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To Study the Clinical Profile of Pulmonary Hypertension

Dr. Madhukar Gaikwad[1], Dr. Ramanand J Patil[2*], Dr. Vikramjit R Padole[3], Dr. P.S. Tampi[4]
[1]Associate Professor, Department of General Medicine, Grant Govt. Medical College & Sir J J Group of Hospitals, Mumbai – 400008, Maharashtra, India
[2]Assistant Professor, Department of Pharmacology, Smt. Kashibai Navale Medical College and General Hospital, Narhe, Pune – 411 041, Maharashtra, India
[3]Ex Senior Resident, Department of General Medicine, Grant Govt. Medical College & Sir J J Group of Hospitals, Mumbai – 400008, India
[4]Assistant Professor, Department of General Medicine, Grant Govt. Medical College & Sir J J Group of Hospitals, Mumbai – 400008, India

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***Corresponding author**
Dr. Ramanand J Patil

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Abstract: This study being carried out in a tertiary care setting caring for patients with respiratory disorders attempts to study the clinical profile of patients with pulmonary hypertension in association with respiratory disorders and enhance our understanding of the same; more so as the study being carried out in Indian setting where diagnosis of pulmonary hypertension itself is lacking. Observational, open, single centric, parallel study. This study will be conducted in the tertiary care hospital of Mumbai & data for the patients of pulmonary hypertension will be procured from Medical Record Section for last one year. Prior start of this study, ethics committee approval will be taken. 100 patients of pulmonary hypertension (PH) will be enrolled in the study to get the significant results after calculating the power of the study. There are 64 males and 36 females. There are 28 smokers among this. 12 patients complained of chest pain among the study group. 16 patients presented with haemoptysis as their primary symptom. 30 patients presented with pedal edema of pitting variety. Among 100 patients 14 presented with syncope as their primary symptom. Totally 89 patients complained of cough as their initial symptom. 98 patients presented with X-ray alteration. In our study 93 patients complained of dyspnea. Among our patients 82 patients presented with fatigue. During the study period 7 patients who were symptomatic due to their cardiovascular problems, were cured following corrective surgery. 5 patients died during this period. 88 patients are still under treatment. In our study design majority were from class 3 being 76 followed by class 5, class 1 and class 4. The above study was an observational study of clinical profile of patients with pulmonary hypertension. In our study of 100 patients with pulmonary hypertension, men outnumbered women. Smoking is one of the major risk factor for respiratory etiology of pulmonary hypertension. The main symptoms at the diagnosis were chest pain (88%), dyspnoea (93%), followed by cough (89%), easy fatigue (82%), pedal oedema (30%), haemoptysis was complained by 84% of the patients. Syncope was present in only 14% patients. On respiratory examination, abnormality was found in almost all the cases except in 8 cases. 98 patients showed the x-ray abnormalities; most were the nonspecific findings. The composition of clinical classes according to Evian's classification in our study was as following. Clinical class 1 had 9 patients, class 3 had 76 patients, class 4 had two patients and clinical class 5 contained 13 patients. Interestingly during our study period we never came across any type 2 cases. Men were outnumbered by women. There was significant delay between symptom onset and diagnosis of pulmonary hypertension. Dyspnoea and easy fatigue were the commonest symptoms. Physical examination findings for PH were less sensitive. Pedal oedema was present in significant number of patients despite absence of right heart failure. Chest radiograph had poor sensitivity in identification of pulmonary hypertension; however when present them signified RV dilatation and dysfunction. Clinical class 3 was the most predominant class. Obliterative bronchiolitis of post infectious aetiology was found to be single largest aetiology associated with pulmonary hypertension in clinical class 3 and overall.

Key words: Pulmonary arterial hypertension (PAH), Obliterative bronchiolitis, Chest pain, Dyspnea, Cough, Easy fatigue, Pedal oedema, Haemoptysis, Syncope.

INTRODUCTION

Pulmonary hypertension (PH) is a disease state characterised by persistent elevation of pulmonary vascular resistance [1]. The pulmonary hypertension (PH) consists of hemodynamic and pathological features. It is a heterogeneous group of disorders seen in association or complicating a variety of pulmonary and cardiac disorders, pulmonary hypertension can exist as isolated pulmonary vasculopathy without an identifiable cause [pulmonary arterial hypertension (PAH)].

