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Research Article

Prognosis Symptoms, Quality of Life and Comorbidity Relationship with Cough in Patients with Idiopathic Pulmonary Fibrosis

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Objective: Cough is one of the most frequent symptoms in patients with idiopathic pulmonary fibrosis (IPF). The aim of this study was to investigate whether there was any difference with respect to quality of life, depression, sleep disturbance and reflux symptoms between IPF patients with and without cough symptom.

Study Design: Cross-sectional study

Materials and Methods: Patients with IPF who were admitted to outpatient clinic were divided into two groups according to the Visual Analog Scale (VAS) scores as cough group and non- cough group. In each group, Leicester cough questionnaire, reflux questionnaire, Beck depression questionnaire, St George's quality of life questionnaire (SGRQ) and Sleep Quality index were evaluated to determine whether there were any differences between groups.

Results: It was shown that the Leicester cough questionnaire score was lower in the cough group (86±24.9 vs 111±18.9) (p 0,02). Beck depression score revealed moderate level of depression in both groups (22±10.74 in cough group vs 18±11.86 in non-cough group) (p 0,4). SGRQ symptom score was significantly higher in the cough dominant group (p 0,04).

Conclusion: It is found that presence of cough in patients with IPF negatively affected the quality of life and was associated with the sleep disorders and depression. Leicester cough questionnaire can be used to assess whether the cough symptom affects patients' quality of life in routine clinical evaluation of patients with IPF. This evaluation is thought to improve quality of life and treatment compliance by increasing cough palliation in IPF patients.

Keywords: Idiopathic pulmonary fibrosis, Cough, Leicester cough questionnaire, Quality of life

1. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common type of interstitial pneumonia and is a chronic, progressive interstitial pneumonia of unknown origin. It is common in adults and is limited only to the lungs.

Progressive fibrosis in IPF leads to impaired gas exchange, reduced functional capacity, exercise intolerance and impaired quality of life.[1] The prognosis of the disease is poor and the average life expectancy is two to five years after diagnosis.[2] However treatment with antifibrotic agents reduced the decline of functional capacity, increased the survival and improved the quality of life in patients with IPF.[3-6] The most important treatment goal is to increase survival but improvement of quality of life and palliation of symptoms are also important, especially in patient's perspective.

It's been shown that severity of dyspnea is associated with anxiety, depression and decreased quality of life in patients with IPF however it is not clear whether presence of cough also related to these conditions.[7]

Technological advances in diagnostic methods, increase in human life expectancy, especially the development of radiological diagnostic methods and the emergence of new treatment options in the treatment of IPF in the recent past have both increased the diagnosis rate in IPF cases and led to more IPF cases in the clinical practice of chest diseases. Although the emergence of new treatment options such as antifibrotic therapies in

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IPF is an important development, improving the quality of life is still important.

The aim of this study was to investigate whether there is any difference in quality of life parameters, presence of depression, sleep disturbances, and reflux symptoms among patients with IPF with and without cough.

2. MATERIALS AND METHODS

1.1. Study population

Twenty patients diagnosed with IPF who were admitted to Kocaeli University Medical Faculty Hospital Chest Diseases Clinic between February 2017 and July 2017 were included in the study. The study was approved by Kocaeli University Ethics Committee (Project No: 201/367). The study is planned according to the International Declaration of Helsinki. The patients were informed about the aim and methods of the study and written informed consent was obtained.

Inclusion and exclusion criteria are presented in Table 1.

Table 1.

Inclusion and exclusion criteria

Inclusion Criteria	Exclusion criteria
Age older than 18 years	Previous diagnosis of chronic airway disease such as COPD and asthma, and use of
IPF diagnosis according to ATS/ERS criteria without any exacerbation in the last three months,	Presence of active malignancy
No respiratory tract infection in the last month	Use of antitussive medication
No need for long-term oxygen therapy at home.	Use of gastric acid suppressant such as antacids, proton pump inhibitors, H2 receptor blockers in the last three months
	Angiotensin Converting Enzyme (ACE) inhibitors and beta-blockers in the last month.

