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Original Research Article

Correlation of grade of pulmonary artery pressure with six minutes walk distance and dyspnoea grading in group 3 pulmonary artery hypertension

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ABSTRACT

Background: Pulmonary Artery Hypertension (PAH) is defined as mean pulmonary artery pressure greater than 25 mmHg at rest as assessed by Right heart catheterization. 1 PAH secondary to lung disease is categorized under Group 3 PAH according to WHO classification, the major causes being COPD, ILD, OSA etc. Only few studies have analyzed the clinico-radiological profile, severity, morbidity and mortality associated with group 3 PAH. Hence this study was undertaken to study the clinic-radiological and functional profile of patients with group 3 pulmonary hypertension and to correlate grade of PAH with six-minute walk distance (6MWD) and Dyspnoea grading by modified Medical Research Council (mMRC). Primary objective was to correlate grade of PAH with 6MWD and dyspnoea grading (mMRC) in group 3 pulmonary artery hypertension. Secondary objective was to study the clinic-radiological and functional profile of patients with group 3 pulmonary hypertension in a tertiary care centre.
Methods: Seventy two patients diagnosed to have PAH by 2D ECHO with underlying lung disease were retrospectively analyzed in Department of Respiratory Medicine, Chettinad Hospital and Research Institute, Chennai. Their demographic data, clinical history, examination, Dyspnoea according to MMRC grading, Chest X ray, CT chest, ECG, 2D ECHO (using VIVID 5), PFT (Easy on PC 2700-1-01. EOPC SN 219295, ATS guidelines), six minute walk test (ATS guidelines) and other Special investigations like CT Pulmonary Angiogram, Polysomnography were included wherever necessary.
Results: Out of the 72 patients with group 3 PAH 44.4% belong to the age group of 46-65 years with a mean age of 57.59±13.6 years along with a slight male preponderance. The commonest cause being COPD (27.7%) followed by ILD (15.30%) and Bronchiectasis (5.50%) and the combined etiology contributing to 48.8%. There was a statistically significant positive correlation between grade of PAH and mMRC score ($p< 0.05$) and significant negative correlation between grade of PAH with 6MWD and FEV1 ($p <0.05$).
Conclusions: This study shows that Simple bed side tools like 6MWD and mMRC score can be used for the evaluation of presence and severity of Group 3 PAH.

Keywords: 3 PAH, FEV1, mMRC score, Six Minute walk distance (6MWD)

INTRODUCTION

The term pulmonary arterial hypertension (PAH) describes patients with mean pulmonary artery pressure greater than 25mmHg at rest, characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) 15 mm Hg and a pulmonary vascular resistance >3 Wood unit as assessed by right heart

catheterization.[1] According to the WHO, PAH is classified into 5 groups.[2]

Group 1: Pulmonary arterial hypertension

- Idiopathic PAH, heritable PAH, Drug and toxin induced, other associated conditions
- Pulmonary veno occlusive disease and/or pulmonary capillary hemangiomatosis
- Persistent pulmonary hypertension of new born (PPHN).

Group 2: pulmonary hypertension due to left heart disease.
Group 3: pulmonary hypertension due to lung disease and/or hypoxia.
Group 4: chronic thromoembolic pulmonary hypertension and other pulmonary artery obstructions.
Group 5: pulmonary hypertension with unclear and /or multifactorial mechanisms.

The lung conditions included under group 3 PAH are as follows.[3]

- Chronic obstructive lung disease.
- Interstitial lung disease.
- Other pulmonary diseases with mixed restrictive and obstructive pattern.
- Sleep disordered breathing.
- Alveolar hypoventilation disorders.
- Chronic exposure to high altitudes.

