(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 1, Page No: 1096-1127
January-February 2022

IJMSCR

Evaluation Of Serum Uric Acid To Creatinine Ratio As A Predictor Of Severity Of Chronic Obstructive Pulmonary Disease

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Type of Publication: Oroginal Research Paper
Conflicts of Interest: Nil

Abstract

Keywords: NIL

Introduction

COPD is a complex heterogenous disease with oxidative stress and inflammation in its development. It has emerged as a global concern and it kills more than 3 million people worldwide annually. As the global population ages, the burden of COPD increases in years to come. It continues to be an important cause of morbidity, mortality and health care costs worldwide .

The airflow obstruction is progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases[1]. Hence, degree of airflow obstruction is generally considered to be the key factor for staging COPD severity and to guide and monitor treatment The severity of COPD is usually assessed on the basis of GOLD CRITERIA with a single parameter – forced expiratory volume in one second (FEV_1). However, the rate of decline in FEV1 is influenced by the number of exacerbations of COPD and it correlates poorly to all the things that matter to COPD patient.

COPD provokes oxidative stress and lung inflammation during exacerbations rising lung parenchyma destruction and regression of lung function.it dimishes oxygen intake with consequential cellular hypoxia.Tissue hypoxia results in increase purine catabolism led into uric acid which contributes to half of the plasma antioxidative capacity.

Thus as it is a strong reducing substance and antioxidant, higher Serum Uric acid levels could be biomarker of oxidative stress,which increases significantly with occurrence of inflammation systemically. As Serum Uric Acid excretion is highly dependent on renal function,the assessment of its corrective ratio with creatinine that is Uric Acid to Creatinine is important. Serum Uric acid to creatinine ratio is the affordable biomarker that can be done easily in a primary care setting.Thus it will be helpful in determining the severity and exacerbation of COPD.

Definition

COPD is defined as a disease state which is characterized by persistent respiratory symptoms and airflow limitation that is not fully reversible.

COPD includes emphysema, an anatomically defined condition characterized by destruction of the lung alveoli with air space enlargement, chronic bronchitis, a clinically defined condition with chronic cough and phlegm and a small airway disease , a condition in which small bronchioles are narrowed and reduced in number.

Epidemiology

COPD is currently the fourth leading cause of death world wide but WHO predicted to be the third leading cause of death by 2030. The Global Burden of Disease Study reports a prevalence of 251 million cases of COPD globally in 2016. It is estimated that 3.17 million deaths were caused by COPD in 2015 worldwide which contributes 5% of all deaths globally in that year.

COPD represents an important public health challenge that can be preventable and treatable and it induces an economic and social burden that is both substantial and increase. It was the eighth leading cause of DALYs lost across the world in 2005 but by 2013,it was ranked as fifth.

Etiology

Risk factors for the development of COPD are environmental and host based. Smoking tobacco is the predominant risk factor in developed countries.Non smokers also develop COPD and women predominate in this category. other factors like indoor air pollution, passive smoking, age, level of education, tuberculosis, hospitalization for respiratory illness before the age of 10 years, number of years worked in dusty jobs and a family history of COPD.

RISK FACTORS FOR FACTORS

ENVIRONMENTAL	HOST BASED
Smoking	Genetic
Indoor air pollution	Airway hyper reactivity
Occupation	
Low socioeconomic status	

Smoking

In 1964,the Advisory Committee to the Surgeon General of the United States concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Some longitudinal studies have shown that accelerated decline in FEV1 in a dose response relationship to the intensity of smoking expressed as pack years which is defined as average number of packs of cigarettes per day multiplied by the total number of years of smoking. The higher rate of smoking among males explained likely the higher prevalence of COPD among males. Pack years of cigarette smoking is the most significant predictor of FEV1 But only 15% of the variability is explained by pack years.

Passive Or Second Hand Smoking Exposure

Exposure of children to maternal smoking results in reduced lung growth. In utero also it contributes some reductions in postnatal pulmonary functions. Though passive smoking exposure causes reduced pulmonary function, it remains uncertain that its role as risk factor in COPD.

Ambient Air Pollution

Prolonged exposure to smoke produced by biomass combustion, a mode of cooking in some countries also appears to be a significant risk factor for COPD among women in those countries. However, it is less important risk factor than smoking.

Occupational Exposures

Some occupational exposures like coal mining, gold mining and cotton textile dust have been suggested to cause increased respiratory symptoms and airflow obstruction in COPD. Some studies suggested that exposure to coal mine dust among coal miners was a significant risk factors for emphysema in both smokers and non smokers.

Respiratory Infections

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Respiratory infections are the most important causes for COPD exacerbations. Recently COPDGene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally. Some recent studies have suggested that childhood pneumonia may lead to increased risk for COPD in later life.

Airway Responsiveness

Many patients of COPD showed airway hyper responsiveness like asthma. In some elderly people, there is an overlap between persons with asthma history and smokers with COPD in terms of airway hyper responsiveness, airflow obstruction and pulmonary symptoms. They likely share common environmental and genetic factors and the chronic form in older ones can present similarly. A recent study from the Childhood Asthma Management Program identified four lung function tractories in children with persistant asthma. Asthmatics with reduced lung function early in life were more likely to meet spirometric criteria for COPD in early aduldhood. Persons with features of both asthma and COPD have been referred as asthma-COPD overlap syndrome.

Genetic Considerations

Severe α1AT deficiency is a proven genetic risk factor for COPD .It contributes approximately 1% of COPD patients and 1 in 3000 in the United States inherits this. Individuals with two Z alleles or one Z and one null allele are referred to as Piz, which is the most common form of severe α1AT deficiency. These Piz individuals often develop early onset COPD. Cigarette smokers among Piz individuals are more likely to develop COPD at early ages. Serum α1AT measurement is used to screen α1AT deficiency. Significant variability has been observed in Piz non smokers and other genetic or environmental factors likely to contribute to this variability. α1AT augmentation therapy can be given as weekly IV infusion for these Piz individuals.

Genome Wide Association Studies (GWAS) have identified more than 20 regions of genome for COPD susceptibility loci including HHIP gene in chromosome 4, IRBE2 gene and nicotinic acetyl choline receptor regulatory gene in chromosome 15 and FAM13A gene.

Pathogenesis

A major physiologic change in COPD, Airflow limitation can result from small airway disease and emphysema. A hallmark of advanced COPD can result from pathogenic changes like small airways narrowed by hyperplasia of cells ,mucus accumulation ,fibrosis and extensive destruction of small airways.

The pathogenesis of emphysema comprises of series of four interrelated events:1.Chronic inflammation in chronic exposure to cigarette smoke in genetic susceptible individuals 2. Extracellular matrix proteolysis 3.Cell death 4. Ineffective repair.

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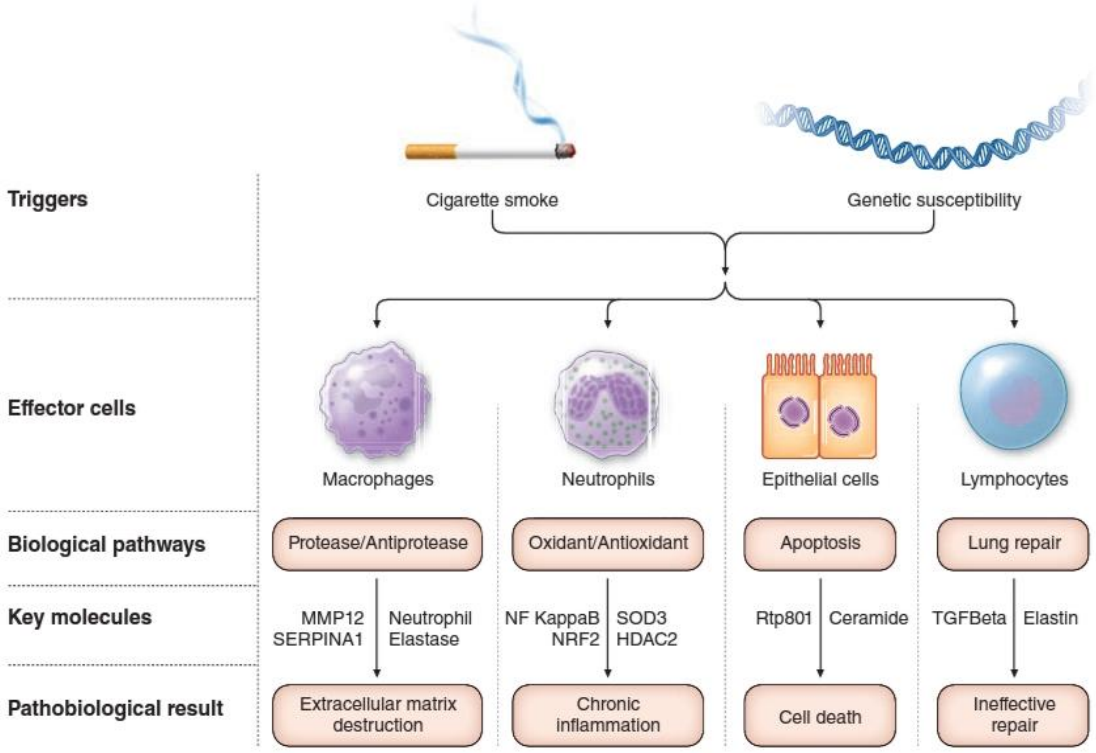

Chronic inflammation and Extracellular matrix proteolysis

Oxidative stress is a key component of COPD pathology. The transcription factor NRF2, a major regulator of oxidant-antioxidant balance and SOD3 a potent antioxidant have been implicated in emphysema. Mitochondrial dysfunction in COPD may worsen oxidative stress. Macrophage activation occurs via oxidant induced inactivation of histone deacetylase-2(HDAC2) exposing nuclear factor kappa B sites(NRF2) resulting in transcription of MMP and proinflammatory cytokines such as IL-8and TNFα which leads to neutrophil recruitment.CD8+ T cells also recruited which releases interferon inducible protein 10 and which in turn leads to macrophage production of macrophage elastase(MMP-12).

The elastase-antielastase hypothesis postulation suggested that the balance of elastin degrading enzymes and their inhibitors determines of susceptibility to lung destruction. Proteolytic cleavage products of elastin as a macrophage chemokine and proline-glycine-proline proteolytic cleavage of collagen as a neutrophil chemokine contributes to airspace destruction.

There is some evidence that autoimmune mechanisms may promote disease by increasing B cells and lymphoid follicles. IgG antibodies against elastin and pulmonary epithelium have the potential to mediate cytotoxicity.

Cell Death

Several mechanisms including excessive ceramide production and Rtp801 inhibition of mTOR leads to cell death as well as inflammation. The genetic determinants of COPD identified by GWAS,Hedge hog interacting protein in a murine model leads to aging related emphysema.

