A dissertation on

A CASE-CONTROL STUDY ON CALCIUM LEVELS IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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CERTIFICATE

This is to certify that the dissertation entitled **"A CASE CONTROL STUDY ON CALCIUM LEVELS IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** is a bonafide work done by **Dr.Rajasekar. G,** Registration No. **201711013,** at Madras Medical College, Chennai in partial fulfillment of the University rules and regulation for the award of M.D., Degree in General Medicine (Branch-I) under our guidance and supervision during the academic year 2017-2020.

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DECLARATION

I, Dr. G. RAJASEKAR, Registration Number 201711013 solemnly declare that this dissertation entitled "**A CASE CONTROL STUDY ON CALCIUM LEVELS IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during 2017-2020 under the guidance and supervision of my Chief **Prof. Dr. R. Muthuselvan, M.D.** This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirements for the award of M.D. Degree in General Medicine (Branch-I).

Place: Chennai - 3. Signature of Candidature

Date

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LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease
IL-6	Interleukin - 6.
TNF Alpha	Tumor Necrosis Factor - Alpha
WHO	World Health Organisation
CT	Computerized Tomography
FEV 1	Forced Expiratory Volume, first second
S.D	Standard Deviation
ECM	Extra cellular Matrix
FVC	Forced vital capacity
V-Q	Ventilation-perfusion
PaO_2	Partial pressure of oxygen in arterial blood
$PaCO_2$	Partial pressure of Carbon dioxide in arterial blood
CAT	COPD Assessment Test
JVP	Jugular venous pressure
GOLD	Global initiative for Chronic Obstructive Lung disease
ABG	Arterial Blood Gas
LAMA	Long Acting Muscarinic Agents
LABA	Long Acting Beta Agonist
ICS	Inhaled Corticosteroid
PDE4	Phosphodiesterase - 4
IV	Intravenous

mMRC	Modified Medical Research Council
NIPPV	Non invasive Positive pressure ventilation
PEEP	Peak End Expiratory Pressure
ECF	Extra cellular Fluid
PTH	Parathyroid Hormone
BMI	Body Mass Index
PFT	Pulmonary Function Test
IRV	Inspiratory Reserve Volume
ERV	Expiratory Reserve Volume
V_c	Vital Capacity
RV	Residual Volume
FRC	Functional Residual Capacity
TLC	Total Lung Capacity
MVV	Maximum Voluntarily Ventilation
PEFR	Peak Expiratory Flow Rate

CONTENTS

INTRODUCTION

Chronic Obstructive Pulmonary Disease is a Chronic Respiratory Disease characterized by progressive, irreversible air flow limitation due to bronchial and alveolar inflammation. The causative agents are Cigarette smoking, exposure to fumes, air pollution and airway hyper responsiveness

COPD is the third most common cause of death in the world. It is the second leading cause of death in India. It includes Emphysema (alveolar destruction), Chronic bronchitis and Small airway disease.

COPD also affects other systems exhibiting as osteoporosis, weight loss, muscle weakness, cardiovascular diseases and renal diseases.

It causes these systemic manifestations through various pathological process. In particular, osteoporosis is caused due to chronic inflammation, cytokines released such as IL 6, TNF - Alpha and secondary Vitamin D deficiency.

Vitamin D deficiency is much commoner in COPD patients and the incidence increases with severity of COPD due to decreased mobility, decreased exposure to sunlight, associated renal dysfunction, chronic steroid use and decreased diet.

Vitamin D deficiency can lead on to hypocalcemia. Hypocalcemia can manifest as carpopedal spasm, arrhythmias and sometimes present as bronchospasm. Thus this bronchospasm could trigger Exacerbations in COPD patients and specifically in Severe disease.

Thus a correlation between calcium levels and exacerbations of COPD could aid in further understanding of triggering factors

AIMS AND OBJECTIVES

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- TO DETERMINE THE LEVELS OF SERUM CALCIUM IN PATIENTS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- TO DETERMINE THE ASSOCIATION OF SERUM CALCIUM LEVELS WITH ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

REVIEW OF LITERATURE

COPD includes three categories which include

- Emphysema, anatomically defined condition where alveolar destruction leads on to air space enlargement

- Chronic Bronchitis, characterized by chronic cough and sputum production

- Small airway disease is a condition characterized by narrowing of small airway and reduction in number

EPIDEMIOLOGY

WHO stated that there were 251 million cases were reported in 2016 and 3.15 million death/year. COPD is associated with smoking and pollution and hence the burden is much higher in low and middle income countries. In India, it is the second biggest cause of death[10]. Its prevalence has increased by 29.2% from 1990 to 2016 which is a serious concern for public health.

RISK FACTORS

Cigarette Smoking

Airway Hyperresponsiveness

Repeated Respiratory Infections

Occupational exposures to dust and fumes

Air pollution and Passive smoking

Genetic factors

TOBACCO SMOKING

Several longitudinal studies have shown progressive decline in lung function with the intensity of smoking in a dose-response relationship. The dose is typically measured in pack-years

(Pack year =Average Number of cigarettes/day X Total number of years of cigarette smoking).

Pack years of smoking is the highest predictor of FEV1 but still the decline in only 15% could be explained, indicating other factors, nonetheless these patients may show evidences of airway diseases on CT scans of chest and signs of decreased exercise capacity. Since smoking is commoner in male sex, the prevalence is also high in male compared to females

AIRWAY HYPER RESPONSIVENESS

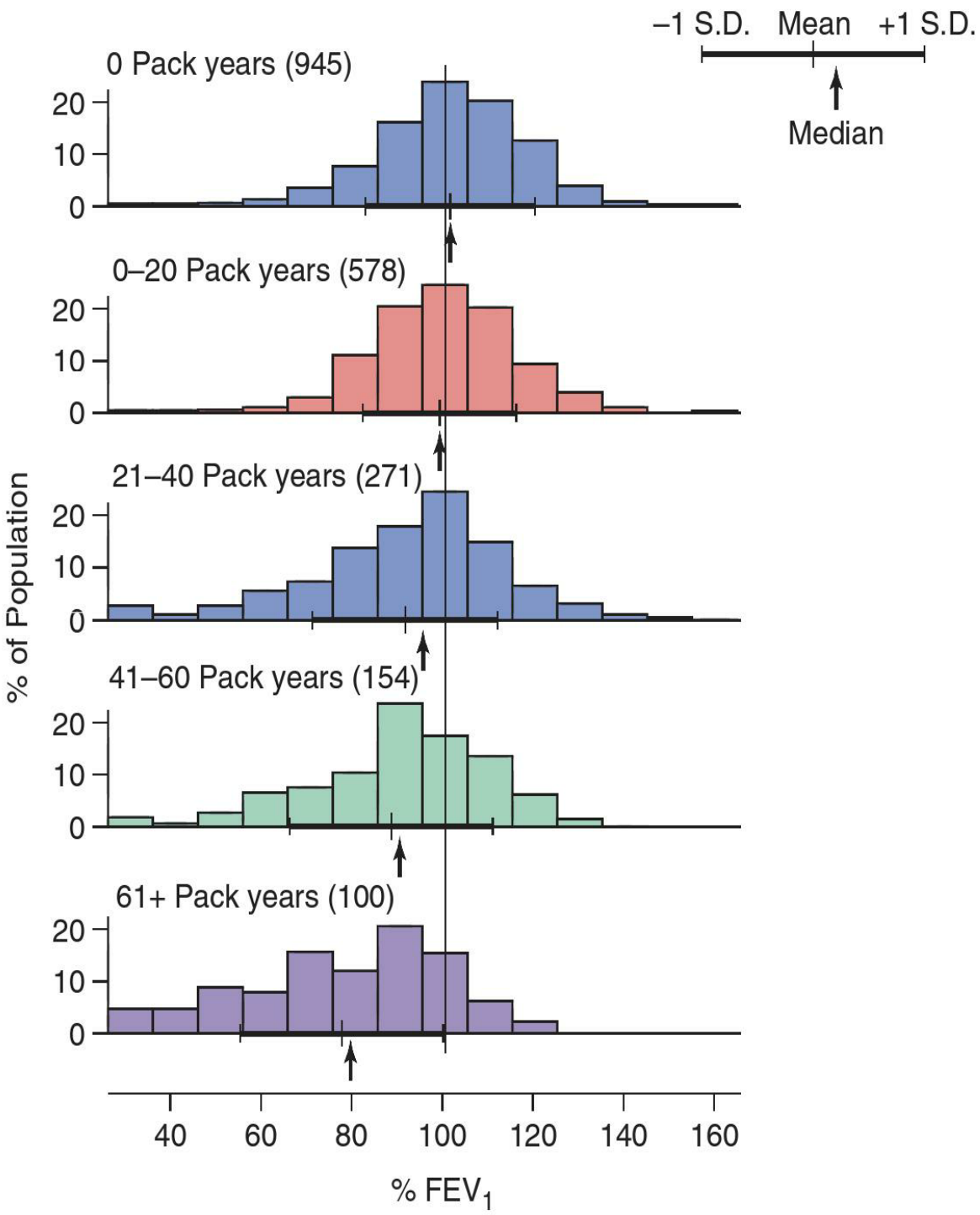
A Tendency to bronchoconstrict vigorously to external stimuli is a feature of asthma. Such feature is shared in many of the COPD patients. Childhood Asthma is also a risk factor for COPD.

RESPIRATORY INFECTIONS

Childhood pneumonia contributes to increased risk of COPD later in life. Further respiratory infections are important cause of exacerbations in COPD and each exacerbations leads to further decline in lung function.

OCCUPATIONAL EXPOSURE

Several occupation poses risk of exposure to dust and fumes such as Coal and gold mining, cotton textile dust, etc which have been implicated in significant reduction in FEV1. Concurrent cigarette smoking increases the risk many times.


–1 S.D. Mean +1 S.D.
Median
0 Pack years (945)
0–20 Pack years (578)
21–40 Pack years (271)
41–60 Pack years (154)
61+ Pack years (100)
20
10
0
% of Population
40
60
80
100
120
140
160
% FEV1

AIR POLLUTION

Several studies show increased respiratory symptoms in urban population in comparison to the rural counterpart. Prolonged exposure to biomass combustion particularly women are at increased risk of COPD.

PASSIVE SMOKING

Passive smoking has been associated with reduction in FEV1. In utero, smoke exposure also results in significant post natal reduction in lung function.

GENETIC CONSIDERATIONS

Severe Alpha 1 Anti Trypsin deficiency is a proven risk factor for COPD. Although only ~1% of COPD patients are positive for Alpha 1 Anti Trypsin deficiency, these patients prove the effect of genetic factors for susceptibility to COPD.

PATHOGENESIS

Pathogenesis of Emphysema comprises four events

- Chronic exposure to cigarette smoking triggers inflammation of large and small Airways and in the alveolus in genetically susceptible individuals

- Inflammatory cells produce enzymes such as proteinases which damage the Extra-cellular matrix(ECM) of Airways, gas exchange surface and vasculature

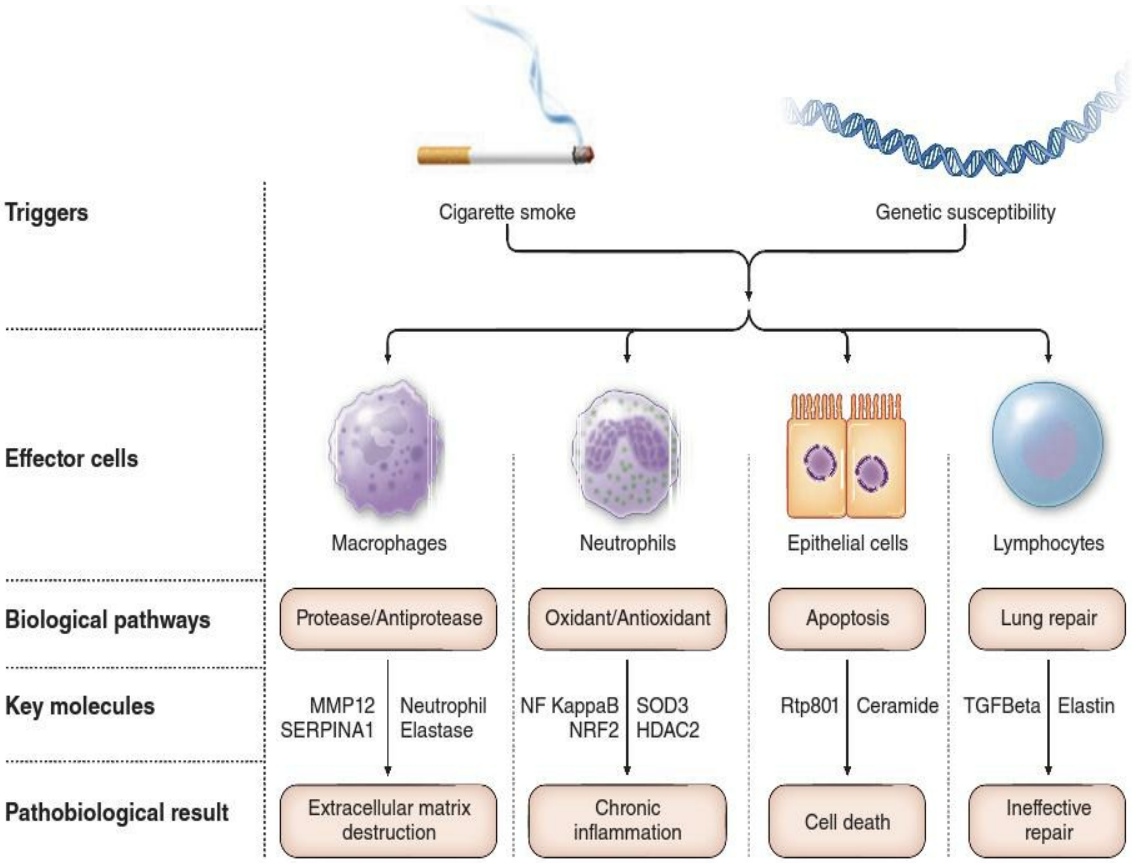
- Structural cell death results in extensive loss of smaller airways, alveolus and vasculature.

- Disordered repair of elastin and ECM contributes to loss of elasticity and in turn air space enlargement

Exposure of oxidants from smoke results in activation of macrophages and epithelial cells, which in turn produces PROTEINASES and chemokines such as TNF- and IL-8 recruiting more inflammatory cells.

