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Survey on the Influence of Living Environment Factors on Diagnosis of Idio-Pathic Pulmonary Fibrosis in Foshan

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ABSTRACT

Purpose of the study: (a) investigate the relationship between the time and diagnosis of IPF and its influencing factors, (b) provide information from patients' real-life diagnostic experiences for the devel-opment of more rational diagnostic pathways and the introduction of more treatment options and tech-nologies, and (c) improve the publics' awareness of IPF and promote the prevention of IPF.

Methods of investigation: A questionnaire was designed to survey 37 patients with IPF in January 2022, including general information questionnaires and age, sex, time for diagnosis, etc. Ridge regression analysis was used to explore the factors influencing the length and difficulty of IPF diagnosis. In addition, 11 respiratory physicians were interviewed by online interview about the difficulty of IPF diagnosis, treatment options, and patient prognosis.

Results: The stress caused by the lack of formal diagnosis ($B=0.617$, $p<0.001$), the high cost of the diag-nosis process ($B=0.509$, $p<0.001$), and the number of misdiagnoses or missed diagnoses ($B=0.177$, $p<0.005$) were significantly related to the length and difficulty of the IPF diagnosis ($p<0.05$).

Conclusions: The findings highlight the need for new appropriate, convenient, and economical diagnos-tic procedures to be developed and designed. Simultaneously, professionals should strengthen the dis-semination of disease understanding among the susceptible population, improve understanding and at-tention to the patients' condition, and conduct more lectures on the basics of avoiding IPF to strengthen the knowledge, which can effectively improve the mental quality of the susceptible population, in con-junction with the advice given by the doctors in the interviews.

Introduction

Idiopathic pulmonary fibrosis（IPF） is a fibrotic lung disease that is chronic and progressive with unknown cause. Idiopathic pulmonary fibrosis is mainly caused by excessive fibrosis of the interstitial tissue and continuous activation of mesenchymal cells due to repeated epithelial cell injury. During this process, the production of fibrotic mediators gradually reduces the ability of epithelial cells to absorb oxygen, resulting in death. IPF is pictured to own a frequency of 4 hundred instances per a hundred thousand humans and is bigger general in males than in females to a lower place the age of fifty(median age at analysis is re-garding sixty-five years.)(Richeldi et al., 2017) As age grow, the incidence and occurrence of IPF upward thrust enormously. Patients with IPF have a dismal prognosis, with survival travel significantly from af-fected patient to patient, with a median survival of 3-5 years barring therapy, which is decrease than many malignancies that have an effect on human beings with same demographics. Age, male sex, extra extreme dyspnea, and greater extreme bodily anomalies have been all linked to a terrible outcome. Mor-tality is appreciably linked to a range of factors, which include sex, age, and bodily anomalies.(Kim et al., 2015) Environmental exposure, smoking,

continual viral infections, and sure comorbidities are all acknowledged to have a position in the progression of IPF. The genetic hazard is that the most compelling of those.(Fingerlin et al., 2013) The exposure of some targeting lung epithelial cells in certain environment is also associated with an expanded threat of IPF, with smoking offering the most consistent evidence in each of the sporadic and familial instances.(Travis et al., 2013)

The most acceptable diagnosis of IPF still follows the following principles: the presence of common in-terstitial pneumonia (UIP) should be determined using HRCT (high resolution computed topography) in order to rule out the potential causes of ILD by asking detailed questions about medication history and environmental exposure at home, work, and other places that are frequently visited by the patient, and serological testing is strongly recommended to rule out connective tissue disease (CTD) as a potential cause of ILD. Surgical lung biopsy is frequently recommended when the features of HRCT are nondiagnos-tic. Surgical lung biopsy is usually avoided in more experienced patients, those with co-diagnoses, clinical-ly substantial physiological handicap. Surgical lung biopsy is usually avoided in more experienced patients, those with co-diagnoses, clinically substantial physiological handicap.(Fell et al., 2010) In summation, the key to the diagnosis and exclusion of other ILD or co-morbidities lies in the determination of multiple criteria including clinical features, lung histology, and chest imaging. The prognosis of IPF is often deter-mined after numerous conversations, adjustments, and determinations between multidisciplinary teams, combined with international standards.(Orens et al., 1995)

