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Serum Inflammatory Markers And Functional Status Correlation With Pulmonary Hypertension In Patients With Stable Bronchiectasis

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Abstract

Context: Bronchiectasis is a pulmonary disorder characterized pathologically by permanent bronchial dilatation and severe bronchial inflammation and clinically by chronic productive cough and recurrent infectious exacerbations.

Aims: To evaluate if inflammatory markers, serum C reactive protein, osteopontin, serotonin, uric acid, IL-6 levels as well as physiological parameters (6MWT, SGRQ) could correlate with pulmonary hypertension in stable bronchiectasis patients.

Methods and Material: Forty-one patients with stable bronchiectasis were recruited from the Outpatient Clinic at PSG Institute of Medical Sciences and Research during one year period.Amongst these twenty patients had pulmonary hypertension and twenty-one did not have pulmonary hypertension. Baseline investigations including (hemogram, biochemistry, Borg scale, and 6-minute walk test) and spirometry were performed in all the patients Assessment of serum inflammatory markers (serum CRP, IL-6, Uric acid, serotonin, osteopontin) were performed in all the patients

Results: The mean age was 54.17 ± 14-83 years. There were 17 males and 24 females. Average duration of illness was 10.51 ± 13.90 years, total number of exacerbations in last one year were more than three in 34 % and between one to three in 36.6% which was statistically significant in group with pulmonary hypertension. Six MWT was statistically significant in between groups with 344.00 ± 123.56 in patients without pulmonary hypertension and 419 ± 85.99 in patients with pulmonary hypertension(p==0.06). Levels of serum CRP, seratonin, osteopontin, IL-6, uric acid were compared in between both groups. There was nostatistically significant difference amongst both groups as regards inflammatory markers.

Conclusions: In our study we found that 6MWT and frequency of exacerbations has predictive ability todiscriminate bronchiectasis patients with and without pulmonary hypertension.

Key-words: Bronchiectasis, Pulmonary Hypertension, osteopontin, seratonin, C Reactive protein, InterleukinL-6, 6Minute Walk Test

Key Messages:

Our study indicates that frequency of exacerbations in last one year and 6 MWT correlates well, in patients of stable bronchiectasis with pulmonary hypertension. Bronchiectasis subjects with Pulmonary Hypertension have worse survival than do bronchiectasis subjects without pulmonary hypertension. 6MWT is a cheap, inexpensive and repeatable test which is technically easy to apply. It can be utilized as diagnostic and prognostic marker of pulmonary hypertension in patients with bronchiectasis.

Introduction

Bronchiectasis is one of the leading causes of death globally, as well as in India. As per study done by Derek Weyeker prevalence of bronchiectasis ranged from 4.2 per 100,000 persons aged 18–34 years to 271.8 per 100,000 among those aged 75 years(1) A recent published systematic review of MEDLINE from inception to 2018 for studies of the epidemiology and natural history of bronchiectasis identified that bronchiectasis is a common respiratory disease worldwide, affecting up to 566 per 100 000 population in high-income countries.(2) Little published data are available from Asia, Africa, South America, or from low-income and middle-income countries more generally. Overall prevalence rates is 18-34 yrs is 4.2/1 lakh population and in above 75 yrs, its 272/1. (3)

Bronchiectasis is a pulmonary disorder characterized pathologically by permanent bronchial dilatation and severe bronchial inflammation and clinically by chronic productive cough and recurrent infectious exacerbations. Advanced chronic lung conditions lead to lung tissue destruction and a decrease in the capillary area. (4)

Pulmonary Hypertension was defined in this study as mPAP of greater than or equal to 45 mmHg. This value was chosen based on the criteria established by the World Health Organization Symposium on Primary Pulmonary Hypertension Review Board of the Office of Regulatory. Affairs at the University of (1998), which defines mild PH as mPAP of 40–50 mm Hg (5). Pulmonary hypertension is common complication of chronic lung diseases. The common mechanisms that lead to pulmonary hypertension in this group are hypoxic vasoconstriction and vascular remodelling of the pulmonary vasculature. (6)

