Idiopathic Pulmonary Fibrosis (IPF) Treatment and Prognosis: A Comprehensive Review

Mohammed Ali Alshahrani, Mosa Theeban Al Garni, Yousef Ali Alzamil, Khaled Jobran Alshahrani, Mohammed Saad Alahmari, Abdullah Ahmed Albeair, Mohammed Abdullah Alamri, Eyad Hassan Jaber Alkadi, Mohammed Moshabbab Alahmari

Respiratory therapist, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia

Abstract: Idiopathic pulmonary fibrosis (IPF), a devastating progressive interstitial lung disease (ILD) with no known cause, is the most common and deadly of the idiopathic interstitial pneumonias. With a median survival of 3–5 years following diagnosis, IPF is characterized by a progressive decline in lung function and quality of life in most patients. Prognostic factors recognized classically that influence mortality include functional, clinical and radiological parameters. However, in recent years, there has also been progress in the knowledge of genetic factors and biomarkers that may be useful in the prognostic evaluation of these patients. On the other hand, the monitoring of the disease throughout its evolution is key to improving the prognosis of the patients, as it allows for taking therapeutic measures based on this evolution, even early remission for lung transplantation. This article reviews the main prognostic factors of the disease, as well as the most useful way to monitor the disease follow-up.

Keywords: idiopathic pulmonary fibrosis, prognostic factors, treatment, monitoring, follow-up

1. Introduction

Idiopathic pulmonary fibrosis is a type of chronic, progressive fibrosing interstitial pneumonia with a poor prognosis, primarily affecting older adults. The disease is characterized by an aberrant deposition of extracellular matrix, leading to extensive remodeling of the lung parenchyma. Patients suffering from this condition experience a gradual decline in pulmonary function, typically resulting in respiratory failure and death within a median survival time of only 2-3 years post-diagnosis [1]. The etiology remains elusive, rendering it a challenging condition to diagnose and manage effectively [2]. This review aims to provide a comprehensive overview of the treatment strategies and prognosis for patients with idiopathic pulmonary fibrosis, focusing on advancements in understanding this disease, recent research findings, and implications for clinical practice.

The pathogenesis of idiopathic pulmonary fibrosis is multifactorial, involving genetic predispositions, environmental factors, and immunological responses. Abnormal wound healing responses after alveolar epithelial injury appear to play a critical role in disease progression. Research has indicated that epithelial cells in the lungs are injured by factors such as cigarette smoke and viral infections, which can trigger an inappropriate repair response leading to fibrotic changes. The role of immune cells, particularly macrophages, has also been emphasized, where monocyte-derived alveolar macrophages persist in the fibrotic lung environment and promote fibrosis through the release of profibrotic mediators. New insights into the relationship between microbiota and lung health have emerged, linking dysbiosis to inflammation and fibrotic processes in the lungs [3].

Despite recent advances in pharmacological treatments, there is no definitive cure for idiopathic pulmonary fibrosis. Treatment options largely focus on slowing disease progression and providing symptomatic relief. The advent of antifibrotic drugs represents a significant breakthrough in managing this condition, improving outcomes by reducing the decline in lung function. Lung transplantation remains the most definitive treatment for patients with advanced idiopathic pulmonary fibrosis, yet it is burdened by limitations including donor shortages and postoperative complications. As the

understanding of this condition continues to evolve, there is a pressing need for further research into novel therapeutic targets and biomarkers that could enhance personalized care for individuals affected by this devastating disease [4].

Epidemiology

IPF is the most common form of ILD. Reported incidence rates for IPF vary considerably depending on the method of data collection and diagnostic case definition. A systematic review of the global incidence of IPF estimated a rate of 2.8–9.3 per 100,000 per year in North America and Europe with significantly lower rates in Asia and South America. Regional variation within countries has also been observed, possibly reflecting exposure to environmental or occupational risk factors [5]. Evidence suggests that the incidence of IPF is rising. A recent analysis of a UK-based primary care data-base calculated a rise in incidence of 78% between 2000 and 2012, as well as a doubling of prevalence, estimated at 38.8 per 100,000 [6], with the consequential growing economic burden on global health care.

Mortality in IPF is high, with a reported median survival of 2–3 years from diagnosis, based on historical data. More recent evidence shows no improvement in survival. Mortality rates also appear to be rising, although this may partly reflect increased recognition and diagnosis. Over the last five years, antifibrotic therapies have become increasingly available, and at present the global impact of this on survival in IPF is unclear. Early evidence from an open label extension of the pirfenidone clinical trials reported an on-treatment median survival of 77.2 months. It is well recognised that IPF is a heterogeneous disease with a variable disease course. Predicting disease outcomes is difficult, particularly as baseline lung function alone is a poor predictor of mortality. Composite scoring systems, such as the Gender-Age-Physiology (GAP) index, which include demographic and physiological parameters, may offer better prognostic accuracy [7].

Diagnosis

Diagnosis of idiopathic pulmonary fibrosis presents a unique array of challenges. The integration of clinical, radiological, and histopathological findings is vital for an accurate diagnosis. High-resolution computed tomography plays a pivotal role in identifying patterns consistent with usual interstitial pneumonia. The identification of honeycombing and reticular opacities on HRCT scans is classically associated with this condition, and these imaging findings are critical in the diagnostic algorithm. According to the relevant guidelines, a multidisciplinary approach involving pulmonologists, radiologists, and pathologists has been recommended to enhance diagnostic accuracy [8].