Ineffective Repair

Uptake of apoptotic cells by macrophages normally results in production of growth factors and dampens inflammation promoting lung repair. Cigarette smoke

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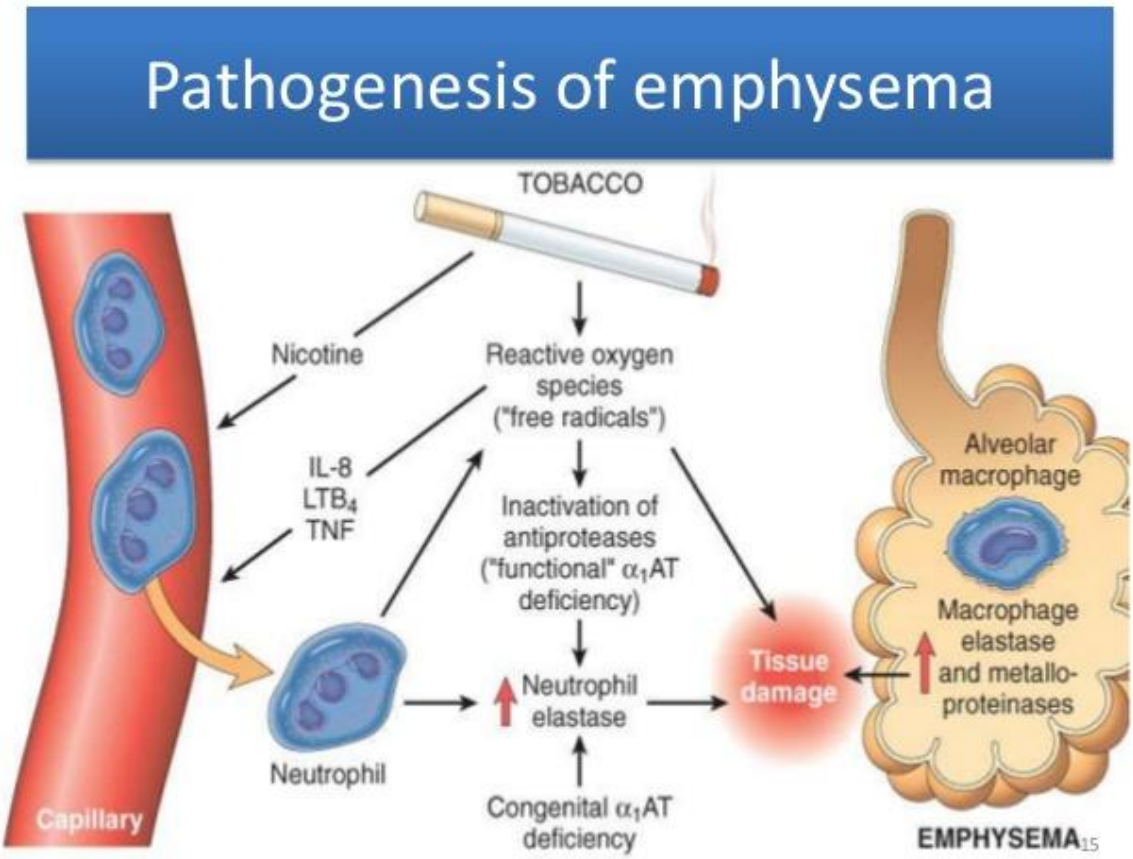
impairs macrophage upatake of apoptotic cells limiting repair.

Pathology

Cigarette smoking may affect the large airways, small airways<2mm in diameter and alveoli. Changes in large airways cause cough and sputum production, while changes in small airways and alveoli are responsible for physiological alterations. The early stages of COPD primarily associated with medium and small airway disease with majority of GOLD1 and GOLD2 demonstrating little or no emphysema, whereas the advanced stages of COPD (GOLD3 and GOLD4) are typically characterized by extensive emphysema.



Large Airways

Cigarette smoke exposure results in mucus gland enlargement and goblet hyperplasia, leading to cough and mucus production that defines chronic bronchitis not airflow limitation. Squamous metaplasia in bronchi predisposing to disruption of mucociliary clearance and carcinogenesis. Some may have smooth muscle hypertrophy and bronchial hyper reactivity leading to airway limitation.

Small Airways

Characteristic cellular changes in small airways<2mm diameter showed goblet cell metaplasia,with replacing surfactant secreting club cells.Smooth muscle hypertroph , luminal narrowing by fibrosis, excess mucus, edema and cellular infiltration also have been seen. Reduced surfactant may increase surface tension at the air tissue interface causing airway narrowing and collapse. Narrowing and drop out of small airways precede the onset of emphysematous destruction.

Lung Parenchyma

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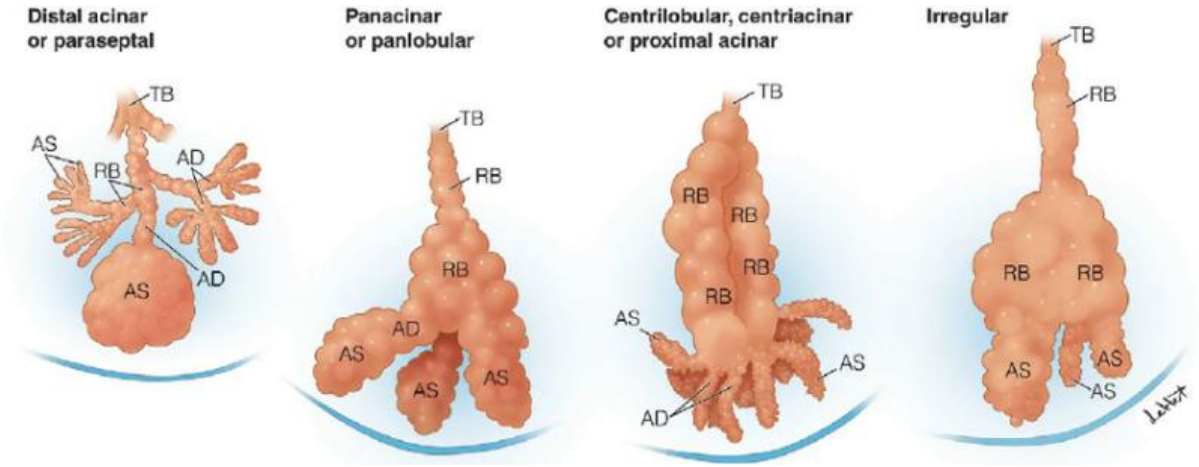
Emphysema is characterized by destruction of gas exchanging air spaces like the respiratory bronchioles, alveolar ducts and alveoli. Their walls become perforated, obliterated with coalescence of delicate alveolar structure into large emphysematous air spaces. Large number of macrophages accumulate in respiratory bronchioles in smokers which is five times higher than non smokers.

Emphysema is classified into distinct pathological types : centrilobular, panlobular , paraseptal and irregular.



Centrilobular emphysema is the most common form among smokers which is characterized by enlarged air spaces along with respiratory bronchioles.It is often focal and is usually prominent in upper and superior segments of lower lobes.

Panlobular emphysema defined as abnormally large air spaces evenly distributed within and across acinar units.It is commonly observed in patients with α1AT deficiency which has a lower lobe predilection.

Paraseptal emphysema occurs in 10%-15% patients and is distributed along the pleural margins with relative sparing of central region of the lungs.It is commonly associated with significant airway inflammation.

Pathophysiology

Persistent reduction in Forced expiratory flow rates is the most typical finding in COPD. Increases in Residual volume and the Residual volume/total lung capacity ratio, ventilation-perfusion mismatch also can occur.

Airflow Obstruction

Airflow limitation or obstruction is typically determined by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity. The parameters from spirometry include the volume of air exhaled within the first second of forced expiratory maneuver (FEV1) and the total volume of air exhaled during the entire spirometric maneuver (FVC).The reduced FEV1 in COPD only shows improvement upto15% after inhaled bronchodilators.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as FEV1/FVC less than 0.7 and FEV1 ≤80%predicted and categorised into 4 stages based on severity on airflow obstruction.

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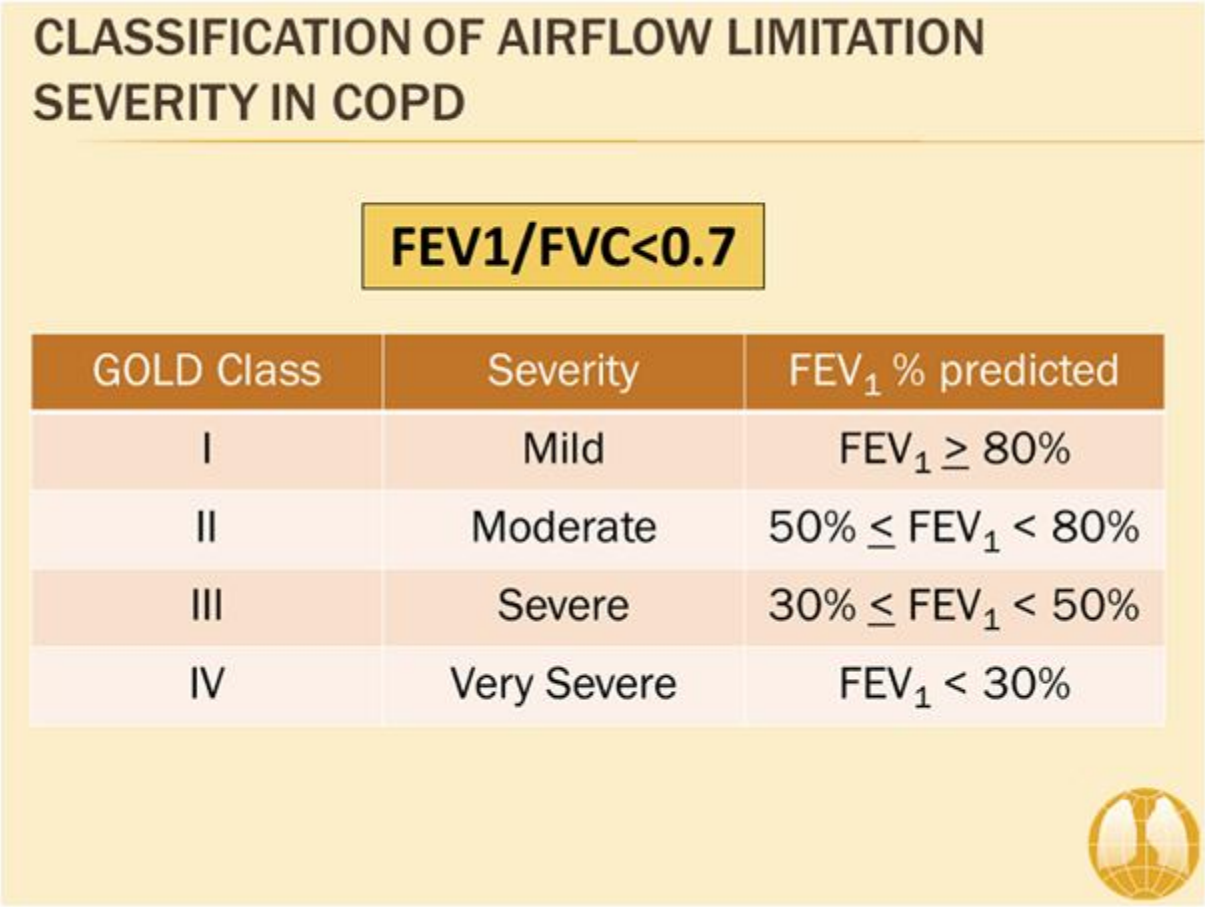

Hyperinflation

Lund volumes are routinely assessed in pulmonary function testing. In COPD there is "air trapping"(increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation (increased total lung capacity) in the disease. Hyperinflation of the thorax during tidal breathing preserves maximum expiratory airflow ,as lung volume increase elastic recoil pressure increases and airways enlarge so that airway resistance decreases.

Hyperinflation can push the diaphragm into a flattened position with a number of effects. First by decreasing te zone of apposition between the diaphragm and the abdominal wall, ineffective positive abdominal pressure during inspiration hinders rib cage movement and impairs inspiration. Secondly the shortened muscle fibers of the flattened diaphragm generate ineffective inspiratory pressure. Third, the flattened diaphragm must generate greater tension to develop the transpulmonary pressure required to produce tidal breathing. Fourth, the inspiratory muscles must work to overcome the resistance of the thoracic cage to further inflation.

Gas Exchange

Non uniform ventilation and ventilation-perfusion mismatching are the characteristic of COPD reflecting heterogenous nature of the disease process within the airways and lung parenchyma. The partial pressure of oxygen in arterial blood(PaO2) remains normal until FEV1 is decreased to less than 50% predicted. Elevated arterial level of CO2(PaCO2) is expected to rise the FEV1is <25%.Pulmonary hypertension and right ventricular failure typically occurs who have marked decrease in FEV1<25% of predicted and chronic hypoxemia(PaO2<55mmHg).However, recent studies suggested that some patients will develop COPD independent of COPD severity.

Clinical Presentation

The three common symptoms in COPD are cough, sputum production and exertional dyspnoea. In early stages, patients have normal physical examination. Smokers may have an odour of smoke or nicotine staining of fingernails.In patients with severe disease,

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the physical examination reveals expiratory wheeze. Patient may have barrel chest due to hyperinflation. They may attain characteristic "Tripod" position and they may develop cyanosis in the lips and nail beds.

The patients with predominant emphysema (pink puffers) are thin and non cyanotic at rest and have prominent use of accessory muscles and patients with predominant chronic bronchitis (blue bloaters) are heavy and cyanotic but currently most patients have elements of both. Advanced disease may be accompanied by cachexia with weight loss, bitemporal wasting and diffuse loss of subcutaneous adipose tissue. Some patients with advanced disease have paradoxical inward movement of the rib cage with inspiration , the result of alteration of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation.

Signs of overt right heart failure termed cor pulmonale may be infrequent. Clubbing is not a sign of COPD and its presence alerts the development of lung cancer.

