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Clinical characteristics and factors associated with mortality in idiopathic pulmonary fibrosis: An experience from a tertiary care center in Pakistan

Ali Bin Sarwar Zubairi | **Huzaifa Ahmad** | **Maryam Hassan** | **Sajjad Sarwar** | **Aamir Abbas** | **Talha Shahzad** | **Muhammad Irfan**

Department of Medicine, Aga Khan University, Karachi, Pakistan

Correspondence
Ali Bin Sarwar Zubairi, Department of Medicine, Aga Khan University, Karachi, Pakistan.
Email: ali.zubairi@aku.edu

Abstract

Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) that predominantly affects older adults. IPF has the highest mortality burden of all ILDs. Data on mortality in patients with IPF is limited in developing countries.

Objectives: To identify factors associated with mortality in patients with IPF at a tertiary care center in Pakistan.

Methods: A retrospective chart review was conducted at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan from January 2005 to December 2015. Patients were assessed for smoking status, clinical onset of disease, pulmonary hypertension, disease severity based on spirometry and hypoxemia.

Results: A total of 239 cases were reviewed, of which 103 were non-survivors. A total of 45 (18%) were current smokers and 71 (29.7%) were ex-smokers. Smoking was more common in non-survivors (56.3% $P \leq .01$). Pulmonary hypertension was present in 18.8% of patients. 95.4% of patients who had received pirfenidone treatment were alive at the time of study. On multivariate analysis, pirfenidone treatment (OR 0.03; 95% CI 0.01-0.08), current smoking (OR 2.60; 95% CI 1.04-6.58), age older than 60 years (OR 2.63; 95% CI 1.04-6.58) and hypoxemia (OR 3.29; 95% CI 1.58-6.84) were the factors associated with mortality.

Conclusion: Smoking, age greater than 60 years and hypoxemia were identified as factors that increased the odds of mortality in IPF patients, whereas pirfenidone was found to lower the odds of mortality.

KEYWORDS
idiopathic pulmonary fibrosis, mortality, pirfenidone, Pakistan

1 | INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive form of interstitial lung disease (ILD) that carries a poor prognosis. It is characterized by the histological pattern of usual interstitial pneumonia (UIP) and primarily occurs in older adults.[1] It has a global prevalence of 20 cases per 100 000 people for males and 13 cases per 100 000 people for females.[2,3]

Mortality associated with IPF is the highest among the ILDs. The average survival duration after diagnosis is 2–4 years. Factors that have been shown to decrease survival

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

include older age, lower body mass index (BMI) and the development of complications like pulmonary hypertension and concomitant emphysema.[4–6] Smoking is the most consistent environmental risk factor for the development of IPF, and studies suggest a history of smoking worsens the prognosis.[4,7]

The heterogeneous clinical course of IPF also has an impact on mortality. Depending on the clinical variant of IPF that a patient presents with, their prognosis can be significantly altered. The majority of cases present after 50 years of age.[3] Comorbid conditions that may have an impact on the clinical course of IPF include obesity, diabetes mellitus, gastroesophageal reflux disease and pulmonary hypertension. Subpopulations of patients, mainly males and cigarette smokers, have shortened survival due to an accelerated course. The prognosis in patients with an acute exacerbation of IPF is poor, with short-term mortality exceeding 50%.[8,9]

Most studies on IPF have been conducted in industrialized nations with well-established healthcare systems. There is a lack of data on mortality associated with IPF. The diagnosis of IPF is delayed in developing countries where access to diagnostic resources like high-resolution computed tomography (HRCT) of the chest and pulmonary function testing (PFT) is limited and costly. In Pakistan, the clinical and radiological presentation of IPF may be masked by tuberculosis, which is endemic to the region, further compounding the delay in diagnosis.

The objective of this study was to identify factors associated with mortality in patients with IPF at a tertiary care center in Pakistan. There is currently no literature on the epidemiology, mortality or morbidity of IPF in Pakistan.

