Internal Medicine Section

Prevalence and Risk Factors of Pulmonary Arterial Hypertension in Interstitial Lung Diseases: A Cross-sectional Study

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ABSTRACT

Introduction: Interstitial Lung Diseases (ILD) is associated with inflammatory and/or fibrotic changes in the lungs. Pulmonary Arterial Hypertension (PAH) is a complication of many end-stage lung diseases due to the remodelling of pulmonary vasculature associated with hypoxia leading to pulmonary vascular resistance. The Association of PAH in ILD contributes significantly to high morbidity and mortality. ILD being a progressive disease it is difficult to predict when the PAH will set in.

Aim: To assess the clinical and radiological profiles of patients with ILD and to associate these with the severity of PAH.

Materials and Methods: The present cross-sectional study was conducted in the Department of Respiratory Medicine at GSL Medical College on 23 patients with ILD from 1st October 2019 to 31st August 2021, in GSL Medical College and Hospital, Andhra Pradesh. Each patient was subjected to Chest X-ray (CXR), Electrocardiogram (ECG), and 2-Dimensional Echocardiogram (2D ECHO). Evidence of PAH in any one investigation was considered. In ECG reports evidence of right ventricular enlargement (R>S in V1/V2 and right axis deviation >110 degrees, R=11 mm) was considered as PAH. CXR showing dilatation of the pulmonary artery with an increased cardiothoracic ratio was considered as PAH. A 2-D ECHO was performed to estimate the right arterial pressure and evidence of pulmonary arterial systemic pressure of >40 mmHg was considered as PAH. All the data were statistically analysed by using IBM Statistical Package for Social Sciences (SPSS) version 20.0.

Results: Fifty-two percent of the population constituted females, and the mean age of the whole population was 59.7±14.4 years and the majority of them (65%) belonged to upper lower socio-economic class. Usual Interstitial Pneumonia (UIP) was the most common pattern observed accounting for 57%. Prevalence of PAH was 65% with a longer duration of symptoms, 57% of the population had grade 3 of Modified Medical Research Council (MMRC) dyspnoea and 52.17% covered less than 200 metres in the 6-Minute Walk Test (6-MWT). Oxygen desaturation after 6-MWT was observed to be the contributing factor for the development of severe pulmonary hypertension in ILD patients.

Conclusion: Factors like delayed seeking of medical care, co-morbidity like hypertension, higher grades of dyspnoea at the time of presentation, shorter 6MWD, and postwalk oxygen saturation were found to be predictors of pulmonary artery hypertension in patients with ILD. Early recognition of these risk factors in patients with ILD and the prompt treatment of the disease can reduce the development of severe PAH.

Keywords: Chest X-ray, Dyspnoea, Echocardiogram, Electrocardiogram, Hypoxia

INTRODUCTION

The interstitial lung diseases are a heterogeneous group of lung diseases associated with inflammatory and fibrotic changes in the lungs [1]. PAH is a very common occurrence in ILDs which deteriorates the quality of life in individuals. It occurs due to the remodelling of pulmonary vasculature associated with hypoxia leading to pulmonary vascular resistance [2]. The occurrence of PAH in ILDs leads to an increase in mortality [3,4]. ILDs have a progressive course and it is difficult to predict when PAH develops. A multicentric study showed that ILD due to systemic sclerosis has a higher mortality risk in comparison to idiopathic PAHs [5]. Another study also observed the development of PAH in mild ILD in systemic sclerosis patients [6]. Ryu JH et al., suggest progressive parenchymal and perivascular fibrosis, vascular inflammation, etc., are contributing factors to the development of PAH [7]. All this literature hints towards the causes of PAH particularly in patients with ILD associated with Connective Tissue Disorders-ILD (CTD-ILD).

In CTD-ILDs vascular involvements are more due to the involvement of the connective tissues. But ILD due to other known and unknown aetiologies also leads to PAH in most instances. But it is difficult to predict who will develop this complication earlier. Very few studies have been conducted to assess the risk factors for the development of PAH in patients with ILDs. The present study was intended to predict the risk factors contributing to PAH in patients with ILDs.

The objectives were to assess the clinical and radiological profiles of patients with ILDs and to associate them with the severity of PAH in the patients.

MATERIALS AND METHODS

The present cross-sectional study conducted in the Department of Respiratory Medicine at GSL Medical College, Rajahmundry, Andhra Pradesh, India, on 23 patients with ILD from 1st October 2019 to 31st August 2021. This study was approved by the Institutional Ethical Committee and institutional review board (GSLMC/RC: 565-EC/565-09/19).

