Study of idiopathic pulmonary fibrosis in a tertiary care centre

Ramakrishna Rachakonda[1,*], Nandeeswara Reddy CV[2]

[1]Professor & HOD, Dept. of Pulmonology, NRI Medical College, Chinakakani, Guntur, Andhra Pradesh, [2]Senior Resident, Appollo Medical College, Chittoor, Andhra Pradesh, India

***Corresponding Author:**
Email: ramakrishna45@yahoo.co.in

Abstract

Introduction: Idiopathic interstitial pulmonary fibrosis is an important debilitating disease among the interstitial lung diseases, frequently diagnosed with the help of HRCT among the symptomatics.

Materials and Methods: We have studied a total of 48 cases of IPF over a span of two and half years. Among a total of 104 ILDs attending our tertiary care centre IPF constituted 48 cases accounting for 46%. IPF cases are diagnosed on the basis of clinical history and hRCT findings.

Results: There is a female preponderance of 1.4:1. Mean age of IPF patients in our study is 57.9 years. Mean age in females is 60.71 and 53.9 in males.Among our 48 cases of radiologically diagnosed IPF forty patients had definite UIP Pattern and 8 patients have possible UIP pattern as defined by the radiologist. The frequency of difinite IPF cases increased with severity of symptoms as measured by MMRC scale and the association is statistically significant. More than 90% of patients expressed tiresomeness and breathlessness. Cough was seen in 60% and pain chest was found in 45% of IPF patients. There is a statistically significant correlation of disease severity measured by MMRC scale with decrease in DLCO. BAL fluid lavage showed predominant neutrophils in >90% of IPF patients. Severity of IPF measured by MMRC correlated with decrease in 6 minute walk distance($p<0.05$). There is a statistically significant correlation with MMRC grade and percentage desaturatiion in 6 minute walk test.($p<.05$). All the patients of IPF in our study had pulmonary arterial hypertension. The severity of PAH has no statististically significant correlation with severity of IPF as measured by MMRC grade of breathlessness. By spirometry 62.5% of IPF patients had restrictive lung disease and 29% had combined obstructive and restrictive lung disease. There is no statistically significant correlation between the severity of IPF as measured by MMRC scale with severity of restriction measured by FVC percentage.

Summary and Conclusion: Idiopathic interstitial pulmonary fibrosis is a debilitating disease. Constitutes significant proportion of ILDs. Females outnumbered males. Tiresomeness and breathlessness are predominat symptoms. Disease occurred at a much earlier age in males. Active and passive smoking possibly contributes to the severity of IPF. MMRC grade correlates significantly with DLCO, 6 minute walk distance and definite UIP. There is no statistically significant correlation of MMRC grade with severity of PAH and FVC values.

Keywords: Interstitial Lung Disease (ILD); Idiopathic Pulmonary Fibrosis (IPF); MMRC Grade, Desaturation; Broncho alveolar lavage; DLCO.

Introduction

Idiopathic pulmonary fibrosis is an important decompensating condition among idiopathic interstitial pneumonias [1]. There is a progressive aggravation of symptoms and death occurs in two to three years after the diagnosis.[1,3] Unlike other interstitial pneumonias they do not respond to corticosteroid drugs[2]. Idiopathic pulmonary fibrosis is often diagnosed by clinical presentation and chest radiology especially high resolution CT scan. Certain radiological presentations are said to be pathognomonic for IPF[1,2]. IPF occurs in relatively older age and is less amenable for treatment[4].

Radiologically IPF is diagnosed by peripheral subpleural lower zone lesions with interstitial pattern with or without honeycombing with heterogenous distribution. Findings probably suggestive of UIP include peripheral subpleural lower zone reticular lesions with bronchiectasis or traction bronchiectasis with minimal GGO.Subpleural basal predominant lesions with subtle reticulation and minimal GGO or distortion along with CT features or distribution of fibrosis not suggestive of any particular disease are considered under the heading indeterminate for UIP[5].

Alternative diagnosis is considered if the CT is suggestive of Pneumonia, Nodules micronodular nodules, centrilobular nodules, predominant GGO, mosaic attenuation or cystic changes. When the lesions are distributed in peribronchovascular region, perilymphatic regions, upper or mid zones alternative diagnosis should be considered. Presence of pleural plaques points to asbestosis and dilated esophagus to connective tissue disease. Pleural effusion and pleural thickening occurs in CTD or drug induced ILD. Distal clavicular erosions occur in RA. The present study is conducted Katuri Medical college Hospital, Department of Pulmonary Medicine and Sanjeevani hospital, Guntur after approval from ethical committee was obtained.

