

**A STUDY ON CLINICAL PROFILE OF CHRONIC OBSTRUCTIVE
PULMONARY DISEASES AND CORRELATION OF HIGHLY
SENSITIVE C-REACTIVE PROTEIN WITH INCREASING
SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES**

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CHENNAI**

CERTIFICATE

This is to certify that this dissertation titled “**A STUDY ON CLINICAL PROFILE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES AND CORRELATION OF HIGHLY SENSITIVE C-REACTIVE PROTEIN WITH INCREASING SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES**” submitted by **Dr.R.VAIRAKKANI** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I, **Dr.R.VAIRAKKANI**, solemnly declare that the dissertation titled “**A STUDY ON CLINICAL PROFILE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES AND CORRELATION OF HIGHLY SENSITIVE C-REACTIVE PROTEIN WITH INCREASING SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASES**” has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai**, in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine.

Place : Madurai

Date :

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INTRODUCTION

Chronic obstructive pulmonary disease, a disorder of expiratory airflow has been projected to be the 3rd leading cause of mortality and 5th cause for disability as measured by DALY in 2020 by the Global burden of Disease study. It is one of the few diseases whose morbidity and mortality are increasing at an alarming rate day by day and imposing a heavy economic burden on the countries particularly the developing countries like others. Reasons for this troubling situation include the reduction in other cause mortality increasing the longevity of the population, increasing tobacco use & increasing environmental pollution. The situation is so alarming that the disease has achieved epidemic proportions. Many advances have been made recently in the diagnosis and management of this disease but the hard fact is that the disease is one of gradual progression, increasing morbidity and incurable and the better way to handle this by prevention by healthy life style, very importantly avoiding tobacco use.

Chronic obstructive pulmonary disease is a disorder of pulmonary inflammation and in contrary to yester years belief that it is confined only to the respiratory system, studies over the recent

years have thrown much light on the systemic component of the disease largely due to oxidant stress and which in addition to the lung manifestations has been attributed to the extra pulmonary manifestations such as coronary artery disease which is the leading cause of mortality in these patients, osteoporosis, development of diabetes, loss of muscle mass – these impose health burden on these patients with already deranged lung function. As the pathophysiology of the varied manifestations of the disease are being unraveled everyday recent studies are on to find a unified marker which could reliably predict the entire disease manifestations, disease course, which could help in making treatment plan and also studies are on to find a way of halting the unrelenting inflammation and disease progression. Among the various markers being tested, one such is highly sensitive C-Reactive Protein.

In the present study the baseline characteristics of our patients are analysed and to possibly see whether highly sensitive C-Reactive Protein correlates with the disease severity.

AIMS AND OBJECTIVES

The present study was done

1. To study the clinical profile of COPD patients with respect to their baseline characteristics – age, sex, occupation, symptoms, signs, X-ray, ECG, ECHO, BMI, pack years of smoking
2. To categorize the patients based on spirometry into different stages and to study the distribution of the baseline characteristics in each stage
3. To determine the value of hs-CRP in these patients and to correlate it with the various stages, smoking pack years, FEV1 and other variables and its significance
4. To study other markers of inflammation such as ESR, serum albumin and their variation with stages and lung function.

REVIEW OF LITERATURE

DEFINITION ⁴

COPD is defined as “a disease state characterized by airflow limitation that is not fully reversible”^{25,31} It includes

I. EMPHYSEMA⁴

Emphysema is defined as “destruction and enlargement of the lung alveoli”

II. CHRONIC BRONCHITIS⁴

Chronic bronchitis is clinically defined with chronic cough and phlegm production.

III. Small Airway disease

GOLD criteria for COPD severity ⁴			
GOLD stage	Severity	Symptoms	Spirometry
0	At risk	Chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	FEV1/FVC < 0.7 and FEV1 ≥ 80% predicted
II	Moderate	With or without chronic cough or sputum production	FEV1/FVC < 0.7 and 50% ≤ FEV1% < 80% predicted
III	Severe	With or without chronic cough or sputum production	FEV1/FVC < 0.7 and 30% ≤ FEV1% < 50% predicted
IV	Very severe	With or without chronic cough or sputum production	FEV1/FVC < 0.7 and FEV1 < 30% or FEV1% < 50% predicted with respiratory failure or signs of right heart failure

EPIDEMIOLOGY^{29,30}

COPD is expected to be the 3rd most common cause of mortality and the 5th for loss of DALY worldwide according to Global Burden of Disease Study.⁴⁶

PREVALENCE IN INDIA

The exact prevalence in our country could not be ascertained with certainty because of misdiagnosis, under assessment, lack of extensive studies, poor statistical information. The prevalence rate have been variably reported from 2-22% in males and 1.2-19% in females. Recently ICMR has undertook the INSEARCH study in four cities and reported prevalence of 5% in males and 3.2% in females in those more than 35 years of age. The total population affected by the disease has increased to 14.84 million in 2011 from 6.45 million in 1971. In India the sex ratio and the smoker to non smoker ratio are not as high when compared to western statistics. This disparity is because of biomass fuel combustion which is an important risk factor in women more so in the villages. Data on mortality statistics are limited; 7% mortality have been attributed to chronic respiratory illness.^{29,30}

RISK FACTORS

SMOKING^{4,5,6,11,25,30,31,35}

Cigarette smoking by far is the major cause for COPD with proven cause-response relationship with approximately half of

smokers developing the disease. The effect of smoking on declining lung function have been proved in many studies. But still not all smokers develop the disease and even among those who smoke there is variation in response to the duration of smoking which suggests that other factors particularly genetic and environmental modulate the effect of smoking in these patients.

AIRWAY RESPONSIVENESS^{4,11}

Though the concept of airway hyperresponsiveness have been proved beyond doubt in bronchial asthma, in COPD there are conflicting reports as to whether it contributes to the development of airflow obstruction with recent studies supporting the hypothesis.

RESPIRATORY INFECTIONS^{4,30}

Infections associated with risk

- a. Previous H/O tuberculosis even when adequately treated with ATT
- b. Childhood respiratory infections⁴³
- c. Inadequately treated bronchial asthma

INDOOR AIR POLLUTION^{4,29,30}

Though in developed countries smoking is the major risk factor, in developing countries like ours causes other than smoking

contribute to 1/3 to 1/2 of all cases. Among them chronic exposure to sulfur dioxide, carbon monoxide, nitric oxide, HCHO and others released from biomass fuel combustion³⁸ is the important risk factor particularly in female patients.

OCCUPATIONAL DUSTS^{4,30}

Several occupations are met with chronic exposure to occupational dust/gas but the impact of these agents in the development of the disease is much less significant than cigarette use.

INCREASING AGE :³⁰

Physiological decrease in pulmonary function could also lead to the disease.

LOW SOCIO-ECONOMIC STATUS^{29,30}

GENETICS^{4,5,6,10,11,30}

The considerable variation in smokers developing the disease could possibly be due to various genetic derangements. As of now, the only proven genetic defect causing the disease is α 1-antitrypsin deficiency which is due to alteration in SERPINA1 locus encoding the enzyme.

Allele	$\alpha 1$ AT
M	Normal
S	Slightly reduced
Z	Markedly reduced
Null	Absent

Pi^Z - most common form.

Treatment for this subset of patients is available as $\alpha 1$ -AT augmentation therapy as weekly intravenous administration.

Apart from $\alpha 1$ -AT deficiency, other genetic factors have also been hypothesized to contribute to the risk factor pool and research on several other genes are underway.⁴

PATHOPHYSIOLOGY

AIRFLOW LIMITATION^{4,11,30}

Airflow limitation due to decreased airway caliber and increased airway resistance, impaired elastic lung recoil during expiration manifested in spirometry as reduction in the ratio of Forced Expiratory Volume₁/Forced Vital Capacity < 0.7 and reduced post

bronchodilator FEV1% predicted value is a cardinal feature for the disease diagnosis and dividing into stages.

HYPER INFLATION^{4,11}

In these patients there is hyper inflation as shown by increased RV and increased ratio of RV/TLC and later increase in TLC.

Mechanism³⁰

The principal mechanism of airflow during expiration from the small airways and alveoli is driven by the inward elastic recoil pressure of the lung which also counteracts thoracic wall outward pressure. At the end of tidal expiration both these balance each other resulting in particular amount of air remaining in the lungs named as FRC (functional residual capacity). In these patients due to the destruction of lung parenchyma, the inward pressures are low and it comes into equilibrium with the outward pressure at increased volumes of FRC resulting in hyperinflation. This state of hyperinflation also causes flattening of diaphragm resulting in functional diaphragmatic paralysis.

GAS EXCHANGE ⁴

Hypercapnea and hypoxia results from deranged gas exchange due to the reduction in surface area caused by destruction of the respiratory units. The chronic hypercapnic state decreases the chemoreceptor sensitivity and hence the respiratory stimulus in these patients is hypoxia stimulating the peripheral chemoreceptors.³⁰

V/Q MISMATCH ⁴

It is due to the inhomogeneous disease distribution in the lungs and airways

PATHOGENESIS

ELASTASE-ANTI ELASTASE HYPOTHESIS ^{4,10,11}

α 1 – AT DEFICIENCY:

Neutrophils in the alveoli are stimulated by various triggers which get activated and recruited and release their granules which have elastase, proteinases, cathepsins & MMP and also releases ROS which inhibit α 1 anti trypsin. In patients with the enzyme deficiency, these elastases cause destruction of the air spaces.

Smoking

In smokers both neutrophils and macrophages are increased in alveoli. Neutrophils upon activation releases a number of proteases mentioned above and activated macrophages release a variety of cytokines, chemokines, ROS and a variety of matrix metalloproteinases which are not inhibited by $\alpha 1$ AT rather these enzymatically degrade $\alpha 1$ AT and thus enhancing pulmonary destruction several fold.¹⁰ CD8 lymphocytes enhance apoptosis of alveoli and CD4 cells trigger autoimmunity against native lung tissue.³⁰

OXIDANT STRESS

The normal lung contains rich anti-oxidants such as glutathione to handle the oxidant stress. Smoking by way of its contents and also by activating inflammatory cells which release free radicals tilt the balance towards oxidant stress which inactivates anti-proteases causing lung destruction in patients even with normal $\alpha 1$ AT. Oxidant stress also results in loss of surfactant, ECM apoptosis, reduction in elastin synthesis.¹⁰

CLINICAL PRESENTATION

HISTORY

SYMPTOMS ^{4,5,6,11}

- i. Chronic cough
- ii. Expectoration
- iii. Dyspnoea on exertion – insidious in onset and gradually progressive over time. Sudden worsening of dyspnoea is due to either an exacerbation or other complications.
- iv. Wheeze
- v. Loss of weight – in severe disease. (other causes to be ruled out before attributing it to the disease per se.)

SIGNS : ^{4,5,6}

The physical examination may be completely normal in patients in the beginning stages till there is significant deterioration in pulmonary function.

GENERAL EXAMINATION

- a. Stigmata of smoking – nicotine stains, etc.
- b. Cyanosis may be present

- c. Clubbing is not a sign of the disease per se and if present a prompt search for other conditions such as lung Ca has to be made.
- d. Pedal edema, ascites, elevated JVP – due to pulmonary hypertension & cor pulmonale.
- e. SPO₂ – patients may have hypoxemia.

RESPIRATORY SYSTEM EXAMINATION

- a. Patients with severe disease have accessory muscles of respiration acting with the patient assuming “tripod” position to enhance the synergistic action of these muscles⁴
- b. Hoover’s sign⁴
- c. Signs of hyperinflation – Barrel shaped chest, hyper resonance on percussion.⁴
- d. On auscultation patient may have prolonged expiratory phase, diminished intensity of breath sounds, expiratory wheeze.^{4,6}
- e. Signs of pulmonary hypertension and cor pulmonale – Loud P2 may not be present due to hyperinflation, Tricuspid regurgitation murmur can be present.⁴

DIFFERENTIAL DIAGNOSIS ⁵

- a. Bronchial asthma – distinguished by near total post bronchodilator FEV1 reversibility.
- b. Bronchiectasis – differentiated by symptoms like hemoptysis, presence of clubbing & radiography.
- c. Cystic fibrosis – history since childhood, recurrent infections, presence of other features such as cirrhosis.
- d. Broncho pulmonary mycosis.
- e. Central airway obstruction such as tumours, stenosis or developmental anomaly – differentiated by history and PFT using flow-volume loops.

COMPLICATIONS ^{5,30}

- i. Recurrent lung/airway infection
- ii. PTE
- iii. Cor pulmonale and pulmonary hypertension
- iv. Bronchogenic carcinoma
- v. Pneumothorax especially in those with emphysema
- vi. Cardiovascular effects – CAD, arrhythmias.

RADIOGRAPHY

X-RAY CHEST ^{4,5}

- i. Chronic bronchitis – Increased bronchovascular markings
- ii. Emphysema – Hyper inflated lung fields

Diaphragm flattening

Decreased peripheral vascular markings

Bulla
- iii. Pulmonary hypertension – enlarged main & right descending pulmonary artery
- iv. To look for co morbidities and complications like malignancy, pneumothorax, etc.