Dyspnoea was graded using MMRC grading system. According to MMRC, dyspnoea was classified into 5 grades. Grade 0 to grade 4. Grade 0 represents breathlessness only with strenuous exercise, while grade 4 represents too breathlessness to leave the house or on dressing or undressing. Higher the grade number, higher the severity of dyspnoea.

Inclusion criteria: All patients who were diagnosed with ILD based on history, clinical examination, and High-resolution Computed Tomography (HRCT). Patients' presentations like dry cough, and progressive dyspnoea and corroborated with HRCT findings like any of the following five patterns-ground glass opacities, miliary pattern, reticular patterns, reticulonodular pattern, and honey-combing were included in the study.

Exclusion criteria: Patients with pre-existing cardiac conditions and other respiratory conditions other than ILDs leading to PAH were excluded from the study.

Sample size calculation: The following formula was used.

$N=Z^2 *P(1-P)/d^2$, considering the ILD prevalence rate of 6.27 per lac [8] and precision (d) of 0.10. The final sample size was 22.

Study Procedure

After informed consent was taken, a detailed history was obtained and a thorough clinical examination was conducted. Modified Kuppuswamy classification was used to assess the socio-economic status of the study population [9]. Radiological findings and other relevant laboratory investigations were done. Each patient was subjected to a CXR, ECG and 2-D ECHO, and evidence of PAH in any one investigation was considered for the study. The independent variables like age, gender, height, weight, Body Mass Index (BMI), socio-economic status, duration of symptoms, and the extent of disease in High-resolution Computed Tomography (HRCT), and dependent variables were degree of PAH. The degree of PAH was estimated on the basis of Right Ventricular Systolic Pressure (RVSP) as none (RVSP <40 mmHg), mild (RVSP 40-50 mmHg), moderate (RVSP 50-60) mmHg), or severe (RVSP >60 mmHg) [10].

The ECG findings of right ventricular enlargement like R wave (R)> S wave (S) in V1/V2 chest leads and right axis deviation >110 degrees, R<S in V6/L1 and R in V1/V2 plus S in V5/V6>11 mm were considered positive for PAH. Chest radiograph showing dilatation of the pulmonary artery with an increased cardiothoracic ratio was one of the criteria for diagnosing PAH. Moreover, 2-D ECHO was performed to estimate the RVSP. RVSP of >40 mmHg was considered for PAH.

STATISTICAL ANALYSIS

All the data were statistically analysed by using IBM SPSS version 20.0. Descriptive data were expressed as mean±standard deviation and percentages. Data were tabulated and graphically represented. The Chi-square test was used to assess the association of various categorical variables. The logistic regression method was used to determine the predictors. A p-value <0.05 was considered statistically significant.

RESULTS

Most of the patients were in the age group of 70-79 years [Table/Fig-1]. The mean age of the study population was 59.7 years and male to female ratio was 11:12 [Table/Fig-2]. All the female patients were house wife's (n=12), among the male patients, 1 was electrician, 1 was lorry driver, 1 was tailor, 4 were daily wage labourers, and 4 were farmers by occupation [Table/Fig-2]. Among all patients, 65% (n=15) of the patients belonged to the upper lower socio-economic class, and 35% (n=8) belonged
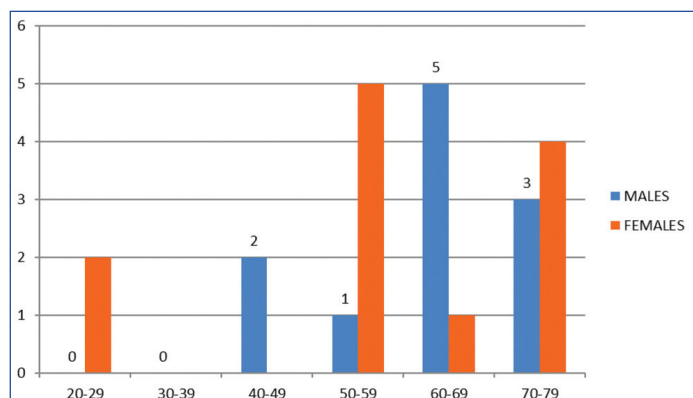
[Table/Fig-1]: Age-wise sex distribution.

to the lower class [Table/Fig-2]. The mean BMI was 22.4±2.73 [Table/Fig-2]. It was noted that the majority, 73.91% (n=17) of the patients in the study were of average build and within the range of normal BMI (18.5-24.9). Among all patients, 21.7% (n=5) patients had diabetes mellitus, and 34.78% (n=8) patients had hypertension [Table/Fig-2]. Majority of the study population were non smokers (n=13) [Table/Fig-2]. Cough and shortness of breath were the most common presenting symptoms [Table/Fig-3]. Digital clubbing was seen in only 17% of patients [Table/Fig-3]. The mean duration of symptoms was 12.78±10.95 [Table/Fig-3,4]. The grade-3 MMRC dyspnoea was seen in 57% of patients [Table/Fig-3,4]. On HRCT examination, a majority had a UIP pattern [Table/Fig-5]. All patients in the study were subjected to a 6-MWT and it was observed that more than half of the patients (n=12) could walk 200 metres in 6-minutes [Table/Fig-4,6]. The mean distance covered by 23 patients in the 6-MWT was 213.91 metres with a standard deviation of 105.06.

