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PREVALENCE AND CLINICAL PROFILE OF PULMONARY ARTERIAL HYPERTENSION IN CASES OF POST TUBERCULAR FIBROSIS

Medicine

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ABSTRACT

Pulmonary Hypertension is a hemodynamic and pathophysiological defect found in many clinical conditions, most commonly heart and lung diseases. The pulmonary circulation normally is a high flow, low-resistance, low pressure system that carries blood to the pulmonary microcirculation where the blood takes up oxygen and unloads excess CO2.

We have correlated CT fibrosis score with ECHO PASP and cardiac catheterization PASP, mPAP and PCWP to assess the presence of pulmonary hypertension and to quantify the severity of the disease. In our study, 30 patients with post tubercular fibrosis were studied in chest medicine department and cardiology department of NRSMCH.

We found from our study that the patients with significant lung damage (CTfibrosis score>10), have higher probability of having P-PULMONALE on ECG signifying pulmonary hypertension and right ventricular hypertrophy.Patients with higher CT fibrosis scores were found to have higher probability of having pulmonary hypertension as evidenced by ECHO PASP, cardiac catheterization PASP, mPAP and PCWP values. All patients who have P-PULMONALE on ECG were found to have pulmonary hypertension from ECHO PASP, cardiac catheterization PASP, mPAP, PCWP values.

KEYWORDS

PULMONARY ARTERIAL HYPERTENSION, TUBERCULAR FIBROSIS, MMRC GRADES, CARDIAC CATHETERISATION

INTRODUCTION

Pulmonary Hypertension is a hemodynamic and pathophysiological defect found in many clinical conditions, most commonly heart and lung diseases. Pulmonary Hypertension is defined as a mean pulmonary artery pressure (mPAP) of ≥ 25mm Hg. This is the universally accepted hemodynamic definition published by the European society of Cardiology and after the 4th world Symposium on Pulmonary Hypertension. Tuberculosis is a very common disease in India and post tubercular fibrosis is one of the most common sequelae of Tuberculosis. Patients with long standing disease eventually develop obstructive disease, chronic hypoxia, pulmonary vascular remodeling and ultimately pulmonary hypertension and features of corpulmonale. [1-3]

The pulmonary circulation normally is a high flow, low-resistance, low pressure system that carries blood to the pulmonary microcirculation where the blood takes up oxygen and unloads excess CO2. PAP is the product of cardiac output (CO) and pulmonary vascularresistance (PVR), i.e., vascular resistance of entire lung, including pulmonary arteries, capillaries and veins.[2]

PAP= CO x (PVR arteries + PVR capillaries + PVR veins) From this equation it is clear that PAP can be raised by an increase in C.O or an increase in arterial, capillary or versus resistance. Increased PVR(pulmonary vascular resistance) seen in pulmonary hypertension is due to collective effects of sustained vasoconstriction, vascular remodeling, insitu thrombosis and increased arterial wall stiffness.[3-8] Vasoconstrictive lesions include medial hypertrophy involving an increase in number and size of pulmonary arterial smooth muscle cells.[9] This leads to pulmonary arterial smooth muscle hypertrophy and hyperplasia which eventually leads to medial atrophy, fibrosis and subsequent thinning of media and dilation of vessel lumen.[10] Hypoxic pulmonary vasoconstriction is an adaptive mechanism important for redirecting blood flow away from poorly ventilated areas of lung and into the better ventilated areas to maximize the ventilation perfusion matching and optimize oxygenation of blood.[11-14]

In chronic hypoxia, two factors contribute to increase PAP – vascular remodelling due to pulmonary arterial smooth muscle cell proliferation and sustained vasoconstriction and structural changes that develop within a matter of weeks.[15-18] Increased proliferation and hypertrophy of pulmonary arterial smooth muscle cells and decreased apoptosis have been implicated in the development of pulmonary hypertension.[19-20] Hypoxia induces proliferation of pulmonary arterial adventitial fibroblasts and plays an important role in vascular remodeling. Complex lesions like plexiform lesions also contribute to vascular remodeling. Plexiform lesions are aneurysmal dilatations of muscular artery that can occur in very small arteries and arterioles. Plexiform lesions often co-exist with other obliterative vascular changes such as concentric laminar intimal thickening [21-36]

In our study, we have attempted to evaluate the diagnosed cases of post tubercular fibrosis by spirometry, CT SCAN of thorax, and evaluating Right heart with both Echocardiography and Cardiac catheterization. In our study, we took sputum negative cases of PTB who were treated with antitubercular drugs in the past, and have now developed evidence of pulmonary hypertension. We have correlated CT fibrosis score with ECHO PASP and cardiac catheterization PASP, mPAP and PCWP to assess the presence of pulmonary hypertension and to quantify the severity of the disease.