Clinical criteria for diagnosing idiopathic pulmonary fibrosis also include the exclusion of other known causes of interstitial lung disease, such as connective tissue disease, drug toxicity, and occupational exposures. A thorough patient history is essential, particularly considering the associations between environmental exposures, such as smoking and this condition. Familial pulmonary fibrosis has been identified as a significant risk factor, which highlights the genetic component that practitioners should consider during initial assessments [9].

Despite these diagnostic advancements, many patients may still face a prolonged period before receiving a definitive diagnosis. A substantial overlap of clinical features among different interstitial lung diseases can lead to misdiagnosis or delayed diagnosis, which can significantly impact prognosis. Additionally, the disease course may include episodes of acute exacerbation, contributing to the overall complexity of managing and diagnosing idiopathic pulmonary fibrosis. Furthermore, recent studies are investigating the role of novel biomarkers identified through machine learning and other methodologies to improve the diagnostic capabilities for this condition. The identification of specific serum biomarkers that correlate with disease severity or predict progression could greatly aid clinicians in tailoring individualized management plans for their patients [10].

Pathogenesis

Understanding the pathogenesis of idiopathic pulmonary fibrosis is crucial for developing targeted therapies. The complex interplay of genetic susceptibility, environmental triggers, and a dysregulated immune response has been highlighted in recent studies. Alveolar epithelial injury, whether due to environmental factors like smoking, viral infections, or genetic predispositions, induces a pathological healing response characterized by excessive fibroblast activation and collagen deposition [11].

The role of cytokines, particularly transforming growth factor-beta, is central to the fibrotic process. This factor facilitates the activation of fibroblasts into myofibroblasts, which are responsible for the

excessive extracellular matrix production seen in fibrosis. Furthermore, abnormalities in cellular signaling pathways have been implicated in promoting fibrosis. It has been observed that monocyte-derived alveolar macrophages persist in fibrotic lungs and secrete pro-inflammatory cytokines and proteases that further exacerbate lung tissue damage [12].

Emerging research has provided insights into the contributions of innate immunity to idiopathic pulmonary fibrosis. Disruptions in the homeostasis of immune cells within the lungs can lead to an exaggerated inflammatory response, contributing to lung fibrosis. In patients with this condition, an increase in CD8+ T cells has been noted, indicating a reactive immune profile. The role of the microbiome in modulating immune responses and influencing lung health presents another exciting avenue of research, where dysbiosis may propagate chronic inflammatory conditions leading to fibrosis [13].

Additionally, the genetic basis of idiopathic pulmonary fibrosis is becoming clearer with the identification of various mutations associated with familial forms of the disease. These findings suggest that some patients may have an inherited predisposition to the disease, highlighting the need for genetic counseling and targeted therapies.

Disease progression

IPF progresses heterogeneously. The best method of determining progression is to identify a decline in FVC (forced vital capacity). Regular lung function checks to measure vital and diffusing capacity are therefore recommended at intervals of three to six months. Functionally stable patients show decline in FVC of a maximum of 5% of the target value over 6 to 12 months. A decline in FVC of 5 to 10 percentage points indicates prognostically relevant progression, while a decline of 10 percentage points or more in six months is associated with a fourfold to eightfold increase in the risk of death in the next 12 months [14].

Acute exacerbations are an important aspect of the clinical progression of IPF. These are characterized by an increase in shortness of breath over a period of 30 days and a high-resolution computed tomography (HRCT) showing new infiltration of the lungs with no identifiable cause. Their frequency is 5 to 15% per year and they are associated with high mortality. Following an acute exacerbation of IPF approximately 50% of patients die within three months, and approximately 80 to 90% within 12 months [15].

Treatment

The treatment approach to IPF has evolved considerably over the last two decades. A typical regimen in the year 2000 involved immunosuppression with prednisolone and azathioprine (2000). The Idiopathic Pulmonary Fibrosis International Group Exploring N-Acetylcysteine I Annual (IFIGENIA) study [16], published in 2005 suggested that the addition of N-acetylcysteine (NAC), an anti-oxidant compound, to this combination would help to preserve lung function. However, the Prednisolone, Azathioprine, and N-Acetylcysteine: A Study That Evaluates Response (PANTHER) study [17] found that patients taking this triple combination therapy were at increased risk of death and hospitalisation compared to patients receiving placebo alone. Furthermore, as compared with placebo, NAC in isolation offered no significant benefit with respect to the preservation of forced vital capacity (FVC) in patients with IPF compared to placebo [18]. This led to a shift away from immunosuppression and NAC, leaving a treatment gap with no apparent effective option available. However, over the last 5 years, two novel antifibrotic therapies, pirfenidone and nintedanib, have been developed, providing treatment options for many patients with IPF [19].