Management of patients with IPF focuses on improving symptoms, improving health, protecting lung function, minimizing adverse effects of treatment and improving survival.(Lamas et al., 2011) For phar-macotherapy, by using a large number of randomized trials, the 2015 International IPF Therapy Guide-lines excluded patients with corticosteroid, Azathioprine (an immunosuppressive), n-acetyl cysteine (NAC) and other drugs that lead to adverse clinical outcomes, and revolutionarily updated two modified thera-pies for idiopathic pulmonary fibrosis according to safety and efficacy in trials- pirfenidone and nintedanib.(Azuma et al., 2005; Richeldi et al., 2014)For non-pharmacotherapy, long-term oxygen therapy may be useful to patients given that many IPF patients experience a sharp drop in blood oxygen levels during strenuous exercise.(Raghu et al., 2014) In spite of the fact that 5-year survival for those with IPF after transplantation is generally 44%, lung transplantation is the as it were treatment that amplifies life in serious IPF. However, because of the lack of lung source and the uncertainty of the perfect minute for lung transplantation, there are very few patients who can get a lung transplant.

Currently, there are not enough relevant studies to explore the length of diagnosis and the difficulty of IPF and their influencing factors. This study aims to (a) investigate the relationship between the time to diagnosis of IPF and its influencing factors, (b) provide information from patients' real-life diagnostic ex-periences for the development of more rational diagnostic pathways and the introduction of more treat-ment options and technologies, and (c) improve the publics' awareness of IPF and promote the preven-tion of IPF.

Resources and Methods

Investigation Methods

Questionnaire: Self-designed and developed information questionnaire. In specific, the contents con-tain: age, sex, time for diagnosis, etc. Inclusion criteria：(a) People with clear mind and no communication difficulties; (b) Surveyors who have informed themselves and agreed to fill out the survey; (c) Age > 18.

Exclusion criteria for questionnaire: (a) people that do not have the habit of smoking; (b) No pollution factors such as dust, fumes, harmful gases or toxins in the working environment (Figure 1).

For questionnaire, strictly follow the inclusion and exclusion criteria for screening. To ensure the uni-formity and authenticity of the questionnaire, the questionnaires were filling out within half an hour. A total of 322

questionnaires were returned, of which the number of questionnaires that met the analysis requirements and passed the screening was 37, and the survey was conducted in January 2022.

Interviews: Interviews with professional respiratory physicians by way of interviews. Independent ques-tions about the difficulty of IPF diagnosis, treatment options, and patient prognosis have been asked, collected the responses given, and finally summarized and analyzed the answers given by different doc-tors.

Statistical Method

SPSS statistical software was used to analyze the data, and the measured data were expressed as mean ± standard deviation (X±SD), and the count data were expressed as [n (%)]. Ridge regression analysis was adopted to explore the relationship between the time to diagnosis of idiopathic pulmonary fibrosis and its influencing factors. $P < 0.05$ was considered a statistically significant difference. The K value for estima-tion is confirmed by the ridge trace plot. In this study, the K value is 0.2.