COMPUTED TOMOGRAPHY ⁴

- a. Not routinely done for diagnostic purposes
- b. To assess patients fit for surgical management.

LABORATORY TESTS

PFT : ^{4,5,6,31}

- a. FEV1/FVC < 0.70
- b. TLC, FRC, RV may increase often more than normal with disease progression.

Apart from diagnostic utility, FEV1 is also used to monitor treatment response and worsening FEV1 is a poor prognostic factor.

ABG : ^{4,6}

- a. Normal in early stages
- b. To determine the degree of hypoxemia and the acid base status and to differentiate between acute exacerbations and chronic respiratory failure.
- c. Yearly assessment is recommended.

TREATMENT

STABLE PATIENTS

Survival improving strategies ^{4,5,6,11,30,35}

1. Smoking cessation
2. Oxygen

3. Lung volume reduction surgery

Other management strategies are to the relief of symptoms, improving the quality of life and to reduce exacerbations.⁴

DRUGS

BRONCHODILATORS^{4,5,6,11,30}

These drugs are the mainstay of management in that they provide symptom relief and enhances the well being of patient but do not prevent the decline in FEV1.

Inhaled β_2 agonists :

i) short acting β_2 : used in all stages of the disease ‘on demand’ basis to provide immediate relief from dyspnoea and not to be used on a routine basis.

Drugs used are salbutamol and levosalbutamol.³⁰

ii) long acting : used on a scheduled basis as maintenance therapy to provide sustained relief.

Drugs commonly used are formoterol, salmeterol.

Side effects : Tachycardia, tremor, decrease in serum K^+ .³⁰

Inhaled Anti-cholinergics :

i) short acting : For symptom relief similar to short acting beta 2 agonists but devoid of their sympathetic side effects and also has prolonged action compared to them.

Drug used ipratropium

ii) long acting : for maintenance therapy

Side effects : dryness of mouth, Primary angle closure glaucoma is an absolute contra indication, symptoms of BPH may aggravate.

COMBINATION THERAPY ³⁰

As the disease worsens, combination therapy with Long acting sympathetic and anticholinergic provides maximum symptom benefit by synergistic mechanisms rather than single drug alone.

CORTICOSTEROIDS

INHALED :

ICS are not to be used as a single agent in management of these patients but used in combination with other inhaled bronchodilators.⁵

Indication : ³⁰

- i. Stage III disease
- ii. ≥ 2 exacerbations / year

Side effects : ³⁰

1. oral candidiasis – prevented by mouth gargling after each use or by spacer
2. hoarseness of voice

SYSTEMIC STEROIDS ^{4,5,6,30}

Oral steroids are not used in the regular treatment of stable patients because the adverse effects outweigh the benefits but they are an important part of acute exacerbation management.

METHYL XANTHINES ^{5,6,30}

Sustained release theophylline is commonly used in patients who do not have adequate symptom relief with inhalational therapy because of its effects on diaphragm function, reducing airway resistance and decreasing inflammation.

Side effects : ^{6,30}

These drugs have a narrow therapeutic window and patients' supervision is essential.

- CVS : increase in heart rate, arrhythmia.
- CNS : tremor, decreases seizure threshold, insomnia.
- GIT : gastritis, nausea.

ANTIBIOTICS - No role in stable patients. ^{5,30}

NON PHARMACOLOGICAL MEASURES

OXYGEN ^{4,5,6,30}

Oxygen therapy by various methods undoubtedly prolongs survival and also provides symptom relief.

Indications ^{6,42}

- Arterial partial pressure of O₂ ≤ 55 mm Hg or oxygen saturation by pulse oximetry ≤ 88%
- Arterial partial pressure of O₂ < 60 mm Hg and oxygen saturation < 90% in the presence of pulmonary hypertension, Hct > 55% or cor pulmonale.

VACCINATIONS ^{6,30,34}

For all stages of the disease yearly influenza vaccine and pneumococcal vaccine (zero dose and a booster after 5 years).

PULMONARY REHABILITATION^{4,5,6,30}

It is a multi system modality including respiratory exercises, adequate nutrition, psychological support that improves exercise tolerance, improves dyspnoea and quality of life indicated in patients failing optimal medical therapy and also for severe disease.

SURGICAL MANAGEMENT

I. LUNG TRANSPLANTATION^{4,5,6}

- a. Done either as one lung or sequential double lung transplant
- b. Requirements include severe disease inspite of optimal medical management, absence of other organ system dysfunction, poor quality of life.
- c. PHT and the region of lung involved are not contra indications.

II. LUNG VOLUME REDUCTION SURGERY^{4,5,6}

Patients with upper lobe emphysema and severely compromised exercise tolerance are ideal candidates. Presence of PHT/cor pulmonale are contra indications.

III. BULLECTOMY⁵

EXACERBATIONS OF COPD

PRECIPITATING CAUSES^{4,30}

I. Infections

- i. Viral infections
- ii. Bacterial infections
 - a. Pneumococcus
 - b. Hemophilus influenza
 - c. Moraxella catarrhalis
 - d. Pseudomonas in special risk groups

II. Environmental

- i. Pollution
- ii. Exposure to toxic gases
- iii. Climate changes

SYMPTOMS^{4,30}

- i. Increase in cough
- ii. Worsening dyspnoea

- iii. Increased sputum with purulence
- iv. Worsening general condition

Complete physical examination is mandatory to assess the severity of the exacerbation. Investigations done include X ray chest to detect the presence of pneumothorax, consolidation, ECG to detect rhythm disturbances- most common being MAT, ABG to detect respiratory failure. The decision as to whether the patient has to be treated at home or hospital or ICU is based on the severity, patient's general health status, supportive care, presence of other co morbidities like CAD, DM, neurological status, ABG measurements and the need for assisted ventilation.^{4,6,30}

DRUGS

BRONCHODILATORS

Short acting beta agonists are used as the primary treatment for an exacerbation, alone or in addition with an anti cholinergic delivered through nebulisation or inhalation if patient can perform.⁶ If patient is already taking methyl xanthines it should not be stopped as it may cause deterioration but monitoring of drug levels is mandatory.

In theophylline naïve patients it should not be prescribed during an exacerbation. ^{5,6}

GLUCOCORTICOIDS

Systemic steroids via oral or parenteral if patient cannot take medication orally for short course is an important cornerstone in management of exacerbation because they decrease hospital stay, improves lung function and decreases the probability of subsequent relapse. ^{4,6,30}

ANTIBIOTICS

They are chosen based on the sensitivity pattern, the likely organism and availability and is particularly useful in patients with purulent sputum production and in those requiring assisted ventilation. ^{4,6}

SUPPLEMENTAL OXYGEN

To maintain $\text{SaO}_2 \geq 90\%$.⁶ Oxygen should not be withheld for fear of respiratory depression due to removal of hypercarbic stimulus because it is essential to prevent tissue hypoxemia but care should be exercised in monitoring the patient. ⁵

ASSISTED VENTILATION

Non invasive ventilation indicated in patients with respiratory failure has shown to decrease mortality, decrease hospital stay, the need for invasive ventilation and lesser risk of hospital acquired infections. Invasive ventilation is indicated when NIV fails or patient has contra indications to NIV or severe acidosis or hypercapnea or the presence of co-morbidities.^{4,5,6,30}

PULMONARY HYPERTENSION IN COPD :

Mild PHT to some extent develops in most of the patients with advanced disease and rarely severe pulmonary HT in few.^{7,37}

CAUSES ⁷

1. Pulmonary vasoconstriction caused by alveolar hypoxia,³⁷ acidosis, hypercapnia.
2. Increased lung volume causing compression of Pulmonary vessels
3. In patients with emphysema due to terminal air space destruction there is a decrease in the small vessels in areas of destroyed lung tissue.

Pulmonary artery pressure increases by approximately 20 mm Hg for every acute exacerbation and this can end up in pulmonary hypertension on repeated occurrence.^{9,30}

MECHANISM OF PULMONARY HYPERTENSION BY HYPOXIA:⁷

1. Vascular intima thickening
2. Distal vessels muscularisation
3. Hypertrophy of the vascula media of proximal vessels
4. Alveolar hypoxia in order to maintain V/Q and PaO₂ is a potent vasoconstrictor in pulmonary circulation.

TREATMENT^{7,44}

- A. Pulmonary vasodilators produce worsening of V/Q mismatch because it is not the level of pulmonary hypertension but the degree of hypoxia which causes the clinical symptoms and that these drugs further worsen the situation.
- B. Only proven treatment of use is O₂ which decreases both morbidity and mortality

C. To maintain the Hb in upper limit of normal because low Hb is not tolerated in these patients due to hypoxemia.

Nocturnal or ambulatory SaO₂ can guide in optimal O₂ concentration.

COR PULMONALE (RIGHT HEART FAILURE) : ⁴⁴

It can occur either acutely during exacerbations or chronically due to disease progression and worsening gas exchange resulting in irreversible vascular remodeling.

DIAGNOSIS

i) Echocardiogram

To detect the presence of right ventricular enlargement but the procedure is difficult due to hyperinflated lungs and rotation of the heart.⁸ It can be supplemented by ABG-showing PaO₂ < 50 mm Hg and PCO₂ > 50 mm Hg.⁴⁴

ii) Electrocardiogram ⁴⁴

Routine criteria to detect RVH cannot diagnose RVH in these patients due to

a. rotation of the heart

b. Hyper inflation causing increased distance between the skin and cardiac surface.

c. It is more of RV dilatation rather than hypertrophy.

iii) Cardiac catheterization – gold standard investigation. ⁴⁴

MANAGEMENT ⁴⁴

1) Acute cor pulmonale

i) treatment of the precipitating cause

ii) supplemental O₂ to maintain adequate oxygenation.

2) Chronic cor pulmonale

i) cautious use of digoxin and diuretics for the fear of precipitating life threatening rhythm disturbances in the presence of hypoxia and acidosis.

ii) Oxygen.

SPIROMETRY IN COPD

The investigation to confirm or refute a diagnosis of the disease is spirometric evaluation as suggested by GOLD. According to them a post bronchodilator Forced expiratory volume 1/ Forced Vital Capacity < 70% is used for diagnosis and the previous concept of

absence of post bronchodilator reversibility has been abandoned. Spirometry has its own limitations and hence a combination of clinical symptomatology and spirometry improves the diagnostic accuracy.³⁰

USES³⁰

1. Diagnosis

2. Grading of severity

In these patients the rate of decrease in Forced expiratory volume₁ per year is about 75-100 ml in sharp contrast to normal persons' 30 ml/year.

3. Lung "age" assessment

By comparing patient's FEV₁(lung age) to the predicted FEV₁ of his age matched control. It could be used to encourage smokers to quit smoking.

4. Detection of Upper airway obstruction

5. Pre-Operative evaluation

These patients have a higher chance of developing post-op pulmonary complications.

i) Thoracic surgery

Predicted Post operative FEV1 is calculated by applying “rule of 5” in which 1/5th function is contributed by each lobe and the PPO value is calculated by subtracting the lobe to be removed. A PPO FEV1 < 40% predicted is a contra indication to surgery.

ii) Non thoracic surgery

Factors predicting post-operative complications are

- a. FEV1/FVC < 50%
- b. Maximum voluntary ventilation < 50%
- c. FEV1 or Diffusing capacity < 20% predicted
- d. High partial pressure of carbon dioxide
- e. Short distance of surgical site from the chest

SYSTEMIC INFLAMMATION ³⁰

It has been recognized from the experiences in past decades that inflammation is no longer confined to lungs in COPD and that GOLD definition of the disease at present includes “some significant extra pulmonary effects that may contribute to the severity in individual

patients” and hence the disease could be renamed as “chronic systemic inflammatory syndrome”.

MARKERS OF SYSTEMIC INFLAMMATION IN COPD ³⁰

1. hsCRP
2. Fibrinogen
3. Ferritin
4. White blood cell count
5. ROS
6. Interleukins
7. TGF β 1
8. TNF α receptor polymorphism

These markers are present even in mild forms of the disease and their levels increase with increasing disease severity.

HYPOTHESIS ³⁰

1. Probable inflammation spreading over from lungs to other systems.
2. A proinflammatory phenotype in which systemic inflammation happens independent of lung component.

TRIGGERS ³⁰

1. Smoking an important risk factor for the disease per se by way of causing oxidative stress & endothelial function derangement
2. Hypoxia of severe disease enhances HIF-1 expression. HIF-1 upregulates genes involved in inflammation, vascular remodeling & new vessel formation. TNF- α levels have been shown to be in relation with hypoxemia severity and that the enhanced survival of patients on LTOT might be due to the fact that oxygen decreases inflammation.
3. Increased leptin levels and its receptors
4. Auto-immune process
5. Oxidative stress of the disease accelerates telomere shortening and causes “ageing” of lungs and other systems.

CONSEQUENCES ³⁰

Consequences of the systemic inflammatory process are the non pulmonary morbidities that have been shown to have immediate cause-effect relationship across studies consistently and also have been proven that their association is not just by chance.

