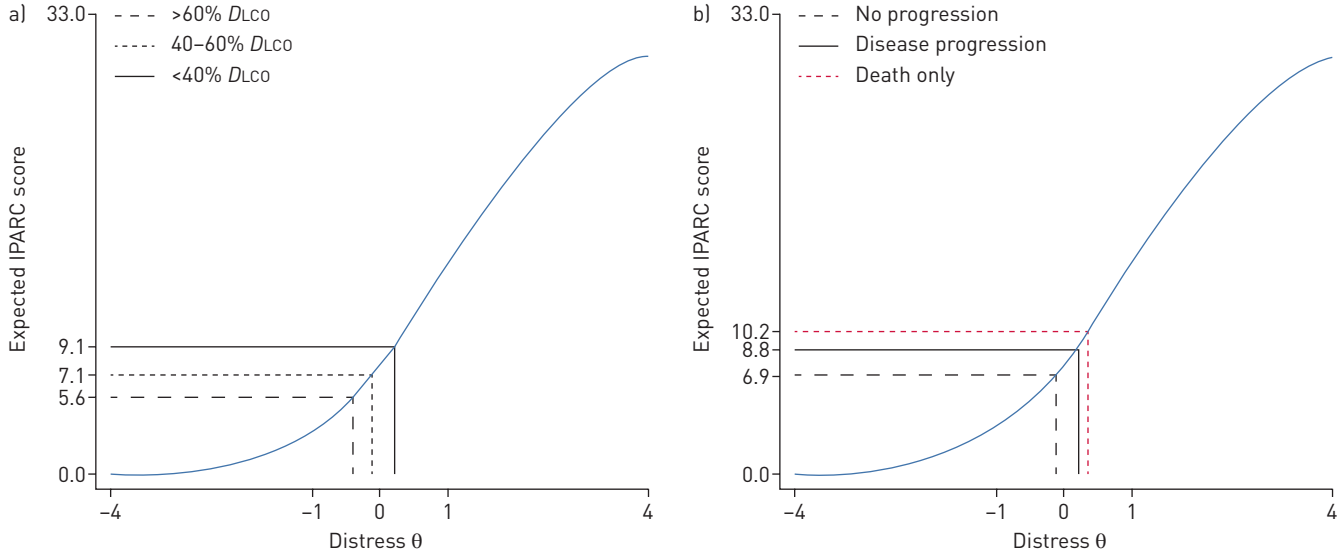

FIGURE 2 Expected IPF Prognostic Assessment and Referral to Care (IPARC) scores from mean distress in lung function categories. Item response theory test characteristic curve from 11 items in final model plots distress (θ) values against expected score. Scale of θ has a mean of 0 and the arbitrary range (4) represents incremental standard deviations. a) Mean θ values plotted for diffusing capacity of the lung for carbon monoxide (*D*LCO) % pred category. One-way ANOVA p=0.006; *post hoc* Tukey's analysis p=0.004, *D*LCO % pred <40% compared with >60%. b) Mean θ values plotted for disease progression in 12 months; lung function decline only not shown. Two-way t-test p=0.0085, disease progression, no progression; one-way ANOVA p=0.003, death, lung function decline, no progression; *post hoc* Tukey's analysis p=0.002, death compared with no progression.