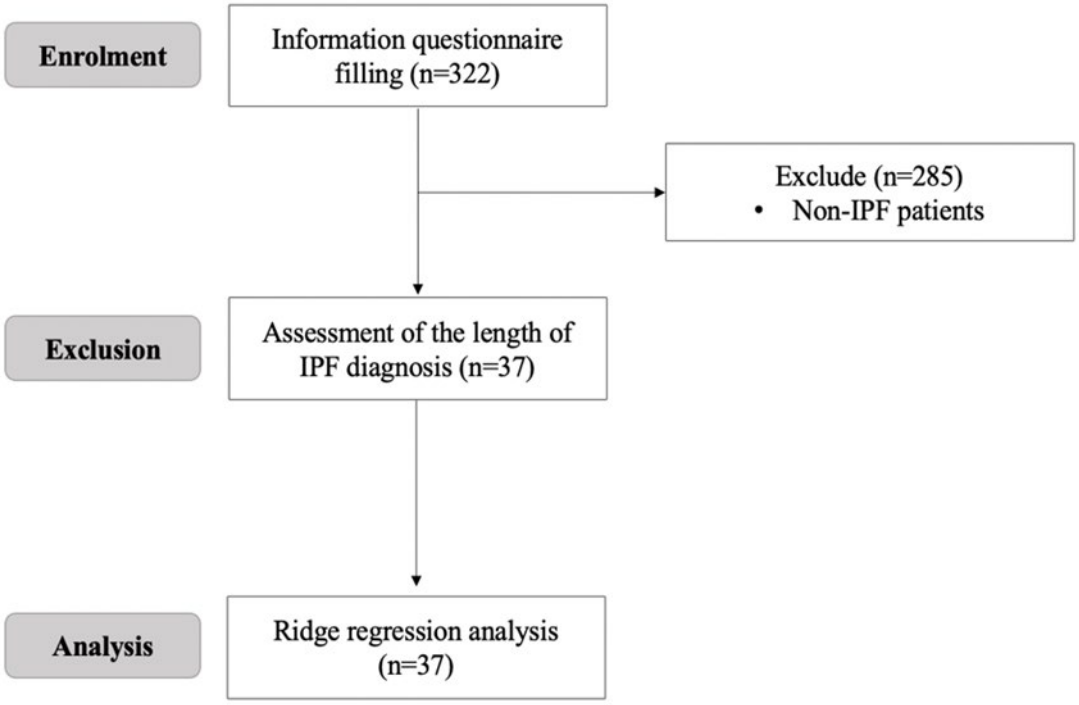

Figure 1. CONSORT flow diagram showing participant enrolment, exclusion, and assessment for the length of IPF diagnosis

Results

Demographic Characteristics

Table 1. and Figure 2. shows the participants' demographic characteristics

Table 1. Participants' demographic characteristics.

Baseline characteristic	Choices	Frequency	Percentage (%)	Cumulative percentage (%)
Gender	Male	23	62.16	62.16
	Female	14	37.84	100.00
Age (years)	<18	1	2.70	2.70
	18-54	35	94.59	97.30
	55-69	1	2.70	100.00
Profession	Engaged in farming/animal husbandry/agricultural production and processing	1	2.70	2.70
	Workers (construction site/machinery manufacturing/ore mining/metal smelting)	7	18.92	21.62
	Government Staff	7	18.92	40.54
	Corporate Staff	18	48.65	89.19
	Other	2	5.41	100.00
Smoking history (years)	More than 5 years	28	75.68	75.68
	Less than 5 years	6	16.22	91.89
	Do not smoking	3	8.11	100.00
Working environment	The presence of harmful dust, fumes, harmful gases or poisons in the work environment	25	67.57	67.57
	There are other special harsh environmental factors in the working environment, such as high heat and pressure	9	24.32	91.89
	Working environment is good	3	8.11	100.00
Total	31		100.0	100.0

The audience of this questionnaire is mainly middle-aged people aged 18-54, accounting for 94.59%. 62.14% of them are male. Most of the respondents were Corporate Staff, followed by government work-ers and construction workers. Also, 91.8% of the patients had a history of smoking, and 75.68%of them had a history of smoking for at least five years. This data set supports the significant role of smoking his-tory in the development of IPF. 91.8% of the questionnaires were filled out by people who reported the presence of risk factors such as hazardous dust, fumes, harmful gases or poisons, high heat and pressure in their work environment, indicating a significant effect of environmental factors on the development of IPF.

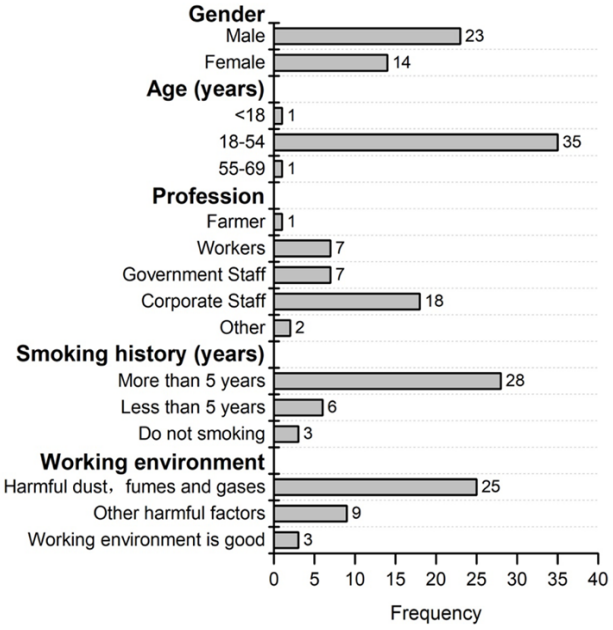

Figure 2. Participants' demographic characteristics. The data provide an initial indication of potential influencing factors for IPF: smoking history, poor working environment, and occupational exposure.

