Original Article

Idiopathic Pulmonary Fibrosis in a Referral Center in Iran: Are Patients Developing the Disease at a Younger Age?

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Abstract

Background: The incidence of idiopathic pulmonary fibrosis (IPF) appears to be increasing. In the western literature, the average age of presentation is in the seventh decade of life while it has been reported to be earlier in the Middle East and India. Given that a paucity of epidemiological data exists in Iran, we sought to describe the clinical pattern and course of the disease at a large Iranian referral center.

Methods: A retrospective review was conducted of 132 patients diagnosed with IPF at the National Research Institute of Tuberculosis and Lung Diseases (NRITLD) in Tehran, Iran from 1988 through 2008. Data were collected from the medical records which consisted of demographics, clinical history, laboratory tests, pulmonary function tests (PFT), radiographic and pathology findings, treatment, and outcomes of the disease.

Results: The mean age at diagnosis was 56.6 years (95% CI: 53.8 – 59.4) with no significant sex predilection. Common presenting symptoms included dyspnea and cough, which occurred for a mean period of 21 months prior to diagnosis. Common signs included end-inspiratory crackles and digital clubbing, which were found in 85.6% and 55.3% of the patients, respectively. Radiographically, reticular and reticulonodular opacities were seen in 47.3% and 20.9% of the patients, respectively on high resolution computed tomography (HRCT). In patients who underwent lung biopsy, diffuse interstitial fibrosis was seen in 91.1%. The mean follow-up time for all patients was 32.8 months (95% CI: 23.2 – 42.4, range: 1 – 257 months). There were 16 patients who died during the study period. The mean age of death was 56.8 years (95% CI: 46.2 – 67.4), which is significantly lower than the life expectancy in Iran (P-value: 0.017). The mean survival time for patients who died was 1.1 years (95% CI: 0.5 – 1.7) after diagnosis. The one- and three- year overall survival rates for all patients were 88% and 79%, respectively.

Conclusion: The clinical characteristics of IPF in Iran are similar to those in the western literature. However, Iranian patients appear to be developing the disease a decade earlier than western patients.

Keywords: Age, idiopathic pulmonary fibrosis, Iran, Middle East, retrospective, survival

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Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common form of the idiopathic interstitial pneumonias, a subgroup of diffuse parenchymal lung diseases. IPF presents with an insidious onset, eventually leading to progressive, irreversible damage of the lung parenchyma through varying patterns of inflammation and fibrosis.[1–2] IPF has been diagnosed more frequently in the last two decades; this could be due to novel techniques in imaging, pathological examinations, and more common use of pulmonary diffusion indices. In most cases, the need for biopsy is eliminated by determining clinical and radiological diagnosing criteria.[3–6] There is no efficient intervention in order to cure or even stabilize the disease.[7–8] It is only recently that some studies reported prifenidone, a novel antifibrotic agent, and BIBF 1120, a tyrosine kinase inhibitor, to be of benefit in patients with IPF.[9–12]

The epidemiology of IPF appears to be changing. An increase in the incidence and prevalence of the disease in the nineties was reported in a study from the United Kingdom.[13] It is estimated that five million persons are affected worldwide.[14] Men are affected with IPF more commonly than women. A large population-based study in the United States reported a higher incidence in men (10.7 per 100,000) compared to women (7.4 per 100,000).[15] Furthermore, the incidence of IPF rises with older age. From a combined registry from the United States and Europe, two thirds of IPF patients were over 60 years of age at the time of diagnosis and had a mean age of 66 years.[1] There are a limited number of epidemiological studies on IPF in the Middle East. Studies from Saudi Arabia, Kuwait, and Iran reported a lower mean age than in western countries (range: 54.7 – 56.2 years).[16–18] However, patient cohort size was small in each study (range: 50 – 61 patients).

The National Research Institute of Tuberculosis and Lung Diseases (NRITLD) is a high-volume referral center for lung diseases from all over Iran. Given the differences in the epidemiological studies from the Middle East compared to western studies and the paucity of larger studies in Iran, we sought to evaluate the clinical characteristics of IPF patients from our center. In this study, we present the largest series of patients with IPF reported in the Middle Eastern literature.