The prevalence of PAH in chronic lung diseases depends on the type and severity of underlying lung disease. About 10-30% of patients with moderate to severe COPD have mild to moderate PAH and less than 5% have severe PAH.[4] ILD has a higher prevalence of PAH (30-40%) which is mild to moderate due to parenchymal and vascular remodelling.[5] PAH was found in 12-34% of patients diagnosed with obstructive sleep apnea.[6]

Pulmonary hypertension in chronic lung diseases is considered to be multifactorial and is due to loss of peripheral pulmonary vessels, chronic or recurrent hypoxia and altered expression of vascular and inflammatory mediators. Therefore, treating the underlying lung condition is the primary objective.[7]

Exertional dyspnoea is the main presenting symptom in patients with PAH in the early stages and it often predisposes to exercise intolerance.[6] It is considered as a hallmark in diagnosing patients with PAH which is attributed to pulmonary vascular abnormalities.

6MWD is simple, bed side repeatable standardized test, which evaluates the exercise tolerance in patients with group-3 PAH. It is a good prognostic marker that helps in measuring the symptomatic improvement and also in assessing the progression of the disease as well as response to treatment.[8]

The lung function and severity of PAH depends on underlying lung disease. In patients with airway obstruction and restriction associated with PAH the lung function may further decline.[9] However according to certain studies there is a poor correlation between lung function and PAH and hence it cannot be used to assess the presence and severity of PAH.[10]

Studies on clinico, radiological and functional profile of patients with Group 3 PAH are limited. Hence this study is being done to correlate grade of PAH with 6MWD and dyspnoea grading (mMRC) in group 3 pulmonary artery hypertension and also to study the clinic-radiological and functional profile of patients with group 3 pulmonary hypertension in a tertiary care centre.

METHODS

Study design

Retrospective observational study

Study period

July 2014 to November 2016

Study settings

Department of Respiratory Medicine, Chettinad Hospital and Research institute

Study population

Patients with pulmonary artery hypertension secondary to lung diseases diagnosed by 2D echo

Inclusion criteria

Adult patients aged from 18-80 years with chronic lung disease diagnosed with pulmonary hypertension by 2D ECHO.

Exclusion criteria

- Other groups of PAH.
- Patients with active PTB, Hemoptysis.
- Patients with unstable cardiac status.
- Pregnancy.

Methodology

- The demographic data, clinical history, examination, Dyspnoea according to mMRC grading was recorded.

MMRC 0: Dyspnoeic on strenuous exercise.
MMRC 1: Dyspnoeic on walking a slight hill.
MMRC 2: Dyspnoeic on walking level ground; must stop occasionally due to breathlessness.

MMRC 3: Must stop for breathlessness after walking 100 yards or after a few minutes.
MMRC 4: Cannot leave house; breathlessness on dressing/undressing.

- Chest X ray, CT chest, ECG, 2D ECHO, PFT (ATS guidelines) using Easy on PC 2700-1-01. EOPC SN 219295, six minute walk test (ATS guidelines) and other special investigations like CT pulmonary angiogram, polysomnography were done wherever necessary.
- 2D ECHO was done using VIVID S5 and mean pulmonary artery pressure (mPAP) was calculated using the following formula mPAP = 0.61 × SPAP + 2 mmHg.[11]
  Where SPAP = systolic pulmonary artery pressure
- Grading of mPAP according to ESC/ERS guidelines.[12]

Mild PAH = 25-40 mmHg
Moderate PAH = 41-55 mmHg
Severe PAH = > 55 mmHg

Statistical method

The data was entered in Microsoft excel worksheet. descriptive data was analyzed using proportions. analysis of variance (ANOVA) was used to study correlation between factors and outcome, Regression equation was obtained using SPSS version 24 and Open Epi Info software.

RESULTS

Table 1 shows age and gender distribution of patients with group 3 PAH. There was a male preponderance. Majority of the patients belonged to the age group of 45-65 years with mean age of 57.59+13.6 years.

Table 1: Age and gender distribution of patients with group 3 PAH (n=72).

Age groups (years)	Male	Female	Total
25-45	10	7	17
45-65	19	13	32
> 65	12	11	23
Total	41	31	72

Table 2: Distribution of mMRC grade among patients with group 3 PAH (n= 72).