Multifactorial ridge regression analysis of factors influencing the length of IPF treatment

Using the length of IPF diagnosis as the dependent variable (in years), the single factor was assigned and then introduced into the ridge regression analysis, and the k-value was selected in conjunction with the ridge trace plot. The number of diagnoses, cost of diagnosis, and psychological stress were found to be influential factors on the length of IPF diagnosis ($p<0.05$). Details are shown in Table 2.

Table 2. Multifactorial ridge regression analysis of factors influencing the length of IPF treatment.

	Unstandardized Coefficients		**Standardized Coefficients**	**t**	**p**	**R^2**	**Adjusted R^2**	**F**
	B	*Standard Error*	*Beta*					
Constant	1.404	0.786	-	1.786	0.084			
Number of diagnoses	0.177	0.066	0.225	2.676	0.012*			
Cost of various diagnostic tests	0.509	0.128	0.275	3.968	0.000**			
Smoking history (more than 5 years)	0.216	0.323	0.048	0.668	0.509			
Psychological stress	0.617	0.116	0.354	5.301	0.000**	0.779	0.735	F (6,30) =17.657, p=0.000
Harsh working environment (toxic gases, high temperature and pressure, etc.)	-0.048	0.321	-0.011	-0.149	0.883			
Basic understanding of IPF	-0.292	0.419	-0.051	-0.697	0.491			

Dependent Variable: How long did it take from the first appearance of symptoms associated with interstitial pneumonia to the diagnosis of idiopathic pulmonary fibrosis (IPF)?

* $p<0.05$, ** $p<0.01$

Table 3. Topics and questions of structured interview.

Topic	Questions
Diagnosis	1. Do you agree with the following: IPF Patients are difficult to diagnose, easily misdiagnosed and delayed?
	2. How long does a patient with IPF typically experience from the first onset of symptoms to the final diagnosis?
	3. IPF Is there a possibility of misdiagnosis or omission in the process of seeking medical diagnosis for patients?
	4. Do you think doctors would choose HRCT (High Resolution CT) as an aid in diagnosing IPF or related diseases?
	5. Do you think HRCT (High Resolution CT) has helped doctors diagnose IPF?
Treatment	6. What is the typical treatment option doctors choose for ILDs disease such as AE-IPF (Acute Exacerbation IPF)?
	7. What could be the reason why you choose not to undergo treatment?
	8. In patients with AE-IPF (acute exacerbation of idiopathic pulmonary fibrosis), do you continue, long-term treatment with glucocorticosteroids or Mycophenolate Mofetil?
	9. Do you choose to proactively administer antifibrotic drugs at the first sign of a patient's PF-ILD (progressive fibrotic ILD) diagnosis?
Risk factor	10. Which of the following options or options would you choose as a prevention strategy for AE-IPF (Acute Exacerbation of IPF)?
	11. What do you think is the biggest problem with the diagnosis of IPF patients at the moment?
	12. What do you think are the most important causative, pathogenic factors for ILDs (acute interstitial lung diseases) at this time?
	13. What do you think is the biggest difficulty for IPF patients (e.g., living, finances, mental health, etc.)?
	14. What advice do you have for IPF patients and susceptible people to improve their quality of life and prevent the disease?

Structured Interview

11 respiratory physicians answer opened-up questions about the current situation for the diagnosis of IPF and the prognosis of patient (Table 3).