Background

Interstitial lung diseases are frequently diagnosed nowadays with the availability of HRCTs. There are nearly two hundred varieties of interstitial lung diseases are diagnosed. The treatment of ILDs with the known

aetilogies lies in the treatment of the background disease. Idiopathic interstitial pneumonias are the ILDs with no known definite causes.

IPF stands among the IIPs as the most debilitating disease with poor prognosis. As the IPF is increasingly diagnosed we studied a total of forty eigtht cases of IPF in our study.

Materials and Methods

We studied the idiopathic pulmonary fibrosis as an extension of our study of interstitial lung diseases. After excluding interstitial lung diseases with known causes we studied the HRCT scans of chest of the patients and included forty eight patients who had UIP pattern or possible UIP pattern in their chest CTs. We analysed the clinical, radiological data, studied the exercise tolerance, measured DLCO and BAL fluid analysis of the forty eight patients. Statistical analysis is done with SPSS 20 software. Statistical test of association is done with chisquare test

Observations and Results

Among a total of one hundred and four ILD patients IPF constituted 46%. The breakup of different ILDs diagnosed during two years of observation are as follows:

Table 1: IPF and Non IPF

	Number of patients n=104	Percentage
IPF	48	46%
NSIP	22	21%
NSIP with CTD	12	12%
Hypersensitivity pneumonitis	14	13%
Rare forms (LAM,LCH)	4	4%
Drug Induced	4	4%

Table 2: IPF AND non IPF

	Number of patients
IPF	48
Non IPF	56

Among 104 patients of interstitial lung disease, 48 patients (46%) are diagnosed as IPF and 56 patients(54%) are diagnosed as non IPF .

Table 3: Age distribution in IPF patients

Age	No. of Males	No. of Females	Percentage	Total
30-40 Years	00	01	2.08%	01
40 to 50 years	06	03	18.75%	09
50 to 60 years	11	09	41.66%	20
60- 70 years	02	09	22.92%	11
70and above	01	06	14.58%	07
Total	20	28		
Mean Age	53.9	60.71		57.91

In the present study the mean age of patients of IPF is 57.91 years. 53.9 among males and 60.71 among females.

Table 4: Sex distribution in IPF

Sex distribution	Number of ipf patients n=24
Males	20
Females	28

Among 48 patients of IPF, 20 were male patients and 28 were female Patients.

Table 5: Symptomatology

Symptom	No. of Patients	Percentage
Cough	29	60.41%
Tiredness	43	93.48%
Breathlessness	46	95.83%
Pain chest	22	45.83%

N=48

Table 6: Grades of MMRC in patients of IPF

Total IPF patients n= 48	Number	Percentage
Grade I MMRC	2	4.16%
Grade II MMRC	14	29.16%
Grade III MMRC	26	54.17%
Grade IV MMRC	6	12.5%

MMRC grades of breathlessness.

Table 7: HRCT findings

No. of Patients	Definite UIP	Possible UIP
No. of Patients	40	08

N=48

Table 8: Correlation MMRC Grade with Radiological Shadows

Grade of MMRC	No.of cases of Definite UIP	No. of Cases of Possible UIP
Grade I	01	01
Grade II	08	06
Grade III	25	01
Grade IV	06	00

The Chi-square statistic is 12.7912. The p-vale is 0.00511. The result is significant at a p-value of <.05.

Table 9: DLCO in IPF

DLCO	No. of IPF Patients	Percentage
30-40%	22	45.83
41-50%	18	37.5
51-60%	06	12.5
61-70%	02	4.17

Table 10

Grade of MMRC	DLCO 30-40%	41-50%	51-60%	61-70%	Total No. of Patients
Grade I	01	00	01	00	02
Grade II	08	04	01	01	14
Grade III	11	13	00	02	26
Grade IV	02	01	03	00	06

Table 11: Correlation of DLCO with MMRC Total No. of Patients N=48

DLCO %	MMRC Grade I	MMRC Grade II	MMRC Grade III	MMRC Grade IV	Total	
30-40%	01	08	11	02	22	45.83%
41-50%	00	04	13	01	18	37.50%
51-60%	01	01	01	03	06	12.50%
61-70% and above	00	01	01	00	02	4.17%
Total	02	14	26	06	48	100%

The Chi-square statistic is 18.7591. The p-value is 0.027321. The value is statistically significant at a p-value of <.05.

Table 12: BAL fluid analysis in IPF patients

Type of cell predominant in BAL fluid	Number of patients n=24	Percentage
Neutrophills	44	91.6%
Lymphocytes	4	8.4%

Table 13: 6 minute walk distance among IPF patients N=24

Distance walked	No. of Patients	Percentage
<200 metres	15	31.25%
200-300 metres	15	31.25%
300-400 metres	10	20.83%
400 metres and above	08	4.16%

Table 14: Correlation of 6 minute walk distance with MMRC scale

Grade of MMRC	Distance walked <200mts	200mts to300 mts	300to 400 metres	>400mts	No. of Patients
Grade I	00	00	01	01	02
Grade II	02	02	04	06	14
Grade III	07	13	05	01	26
Grade IV	06	00	00	00	06
No. of Patients	15	15	10	08	48

The Chi-square statistic is 31.0198. The p-value is .000294. The result is significant at p-value of <.05.