Dyspnoea grade	Number	Percentage
0	1	1.8
1	10	13.8
2	28	38.8
3	19	26.3
4	14	19.3
Total	72	100

Table 2 65.1% of the patients had dyspnoea of mMRC grade 2 and mMRC grade 3, 19.4% had mMRC grade 4 and 13.8% had mMRC grade 1.

Table 3 shows the commonest cause was COPD (27.7%) followed by ILD (15.3%), bronchiectasis (5.50%), bronchial asthma (2.70%), OSA (1.38%).

Table 3: Distribution of underlying chronic lung disease among patients with group 3 PAH (n = 72).

Diagnosis	Number	Percentage
COPD	20	27.7
Bronchiectasis	4	5.5
ILD	11	15.3
OSA	1	1.38
Bronchial asthma	2	2.7

Table 4 shows 16.6% of patients with group 3 PAH had two or more underlying lung diseases in the form of post PTB OAD, bronchiectasis followed by 12.5% of patients with ILD, bronchiectasis and post PTB OAD, 8.4% had OAD, OSA, 2.7% had bronchiectasis, OSA, OAD, 2.7% had bronchiectasis, ILD, 2.7% had bronchiectasis and OAD.

Table 4: Distribution of two or more underlying chronic lung disease among patients with group 3 PAH (n=72).

Diagnosis	Number	%
Post PTB OAD, bronchiectasis	12	16.66
ILD, bronchiectasis, OAD	1	1.8
ILD, bronchiectasis, post PTB, OAD	9	12.5
OAD, OSA	6	8.4
Bronchiectasis, OSA, OAD	2	2.7
Bronchiectasis, ILD	2	2.7
Bronchiectasis, OAD	2	2.7

Table 5: Distribution of X-ray findings among patients with group 3 PAH (n=72).

X-ray findings	Number	%
Normal	2	2.8
B/L hyperinflation	24	33.4
Reticulo- nodularity	15	20.8
Cystic changes	17	23.6
Nonhomogenous opacities	7	9.7
CP angle obliteration	1	1.4
B/L linear fibrotic strands	4	5.5
B/L hyperinflation and reticulo-nodularity	1	1.4
B/L hyperinflation and B/L linear fibrotic strands	1	1.4

Table 5 shows 33.4% of the patients had B/L hyperinflated lung fields on chest X-ray followed by cystic changes in 23.6% of the cases, 20.8% had reticulonodularity, 9.7% had non-homogenous opacities, 5.5% had bilateral linear fibrotic strands, 2.8% had

normal x-ray while 1.45 had both B/L hyperinflation of lungs and reticulonodularity and 1.4% had both B/L hyperinflation of lungs B/L linear fibrotic strands.

Table 6 shows out of the 72 patients 68 patients had CT chest findings, 38.23% (26 patients) showed ectatic changes, followed by 14.70% (10 patients) with emphysema, 11.76% had dilated pulmonary artery, 11.6% had mosaic attenuation, 10.29% had honey combing, 5.88% had consolidation, 4.41% had fibrotic changes, 2.94% had B/L nodules on CT chest.

Table 6: Distribution of CT scan findings among patients with group 3 PAH (n= 68).

CT chest findings	Number	%
Dilated pulmonary artery (PA)	8	11.76
Ectatic changes	26	38.23
Consolidation	4	5.88
Mosaic attenuation	8	11.76
Emphysema	10	14.70
Fibrotic changes	3	4.41
Honey combing	7	10.29
B/L nodules	2	2.94
Total	68	100

Table 7 shows majority of the cases (51.4%) had mild grade of pulmonary artery hypertension followed by 25% with severe PAH and 23.6% with moderate PAH.

Table 7: Distribution of study subjects as per the grades of pulmonary artery hypertension (PAH) among patients with group 3 PAH (n = 72).