2.2. Study plan

Demographic characteristics (age, gender, occupation, education level, smoking habits, history of comorbidities, occupational exposures, family history, symptom questioning, vaccine applications, diagnostic and therapeutic procedures) and anthropometric measurements (height, weight, body mass index) of patients who met the inclusion criteria (Table 1) and agreed to participate in the study by signing an informed consent form were evaluated. Detailed physical examinations were performed, and pathological findings, especially the presence of clubbed toe and fibrotic rale, were recorded. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m2).

Visual Analogue Scale (VAS) was used to evaluate the presence of cough symptom. The patients were asked to mark level of cough disturbance on a 100 mm scale; markings of 40 mm or less were classified as non-cough group whereas markings higher than 40 mm was defined as cough group.

Leicester Cough Questionnaire (LCQ), reflux symptom questionnaire, Beck depression questionnaire, St. George quality of life questionnaire (SGRQ) and sleep quality index were compared between the groups. In addition, GAP scores (Gender, Age, Physiological evaluation) were used as indicator of disease severity and risk of mortality.

2. Measurements

2.3.1. Pulmonary function tests

Pulmonary function test was performed according to ATS/ERS criteria and forced vital capacity (FVC), forced expiratory volume in 1

second (FEV1) and FEV1 / FVC levels were measured via a spirometer (ZAN™, Germany). After resting for 15 minutes, at least 3 tests were performed in the sitting position. The test was repeated for a maximum of eight maneuvers until three technically acceptable results were obtained. It was terminated if acceptable results could not be achieved despite 8 attemps or if the patient got tired. Diffusing capacity for carbonmonoxide (DLCO) was measured using the single-breath manuever.

2.3.2. Visual analog scale

The VAS scale is used to evaluate symptoms such as cough and pain that can not be measured numerically. The straight horizontal line with the length of 100 mm was used in this study. The two ends were defined as no-cough and the worst cough and the level for the presence of clinically significant cough was accepted as 40 mm.

2.3.3. Leicester cough questionnaire

Leicester cough questionnaire is a short, easy-to-perform questionnaire that is developed to investigate the effect of chronic cough on quality of life.[8]

2.3.4. Sleep, depression, reflux and quality of life surveys

Pittsburgh Sleep Quality Index (PSQI): It is a self-report questionnaire to assess sleep quality over one month period and consists of 19 items and 7 components which are subjective sleep quality, sleep latency, sleep time, habitual sleep efficiency, sleep disturbances, sleep medication use and daytime functions.[9]

Beck Depression Scale (BDS): It is a self-assessment inventory consisting of 21 questions developed to measure physical, emotional, cognitive and motivational symptoms of depression.[10]

St. George's Respiratory Questionnaire (SGRQ): The SGRQ consists of 50 items, within three sections representing the symptom, activity and impact domains.[11]

Reflux questionnaire (GERDQ): It is a self-administered tool that scores the frequency of six items (heartburn, regurgitation, dyspepsia, nausea, need for treatment and sleep disturbance) during the past 7 days according to a 4-point scale.[12]

2.3.5. GAP score

The GAP (Gender, Age, Physiology) model measures clinical and physiological variables to predict mortality in patients with IPF. There are four clinical variables; gender (woman: 0 points, man: 1 point), age (0–2 points), FVC (%) (0–2 points), and DLCO (%) (0–3 points) and three stages to predict mortality in GAP model. In the study of Ley et al, 1-year mortality of of GAP stage I, II and III were 6%, 16%, and 39%, respectively.[13]

2.4. Statistical analysis

Statistical analysis was performed with IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program. Normal distribution was assessed by Kolmogorov-Smirnov Test. Numerical variables with normal distribution were presented as mean ± standard deviation, numerical variables not showing normal distribution were given as median (25th - 75th percentile) and categorical variables as frequency (%). The difference between the groups was tested by independent samples t test for numerical variables with normal distribution, and with Mann Whitney U Test for numerical variables without normal distribution, and FisherExactkikare and Monte Carlo chi-square test for categorical variables. For the testing of bidirectional hypotheses, $p < 0.05$ was considered sufficient for statistical significance.