Though pulmonary hypertension is a clinical entity, it has got both hemo-dynamic and pathological aspects. It is defined hemo-dynamically as persistent elevation of mean pulmonary artery pressure of >25 mmHg at rest, measured by right heart catheterisation (RHC) [2]. The definition of pulmonary hypertension on exercise as mean PAP >30mmHg has been abandoned in view of lack of supporting evidence and fact that normal individuals can reach much higher values on exercise [3,4]. The pulmonary hypertension can be estimated non-invasively by trans-thoracic Doppler echocardiography by estimating tricuspid regurgitation jet velocity using modified Bernoulli equation [5]. The estimated pulmonary artery systolic pressure by trans-thoracic echocardiography has better correlation with invasively measured mean pulmonary artery pressures [6]. The error of calculation is of the order of only 5-9 mmHg [7]. Overestimation of pulmonary pressure may occur, however Doppler echocardiography has a good negative predictive value [8].

Uncontrolled pulmonary hypertension progresses into corpulmonale and later with decompensation of right ventricular function leads to right ventricular pump failure or right heart failure. The level of pulmonary hypertension associated with chronic respiratory disorders typically is relatively mild [9].

Mean pulmonary artery pressure in patients with pulmonary hypertension due to lung disorders is relatively lower than in patients with pulmonary arterial hypertension (PAH). Despite relatively milder pulmonary hypertension patients with pulmonary hypertension due to lung disorders may show right ventricular decompensation and right ventricular pump failure underlining the fact that it is the severity of underlying disease that determines the clinical symptomatology. Because of underlying hypoxemia the right ventricle in these patients behaves as ischemic right ventricle instead of pressure loaded ventricle [10]. Further in patients with pulmonary hypertension due to respiratory diseases it is the underlying disease and its clinical signs and symptoms that will predominate over clinical symptoms due to pulmonary hypertension. The presence of pulmonary hypertension in lung disorders signals severity and advanced level of underlying disease and is associated with frequent exacerbations and poor survival.

Most of the understanding regarding pulmonary hypertension is relatively recent and is mostly centred around pulmonary arterial hypertension whilst studies involving pulmonary hypertension due to hypoxia or due to lung disorders are being sparse.

This study being carried out in a tertiary care setting caring for patients with respiratory disorders attempts to study the clinical profile of patients with pulmonary hypertension in association with respiratory disorders and enhance our understanding of the same; more so as the study being carried out in Indian setting where diagnosis of pulmonary hypertension itself is lacking.

MATERIALS & METHODS

Observational, open, single centric, parallel study was conducted in the tertiary care hospital of Mumbai & data for the patients of pulmonary hypertension was procured from Medical Record Section for last one year. Prior start of this study, ethics committee approval will be taken. 100 patients of pulmonary hypertension (PH) were enrolled in the study to get the significant results after calculating the power of the study.

Inclusion Criteria

- Patients of either gender.
- Patients with age >18 years.
- Patients who were diagnosed as cases of pulmonary hypertension (PH) by specialist and were treated in the same institute for the pulmonary hypertension (PH).

Exclusion Criteria

- Patients with age <18 years.
- Patients whose diagnosis of pulmonary hypertension (PH) is not confirm.

Objectives

- To study the prevalence of patients of pulmonary hypertension.
- To study the demographic profiles of patients with pulmonary hypertension.
- To study the various symptoms & signs of patients of pulmonary hypertension.
- To study the outcomes in the patients of pulmonary hypertension.

Statistical Analysis

The data procured will be noted in a case record form and will be compiled in Microsoft excel sheet & analyzed in tabular & graphical forms. For the quantitative data, mean with standard deviation will be calculated. Appropriate statistical test will be applied wherever necessary.

