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ORIGINAL INVESTIGATION / ÖZGÜN ARAŞTIRMA

Idiopathic Pulmonary Fibrosis: A Study of 46 Patients from Western India: Clinical Presentations and Survival

İdiyopatik Pulmoner Fibrozis: Batı Hindistan'dan 46 Hastalık Çalışma: Klinik Prezentasyon ve Sağkalım

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Abstract

OBJECTIVES: Idiopathic pulmonary fibrosis (IPF) is the most common form of interstitial lung disease (ILD) diagnosed all over the world as well as in India. The objective was to study the clinical presentations, treatment options, and survival of patients diagnosed with IPF.

MATERIALS AND METHODS: This was a 6-year retrospective observational study. All patients diagnosed with ILD underwent a comprehensive evaluation to confirm the diagnosis of IPF and were subsequently included in the study. Clinical data and laboratory data were recorded. Patients were treated as per current guidelines.

RESULTS: Out of the total number of patients (n=123) diagnosed with ILD, 46 (37.4%) patients were included in the study [Males, n=19 (41%) and females, n=27 (59%)]. Sixty-seven percent (n=31) of the patients were in the age group of 61-80 years. The mean age of males and females was 68.36 and 66.25 years, respectively. Clubbing was observed in 67% (n=29) of the patients. The mean forced vital capacity (FVC) was 52%. High-resolution computed tomography (HRCT) of the chest showed a definite usual interstitial pneumonia (UIP) pattern of honeycombing in 60% (n=28) of the patients. Desaturation on a 6 min walk distance was noted in 60% (n=28) of the patients. Ten patients wrongly received-anti tuberculosis treatment (21%) before they were diagnosed with IPF. The median delay in diagnosis was 20 months. The 5-year survival rate was 25%; the average survival was 39 months. Patients receiving pirfenidone showed a survival benefit compared with those having received triple therapy. Survival in IPF was significantly low compared with that in other ILDs. Twenty-four (52%) patients died during the study.

CONCLUSION: IPF is a disease which affects the fourth to seventh decade of the Indian population with low survival.

KEYWORDS: Idiopathic pulmonary fibrosis, survival, pirfenidone

Özet

AMAÇ: İdiyopatik pulmoner fibrozis (İPF) tüm dünyada olduğu gibi Hindistan'da da tanı almış interstisyel akciğer hastalığı (İAH)'nın en yaygın şeklidir. Amaç İPF tanısı almış hastaların klinik prezentasyonları, tedavi seçenekleri ve sağkalımlarını incelemekti.

GEREÇ VE YÖNTEMLER: Bu, altı yıllık prospektif gözlemsel bir çalışmaydı. İAH tanısı almış bütün hastalar İPF tanısını doğrulamak için kapsamlı bir değerlendirmeden geçtiler ve çalışmaya dâhil edildiler. Klinik ve laboratuvar verileri kaydedildi. Hastalar güncel kılavuzlara göre tedavi edildi.

BULGULAR: İPF tanısı konulan toplam 123 hastanın 46'sı (%37,4) çalışmaya dahil edildi [Erkek hasta sayısı, n=19 (%41), kadın hasta sayısı, n=27 (%59)]. Hastaların %67'si (n=31) 61-80 yaş grubundaydı. Yaş ortalaması erkeklerde 68,36 ve kadınlarda 66,25 idi. Çomak parmak hastaların %67'sinde (n=29) görüldü. Ortalama zorlu vital kapasite (FVC) %52'ydi. Yüksek çözünürlüklü bigisayarlı toraks tomografisi (YÇBT) hastaların %60'ında (n=28), bal peteği görünümlü usual interstisyel pnömoni (UIP) varlığını açıkça ortaya koydu. Hastaların %60'ında (n=28) altı dakika yürüme mesafesinde desatürasyon görüldü. On hasta İPF tanısı konulmadan önce hatalı olarak antitüberküloz tedavi almıştı (%21). Tanıda gecikme ortanca 20 aydı. Beş yıllık sağkalım hızı %25, ortalama sağkalım 39 aydı. Pirfenidon alan hastalar üçlü terapi alan hastalara kıyasla sağkalım avantajı gösterdiler. İPF'de sağkalım diğer İAH'lere kıyasla anlamlı olarak düşüktü. Çalışma süresince 24 hasta (%52) öldü.

SONUÇ: İdiyopatik pulmoner fibrozis düşük sağkalım ile birlikte Hindistan nüfusunun 40. ila 70. dekatını etkileyen bir hastalıktır.

