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Title: Diagnosis, management and attitudes about idiopathic pulmonary fibrosis among Turkish pulmonologists

Short title: Idiopathic pulmonary fibrosis survey-Turkey

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ABSTRACT

Objective: The aim of this study is to determine the approaches of Turkish pulmonologists to the diagnosis and treatment of patients with idiopathic pulmonary fibrosis (IPF) in daily clinical practice.

Material and methods: A questionnaire containing 38 questions about IPF diagnosis and treatment was applied to pulmonologists between 22-29 January 2018 and data of 158 physicians who responded to the questionnaire were evaluated.

Results: Results of this survey showed that mean number of patients that physicians follow-up and managed annually was 8.3 and 5 respectively. The mean symptom duration of the patients before the diagnosis was 9-12 months. Patients have been seen by average three physicians prior to confirmed diagnosis. Almost 80% of the physicians have opportunity to access a pathologist and radiologist who are specialized in IPF. However only 26% of them have opportunity to access regular multidisciplinary meetings. Although the most commonly prescribed drugs were antifibrotics, approximately 10% of patients were prescribed steroids, N-acetylcysteine and immunosuppressive drugs. Most of the physicians (81%) were aware of international guidelines however Turkish Thoracic Society Idiopathic Pulmonary Fibrosis Diagnosis and Treatment Consensus Report was read by only 41% of them.

Conclusion: This survey may lead to IPF awareness in Turkey, and may help closing the gaps on diagnosis and treatment.

KEYWORDS: idiopathic pulmonary fibrosis; survey; Turkey

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INTRODUCTION

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive disease of the lungs with irreversible fibrosis. The pathogenetic mechanisms are not fully explained [1, 2]. There is rapid loss of respiratory function and unpredictable prognosis. The average life expectancy of the patients is 3-5 years. There are serious problems in diagnosis and treatment of IPF.

IPF is an orphan disease with an estimated incidence in United States is between 6.8 and 8.8/100.000 [3, 4], in United Kingdom 2.85/100.000 [5]. In Turkey there is no data about incidence and prevalence of IPF but estimated incidence of all interstitial lung diseases is 25.8/100.000 [6].

In 2011, an international consensus report (by ATS / ERS / JTS / ALAT) and in 2018 a national consensus report by the Turkish Thoracic Society were published to standardize the diagnosis and treatment of IPF [7, 8]. According to these guidelines, high resolution computed tomography (HRCT) plays key role in the diagnosis of IPF. In HRCT, the diagnosis of IPF is made by the existence of usual interstitial pneumonia (UIP) pattern and after exclusion of known causes of interstitial lung disease. Surgical lung biopsy is recommended in patients with possible UIP pattern in HRCT. It is emphasized that multidisciplinary council meetings where clinical, radiological and pathological findings are discussed together are very important in the diagnosis of IPF.

Studies about the treatment of IPF have shown that steroids, N-acetylcysteine, anticoagulant and immunosuppressive drugs have no place in treatment. Currently antifibrotic drugs such as pirfenidone and nintedanib are recommended for the treatment of IPF [7, 9, 10].

MATERIALS AND METHODS

This study was planned and performed by the Turkish Thoracic Society Clinical Problems Study Group. This is a survey study performed on physicians. All of the physicians voluntarily gave their informed consent and answered the questionnaire sent by e-mail. The study was carried out according to the principles of the Declaration of Helsinki. Advancing IPF Research (AIR) Survey questionnaire used in European countries has been applied. The AIR Survey questionnaire consisted of 28 questions [11]. We added several questions to assess the approaches and attitudes of

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pulmonologist about IPF. The questionnaire consists of 38 questions relating to the diagnosis and treatment of IPF. The questions were about the approaches of physicians in daily clinical practice for the diagnosis and treatment of IPF. The questionnaire was sent by e-mail to the chest physicians who are listed in Turkish Thoracic Society database. Physicians were given a week between 22th and 29th of January 2018 to complete the questionnaire. The responses of the physicians who completed the questionnaire were analyzed.