PAH grade	Number	Percentage
Mild	37	51.4
Moderate	17	23.6
Severe	18	25

Table 8 shows distribution of grade of PAH in underlying lung diseases among patients with group 3 PAH. Mild PAH was seen in 21.62% of COPD patients. Moderate PAH in 35.29% of the cases. Severe PAH in 33.33% of COPD patients.

Table 9 shows mild PAH was seen in 24.32% of patients with post PTB OAD, bronchiectasis followed by 11.11% of severe PAH. 17.64% of patients with ILD, bronchiectasis, post PTB OAD had moderate PAH with 11.11% having severe PAH.2.7% of patients with ILD, bronchiectasis, OAD had mild PAH, 10.81% of patients with OAD, OSA had mild PAH and 11% had severe PAH.

Table 8: Distribution of grade of PAH in underlying lung diseases among patients with group 3 PAH (n = 72).

	Mild	%	Moderate	%	Severe	%	Total
COPD	8	21.62%	6	35.29%	6	33.33%	20
BXIS	3	8.1%	1	5.88%	0	0	4
ILD	2	5.4%	3	17.64%	6	33.33%	11
OSA	0	0%	1	5.88%	0	0	1
BA	1	2.70%	1	5.88%	0	0	2

Table 9: Distribution of grade of PAH in two or more underlying chronic lung diseases among patients with group 3 PAH (n = 72).

Diagnosis	Mild	%	Moderate	%	Severe	%	Total
Post PTB OAD, Bronchiectasis	9	24.32%	1	5.88%	2	11.11%	12
ILD, Bronchiectasis, Post PTB OAD	4	10.81%	3	17.64%	2	11.11%	9
ILD, Bronchiectasis, OAD	1	2.70%	0	0	0	0	1
Bronchiectasis, ILD	1	2.70%	1	5.88%	0	0	2
Bronchiectasis, OAD	2	5.40%	0	0	0	0	2
OAD, OSA	4	10.81%	0	0	2	11.11%	6
Bronchiectasis, OSA, OAD	2	5.40%	0	0	0	0	2

Table 10 shows correlation between PAH and dyspnoea. It has been found that as the grade of dyspnoea increased, the mean pulmonary artery hypertension increased. This increase was uniform. This correlation between PAH and dyspnoea was found to be statistically significant. ($p < 0.005$).

Table 11 shows correlation between PAH and 6 minute walk distance (6 MWD). It has been found that as the severity of pulmonary artery hypertension increased, the mean duration of 6 MWD decreased. This decrease was uniform.

The correlation between PAH and 6 MWD was found to be statistically significant (p<0.05).

A regression equation was obtained y = 75.6546+(-0.1229) x. Where y = PAP and x=6MWD.

Table 10: Correlation between pulmonary artery hypertension and mMRC grade of dyspnoea.

Variable	Grade	Pulmonary artery hypertension				ANOVA			
		N	Mean	SD	SE	Sum of squares	Df	F value	P value
Dyspnoea (mmrc)	1	11	44.1	10.7	3.2	32520.5	71	3.78	0.014
	2	28	53.4	18.86	3.56				
	3	19	56	20.43	4.68				
	4	14	70.4	27.28	7.29				

Table 11: Correlation between PAH and 6 minutes walk distance (6 MWD).

Variable	Grade	6 minute walk test (6 MWD)				ANOVA			
		N	Mean	SD	SE	Sum of squares	Df	F value	P value
PAH grades	1 (mild)	37	188.4	69.6	11.4	246420	71	9.34	0.0002
	2 (moderate)	17	194.5	67.5	16.4				
	3 (severe)	18	128.2	29.9	16.4				

Table 12 Shows the correlation between 6MWD and mMRC grade of dyspnoea, where in as the grade of dyspnoea increased the six minute distance walked was less which was statistically significant p<0.005.

Table 12: Correlation between dyspnoea and 6 minute walk distance (6MWD).

Variable	Grade	6 minute walk distance				ANOVA			
		N	Mean	SD	SE	Sum of squares	Df	F value	P value
Dyspnoea	0	130	130	0	0	314190	71	18.32	<0.0001
	I	11	234.27	80.4	24.2				
	II	28	204.64	55.87	10.5				
	III	19	143.8	37.41	8.6				
	IV	14	110.3	7.12	1.9				

Table 13: Correlation between PAH and FEV1.

