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A COMPARITIVE STUDY OF PRE AND POST TREATMENT ECG AND ECHO FINDINGS IN ACUTE EXACERBATION OF COPD PATIENTS

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD)- refers to chronic bronchitis and emphysema,a pair of two commonly co existing diseases of the lungs in which the airways becomes narrowed. Chronic obstructive pulmonary disease (COPD), defined by GOLD as a preventable and treatable disease with some significant extrapulmonary effects, is a very common clinical entity in clinical practice.

COPD is a leading cause of death and disability worldwide. According to World Bank data it is expected to move from its status in 2000 as the 4 th and 12 th most frequent cause of mortality and morbidity, respectively, to the 3 rd and 5 th leading cause of mortality and morbidity, respectively, in 2020.[1,2]

COPD exacerbation was defined according gold 2010 guidelines as An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD.[3]

COPD is associated with significant extrapulmonary (systemic) effects among which cardiac manifestations are most common. Cardiovascular disease accounts for approximately 50% of all hospitalization and nearly one third of all deaths, if forced expiratory volume in one second (FEV 1)< 50% of predicted.[4] In more advanced disease cardiovascular disease account for 20%-25% of all deaths in COPD.[5] COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to development of pulmonary hypertension, corpulmonale, right ventricular dysfunction, and left ventricular dysfunction too.

In COPD, changes in the activity of the heart is reflected in the electrocardiography as change in P-wave axis and amplitude, rightward displacement of QRS and T-axis, reduction of amplitude of QRS complex in limb and precordial leads, sinus tachycardia, Right bundle branch block (RBBB) and atrial fibrillation.[6-10]

Echocardiography provides a rapid, non invasive portable and accurate method to evaluate the right ventricle function, right ventricular filling pressure, tricuspid regurgitation, left ventricular function and valvular function.[11] Many studies have confirmed that echocardiographically derived estimates of pulmonary arterial pressure co-relate closely with pressures measured by right heart catheter ($r > 0.7$).[12,13]

Present study had been planned because no previous studies were available on the changes in pulmonary artery hypertension before and after treatment of acute exacerbation of COPD with bronchodilators.

MATERIALS AND METHOD

- study design : Time bound prospective study
- sample number : 108 patients
- Study period : December 2011 – January 2013
- Data analysis was done using SPSS v.20 and statistical method used for determining significance was paired T test and 95% confidence interval was calculated using chi square test.

INCLUSION CRITERIA

- Males aged more than 40 years.
- COPD patients admitted with acute exacerbation.
- COPD patients having Tricuspid regurgitation.

EXCLUSION CRITERIA

1. Coronary artery disease.
2. Congenital heart disease
3. Valvular heart diseases.
4. Systemic hypertension.
5. Old pulmonary tuberculosis.
6. Interstitial lung disease
7. Diabetes mellitus

8. Psychiatric illnesses
9. Persistent dyselectrolytemia
10. Patients who lost follow up/ died during study period.

DATA COLLECTION

- The study was conducted after obtaining institutional ethics committee clearance, Kasturba hospital, manipal for period of 1 year 2 months from December 2011 to January 2013.
- Patients of COPD meeting the inclusion criteria were selected. For the study Informed consent had been taken from all the subjects, clinical features, laboratory values were noted and entered in data chart. Cases were followed regularly to record the treatment given.
- At no point of time the study or the investigator's observations had been used to alter the management plan who had been managed as per the existing – management protocols of the hospitals according to physician preference.
- All selected patients were subjected to routine blood investigations and electrocardiography within 24 hours of admission. All patients received standard treatment of nebulised and systemic bronchodilators, antibiotic, and oxygen based on requirement.
- Once stable clinically all the patients were subjected to spirometry to confirm the diagnosis and classified according to GOLD guidelines (postbronchodilator FEV_1 /forced vital capacity (FVC) ratio < 70% predicted) as GRADE I-mild COPD ($FEV_1 \geq 80\%$ of predicted), GRADE II- moderate COPD ($50\% \leq FEV_1 < 80\%$ predicted), GRADE III-severe COPD ($30\% \leq FEV_1 < 50\%$ predicted), and GRADE IV-very severe COPD ($FEV_1 < 30\%$ predicted) .
- Within 24-48 hours of admission resting two-dimension transthoracic Doppler echocardiography was done by cardiologists and valvular anatomy and function, left and right side chamber size and cardiac function were assessed.

- Tricuspid regurgitant flow was identified by colour flow Doppler technique and the maximum jet velocity was measured by continuous wave Doppler. Right ventricular systolic pressure was estimated based on the modified Bernoulli equation and is considered to be equal to the systolic Pulmonary Artery Pressure (sPAP) in the absence of right ventricular outflow obstruction: sPAP (mmHg) = right ventricular systolic pressure (RVSP) = trans-tricuspid pressure gradient (TTPG) + right atrial pressure (RAP), where trans-tricuspid gradient is $4V^2$ (V = peak velocity of tricuspid regurgitation, m/s).[5,12,13] RAP was estimated to be 5, 10, or 15 mmHg based on the variation in the size of inferior vena cava with inspiration, complete collapse, RAP = 5 mmHg; partial collapse, RAP = 10 mmHg; and no collapse, RAP = 15 mmHg.[20]

In the present study Pulmonary artery hypertension (PAH) was defined as Resting PAP ≥ 30 mmHg.[21] PAH was further classified into classified into mild, moderate, and severe category as resting PAP 30-50, 50-70, >70 mmHg, respectively.[22] .pulmonary artery pressure as measured by 2D resting echocardiography equals the right ventricular systolic pressure (RVSP) which is determined using trans-tricuspid pressure gradient (TTPG) and right atrial pressure (RAP) (RVSP=TTPG + RAP), where trans-tricuspid gradient is $4V^2$ (V = peak velocity of tricuspid regurgitation, m/s).[4,12,13]

- In case of weak Tricuspid regurgitation signals, saline Bubble Contrast was used for augmentation of signals and assessment of PAH. Right ventricle dimension was measured by M-Mode echo and right ventricular hypertrophy or corpulmonale was said to be present when right ventricular free wall thickness exceeded 0.4 cm. Right ventricle contractility was measured using Tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic dysfunction was said to be present when TAPSE was less than 1.8cm.[23] Left ventricular systolic function was said to be normal, when left ventricle ejection Fraction was more than 50%.

- All Patients enrolled in the study received a standard treatment with according to fixed protocol designed by physician according to COPD gold guidelines 2010 and pulmonary artery hypertension treated as per cardiologist advice. Hence patients of COPD with mild pulmonary artery hypertension received only inhaled bronchodilators along with short term xanthine derivative(oral doxophylline). COPD patients with moderate PAH and pedal edema received short term diuretics along with inhaled bronchodilators along with short term xanthine derivative (oral doxophylline). COPD patients with severe PAH and received vasodilators (selective phosphodiesterase inhibitors) along with short term diuretics, inhaled bronchodilators and short term xanthine derivative (oral doxophylline).

- 2 D echocardography and electrocardiogram were done in all patients after 1 month to reassess the cardiac status and pulmonary artery pressure.

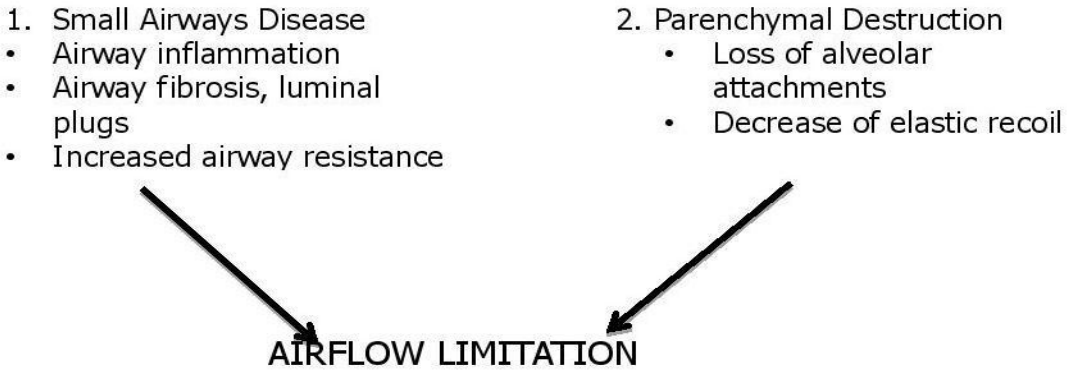
- Pre treatment and post treatment quality of life and symptoms scoring was done using a COPD assessment test (CAT scoring) questionnaire for each patient (Appendix 2).[24]

REVIEW OF LITERATURE

EPIDEMIOLOGY

- COPD, a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

- Exacerbations and comorbidities contribute to the overall severity in individual patients.
- Mechanism underlying airflow limitation in COPD includes