1. CARDIO VASCULAR SYSTEM : ³⁰

i) Coronary Artery Disease:

These patients have a 3-fold greater risk of developing CAD and that the mortality rates in these patients due to CAD are comparable to those due to worsening of the disease per se. Cardiac injury biomarkers have been shown to be increased in studies during acute exacerbations when the level of systemic inflammation is high.

ii) Cardiac failure:

Cardiac failure is precipitated by end diastolic pressure changes induced by pressure variation caused by hyper inflation which interferes with ventricular remodeling. Cardiac failure and air flow limitation is a vicious cycle – one perpetuating the other in that airflow resistance is worsened by the electrolyte changes, mucosal congestion & decreased lung compliance in heart failure.

iii) Arrhythmias:

The common rhythm disturbances include

- a. Multifocal Atrial Tachycardia
- b. Atrial Fibrillation
- c. Ventricular arrhythmias.

2. BONE: ³⁰

The prevalence of osteoporosis is high in these patients independent of glucocorticoid use. Inflammatory mediators such as TNF- α and IL-1 stimulates mesenchymal cells to release receptor activator of NFKB ligand which mediates macrophage transformation to osteoclasts & accelerates osteoporosis. Other factors such as old age, decreased BMI, smoking and sedentary life style may contribute.

3. DIABETES MELLITUS: ³⁰

Undoubtedly there is an increased prevalence of T2DM in these patients due to systemic inflammation which is strengthened by the finding of elevated levels of inflammatory markers such as tumour necrosis factor α , interleukin 6 & C-reactive protein which further compounds the risk of developing CVD.

4. MUSCULOSKELETAL SYSTEM : ^{27,30}

Progressive muscle wasting with preserved fat mass is a feature of the disease.

Mechanism

- Increased IL-6
- Decreased diet intake

- Endocrine abnormalities
 - i. Decreased Insulin like Growth Factor-1 expression and its binding proteins
 - ii. Decreased testosterone
 - iii. GH resistance

- Hypoxia

Muscle dysfunction-respiratory and non-respiratory muscles adversely affect the exercise tolerance & health status of the patient & the loss of skeletal muscle is an important negative predictive factor for survival in these patients and also the BODE index – validated index incorporates BMI as one of its four parameters predicting prognosis of the disease.

5. DEPRESSION : ³⁰

Increased prevalence due to

- i. Systemic inflammation
- ii. Dependence due to increasing disability
- iii. Impaired Quality of Life

NEED FOR IDENTIFYING CONSEQUENCES:³⁰

A knowledge of the systemic consequences enlightens us the need for investigating these patients for the comorbidities and to intervene early so as to decrease the morbidity and mortality and improving the QOL and also to look for the disease in patients presenting with any of these co-morbidities.

C-REACTIVE PROTEIN

It is an acute phase reactant produced by the hepatocytes and to some extent by vascular endothelial and smooth muscle cells in response to inflammatory mediators released by macrophages and adipocytes. It belongs to the pentraxin family of proteins. The name is derived from its finding as an agent in patients with inflammation that reacted with the C-polysaccharide of *Streptococcus pneumoniae*. The gene encoding is on chromosome 1q21-q23.^{16,41}

FUNCTION

BENEFICIAL EFFECTS

It binds to phosphocholine exposed on micro organisms and damaged cells and enhances their removal by phagocytosis by macrophages (opsonisation). It is also a part of innate immunity.^{14,16}

NEGATIVE EFFECTS

CRP is a pro-inflammatory agent. It directly activates the complement cascade by binding to C1q causing tissue destruction. It also enhances NF κ B to induce the synthesis of various cytokines perpetuating inflammation which when unchecked results in extensive host tissue damage.¹⁶

CLINICAL IMPLICATIONS

CRP is increased in acute and chronic inflammation, autoimmune diseases, malignancy, and conditions associated with tissue damage.¹³ It is a more sensitive and more accurate marker of acute inflammation than ESR. The degree of increase correlates with the severity of inflammation. It returns to normal with subsidence of inflammation rapidly with a $t_{1/2}$ of 18 hrs and hence can be used to monitor response to treatment.

Value of Highly Sensitive C-Reactive protein above 3 mg/L is considered abnormal.⁴¹

Highly sensitive methods for assaying CRP known as hs-CRP was developed to enhance the sensitivity of detecting the low grade inflammation in disease process such as atherosclerosis which routine

assays could not detect. Highly Sensitive C-Reactive protein is a predictor of CVA, sudden cardiac death, CAD and peripheral vascular diseases.¹³ It is a prognostic indicator and mortality predictor in acute coronary syndrome.⁴¹

Highly Sensitive C-Reactive protein in COPD:

MECHANISM OF ELEVATION

Interleukin 6 is the important molecule that upregulates the hepatic production of C-Reactive Protein.^{15,16,17}

SOURCE OF INCREASED INTERLEUKIN 6 :

- i. Interleukin 6 may be released by the activated inflammatory cells – macrophages in the pulmonary circulation and alveolar epithelial cells.¹⁴
- ii. Oxidant stress induced derangement in muscle metabolism homeostasis causing enhanced expression of interleukin 6.⁴⁰

The increased plasma levels of IL-6 stimulates the hepatocytes to express C-Reactive Protein.

CLINICAL IMPLICATIONS

Highly Sensitive C-Reactive protein

- i. Is increased even in stable patients^{16,17,18}
- ii. Predictor of mortality^{14,18,40}
- iii. Increased significantly in patients with low body mass index than others signifying malnutrition
- iv. Marker of low grade systemic inflammation in these patients^{13,16,18,40}
- v. Marker of increasing severity of the disease
- vi. Predicts exacerbations, hospitalization^{14,18}
- vii. Negative correlation with decline in lung function^{12,16,18,21,24,28,40}
- viii. Elevated levels are associated with poor quality of life & reduced exercise tolerance.^{14,18}

SMOKING CESSATION^{4,30}

Smoking cessation is by far the best effective intervention in halting the disease process.

Approach

- a. Counseling
- b. Pharmacological assistance

CONSELLING

Counseling either by the clinician or non clinician enhances cessation rate several fold than self initiated attempts.

5A intervention approach

- I. ASK – information about tobacco use at every visit.
- II. ADVICE – should be strong and individualized depending on patient's health status and other considerations.
- III. ASSESS – patient's willingness. If patient is not willing he/she should be urged to quit.
- IV. ASSIST – by discussing with the patient a quit plan; setting a date to stop smoking in next 2 weeks, to reduce alcohol use, educate households and providing psycho social support.
- V. ARRANGE – follow-up.

PHARMACOTHERAPY ^{4,6,30}

First line agents

Nicotine Replacement Therapy

Formulations available

Gum

Dose : 2 mg – 1-24 cigarettes/d ; 4 mg - >25 cigarettes/d

Duration : 12 weeks

Adverse effects : dyspepsia

Lozenge

Dose : 2 mg – first smoke > 30 min after waking up from bed; 4 mg – first smoke < 30 min after waking up from bed

Maximum of 20 mg/d

Duration : 12 weeks

Side effects : nausea, insomnia.

Inhaler

Dose : 6 – 16 cartridges of 4 mg each/d

Duration : 6 months with dose reduction in last 3 months

Side effects : rhinitis, local irritation

Spray

Dose : 0.5 mg in each nostril 1-2 doses/hr

Maximum 5/hr

Duration : 3-6 months

Side effects : local irritation

Patch

Dose : 16 or 24 hr patch for total duration of 8 weeks with dose reduction

Side effects : local skin reaction, insomnia

Advantage : good compliance, requires less skill.

Contra indication to NRT :

- Coronary artery disease – MI or unstable angina
- Cerebrovascular accident
- Untreated Acid peptic disease

Bupropion sustained release

Mechanism of action

Nor-epinephrine and dopamine reuptake inhibitor

Dose : 150 mg once daily x 3 days; 150 mg bd x 7- 12 weeks

Duration : 6 -12 months

Side effects : insomnia, dry mouth

Contra indications : epilepsy, MAOI use in past 2 weeks

Particularly preferred in patients with concomitant depression

Varnecline

Mechanism of action

Partial agonist of nicotinic Ach receptor

Dose : 0.5 mg od x 1-3 days; 0.5 mg bd x 4-7 days; 1 mg bd from then up to 8 weeks.

Side effects : CNS – suicidal intention which has resulted in FDA warning.

Second line agents

1. Clonidine :

Mechanism of action : post synaptic α_2 agonist

Dose : 0.1 – 0.4 mg/d x 2 -6 weeks

2. Anxiolytics

Diazepam, buspirone, beta blockers

3. Sensory replacement

Citric acid inhaler, denicotinised tobacco, black pepper extract

4. Acupuncture : by releasing endorphins

Antagonists

a. Mecamylamine

non competitive CNS and PNS nicotine receptor antagonist

b. Naltrexone.

Aversion causing drugs

Silver acetate – poor compliance

SMOKING PREVENTION^{4,30}

Smoking behavior in around 90% smokers were initiated during adolescence. So prevention is more important and effective than cessation after the behavior has begun.

Measures :

1. Health education – target population : adolescents, young adults
2. Public health programs
3. Smoke free public places.

EMERGING THERAPIES

Newer drugs have been developed with the aim of inhibiting one of the several steps involved in the inflammatory pathogenesis of COPD with the concern of developing effective but also safe drugs.

Oxidative stress – imbalance between pulmonary oxidant load and anti-oxidants causing inflammation and airway modeling – an important pathogenetic mechanism – probably the reason for steroid resistance has been the target for newer therapies.³⁰

SMOKING CESSATION

An important and effective intervention to arrest the decline of lung function is smoking cessation.

Recent research has developed anti-free nicotine antibodies which bind with free nicotine denying its access across the BBB and hence cannot stimulate nicotine receptors causing smoking an unpleasant experience.³⁰

NEWER BRONCHODILATORS

Bronchodilators though they do not arrest the disease process – provide immediate symptom relief and improves well being of the patient are an important component of treatment plan.

Newer long & ultra long acting bronchodilators have been developed to meet the short comings of short acting ones – poor compliance due to multiple dosing. These include ultra-long acting muscarinic antagonists and ultra-long acting β 2 agonists.³⁰

ULTRA-LONG ACTING MUSCARINIC ANTAGONISTS

These agents besides providing long acting bronchodilatation have been shown to decrease the number of exacerbations and so they have the ability to attenuate the disease process partially and hence provide mortality benefit.³⁰

Drugs under research:

- i. Aclidinium
- ii. Dexpironium
- iii. TD-4208
- iv. Daratropium bromide
- v. GSK-573719
- vi. Glycopyronium bromide

ULTRA-LONG ACTING β 2 AGONISTS³⁰

This includes

- i. Indacaterol – approved in Europe & USA
- ii. Vilanterol – safe & efficacious
- iii. Carmoterol – using modulate technology, the amount of inhaled drug reaching the target has been increased

- iv. Milveterol – proved efficacious in asthma, not yet researched on COPD
- v. GSK-642444
- vi. UK-503590
- vii. BI-1744-CL
- viii. Compound X

NOVEL COMBINATIONS

Rationale of combing long acting drugs

- a) Synergism between the two agents
- b) Patients based on whether beta or muscarinic receptor predominance in their airway respond to their respective drugs more than the other and hence their combination can overcome their problem of receptor variation.

Several combination of these agents along with steroids to decrease exacerbations are under development but a potential limitation of using these combination is delivery of these agents at different site which decrease their synergism. To overcome these limitation combining them into a dimer which serves to deliver the

agents at same site – dual acting muscarinic antagonist beta 2 agonist have emerged.

Other combinations under development are combining a LABA with an ICS or combining LABA with inhaled steroid and LAMA.³⁰

ANTI INFLAMMATORY DRUGS

The search for an effective and safe anti inflammatory drug with the potential of reducing lung inflammation over the decades have been in vain. One of the recent break through finding is that oxidative stress causing decrease in HDAC in these patients has been the reason for corticosteroid unresponsiveness in them and that this enzyme at cellular levels can be increased by theophylline. Hence theophylline has staged a comeback in management of the disease with the potential of additive anti-inflammatory effect when given with steroids and studies are underway on this aspect.³⁰

PDE-4 INHIBITORS³⁰

Phosphodiesterase-4 an enzyme found specifically in most inflammatory cells have been targeted to reduce the inflammatory process of the disease. Roflumilast selective PDE-4 inhibitor has been approved for use. It has shown to increase FEV1 significantly than

tiotropium. These drugs could be the best adjuvant therapy with bronchodilators. An inhalational form of this class is under study. But the side effects of this drug – gastrointestinal and upper respiratory tract effects have led to search for development for specific inhibitors.

ANTI PROTEASES³⁰

An imbalance between proteases (matrix metallo proteinases) – anti proteases is an important pathogenetic mechanism of emphysema. Anti proteases – MMP inhibitors have shown promising results in preventing emphysema. Few drugs of this class are under phase II and III trials.

