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Pulmonary Tuberculosis; A Dominant Etiology of Pulmonary Hypertension in Endemic Areas

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ABSTRACT

Background: Many patients with chronic lung disorders like infections, COPD, ILD, OSA & Thrombo-embolism, present with dyspnea, not showing adequate improvement by conventional treatment. Most of these were diagnosed as pulmonary hypertension by further multidisciplinary work-up. Such patients show reduced life expectancy due to late diagnosis and insufficient treatment. Many TB patients often remain undiagnosed in this context. The understanding of etiology and risk factors is essential for a high index of suspicion. **Objective:** To explore the etiology of Pulmonary Hypertension in chronic respiratory patients. **Study Design:** A Retrospective Observational Study. **Settings:** Male pulmonology ward, Gulab Devi Chest Hospital, Lahore Pakistan. **Duration:** 37 months from January 2014 to February 2017. **Methodology:** 231, consecutive cases, having Age >14 years with clinical and radiological suspicion of pulmonary hypertension were included. Patients having Age >90 years and <14years, not willing for further investigations were excluded. Detailed history, physical examination, radiological, hematological, bacteriological biochemical and immunologic findings were recorded. PH was diagnosed by ECG, Echocardiography, CT-Angiography. HRCT thorax & PFTs, were employed to recognize the underlying lung disorders. Risk factors were identified. Data tabulated, analyzed statistically and conclusions were drawn. **Results:** 69/231 (29.87%) cases with active and 76/231(32.90%) with old-treated TB, 50(21.64%) COPD, 10(4.32%) pneumonia, 5(2.16%) CLD, six bronchiectasis and three cases of chest deformities were diagnosed PH. Cigarette smoking, DM and obesity were major risk factors. **Conclusion:** Pulmonary Tuberculosis can be the dominant etiology of PH in high prevalence populations.

Keywords: *Pulmonary tuberculosis, Pulmonary hypertension, High prevalence population.*

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INTRODUCTION

Pulmonary hypertension (PH) is a devastating disease associated with increasing debility and poor prognosis, resulting from architectural lung damage and hypoxia. It is characterized by persistent elevation of mean pulmonary arterial systolic pressure > 25 mmHg at rest and > 30 mmHg on exercise. It is considered as an uncommon entity but shows high morbidity and mortality.[1] Previously it was recognized as a disease of the young and middle-aged but currently it is considered as disease of elderly with multiple co-morbidities.[2-3] These patients usually present with debilitating symptoms and show reduced life expectancy while late diagnosis and inadequate treatment contributes to the poor survival.[4]

It is classified into five main groups, (group-1) pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, (group-2) due to left heart disease- left ventricular systolic and diastolic dysfunction, valvular disease, left heart inflow or outflow tract obstruction & congenital cardiomyopathies, (group-3)lung disease like COPD, ILD, mixed obstructive and restrictive disorders, sleep disorders, alveolar hypoventilation, high altitude & developmental lung disorders, (group-4), chronic thrombo embolic phenomena, (group-5) PH with unclear /multifactorial mechanisms like hematologic, systemic disorders (sarcoidosis, Histiocytosis & Lymphangiomyomatosis), metabolic and tumoric obstructive diseases.[5] PH can be caused by HIV infection, chronic hepatitis B and C, hereditary haemoglobinopathies and tuberculosis can also be the possible etiology.[6-7]

These patients usually present with shortness of breath disproportionate to radiological picture, not showing adequate improvement, on conventional treatment but multidimensional diagnostic work-up reveals the diagnosis. PH remains associated with significant morbidity and mortality, and a substantial reduction in

quality of life. After failure of medical treatments, the lung transplantation remains the only but difficult option.[8-9] Although identification of the etiology can be challenging but is essential because it determines the correct management options which can ameliorate the severity of PH. We conducted this study to explore the etiology of pulmonary hypertension in daily pulmonology practice.