OBSERVATIONS AND RESULTS

Table-1: Sex distribution of the study population

Sex	Frequency	Percent
F	36	36.00%
M	64	64.00%
TOTAL	100	100.00%

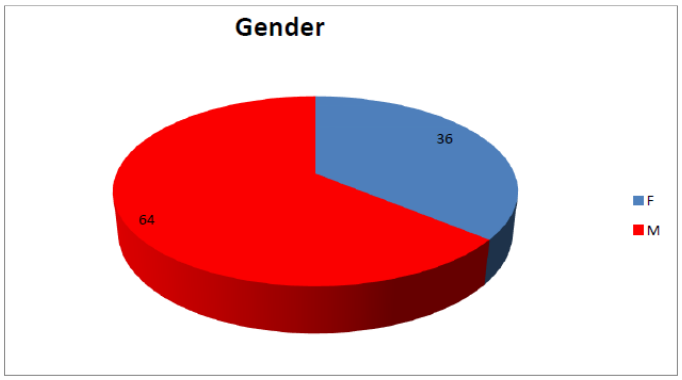

Fig-1: Sex distribution of the study population

Table and Figure 1 show sex distribution of the study population. There are 64 males and 36 females. The sex difference attributes to many factors.

Table and figure 2: Denotes the smoking behavior of our study population. There are 28 smokers among this. The smoking is a very important risk factor for the pulmonary hypertension as we shall see in the analysis.

Table-2: Smoking behavior of study population

Smoking	Frequency	Percent
NO	72	72.00%
YES	28	28.00%
TOTAL	100	100.00%

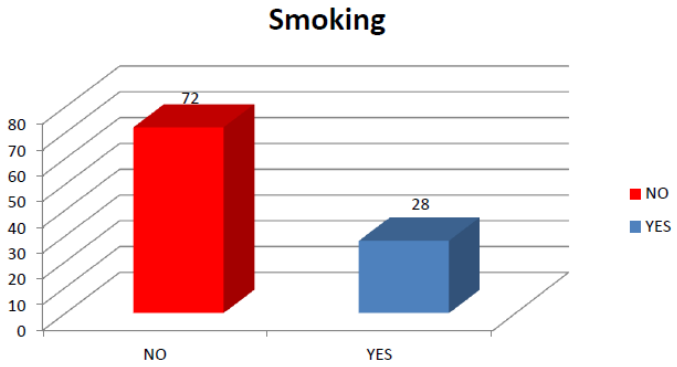

Fig-2: Smoking behavior of study population

Table-3: Chest pain among study population

Chest pain	Frequency	Percent
NO	88	88.00%
YES	12	12.00%
TOTAL	100	100.00%

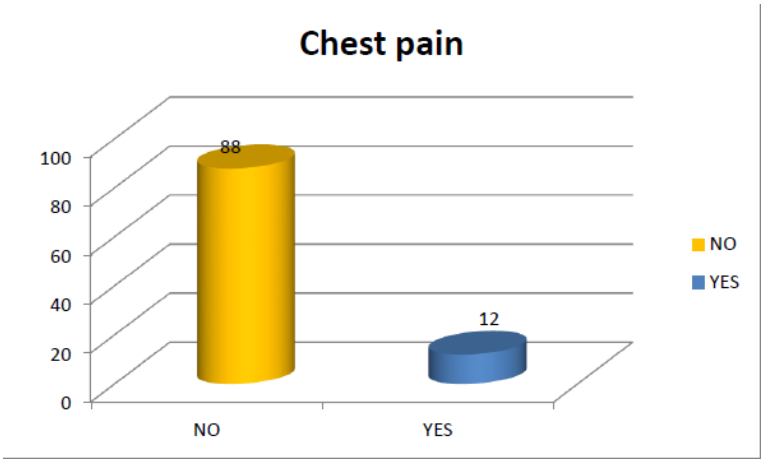

Fig-3: Chest pain among study population

Table and Figure 3 show the distribution of chest pain among subjects. 12 patients complained of chest pain among the study group. Chest pain can be easily attributes to cardio vascular symptoms. So high index of suspicion is needed