BURDEN OF COPD

- COPD is a leading cause of morbidity and mortality worldwide.
- The burden of COPD is projected to increase in coming decades due to continued exposure to COPD risk factors and the aging of the world's population.
- COPD is associated with significant economic burden.
- COPD is a leading cause of death and disability worldwide. According to World Bank data it is expected to move from its status in 2000 as the 4 th and 12 th most frequent cause of mortality and morbidity, respectively, to the 3 rd and 5 th leading cause of mortality and morbidity, respectively, in 2020.
- COPD affects more than 400 million people worldwide. The reported prevalence of COPD is highly variable ranging from 0.2% in Japan to 37% in the United States. According to the 12-site Burden of Obstructive Lung Disease (BOLD) study, the average prevalence of COPD is 10.1%, with wide variations.[19]
- Prevalence estimates based on spirometry are reported to be higher than those based on questionnaire-based studies.[20,21]
- Before the turn of 20th century, there were few studies from India, which reported the prevalence of COPD. Most of them were limited by small sample size and were based on unvalidated questionnaire interviews making them unreliable for any national assessment.[22,23,24] Nevertheless, the prevalence of COPD reported in these studies varied from 2-22% in men and from 1.2-19% in women.
- There were three attempts to systematically review and analyze available data until the results of the 'Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults' (INSEARCH) phase II was published.[23,24,25] All the reviews concluded that data was insufficient to derive national representative figures of prevalence of COPD. After publication of the results of INSEARCH II, some nationwide prevalence data are available.
- Together, the INSEARCH I and II involved 16 centers across the country, included 121,776 individuals of more than 35 years of age, and was based on a well-validated questionnaire.[26] The study population had rural and urban representation of both genders.[27,28] The prevalence of COPD in India according to these studies was 3.67% (4.46 and 2.86% among males and females, respectively). The estimated burden of COPD in India is about 15 million cases (males and females contributing to 9.02 and 5.75 million, respectively).
- These figures may however underestimate the true burden since questionnaire based prevalence rates tend to underestimate the true spirometry-based prevalence of COPD.
- As of now, valid spirometry based nationwide prevalence data for COPD in India are not available. In most of the critical analyses, validated questionnaire based data has been accepted as reasonable for assessment of prevalence of COPD despite its limitations.
- Globally, COPD is the ninth leading cause of loss of disability adjusted life years (DALYs) according to the baseline projections made in the Global Burden of Disease Study (GBDS).[29]
- In India, chronic respiratory diseases (CRDs) account for 3% of DALYs, and COPD is the major cause among CRDs.[30]
- COPD also accounts for more than 3 million deaths per year globally making it the third leading cause of death worldwide.[31] It accounts for 2.3-8.4% of all deaths. This proportion is more among men than women, and more among the elderly as compared to the young.[21,32]
- In India, COPD causes about 500,000 deaths per year.[33] A review of data from multiple sources suggested that COPD causes more death than tuberculosis and pneumonia.[34 Recently, the State Health Systems Resource Center reported that COPD is the leading cause of death in Maharashtra

state; surpassing coronary artery disease, cerebrovascular accident, and diabetes combined together.[35]

- According to the preliminary report of the "Million Death Study", CRDs were the second common cause of death among Indian adults. They are second and the third common causes of death in rural and urban population, respectively.[36]
- The estimated economic loss in India due to COPD is about Rs. 35,000 crores for year 2011 and is predicted to exceed Rs. 48,000 crores for year 2016. These economic losses are more than the annual budget of the Ministry of Health and Family Welfare (MOHFW) for year 2010-2011, which was Rs. 25,124 crores.[33]
- In a study that assessed the costs of treatment amongst 423 COPD patients in India, it was found that patients spent 15% of their annual income on smoking products and 30% on disease management.[37]
- It has been calculated that proper program-based or guideline-based management of COPD can reduce these costs by approximately 70%.[30]

RISK FACTORS

There are numerous factors that are thought to affect lung function at various stages of development and ageing of lung. Some of them have strong evidence to qualify as being causative for COPD; however there are others for which such causative associations are yet to be established. Exposure to multiple risk factors tends to have an additive effect. Listed in table 1.

Established	Probable
Tobacco smoking	Outdoor air pollution
Environmental tobacco smoke	Pulmonary tuberculosis
Exposure to biomass fuel smoke	Poorly treated asthma
Occupational exposure	Intrauterine growth retardation
Alpha-1 antitrypsin deficiency	Poor nourishment
	Repeated lower respiratory infections during childhood
	Others
	Age
	Male gender
	Low socioeconomic status

COPD: Chronic obstructive pulmonary disease

Tobacco smoking

- Noncommunicable diseases (NCDs) account for approximately 36 million deaths per year across the globe; among them tobacco alone causes approximately 6 million deaths and is the leading modifiable risk factor for NCDs. [38,39]

- Tobacco is abused in two main forms, mainly smoking and smokeless tobacco. Globally, the rate of current smokers is estimated to be about 1 billion. [39] In the INSEARCH study, prevalence of tobacco use was 28.5 and 2.1% among adult men and women, respectively. [28]

- According to the Global Adult Tobacco Survey (2009-2010) conducted in India, the prevalence of tobacco use in any form was 34.6% (47.9 and 20.3% among men and women, respectively). Of them, 14% (24.3% men and 2.9% women) smoked tobacco. The rise in COPD incidence has paralleled the rise in tobacco smoking throughout the world.[40,41] There is a strong dose-response relationship (for amount and duration) between tobacco smoking and COPD. [26,42]

- In INSEARCH II, the adjusted odds ratio (OR) for developing COPD among smoker as compared to non smoker was 4.08. In addition, smoking tobacco has additive effect with most of the other risk factors for COPD. [39]

- The risk of COPD increases with increase in the number of cigarettes/ bidis as well as with the duration of smoking. Any amount of smoking is harmful, although the risks are lower at low dose.[43] In one study the prevalence of CRDs among smokers with 2.5 and > 13.5 pack years was found to be approximately 13 and 60%, respectively.[42] Similarly, another study reported that prevalence of COPD in smokers with less than 20 pack years was 9.6%, which increased to 18% in subjects who smoked more than 20 pack years.[26]

ETS

- About 25-45% of patients with COPD are never smokers. Recent evidence suggests that factors other than smoking are strongly associated with COPD.[44,45]

- In INSEARCH phase II study, approximately 60% of chronic bronchitis patients were nonsmokers.[28] ETS exposure among nonsmokers, especially women and children is common in many Asian countries. The INSEARCH study established

the association of ETS exposure with COPD. The adjusted OR for COPD among those with ETS exposure was reported to be 1.99 (95% confidence intervals (CI), 1.69-2.34).[28] The odds for combined childhood and adult exposure was higher than that with ETS exposure during either childhood or adulthood alone, suggesting a cumulative effect.

Burning of biomass fuel

- The combustion of biomass fuel such as dried dung, wood, and crop residue is associated with generation of several toxic gases and particles which are responsible for various health hazards, including respiratory problems.[46,47]
- Globally, about 3 billion people are exposed to biomass fuel smoke, compared with 1.01 billion people who smoke tobacco.[45,48]
- According to the third National Family Health Survey, about 75% of households in India still continue to use biomass fuel for cooking. Respiratory symptoms were reported in 13% of 3,608 nonsmoking women involved in domestic cooking.[49]
- One study found the prevalence of airflow limitation to be almost double in residents of households using biomass fuel compared to households using liquefied petroleum gas (LPG) (8.1 vs 3.6%).[50]
- Contrary to previous studies, this study displayed similar patterns for males as well as females. Two recent meta-analyses suggest that exposure to biomass fuel combustion is an important risk factor for COPD.[51,52]
- In fact, it has been argued that in India, where more than 70% people use biomass fuel for cooking purposes compared to 25% who smoke, exposure to biomass fuel may be a bigger risk factor for COPD in India.[52]

Occupational exposures

- A systematic review of epidemiological data by the ATS suggests that about 15% of COPD cases might be related to exposure at workplace.[47] In subsequent studies, the proportion of patients with COPD attributable to occupation was about 19% overall and 31% in never smokers.[53]
- The list of occupations associated with increased risk of COPD include; rubber, plastics, and leather manufacturing; textile mill product manufacturing; and food product manufacturing.[54,55]

Alpha-1 antitrypsin deficiency and other genetic factors

- AAT deficiency is the only well-known genetic risk factor for emphysema.[56] While the prevalence of AAT deficiency is significant in Europe and North America, it is not very commonly reported from the Asian continent including India. Two studies from India suggest that few interleukin genotypes, and mutations in glutathione s-transferase 1, have some association with COPD.[57,58]

Outdoor air pollution

- Ambient air pollution in metropolitan cities has been frequently implicated as a causative agent for various respiratory diseases including COPD, especially in Asian countries where urban air pollution is high.[59] In one study, respiratory symptoms were found to be more common in the higher pollution zones among 4,171 randomly selected residents. Also, the emergency room visits for COPD increased by 24.9% when the levels of pollutants in ambient air exceeded the acceptable limits.[60]

Pulmonary tuberculosis

- The association of pulmonary tuberculosis with COPD has occasionally been described. The prevalence of airflow obstruction varies from 28 to 68% of patients with treated pulmonary tuberculosis.[61] In a nationwide survey of 13,826 adults in South Africa, a history of pulmonary tuberculosis was associated with COPD with odds of 4.9 for men and 6.6 for women.[62] Whether this finding of obstructive functional defect in post tubercular sequel behaves as COPD, or is different, remains to be established in long term-prospective cohort studies.