The recruited Neutrophils produce NEUTROPHIL ELASTASE and CD8+ T cells release cytokines that causes macrophages to release MATRIX METALLOPROTEINASES (MMP -12). These enzymes (MMP, NEUTROPHIL ELASTASE AND PROTEINASES) work synergistically to cause lung destruction. Further end product of these proteolytic

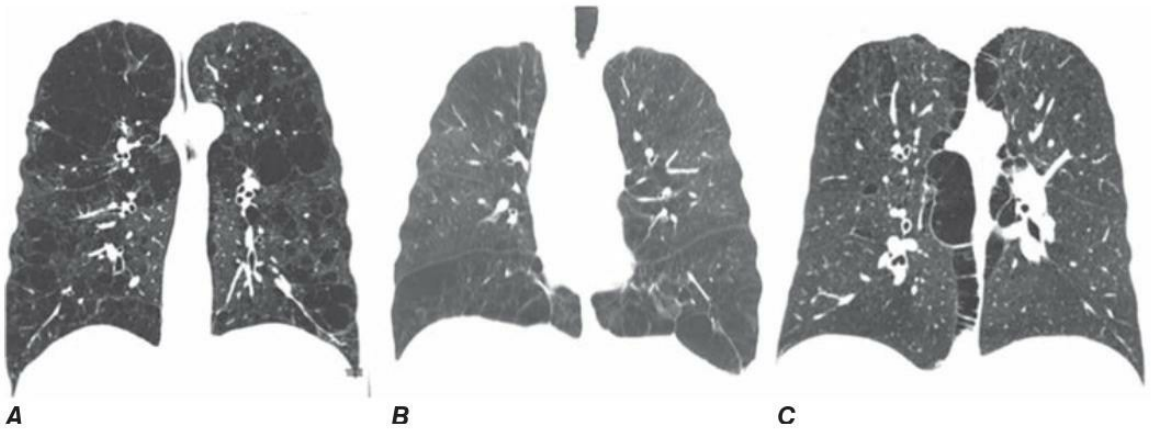
cleavage of elastin and collagen acts as chemokines for Macrophages and Neutrophils respectively resulting in a positive feedback loop.



Cigarette smoke oxidant induced cell death occurs directly via other mechanisms. The ability of lung to replace damaged tissue becomes limited due to macrophage impairment of uptake of apoptotic cells.

Pathologically, Emphysema is classified into

1. Centrilobular - prominent in upper loves and upper parts of lower lobes
2. Panlobular - abnormally large air spaces evenly distributed
3. Paraseptal - distributed along the pleural margins



CENTRILOBULAR PANLOBULAR PARASEPTAL

Pathogenesis of Chronic Bronchitis

Chronic Smoking results mucus gland enlargement, goblet cell hyperplasia and smooth muscle hypertrophy leading on to cough, sputum production and airflow limitation.

Pathogenesis of Small Airways

The major site of resistance is in Airways 2 mm diameter. The surfactant producing cells are replaced by goblet cells which produce mucus this increasing resistance to air flow and tendency to collapse. Added elastin damage and fibrosis leads on to further luminal narrowing

PATHOPHYSIOLOGY

- *Persistent reduction in forced expiratory flow rates*

Measured by spirometry. Key parameters include

FEV1 - air exhaled during the first second by the forced expiratory maneuver

FVC - total volume of air exhaled during the maneuver

FEV1/FVC - ratio of above two parameters

In COPD, FEV1 is reduced and does not improve with bronchodilators not more than 15%

- *Increase in residual volume and total lung capacity*

Hyperinflation of the lung occurs as a compensation for airway obstruction. Increased lung volume increases the elastic recoil pressure and opens airway thereby decreasing airflow residence. However this hyperinflation causes flattening of diaphragm thereby increases the effort required to attain inspiratory pressures.

- *Non uniform distribution of ventilation*

Non uniform ventilation and mismatching of ventilation-perfusion is characteristically seen in COPD. V-Q mismatching accounts for all the changes in PaO2 that occurs in COPD, while shunt is minimal. Hence mild elevation in inspiratory oxygen is effective in treating hypoxemia in COPD patients.

PaO2 remains normal until FEV1 decreases to ~50% of predicted. PaCO2 increases usually only after <25% of FEV1. Pulmonary Hypertension also occurs at FEV1 levels <25% of predicted and chronic hypoxemia PaO2 levels < 55 mm Hg.

EXACERBATIONS OF COPD

- Exacerbations are episodic worsening of symptoms such as increased cough, wheezing, breathlessness and change in the quantity of sputum. They may or may not be associated with other symptoms but the strongest predictor is a history of previous exacerbation. The frequency increases with the severity of airflow obstruction.

- *Precipitating factors* - Bacterial infections that are new stains for the patient, viral respiratory infections, Gastro oesophageal reflux disease and no specific causes in some cases

CLINICAL HISTORY

The usual Age of onset is 5th to 6th decade. Cough, sputum production and existing dyspnoea are the three major symptoms of COPD.

The development of exertional dyspnoea will be usually gradual. Although the patient may provide a history of sudden onset after exacerbations. A careful history elicitation brings out the gradual onset of dyspnoea.

Cough after dyspnoea and before dyspnoea are seen in Emphysema and Chronic Bronchitis respectively. Sputum production is usually scanty in Emphysema whereas copious and purulent in chronic Bronchitis.

Dyspnoea is graded based on severity according to Modified Medical Research Council Classification (MMRC) and SHERWOOD JONES CLASSIFICATION

MMRC CLASSIFICATION

1. Shortness of breath when walking up hill or hurrying on a level ground
2. Shortness of breath when walking on a level ground with people of same age group
3. Shortness of breath when walking at own pace on level ground.
4. Shortness of breath lying daily activities.

SHERWOOD JONES CLASSIFICATION

1. Able to do housework
    - With moderate difficulty
    - With great difficult
2. Confined to chair or bed
    - Able to get up with moderate difficulty
    - Able to get up with great difficulty
3. Totally confined to chair or bed
4. Moribund

COPD ASSESSMENT TEST

Quantifies the impact of the symptoms on patients health

1. Cough - 0 to 5 points
2. Sputum production - 0 to 5 points
3. Chest tightness - 0 to 5 points
4. Breathlessness - 0 to 5 points
5. Activities - 0 to 5 points
6. Confidence to leave home - 0 to 5 points
7. Sleep - 0 to 5 points
8. Energy - 0 to 5 points

It is used as one of the components in grading symptom burden and categorise the patients into one of four groups (A to D), which aids in treatment.

History of smoking - The number of cigarettes/beedis smoked per day and the number of years of smoking represented as pack years as discussed already. Smoking index is a similar tool to identify the risk for COPD and bronchogenic carcinoma

Smoking Index = Number of cigarettes/day X Number of years of smoking.

Several studies have proven that duration of smoking poses higher risk than number of cigarettes/day. Even after cessation of smoking the progression of the severity of the disease does continue.

A History of occupational exposure to dust and fumes for a long time is a risk factor and increases manifolds if there is additional history of chronic smoking.

PHYSICAL FINDINGS

GENERAL EXAMINATION:

- Signs of smoking such as odour of smoke and nicotine attain in fingernails.

- Cachexia, weight loss, bitemporal wasting and diffuse loss of subcutaneous tissue due to poor oral intake and tired levels of inflammatory cytokines.

- Signs of right heart failure (cor pulmonale) such as raised JVP, B/L pedal edema, para-sternal heave, epigastric pulsation, apical impulse shifts laterally, loud P2, ascites and hepatomegaly.

- Pink puffers and blue boaters - Thin, non cyanotic, with predominant emphysema are termed 'pink puffers', while heavy, cyanotic, with predominant chronic bronchitis are termed 'blue boaters'.

- Clubbing is not a sign of COPD and is presence should warrant evaluation for causes of clubbing, especially incidence of lung cancer is more common in these patients.

INSPECTION

- Barrell shaped chest wall - The Anteroposterior to traverse diameter becomes 1:1.
- Accessory muscles of expiration abdominal muscles and latissimus dorsi will be recruited.

PALPATION

- Increased inspiratory tracheal descent seen in the suprasternal region.
- Generalized restriction of expansion. Normal expansion of the chest is 5-8cm. In Severe COPD the expansion may become < 1cm

AUSCULTATION

- Prolonged expiratory phase of breathing due to obstruction of air flow. In some advanced conditions, patient may have paradoxical inward movement of thoracic cage during inspiration (Hoover's sign) as a result of hyperinflation causing resultant contraction of diaphragm altered
- Diminished breath sounds due to airflow obstruction.
- Monophasic or polyphonic wheeze -usually expiratory, complex musical sounds due to compression of large airways.

LABORATORY FINDINGS

Spirometry

- FEV1 reduced
- FEV1/FVC reduced
- Increase in TOTAL LUNG CAPACITY (TLC)
- Increase in FUNCTIONAL RESIDUAL CAPACITY (FRC)
- Increase in RESIDUAL VOLUME (RV)

The degree of airflow obstruction is measured from the above spirometry values and graded as mild, moderate, Severe and very Severe based on GOLD Criteria (GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE).

TABLE 286-1 GOLD Criteria for Severity of Airflow Obstruction in COPD

GOLD STAGE	SEVERITY	SPIROMETRY
I	Mild	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 50\%$ but $< 80\%$ predicted
III	Severe	$FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ but $< 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted

However, GOLD severity classification alone is not perfect in grading. Hence when spirometry measurements were considered along with clinical features, it turned out to be better predictor of mortality rate.

BODE INDEX

B -BMI

O -OBSTRUCTION TO AIRFLOW

D- DYSPNOEA

E - EXERCISE PERFORMANCE

Calculation of the BODE Index*

	Points on the BODE Index			
Variable	**0**	**1**	**2**	**3**
FEV_1 (% predicted)	≥65	50–64	36–49	≤35
Distance walked in 6 min (meters)	≥350	250–349	150–249	≤149
MMRC dyspnea scale	0–1	2	3	4
Body-mass index (kg/M^2)	> 21	≥21		

- *Arterial Blood Gas*

ABG provides a valuable information regarding alveolar ventilation and acid base disturbances. The change in pH with change in pCO2 above 45 mmHg is 0.08 units/10 mmHg and 0.03 units/10 mmHg in the acute and chronic state respectively. Thus, it allows the classification of ventilatory failure into acute and chronic conditions.

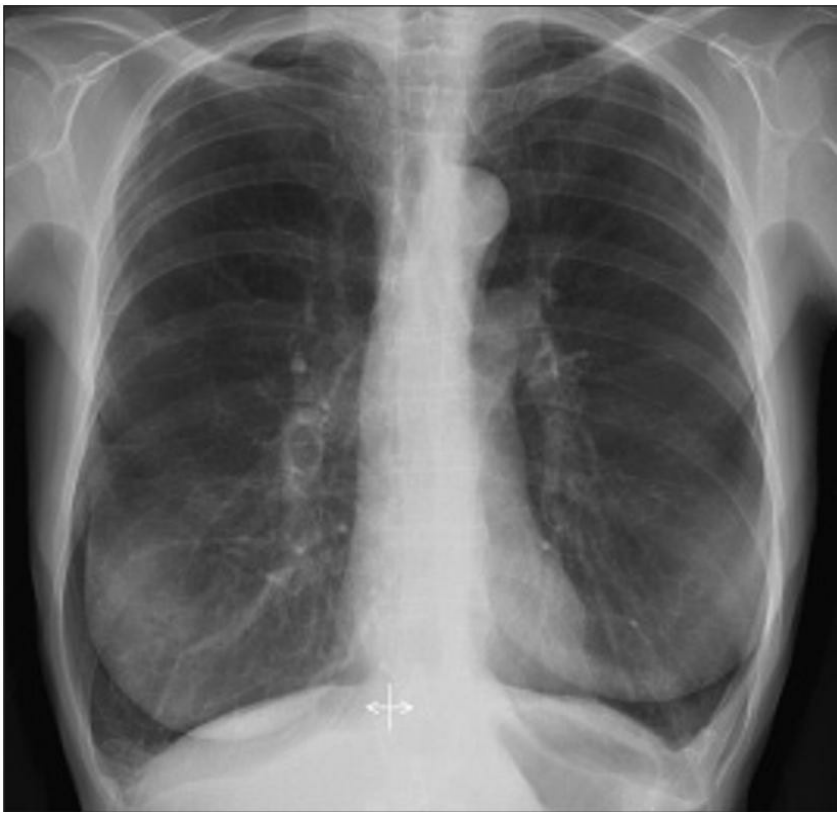
- *Other investigations*

Sputum culture analysis to rule out infective causes of exacerbation. Usual infective agents are H. influenza, S. Pneumoniae and M. catarralis.

Measurement of serum Alpha 1 Anti Trypsin levels to be done. If it is low, definitive diagnosis requires genetic determination of PI locus.

- *Radiographic Studies*

X ray chest - bullae, paucity of parenchymal markings, hyperlucency extend anteriorly up to the 7th rib and posteriorly to 9th rib. flattening of diaphragm, widened intercostal spaces and tubular heart suggests Emphysema.

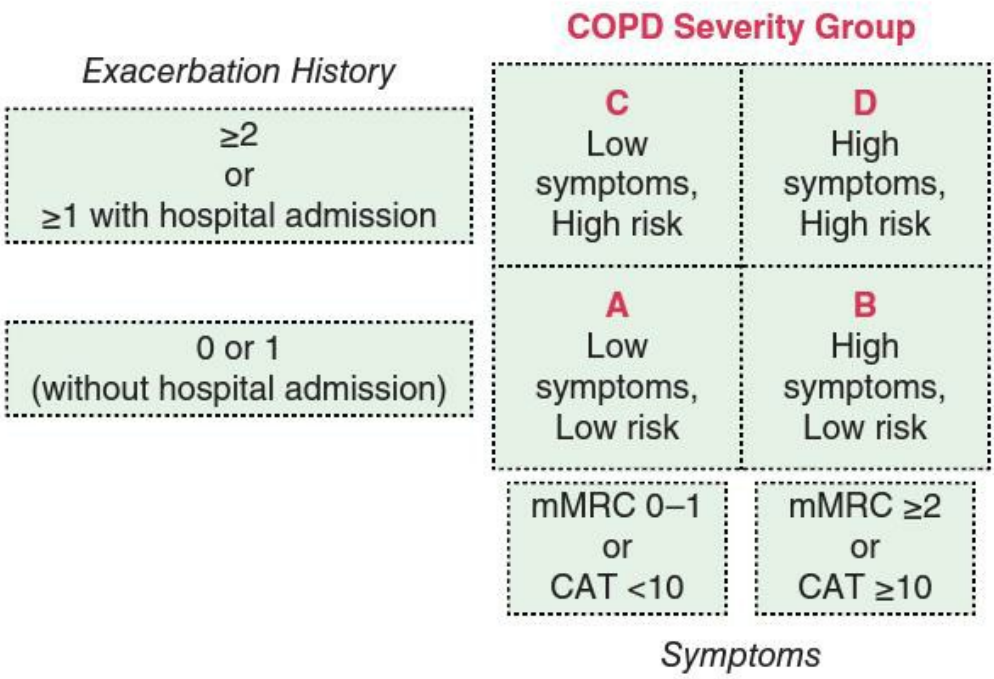


Xray showing low, flat diaphragm with large main pulmonary arteries evidencing pulmonary artery Hypertension

CT Chest - definitive test to diagnose the presence or absence of Emphysema, the type of emphysema and any co-existing interstitial lung disease, bronchiectasis and lung cancer.
Echocardiogram - features of Pulmonary Hypertension and Right heart failure suggestive of cor pulmonale.

