



An Observational Study of Anxiety and Depression in Idiopathic Pulmonary Fibrosis

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Authors' contributions

This work was carried out in collaboration between all authors. Author KP collected the data, performed the statistical analysis, managed the literature searches and wrote the first draft of the manuscript. Author JB collected the data. Author BHG designed the study. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: Anxiety and depression are common in idiopathic pulmonary fibrosis (IPF). The longitudinal relationships between mental health and disease severity, progression and symptom burden are unknown. This study aims to identify if the prevalence and severity of anxiety and depression in IPF is associated with disease severity and progression. Also, to observe whether changes in cough and breathlessness symptom severity are associated with changes in mental health.

Study Design: Retrospective case note review.

Place and Duration of Study: Department of Respiratory Medicine, University Hospital Llandough, Cardiff between November 2010 and August 2012.

Methodology: Data was collected from 37 patients with IPF from two out-patient visits 12 months apart. Data included patient demographics, lung function measurements (FVC/TLco), hospital anxiety and depression scores, Denver ILD breathlessness score and Leicester cough questionnaire.

Results: The proportion of patients with depressive symptoms increased from 24.3% at baseline to 43.6% at 12 months. Anxiety rates fell from 40.5% at baseline to 35.1%. 12 patients (32%) had severe pulmonary fibrosis and 14 patients (38%) had progressive fibrosis. Patients with severe or progressive disease were more likely to have a clinically important increase in anxiety (severe $P = .02$, progressive $P = .008$) and depression scores (severe $P = .008$, progressive $P = .04$) compared with those with mild or stable

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disease. An association was identified between worsening depression and increasing dyspnoea ($r = .60, P = .01$) and cough related quality of life ($r = -.47, P = .01$). Increasing anxiety was also associated with dyspnoea ($r = .38, P = .05$) and cough ($r = -.39, P = .05$).

Conclusion: Anxiety and depression are highly prevalent in IPF and are associated with severe and progressive disease. Increasing symptom burden is associated with worsening mental health.

Keywords: *Idiopathic pulmonary fibrosis; depression; anxiety; quality of life.*

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive, life-limiting condition characterised by inflammation and fibrosis of the lung parenchyma [1]. It is a common disorder with a rising incidence in the United Kingdom [2] and a median survival of 2.8 years [3]. Symptoms include progressive breathlessness and a dry cough, which is frequently resistant to conventional therapy. Treatment options are limited and there is currently no drug therapy proven to improve survival. Management is therefore supportive; focusing on improving quality of life which is significantly impaired in these patients [4]. Despite the prevalence and poor prognosis of IPF little is known about the specific care needs of this population.

Anxiety and depression are prevalent in other chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) [5]. Depression also occurs more frequently in patients with underlying physical ill-health, however, the longitudinal relationship between IPF and mental health is not clear. The reported prevalence of anxiety and depression in pulmonary fibrosis is between 21-49% [6-9]. It has previously been shown in a group of patients suffering from IPF that increasing disease duration is associated with increasing anxiety and depression [10]. Further studies have shown degree of dyspnoea to be correlated with symptoms of depression in interstitial lung disease (ILD) [6,7] and a low transfer factor for carbon monoxide (TLco) has been identified as a risk factor for worsening depression [6]; suggesting a link with disease severity or progression. In addition, clinically meaningful depression at baseline has been identified as an important predictor of depressive symptoms at follow up. A recent study by Ryerson et al showed that depression persisted in 75% of patients over a six-month period [6].

There is a paucity of literature regarding anxiety in patients with IPF. Specifically, the longitudinal relationships between anxiety, depression and pulmonary fibrosis-related disease severity, progression and symptom burden are unknown.

Given the current emphasis on supportive care for patients with IPF it is important to identify which groups of patients are most susceptible to symptoms of worsening anxiety and depression, as these patients may benefit from particular surveillance and treatment where indicated.