In the recent revised classification of pulmonary hypertension (PH), chronic lung diseases or conditions with alveolar hypoxia are included in WHO Group III of PH-related diseases chronic lung diseases of a mixed obstructive and restrictive pattern, which includes chronic bronchiectasis, cystic fibrosis and a syndrome characterized by the combination of pulmonary fibrosis (mainly of the lower zones of the lung) and emphysema (mainly of the upper zones of the lung), the prevalence of pulmonary hypertension is almost 50%. In a study of 94 patients with bronchiectasis done by Alzeer et al, 31(32.9%) had pulmonary hypertension. (7) Pulmonary hypertension related to respiratory diseases is mostly mild to moderate, and the severity is associated with the category of respiratory diseases.

Gold standard for diagnosis of pulmonary hypertension is right heart catheterization which is an invasive test and therefore echocardiography is done in majority of such patients. A cross-sectional study done by Abdulaziz H Alzeer et al has shown that RV systolic dysfunction and Pulmonary Hypertension were more common than LV systolic dysfunction in bronchiectasis patients. (7) Previous study done by Anand Devaraj et al have shown Pulmonary hypertension, reflected by pulmonary arterial enlargement on CT scans, is a highly significant prognostic indicator in the evaluation of patients with bronchiectasis(8)

Patients with bronchiectasis in a stable phase have raised systemic markers of inflammation and this is not dependent on the presence of infected sputum. A study done by Elaine Soon et al illustrates dysregulation of a broad range of inflammatory mediators in idiopathic and familial PAH and demonstrates that cytokine levels have a previously unrecognized impact on patient survival. (8)

Non-invasive modalities that might raise suspicion for the presence of Pulmonary Hypertension in Chronic Lung Diseases include circulating biomarkers, pulmonary function testing, echocardiography and imaging. (9) Several studies have investigated markers of inflammation in the blood as indicators of Pulmonary Hypertension in non-Cystic Fibrosis Bronchiectasis. Gabriel Olveira et al in 2012 shown Biomarkers of oxidative stress such as catalase activity and lipid peroxidation, both in plasma and intracellular were raised in patients with bronchiectasis compared with controls (10). In a retrospective study of 70 patients Lorenzen et al in 2011 found the baseline levels of Osteopontin is increased in Idiopathic Pulmonary hypertension when compared to healthy subjects (11).

Gabril et al in a cross-sectional study of 90 stable bronchiectasis patients measured the serum oxidative stress biomarkers and found that intracellular superoxide was significantly elevated when compared to controls (15). Soon et al in a cohort study of 60 pts found that increased serum cytokines

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level predicts survival in PAH patients (8). In a study done by Quarck et al in 2009 among 144 pts it was found that PAH pts has increased circulating CRP levels when compared with controls. (12)

Wilson et al evaluated the clinical characteristics (6MWD&NYHA Class), hemodynamic parameters (PAP, PVR & cardiac output) and correlated to uric acid level in a retrospective study of 29 patients. (13)

Whether a link exists between biomarkers of systemic inflammation, 6MWT and pulmonary hypertension in bronchiectasis patients is unclear. Biomarkers that specifically indicate the pathologic mechanism, the severity of the disease, and the treatment response would be ideal tools for the management of Pulmonary Hypertension. (14) Our study was aimed to assess predictive ability of serum inflammatory markers levels, physiological and clinical parameters in stable bronchiectasis patients with and without pulmonary hypertension.

Subjects and Methods:

Forty-one patients with stable bronchiectasis were recruited from the Outpatient Clinic at PSG institute of medical sciences and research during one year period (2016-2017). Amongst these twenty patients had pulmonary hypertension and twenty-one did not have pulmonary hypertension. Diagnosis of pulmonary hypertension was based on 2 D echocardiography findings. Diagnosis of bronchiectasis was based on gold standard HRCT. All patients should have been clinically stable for at least 3 months prior to enrolment. Patients with a clinical diagnosis of asthma and other established alternative diagnoses like COPD, pneumonia, tuberculosis, or other inflammatory diseases such as malignancy, connective tissue disorders, arthritis, inflammatory bowel diseases, liver cirrhosis, thyroid disease, and end-stage renal failure or those who had recently undergone a surgical procedure were excluded. Written informed consent was obtained from all the participants and participants who refused consent were excluded. The study was approved by the Institute Ethics Committee. All participants were informed in detail regarding the proposed investigations.