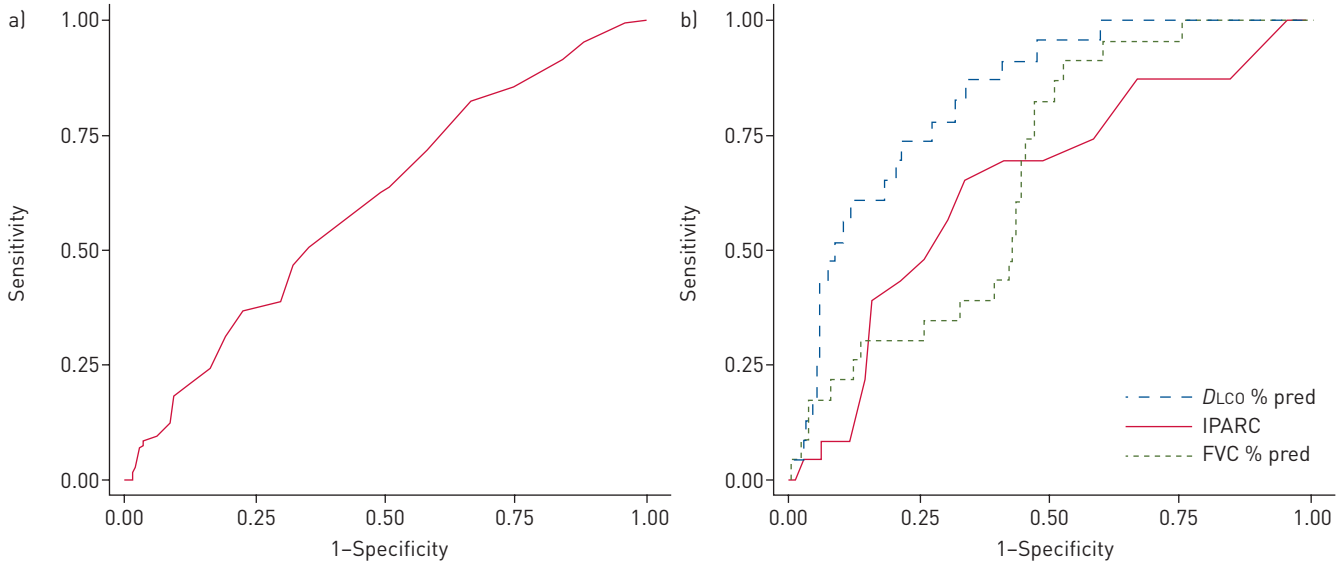

FIGURE 3 Receiver operating characteristic (ROC) curve assesses sensitivity and specificity of measures in predicting progression of idiopathic pulmonary fibrosis (IPF). a) Ability of IPF Prognostic Assessment and Referral to Care (IPARC) score to predict disease progression: area under curve (AUC) 0.60 (95% CI 0.53–0.68); n=243. b) Ability to predict 12-month mortality: IPARC score, AUC 0.64 (95% CI 0.52–0.77); diffusing capacity of the lung for carbon monoxide (*D*LCO) % pred, AUC 0.83 (95% CI 0.75–0.91); and forced vital capacity (FVC) % pred, AUC 0.66 (95% CI 0.56–0.76); n=167. *D*LCO % pred AUC greater than IPARC AUC, p=0.013.

patients who died provided an expected score of 10.2 (θ=0.39); significance was identified across categories of disease progression (p=0.003), largely driven by the difference between those who died and those with no disease progression (p=0.002) (figure 2b).

Lung function recordings require a suitable level of fitness to provide acceptable and repeatable measurements, introducing selection bias if individuals struggle to perform them. To understand the influence of missing data, we evaluated distress according to completion of lung function measurements (supplementary table S2). Patients with missing FVC % pred data were more likely to have died (61.9%) than patients with complete FVC % pred data (16.2%, p<0.0001). However, there was no difference in mean distress between people with missing FVC % pred data and those with complete data (scores of 8.8 *versus* 7.6, p=0.384). Similarly, patients with missing *D*LCO % pred data were more likely to have died (34.7% *versus* 13.7%, p<0.0001), although those missing data were also more distressed (scores 9.5 *versus* 7.0, p=0.002). In total, 75 people (31%) were missing *D*LCO measures; analyses based on non-missing *D*LCO recordings will underestimate actual effect sizes as they exclude a large sample of distressed patients.