2 | METHODS

2.1 | Study design and setting

This retrospective chart review was conducted at Aga Khan University Hospital (AKUH). AKUH is a tertiary care referral hospital with 640 beds located in the major metropolitan city of Karachi, Pakistan.

2.2 | Study population

Data of 239 patients was collected via review of patient's medical records. ICD-9 coding was used to retrieve the patients' files. A multidisciplinary team comprising of a pulmonologist, a chest radiologist and a pathologist with special interest in ILDs reviewed the files. Cases of post-infectious fibrosis, bronchiectasis and other interstitial pneumonias that mimic IPF such as connective-tissue disease related ILD (CTD-ILD) and hypersensitivity pneumonitis were excluded from the study based on detailed environmental and occupational history, meticulous physical examination and serology.

2.3 | Data collection

This study was reviewed and approved by the AKUH ethics review committee. Patient medical records were retrieved using ICD-9 coding from January 2005 till December 2015. A standardized questionnaire was used to collect information about patient demographic variables, occupation, environmental exposures, clinical features, smoking, radiological and pathological pattern, disease severity, treatment and outcome of the disease.

Smoking status, clinical onset of disease, severity of disease based on forced vital capacity (FVC) on spirometry, pulmonary artery hypertension on transthoracic echocardiography and hypoxemia were assessed by classifying patients into sub groups. Smokers were classified as current smokers, ex-smokers and non-smokers. The clinical onset of disease was divided into sub-acute and chronic group. On spirometry disease severity was classified into mild (FVC >70% predicted), moderate (FVC 50%-70% of predicted) and severe (FVC <50% predicted). The patients who were assessed for pulmonary artery hypertension on echo were divided into mild (mean pulmonary artery systolic pressure-PASP 25–35 mm Hg), moderate (mean PASP 36–45 mm Hg), and severe (mean PASP >45 mm Hg) pulmonary artery hypertension (PAH). Hypoxemia was defined as having an oxygen saturation of less than 88% on room air at rest and requiring long-term oxygen therapy (LTOT).

The American Thoracic Society/European Respiratory Society Statement on Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias 2013 was used as a template for the diagnosis of IPF. Based on this classification patients were diagnosed with IPF if their HRCT findings met the following criteria: presence of bilateral honeycombing, reticular opacities, traction bronchiectasis, with minimal or no ground glass opacities and predominant basal or peripheral involvement.[10]

3 | STATISTICAL ANALYSIS

Data was analyzed using SPSS version 19. Mean and standard deviation were reported for quantitative variables. Frequencies with percentages were reported for qualitative variables. Logistic regression was used to identify factors associated with mortality. Factors with P value of <.20 were considered for multivariable model. Crude and adjusted odds ratio were reported in the final model.

4 | RESULTS

Out of 791 files that were reviewed, 239 met the criteria for our study. Of these 122 (51%) were males and average age was 67.4 years (±12.0). There were a total of 136 survivors

TABLE 1 Association of patient characteristics and IPF variables with mortality

Variable	Alive $n = 136$	Dead $n = 103$	P value
Age Mean (SD)	64.4 (11.3)	71.4 (11.8)	<.01
Gender			
Male	70 (51.5)	52 (50.5)	.9
Female	66 (48.5)	51 (49.5)	
Smoking *n* (%)			
Current smoker	15 (11.0)	30 (29.1)	<.01
Non-Smoker	78 (57.4)	45 (43.7)	
Ex-smoker	43 (31.6)	28 (27.2)	
Clinical Onset *n* (%)			
Sub-acute	8 (5.9)	2 (1.9)	.13
Chronic	128 (94.1)	101 (98.1)	
Clubbing *n* (%)	22 (16.2)	16 (15.5)	.89
Pulmonary Hypertension on Echo			
None	17 (50.0)	10 (20.8)	.04
Mild	8 (23.5)	20 (41.7)	
Moderate	6 (17.6)	9 (18.8)	
Severe	3 (8.8)	9 (18.8)	
Severity of disease based on spirometry ($n = 60$)			
Mild	24 (42.9)	1 (25)	.68
Moderate	15 (26.8)	2 (50)	
Severe	17 (30.3)	1 (25)	
HRCT Chest			
Lower lobe predominant	111 (81.6)	82 (79.6)	.6
Diffuse	25 (18.4)	21 (20.4)	
Treatment			
Pirfenidone	84 (67.5)	4 (3.9)	<.01
Prednisolone	39 (31.0)	89 (86.4)	
Prednisolone + Azathioprine	2 (1.6)	10 (9.7)	
Hypoxemia *n* (%)	31 (22.8)	54 (52.4)	<.01