RESULTS

Characteristics of respondents

At the end of the determined period, 247 physicians completed the questionnaire. The responses of 158 pulmonologists who followed at least one IPF patient are evaluated. More than half of the physicians participating in the survey were women (n=87, 55%) and 71 (45%) were men and 112 (71%) of them were older than 40 years of age. Most of the physicians were working in academic centers (n=124, 80%) and 34 physicians (20%) were working in non-academic hospitals.

The survey responses showed that the total number of IPF patients followed by respondents were about 940. The number of patients followed by each physician ranged from 2 to 200 (mean 8.3). Total number of patients who received treatment in the last year was 530, ranged 1 to 50 per physician. The average number of IPF patients treated by a physician per year is 5 (Table 1).

Diagnosis of IPF

Approximately two thirds of the survey respondents had access to a radiologist (71%) and a pathologist (67%) at their institution, but one third did not have this opportunity (Figure 1).

Multidisciplinary team (MDT) discussion including pulmonologist, radiologist and pathologist is crucial for the diagnosis of IPF. However, 26% of the respondents have regular MDT meetings, 36% have irregular and 38% have no MDT meeting (Figure 2).

The average symptom duration was 9-12 months before the diagnosis and patients were seen by average 3 physicians before the confirmed diagnosis of IPF. One third of the patients had been seen by four or more physicians (Figure 3).

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At the diagnosis of IPF almost all the physicians explored the occupational risk factors and 82% of them asked whether there is a family history of fibrotic interstitial lung disease or not. Genetic tests were performed by 20% of the physicians if there is a family history.

Only 15% of the physicians always perform bronchoalveolar lavage (BAL) examination in the diagnosis of IPF and 85% of them perform in only selected patients such as younger, non-smoker patients, patients with pre-diagnosis of hypersensitivity pneumonia and patients with possible UIP pattern in HRCT. The ratio of physicians who always recommend surgical lung biopsy for the diagnosis of IPF is 22%. Surgical biopsy is usually recommended in younger patients.

ATS / ERS / JRS / ALAT IPF guidelines were considered useful by 81% of physicians, while 16% stated that they did not read the guideline in detail. Only 41% of the physicians read the Turkish Thoracic Society IPF Consensus Report, 46% of them were aware of the report but they have not read yet and 13% have not heard about it.

IPF Treatment

IPF treatment decision was made on their own by 27%, discussing with other pulmonologist by 31% and multidisciplinary team discussion by 27% of respondents. The most commonly initiated treatments are pirfenidone and nintedanib.

Corticosteroids, NAC, immunosuppressive drugs are used alone or in combination in 10-15% of the patients (Figure 4).

For patients with the diagnosis of definite IPF; 68% of the physicians started the antifibrotic drugs early, 27% of them followed the progression of the disease for at least 3 months and decided to treat according to the progression of the disease. For the patients with the diagnosis of possible IPF, 18% of the physicians started treatment early, 67% followed the patients for at least 3 months and they started treatment according to the progression of the disease (Figure 5).

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Approximately 80% of physicians assess the progression of the disease by FVC, DLCO and 6 minutes walking test. Lung transplantation was performed to 17 of the patients who were followed-up by the physicians in this survey.

When IPF treatment is considered, 75% of physicians give priority to early diagnosis, 70% to effectiveness of treatment and monitoring of side effects, 61% to follow-up plan, 59% to reach a definitive diagnosis and 57% to treatment of comorbidities.

Comorbidities

Comorbidities are very common in IPF patients. The most common comorbidities were pulmonary hypertension, gastroesophageal reflux (GER), emphysema, cardiovascular diseases and lung cancer (Figure 6).

In patients diagnosed with IPF, 83% of the physicians always investigate the symptoms of GER. 26% of the respondents routinely treat GER whether the patients have GER symptoms or not, but 73% only treat patients with symptomatic or documented GER.

