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Are idiopathic pulmonary fibrosis patients more anxious and depressive than patient's with other interstitial lung disease?

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Abstract. *Background and aim:* Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) with unknown etiology that occurs primarily in older adults with a median survival time of 2.5±3.5 years. Since there is no curative treatment for IPF, patients with IPF may have symptoms of depression and anxiety more than those of other interstitial lung diseases. There is a few studies about comparison of anxiety depression with other interstitial lung disease and IPF. In this study, we investigated whether anxiety depression in IPF was more frequent than other ILDs and its effect on quality of life. *Methods:* The study was designed as a prospective study. Age, sex, smoking status, respiratory symptoms, comorbidities, pulmonary function tests, diffusion capacity of the lungs for carbon monoxide (TLCO), SF-36, and depression/anxiety levels, radiological findings, erythrocyte sedimentation rate (ESR), CRP level, blood gas analysis, complete blood count parameters were recorded. *Results:* The mean age of 50 IPF and 42 non-IPF interstitial lung disease patients were 67.4±7.1 and 64.9±7.2, respectively. Compared with the non-IPF group, SF-36 total, SF-36 physical function and SF-36 physical role severity were significantly lower in the IPF group, while the GAP score was significantly higher. There was no significant difference between the two groups in HAM-Anxiety and HAM-depression for total scores. But mild anxiety was present in most of non-IPF group. No severe anxiety was observed in this group. Forty-nine of 50 patients with IPF patients had moderate-severe anxiety and the difference was statistically significant compared to non-IPF patients. *Conclusions:* This is one of the first studies of anxiety and depression symptoms are also important in non IPF ILD like IPF. Patients with non-IPF ILD have similar anxiety depression with IPF patients in this study. This study led to the conclusion that anxiety depression should also be evaluated in non-IPF ILD patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (4): 294-301)*

Key words: anxiety, depression, interstitial lung disease, IPF

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease with unknown etiology that occurs primarily in older adults, with a median survival time of 2.5±3.5 years (1). Since there is no curative treatment for IPF, and lung transplantation is the only effective treatment. Patients with IPF may have symptoms of depression and anxiety more than other non IPF interstitial lung diseases. Because of the high morbidity and mortality, primary target for management of these patients is improving the symptoms and quality of life (QOL). The probability of developing depression is 1.5-7 times higher in these group of patients than the general population (2-4). Recent studies have shown increased depressive symptoms among patients with chronic respiratory disease (5). However, while several studies have shown that psychological factors affect the quality of life or health status in chronic obstructive pulmonary

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disease (COPD) patients, studies also started for IPF patients (6,7). Some studies studies have revealed that the prevalence of depression ranges from 24.3±49.2%, while that of anxiety may be as high as 60%, in patients with IPF (8-10). Additional studies have reported that depression and anxiety are more common in patients with severe, progressive forms of IPF (11).

Depression has been associated with the severity of dyspnea, cough, and pulmonary dysfunction which is a major determinant of quality of life (QOL) in patients with IPF (12-14). Although anxiety is also likely associated with poorer health status in patients with IPF, comparatively less is known regarding the association between anxiety and IPF. Despite the study of how anxiety and depression affect quality of life and disease in IPF patients, there is a few comparative studies regarding anxiety and depression with other interstitial lung disease and IPF(12,13).

In this study, we investigated whether anxiety depression in IPF was more frequent than other ILDs and its effect on quality of life.

Methods

The study was designed as a prospective nature. All patients were informed about study and consent form were obtained from them. Ethical approval was received. Patients were recruited from our ILDs outpatient clinic of tertiary teaching hospital with a high bed capacity, between January 2016 and January 2017. Patients with IPF and other interstitial lung disease who had completed the Hamilton Anxiety and Depression Scale (HADS) questionnaire were enrolled.

Diagnosis: IPF was diagnosed after multidisciplinary discussions in accordance with criteria outlined by the 2011 consensus of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society, and the Latin American Thoracic Association (1).

Non IPF Interstitial lung diseases include 15(35%) cases with chronic hypersensitivity pneumonia, 5(12%) cases with asbestosis, 3(7%) cases with sarcoidosis , 12 cases (28%) with non-specific interstitial pneumonia (NSIP), unidentified in 7 cases (17%) . The common feature of all was ILD with fibrosis.