Baseline evaluation included a detailed proforma containing demographic characteristics, history of smoking, and socioeconomic status, frequency of exacerbations, clinical characteristics like finger clubbing, oxygen saturation. Baseline investigations including (hemogram, biochemistry, Borg scale, and 6-minute walk test) and spirometry were performed in all the patients Assessment of serum inflammatory markers (serum CRP, IL-6, Uric acid, serotonin, osteopontin) were performed in all the patients. Six-minute walk test was performed as per the ATS guidelines (2007).

Determination of C-reactive protein, IL-6, Uric acid, serotonin, osteopontin

Venous blood sample (10 ml) was drawn after an overnight 12h fasting. The blood sample was centrifuged at 3000 rpm for 15 min; sera were separated and stored at −80°C until assayed. Serum CRP (Nephelometry), IL-6 (Biotube method), serotonin, osteopontin (ELISA) and uric acid (Calorimetry) were assayed. All measurements were performed according to the instructions as specified in the manual by the manufacturer.

Spirometry

Spirometry was performed using a electronic spirometer (PESO Smart spirometer) The results were reported in absolute volumes as well as percent predicted. The highest value of at least three measurements of FEV1 and forced vital capacity was used.

Statistical analysis

Statistical analysis was carried out using SPSS 17 software. The data were examined initially for normality of distribution and homogeneity of variance. The comparison of quantitative variables between the groups was carried out by using Student t-test. Categorical variables were compared by using Chi-square test and odds ratio was evaluated for significant variables using logistic regression after adjusting for important confounders Frequency of one year exacerbations among bronchiectasis patients was correlated with RVSP, and Pearson's correlation coefficient was derived. A P value of <0.05 was considered significant ROC curve was drawn (figure 4) by a nonparametric method using SPSS software (AUC=0.79, 95% confidence interval: 0.74-0.84, $p<0.001$).

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Results:

Forty-one patients with stable Bronchiectasis were recruited in our study [Figure 1]. Amongst them twenty patients had pulmonary hypertension and twenty-one patients did not have pulmonary hypertension. The mean age was 54.17 ± 14-83 years. There was 17 males and 24 females. The details of baseline characteristics are summarized in Table 1 Average duration of illness was 10.51 ± 13.90 years, total number of exacerbations in last one year were more than three in 34% and between one to three in 36.6% which was statistically significant in group with pulmonary hypertension (p=0. 2D echocardiography findings revealed average right ventricular systemic pressure (RVSP) of 43.75 ± 7.11mm Hg in patients with pulmonary hypertension and 25.14 ± 0.655 in patients without pulmonary Hypertension. Six MWT was statistically significant in between groups with 344.00 ± 123.56 in patients without pulmonary hypertension and 419 ± 85.99 in patients with pulmonary hypertension(p=0.06). Details of echo findings, number of exacerbations and 6MWT are summarised in Table 2. Among bronchiectasis patients with pulmonary hypertension 6 MWT correlated very well with RVSP in echo. (Pearson correlation coefficient r2 = -0.315; P value = 0.045) (Figure 2)

This correlation persisted after controlling for age, BMI, and duration of illness. Levels of serum CRP, seratonin, osteopontin, IL-6, uric acid were compared in between both groups There was no statistically significant difference amongst both groups as regards inflammatory markers. Total score determining health related quality of life through SGRQ questionnaire was comparable in between both groups at 24.15 ± 4.44 and 23.5 ± 5.38 respectively. Details of above are summarised in Table 3.