MATERIALS AND METHODS

Sample design

30 patients with pulmonary fibrosis with a past history of diagnosed PTB and ATD intake and have now developed evidence of pulmonary hypertension at Department of respiratory medicine, NRSMCH, Kolkata from April 2016 to March 2017. This is prospective randomized open labeled study

Inclusion criteria

- Confirmed case with a history of pulmonary tuberculosis (diagnosed by sputum or radio logically) and patients having a history of ATD intake.
- Patients having definite pulmonary fibrosis as evidenced by chest Xray and chest CT scan.

Exclusion criteria

- Patients having active pulmonary tuberculosis
- Patients who are taking ATD presently
- Patients having severe artery disease/cerebrovascular disease, cardiomyopathy, valvular heart disease.
- Patients who do not give informed consent

Statistical Analysis:
For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test where in the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered for statistically significant.

RESULT AND ANALYSIS

We had found that 16 patients were male and 14 patients were female. The age group range had 55-70 yrs. Scores were calculated separately for upper, middle and lower zones for each lung. Finally scores for all zones of both lungs were added to get the final CT fibrosis score. It is then divided into MILD (score 0-5), MODERATE (score 6-10) and SEVERE (score >10).

ECHO PASP and Cardiac Catheterization PASP was divided into two groups- <30 and ≥30(having pulmonary hypertension).Cardiac Catheterization mPAP was divided into two groups- <25 and ≥25(having pulmonary hypertension).Cardiac Catheterization PCWP was divided into two groups-≤10 and >10(having pulmonary hypertension)

We observed that among patients who have PULMONARY ARTERIAL HYPERTENSION (ECHO PASP≥30), 40% of patients have moderate CT fibrosis score and 46.7% of patients have severe CT Fibrosis score and the association between ECHO PASP and CT FIBROSIS SCORE three groups was statistically significant (p<0.0001)

We observed that among patients with pulmonary hypertension based on cardiac catheterization PASP (≥30), 43.8% of patients have moderate CT Fibrosis score and 43.8% of patients have severe CT Fibrosis score. On the other hand, 100% of patients with severe CT Fibrosis score were found to have pulmonary hypertension in our study and association between Cardiac Catheterization PASP and CT FIBROSIS SCORE was statistically significant (p<0.0001).

We observed that among patients with mPAP value ≥25, 46.2% of patients have moderate CT fibrosis score and 53.8% of patients have severe CT fibrosis score. On the other hand, 100% of patients having severe CT fibrosis are found to have pulmonary hypertension (mPAP≥25) in our study and the association between mPAP and CT FIBROSIS SCORE three groups was statistically significant (p<0.0001).

We observed that among patients with PCWP>10, 41.2% of patients have moderate CT fibrosis score and 41.2% of patients have severe CT fibrosis score. On the other hand, 100% of patients with severe CT fibrosis score are found to have PCWP>10 in our study and association between PCWP and CT FIBROSIS SCORE was statistically significant (p<0.0001)

We observed that correlation between SEX and CT fibrosis score was NOT statistically significant.

We observed that correlation between SMOKER/NON-SMOKER with CT fibrosis score was NOT statistically significant.

We observed that in mild, the age (mean± s.d.) of patients was 58.5000 ± 10.5515 years. In moderate, the age (mean± s.d.) of patients was 59.5714 ±9.3069 years. In severe, the age (mean± s.d.) of patients was 68.4286 ± 5.8269 years. Distribution of mean age in three CT fibrosis score was not statistically significant (p=0.0771).

We observed that among all patients who have P-PULMONALE in ECG, 37.5% of patients have moderate CT fibrosis score and 62.5% of patients have severe CT fibrosis score. On the other hand, 71.4% of patients with severe CT fibrosis score are found to have P-PULMONALE in ECG in our study and the association between ECG (P-PULMONALE) and CT FIBROSIS SCORE was statistically significant (p=0.0009).

We observed that among patients with moderate CT fibrosis score, 57.1% of patients have grade 3 MMRC and 28.6% of patients have grade 4 MMRC. Among patients with severe CT fibrosis score, 28.6% of patients have grade 3 MMRC and 71.4% of patients have grade 4 MMRC and the association between MMRC Grade and CT FIBROSIS SCORE was statistically significant (p=0.0001).

We observed that correlation of HOW PTB WAS DIAGNOSED with CT fibrosis score was not statistically significant.