In patients with pulmonary hypertension, 11% of the physicians regularly treat pulmonary hypertension in patients with IPF, 41% treat occasionally and 48% never give any specific treatment for pulmonary hypertension.

DISCUSSION

This is the first survey to assess the attitudes and current approaches of Turkish pulmonologists about the diagnosis and management of IPF. With this survey we had the opportunity of comparing our results with other international surveys.

Seventy nine percent of respondents were working in university hospitals or in education hospitals of the ministry of health. Because of the difficulties in diagnosis and management of IPF, majority of the patients were followed by tertiary care settings and this may explain the higher rate of respondents from academic centers.

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The mean number of patients treated annually by each physician was five. Forty one percent of physicians report that they treat less than 5 patients per year and 51% of them treat between 5-20 patients. Similarly in Polish survey with 150 participants; 52% of the physicians managed less than 5 IPF patients per year and 9% of them manage more than 20 patients [12]. In Latin American survey the average number of IPF patients managed previous year was 13.8 [13]. In French survey the mean number of patients managed annually was 56 [14] and in European survey it was 39 [11]. The reason for this higher number of patients in France and Europe may be explained by that majority of the respondents in French and European survey was from IPF centers.

In order to reveal the awareness of participants about the national and international guidelines, our survey had several questions about the guidelines. Most of the respondents (81%) declared that they read the ATS/ERS/JRS/ ALAT IPF guidelines and considered it useful for the management of IPF. In contrast only 41% read, and another 46% was aware of but did not read the Turkish Thoracic Society IPF Consensus Report and 13% did not hear about the report. In our opinion, the reason for this was that the survey was done just a few months after the publication of the national consensus report so there was a very short period of time between the publication of national consensus report and the survey. We believe that future studies will reflect the actual usage of the national report more accurately.

At diagnosis 96% of physicians explore lung fibrosis in families of IPF patients, and perform genetic tests for %20 of those patients who have family history of fibrotic interstitial lung disease. In the European survey the rate of questioning of fibrotic disease in the family is 94% and 29% of them performing genetic tests [11]. This rate is 77% in French study [14]. Although there is no recommendation for genetic study in ATS / ERS / JRS / ALAT IPF guidelines, such high rates of genetic testing is surprising [15].

A patient who presented with symptoms compatible with IPF has a period of approximately one year before the confirmed diagnosis of IPF and every patient is seen by 3 physicians before the diagnosis. Similarly in the IPF survey conducted in Europe, it is stated that there is an average delay of one year for the diagnosis and the patients seen by two or more physicians prior to the diagnosis of IPF.

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In Turkey approximately 71% of the respondents have opportunity to access a radiologist and 67% to a pathologist in their institution. Access to radiologist and pathologist in Latin America is 39% and 28%, in France 63% and 66% and in Europe 85% and 74% respectively [11, 13, 14]. Although the higher availability and easy accessibility to radiologist and pathologist in our country we have two main problems in the diagnosis of IPF. First we have few numbers of experienced radiologist and pathologist in IPF, and the second is the inability in gathering a MDT. This results show us that only 26% of participating institutions have regular multidisciplinary meeting discussion. Nearly one third (36%) have irregular meetings and 38% have no MDT meeting in their hospitals. In French and European surveys the vast majority of IPF cases were diagnosed by multidisciplinary discussion. Only 7% of European responders and 3% of French pulmonologists reported that the diagnosis of IPF was made without multidisciplinary discussion [11, 14]. In Latin American survey access to multidisciplinary team was 41.1% among pulmonologist [13].

In Turkey IPF treatment decision was made alone by 27% of the physicians, 31% by consulting with other chest diseases specialists, and 27% by the multidisciplinary discussion. The rate of physicians who stated that they gave treatment decisions alone in Europe was 7% and in Latin America it was 20%. Treatment decision should be given by multidisciplinary council discussions, but the rate of making decision alone by a physician is quite high.