Table-4: Haemoptysis among study population

Haemoptysis	Frequency	Percent
NO	84	84.00%
YES	16	16.00%
TOTAL	100	100.00%

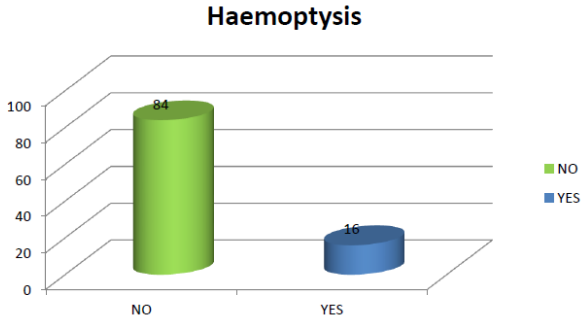

Fig-4: Haemoptysis among study population

Table and figure 4: 16 patients presented with haemoptysis as their primary symptom. Among smokers it can be easily confounded with pulmonary Koch or bronchiectasis. So again it necessitates the careful approach.

Table-5: Pedal edema among study population

Pedal edema	Frequency	Percent
NO	70	70.00%
YES	30	30.00%
TOTAL	100	100.00%

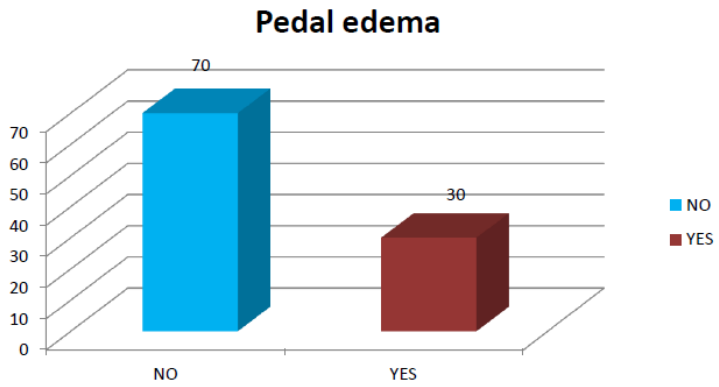

Fig-5: Pedal edema among study population

Table and Figure 5: it is clear that 30 patients presented with pedal edema of pitting variety. Again there are important differentials of this symptom. It underscores the importance of careful approach.

Table-6: Syncope among study population

Syncope	Frequency	Percent
NO	86	86.00%
YES	14	14.00%
TOTAL	100	100.00%

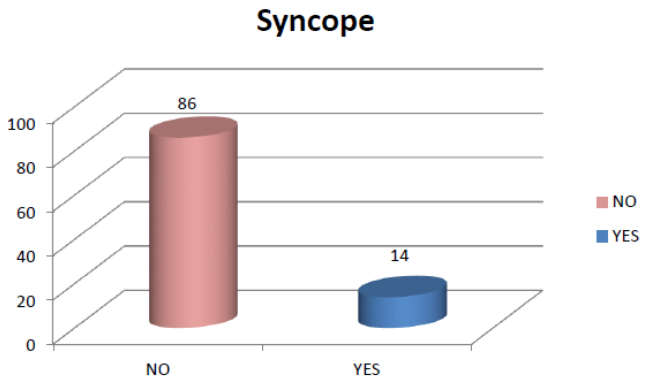

Fig-6: Syncope among study population

Table and figure 6: Indicates the pattern of syncope in study group. Among 100 patients 14 presented with syncope as their primary symptom. There are lots of differentials of syncope depending upon the age structure.

Table-7: Cough among study population.

Cough	Frequency	Percent
No	11	11.00%
Yes	89	89.00%
TOTAL	100	100.00%

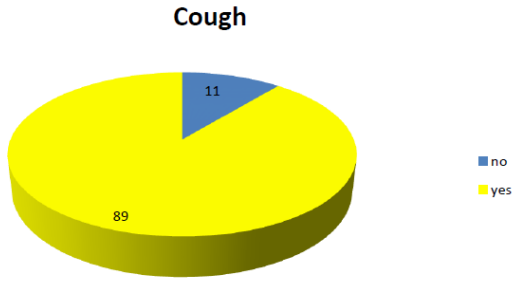

Fig-7: Cough among study population

Table and Figure 7: Dry cough is one of the major symptoms of the pulmonary hypertension. This is aggravated by the supine position. Our study reflects the same fact. Totally 89 patients complained of cough as their initial symptom.

