Section: Miscellaneous

Original Research Article

MORTALITY AND MORBIDITY IN PATIENTS WITH INTERSTITIAL LUNG DISEASES. A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Interstitial lung diseases (ILDs),are a group of diseases also described as diffuse parenchymal lung diseases. The ILDs include diseases of unknown aetiology, those secondary to drugs, collagen vascular disease, granulomatous conditions like sarcoidosis and other forms of ILDs like lymphangioleiomyomatosis or Histiocytosis X. There is a paucity of data on follow up of patients with interstitial lung diseases in India. The primary aim of study was to study the mortality and morbidity in patients with interstitial lung disease. The secondary aim of the study was to study the change in pulmonary function during follow up and the complications of interstitial lung disease. **Materials and Methods:** This Retrospective cohort study was done in a tertiary care centre. Data was collected from records of 54 patients at interval of 6 months for a period of 2 years. Data collected include demographic details, Spirometry, six-minute walk test, chest X ray, CT scan, two-dimensional echocardiogram and routine blood investigations including autoimmune workup. The mortality was studied using GAP index for IPF. Although the GAP index was designed for IPF it was applied for non-IPF patients also. Since there was no established scale available for the study of morbidity, GAD6 index was formulated and it was used to study the morbidity in IPF and non-IPF patients. Analysis was done using chi-square test, SPSS version 23. **Result:** In this study, the mean age was 47.2 yrs. In this study 31(57%) were females and 23(43%) were males. Among 54 patients, 18(33.3%) were IPF, 11(23.3%) were Rheumatoid arthritis associated ILD (RA-ILD), 10(18.5%) were Systemic sclerosis associated ILD (SS-ILD), 6(11.1%) were Hypersensitivity pneumonitis (HP), 5(9.2%) were Sarcoidosis. In this study, dyspnea was the most common symptom (100%). P values were statistically significant for mortality and morbidity at 0,6,12,18 and 24 months in both IPF & Non-IPF group by GAP and GAD6 index respectively. **Conclusion:** GAP index and GAD6 index had significant correlation with mortality and morbidity respectively in IPF and non-IPF patients, hence these scores can be utilized as useful tool in measuring mortality and morbidity irrespective of the type of ILD.

INTRODUCTION

The interstitial lung diseases (ILDs) are a clinically challenging and diverse group of over 150 disorders. They are characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium.[1,2] They are also referred to as diffuse parenchymal lung diseases and are a diverse group of pulmonary disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestation.[1,2] There had been a significant progress made in the understanding of interstitial lung diseases with the recognition of collagen vascular diseases, drugs and occupational exposures as potential causes. However, a wide spectrum of pathologies, presentations and outcomes still remain unknown.[2] Hamman and Rich in 1944 described several cases of "diffuse interstitial fibrosis of the lungs" which rapidly progressed and were fatal within a few weeks or months.[3] Later, many cases of diffuse pulmonary fibrosis with a chronic course were described and were thought to be the chronic

stage of Hamman–Rich syndrome. They were termed as "idiopathic pulmonary fibrosis" (IPF). Subsequent studies had shown that Hamman–Rich syndrome had no chronic stage. The condition similar to this is now termed as acute interstitial pneumonia (AIP). Liebow and Carrington were first to classify idiopathic interstitial pneumonias (IIP) into five histologic subgroups : usual interstitial pneumonia (UIP), bronchiolitis interstitial pneumonia, desquamative interstitial pneumonia (DIP), giant interstitial pneumonia (GIP) and lymphoid interstitial pneumonia (LIP).[4] Subsequently, in 1998, Katzenstein and Muller and Colby provided classifications that retained UIP and DIP as distinct entities and added new entities such as respiratory bronchiolitis associated interstitial lung disease (RB–ILD), bronchiolitis obliterans organizing pneumonia (BOOP), acute interstitial pneumonia (AIP), and non-specific interstitial pneumonia (NSIP).[5,6] The terms GIP and LIP were removed from their classifications because GIP was found to be associated with hard metal pneumoconiosis and LIP was found to develop into lymphomas.[5,6] In the modern classification which was recognized by American Thoracic Society and European Respiratory Society also included another entity called as cryptogenic organizing pneumonia (COP).[7]