METHODOLOGY

Study Design: A Retrospective Observational Study.
Settings: Male ward of Pulmonary Medicine, Gulab Devi Chest Hospital, Lahore Pakistan.
Duration: 37 months from January 2014 to February 2017.
Sample Technique: Non-probability consecutive sampling.
Sample Size: 231 consecutive male patients.
Inclusion Criteria: Male patients, having Age ≥14 years, dyspnea not responding to conventional treatment, and clinical and radiological suspicion of pulmonary hypertension were included in the study.
Exclusion Criteria: Patients having Age >90 years and <14 years, not willing for further investigations were excluded.
Data Collection Procedure: Pulmonary hypertension was suspected by an unexplained dyspnea, desaturation even at minimal activity like changing dress, visiting toilet, saying prayer or walking a short distance and sometimes an overt heart failure associated with raised JVP, pedal edema, tender hepatomegaly and prominent pulmonary artery & reticulations on x-ray chest. The patients were re-evaluated with detailed history, thorough physical examination and a multidisciplinary diagnostic work-up. Basic hematological, biochemical and immunological tests were performed. Sputum for Acid Fast Bacilli and G-Xpert was done. ECG and echocardiography were employed to evaluate the cardiac status. Pulse oximetry and ABGs were used to evaluate oxygen saturation. Multiple view radiography, HRCT thorax & PFTs, were utilized to recognize the lung disorders. Ultrasound abdomen & chest were used to identify the risk factors. PH was diagnosed by Doppler Echocardiography and CT- Angiography. The severity was classified into mild (30----45 mmHg), moderate (46---60 mmHg) and severe (> 60 mmHg) groups. Six-Minute Walk-Test was employed for objective assessment of exercise capacity and to monitor the response of treatment. TB-cases were treated according to the WHO & COPD cases on the Global initiatives guide-lines and all cases were followed up for six months, at least. Risk factors and co-morbidities were identified. The files were retrieved from the hospital registry, all multidisciplinary findings were noted, tabulated, data analyzed and conclusions were drawn by applying statistics.
Data Analysis: SPSS-16 was utilized for statistical analysis. Quantitative results were expressed as mean ±SD, categorical data was presented as percentage. Fisher exact test was utilized for the calculation of *p-value*. A *p-value* < 0.05 was taken as significant.

RESULTS

231-male patients were enrolled. Age range was 14 – 90 years with median age 46 years, mean 48.68 with SD ± 10.79, 95% CI for the mean 47.28-50.08 and Std. Error : ± : 0.71. The clinical presentation of 231 patients is shown in table 1.

Table 1: Frequency of clinical picture in 231 patients

Clinical Features Total cases	Observed cases	Percentage
Unexplained dyspnea	231	100.00 %
Cough	217	93.93 %
Expectoration	200	86.58 %
Fever	145	62.77%
Chest Pain	138	59.74%
Hemoptysis	32	13.85 %

Percentage is calculated for 231 patients

Table-1 shows that 100% patients presented with un-explained dyspnea. Cough, expectoration & fever were the main symptoms while chest pain and hemoptysis were less common. The findings of physical examination are shown by figure 1.