Pirfenidone is a novel compound with anti-inflammatory and anti-fibrotic properties [19]. Early phase II and III studies in Japan identified it as a potential therapeutic option in IPF [20]. This was followed internationally by the Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes (CAPACITY) trials (PIPF-004 and PIPF-006) [21], concurrent randomised control trials (RCT) in IPF comparing pirfenidone at doses of 2403 mg/day and 1197 mg/day against placebo over 72 weeks. In the PIPF-004 trial, pirfenidone at the 2403 mg/day dose achieved a significant reduction in FVC decline. Although this was not matched in the PIPF-006 trial, a pre-specified pooled analysis identified a significant treatment effect with an 8% decline in FVC in the pirfenidone group compared to 11% receiving placebo. Significantly fewer patients suffered a decline in FVC of 10% or greater and progression-free survival was improved by 26%.

A further phase III trial, the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study [22], was requested by the United States Food and Drug Administration (US FDA) due to discrepancies between the two CAPACITY trials in meeting their primary endpoints. In this study 555 patients with IPF were randomised to receive pirfenidone (2403 mg/day) or placebo for 52 weeks. Treatment with pirfenidone led to a significant reduction in the proportion of patients suffering disease progression (absolute decline in FVC of ≥10% or death), which was the primary endpoint. Pooled analysis of the CAPACITY and ASCEND studies found that treatment with pirfenidone at 2403 mg/day reduced the proportion of patients experiencing a FVC of ≥10% or death by 43.8% [23]. In addition, there was a reduction in the relative risk of all-cause and IPF-related mortality at 52 weeks with pirfenidone treatment [24]. Post-hoc analysis indicates that the efficacy of pirfenidone is independent of baseline disease severity or demographics [22.23].
Nintedanib, a tyrosine kinase inhibitor initially developed as an anti-tumour agent, was noted to have activity against fibroblasts through inhibition of vascular endothelial growth factor (VEGF) and other profibrotic mediators such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)-β [25]. An initial phase II study, the To Improve Pulmonary Fibrosis with BIBF 1120 (TOMORROW) study [27], suggested that nintedanib at a dose of 150 mg twice daily was effective at reducing FVC decline although failed to reach statistical significance. Subsequently, the INPULSIS trials (INPULSIS-1 and 2) [26], parallel phase III, multicentre RCTs, demonstrated a significant reduction in the rate of FVC decline over a 52-week period, in IPF patients receiving nintedanib compared to placebo. In the pooled analysis, the mean difference in FVC decline was 109.9 mL/year and significantly fewer patients suffered a 5 or 10% decline in FVC with nintedanib. No mortality benefit was noted with nintedanib treatment in the INPULSIS trials or when the data was pooled with the TOMORROW study [27]. Evidence from TOMORROW and INPULSIS-2 suggests that nintedanib may reduce the frequency of acute exacerbations of IPF however this was not observed in INPULSIS-1 and there was no evidence from pooled data that mortality post-exacerbation improved with nintedanib [28]. In similarity to pirfenidone, post-hoc analysis has suggested that nintedanib is equally efficacious in patients with mild or severe disease, irrespective of baseline characteristics and appears to be equally effective in patients with a 'possible UIP' pattern compared to those with 'definite UIP' radiologically [25].
Meta-analysis indicates similar efficacy between both antifibrotics. Treatment decisions are generally driven by tolerance to side effect profiles. Adverse events were common in all the major anti-fibrotic studies with discontinuation rates of 11.9% for pirfenidone in the CAPACITY and ASCEND studies and 19.3% for nintedanib in INPULSIS. Gastrointestinal side effects are common with both antifibrotics, with high rates of diarrhoea (62.4%) reported with nintedanib in INPULSIS, while a photosensitivity rash was observed in 29.2% of patients receiving pirfenidone. Both drugs reported higher proportions of patients suffering a rise in liver function tests in comparison to placebo. Despite frequency of adverse events, results from real-world studies suggest that both drugs are well tolerated in practice, particularly with support to manage side effects. Recent studies have assessed combination therapy with both antifibrotics and have reported adequate tolerability with promising secondary efficacy data [23,25].

Comorbidities

In addition to targeted antifibrotic treatment of the underlying disease, treatment of comorbidities also plays an important role. For example, treating severe pulmonary hypertension or sleep apnea can improve the condition of individual patients [29]. Strict indication criteria should be applied for the treatment of pulmonary hypertension, and efforts should be made to achieve evidence of a response to treatment in the individual patient [30]. Approximately 25% of IPF patients have an additional disorder of left ventricular function that requires treatment. Gastro-esophageal reflux (GER) is observed in up to 80% of IPF patients; it is being discussed as a trigger for disease progression and acute exacerbations. GER should therefore be routinely treated in IPF patients. Reactive depression requiring treatment is often observed in IPF patients. In advanced stages of the disease, where there is no prospect of transplantation, timely palliative care should be initiated and end-of-life scenarios should be discussed with patients and their relatives [31].

Prognosis:

The prognosis of idiopathic pulmonary fibrosis (IPF) is generally poor, with median survival rates ranging from 2 to 5 years after diagnosis. Factors such as age, disease progression, and treatment options

significantly influence outcomes, leading to a decline in lung function and quality of life. Patients with IPF often experience a gradual deterioration in respiratory function, which can culminate in respiratory failure. The variability in individual responses to treatment, along with the presence of comorbidities, complicates the prognosis further. Lung transplantation is a potential option for some patients, offering a chance to improve survival rates; however, it is not universally accessible due to donor shortages and strict eligibility criteria. Ongoing research is focused on identifying biomarkers and developing new therapeutic strategies that may enhance patient outcomes, aiming for a more personalized approach to managing this challenging condition. The overall outlook for individuals with IPF remains concerning, emphasizing the need for continued advancements in treatment and care strategies to improve survival and quality of life for affected patients [32].