Most published series on ILDs are from the Western countries. There is paucity of data on ILD in India, where these diseases are under-estimated and remain under-diagnosed and under-reported for various reasons. This is probably due to lack of awareness among physicians due to overshadowing of tuberculosis (TB) problems of lungs and lack of availability of diagnostic modalities like computed tomography (CT), bronchoscopy and video assisted thoracoscopic surgery (VATS) and the high cost involved in getting these investigations done. TB mimics some of the ILDs, like sarcoidosis, leading to diagnostic errors and delay. Thus, the incidence of ILDs in the developing countries has been considerably under-estimated. In the last few decades scattered case reports have emerged including various etiological factors responsible for ILDs from India.[3,8] However there is a paucity of data on follow up. This study was therefore, planned to analyse the mortality and morbidity in patients with ILDs. The secondary objective of the study is to analyse the change in pulmonary function during follow up and the complications of ILDs.

MATERIALS AND METHODS

This retrospective cohort study, was conducted in a tertiary care medical college & teaching hospital, in India, during January 2023, from data of patients with interstitial lung disease treated between October 2016 and September 2018.

Inclusion Criteria

All patients who were diagnosed clinically and radiologically as interstitial lung disease.

Exclusion Criteria

Patients with coronary artery disease, chronic kidney disease, malignancy, pregnant females, age less than 12 yrs.

A total of 58 patients who satisfied inclusion criteria were enrolled in the study out of which 4 patients who met the exclusion criteria were excluded. The total number of patients enrolled in the study was 54. Patient's demographic details, occupational and environmental exposure, symptoms suggestive of collagen vascular diseases, co-morbidities were noted. Their spirometry, six-minute walk test (6MWT), chest X ray (CXR), computerized tomographic (CT) scan, two-dimensional echo (2D ECHO) and routine blood investigations including autoimmune workup was obtained from the records of these patients. The data was extracted at an interval of 6 months for a period of 2 years (October 2016 and September 2018) for all the 54 patients.

Statistical Analysis

Analysis was done using chi-square test, SPSS version 23. A p-value of < 0.05 considered as statistically significant.

a) Mortality

The mortality was studied using gender, age, physiology (GAP) index for IPF. Though the GAP index was designed for IPF it was applied for non-IPF patients also. The scoring is given in Table 1.[6]

b) Morbidity

Since there was no established scale available for the study of morbidity GAD-6 index was formulated by using commonly measured clinical and physiologic variables and it was used to study the morbidity in IPF and non-IPF patients.GAD-6 score consists of Gender, age, dyspnea, 6MWT. The scoring was given in Table 2.

The change in pulmonary function and complications was also analysed from the data collected at an interval of 6 months for a period of 2 years.

RESULTS

In this current study, majority of them were in the age group of 40-50 years (Figure 1) with a mean age of 47.2 yrs. Most of them 31(57%) were females and 23(43%) were males (Figure 2). Among 54 patients,18(33.3%) was IPF, 11(23.3%) were RA-ILD, 10(18.5%) were SS-ILD, 6(11.1%) were HP, 5(9.2%) were Sarcoidosis. Remaining 4.6% were contributed by Eosinophilic pneumonia, NSIP, MCTD-ILD and SLE-ILD (Figure 3). In our study, dyspnea was the most common symptom (100%) while cough was the second most common symptom (90.7%). Skin manifestations in the form of digital ulcers, skin thickening and restricted mouth opening (Fish mouth appearance) was present in 18.5%, small joint involvement in the form of hand and foot deformities was present in 14.8% and dysphagia was present in 7.4% (Table 3).

GAP index was used to study mortality. GAP index was calculated with data collected at every 6 monthly

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intervals for the study period of 2 years, separately for IPF and Non-IPF patients and mortality was analysed using chi-square test. p values were statistically significant in IPF and non-IPF group. In IPF group p values at 0,6,12,18,24 months were 0.016, 0.042, 0.048, 0.033, 0.022 respectively. In non-IPF group p values at 0,6,12,18 and 24 months were 0.002, 0.010, 0.040, 0.022, 0.035 respectively.