This study aimed to investigate the association between anxiety and depression and disease severity and progression in patients with IPF. In addition we aimed to identify whether a change in cough and breathlessness was associated with a change in severity of anxiety and depressive symptoms.

2. METHODOLOGY

A retrospective case note review of routinely recorded clinical data was undertaken. All patients with a diagnosis of IPF attending the Cardiff Interstitial Lung Disease clinic between 2010 and 2012 were included. All diagnoses of IPF were made by multidisciplinary review of clinical, pathological and radiological data in accordance with published guidelines [1,11].

Data was collected as part of routine clinical evaluation from two outpatient appointments at least nine months apart between November 2010 and August 2012; including age, sex, presence of co-morbidity, use of oxygen therapy, lung function (forced vital capacity (FVC) and transfer factor for carbon monoxide (TLco)), hospital anxiety and depression score (HADS) [12], Denver ILD breathlessness score [13] and Leicester cough questionnaire score [14]. Patients were excluded if anxiety and depression symptom scores were not available in their medical notes from two out-patient appointments 9-12 months apart. Patients were not routinely started on treatment within the respiratory clinic.

The HADS is a well-validated screening tool for symptoms of anxiety and depression [12]. It has not been specifically validated in patients with IPF. However, in patients with chronic obstructive pulmonary disease the minimally important change has been shown to be 1.5 [15]. For the purposes of our analysis we have assumed that the clinically important change is of a similar magnitude in IPF.

The Denver ILD breathlessness score is a self-administered questionnaire that scores the amount of exertion required to precipitate dyspnoea [13]. Scores range from 2 to 20 with a higher score indicating more severe breathlessness and interval scores of 2 or more representing a recognisable change in exercise tolerance.

The Leicester cough questionnaire has been validated for use in chronic cough related to a number of chronic respiratory conditions although not specifically for IPF. The minimally important difference has been defined as 1.3 in patients with chronic cough [16].

Patients were retrospectively stratified into four subgroups; mild (FVC >50% and TLco ≥40%), severe (FVC < 50% or TLco <40%), stable (FVC decrease ≤10% or TLco decrease ≤15%) and progressive (FVC decrease >10% or TLco decrease >15%) [1,11].

Data analysis was performed using Statistical Package for Social Sciences, version 20.0 (SPSS Inc, Chicago, IL, USA), $P = .05$ was considered statistically significant. Parametric data was expressed as mean +/- standard deviation and was compared using the paired or independent student t test. Pearson's correlation coefficient was used to calculate correlations between HADS and change in symptoms. Fisher's exact test was used to identify associations between change in HADS and disease severity or disease progression.

Data used for analysis was collected as part of routine clinical practice; therefore following advice from the local ethics committee formal approval was not sought.