The most common initiated drugs for the treatment of IPF are antifibrotics. Most of the Turkish physicians (78%) reported that they prescribe pirfenidone as an antifibrotic and 50% nintedanib. The prescription rate of antifibrotic drugs was 81% in Europe, 60% in Latin America and 11% in Poland [11-13]. The low rate of prescription in Poland can be explained by the late reimbursement of these drugs for IPF. Corticosteroid therapy in monotherapy or in different combinations was recommended by 37% of respondents. Very similarly, 43%, 57% and 83% of the physicians from Poland, Europe and Latin America respectively prescribe corticosteroids alone or with combinations for treatment of IPF [11-13]. As mentioned in European survey report the possible reasons for prescription of non-antifibrotic drugs may be that in clinical practice such therapies demonstrate a benefit in some patients with conditions similar to IPF, or that the patients themselves may be reluctant to stop

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certain medications. Fifteen percent of responders tried immunosuppressive therapies before starting antifibrotic drugs in patients with possible IPF.

Early initiation of antifibrotic drug for treatment of IPF is recommended [16]. From the point of view of initiation time of antifibrotic drugs, 68% of physicians start treatment upon diagnosis irrespective of symptoms in patients with the diagnosis of definite IPF and 27% of the responders follow the patient at least 3 months to evaluate the progression of the disease and started treatment if progression occurs. In patients with the diagnosis of possible IPF, 18% of physicians initiate treatment early, 67% started after 3 months follow-up.

The most common reported comorbidities in patients with IPF are emphysema, GER, cardiovascular diseases and pulmonary hypertension. Most of physicians (83%) always ask the patient if they have GER symptoms. Twenty six percent of the physicians routinely treat GER irrespective of symptoms, but 73% of them treat only patients with symptoms. Regarding to pulmonary hypertension; 11% of the physicians regularly treat pulmonary hypertension. In European survey, this rate is 4% and in Latin America it is 50% [11, 13]. Although there is no recommendation for the treatment of pulmonary hypertension in the guidelines, it is also interesting that the rates of treatment are as high as 50% and there are significant differences between countries.

In summary, the results of this survey provide a snapshot showing the approaches of Turkish pulmonologists for the diagnosis and treatment of IPF in daily clinical practice. Majority of the Turkish pulmonologists are aware of the international guideline recommendations. Despite this awareness and despite having a new national consensus report there are gaps in diagnosis and treatment of IPF.

The study was carried out according to the principles of the Declaration of Helsinki.

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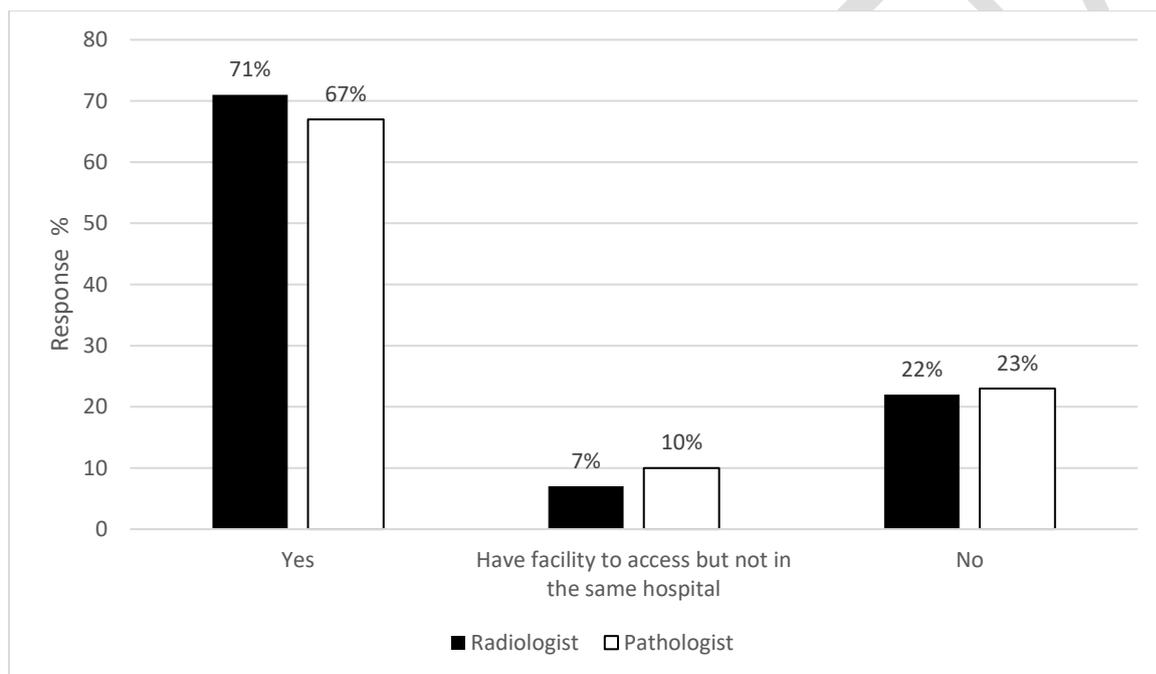
Table 1: Characteristics of the physicians participating in the survey