3. RESULTS

Totally 20 patients, 5 female (25%) and 15 male (75%), diagnosed as IPF according to ATS/ERS criteria were included in the study.[14] Patients were divided into two categories according to VAS scores as cough and non-cough groups. Cough group consisted of 11 patients (%55) who had a VAS score of 40 mm or higher. Demographic data and pulmonary function test parameters of the patients are shown in Table2. Gender distribution was similar between the groups.

Table 2.

Demographic data and pulmonary function test parameters of the patients

Gender	Female	5 (%25)
	Male	15 (%75)
Education level	Primary education	14 (%70)
	Middle School	-
	High school	1 (%5)
	University / College	1 (%5)
Smoking history	Current smoker	0
	Ex smoker	15 (%75)
	Non smoker	5 (%25)
Occupational exposure	(+)	20 (%100)
Family history	(+)	1 (%5)
Comorbidities	(+)	14 (%70)
Symptoms	Dyspnea	17 (%85)
	Cough	11 (%55)
	Gastro esophageal reflux	6 (%30)
Physical examination	Velcro crackles	20 (%100)
	Clubbing	7 (%35)
m MRC dyspnea score	1	4 (%20)
	2	8 (%40)
	3	8 (%40)
	4	-
Diagnostic assesment	Fiberoptic bronchoscopy	12 (%60)
	Surgical lung biopsy	4 (%20)
Treatment	Follow up without treatment	10 (%50)
	Pirfenidone	6 (%30)
	Nintedanib	4 (%20)

In cough group DLCO, FVC and FEV1 values were lower than the non-cough group however the difference was not statistically significant (Table 3).

Table 3.

Pulmonary function test parameters of the cases

Pulmonary function test	**VAS<40**	**VAS≥40**	**p**
FVC, L	2,24 ± 0,75	2,08 ± 0,58	0,6
FVC, %	66,17 ± 20,3	62,31 ± 11,43	0,6
FEV_1, L	1,98 ± 0,65	1,83 ± 0,44	0,5
FEV_1, %	71,43 ± 20,81	70,19 ± 12,68	0,9
FEV_1/FVC, %	87,80 ± 7,86	85,87 ± 8,03	0,6
DLCO, %	43,01 ± 15,39	34,73 ± 7,27	0,2

Leicester Cough Questionnaire, Gastroesophageal Reflux Questionnaire, Pittsburgh Sleep Quality Questionnaire, St. George Respiratory Questionnaire (SGRQ) and Beck Depression Questionnaire were applied to all patients who were divided into two groups according to VAS score (Group-1 VAS<40, Group-2 VAS≥40). The Leicester Cough Questionnaire score was higher in the non-cough group (111 ± 18.9 vs 86 ± 24.9). There was a correlation between VAS score and Leicester Cough Questionnaire (p=0.02). Apart from this, there was no statistically significant difference between the scores of the Beck Depression Questionnaire and the Pitsburgh Sleep Quality Questionnaire of the two groups (Table 4)

Table 4.

LCQ, BDI and Pittsburgh SQI results according to VAS

	VAS<40	**VAS≥40**	**p**
Leicester Cough Questionnaire	111,63 ± 18,87	86,11 ± 24,87	**0,02**
Beck Depression Questionnaire	18 ± 11,86	22 ± 10,74	0,4
Pitsburgh Sleep Quality Questionnaire	5,81 ± 6,27	10 ± 4,74	0,1

Patients were asked whether they had reflux symptoms and six of them (30%) responded positively. Patients also fulfilled the GERDQ and again no difference was found between the two groups (Table 4).