TREATMENT OF COPD

Goals of the treatment are symptomatic relief and reduce future risk. To maximise the benefits and reduce side effects, COPD patients are categorised into groups based on severity of symptoms and risk for exacerbations.



I. SMOKING CESSATION

Middle aged smokers who quit smoking experienced significant improvement in the pulmonary function decline. Hence smoking cessation should be counselled. Combining with pharmacological approach helps in successful cessation. Nicotine, bupropion and varneciline are the three drugs available that helps to quit smoking.

II. *PHARMACOTHERAPY*

BRONCHODILATORS

1. *Anticholinergic muscarinic antagonists*

A. Short acting - ipratropium

B. Long acting (LAMA) - aclidinium, (LAMA) - glycopyrolate, tiotropium and umeclidinium

2. *Beta agonists*

A. Short acting - terbutaline, salbuterol

B. Long acting (LABA) (LABA)- arformetrol, formoterol, indaceterol, olodaterol, salmeterol andvilanterol

3. *Combination of anticholinergic and beta agonist*

CORTICOSTEROID

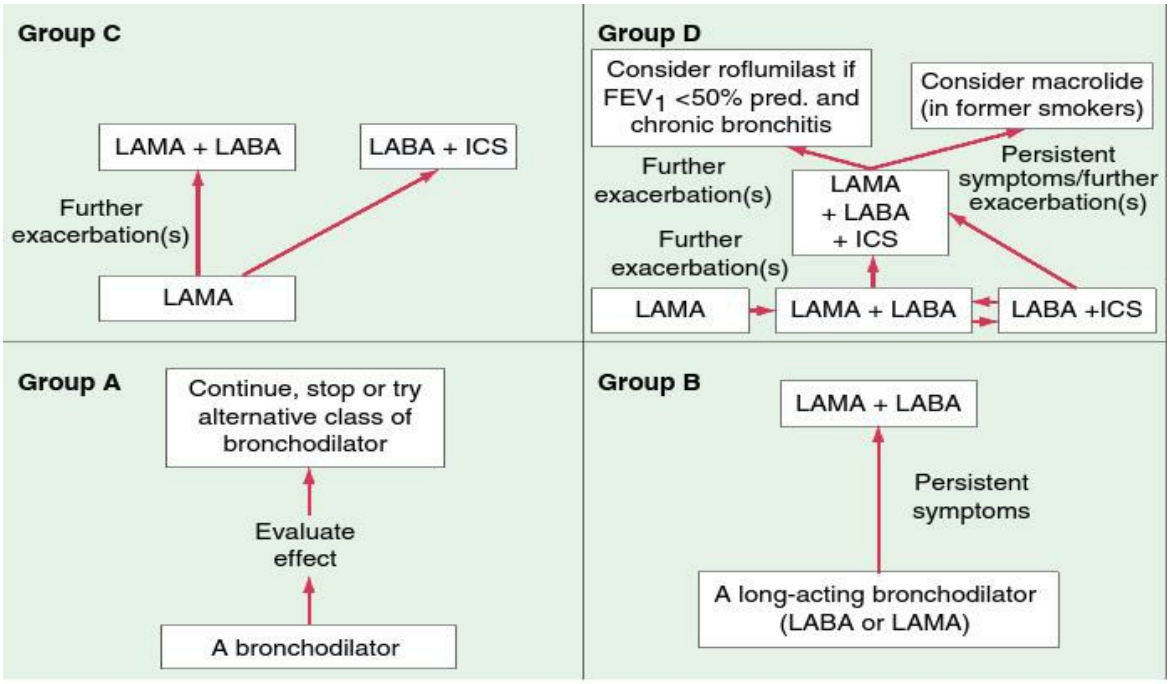
1. *Inhaled corticosteroid (ICS)* - Reduces exacerbations, but associated with increased risk of oropharyngeal candidiasis and pneumonia

2. Oral corticosteroid - it is not recommended because of low benefit/risk ratio. But tapering the dose gradually may reduce the adverse effects

OTHER DRUGS

- Theophylline produces modest improvement in vital capacity and air flow
- PDE4 inhibitors - roflumilast produce similar modest improvement
- Antibiotics - Bacteria that are commonly associated with COPD exacerbations are *Streptococcus pneumoniae, Haemophilus influenza and Moraxella catarrhalis.* Also *Chlamydia pneumoniae and Mycoplasma pneumoniae* are seen in some cases. Antibiotics such as Azithromycin, demonstrated reduced frequency of exacerbations and longer exacerbation free periods.
- Alpha 1 antitrypsin augmentation therapy through IV administration is available for Alpha 1 deficiency. Several studies prove decreased progression too Severe emphysema. Eligibility for IV administration is Alpha 1 levels < 11 micromole

GOLD GUIDELINES



- Group A: Patients with *low symptoms and low risks* of Exacerbations (without hospital admission 0-1 exacerbations + mMRC 0-1 or CAT <10). A bronchodilator may alleviate symptoms, if still persists, continue the same drug or alternate drug till the symptom subsides.

- Group B: Patients with *High symptoms but low risks of exacerbations* (without hospital admission 0 to 1 exacerbations + mMRC > 1 or CAT > 10). A long acting bronchodilator (LABA or LAMA). If symptoms are persisting, combining both LABA and LAMA will provide relief

- Group C: Patients with *Low symptoms but high risks of exacerbations* (>1 exacerbations with hospital admission or > 2 exacerbations + mMRC 0-1 or CAT < 10). LAMA initially, if still exacerbations occur, combining LAMA with LABA or LABA and ICS.

- Group D: Patients with *High symptoms and high risks of exacerbations* (>1 exacerbation with hospital admission or >2 exacerbations + mMRC >1 or CAT >10). LAMA initially, further exacerbations LAMA + LABA (or) LABA + ICS. If still symptoms persists, LAMA+LABA+ICS and still further exacerbations consider adding roflumilast and macrolides.

III. OXYGEN THERAPY

- Supplemental oxygen is the only proven therapy which decrease mortality rate in patients with COPD. Patients with resting hypoxemia <89% or with signs of pulmonary Hypertension, supplemental oxygen has demonstrated significant improvement in mortality.

IV. MECHANICAL VENTILATORY SUPPORT

- *NIPPV* - Patients with respiratory failure, defined as PaCO2 > 45 mmHg, needs initiation of non-invasive positive pressure ventilation. Contraindicated when there is cardiovascular instability, altered sensorium, copious secretion or inability to clear secretion, extreme obesity or craniofacial abnormalities.

- *Invasive mechanical ventilation* by endotracheal intubation is indicated in conditions such as life threatening hypoxia, respiratory distress, hypercapnia, acidosis, altered sensorium and hemodynamic instability. Factors to be noted in mechanical ventilation allowing sufficient expiratory time and the presence of auto-PEEP which demands more respiratory effort.

NON PHARMACOLOGICAL THERAPIES

- *Pulmonary Rehabilitation* - Exercise, education, psychosocial and nutritional counseling

- *Lung volume reduction surgery* - Removing most emphysematous portions of lung improves lung function and survival. Patients with upper lobe involvement and low exercise capacity post rehab benefit most with these surgeries.

- *Lung transplantation* - COPD is the second most common cause of lung transplantation. Indicated when despite maximal support did not improve the morbidity

- Vaccination against pneumococcus, influenza and *Bordetella pertussis*

CALCIUM

- Calcium is essential for bone mineralisation, neurological function, cardiac contractility, hormone secretion and blood coagulation. By far, calcium is the most abundant cation in the body accounting to 1.2 to 1.4 kg in a healthy adult. Of this, 99% is found in the bone and rest in other tissues and ECF.

- Normal serum concentration is 8.5 to 10.5 mg/dL but values may vary according to different laboratories. Of that 50-55% is in the ionised or free form, while 40-45% are bound to albumin.. Hence the total calcium is sum of both ionised+bound calcium

- Ionised calcium is the source of physiologically active calcium. But the measurement of ionised calcium is influenced by various factors hence lacks accuracy.

- Hence total calcium is measured, however, when albumin levels are low, the total calcium measured will be low but the ionised will be normal. Hence a correction factor is to be added, whenever the serum albumin is low, which is given by the formula

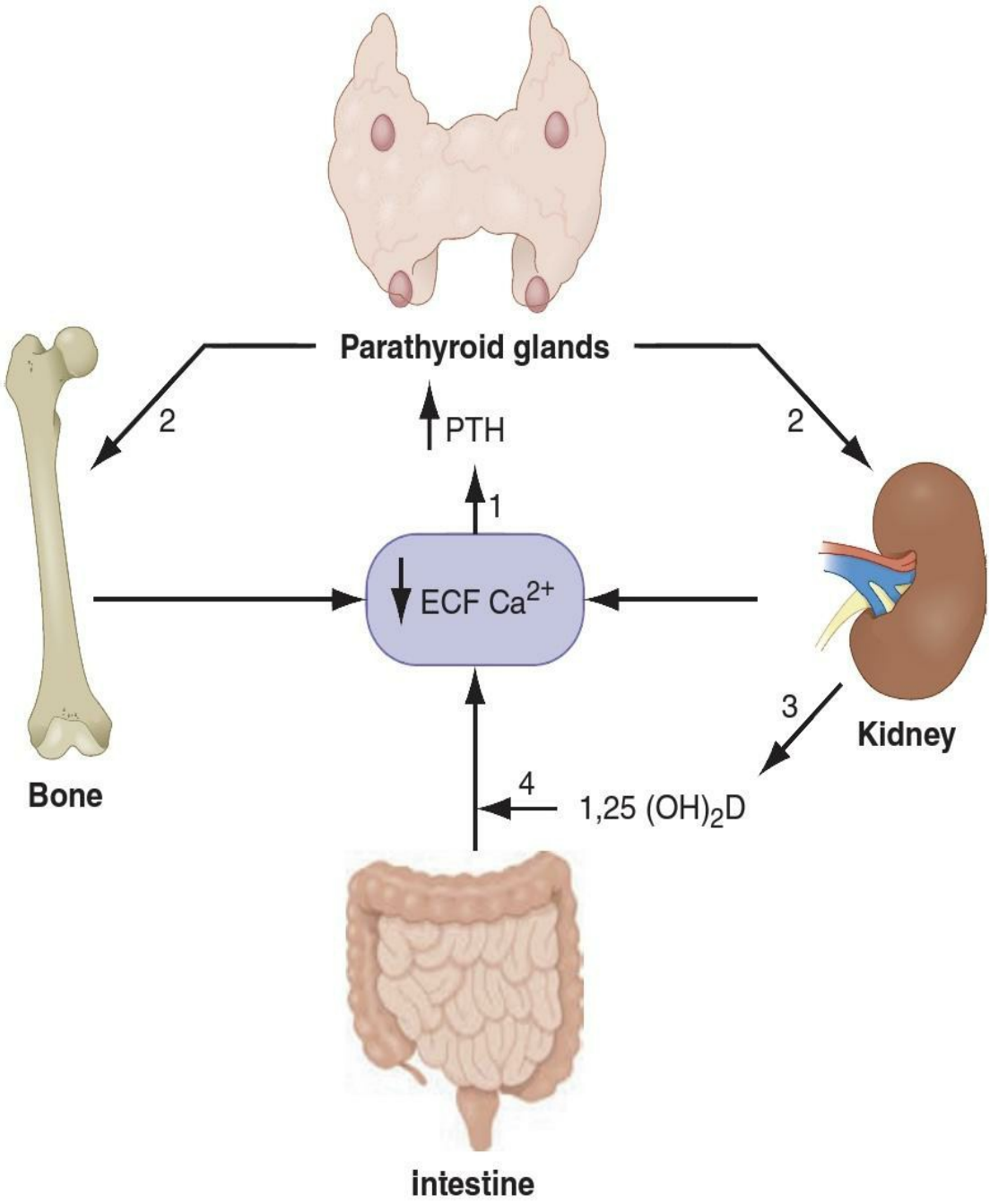
  Corrected calcium = Total calcium + 0.8 X (4.0 - serum albumin)

- The calcium levels in the serum are maintained by two hormones namely

  Parathyroid Hormone (PTH) and Vitamin D

- PTH increases serum calcium levels by stimulating bone resorption, renal absorption and conversion of vitamin D to is active form. Serum calcium also down regulates PTH secretion from Parathyroid gland by negative feedback mechanisms.

- Vitamin D in its active form (calcitriol) increases calcium reabsorption from kidneys, absorption from intestines and bone reabsorption, thereby necessary for bone mineralisation. Vitamin D production is stimulated by hypophosphatemia and increased PTH levels and down regulated by increased serum phosphate levels.



FEEDBACK MECHANISMS MAINTAINING CALCIUM HOMEOSTASIS

COPD AND VITAMIN D DEFICIENCY

- Normal vitamin D levels 20 - 50 ng/mL. A level <12 is indicative of vitamin D deficiency. Vitamin D is important not only for skeletal integrity, but also is protective against chronic diseases like cancer, autoimmune diseases, cardiovascular disease and infectious diseases.

- Several studies have proven that vitamin D deficiency is much commoner in COPD patients due to various reasons such as decreased physical activity and thereby decreased outdoor exposure to sunlight, decreased intake of food, chronic use of inhaled steroids and beta agonists (hypomagnesemia) renal dysfunction in Severe disease.