and 103 non-survivors at the time of study. The characteristics of survivors and non-survivors are presented in Table 1.

A total of 45 (18%) were current smokers and 71 (29.7%) were ex-smokers. Smoking was more common in non-survivors (56.3%). Almost all the patients 229 (95.8%) had chronic onset of disease, while 10 (4.1%) had sub-acute onset. Clubbing was found in 38 (15.8%). Pulmonary hypertension was present in 45 (18.8%). Mild PAH was present in 18 (40%) patients, moderate in 15(33%), and 12 (27%) had severe PAH. The PAH was found to be significantly associated with mortality. Based on spirometry findings, 25 (10.4%) patients were found to have mild disease, 17 (7.1%) had moderate disease, 13 (5.4%) had severe, and 5 (2%) had very severe disease. HRCT findings showed lower lobe predominance in 193 (80.7%) subjects and diffuse distribution in 46 (19.2%) patients. Surgical lung biopsy was conducted in 4 of these patients; the remaining 42 patients were diagnosed by a multidisciplinary team.

When assessed for treatment, of the 88 (36.8%) patients who had received pirfenidone, 84 (95.4%) were still alive and 4 (4.5%) had died. Prednisolone was given to 128 (53.5%), of whom 39 (30.4%) were alive and 89 (69.5%) had died. A combination of prednisolone and azathioprine was received by 12 (5%) of the patients, of which 2 (16.6%) were alive while 10 (83.3%) had died. LTOT was administered to a total of 85 (35.5%) patients with hypoxemia, of which 31 (36.4%) were alive and 54 (63.6%) had died.

On the basis of multivariable model, treatment with pirfenidone (OR 0.03; 95% CI 0.01 to 0.08), age greater than 60 years (OR 2.63; 95% CI 1.04 to 6.58), current smoking (OR 2.60;

TABLE 2 Univariate and multivariable logistic regression models for mortality

	Univariate		Multivariate	
Variable	**Unadjusted OR**	**95% CI**	**Adjusted OR**	**95% CI**
Treatment				
Pirfenidone	0.02	0.01 to 0.07	0.03	0.01 to 0.08
Other treatments	1		1	
Age				
> 60	2.83	1.53 to 5.25	2.62	1.04 to 6.58
≤ 60	1		1	
Smoking				
Smoker	3.32	1.67 to 6.57	2.6	1.04 to 6.58
Non-smoker	1		1	
Hypoxemia				
Yes	3.73	2.14 to 6.51	3.29	1.58 to 6.84
No	1		1	

95% CI 1.04 to 6.58) and hypoxemia (OR 3.29; 95% CI 1.58 to 6.84) were the factors associated with mortality (Table 2).

5 | DISCUSSION

This study is the first to address factors associated with mortality in IPF in Pakistan. As one of the few tertiary care centers in the country, this hospital receives referrals from all parts of the country. The patient population thus reflects a range of socioeconomic and cultural backgrounds. We identified older age, smoking, and hypoxemia as factors that increased the odds of mortality in IPF, while pirfenidone was identified as having a protective effect on mortality.

