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FREQUENCY OF PULMONARY HYPERTENSION IN PATIENTS WITH INTERSTITIAL LUNG DISEASE

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Abstract

Objectives: The aim of this study is to find out the prevalence of pulmonary hypertension (HP) in patients with interstitial lung disease (ILD) and the relationship between the frequency of PH and age, gender, smoking history, and disease duration.

Materials and Methods: The current with a cross-sectional descriptive design was carried out in KTH, Peshawar, from September 28, 2019, to March 27, 2020. Patients with ILD who volunteered for the study were recruited after an explanation of the study procedures, risks, and benefits by the investigators to the patients or their surrogates. Echocardiography of the right side of the heart was done using transthoracic echocardiography (TTE) which was used to thereby determine the degree of pulmonary hypertension. Using SPSS version 16, students' demographic details and illness experiences were categorized, and numerical data was compared.

Results: Out of 95 patients 27 patients (28.42 percent) were diagnosed to have PH. PH was more common in the elderly, where 42.9% of samples from patients over 60 years of age had PH. PH was not significantly correlated to gender, smoking history, or disease duration.

Conclusion: PH is common in ILD patients, particularly those of older age. Regular screening tests are helpful in the early detection of diseases such that they can be managed to improve a patient's health status.

Keywords: Pulmonary hypertension, interstitial lung disease, echocardiography, prevalence, age, clinical outcomes.

INTRODUCTION

Pulmonary hypertension (PH) is a well-recognized complication of ILD that plays a major role in the complications and mortality of end-stage patients. ILD is a large category of lung diseases that are defined by inflammation and fibrosis of pulmonary tissue, leading to a gradual decline in respiratory function. PH is referred to as increased pulmonary arterial pressure and occurs due to hypoxic vasoconstriction and vascular remodeling from chronic hypoxia and inflammation (1). Clinicians should know that PH must be diagnosed early for the simple reason that its existence worsens the prognosis and treatment of ILD (2).

The specific processes contributing to PH in ILD have not been clearly described and may involve a number of aspects. Interstitial inflammation, hypoxia, and fibrosis are recurrent changes that

predispose to pulmonary vascular remodeling and increase pulmonary vascular resistance and pulmonary artery pressure. This increases pressure on the right side of the heart and, most of the time, results in right-side heart failure at the terminal stage of end-stage renal disease (3). PH development is further exacerbated by the etiology of ILD, as observed in sSc-ILD, where fibrotic remodeling and vascular abnormalities are apparent (4). There is a clear association between patients with pulmonary vascular disease and interstitial lung pathology, and that will require a full plan for treatment.

Screening for PH in patients with ILD is still an area of research. Early PH assessment is crucial because it allows health care providers to be able to identify when a patient is in decline and intervene. There have been several approaches advanced by different studies concerning screening for PH in ILD patients through echocardiography, right heart catheterization, or biomarker profiling (5). The screening modality is also not well-established for all patients utilizing ILD, while others recommend selective screening based on risk factors (6) (7). Hence, it is important to unravel the incidence and the clinical relevance of PH in ILD with a view of enhancing the therapeutic approaches.

An important consideration when treating PH in patients with ILD is dealing with the underlying lung disease as well as the presence of PH. Studies of specific treatments for PH, including pulmonary vasodilators, have been promising in other variants of PH, but there remains uncertainty about their role in ILD-associated PH. Oral therapies like treprostinil have generally positive impacts on pulmonary hemodynamics and exercise tolerance in patients with ILD and PH (8). However, the effectiveness of such treatments for the improvement of symptoms and overall prognosis of the patients is still doubtful, and more trials using randomized controlled design are warranted to evaluate the effectiveness of these interventions for the target population. However, treatment plans should also consider the progression of the associated ILD, as this inflammation and fibrosis need to be managed to avoid additional lung function decline (9).