1. Marimastat – non selective MMP inhibitor
2. AZ11557272 – dual MMP-9/MMP-12 inhibitor

CYTOKINE INHIBITORS³⁰

Tumour necrosis factor – α and other interleukins – notably IL-7, IL-1 β , IL-6 are important cytokines implicated in the systemic inflammatory process in the disease. Drugs targeting these cytokines are in the infant phase.

CHEMOKINE ANTAGONISTS ³⁰

Oral AD28309 – CXCR1/2 receptor antagonist – the receptor which mediates the effects of chemokines on inflammatory cells has shown to reduce inflammation in man. Other receptors targeted are CXCR 3 and 5 and drugs involved in these have finished phase I trials.

TGF- β INHIBITORS ³⁰

SD-280 which inhibits the fibrogenic cytokine TGF- β causing small airway fibrosis resulting in decrease in FEV1 and reduced exercise capacity has been developed but the long term consequences of this class are yet unknown.

NFKB INHIBITORS ³⁰

Inhibition of NFKB – a transcription factor involved in upregulating the production of various chemokines, TNF- α and MMP-9 seems to be a potential option. Such inhibitors are presently under research.

P38MAPKinase INHIBITORS : ³⁰

Inhaled formulation of inhibitors of this enzyme which upregulates the production of interleukin 8, TNF α and few other mediators causing inflammation are now in development period.

PHOSPHOINOSITOL-3-KINASE INHIBITORS under research. ³⁰

PPAR AGONISTS ³⁰

Immunomodulatory effects of PPAR α and γ (also inhibits TGF- β) are being exploited and the drugs currently being studied are rosiglitazone and SB-219994.

ANTIOXIDANTS ³⁰

Anti oxidant drugs being used are

I. NAC and its derivatives

a. N-Acetyl Cysteine

- i. Decreases systemic and pulmonary oxidative stress
- ii. Mild bronchodilation
- iii. Halts decrease in FEV1
- iv. Reduces exacerbation

b. N-acetylcysteine – well tolerated

c. Erdosteine – added advantage of reducing bacterial adhesion thereby reducing exacerbations.

d. Carbocysteine

e. Procysteine – toxic

f. N – isobutyryl cysteine – less effective

II. NRF-2 Activators

STATINS³⁰

The pleomorphic action of statins apart from lipid lowering such as anti-oxidant, endothelial protection and anti inflammatory properties in retrospective analysis have shown to decrease mortality, reduce exacerbations, decreasing need for assisted ventilation, improving functional capacity and reduce FEV1 decline. But randomized controlled trials are required to confirm their effectiveness before being part of management plan of the disease.

REGENERATIVE THERAPIES

Currently research is focusing on a modality of treatment that could actually bring back the destroyed lung tissue and hence restoring the normal anatomy which in future if discovered can revolutionize the COPD management.³⁰

STEM CELLS

Allogenic mesenchymal stem cells have the prospect of restoring alveolar tissue but clogging of pulmonary vasculature with

these cells resulting in death is an undesirable outcome. Trials are currently under research to overcome this side effect.³⁰

RETINOIC ACID

ATRA can cause regeneration of distal respiratory unit and hence reverse emphysema but in clinical trials have not shown such benefits.³⁰

ANTI-AGEING THERAPY

Oxidative stress causing accelerated ageing by increasing DNA damage mediated by inactivation by SIRT1 or SIR2 protein1 being focused as a target for arresting the disease process.³⁰

Besides these discoveries, research are also on to find a better way of enhancing the amount of drugs delivered to the desired segment of lung by using either new carrier formulation, nanotechnology, liposomal formulations or agents to enhance absorption such as surfactant, hyaluronic acid, taurocholate,etc.

Several hundreds or thousands of newer treatment modalities/drugs may emerge but still the best and most effective intervention is cessation of smoking.³⁰

MATERIALS AND METHODS

DESIGN OF STUDY : Cross sectional study

PERIOD OF STUDY : April 2012 – October 2012

SELECTION OF STUDY SUBJECTS : Outpatients attending the medical and thoracic medicine department

STUDY POPULATION : 70 cases

ETHICAL CLEARANCE : Obtained

CONSENT : Informed consent obtained

CONFLICT OF INTEREST : Nil

FINANCIAL SUPPORT : Nil.

INCLUSION CRITERIA

Patients attending the out patient department with symptoms suggestive of chronic obstructive pulmonary diseases (chronic cough with sputum , shortness of breath, wheeze) who were clinically stable were subjected to PFT and whose $FEV_1/FVC < 0.70$ (GOLD guidelines) were chosen.

EXCLUSION CRITERIA

- a. PFT showing features of bronchial asthma (post bronchodilator reversibility $> 15\%$ baseline value)
- b. Patients in acute exacerbations or clinically unstable

- c. Pulmonary tuberculosis
- d. Diabetes mellitus
- e. Ischaemic heart disease
- f. Cerebrovascular accident
- g. Any acute infection or inflammation (rheumatoid arthritis, autoimmune diseases)
- h. Malignancy
- i. Hepatic or renal impairment

STUDY

70 cases were selected for the study after applying the inclusion and exclusion criteria as stated above and subjected to the following

Baseline data and clinical characteristics

The baseline characteristics of the patients – age, sex, occupation, smoking habit and the clinical characteristics – symptoms and signs by thorough examination were recorded in the proforma prepared according to the need of study.

Spirometry

Pulmonary function test was done using the spirometer machine in the department of thoracic medicine after properly instructing the patient and post bronchodilator values after 20 min of salbutamol

nebulisation were recorded and the test was repeated twice and the best of the two was taken and based on FEV1 % predicted value patients were classified into stages based on GOLD guidelines.

Other investigations

- Height, weight were recorded and BMI calculated.
- X-ray chest Postero-anterior view was taken for all patients and the nature of COPD was ascertained
- ECG was taken and analysed for signs of pulmonary hypertension, cor pulmonale or coronary artery disease.
- Echocardiography was done in the department of cardiology to assess for the presence of pulmonary hypertension, its severity and right heart enlargement/dysfunction
- Blood investigations – basic blood investigations, ESR and serum albumin were done. hs-CRP was assayed by nephelometric method.

OBSERVATION AND RESULTS

A total of 70 cases were studied. Data collected from the patients were entered in Microsoft excel 2007 spread sheet and analysed with simple statistical analysis.

TABLE – 1

STAGES OF COPD

STAGE	NO.OF CASES	PERCENTAGE	MEAN FEV1% PV	S.D
I	8	11.4	84.00	2.39
II	33	47.1	67.94	6.89
III	24	34.3	42.21	4.19
IV	5	7.2	28.20	1.48
TOTAL	70	100		

Of the 70 patients, 8 patients (11.4%) were in stage I, 33(47.1%) were in stage II, 24(34.3%) were in stage III and 5(7.2%) were in stage IV during the period of study. The mean FEV1% of predicted value of each stage is also shown in the table.(fig 1)

fig 1.STAGES OF COPD

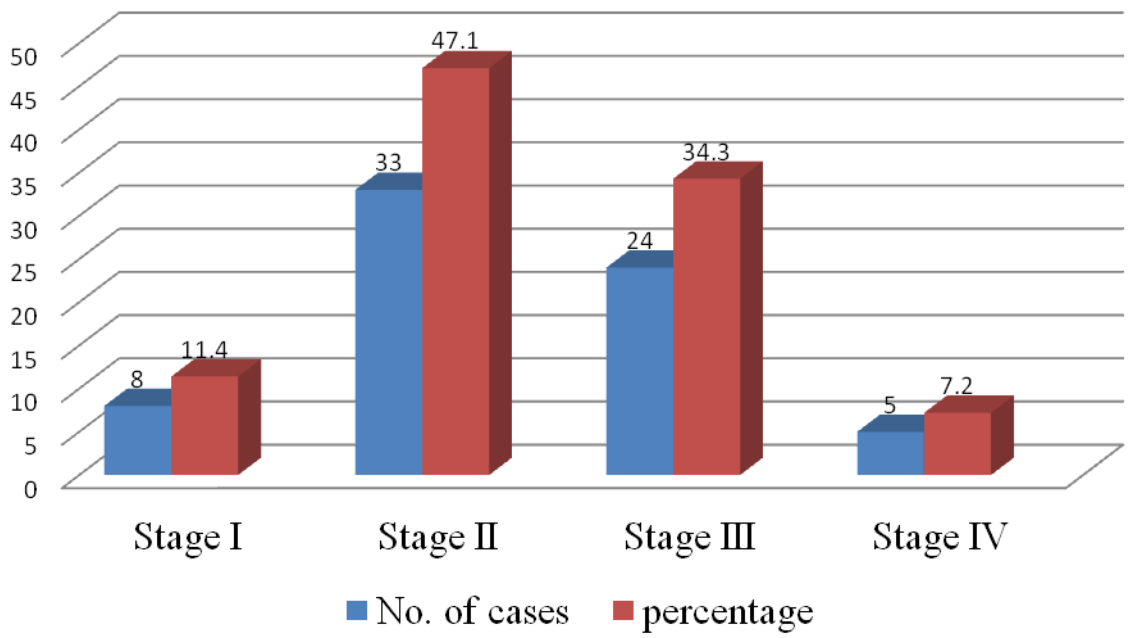


TABLE – 2**AGE DISTRIBUTION**

	21-30	31-40	41-50	51-60	61-70	71-80	TOTAL
I	1	5	-	2	-	-	8
II	3	9	10	11	-	-	33
III	-	1	6	7	7	3	24
IV	-	-	-	-	1	4	5
TOTAL	4	15	16	20	8	7	70
%	5.7	21.4	22.9	28.6	11.4	10	100

The maximum number of patients belonged to the 51-60 age group (28.6%) and 21-30 age group (5.7%) constituted the minimum.(fig 2)

fig 2.AGE DISTRIBUTION

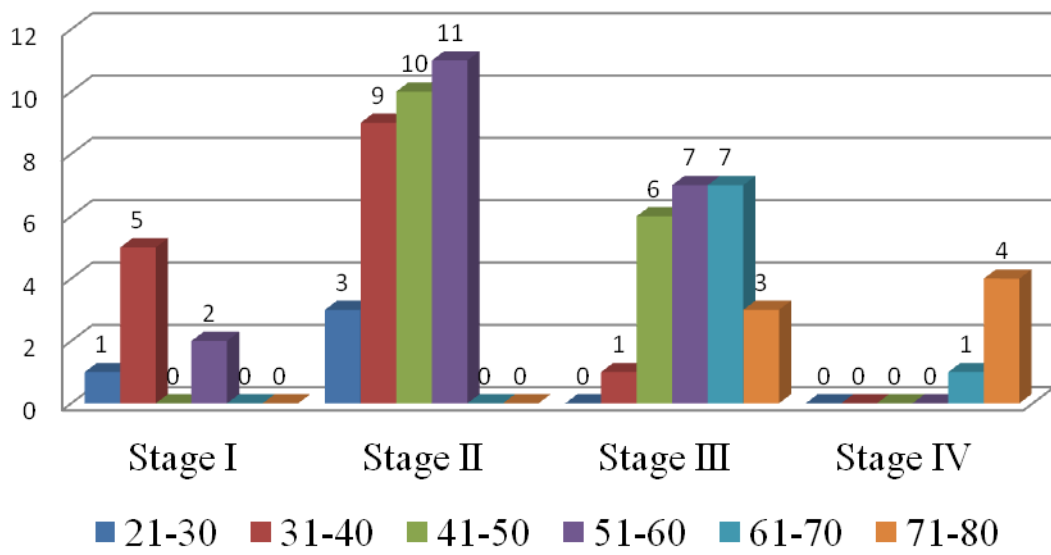


TABLE – 3

AGE DISTRIBUTION ACCORDING TO STAGE

AGE	MEAN	S.D
I	39.25	10.58
II	44.91	9.17
III	57.21	10.13
IV	73.20	4.21
p < 0.001 Significant		