- Vitamin D deficiency manifests as osteoporosis, osteopenia, recurrent respiratory infections, hypocalcemia and its manifestations.

HYPOCALCEMIA

Serum calcium levels less than 8.5 mg/dL. The most commonest cause of hypocalcemia is false hypocalcemia due to hypoalbuminemia. True hypocalcemia is caused by

1. Hypoparathyroidism - post surgical, hypomagnesemia and idiopathic

2. Vitamin D defect - nutritional, lack of exposure to sunlight, malabsorption, drugs, liver disease, renal disease and Vitamin D dependent rickets

3. Miscellaneous - metabolic or respiratory alkalosis, sepsis, toxic shock syndrome, massive transfusion of blood, acute pancreatitis and burns

4. Severe acute hyperphosphatemia - acute renal failure, tumor lysis syndrome and rhabdomyolysis

CLINICAL FEATURES of hypocalcemia are due to neuromuscular excitability that cause weakness, parasthesia, muscle spasm, carpopedal spasm, bronchospasm, tetany and mental changes. The symptoms vary depending upon the depth and rate of development of hypocalcemia. On physical examination, patient may show signs of Chovstek's sign and Trousseau's sign.

Chovstek's sign - facial twitch elicited by tapping on the facial nerve anterior to the ear lobe, below zygomatic arch with the open mouth.

Trousseau's sign - wrist flexion, metacarpophalangeal joint flexion, thumb flexion and hyper extended fingers when BP cuff inflated around the arm with a pressure more than systolic BP for> 3 minutes.

PATHOPHYSIOLOGY responsible for this neuronal excitability can be explained by the inhibition of sodium channels to open in the presence of calcium in ECF. When there is low calcium in the ECF, this inhibition is lost. Thus the sodium channels open with minimal stimulus and depolarize easily.

TREATMENT

Acute management

- Symptomatic hypocalcemia is usually treated as emergency with 10% calcium glucose 10-20 ml IV slowly over 10 minutes.

- In Severe hypocalcemia 60 ml of calcium glucose in 500 ml of 5% dextrose infused at a rate of 0.5 to 2 mg/kg/hour.

Long term management

- Treating the cause and calcium supplementation (oral elemental calcium 1 to 3 grams/day)

- Vitamin D supplementation

TABLE 50-2 Causes of Hypocalcemia
Low Parathyroid Hormone Levels (Hypoparathyroidism)
Parathyroid agenesis
Isolated
DiGeorge's syndrome
Parathyroid destruction
Surgical
Radiation
Infiltration by metastases or systemic diseases
Autoimmune
Reduced parathyroid function
Hypomagnesemia
Autosomal dominant hypocalcemia
High Parathyroid Hormone Levels (Secondary Hyperparathyroidism)
Vitamin D deficiency or impaired $1,25(OH)_2D$ production/action
Nutritional vitamin D deficiency (poor intake or absorption)
Renal insufficiency with impaired $1,25(OH)_2D$ production
Vitamin D resistance, including receptor defects
Parathyroid hormone resistance syndromes
PTH receptor mutations
Pseudohypoparathyroidism (G protein mutations)
Drugs
Calcium chelators
Inhibitors of bone resorption (bisphosphonates, plicamycin)
Altered vitamin D metabolism (phenytoin, ketoconazole)
Miscellaneous causes
Acute pancreatitis
Acute rhabdomyolysis
Hungry bone syndrome after parathyroidectomy
Osteoblastic metastases with marked stimulation of bone formation (prostate cancer)

HYPOCALCEMIA AND EXACERBATIONS OF COPD

- Several studies have shown that hypocalcemia could cause bronchospasm which may trigger an exacerbation.

- These patients, usually, had Severe airflow obstruction and routine bronchodilators didn't improve the symptoms completely.

- In some patients even correction of calcium, reduced the exacerbation. Thus a correlation between the exacerbations and calcium has to be quantified which would definitely aid in further management of COPD.

MATERIALS AND METHODS

MATERIALS AND METHODS

- **STUDY DESIGN -** Analytical Case-Control Study

- **DURATION OF THE STUDY** - 6 months (June 2018 - December 2018)

- **SAMPLE SIZE** - 50 cases and 50 controls, selected from the patients who got admitted and also gave consent for the study.

- **STUDY CENTRE** - Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, Chennai.

- **SELECTION OF STUDY SUBJECTS** - COPD patients who attended medicine ward and gave willingness for the study

- **ETHICAL CLEARANCE** - Approved on 03.04.2018

- **CONSENT** - Individual written and informed consent

- **ANALYSIS** - Quantitative Statistical Analysis

- **CONFLICT OF INTEREST** - Nil

- **INCLUSION CRITERIA FOR CASES**

  Spirometrically confirmed COPD patients, who belonged to Severity Group C and D

  1. FEV 1 30-49% (GOLD 3)
  2. FEV 1 <30% (GOLD 4)
  3. Exacerbations history of $\geq$ 1 or 2 leading to hospital admissions
  4. MMRC 0-1 & $\geq$ 2
  5. CAT < 10 & > 10
  6. BMI similar to that of Controls (19-25)
  7. Smoking history of atleast 10 pack years

- **INCLUSION CRITERIA FOR CONTROLS**

  Spirometrically confirmed COPD patients who belonged to Severity Group A and B

  1. FEV 1 >80% but FEV 1/FVC < 0.7 (GOLD 1)
  2. FEV 1 50-80% (GOLD 2)
  3. Exacerbations history of $\geq$ 1 without hospital admissions
  4. MMRC 0-1 & $\geq$ 2
  5. CAT < 10 & CAT > 10
  6. BMI similar to that of Cases (19-25)
  7. Smoking history of atleast 10 pack years.

EXCLUSION CRITERIA FOR CASES

- Similar respiratory disease like bronchiectasis, pleural effusion, bronchogenic carcinoma, etc.,
- Diagnosis of asthma
- Chronic treatment with steroids
- History of cystic fibrosis
- Upper and lower respiratory tract infections
- COPD patients who were not capable of performing PFT
- Hypoparathyroidism

EXCLUSION CRITERIA FOR CONTROLS

- Similar respiratory disease like bronchiectasis, pleural effusion, bronchogenic carcinoma, etc.,
- Diagnosis of asthma
- Chronic treatment with steroids
- History of Cystic fibrosis
- Upper and lower respiratory tract infections
- COPD patients who were not capable of performing PFT
- Hypoparathyroidism

DATA COLLECTION

- 50 cases and 50 controls were selected for the study after applying the Inclusion and Exclusion criteria as described above. These patients were subjected to following investigations and clinical characteristics line.

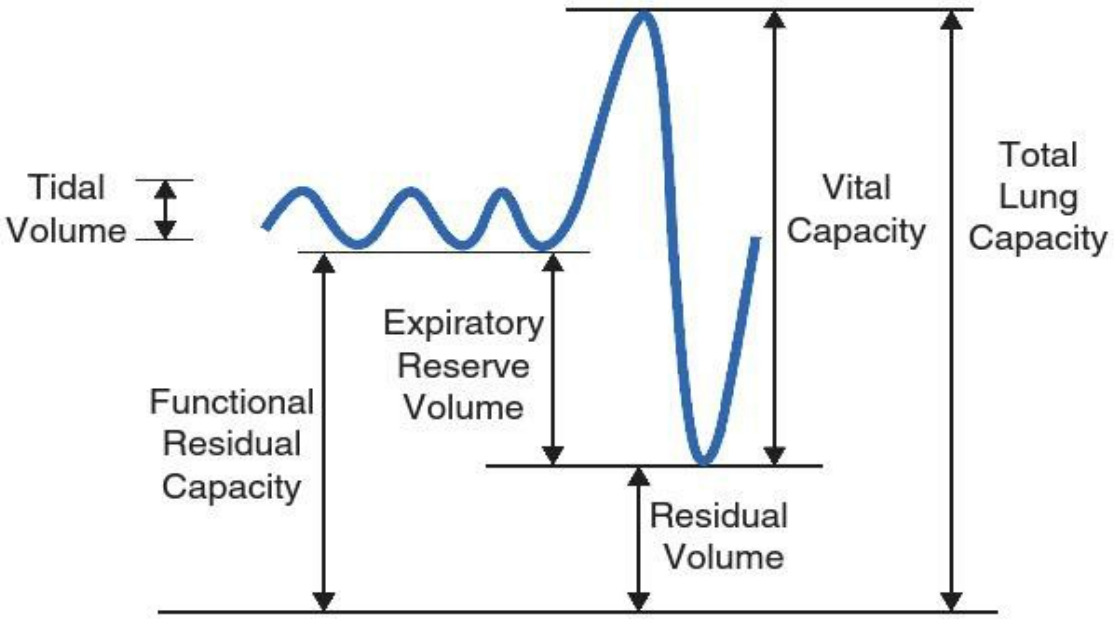
- The relevant studies and investigations done were

  Age, Sex, FEV 1, FEV/FVC, GOLD Criteria, Severity Group, pCO_2 and total Calcium among the selected COPD patients recorded in Proforma prepared according to the need of study.

1. SPIROMETRY

Asked the patient to breathe out through a mouth piece, with closed nostrils, which was connected to a spirometer and the recordings were noted.

- A normal wave of breathing in and out recorded Tidal Volume (**TV)**



NORMAL SPIROMETRY

- Breathing in as much as possible after a normal expiration recorded Inspiratory Reserve Volume (**IRV)**
- Breathing out forcefully and then breathing in normally measured Expiratory Reserve volume (**ERV)**
- Breathing out as much as possible and breathing in as much as possible measured the vital capacity (**V_c = IRV + ERV + TV)** or Forced Vital capacity (**FVC)**
- The volume of air remaining, at the end of maximal expiration, in the lungs was Residual Volume (**RV)**
- Functional Residual Capacity is the summation of Expiratory Reserve volume and Residual Volume which could not be measured by Spirometry. (**FRC = ERV + RV)**
- Total Lung Capacity (**TLC = IRV + TV + ERV + RV)**

NORMAL VALUES OF PFT

1. TIDAL VOLUME TV - 400 to 600 ml
2. INSPIRATORY RESERVE VOLUME IRV - 3000 ml
3. EXPIRATORY RESERVE VOLUME ERV - 1100 ml
4. FORCED VITAL CAPACITY FVC - 4600 ml
5. FORCED EXPIRATORY VOLUME, FIRST SECOND FEV1 - >80% predicted of FVC
6. MAXIMUM VOLUNTARY VENTILATION MVV - 125-175L/min
7. PEAK EXPIRATORY FLOW RATE PEFR - 400-600L/min
8. RATIO OF FEV 1/FVC - 0.75 - 0.80

- PEFR -Peak expiratory flow rate. It is the highest flow rate during expiration
- MVV - Volume of expired air during maximal breathing effort over a given period of time
- FEV 1/FVC - This is more sensitive predictor of air flow obstruction than what FEV 1 and FVC can predict alone.

CALCIUM ESTIMATION

- Preferred specimen was serum
- Container used for collection was Red- top tube (clot activator)
- Specimen volume collected was 0.5 ml of blood
- Collection technique - samples were collected with the patients in the sitting position. Standing, clenching the first or forearm and hemolysis of the sample creates increased calcium values, hence avoided.
- After obtaining the total calcium value, correction with serum albumin level was done by the formula

  Corrected calcium(mg/dL) = total calcium(mg/dL) + 0.8 X [4- serum albumin(g/dL)]
- **GOLD CRITERIA** and Severity Group Were obtained by applying GOLD guidelines.
- pCO_2 was obtained from an Arterial blood gas analysis.

OBSERVATIONS AND RESULTS

Table 1. Comparison of the Cases and Controls based on Age distribution

Age Group	Controls	Cases	Percent	Total
40-50 years	12	10	22%	22
51-60 years	23	23	46%	46
>60 years	15	17	32%	32
Total	50	50	100%	100

Pearson Chi-Square=0.307 P= 0.858

In this study,

22% of the patients belonged to 40-50 years of age (12 controls & 10 cases)

46% of the patients belonged to 51-60 years of age (23 cases & 23 controls)

32% of the patients belonged to above 60 years (15 controls & 17 cases)

Majority of the patient belonged to 51-60 years of patients

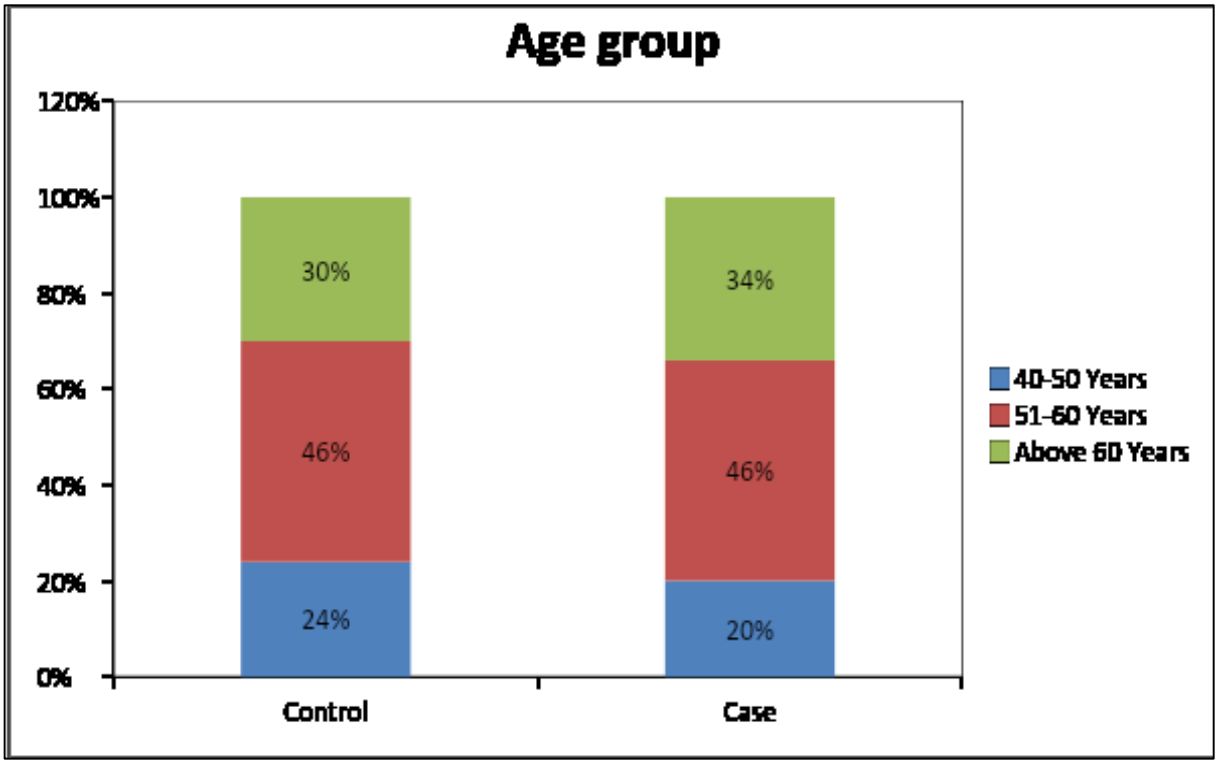


Chart 1. With this graphical representation, it is quite evident that the patients chosen for Cases and Controls were age matched

Table 2. Comparison of Sexual distribution among the Controls and Cases

Sex Distribution among Cases and Controls				
Sex	Controls	Cases	Total	Percent
Male	41	39	80	80%
Female	9	11	20	20%
Total	50	50	100	100%

Pearson Chi-Square=0.250 P= 0.617

In this study,

80% were males (41 Controls & 39 Cases)

20% were females (9 Controls & 11 cases)

Majority of the patients selected were males.