The following characteristics were assessed during baseline clinical examinations: age, sex, smoking status, respiratory symptoms, comorbidities, pulmonary function test results (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], and diffusing capacity of the lungs for carbon monoxide [TLCO]), SF-36, and depression/anxiety levels, radiological findings, erythrocyte sedimentation rate (ESR), CRP level, blood gas analysis, complete blood count parameters.

Pulmonary function tests (PFT): Pulmonary function tests were performed by trained professionals in accordance with standardized ATS guidelines (15). The Gender-Age-Physiology Index for IPF (GAP Index) was also calculated for each patient in accordance with methods described by Ley et al. (16).

PFT had been performed using a ZAN 300 device (ZAN Messgerate, Oberthulba, Germany), in the sitting position. The highest value of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC), from at least three technically satisfactory maneuvers differing by less than 5%, was recorded.

Psychological Symptoms: The Hamilton Anxiety and Depression (HAD) scale, consisting of 14 questions, is used to determine the psychological status of the patients (17,18).

Exercise Capacity: The 6MWT is performed according to the ATS guidelines and the distance walked for six minutes was recorded.

Quality of Life: Overall quality of life is assessed by SF-36 Quality of Life Questionnaire (19). Increased scores are considered in favor of improved quality of life.

Statistical analysis: Data were analyzed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, US) computer software. Nominal variables were given by their frequencies and percentages and compared by cross tables. Independent groups were compared using a Chi-square test. The mean, standard deviation, median, minimum, and maximum values of the continuous variables were presented, and the normal distribution of these variables was examined. According to normal distribution, student's *t*-test and Mann-Whitney U-test were used to compare continuous variables between groups. A value of $P < 0.05$ was considered statistically significant.

Results

The mean age of 50 IPF and 42 non-IPF interstitial lung patients were 67.4 ± 7.1 and 64.9 ± 7.2, respectively (p = 0.08). The most common symptom was dyspnea, with 74% in the IPF group, 44% in the non-IPF group, and the second most common symptom was cough (IPF 56%, non-IPF 44%). The most frequently observed physical examination finding was thin rales in both groups. Demographic data and laboratory characteristics of the patients are summarized in Table 1.

Six of the IPF patients (12%) had family history. Clubbing was seen in 15 IPF patients (30%) and 3 (6%) in the non-IPF group, which is statistically significant (p = 0.015). Long-term oxygen therapy (LTOT) was used by 4 of the IPF and 1 of the non-IPF patients. In IPF patients, high resolution com-

Table 1. Demographic and laboratory findings of patients

	IPF (n=50)	Non-IPF (n=42)	p value
Age (Mean±SD)	67.4±7.1	64.9±7.2	0.08
Gender (n) (Female/Male)	12/38	13/29	
Non-smoker (n) Smoker Ex-smoker	16 10 23	15 6 20	0.76
BMI	27.3±3.9	29±4.1	**0.04**
6DYT = 6MWT(mt)	342.8±93	362.787.8	0.30
FEV_1%	69.6±14.4	77.8±17.7	**0.01**
FVC %	63±15.2	71.6±15.9	**0.01**
TLCO %	42.2±15	53.2±20.9	**0.006**
Clubbing, n	15	3	**0.015**
Symptom *, n(%) Dispnea Coughing Sputum	 46 (92%) 28 (56%) 10 (20%)	 33 (78,6%) 21 (50%) 16 (38%)	 0,123 0,71 0,09
Comorbidity* (n) Total (+/-) Hypertension Diabetes Coronary Artery Disease COPD Others	 32/18 12 16 18 5 2	 32/10 16 16 8 5 3	 0.51
Radiological findings* (n) Traction bronchiectasis Honeycomb Fibrosis Glossy opacity Emphysema	 23 41 44 28 13	 8 18 35 35 10	 **0.006** **<0.001** 0.72 **0.005** 0.82
Sedimentation	26 (8,100)	26 (4,119)	0.74
CRP	0.6 (0.1 , 25)	0.6 (0.1,13.5)	0.36

*= more than one finding in a patient
Abbrevations: IPF:Idiopatic Pulmonary Fibrosis; BMI: Body mass index; 6MWT: Six minute walk test

puted tomography (HRCT) showed a typical UIP pattern in 25 patients and a possible UIP pattern in 25 patients. Among patients with probable UIP pattern, pathologic diagnoses were obtained in 17 patients, in 6 with cryo-biopsies and 11 with VATS. In 8 patients, biopsies were not performed due to high risk and rejection. Exacerbation was observed in 13 patients (26%) with IPF patients and 10 of them were hospitalized. Twenty-five patients with IPF used pirfenidone, 9 patients used Nintedanip and 16 patients did not use anti-fibrotic agent.