Parameters	Sample size (n=23)
Mean age	59.7±14.4
M:F	11:12
Occupation	
House wife	12
Farmer	4
Daily wage labourer	4
Electrician	1
Lorry driver	1
Tailor	1
Socio-economic status (Modified Kuppuswamy Classification)	
Lower class	8
Upper class	15
Body Mass Index (BMI)	
Underweight	2
Healthy	17
Overweight	4
Obese	0
Mean body mass index (kg/m²)	22.4±2.73
Co-morbidities	
Diabetes	5
Hypertension	8
Non-smokers	13 (56.52%)
Smokers	10 (43.48%)

[Table/Fig-2]: Demographic data.

Symptoms and signs	N
Cough	22
Shortness of breath	22
Chest pain	7
Fever	7
Expectoration	14
Clubbing	4
Mean duration of symptoms (Months)	12.78±10.95
Modified Medical Research Council (MMRC) dyspnoea [11]	
Grade 0	1
Grade 1	0
Grade 2	6
Grade 3	13
Grade 4	3

[Table/Fig-3]: Clinical signs and symptoms, mean duration of symptoms, MMRC grade.

Indicator	p-value	Pearson correlation
Duration of symptoms	0.05	0.411
MMRC grade	0.01	0.521
6-minute walk distance	<0.001	-0.697
Oxygen saturation after 6 MWT	0.001	-0.649

[Table/Fig-4]: Correlation with Right Ventricular Systolic Pressure (RVSP) value.

Variables	N	No PAH	Mild PAH	Mod PAH	Sev PAH	p-value
Usual interstitial pneumonia	13	3	5	5	0	
Non specific interstitial pneumonia	8	3	1	2	2	0.389
Lymphoid interstitial pneumonia	1	1	0	0	0	
Sarcoidosis	1	1	0	0	0	

[Table/Fig-5]: Type of ILD based on HRCT.

Total 15 patients (65%) had PAH based on 2-D echo and 8 patients (35%) did not have any evidence of PAH, 7 (30%) patients have moderate PAH as assessed by 2D Echo by measuring RVSP [Table/Fig-6]. The mean RVSP value as assessed by 2D Echo was 49.65 mmHg with a standard deviation of 13.72. The median RVSP was 46 mmHg.

Variables	Frequency
6-minute walk test	
<200 metres	12
200-400 metres	9
>400 metres	2
Severity of PAH	
No PAH	8
Mild PAH	6
Moderate PAH	7
Severe PAH	2

[Table/Fig-6]: 6-Minute Walk Test (6-MWT) and severity of PAH.

DISCUSSION

The mean age of study participants in the present study was 59.7. The suffering of middle-aged people with ILD is evident in the Indian prospective ILD registry by Singh S et al., [1]. A study by Lettieri CJ et al., revealed a mean age of 56 years in patients of ILD with PAH [2]. Slight female preponderance among index study was observed, participants and similar observations have been reported in various other studies conducted on ILD patients [1,4,12]. The median RVSP in the 2D echo study in present study group was 46 mmHg. This observation agrees with the observation of the study by Teramachi R et al., where the median RVSP value was 47 mmHg, in their study of 125 ILD patients [13].

All patients in the present study belonged to lower and upper-lower socio-economic groups (as per the modified Kuppuswamy classification of Socio-economic status) [9]. This was because the study institution caters to mostly rural and semi-urban catchment areas nearby. All female patients were housewives, and most of the males were either daily wage laborers or farmers by occupation. Hence socio-economic status may not be considered a predictor of the development of PAH in ILD in the setup. None of the earlier studies could establish any significant correlation between socio-economic status and ILD [14,15]. The BMI of most of the study participants was in the range of average (Mean BMI=22.4 Kg/m²). This observation agrees with the inferences made in studies of various other authors [13,16]. In a study by Yogeshwaran A et al., the mean BMI was 28 in ILD patients with severe pulmonary hypertension [17]. There was no significant relationship between

age, gender, socio-economic status, height, weight, and BMI with the severity of PH [Table/Fig-1]. A study by Anderson CU et al., also could not establish any statistically significant relationship between parameters like BMI, gender, and socio-economic status with the prevalence of PH but they found the mean age of ILD patients was higher (65 years) than those without PH (60 years) [4].