IPARC score can predict disease progression and mortality

Area under the curve (AUC) of the ROC curve initially assessed the ability of the IPARC score to predict disease progression in the complete dataset (figure 3), resulting in an AUC of 0.60 (95% CI 0.53–0.68). ROC subsequently assessed the ability of the IPARC score to predict death compared with lung function recordings in 167 people with complete data. We identified *D*LCO % pred as having the largest AUC of 0.83 (95% CI 0.75–0.91), whilst FVC % pred had an AUC of 0.66 (95% CI 0.56–0.76). The cumulative IPARC score provided an AUC of 0.64 (95% CI 0.52–0.77); a minimum score of 9 resulted in 59.2% sensitivity and 62.9% specificity. No statistical difference was observed between the AUC of IPARC score and FVC % pred (p=0.8), although *D*LCO % pred was significantly better at predicting mortality (p=0.013). The ability of the IPARC score to predict mortality was also assessed independently from lung function recordings in the complete dataset (supplementary figure S2), resulting in a greater AUC of 0.66 (95% CI 0.57–0.74).

Kaplan–Meier curves of time to event were plotted separately for disease progression and death according to the observed IPARC score (figure 4), categorised using expected score from mean distress when *D*LCO % pred was <40% (score of 9). A large proportion of people scoring over 18 from the 11 IPARC items had rapid disease progression; 51.5% of people scoring at least 9 progressed within 12 months. Fewer than 75% of people who scored 9–18 survived 12 months (figure 4b). A total of 101 people scored 9 or more and 29 died within 12 months, providing a positive predictive value of 28.7%; this is compared with 20 people from the 142 scoring 8 or less, which provided a positive predictive value of 14.1%. Scoring over 18 increased the positive predictive value to 42.9% from a total of 14 people; all deaths in this group occurred within 105 days.