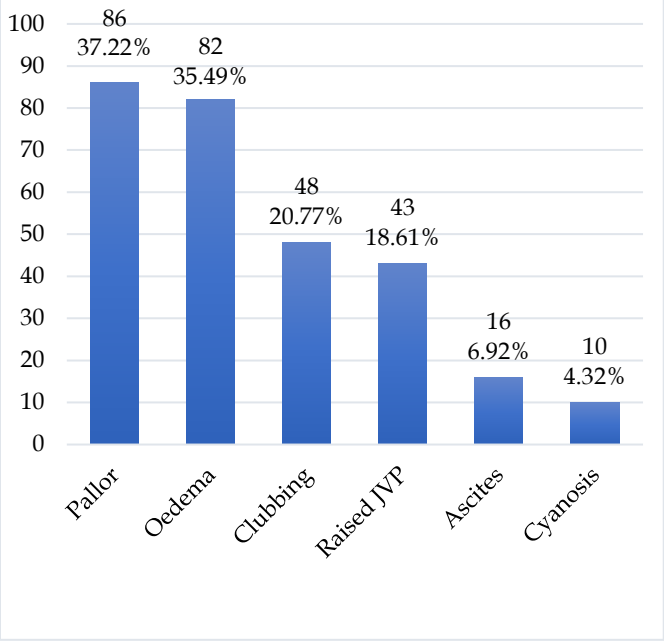

Figure 1: Frequency of Physical Signs in 231 Patients

Dyspnea was classified according to m-MRC scale as grade 0 to grade 4. Its frequency is shown by the table 2, in 231 patients.

Table 2: Frequency of severity of dyspnea (m MRC Scale) n=231

Dyspnea Severity	Observed cases	Percentage
Grade-0	0.00	0.00%
Grade-1 +	0.00	0.00%
Grade-2 ++	155	67.09%
Grade-3 +++	66	28.57%
Grade-4 ++++	10	4.32%

Percentage is calculated for 231 patients.

Majority of the patients showed m-MRC grade 2 & 3 dyspnea. The identified risk factors are shown in table 3.

Table 3: Frequency of risk-factors for pulmonary hypertension (n = 231)

Risk Factors	Observed Cases	Percentage
Cigarette Smokers	174	75.32%
Diabetes Mellitus	24	10.38%
Obesity	09	3.89 %
Chronic Liver Disease	05	2.16 %
Pectus Excavatum	03	1.29 %

Percentage is calculated for 231 patients.

Cigarette smoking was the most common (75.32%) risk factor. 174 smoker patients showed mean age 50.33 with SD ± 11.34, range 48 and variance 129.8. while 57 non-smoker patients, displayed mean age 41.7, SD. ± 7.67, range 36 and variance 58.88. Fisher exact test statistic value is 0.0005, which is highly significant at < 0.05. The PASP value ranged from 35 to 105 mmHg, the mean value was 53.69 with SD ± 16.89 with 95% CI: 51.50-55.88, Std. Error ± 1.11, variance 285.37 and range 75. The mean PASP value for TB-cases was 55.46 mmHg with SD ±16.06, 95% CI for the mean:52.82-58.09, variance 257.9 and range 75. COPD patients showed mean PAH value of 51.52 mmHg with SD ±15.58, 95% CI:47.09-55.94, variance 242.9 and range 60. The *p-value* for PASP, by Fisher exact test was 0.0001 with significance level at p < *0.05*. The frequency of dyspnea severity is shown in figure 2.

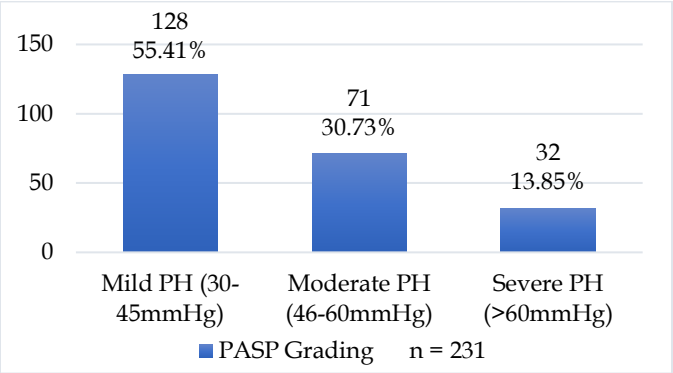

Figure 2: Frequency of PH Severity in 231 patients

Only103 patients (44.58%) could perform lung function test successfully. 20 patients showed mild obstruction, 28 moderate obstruction, 15 moderate restriction and 40 cases with severe restriction were noted. 12/231 cases (5.19%) were with cardiac etiologies while 219 patients (94.80%) were with non-cardiac causes. Among cardiac group, one case (8.33%) was of ASD secundum,03 cases (25.0%) of DCMP, 05 cases (41.66%) of severe LV systolic dysfunction, and 03 cases (25.00%) of severe mitral stenosis were found. The frequency of non-cardiac etiologies is shown in figure 3.