We observed that among patients who have FEV1<0.75, 33.3% of patients have moderate CT fibrosis score and 41.7% of patients have severe CT fibrosis score. Only 11.1% of patients with FEV1≥0.75 have severe CT fibrosis score and the association between FEV1 and CT FIBROSIS SCORE was statistically significant (p=0.0342).

We observed that among patients with pulmonary hypertension (ECHO PASP≥30), 33.3% of patients have MMRC grade 3 and 53.3% of patients have MMRC grade 4and the association between MMRC Grade and ECHO PASP was statistically significant (p=0.0001).

We observed that among patients with mPAP≥25, 46.2% of patients have MMRC grade 3 and 53.8% of patients have MMRC grade 4 and the association between MMRC Grade with mPAP was statistically significant (p<0.0001).

We observed that among patients with PASP≥30, 37.5% of patients have MMRC grade 3 and 50% of patients have MMRC grade 4 and the association between MMRC Grade and PASP was statistically significant (p<0.0001).

We observed that among patients with PCWP>10, 35.3% of patients have MMRC grade 3 and 47.1% of patients have MMRC grade 4 and the association between MMRC Grade and PCWP was statistically significant (p=0.0001).

We observed that all patients (100%) with P-PULMONALE on ECG are having pulmonary hypertension (ECHO PASP≥30) and the association between ECG (P-PULMONALE) andECHO PASP was statistically significant (p=0.0009).

We observed that all patients (100%) showing P-PULMONALE in ECG are having pulmonary hypertension (mPAP≥25) and the association between ECG(P-PULMONALE) and mPAP was statistically significant (p=0.0001).

We observed that all patients (100%) with P-PULMONALE on ECG are having pulmonary hypertension (PASP≥30) and the association between ECG (P-PULMONALE) and PASP was statistically significant (p=0.0020).

We observed that all patients (100%) with P-PULMONALE on ECG are having pulmonary hypertension (PCWP>10) and the association between ECG (P-PULMONALE) with PCWP was statistically significant (p=0.0038).

DISCUSSION

In our study, 30 patients with post tubercular fibrosis were admitted in chest Medicine department of NRSMCH. We did HRCT -thorax, ECG, ECHO and cardiac catheterization in all these patients. CT scan, PFT, ECG were done in our department while ECHO study and cardiac catheterization study was done in the cardiology department of NRSMCH.

We initially stratified all patients on whether they are smokers or nonsmokers, severity of their dyspnea based on MMRC grade and how was PTB initially diagnosed in all these patients (sputum/radiological/ both).

After we did a CT scan in all these patients, we calculated the CT fibrosis score. Score was calculated as follows-

Initially each lung was divided into 3 zones-upper, middle and lower zones. Upper zone was defined as area above the carina. Middle zone was defined as area between carina and junction of inferior pulmonary veins with left atrium. PFT was done in our department and FEV1 was taken into account in each patient for our study. ECHO was done in cardiology department of NRSMCH and PASP was calculated. After doing ECHO, cardiac catheterization was done in every patient in catheterization laboratory of cardiology department of NRSMCH. In

our study we compared CT fibrosis score with ECG (P-PULMONALE), ECHO PASP score, cardiac catheterization PASP, mPAP and PCWP.

Also CT fibrosis score was studied separately in males and females, smokers and nonsmokers, different age groups, patients with different MMRC grades and also the correlation between CT fibrosis score and how PTB was initially diagnosed-sputum/radiological/both. From PFT, we compared the FEV1 values with different severity of CT fibrosis score.

We also studied the correlation of MMRC grades of patients admitted in our ward with the ECHO PASP and cardiac catheterization PASP, PCWP and mPAP values. Also the correlation between ECG (P-PULMONALE) and ECHO PASP and cardiac cath. PASP, mPAP and PCWP was studied in our work. It was found that correlation between CT fibrosis score was statistically significant with ECHO PASP, cardiac catheterization PASP, mPAP, PCWP values. 46.7% of patients with severe CT fibrosis score was found to have ECHO PASP≥30 while 93.3% of patients with mild CT fibrosis score have ECHO PASP<30.Among patients with pulmonary hypertension based on cardiac catheterization PASP (≥30), it is seen that 43.8% of patients have severe CT fibrosis score. Among patient with pulmonary hypertension based on mPAP value (≥25), 53.8% of patients have severe CT fibrosis score. Among patients with pulmonary hypertension based on PCWP value (>10), 41.2% of patients have severe CT fibrosis score.