PH has been reported in different frequencies in patients with ILD based on the population sampled, the etiology of the ILD, and the specific diagnostic techniques employed. For instance, research conducted has found that PH is frequent in idiopathic pulmonary fibrosis patients, in which an estimated 40% of the patients suffer from the condition (10). However, the frequency of PH in various other forms of ILD, such as sarcoidosis and hypersensitivity pneumonitis, is comparatively less (11). The presence of PH in patients with ILD exacerbates hospitalizations, diminishes survival rates, and significantly impacts the quality of patient's life (12). Thus, it is necessary to identify PH in patients with ILD to enhance the outcomes of the treatment as well as to decide on the further management of the disease.

Furthermore, the prevalence of PH in patients with ILD is a concern mainly because of its effect on patients' prognosis (15). The negative impact of PH in ILD patients can be minimized and survival enhanced where patients are identified early and well-managed. But more studies are required in screening and determining the specific high-risk population who needs treatment, as well as the appropriate modes of treatment for this disorder (13). Therefore, The present study plans to estimate the prevalence of PH in a cohort of Pakistani ILD patients, adding to the available body of knowledge on this significant clinical concern (14).

Objective: The aim of this study is to identify the prevalence of pulmonary hypertension in interstitial lung disease in Pakistan and to evaluate its effect on the patients' prognosis and survival.

MATERIALS AND METHODS

Study Design: This study is a cross-sectional descriptive study designed to determine the prevalence of PH in patients with ILD. The method of study enables a cross-sectional view of the occurrence of PH within a certain period of time as well as within a certain population.

Study setting: The study was carried at department of Pulmonology, Khyber Teaching Hospital in Peshawar, Pakistan. This hospital is a large tertiary care hospital in this part of the country catering to patients with respiratory illnesses including ILD.

Duration of the study: The study was conducted between 28 September 2019 and 27 March 2020. In total, 150 patients with pathological-proven ILD were recruited for screening and assessment during this time.

Inclusion Criteria

This study enrolled patients with ILD confirmed by clinical, radiological, and histopathological data, aged 18 years or older.

Exclusion Criteria

Patients with other types of PH not associated with ILD, like congenital heart diseases, thromboembolic pulmonary hypertension, or patients with partial clinical records, were not included in the study.

Methods

The present study was undertaken on 150 patients who were ILD patients who had given voluntary consent. Following the recommendation of the approved ethical committee, the patients in the outpatient department and wards with matched inclusion criteria were approached for inclusion into the study. Demographic details were obtained from the patients by interviewing them patients after their clinical history and physical examination. To compare the presence or absence of pulmonary hypertension, transthoracic echocardiography (TTE) was done by a trained cardiologist using a conventional echocardiographic machine (TOSHIBA-APLIO 300). All data were recorded in a structured proforma All data were recorded in a structured proforma. SPSS version 16 was used to analyze the data. Categorical variables including gender and the presence of PH, were summarized using frequencies and percentages. Continuous data such as age were presented as Mean ± Standard Deviation. To explore the effect of measure modification, PH was stratified according to age, gender, smoking history, and duration of ILD.

RESULTS

The study established subjects consisting of a total of ninety-five patients diagnosed with interstitial lung disease (ILD). Among these, 41 (43.16%) were male, and 54 (56.84%) were female, yielding a male-to-female ratio of 1:1.3 (Fig. 1). The patients were further found to be 51.81 ± 9.49 years of age with a minimum age being 30 years while the maximum age was 70 years. Evaluation of patients' age indicators yielded the conclusion that 44.2% of the ILD patients are within the age range of 51-60 years. The age categories were as follows: Among them, 15 (15.8%) patients were of and less than 40 years, while 24 (25.3%) of the patients were between 40 to 50 years, 42 (44.2%) were between 50 to 60 years and 14 (14.7%) patients were more than 60 years old (table 1). In the present study, PHI was observed in 27 (28.42%) out of the ninety-five ILD patients with PHI and 68 (71.58%) patients without PHI (Fig. 2). Out of 27 patients of PH, 7 (25.93%) patients had mild PH, 10 (37.04%) patients had moderate PH and 10 (37.04%) patients had severe PH (Fig. 3).