3. RESULTS

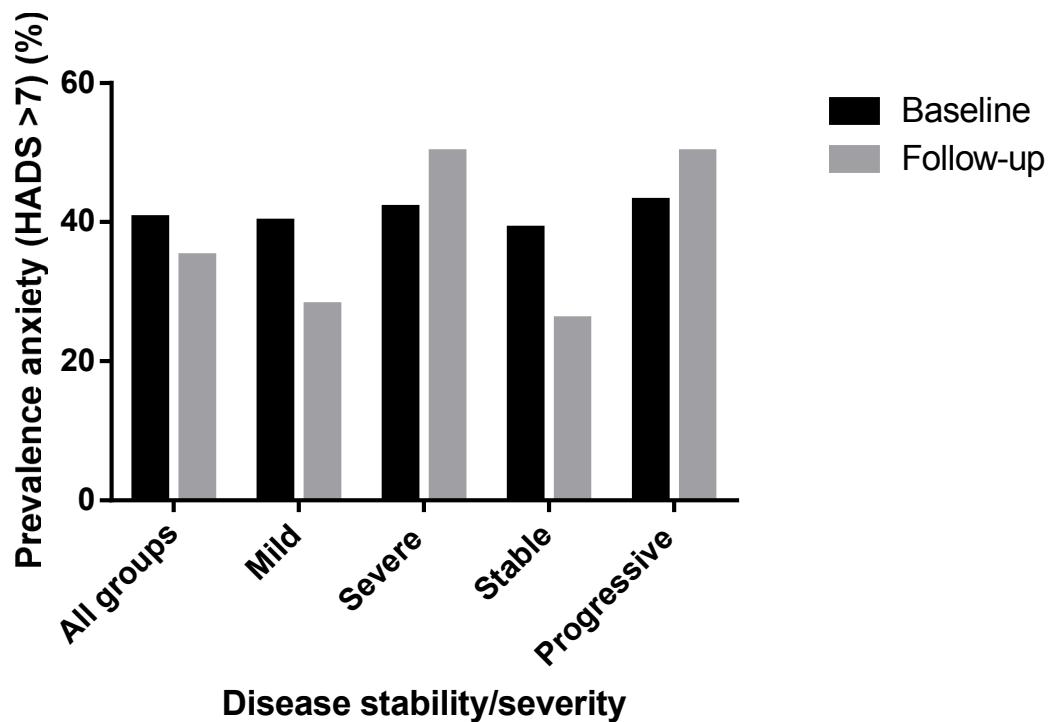
Table 1 shows the subject characteristics.

Table 1. Subject characteristics

Demographics	
Number of case notes reviewed	128
Number of patients with complete data available	37
Male: Female (n, %)	24 (65%): 13 (35%)
Months between data collection (mean, SD)	12.1 (1.6)
Comorbidity (n, %)	33 (89%)
Oxygen prescription (n, %)	2 (5.4%)
Mild disease (n, %)	25 (68%)
Severe disease (n, %)	12 (32%)
Stable disease (n, %)	23 (62%)
Progressive disease (n, %)	14 (38%)

3.1 Anxiety and Depression Symptoms and Disease Severity

The proportion of patients with depressive symptoms increased from 24.3% at baseline to 43.6% at 12 months. The proportion of patients with symptoms of anxiety was 40.5% at baseline and 35.1% at 12 months. The proportion of patients with symptoms of anxiety and depression in each subgroup (mild, severe, stable and progressive IPF) is shown in Figs. 1 and 2.