Materials and Methods

Study design and population

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This was a retrospective descriptive study. Medical records of the patients diagnosed with IPF or suspected of having the disease based on clinical presentation, radiographic, and/or pathologic findings were identified using the keywords IPF, cryptogenic fibrosing alveolitis, and usual interstitial pneumonia at the NRITLD in Tehran between 1988 and 2008. A total of one hundred and eighty-eight records were identified. Medical records were reviewed and fifty-six of these patients were excluded since they were found to have disorders other than IPF, such as collagen vascular diseases, sarcoidosis, lung cancer, lymphoma, and hypersensitivity pneumonitis. Also, patients with the suspicion of drug toxicity or a history of chronic exposure to an environmental agent known to cause pulmonary fibrosis were excluded from the study. The following data were collected and recorded for analysis: age, sex, occupation, smoking history, past medical history, medication history, onset of symptoms, signs, and symptoms at presentation, laboratory test results, pulmonary function tests (PFT), radiographic and pathologic findings, treatments, and disease outcome. In cases where all data were not available, phone follow-up or face-to-face interview was done when possible.

Data analysis

Missing and discrepant data were checked by direct inquiry to the physician or by calling the patient. Data were statistically analyzed using SPSS version 16.0.2 (SPSS Inc., Chicago, IL, USA). T-test and logrank statistical tests were used to compare Kaplan-Meier survival curves.

Results

Demographics

Table 1 describes the characteristics of the patients. Follow-up data were available in 107 patients, while post- diagnosis follow-up was not available for 25 patients. There were 67 men and 65 women with a mean age of 56.6 years (95% CI: 53.8 – 59.4) at the time of diagnosis (range: 9 – 90 years). There was no statistically significant difference in the age of diagnosis between men and women. Eighty-six patients (65.15%) were over 50 years of age.

Occupational and smoking history

Occupational exposures were reported in ten patients (contact with livestock in one, farming in three, exposure to stone dusts in two, and exposure to chemicals in four). Thirty-one patients (23.4%) were current or previous smokers (25 men, 6 women; mean use = 28.1 pack-years). The mean age at diagnosis in this group was 59 years (95% CI: 53.4 – 64.6).

Clinical features

Breathlessness (68.2%) and cough (60.6%) were the most common presenting symptoms while inspiratory crackles (85.6%) and finger clubbing (55.3%) were the most common signs (Table 1). The patients experienced onset of symptoms for a mean of 21 months (95% CI: 15.8 – 26.2, range: 1 – 60 months) prior to diagnosis.

Radiographic findings

Radiographic features are shown in Table 2. The most common finding was a reticular (47.3%) or reticulonodular pattern (20.9%), which was bilateral in 87.9% of the cases. Out of the ten patients with a normal chest x-ray (CXR), eight had evidence of disease on HRCT. The two patients who had both a normal CXR and HRCT underwent lung biopsy, given the strong clinical suspicion of IPF. In both cases, pathological evaluation demonstrated diffuse fibrosis. Figures 1 and 2 show HRCT patterns of extensive disease.

Pulmonary studies

Out of 132 patients, 122 patients (92.4%) underwent PFT. A restrictive pattern was seen in 77 patients (58.3%), an obstructive pattern was seen in 11 patients (8.3%), and a mixed pattern was seen in 16 patients (12.1%). Additionally, 18 patients (13.6%) had PFT results that were nonspecific.

Transbronchial lung biopsy (TBLB) was performed in 79 patients (59.8%). Of these, histopathologic examination revealed interstitial fibrosis in 72 patients (91.1%). An open lung biopsy was performed in four out of the seven patients who had nonspecific findings on TBLB, which revealed diffuse interstitial fibrosis in all four patients. In the remaining three patients, the diagnosis of IPF was made based on the major and minor IPF diagnostic

Table 1. Clinical features of patients with IPF at the time of diagnosis

Characteristic		No (N %)
Age (years)		---
Mean ± SD:	56.6 ± 16.2	---
Range:	9–90	---
Sex		
Male		67 (50.8 %)
Female		65 (49.2 %)
Smoking history		
Current smoker		6 (4.5 %)
Former smoker		26 (19.7 %)
Never smoker		100 (75.8 %)
Symptoms and signs		
Crackles		113 (85.6 %)
Dyspnea		90 (68.2 %)
Cough		80 (60.6 %)
Finger clubbing		73 (55.3 %)
Chest pain		11 (8.3 %)
Fatigue		10 (7.6 %)
Cyanosis		9 (6.8 %)
Fever		6 (4.5 %)
Pulmonary function (n = 122)		
Restrictive		77 (58.3 %)
Mixed		16 (12.1 %)
Obstructive		11 (8.3 %)
Nonspecific		18 (13.7 %)
Unknown		10 (7.6 %)