Diagnosis

All physicians interviewed agreed that IPF patients are difficult to diagnose, easily misdiagnosed, and delayed. 7 of 11 doctors implies that biggest problem in the diagnosis of IPF patients is that the etiology is not easy to diagnose, in other words, the differential diagnosis with other pneumonia is difficult. For the number of misdiagnoses, eight physicians believe that depending on the complexity of the patient's own condition, the diagnosis of IPF will typically experience 1-2 misdiagnoses. 2 physicians believed that the number of misdiagnoses would typically reach 4 or more. One physician thought there would be no misdiagnosis. All respondents agreed that HRCT (high resolution CT) is extremely helpful in the diagnosis of IPF. Three of the physicians thought that HRCT was not sufficiently prevalent in non-first tier cities.

Risk Factors

5 of 11 doctors contends that the most important risk factors for IPF are environmental exposure (smok-ing, dust, harmful gases, livestock hair, etc.). The second most common cause was viral infection, held by four of the 11 people interviewed. For the risk factors of patients with AE-IPF (acute exacerbation of IPF), there was little agreement among the answers of the 11 surveyed physicians, but they could be roughly divided into in-fections caused by occupational exposure, genetic factors, the complexity of the disease itself, and respiratory failure. Among all these factors, infections caused by occupational exposure is the answer that more physicians gave. In addition to this, two doctors gave the answer of respiratory failure.

Difficulties

On the topic of the biggest problems faced by IPF patients, 3 doctors identified the financial pressure of treat-ment as the most significant difficulty faced by patients, 3 doctors identified the ability to live a normal life after the disease as the biggest difficulty faced by patients, and 2 doctors identified the psy-chological pressure of not being able to cure the disease completely as the most significant difficulty faced by patients. The remain-ing three doctors believed that the difficulties experienced by IPF patients could not be explained in a single way but were the result of the interaction of multiple factors.

Treatments

For patients with AE-IPF (acute exacerbation of idiopathic pulmonary fibrosis), four physicians indicated con-tinued, long-term treatment with glucocorticoids or Mycophenolate Mofetil, and seven indicated that although they would choose glucocorticoids or Mycophenolate Mofetil, they would not use them for long periods of time.

Also, 4 doctors did not choose to continue treatment if the patient was treatment intolerant or did not respond to treatment, and 2 doctors thought that they should try to get treatment regardless of the con-dition (Figure 3)

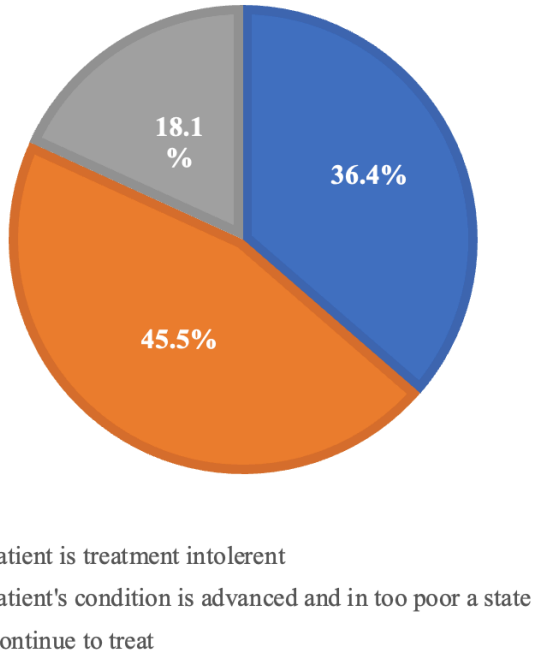

Figure 3. Reasons for not continuing treatment. A large proportion of physicians choose not to continue treat-ment for various reasons, demonstrating a bias in physicians' understanding of IPF

Suggestions

To improve the quality of life of IPF patients, 11 interviewed physicians gave their advice. All doctors suggested that self-protection should be taken to prevent colds. Also improve the working and living envi-ronment to ensure air quality and stay away from occupational exposure. Among them, four doctors thought that patients should pay attention to improving their lifestyle, eating less spicy and oily food, not staying up late, and having a balanced diet. Also quit smoking and alcohol. One doctor pointed out that patients need long-term oxygen therapy at home.