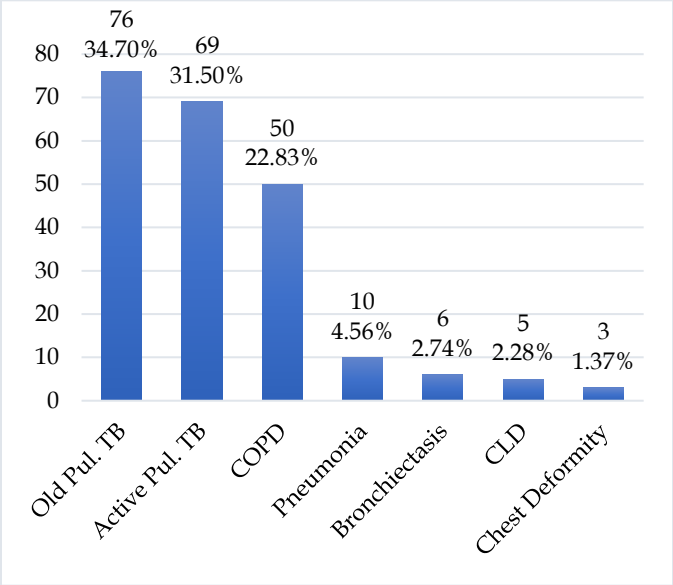

Figure 3: Non-cardiac Etiologies in 219 pulmonary hypertension patients

145/219 cases (66.21%) of Tuberculosis and 50/219 cases (22.83%) of COPD were the main contributors.
The PASP values were higher for TB than COPD patients.

DISCUSSION

231 male patients with mean age 48.68 were diagnosed pulmonary hypertension. The literature demonstrated mean ages between 45 ± 17 and 65 ± 15 years at diagnosis.[6,7]
Previously, pulmonary hypertension was considered as the disease of the young and middle aged but changes in the phenotype were observed in the past decades. Many Western authors have reported it as a disease of elderly with multiple co-morbidities.[4-8] PH secondary to Left Heart Disease is found in elderly patients which later on develop right heart failure and PH also. The higher prevalence of PH in the elderly may be related to decreasing compliance of the pulmonary arteries with aging.
Clinically, 100% patients presented with un-explained dyspnea which is the most prominent finding of this study. Even 128 patients (55.41%) could not perform lung

function test successfully because of poor control on breathing.

Cough, expectoration & fever have also significant contribution but these are non-specific symptoms, can be found in any respiratory disorders. Hemoptysis signifies tuberculosis, bronchiectasis or pneumonia. Oedema, ascites and raised JVP, points towards cardiac involvement, cyanosis can be found in advanced respiratory and cardiac disorders while clubbing is a feature of bronchiectasis, COPD, ILD, cyanotic heart diseases & CLD. Pallor is a non-specific finding which can be related to poor socio-economic status, malnutrition and poor health education in addition to pathological processes.

In this study, PASP was measured in the range of 30 to 105 mmHg by Doppler echocardiography. Which indicated that echocardiography is an excellent modality capable of diagnosing PH at an earlier stage, enabling early diagnosis, prompt management and reducing morbidity and mortality just by having a high index of suspicion. Furthermore, it has eliminated the need of diagnostic right heart catheterization for PH.[9]

174 cases (75.32%) with cigarette smoking is a big risk factor. Cigarette smoking has direct effect on intra-pulmonary vessels & is the major risk-factor for pre-disposing a wide spectrum of chronic respiratory disorders like COPD, recurrent respiratory infections, respiratory failure and malignancies and is a big risk factor for PH.[10]

We came across 09(3.89%) cases of obesity, which is an independent risk factor for PH.[11] Obesity directly contributes to the development of PH because up to 5% of otherwise healthy individuals with a BMI >30 kg·m^{-2} have been found with moderate or severe PH. The possible explanation is that these patients are at increased risk of left heart-disease, pulmonary thrombo-embolism and sleep-disordered breathing. A recent meta-analysis has demonstrated that bariatric surgery leads to clinical improvements in PH, in obese patients.