TABLE – 4

AGE WITH FEV1 % OF PREDICTED VALUE

FEV1 % PV	p VALUE
AGE	0.004 Significant

The increase in age with the increasing stage of the disease was found to be statistically significant with $p < 0.001$ and the correlation of age with FEV1% of predicted value was also found to be statistically significant.(fig 3)

fig 3.AGE DISTRIBUTION ACCORDING TO STAGE

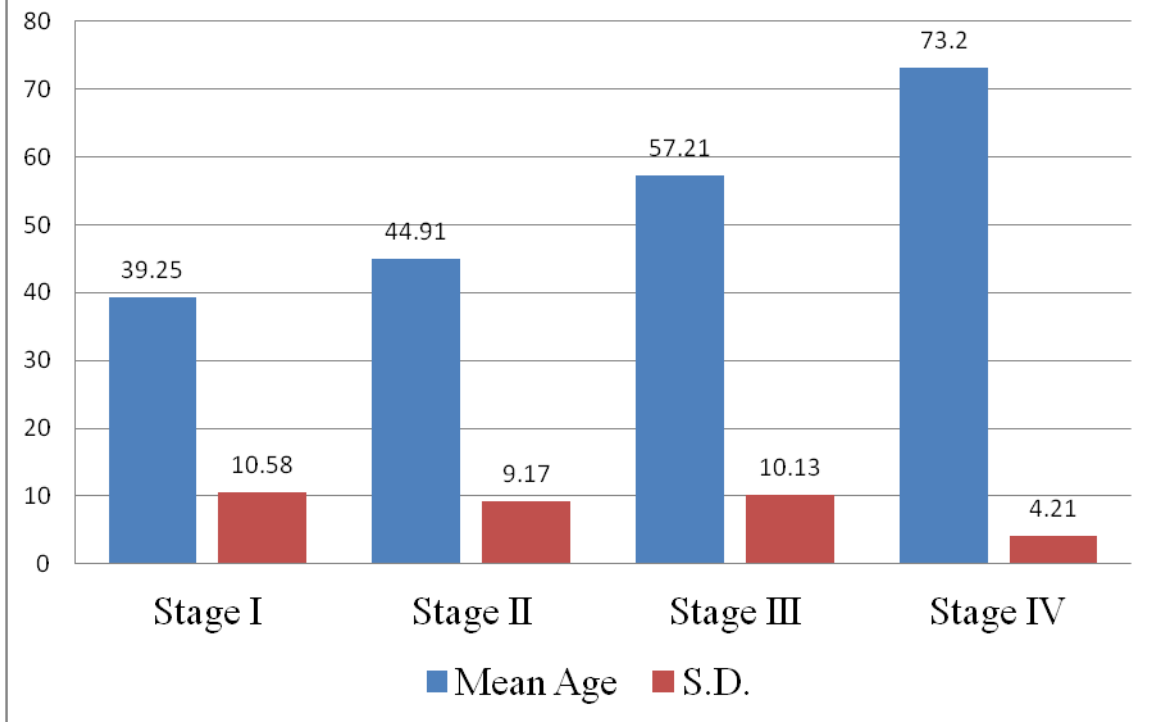


TABLE – 5

SEX

	N	MALE	%	FEMALE	%
I	8	6	8.9	2	66.7
II	33	32	47.8	1	33.3
III	24	24	35.8	-	-
IV	5	5	7.5	-	-
TOTAL	70	67	100	3	100

Of the total 70 patients, 67 (95.7%) were males and 3 (4.3%) were females.(fig 4)

fig 4.SEX

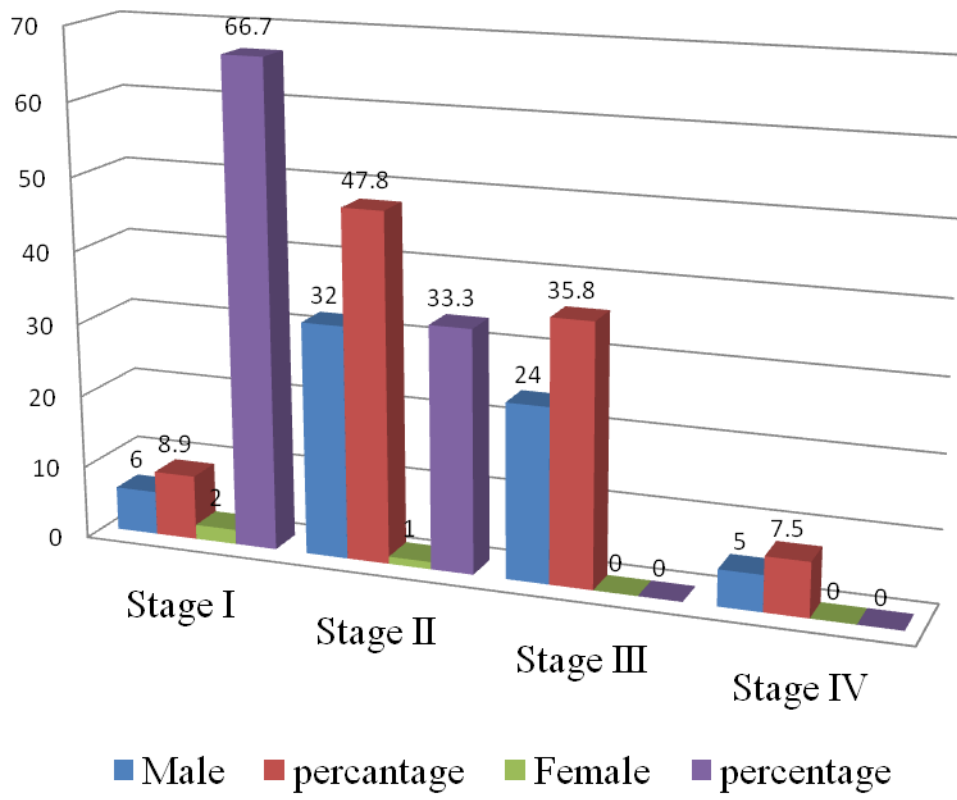


TABLE - 6
OCCUPATION

OCCUPATION	N	%
MANUAL LABOURERS	53	75.8
COTTON INDUSTRY	5	7.1
FLOUR MILL	6	8.6
BUSINESS	4	5.7
PROFESSIONAL	1	1.4
DYE INDUSTRY	1	1.4
TOTAL	70	100

Of the total 70 patients, 53(75.8%)were manual labourers, 6(8.6%) were working in flour mill, 5(7.1%) in cotton industry, 4(5.7%) were in business,1 (1.4%) in dye industry and 1(1.4%) was a professional.(fig 5)

fig 5. OCCUPATION

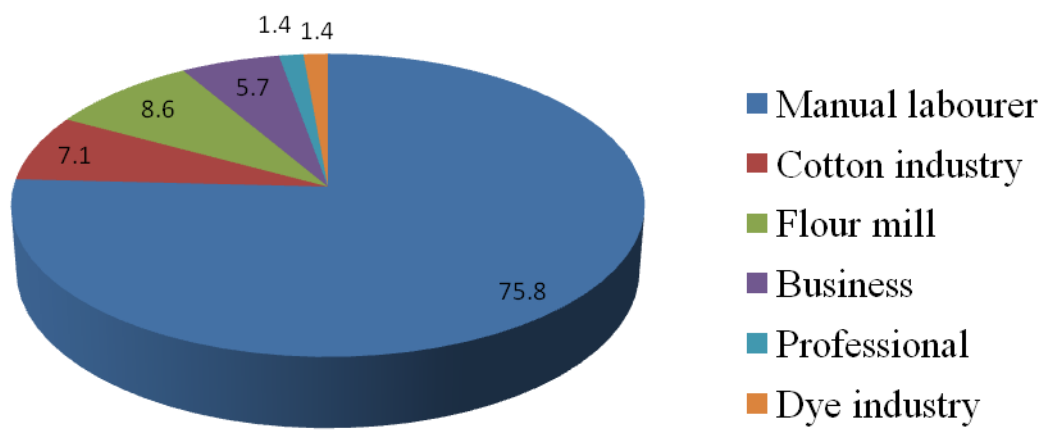


TABLE – 7

SYMPTOMS

SYMPTOMS	N	%
Chronic cough	70	100
Sputum production	70	100
Shortness of breath	62	88.6
Wheeze	51	72.9

All the patients had chronic cough with sputum production, 88.6% had shortness of breath and 72.9% gave a history of wheeze.(fig 6)

fig 6. SYMPTOMS

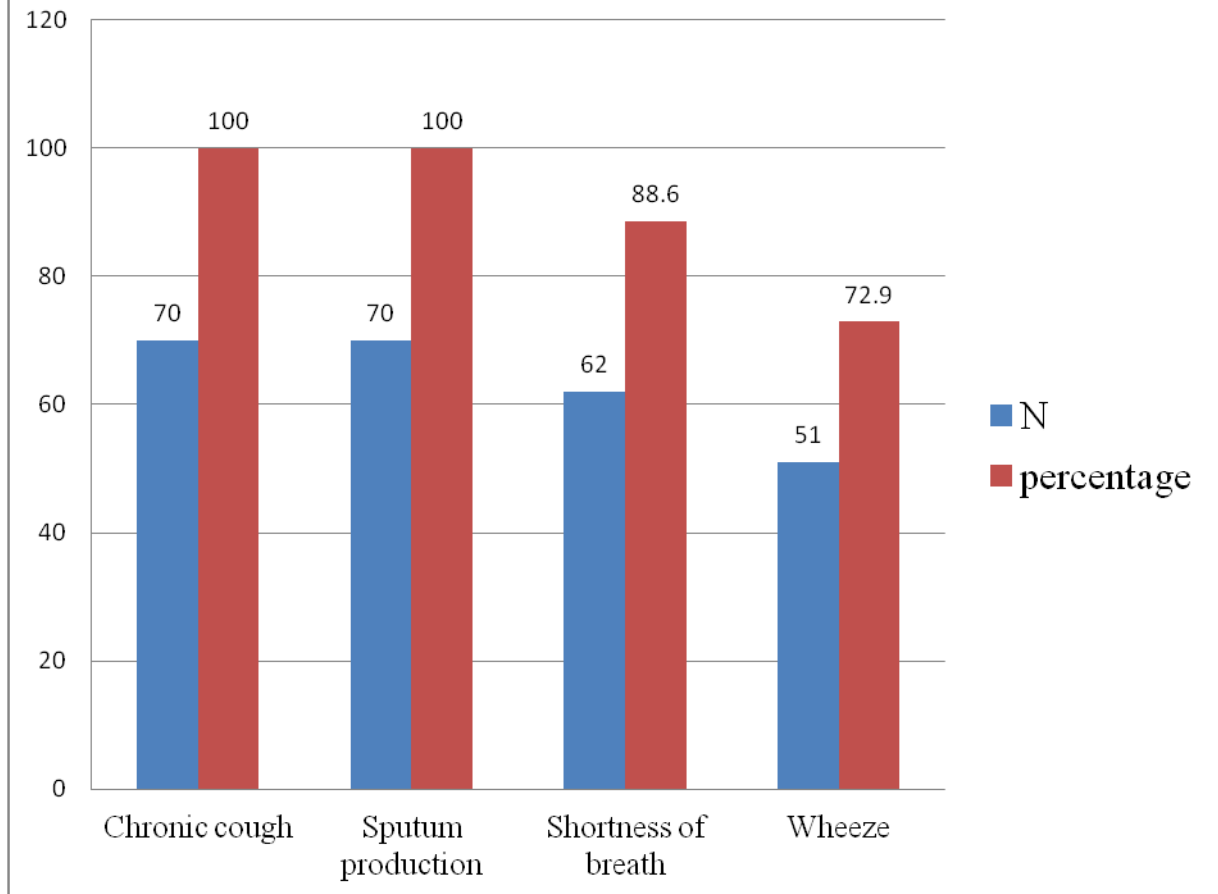


TABLE - 8

SIGNS

SIGNS	N	%
Elevated JVP	15	21.4
Pedal edema	11	15.7
Diminished air entry	31	44.3
Wheeze	47	67.1
Crackles	39	55.7
Downward liver displacement	24	34.3

Of the 70 patients, 15(21.4%) had elevated JVP, 11(15.7%) had pedal edema, 31(44.3%) diminished air entry, 47(67.1%) wheeze, 39(55.7%) crackles on auscultation and 24(34.3%) had downward displacement of liver due to air trapping and hyperinflation.(fig 7)

fig 7. SIGNS

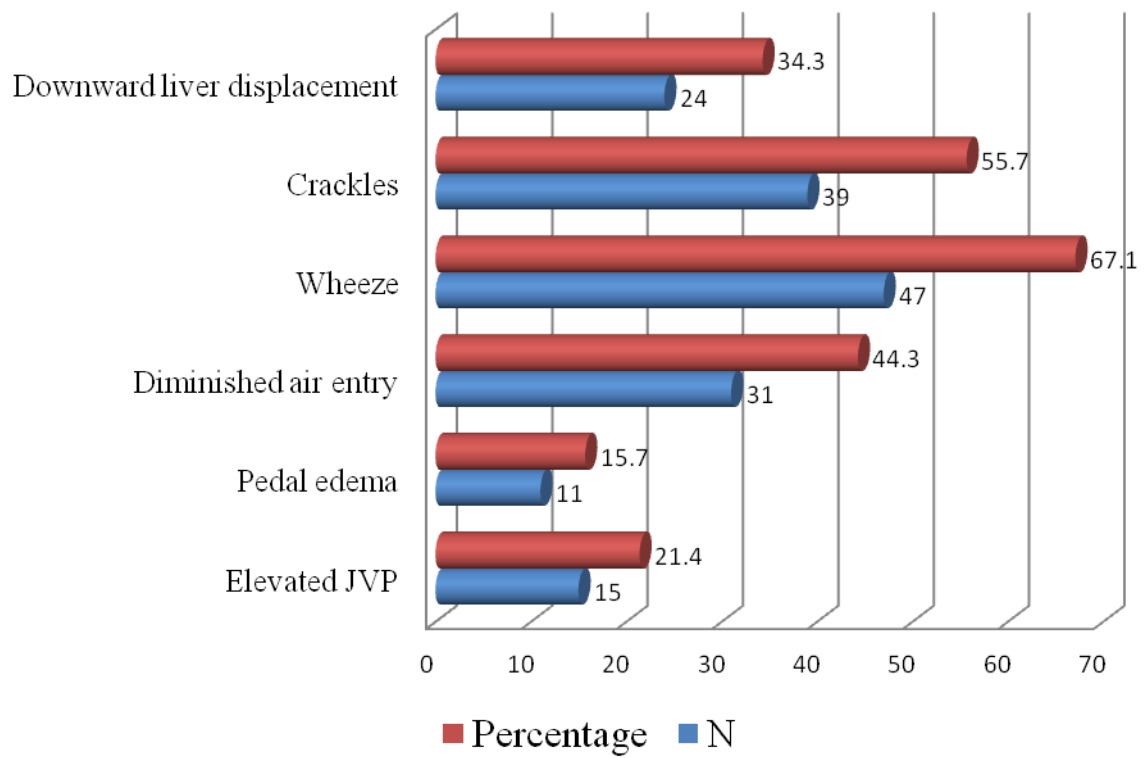


TABLE - 9

X-RAY CHEST PA VIEW

Stage	N	Normal	%	CB	%	E	%	CB + E	%
I	8	8	100	-	-	-	-	-	-
II	33	5	15.2	10	30.3	10	30.3	8	24.2
III	24	-	-	6	25	10	41.7	8	33.3
IV	5	-	-	1	20	1	20	3	60