The clinical conditions that have been associated with a worse prognosis are diverse and depend on epidemiological data such as male gender and age, symptoms such as baseline dyspnoea, or characteristics of the disease evolution expecting a phenotype or another depending on the exacerbations. In addition, the presence of comorbidities and complications such as emphysema, pulmonary hypertension, cardiovascular diseases and bronchogenic carcinoma are clinical factors that also have been associated with more rapid progression of IPF. Therefore, a rapid progression of IPF is more common in males with a personal smoking history and other co-morbidities, altogether with a delay in diagnosis [33]. Thus, the delay in the evaluation by a team of experts in IPF may be related to a shorter survival, regardless of the level of severity or other prognostic factors [34]. In the same way, it is known that not all patients with IPF evolve in the same way. This is why different phenotypes of IPF are now being highlighted, with two distinct groups—on the one hand, those whose evolution is slowly progressive, with interspersed exacerbation episodes that can be a clear decline in the survival of the patient, and, on the other hand, those who suffer exacerbations frequently, encouraging to a clinical and functional faster decline and consequently to an earlier mortality [35]. This situation is concerning because there are no predicting factors strong enough to identify who will evolve in one way or another.

The explorations to be performed in the follow-up and patient monitoring will differ depending on the clinical status of the patient at the time of diagnosis. In those cases with very little functional impact and absence of limitation to the exercise assessed by the six minutes walking test (6 MWT), evaluation of the patient every three or six months should include the degree and intensity of cough using the questionnaire of Leicester and dyspnoea, using valid scales such as the modified Medical Research Council (MRC), Borg, and both initial and transition dyspnoea indexes [36]. In cases of rapid and progressive disease, the visits should be more frequent (every three months or less, according to evolution), and should also review the cough, the degree of dyspnoea and the progression of the functional limitation by PFT, including arterial blood gases and the 6 MWT. The plain chest X-ray can provide a lot of information showing complications that could be influencing the clinical and or functional worsening of the patient. Registering hospitalizations related to any respiratory cause (exacerbations, infections, etc.) is very important because of their close association with an increase in mortality during the follow-up [33].

Follow-Up

The main reasons for monitoring patients with Idiopathic Pulmonary Fibrosis are to evaluate the disease progression that can lead to a change in treatment and identify comorbidities and complications that may influence when to initiate or stop antifibrotic treatment, when to establish oxygen therapy, when to refer to lung transplantation and when to initiate palliative measures [37].

Currently, there is no consensus on how to monitor these patients. Most recommendations are based on expert opinion and extrapolated evidence. The follow-up strategy is based on clinical need assessed on a case-by-case basis. The frequency and type of follow-up varies with the disease course with symptom assessment and pulmonary function measurements being the cornerstones of disease monitoring.

- Evaluation of Symptoms

The most frequent symptoms in IPF are dyspnoea, reduced exertional capacity and unproductive or minimally productive cough. These symptoms are present at the time of diagnosis in most patients and their frequency and severity increase as the disease progresses.

Worsening dyspnoea is a primary indicator of disease progression [38], including acute exacerbations, and should be evaluated at each visit. The optimal evaluation method has not been determined, but, in clinical practice, dyspnoea is usually assessed by a qualitative history or simple measures such as the modified Medical Research Council (mMRC) breathlessness scale. Dyspnoea is also a common

manifestation of multiple comorbidities such as COPD, pulmonary hypertension and cardiovascular disease, and it is necessary to consider the worsening of dyspnoea in the context of other measures of disease progression. This allows us to determine whether dyspnoea worsening is due to IPF progression or not, and make decisions related to IPF pharmacotherapy, lung transplantation and/or palliative therapies.

Exercise capacity worsens as IPF progresses and increases morbidity and loss of independence. There is no established strategy for measuring physical function in IPF. Patients should be questioned about their ability to exercise at each visit. These questions focus on how far the patients can walk and whether they can climb stairs, with or without oxygen, as well as other questions related to the management of the patient at home [39].

Cough negatively affects quality of life in patients with IPF and tends to worsen as the disease progresses. In clinical practice, cough is evaluated qualitatively by frequency and severity.

In addition, we must also explore other symptoms such as sleep disturbance, depression, anxiety and pulmonary hypertension at each visit. Finally, we should assess the adverse effects derived from antifibrotic therapy [40].

- Pulmonary Function Tests

Pulmonary function tests are an essential component of the disease control in IPF patients. The variables that are regularly monitored are FVC and DLco (both % predicted), strong predictors of mortality and key variables in timing for lung transplantation.

Spirometry, DLco and 6 MWT are usually performed at intervals of three to six months in patients with IPF, with more or less frequent testing depending on severity of symptoms and rate of worsening [41].