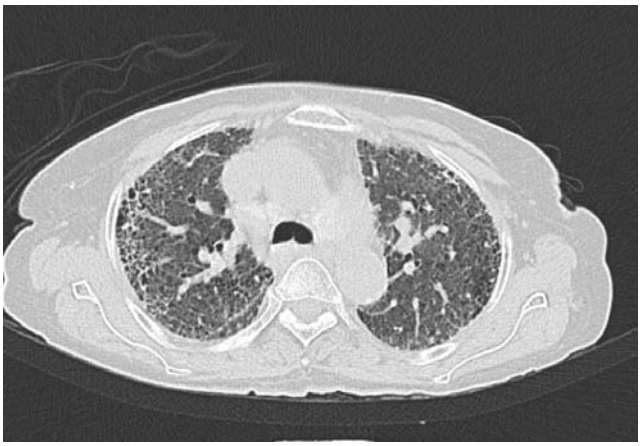

Figure 1. Axial HRCT through the lungs showing pulmonary fibrosis evidenced by subpleural honeycombing and interlobular septal thickening predominantly in the lower lobes.

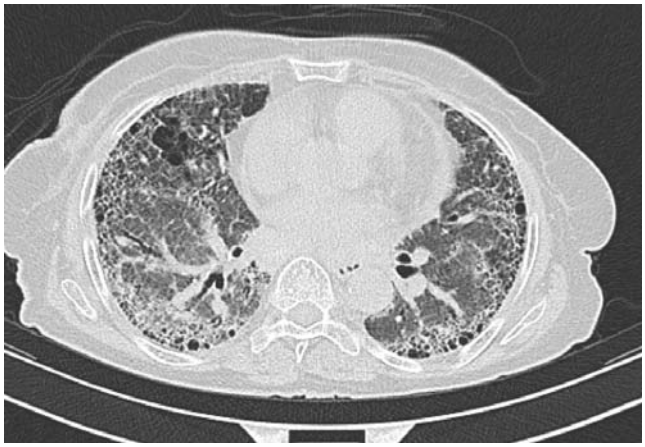

Figure 2. Axial HRCT through the lungs showing predominant abnormality, extensive honeycombing, some with confluence, and air cyst formation.

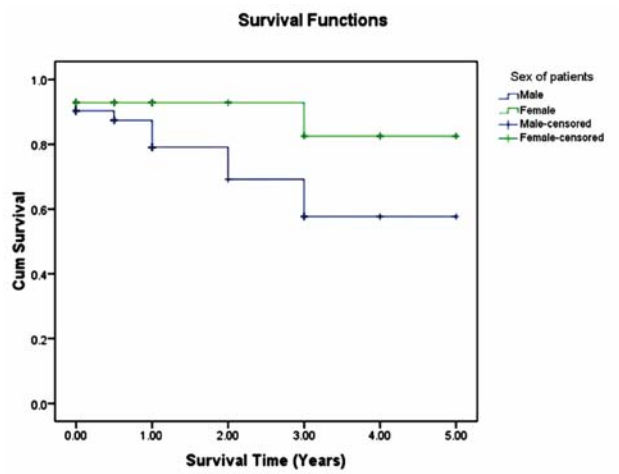

Figure 3. Kaplan-Meier curve of survival from the time of initial visit stratified by sex.

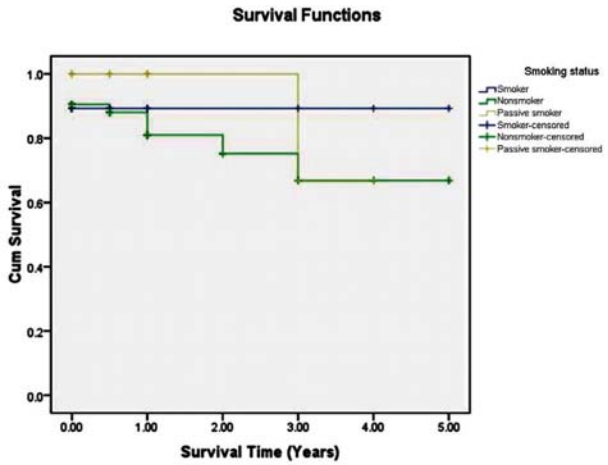

Figure 4. Kaplan-Meier curve of survival from the time of initial visit stratified by smoking history.

criteria defined by the American Thoracic Society.[1] Of note, all 11 patients who had an obstructive pattern on PFT had interstitial fibrosis on TBLB.