Table-8: Chest X-ray among study population

CXR changes	Frequency	Percent
NO	2	2.00%
YES	98	98.00%
TOTAL	100	100.00%

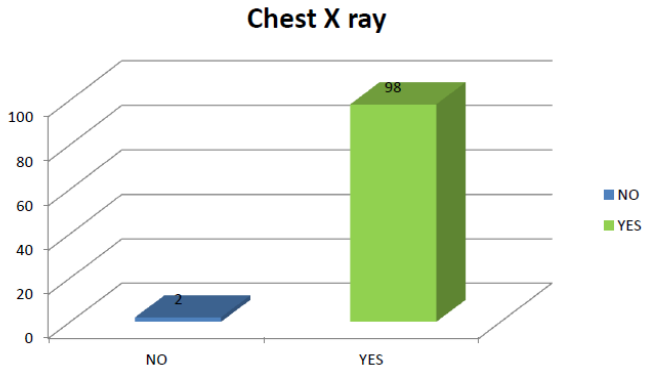

Fig-8: Chest X-ray among study population

Table and Figure 8: Chest X-ray findings are almost always present whenever patient is symptomatic. 98 patients presented with X-ray alteration.

Table-9: Dyspnea among study population.

Dyspnea	Frequency	Percent
NO	7	7.00%
YES	93	93.00%
TOTAL	100	100.00%

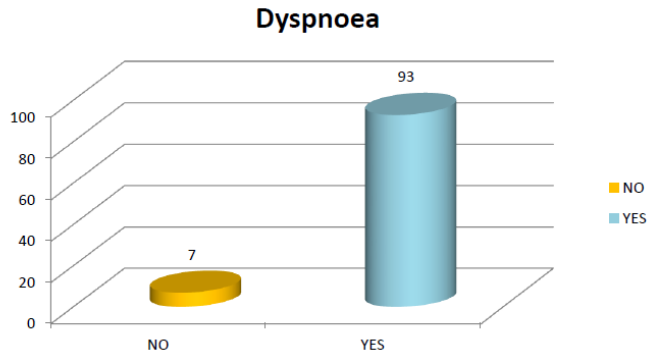

Table 9: Dyspnea among study population

Table and Figure 9: Dyspnoea initially with activity and then even at rest is also one of the major symptom. In our study 93 patients complained of dyspnea.

Table 10: Easy fatigue among study population

Easy fatigue	Frequency	Percent
NO	18	18.00%
YES	82	82.00%
TOTAL	100	100.00%

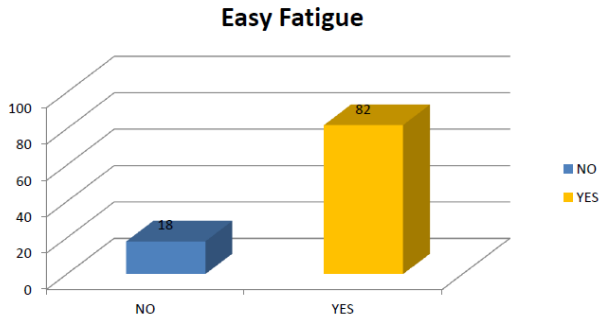

Table-10: Easy fatigue among study population

Table and Figure 10: Whenever patients present with dyspnoea, they simultaneously start having easy fatigability. This could be attributed to the defects of metabolic aspects. Among our patients 82 patients presented with fatigue.

Table-11: Outcome of the study population

Outcome	Frequency	Percent
Cured	7	7.00%
Died	5	5.00%
Under treatment	88	88.00%
TOTAL	100	100.00%

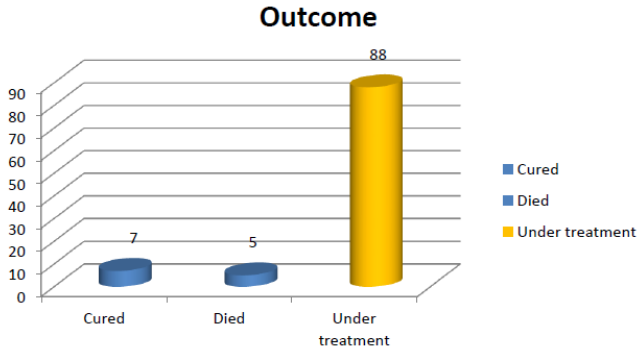

Fig-11: Outcome of the study population

Table and Figure 11: During the study period 7 patients who were symptomatic due to their cardiovascular problems, were cured following corrective surgery. Mainly these were the patients who were suffering from valvular heart diseases. 5 patients died during this period. These were the patients who were at their age extremes and had significant morbidity as well. 88 patients are still under treatment.