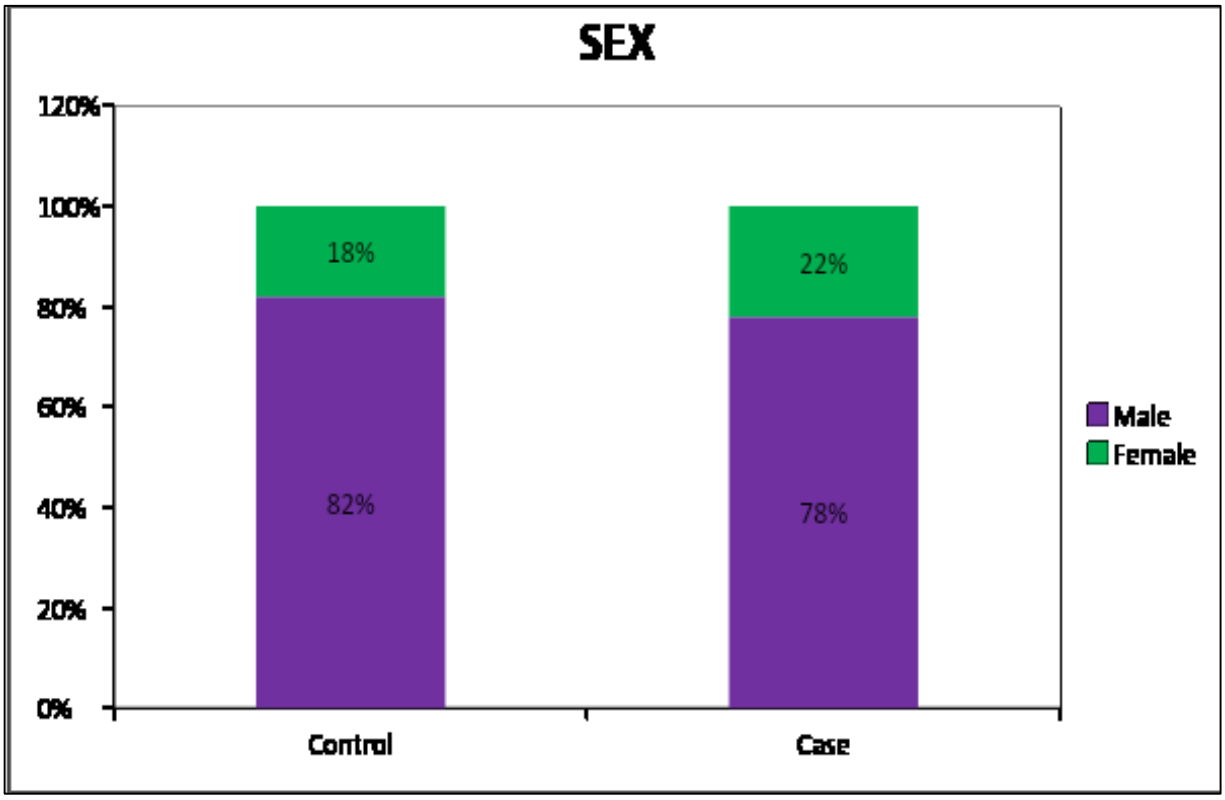


Chart 2. This figure illustrates the unequal distribution of sex among the selected patients, but the Cases are Controls were appropriately sex matched

Table 3. Distribution of patients into Cases and Controls group based on GOLD classification.

GOLD CLASSIFICATION	Control	Case	Total	Percent
GOLD 1	7	0	7	7%
GOLD 2	43	0	43	43%
GOLD 3	0	36	36	36%
GOLD 4	0	14	14	14%
Total	50	50	100	100%

Pearson Chi-Square=100.00** P< 0.001

In this study, after applying GOLD criteria according to GOLD guidelines, patients are gripped into 4 categories

1 - 7 patients (7 in Controls)

2 - 43 patients (43 in Controls)

3 - 36 patients (36 in Cases)

4 - 14 patients (14 in Cases)

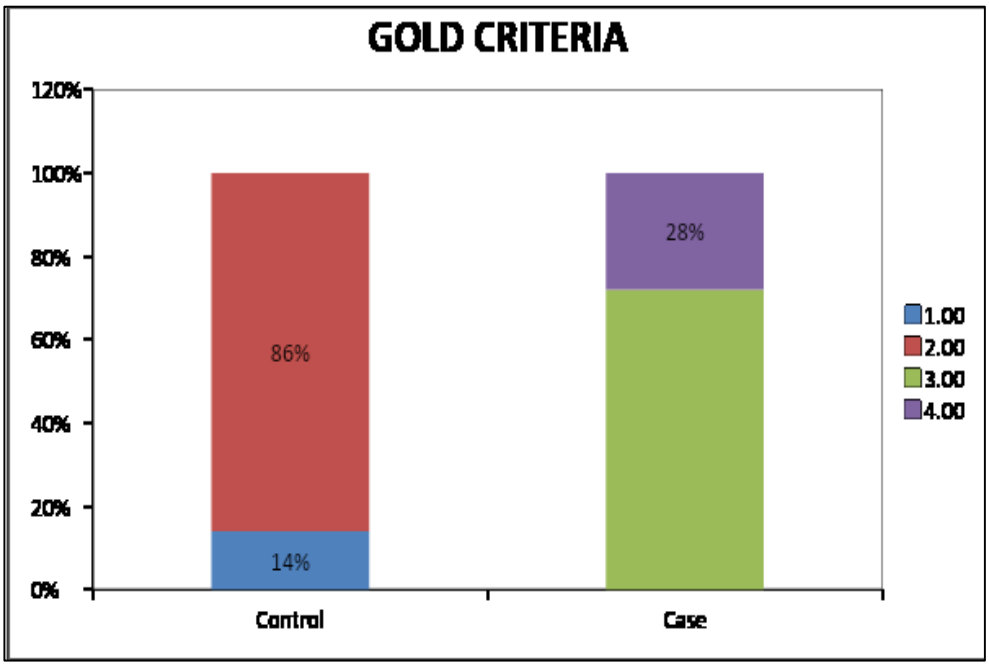


Chart 3. This figure demonstrates the distribution of patients with less severity of lung function among the Controls while more severe in the Cases group

1 - GOLD 1 FEV1/FVC < 0.7 & FEV1> 80%

2 - GOLD 2 FEV1/FVC < 0.7 & FEV1 <80% but >50%

3 - GOLD 3 FEV1/FVC <0.7 & FEV1 <50% but >30%

4 - GOLD 4 FEV1/FVC <0.7 & FEV1 <30%

Table 4. Distribution of patients in control & Cases based on the severity classification according to GOLD guidelines

Severity Group	Control	Case	Total	Percent
A	22	0	22	22%
B	28	0	28	28%
C	0	31	31	31%
D	0	19	19	19%
Total	50	50	100	100%

Pearson Chi-Square=100.00** P< 0.001

After applying GOLD guidelines, patients are categorised into four groups

A - 22 patients (22 in Controls)

B - 28 patients (28 in controls)

C - 31 patients (31 in Cases)

D - 19 patients (19 in Cases)

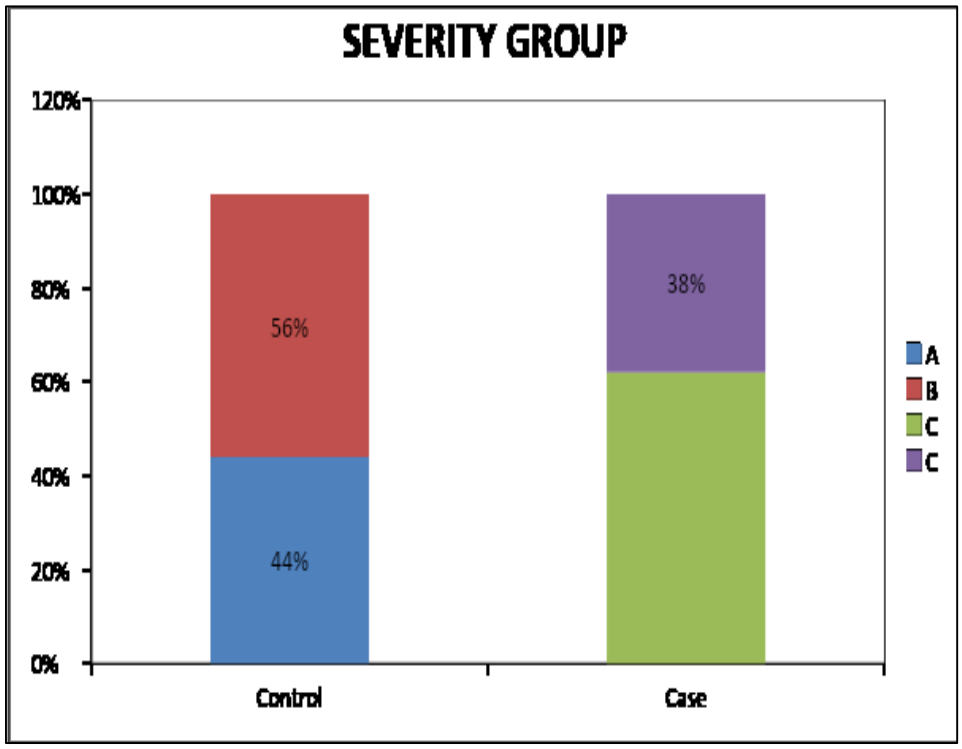


Chart 4. As illustrated, Group A & B were distributed in Controls, while Group C & D were distributed as Cases

Group A - Low symptoms and low risks of exacerbation

Group B - High symptoms but low risks of exacerbation

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks of exacerbation

Table 5. Comparison of FEV1/FVC, FEV1, pCO_2 & Calcium of Cases vs Controls

Variables	Group	N	Mean	Std. Deviation	Std. Error Mean	t value	P value
FEV 1/ FVC	Control	50	.6016	.10187	.01441	8.767**	p<0.001
	Case	50	.4376	.08436	.01193		
FEV1	Control	50	64.3200	9.57556	1.35419	15.400**	p<0.001
	Case	50	37.7600	7.55270	1.06811		
pCO2	Control	50	55.5800	7.37367	1.04279	4.799**	p<0.001
	Case	50	62.5400	7.12630	1.00781		
Calcium	Control	50	8.7080	.76127	.10766	2.930**	0.004
	Case	50	9.1400	.71257	.10077		

In this study, FEV1/FVC, FEV 1, pCO_2 and Calcium levels were measured and compared for Cases and Controls.

Mean FEV 1/FVC - 0.6 (controls) & 0.43 (Cases)

Mean FEV 1 - 64.3% (Controls) & 37.76% (Cases)

Mean pCO_2 - 55.58mmHg (Controls) & 62.54mmHg (Cases)

Mean Calcium - 8.7080 (Controls) & 9.1400 (Cases)

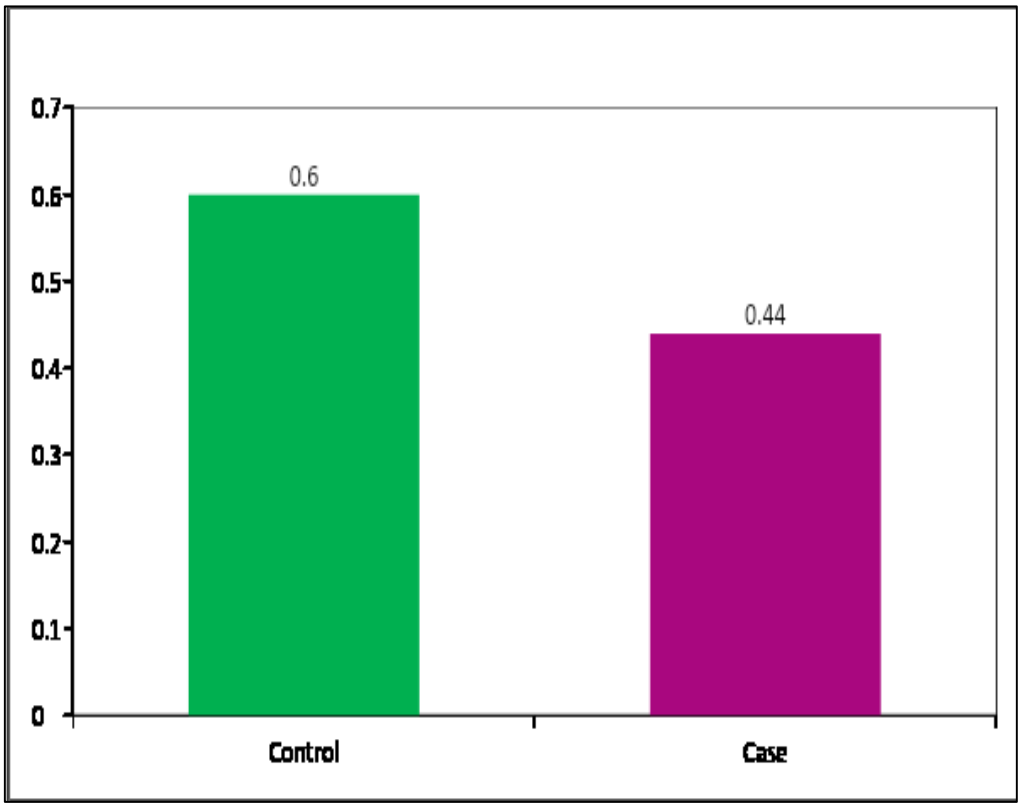


Chart 5. Mean FEV 1/FVC ratio of Controls and Cases is graphically represented, which shows that the ratio is lower in Cases