Asthma

- Patients with active asthma were found to have 10-fold increased risk of chronic bronchitis and 17-fold increased risk of emphysema as compared to those without asthma even after adjustment for confounding factors.[63] A subsequent review also suggests that a subset of patients with asthma may have COPD phenotype.[64]

Miscellaneous factors

- An increased association of COPD is reported with demographic and socioeconomic factors such as advancing age, low socioeconomic status, and urban residence with lower socioeconomic status. This association may perhaps be attributed to the greater prevalence of smoking and cumulative effects of smoking and other exposures with age. Low socioeconomic status and infections have been listed as additional risks.

DIAGNOSIS AND ASSESSMENT OF COPD

COPD is one of the important differential diagnosis in patients presenting with symptoms of chronic cough, sputum production, breathlessness, and/or wheezing.[65,66,67] This is especially true when patients have a history of prolonged exposure to risk factors. There is no definite duration of exposure to the risk factors that can result in COPD. However, in general, a prolonged exposure to risk factors is required for the development of disease.

SYMPTOMS OF COPD

COPD patients may present to a healthcare facility in four typical ways

a. With one or more of the characteristic respiratory symptoms of chronic progressive breathlessness, cough, sputum production, wheezing, and/or chest tightness. Recent studies reveal that presence of one or more of these symptoms increases the odds for the diagnosis of COPD. [65,66,67]
b. Without respiratory symptoms like breathlessness, because patients might have reduced their physical activity unknowingly to very low levels. They might just complain of fatigue.
c. With symptoms attributed to complications of the disease like weight loss (COPD related cachexia) or leg swelling (due to corpulmonale).
d. With an exacerbation (as discussed in the section on exacerbation).

Breathlessness

Patients may variously describe their breathlessness as: "My breathing requires effort", "I cannot get enough air in", "I feel out of breath", or "I feel hunger for more air".[68] There may be individual and cultural variations in the description of breathlessness.[69] Breathlessness is usually present on exertion until late in the course of the disease. Orthopnea occurs early and more commonly in heart failure, which is an important differential diagnosis, while it is reported infrequently and late (if ever) in patients with COPD. The severity of breathlessness may be graded on various scales. A simple and widely used scale is the modified Medical Research Council (mMRC) questionnaire,[70] illustrated in table 2.

Grade	Patient's description of breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on the level or walking up a slight hill
Grade 2	I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on the level
Grade 4	I am too breathless to leave the house or I am breathless when dressing

Cough and sputum production

Cough may be the only presenting symptom. On the other hand, a smoker might consider his cough to be a natural consequence of smoking, and might neglect it as a symptom. An increasing intensity, or change in the nature, of cough may be reported. It may be more prominent in the morning. Cough may be accompanied by mucoid or purulent sputum production that may vary greatly in amount.[71] Again, patients may find it a normal phenomenon associated with smoking and might even feel that smoking helps in easing out the passage of sputum. Immediately following smoking cessation, cough and sputum may become more bothersome, but generally improve with continued abstinence.[69] The epidemiological definition of chronic bronchitis (regular production of sputum for 3 or more months for 2 consecutive years) is arbitrary and might not apply to a given patient. However, it might identify an "at risk" individual.

Wheezing

Patients may complain of wheezing, variously described as noisy breathing or a whistling sound. Wheezing may have diagnostic value when seen in the light of other clinical features.[65,66,67]

Chest tightness

Patients may complain of chest tightness, chest congestion, or an obstructed chest.

Chest pain and hemoptysis

These are not the usual symptoms of COPD. Their presence is often a pointer to an alternative diagnosis (e.g., lung malignancy, pulmonary tuberculosis, etc.)

SIGNS OF COPD

COPD patients may demonstrate various physical signs that may either be due to the primary disease or an associated complication [Table 3].[72,73] Diminished breath sounds and wheezing on auscultation have been shown to increase the odds for a diagnosis of COPD.[71] An important clinical sign is the forced expiratory time (FET).[74] An FET of more than 6 seconds suggests airway obstruction

Inspection
Pursed-lip breathing
Use of accessory muscles of respiration
Jugular venous distension during expiration
Retraction of suprasternal, supraclavicular and intercostal spaces during inspiration
Short trachea
Pulsus paradoxus
Increased anteroposterior diameter of the chest (barrel-shaped chest)
Reduced chest movements
Peripheral edema
Dyspnea-relieving posture
Muscle wasting
Palpation
Restricted chest expansion
Subxiphoid shift of maximum impulse of the heart
Percussion
Chest hyperresonance
Obliteration of cardiac dullness
Lower level of liver dullness
Lower diaphragmatic levels
Auscultation
Diminished breath sounds
Early inspiratory crackles
Loud pulmonic component of second heart sound
Special maneuver
Forced expiratory time
Snider's match test

COPD: Chronic obstructive pulmonary disease

ROLE OF SPIROMETRY IN DIAGNOSING COPD

Demonstration of airflow obstruction is essential to make a definitive clinical diagnosis of COPD. Spirometry is a simple and accurate tool to assess airflow obstruction. Spirometry should be performed as per standard guidelines.[75,76] [Table 4] summarizes some of the important points elaborated in these guidelines regarding the equipment and performance of spirometry.[75,76] Both FEV_1 and FVC should be assessed, and the FEV_1/FVC ratio calculated.

Equipment
It is the responsibility of the manufacturers to manufacture pulmonary function systems that satisfy the latest accepted published guidelines. It is also the duty of the user that the system being used complies with the latest recommendations and gives accurate measurements during the course of its running
The equipment should meet the recommended requirements for volume, flow, resistance, and time of flow
Calibration checks for volume, leak, and volume and flow linearity should be performed regularly
Performance
Each test performed should meet certain within-maneuver and between-maneuver criteria
Individual spirograms are acceptable if they are free from artifacts (cough during first second of exhalation, glottis closure, early termination, submaximal effort, or obstructed mouthpiece), have good starts with extrapolated volume < 5% of FVC or 0.15 L, whichever is greater and show satisfactory exhalation (duration of ≥ 6 seconds or a plateau in the volume-time curve)
Acceptable spirograms should meet the between-maneuver criteria. Out of three acceptable spirograms, the two largest values of FVC should be within 0.15 L of each other, the two largest values of FEV_1 should also be within 0.15 L of each other. If these criteria are not met, testing should be continued until the above criteria are met with additional acceptable spirograms or a total of eight maneuvers have been performed
Bronchodilator administration and post-bronchodilator testing
Four separate doses of salbutamol 100 μg and/or ipratropium bromide 40 μg are delivered through a valved spacer device at 30 seconds intervals. Spirometry should be performed after 10-15 min later for salbutamol and 30 min later for ipratropium bromide
Evaluation
A post-bronchodilator FEV_1/FVC less than the lower limit of normal, signifies obstruction. Further severity classification is done according to the FEV_1 value
Appropriate reference equations should be used for determining the lower limit of normal

FEV_1/FVC: Forced expiratory volume in first second/forced vital capacity

The criterion for defining airflow obstruction has been a subject of much debate in recent years.[77,78] The GOLD committee suggests use of a post-bronchodilator FEV_1 /FVC less than an arbitrarily fixed value of 0.7 ($FR_{0.7}$) as the criterion for diagnosis of COPD.[3] However, guidelines on spirometry recommend the use of statistically derived LLN of FEV_1 /FVC as the cutoff to define airflow obstruction.[75] The LLN is defined as the lower fifth percentile of values in the reference population. The age and gender adjusted reference equations for this purpose are generated from spirometric data from a cohort of normal healthy nonsmoking individuals sampled from the particular population in a geographical area. LLN is then computed as the difference between predicted value and 1.645 times the standard error of estimate of the reference equation.

A systematic review analyzed the findings of 18 studies that compared these two spirometric definitions.[79] Most of these studies reported that use of $FR_{0.7}$ leads to a much higher proportion of subjects being diagnosed as having airflow obstruction than use of LLN.[80,81,82,83,84,85,86,87,88,89,91]

CO MORBIDITIES ASSOCIATED WITH COPD

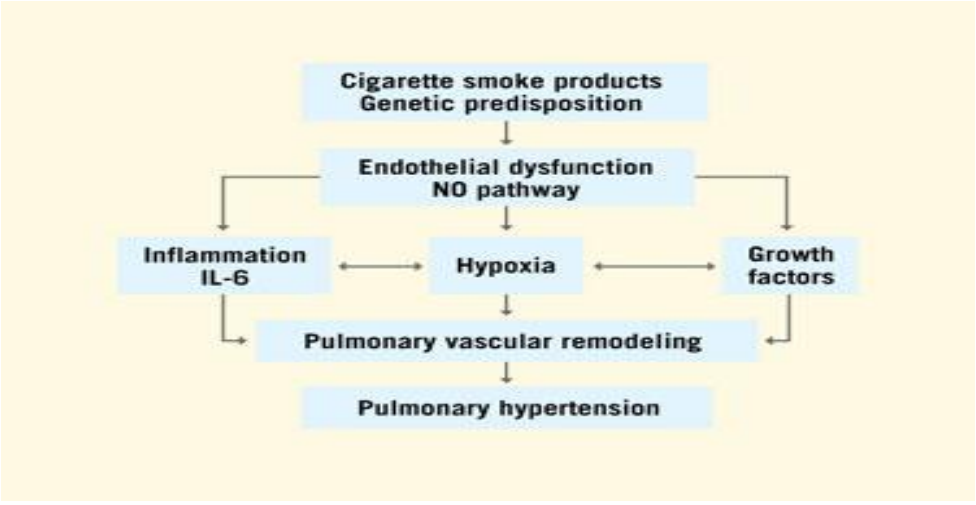
COPD is associated with many comorbid diseases, which may be pulmonary or extrapulmonary (coronary vascular disease, congestive heart failure, diabetes mellitus, metabolic syndrome, obstructive sleep apnea, skeletal muscle dysfunction, cachexia, osteoporosis, depression, lung cancer).[92,93,94] Comorbid diseases in COPD are independently associated with a higher risk of hospitalization and mortality.[95]

