Original Article

Access this article online
Quick Response Code:

Website:
https://eurasianjpulmonol.org
DOI:
10.14744/ejp.2022.1202

Factors associated with mortality in cases of idiopathic pulmonary fibrosis with mild to moderate functional impairment

Aysun Şengül, Berna Akıncı Özyürek[1], Funda Coşkun[2], Onur Yazıcı[3], Fulsen Bozkuş[4], Pınar Yıldız Gülhan[5], Celal Satıcı[6]

Department of Chest Diseases, Sakarya Üniversitesi University, Sakarya, Türkiye, [1]Department of Pulmonary Medicine, Ataturk Chest Diseases and Chest Surgery Training and Research Hospital, Ankara, Türkiye, [2]Department of Chest Diseases, Bursa Uludağ University Faculty of Medicine, Bursa, Türkiye, [3]Department of Chest Diseses, Aydın Adnan Menderes University Faculty of Medicine, Aydin, Türkiye, [4]Department of Chest Diseases,Kahramanmaraş Sütçü İmam University Faculty of Medicine, Kahramanmaraş, Türkiye, [5]Department of Chest Diseases, Düzce University Faculty of Medicine, Düzce, Türkiye, [6]Department of Chest Diseases, University of Health Sciences, Gaziosmanpasa Training and Research Hospital, İstanbul, Türkiye

ORCID:
Aysun Şengül: 0000-0002-8084-1322
Berna Akıncı Özyürek: 0000-0003-0206-7615
Funda Coşkun: 0000-0002-4400-3380
Onur Yazıcı: 0000-0003-3487-7735
Fulsen Bozkuş: 0000-0002-6498-4390
Pınar Yıldız Gülhan: 0000-0002-5347-2365
Celal Satıcı: 0000-0002-5457-9551

Address for correspondence:
Dr. Pınar Yıldız Gülhan, Department of Chest Diseases, Düzce University Faculty of Medicine, Düzce, Türkiye.
E-mail
pinaryildiz691@hotmail.com

Received: 14-01-2023
Revised: 24-02-2023
Accepted: 19-06-2023
Published: 10-11-2023

Abstract:

BACKGROUND AND AIM: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease with a poor prognosis, characterized by advanced fibrosis. The course of the disease varies from patient to patient. The factors that determine the course of the disease are yet to be clarified. Here, we aimed to assess patient characteristics, overall mortality, and mortality-associated factors in our IPF patient cohort.

METHODS: Our multicenter, retrospective cohort study reviewed the records of 169 patients diagnosed with IPF who had mild-to-moderate functional impairment and were followed up for at least one year from diagnosis until death between 2009 and 2019.

RESULTS: The mean age of the 169 IPF patients was 69.7±8.8 years, and 73.4% were male. The diagnosis was established clinically and radiologically in 152 (89.9%) patients and histopathologically in 17 (10%) patients. A smoking history was found in 72.2% of the patients, with an average smoking quantity of 35.6±14.7 pack-years. Among the patients, 28 (16.6%) did not receive treatment, 87 (51.5%) received pirfenidone, and 54 (31.9%) nintedanib treatment. The median Gender, Age, and Physiology (GAP) score of the patients was 3. The mean forced vital capacity (FVC) was 79.6%±19.7%, the mean diffusing capacity of the lungs for carbon monoxide (DLCO) was 52.8%±14.5%, the median pulmonary hypertension score was 2, the mean pulmonary artery-to-aorta (PA/Aorta) ratio was 0.85±0.15, the mean arterial partial pressure of oxygen (PaO_2) was 66±10.7 mmHg, and the median right ventricular systolic pressure (RVSP) was 30 (range: 19–60) mmHg. The one-year mortality rate was 7.1%, the two-year mortality rate was 19.6%, and the three-year mortality rate was 42.5%. The factors associated with one- and two-year mortality were age, GAP score, RVSP, and non-treatment. The factors associated with three-year mortality were age, GAP score, non-treatment, and the PA/Aorta ratio.

How to cite this article: Şengül A, Akıncı Özyürek B, Coşkun F, Yazıcı O, Bozkuş F, Yıldız Gülhan P, Satıcı C. Factors associated with mortality in cases of idiopathic pulmonary fibrosis with mild to moderate functional impairment. Eurasian J Pulmonol 2023;25:166-73.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: kare@karepb.com

© 2023 Eurasian Journal of Pulmonology Published by Kare Media

CONCLUSIONS: Antifibrotic therapy improves disease prognosis and can reduce mortality in patients diagnosed with IPF. Elevation of RVSP on echocardiography and PA/Aorta ratio on thoracic computed tomography can be used as predictors of mortality, similar to the GAP score.