Discussion

IPF is a serious threat to the life and health of patients, with a median survival of only 3-5 years.(Richeldi et al., 2014) There is no effective treatment to reverse the progression of fibrosis.(Somogyi et al., 2019) Patients with IPF are managed with the goal of relieving symptoms, increasing health, protecting lung function, minimizing therapy side effects, and, ideally, improving survival.(Noth et al., 2012) The difficulty of diagnosis of IPF makes it hard for patients to receive effective treatment in time, which ultimately re-duces survival.

This study shows the relationship between the time to diagnosis of IPF and its influencing factors. Also hope to demonstrate the difficulty of diagnosis of IPF through the perspective of patients with IPF. Based on the results of ridge regression, we found that the psychological stress caused by uncertainty about one's illness before being diagnosed is positively related to the time for diagnosis ($B=0.617$, $p<0.001$). In fact, this was found to be the strongest factor that contribute to the time spend on the diagnosis of IPF. That is, compared to all the other variables in the model, it accounted for the most variance in the time spend on the diagnosis of IPF. This suggests that whether the prices of various diagnostic processes in-volved in the future IPF are easy to bear determines the diagnostic difficulty of IPF to a certain extent, that is, the time it takes. The result also indicate that the cost incurred in the diagnosis process is posi-tively related to the duration of diagnosis ($B=0.509$, $p<0.001$). In other words, due to the fact that IPF is prone to misdiagnosis and missed diagnosis, patients are prone to have negative psychology in the diag-nosis process, which leads to increased psychological stress. This increase in psychological stress will then lead to an increase in diagnostic time. The reason for this phenomenon may be due to the fact that the increased psychological stress of patients can lead to a vicious cycle in which patients face diagnostic tests in a more negative posture during various diagnostic procedures, and even avoid testing and diagnosis to some extent. Further, the number of diagnoses before formal diagnosis of IPF was identified to be posi-tively associated with the diagnostic time for IPF ($B=0.177$, $p<0.005$).

Surprisingly, there was no significant relationship between smoking history and the length of time to diagnosis of IPF（$B=0.216$, $p=0.479$）. Similar results were found for the impact of a harsh working environment ($B=-0.048$, $p=0.883$) and basic knowledge of IPF ($B=-0.292$, $p=0.491$) on the length of treatment for IPF. The data suggest that the increased risk of IPF from occupational exposure and a history of smok-ing does not appear to increase the difficulty or length of diagnosis.

This is contrary to the results obtained from interviews with medical professionals. The phenomenon may be due to several reasons. (a) Ridge regression model itself may have deviation, that is, the error between mathematical model and practical problems may occur. (b) Questionnaire data may be prob-lematic. Bias can find its way into any research program. In this study, habituation may be the reason that leads to this bias. Respondents give the same answers to questions that are phrased similarly in cases of habituation bias. This is a physiologic response: it takes a lot of energy to be responsive and pay attention. Our brains habituate or go on autopilot to save energy. Respondents frequently display signs of exhaus-tion, such as remarking on how repetitive the questions are or giving similar responses to many ques-tions(Sarniak, 2015). In this study, there were five questions addressing environmental factors and smoking history, which inevitably overlapped to some extent. And this overlap led to a certain amount of inertia among the questionnaire completers, so that they may not have paid attention to the differences between the questions and still gave similar responses. This affects

the quality of the data and leads to bias in the results of the ridge regression analysis. At the same time, this deviation may also lead by the Question-order bias. Question-order bias occurs when one question influences the replies to following questions. The words and concepts offered in questions prime respondents, influencing their thoughts, feelings, and attitudes in following inquiries. The unreasonable order in which the questionnaire questions were asked in this study may have led to unsatisfactory questionnaire data(Qualtrics). The perceived sta-tistics results result explained a significant proportion of variance in the regression model ($R2=0.735$, $F(6,30)=17.657$, $p<0.01$). The results of the analysis are presented in Table 1.