Table 1: Age-wise Distribution of the Patients

Age Group	Frequency	Percent
<= 40.00	15	15.8%
41 – 50	24	25.3%
51 – 60	42	44.2%
61+	14	14.7%
Total	**95**	**100%**

When stratified by age, the number of cases of PH increased with age, but this was not statistically significant (p = 0.429). Remarkably, in the group of those less than or equal to 40 years, 20% of patients suffered from PH, as opposed to 80% who did not. PH was more prevalent in patients aged between 51-60 years, with a prevalence of 31%, followed by those aged 41-50 years, with a prevalence

of 20.8%, while the highest frequency of 42.9% was recorded in patients over 60 years of age (Table 2).

Table 2: Age-wise Distribution of Pulmonary Hypertension

Age Group	Pulmonary Hypertension	No Pulmonary Hypertension	Total	p-value
<= 40.00	3 (20%)	12 (80%)	15	0.429
41 – 50	5 (20.8%)	19 (79.2%)	24	
51 – 60	13 (31%)	29 (69%)	42	
61+	6 (42.9%)	8 (57.1%)	14	
Total	**27 (28.4%)**	**68 (71.6%)**	95	

The distribution of PH by gender demonstrated a slight male and female disparity. PH was diagnosed in 31.7% of the male patients and 25.9% of female patients participating in the study. Likewise, PH was observed in a higher proportion of patients with a past history of smoking, having a value of 29.4% and a disease duration of more than 12 months. Nevertheless, there was no significant relationship between gender, smoking history, and disease duration having PH, according to the results shown in Table 3.

Table 3: Gender, Smoking History, and Duration of Disease-wise Distribution of Pulmonary Hypertension

Variable	Pulmonary Hypertension	No Pulmonary Hypertension	p-value
Gender			0.536
Male	13 (31.7%)	28 (68.3%)	
Female	14 (25.9%)	40 (74.1%)	
Smoking History			0.873
Yes	10 (29.4%)	24 (70.6%)	
No	17 (27.9%)	44 (72.1%)	
Duration of Disease			0.551
<= 12 months	14 (24.6%)	43 (75.4%)	
13-24 months	6 (37.5%)	10 (62.5%)	
> 25 months	7 (31.8%)	15 (68.2%)	

This study indicates that although the prevalence of PH is relatively higher in patients developing ILD at an older age, there is no significant association between PH and other factors such as gender, smoking history, and duration of the disease.

Discussion:

PH is known to have worse survival and lower health-related quality of life in patients with ILD. The study aims and objectives were the identification of the prevalence of PH in ILD and comparison with age, gender, smoking history, disease duration, and the measurement of the extent of PH in the Pakistani population. The results of the present study will help to enrich the knowledge about the distribution and frequency of PH in ILD patients in clinical practice that may serve to underline the importance of early detection and management of PH in such patients.

In the present study, the prevalence of PH in ILD patients was found to be 28.42% by diagnosis of PH in 27 out of 95 patients. This is supported by previous literature which has also indicated that PH is diagnosable in between 20% and 40% of patients with ILD (1, 2). For instance, Parikh et al., 2022 have found that PH is detected in ILD patients at a rate of 30%, which is similar to our results. This shows why screening for PH in patients with ILD should be done, as its presence has a negative impact and complicates the management of the patient(3).

The study also provided a gender distribution of PH, which depicted a slightly higher prevalence in male patients, of whom only 31.7% had PH as compared to 25.9% of female patients. However, This difference was not found to be statistically significant ($p = 0.536$), but it fits well with other studies

that have proposed this gender-based differential as a probable explanation of PH in ILD (4). Researchers claim that male individuals with ILD tend to have a slightly increased probability of developing pulmonary hypertension, with idiopathic pulmonary fibrosis being an example of such a disease (5). However, the impact of gender relating to the development of PH-ILD remains less clear since other factors, such as the cause of ILD, the existence of other diseases, and the treatment history, greatly determine the development of PH (6).