Of the 70 patients, 13 patients had normal X-ray, 17 patients had features of chronic bronchitis, 21 had findings suggestive of emphysema and 19 patients showed features of both chronic bronchitis and emphysema.(fig 8)

fig 8. X-RAY CHEST PA VIEW

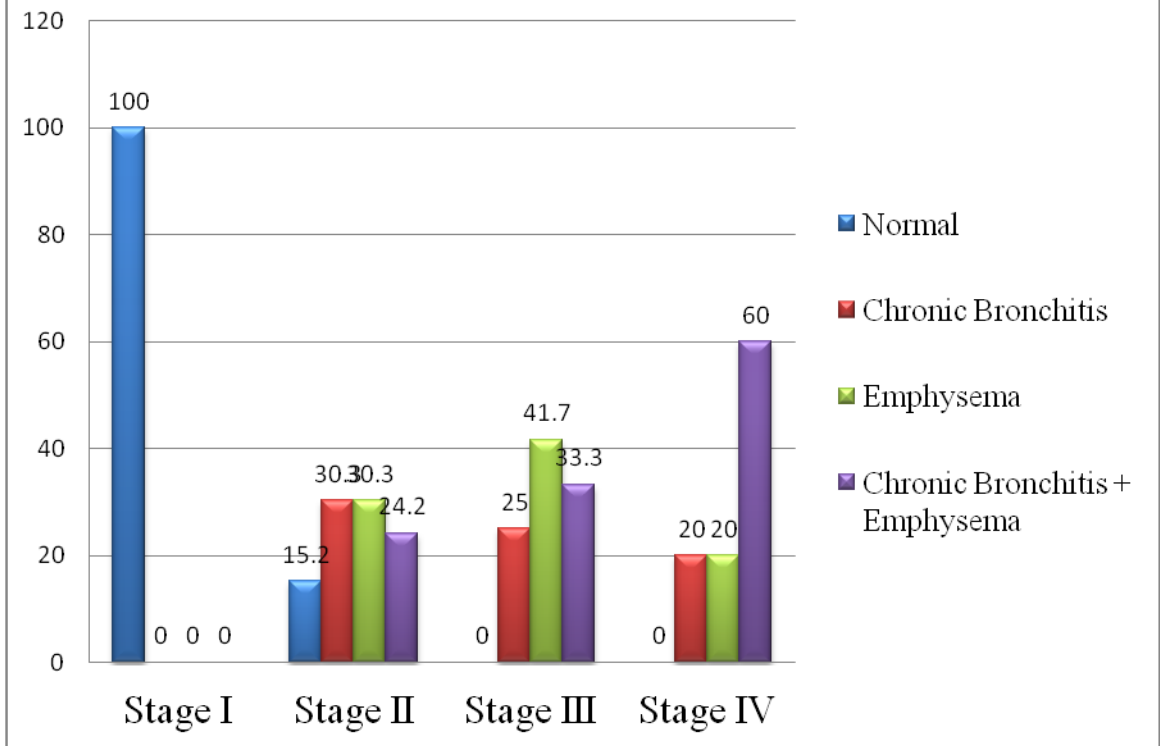


TABLE - 10

ELECTROCARDIOGRAM

	I	II	III	IV	TOTAL
RAE	-	1	6	5	12
RVH	-	2	5	3	10
Right axis deviation	-	1	2	3	6
Right Bundle Branch Block	1	3	4	2	9
Lead I sign	-	9	8	3	20
PPRW	-	6	9	2	17

Among patients with stage I disease (8) 1 patient had ECG criteria for right bundle branch block, stage II disease(33) 1 patient showed features of right atrial enlargement (p wave > 2.5mm), 2 patients had right ventricular hypertrophy (R in V1 > 7mm or R/S in V1>1), 1 had right axis deviation,3 showed right bundle branch block, 9 had lead I sign (small equiphasic QRS complex in lead I – due to hyperinflation of lungs and rotation of heart) and 6 had poor R wave progression. Among patients with stage III disease, 6 showed RAE, 5 RVH, 2 right axis deviation, 4 right bundle branch block, 8 lead I sign and 9 poor progression of R wave. In stage IV disease 5 had right atrial enlargement,3 right ventricular hypertrophy, 3 had right axis deviation,2 RBBB,3 lead I sign and 2 had poor R wave progression.(fig 9)

fig 9. ELECTROCARDIOGRAM

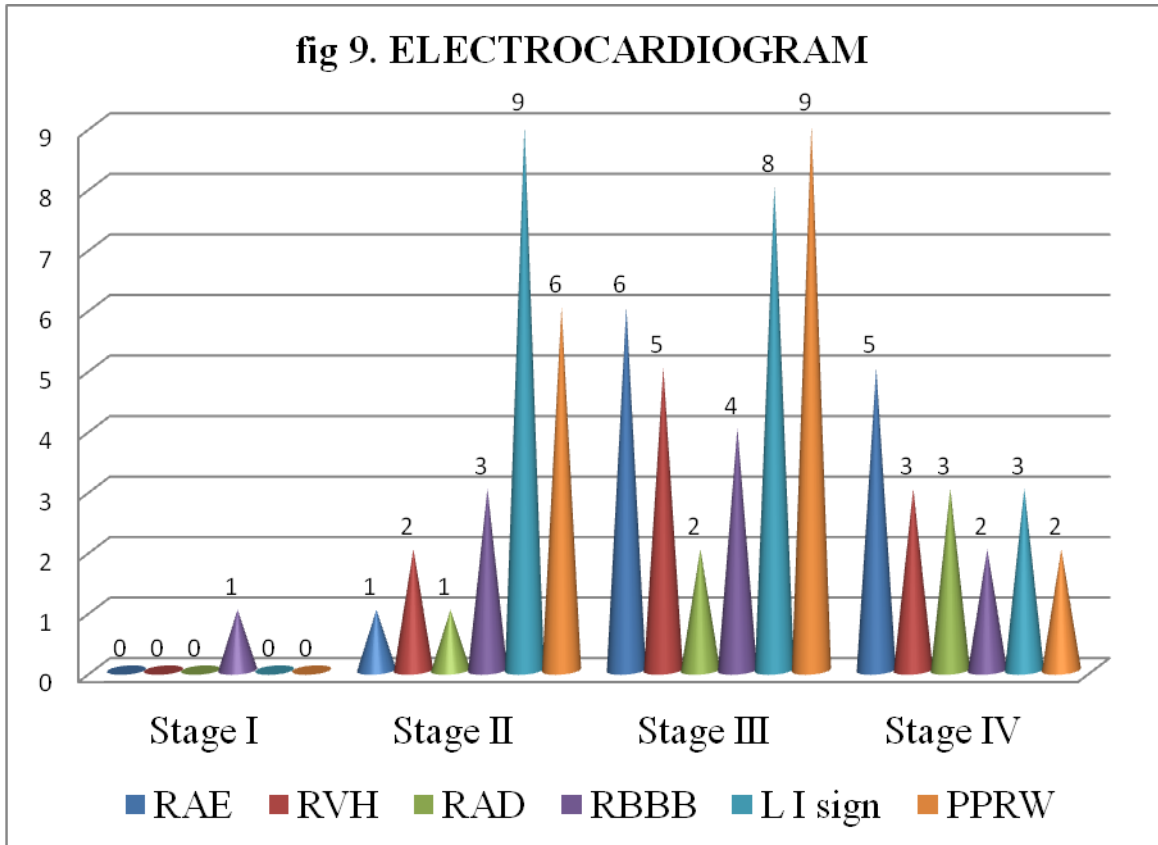


TABLE - 11

ECHOCARDIOGRAPHY

Stage	N	Mild	%	Moderate	%	Severe	%	RV dilatation	%
I	8	-	-	-	-	-	-	-	-
II	33	3	42.9	1	10	-	-	-	-
III	24	4	57.1	5	50	2	66.7	2	33.3
IV	5	-	-	4	40	1	33.3	4	66.7
TOTAL	70	7	100	10	100	3	100	6	100

Of the total 70 patients, 7 patients – 3 in stage II and 4 in stage III had mild pulmonary hypertension, 10 patients – 1 in stage II, 5 in stage III and 4 in stage IV had moderate pulmonary hypertension, 3 patients – 2 in stage III and 1 in stage IV had severe pulmonary hypertension. Of the 6 patients with RV enlargement 2 were in stage III and 4 in stage IV.(fig 10)

fig 10. ECHOCARDIOGRAM

■ RV dilatation ■ Severe ■ Moderate ■ Mild

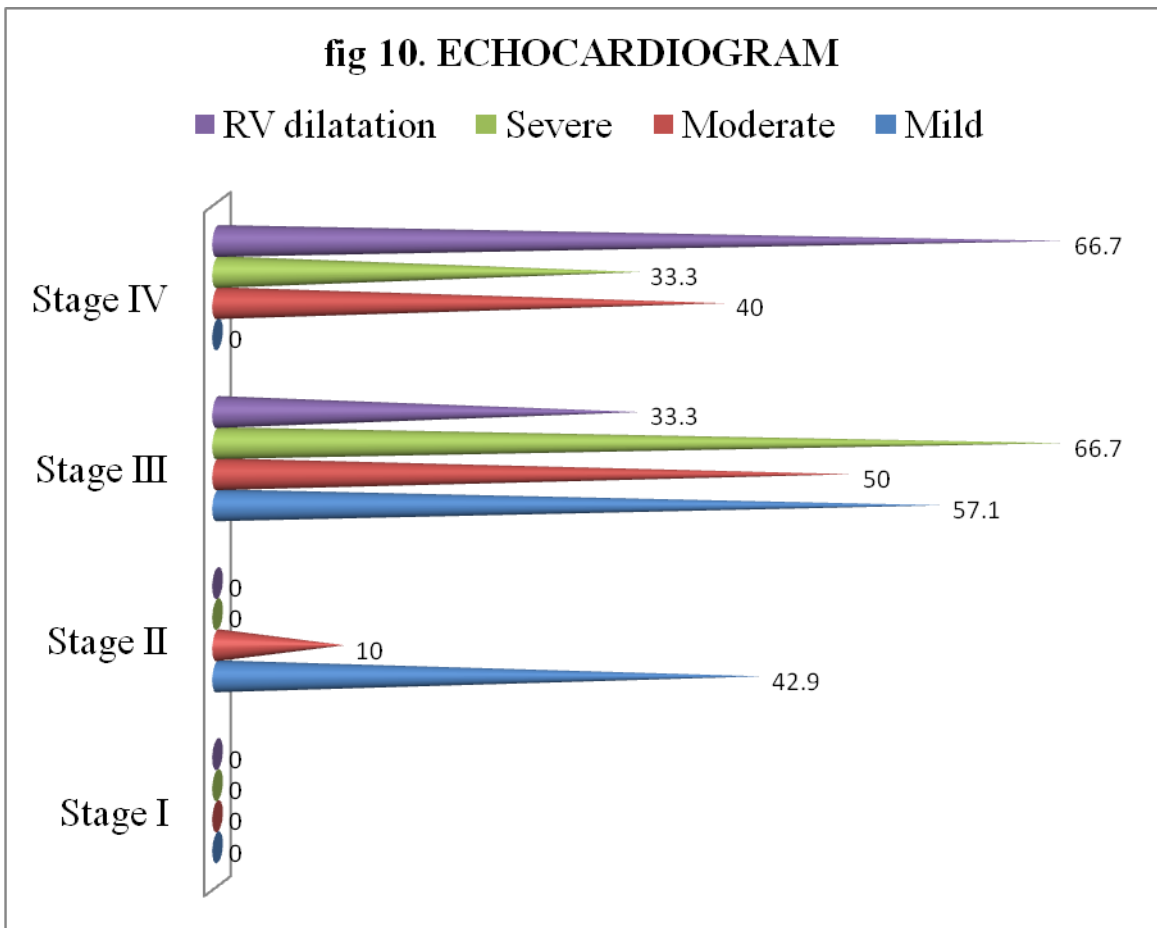


TABLE –12

BODY MASS INDEX WITH STAGE

BODY MASS INDEX	MEAN	S.D
I	26.43	4.16
II	23.91	1.84
III	21.50	2.07
IV	18.78	1.98
p < 0.001 Significant		