SGRQ symptom score was significantly higher in cough group. However activity, effect and total scores were not statistically significant between the two groups. (Table 5).

Table 5.

Reflux questionnaire and SGRQ results

	Median (25.-75. percentil)	**P value**
Reflux questionnaire	2,5 (0- 9,75)	0,9
SGRQ activity	874,1 (465,82-956,7)	0,8
SGRQ effect	872,6 (412,65 – 1299,15)	0,5
SGRQ symptom	344,8 (270,8 – 487,63)	**0,04**
SGRQ total scores	2106,5 (1214,85 – 2683,33)	0,6

There was no significant difference between the groups in terms of GAP scores. In the dominant cough group, 1 patient was evaluated as stage-1, 3 patients as stage-2 and 3 patients as stage-3. In the non-cough group, 3 patients were evaluated as stage-1, 3 patients as stage-2 and 3 patients as stage-3.

4. DISCUSSION

In this study, the presence of cough in IPF patients correlated with the Leicester Cough Questionnaire and the symptom domain of the SGRQ. In the cough group, pulmonary functions were lower, Beck depression scores were higher and sleep quality was lower but these differences did not reach statistical significance level.

Interstitial lung diseases consist of several diseases, ranging from simple inflammation to fibrosis, affecting lung parenchyma and airways. IPF is the most common subgroup among idiopathic interstitial pneumonias.[15] The most common symptoms are shortness of breath and dry cough and 70 to 85% of patients have cough at the time of diagnosis.[16,17]

In IPF patients, cough is generally dry and increases during exercise and speech and generally does not respond the treatment. In a previous study, the frequency of cough in patients with IPF was found to be 9.4 times per hour and frequent in daytime.[18] In this study 11 out of 20 (55%) patients had severe cough with a VAS score above 40 mm.

Since cough is a common symptom in the community, it is also important to identify pathologies that may cause of cough in IPF patients. Previous study by Madison JM et al. reported that half of the patients had additional factors that may be cause of cough symptom such as reflux, cough variant asthma, upper airway cough syndrome and medication.[19] Since we aimed to investigate cough associated with IPF, patients who had a history of comorbid disease

and/or medication that could cause cough were excluded from this study.

The Leicester Cough Cuestionnaire is a short, easy to apply and valid questionnaire developed to investigate the effect of chronic cough on quality of life.[8] In a study involving 19 patients investigating the frequency of cough and its effect on quality of life in IPF patients, it was shown that cough was a common symptom in IPF patients and VAS score and Leicester Cough Questionnaire were effective in determining the frequency of cough in these patients.[18] In our country, it was validated by Havlucu et al. with 100 patients and its validity and reliability in our language was shown.[20] In our study, patients were divided into two groups according to VAS score in terms of the presence of cough and Leicester Cough Questionnaire scores were found to be significantly different between the groups. It is thought that the Leicester questionnaire, which can be considered as a cough-specific quality of life questionnaire to show the effect of cough on quality of life in IPF, can be included in the routine clinical evaluation of these patients. It is thought that the use of this short, easy-to-administer and patient-administered questionnaire in the evaluation of cough will provide additional information in terms of the severity of this symptom and increase the physician's awareness of cough symptoms, leading to symptom palliation and thus improvement in the patient's quality of life indicators.

Gastroesophageal reflux is more common in IPF patients than in the normal population.[21] It is thought that there is a relationship between microaspirations caused by reflux and disease development. In a case-control study, erosive esophagitis secondary to reflux was reported to be associated with pulmonary fibrosis.[22] Although the mechanism of action has not been determined, there are several studies reported stable pulmonary function, lower number of attacks and prolonged survival in patients with IPF receiving proton-pump inhibitor (PPI).[21,23] However there are other studies reported no favorable effects in disease course with PPI moreover it is associated with increased frequency of lung infection.[24] Therefore routine use of PPI in patients with IPF is not recommended. In this study we have excluded patients with anti-reflux therapy considering this may affect cough frequency. Still %30 of the patients stated they had reflux symptoms and GERDQ scores showed impact of reflux in study population however there was no difference between the groups.