Questions	Responses	N	%
Gender	Female	87	55
	Male	71	45
Age	<30	1	1
	31-40	45	28
	41-50	62	39
	51-60	44	28
	>60	6	4
Institution	Public Hospital	17	10
	MH Academic Hospital	44	29
	University Hospital	80	51
	Private Hospital	17	10
Title	Specialist	57	36
	Assistant professor	13	8
	Associate professor	35	22
	Professor	53	34
Number of IPF patients treated by a physician in one year	<5	48	41
	6-20	59	51
	21-50	9	8
	>51	0	0

MH: Ministry of Health

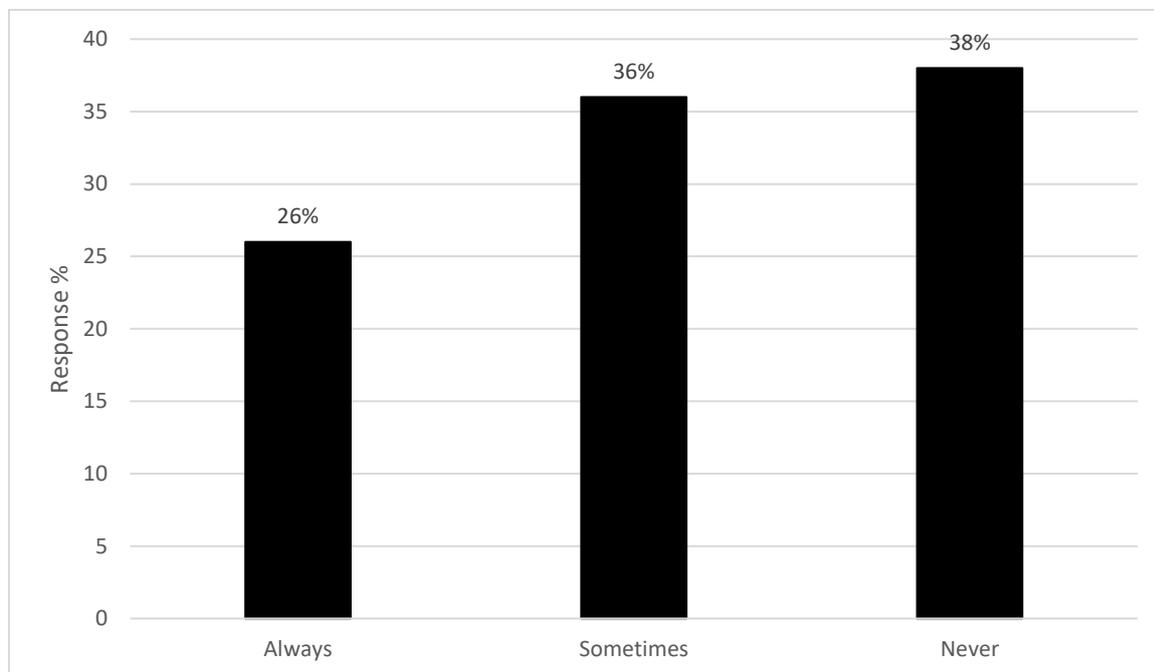
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Figure 1: Proportion of physicians with access to radiologist and pathologist