In addition to the study of IPF patients, this interview with professional physicians once again demon-strates the great difficulty of diagnosing and treating IPF. This interview also shows the current challenges and opportunities facing IPF. In the question "What do you think is the biggest problem in the diagnosis of IPF patients today?" seven physicians demonstrated their concern about the similarity of the clinical course of all fibrotic ILDs. This is even more important in IPF, the interstitial lung disease with the highest morbidity and mortality(KENT A. GRIFFITH & ENRIGHT, 1999). The natural course and outcome of IPF varies widely among individuals and is difficult to predict. Some patients progress more rapidly, experi-encing one or several acute exacerbations and progressing to respiratory failure or death. And worryingly, excluding IPF, there are many other diseases with equally poor prognosis and similar nature of lesions. Based on an online survey of 486 internists from the United States, Japan, Germany, France, Italy, Spain, and the United Kingdom, 18%-32% of non-IPF ILDs will develop a progressive fibrosis phenotype. And some CTD-ILD patients develop progressive fibrosis in more than a quarter of them, with RA-ILD (rheu-matoid arthritis-associated interstitial pneumonia) and SSc-ILD (systemic sclerosis-associated interstitial lung disease) as representatives(Raghu et al., 2011).

All 11 physicians agreed that patients with IPF are difficult to diagnose. This is consistent with the re-sults presented in the questionnaire study. This demonstrates the reality that IPF patients are difficult to diagnose and face difficulties. At the same time, one study showed that approximately 25-50% of patients with ILD are currently not receiving adequate pharmacological medication. As for the reasons for not re-ceiving treatment, this study showed that the percentage of reasons why respiratory physicians believe that patients do not need treatment in advanced stages, have mild disease, are intolerant to treatment, and have no effective treatment options are 45%, 34%, 45%, 33%. The percentages of rheumatologists who thought patients were mildly ill, slow to progress, intolerant of treatment and had no effective treatment were 49%, 37%, 34%, and 32%, respectively(Jain & Lethagen, 2020). This data is similar to the results obtained from the interviews conducted in this study. In this study, the percentages of doctors interviewed who believed that patients were intolerant of treatment and had no effective treatment in the late stages were 36% and 45%, respectively. At the same time, 38% of the physicians interviewed cited mild disease as a reason for not treating patients.

In fact, Professor Luo qun, head of the interstitial lung disease subspecialty group of the Department of Respiratory and Critical Care Medicine, First Hospital of Guangzhou Medical University, said in the 4th ILD Innovation Leading Development Forum that these reasons are actually not reasonable enough. In other words, most of these reasons are caused by the incorrect perception of doctors. In response to the idea that patients cannot tolerate treatment, Prof. Luo qun said that although some people will have side ef-fects from either Pirfenidone or Nintedanib, these side effects are manageable. The most common side effect of Nintedanib, for example, is diarrhea, but according to available data, all diarrhea is manageable. So, there will not be so many patients who cannot tolerate the treatment. At the same time, Prof. Luo qun said that slow disease progression should not be a reason not to receive treatment. On the contrary, timely treatment and timely intervention may lead to better results. Current research suggests that the vast majority of patients with IPF continue to be treated early with hormones and immunosuppressive drugs. However, when patients develop fibrosis, some physicians continue to use anti-inflammatory therapy and do not choose to actively intervene in the fibrotic component. This is consistent with the responses given by the physicians in the interviews. 4 physicians indicated that they would choose to use anti-inflammatory drugs such as glucocorticoids for a long time. Current research suggests

that antifi-brotic drugs, if proven effective and safe, should be administered immediately after a patient is diagnosed with PF-ILD(Wu et al., 2019). This treatment approach has been agreed upon by several experts. This demonstrates the current barrier to understanding IPF by some physicians.

Conclusion

Both studies of IPF patients and interviews with respiratory physicians have very clearly demonstrated the current difficulties in the diagnosis and treatment of IPF. Among them, financial stress, psychological stress and the number of misdiagnoses and missed diagnoses are significantly related to the time and difficulty of IPF diagnosis for patients. This demonstrates the need to develop and design more reasona-ble, convenient, and affordable diagnostic methods. At the same time, in conjunction with the advice given by the doctors in the interviews, professionals should strengthen the dissemination of knowledge about the disease among the susceptible population, enhance the understanding and attention to the patients' condition, and conduct more lectures on the basics of avoiding IPF to strengthen the knowledge, which can effectively improve the mental quality of the susceptible population. For physicians, it is clear from this study that some physicians still have some outdated ideas about the accurate use of drugs and the selection of appropriate treatment options. Physicians should aim to improve patient survival and quality of life by actively following up on the latest research and proactively adjusting treatment plans.

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