ANAHTAR SÖZCÜKLER: İdiyopatik pulmoner fibrozis, sağkalım, pirfenidon

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INTRODUCTION

Interstitial lung diseases (ILD) are a group of disorders characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium [1]. Combining clinical, radiological, and pathological information is pivotal to accurate diagnosis in interstitial lung diseases. Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD diagnosed worldwide as well as in India. IPF portends a poor prognosis as well as increased morbidity and poor quality of life. In India where lung transplantation is in a nascent stage, patients presenting with IPF have a poor prognosis. We present the analysis of our data from the western Indian population.

The objective was to study the clinical presentations, treatment options, and survival of patients diagnosed with IPF.

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MATERIALS AND METHODS

Design and setting: This was a retrospective observational study of patients presented to our specialty respiratory clinics in the period from January 2008 to March 2014. Data analysis was performed subsequently.

Eligibility: All patients presented to the outpatients department with a history and examination suggesting interstitial lung disease were confirmed with a high-resolution computed tomography (HRCT) scan of the chest. The patients subsequently underwent a comprehensive evaluation of their case record forms to confirm the diagnosis of IPF and were then included in the study. Informed consent was obtained from all individual participants who were included in the study.

Data Collection

Clinical data: Case record forms (CRF) were reviewed for the following details: age, gender, education, occupation, family income, addictions, duration of cough and breathlessness, and history of treatment with anti-tuberculous drugs. Delay (in months) of diagnosis of ILD was calculated from the CRFs. Clubbing, identifiable respiratory risk factors, occupational history, exposure to birds, ship breaking, and demolition work to exclude other forms of ILD, which may mimic IPF, were also recorded.

Laboratory data: Baseline spirometry forced vital capacity (FVC) maneuver and subsequently every 3 monthly spirometry data were noted. Diffusion capacity of the lungs (DLCO) had not been performed in all patients. HRCT of the chest was performed on the scanner with prone cuts and expiratory cuts. The protocols consisted of 1-1.5 mm collimation sections reconstructed with a high spatial frequency algorithm at 1.25-1.5 cm intervals. The images were photographed at window settings appropriate for viewing the lung parenchyma (window level from -600 to -700 Hounsfield units (HU); window width from 1,200 to 1,500 HU). A panel of experienced radiologists noted the HRCT findings as per the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) joint statement [2-6]. CT findings were recorded and each case was classified into one of the following three categories: (1) Definite usual interstitial pneumonitis (UIP) pattern, (2) Possible with UIP pattern, and (3) suggestive of alternative diagnosis or NOT UIP pattern. Definite UIP pattern was recorded when honeycombing, traction bronchiectasis, bronchiolectasis, and lower lobe volume loss were prominent. UIP pattern was unlikely when HRCT showed ground-glass attenuation, decreased attenuation, mosaic attenuation, and centrilobular nodules, or when there was an upper lobe predominance of abnormality. CT scans were generally repeated after 1 year of treatment. Patients showing a CT pattern NOT UIP were excluded. Patients were classified under various subgroups of ILDs according to the latest guidelines [7]. In the 6-minute walk distance test (6MWD), the distance covered and the desaturation were noted. Details of the 6MWD test, which was repeated every 3 months, were also noted. Patients showing positive serological studies of serum rheumatoid (RA) factor, anti Scl-70 (Anti topoisomerase 1) antibody, and anti double stranded (ds)-DNA antibodies with correlating history were excluded from the study. Indications for bronchoscopy when performed were noted as follows: 1) Age <50 years with HRCT suggestive of UIP pattern and 2) CT suggestive of a possible UIP pattern. Bronchoscopy with bronchoalveolar lavage (BAL) collection and a transbronchial lung biopsy (TBLB) was performed. We chose patients under the age of 50 years for a bronchoscopy based on the ATS/ERS 2002 criteria [2] for the diagnosis of IPF in the absence of a surgical lung biopsy. The differential count performed on the BAL samples was noted. The histopathological diagnosis was noted during the analysis. 2D Echocardiography with resting pulmonary artery pressures on treatment initiation was noted.

Treatment data: Treatment in patients diagnosed as IPF from 2008 to 2012 were given as per the ATS/ERS joint statement 2002 [2,8]. Patients were treated with the combination of prednisolone, azathioprine, and N-acetyl cysteine (triple therapy). Patients were administered with 50 mg per day of azathioprine and subsequently the dosage was increased by 0.25 mg/kg/day every week to a maximum of 2 mg/kg/day i.e. 125-150 mg/day. Any cytopenias or hepatic derangements due to treatment were noted. From 2012, after the National Heart Lung Blood Institute (NHLBI) update [9], patients surviving on triple therapy were slowly withdrawn from this regimen and started on Pirfenidone. All new patients diagnosed with IPF from 2012 were also started on pirfenidone at a dose of 1200-1800 mg/day. The number of infective and non-infective exacerbations and mortality were noted.