Table 15: MMRC Grade of Breathlessness and Desaturation in IPF patients on six minute walk Test N=48

MMRC Grade	Desaturation <4%	Desaturation 4-8%	Desaturation 8-12%	Desaturation >12%	Total number
Grade I	01	01	00	00	02
Grade II	00	03	09	02	14
GradeIII	00	07	10	09	26
H Grade IV	00	00	04	02	06
Total	01	11	23	13	

When percentage desaturation is correlated with MMRC grade there is a statistically significant correlation of increased desaturation on exercise with increased grade of MMRC. The chi-square statistic is 29.8967. The p-value is .000457 and the result is significant at a p value of <0.5

Table 16: PAH in IPF Patients

Grade of PAH	No. of Patients	Percentage
Mild	4	8.33%
Moderate	28	58.33%
Severe	16	33.33%

Table 17: Correlation of PAH with MMRC Grade

MMRC	Mild PAH	Moderate PAH	Severe PAH	Total
Grade I	01	01	00	02
Grade II	02	04	08	14
Grade III	02	06	18	26
Grade IV	00	00	06	06
No.of Patients	05	11	32	48

Chi-square satatistic is 8.78. The p-value is .186333. The value is not significant at p <.05.

Among 48 patients of IPF 18 of the twenty male patients were smokers. Two male patients were non-smokers. Among twenty eight female IPF patients twenty seven were non smokers. One patient gave history of limited cigar smoking. Among twenty seven non smoker female IPF patients twenty gave history of passive smoking their spouses being smokers.

Final 18: Smoking among IPF patients n=48

Category	Males	Females	Total	Percent
Smokers	18	01	19	39.58%
Nonsmokers	02	27	29	60.42%
Passive Smoking among females			20	71.43%

Among 48 patients 30 patients (62.5%) showed restrictive pattern, 14
Patients (29.16%) showed mixed **spirometry** pattern and 4 patients (8.33%) Obstructive pattern in showed.

Final 19: Spirometry among IPF patients

Spirometry Pattern	Males	Females	Total	Percentage
Restrictive	16	14	30	62.5%
Combined Obstructive and Restrictive	02	12	14	29.16%
Obstructive	02	02	04	8.33%

Final 20: Correlation of MMRC Grade with Spirometry pattern among 48 patients of IPF

MMRC Grade	Restrictive Disease	Combined disease	obstructive Disease	
Grade I	01	01	00	02
Grade II	09	04	01	14
Grade III	18	06	02	26
Grade IV	02	03	01	06
Total	30	14	04	48

Final 21: MMRC and Percentage of FVC. Mean FVC in our patients is 48% predicted

MMRC Grade	FVC <45%	45-60%	60% and above	Total
Grade I	00	01	01	02
Grade II	04	08	02	14
Grade III	15	08	03	26
Grade IV	05	01	00	06
Total	24	18	06	

The chisquare statistic is 9.514. The p-value is .146665. The result is not statistically significant.

Discussion

Our study showed a female preponderance among cases IPF in a ratio of 1:4. Harold R. Collard study showed IPF is a disease of old age and mean age of their patients was 65 years[6] and it is rare in younger age group. In our study we didnot have any patients in the above 65 years age group.

Jürgen Behr study *also confirmed a mean age of IPF was 68.They found HRCT could diagnoseniPF in 90% of patients*[7]. So-My et al. koo also agreed that IPF occured in old age and duration of survival was the same even for those diagnosed at an earlier age[8].

Luba Nalysnyk et al found a male preponderance among their IPF patients. Our study showed a female prepondeance in aratio of 1:4[9].

M. K. Han, S. Murray study also found a male preponderance but they felt that survival was better among females and among patients who did not desaturate below 88% on ambulation[10].

Brett Ley et al. In their study found that Incidence and mortality from IPFare increasing. Occupational and environmental exposure, tobacco smoking, gastroesophageal reflux and genetic factors are the risk factors[11].

Virendra Singh study showed female preponderance in ILD patients. IPF was more common among males in a male:Female ratio of 2:1. Prevalence of IPF in their study was 27% where as in our study of IPF we had female preponderance and IPF constituted 46% of ILD patients[12].