Similarly, GAD6 index was used to study morbidity. GAD6 index was calculated with data collected at every 6 monthly intervals for the study period of 2 years separately for IPF and Non-IPF patients and morbidity was analysed using chi-square test. p values were statistically significant in IPF and non-IPF group. In IPF group p values at 0,6,12,18,24 months were 0.018, 0.020, 0.011, 0.007, 0.039 respectively. In non-IPF group p values at 0,6,12,18 and 24 months were 0.009, 0.019, 0.043, 0.012, 0.036 respectively.

In pulmonary function tests which was done at interval of 6 months for the study period of 2 years there was gradual decline in mean forced vital capacity (FVC) in IPF, RA-ILD and SS-ILD. The FVC decline in IPF group was steeper when compared to other interstitial lung diseases (Figure 4). The mean decline in FVC in IPF, RA-ILD and SS-ILD over a period of 2 years was 0.29L, 0.18L and 0.04L/min respectively. In patients with HP there was a gradual increase in mean FVC. The mean increase in FVC over a period of 2 years was 0.43L/min (Figure 4).

In this study the complications were pulmonary hypertension 26(48.1%) followed by respiratory failure 24(44.4%) and pneumothorax 5(9.2%) (Figure 5). In this study 50% of patients developed one or more of the above-mentioned complications.

In 26 patients who has developed pulmonary hypertension 14 were IPF, 5 were SS-ILD, 4 were RA-ILD and the remaining 3 were HP, SLE-ILD and NSIP. Among 18 IPF patients, 14(77.7%) developed pulmonary hypertension followed by 5(50%) out of 10 patients with SS-ILD and 4(36.3%) out of 11 patients with RA-ILD.

In 24 patients who has developed respiratory failure 13 were IPF, 4 were RA-ILD, 3 were SS-ILD, 2 were HP and the remaining were SLE-ILD and NSIP. Among 18 IPF patients,13(72.2%) developed respiratory failure followed by 4(36.3%) out of 11 patients with RA-ILD, 3(30%) out of 10 patients with SS-ILD and 2(33.3%) out of 6 patients with HP.

In 5 patients who developed pneumothorax, 3 were IPF and 2 were HP. Among 18 IPF patients 3(16.6%) developed pneumothorax followed by 2(33.3%) out 6 patients with HP.

Table 1: Gender-Age-Physiology (GAP) Index

Gender-Age-Physiology (GAP) Index		
Factor		**Points**
Gender:	Female	0
	Male	1
Age:	61-65 year	1
	>65 years	2
Physiology	FVC 50-75% predicted	1
	FVC < 50% predicted	2
	DLCO 36-55% predicted	1
	DLCO < 36% predicted	2
	Patient cannot perform	3

FVC = Forced Vital Capacity, DLCO = Diffusing Capacity of Lung for Carbon Monoxide

Table 2: Gender-Age-Dyspnea-6MWT (GAD6) Index

Generalized Anxiety Disorder6 (GAD6) Index		
Factor		**Points**
Gender:	Female	0
	Male	1
Age:	61-65 year	1
	>65 years	2
Dyspnoea: (mMRC Scale)	Grade 0	0
	Grade 1	1
	Grade 2	2
	Grade 3	3
	Grade 4	4
6MWT: (Distance covered)	>350 meters	0
	250-349 meters	1
	150-249 meters	2
	<150 meters	3
6MWT: (Mean of Pre & Post walk SPO2)	>90 %	0
	80-89 %	1
	70-79 %	2
	<70 %	3

mMRC Scale: Modified Medical Research Council Scale, 6MWT: Six Minute Walk Test

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Table 3: Presenting symptoms in the study population

Symptoms	No. of patients
Dyspnoea	54(100%)
Cough	49(90.7%)
Skin manifestation	10(18.5%)
Small joint involvement	8(14.8%)
Dysphagia	4(7.4%)