Laboratory Findings

Pulmonary function testing show airflow obstruction with a reduction in FEV1/FVC. The degree of airflow obstruction is an important prognostic factor in COPD and it is the basis for the GOLD spirometric severity classification. Artetial blood gases and oximetry may demonstrate resting and exertional hypoxemia. An elevated hematocrit suggests the presence of chronic hypoxemia, as does te presence of signs of right ventricular hypertrophy.

Radiographic studies assist in classifying the types of COPD. Obvious bullae, paucity of parenchymal markings or hyperlucency, flattening of diaphragm on chest Xray suggests the presence of emphysema. Chest CT scan is the definitive test for establishing pattern of emphysema, involvement of medium and large airways.

Measurement of the serum α1AT level can be used as an initial test in α1AT deficiency in COPD patients. Molecular genotyping of DNA can be performed for the common PI alleles(M,S and Z).

Treatment

The two main goals of therapy are to provide sympatomatic relief and reduce future risk. The current protocol suggested categories of COPD based on respiratory symptoms and risk for exacerbations. Response to therapy should be assessed and decisions should be made whether or not to continue.

COPD severity assessment are based on respiratory symptoms (mMRC or CAT scales) and annual frequency of COPD Exacerbations. mMRC-Modified Medical Research Council provides grading of degree of breathlessness;0-only with strenuous activity;1-hurrying on level ground or walking up a slight hill;2-walk slower than peers or stop walking at their own pace;3-walking about 100yards or after a few minutes on level ground;4-too breathless to leave the house or when dressing.CAT-COPD Assessment Test. An 8 item COPD health questionare about cough, phlegm, chest tightness, dyspnoea on one flight of stairs, limitation in home activities, confidence in leaving the home, sleep and energy. Total score is 0-40.

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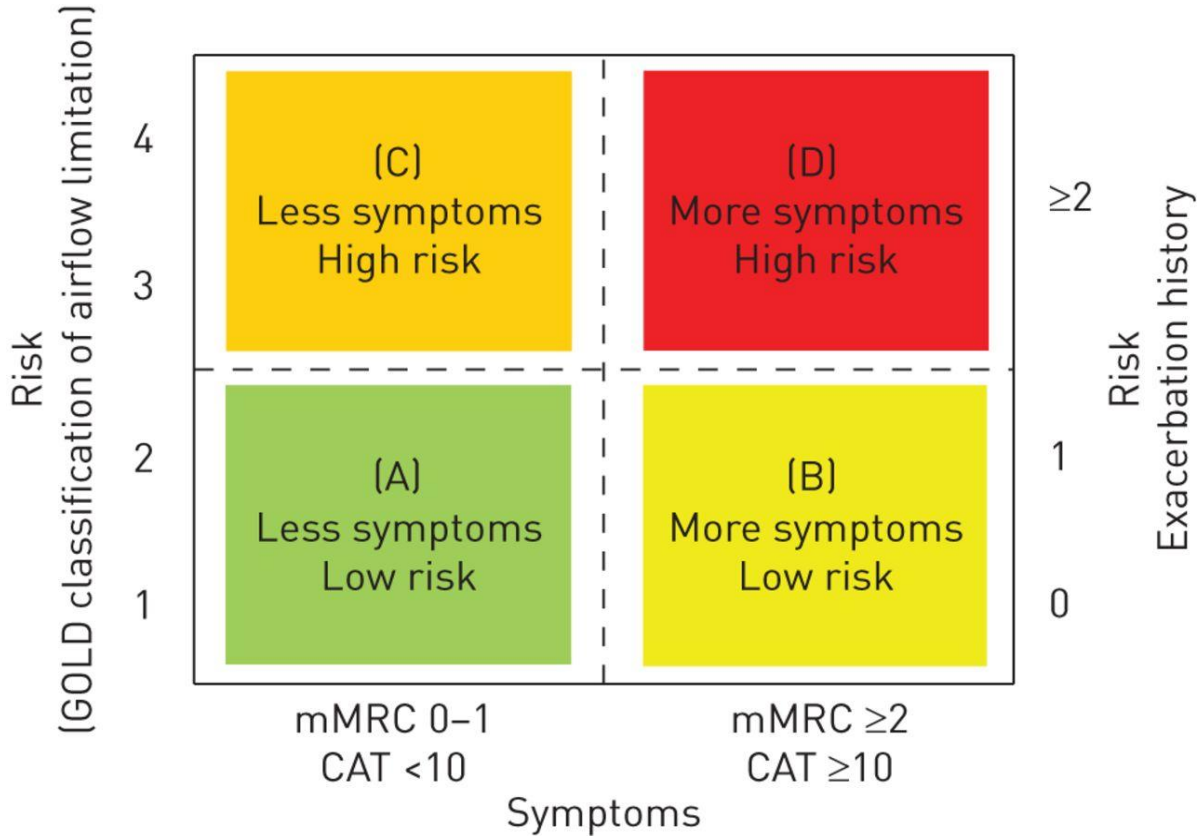

Smoking cessation, oxygen therapy in chronically hypoxic patients and lung volume reduction surgery in selected patients of emphysema have been implicated to improve survival of patients in COPD.

Smoking cessation

Some studies suggested that stopping smoking revealed a significant improvement in the rate od decline in pulmonary function. There are some pharmacological approach to stop smoking such as nicotine replacement therapy as gum transdermal patch, lozenge, inhaler and nasal spray; nicotinic acid receptor agonist/antagonist varenicline and bupropion.

Bronchodilators

Bronchodilators are the primary treatment for all COPD patients and used for symptomatic benefit and to reduce exacerbations. The inhaled route is preferred because systemic side effects are less. In symptomatic patients, both long acting agents and as needed short acting medications are indicated.

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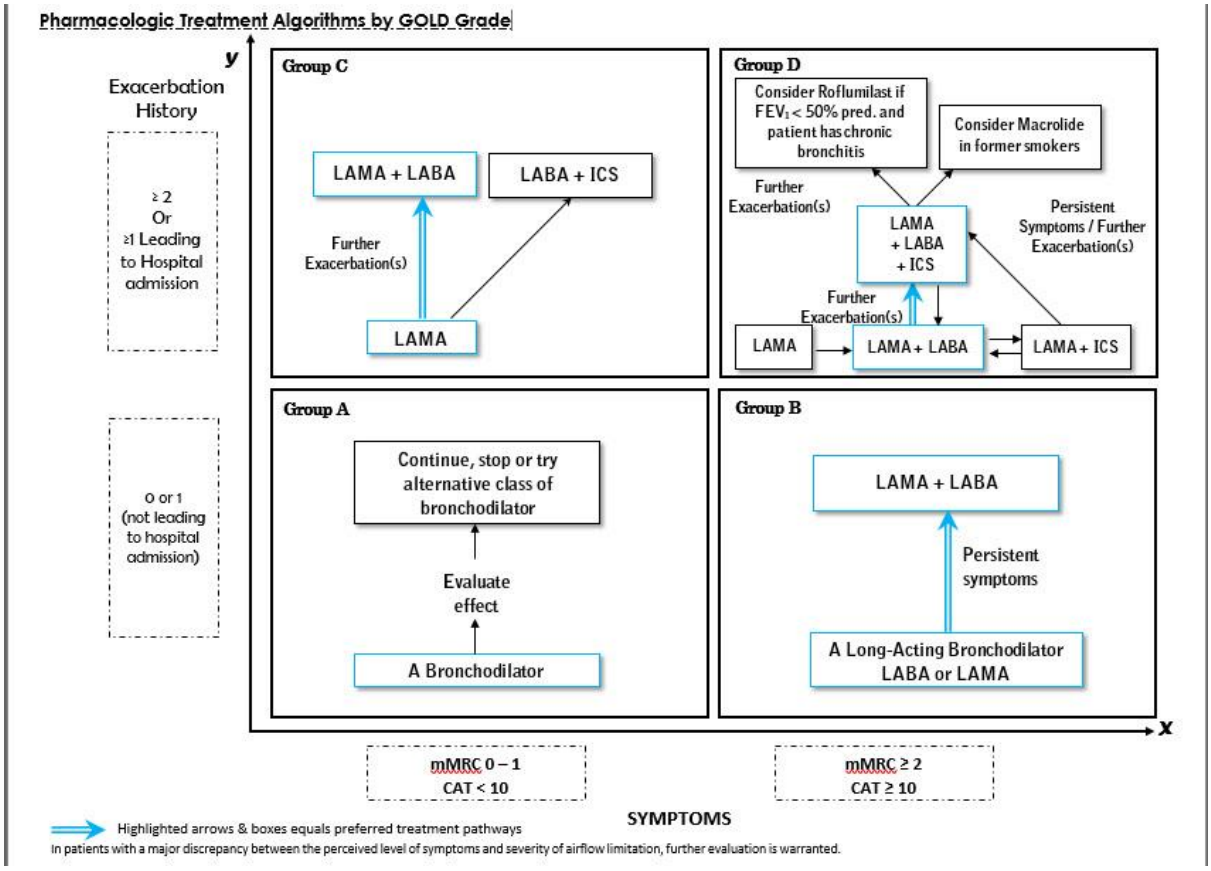

Anticholinergic Muscarinic Antagonists

Short acting ipratropium bromide improve symptoms with acute improvement in FEV1. Long acting muscarinic antagonists (LAMA, including aclidinium, glycopyrulate, tiotropium and umeclidinium) improve symptoms and reduce exacerbations. Dry mouth is the only minor side effect.

Beta agonist

Short acting beta agonists ease symptoms with acute improvements in lung function. Long acting agents (LABA) provide symptomatic benefit and reduce exacerbation. Currently available long acting inhaled β agonists are arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol. The main side effects are tremor and tachycardia.

Inhaled corticosteroids

The main role of ICS is to reduce exacerbations. ICS can be initiated in patients with frequent exacerbations defined as two or more exacerbations per year. In stable patients, ICS can be withdrawn and it may cause a small decline in lung function.

Oral glucocorticoids

The chronic use of oral glucocorticoids is not recommended in view od unfavourable risk/benefit ratio.The significant side effects are osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection.

Theophylline

Theophylline produces modest improvement in airflow and vital capacity but it is not first line therapy due to its side effects and drug interactions. Nausea, tachycardia and tremors are the adverse effects .Monitoring of blood theophylline levels is required to minimize its toxicity.

PDE4 Inhibitors

The selective phosphodiesterase 4 inhibitor roflumilast has been demonstrated to reduce exacerbation in severe COPD.

Antibiotics

There are some strong evidence implicating bacterial infection as a precipitant of an exacerbation. The macrolide treated cohort study in 6 months

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demonstrated a reduced exacerbation frequency with hazard ratio of 0.73.

Oxygen

Supplemental O2 is the only pharmacologic therapy in decreasing mortality unequivocally in COPD. In patients with resting hypoxemia≤88% or ≤89% with signs of pulmonary hypertension or right heart failure, the judicial use O2 has been demonstrated to have a significant impact on mortality.

Mechanical ventilation

The initiation of non invasive positive pressure ventilation in patients with respiratory failure defined as Paco2.45mmhg,results in significant reduction in mortality rate, need for intubation, hospital stay. Invasive mechanical ventilation via endotracheal tube is indicated in patients with severe respiratory distress. the mortality of the patients requiring mechanical ventilatory support is 17% -30%.

α1AT Augmentation Therapy

Specific α1AT therapy may be indicated in severe deficiency of α1AT deficiency to reduce the progression of emphysema. Indication for α1AT Augmentation therapy is serum α1AT level <50mg/dl. As only a small fraction of α1AT deficiency patients will develop COPD, it is not recommended in severe α1AT deficiency patients with normal pulmonary function and normal chest CT scan.

Pulmonary rehabilitation

It is a comprehensive treatment program that incorporates exercise, education, psychosocial and nutritional counselling. Pulmonary rehabilitation has been implicated to improve quality of life, dyspnoea and exercise capacity.

Lung Volume Reduction Surgery

LVRS surgeries may be indicated to remove the most emphysematous parts of lung in carefully selected patients to improve exercise, lung function and survival. Patients with upper lobe predominant emphysema and a low post rehabilitation exercise capacity are capable to benefit from reduction surgeries.