CARDIOVASCULAR ABNORMALITIES IN COPD

The cardiac manifestations of COPD are numerous. Impairment of right ventricular dysfunction and pulmonary blood vessels are well known to complicate the clinical course of COPD and co-relate inversely with survival. Significant structural changes occur in the pulmonary circulation in patients with COPD. The presence of hypoxemia and chronic ventilator insufficiency is associated with early evidence of intimal thickening and medial hypertrophy in the smaller branches of the pulmonary arteries. Coupled with these pathological changes are pulmonary vasoconstriction arising from the presence of alveolar hypoxemia, destruction of pulmonary vascular bed, changes in intrinsic pulmonary vasodilator substances (such as decrease in PGI_2s (prostacyclin synthase), decrease in eNOS (endothelial nitric oxide synthase), and increase in ET1 (endothelin1) leads to remodeling, increase in blood viscosity, and alteration in respiratory mechanics. All these lead to a significant increase in pulmonary vascular resistance, the consequence of which is pulmonary hypertension. Severe PH increases right ventricular after load with a corresponding increase in right ventricular work, which results in uniform hypertrophy of the right ventricle. In patients with COPD, hypoxic vasoconstriction is associated with not only right ventricular hypertrophy but also right ventricular dilation which eventually leads to clinical syndrome of right heart failure with systemic congestion and inability to adapt right ventricular output to the peripheral demand on exercise.

Pulmonary artery hypertension in COPD

Pulmonary arterial hypertension (PAH) is defined as a group of diseases characterised by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death.[97] The median life expectancy from the time of diagnosis in patients with idiopathic PAH (IPAH), formerly known as primary pulmonary hypertension (PPH), before the availability of disease-specific (targeted) therapy, was 2.8 years through the mid-1980s.[98] PAH includes IPAH[99] and pulmonary hypertension associated with various conditions such as connective tissue diseases (CTD), congenital systemic-to-pulmonary shunts, portal hypertension and Human Immunodeficiency Virus (HIV) infection.[100] All these conditions share equivalent obstructive pathological changes of the pulmonary microcirculation.[101,102] suggesting shared pathobiological processes among the disease spectrum of PAH.[103]



In COPD, the presence of PH is associated with shorter survival[103] and frequent episodes of exacerbation.[104] In our study pulmonary artery hypertension was defined as Pulmonary hypertension (PH) was defined in this study as Resting PAP ≥ 30 mmHg.[14] This value is chosen according to the definition of pulmonary hypertension. PH is classified into mild, moderate, and severe category as resting PAP 30-50, 50-70, >70 mmHg, respectively with equals to right ventricular systolic pressure (RVSP) = trans-tricuspid pressure gradient (TTPG) + right atrial pressure (RAP), where trans-tricuspid gradient is$4V^2$ (V = peak velocity of tricuspid regurgitation, m/s).[10,12,13]

Currently there is no specific therapy for PH associated with COPD or interstitial lung diseases. Long-term O2 administration has been shown partially to reduce the progression of PH in COPD. Nevertheless, with this treatment PAP rarely returns to normal values and the structural abnormalities of pulmonary vessels remain unaltered.[105]

Although the true prevalence of PH in COPD is unknown, an elevation of pulmonary arterial pressure is reported to occur in 20%–90% of patients when measured by right heart catheterization with some evidence that pulmonary hemodynamic worsens with worsening airflow obstruction.[106,107,108,109,110,111] Two studies have shown an abnormal increase in mean pulmonary arterial pressure (Ppa) in COPD of 0.4–0.6 mmHg per year. These studies illustrate that PH in COPD progresses slowly and occurs in mild as well as severe forms of disease.[112,113]

The level of PH has a prognostic value in COPD patients that has been demonstrated by several studies. In one of these studies, the 5-year survival rates were 50% in patients with mild PH (20–30 mmHg), 30% in those with moderate-to-severe PH (30–50 mmHg), and 0% in the small group of patients with very severe PH (>50 mmHg). Thus a high degree of PH bears a poor prognosis, and this also has been observed in COPD patients receiving long-term oxygen therapy.[114]

Approximately 25% patients with COPD eventually develop cor pulmonale.[115] Cor pulmonale was found in 40% patients with COPD in one autopsy study.[116,109] It is estimated that every year between 10% and 30% of all hospital admissions for heart failure in the United States are due to cor pulmonale[117] and approximately 85% patients with cor pulmonale have COPD.[115]

Management of a patient with COPD exacerbation

COPD exacerbation was defined according gold 2010 guidelines as An event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD.[3]

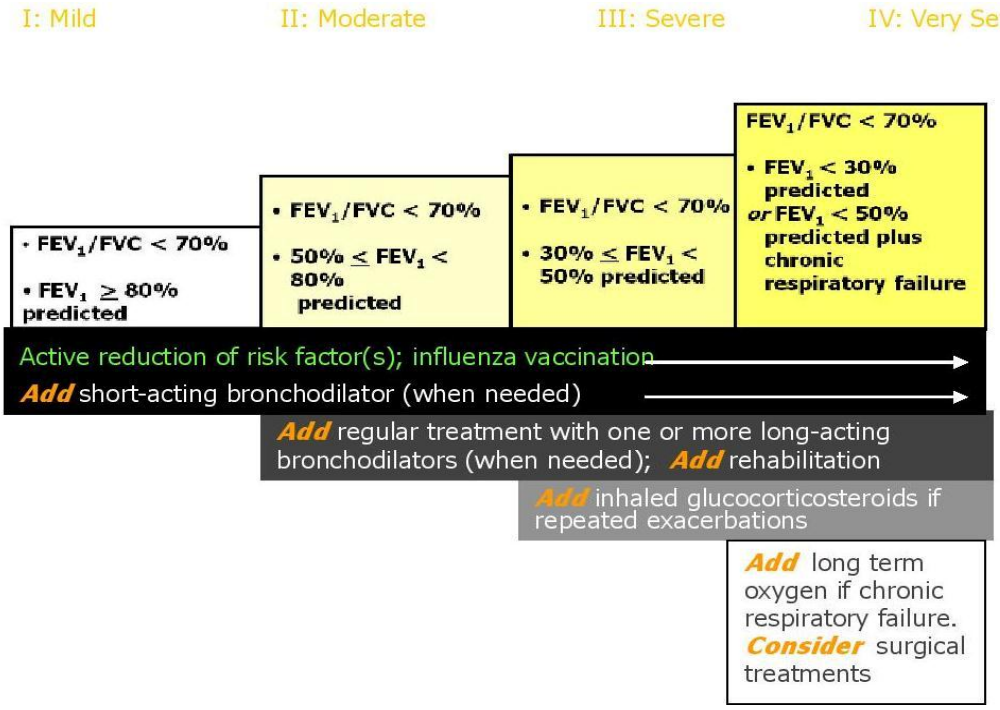
More than 80% of exacerbations can be managed on an outpatient basis.[118,120,121] SABA, with or without anticholinergic, are essential for symptomatic relief of airway obstruction, and constitute the first line of treatment.[119,122,123,124,125] Few studies have evaluated the use of bronchodilators in management of AECOPD. There were no significant differences in FEV_1 change in patients treated with beta-agonists or ipratropium bromide, and no additive benefit of adding ipratropium to beta-agonist.[126] Also, the optimal dosing and frequency of bronchodilators in AECOPD is not established. There was no difference in clinical outcomes in patients treated every 4 hours with either 2.5 or 5 mg of nebulized salbutamol.[127] There was also no significant difference in improvement in FEV_1 between hourly and 20-min dosing of salbutamol.[128] Post-hoc analysis however revealed significantly better improvement with the 20-min protocol in those with $FEV_1 < 20\%$.[128] The drugs can be delivered by the inhaled route either using pMDI with spacer or nebulizer. There is no significant difference in outcomes based on either method of administration.[125] In severe exacerbations, altered mental status favors the use of nebulized bronchodilators, while in others pMDI with spacer is preferred due to lower costs and lesser chances of infection. In any case, the patient should be switched over to pMDIs with spacer at the earliest. Importantly, the drugs should not be nebulised using oxygen. Rather patients should receive supplemental oxygen separately through nasal prongs while nebulising drugs using compressed air, with monitoring of oxygen saturation.