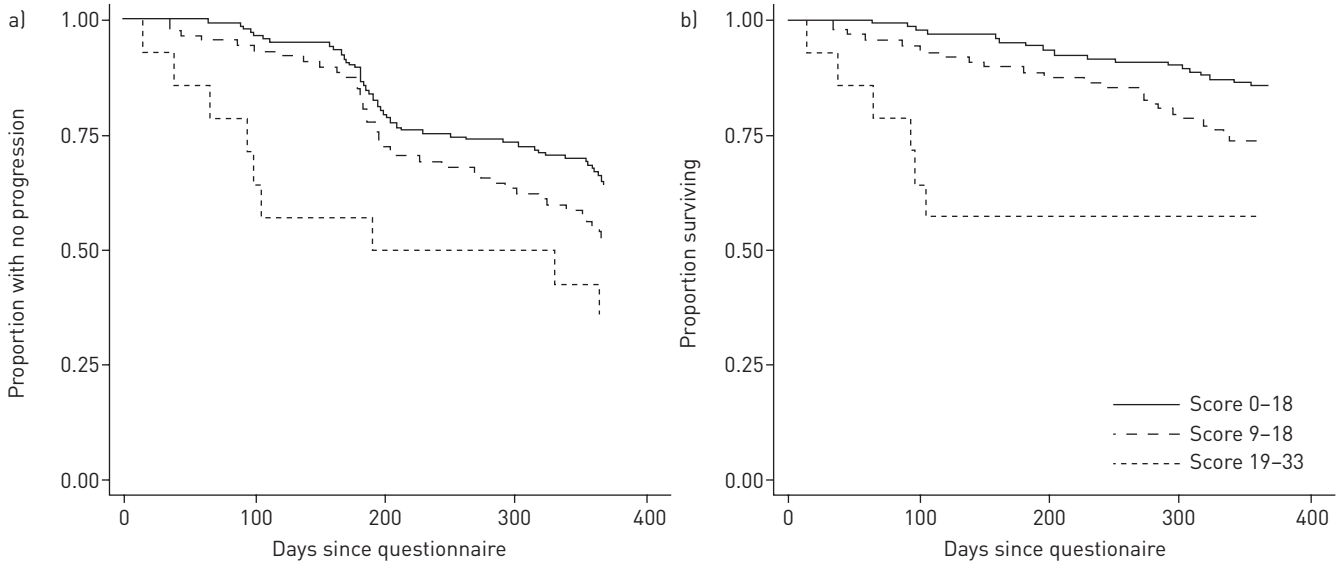

FIGURE 4 Kaplan–Meier analyses of time to event in idiopathic pulmonary disease (IPF), categorised by IPF Prognostic Assessment and Referral to Care (IPARC) score. a) Proportion of people with no disease progression against time since completing questionnaire. b) Proportion of people surviving against time since completing questionnaire.

Cox regression estimates of the risk of disease progression and risk of death in 12 months for each unit increment of the IPARC score are reported in table 2. For every point increase, the risk of disease progression increased by 5% (HR 1.05, 95% CI 1.02–1.09) whilst risk of death increased by 10% (HR 1.10, 95% CI 1.05–1.15). Disease progression was almost 60% more likely for people scoring 9–18 (HR 1.59,

TABLE 2 Cox regression risk estimates of disease progression and overall mortality by IPARC score

	Subjects n	Fail %	HR (95% CI)	Adjusted HR[#] (95% CI)
12-month disease progression risk[¶]				
IPARC score	243	42.39	1.05 (1.01–1.08)	1.05 (1.02–1.09)
IPARC category				
Score 0–8	142	35.92	1	1
Score 9–18	87	49.43	1.50 (1.00–2.26)	1.59 (1.04–2.44)
Score 19–33	14	64.29	2.69 (1.32–5.47)	3.19 (1.53–6.64)
12-month mortality risk[¶]				
IPARC score	243	20.16	1.08 (1.03–1.12)	1.10 (1.05–1.15)
IPARC category				
Score 0–8	142	14.08	1	1
Score 9–18	87	26.44	2.02 (1.11–3.68)	2.43 (1.30–4.55)
Score 19–33	14	42.86	4.44 (1.78–11.08)	5.74[+] (2.20–14.97)
6-month mortality risk[¶]				
IPARC category				
Score 0–8	142	4.93	1	1
Score 9–18	87	11.49	2.43 (0.92–6.37)	2.82 (1.03–7.68)
Score 19–33	14	42.86	11.69 (3.92–34.86)	12.32 (3.84–39.55)
3-month mortality risk[¶]				
IPARC category				
Score 0–8	142	0.70	1	1
Score 9–18	87	5.75	8.37 (0.98–71.61)	7.69 (0.89–66.28)
Score 19–33	14	21.43	34.25 (3.56–329.37)	19.47 (1.98–191.13)

IPARC: IPF Prognostic Assessment and Referral to Care; IPF: idiopathic pulmonary fibrosis; HR: hazard ratio. [#]: adjusted for age group, comorbidity count, sex, age–comorbidity interaction; [¶]: 12-month, 6-month and 3-month analyses were assessed at 365 days, 180 days and 90 days, respectively; [+]: proportional hazard assumption not met.

95% CI 1.04–2.44) compared to those scoring less, whilst those scoring highest were at three times the risk (HR 3.19, 95% CI 1.53–6.64). People scoring 9–18 were more than twice as likely to die within 12 months as those scoring less than 9 (HR 2.43, 95% CI 1.30–4.55). Estimates for those scoring over 18 did not meet proportional hazard assumptions at 12 months, although their risk of death in 6 months was 12-fold that of those scoring less than 9 (HR 12.32, 95% CI 3.84–39.55), whilst the risk for those scoring 9–18 more than doubled (HR 2.82, 95% CI 1.03–7.68). Similar results were estimated at 3 months for those scoring highest (HR 19.47, 95% CI 1.98–191.13), though scoring 9–18 was not statistically different from scoring less than 9 (HR 7.69, 95% CI 0.89–66.28).