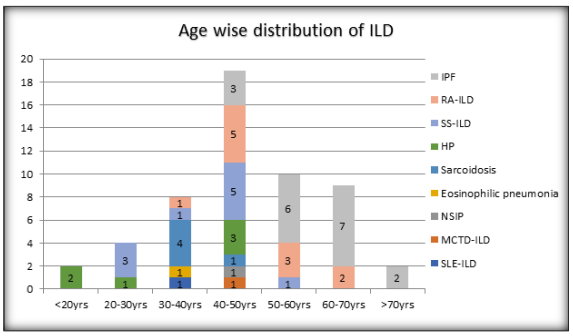

Figure 1: Age wise distribution of Interstitial Lung Diseases in the study population

ILD: Interstitial Lung Disease, IPF: Idiopathic pulmonary fibrosis, RA-ILD: Rheumatoid arthritis associated ILD, SS-ILD: Systemic sclerosis associated ILD, HP: Hypersensitivity pneumonitis, NSIP: Nonspecific interstitial pneumonia, MCTD-ILD: Multiple connective tissue disorder associated ILD, SLE-ILD: Systemic lupus erythematosus associated ILD.

ILD: Interstitial Lung Disease

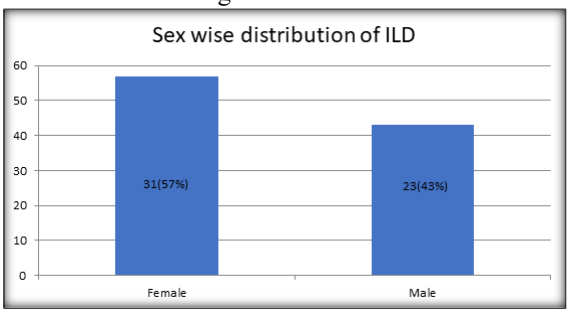

Figure 2: Sex wise distribution of Interstitial Lung Diseases in the study population

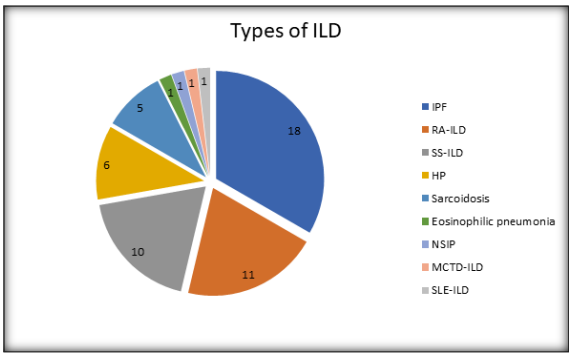

Figure 3: Types of Interstitial Lung Diseases in the study population

Interstitial Lung Disease, IPF: Idiopathic pulmonary fibrosis, RA-ILD: Rheumatoid arthritis associated ILD, SS-ILD: Systemic sclerosis associated ILD, HP: Hypersensitivity pneumonitis, NSIP: Nonspecific interstitial pneumonia, MCTD-ILD: Multiple connective tissue disorder associated ILD, SLE-ILD: Systemic lupus erythematosus associated ILD.

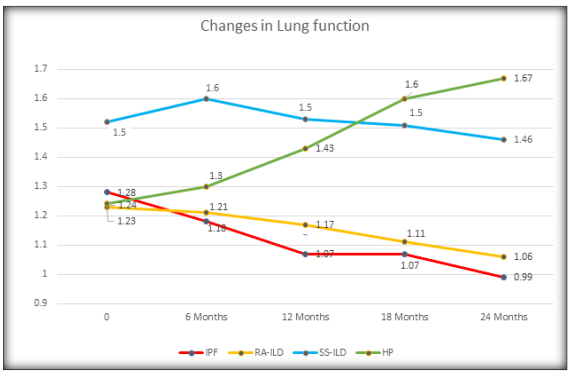

Figure 4: Changes in the forced vital capacity in study population

FVC: Forced Vital Capacity, IPF: Idiopathic pulmonary fibrosis, RA-ILD: Rheumatoid arthritis associated ILD, SS-ILD: Systemic sclerosis associated ILD, HP: Hypersensitivity pneumonitis.