Keywords:

GAP score, idiopathic pulmonary fibrosis, mortality, nintedanib, PA/Aorta ratio, pirfenidone, pulmonary hypertension

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of interstitial lung disease (ILD) characterized by fibrosis and declining lung function. It typically occurs at the age of 50 years and above.[1,2] Various causes, such as genetic predisposition, environmental risk factors and exposure, smoking, gastroesophageal reflux, and viral infections, have been suggested in the literature; however, the etiology is still unknown. Repeated exposures lead to micro-injuries in the lung tissue and vascular system, triggering inflammatory response and fibrosis.[2] Symptoms are nonspecific, with most patients initially experiencing exertional dyspnea and dry cough. In some cases, symptoms may appear after the onset of radiological changes. The prognosis and surveillance of IPF are poorer than many cancers, with a mean survival of three to five years following diagnosis.[3–5] Although antifibrotic therapies have been used in recent years to reduce disease progression, exacerbations, hospitalizations, and mortality rates remain high. Currently, lung transplantation is the only definitive treatment option available. The course of the disease varies among patients. Some patients with IPF remain stable over an extended period, while others experience frequent exacerbations leading to early mortality. The factors influencing disease course have yet to be fully understood. Several clinical models have been proposed to predict the course of the disease, with Gender, Age, and Physiology (GAP) index being the most commonly utilized.[6]

In addition, most patients with IPF have comorbidities such as gastroesophageal reflux, obstructive sleep apnea, lung cancer, cardiomyopathy, and pulmonary hypertension, which significantly impact the disease course. These comorbidities contribute to more frequent exacerbations and loss of function, resulting in a rapid decline in survival. Consequently, identifying and treating comorbidities may lead to improved overall outcomes, including quality of life and survival.[7] Approximately 30–50% of patients with advanced IPF develop pulmonary hypertension.[7] Pulmonary hypertension should be suspected in patients with severe hypoxemia, disproportionate desaturations during the six-minute walk test, or IPF patients who have disproportionate decrease in Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO) relative to the disease.[8–10]

The present study aims to evaluate the significance of demographic characteristics, pulmonary function parameters, GAP scores, measurements, and scores potentially indicative of pulmonary hypertension, as well as radiological findings, in predicting mortality among our IPF patients. Additionally, we aim to assess overall mortality and factors associated with mortality.

Materials and Methods

Our multicenter, retrospective cohort study included 169 adult patients diagnosed with IPF clinically, radiologically, or histopathologically.[1,11] According to current guidelines, we specifically selected patients with mild-to-moderate functional impairment (Forced Vital Capacity (FVC) ≥ 50%, DLCO ≥ 30%) who were followed up for at least one year from diagnosis or until death between 2009 and 2019. Patients with IPF who had severe functional impairment and were followed up for less than one year were excluded. Additionally, cases with severe functional impairment where antifibrotic treatment was not indicated were not included in the study, enabling a comparison between cases that received and did not receive treatment. The medical records of the patients were retrospectively reviewed.

We evaluated our patients for demographic characteristics, diagnostic methods, pulmonary function parameters, pulmonary artery diameter on thoracic Computed Tomography (CT), oxygenation, echocardiographic findings, survival during the follow-up period, and the treatments received. The GAP score was calculated for all patients using the method suggested by Ley et al.[6] This total GAP score considered four clinical variables: gender (female: 0 points, male: 1 point), age (0–2 points), forced vital capacity (FVC) (%) (0–2 points), and DLCO (%) (0–2 points). Subsequently, the patients were classified into three stages based on their GAP scores: Stage I (0–3 points), Stage II (4–5 points), and Stage III (6–8 points).

Pulmonary function tests (PFTs), including spirometry and the test of diffusing capacity of the lungs for carbon monoxide (DLCO), were performed following the current American Thoracic Society/European Respiratory Society (ATS/ERS) pulmonary function guidelines of that period.[12]

Measurements of pulmonary artery diameter and aortic diameter were taken at the level of the pulmonary artery bifurcation on High-Resolution Computed Tomography (HRCT), and the Pulmonary artery/Aortic diameter ratio (PA/Ao) was calculated.[13]

Transthoracic echocardiography was used to measure the estimated right ventricular systolic pressure (RVSP).