Since there is no quality of life questionnaire specific to IPF patients therefore we used SGRQ, a questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with respiratory disease. Dyspnea has been shown to be the most important symptom associated with deterioration of quality of life in patients with IPF.[11,25] According to the data obtained from the meta-analysis in which 60 studies were included in the literature, it was shown that there was a relationship between the decrease in quality of life and the severity of the disease in patients followed up with the diagnosis of interstitial lung disease. It was revealed that SGRQ scores increased as the severity of the disease increased.[26] In our study, it was seen that the symptom score of the SGRQ questionnaire was significantly higher in the group with cough than in the other group. However no differences were found in other domains.

Panic, anxiety and fear were reported to be common in patients with IPF. Studies related to depression and anxiety in these patients have shown that the Hospital Anxiety Depression (HADS) scale is significantly higher than the control group.[27,28] The frequency of long-term anxiety and depression was found to be higher in symptomatic IPF patients. In a study included 102 participants in Australia, patients were assessed by the Hospital Anxiety and Depression Scale and 20 of them (21%) had long-term anxiety.[29] Prolonged anxiety was associated with initial dyspnea, need for additional oxygen, presence of comorbidities and severe cough. Anxiety-related increase in HADS score was detected in 13% of the patients and this deterioration was attributed to an increase in cough severity and shortness of breath at 12-month follow-up. Prolonged depression was detected in 14 patients and multivariate analysis indicated that the increase in initial cough severity could be an independent

marker for depression. It was reported that a 10 mm increase in cough severity during follow-up increases the risk of long-term depression by 45%.[29] In our study, the mean Beck Depression Scale score was high in both groups suggesting moderate depression in the study population. Although there was no significant difference between the two groups, depression scores were higher in the group with cough symptoms. In IPF, especially in patients with higher symptom burden, depression and anxiety questioning is thought to be important in terms of increasing the compliance of patients to the treatment.

Mortality and morbidity in IPF is high and the average survival is between 2.3 and 3.5 years. Clinical course and prognosis may vary between individuals.[30] This causes difficulties in predicting prognosis and planning treatment. Therefore, prognostic factors such as age, sex and radiological evaluation have been tried to predict the clinical course of the disease.[31] Ley et al. developed a 4-parameter GAP score (Gender, Age, Physiological evaluation) in 2012 to predict disease prognosis.[32] In the study, which included 1262 patients the survival of patients in Group-3 was significantly lower than in Group-1 and Group-2. However, this study did not find any significant difference between cough and non-cough group which may be related to relatively low number of patients included in the study.

The study has some limitations. First, the study was a single centered and the number of patients was low. Second, the fact that some of the patients were on antifibrotic therapy might have affected the frequency of cough. However, since half of the patients were not receiving treatment and there was no difference between the groups in terms of treatment used, it was thought that treatment did not significantly affect the study findings.

As a result, it is found that presence of cough in patients with IPF negatively affected the quality of life and was associated with the sleep disorders and depression. Leicester cough questionnaire can be used to assess whether the cough symptom affects patients' quality of life in routine clinical evaluation of patients with IPF. This evaluation is thought to improve quality of life and treatment compliance by increasing cough palliation in IPF patients. There is a need for multicentre studies involving more patients.

Article Information Form

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Salih Küçük, İlknur Başyiğit, Serap Argun Barış and Haşim Boyacı. The first draft of the manuscript was written by Salih Küçük, İlknur Başyiğit, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

The Declaration of Conflict of Interest/ Common Interest

No conflict of interest or common interest has been declared by authors.

The Declaration of Ethics Committee Approval

The study was approved by Kocaeli University Ethics Committee (Project No: 201/367).

Artificial Intelligence Statement

No artificial intelligence tools were used while writing this article.

Copyright Statement

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