Variable	Values	PAH				ANOVA			
		N	Mean	SD	SE	Sum of squares	Df	F stat	P value
FEV1 values	0	20	61.6	18.9	4.2	32460.9	71	2.92	0.04
	0.1 to 0.99	17	60.7	23.5	5.7				
	1 to 1.99	21	56	24.4	5.3				
	2 & > 2	14	42.1	9.7	2.6				

Table 14: Correlation between PAH and FEV1/FVC.

Variable	Values	PAH				ANOVA			
		N	Mean	SD	SE	Sum of squares	Df	F stat	P value
FEV1 values	0	20	61.6	18.9	4.2	32596	71	1,58	0.21
	0 to 0.8	17	60.7	23.5	5.7				
	> 0.8	21	56	24.4	5.3				

Table 13 shows correlation between PAH and FEV1. It has been found that as the severity of PAH increased the value of FEV1 decreased which was statistically significant ($p<0.05$).

Table 14 shows correlation between PAH and FEV1/FVC. It has been found that as the severity of PAH increased the FEV1/FVC ratio decreased. The decrease was uniform. But this was not found to be statistically significant ($p > 0.05$).

DISCUSSION

Out of the 72 patients with Group 3 PAH, majority of the subjects were in the age group of 46-65 years (44.4%) with a mean age of 57.59+13.6 years. According to a study by Andersen CU et al, the mean age was 61+0.9 years in their sample of 212 patients with Group 3 PAH.[12] Neal JE et al found that in their study with 46 patients the mean age was 61+13 years.[13] Ozpelit E et al in their study grouped the patients into elderly and young where the mean age among the elderly was 71.5+5.5 years and 44.5+15.2 years among the young.[14] In contrast to this Mehrotra R et al showed that in his study the mean age was 35.6±14.3 years in young adults with Group 3 PAH.[15]

There was a slight male preponderance (56.9%) in the present study. A study done by Parthiban N et al in patients with PAH males constituted 65.4% of the cases.[16] In contrast Female preponderance (52%) was reported in a study by Andersen CU et al in patients with Group 3 PAH.[12]

Majority of the patients had lung signs in the form of both wheeze and crepts (48.8%) only three patients had bronchial breath sounds. On ECG Majority of the patients had P pulmonale (43.1%) followed by normal ECG in 26.3% of the cases. Only four patients had right ventricular hypertrophy.

In the present study the common cause was COPD (27.7%) followed by ILD in 15.3% of the cases, Bronchiectasis in 5.50%. A combined diagnosis of 48.8% was observed with post PTB OAD, Bronchiectasis being the common cause. According to Elwing J et al, 10-20% of patients with COPD had PAH.[7] Whereas Launay D et al stated from their study that PAH was more common in patients with ILD compared to patients without ILD.[17] Andersen CU et al reported a very high incidence of ILD in 41% of the cases in their study in patients with Group 3 PAH.[12] However out of the 92 patients with bronchiectasis 32.9% had PAH according to a study by Alzeer A et al.[18]

Majority had MMRC dyspnoea of grade 2 and grade 3 (65.1%) in the present study. Serap ACAR et al found that in patients with PAH, as per MMRC dyspnoea scale, 54.8% had mild dyspnoea (grade I-II), 22.6% had moderate dyspnoea (grade II-III) and 6.5% had severe dyspnoea (grade IV).[19] In the study done by Andersen CU et al, Borg scale was used to grade dyspnoea in patients with Group 3 PAH and it was found that a higher score was recorded in patients with severe PAH.[12]

The mean six minute walk distance (SMWD) was 174±7.85 in patients with group 3 PAH, Andersen CU et al found in their study among group 3 PAH that the mean SMWD was 267±78 in patients with moderate to severe PAH.[12]

Out of the 72 patients in the study 52 patients performed PFT under acceptable guidelines, whereas 20 patients were unable to produce acceptable PFT. The mean FEV1 was 1.52±0.094 and mean FEV1/FVC was 0.59±0.16 among patients with group 3 PAH. Majority of the patients showed a restrictive pattern.