Lung transplantation

COPD is the second leading indication for lung transplantation. The ideal candidates for lung transplantation should have very severe airflow limitation, severe disability despite maximal medical therapy and free of significant comorbid conditions like cardiac, liver or renal diseases.

Aim

To assess whether Serum Uric Acid to Creatinine Ratio can be used to assess the severity of COPD in stable patients

Objectives

1.To assess Serum Uric Acid to Creatinine Ratio in stable COPD patients.

2.To study the correlation of Serum Uric Acid to creatinine ratio with GOLD criteria in COPD patients.

Review Of Literature

A study by Nagihan Durmus Kocak et al proved 110 patients with COPD having higher Serum Uric Acid to Creatinine ratio in predicting exacerbation risk and disease severity

Another study done by Hesham A AbdelHalim et al evaluated 283 patients and 123 healthy controls and proved that Serum Uric Acid to Creatinine ratio have a supplementary role in anticipating the severity and in predicting future exacerbations.

Yet in an another prospective study showed that Serum Uric Acid to Creatinine Ratio values were found to be increase along with increasing severity of hypoxemia.

Another study by Lada Rumora et al , after evaluating 153 COPD patients, Serum Uric Acid to Creatinine Ratio present significant correlation with important variables expressing COPD severity both on exacerbation and in stable condition. These patients presented more exacerbations and hospitalisations in the year of follow up.

Another recent cross sectional study done by Dishan Y P et al among 80 COPD patients in puducherry has shown Serum Uric Acid/Creatinine Ratio were increased which correlates with severity of obstruction and it is useful tool in predicting the morbidity and mortality in COPD patients.

Materials And Methods

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Setting

Department of General Medicine, Government kilpauk Medical College, Chennai.

Institutional Ethical Committee Clearance : Obtained

Study Design

Prospective Study was chosen to assess the correlation of serum uric acid to creatinine ratio with severity of COPD by GOLD CRITERIA.

Study Period

SEPTEMBER 2019 TO AUGUST 2020

Study Population

Patients diagnosed as COPD based on spirometry from the department of medicine, Government Kilpauk medical college & hospital, Chennai during the period, were included in the study.

Sample Size

$$n = \frac{2SD^2(Z\alpha/2 + Z\beta)^2}{d^2}$$

where n-sample size

SD- Standard Deviation from previous study

Zα/2 - 1.96 at type 1 error of 5%

Zβ - 0.842 at 80% power

D - effect size -difference between mean values

$$= \frac{2 * 2.47^2 * (1.96+0.842)^2}{1.38^2} = 50 \text{ per group}$$

Thus Sample size of 100 was calculated to have 80% chance (type I error of 5%/p-0.05)

Inclusion Criteria

Patients with symptoms suggestive of COPD as diagnosed by spirometry in stable condition.

MALE patients age more than 40 years

Exclusion Criteria

Patients with acute exacerbation of COPD

H/O Exacerbation in the past 4 weeks

Spirometry proved Bronchial asthma.

Known comorbidities –systemic hypertension, cardiovascular diseases,diabetes mellitus

Inability to perform spirometry or 6 minute walk test

Chronic kidney disease

Gout

Patients on drugs that might affect Serum uric acid levels like allopurinol, probenecid, febuxostat, losartan, fenofibrate, pyrazinamide, ethambutol, cyclosporine, heparin

Females

Methodology

The patients diagnosed as having COPD according to the GOLD guidelines attending Out patient department, department of General Medicine were screened based on inclusion and exclusion criteria. The eligible patients were explained about our study and those who all were willing to participate were enrolled in our study.

Written informed consent were obtained after for each enrolled patient.

Detailed history of smoking, occupation, previous exacerbations/hospitalisations , personal and family medical history were obtained .

Pack years were calculated based on their smoking history and by anthropometry measurements BMI were calculated.

Under aseptic precautions, blood samples were collected for Serum Uric Acid and creatinine between 10am to 12pm to minimize the diurnal variation.

Serum Uric Acid was measured by Uricase based enzymatic oxidative method and Serum Creatinine was measured by modified Jaffe's method. Serum Uric acid Creatinine ratio of each patient calculated.

Spirometry was performed with equipment which met the American Thoracic Society performance criteria . The test was done as per the ATS guidelines after giving salbutamol nebulization in all cases. Predicted FEV_1 and forced vital capacity (FVC) standardized for ethnicity, height, age and sex was used. FEV1 /FVC and predicted FEV1% post bronchodilator were calculated.

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Patients were categorised by GOLD STAGING based on spirometry and GOLD ABCD assessment based on history.

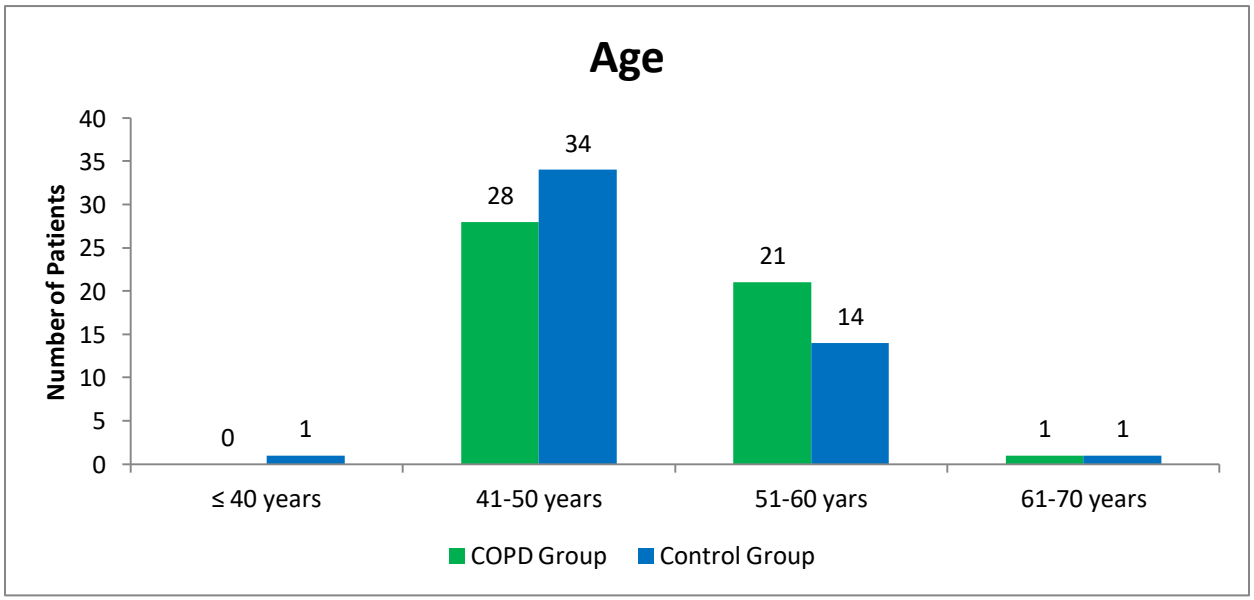
Master chart was made ready with all the above details for statistical analysis.

After applying the inclusion and exclusion criteria 50 patients diagnosed with COPD following GOLD guidelines as diagnostic criteria were selected for the study along with 50 patients without COPD as controls, to assess whether Serum Uric Acid to Creatinine Ratio can be used to predict the severity of COPD in stable patients.

Groups	Description	Number
COPD Group	Patients clinically diagnosed to have COPD (GOLD guidelines as diagnostic criteria)	50
Control Group	Normal participants	50

Data collected from selected subjects was tabulated, analysed and interpreted by using descriptive and inferential statistics based on the formulated objectives of the study. Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired test. Categorical variables were analysed with the Chi-Square Test and Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS Version 16. Microsoft Excel 2007.was used to generate charts.

Results And Observations



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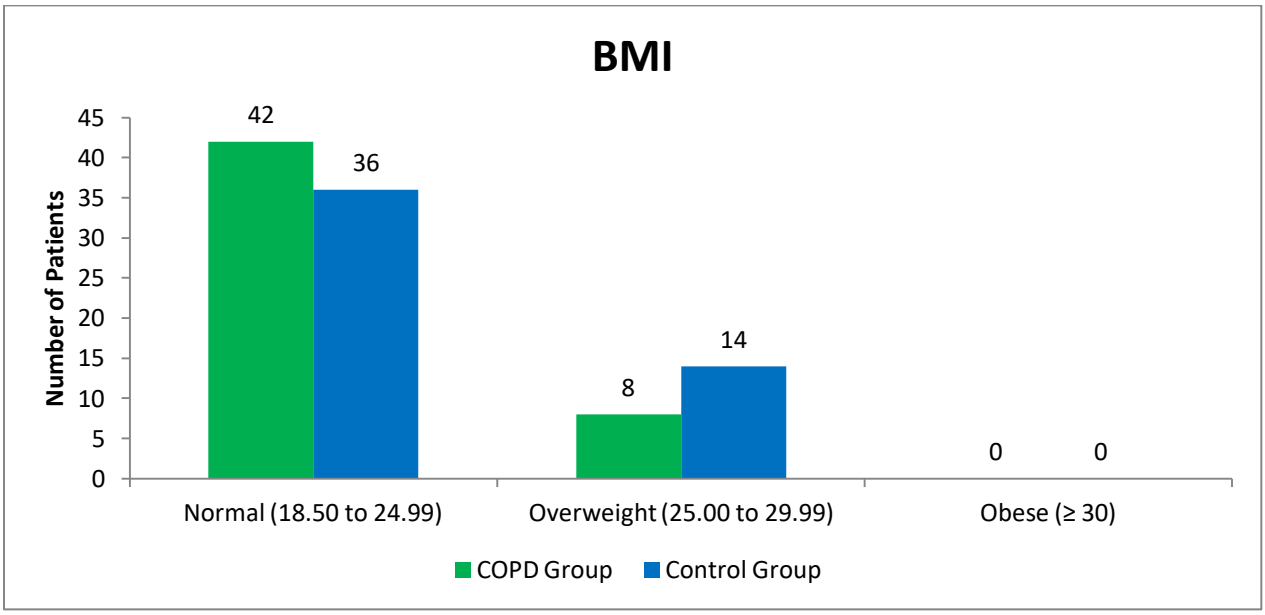
Age	COPD Group	%	Control Group	%
≤ 40 years	0	0.00	1	2.00
41-50 years	28	56.00	34	68.00
51-60 years	21	42.00	14	28.00
61-70 years	1	2.00	1	2.00
Total	50	100.00	50	100.00

Age Distribution	COPD Group	Control Group
Mean	49.92	48.08
SD	5.20	5.91
P value Unpaired t Test	0.102	

On analysis of age distribution between study groups, most of the COPD Group patients fell in the 41-50 years age category (56.00%) followed by 51-60 years age category (42.00%) with a mean age of 49.92 years. Similarly most of the control Group patients fell in the 41-50 years age category (68.00%) followed sby 51-60 years age category (28.00%) with a mean age of 48.08 years. There was no statistically significant difference in relation to age distribution between the study groups with a p value of >0.05 as per unpaired t test.