Spirometry revealed post FEV1 was comparable in between both groups 52.55 ± 19.67 and 57.40±18.89 respectively Details of spirometry values are summarised (table 4) ROC curve was drawn in figure 4 by a nonparametric method using SPSS software (Area under curve (AUC): 0.730, 95% confidence interval: 0.574 – 0.885, P value: 0.012) Results of logistic regression analysis of variables significantly associated with pulmonary hypertension in bronchiectasis are given in figure2. Frequency of exacerbations was significantly associated with pulmonary hypertension with an odds ratio of 5.385(95% confidence interval [CI] 1.125-25.78) after adjusting for important covariates such as age, gender, and duration of illness. In our study we observed a significant correlation between the six-minute walk test and the pulmonary function test. Patients with altered PFT show low score in six-minute walk test. There was a positive correlation (r=0.25) in the study population with significant alteration in the FEV1/FVC. However, this was not significant for presence of pulmonary hypertension in bronchiectasis patients.

ROC curve and the corresponding AUC show that 6MWT and frequency of exacerbations has predictive ability to discriminate bronchiectasis patients with and without pulmonary hypertension.

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Figure 1: Flow of participants through the study

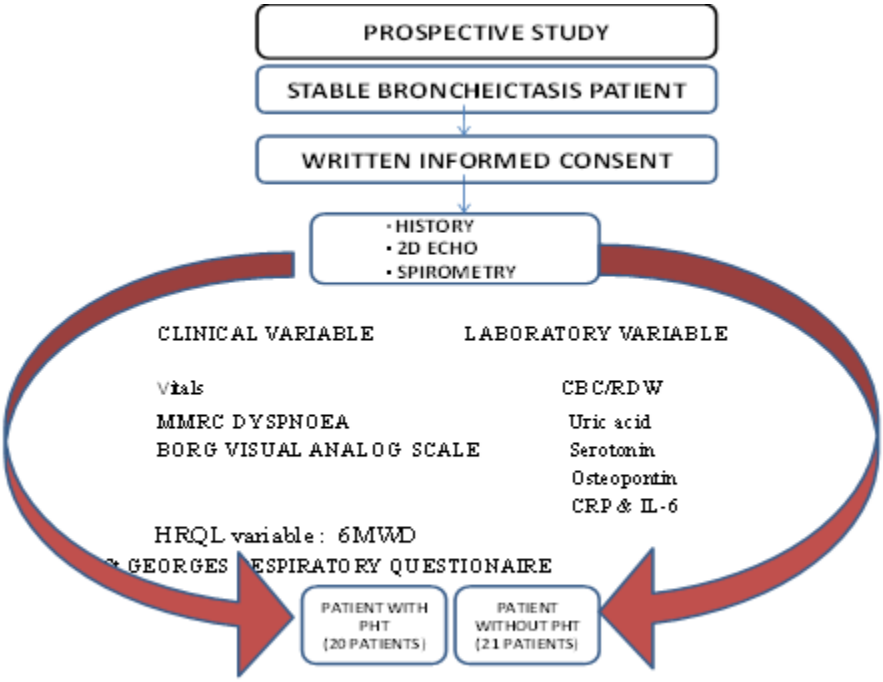

Table 1 Socio-demographic Characteristics Between Subgroups

Table 2:

Variables	Bronchiectasis with pulmonary hypertension (n=20)	Bronchiectasis without pulmonary hypertension (n=21)	p value
Age (years)	56.60 ± 13.43	51.86 ± 16.06	0.311
Female gender (n=24)	11 (45.8%)	13 (54.2%)	0.654
Body Mass Index (kg/m²)	22.07 ± 4.99	21.86 ± 5.06	0.899
Lower socio-economic classes*	9 (60.0%)	6 (40.0%)	0.275
Dwelling (Urban)	8 (38.1%)	13 (16.9%)	0.161

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Table 2 Comparison of Clinical Characteristics Between Subgroups