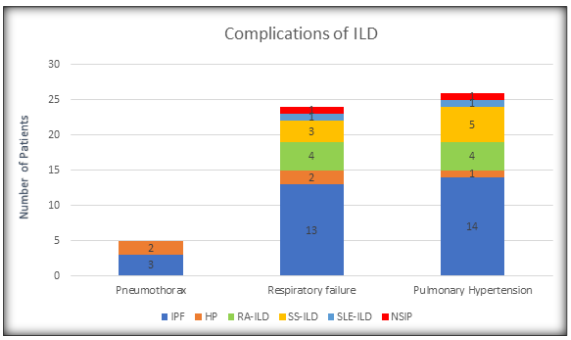

Figure 5: Complications of Interstitial Lung Diseases in study population

ILD: Interstitial Lung Disease, IPF: Idiopathic pulmonary fibrosis, RA-ILD: Rheumatoid arthritis associated ILD, SS-ILD: Systemic sclerosis associated ILD, HP: Hypersensitivity pneumonitis, NSIP: Nonspecific interstitial pneumonia, SLE-ILD: Systemic lupus erythematosus associated ILD.

DISCUSSION

This study was done during January 2023, from the data of patients with interstitial lung disease treated between October 2016 and September 2018.

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Total of 54 patients were included in this study. Majority of them were in the age group of 40-50 years. The mean age was 47.2 years. In an Indian study by Tiyas sen, the mean age of patients was 48 yrs.[9] Out of 54 patients, in this study 31(57%) were females and 23(43%) were males. In the same Indian study, the male: female ratio was 1:2.[9] The ILD Indian registry showed that ILDs occur at a younger age compared to the western countries, and females are affected more.[9] Among 54 patients, 18(33.3%) were IPF, 11(23.3%) were RA-ILD, 10(18.5%) were SS-ILD, 6(11.1%) were HP, 5(9.2%) were Sarcoidosis. Remaining 4.6% were contributed by Eosinophilic pneumonia, NSIP, MCTD-ILD and SLE-ILD. In Indian ILD registry, the most common ILD was IPF (27.5%).[9] In another Indian study with 274 ILD patients, majority was IPF (43%).[8] In the same study ILD secondary to connective tissue disease was 18%.[9] In the present study it was 42%.

In this current study, dyspnea was the most common symptom (100%) while cough was the second most common symptom (90.7%). Skin manifestation was present in 18.5%, small joint involvement was present in 14.8% and dysphagia was present in 7.4%. In Indian ILD registry it was also observed that breathlessness and dry cough were the most predominant symptoms.[9] In this study clubbing was present in 75.9%. It is generally seen in 40% of patients with ILD while in 60% patients with IPF.[10] In this study all 18 patients of IPF had clubbing (100%).

GAP index was used to study mortality. GAP index was also used to assess the mortality in a study done by Ley B et al.[11] GAP index was calculated with data collected at 6 monthly intervals for the study period of 2 years separately for IPF and Non-IPF patients and mortality was analysed using chi-square test. p values were statistically significant in IPF and non-IPF group. In IPF group p values at 0,6,12,18,24 months were 0.016, 0.042, 0.048, 0.033, 0.022 respectively. In non-IPF group p values at 0,6,12,18 and 24 months were 0.002, 0.010, 0.040, 0.022, 0.035 respectively.

Since there was no established scale available for the study of morbidity GAD6 index was formulated and it was used to study the morbidity in IPF and non-IPF patients. GAD6 index was calculated with data collected at 6 monthly intervals for the study period of 2 years separately for IPF and Non-IPF patients and morbidity was analysed using chi-square test. p values were statistically significant in IPF and non-IPF group. In IPF group p values at 0,6,12,18,24 months were 0.018, 0.020, 0.011, 0.007, 0.039 respectively. In non-IPF group p values at 0,6,12,18 and 24 months were 0.009, 0.019, 0.043, 0.012, 0.036 respectively.No earlier studies regarding morbidity was available for comparison.