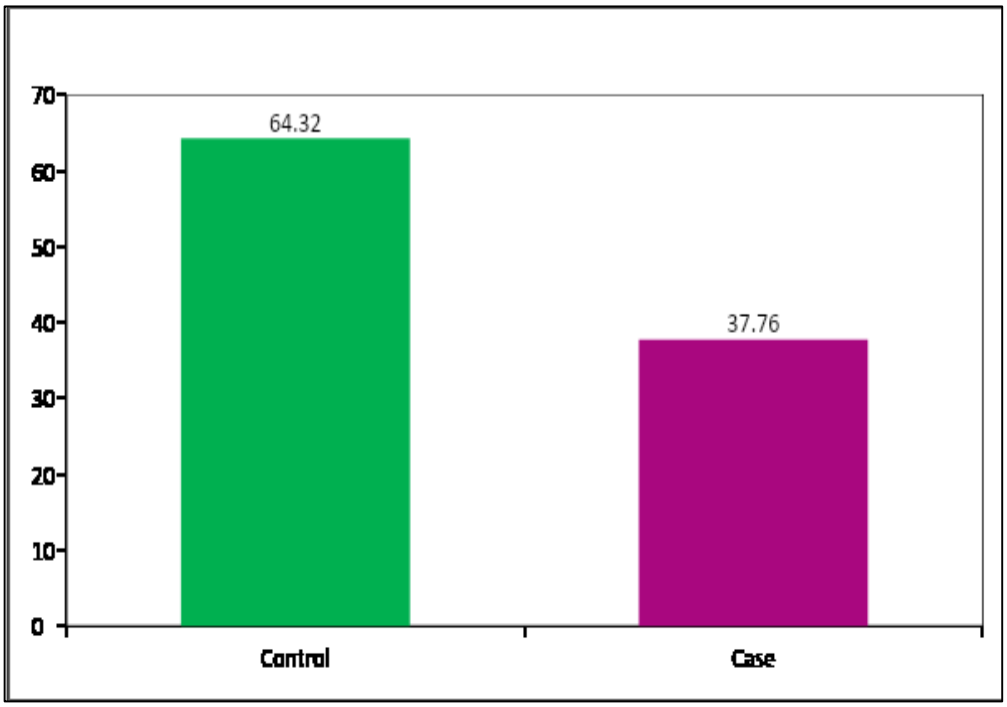


Chart 6. Mean FEV1 of Cases and Controls also represents the lower FEV1 levels in Cases compared to that of Controls

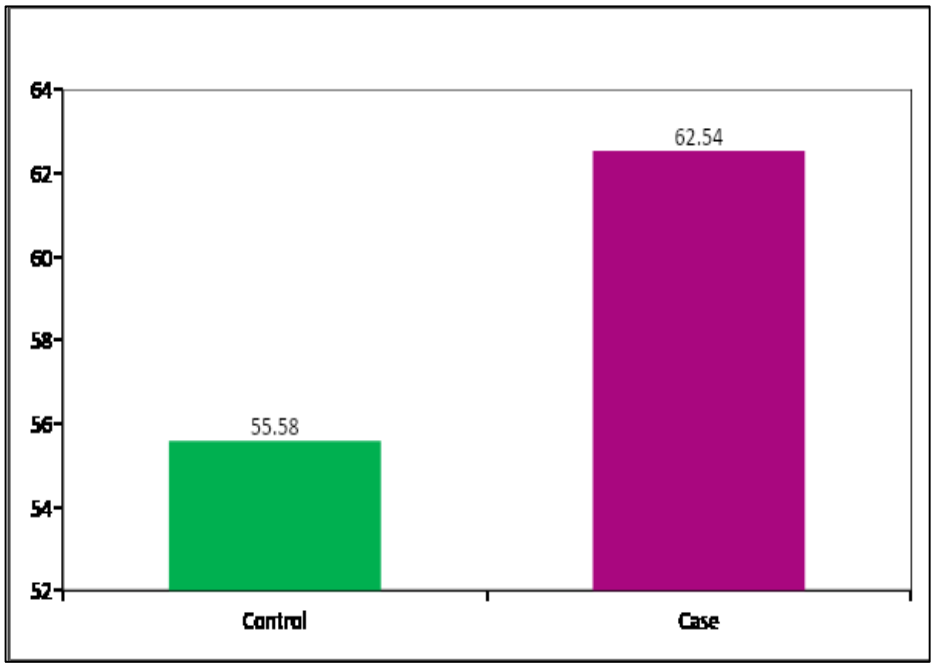


Chart 7. Mean pCO2 of Controls and Cases represented above shows a direct relationship of severity of airflow obstruction with pCO2

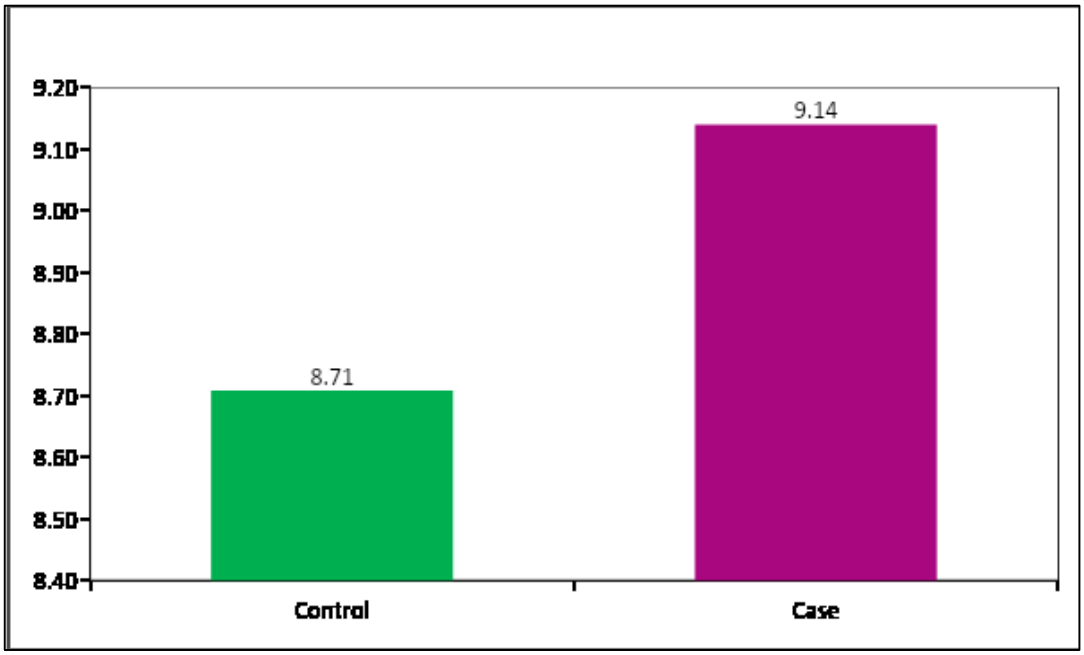


Chart 8. Mean Calcium levels of Controls vs Cases depicts a relatively lower calcium levels in Controls compared to that of Cases

Table 6. Comparison of FEV1/FVC, FEV1, pCO2 & calcium among the classified Severity Groups

Variables & Severity Groups		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min.	Max.	F value	P value
						Lower Bound	Upper Bound				
FEV1/ FVC	A	22	.6473	.03089	.00659	.6336	.6610	.55	.69	32.023	P<0.001
	B	28	.5656	.12267	.02318	.5181	.6132	.04	.68		
	C	31	.4490	.09695	.01741	.4134	.4845	.04	.55		
	D	19	.4189	.05587	.01282	.3920	.4459	.33	.55		
	Total	100	.5196	.12430	.01243	.4949	.5442	.04	.69		
FEV1	A	22	70.04	9.63366	2.0539	65.774	74.316	55.00	83.00	144.797	P<0.001
	B	28	59.82	6.82074	1.2890	57.176	62.466	51.00	75.00		
	C	31	42.03	5.02980	.90338	40.187	43.877	29.00	49.00		
	D	19	30.78	5.51341	1.2648	28.132	33.446	24.00	42.00		
	Total	100	51.04	15.86682	1.5866	47.891	54.188	24.00	83.00		
pCO2	A	22	53.04	7.13461	1.5211	49.882	56.208	44.00	70.00	20.766	P<0.001
	B	28	57.57	7.05234	1.3327	54.836	60.306	42.00	72.00		
	C	31	58.96	5.21845	.93726	57.053	60.881	50.00	70.00		
	D	19	68.36	5.91806	1.3577	65.516	71.220	54.00	78.00		
	Total	100	59.06	8.01743	.80174	57.469	60.650	42.00	78.00		
Calcium	A	22	8.795	.78284	.16690	8.4484	9.1425	7.40	10.60	8.859	P<0.001
	B	28	8.639	.75097	.14192	8.3481	8.9305	7.60	10.10		
	C	31	9.445	.58186	.10450	9.2317	9.6586	8.00	10.40		
	D	19	8.642	.62921	.14435	8.3388	8.9454	7.80	9.90		
	Total	100	8.924	.76503	.07650	8.7722	9.0758	7.40	10.60		

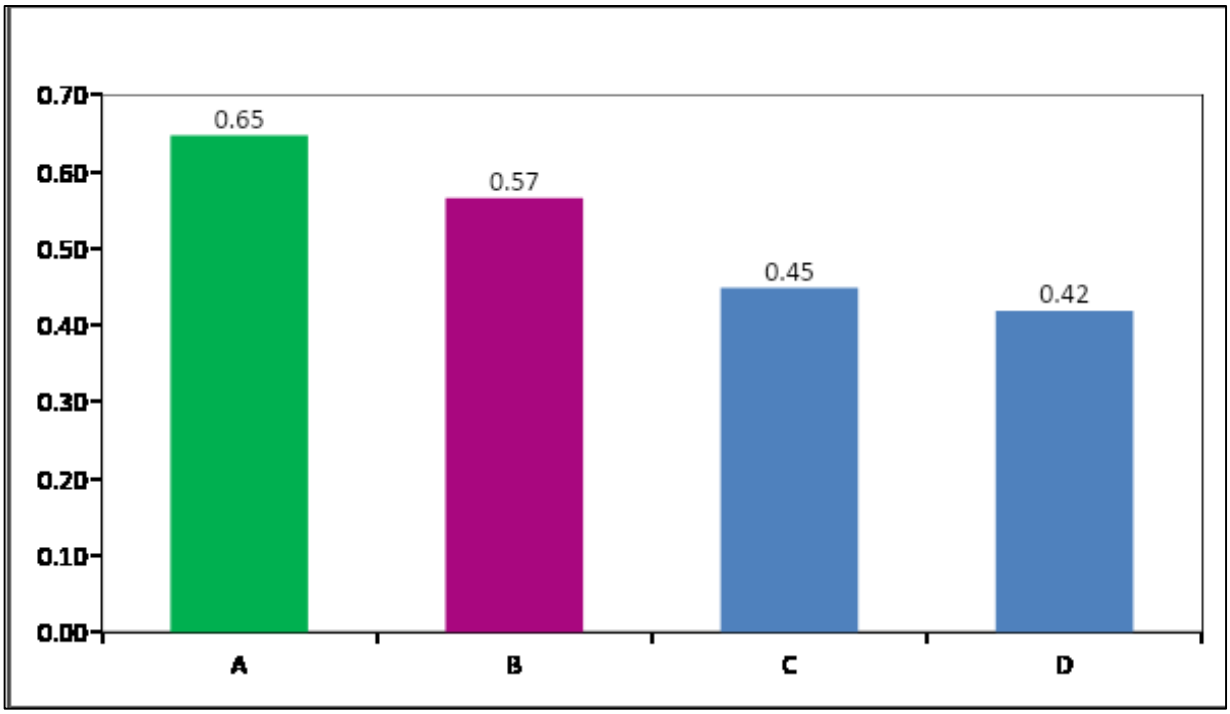


Chart 9. Mean FEV 1/FVC ratio of Group A,B,C & D shows an inverse relationship between the ratio and Severity of airflow obstruction

Group A - Low symptoms and low risks of exacerbation

Group B - High symptoms but low risks of exacerbation

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks of exacerbation

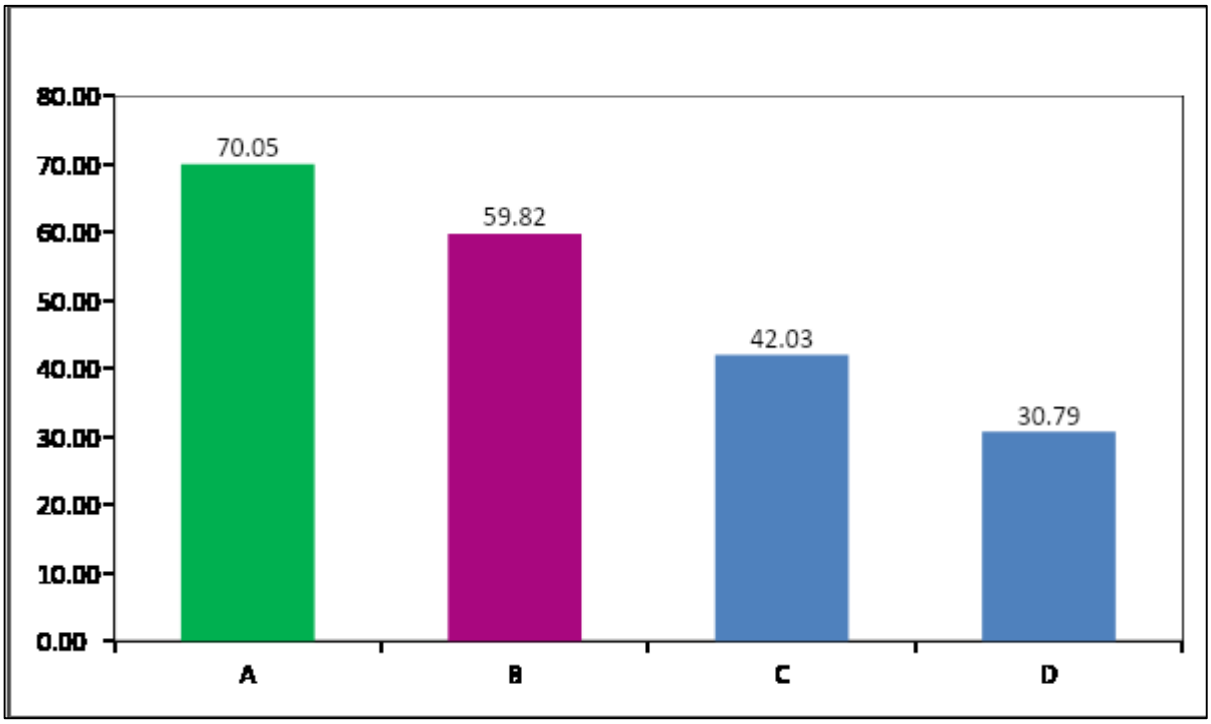


Chart 10. Graphical representation of Mean FEV1 values of Severity Groups A,B,C & D depicting the inverse relationship between FEV1 and Severity of airflow obstruction