The body mass index showed a decreasing trend with increasing stage of the disease and the association was found to be statistically significant. (p < 0.001) (fig 11)

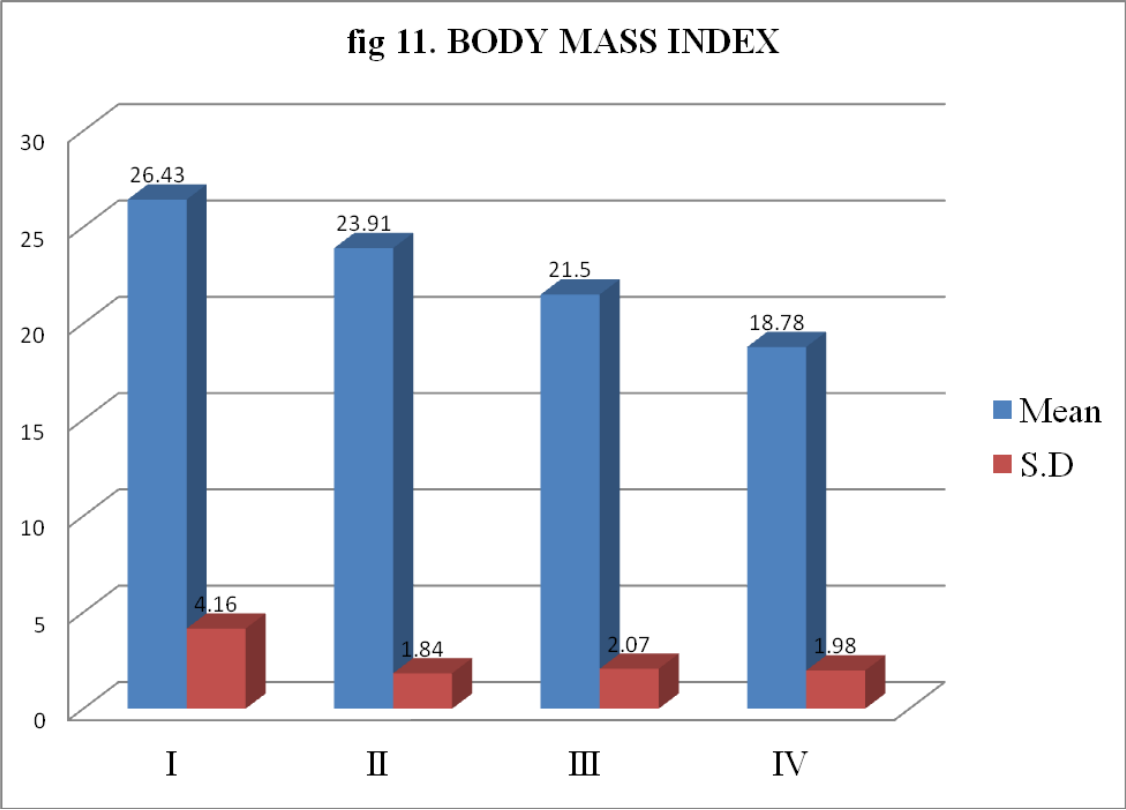


TABLE – 13

PACK YEARS OF SMOKING WITH STAGE

PACK YEARS OF SMOKING	MEAN	S.D
I	13.75	9.91
II	30.61	10.81
III	41.25	6.29
IV	52.00	4.47
p < 0.001 Significant		

TABLE – 14

FEV1% OF PREDICTED VALUE WITH PACK YEARS

FEV1% OF PV	P
PACK YEARS OF SMOKING	< 0.001 Significant

The study showed that there is an increase in severity of the disease as depicted by GOLD stage with the increase in the number of pack years of smoking and it was statistically significant ($p < 0.001$). Also the decline in FEV1 % of predicted value also showed a significant association with the number of pack years of smoking.(fig 12)

fig 12. PACK YEARS OF SMOKING

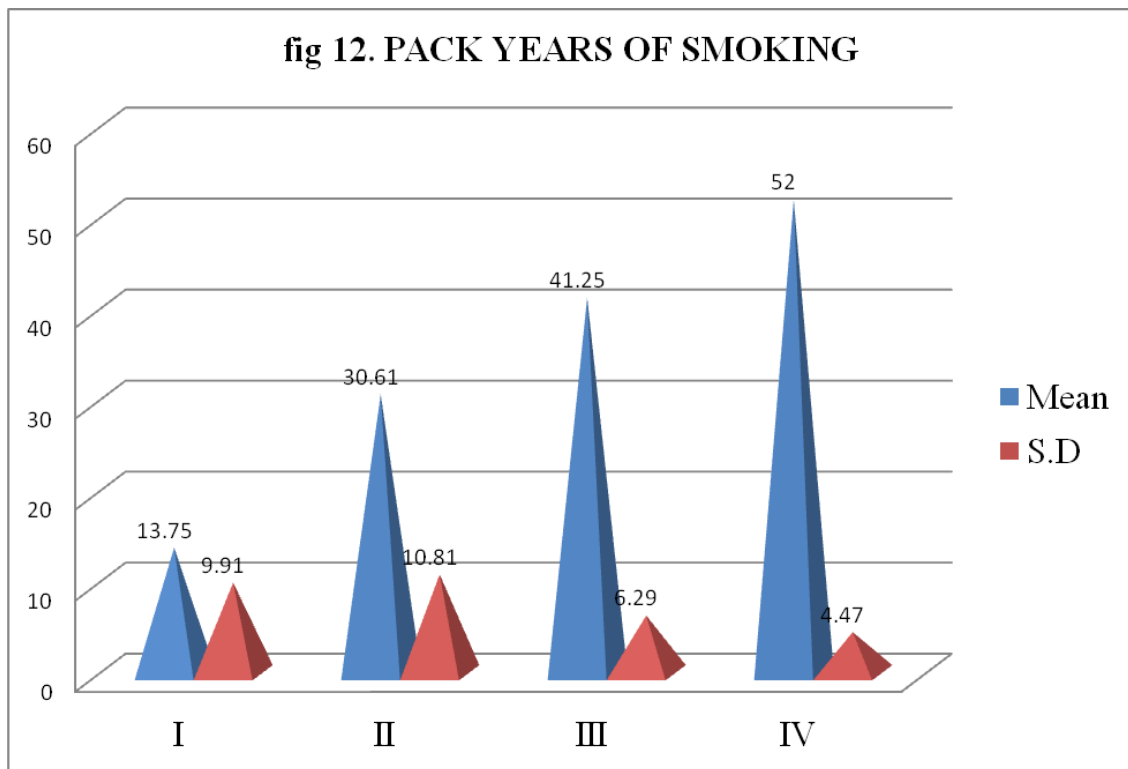


TABLE – 15

ERYTHROCYTE SEDIMENTATION RATE WITH STAGE

ERYTHROCYTE SEDIMENTATION RATE	Mean	S.D
I	22.13	11.13
II	23.18	8.37
III	26.04	6.28
IV	36.00	11.23
p = 0.012 Significant		

TABLE – 16

FEV1% OF PREDICTED VALUE WITH ERYTHROCYTE
SEDIMENTATION RATE

FEV1% OF PV	P
ERYTHROCYTE SEDIMENTATION RATE	< 0.001 Significant

The mean erythrocyte sedimentation rate in each stage were tested for significance and was found to be statistically significant with p value = 0.012. Similarly the correlation between erythrocyte sedimentation rate and FEV1% of predicted value was also found to be significant.(fig 13)

fig 13. ERYTHROCYTE SEDIMENTATION RATE

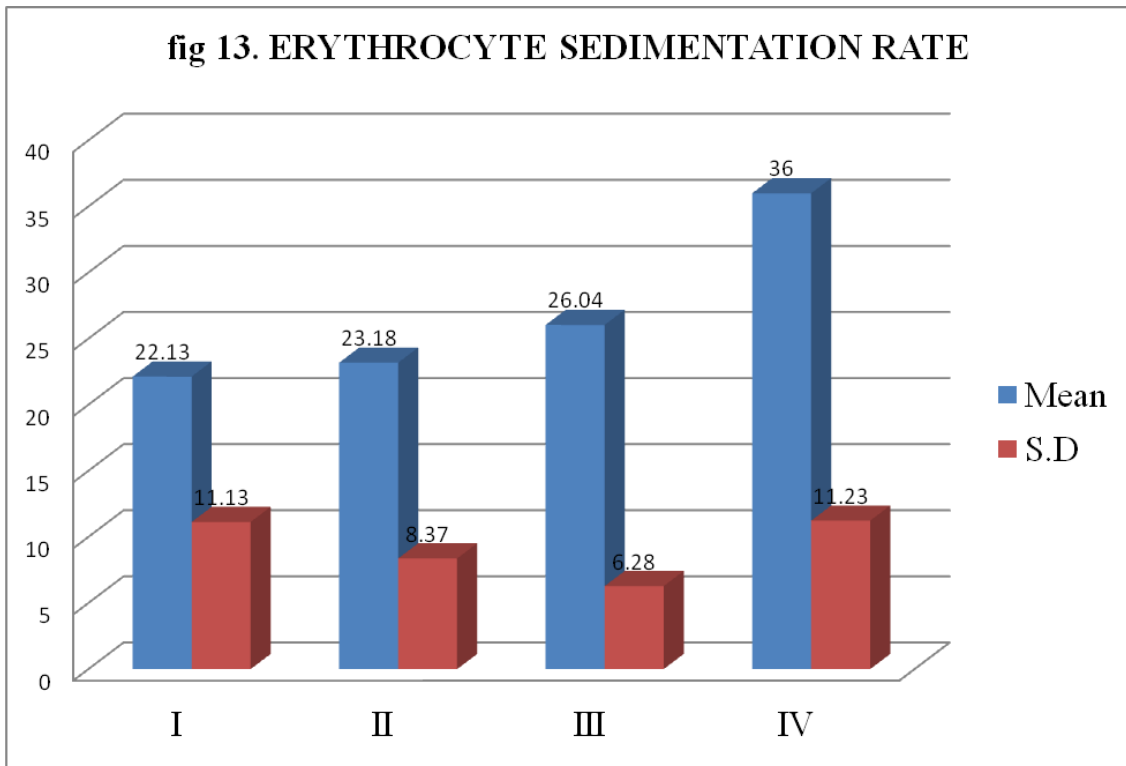


TABLE – 17

SERUM ALBUMIN WITH STAGE

SR. ALBUMIN	MEAN	S.D
I	4.43	0.35
II	3.91	0.36
III	3.62	0.35
IV	2.56	0.39
p < 0.001 Significant		

TABLE – 18

FEV1% OF PREDICTED VALUE WITH SERUM ALBUMIN

FEV1% OF PV	P
SERUM ALBUMIN	< 0.001 Significant

Serum albumin concentration was found to decrease among patients with increasing disease severity and the decrease was found to be statistically significant ($p < 0.001$). Also with declining FEV1% of predicted value serum albumin was found to significantly decrease. ($p < 0.001$) (fig 14)

fig 14. SERUM ALBUMIN

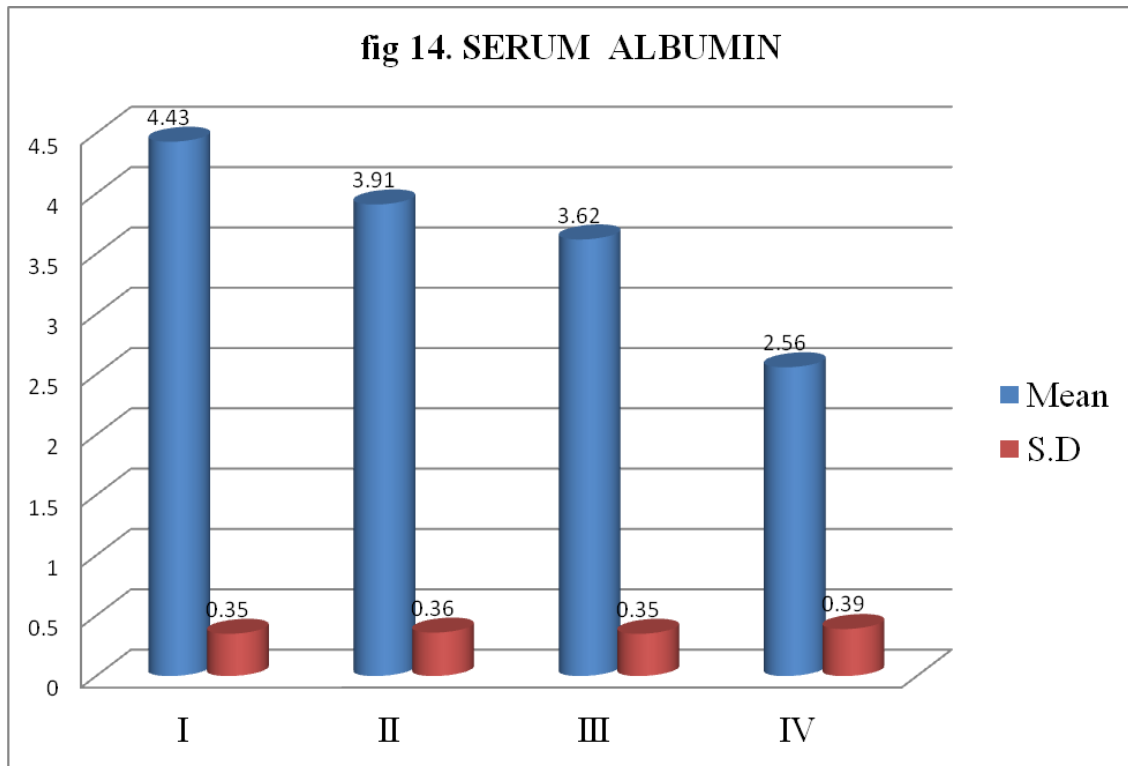


TABLE – 19

HIGHLY SENSITIVE CRP WITH STAGE

HIGHLY SENSITIVE CRP	MEAN	S.D
I	3.91	1.26
II	5.79	1.23
III	9.01	0.96
IV	11.98	0.73
p < 0.001 Significant		