Treatment and clinical course

A corticosteroid was prescribed as the basic therapy for 124 patients (93.9%). Azathioprine and N-acetylcystein were also added in the regimen of 40 (30.3%) and 20 (15.2%) of the patients, respectively. Forty-eight patients (36.4%) experienced a stable clinical course. Disease progression was seen in 40 patients (30.3%) despite being placed on one of the above treatment regimens. The disease course could not be determined in 44 patients (33.3%).

Follow-up data were available for 107 (81.6%) of the 132 patients. The mean follow-up period was 32.8 months (95% CI: 23.2 – 42.4, median: 11.1 months, range: 1 – 257 months). Sixteen patients died during the study period, with a mean survival of 12.9 months (95% CI: 5.5 – 20.3) from the time of their diagnosis. In 13 of these patients death was due to respiratory failure. The patients had a mean age of 56.8 years (95% CI: 46.2 – 67.4) at their death, which is significantly lower than the life expectancy in Iran (70.8 years, P-value = 0.017). Age standardization of the mortality rate in the patients is shown in Table 3. The one- and three- year overall survival rates were 88% and 79%, respectively. Kaplan-Meier curves were drawn in different groups. Overall survival was higher in women versus men. However, comparison using logrank test showed no statistical significance. Overall survival was also higher in the smoker group, yet this was also statistically insignificant. The Kaplan-Meier curves are shown in Figures 3 and 4.

Discussion

In this study, the mean age at the time of IPF diagnosis was 56.6 years. Although two studies in the western literature reported a similar mean age at diagnosis,[19–20] most western studies report the mean age of diagnosis to be significantly higher (range: 61.5 – 73.5 years).[13,15, 21–29] In a series of 50 Iranian patients diagnosed with IPF, Jammati, et al. reported the mean age of diagnosis to be 56.2 years, which is consistent with our findings.[18] In IPF epidemiological studies from other Middle Eastern countries, a lower mean age of diagnosis has also been seen. In a series of 61 patients treated in Saudi Arabia, Alhamad, et al. reported a mean

Table 2. Radiographic features in patients with IPF (n=129).

	No (N %)
Pattern	
Reticular	61 (47.3 %)
Reticulonodular	27 (20.9 %)
Honeycombing	21 (16.3 %)
Hazy changes	13 (10.1 %)
Ground-glass	5 (3.9 %)
Normal	2 (1.5 %)
Distribution	
Diffuse	70 (54.2 %)
Subpleural	28 (21.7 %)
Lower lobe	20 (15.5 %)
Peripheral	1 (0.8 %)
Unknown	10 (7.8 %)

Table 3. Age standardization of the mortality rate in patients with IPF.

Age	No. of Patients	Mortality Rate in Patients, %	Reference Population*	Mortality Rate in Reference Population**, %	Expected No. of Death
< 40years	18	16.7	53,119,419	0.1	0.02
40–49	24	12.5	7,611,919	0.3	0.07
50–59	24	4.2	4,643,401	0.6	0.14
60–69	35	14.3	2,662,002	1.5	0.52
≥ 70	31	12.9	2,459,041	6	1.86

*Based on a report from Statistical Center of Iran, general census of 2006– 2007; ** Based on a report from National Organization for Civil Registration, census of 2006–2007.

age at the time of IPF diagnosis to be 54.7 years.[16] In a series of 52 patients treated in Kuwait, Khadadah and colleagues reported a mean age at the time of IPF diagnosis to be 55.4 years.[17] Similar observations have been reported in Indian subcontinent. In a series of 76 patients treated in India, Maheshwari and coworkers reported a mean age at the time of IPF diagnosis to be 50.6 years.[30] These findings indicate that in Iran and other regional countries, patients develop IPF almost one decade earlier than their counterparts in the west. It is unclear why such a discrepancy exits, however, there may be underlying genetic and/or environmental factors that affect the earlier development of IPF.