A sub-analysis was performed on a small sample of patients who had an IPARC score before and after pirfenidone treatment to preliminarily assess therapy modification of the IPARC score (supplementary figure S3). Overall, in 12 patients with matched scores taken at a 12-month interval, there was a nonsignificant trend towards increased distress following therapy with pirfenidone. The change in level of distress with treatment was driven by the IPARC category prior to therapy; patients scoring under 9 (mild distress) demonstrated more distress following therapy (p=0.0086), whilst those scoring 9 or over (high level of distress) had a more varied response, including some reduction in IPARC score.

Discussion

The SPARC questionnaire is recognised within the UK National Health Service as a way to help address and improve end-of-life care management [5, 6, 9, 24]. We have utilised a unique clinical cohort of patients with IPF [19], determining that items specified within the IPARC list can identify patients at high risk of death within 3–6 months, providing an opportunity for earlier supportive care and improving patient outcomes (box 1).

We applied IRT in a novel way to assess patient-reported outcome measures [11], identifying a concise list of 11 items from an original 45 questions that captures the majority of information distinguishing people with high distress. Disease distress correlated with measures of lung function and could characterise disease progression. Furthermore, scores could predict mortality, with those scoring highest also at greatest risk of death. The associations of disease distress with lung function, disease progression and mortality support the IPARC score as a valid tool to inform prognoses.

Previous studies using alternative patient-reported outcomes to measure quality of life in IPF have similarly noted weak to moderate correlations with lung function measures, including the Medical Research Council (MRC) dyspnoea scale, the A Tool to Assess Quality of Life in IPF (ATAQ-IPF) and the COPD Assessment Test (CAT) [25–27]. Imperfect correlations indicate that lung function alone cannot account for all differences in patient-reported outcomes, but in combination they offer tremendous clinical value [28]. However, the MRC dyspnoea scale is one dimensional, ATAQ-IPF remains extensive at 75 items and CAT was developed for COPD, and so although convenient with just eight items, it may not have the sensitivity to capture IPF traits [29]. Whilst the original SPARC is a broad palliative assessment survey, answers provided by an IPF population specify appropriate items in the IPARC tool. The

BOX 1 Scoring of items in final model

Original SPARC item	IPARC score item	In the past month, have you been distressed or bothered by:	Not at all	A little bit	Quite a bit	Very much
7	1	Shortness of breath	0	1	2	3
13	2	Feeling weak	0	1	2	3
14	3	Feeling tired	0	1	2	3
16	4	Feeling sleepy in the day	0	1	2	3
17	5	Loss of appetite	0	1	2	3
21	6	Feeling restless and agitated	0	1	2	3
22	7	Uncontrolled symptoms	0	1	2	3
41	8	Side effects of treatment	0	1	2	3
34	9	Losing independence	0	1	2	3
35	10	Ability to carry out daily activities	0	1	2	3
36	11	Ability to carry out household tasks	0	1	2	3
		TOTAL		<9	9–18	>18

Items from final model presented. Highest scores, >19, may be considered an indicator for follow-up within 3 months; intermediate scores, 9–18, support review within 6 months; lower scores, <9, support review within 12 months.

unabbreviated name, IPF Prognostic Assessment and Referral to Care, reflects the purpose and cohort it was developed with, as well as the tool it originated from.

Strengths and limitations of item response theory application

IRT is an increasingly applied methodology that lends itself to parametric tests, providing an evidence base for reusing questions that can be used to distinguish traits of interest [16, 18, 30]. This study supports the use of IRT methodology in optimising questions within healthcare surveys to predict patient outcomes. Questions that did not distinguish levels of distress, such as those which scored low for the vast majority (*e.g.* Q33: Religious or spiritual needs not being met), or those that can show clustering of responses (*e.g.* Q30: Thoughts about ending it all; Q32: Worrying thoughts about death or dying) can be dropped in order to retain items offering the most discriminatory value.