Statistical Analysis

Statistical analysis was performed with Windows Med calc Version 12. Descriptive statistics were completed using medians and means, as appropriate. P values (determined by χ^2 or Mid- P exact or Fisher's exact tests) were reported; alpha was inferred at 0.05. Two-sided P values were reported. Survival analysis was calculated using the Kaplan-Meier survival estimates and was plotted on separate graphs.

RESULTS

Out of the total 123 patients diagnosed with ILD, 46 patients (37.4%) were diagnosed with IPF with a combined clinico-pathological and radiological correlation and were included in the study. Females were predominant (59%). Majority of the patients were in the age group of 61-80 years (67%). The mean age in males and females was 68.36 and 66.25 years. Four patients were below the age of 50 years and two patients were above 80 years. Three patients were smokers, and the rest were non-smokers.

Clubbing was observed in 67% of the patients (n=29). The duration of cough varied from 3 months to 7 years, the mean being 26 months. The duration of breathlessness varied from 2 months to 7 years, the mean being 23 months. Four patients presented with fever along with breathlessness and cough.

Desaturation on 6MWD was noted in 60% of the patients (n=28). Eight patients had resting oxygen saturation <90% on presentation. The mean FVC was 52% on presentation.

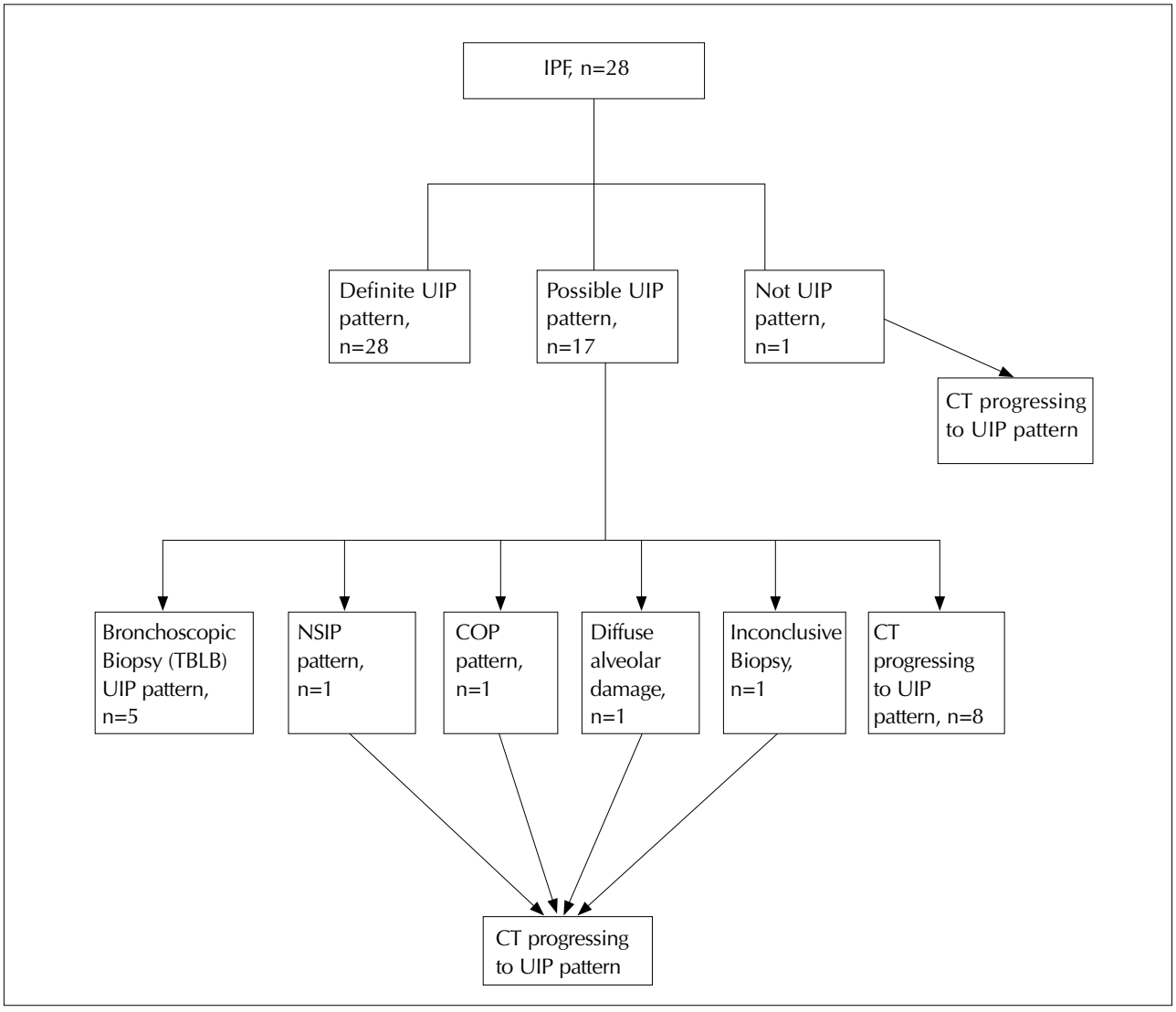

Figure 1. Algorithm for the computed tomographic diagnosis of IPF patients
TBLB: transbronchial lung biopsy, NSIP: nonspecific interstitial pneumonia, COP: cryptogenic organising pneumonia, IPF: idiopathic pulmonary fibrosis, UIP: usual interstitial pneumonia

HRCT of the chest showed a definite UIP pattern in 60% of the patients (n=28). Thirty-seven percent of the patients showed predominant reticulation with few areas of honeycombing in the lower lobes, suggesting a possible UIP pattern (n=17). One patient had patchy ground glass opacities with reticulation in bilateral lower lobes (n=1).

Out of these 18 patients, five were diagnosed with UIP on bronchoscopic biopsy (TBLB). Eight patients (n=8) on treatment with steroids progressed to a UIP pattern on follow-up CT scans. One patient was diagnosed with non-specific interstitial pneumonitis (NSIP) and one patient with cryptogenic organising pneumonia (COP) on bronchoscopic biopsy. Two patients were diagnosed with diffuse alveolar damage (DAD). One biopsy was inconclusive. Patients diagnosed with NSIP and COP on biopsy progressed on treatment to a UIP pattern on follow-up CT scans (Figure 1). Ten patients had been incorrectly diagnosed with tuberculosis and were administered anti-tuberculosis treatment (21%) before they were diagnosed with ILD in our clinics. These patients had a delay in the diagnosis of at least 6 months and in some cases up to 2 years. This data was statistically compared to determine whether the death rates were higher in these patients. The survival rate was 20% (n=2) in patients administered with anti-tuberculosis medications, whereas it was 50% (n=18) in patients not administered with anti-tuberculosis medications (p=0.05, OR 3.88, RR 1.02).

The median delay in diagnosis from the symptom onset was 20 months in our study. The duration of survival varied from 4 to 96 months from the symptom onset. Patients survived for 39 months on an average after the first visit and 45 months from symptom onset. The 5-year survival rate was barely 25% in our patients (Figure 2).

Seventeen patients were on pirfenidone and completed 2 years of this treatment at the time of analysis. Of these, four died while on pirfenidone. A comparison was made between patients who received pirfenidone and those who were on triple therapy. Patients receiving pirfenidone showed a survival benefit compared with those who received triple therapy; however, this was not statistically significant (Figure 3). At

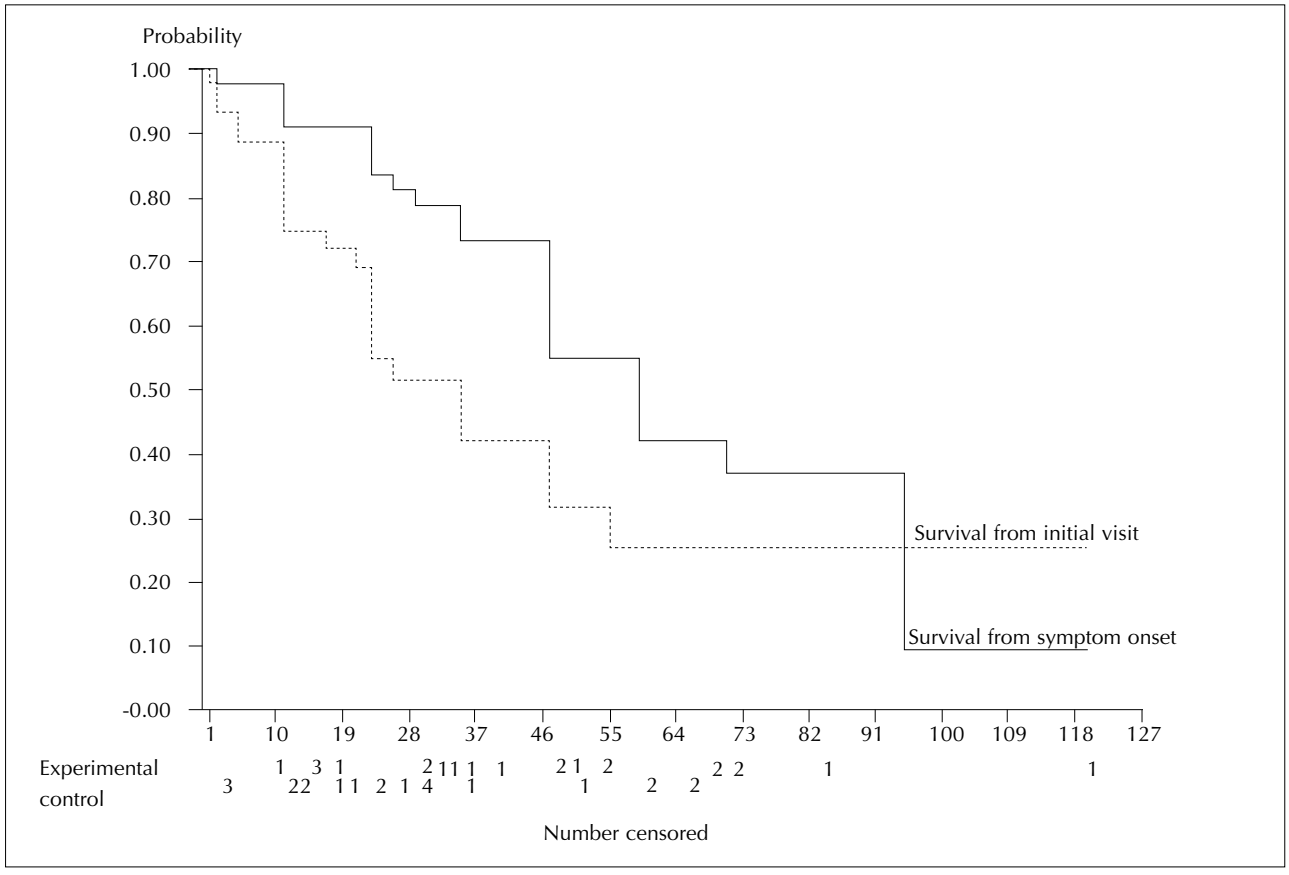

Figure 2. Survival in idiopathic pulmonary fibrosis
Kaplan–Meier curves showing the survival curves in patients with IPF (n=46). Time in months

the end of 3 years, the survival estimates showed a 75% survival in the pirfenidone group compared to the 40% survival in the triple therapy group but showed no survival difference in either group at the end of 4 years. The patients who were on pirfenidone showed a change in FVC from baseline at the end of 6 months that varied between -5% and +20%, the mean being +5%, and also a change at the end of a year from +5% to +19%, the average being 14%.

In our study, Kaplan-Meier survival estimates showed that the survival rate in IPF was significantly low compared with that in other ILDs (Figure 4). Twenty-four patients died during the study (52%). The causes of death in our patients were pneumothorax (n=3), acute exacerbation (n=6), cardiac disease (n=3), and slow progression of disease (n=12).

DISCUSSION

Our study on IPF has shown certain important points. A female predominance with involvement in the seventh and eighth decade was seen. The mean duration of cough and breathlessness was on 2 years (23 months and 26 months, respectively), thus showing that there is a delay in diagnosis. Non-smokers were predominantly observed in the cohort as opposed to studies from the western world, wherein smoking has been identified as a clear risk factor.

HRCT of the chest showed a definite UIP pattern in 60% of the patients (n=28). The HRCT of the chest findings were not confirmatory of the UIP pattern (IPF) in 18 of our patients. Nine underwent bronchoscopic biopsy. Of these, two patients were diagnosed with NSIP and COP patterns on histology. It is a well-known fact that transbronchial lung biopsy yields smaller tissue than open lung biopsy. In addition, rare early IPF may have an occasional focal organizing pattern on histopathology, leading to false diagnosis [10]. Moreover, the histologic pattern of NSIP may be present in lung biopsies in a variety of clinical disorders, including IPF [11]. Both COP and NSIP have excellent prognosis on treatment with steroids, with CT scans and PFTs showing improvement or stabilization [2,11]. However, both these patients showed progression to the UIP pattern on follow-up CT scans. Nine patients who did not undergo biopsy showed progression to honeycombing on HRCT of the chest and worsening symptoms despite adequate treatment with steroids.

The mean FVC was 52% of the predicted values on presentation. In our study, some patients were incorrectly administered with anti-tuberculosis medications, thus delaying the diagnosis and treatment had a higher mortality. The 5-year survival rate was 25% in our patients. Progression of disease was the cause of death in half of our patients. However, other causes such as cardiac failure and infections also contributed to mortality in significant numbers.

We analyzed all the available Indian data and also some international articles on ILD, which were available on PubMed.

All studies showed female predominance [12-14]. As in our study, other studies showed a prevalence of 43%-45% of IPF

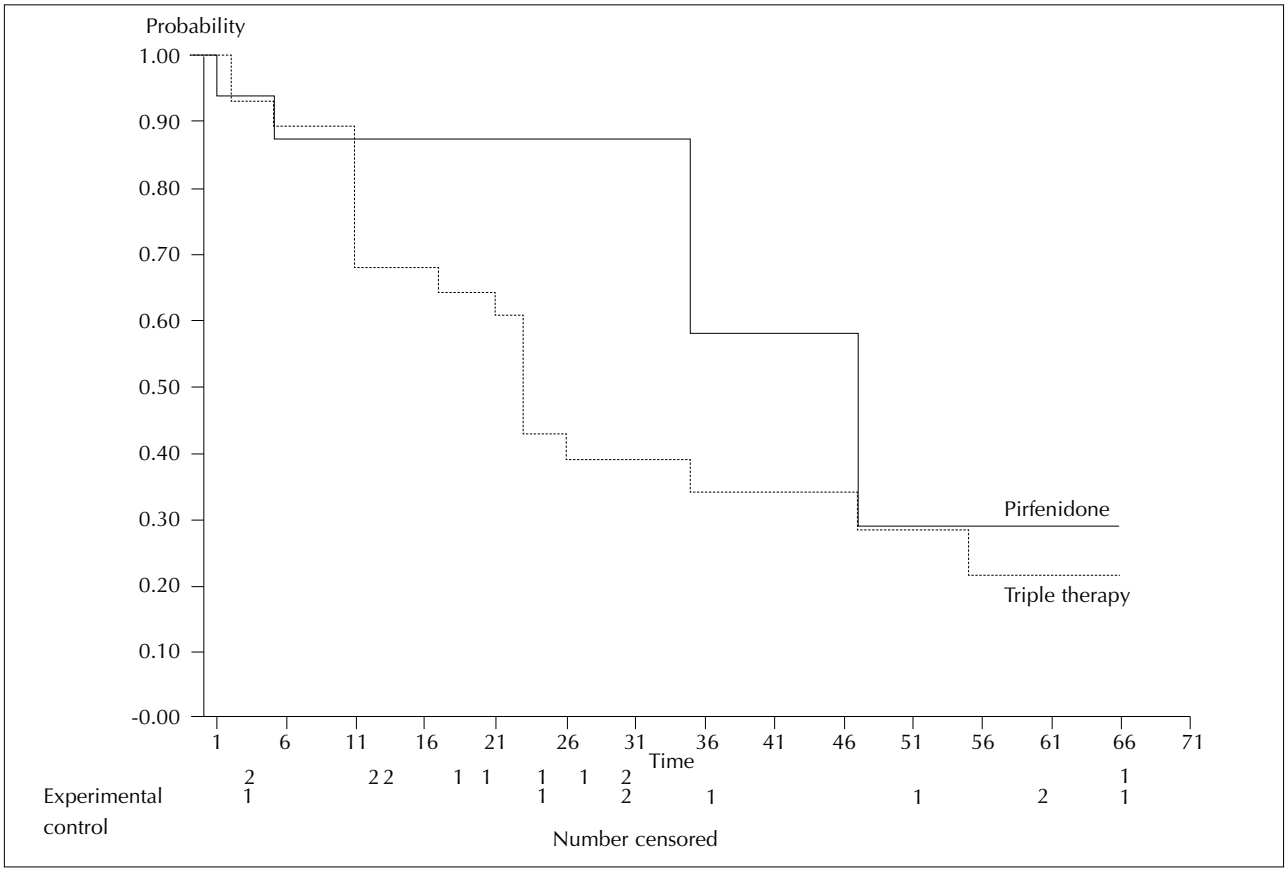

Figure 3. Survival in patients on pirfenidone compared with that on triple therapy
Kaplan–Meier curve showing the probability of survival on pirfenidone compared with that in patients on triple therapy. P=2.33.