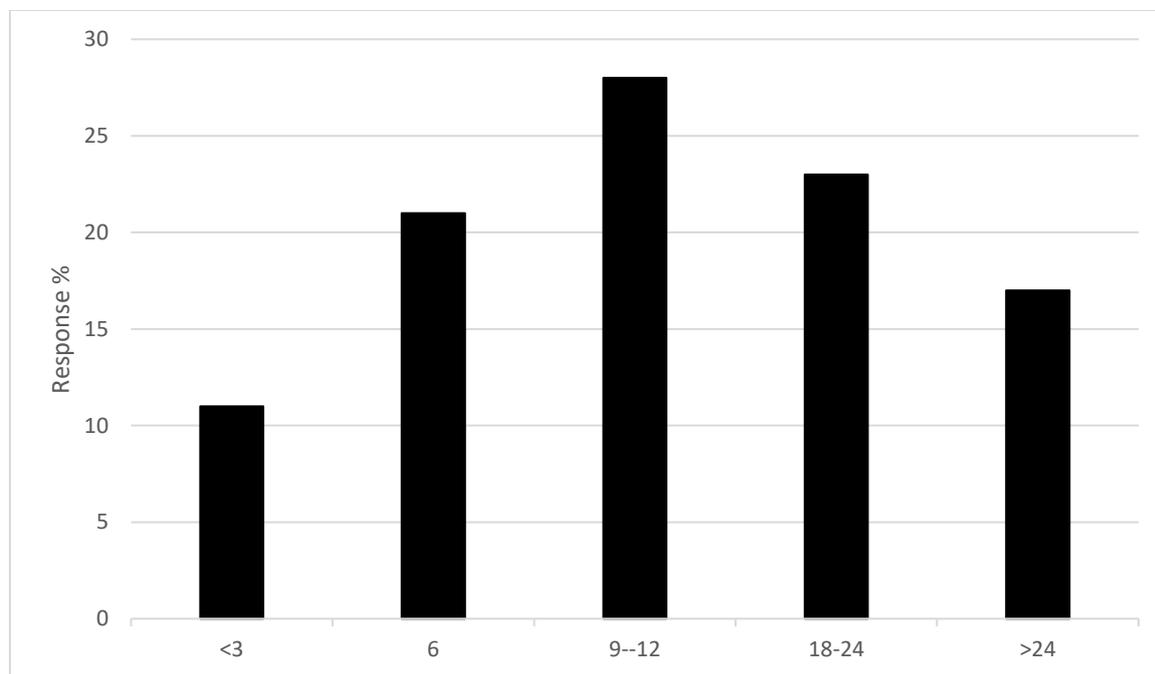
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Figure 2: Proportion of physicians with access to multidisciplinary discussion