Variables	Bronchiectasis with pulmonary hypertension (n=20)	Bronchiectasis without pulmonary hypertension (n=21)	p value
Duration (years)	10.60 ± 13.9	10.43 ± 14.25	0.969
Clubbing	11 (44.0%)	14 (56%)	0.444
SpO2 (%) in RA	94.30 ± 5.69	96.48 ± 1.21	0.095
No of exacerbations			
0	3 (25%)	9 (75%)	
1	7 (46.7%)	8 (53.3%)	0.06
2	10 (71.4%)	4 (28.6%)	
Right Ventricular Systolic Pressure (mm Hg)	43.75 ± 7.11	25.14 ± 0.655	0.000
Six Minute Walk Distance (metres)	344.00 ± 123.56	419 ± 85.99	0.028

Table 3: Comparison of Measures Of Health Related Quality Of Life Between Subgroups

St .George's Respiratory Questionnaire	Bronchiectasis with pulmonary hypertension (n=20)	Bronchiectasis without pulmonary hypertension (n=21)	P value
Total score	24.15 ± 4.44	23.5 ± 5.38	0.676
Symptom score	49.57 ± 14.02	57.14 ± 17.61	0.753
Activity score	12.52 ± 0.343	12.44 ± 0.358	0.446
Impact score	22.83 ± 4.33	21.13 ± 5.20	0.262

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Table 4: Comparison of Physiological Characteristics Between Subgroups

Spirometry	Bronchiectasis with pulmonary hypertension (n=20)	Bronchiectasis without pulmonary hypertension (n=21)	P Value
FEV1/FVC	76.85 ± 18.76	76.81 ± 14.08	0.995
Pre FEV1 (%)	47.8 ± 19.53	53.71 ± 18.69	0.328
Pre FVC (%)	54.20 ± 18.30	60.14 ± 17.25	0.292
Post FEV1 (%)	52.55 ± 19.67	59.05 ± 21.44	0.318
Post FVC (%)	57.40 ± 18.89	64.52 ± 18.07	0.225

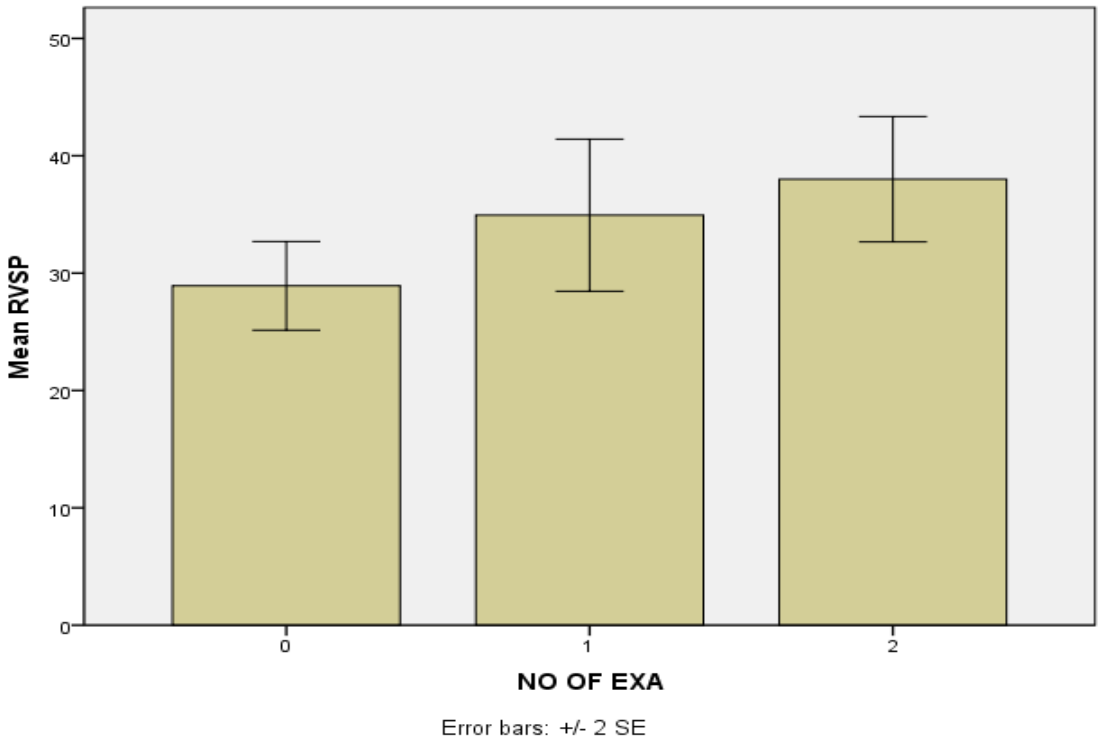

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Figure 2: Association between Right Ventricular Systolic Pressure (RVSP) and frequency of exacerbation of Bronchiectasis