Intravenous or subcutaneous routes of administering beta-agonists are associated with significant adverse events without significant additional bronchodilatation. Intravenous methylxanthines (theophylline or aminophylline) are considered second-line therapy, to be used only in select cases when there is insufficient response to short-acting bronchodilators.[129,130] Two randomized controlled trials have compared intravenous magnesium sulfate (1.5 or 1.2 g) with placebo in patients with AECOPD, and have found modest improvements in lung function.[131,132]

The pathophysiology of AECOPD is due to severe inflammation triggered by infective and/or noninfective causes, and thus systemic corticosteroids have a role in managing this condition. In a systematic review involving ten studies (n = 1051), steroid use resulted in significantly fewer treatment failures (defined as the need to seek additional medical therapy within 30 days), shorter duration of hospitalization, improvement in breathlessness, and FEV_1 ; but with no significant effect on mortality. There was an increased likelihood of an adverse event (hyperglycemia, weight gain, or insomnia) associated with corticosteroid treatment with a number needed to harm of any adverse event being 5 (95% CI 4-9).[133] In a study of approximately 80,000 hospitalizations for COPD, there was no advantage of high-dose corticosteroids over low-dose regimens; in fact

lower-dose regimens actually improved outcomes. [134] The study of ICS has been restricted largely to its role as chronic therapy for the prevention of exacerbations. Few studies have investigated the role of ICS in management of AECOPD.[135,136,137]
criteria (TABLE 6):

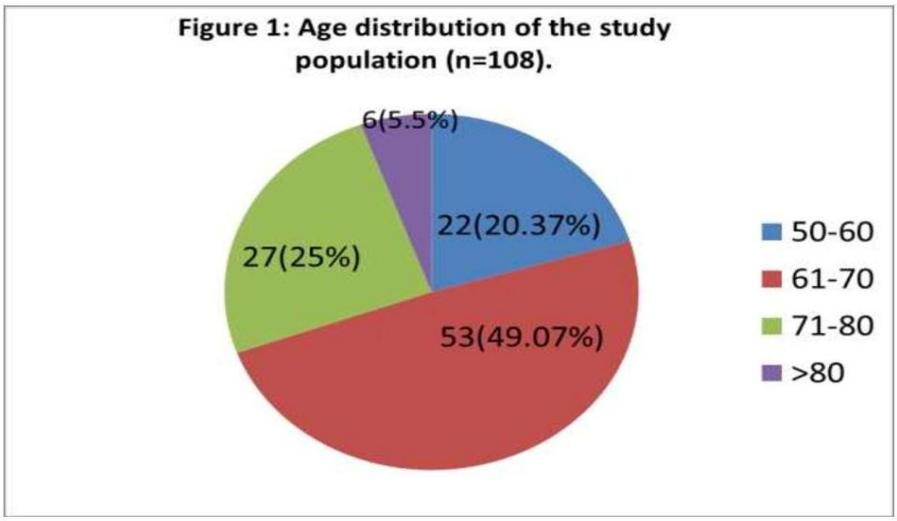
Management of post COPD exacerbation status
During post exacerbation status patients are managed according to gold guidelines 2010 according to spirometry



RESULTS
DEMOGRAPHY(AGE)
TABLE 7: demography of the study population

	NUMBER	MEAN AGE	STANDARD DEVIATION
MALES	108	66.78	7.589

- In our study we included only male patients with age more than 40years. However in the present study there were no patients in the age group of 40-50 years
- Most of the patients were within the age group 61 – 70 years (49.07%).

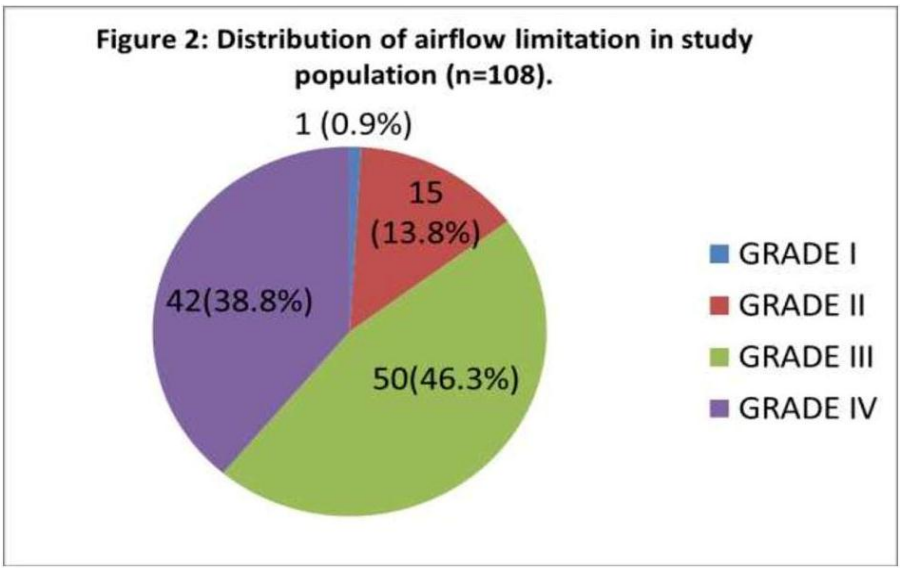


PULMONARY FUNCTION TEST

In our study all patients were classified according to GOLD guidelines (postbronchodilator FEV $_1$ /forced vital capacity (FVC) ratio < 70% predicted) as GRADE I-mild COPD (FEV $_1$ ≥ 80% of predicted), GRADE II-moderate COPD (50% ≤ FEV $_1$< 80% predicted), GRADE III-severe COPD (30% ≤ FEV $_1$< 50% predicted), and GRADE IV-very severe COPD (FEV $_1$< 30% predicted).

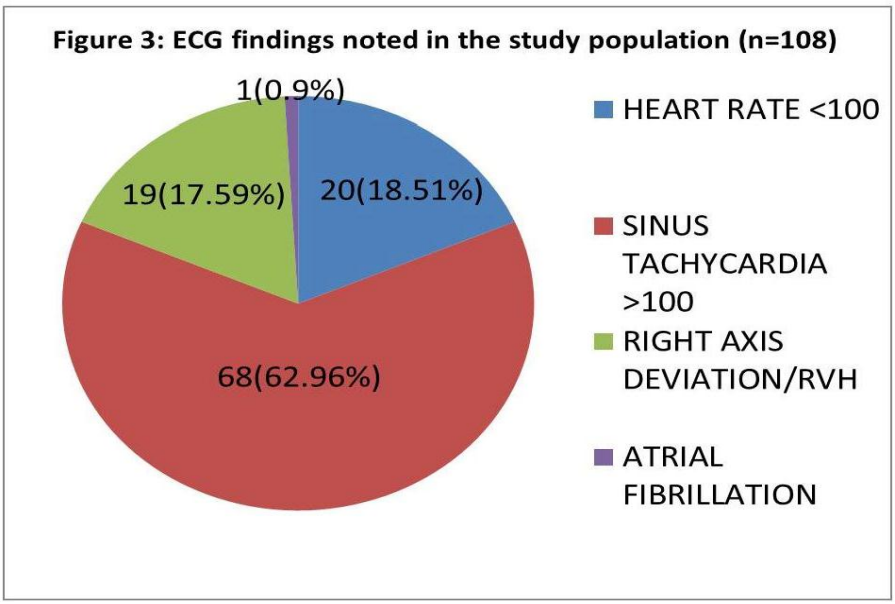
Table 8: Distribution of airflow limitation in the study population

GRADE	NUMBER	MEAN	STANDARD DEVIATION	95%CONFIDENCE INTERVAL	P VALUE
GRADE I	1	81%	-	-	-
GRADE II	15	57.93%	5.035%	55.14-60.72	0.000
GRADE III	50	39.36%	5.348%	37.84-40.88	0.000
GRADE IV	42	25.95%	3.870%	24.75-27.16	0.000



- Majority of patients who were recruited falls under grade III COPD(severe) which included 46.3% (50 patients) and grade IV COPD (very severe) which included 38.8%(42 patients) severity of air flow limitation based on post bronchodilator FEV1% on spirometry as per GOLD criteria.

ELECTROCARDIOGRAPHY FINDINGS



Among 108 COPD patients admitted with exacerbation, maximum i.e. 68 (62.96%) patients were having sinus tachycardia, while 20 (18.51%) were having normal heart rate. The mean heart rate recorded among COPD patients was 106.14 per minute, followed by 19(17.59%) were having peaked p wave (p wave amplitude > 2.5mm) with right axis deviation and one patient (0.9%) with atrial fibrillation with irregularly irregular rhythm with loss of p wave. Duration of QRS and ST segment were normal in this patients.

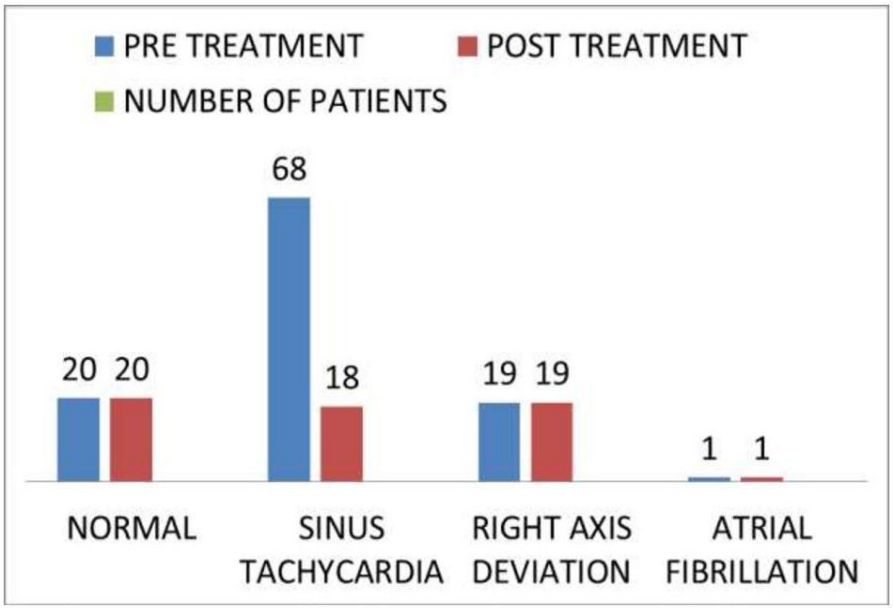


Figure 4: Pre and post treatment ECG variation observed in the study population (n=108)

During follow up post treatment there were no ECG changes compared to ECG taken during exacerbation status except sinus tachycardia has been normalised in 50 patients (73.5%) among 68 patients of sinus tachycardia of heart rate more than 100.