As far as pulmonary functions are considered there was gradual decline in mean FVC in IPF, RA-ILD and SS-ILD. The FVC decline in IPF group was steeper when compared to other interstitial lung diseases (Figure 4). The mean decline in FVC in IPF, RA-ILD and SS-ILD over a period of 2 years was 0.29L, 0.18L and 0.04L respectively. In patients with HP there was a gradual increase in mean FVC. The mean increase in FVC over a period of 2 years was 0.43L(Figure 4). ILD is known to have restrictive ventilatory defect in which the static expiratory pressure-volume (P-V) curve of the lung is shifted downward and to the right compared with normal subjects due to a reduced distensibility of the lung parenchyma.[12,13,14] It merely reflects fewer functioning alveolar units because of obliteration by the disease process and filling of the alveoli with exudate, edema or inflammatory material.[12,15,16] Combining data from several large series applicable to ILD in general, Gottlieb and Snider reported that the mean FVC and TLC were reduced to 63 and 72% predicted normal, respectively.[12,17]

In this study the complications were pulmonary hypertension 26(48.1%) followed by respiratory failure 24(44.4%) and pneumothorax 5(9.2%). Above mentioned complications were observed in 50% of patients. In a study by Nathan et al, which included 118 patients, pulmonary hypertension was present in 40.7% of patients.[18] In another study by Charlie Strange, pulmonary hypertension was present in 33.7% cases.[19] In the present study it was 48.1%. In 26 patients who has developed pulmonary hypertension 14 were IPF, 5 were SS-ILD, 4 were RA-ILD and the remaining 3 were HP, SLE-ILD and NSIP. Among 18 IPF patients, 14(77.7%) developed pulmonary hypertension. In a study by Steven Nathan, 33.5% of patients with IPF had PH.[20] In this study 5(50%) out of 10 patients with SS-ILD and 4(36.3%) out of 11 patients with RA-ILD also had pulmonary hypertension. In a study done by Marie et al, PH was present in 21% of patients with interstitial lung disease.[21]

In 24 patients who has developed respiratory failure 13 were IPF, 4 were RA-ILD, 3 were SS-ILD, 2 were HP and the remaining were SLE-ILD and NSIP. In this study among 18 IPF patients,13(72.2%) developed respiratory failure. In a study by Steven Nathan, 51.3% of patients with IPF had respiratory failure.[20] In our study respiratory failure was also seen in 4(36.3%) out of 11 patients with RA-ILD, 3(30%) out of 10 patients with SS-ILD and 2(33.3%) out of 6 patients with HP.

In 5 patients who developed pneumothorax, 3 were IPF and 2 were HP. In this study among 18 IPF patients 3 (16.6%) developed pneumothorax. In a study by King TE et al, pneumothorax in IPF patients was 31.4%.[22] In the present study 2(33.3%) out 6 patients with HP also developed pneumothorax.

Limitation: It was a retrospective cohort study. In this study majority of patients were IPF, GAP index and GAD6 index should be studied in large number with all other subset of Interstitial lung diseases like RA-ILD, SS-ILD, NSIP, HP and sarcoidosis to find out their utility. More prospective studies in large number are needed to overcome the gap in literature.

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CONCLUSION

1. In this study a total of 54 patients were included of which majority of them were in the age group of 40-50 years with a mean age of 47.2 yrs. Most of them 31(57%) were females and 23(43%) were males.
2. Among 54 patients, 18(33.3%) were IPF, 11(23.3%) were RA-ILD, 10(18.5%) were SS-ILD, 6(11.1%) were HP, 5(9.2%) were Sarcoidosis. Remaining 4.6% were contributed by Eosinophilic pneumonia, NSIP, MCTD-ILD and SLE-ILD.
3. Dyspnea was the most common symptom (100%) while cough was the second most common symptom (90.7%). Clubbing was present in 75.9%.
4. In this study GAP and GAD6 index had significant correlation with mortality and morbidity respectively in both IPF and non-IPF groups.
5. In PFT there was a gradual decline in mean FVC in patients with IPF, RA-ILD and SS-ILD despite treatment whereas in patients with HP there was a gradual increase in FVC with treatment.
6. Complications was present in 50% of the patients the most common being pulmonary hypertension 48.1% followed by respiratory failure 44.4% and pneumothorax 9.2%.

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