Most western studies support a male predilection for IPF,[21, 31–35] while a selected group of studies report equal male: female ratios[15,19–20,25] or even a female predominance.[28] In our study, a near equal male: female ratio was seen, which is consistent with the pattern previously reported in Iran, other areas of the Middle East, and India.[16–18,30]

The mean time elapsed from early onset of symptoms to the time of diagnosis was 21 months in the patients. This was similar to previous studies reporting a range of one to four years of symptoms before getting diagnosed.[16,19,36–37]

The overall survival for IPF patients has been reported to be two and a half to five years; however, the clinical course can be highly variable as some patients remain stable or progress very slowly for long periods of time while some others demonstrate an expedited course or experience frequent exacerbations leading to respiratory failure and death. Therefore, the overall survival can vary from a few months to over a decade in different studies.[38–41] Although we found a survival of 1.1 year in the 16 patients who died on follow-up, we cannot attribute this to our whole patient population since 66% of the patients were eventually lost during follow-up and consequently, we were not able to calculate survival due to the fairly large number of missing data.

Our study had some limitations. This was a retrospective study covering a wide range of years. Therefore, some clinical or paraclinical parameters were not available in the diagnostic or follow-up records of all the patients. Also, again due to the retrospective nature of the study, many patients were lost in follow-up and we couldn't figure out the outcome of their disease.

In conclusion, this study indicates that despite similar clinical features, the age at which patients develop IPF in Iran seems to be lower than the majority of literature from the west, yet comparable with studies from other regional countries. This is likely due to differences in environmental and genetic factors that are not yet elucidated.

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Abbreviations

CI = confidence interval, CXR = chest x-ray, HRCT = high-resolution computed tomography, IPF = idiopathic pulmonary fibrosis, NRITLD = National Research Institute of Tuberculosis and Lung Diseases, PFT = pulmonary function test, TBLB = transbronchial lung biopsy.

References

1. 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:** 646 – 664.
2. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002; **165:**