**Fig. 1. Prevalence of symptoms of anxiety at baseline and follow-up
(mean interval 12.1 months)**

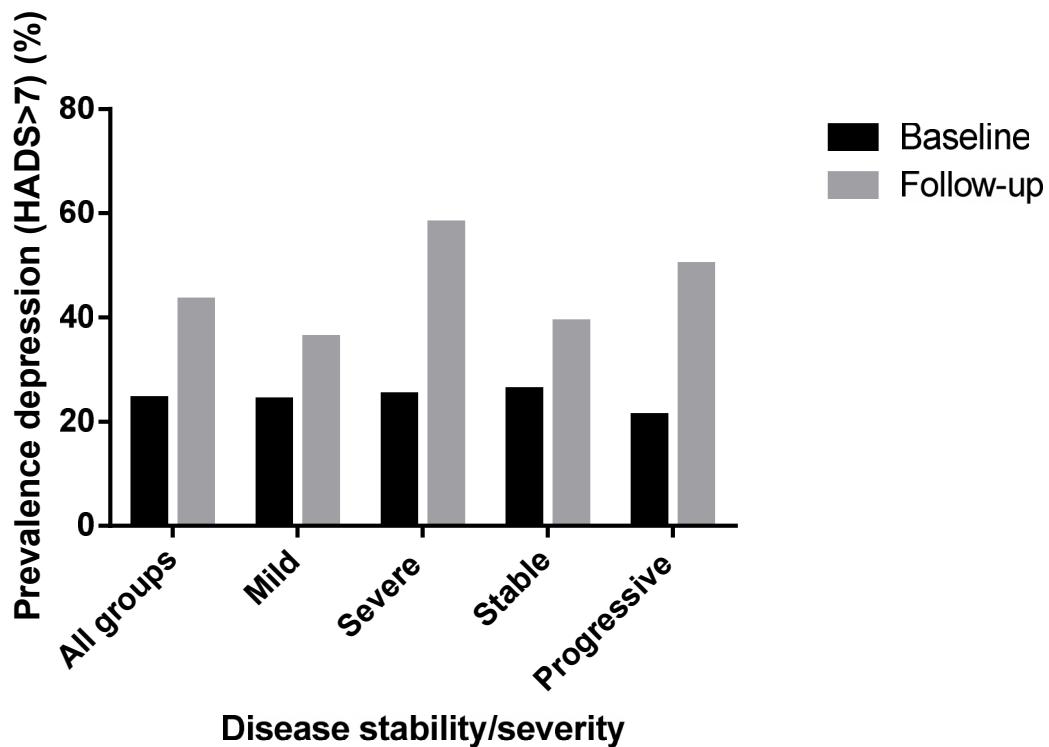


Fig. 2. Prevalence of symptoms of depression at baseline and follow-up (mean interval 12.1 months)

The mean HADS (depression) increased in all subgroups but was only significant in those with progressive disease (increase from baseline mean HADS 5.0 to follow-up mean 7.14, $P = .02$) (Table 2). There was no statistically significant change in the mean HADS (anxiety) between baseline and follow-up visits although non-significant trends of decreasing anxiety in patients with mild and stable disease and increasing anxiety in severe and progressive disease were observed (Table 2).

Table 2. Mean HADS at baseline and follow-up

	Baseline mean (SD)	Follow-up mean (SD)	P value (CI)
Depression			
Mild IPF	5.56 (4.6)	5.32 (3.9)	.59 (-0.68-1.16)
Severe IPF	5.42 (3.03)	7.33 (5.2)	.08 (-4.09-0.23)
Stable IPF	5.83 (4.7)	5.26 (4.2)	.22 (-0.36-1.49)
Progressive IPF	5.00 (3.0)	7.14 (4.6)	.02* (-3.89- -0.39)
Anxiety			
Mild IPF	6.16 (4.9)	5.32 (4.8)	.30 (-0.8-2.48)
Severe IPF	7.17 (5.08)	7.42 (6.4)	.83 (-2.76-2.26)
Stable IPF	6.26 (5.14)	5.13 (5.3)	.20 (-0.64-2.9)
Progressive IPF	6.86 (4.7)	7.43 (5.4)	.56 (-2.63-1.49)

The mean change in depression symptom score over the follow up period was significantly higher in the severe and progressive groups (Table 3).

Table 3. Mean individual change in depression and anxiety symptom scores during 12 month follow up period

	Mild IPF	Severe IPF	P value
Mean change in HADS (depression) (SD, range)	-0.12 (2.37) (-5, +4)	1.92 (3.4) (-2, +8)	.05*
Mean change in HADS (anxiety)	-0.76 (3.99) (-10, +9)	0.33 (3.9) (-9, +4)	.44
		Stable IPF Progressive IPF	
Mean change in HADS (depression)	-0.43 (2.33) (-5, +4)	2.14 (3.03) (-2, +8)	.01*
Mean change in HADS (anxiety)	-1 (4.1) (-10, +9)	0.57 (3.6) (-9, +4)	.25

Patients with severe or progressive disease were more likely to have a clinically important increase in both anxiety and depression scores compared with those with mild or stable disease (Table 4).