IRT methodology can also assess the way in which an item may be answered differently according to demographic traits that are unrelated to the latent trait of distress, termed differential item functioning (DIF) [16, 17]. We identified no DIF in the final model according to sex, indicating that men and women with IPF report distress similarly. Of the 243 individuals sampled in this study, two were of non-white origin, and thus we were not able to assess the influence of ethnicity on patient responses. Further study in more ethnically diverse populations is warranted to determine whether IPARC retains prognostic value. DIF by demographics of age category and comorbidity count was identified for item 21 (Feeling restless and agitated); however, the analyses indicate an underlying relationship between these demographics and disease distress, so are not defined as DIF. The original SPARC questionnaire collects distress information from an extensive list of possible issues, with a response of "very much" (score of 3) in any of the 41 scaled items acting as a flag that the individual would benefit from an immediate palliative care assessment. Within clinical settings, the SPARC questionnaire could be considered too sensitive, or excessive, depending on health status [6, 9], whilst under-reporting of distress is an issue in progressive disease [10, 31]. Use of the cumulative score over 11 items provides a greater opportunity to capture distress when under-reported, whilst shorter health questionnaires can provide similar insight to lengthier ones [32].

The mean distress for those with the lowest *D*LCO % pred equated to a score of 9.1, with a score of 9 being subsequently used as a threshold point for grouping people who may undergo disease progression within 12 months. Lung function measures are a valuable tool in defining disease progression, although they are limited by the scheduling of measurement recordings that may not reflect the actual timing of progression. Those who progressed had an average score of 8.8, which supports an IPARC score of 9 as a suitable benchmark, particularly as those who died had an average score of 10.2.

Other self-reported surveys exist to measure health status in those with progressive lung disease, including King's Brief Interstitial Lung Disease (K-BILD) questionnaire [15]. The authors of K-BILD used patient interviews to define a series of pertinent questions, and Rasch analysis to refine the item list to 15, with four domains and a seven-point Likert scale. We used similar methodology to refine the list of predetermined SPARC items, as answered by a sample of 243 IPF patients, to a set of 11 within a single domain and a four-point Likert scale. Whilst K-BILD offers an empowering way to self-monitor respiratory health, IPARC should be completed within clinical settings in which rapid disease progression is a factor.

IPARC score offers prognosis estimates for clinical decisions

ROC analysis confirmed that *D*LCO % pred was the best measure for predicting 12-month mortality in this cohort [33]. The IPARC score appeared to identify true positives slightly better than FVC % pred when the accepted proportion of false positives was restricted to 50%. Lung function measurements can be challenging for patients with severe disease to provide, and this appears particularly apparent in people missing *D*LCO values, who were significantly more distressed than those without missing *D*LCO values. These data illustrate the considerable survival bias associated with lung function data in studies of patients with progressive lung disease. As a result, these analyses may underestimate IPARC performance relative to lung function measures, yet demonstrate the value of patient-reported measures.

Therapy-modified quality of life measures can inform whether an intervention is necessary or successful [34]. In our study, a preliminary analysis undertaken on a very small subset of patients indicated that treatment with pirfenidone in patients with mild levels of distress may be associated with increased levels of distress following anti-fibrotic therapy. This is consistent with the known adverse effect profile of pirfenidone, though we do not account for clinical presentation or disease progression on therapy. We recommend that further trials measure distress modification following therapeutic intervention to assess whether IPARC can be used to define individuals for whom a particular therapy may be heightening distress.

Survival curves indicated that whilst the majority of the cohort survived 12 months after completing their SPARC questionnaire, those with the highest IPARC scores had poorer life expectancy than those scoring

lowest. The positive predictive value of mortality in 12 months was 29% for those scoring above the threshold of 9, and increased to 43% for those scoring 19 or more. The findings provide evidence that patient-reported distress can predict early mortality with similar accuracy to predictions made with FVC lung function recordings.