PULMONARY ARTERY HYPERTENSION

In our study patients were further classified into classified into mild, moderate, and severe pulmonary artery hypertension category as resting PAP 30-50, 50-70, >70 mmHg, respectively[10] , which was measured by 2D resting echocardiography equals the right ventricular systolic pressure (RVSP) which is determined using trans-tricuspid pressure gradient (TTPG) and right atrial pressure (RAP) (RVSP=TTPG + RAP), where trans-tricuspid gradient is $4V^2$ (V = peak velocity of tricuspid regurgitation, m/s).

Table 9: Distribution of pulmonary artery hypertension in the study population

GRADING	NUMBER	MEAN RVSP	STANDARD DEVIATION
MILD	88 (81.48%)	38.59MMHG	4.968MMHG
MODERATE	17 (17.04%)	52.47MMHG	3.484MMHG
SEVERE	3 (2.77%)	70.33MMHG	0.577MMHG

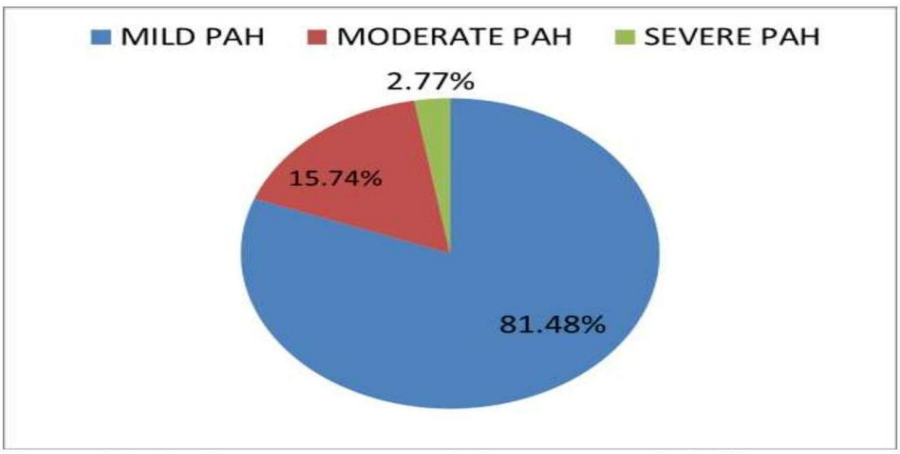


Figure 5: Distribution of pulmonary artery hypertension in the study population (n=108)

COMPARISON OF PULMONARY ARTERY HYPERTENSION WITH AIRFLOW LIMITATION

Table 10: comparison of pulmonary artery hypertension with airflow limitation

PAH GRADING	SPIROMETRY GRADING	NUMBER (%)	MEAN FEV1 (%)
MILD PAH (N= 88 PATIENTS)	GRADE I	1 (1.13%)	81%
	GRADE II	14 (15.99%)	58.33%
	GRADE III	45 (51.13%)	39.29%
	GRADE IV	28 (31.81%)	25.89%
MODERATE PAH (N=17 PATIENTS)	GRADE II	1 (5.8%)	57%
	GRADE III	5 (29.81%)	43%
	GRADE IV	11 (64.70%)	26.45%
SEVERE PAH (N=3 PATIENTS)	GRADE IV	3 (100%)	24.66%

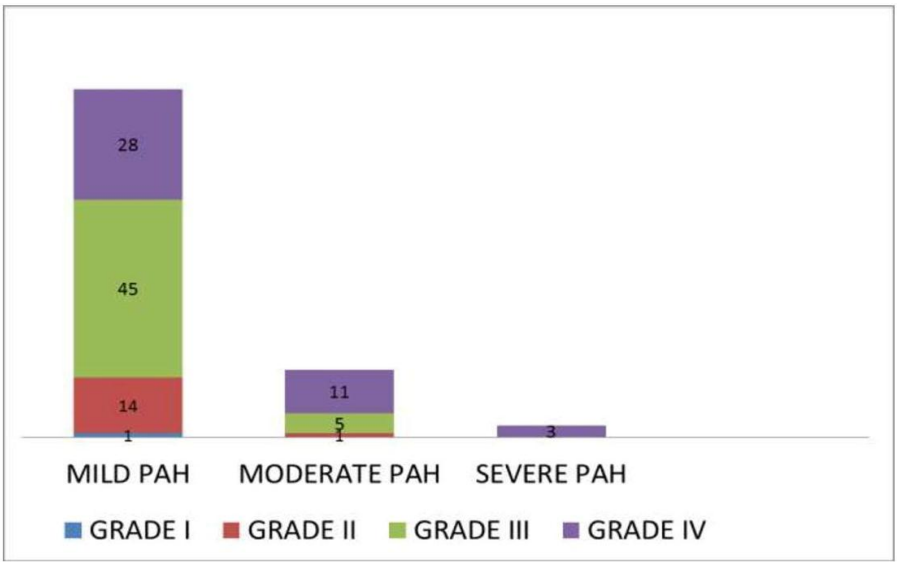


Figure 6: Distribution of air flow limitation with severity of pulmonary artery hypertension in study population (n=108)

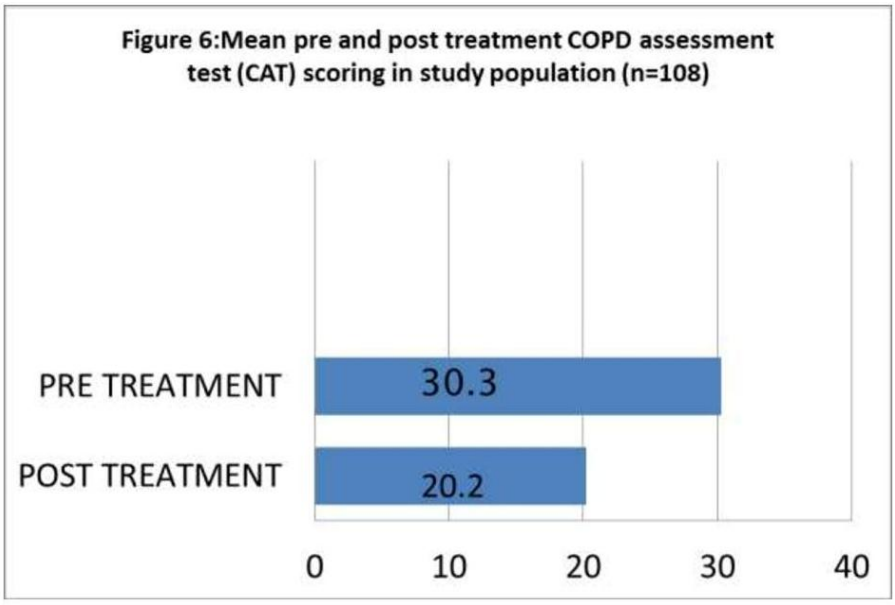
- Mild PAH was observed in 88 patients(81.48%) with mean RVSP=38.59mmHg. Among them 1 patient(1.13%) was grade I (fev1%=81%) ,14(15.99%) patients were grade II COPD(mean fev1%=58.33%), 45 patients(51.13%) were grade III(mean fev1%=39.288%) and 28 patients(31.81%) were grade IV(mean fev1%=25.89%) COPD.

- Moderate PAH was observed in 17 patients(15.74%) with mean RVSP=52.47mmHg. Among them 1 patient(5.8%) was grade II COPD (mean fev1%=57%), 5Patients(29.41%) were grade III(mean fev1% =43%) and 11 patients(64.70%) were grade IV COPD(mean fev1%=26.45%).

- Severe PAH was observed in 3 patients (2.77%) with mean RVSP=70.33mmHg among them all 3 patients(100%) were of grade IV COPD(mean fev1%=24.66%).

TREATMENT OPTIONS

- COPD patients with Mild pulmonary artery hypertension- inhaled bronchodilators + short term oral xanthine drugs (doxophylline).
- COPD patients with Moderate pulmonary artery hypertension and pedal edema- inhaled bronchodilators + short term oral xanthine drugs (doxophylline) + short term diuretics.
- COPD patients with Severe pulmonary artery hypertension and pedal edema - inhaled bronchodilators + short term diuretics + selective Phosphodiesterase inhibitors (selective PDE inhibitors).
- Pre treatment and post treatment quality of life and symptoms scoring was done using eight questions based COPD questionnaire called COPD assessment test (CAT scoring) for each patient. Pre treatment mean CAT scoring was 30.33 and post treatment mean CAT score had been reduced to 20.20 with a symptomatic reduction of 10.13 score with p value of 0.000 ($p < 0.01$).