For many years, a combination therapy of prednisone, azathioprine, and n-acetylcysteine was used to treat IPF.[11] In 2012, the PANTHER-IPF study concluded that the three-drug regimen increased mortality, frequency of hospitalization and treatment-related severe adverse events when compared with placebo.[12] Five randomized controlled trials have investigated the use of pirfenidone for this disease. Pirfenidone was shown to significantly decrease the rate of decline of lung function, as measured by forced vital capacity (FVC), slowing the rate of progression of IPF.[13–15] A meta-analysis by Rochwerg et al. established that pirfenidone was among the top three medications that reduced mortality in IPF.[16]

As data on the effect of pirfenidone on mortality is limited it is difficult to compare our findings with other regions. A meta-analysis of three randomized controlled trials found that pirfenidone decreased all-cause and IPF-related mortality when compared to placebo.[13] Further research is required to establish the effect of pirfenidone on mortality, including long-term follow up of patients to document mortality benefit.

Smoking is an established risk factor for IPF, but the effect of smoking status on mortality has been variable. Older studies have shown that being a current smoker had a protective effect resulting in longer survival times.[4] This effect however has been attributed to selection bias, and non-smokers have overall better odds of survival than current and former smokers.[17] Our study supports the evidence that smokers have higher odds of mortality than non-smokers.

We identified age greater than 60 as a risk factor for IPF. The median age of patients at diagnosis with IPF is 66 years.[18] Older age has been established in the literature as an IPF risk factor, but the mechanism behind aging and the development of IPF remains elusive. The diagnosis and management of the disease is complicated in the elderly population where the non-specific symptoms of cough and dyspnea can be attributed to other comorbidities like heart failure and chronic obstructive pulmonary disease. Although IPF and comorbid conditions may share risk factors, the likelihood for the presence of pulmonary and extrapulmonary comorbidities such as coronary artery disease and gastroesophageal reflux disease is higher in elderly patients with IPF.[19] Older age has been shown to worsen the prognosis of patients with IPF, supporting the results of this study.[20]

Patients with hypoxemia had higher odds of mortality than patients without hypoxemia. Low oxygen saturation is a manifestation of progressively worsening IPF with decreased lung function. Over half of the patients who had not survived at the time of this study had hypoxemia and required LTOT. Supplemental oxygen therapy is commonly needed for hypoxia that worsens with exercise.[20] Exertional desaturation with a SpO_2 drop of greater than 10% has been associated with increased mortality in patients with IPF.[21] Low mixed venous oxygen saturation has also been shown to be a poor

predictor of survival in patients with pulmonary hypertension associated with chronic fibrosing idiopathic interstitial pneumonia.[22] Our results support data indicating hypoxemia as a poor prognostic factor in patients with IPF.

Insufficient information from medical records precluded the assessment of risk factors such as gastroesophageal reflux disease, family history, occupational and avocational exposures of IPF and was a limitation of this study. Spirometry and echocardiography were not performed in all the cases due to limited financial resources.

6 | CONCLUSIONS

Smoking, age greater than 60 and hypoxemia requiring LTOT increased the odds of mortality in our population whereas pirfenidone reduced the odds of mortality. Further randomized controlled clinical trials are needed to study the effect of pirfenidone on mortality in our population.

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AVAILABILITY OF DATA AND MATERIALS

The dataset generated during and/or analyzed during the current study are not publicly available due to confidentiality of the patients but is available from the corresponding author on request.

CONFLICT OF INTERESTS

None of the authors have competing interests.

AUTHOR CONTRIBUTIONS

Study design: Ali Bin Sarwar Zubairi, Talha Shahzad
Ethical approval: Ali Bin Sarwar Zubairi
Paper writing: Ali Bin Sarwar Zubairi, Huzaifa Ahmad, Maryam Hassan, Talha Shahzad, Aamir Abbas
Data collection: Ali Bin Sarwar Zubairi, Huzaifa Ahmad, Maryam Hassan, Sajjad Sarwar
Data entry: Ali Bin Sarwar Zubairi, Maryam Hassan, Sajjad Sarwar
Data analysis: Ali Bin Sarwar Zubairi, Huzaifa Ahmad, Aamir Abbas
Reviewed the manuscript: Muhammad Irfan

ETHICS

This study was approved by Ethical Review Committee (ERC) 3510-Med-ERC-15.

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