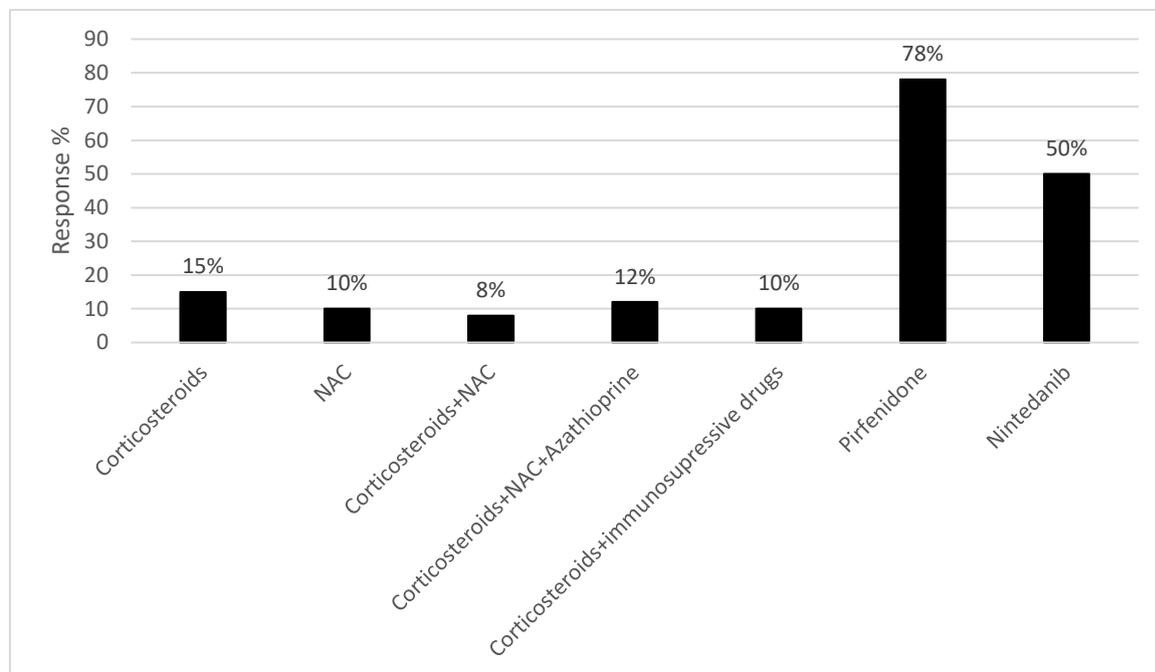
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Figure 3: Average symptom duration (months) before diagnosis of IPF



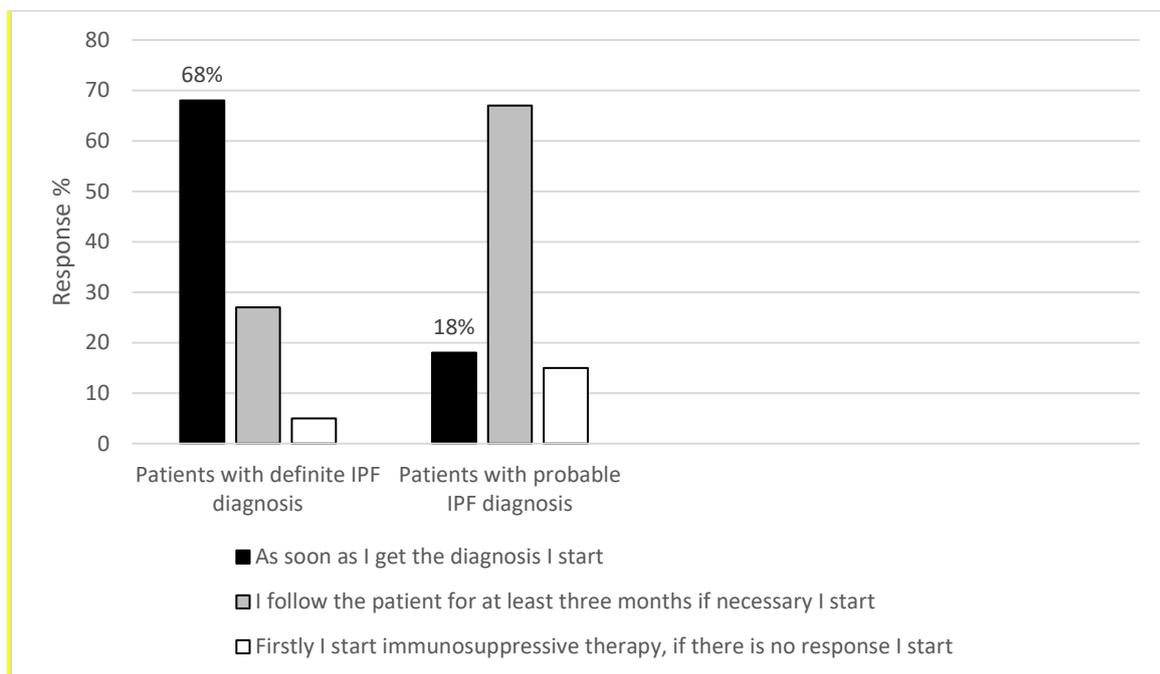
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Figure 4: Percentage of physicians who prescribe treatment for IPF