COMPARISON OF PRE AND POST TREATMENT PULMONARY ARTERY HYPERTENSION USING RIGHT VENTRICULAR SYSTOLIC PRESSURE

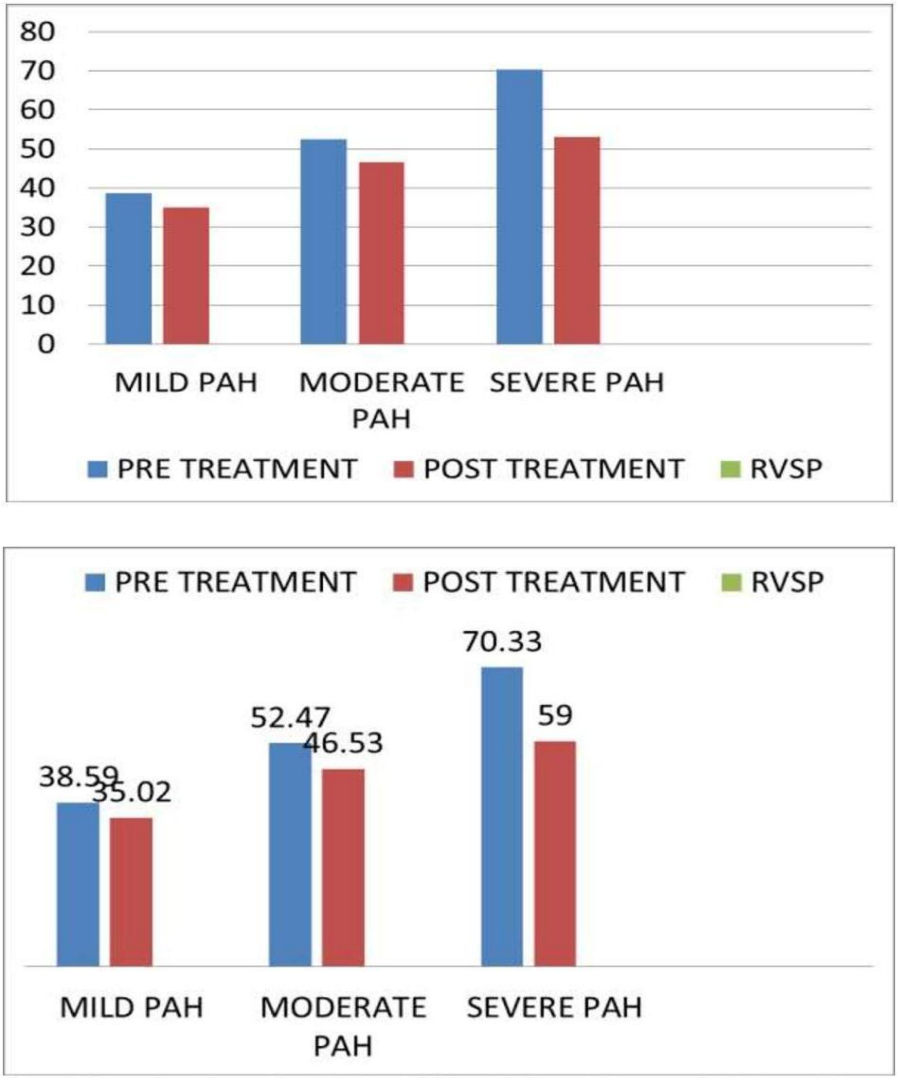


Figure 7: Comparison of pre and post treatment right ventricular systolic pressure in study population

Table 10: Comparison of pre and post treatment right ventricular systolic pressure in study population

PAH GRADING	SPIROMETRY GRADING	MEAN PRE TREATMENT RVSP	MEAN POST TREATMENT RVSP	DIFFERENCE
MILD PAH (N= 88 PATIENTS)	GRADE I (N=1)	32 MMHG	30 MMHG	-2MMHG
	GRADE II (N=15)	39.07MMHG	34 MMHG	-5.07MMHG
	GRADE III (N=45)	38.71MMHG	35.11MMHG	-3.6OMMHG
	GRADE IV (N=28)	38.46MMHG	35.50MMHG	-2.96MMHG
MODERATE PAH (N=17 PATIENTS)	GRADE II (N=1)	51MMHG	41MMHG	-10MMHG
	GRADE III (N=5)	53.40MMHG	44.80MMHG	-8.60MMHG
	GRADE IV (N=11)	51.81MMHG	47MMHG	-4.81MMHG
SEVERE PAH (N=3 PATIENTS)	GRADE IV (N=3)	70.33MMHG	59MMHG	-11.33MMHG

Table 10: Statistical analysis of pre and post treatment right ventricular systolic pressure in study population (N=108)

PAH STATUS	RVSP	MEAN RVSP	STANDARD DEVIATION	95% CONFIDENCE LIMITS	P VALUE
MILD PAH (N=88)	PRE TREATMENT	38.59MMHG	4.968MMHG	2.033-5.103	.000 (<0.01)
	POST TREATMENT	35.02MMHG	5.121MMHG		
MODERATE PAH (N=17)	PRE TREATMENT	52.47MMHG	3.484MMHG	1.940-9.942	.000 (<0.01)
	POST TREATMENT	46.53MMHG	5.928MMHG		
SEVERE PAH (N=3)	PRE TREATMENT	70.33MMHG	0.577MMHG	7.539-15.128	.006 (<0.01)
	POST TREATMENT	59.00MMHG	1.000MMHG		
TOTAL (N=108)	PRE TREATMENT	41.66MMHG	8.441MMHG	2.756-5.559	.000 (<0.01)
	POST TREATMENT	37.50MMG	7.587MMHG		

- All COPD Patients with mild PAH=88 patients(81.48%) with mean RVSP=38.59mmHg with standard deviation of 4.968mmHg were treated with standard treatment protocol with inhaled bronchodilators with short term oral xanthine (doxophylline) and were kept under follow up and PAH status was re analysed using 2D echocardiography showed mean RVSP = 35.02mmhg with standard deviation of 5.121mmHg. pre and post treatment RVSP analysis showed reduction of RVSP of 3.57mmHg with 95% confidence limit of 2.033-5.013 with p value of 0.000(<0.01) along with improvement in quality of life and symptoms.

- COPD Patients with moderate PAH=17 patients(15.74%) with mean RVSP=52.47mmHg with standard deviation of 3.484mmHg were treated with short term diuretics along with inhaled bronchodilators with short term oral xanthine (doxophylline) and were kept under follow up and PAH status re analysed using 2D echocardiography which showed mean RVSP = 46.53mmHg with standard deviation of 5.121mmHg. Pre and post treatment RVSP analysis showed reduction of RVSP of 5.928mmHg with 95% confidence limit of 1.940-9.942 with p value of 0.000(<0.01) along with improvement in quality of life and symptoms.

- COPD Patients with severe PAH=3 patients(2.77%) with mean RVSP=70.33mmHg with standard deviation of 0.577mmHg were treated with vasodilators(selective phosphodiesterase inhibitor) with short term diuretics along with inhaled bronchodilators with short term oral xanthine (doxophylline) and were kept under follow up and PAH status was re analysed using 2D echocardiography which showed mean RVSP = 59mmHg with standard deviation of 1.000mmhg. Pre and post treatment RVSP analysis showed reduction of RVSP of 11.330mmHg with 95% confidence limit of 7.539-15.128 with p value of 0.006(<0.01) along with improvement in quality of life and symptoms.

- Among 108 COPD patients who were recruited 2D resting echocardiography showed mean pre treatment RVSP of 41.66mmHg with standard deviation of 8.441mmHg where started on treatment and kept under follow up. Re evaluation of pulmonary artery hypertension status showed mean post treatment RVSP of 37.50mmHg with standard deviation of 7.587mmHg with reduction of RVSP of 4.16mmHg with 95% confidence interval 2.756-5.559 with p value of 0.000 (<0.01). This analysis showed reduction in pulmonary hypertension status with treatment of COPD along with improvement in quality of life and symptoms.

- Among 108 COPD patients considered for the present study 6 patients(5.54%) had cor-pulmonale. Of the 6 patients, 3 patients had severe PAH(100%) and 3 patients had moderate PAH(17.64%).

DISCUSSION

Chronic obstructive pulmonary disease (COPD), defined by GOLD as a preventable and treatable disease with some significant extrapulmonary effects, is a very common clinical entity in clinical practice. COPD is associated with significant extrapulmonary (systemic) effects among which cardiac manifestations are most common. Cardiovascular disease accounts for approximately 50% of all hospitalization and nearly one third of all deaths, if forced expiratory volume in one second (FEV 1)<50% of predicted.[4]

In more advanced disease cardiovascular disease account for 20%-25% of all deaths in COPD.[5] COPD affects pulmonary blood vessels, right ventricle, as well as left ventricle leading to development of pulmonary hypertension, corpulmonale, right ventricular dysfunction, and left ventricular dysfunction too. ECG provides a rapid, cheap, non- invasive, portable method to measure gross cardiac changes including P Pulmonale, Right ventricular hypertrophy and Left ventricular hypertrophy,ischaemic changes.