Table-12: Class wise distribution of the study population

Clinical class	Frequency	Percent
class 1	9	9.00%
class 3	76	76.00%
class 4	2	2.00%
class 5	13	13.00%
TOTAL	100	100.00%

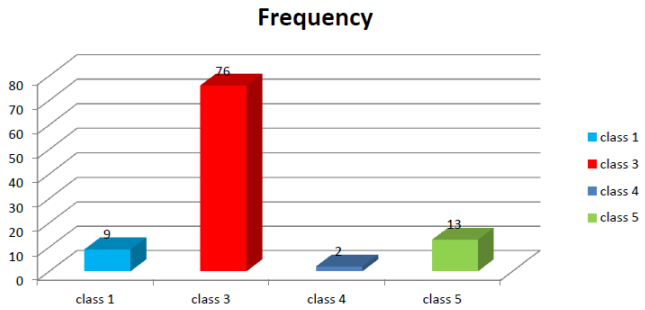

Fig-12: Class wise distribution of the study population

Table and Figure 12: In our study design majority were from class 3 being 76 followed by class 5, class 1 and class 4.

DISCUSSION

The above study was an observational study of clinical profile of patients with pulmonary hypertension. The study included 100 consecutive patients who were diagnosed by specialists already and were undergoing treatment.

Demography

In our study of 100 patients with pulmonary hypertension (PH), men outnumbered women. The interesting fact is that the male to female ratio is reversed in our study as compared to previous observations elsewhere. In French registry [1] data women formed 65.3% in overall cases, whereas in Swiss registry data; women formed 59% of the study population.[2] This difference in sexes in our study group could be explained due to the fact that it involved subjects with respiratory symptoms and bias in seeking medical care and absence of tobacco smoking in women. Smoking is one of the major risk factor for respiratory etiology of pulmonary hypertension. In our study only 28 patients accepted the fact that they were smokers. This paradox can be due to hiding of the history by them. Similar studies underscore this fact.

Symptoms

The symptoms in pulmonary hypertension are often nonspecific and may not be present till the disease is advanced. The symptoms include breathlessness, easy fatigue, weakness, chest pain, syncope [1]. Syncope and angina are rarely seen early in the disease and when present signify the reduced cardiac output. The main symptoms at the diagnosis were chest pain (88%), dyspnoea (93%), followed by cough (89%), easy fatigue (82%), pedal oedema (30%), haemoptysis was complained by 84% of the patients. Syncope was present in only 14% patients. Thus patients with pulmonary hypertension in our study group had non-specific symptoms, of long standing duration. Dyspnoea, easy fatigue and cough were most common symptoms. Various authors have reported dyspnoea and easy fatigue to be the most common symptoms in patients with pulmonary hypertension (PH). In a national prospective study Rich and colleagues reported symptoms were nonspecific and dyspnoea accounted for 60%, fatigue was seen in 73%, chest pain in 47%, syncope in 36% and oedema feet was seen in37% [11].

Physical examination

On respiratory examination, abnormality was found in almost all the cases except in 8 cases. The findings included crackles, rhonchi, reduced breathe sounds ad bronchial breathe sounds. The respiratory physical examination findings depended upon the underlying aetiology. On cardiovascular examination, findings associated with pulmonary hypertension (PH) included loud or accentuated pulmonary component of second heart sound, systolic murmur, parasternal heave, hepatojugular reflex and raised jugular venous pressure. Loud p2 was the most common physical examination finding and was present in 58 patients with pulmonary hypertension. In a study conducted by Julian sleeper and workers it was found that accentuated pulmonary component of second heart sound was present in all (100%) cases of pulmonary arterial hypertension and parasternal heave was present in 93% of cases[5]. The physical examination findings for evidence of pulmonary hypertension though having high specificity are lacking in sensitivity and are subjective and affected by the underlying lung diseases.