A decline in FVC or DLco of at least 10% over six to 12 months predicts an increased risk of mortality and some studies suggest that decreases in 5% of FVC also portend a worse prognosis [42]. Those patients who present a decline in FVC and/or DLco should have this worsening interpreted in the context of other features of disease progression, such as symptoms and HRCT, given the inherent variability of the pulmonary function tests and the lack of specificity.

For patients with Combined Pulmonary Fibrosis and Emphysema (CPFE) or discordant changes in FVC and DLco, lung volumes by plethysmography may help clarify physiology. These patients have a relative preservation of spirometric values and a slower decrease in FVC compared to patients with isolated IPF, indicating the need to consider other functional parameters of disease progression in these patients.

Furthermore, 6 MWT is the most common method of measuring exercise capacity in patients with IPF. The most important variables obtained from the 6 MWT are the distance walked and extent of hypoxemia measured by pulse oximetry. A change in 6 MWD of approximately 30 meters is considered a clinically important change in IPF. However, it is unknown what amount of change in oxygenation is clinically significant [43].

Both baseline and change in 6 MWD over six months are strong and independent predictors of mortality. Lower values for the oxygen saturation nadir also indicate a worse prognosis. These findings suggest that there may be a prognostic role to repeat the 6 MWT every six months, and particularly in patients with more severe disease.

The 6 MWT also provides data on when to start ambulatory oxygen supplementation. Patients with IPF who have exertional desaturation obtain symptomatic benefits from supplemental oxygen during exercise, although the long-term benefit of supplemental oxygen is not established in patients with isolated exertional hypoxemia and preservation of resting oxygen saturation.

Recently, more frequent monitoring of lung function by daily home spirometry is being explored as a way to identify acute exacerbations more rapidly as well as worsening of disease [44].

- Oxygenation

Patients with advanced IPF often have hypoxemia at rest and require the administration of supplemental oxygen, which can be administered continuously, with ambulation, and at night as needed.

Development of worsening hypoxemia and increased oxygen requirements are common indicators of disease progression and increased mortality risk. However, there is no established method to identify which patients require an assessment of resting, exertional, or nocturnal hipoxemia. Severe dyspnoea with ambulation, functional limitation secondary to dyspnoea, moderately or severely reduced DLco and the presence of pulmonary hypertension are common features to consider ambulatory oxygen administration [45].

Assessment of resting oxygenation by pulse oximetry is easily performed and often obtained in each clinical visit, particularly in patients with advanced disease.

Overnight oximetry is obtained in patients with clinical suspicion of nocturnal hypoxemia and/or sleep disorders. Given the absence of clear guidance on the frequency that patients should be evaluated, most patients are tested at baseline and when there is evidence of worsening disease with concern for nocturnal hypoxemia. The high prevalence of obstructive sleep apnea in patients with IPF indicates the need to consider nocturnal oximetry and polysomnography in all patients with IPF, even when there is a low suspicion of nocturnal hypoxemia [46]].

An arterial blood gas is obtained in some patients as a complementary study of pulse oximetry in patients with borderline findings; however, this is a more invasive test and is often not necessary to demonstrate the presence of clinically significant hypoxemia. Respiratory acidosis is a rare finding in IPF and arterial blood gases are rarely obtained for the acid-base evaluation.

- Chest Imaging

High-resolution computed tomography is essential for diagnosis of interstitial lung diseases, particularly in IPF. However, chest radiography has a limited role for routine monitoring of disease progression in patients with IPF, but it may be useful for the initial screen for potential aetiologies of acute respiratory worsening and may occasionally suggest other comorbidities.

High-resolution computed tomography, with or without a rule-out pulmonary embolism protocol, is an important test in the evaluation of an acute respiratory worsening (acute IPF exacerbation). Given the baseline abnormalities in IPF, comparison of HRCT findings during an episode of acute worsening of dyspnoea with a previous exam is essential [47].

The role of HRCT for monitoring IPF progression is less clear. In clinical practice, HRCTs are primarily assessed qualitatively to confirm or exclude significant disease progression, particularly in patients with discordant symptoms and physiology. Many clinicians repeat the HRCT every one or two years in patients with IPF, to identify any change in morphology, to clarify disease progression or to detect a new comorbidity (i.e., lung malignancy), even follow-up HRCT can identify a change in morphology that indicates the need to reconsider an initial diagnosis of IPF [42].

In addition to qualitative assessment, an experienced chest radiologist can visually score the severity of fibrosis on HRCT to obtain a total fibrosis score (percentage of affected lung) or calculate quantitatively using a computer algorithm to re-produce a fibrosis score. Previous studies have shown that both visual and computer-based scoring of fibrosis severity provide prognostic information beyond standard clinical and physiological variables [38,39]; however, these scores have been used mainly as research tools in specialized settings.

2. Conclusion

Idiopathic pulmonary fibrosis remains a complex and challenging disease to manage effectively. While advancements in diagnostic imaging and the understanding of disease mechanisms have improved the accuracy of diagnosing IPF, patients continue to face significant hurdles in terms of treatment options and prognosis. The introduction of antifibrotic therapies has revolutionized the management of IPF, but the search for a cure is ongoing. Future therapeutic approaches may hinge on a deeper understanding of the genetic, immunological, and environmental factors influencing the pathogenesis of this disease. Continuous research efforts are crucial to uncovering new biomarkers and therapeutic targets that can extend survival and improve the quality of life for individuals affected by idiopathic pulmonary fibrosis.