Echocardiography provides a rapid, noninvasive portable and accurate method to evaluate the right ventricle function, right ventricular filling pressure, tricuspid regurgitation, left ventricular function and valvular function.[11] Many studies have confirmed that echocardiographically derived estimates of pulmonary arterial pressure co-relate closely with pressures measured by right heart catheter (r >0.7).[12,13]

In the present study we decided to evaluate the correlation of severity of airflow limitation and pulmonary artery hypertension in COPD patients based on spirometry and 2 D resting echocardiography and as well as analysed right ventricular systolic pressure was analysed before and after treatment of acute exacerbation of COPD. This study was a time bound comparative study conducted on 108 patients diagnosed to have chronic obstructive pulmonary disease patients aged above 50 years of age admitted with acute exacerbation status and during follow up after 1 month.

Demography variation

In our study we included only male patients aged more than 40 years . (However in the present study there were no patients in the age group of 40-50 years). Most of the patients were within the age group 61 – 70 years (49.07%) with mean age of 66.78 years with standard deviation of 7.589 . A population based prevalence study of COPD in five latin American cities (PLATINO STUDY) in post bronchodilator airflow limitation in persons aged above 40 years showed increased prevalence of COPD in patients aged above 60 years of age which is comparable with our study.[138]

Pulmonary function test

In our study Majority of patients who were recruited fell under grade III (severe) which included 46.3%(50 patients) and grade IV (very severe) which included 38.8%(42 patients). Severity of air flow limitation based on FEV1% of spirometry GOLD criteria which is comparable with patients admitted with frequent hospitalization and nearly one third of all deaths, if forced expiratory volume in one second (FEV 1) < 50% of predicted[4] . Grade I COPD with FEV1% of 81 % was observed in one patient (0.9%). Grade II COPD (fev1% = 51% - 80%) was observed in 15 patients(13.8%) with mean fev1% of 57.93% with standard deviation of 5.035% with p value of 0.000 and 95 % confidence interval between 55-14-60.72. Grade III COPD (fev1% = 31% - 50%) was observed in 50 patients(46.3%) with mean fev1% of 39.36% with standard deviation of 5.348% with p value of 0.000 and 95 % confidence interval between 37.84-40.88. Grade IV COPD (fev1% = <30%) was observed in 42patients(38.8%) with mean fev1% of 25.95% with standard deviation of 3.870% with p value of 0.000 and 95 % confidence interval between 24.75-27.16. There is good quality evidence from large studies that worsening airflow limitation is associated with increasing mortality and hospitalization rates, as well as increased risk of exacerbations.[139,140,141]

In our study the distribution of pulmonary artery hypertension in mild, moderate, severe, and very severe COPD were 0.09 %, 13.8%, 46.3% %, and 38.8 %, respectively which showed as severe the COPD the incidence of PAH is high if spirometry FEV1% <50%. Similar study which analysed frequencies of PH in mild, moderate, severe, and very severe COPD were 16.67 %, 54.55 %, 60.00 %, and 83.33 %, respectively.[148] In another study, the frequency of PAH was also found to be 25 %, 43 %, and 68 % in mild, moderate, and severe COPD, respectively.[147]

Electrocardiogram

Among 108 COPD patients admitted with exacerbation, maximum i.e. 68 (62.96%) patients were having sinus tachycardia, while 20 (18.51%) were having normal heart rate. The mean heart rate recorded among COPD patients was 106.14 per minute. Followed by 19(17.59%) were having peaked p wave (p wave amplitude > 2.5mm) with right axis deviation and one patient (0.9%) with atrial fibrillation with irregularly irregular rhythm with loss of p wave. Duration of QRS and ST segment were normal in this patients.

The mean heart rate in the present study was recorded as 106.14 per minute as compared to 86 per minute obtained by Calatayudet al.[145] Normal sinus rhythm was recorded in 57.1% cases. Sinus tachycardia was present in 28.6% cases. Scott RC et al[146] reported arrhythmias other than sinus tachycardia to be uncommon in chronic corpulmonale.

During follow up post treatment there were no ECG changes compared to ECG taken during exacerbation status except sinus tachycardia has been normalised in 50

patients(73.5%) among 68 patients. No similar follow up studies were available to compare this outcome.

ECHOCARDIOGRAPHY

Among 108 patients recruited Mild PAH was observed in 88 patients(81.48%) with mean RVSP=38.59mmHg with standard deviation of 4.968mmHg. Moderate PAH was observed in 17 patients (15.7%) with mean RVSP=52.47mmHg with standard deviation of 3.484mmHg. Severe PAH was observed in 3 patients(2.77%) with mean RVSP=70.33mmHg with standard deviation of 70.33mmhg. It is similar to the studies which showed incidence of pulmonary artery hypertension directly proportional to severity of airflow limitation .[142,143,144]

Comparison of pulmonary artery hypertension with airflow limitation

Mild PAH was observed in 88 patients(81.48%) with mean RVSP=38.59mmHg. Among them 1 patient (1.13%) was grade I (fev1%=81%), 14(15.99%) patients were grade II COPD(mean fev1%=58.33%), 45 patients(51.13%) were grade III(mean fev1%=39.288%) and 28 patients(31.81%) were grade IV(mean fev1%=25.89%) COPD.Moderate PAH was observed in 17 patients (15.7%) with mean RVSP=52.47mmHg. Among them 1 patient(5.8%) had grade II COPD (mean fev1%=57%), 5Patients(29.41%) were grade III(mean fev1% =43%) and 11 patients(64.70%) were grade IV COPD(mean fev1%=26.45%). Severe PAH was observed in 3 patients (2.77%) with mean RVSP=70.33mmHg among them all 3 patients(100%) were of grade IV COPD(mean fev1%=24.66%).Which showed a positive correlation of airflow limitation with pulmonary artery hypertension. It is similar to the studies which showed incidence of pulmonary artery hypertension directly proportional to severity of airflow limitation .[147,148,149]

In our study the distribution of pulmonary artery hypertension in mild, moderate, severe, and very severe COPD were 0.09 %, 13.8%, 46.3% %, and 38.8 %, respectively which showed the severe the COPD, the incidence of PAH is high if in spirometry FEV1% <50%. Similar study which analysed frequencies of PAH in mild, moderate, severe, and very severe COPD were 16.67 %, 54.55 %, 60.00 %, and 83.33 %, respectively.[148] In another study, the frequency of PH was also found to be 25 %, 43 %, and 68 % in mild, moderate, and severe COPD, respectively.[147]

In our study showed all patients with grade I, grade II, grade III spirometry had only mild to moderate pulmonary artery hypertension. Among patients with grade II spirometry grading 28/18(25.92%) had mild PAH, 11/108 (10.18%) had moderate PAH and 3/18 (2.77%) had severe PAH. All patients with severe PAH during acute exacerbation of COPD (3/108-2.77%) had grade IV spirometry grading.

Comparison of pre and post treatment pulmonary artery hypertension using right ventricular systolic pressure

The pathophysiology of the development of PAH in COPD is poorly understood and is likely multifactorial. The central stimulus to these processes remains chronic exposure of airways to noxious stimuli like tobacco and biomass smoke. Hypoxia has been classically considered to be the major pathogenic mechanism of pulmonary hypertension in COPD.[149,150] Chronic hypoxia induces predominant medial hypertrophy and is associated with complete reversal of pulmonary hypertension a few weeks after return to sea level[151,152] Pathologic studies of lung specimens from patients with COPD have shown all vessel wall layers to be involved extensive pulmonary vascular remodeling with prominent intimal thickening, medial hypertrophy, and muscularization of small arterioles.[153]

No studies are available on any correlation of PAH status with pre and post treatment of underlying airflow limitation and hypoxemia. In our study we analysed pulmonary artery systolic pressure before and after treatment of acute exacerbation of COPD with use of right ventricular systolic pressure which was calculated using 2D resting echocardiography.

Among 108 COPD patients who were recruited 2D resting echocardiography showed mean pre treatment RVSP of 41.66mmHg with standard deviation of 8.441mmHg where started on treatment and kept under follow up. Re evaluation of pulmonary artery hypertension status showed mean post treatment RVSP of 37.50mmHg with standard deviation of 7.587mmHg with reduction of RVSP of 4.16mmHg with 95% confidence interval 2.756-5.559 with p value of 0.000 (<0.01). Our study showed significant reduction in right ventricular systolic pressures in all three groups of mild, moderate and severe PAH patients with significant p value of <0.01 on one month follow up with optimum medical management and symptomatic improvement. This analysis showed reduction in pulmonary artery pressure with treatment of COPD. No similar studies had done in the past to compare the outcome. Hence study with larger sample size is recommended.

CONCLUSION

- Most of the patients admitted with acute exacerbation of COPD had only mild to moderate pulmonary artery hypertension.
- The pulmonary artery pressure comes down significantly on one month follow up with optimum medical management and symptomatic improvement.
- Most common ECG abnormality during an exacerbation was sinus tachycardia and close to 75% had normalized during the follow up.

- Echocardiography screening of COPD patients is beneficial to assess the pulmonary artery pressure and identify patients with severe pulmonary artery hypertension, who may benefit with addition of phospho diesterase inhibitors. Study with larger sample size is recommended.

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