The values of BMI, FEV1%, FVC%, diffusion (TLCO%) were significantly lower in the IPF group than in the non-IPF group and clubbing was significantly higher in the IPF group (p values 0.04, 0.01, 0.01, 0.006 and 0.015 respectively). In the radiological parameters, honeycomb and traction bronchiectasis were significantly higher in the IPF group and the ground glass opacity was significantly lower (p values <0.001, 0.006 and 0.005 respectively) (Table 1).

Compared with the non-IPF group, SF-36 total, SF-36 physical function and SF-36 physical role severity were significantly lower in the IPF group, while the GAP score was significantly higher (p value 0.007, 0.02, 0.02 and 0.001 respectively). GAP scores could not be calculated in some patients because of the absence of the DLCO values. There was no significant difference between the two groups for total HAM-Anxiety and HAM-depression scores. But, mild anxiety was present in 81% of non-IPF group. No severe anxiety was observed in this group. Forty-nine of 50 patients with IPF patients had moderate-severe anxiety and the difference was statistically significant compared to non-IPF patients. Depression was similar in both groups (Table 2).

HAM-A in IPF patients; was negatively cor-

Table 2. The quality of life of the patients and Hamilton anxiety-depression scale values

	IPF (n=50)	Non-IPF (n=42)	p value
SF-36 Physical function	45 (0,100)	70 (10,100)	**0.02**
SF-36 Physical role severity	12.5 (0,100)	62.5 (0,100)	**0.02**
SF-36 Emotional role difficulty	33.3 (0,100)	66.7 (0,100)	0.08
SF-36 Vitality	45 (5,100)	45 (10,95)	0.71
Mental health	60 (20,92)	52 (20,100)	0.31
Social function	50 (0,100)	56.2 (12.5,100)	0.59
Pain	100 (32.5,100)	82.5 (10,100)	0.12
General health	42.5 (0,86)	47.5 (15,85)	0.39
Total	79.2±17.6	88±12.1	**0.007**
GAP Score	4.5±1.6	3.3±1.3	**0.001**
GAP Score Stage I Stage II Stage III	15 20 13	19 15 1	**0,008**
HAM-A	27.1±6.3	26.7±7.5	0.78
Psychological	10±2.4	10.4±4	0.56
Somatic	16.8±4.6	17.2±5.1	0.66
HAM-D	35±7.1	34.5±8	0.76
HAM-A Mild Moderate Severe	1 (%2) 20 (%40) 29 (%58)	34 (%81) 8 (%19) 0 (%0)	**0,000**
HAM-D Moderate Severe	5 45	8 34	0,347

SF-36 = Short form-36 Quality of Life; HAM-A = Hamilton Anxiety score; HAM-D = Hamilton Depression score; GAP = Gender Age Physiologic index; 6MWT = 6 Minute walk Test

related with SF-36 physical function, SF-36 emotional role, vitality, mental health, social function, general health and 6M and positively correlated with HAM-D. HAM-D; was negatively correlated SF-36 physical function, SF-36 emotional role, vitality, pain, general health and 6MWT, and positively correlated with HAM-A (Table 3).

HAM-A in non-IPF patients was negatively correlated with mental health and 6MWT, and positively correlated with HAM-D. HAM-D correlated negatively with vitality, mental health, social function, and 6MWT, and positively correlated with HAM-A (Table 4).

Discussion

There are few studies on anxiety and depression in IPF and other interstitial lung diseases (10,16). The study comparing IPF and non-IPF patients in