277 – 304.
3. Lynch JP, Saggar R, Weigt SS, Zisman DA, White ES. Usual Interstitial Pneumonia. *Critical Care*. 2006; **1:** 634 – 651.
4. Demedts M, Wells aU, Antó JM, Costabel U, Hubbard R, Cullinan P, et al. Interstitial lung diseases: an epidemiological overview. *The European respiratory journal Supplement*. 2001; **32:** 2s – 16s.
5. Hunninghake GW, Zimmerman MB, Schwartz Da, King TE, Lynch J, Hegele R, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *American journal of respiratory and critical care medicine*. 2001; **164:** 193 – 196.
6. Silva CI, Muller NL. Idiopathic interstitial pneumonias. *J Thorac Imaging*. 2009; **24:** 260 – 273.
7. Collard HR, Loyd JE, King TE, Lancaster LH. Current diagnosis and management of idiopathic pulmonary fibrosis: a survey of academic physicians. *Respiratory medicine*. 2007; **101:** 2011 – 2016.
8. Castriotta RJ, Eldadah BA, Foster WM, Halter JB, Hazzard WR, Kiley JP, et al. Workshop on idiopathic pulmonary fibrosis in older adults. *Chest*. 2010; **138:** 693 – 703.
9. Wuyts WA, Thomeer M, Demedts MG. Newer modes of treating interstitial lung disease. *Curr Opin Pulm Med*. 2011; **17:** 332 – 336
10. Hauber HP, Blaukovitsch M. Current and future treatment options in idiopathic pulmonary fibrosis. *Inflamm Allergy Drug Targets*. 2010; **9:** 158 – 172.
11. Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med*. 2011; **365:** 1079 – 1087.
12. Maher TM. Pirfenidone in idiopathic pulmonary fibrosis. *Drugs Today (Barc)*. 2010; **46:** 473 – 482.
13. Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax*. 2006; **61:** 980 – 985.
14. Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. *Orphanet journal of rare diseases*. 2008; **3:** 8.
15. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med*. 1994; **150:** 967 – 972.
16. Alhamad EH, Masood M, Shaik SA, Arafah M. Clinical and functional outcomes in Middle Eastern patients with idiopathic pulmonary fibrosis. *Clin Respir J*. 2008; **2:** 220 – 226.
17. Khadadah ME, Onadeko BO, Abul AT, Behbehan NA, Cerna M, Cherian JM, et al. Clinicopathological and therapeutic patterns of idiopathic pulmonary fibrosis in Kuwait: a prospective study. *Int J Clin Pract*. 2003; **57:** 879 – 884.
18. Jammati HR TP, Emami H, Mohammadi F, Bakhshayesh Karam M, Masjedi MR. Clinical pattern of idiopathic pulmonary fibrosis: a retrospective study. *Tanaffos*. 2006; **5:** 27 – 32.
19. Erbes R, Schaberg T, Loddenkemper R. Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? *Chest*. 1997; **111:** 51 – 57.
20. Gay SE, Kazerooni EA, Toews GB, Lynch JP, Gross BH, Cascade PN, et al. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med*. 1998; **157:** 1063 – 1072.
21. Johnston ID, Prescott RJ, Chalmers JC, Rudd RM. British Thoracic Society study of cryptogenic fibrosing alveolitis: current presentation and initial management. Fibrosing Alveolitis Subcommittee of the Research Committee of the British Thoracic Society. *Thorax*. 1997; **52:** 38 – 44.
22. Barlo NP, van Moorsel CH, van den Bosch JM, van de Graaf EA, Kwakkel-van Erp JM, Grutters JC. [Idiopathic pulmonary fibrosis; description of a Dutch cohort]. *Ned Tijdschr Geneeskd*. 2009; **153:** B425.
23. Antoniou KM, Hansell DM, Rubens MB, Marten K, Desai SR, Siafakas NM, et al. Idiopathic pulmonary fibrosis: outcome in relation to smoking status. *American journal of respiratory and critical care medicine*. 2008; **177:** 190 – 194.
24. Collard HR, King TE, Jr., Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003; **168:** 538 – 542.
25. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1998; **157:** 199 – 203.
26. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: Impact of oxygen and colchicine, prednisone, or no therapy on survival. *Am J Respir Crit Care Med*. 2000; **161:** 1172 – 1178.
27. Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. *Chest*. 1998; **113:** 396 – 400.
28. von Plessen C, Grinde O, Gulsvik A. Incidence and prevalence of cryptogenic fibrosing alveolitis in a Norwegian community. *Respiratory medicine*. 2003; **97:** 428 – 435.
29. Fernandez Perez 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:** 129 – 137.
30. Maheshwari U, Gupta D, Aggarwal AN, Jindal SK. Spectrum and diagnosis of idiopathic pulmonary fibrosis. *Indian J Chest Dis Allied Sci*. 2004; **46:** 23 – 26.
31. Turner-Warwick M, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: response to corticosteroid treatment and its effect on survival. *Thorax*. 1980; **35:** 593 – 599.
32. Hubbard R, Johnston I, Coultas DB, Britton J. Mortality rates from cryptogenic fibrosing alveolitis in seven countries. *Thorax*. 1996; **51:** 711 – 716.
33. Mannino DM, Etzel RA, Parrish RG. Pulmonary fibrosis deaths in the United States, 1979 – 1991. An analysis of multiple-cause mortality data. *Am J Respir Crit Care Med*. 1996; **153:** 1548 – 1552.
34. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, et al. Determinants of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1994; **149:** 450 – 454.
35. Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. *Eur Respir J*. 1998; **12:** 1010 – 1019.
36. 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:** 639 – 644.
37. Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed Access and Survival in Idiopathic Pulmonary Fibrosis: a Cohort Study. *Am J Respir Crit Care Med*. 2011. **184:** 842 – 847.
38. Hoo ZH, Whyte MK. Idiopathic pulmonary fibrosis. *Thorax*. 2011. **67:** 742 – 746.
39. Barlo NP, van Moorsel CH, van den Bosch JM, Grutters JC. Predicting prognosis in idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 2010; **27:** 85 – 95.
40. Harari S, Caminati A. IPF: new insight on pathogenesis and treatment. *Allergy*. 2010; **65:** 537 – 553.
41. Selman M, Pardo A, Richeldi L, Cerri S. Emerging drugs for idiopathic pulmonary fibrosis. *Expert Opin Emerg Drugs*. 2011; **16:** 341 – 362.