24 cases (10.38%) of diabetes mellitus is a significant risk factor displayed by this study. It has been demonstrated that long-term survival appears worse in PH patients with diabetes in comparison to PH patients without diabetes.[12]

We encountered 05/219 cases (2.28%) of PH with chronic liver disease having portal hypertension. Several researchers have reported that 5% cases of portal hypertension, irrespective of the cause, develop porto-pulmonary hypertension.

Three cases (1.29%) with gross chest deformity (kypho-scoliosis + Pectus Excavatum) were found in our series. Such cases have reduced chest wall compliance, alveolar hypoventilation, alveolar hypoxia and hypercapnia causing pulmonary vasoconstriction and elevated PASP levels.[13]

Out of 231, we came across 12 patients (5.19%) with cardiac etiology. The cardiac cases included Mitral Stenosis, DCMP, LV-systolic dysfunction and ASD secundum. PH is a complication of Left Heart disease including systolic and diastolic left ventricular dysfunction and left-sided valvular heart disease.[4-8]

In non-cardiac group, 50/219 cases (22.83%) of PH associated with COPD were found which can be due to cigarette smoking active or passive or working at smoky and polluted environment.[11] Tuberculosis itself is proposed to be etiologically responsible for the development of COPD.[14]

06 cases (2.74%) of bronchiectasis and 10 patients (4.56%) of slow resolving pneumonia were encountered in this study. Although the level of PASP was lower in COPD as compared to TB patients but it is an undisputed fact that COPD with PH has the worst prognosis. In COPD, hypoxia and emphysematous destruction of pulmonary vascular bed is the main responsible factor. In this condition PASP > 45 mmHg has five-year survival less than 10%. Because pulmonary hypertension progresses slowly in chronic obstructive pulmonary disease, these cases remain unidentified several times and a poor out-come is the result. A high index of suspicion is the only tool to pick such cases. Andersen KH et al showed 36% PH in COPD patients.[15] A single study from Egypt, reported a prevalence of 62.7% among those with chronic obstructive pulmonary disease.

It is amazing that out of 219 non-cardiac cases, 145 patients (66.21%) had tubercular etiology. 69/145 cases (47.58%) were with active disease while 76/145 cases (52.41%) were, old-treated cases of tuberculosis, again admitted for worsening chest symptoms. In chronic tuberculosis when there is significant parenchymal damage, there is destruction of vascular bed, vasculitis and endarteritis, resulting into reduced cross-sectional area of the pulmonary vasculature and PAH.[16] This is the reason that these patients present with dyspnea, out of proportion to their radiological picture, desaturation with minimal activity and some-times as overt heart failure with pedal edema, raised JVP and tender hepatomegaly that is why we had 60/219 patients (27.39%) of cor-pulmonale in our study.[17] Ahmed AE et al In their cross-sectional study, described 14 patients of PH after successful treatment of pulmonary tuberculosis, with PASP values ≥ 40 mm Hg estimated by Doppler echocardiography.[18] Most of them had fibro-cavitary or fibrotic changes in the chest X-ray. Another study by Bhattacharya *et al*. has also reported PH in patients with tuberculosis.[19] Patel *et al*. have described 12% cases of PH to develop from tuberculosis.[20]