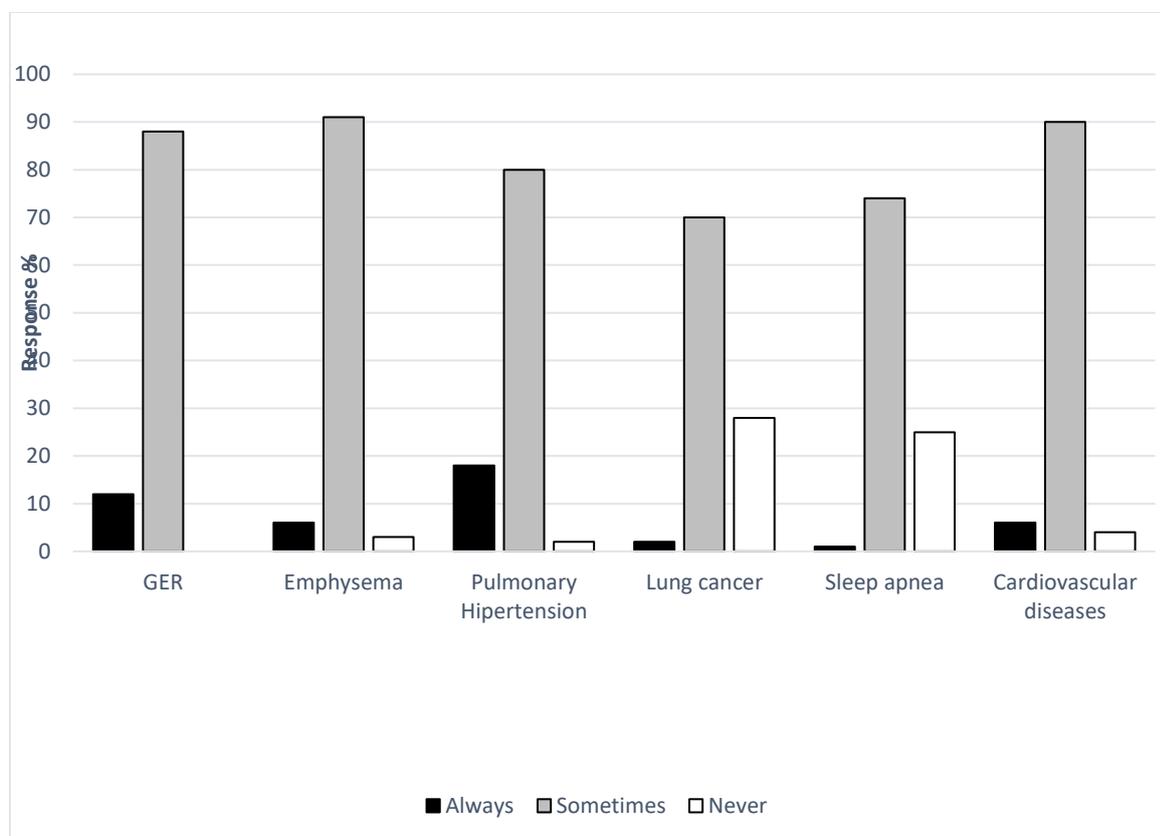
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Figure 5: Percentage of physicians who prescribe antifibrotic drugs for patients with definite and probable IPF



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Figure 6: The most common comorbidities in IPF patients



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