The pulmonary hypertension score, proposed by Furukawa et al.[13] as predictor of pulmonary hypertension, was calculated using DLCO, PA/Ao ratio on CT, and partial arterial oxygen pressure (PaO_2).

At the end of the first year, 157 out of 169 patients survived. In the second year, 45 patients were lost to follow-up, while 112 patients remained in the study and their data were evaluated. By year three, 10 out of the 90 patients who had survived until the end of the second year were lost to follow-up. The data of the remaining 80 patients who continued to be in follow-up were evaluated.

Descriptive statistics were used to present the variables. Categorical data were reported as proportions and counts, while normally distributed continuous data were presented as means and standard deviation (SD). Median and interquartile range values were provided for non-normally distributed continuous data. The Chi-square test was used to compare categorical variables, and the Student t-test and Mann-Whitney U test were performed to compare normally and non-normally distributed continuous data between two groups, respectively.

Results

The mean age of the 169 IPF patients was 69.7±8.8 years. The study sample consisted of 124 (73.4%) male patients and 45 (26.6%) female patients. The diagnosis was established clinically and radiologically in 152 (89.9%) patients based on typical radiological findings along with compatible clinical findings, and histopathologically in 17 (10%) patients. Among the patients, 72.2% were active smokers or had a history of smoking. The mean smoking quantity was 35.6±14.7 pack-years. Out of all the patients, 28 (16.6%) did not receive treatment, 87 (51.5%) received pirfenidone, and 54 (31.9%) received nintedanib treatment. The median GAP score of the patients was 3. The mean FVC was 79.6%±19.7%, the mean DLCO was 52.8%±14.5%, the median pulmonary hypertension score was 2, the mean PA/Aorta ratio was 0.85±0.15, the mean PaO_2 was 66±10.7 mmHg, and the median RVSP was 30 (19–60) mmHg. The one-year mortality rate was 7.1%, the two-year mortality rate was 19.6%, and the three-year mortality rate was 42.5% (Table 1).

Table 1: Characteristics of IPF patients with mild-to-moderate functional impairment

	n*		%
Age (years, mean±SD)	169	69.7±8.8	
Gender	169		
Male	124		73.4
Type of diagnosis	169		
Clinical-radiological	152		89.9
Histopathological	17		10.1
Smoking	126		
Never-smoker	35		27.7
Ex-smoker	75		59.5
Current smoker	16		12.7
Smoking pack years	85	35.6±14.7	
Antifibrotic therapy	169		
Not received	28		16.6
Pirfenidone	87		51.5
Nintedanib	54		31.9
FVC (%) (mean±SD)	169	79.6±19.7	
DLCO (%) (mean±SD)	169	52.8±14.5	
PaO_2 (mmHg) (mean±SD)	156	66±10.7	
PA/Ao (mean±SD)	145	0.85±0.15	
GAP score (median, IQR)	169	3 (1–6)	
PH score (median, IQR)	133	2 (0–3)	
RVSP (mmHg) (median, IQR)	57	30 (19–97)	
Year mortality	169		
1	12		7.1
Year mortality	112		
2	22		19.6
Year mortality	80		
3	34		42.5

*: Cases with available data. IPF: Idiopathic pulmonary fibrosis, SD: Standard deviation, FVC: Forced vital capacity, DLCO: Diffusing capacity of the lungs for carbon monoxide, PaO_2: Arterial partial pressure of oxygen, PA/Ao: Pulmonary artery-to-aorta, GAP: Gender, Age, and Physiology, PH: Pulmonary hypertension, RVSP: Right ventricular systolic pressure, IQR: Interquartile range

The factors associated with one- and two-year mortality were age, GAP score, RVSP, and non-treatment. Similarly, for three-year mortality, age, GAP score, non-treatment, and the PA/Aorta ratio were identified as significant factors (Table 2).