BMI



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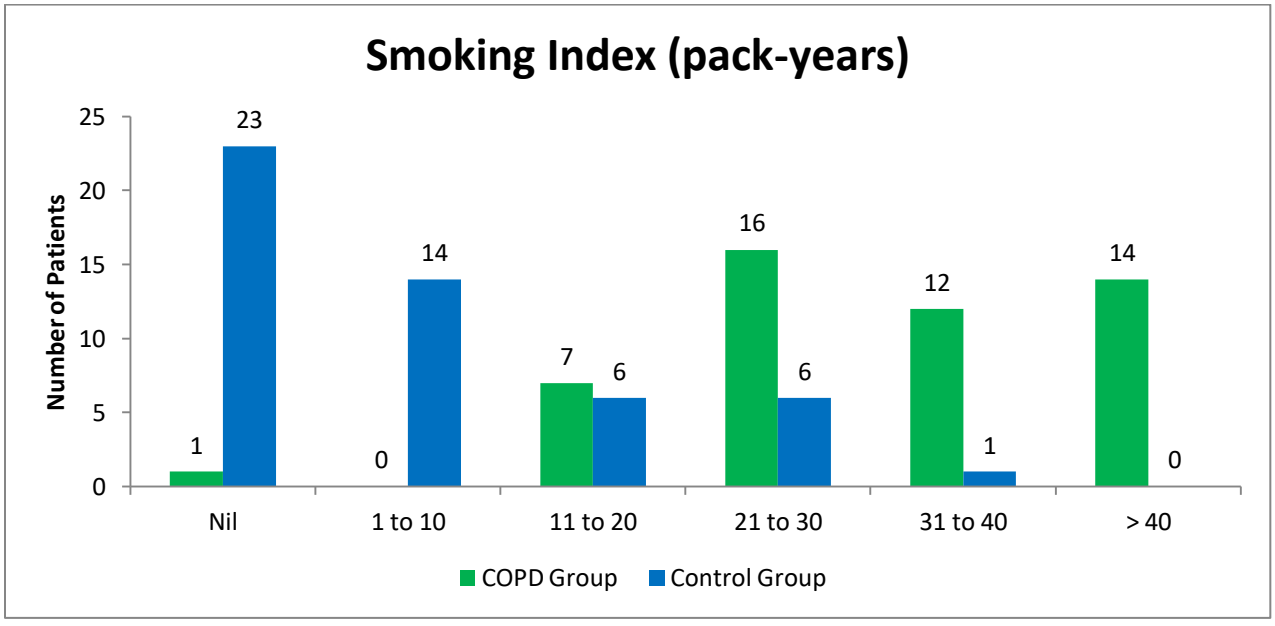
BMI	COPD Group	%	Control Group	%
Normal (18.50 to 24.99)	42	84.00	36	72.00
Overweight (25.00 to 29.99)	8	16.00	14	28.00
Obese (≥ 30)	0	0.00	0	0.00
Total	50	100.00	50	100.00

BMI Distribution	COPD Group	Control Group
Mean	23.12	24.00
SD	2.01	1.67
P value Unpaired t Test	0.019	

On analysis of BMI distribution between study groups, most of the COPD Group patients fell in the normal BMI category(84.00%) followed by overweight BMI category (18.00%) with a mean BMI of 23.12. Similarly most of the control Group patients fell in the normal BMI category (72.00%) followed by overweight BMI category (28.00%) with a mean BMI of 24.00. There was a statistically significant difference seen in relation to BMI distribution between the study groups with a p value of <0.05 as per unpaired t test.



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Smoking Index (pack-years)	COPD Group	%	Control Group	%
Nil	1	2.00	23	46.00
1 to 10	0	0.00	14	28.00
11 to 20	7	14.00	6	12.00
21 to 30	16	32.00	6	12.00
31 to 40	12	24.00	1	2.00
> 40	14	28.00	0	0.00
Total	50	100.00	50	100.00

Smoking Index (pack-years) Distribution	COPD Group	Control Group
Mean	35.86	7.38
SD	14.38	9.81
P value Unpaired t Test	<0.001	

On analysis of smoking index distribution between study groups, most of the COPD Group patients fell in the 21 to 30 pack years smoking index category (32.00%) followed by > 40 pack years smoking index category (28.00%) with a mean smoking index of 35.86. Similarly most of the control Group patients fell in the nil pack years smoking index category (46.00%) followed by 1-10 pack years smoking index category (28.00%) with a mean smoking index of 7.38. There was a statistically significant difference seen in relation to smoking index distribution between the study groups with a p value of <0.05 as per unpaired t test.

mMRC Dyspnea Scale

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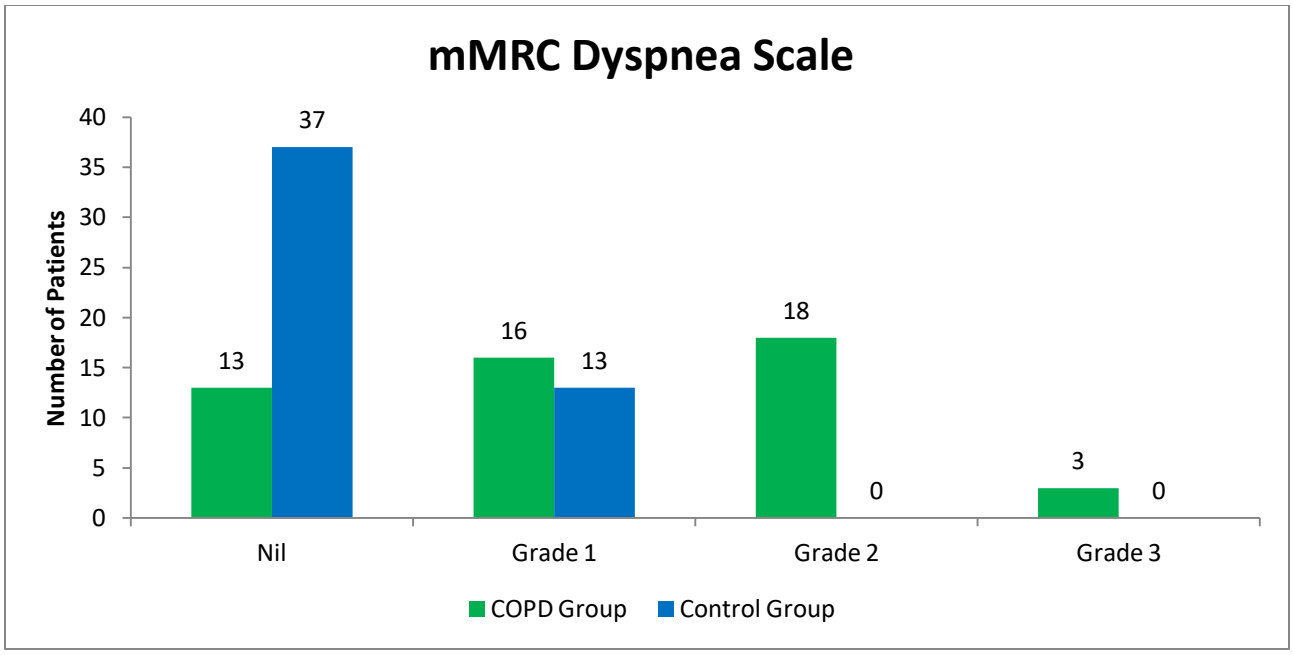

mMRC Dyspnea Scale	COPD Group	%	Control Group	%
Nil	13	26.00	37	74.00
Grade 1	16	32.00	13	26.00
Grade 2	18	36.00	0	0.00
Grade 3	3	6.00	0	0.00
Total	50	100.00	50	100.00
P value Fishers Exact Test	<0.001			

On analysis of mMRC Dyspnea Scale status between study groups, most of the COPD Group patients had higher incidence of Grade 2 dyspnea (36.00%) followed by Grade 1 dyspnea (32.00%). Similarly most of the control Group higher had higher incidence of no dyspnea (74.00%) followed by Grade 1 dyspnea (26.00%). There was a statistically significant difference seen in relation to mMRC Dyspnea Scale status between the study groups with a p value of <0.05 as per fishers exact test.

FEV1/FVC %

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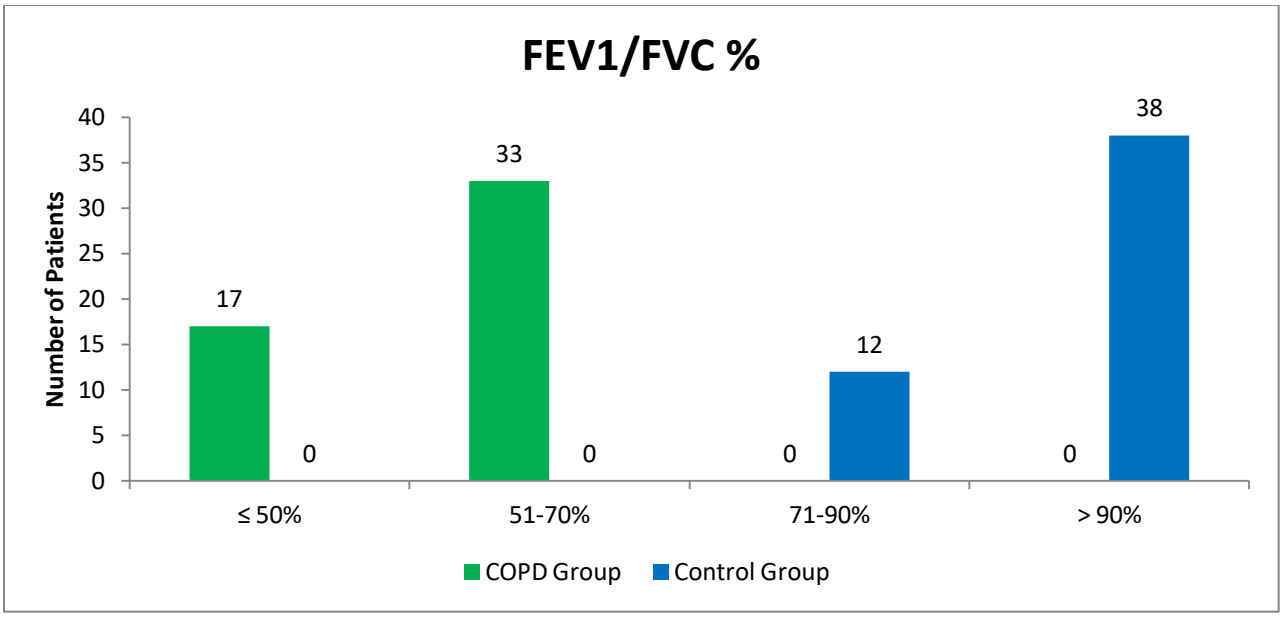

FEV1/FVC %	COPD Group	%	Control Group	%
≤ 50%	17	34.00	0	0.00
51-70%	33	66.00	0	0.00
71-90%	0	0.00	12	24.00
> 90%	0	0.00	38	76.00
Total	50	100.00	50	100.00

FEV1/FVC % Distribution	COPD Group	Control Group
Mean	53.26	97.18
SD	11.95	9.61
P value Unpaired t Test	<0.001	

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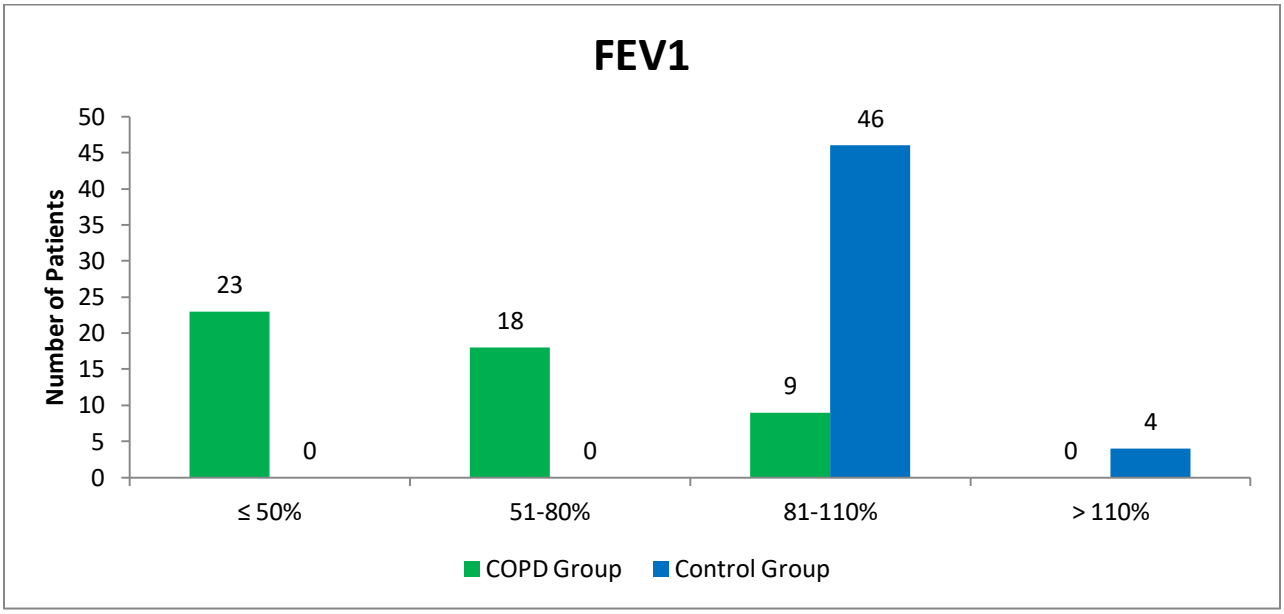
On analysis of FEV1/FVC % distribution between study groups, most of the COPD Group patients fell in the 51-70% FEV1/FVC % category (66.00%) followed by ≤ 50% FEV1/FVC % category (34.00%) with a mean FEV1/FVC % of 53.26. Similarly most of the control Group fell in the > 90% FEV1/FVC % category (76.00%) followed by 71-90% FEV1/FVC % category (24.00%) with a mean FEV1/FVC % of 53.26. There was a statistically significant difference seen in relation to FEV1/FVC % distribution between the study groups with a p value of <0.05 as per unpaired t test.

FEV1



FEV1	COPD Group	%	Control Group	%
≤ 50%	23	46.00	0	0.00
51-80%	18	36.00	0	0.00
81-110%	9	18.00	46	92.00
> 110%	0	0.00	4	8.00
Total	50	100.00	50	100.00

FEV1 Distribution	COPD Group	Control Group
Mean	54.38	98.60
SD	21.29	8.29
P value Unpaired t Test	<0.001	

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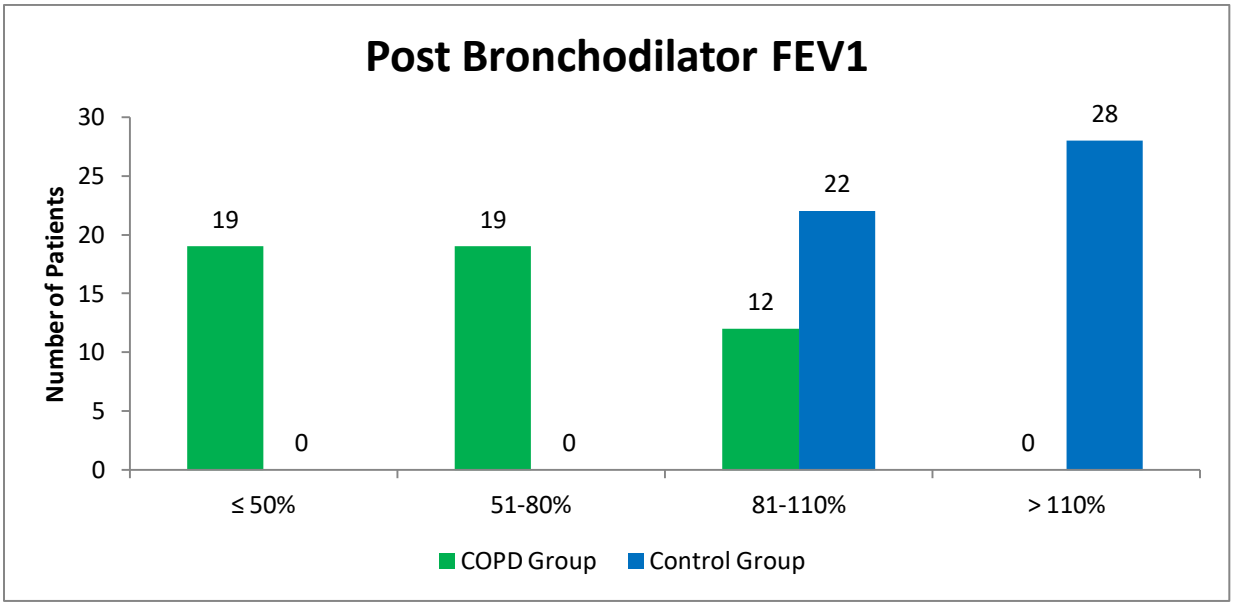
On analysis of FEV1 distribution between study groups, most of the COPD Group patients fell in the ≤ 50% FEV1 category (46.00%) followed by 51-70% FEV1 category (36.00%) with a mean FEV1of 54.38. Similarly most of the control Group fell in the 81-110% FEV1 category (92.00%) followed by > 110% FEV1 category (8.00%) with a mean FEV1 of 98.60. There was a statistically significant difference seen in relation to FEV1 distribution between the study groups with a p value of <0.05 as per unpaired t test.

Post Bronchodilator FEV1



Post Bronchodilator FEV1	COPD Group	%	Control Group	%
≤ 50%	19	38.00	0	0.00
51-80%	19	38.00	0	0.00
81-110%	12	24.00	22	44.00
> 110%	0	0.00	28	56.00
Total	50	100.00	50	100.00

Post Bronchodilator FEV1 Distribution	COPD Group	Control Group
Mean	63.12	111.84
SD	23.48	7.93

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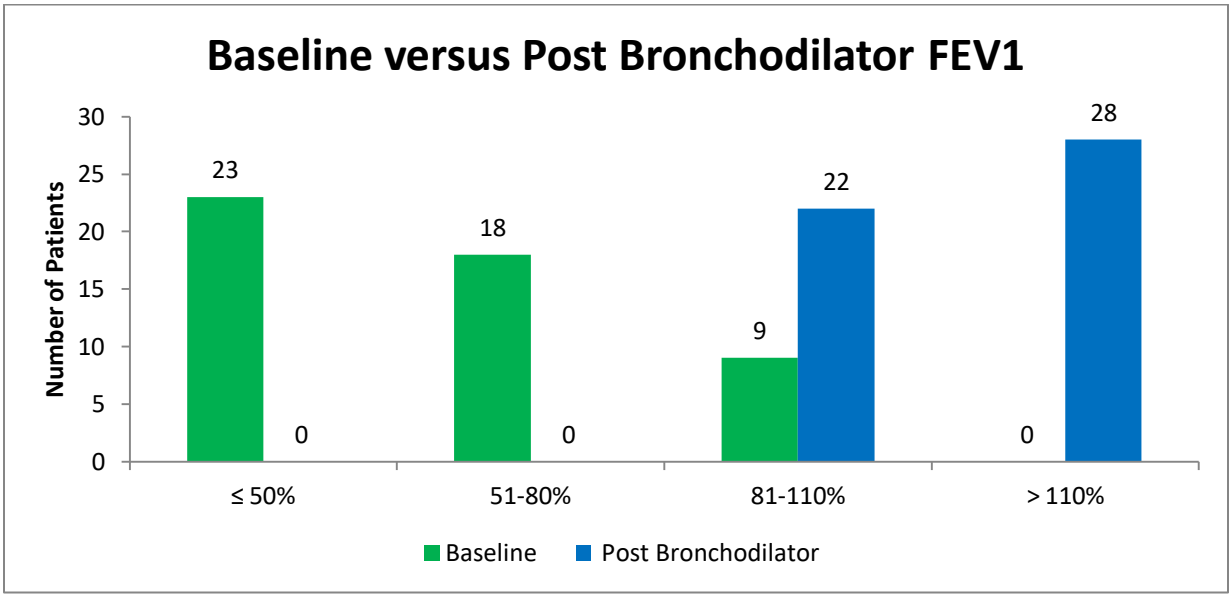
P value Unpaired t Test	<0.001

On analysis of post bronchodilator FEV1 distribution between study groups, most of the COPD Group patients fell equally in ≤ 50% post bronchodilator FEV1 category (38.00%) and 51-70% post bronchodilator FEV1 category (38.00%) with a mean post bronchodilator FEV1of 63.12. Similarly most of the control Group fell in the > 110% post bronchodilator FEV1 category (56.00%) and followed by 81-110% post bronchodilator FEV1 category 44.00%) with a mean post bronchodilator FEV1of 118.84. There was a statistically significant difference seen in relation to post bronchodilator FEV1 distribution between the study Baseline versus Post Bronchodilator FEV1.



Baseline versus Post Bronchodilator FEV1	Baseline	%	Post Bronchodilator	%
≤ 50%	23	46.00	0	0.00
51-80%	18	36.00	0	0.00
81-110%	9	18.00	22	44.00
> 110%	0	0.00	28	56.00
Total	50	100.00	50	100.00

Baseline versus Post Bronchodilator FEV1	Baseline	Post Bronchodilator

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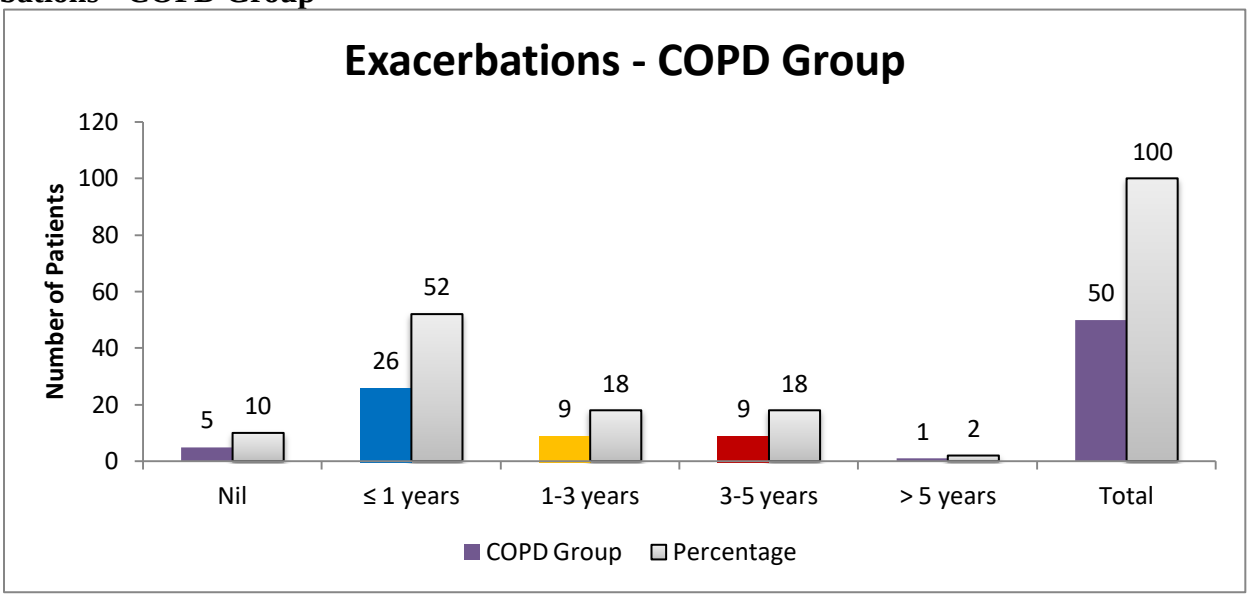
Distribution		
Mean	54.38	63.12
SD	21.29	23.48
P value Paired t Test	0.027	

On analysis of baseline versus post bronchodilator FEV1 distribution between study groups, the mean baseline FEV1 was 54.38 and the mean post bronchodilator FEV1 was 63.12. There was a statistically significant difference in relation to mean baseline versus post bronchodilator FEV distribution with a p value of <0.05 as per paired t test.

Exacerbations - COPD Group



Exacerbations - COPD Group	COPD Group	Percentage
Nil	5	10.00
≤ 1 years	26	52.00
1-3 years	9	18.00
3-5 years	9	18.00
> 5 years	1	2.00
Total	50	100.00

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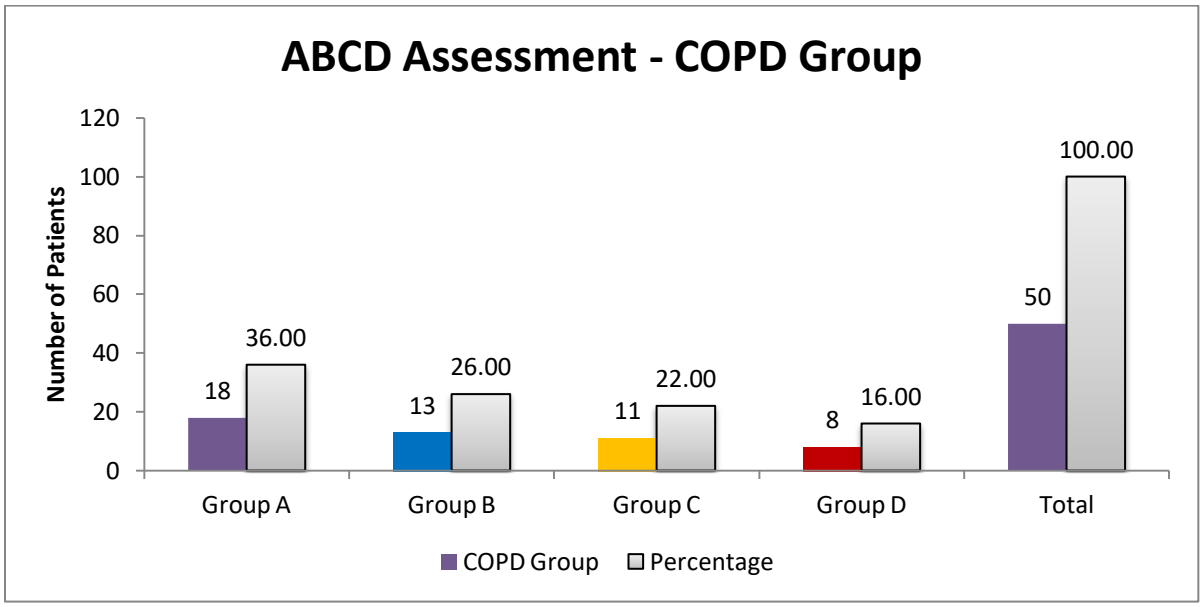
On analysis of incidence of exacerbations in COPD group, most had higher incidence of exacerbations (52.00%) within the first year followed equally between 1-3 years and 3-5 years (18.00%).

ABCD Assessment - COPD Group



ABCD Assessment - COPD Group	COPD Group	Percentage
Group A	18	36.00
Group B	13	26.00
Group C	11	22.00
Group D	8	16.00
Total	50	100.00

On analysis of ABCD assessment in COPD group, most belonged to Group A – low risk less symptom category (36.00%) followed by Group B - low risk more symptom category (26.00%).

Airflow Obstruction - GOLD Staging - COPD Group

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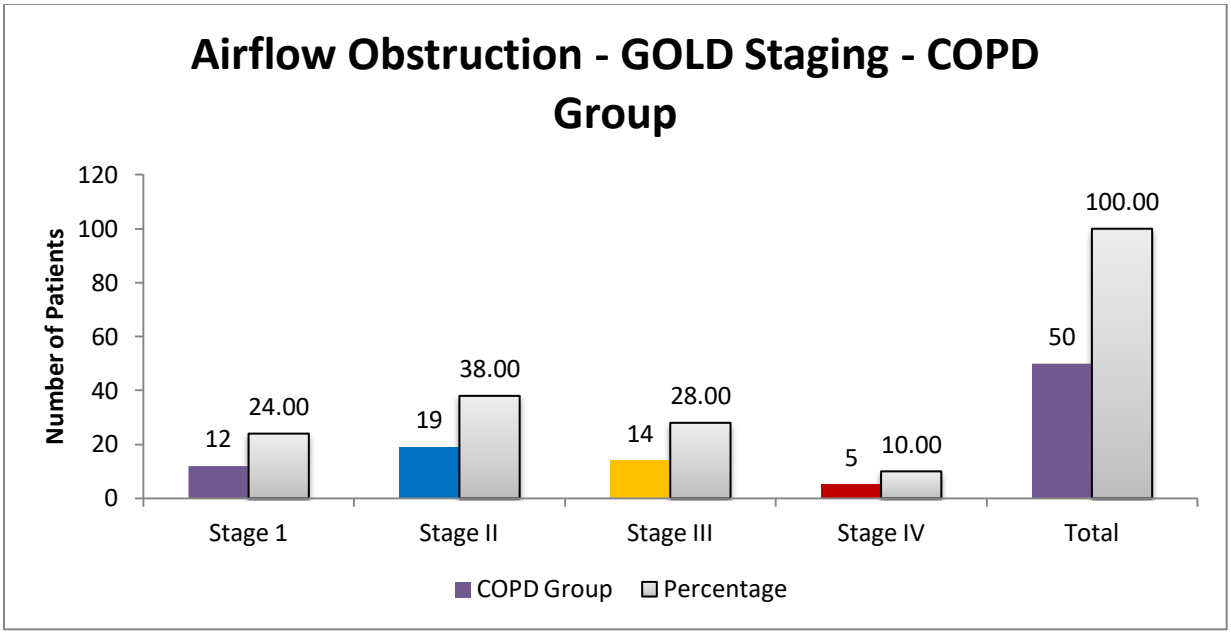

Airflow Obstruction - GOLD Staging - COPD Group	COPD Group	Percentage
Stage 1	12	24.00
Stage II	19	38.00
Stage III	14	28.00
Stage IV	5	10.00
Total	50	100.00

On analysis of GOLD staging in COPD group, most belonged to Stage II – low moderate category (38.00%) followed by Stage III - severe category (28.00%).

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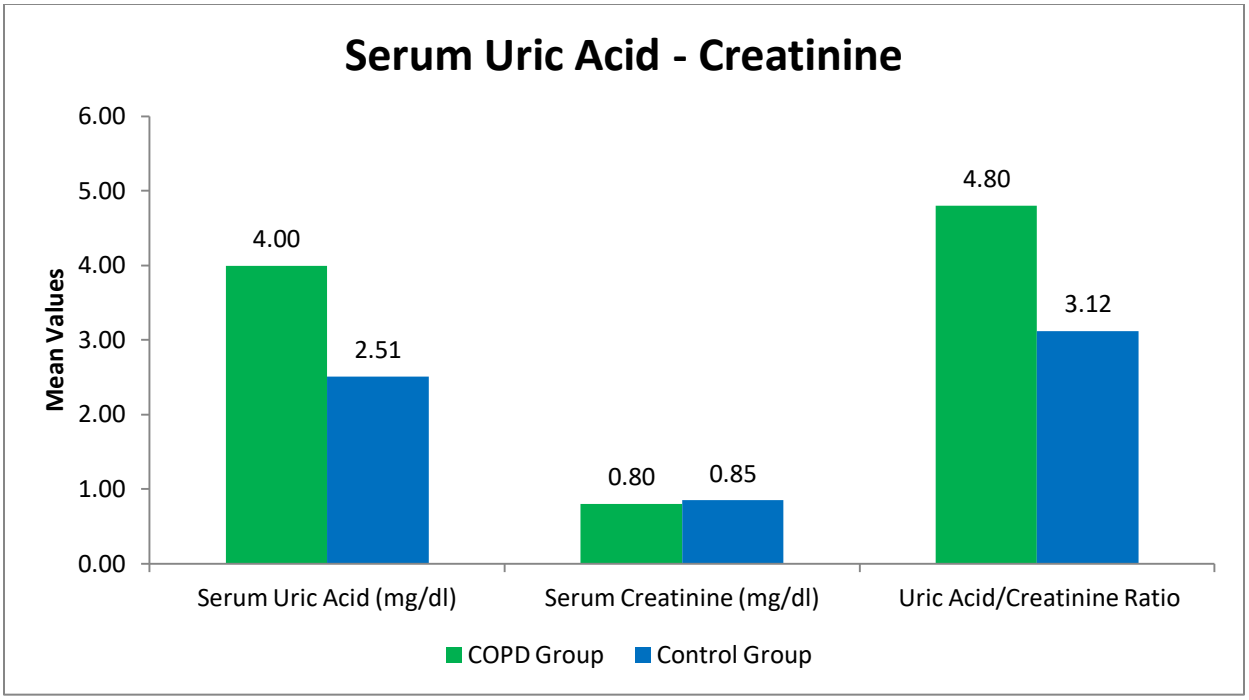
Serum Uric Acid - Creatinine



Serum Uric Acid – Creatinine		Serum Uric Acid (mg/dl)	Serum Creatinine (mg/dl)	Uric Acid/Creatinine Ratio
COPD Group	Mean	4.00	0.80	4.80
	SD	1.40	0.12	1.84
Control Group	Mean	2.51	0.85	3.12
	SD	0.40	0.11	0.47
P value Unpaired t Test		<0.001	0.026	<0.001

On analysis of serum uric acid - creatinine distribution between study groups, the mean serum uric acid level in COPD group was 4.00 mg/dl compared to mean serum uric acid level in Control group of 2.51 mg/dl , the mean serum creatinine level in COPD group was 0.85 mg/dl compared to mean serum uric acid level in Control group of 0.80 mg/dl and the mean serum uric acid/creatinine ratio level in COPD group was 4.80 compared to mean serum uric acid/creatinine ratio level in Control group of 3.12. There was a statistically significant difference in relation to serum uric acid , serum creatinine and serum uric acid/creatinine ratio distribution with a p value of <0.05 as per paired t test.

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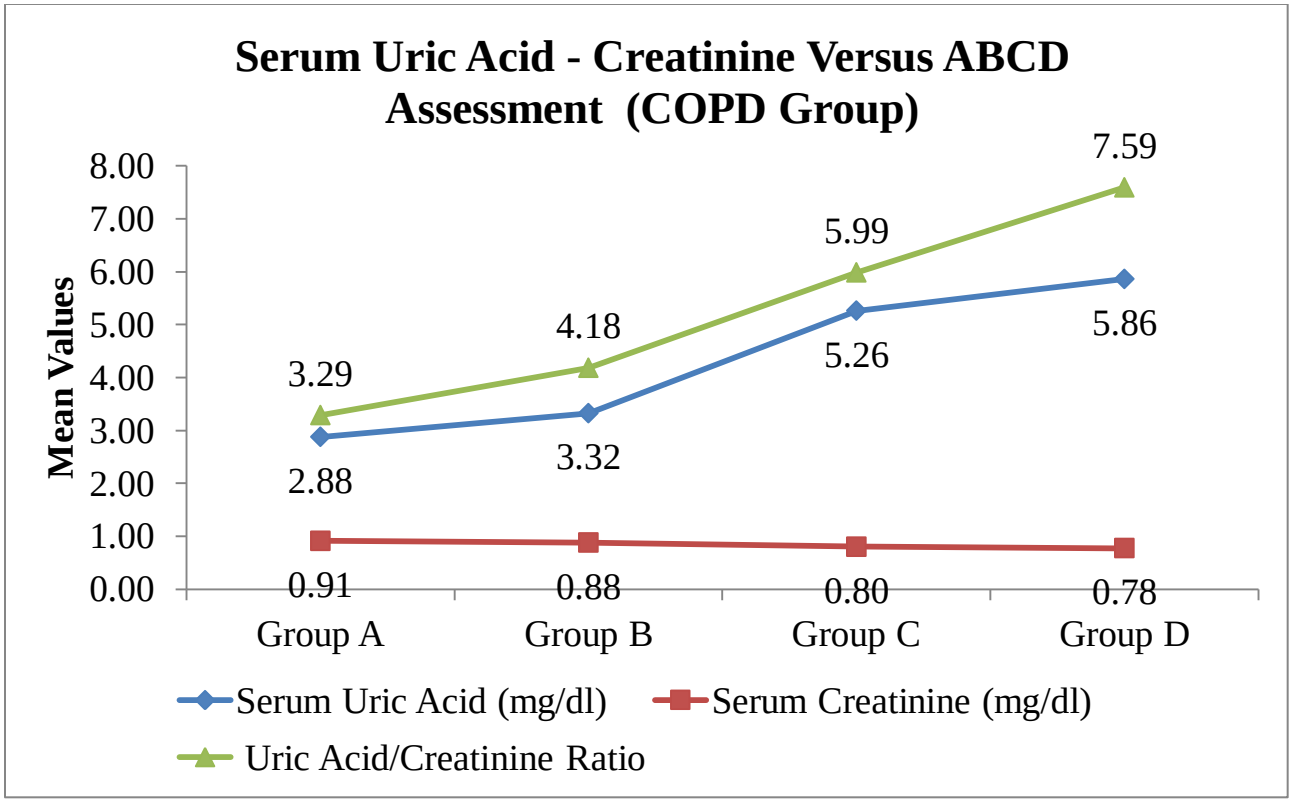
Serum Uric Acid - Creatinine Versus ABCD Assessment (COPD Group)



Serum Uric Acid - Creatinine Versus ABCD Assessment (COPD Group)		Serum Uric Acid (mg/dl)	Serum Creatinine (mg/dl)	Uric Acid/Creatinine Ratio
Group A	Mean	2.88	0.91	3.29
	SD	0.77	0.13	1.05
Group B	Mean	3.32	0.88	4.18
	SD	0.63	0.13	0.87
Group C	Mean	5.26	0.80	5.99
	SD	0.49	0.08	0.65
Group D	Mean	5.86	0.78	7.59
	SD	0.80	0.07	1.18
P value One Way ANOVA		<0.001	0.012	<0.001

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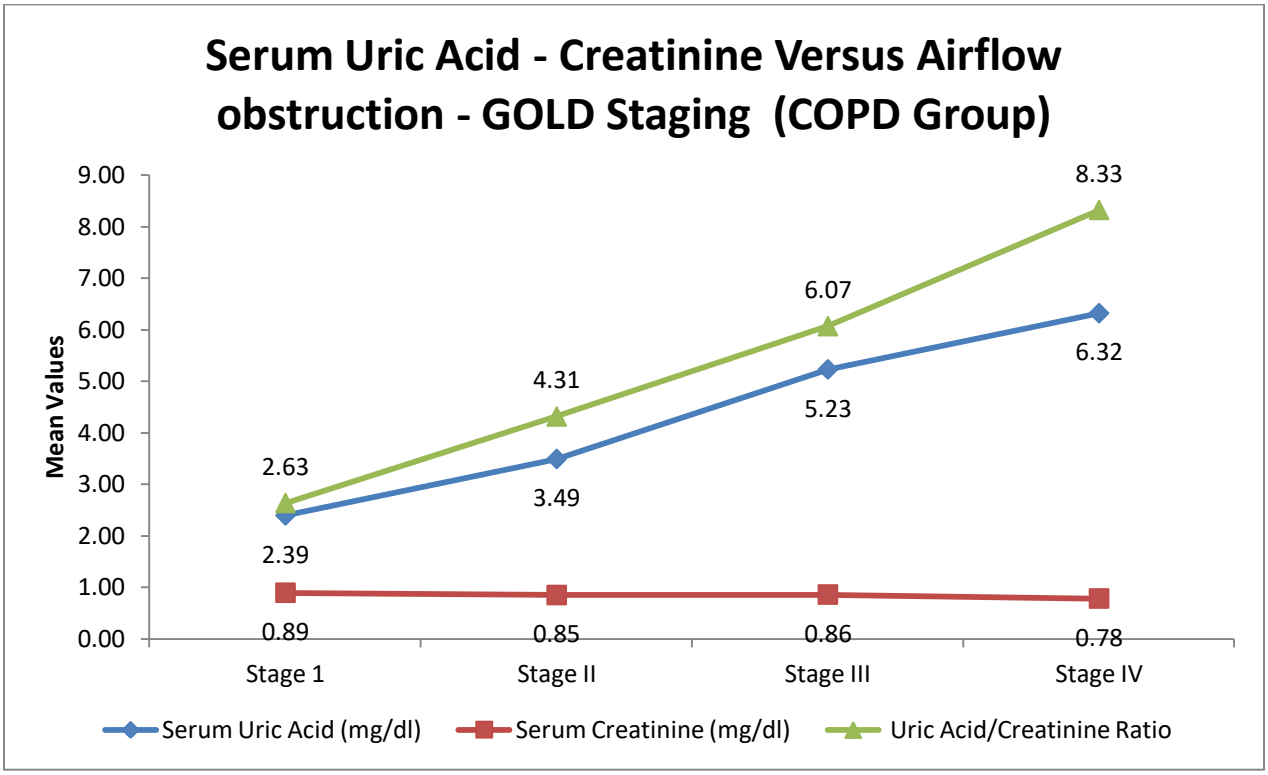
On analysis of serum uric acid – creatinine versus ABCD assessment distribution in COPD group, the mean serum uric acid level in COPD group was 2.88 mg/dl in Group A, 3.32 mg/dl in Group B, 5.26 mg/dl in Group C and 5.86mg/dl in Group C. Similarly the mean creatinine level in COPD group was 0.91 mg/dl in Group A, 0.88 mg/dl in Group B, 0.80 mg/dl in Group C and 0.78 mg/dl in Group C. Likewise the mean uric acid/creatinine ratio level in COPD group was 3.29 in Group A, 4.18 in Group B, 5.99 in Group C and 07.99 in Group D. There was a statistically significant difference seen in relation to serum uric acid , serum creatinine and serum uric acid/creatinine ratio versus ABCD assessment distribution with a p value of <0.05 as per one way ANOVA test.

Serum Uric Acid - Creatinine Versus Airflow obstruction - GOLD Staging (COPD Group)



Serum Uric Acid - Creatinine Versus Airflow obstruction - GOLD Staging (COPD Group)		Serum Uric Acid (mg/dl)	Serum Creatinine (mg/dl)	Uric Acid/Creatinine Ratio
Stage 1	Mean	2.39	0.89	2.63
	SD	0.45	0.14	0.34
Stage II	Mean	3.49	0.85	4.31
	SD	0.54	0.14	0.80
Stage III	Mean	5.23	0.86	6.07
	SD	0.47	0.09	0.63

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Stage IV	Mean	6.32	0.78	8.33
	SD	0.58	0.08	0.69
P value One Way ANOVA		<0.001	0.403	<0.001

On analysis of serum uric acid – creatinine versus airflow obstruction - GOLD staging distribution in COPD group, the mean serum uric acid level in COPD group was 2.39 mg/dl in Stage I, 3.49 mg/dl in Stage II, 5.3 mg/dl in Stage III and 6.32 mg/dl in Stage IV. Similarly the mean creatinine level in COPD group was 0.89 mg/dl in Stage I, 0.85 mg/dl in Stage II, 0.86 mg/dl in Stage III and 0.78 mg/dl in Stage IV. Likewise the mean uric acid/creatinine ratio level in COPD group was 2.63l in Stage I, 4.31 in Stage II, 6.07 in Stage III and 8.33 in Stage IV. There was a statistically significant difference seen in relation to serum uric acid and serum uric acid/creatinine ratio versus ABCD assessment distribution with a p value of <0.05 as per one way ANOVA test and statistically insignificant difference was seen in relation to serum creatinine versus ABCD assessment distribution with a p value of >0.05 as per one way ANOVA test.

Discussion

COPD is the third most leading cause of death worldwide . For many years, more researchers has been trying to formulate a simple and effective index for assessing the severity of COPD. But most prognostic markers has been found to have some limitation in predicting the morbidity and mortality in patients with COPD. In our study we tried to evaluate serum uric acid creatine ratio as a prognostic indicator in predicting the severity of COPD in terms of correlations with many variables. The results which we got in our research would definitely bring a significant impact in the management of COPD in the near future.

We used male patients only in our study as males are more commonly affected in COPD. Thus we could make an uniform study group to remove the gender related differences in Forced End expiratory Volume in 1 second and Body Mass Index (BMI)

Dujirila pujira Chowdary et al proposed in their study that there was no

significant difference in age in serum uric acid creatinine ratio in copd severity

groups.In our study, analysed data expresses that variables like age and Serum

Uric Acid - Creatinine Versus Airflow obstruction - GOLD Staging (COPD

Group) analysis showed no significant difference and effects on outcomes.

The mean BMI was meaningfully and significantly lowered in COPD Group study subjects by 4.00 % (mean difference of 0.88) compared to Control Group study subjects. This significant 4.00 % decrease in BMI among COPD Group study subjects and the proportion of overweight COPD patient was significantly less as compared to control group study subjects. This significant in decrease in BMI in COPD Group study subjects was consistent with the results of Yuvarajan s et al. This may be due to decline in BMI with severity of COPD.

The mean smoking index represented by pack years was meaningfully and significantly higher in COPD Group study subjects by 80.00 % (mean difference of 28.48 pack years) compared to Control Group study subjects. This significant 80.00 % increase in smoking index among COPD Group study subjects and the proportion of non smokers among COPD patient was significantly less as compared to control group study subjects. This significant increase in smoking index in COPD Group study subjects was consistent with the results of Dishan P.Y.et al. This could be explained by smoking years will increase the severity of obstruction in COPD patients in terms of decline in FEV1.

The incidence of disability attributable to dyspnoea as quantified by mMRC dyspnoea scale was

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meaningfully and significantly higher in COPD Group study subjects by 65.00 % (percentage difference of 48.00 points) compared to Control Group study subjects. This significant 65.00 % increase in disability attributable to dyspnoea among COPD Group study subjects and the proportion of subjects with no disability attributable to dyspnoea among COPD patient was significantly less as compared to control group study subjects. This significant increase in mMRC dyspnoea scale scores in COPD Group study subjects was consistent with the results of Hesham A AbdelHalim et al. This may be due to progression of the disease severity.

The mean serum uric acid was meaningfully and significantly higher in COPD Group study subjects by 37.00 % (mean difference of 1.49) compared to Control Group study subjects. This significant 37.00 % increase in serum uric acid levels among COPD Group study subjects explains the role of serum uric acid level in hypoxemia in COPD patients.

Durmus kocak n et al has proved in their study that there is positive association between serum uric acid creatinine ration with severity of COPD. In our study, the mean uric acid/creatinine ratio was meaningfully and significantly higher in COPD Group study subjects by 35.00 % (mean difference of 1.69) compared to Control Group study subjects. This significant 35.00 % increase in serum creatinine levels among COPD Group study subjects

The mean uric acid/creatinine ratio levels was meaningfully and significantly higher in Group D versus Group C COPD study subjects by 21.00 % (mean difference of 1.60) , higher in Group C versus Group B COPD study subjects by 30.00 % (mean difference of 1.80) and higher in Group B versus Group A COPD study subjects by 21.00 % (mean difference of 0.89).

Similarly the mean uric acid/creatinine ratio levels was meaningfully and significantly higher in stage IV versus stage III COPD study subjects by 39.00 % (mean difference of 2.26) , higher in Group C versus Group B COPD study subjects by 29.00 % (mean difference of 1.76) and higher in Group B versus Group A COPD study subjects by 27.00 % (mean difference of 1.68). This significant increase in severity of COPD with rising uric acid/creatinine ratio levels was consistent with Dishan P.Y et al. Thus our study has proved the nature of the study and the disease progression in COPD.

Limitations

Low sample size. So little space for robust statistical analysis.

Study population restricted to patients referred to our department. So a selection bias may have influenced the results.

Lack of longitudinal study design might hinder the generalization of results to clinical community.

Poor financial support

Paucity of time and resources

Study limited to 1 year only

Absence of female patients

Conclusions

These novel findings support the obesity paradox in COPD: compared to normal BMI, low BMI is a risk factor for accelerated lung function decline (2 times higher risk), whilst high BMI has a protective effect.

Smoking is a risk factors for COPD (5 times higher risk)

An increasing mMRC score reflects impaired quality of life and a high symptom burden (3 times higher risk). It can be used to predict hospitalization, exacerbation and significantly poorer prognosis.

These results support the use of FEV1/FVC less than 70% and FEV1: less than 80% to identify individuals at risk of clinically significant COPD.

Our findings suggest that post bronchodilator spirometry may be a more accurate measure of COPD burden and should be used for COPD diagnosis and classification.

In our study population the frequency of a positive bronchodilator response in patients with less than 80% FEV1 to normal FEV1 levels is 1.2 times more. FEV1 detected a larger percentage of patients with significant responsiveness

Serum Uric acid/creatinine ratio may be useful in risk stratification of subjects with chronic obstructive pulmonary disease

To conclude elevated serum uric acid level may serve as a simple, cost effective noninvasive indicator for

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COPD severity and hypoxemia in COPD patients in addition to spirometric parameters like FVC, FEV1 and FEV1/FVC.

Serum Uric acid/Creatinine ratio is a better predictor of COPD severity and hypoxemia in COPD patients among the three

This study is a hypothesis proving study. Hence results have high clinical significance.

Summary

These results support:

1. The reduction in BMI is significantly associated with higher COPD incidence.
2. Subjects with COPD had a higher exposure to smoking compared with non-COPD control subjects.
3. Patients with COPD tend to land up with higher mMRC scale grade
4. Patients with COPD were associated with lowered FEV1:FVC (less than 70%), FEV1: (less than 80%) and increased post bronchodilator FEV1 (more than 80%)
5. Patients with COPD were associated with elevated serum uric acid and uric acid/creatinine ratio in addition to lowered serum creatinine levels
6. The levels of serum uric acid (positively) and uric acid/creatinine ratio (positively) correlates with increase in COPD symptoms and exacerbations – ABCD ASSESSMENT groups
7. The levels of serum uric acid (positively) and uric acid/creatinine ratio (positively) correlates with increase in severity grade of COPD – GOLD severity groups

Scope For Future Studies

Larger and meticulously designed studies with larger sample size from multiple centers and longer follow up period is required for more elaborate statistical analysis. for better clinical decision making to develop informed evidence based recommendations

Further studies investigating this issue are needed to further develop and standardize the predicting capacity of serum uric acid, serum creatinine, and uric acid/creatinine ratio.

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