TABLE – 20

HIGHLY SENSITIVE CRP

	I	II	III	IV	'p' value
≤ 3 mg/L (3)	2	1	0	0	0.421 Not Significant
>3 mg/L (67)	6	32	24	5	< 0.001 Significant

TABLE – 21

FEV1% OF PREDICTED VALUE WITH HIGHLY
SENSITIVE CRP

FEV1% OF PV	P
HIGHLY SENSITIVE CRP	< 0.001 Significant

Among the 4 stages, the concentration of highly sensitive C-Reactive Protein was highest in stage IV disease and the increase in highly sensitive C-Reactive Protein with disease severity was found to be statistically significant with $p < 0.001$.(fig 15). Also among the total 70 patients, 67 patients had increased highly sensitive C-Reactive Protein of > 3 mg/L and only 3 patients had normal values. When statistically tested between the normal vs abnormal groups among the stages it was found to significant.(fig 16). Similarly, the correlation between FEV1% of predicted value with this marker of inflammation was also statistically significant ($p < 0.001$).

fig 15. Highly sensitive CRP (mg/L)

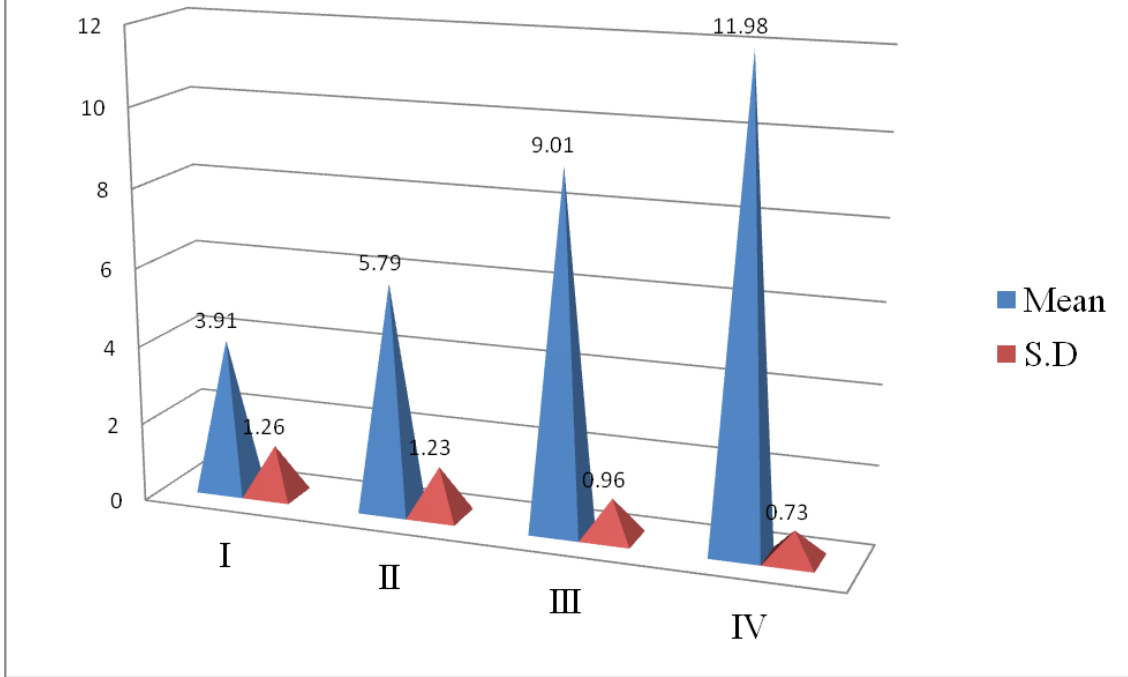
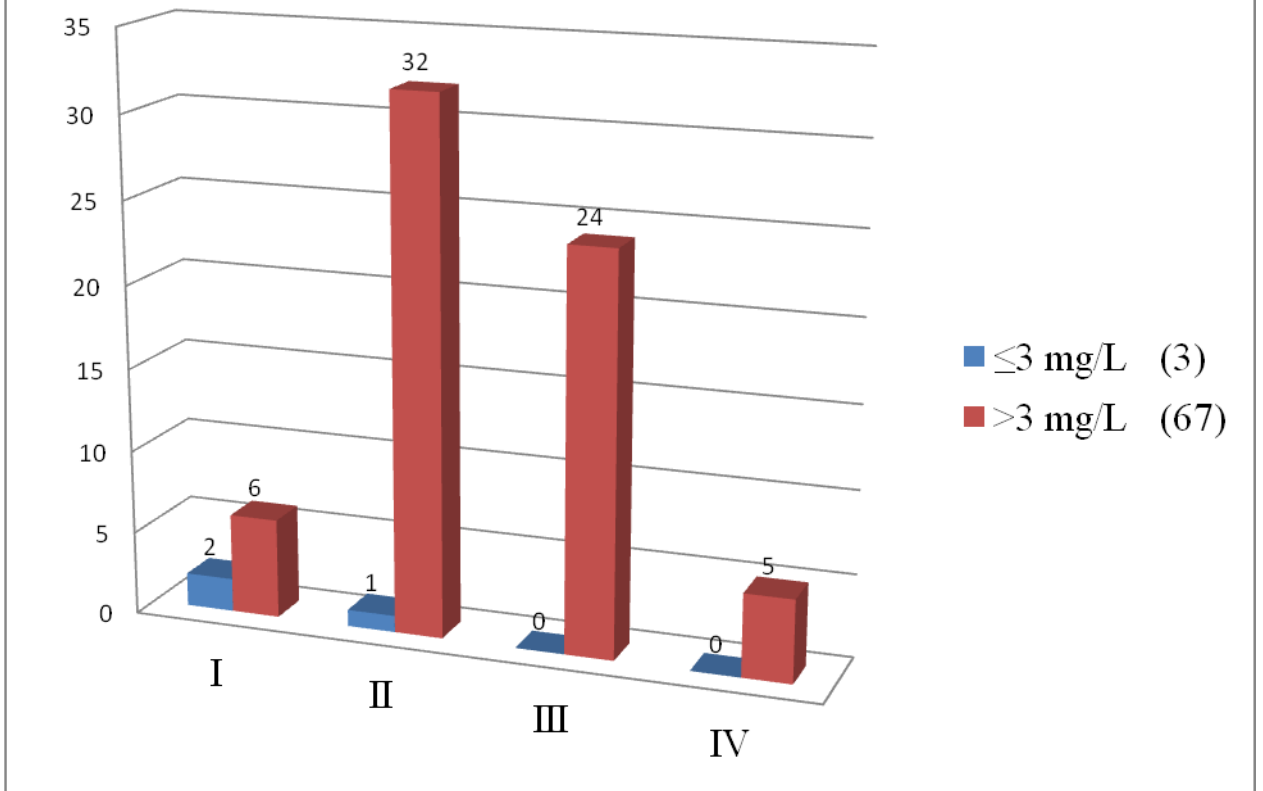


fig 16. Highly Sensitive C-Reactive Protein



DISCUSSION

COPD is one of the several diseases whose morbidity and mortality is increasing day by day at an alarming rate and imposing economic burden on the nation.³⁴ Despite advances in diagnosis and management the disease still remains untamed. The disease has been recognized as one with systemic manifestations and several markers are being tested everyday to possibly reflect the entire disease process, but the 'ideal' marker still remains an enigma. In our study, a total of 70 patients were studied after applying the inclusion and exclusion criteria; their clinical status analysed and markers of inflammation were correlated with severity to determine their significance.

AGE

In our study, the increase in age with the increasing stage of the disease was found to be statistically significant with $p < 0.001$ and the correlation of age with FEV1% of predicted value was also found to be statistically significant. The risk of developing the disease has been shown to increase with age.⁴³ This may be due to the age related deterioration of lung function or increase in duration of smoking or

sustained exposure to environmental risk factors or a combination of any these, one compounding the effects of the other.

SEX

Of the total 70 patients, 67 (95.7%) were males and 3 (4.3%) were females. This is because smoking, the important risk factor is common in males. ⁴

SMOKING

The study showed that there is an increase in severity of the disease as depicted by GOLD stage with the increase in the number of pack years of smoking and it was statistically significant. Also the decline in FEV1 % of predicted value also showed a negative correlation with the number of pack years of smoking which is consistent with other studies. Smoking in any form has been regarded as the most important risk factor in almost every study for developing the disease and has been proven to have a dose – response relationship. ^{4,5,6} On reviewing several studies on Indian male patients, 82.3% were associated with smoking. ³⁹

OCCUPATION

Of the total 70 patients, 53(75.8%) were manual labourers, 6(8.6%) were working in flour mill, 5(7.1%) in cotton industry, 4(5.7%) were in business, 1 (1.4%) in dye industry and 1(1.4%) was a professional. Several occupation which are associated with chemicals, noxious gases, minerals, dust, cotton industry have been identified as risk factors and the risk is further compounded if smoking is also present. ³⁰

SYMPTOMS

In our study, all the patients had chronic cough with sputum production and a majority had shortness of breath and wheeze – the cardinal symptoms of the disease.

SIGNS

Of the 70 patients, 15 had raised JVP, 11 had pedal edema which could be due to hypoalbuminemia or cor pulmonale, 31 diminished air entry, 47 wheeze, 39 crackles on auscultation and 24 had downward displacement of liver due to air trapping and hyperinflation.

X-RAY CHEST PA VIEW

Among the 70 patients, 13 patients had normal X-ray, 17 patients had features of chronic bronchitis, 21 had findings suggestive of emphysema and 19 patients showed features of both chronic bronchitis and emphysema. These inferences show that imaging could not be used to diagnose the disease particularly in its early stages and also that the two forms of the disease is not mutually exclusive as patients over time may develop features of the two.¹⁰

ELECTROCARDIOGRAM

Among patients with stage I disease (8) 1 patient had ECG criteria for right bundle branch block, stage II disease(33) 1 patient showed features of right atrial enlargement, 2 patients had right ventricular hypertrophy, 1 had right axis deviation,3 showed right bundle branch block, 9 had lead I sign and 6 had poor R wave progression. Among patients with stage III disease, 6 showed RAE, 5 RVH, 2 right axis deviation, 4 right bundle branch block, 8 lead I sign and 9 poor progression of R wave. In stage IV disease 5 had right atrial enlargement,3 right ventricular hypertrophy, 3 had right axis deviation,2 RBBB,3 lead I sign and 2 had poor R wave progression.

Several studies have demonstrated the ECG changes including right atrial enlargement, right axis deviation, right bundle branch block, low voltage complexes in these patients as the disease progresses.³⁶ The criteria for diagnosing right ventricular hypertrophy cannot detect all cases in these patients due to cardiac rotation and hyperinflation of lungs.⁴⁴ Antonelli incalzi et al showed that SI SII SIII pattern and right atrial overload was significantly associated with increased risk of death. ECG findings though less sensitive are highly specific.²²

ECHOCARDIOGRAPHY

Of the total 70 patients, 7 patients – 3 in stage II and 4 in stage III had mild pulmonary hypertension, 10 patients – 1 in stage II, 5 in stage III and 4 in stage IV had moderate pulmonary hypertension, 3 patients – 2 in stage III and 1 in stage IV had severe pulmonary hypertension. Of the 6 patients with RV enlargement 2 were in stage III and 4 in stage IV. