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

Aysun Şengül, Berna Akıncı Özyürek, Funda Coşkun, Onur Yazıcı, Fulsen Bozkuş, Pınar Yıldız Gülhan, Celal Satıcı

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 (PaO₂) 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.

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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. 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. 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. 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.

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. Approximately 30–50% of patients with advanced IPF develop pulmonary hypertension. 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.

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. 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. 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. 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.

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

The pulmonary hypertension score, proposed by Furukawa et al. as predictor of pulmonary hypertension, was calculated using DLCO, PA/Ao ratio on CT, and partial arterial oxygen pressure (PaO₂).

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 mean PaO₂ (mmHg) was 66±10.7, the mean PA/Ao was 0.85±0.15, the mean GAP score was 2, the mean PH score was 3 (1–6), the mean RVSP was 30 (19–97) mmHg, and 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).

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/Ao 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

<table>
<thead>
<tr>
<th></th>
<th>1-year mortality</th>
<th>2-year mortality</th>
<th>3-year mortality</th>
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<tr>
<td></td>
<td>(+) (n=12)</td>
<td>(+) (n=22)</td>
<td>(+) (n=34)</td>
</tr>
<tr>
<td></td>
<td>(–) (n=157)</td>
<td>(–) (n=90)</td>
<td>(–) (n=46)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>78.9±10.6</td>
<td>78.1±8.8</td>
<td>77±9.4</td>
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<tr>
<td>(mean±SD)</td>
<td>68.9±8.2</td>
<td>68.5±8.0</td>
<td>67.8±7.5</td>
</tr>
<tr>
<td>Female</td>
<td>8.3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Smoking history</td>
<td>0.66</td>
<td>0.81</td>
<td>0.81</td>
</tr>
<tr>
<td>Never smoker</td>
<td>2</td>
<td>3</td>
<td>5</td>
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<tr>
<td>Active smoker</td>
<td>5</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Smoking pack (years)</td>
<td>32.1±12.3</td>
<td>34.7±13.5</td>
<td>34.4±13.2</td>
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<tr>
<td>(mean±SD)</td>
<td>35.9±14.9</td>
<td>36±15.7</td>
<td>35.2±18</td>
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<tr>
<td>Treatment</td>
<td></td>
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<tr>
<td>Not received</td>
<td>8</td>
<td>13</td>
<td>18</td>
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<tr>
<td>Pirfenidone</td>
<td>4</td>
<td>7</td>
<td>11</td>
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<tr>
<td>Nintedanib</td>
<td>0</td>
<td>2</td>
<td>5</td>
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<tr>
<td>RVSP (mmHg)</td>
<td>50</td>
<td>47.5</td>
<td>45</td>
</tr>
<tr>
<td>(median, IQR)</td>
<td>(37–40)</td>
<td>(34.7–69.2)</td>
<td>(30–60)</td>
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<tr>
<td>GAP score</td>
<td></td>
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<tr>
<td>0–3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4–8</td>
<td>6</td>
<td>2</td>
<td>5</td>
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<tr>
<td>FVC (%)</td>
<td>69.5</td>
<td>74</td>
<td>66</td>
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<tr>
<td>(median, IQR)</td>
<td>(61.2–80.7)</td>
<td>(60.5–81.5)</td>
<td>(56.2–87.7)</td>
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<td>DLCO (%)</td>
<td>50.8±4.7</td>
<td>51.5±4.3</td>
<td>50.7±8.7</td>
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<tr>
<td>(mean±SD)</td>
<td>52.8±14.7</td>
<td>54.3±16.1</td>
<td>56.8±18</td>
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<tr>
<td>pO2 (mmHg)</td>
<td>66.1±21.8</td>
<td>64.2±19.6</td>
<td>64.2±17.1</td>
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<tr>
<td>(mean±SD)</td>
<td>65.9±10.0</td>
<td>66.8±11.5</td>
<td>67.3±10.9</td>
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<tr>
<td>PA/Ao</td>
<td>0.93±0.21</td>
<td>0.91±0.21</td>
<td>0.90±0.18</td>
</tr>
<tr>
<td>(means SD)</td>
<td>0.84±0.14</td>
<td>0.82±0.12</td>
<td>0.83±0.13</td>
</tr>
<tr>
<td>PH score</td>
<td></td>
<td>0.75</td>
<td>0.99</td>
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</table>

*: 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, pO2: 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. 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. 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.

Several studies have demonstrated an association between advanced age and male gender with mortality. 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. The risk of developing IPF increases with the quantity of smoking, and most patients have a smoking history of more than 20 pack-years. 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. 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. A meta-analysis by Fleetwood et al. demonstrated that pirfenidone reduced lung function decline and mortality. Lancaster et al. in a pooled analysis of six studies, found that nintedanib could increase life expectancy. A recent meta-analysis by Petnak et al., 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. Additionally, the study by Moğulkoç et al. 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. Lee et al. 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. Pulmonary hypertension often coexists with IPF, 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.[31] 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 PaO2 <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).

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Peer-review

Externally peer-reviewed.

Authorship Contributions

References