Table 4. Number of patients with a clinically important change in HAD score (>1.5) over the 12 month follow up period

	Mild	Severe	P value
Change HADS (depression)	2/25 patients	6/12 patients	.008*
Change HADS (anxiety)	4/25 patients	7/12 patients	.02*
	Stable	Progressive	
Change HADS (depression)	2/23 patients	6/14 patients	.04*
Change HADS (anxiety)	3/23 patients	8/14 patients	.008*

3.2 Anxiety and Depression and Symptom Severity

Increasing depression score was strongly associated with worsening breathlessness ($r = .60$ $P = .01$, Fig. 3). A weaker association was identified between change in HADS (anxiety) and change in Denver score ($r = .38 P = .05$).

Increasing depression score was associated with worsening cough related quality of life ($r = -.47 P = .01$, Fig. 4). There was also a weak association between increasing anxiety and worsening cough ($r = -.39 P = .05$).

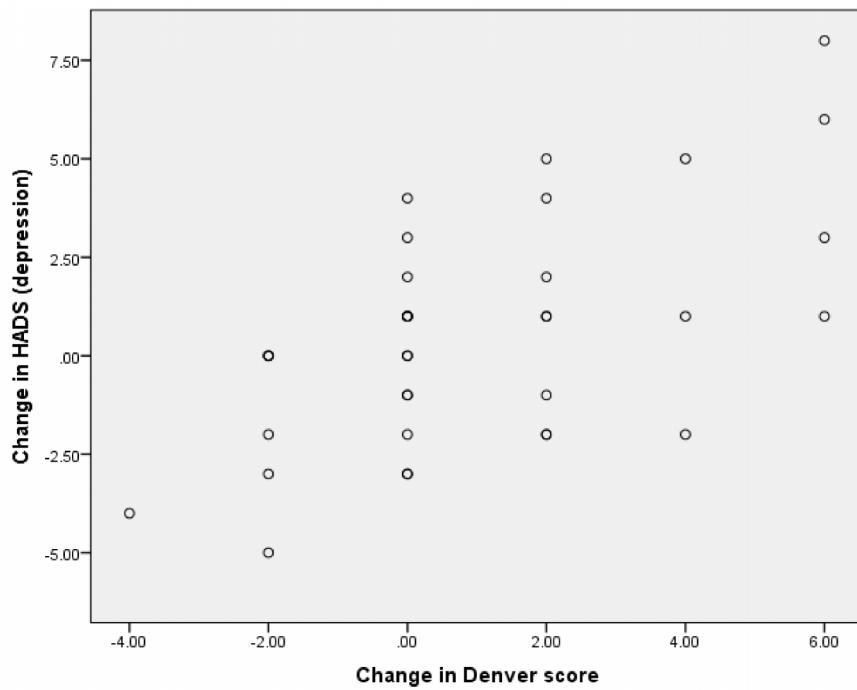


Fig. 3. Association between breathlessness and depression ($r = 0.60, P = .01$)