Tuberculosis is the dominant etiology of PH in (66.21%) this study. The high percentage of tuberculosis may be due to the fact that we rank 5th among the high burden countries with majority of the patients belonging to a class, below the poverty line, and people are not well

aware of the health education.[21] Furthermore, the study was conducted in a tertiary care hospital where TB patients are referred from all corners of the country. Anyhow it is clear from our results that tuberculosis irrespective of active or inactive, is a dominant etiology of PH in the community, which is often over-looked. Refractory shortness of breath and poor clinical states are usually not given due consideration and are attributed to advanced TB-disease, MDR, malnutrition, poor socio-economic status and various other factors without any thought about PH. The old treated cases presenting with worsening dyspnea are incorrectly interpreted as relapse of TB and are put again on anti-TB treatment or bronchodilators, for the treatment of dyspnea, without precise diagnosis. Such mismanagement, resulting into unhappy out-comes, needs to be avoided. Furthermore, the development of PH and ultimately cor-pulmonale can also be prevented by adequate and timely management of pulmonary TB which otherwise, destroys lung parenchyma & significantly reduces the span and quality of life as well.

The prevalence of PH varies widely across different populations with different etiologies and risk-factors. An Egyptian study reported a prevalence of 62.7% among COPD patients while the main class of PH in Africa is due to left heart diseases. On the other hand, this study revealed tuberculosis as the most common etiology.[21,22]

PH is no more a rare disease rather it is under-diagnosed. Average time between the appearance of the symptoms and confirmed diagnosis ranges from 1 to 4 years.[23,24] This is because pulmonary hypertension is present in the back-ground of chronic lung disorders, for which patients remain under treatment for longer periods & disease is identified as diagnosis of exclusion. It is diagnosed usually after a hectic multidisciplinary diagnostic work-up. A high index of suspicion is the only tool, which can take us to the early diagnosis.

This study has not only revealed the relevance of PH with pulmonary tuberculosis, but also highlighted that tuberculosis is the commonest culprit in high burden populations, which is often over-looked for the etiology of PH.

It is clear from this discussion that pulmonary hypertension is associated with increasing morbidity, mortality and poor quality of life. Early diagnosis & prompt management is the golden rule to escape unpleasant out-come. The findings of this study are adequate to alert the physicians for diagnosing PH at an early stage for the right treatment and favorable out-come. One should make a positive search for PH in cases of TB and other chronic lung disorders with shortness of breath, mismatched with radiological picture and refractory to conventional treatment.

In short, PH remains a fatal disease & tuberculosis is the most common etiology, followed by COPD and Slow Resolving Pneumonia. Cigarette smoking, DM, obesity, CLD and chest deformities are the significant risk factors.

CONCLUSION

- Tuberculosis is the dominant etiology of pulmonary hypertension in high burden populations.
- COPD is also a significant contributor followed by Bronchiectasis and pneumonia.
- Cigarette smoking, DM, obesity, CLD and chest deformities are significant risk factors.
- All the patients with shortness breath, refractory to conventional treatment must be investigated in the perspective of PH and treated on priority to reduce the morbidity and mortality in the community.

LIMITATIONS

The main limitations of this study is that it is a single centered, retrospective, observational study which usually is considered, having lesser credibility as compared to a prospective trial. Secondly the value of PH has not been confirmed by right heart catheterization which is the gold-standard, but is highly invasive, expensive and unsuitable for screening. On the other hand, echocardiography has emerged as a safe, sensitive & specific modality for screening purpose. Calculation of PASP in patients with severe tricuspid regurgitation can be under or overestimated, so an experienced hand is essential for the echocardiography of suspected cases. Although current study successfully shows the association of PH with TB but the questions about the screening of TB patients for PH, like when to go for screening, what tool should be opted and which intervention can improve the out-come in TB-patients with detected PH are still needing satisfactory answers. Our setting is very much popular for the treatment of tuberculosis and other chest disorders. Patients from every corner of the country rush to our hospital for unique facilities and high-class treatment, that is why, more TB patients are found in our wards which can be a source of bias but it does not affect the objectives of this research.

SUGGESTIONS / RECOMMENDATIONS

Further nation-wide, multi-centered, prospective studies with large sample size, preferably RCT should be performed to additionally explore the subject and reduce the bias, using protocols capable of answering the questions regarding screening TB-patients & screening tools for PH.

CONFLICT OF INTEREST / DISCLOSURE

No conflict of interest exists among the authors in this article.

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