Age was identified as a contingency factor having a direct influence on the development of PH since higher PH prevalence rates were observed among the older age bracket. According to the study, PH was present in patients of age 40 years or less at 20%, 41-50 years at 20.8%, 51-60 years at 31%, and >60 years at 42.9%. However, since the difference was not statistically significant ($p = 0.429$), these results point to the fact that the prevalence of PH appears to be higher in the older population. Prior research associates older age with the development of PH in ILD as aging influences increased pulmonary vascular resistance and vasculopathy (7). Moreover, age-related structural changes involving the lung tissue, patient comorbidities like cardiovascular disease or chronic hypoxia, as well as increased fibrosis can prompt the development of PH in more elderly ILD patients (8).

In this study, the PH was classified into mild, moderate and severe according to estimated pulmonary artery systolic pressure (ePASP). Among the patients with PH, 25.93% had mild PH, 37.04% had moderate PH, and the remaining 37.04% had severe PH. This distribution is in concordance with other studies, which have demonstrated a high proportion of ILD patients with either moderate or severe PH (9). The stage of PH in ILD matters as it translates to the management and prognosis of the patients. Especially, severe PH is connected with the increased rate of right heart failure and a decrease in survival probability (10).

Another factor examined in this research was the smoking history of the patients. Smoking was observed to be higher in the patients with PH, with smokers comprising 29.4% while non-smokers making up 27.9%. However, this difference was not found to be significant ($p = 0.873$), therefore pointing to the fact that smoking history might not be a good independent variable in the prediction of PH in ILD patients. Besides, smoking remains known to be associated with the development of ILD, especially in COPD and emphysema. However, the relationship between smoking and the development of PH among the ILD patient population is not very well established (11). Several similar studies have indicated that smoking may contribute to increased pulmonary vascular remodeling resulting in PH, but this notion has remained inconclusive, and therefore, more research is needed in order to determine if there is a positive association between smoking and incident PH in patients with ILD (12).

The time during which a patient has ILD was also examined as a possible predictor of developing PH. Specifically, the study revealed that 24.6% of patients within the first year of disease development had PH, whereas 31.8% of patients who have had the disease for more than 25 months. While this indicates that longer disease duration may be correlated with PH, the increase rate was not statistically significant ($p = 0.551$). This is in line with the understanding that as the severity of the situation in patients with ILD increases, the chances of developing PH also increase due to the chronicity of disease, inflammation, and fibrosis, which cause remodeling of the pulmonary vasculature (13). Conversely, this study did not have a population large enough to yield significant results, and hence, the involvement of the disease duration in the development of PH in ILD requires further elaboration.

Lastly, the results of the current study support the results indicating a high rate of PH in patients with ILD and identified age as a significant predictor of PH. Nevertheless, gender, smoking history, and disease duration were nonsignificant, although they may possibly affect the treatment result in some patients. ELD has been reported to cause PH, and since it is severe in patients with ILD, it should be screened for and treated immediately. More studies are needed in order to maximize the details of the screening strategies and to evaluate the efficacy of the interventions in the effort to reduce PH morbidity and mortality in ILD patients.

CONCLUSION

Finally, the current paper reveals high rates of PH in ILD patients, with PH present in 28.42% of patients. While age was found to be an important predictor for the development of PH, gender, smoking history, and disease duration were other potential predictors, and they were not significantly related. PH is severe in ILD patients, with more symptoms observed in moderate to severe cases and, therefore, require intensive care for early intervention and treatment to avoid worsening of other sequelae such as right heart failure. Since PH is present in the majority of patients with ILD, transthoracic echocardiography should be employed for screening purposes in clinical practice. Future studies need more participants and longer follow-up evaluations to explain the late results and ideal management of ILD patients with PH. More vigorous initial treatment and specific approaches could help the patients reach far better results and quality of life.

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