Cough and shortness of breath were the most common presenting symptoms in the present study population, similar to other studies [12,18,19]. It can be inferred that interstitial involvement leads to cough and patients attend the tertiary care centre mostly after developing shortness of breath. The mean duration of symptoms of patients in the present study was 12.78 months, where 47% of them presented within 6 months of the onset of symptoms. Only 30% of patients presented with PAH after one year of symptoms. But many studies conducted earlier observed patients' presentation after three years of starting symptoms [1,12,20]. Geographical, social, and cultural factors might have led to early presentation in the present study. There was a positive correlation between the duration of symptoms and RVSP values in the present study. In the linear regression model also, the duration of presenting symptoms was found to be a contributing factor to the development of PAH in patients with ILD. It is inferred from these observations that the longer the duration of symptoms, the more severe the PH.

The mean mMRC grade was 2.73 and 57% of them presented with dyspnoea of grade-3 mMRC. The higher grade of dyspnoea in the series may be because of the presence of PAH in them. The mean dyspnoea grading among 101 ILD patients in the retrospective study by Kimura M et al., was only 1.5 [16]. The present study found that when the patients had higher mMRC grades, there were higher RVSP values. It is observed that when patients present with a severe grade of dyspnea severity of pulmonary hypertension is more indicated by high RVSP values. Kimura M et al., noted similar statistically significant observations which indicated a higher grade of mMRC in patients with PAH [16]. Hypertension was more often noted in patients with severe PAH and there is an increasing trend toward diabetes mellitus as per the report given by Shorr AF et al., [21]. In this study, also 35% of patients had hypertension and 21% had diabetes. Among all patients, 43% were active smokers. The percentage of active smokers varies between different studies. The proportion of non smokers was more in other studies [22,23]. On clinical examination, clubbing was observed in only 17% of study participants. In earlier studies by Kumar R et al., and Nadrous HF et al., also the prevalence of clubbing among ILD patients was less than 20% [12,23]. High-resolution CT scans of patients revealed a UIP pattern in 57% of patients and an Non Specific Interstitial (NSIP) pattern in only 35%. In the Indian prospective ILD registry, only 24% of patients have UIP patterns and 14% have NSIP patterns [1]. This discrepancy might be due to the smaller sample size in the index series. Also, the causes of ILD in these patients are different from case to case.

The mean distance walked by the patients in the 6-MWT was 213.9 metres which is almost similar to the observation made by Yogeshwaran A et al., (214 metres) [17]. The patients with PAH could walk shorter distances in the test. There was a negative correlation between the 6-MWT distance and RVSP values in the present study (p<0.001). A similar observation was found in the study of Anderson CU et al., (p=0.01) in a series of 212 patients [4]. They also mentioned that compared to patients without PAH, PAH patients had shorter 6MWD. They also suggested that a 6-MWT distance below 345 metres is an independent risk factor for PH. A negative correlation was also observed between oxygen saturation after 6-MWT and RVSP values as depicted by Pearson correlation (Pearson correlation-0.649; p=0.01). The logistic regression method revealed that postwalk oxygen desaturation is also a factor in the development of PH (p 0.001). Lettieri CJ et al., also observed a similar correlation between oxygen desaturation after 6-MWT

and PH, they also obtained a statistically significant correlation (p=<0.001). They noted that patients with pulmonary hypertension had greater desaturation after 6-MWT [2].

Limitation(s)

Sample size was less and more of the seriously ill patients might have led to selection bias in sampling. Proper measurement of PAH needs right heart catheterisation, but being an invasive procedure this was not used. To assess the risk factors for the development of PAH, a prospective study could have given more information than the present cross-sectional study.

CONCLUSION(S)

Early recognition of risk factors in patients with ILDs and the prompt treatment of the disease can reduce the development of severe pulmonary hypertension. Factors like delayed seeking of medical care, co-morbidity like hypertension, higher grades of dyspnoea at the time of presentation, shorter 6MWD, and postwalk oxygen saturation are predictors of pulmonary artery hypertension in patients with ILDs. So, early diagnosis, and prompt initiation of treatment may prevent the development of this complication. Adequate pulmonary rehabilitation will help increase in quality of life of these patients. A large, multi-centric prospective study may give us more information, help in further risk factor identification, and can enhance treatment outcomes in patients with ILD having pulmonary hypertension.

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