Table 2. Factors associated with 1-, 2-, and 3- year mortality in IPF cases with mild-to-moderate functional impairment

	1-year mortality (+) (n=12)		1-year mortality (–) (n=157)		p	2-year mortality (+) (n=22)		2-year mortality (–) (n=90)		p	3-year mortality (+) (n=34)		3-year mortality (–) (n=46)		p
	n	%	n	%		n	%	n	%		n	%	n	%	
Age (years) (mean±SD)	78.9±10.6		68.9±8.2		<0.001*	78.1±8.8		68.5±8.0		<0.001*	77±9.4		67.8±7.5		<0.001*
Female	1	8.3	44	28	0.18	2	9.1	18	20	0.35	3	8.8	9	19.6	0.22
Smoking history					0.66					0.81					0.81
Never smoker	2	22.2	33	28.2		3	16.7	16	20.8		7	24.1	11	26.2	
Active smoker	5	55.6	70	59.8		12	66.7	52	67.5		17	58.6	26	61.9	
Ex-smoker	2	22.2	14	12		3	16.7	9	11.7		5	17.2	5	11.9	
Smoking pack years (mean±SD)	32.1±12.3		35.9±14.9		0.51	34.7±13.5		36±15.7		0.77	34.4±13.2		35.2±18		0.87
Treatment					<0.001*					<0.001*					<0.001*
Not received	8	66.7	20	12.7		13	59.1	12	13.3		18	52.9	6	13	
Pirfenidone	4	33.3	83	52.9		7	31.8	56	62.2		11	32.4	33	71.7	
Nintedanib	0	0	54	34.4		2	9.1	22	24.4		5	14.7	7	15.2	
RVSP (mmHg) (median, IQR)	50 (37–)		30 (26.7–40)		0.03*	47.5 (34.7–69.2)		30 (25.5–39)		0.01*	45 (30–60)		30 (25.2–37.5)		0.054
GAP score					0.04*					0.002*					<0.001*
0–3	1	14.3	87	59.6		2	16.7	48	55.2		5	21.7	26	57.8	
4–8	6	85.7	59	40.4		10	83.3	39	44.8		18	78.3	19	42.2	
FVC (%) (median, IQR)	69.5 (61.2–80.7)		78 (65–95)		0.27	74 (60.5–81.5)		75 (60.7–88)		0.83	66 (60–81)		74.5 (56.2–87.7)		0.70
DLCO (%) (mean±SD)	50.8±4.7		52.8±14.7		0.36	51.5±4.3		54.3±16.1		0.17	50.7±8.7		56.6±18		0.06
pO_2 (mmHg) (mean±SD)	66.1±21.8		65.9±10.0		0.98	64.2±19.6		66.8±11.5		0.63	64.2±17.1		67.3±10.9		0.34
PA/Ao (mean±SD)	0.93±0.21		0.84±0.14		0.07	0.91±0.21		0.82±0.12		0.10	0.90±0.18		0.83±0.13		0.04*
PH score					0.49					0.75					0.99
0	1	14.3	7	5.6		2	14.3	6	7.5		2	8.3	4	9.3	
1	2	28.6	46	36.5		4	28.6	33	41.3		10	41.7	18	41.9	
2	2	28.6	56	44.4		6	42.9	31	38.8		8	33.3	15	34.9	
3	2	28.6	17	13.5		2	14.3	0	(12.5		4	16.7	0	14	

*: p<0.05. IPF: Idiopathic pulmonary fibrosis, SD: Standard deviation, RVSP: Right ventricular systolic pressure, IQR: Interquartile range, GAP: Gender, Age, and Physiology, DLCO: Diffusing capacity of the lungs for carbon monoxide, pO_2: Partial pressure of oxygen, PA/Ao: Pulmonary artery-to-aorta, PH: Pulmonary hypertension

Discussion

IPF is a chronic and progressive ILD with a worse prognosis compared to many cancers. The disease course varies, with some patients experiencing long-term stability while others face early mortality. Despite efforts to predict the disease course, it remains challenging to accurately determine individual outcomes. In our study involving IPF patients with mild-to-moderate functional impairment, the one-year mortality rate was 7.1%, the two-year mortality rate was 19.6%, and the three-year mortality rate was 42.5%. Age, GAP score, RVSP, non-treatment, and the PA / Aorta ratio were identified as factors associated with mortality.

IPF predominantly affects individuals at an advanced age and is more common in males.[14,15] In our study, 73.4% of the patients were male, with a mean age of 69.7 years. The diagnosis of IPF can be established through a multidisciplinary assessment without the need for biopsy in cases demonstrating a typical pattern of usual interstitial pneumonia (UIP) on HRCT scans, and when other potential causes of UIP are ruled out in the presence of characteristic clinical findings.[16,17] In our study, the diagnosis of IPF was established clinically and radiologically in 152 (89.9%) patients based on typical radiological findings, while histopathological confirmation was obtained in 17 (10%) patients.

The course of IPF exhibits high variability, which poses challenges in developing personalized treatment plans. Several studies have investigated factors that may indicate the prognosis of IPF, including demographic characteristics, pulmonary function test parameters, radiological features, and various biomarkers.[4,18–20]

Several studies have demonstrated an association between advanced age and male gender with mortality.[4,21] However, in our study, advanced age was found to be associated with one-, two-, and three-year mortality, while male gender did not show a significant association with mortality.

In our study sample, 72.2% of the patients were active smokers or had a history of smoking, with a mean smoking quantity of 35.6 pack-years. Previous studies have reported a smoking rate of 60–75% in IPF patients.[22–24] The risk of developing IPF increases with the quantity of smoking, and most patients have a smoking history of more than 20 pack-years.[1] Smokers or former-smokers are at an elevated risk of developing IPF and generally have a worse prognosis compared to IPF patients who never smoked.[22–24] However, our study did not establish a significant association between smoking, smoking quantity, and mortality.

Among our patient, 29 did not receive treatment as they were followed up before the use of antifibrotic therapies. In our study, patients who did not receive antifibrotic treatment had higher one-, two-, and three-year mortality rates. Antifibrotic therapies have well-known effects on reducing the decline in pulmonary function and slowing disease progression. Some studies have reported relatively extended survival with these therapies.[24] A meta-analysis by Fleetwood et al.[25] demonstrated that pirfenidone reduced lung function decline and mortality. Lancaster et al.,[26] in a pooled analysis of six studies, found that nintedanib could increase life expectancy. A recent meta-analysis by Petnak et al.,[27] which included 26 studies, concluded that antifibrotic therapies reduced mortality.

Our study investigated the association between PFT parameters, specifically FVC and DLCO, and mortality. However, we found that these parameters alone were not associated with one-, two-, and three-year mortality. In contrast, the study by Natsuizaka, which evaluated 553 IPF patients, identified Vital Capacity (VC) and DLCO as mortality-associated factors, while Song et al. identified FVC and DLCO as such.[18,28] Additionally, the study by Moğulkoç et al.[29] reported that the percent predicted DLCO was an independent predictor of mortality in patients awaiting transplantation. We believe that the lack of any effect of pulmonary function test parameters on mortality in our study may be attributed to the exclusion of patients with severely impaired pulmonary function.

The GAP model, which incorporates clinical and physiological variables such as gender, age, FVC, and DLCO, has also been used to predict mortality associated with IPF in recent years. Many studies have predicted mortality using this model.[6,28,30] Lee et al.[31] established that the GAP score and composite physiologic index (CPI) could predict mortality, with CPI being superior. In our study, we found an association between the GAP score and one-, two-, and three-year mortality.

Comorbidities are more common in IPF patients compared to the general population, with most patients usually having more than two comorbidities.[1] Pulmonary hypertension often coexists with IPF,[8] as observed in

various studies where it accompanies 30%–50% of IPF cases.[7] The presence of pulmonary hypertension (HT) in IPF patients has been associated with increased mortality and a higher mortality risk correlated with elevated mean pulmonary artery pressures (mPAP).[8,9,28,32] The definitive diagnosis of pulmonary hypertension requires Right Ventricle (RV) catheterization, which is an invasive diagnostic method. Although the diagnostic accuracy of transthoracic echocardiography is unclear, it is a non-invasive method that can indicate the presence of pulmonary hypertension.[33] Some studies have suggested that RVSP elevation alone is not be sufficient to predict pulmonary hypertension, and the addition of other functional and echocardiographic methods would provide a more appropriate prediction.[34]

Alkukhun et al.[35] evaluated non-invasive methods to predict pulmonary hypertension in 235 IPF patients who underwent right heart catheterization. They identified impaired right ventricular function and high PA/Ao ratios as risk factors for precapillary pulmonary hypertension. Another study found that the PA/Ao was a reliable method to predict elevated mPAP in IPF patients with pulmonary hypertension confirmed by right heart catheterization (RHC).[36]

The study by Lettieri et al.[9] found that the need for oxygen and low DLCO values were associated with the presence of pulmonary hypertension in IPF patients. Nadrous et al.[8] established a negative correlation between DLCO, one of the pulmonary function test parameters, and pulmonary artery pressure (PAP). Additionally, another study found that pulse oximetry at rest in room air and the FVC/DLCO ratio had a high negative predictive value for pulmonary HT.[10]

Furukawa et al.[13] introduced a scoring system based on various factors associated with pulmonary hypertension in the literature. The authors used a scoring system that included DLCO <50%, PA/Ao ratio on CT, and PaO_2 <80 mmHg to predict pulmonary hypertension and concluded that this system could predict pulmonary hypertension.