Group A - Low symptoms and low risks of exacerbation

Group B - High symptoms but low risks of exacerbation

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks of exacerbation

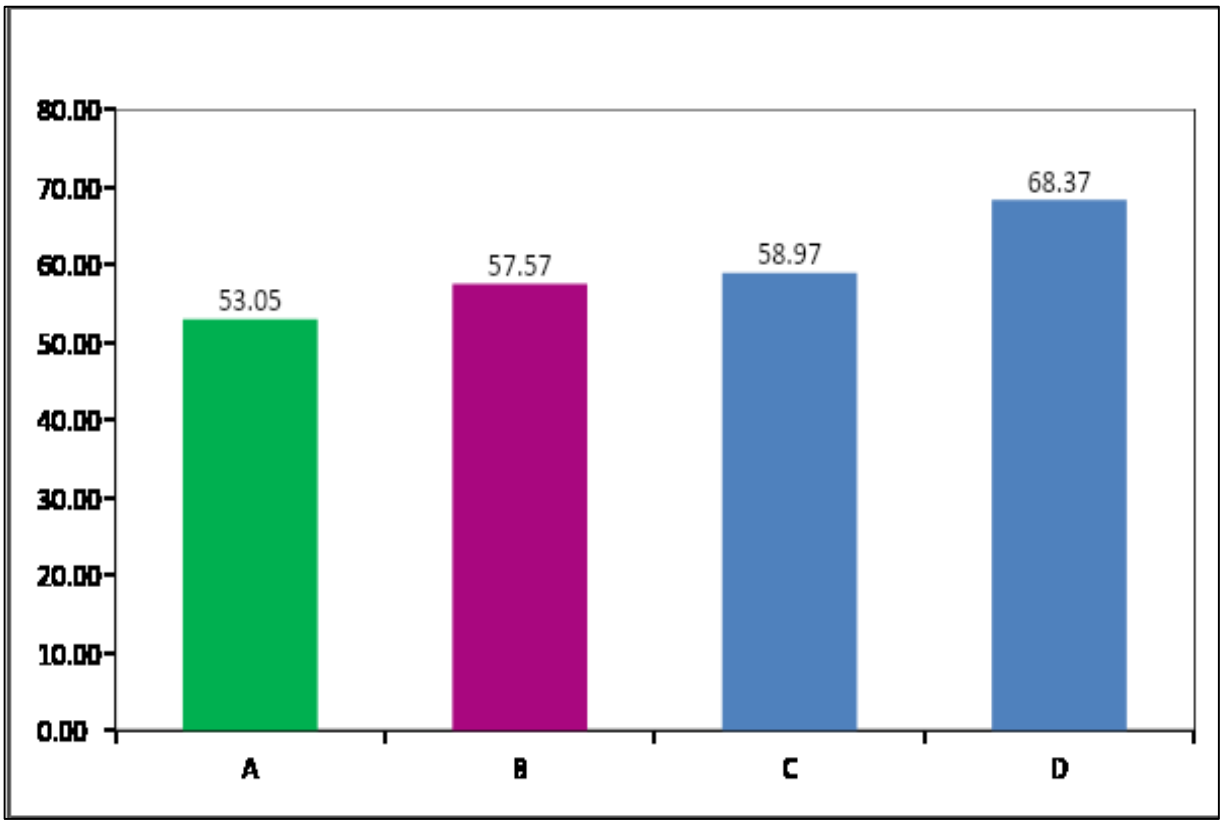


Chart 11. Mean pCO2 levels of individual Severity Groups represented here show a direct relationship between pCO2 and Severity of airflow obstruction

Group A - Low symptoms and low risks of exacerbation

Group B - High symptoms but low risks of exacerbation

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks of exacerbation

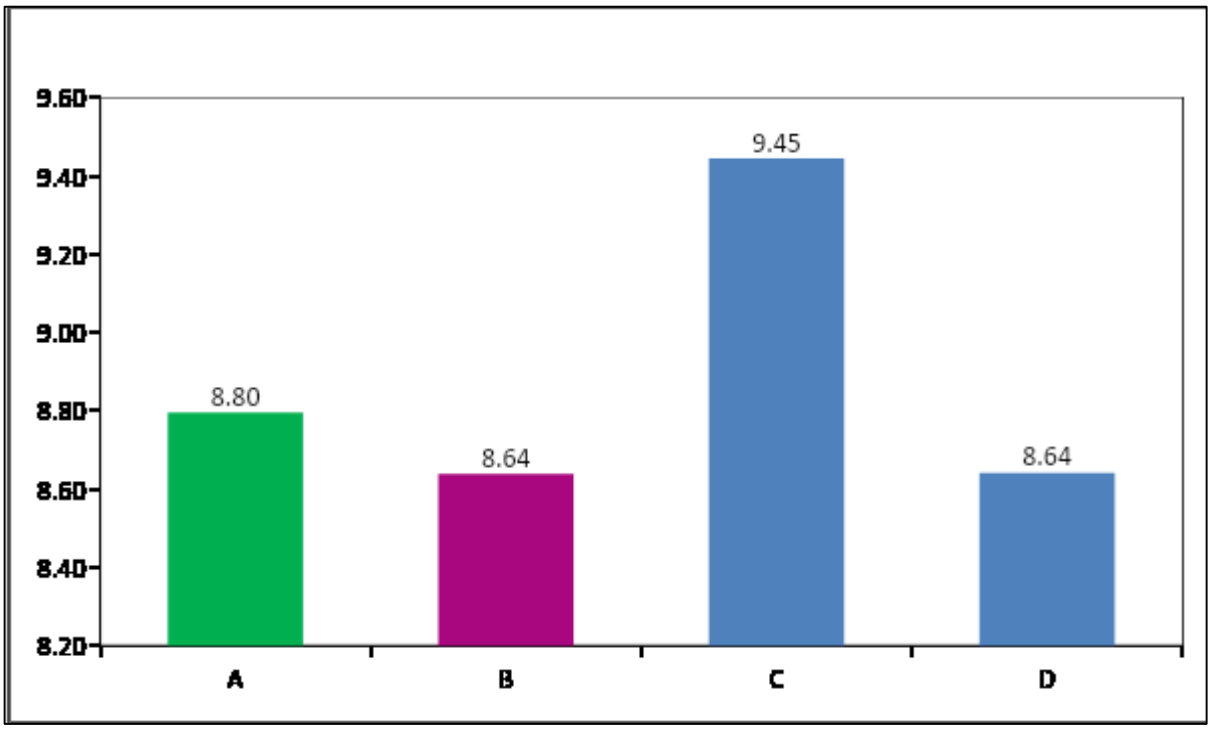


Chart 12. Relationship between Mean Calcium levels and Severity Groups A,B,C & D represented graphically

Group A - Low symptoms and low risks of exacerbation

Group B - High symptoms but low risks of exacerbation

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks of exacerbation

DISCUSSION

This study involved 100 COPD patients, who gave consent, and whose pulmonary functions evaluated and categorised according to the GOLD GUIDELINES and their serum total calcium levels determined.

The values were recorded and the results analysed

AGE DISTRIBUTION

Among the study population, 46 patients belonged to 51-60 years of age. Of these 46 patients, 23 each to Cases and Controls. Of these patients 9 were females and 37 were male patients. **(Table 1)**

32 patients belonged to > 60 years of age. Out of which 15 patients belonged to controls group and 17 belonged to Cases group. 6 females and 26 males was the sex distribution within these groups.

22 patients belonged to 40-50 year group. Of this 12 were from controls group and 10 from cases group, while 5 were females and 17 were males.

From above discussion, it can be understood, the Controls and cases were similarly age matched. **(Chart 1)**

SEX DISTRIBUTION

Out of the 100 patients, 80 patients were males, while 20 were females.

Of the 80 male patients, 41 patients belonged to controls and 39 patients belonged to Cases and 9 female patients belonged to controls, while 11 patients belonged to Cases

Thus it is similarly matched in sex distribution. **(Chart 2)**

GOLD CRITERIA

Controls and Cases were categorised, primarily based on GOLD guideline, into 1, 2 and 3, 4 respectively, which in turn are spirometry defined values as discussed earlier.

Of the 50 patients from controls group, 7 belonged to GOLD classification 1 & 43 belonged to GOLD classification 2

Of the patients from cases group, 36 belonged to GOLD classification 3 & 14 belonged to GOLD classification 4.

Thus, the controls and cases were divided based on spirometry values, with an underlying logic of more Severe patients belonging to Cases, while less severe in controls group. **(Chart 3)**

SEVERITY GROUP

Based on GOLD classification and clinical details, patients were classified into 4 groups

Group A - Low symptoms and low risks of exacerbations

Group B - High symptoms but low risks of exacerbations

Group C - Low symptoms but high risks of exacerbation

Group D - High symptoms and high risks for exacerbations

In our study, no of patients in **(Table 4)**

Group A - 22 patients (22 Controls), Group B - 28 patients (28 controls), Group C - 31 patients (31 Cases) & Group D - 19 patients (19 Cases)

COMPARISON OF THE VARIABLES BETWEEN CASE AND CONTROLS(Table 5)

Mean FEV 1/FVC was lower in cases. It was 0.6016 in controls and 0.4376 in Cases. This was as predicted since cases had patients with more declined lung function.**(Chart 5)**

Mean FEV 1 also showed a similar pattern as one would anticipate. It was much lower in cases as compared to that of Controls. It was 64.32% in controls, whereas 37.760 in cases. **(Chart 6)**

Mean pCO2 was higher in Cases as compared to that of Controls, indicating more CO2 retention in patients belonging to Cases as a consequence of higher airflow obstruction.**(Chart 7)**

Whereas, in contradiction to what was predicted, Calcium was lower in controls compared to that of Cases. The Mean Calcium levels of controls was 8.7080, while that of Cases was 9.1400 **(Chart 8)**

So, this statistical analysis gave us the correlation between Cases, Controls and calcium.

Although, the Mean Calcium level was lower in controls, we should analyse little more about the variables by Severity Group wise distribution.

COMPARISON OF VARIABLES AMONG INDIVIDUAL SEVERITY GROUP. (Table 6)

Mean FEV 1/ FVC for each group is as follows **(Chart 9)**

Group A - 0.6473, Group B - 0.5656, Group C - 0.4490 & Group D - 0.4189

It declined as the severity increased. Thus FEV 1/FVC ratio forms an inverse relationship with the grade of severity of the disease.

Mean FEV1 for each group is as follows **(Chart 10)**

Group A - 70.0455, Group B - 59.8214, Group C - 42.0323 & Group D - 30.7895

Similar to FEV 1/ FVC, this also declined with increasing severity. Thus FEV 1 forms an inverse relationship with the grade of severity of the disease

Mean pCO2 for each group is as follows **(Chart 11)**

Group A - 53. 0455, Group B - 57.5714, Group C - 58.9677 & Group D - 68.3684

The pCO2 value increases with increase in the severity of the disease. Thus pCO2 forms a direct relationship with the grade of severity of the disease

Mean Calcium levels for each group is as follows **(Chart 12)**

Group A - 8.7955, Group B - 8.6393, Group C - 9.4452 & Group D - 8.6421

From the above values, there is no obvious relationship that could be established. But, once, when the definition of each groups are carefully noted and taken into account, a good quantifiable relationship could be obtained.

Although, the Mean Calcium was lower in Controls compared to that of Cases, within the Controls Group B had lower Mean Calcium comparing to that of Group A. As already defined, Group B contains patients with low symptoms, but high risks of exacerbations.

Similarly though, the Mean Calcium levels were higher in Cases compared to that of Controls, within the Cases, Group D had much lower Calcium levels to that of Group C. As defined, Group D contains High symptoms and high risks of exacerbations.

Thus, from above discussion, it could be derived that Calcium levels were lower in patients with High symptoms, whatever maybe the risks of exacerbations associated. Hence, an inverse relationship could be established between Serum calcium and the degree of symptoms of COPD patients.

SUMMARY OF THE RESULTS

The Age group with highest number of patients - 51-60 years of age (46 patients) The sex group with highest number of patients - Male (80 patients) FEV 1/FVC forms an inverse relationship with the grade of severity of the patients. Similarly FEV 1 forms an inverse relationship with the grade of severity of the patients PCO2 forms a direct relationship with the grade of severity of the patients. Serum Calcium levels forms an inverse relationship with the grade of symptoms in COPD patients.

CONCLUSION

The serum Calcium levels were found to be decreased in Chronic Obstructive Pulmonary Disease patients, who had high symptoms such as breathlessness of grade ≥ 2 according to MMRC Classification or COPD Assessment test (CAT Score) > 10, whether the patient had high or low risks of exacerbation. Thus, Serum Calcium forms an inverse relationship with grade of symptoms of COPD patients. Hence, I conclude measuring Serum Calcium in a highly symptomatic COPD patients could aid in further management of these patients.

LIMITATIONS OF THE STUDY

Although the number of COPD patients who attended the ward during the study were competitively more than the selected sample size, most of them could not be included in the study, because many of the patients were either not willing to do PFT or unable to do PFT.

The Past history of the patients, especially, previous exacerbation in the last year was vital in this study. And it was not re-produced properly by some of the patients and they were not included in the study.