cases amongst all ILD cases [14-16] and 28% in the study by Sharma et al. [16]. In the study by Subash et al. [15] from Vellore, the mean age group was 60 years in contrast to the study by Jindal et al. [12] from North India [13] where the mean age was 50 years. Jindal et al. [12] have mentioned that presentation of IPF may be in an earlier decade in India than in the western population. However, we do not agree with this statement because IPF in India was observed right from the fifth to seventh decade and predominantly in the seventh decade in our study. A large multicentric study needs to be undertaken before this statement can be validated. Clubbing was noted in 55% of the patients with IPF in the study by Jindal et al. [12]. The mean duration of cough and breathlessness in the study by Jindal et al. [12] was 18 and 16 months, respectively [12,13]. In the study by Sen et al. [14], the duration of cough and dyspnoea varied from 2 months to 5 years. Over the last four decades, from the study by Jindal et al. [12] to our study, the mean duration of presentation has not changed, thus reflecting the low awareness about this disease amongst primary care physicians and the general population.

Maheshwari et al. [13] reported honeycombing (n=61, 88.4%), ground-glass haziness (n=16, 23.2%), parenchymal nodules (n=5, 7.2%), and insignificant mediastinal lymphadenopathy (n=4, 5.7%) on CT scans of patients with IPF (n=69). The distribution of UIP on CT is characteristically basal and peripheral, although it is often patchy [2]. The presence of honeycombing as a predominant feature had a specificity of 98% and a positive predictive value of 96% for UIP [3]. Also in the same review by Misumi and Lynch [3], UIP pattern could be confidently diagnosed in 50%-75% of the cases of IPF by CT alone. In a study of 91 patients with suspected IPF, Hunninghake et al. [17] found that lower lobe honeycombing was present in 79% of the patients with UIP. The authors have also shown that lower lobe honeycombing was an independent predictor for the diagnosis of IPF. In the study by Lynch et al. [4], 283 of 313 patients had their diagnosis confirmed with IPF. Honeycombing was observed in 91.7%, reticulation in 100%, traction bronchiectasis in 92%, bronchiolectasis in 93%, and ground-glass opacities in 23% of the patients. Honeycombing is a definite marker for IPF. However, HRCT of the chest can sometimes have different patterns, thus mandating biopsy in these patients and also warranting a combined clinical, radiological, and pathological approach.

The mean vital capacity among Indian subjects with DPLD was noted to be around 55%-61% for the predicted value [12,18]. Indian patients have a moderate to severe disease on presentation.

To the best of our knowledge, there are no studies in India that have shown the mortality and survival curves on patients suffering from IPF in Indian patients. In many studies all over the world, IPF carries the worst prognosis, with median survival ranging from 2.5 to 3.5 years [19-23]. The 5-year mortality is around 70% in patients with IPF [24-26]. Similarly in studies reported in the United States[20,27], the symptoms preceded the diagnosis by 1-2 years.