Adjusted survival analyses further showed that risk of 12-month mortality increased by 10% with each incremental point, whilst risk of progression increased by 5%. Intermediate scoring of 9–18 heightened the likelihood of progression and more than doubled the risk of death, compared to a low score. A large proportion of the highest scorers did not survive beyond 105 days, although these estimates are based on low numbers. This relatively large sample of people with confirmed IPF supports the benefit of patient-reported distress in predicting disease progression and death.

Given that it is challenging to perform lung function measurements in patients with progressive disease, it is important to develop clinical markers of prognosis as well as to assess health status. The IPARC score requires no specialist equipment or training to complete or calculate, takes into consideration the individual's concerns, can be undertaken at any time without requiring repeated measures and can aid decisions on whether to review patients earlier. Combined with its associations with lung function and mortality, this patient-reported outcome is a potential component of composite endpoints in clinical trials, although further validation and studies on treatment sensitivity are essential [35]. The predictive capacity could not exclude all false positives, yet we recognise that early integration of palliative care can improve outcomes in other progressive diseases [3, 4, 36]. Future studies may include the IPARC score as part of a composite scoring system for accurately predicting IPF prognosis, adding value in treatment recommendations [33]. We recommend utilising it in combination with available lung function recordings when making clinical decisions (box 1).

The simple practicality of the tool allows an assessment of factors impacting quality of life to identify appropriate clinical management strategies, *e.g.* supplemental oxygen for those reporting high distress with shortness of breath, or domiciliary support and assistive living devices to reduce distress from losing independence. Where best supportive care is indicated through a high score and clinical presentation, the tool encourages a focus on the most distressing features for the individual [28]. We welcome further studies to validate the IPARC tool in separate cohorts of patients with progressive lung disease, including IPF.

Conclusion

The IPARC score, developed using the SPARC holistic tool, offers an encouraging method to assess prognosis and recognise palliative care needs in those with progressive disease. In producing a standardised model based on the latent trait of distress in people with IPF, we generated an abridged list of items that could distinguish those who died within 12 months, with higher scores indicating a worse prognosis. This brief and simple tool offers utility in the clinical care of patients with progressive lung fibrosis, whilst future study should address its validity following anti-fibrotic therapy and in other progressive lung diseases.

Conflict of interest: I. Stewart has nothing to disclose. T. McKeever has nothing to disclose. R. Braybrooke has nothing to disclose. E. Oballa is an employee of GlaxoSmithKline. J.K. Simpson is an employee of and shareholder in GlaxoSmithKline. T.M. Maher has, *via* his institution, received industry–academic funding from GlaxoSmithKline R&D and UCB, and has received consultancy or speakers fees from Apellis, AstraZeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Galapagos, GlaxoSmithKline R&D, Indalo, Pliant, ProMetic, Roche, Samumed and UCB. R.P. Marshall was a paid employee of GlaxoSmithKline when the work was carried out and remains a shareholder in GlaxoSmithKline. P.T. Lukey reports that during the PROFILE study, she was an employee of, and still owns shares in, GlaxoSmithKline. For the last 3 years, she has worked, and in some cases is still working, as an independent consultant to GlaxoSmithKline R&D, the Francis Crick Institute, Syncona, Peptinnovate, Mereo BioPharma, LiFT BioScience, DJS antibodies, BergenBio and Galecto. W.A. Fahy is an employee of and shareholder in GlaxoSmithKline. G. Jenkins reports grants from GlaxoSmithKline during the conduct of the study; grants from Biogen and Galecto, personal fees from Boehringer Ingelheim, Galapagos, Heptares, Pliant and Roche, grants and personal fees from GlaxoSmithKline and MedImmune, and service on advisory boards (no fees received) for NuMedii and Redex, outside the submitted work; and is a trustee of the British Thoracic Society and Action for Pulmonary Fibrosis. G. Saini has nothing to disclose.

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