The present study shows that 51.4% had mild grade of pulmonary artery hypertension followed by 25% with severe PAH. Andersen CU et al in their study in patients with group 3 PAH observed that mild PAH was present in 14% of the cases, moderate PAH was seen in 8% of the patients and severe PAH was noted in 6% of the cases.[12] In contrast to this a study by Parthiban N et al in patients with PAH showed that 51.9% had moderate PAH while 41.9% had severe PAH.[16]

When correlations were done between PAH and Dyspnoea (mMRC), 6MWD, FEV1, FEV1/FVC, Dyspnoea and 6MWD in patients with Group 3 PAH, it was found that as the mMRC grade of dyspnoea increased, the mean pulmonary artery pressure increased showing that there was a positive correlation between dyspnoea and PAH which was statistically significant. ($p < 0.05$). Chaouat A et al showed similar findings in their study in patients with group 3 PAH where there was a significant positive association between dyspnoea and PAH.[20] Similar findings were noted by Dumetrescu D et al where the grade of dyspnoea increased with increasing severity of PAH.[6]

Patients with group 3 PAH included in this study showed that as the severity of pulmonary artery hypertension increased, the mean duration of 6 MWD decreased indicating a negative correlation between PAH and 6 MWD which was statistically significant ($p<0.05$). Similar finding was given by Leuchte HH et al and Modrykamien AM et al where in 6 minute walk test distance covered by PAH patients was lower when compared to patients without PAH in patients with group 3 PAH.[21,22] According to Demir R et al patients with PAH had significantly less 6 minute walk distance and that it can be used a good prognostic indicator to assess PAH pre and post treatment.[8]

It has been found that as the dyspnoea grade increased, the mean duration of 6 minute walk test decreased in the present study. There was a negative correlation between dyspnoea severity and mean duration of 6 minute walk

test which was statistically significant (p<0.05). In a study by Andersen CU et al when the Borg scale for dyspnoea was analyzed with six minute walk distance it was found that less distance was walked with increasing Borg score.[12]

According to the present study there was a negative correlation between PAH and FEV1 which was statistically significant (p < 0.05) indicating that as the severity of PAH increased the FEV1% decreased. It was also noted that as the severity of PAH increased the FEV1/FVC ratio decreased thought the decrease was uniform it was not statistically significant (p>0.05). Andersen CU et al observed in their study that FEV1 decreased with increasing PAH (mean 55±4).[12]

However, a study done by Nathan SD et al showed that their spirometry values were not significantly associated with pulmonary artery pressure.[23] Hence it can be noted that the lung function is not as reliable as the above parameters in assessing the severity of pulmonary hypertension in patients with group 3 PAH.

Therefore, this study shows that out of the 72 patients with Group 3 PAH, 44.4% belong to the age group of 46 -65 years with a mean age of 57.59±13.6 years along with a slight male preponderance. The commonest cause being COPD (27.7%) followed by ILD (15.30%) and bronchiectasis (5.50%) and the combined etiology contributing to 48.8% with post PTB OAD, bronchiectasis being the major cause (16.66%). Majority had mMRC grade 2 and grade 3 and a mean six minute walk distance (6MWD) of 174±7.85. Mild PAH was seen in 51.4%, moderate PAH in 23.6% and severe PAH in 25%. There was a statistically significant positive correlation between grade of PAH and mMRC score (p <0.05) and significant negative correlation between grade of PAH with 6MWD and FEV1 (p<0.05).

CONCLUSION

COPD followed by ILD were the most common etiologies in patients with group 3 PAH. Simple bed side tools like 6MWD and mMRC score for Dyspnoea showed a significant correlation with the presence and severity of PAH.

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