Table 3. In IPF, quality of life, HAM-A, HAM-D, GAP score , 6MWT correlations

	SF-36 total	GAP score	HAM-A	HAM-D	6MWT
SF36 Physical function	r: 0.23 p:0.10	r: -0.25 p:0.07	r: -0.52 p<0.001	r: -0.52 p<0.001	r:0.31 p:0.03
SF36 Physical role severity	r:0.19 p:0.18	r:-0.29 p:0.04	r:-0.25 p:0.07	r: -0.32 p:0.023	r:0.15 p:0.28
SF36 emotional role difficulty	r: 0.10 p:0.47	r: -0.19 p:0.18	r: -0.41 p:0.003	r: -0.52 p<0.001	r:0.38 p:0.008
Vitality	r:0.12 p:0.38	r:-0.04 p:0.74	r: -0.41 p:0.003	r: -0.42 p:0.002	r:0.26 p:0.07
Mental health	r:0.17 p:0.21	r:-0.29 p:0.045	r: -028 p:0.04	r: -0.27 p:0.056	r:0.29 p:0.044
Social function	r: 0.08 p:0.55	r: -0.21 p:0.13	r: -0.36 p:0.009	r: -0.27 p:0.055	r:0.12 p:0.39
Pain	r:-0.03 p:0.82	r:-0.18 p:0.21	r: -0.16 p:0.25	r: -0.30 p:0.033	r:0.08 p:0.55
General health	r:0.38 p:0.005	r:-0.17 p:0.24	r: -0.30 p:0.03	r: -0.37 p:0.007	r:0.37 p:0.10
SF-36 total	-	r:-0.01 p:0.92	r: 0.10 p:0.94	r: -0.11 p:0.42	r:0.04 p:0.78
GAP-score	r:-0.01 p:0.92	-	r: 0.20 p:0.17	r: 0.17 p:0.23	r:-0.10 p:0.50
HAM-A	r: 0.10 p:0.94	r: 0.20 p:0.17	-	r: 0.84 p<0.001	r:-0.41 p:0.004
Psychological	r:0.00 p:0.99	r:0.10 p:0.47	r:0.81 p<0.001	r: 0.66 p<0.001	r:-0.23 p:0.11
Somatic	r:0.04 p:0.73	r:0.21 p:0.15	r:0.95 p<0.001	r: 0.81 p<0.001	r:-0.42 p:0.003
HAM-D	r: -0.11 p:0.42	r: 0.17 p:0.23	r: 0.84 p<0.001	-	r:-0.40 p:0.005
6 MWT	r:0.04 p:0.78	r:-0.10 p:0.50	r:-0.41 p:0.004	r:-0.40 p:0.005	-

SF-36 = Short form-36 Quality of Life; HAM-A = Hamilton Anxiety score; HAM-D = Hamilton Depression score; GAP = Gender Age Physiologic index; 6MWT = 6 Minute walk Test

Table 4. In Non-IPF , quality of life, HAM-A, HAM-D, GAP score, 6MWT correlations

	SF36 total	GAP score	HAM-A	HAM-D	6MWT
SF36 physical function	r:0.19 p:0.21	r: -0.14 p:0.40	r: -0.15 p:0.33	r: -0.16 p:0.28	r:0.22 p:0.16
SF36 physical role severity	r:0.20 p:0.19	r:-0.23 p:0.17	r:-0.01 p:0.91	r: -0.12 p:0.44	r:-0.06 p:0.70
SF36 emotional role difficulty	r: 0.22 p:0.15	r: -0.17 p:0.32	r: -0.10 p:0.52	r: -0.18 p:0.25	r:-0.05 p:0.74
Vitality	r:0.21 p:0.17	r:-0.13 p:0.42	r: -0.27 p:0.08	r: -0.48 p:0.001	r:0.13 p:0.38
Mental health	r:0.02 p:0.86	r:-0.17 p:0.30	r: -031 p:0.040	r: -0.48 p:0.001	r:0.24 p:0.12
Social function	r: 0.14 p:0.37	r: -0.09 p:0.57	r: -0.20 p:0.19	r: -0.35 p:0.020	r:0.21 p:0.18
Pain	r:0.21 p:0.17	r:-0.04 p:0.81	r: -0.17 p:0.26	r: -0.23 p:0.13	r:0.19 p:0.23
General health	r:-0.10 p:0.49	r:-0.19 p:0.27	r: -0.19 p:0.22	r: -0.24 p:0.11	r:0.13 p:0.40
SF36 total	-	r:-0.06 p:0.72	r: -0.15 p:0.34	r: -0.25 p:0.11	r:-0.11 p:0.46
GAP score	r:-0.06 p:0.72	-	r: -0.27 p:0.11	r: -0.12 p:0.48	r:0.06 p:0.73
HAM-A	r: -0.15 p:0.34	r: -0.27 p:0.11	-	r: 0.72 p<0.001	r:-0.46 p:0.002
Psychological	r:-0.06 p:0.70	r:-0.23 p:0.17	r:0.77 p<0.001	r: 0.63 p<0.001	r:-0.56 p<0.001
Somatic	r:-0.23 p:0.13	r:-0.18 p:0.28	r:0.62 p<0.001	r: 0.72 p<0.001	r:-0.31 p:0.047
HAM-D	r: -0.25 p:0.11	r: -0.12 p:0.48	r: 0.72 p<0.001	-	r:-0.41 p:0.007
6MWT	r:-0.11 p:0.46	r:0.06 p:0.73	r:-0.46 p:0.002	r:-0.41 p:0.007	-