In our study, we found that RVSP was associated with one- and two-year mortality rates in measurements that could indicate pulmonary hypertension in IPF patients with mild-to-moderate functional involvement. In contrast, the PA/Ao ratio on CT was associated with three-year mortality. It could be thought that PA/Ao ratio was not related to early mortality but rather to the late mortality rate. However, the pulmonary hypertension score was not associated with mortality.

Our study has some limitations. In our retrospective study, there were cases with missing data. Additionally, due to some of our patients being lost to follow-up, we could only assess their treatment outcomes for the duration of their follow-up. Furthermore, our study focused on patients with mild-to-moderate functional involvement, and therefore, our findings may not fully reflect overall IPF mortality and factors associated with it.

Conclusion

In conclusion, advanced age, not receiving antifibrotic therapy, high GAP scores, high RVSP on echocardiography, and increased PA/Ao ratios on thoracic CT were associated with mortality in IPF patients with mild-to-moderate functional impairment. We believe that pulmonary hypertension is a poor prognostic factor in IPF patients, and antifibrotic therapy improves the disease prognosis and can reduce mortality in patients diagnosed with IPF. RVSP elevation on echocardiography (ECHO) and PA/Ao on thoracic CT can be used as predictors of mortality, similar to the GAP score.

Conflicts of interest
There are no conflicts of interest.

Ethics Committee Approval
The study was approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (No: 13 Date: 09/01/2020).

Financial support and sponsorship
Nil.

Peer-review
Externally peer-reviewed.