Chest radiography

Chest radiography has been found to be abnormal in 98% of the cases during initial evaluation of pulmonary arterial hypertension (PAH). The chest radiography findings that are associated with pulmonary hypertension include main and hilar pulmonary arterial dilation (hilarthoracic ratio greater than 0.44), a transverse diameter of right descending pulmonary artery ≥17mm on frontal chest radiograph and cardiomegaly (cardio-thoracic ratio greater than 0.5). Chest radiograph as an initial investigation may provide important clues for diagnosis. Pulmonary parenchymal changes when present are easily identified by the chest radiograph. However severity of parenchymal changes is not associated with severity of pulmonary hypertension.

In our study chest radiograph changes on frontal radiograph were classified as cardiothoracic changes and pulmonary parenchymal changes. Though 98 patients showed the x-ray abnormalities; most were the nonspecific findings. Thus the sensitivity of chest radiograph in identification of PH was only 25%. S Algeo and workers who evaluated frontal chest radiograph for signs associated with PH found varying levels of sensitivity for different radiological signs. And the most sensitive parameter was enlargement of main pulmonary artery with a sensitivity of 62% at high levels of PH. For mild Pulmonary Hypertension (PH) they found a sensitivity of less than 33% for chest radiograph changes in detection of Pulmonary Hypertension (PH)[6].

Clinical classes

The composition of clinical classes according to Evian's classification in our study was as following. Clinical class 1 had 9 patients, class 3 had 76 patients, class 4 had 2 patients and clinical class 5 contained 13 patients. Interestingly during our study period we never came across any type 2 cases.

In class 1 (pulmonary arterial hypertension) out of 9; 1 case was due to HIV associated pulmonary arterial hypertension (PAH).

Class 3 was the largest class and had 76 patients; its composition was as following

a) Obliterative bronchiolitis (n=34), b) Chronic Obstructive Pulmonary Disease (COPD) (n=14), c) Interstitial lung disease (n=16), d) Combined pulmonary fibrosis and emphysema (n=4), e) Bronchiectasis (n=4), f) Obstructive sleep apnea syndrome (n=2), g) Obesity hypoventilation syndrome (n=1), h) Bronchoalveolar cell carcinoma (n=1). Among the class 3, obliterative bronchiolitis was the most common aetiology which accounted for 34 cases out of 76 patients. Among these cases all were of post infectious in nature except one; which was of idiopathic variety. Most of these cases were preceded by prior pulmonary infections mostly tuberculosis, majority of them were non-smokers only three patients were smokers (20%) thus differing from Chronic Obstructive Pulmonary Disease (COPD). Further on high resolution computed tomography the scenario was totally different in the form of absence of centrilobular emphysema and instead there was presence varying degrees of air trapping and mosaic perfusion. Chronic Obstructive Pulmonary Disease (COPD) was present in 14 and was most common after obliterative bronchiolitis and accounted for 17% of clinical class 3 and 12% of overall cases. Out of these 2 patients were cases of overlap syndrome in that they had in addition to Chronic Obstructive Pulmonary Disease (COPD) obstructive sleep apnoea syndrome (OSAS). Thus the subgroup of patients with Chronic Obstructive Pulmonary Disease (COPD), were relatively older individuals with reduced lung volumes and had hypoxemia and hypercapnia with limited functional capacity. There were 2 (3.6%) patients with combined pulmonary fibrosis and emphysema. In one case, patient had bronchoalveolar carcinoma with resultant hypoxemia and pulmonary hypertension. There were 1 case each of obstructive sleep apnoea syndrome and obesity hypoventilation syndrome. In contrast to other studies there was only one case due to chronic pulmonary thromboembolism.

In class 5 there were total 13 cases and clinical class 5 was most heterogeneous of all classes in that it contained a variety of disorders with associated pulmonary hypertension. That included mediastinal fibrosis in 5 cases in which there direct involvement and luminal compromise of main, left and right pulmonary arteries. 6 cases were due to sarcoidosis and one case each of tropical pulmonary eosinophilia and chronic renal failure.