Kaisa Rajala study found Predominant symptoms were tiredness, breathlessness, cough and pain in movement. Increased mMRC correlated with decreased HRQOL. chest pain ($p<0.001$) had a positive linear relationship to increased mMRC score. An increasing mMRC score reflects impaired HRQoL and a high symptom burden[13].

Tomoo Kishaba study showed that never-smoking IPF patients developed more acute exacerbation (AE) than smoking IPF patients but in our study majority of our patients are non smokers. But when passive smoking is considered exposure to environmental tobacco smoke is high among our patients of IPF[14].

Hasti Robbie et. al. Proposed that IPF is the commonest IIP. It is associated with poor prognosis. A chronic progressive IIP. Results in stepwise loss of pulmonary function. Progress of the disease is variable in different individuals. In general IPF is associatecd with poor prognosis with a median survival rate of 2-3 years. Ours is a cross sectional observation study wherein we didnot follow the patient's progress. Nevertheless in our setting IPF occured at a much lesser age than in Europe and severity of the disease at the time of presentation is comparable[15].

Martin Kolb study proposed Severity of IPF was measured by pulmonary function tests. GAP model of measuring the severity of IPF involves Gender (G), Age (A)), and two lung variables namely FVC and DLCO. GAP model can help in management of IPF. Ij our study also In our study of iPF patients grades of mMRC correlated with severity of IPF.DLCO also correlated with mMRC grade. Lower the DLCO values greater is the MMRC grade. The value is statistically significnt at a p-value of 0.027321[16].

HRCT is a useful paramweter to assess the severity of IPF. In our study we compared the MMRC grade with radiological finding of difinite UIP or possible UIP. With the increase in MMRC grades number of cases of definite UIP are high and the value is statistically significant at a p-value of *0.00511*

Fernando J, et al study revealed Restrictive ventilatory defect, reducing DLCO and exertional desaturation to less than 88% are important prognostic factors[17]. In our study MMRC grade of breathlessness statistically correlated with DLCO, 6 minute walk distance and percentage desaturation making them valuable tools for the assessment of patient with IPF

Antoni xaubet et. al. Proposed that Extent of lung involvement in HRCT correlated with decrease in FVC. Extent of ground glass pattern correlated with FVC. Arterial saturation at peak exercise correlated with HRCT and FVC values. Changes in HRCT among patients of IPF correlated with changes in DLCO and FVC over a span of time[18]. Spirometry is an important tool in the assessment of IPF patients

Estrella Fernández Fabrellas proposed that IPF is a devastating disease with progressive loss of lung function. Survival period from the time of diagnosis is 3-5 years.Functional, clinical and radiological parameters influence the mortality. Genetic and biomarkers may be useful in assessing the prognosis. Early lung transplantation may be useful in selective patients[19].

IPF is adisease with poor prognosis. Ganesh Raghu et al. In the 2015 ATS guidelines gave conditional recommendations for the use of Nintedanib, as a tyrosine kinase inhibitor, antifibrotic drug pirfenadone, endothelin receptor blockers bosentan and masitentan for accomanying Pulmonary arterial Hypertension, PDE5 inhibitor and antacid therapy[1].

Pulmonary arterial hypertension develops in hypoxic and fibrotic lung diseases and also in IPF. In our study PAH was seen in all the patients by echocardiography. Majority of our IPF patients have moderate to severe PAH (91%). ATS recommends treatment for PAH associated with IPF. Severity of pAH in our study did not correlate with the severity of MMRC statistically.

Steven D Nathan felt treatment of PAH in IPF patient improves six minute walk distance and quality of life [20]. According to Georgia Pitsiou et al. PAH in IPF patients indicates poor prognosis. PAH is best assessed by right heart catheterization . Echocardiography is a useful alternative [21]. Our study showed all the patients of IPF had pulmonary arterial Hypertension and most of them have moderate to severe hypertension indicating that majority of our patients have advanced disease.

Subramanian Natarajan et. al. study from western India showed a female preponderance. Mean age of diagnosis of IPF was 68 and 66 in males and females respectively. Clubbing was seen in 67%. Mean FVC was 52% of predicted. Definite UIP pattern was seen in 60%. Desaturation was seen in 60%. They felt that survival in IPF was lower than in other ILDs[22].

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Conflicts of interest: We have no conflicts of interest

Summary and Conclusion

Idiopathic interstitial pulmonary fibrosis is a debilitating disease. Constitutes significant proportion of ILDs. Females outnumbered males. Female preponderance. Tiresomeness and breathlessness are predominat symptoms

Disease occurred at a much earlier age in males. Active and passive smoking possibly contributes to the severity of IPF. MMRC grade correlates significantly with DLCO, 6 minute walk distance and definite UIP. There is no statistically significant correlation of MMRC grade with severity of PAH and FVC values.

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