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PROFORMA

A CASE CONTROL STUDY ON SERUM CALCIUM LEVELS IN EXACERBATIONS OF COPD.

NAME :

AGE/ SEX :

OP/IP NO:

OCCUPATION:

ADDRESS:

CONTACT NUMBER :

SYMPTOMS:

1. Breathlessness (mMRC dyspnea scale)
2. Cough with our without sputum production
3. Chest discomfort

PAST HISTORY :

History of similar complaints in the past

History of any other co morbid illness

PERSONAL HISTORY :

History of alcohol intake : type of alcohol, quantity and duration

History of other substance abuse

GENERAL EXAMINATION :

Consciousness, orientation to time, place and person

Pallor/ Icterus / Cyanosis / Clubbing / Pedal edema / lymphadenopathy

Blood pressure / Pulse rate / respiratory rate / Temperature

SYSTEMIC EXAMINATION :

Cardiovascular system:

Respiratory system

Per abdomen:

Central nervous system:

INVESTIGATIONS :

✓ Complete blood count

✓ Renal function test

✓ Liver function test

✓ Serum Calcium levels

✓ X ray chest

✓ Spirometry

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.G.Rajasekar
I Year PG in M.D. General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai

Dear Dr.G.Rajasekar,

The Institutional Ethics Committee has considered your request and approved your study titled "**A CASE CONTROL STUDY ON SERUM CALCIUM LEVELS IN EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE** " - **NO.15042018**

The following members of Ethics Committee were present in the meeting held on **03.04.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar	:Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH	: Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
9. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
10.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
11.Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3	: Member
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
14.Thiru K.Ranjith, Ch- 91	: Lay Person

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

6/4/18
Member Secretary – Ethics Committee

URKUND

Urkund Analysis Result

Analysed Document: CASE CONTROL STUDY OF CALCIUM LEVELS IN COPD.docx (D58408322)
Submitted: 11/7/2019 6:12:00 AM
Submitted By: sachinraja15@gmail.com
Significance: 1 %

Sources included in the report:

https://www.slideshare.net/drkhanamirzada/copddramirzadah
https://www.karger.com/Article/FullText/355526

Instances where selected sources appear:

5

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"A CASE CONTROL STUDY ON CALCIUM LEVELS IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**" of the candidate **Dr.Rajasekar. G**., Post graduate in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital,Chennai-03, for the award of M.D., DEGREE in the branch of BRANCH-I (GENERAL MEDICINE). I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 1 percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

INFORMATION TO PARTICIPANTS

INVESTIGATORS: Dr. G. Rajasekar

Dr. R. Muthuselvan, M.D.,

NAME OF THE PARTICIPANT :

You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please free to ask if you have any queries or concerns

We are conducting "A CASE-CONTROL STUDY ON SERUM CALCIUM LEVELS IN EXACERBATIONS OF COPD" among patients attending Rajiv Gandhi Government General Hospital, Chennai. Your co-operation to undergo relevant investigations as per need may be valuable to us.

The purpose of this study is to find the correlation between serum Calcium levels and exacerbations of COPD.

We are selecting certain cases and if you are found eligible, we would like to perform extra tests and you will be subjected to a blood investigation which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Right /left thumb impression of Participant

Date:

Place:

ஆய்வு தகவல் தாள்

ஆய்வு தலைப்பு : **நாள்பட்ட தடுப்பு நுரையீரல் நோயின் கடுமையான அதிகரிப்புகளில் கால்சியம் அளவைப் பற்றிய ஒரு வழக்கு கட்டுப்பாட்டு ஆய்வு**

ஆய்வாளர் பெயர் : **டாக்டர். ராஜசேகர். G**

ஆய்வு நிலையம் : பொது மருத்துவப் பிரிவு,
சென்னை மருத்துவக் கல்லூரி, சென்னை-3.

இந்த ஆய்வில் தங்களை பங்கேற்க அழைக்கிறோம். இந்த தகவல் அறிக்கையில் கூறப்பட்டிருக்கும் தகவல்கள் தாங்கள் இந்த ஆராய்ச்சியில் பங்கேற்கலாமா வேண்டாமா என்பதை முடிவு செய்ய உதவியாக இருக்கும். இந்த படிவத்தில் உள்ள தகவல்கள் பற்றி உள்ள சந்தேகங்களை நீங்கள் தயங்காமல் கேட்கலாம்.

இதில் பெரியவர்களுக்கு இரத்த அழுத்தம் அளவீடு - மெர்குரி ஸ்பைக்மோமனோமீட்டர்க்கு மாற்றாக அனிராய்டு அல்லது அசெல்லோமெட்ரி - ஒரு சரிபார்த்தல் ஆய்வு நடைபெறுகிறது. அதற்கு இரத்த அழுத்தம் அளவீடு அவசியம், அதற்குத் தங்கள் ஒத்துழைப்புத் தேவை.

நீங்கள் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியில் இருந்து பின் வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்புப் பரிசோதனையின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவில் தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம்

தேதி :

பங்கேற்பாளர் கையொப்பம் /
இடது கட்டைவிரல் ரேகை
தேதி :

PATIENT CONSENT FORM

Study Detail: “A CASE-CONTROL STUDY ON SERUM CALCIUM LEVELS IN EXACERBATIONS OF COPD”

Study Centre: Rajiv Gandhi Government General Hospital, Chennai.

Patient’s Name :

Patient’s Age:

Identification Number :

Documentation of the informed consent :

1. I _____ have read the information in this form (or it has been read for me). I was free to ask any questions and they have been answered. I am over 18 years of age and exercising my free power of choice, hereby give my consent to be included as a participant in the study.

2. I have read and understood this consent form and the information provided to me.

3. I have had the consent document explained to me.

4. I have been explained about the nature of the study.

5. I have been explained about my rights and responsibilities by the Investigator.

6. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

7. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, govt. agencies and IEC.I understand that they are publicly published

8. I have understood that my identity will be kept confidential if my data are publicly presented.

9. I have had my questions answered to my satisfaction.

10. I have decided to be in the research study

11. I am aware that if I have any question during this study, I should contact at one of the addresses listed above. By signing this consent form I attest that the information given in

this document has been clearly explained to me and apparently understood by me. I will be given a copy of this consent document.

Name and signature/thumb impression of the participant (or legal representative if participant incompetent)

_____	_____	_____
Name	Signature	Date

Name and Signature of the investigator or his representative obtaining consent:

_____	_____	_____
Name	Signature	Date

ஆய்வு ஒப்புதல் படிவம்

ஆய்வு தலைப்பு : **நாள்பட்ட தடுப்பு நுரையீரல் நோயின் கடுமையான அதிகரிப்புகளில் கால்சியம் அளவைப் பற்றிய ஒரு வழக்கு கட்டுப்பாட்டு ஆய்வு**

பெயர் :
வயது :
பால் :

தேதி :
வெளிநோயாளி எண் :
ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பெரியவர்களுக்கு இரத்த அழுத்தம் அளவீடு - மெர்குரி ஸ்பைக்மோமனோமீட்டர்க்கு மாற்றாக அனிராய்டு அல்லது அசெல்லோமெட்ரி - ஒரு சரிபார்த்தல் ஆய்வு நடைபெறுகிறது என்பதை ஆராய்ச்சியாளர் கூற அறிந்துகொண்டேன்.

மேற்கண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

நான் ஆராய்ச்சியாளருடன் ஒத்துழைப்பேன் என்றும், எனக்கு ஏற்படக்கூடிய ஆசாதாரண நிகழ்வுகள் பற்றியும் உடனடியாக ஆராய்ச்சியாளரிடம் தெரிவிப்பேன் என்று உறுதி கூறுகிறேன். இந்த ஆய்விலிருந்து எப்போது வேண்டுமானாலும் எக்காரணமும் கூறாமல் என்னை விடுவித்துக்கொள்ளலாம் என்பதை அறிவேன்.

என்னிடம் இருந்து பெறப்படும் தகவல்களை அரசு, வரைமுறை அதிகாரிகள் ஆகியோர்களுடன் பகிர்ந்துகொள்ள ஆராய்ச்சியாளருக்கு அனுமதி அளிக்கிறேன். என்னுடைய சிகிச்சைக்கட்டுகளை பார்வையிட உரிமை உண்டு. என்னுடைய தகவல்களின் அடையாளம் இரகசியமாக வைக்கப்படும் என்பதை அறிவேன்.

இந்த ஆராய்ச்சியில் பங்கேற்க தன்னிச்சையாக முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் / ரேகை

பங்கேற்பவர் பெயர்

இடம் :

தேதி :

ஆய்வாளர் கையொப்பம்

ஆய்வாளர் பெயர்

இடம் :

தேதி :

	Controls							
S.No	Age	Sex	FEV1/FVC	FEV1%	GOLD Criteria	Severity Group	pCO2	Calcium
1	47	Male	0.62	64	2	A	60	8.6
2	50	Female	0.67	75	2	B	56	8.8
3	46	Male	0.63	70	2	A	61	9.2
4	51	Male	0.55	59	2	A	70	9.1
5	64	Male	0.68	73	2	B	51	8.6
6	62	Male	0.63	77	2	A	49	8.4
7	67	Male	0.65	55	2	A	59	7.9
8	69	Male	0.67	62	2	B	60	9.6
9	64	Female	0.55	53	2	B	57	8.7
10	51	Male	0.54	53	2	B	61	8.1
11	62	Male	0.65	72	2	B	47	8.5
12	64	Male	0.67	74	2	A	49	9
13	52	Male	0.67	81	1	A	51	9.1
14	54	Male	0.62	61	2	A	62	8.8
15	42	Male	0.54	54	2	B	66	7.9
16	47	Female	0.45	54	2	B	67	7.6
17	61	Male	0.61	62	2	A	56	10.3
18	49	Male	0.65	80	1	A	48	9.9
19	67	Female	0.63	62	2	B	51	9.2
20	69	Male	0.65	67	2	B	56	8.9
21	41	Male	0.67	81	1	A	48	8.6
22	57	Male	0.54	57	2	B	62	7.6
23	67	Female	0.57	55	2	B	61	9.2
24	58	Male	0.59	58	2	B	59	8.2
25	51	Male	0.67	82	1	A	51	8.1
26	63	Male	0:54	52	2	B	63	7.9
27	53	Male	0.64	57	2	B	64	7.6
28	60	Male	0.64	56	2	A	62	7.4
29	55	Male	0.67	58	2	A	61	8
30	56	Female	0.56	65	2	B	56	9.1
31	44	Male	0.68	80	1	A	46	8.8
32	58	Male	0.63	63	2	A	52	8.6
33	60	Male	0.67	62	2	A	49	10.6
34	45	Male	0.58	61	2	B	50	10.1
35	54	Female	0.64	72	2	A	46	9.4
36	55	Male	0.66	66	2	B	47	8.9
37	50	Male	0.69	70	2	A	44	8.4
38	51	Male	0.65	69	2	A	51	8.2
39	45	Male	0.66	82	1	A	48	8
40	63	Female	0.59	54	2	B	57	9.6
41	60	Male	0.67	66	2	B	52	8.8
42	43	Male	0.67	83	1	A	44	9.1
43	54	Male	0.45	51	2	B	68	7.6
44	68	Male	0.49	52	2	B	72	7.7
45	56	Male	0.58	61	2	B	60	8.1
46	61	Male	0.54	56	2	B	62	8.2
47	54	Male	0.64	62	2	B	50	9.6
48	60	Male	0.53	54	2	B	60	9
49	60	Male	0.62	66	2	B	42	8.8
50	57	Female	0.52	57	2	B	55	10

Cases								
S.No	Age	Sex	FEV1/FVC	FEV 1%	GOLD Criteria	Severity Group	pCO2	Calcium
1	60	Female	0.48	24	4	D	74	8
2	47	Male	0.48	45	3	C	62	8.9
3	57	Male	0.55	40	3	C	60	8.8
4	72	Female	0.47	32	3	D	76	7.9
5	60	Male	0.45	26	4	D	68	9.6
6	65	Male	0.48	27	4	D	66	9.9
7	50	Male	0.5	45	3	C	56	9
8	62	Male	0.47	36	3	C	60	9.2
9	54	Female	0.44	38	3	D	64	9.6
10	47	Male	0.48	49	3	C	56	10
11	51	Male	0.42	39	3	C	64	9.1
12	62	Male	0.39	27	4	D	72	8.4
13	47	Male	0.55	42	3	C	63	9.7
14	52	Female	0.42	39	3	C	62	9.9
15	61	Male	0.55	42	3	D	64	9.1
16	54	Male	0.43	40	3	C	65	8.7
17	50	Male	0.39	28	4	D	72	8.1
18	42	Male	0.4	29	4	C	70	8
19	63	Female	0.51	36	3	C	54	10.3
20	61	Male	0.44	30	4	D	70	8.2
21	60	Male	0.39	28	4	D	66	9.1
22	44	Male	0.52	46	3	C	58	9.4
23	55	Male	0.44	38	3	C	60	9.1
24	64	Male	0.54	47	3	C	52	10
25	71	Male	0.38	29	4	D	78	7.9
26	60	Female	0.42	36	3	C	63	8.7
27	54	Male	0.55	41	3	C	59	9.5
28	62	Male	0.45	39	3	D	61	8.8
29	59	Female	0.42	44	3	C	64	9.4
30	44	Male	0:55	48	3	C	50	10.1
31	66	Male	0.46	41	3	C	55	9.8
32	72	Male	0.38	26	4	D	73	8.4
33	44	Female	0.48	45	3	C	63	9.2
34	47	Male	0.44	48	3	C	57	10.2
35	52	Male	0.53	47	3	C	51	9
36	54	Male	0.4	44	3	C	56	9.6
37	62	Male	0.47	39	3	C	54	10.4
38	60	Male	0.36	29	4	D	75	7.8
39	57	Female	0.44	48	3	C	58	8.7
40	64	Male	0.44	37	3	D	62	8.9
41	55	Male	0.34	29	4	D	68	8.8
42	61	Male	0.46	41	3	C	63	9.5
43	70	Male	0.37	26	4	D	69	8.2
44	55	Female	0.29	31	3	C	70	9.1
45	61	Male	0.34	44	3	C	62	9.7
46	52	Male	0.33	28	4	D	67	8.5
47	55	Male	0.46	45	3	C	57	10.4
48	60	Male	0.51	48	3	C	52	9.6
49	52	Female	0.43	40	3	D	54	9
50	51	Male	0.5	42	3	C	52	9.8