In a study carried out at an echocardiographic centre by Gabby E and workers of the patients who were diagnosed to have pulmonary hypertension echoed the similar findings as that of our study [12]. In an Indian registry for PH of the 57 patients, 72% had Pulmonary Arterial Hypertension (PAH), 5% had left heart disease, only 7% had chronic lung disease or hypoxemia, and remaining 16% had Chronic Thromboembolic Pulmonary Hypertension (CTEPH). In a study by Joshi JM, Obliterative bronchiolitis was the second most common (22.85%) chronic airway disease associated with pulmonary hypertension followed by Chronic Obstructive Pulmonary Disease (COPD)[13].

Interstitial lung disease (ILD) with pulmonary hypertension PH

In patients with IPF (Idiopathic pulmonary fibrosis) pulmonary hypertension (PH) has been reported in 8-80% of cases and prevalence of PH increases with disease progression. The presence of PH markedly increases mortality in patients with ILD [14-16]. The pulmonary hypertension in interstitial lung disease (ILD) is typically of mild to moderate degree and progression is slow and occurs in tandem with disease progression. There were total of 16 cases with interstitial lung disease of clinical class 3. Out of these two cases were connective tissue disease related interstitial lung diseases while rests were idiopathic interstitial pneumonias. The male to female sex ratio in interstitial lung disease (ILD) was 4:3.The median age was 34.5 years. 2 Patients (25%) had corpulmonale and previous history of right heart failure.

The treatment strategies for the pulmonary hypertension are evolving. There are lots of studies which are going on in this field. A Swiss study showed that antiviral therapy appeared to have no effect on preventing the development of Pulmonary Arterial Hypertension (PAH), as two-third of patients

developed Pulmonary Arterial Hypertension (PAH) while receiving antiviral therapy. Of note, this study showed no significant survival benefit in patients treated with antiviral therapy compared to those not treated [17]. However, Cicalini, *et al*. in their study showed a survival rate of 55% among patients treated with antiviral therapy compared to 22% amongst a non-treatment group (p = 0.02)[18]. This study also recommended an endothelin receptor antagonist, prostacyclin analogs, and type 5 phosphodiesterase inhibitors for treatment of PAH associated with HIV infection [19]. However, the role of antiviral therapy remains unclear in the setting of HIV infection and concomitant Pulmonary Arterial Hypertension (PAH).

SUMMARY AND CONCLUSION

Pulmonary hypertension has multifactorial etiology and varying effects on all body systems. The development of pulmonary hypertension determines further natural course of disease and predicts survival and poor outcome. The progressive and untreated pulmonary hypertension leads to progressive deterioration in the right ventricular function which heralds different clinical features associated with pulmonary hypertension. The diagnosis of pulmonary hypertension is often delayed; the early identification of pulmonary hypertension has both prognostic and treatment implications.

Our study was an observational study carried out at Medicine department in already diagnosed pulmonary hypertension cases by specialist involving 100 consecutive patients. Once patients were enrolled into study after informed consent; detailed clinical evaluation as carried out including clinical history and physical examination. Further patients were evaluated for aetiology and functional status.

Men were outnumbered by women. Median age at presentation for men and women was almost similar. There was significant delay between symptom onset and diagnosis of Pulmonary Hypertension (PH). The symptoms were non-specific; dyspnoea and easy fatigue were the commonest symptoms. Physical examination findings for Pulmonary Hypertension (PH) were less sensitive. Pedal oedema was present in significant number of patients despite absence of right heart failure; implying factors other than right heart failure were responsible for presence of pedal oedema in patients with Pulmonary Hypertension (PH). Chest radiograph had poor sensitivity in identification of pulmonary hypertension; however when present them signified Right Ventricular (RV) dilatation and dysfunction. Clinical class 3 was the most predominant class .There were no cases belonging to clinical class 2. Obliterative bronchiolitis of post infectious aetiology was found to be single largest aetiology associated with PH in clinical class 3 and overall. The level of Pulmonary Hypertension (PH) was relatively mild to moderate; despite which significant number of patients had corpulmonale and had previous history of right heart failure.

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