Thus from this it can ascertained that the more the lung damage due to post tubercular fibrosis (indicated by higher CT fibrosis scores), the higher the chance of patient developing pulmonary hypertension as corroborated by the findings from ECHO PASP, cardiac catheterization PASP, mPAP and PCWP. Statistically significant correlation was also found between CT fibrosis score and ECG(P-PULMONALE).Of all patients who have P-PULMONALE on ECG, 62.5% of patients were found to have severe CT fibrosis score. Thus it can concluded that the more the lung damage , the higher the chance of developing pulmonary hypertension manifested by Right ventricular Hypertrophy and eventually Right Heart Failure.

From PFT it was found that 41.7% of patients with FEV1<0.75 have severe CT fibrosis score while only 11.1% of patients with FEV1 ≥0.75 have severe CT fibrosis score. Thus it can conclude that the more the lung damage, the more severe is the airflow obstruction as can be seen from PFT findings. Correlation of MMRC grade with CT Fibrosis score was found to be statistically significant. It is found that 71.4% of patients with severe CT fibrosis score have MMRC grade 4 on presentation to us. Thus the greater the lung damage, the more severe the dyspnea is as shown by higher grades on MMRC scale. Correlation of MMRC grades with ECHO PASP, cardiac catheterization PASP, mPAP, PCWP were also found to be statistically significant. From this correlation it can be concluded that the greater the lung damage and the greater is the grade of dyspnea in the patients(as shown by higher grades on MMRC scale) and higher the chance of these pts developing pulmonary hypertension as evidenced by ECHO PASP, cardiac catheterization PASP, mPAP, PCWP values. Correlation of ECG (P-PULMONALE) with ECHO PASP, cardiac catheterization PASP, mPAP, PCWP values were found to be statistically significant. From this correlation it can be concluded that the greater the lung damage, the greater the chance of the patient developing pulmonary hypertension, right ventricular hypertrophy and eventually right heart failure and this is evidenced from corroboration of values that were found on ECHO PASP, cardiac catheterization PASP, mPAP, PCWP.

CONCLUSION

- Patients with post tubercular fibrosis who have more severe lung damage (as found from CT scan of thorax) have higher chance of having more severe dyspnea on presentation (higher MMRC grades).
- Patients with post tubercular fibrosis who have more severe lung damage have more obstructive changes (low FEV1 value from PFT).
- Patients with post tubercular fibrosis who have more severe lung damage have higher chance of having P-PULMONALE on ECG.
- Patients with post tubercular fibrosis who have more severe lung damage have higher chance of having pulmonary hypertension as evidenced from investigations of ECHO and CARDIAC CATHETERISATION(higher values of ECHOPASP, higher values of cardiac catheterization PASP, mPAP, PCWP).
- There is a definite (statistically significant) correlation between degree of pulmonary fibrosis and severity of pulmonary hypertension.
- All patients who have P-PULMONALE on ECG were found to have pulmonary hypertension from ECHO PASP, cardiac catheterization PASP, mPAP, PCWP values.

Table: Distribution of CT FIBROSIS SCORE according to parameters

		Mild	Moderate	Severe	Total	Chi-square Value	p- value
ECHO	<30 Row % Col %	14 93.3 87.5	1 6.7 14.3	0 0.0 0.0	15 100.0 50.0	19.5714	0.0001
	≥30 Row % Col %	2 13.3 12.5	6 40.0 85.7	7 46.7 100.0	15 100.0 50.0		
PASP	<30 Row % Col %	14 100.0 87.5	0 0.0 0.0	0 0.0 0.0	14 100.0 46.7	22.9688	<0.00001
	≥30 Row % Col %	2 12.5 12.5	7 43.8 100.0	7 43.8 100.0	16 100.0 53.3		
mPAP	<25 Row % Col %	16 94.1 100.0	1 5.9 14.3	0 0.0 0.0	17 100.0 56.7	26.5094	<0.0001
	≥25 Row % Col %	0 0.0 0.0	6 46.2 85.7	7 53.8 100.0	13 100.0 43.3		
PCWP	≤10 Row % Col %	13 100.0 81.3	0 0.0 0.0	0 0.0 0.0	13 100.0 43.3	20.0735	<0.00001
	>10 Row % Col %	3 17.6 18.8	7 41.2 100.0	7 41.2 100.0	17 100.0 56.7		
SEX	Female Row % Col %	10 71.4 62.5	2 14.3 28.6	2 14.3 28.6	14 100.0 46.7	3.4534	0.1779
	Male Row % Col %	6 37.5 37.5	5 31.3 71.4	5 31.3 71.4	16 100.0 53.3		