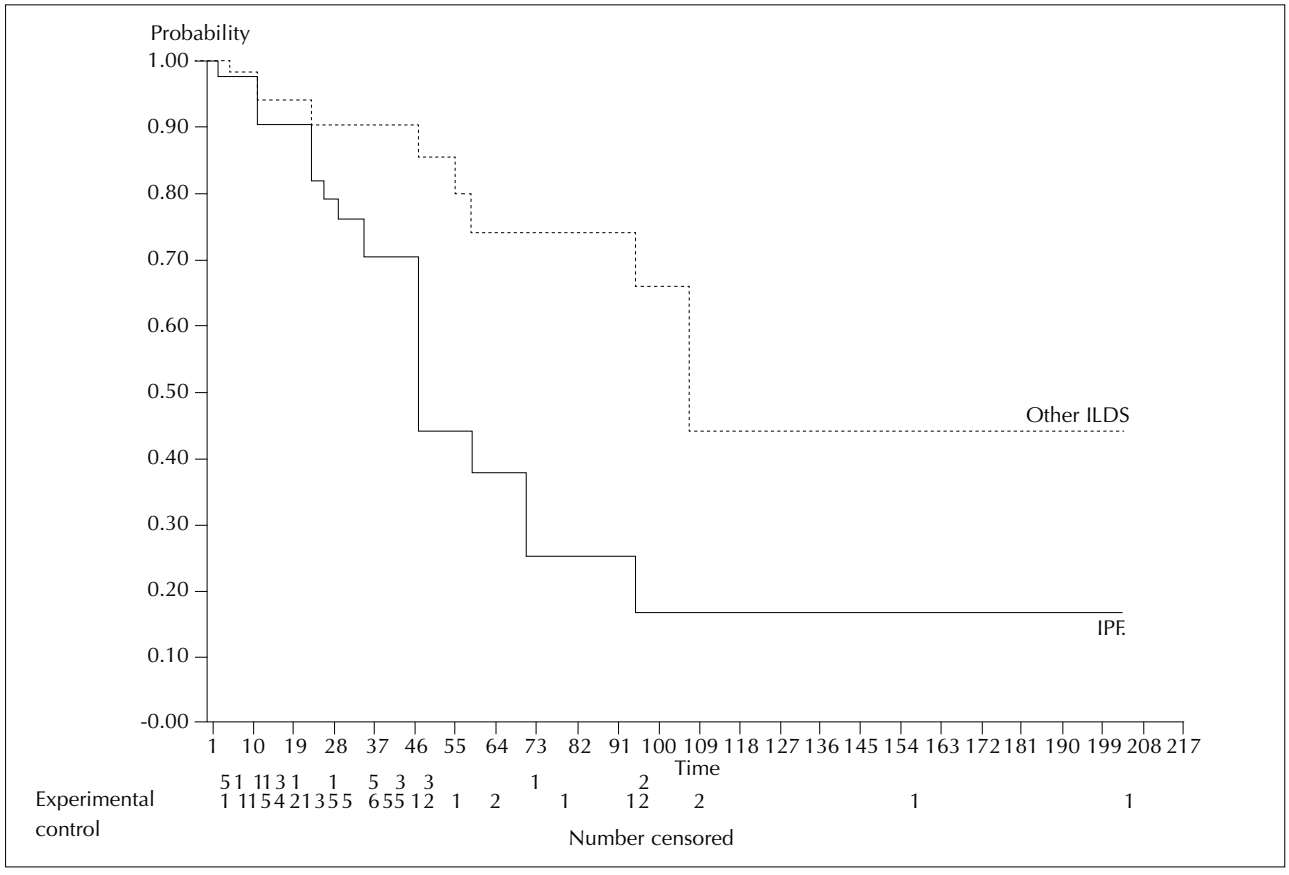

Figure 4. Survival in idiopathic pulmonary fibrosis compared with that in other ILDs.
Kaplan–Meier survival curves showing the comparison between the patients with IPF (n=46) and other ILDs (n=77) (Total patients=123). P=0.0001

In a cohort study of 129 patients by Lamas et al. [28], a longer delay was associated with an increased risk of death, median delay was 2.2 years (inter-quartile range 1.0-3.8 years), HR 1.3, and 95% confidence interval (CI) 1.03-1.6. This is the only study which discusses the mortality associated with a delay in diagnosis. As in our study, many patients who received anti-tuberculosis medications resulted in delayed diagnosis and treatment. The study by Lamas et al. [28] reflects the importance of early diagnosis and early referral for treatment for reducing all-cause mortality.

As in our study, half of the deaths were because of progression of fibrosis in the study by Martinez et al. [29]. In the concise clinical review by Ley et al. [20], 77% of the deaths were due to a respiratory cause, whereas 61% were due to progression of fibrosis. Non-respiratory deaths were due to cardiac causes, sepsis, gastrointestinal conditions, stroke, cancer, and other causes. As in our study, all studies which have examined the causes for mortality show that a significant proportion of patients die because of a non-respiratory cause. All the centers that are treating IPF may introduce algorithms such as regular cardiac checkup, screening for malignancies etc. in the treatment plans for timely interventions and to prevent mortality.

CAPACITY trial showed a significant change in FVC at week 72 and had fewer deaths in patients with IPF than in placebo groups [30,31]. In addition, some reports [32] now suggest that a combination of pirfenidone with N-acetyl cysteine decreased the rate of decline in FVC even in severe IPF, although this was in a small group of patients (n=18). Pirfenidone treatment results in improvement in the lung functions. However, whether it improves the survival is still a question to be answered.

Interstitial lung diseases studies and treatment protocols are still in nascent stages in India. The ILD registry, as mooted by Singh et al. [33], may try to answer some of these crucial problems faced in India.

Many of our patients who had a possible UIP pattern on HRCT of the chest could not undergo surgical lung biopsy. This study was analyzed at the end of 2 years after starting pirfenidone in the study subjects. More time and a larger cohort study may be required to support the beneficial effects of pirfenidone on the mortality. There are recent case reports and statements which contradict each other to show that all-cause mortality and/or functional vital capacity may be used as a clinically useful endpoint in drug trials of patients suffering from IPF [34-36]. However, for patients with IPF, there are currently no validated surrogate end-points [34].

In conclusion, idiopathic pulmonary fibrosis affects the fourth to seventh decade of the western Indian population with a very low survival. A Delay in diagnosis portends worse prognosis.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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