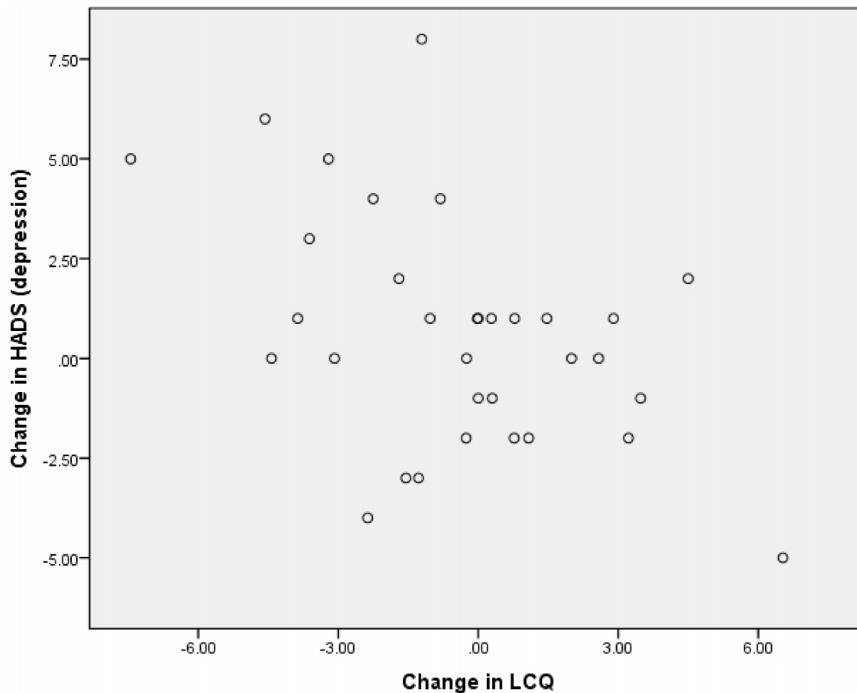


Fig. 4. Association between cough related quality of life and depression ($r = -0.47, P = .01$)

4. DISCUSSION

Symptoms of depression were frequent in our population of patients with IPF (24.3%). This is in accordance with previous studies (21-49%) [6-10]. This compares to an estimated UK adult prevalence of 2.6% [17] and is comparable with patients suffering from COPD (estimated prevalence rates of 7-42%) [18]. This study shows that the proportion of patients suffering depressive symptoms increases over a twelve month follow-up period (43.6%) and is associated with disease severity and progression. Perhaps unsurprisingly all patients with evidence of depression at the start of the study remained depressed at follow-up. A previous study has shown a correlation between disease duration and HADS (depression) ($r=0.629$, $p=0.001$) [10]. In contrast a larger, more recent study showed no correlation [9]. The reasons behind the increasing rates of depression are unknown. We would suggest this may be related to disease progression and progressive physical decline and loss of independence. Certainly these domains are associated with impaired health related quality of life in previous studies [4]. Furthermore, as discussed below, increasing dyspnoea over time is likely to influence depression rates.

The finding that worsening IPF severity and progression is associated with depression is supported by the results of previous studies. Ryerson et al studied the natural history of depression in patients with ILD [6]. They found that baseline depression score was significantly associated with TLco and forced vital capacity was an independent predictor of depressive symptoms. Furthermore a lower TLco was an independent risk factor for worsening depression with time. A recent study by Akhtar et al found weak correlations between depression score and FEV1, FVC and gas transfer factor (all $P = .05$) [9]. However the significance of this finding was questioned due to weak correlations ($r= -0.2$, -0.2 and -0.23 respectively). A study by Tzanakis et al has shown a significant correlation between HADS (depression) and PaO₂ at rest ($r= -0.61$, $P = .001$) and during exercise ($r = -.56$, $P = .004$) [10]. The same study showed correlations between the hospital depression scale and PaO₂ at rest ($r = 0.61$, $P = .001$) and during exercise ($r = .56$, $P = .004$). These findings would seem to corroborate the findings from this study that depression is associated with worsening IPF severity and progression.

The prevalence of anxiety symptoms was high at baseline (40.5%) but had reduced by twelve months (35.1%). This was largely reflective of those patients with mild or stable disease. In contrast the prevalence of anxiety symptoms remained high in those with severe (baseline 42%, 12 months 50%) and progressive fibrosis (baseline 43%, 12 months 50%). There was a non-significant trend towards increasing anxiety in severe and progressive disease and these sub-groups were more likely to have a clinically important increase in anxiety score during the follow-up period ($P = .02$, $P = .008$).

There are few previous studies investigating anxiety in IPF; with prevalence varying between 27-60% [7,19]. Larger studies are required to clarify relationships between symptoms of anxiety and IPF behaviour. It is possible that reduced anxiety at follow-up may relate to greater understanding of the nature of IPF or that those with mild or stable disease became habituated to symptoms, thus reducing anxiety levels. However, a study by Lindell et al in 2010 showed that a disease modifying program increased symptoms of anxiety in the intervention group; an observation considered to be related to full disclosure of details regarding prognosis and disease behavior [20].