Smoker Yes/no	NO	8	4	1	13	3.2385	0.1980
	Row %	61.5	30.8	7.7	100.0		
	Col %	50.0	57.1	14.3	43.3		
	YES	8	3	6	17		
	Row %	47.1	17.6	35.3	100.0		
	Col %	50.0	42.9	85.7	56.7		
Ecg (p-pulmonale) Yes/no	NO	16	4	2	22	13.9286	0.0009
	Row %	72.7	18.2	9.1	100.0		
	Col %	100.0	57.1	28.6	73.3		
	YES	0	3	5	8		
	Row %	0.0	37.5	62.5	100.0		
	Col %	0.0	42.9	71.4	26.7		

Table: Distribution of CT FIBROSIS SCORE according to MMRC Grade, and How was PTB Diagnosed- SPUTUM/ RADIOLOGICAL/ BOTH?

		MILD	MODERATE	SEVERE	TOTAL	Chi-square value	p-value
MMRC Grade	I	11	0	0	11	27.5379	0.0001
	Row %	100.0	0.0	0.0	100.0		
	Col %	68.8	0.0	0.0	36.7		
	II	4	1	0	5		
	Row %	80.0	20.0	0.0	100.0		
	Col %	25.0	14.3	0.0	16.7		
	III	0	4	2	6		
	Row %	0.0	66.7	33.3	100.0		
	Col %	0.0	57.1	28.6	20.0		
	IV	1	2	5	8		
	Row %	12.5	25.0	62.5	100.0		
	Col %	6.3	28.6	71.4	26.7		
How was PTB Diagnosed- SPUTUM/ RADIOLOGICAL/BOTH?	BOTH	5	3	5	13	6.3585	0.1739
	Row %	38.5	23.1	38.5	100.0		
	Col %	31.3	42.9	71.4	43.3		
	RADIOLOGICAL	7	1	0	8		
	Row %	87.5	12.5	0.0	100.0		
	Col %	43.8	14.3	0.0	26.7		
	SPUTUM	4	3	2	9		
	Row %	44.4	33.3	22.2	100.0		
	Col %	25.0	42.9	28.6	30.0		
FEV1	<75	3	4	5	12	6.7485	0.0342
	Row %	25.0	33.3	41.7	100.0		
	Col %	18.8	57.1	71.4	40.0		
	≥75	13	3	2	18		
	Row %	72.2	16.7	11.1	100.0		
	Col %	81.3	42.9	28.6	60.0		

Table: Distribution of MMRC Grade according to parameters

	ECHO		mPAP		PASP		PCWP	
MMRC Grade	<30	≥30	<25	≥25	<30	≥30	≤10	>10
I	11	0	11	0	11	0	10	1
Row %	100.0	0.0	100.0	0.0	100.0	0.0	90.9	9.1
Col %	73.3	0.0	64.7	0.0	78.6	0.0	76.9	5.9
II	3	2	5	0	3	2	3	2
Row %	60.0	40.0	100.0	0.0	60.0	40.0	60.0	40.0
Col %	20.0	13.3	29.4	0.0	21.4	12.5	23.1	11.8
III	1	5	0	6	0	6	0	6
Row %	16.7	83.3	0.0	100.0	0.0	100.0	0.0	100.0
Col %	6.7	33.3	0.0	46.2	0.0	37.5	0.0	35.3
IV	0	8	1	7	0	8	0	8
Row %	0.0	100.0	12.5	87.5	0.0	100.0	0.0	100.0
Col %	0.0	53.3	5.9	53.8	0.0	50.0	0.0	47.1
TOTAL	15	15	17	13	14	16	13	17
Row %	50.0	50.0	56.7	43.3	46.7	53.3	43.3	56.7
Col %	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Chi-square value	21.8667		26.4367		25.1786		21.4109	
p-value	0.0001		<0.00001		<0.00001		0.0001	

Table: Distribution of ECG (P-PULMONALE) according to parameters

	ECHO		MPAP		PASP		PCWP	
ECG (P-PULMONALE) YES/NO	<30	≥30	<25	≥25	<30	≥30	≤10	>10
NO	15	7	17	5	14	8	13	9
Row %	68.2	31.8	77.3	22.7	63.6	36.4	59.1	40.9
Col %	100.0	46.7	100.0	38.5	100.0	50.0	100.0	52.9
YES	0	8	0	8	0	8	0	8
Row %	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0
Col %	0.0	53.3	0.0	61.5	0.0	50.0	0.0	47.1
TOTAL	15	15	17	13	14	16	13	17
Row %	50.0	50.0	56.7	43.3	46.7	53.3	43.3	56.7
Col %	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Chi-square value	10.9091	14.2657	9.5455	8.3422
p-value	0.0009	0.0001	0.0020	0.0038

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