SF-36 = Short form-36 Quality of Life; HAM-A = Hamilton Anxiety score; HAM-D = Hamilton Depression score; GAP = Gender Age Physiologic index; 6MWT = 6 Minute walk Test

terms of anxiety and depression is almost non-existent. Therefore, we investigated whether anxiety depression status in IPF patients was different from non-IPF patients. When IPF patients were compared with non-IPF patients, SF-36 total score, SF-36 physical role severity and SF-36 physical function scores were significantly lower and GAP score was significantly higher in patients with IPF. SF-36 score indicates that health status deteriorates with decreasing score, whereas with the increasing in the GAP score the risk of mortality also increases. Therefore, lower SF-36 scores in IPF patients led us to conclude that the overall health status of these patients was worse than non-IPF patients. The higher the GAP score in the IPF group, the higher the risk of mortality in the IPF group.

In consistent with the literature, we found significantly higher GAP score, which is a determinant

for mortality and prognosis, especially in the stage 3, in the IPF group and we found a negative correlation with quality of life.

In other studies investigating the anxiety and depression in interstitial lung diseases and IPF, Lee et al. found the prevalence of depression in IPF patients similar to the values in western countries. In the normal population of Korea, depression is about 4%, while 6 times more in patients with IPF (20). However, there is no study describing the mechanism of depression and anxiety, but it has been found associated with dyspnea in interstitial lung diseases. Dyspnea has been reported to be more progressive and irreversible in patients with IPF so depression was more (10,13). In Lee's study, depressed patients showed poorer quality of life. This has led to the conclusion that treatment of depression plays a critical role in improving quality of life in IPF patients.

We thought that depression may be seen more frequently in IPF patients than in non-IPF patients when we started to study, but at the end of the study we have seen no difference between the two groups. Whereas Ryerson et al., found that, depression was found to be correlated with the severity of dyspnea and depression scores in patients with ILD. And the authors suggested that treatment of depression would treat not only mood but also dyspnea (10). In our study, in the IPF group, dyspnea symptoms were more frequent but not statistically significant. However, the correlation between anxiety- depression and dyspnea could not be evaluated because it was a retrospective study and dyspnea scores did not exist. However, depression was observed at a similar rate in both groups. There was no difference in the severity of depression.

In various studies, the prevalence of anxiety in IPF patients was found to be higher (31-60%) than depression (11, 13). In Lee's study, it was found to be lower than the literature and similar to depression rate . Patients are more anxious when they feel having irreversible and coming-to-end disease. Although, incidence of anxiety in IPF was seen similar to the anxiety in other ILD, when we looked at the level of the anxiety, while non-IPF patients had mild anxiety, the IPF patients had moderate and severe anxiety.

In our study, the quality of life was assessed by SF 36 and a significant difference was found between SF 36 scores of IPF and other ILD patients. SF 36 scores of other ILD patients were found to be better. Although, previous studies revealed a correlation between anxiety depression scores and the quality of life, we did not find any correlation between anxiety depression scores and overall quality of life. It has been suggested that improvement of functional capacity and dyspnea by pulmonary rehabilitation may provide more positive contributions to quality of life besides treatment of anxiety depression to improve the quality of life (21,22). Therefore, patients should be referred to psychological support and pulmonary rehabilitation to manage anxiety and depression and to improve the quality of life.

The results of this study suggest that clinicians should be alert to symptoms of anxiety and depression both in patients with IPF and non-IPF interstitial lung diseases; particularly in those with progressive disease and increasing symptom burden. Disease modifying treatment options are currently limited for IPF and also in some ILD to prolong survival. Therefore supportive care remains a mainstay of patient management, with a focus on improving quality of life. 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 (6). Patients with IPF show similar benefits in exercise tolerance and quality of life (21,22). Though there is no data, we think that pulmonary rehabilitation may show similar benefits in non IPF-ILD patients.

Conclusion

The current study is one of the few study that showed anxiety and depression symptoms are also important in non-IPF ILD like IPF. There were studies about the relation of anxiety depression and IPF, whereas patients with non-IPF ILD have similar depression with IPF patients in this study. This study led to the conclusion that anxiety especially the depression should also be evaluated in non-IPF ILD patients.

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