Authorship Contributions
Concept – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Design – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Supervision – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Funding – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Materials – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Data collection &/or processing – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Analysis and/or interpretation – A.Ş., B.A.Ö., F.C., C.S.; Literature search – A.Ş., B.A.Ö., F.C.; Writing – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.; Critical review – A.Ş., B.A.Ö., F.C., O.Y., F.B., P.Y.G., C.S.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. 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(6):788–824. [CrossRef]
2. Sharif R. Overview of idiopathic pulmonary fibrosis (IPF) and evidence-based guidelines. Am J Manag Care 2017;23(11 Suppl):S176–82.
3. Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. Respir Med 2015;109(6):661–70. [CrossRef]
4. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183(4):431–40. [CrossRef]
5. Luppi F. Predicting the future of patients with idiopathic pulmonary fibrosis: another step forward. Lancet Respir Med 2017;5(12):911–3.
6. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012;156(10):684–91. [CrossRef]
7. Raghu G, Amatto VC, Behr J, Stowasser S. Comorbidities in idiopathic pulmonary fibrosis patients: A systematic literature review. Eur Respir J 2015;46(4):1113–30. [CrossRef]
8. Nadrous HF, Pellikka PA, Krowka MJ, Swanson KL, Chaowalit N, Decker PA, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005;128(4):2393–9. [CrossRef]
9. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129(3):746–52. [CrossRef]
10. Zisman DA, Ross DJ, Belperio JA, Saggar R, Lynch JP 3rd, Ardehali A, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2007;101(10):2153–9. [CrossRef]
11. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161(2 Pt 1):646–64. [CrossRef]
12. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26(2):319–38. [CrossRef]
13. Furukawa T, Kondoh Y, Taniguchi H, Yagi M, Matsuda T, Kimura T, et al. A scoring system to predict the elevation of mean pulmonary arterial pressure in idiopathic pulmonary fibrosis. Eur Respir J 2018;51(1):1701311. [CrossRef]
14. Navaratnam V, Fleming KM, West J, Smith CJ, Jenkins RG, Fogarty A, et al. The rising incidence of idiopathic pulmonary fibrosis in the U.K. Thorax 2011;66(6):462–7. [CrossRef]
15. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: A population-based study. Chest. 2010;137(1):129–37. [CrossRef]
16. Sumikawa H, Johkoh T, Colby TV, Ichikado K, Suga M, Taniguchi H, et al. Computed tomography findings in pathological usual interstitial pneumonia: Relationship to survival. Am J Respir Crit Care Med 2008;177(4):433–9. [CrossRef]
17. Quadrelli S, Molinari L, Ciallella L, Spina JC, Sobrino E, Chertcoff J. Radiological versus histopathological diagnosis of usual interstitial pneumonia in the clinical practice: Does it have any survival difference? Respiration 2010;79(1):32–7. [CrossRef]
18. Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, et al. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med 2014;190(7):773–9. [CrossRef]
19. Jegal Y, Kim DS, Shim TS, Lim CM, Do Lee S, Koh Y, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171(6):639–44. [CrossRef]
20. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001;164(7):1171–81. [CrossRef]
21. Zubairi ABS, Ahmad H, Hassan M, Sarwar S, Abbas A, Shahzad T, et al. Clinical characteristics and factors associated with mortality in idiopathic pulmonary fibrosis: An experience from a tertiary care center in Pakistan. Clin Respir J 2018;12(3):1191–6. [CrossRef]
22. Ohno S, Nakaya T, Bando M, Sugiyama Y. Idiopathic pulmonary fibrosis--results from a Japanese nationwide epidemiological survey using individual clinical records. Respirology 2008;13(6):926–8. [CrossRef]
23. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997;155(1):242–8. [CrossRef]
24. Raghu G. Idiopathic pulmonary fibrosis: lessons from clinical trials over the past 25 years. Eur Respir J 2017;50(4):1701209. [CrossRef]
25. Fleetwood K, McCool R, Glanville J, Edwards SC, Gsteiger S, Daigl M, et al. Systematic review and network meta-analysis of idiopathic pulmonary fibrosis treatments. J Manag Care Spec Pharm 2017;23(3-b Suppl):S5–S16. [CrossRef]
26. Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, et al. Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: Pooled data from six clinical trials. BMJ Open Respir Res 2019;6(1):e000397. [CrossRef]
27. Petnak T, Lertjitbanjong P, Thongprayoon C, Moua T. Impact of antifibrotic therapy on mortality and acute exacerbation in idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Chest 2021;160(5):1751–63. [CrossRef]
28. Song H, Sun D, Ban C, Liu Y, Zhu M, Ye Q, et al. Independent clinical factors relevant to prognosis of patients with idiopathic pulmonary fibrosis. Med Sci Monit 2019;25:4193–201. [CrossRef]
29. Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ; Greater Manchester Pulmonary Fibrosis Consortium. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. Am J Respir Crit Care Med 2001;164(1):103–8. [CrossRef]
30. Lacedonia D, Correale M, Tricarico L, Scioscia G, Stornelli SR, Simone F, et al. Survival of patients with idiopathic pulmonary fibrosis and pulmonary hypertension under therapy with nintedanib or pirfenidone. Intern Emerg Med 2022;17(3):815–22. [CrossRef]
31. Lee SH, Park JS, Kim SY, Kim DS, Kim YW, Chung MP, et al. Comparison of CPI and GAP models in patients with idiopathic pulmonary fibrosis: A nationwide cohort study. Sci Rep 2018;8(1):4784.
32. Song JW, Song JK, Kim DS. Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. Respir Med 2009;103(2):180–6. [CrossRef]
33. Nowak J, Hudzik B, Jastrzębski D, Niedziela JT, Rozentryt P, Wojarski J, et al. Pulmonary hypertension in advanced lung diseases: Echocardiography as an important part of patient evaluation for lung transplantation. Clin Respir J 2018;12(3):930–8. [CrossRef]

34. Nathan SD, Shlobin OA, Barnett SD, Saggar R, Belperio JA, Ross DJ, et al. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2008;102(9):1305–10. [CrossRef]
35. Alkukhun L, Wang XF, Ahmed MK, Baumgartner M, Budev MM, Dweik RA, et al. Non-invasive screening for pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 2016;117:65–72. [CrossRef]
36. Yagi M, Taniguchi H, Kondoh Y, Ando M, Kimura T, Kataoka K, et al. CT-determined pulmonary artery to aorta ratio as a predictor of elevated pulmonary artery pressure and survival in idiopathic pulmonary fibrosis. Respirology 2017;22(7):1393–9. [CrossRef]