A further study by Tzanakis et al. [10] identified a significant correlation between HADS (anxiety) and disease duration ($r = .64$, $P = .001$) over a five year follow-up suggesting

increasing symptoms of anxiety with time. This study contradicts our findings and highlights the need for further research in this area. The discrepancy could be explained by differences in disease severity or follow up period between the studies.

There is a paucity of evidence regarding the effect of disease severity on anxiety. Tzanakis et al showed a significant correlation between HADS (anxiety) and PaO₂ at rest ($r = .44, P = .03$) and on exertion ($P = .43, P = .03$) suggesting a link with disease severity. However, TLco was not significantly correlated with HADS (anxiety) in this study [10].

We have shown that increasing depression and anxiety are associated with worsening breathlessness and cough. Previous studies have shown that dyspnoea is a major influence on health related quality of life in patients with IPF [4,8] and dyspnoea is strongly associated with depressive symptoms [6,7]. To our knowledge the relationships between anxiety and dyspnoea have not been studied in IPF. Cough has been shown to be the factor most strongly influencing health related quality of life in IPF [21], however the specific association between worsening anxiety and depression and cough has not been identified previously. A study of chronic cough in the community showed a high prevalence of psychological morbidity such as anxiety (69%) and depression (55%) [22]. In addition, in patients with chronic cough, cough-related quality of life has been shown to be related to HADS ($r = .43$ anxiety, $r = .42$ depression, $P = .05$) [23].

In patients with COPD it is known that complex relationships exist between dyspnoea and anxiety [18] and that anxiety is one of the main determinants of quality of life [24]. A longitudinal study of patients with COPD showed worsening dyspnoea and HADS (anxiety and depression) over a five year follow-up. Changes in dyspnoea correlated with changes in HADS (anxiety and depression) ($r = .33 - .46, P = .01$) [25]. Qualitative studies also support the dyspnoea-anxiety-dyspnoea cycle [26]. A further study in a COPD population identified that the increased frequency of anxiety symptoms correlated with disease severity according to GOLD criteria ($\chi^2 = 27.47, P = .001$). The prevalence of anxiety symptoms also increased with the BODE quartiles ($\chi^2 = 78.69, P = .0001$) [27]. Furthermore there was a significant correlation between symptoms of anxiety and depression ($r = .7, P = .0001$) highlighting that if a patient has symptoms of anxiety or depression the other condition should be suspected as well. It seems likely that similar relationships exist in the IPF population and future research should focus on defining these associations.

There are several limitations to this study. It is a small, retrospective, observational study with no control group. Whilst the Hospital Anxiety and Depression score is a well-validated screening tool for depression it is not a diagnostic test but relies on self-reported questionnaires rather than a full psychiatric assessment. In addition, confounding factors such as life circumstances, antidepressant medication use and type of co-morbidity were not adjusted for.

Despite these limitations, the results of this study suggest that clinicians should be alert to symptoms of anxiety and depression in patients with IPF; particularly in those with progressive disease and increasing symptom burden. Disease modifying treatment options are currently limited for IPF with no drug therapy proven to prolong survival. Therefore supportive care remains a mainstay of patient management, with a focus on improving quality of life. There are no previous studies that have evaluated treatment of depression or anxiety in this population; an area that clearly requires further investigation. Future studies of symptom control should also include an assessment of anxiety and depression given the associations identified in this cohort. For example, pulmonary rehabilitation is a well-

established treatment for COPD and has been shown to improve breathlessness symptoms, functional capacity and health related quality of life; including symptoms of anxiety and depression. Patients with IPF show similar benefits in exercise tolerance and quality of life [28]. However, a reduction in anxiety and depression has not been shown.

5. CONCLUSION

This is one of the first studies of anxiety and depression symptoms in patients with IPF to show a relationship between disease severity and progression and deteriorating mental health over time. We have also shown an association between increasing symptoms of anxiety and depression and increasing breathlessness and cough. Patients with these characteristics should be targeted for surveillance and treatment.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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