References

1. Al-Githmi, I. (2013). Early experience with lung transplantation in patients with idiopathic pulmonary fibrosis. Surgery Current Research, 03(01). https://doi.org/10.4172/2161-1076.1000128
2. Arai, T., Kagawa, T., Sasaki, Y., Sugawara, R., Sugimoto, C., Tachibana, K., … & Inoue, Y. (2016). Heterogeneity of incidence and outcome of acute exacerbation in idiopathic interstitial pneumonia. Respirology, 21(8), 1431-1437. https://doi.org/10.1111/resp.12862
3. Baydar, O., Özyılmaz, E., HANTA, İ., KULECİ, S., & Güzel, E. (2022). Lung ultrasound in the follow-up of stable idiopathic pulmonary fibrosis. Journal of Experimental and Clinical Medicine, 39(4), 1190-1193. https://doi.org/10.52142/omujecm.39.4.45

4. García-Sancho, C., Buendía-Roldán, I., Fernández-Plata, M., Navarro, C., Pérez-Padilla, R., Vargas, M., … & Selman, M. (2011). Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. Respiratory Medicine, 105(12), 1902-1907. https://doi.org/10.1016/j.rmed.2011.08.022
5. Navaratnam V., Fleming K.M., West J., Smith C.J., Jenkins R.G., Fogarty A., Hubbard R.B. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax. 2011;66:462–467. doi: 10.1136/thx.2010.148031. [DOI] [PubMed] [Google Scholar]
6. Raghu G., Chen S.Y., Yeh W.S., Maroni B., Li Q., Lee Y.C., Collard H.R. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: Incidence, prevalence, and survival, 2001–11. Lancet Respir. Med. 2014;2:566–572. doi: 10.1016/S2213-2600(14)70101-8. [DOI] [PubMed] [Google Scholar]
7. Hopkins R.B., Burke N., Fell C., Dion G., Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Eur. Respir. J. 2016;48:187–195. doi: 10.1183/13993003.01504-2015. [DOI] [PubMed] [Google Scholar]
8. Oh, C., Murray, L., & Molfino, N. (2012). Smoking and idiopathic pulmonary fibrosis. Pulmonary Medicine, 2012, 1-13. https://doi.org/10.1155/2012/808260
9. Prasad, J., Holland, A., Glaspole, I., & Westall, G. (2016). Idiopathic pulmonary fibrosis: an australian perspective. Internal Medicine Journal, 46(6), 663-668. https://doi.org/10.1111/imj.13078
10. Senoo, S., Miyahara, N., Taniguchi, A., Oda, N., Itano, J., Higo, H., … & Kiura, K. (2020). Nintedanib can be used safely and effectively for idiopathic pulmonary fibrosis with predicted forced vital capacity ≤ 50%: a multi-center retrospective analysis. Plos One, 15(8), e0236935. https://doi.org/10.1371/journal.pone.0236935
11. Shao, R., Wang, F., Lyu, M., Yang, J., Zhang, P., & Zhu, Y. (2019). Ability to suppress tgf-β-activated myofibroblast differentiation distinguishes the anti-pulmonary fibrosis efficacy of two danshen-containing chinese herbal medicine prescriptions. Frontiers in Pharmacology, 10. https://doi.org/10.3389/fphar.2019.00412
12. Wu, Z., Chen, H., Ke, S., Mo, L., Qiu, M., Zhu, G., … & Liu, L. (2023). Identifying potential biomarkers of idiopathic pulmonary fibrosis through machine learning analysis. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-43834-z
13. Behr J, Günther A, Ammenwerth W, et al. S2K-Leitlinie zur Diagnostik und Therapie der idiopathischen Lungenfibrose. Pneumologie. 2013:;67:81–111. doi: 10.1055/s-0032-1326009. [DOI] [PubMed] [Google Scholar]
14. Raghu G, Freudenberger TD, Yang S, et al. High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J. 2006;27:136–142. doi: 10.1183/09031936.06.00037005. [DOI] [PubMed] [Google Scholar]
15. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012;21126:355–361. doi: 10.1183/09059180.00002512. [DOI] [PMC free article] [PubMed] [Google Scholar]
16. Demedts M., Behr J., Buhl R., Costabel U., Dekhuijzen R., Jansen H.M., MacNee W., Thomeer M., Wallaert B., Laurent F., et al. High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis. N. Engl. J. Med. 2005;353:2229–2242. doi: 10.1056/NEJMoa042976. [DOI] [PubMed] [Google Scholar]
17. The Idiopathic Pulmonary Fibrosis Clinical Research Network Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. N. Engl. J. Med. 2012;366:1968–1977. doi: 10.1056/NEJMoa1113354. [DOI] [PMC free article] [PubMed] [Google Scholar]
18. Martinez F.J., de Andrade J.A., Anstrom K.J., King T.E., Raghu G., Idiopathic Pulmonary Fibrosis Clinical Research Network Randomized trial of acetylcysteine in idiopathic pulmonary fibrosis. N. Engl. J. Med. 2014;370:2093–2101. doi: 10.1056/NEJMoa1401739. [DOI] [PMC free article] [PubMed] [Google Scholar]
19. Raghu G., Rochwerg B., Zhang Y., Garcia C.A., Azuma A., Behr J., Brozek J.L., Collard H.R., Cunningham W., Homma S., et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am. J. Respir. Crit. Care Med. 2015;192:e3–e19. doi: 10.1164/rccm.201506-1063ST. [DOI] [PubMed] [Google Scholar]
20. Kaneko M., Inoue H., Nakazawa R., Azuma N., Suzuki M., Yamauchi S., Margolin S.B., Tsubota K., Saito I. Pirfenidone induces intercellular adhesion molecule-1 (ICAM-1) down-regulation on cultured human synovial fibroblasts. Clin. Exp. Immunol. 1998;113:72–76. doi: 10.1046/j.1365-2249.1998.00618.x. [DOI] [PMC free article] [PubMed] [Google Scholar]
21. Oku H., Shimizu T., Kawabata T., Nagira M., Hikita I., Ueyama A., Matsushima S., Torii M., Arimura A. Antifibrotic action of pirfenidone and prednisolone: Different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. Eur. J. Pharmacol. 2008;590:400–408. doi: 10.1016/j.ejphar.2008.06.046. [DOI] [PubMed] [Google Scholar]
22. Azuma A., Nukiwa T., Tsuboi E., Suga M., Abe S., Nakata K., Taguchi Y., Nagai S., Itoh H., Ohi M., et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am.

J. Respir. Crit. Care Med. 2005;171:1040–1047. doi: 10.1164/rccm.200404-571OC. [DOI] [PubMed] [Google Scholar]

23. Taniguchi H., Ebina M., Kondoh Y., Ogura T., Azuma A., Suga M., Taguchi Y., Takahashi H., Nakata K., Sato A., et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur. Respir. J. 2010;35:821–829. doi: 10.1183/09031936.00005209. [DOI] [PubMed] [Google Scholar]
24. Noble P.W., Albera C., Bradford W.Z., Costabel U., Glassberg M.K., Kardatzke D., King T.E., Lancaster L., Sahn S.A., Szwarcberg J., et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomised trials. Lancet. 2011;377:1760–1769. doi: 10.1016/S0140-6736(11)60405-4. [DOI] [PubMed] [Google Scholar]
25. Barratt SL, Creamer A, Hayton C, Chaudhuri N. Idiopathic Pulmonary Fibrosis (IPF): An Overview. J Clin Med. 2018 Aug 6;7(8):201. doi: 10.3390/jcm7080201. PMID: 30082599; PMCID: PMC6111543.
26. King T.E., Jr., Bradford W.Z., Castro-Bernardini S., Fagan E.A., Glaspole I., Glassberg M.K., Gorina E., Hopkins P.M., Kardatzke D., Lancaster L., et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N. Engl. J. Med. 2014;370:2083–2092. doi: 10.1056/NEJMoa1402582. [DOI] [PubMed] [Google Scholar]
27. Noble P.W., Albera C., Bradford W.Z., Costabel U., Bois R.M.d., Fagan E.A., Fishman R.S., Glaspole I., Glassberg M.K., Lancaster L., et al. Pirfenidone for idiopathic pulmonary fibrosis: Analysis of pooled data from three multinational phase 3 trials. Eur. Respir. J. 2016;47:243–253. doi: 10.1183/13993003.00026-2015. [DOI] [PMC free article] [PubMed] [Google Scholar]
28. Richeldi L., du Bois R.M., Raghu G., Azuma A., Brown K.K., Costabel U., Cottin V., Flaherty K.R., Hansell D.M., Inoue Y., et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N. Engl. J. Med. 2014;370:2071–2082. doi: 10.1056/NEJMoa1402584. [DOI] [PubMed] [Google Scholar]
29. Richeldi L., Cottin V., Bois R.M.d., Selman M., Kimura T., Bailes Z., Schlenker-Herceg R., Stowasser S., Brown K.K. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS((R)) trials. Respir. Med. 2016;113:74–79. doi: 10.1016/j.rmed.2016.02.001. [DOI] [PubMed] [Google Scholar]
30. Collard H.R., Richeldi L., Kim D.S., Taniguchi H., Tschoepe I., Luisetti M., Roman J., Tino G., Schlenker-Herceg R., Hallmann C., et al. Acute exacerbations in the INPULSIS trials of nintedanib in idiopathic pulmonary fibrosis. Eur. Respir. J. 2017;49 doi: 10.1183/13993003.01339-2016. [DOI] [PubMed] [Google Scholar]
31. Hoeper MM, Andreas S, Bastian A, et al. German Society of Cardiology (DGK), the German Society of Respiratory Medicine (DGP) and the German Society of Pediatric Cardiology (DGPK) Pulmonary hypertension due to chronic lung disease: updated recommendations of the Cologne Consensus Conference 2011. Int J Cardiol. 2011;152:45–53. [Google Scholar]
32. Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J. 2010;35:496–504. doi: 10.1183/09031936.00077309. [DOI] [PubMed] [Google Scholar]
33. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364:1503–1512. doi: 10.1056/NEJMoa1013660. [DOI] [PMC free article] [PubMed] [Google Scholar]
34. Lamas D.J., Kawut S.M., Bagiella E., Philip N., Arcasoy S.M., Lederer D.J. Delayed Access and Survival in Idiopathic Pulmonary Fibrosis. A Cohort Study. Am. J. Respir. Crit. Care Med. 2011;184:842–847. doi: 10.1164/rccm.201104-0668OC. [DOI] [PMC free article] [PubMed] [Google Scholar]
35. Raghu G., Collard H.R., Egan J.J., Martinez F.J., Behr J., Brown K.K., Colby T.V., Cordier J.F., Flaherty K.R., Lasky J.A., et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011;183:788–824. doi: 10.1164/rccm.2009-040GL. [DOI] [PMC free article] [PubMed] [Google Scholar]
36. Selman M., Carrillo G., Estrada A., Mejia M., Becerril C., Cisneros J., Gaxiola M., Pérez-Padilla R., Navarro C., Richards T., et al. Accelerated variant of idiopathic pulmonary fibrosis. PLoS ONE. 2007;2:e482. doi: 10.1371/journal.pone.0000482. [DOI] [PMC free article] [PubMed] [Google Scholar]
37. Nishiyama O., Taniguchi H., Kondoh Y., Kimura T., Kato K., Kataoka K., Ogawa T., Watanabe F., Arizono S. A simple assessment of dyspnea as a prognostic indicator in idiopathic pulmonary fibrosis. Eur. Respir. J. 2010;36:1067–1072. doi: 10.1183/09031936.00152609. [DOI] [PubMed] [Google Scholar]
38. Swigris J.J., Kuschner W.G., Jacobs S.S., Wilson S.R., Gould M.K. Health-related quality of life in patients with idiopathic pulmonary fibrosis: A systematic review. Thorax. 2005;60:588–594. doi: 10.1136/thx.2004.035220. [DOI] [PMC free article] [PubMed] [Google Scholar]
39. Durheim M.T., Collard H.R., Roberts R.S., Brown K.K., Flaherty K.R., King T.E., Jr., Palmer S.M., Raghu G., Snyder L.D., Anstrom K.J., et al. Association of hospital admission and forced vital capacity endpoints with survival in patients with idiopathic pulmonary fibrosis: Analysis of a pooled cohort from three clinical trials. Lancet. Respir. Med. 2015;3:388–396. doi: 10.1016/S2213-2600(15)00093-4. [DOI] [PMC free article] [PubMed] [Google Scholar]