Multiple logistic regression analysis:

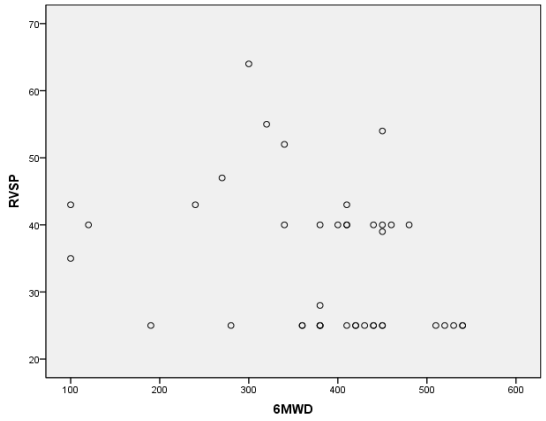
Adjusted Odds Ratio : 5.385

95% confidence interval : 1.125 – 25.78

P value : 0.035

Adjustment model : Age, Gender and Duration of illness

Figure 3: Relationship between Right Ventricular Systolic Pressure (RVSP) and six-minute walk distance



Multiple logistic regression analysis:

Adjusted Odds Ratio : 0.992

95% confidence interval : 0.985 – 0.999

p value : 0.046

Adjustment model : Age, Gender and Duration of illness.

Pearson's correlation co-efficient:

$r^2 = -0.315$; p value = 0.045

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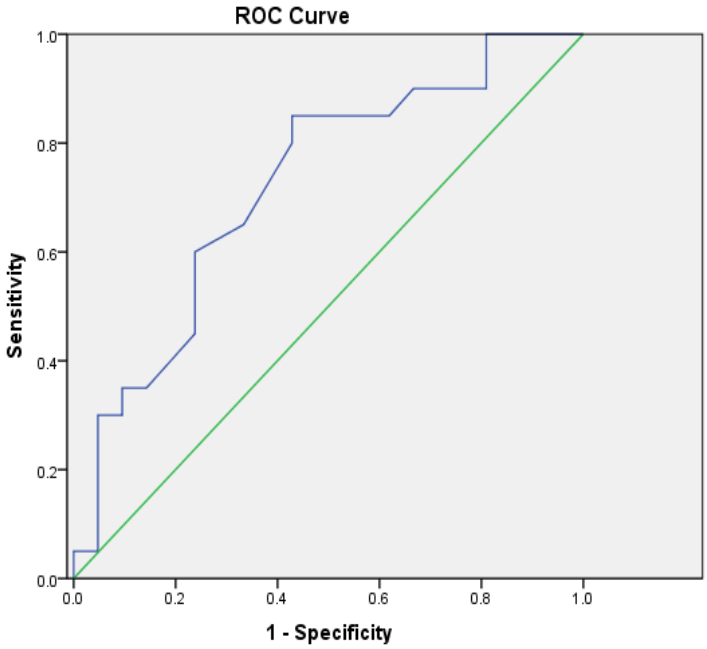
Figure 4: ROC analysis of Prediction model using frequency of exacerbation and six-minute walk distance as predictive variables



Receiver operating characteristic:

Area under curve (AUC)	: 0.730
95% confidence interval	: 0.574 – 0.885
p value	: 0.012
Sensitivity	: 80%
Specificity	: 53%

Discussion:

We studied and compared serum inflammatory biomarkers, spirometry and functional parameters in patients of stable bronchiectasis with and without pulmonary Hypertension. The results of the current study indicate that frequency of exacerbations in last one year and 6 MWT correlated well, in patients of stable bronchiectasis with pulmonary hypertension. This association was independent of age, gender and socioeconomic status. There was no correlation between pulmonary hypertension and physiological parameters like HRQL questionnaire, spirometry unlike other studies. Bronchiectasis subjects with Pulmonary Hypertension have worse survival than do bronchiectasis subjects without Pulmonary hypertension (23). Our study has revealed statistically significant correlation between 6 MWT and pulmonary Hypertension. which correlates well to meta-analysis comprising 12 studies done by Savarese et al (15), reported a significant inverse

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correlation between the changes in 6MWT and pulmonary vascular resistance. 6MWT is a cheap, inexpensive and repeatable test which is technically easy to apply, appropriate for large patient groups and well tolerated by the patients. Despite limitations, 6 MWT plays key role in the evaluation and treatment of PAH patients. 6MWT can be utilized as diagnostic and prognostic marker of pulmonary hypertension in patients with bronchiectasis.(16) Early declines in 6MWD (within the first 6 months) predict future clinical worsening of PAH with high specificity(17) W-T.N. Lee et al in 2010 has shown that absolute 6-min walk distance (6MWD) has been established as the principal clinical outcome measure in pulmonary arterial hypertension (PAH) and has been used as the primary end-point in most clinical trials (18) An extensive analysis has recently been performed by Gabler and colleagues who pooled results from 10 randomized clinical trials of PAH-targeted therapy and used the time to clinical worsening as the clinically meaningful comparator for 6MWT change.(19) The 6-min walk test (6MWT) provides information regarding functional capacity, response to therapy and prognosis across a range of chronic cardiopulmonary conditions. A distance less than 350m is clinically significant in most disease states. (20)

Recurrent exacerbations can increase pulmonary vascular resistance leading to pulmonary hypertension due to airway and systemic inflammation and are associated with progressive lung damage, worse quality of life, accelerated lung function decline and increased mortality (21) Our study has shown positive correlation between frequency of exacerbations in bronchiectasis patients and pulmonary hypertension. This is similar to a Cross-sectional Study done by Christian Goeminne et al in 539 patients with a radiographic diagnosis of non -cystic bronchiectasis showed Bacterial colonization status was associated with more deaths, exacerbation rate, symptoms and reduced pulmonary function. Pulmonary hypertension was found in 48% of outpatients. (22)

In our study, none of inflammatory biomarkers such as osteopontin, serationin, 1L-6, CRP, uric acid correlated with presence of pulmonary hypertension in stable bronchiectasis patients. This was unlike many other studies previously done with above biomarkers. Similarly, no correlation was seen with SGRQ health questionnaire, symptoms and impact scores in our study unlike study done by C.B. Wilson et al who had shown relationship between levels of various systemic markers of inflammation and extent of disease on computed tomographic scan, lung function, sputum bacteriology and health related quality of life (HRQoL) in 87 non-cystic fibrosis bronchiectasis patients (13).

Limitation of study, is that this is cross sectional study and age, gender matched normal healthy controls were not studied. Though the gold standard for diagnosing pulmonary artery hypertension is right heart catheterization, in our study pulmonary hypertension was assessed by Echocardiography. Another limitation was smaller sample size in our study, which needs to be further studied in larger group of patients.

Conclusion:

In our study we found that 6MWT and frequency of exacerbations has predictive ability to discriminate bronchiectasis patients with and without pulmonary hypertension. If 6MWT is done in every outpatient visit for stable brocheicstasis patients, we might be able to predict co- existance of pulmonary hypertension and initiate treatment before clinical worsening occurs. Presently most clinicians do 6MWT in patients of chronic obstructive airway diseases for CAT scoring. The FACED (Fev1, age, colonization, extent of involvement, dyspnoea score) is an assessment of severity tool, validated for people with non-cystic fibrosis bronchiectasis. This does not include 6MWT as parameter. However simple test like 6MWT could predict PAH in stable bronchiectasis patients, this need to be studied further in larger group of such patients.

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