40. Richeldi L., Ryerson C.J., Lee J.S., Wolters P.J., Koth L.L., Ley B., Elicker B.M., Jones K.D., King T.E., Jr., Ryu J.H., et al. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. Thorax. 2012;67:407–411. doi: 10.1136/thoraxjnl-2011-201184. [DOI] [PubMed] [Google Scholar]
41. Zappala C.J., Latsi P.I., Nicholson A.G., Colby T.V., Cramer D., Renzoni E.A., Hansell D.M., du Bois R.M., Wells A.U. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. Eur. Respir. J. 2010;35:830–836. doi: 10.1183/09031936.00155108. [DOI] [PubMed] [Google Scholar]
42. Schmidt S.L., Nambiar A.M., Tayob N., Sundaram B., Han M.K., Gross B.H., Kazerooni E.A., Chughtai A.R., Lagstein A., Myers J.L., et al. Pulmonary function measures predict mortality differently in IPF versus combined pulmonary fibrosis and emphysema. Eur. Respir. J. 2011;38:176–183. doi: 10.1183/09031936.00114010. [DOI] [PMC free article] [PubMed] [Google Scholar]
43. Ryerson C.J., Hartman T., Elicker B.M., Ley B., Lee J.S., Abbritti M., Jones K.D., King T.E., Jr., Ryu J., Collard H.R. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. Chest. 2013;144:234–240. doi: 10.1378/chest.12-2403. [DOI] [PubMed] [Google Scholar]
44. Nathan S.D., du Bois R.M., Albera C., Bradford W.Z., Costabel U., Kartashov A., Noble P.W., Sahn S.A., Valeyre D., Weycker D., et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir. Med. 2015;109:914–922. doi: 10.1016/j.rmed.2015.04.008. [DOI] [PubMed] [Google Scholar]
45. Lederer D.J., Arcasoy S.M., Wilt J.S., D'Ovidio F., Sonett J.R., Kawut S.M. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 2006;174:659–664. doi: 10.1164/rccm.200604-520OC. [DOI] [PMC free article] [PubMed] [Google Scholar]
46. Albert R.K., Au D.H., Blackford A.L., Casaburi R., Cooper J.A., Criner G.J., Diaz P., Fuhlbrigge A.L., Gay S.E., Kanner R.E., et al. Long-term oxygen treatment trial research group. A randomized trial of long-term oxygen for COPD with moderate desaturation. N. Engl. J. Med. 2016;375:1617. doi: 10.1056/NEJMoa1604344. [DOI] [PMC free article] [PubMed] [Google Scholar]
47. Russell A.M., Adamali H., Molyneaux P.L., Lukey P.T., Marshall R.P., Renzoni E.A., Wells A.U., Maher T.M. Daily home spirometry: An effective tool for detecting progression in idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 2016;194:989–997. doi: 10.1164/rccm.201511-2152OC. [DOI] [PMC free article] [PubMed] [Google Scholar]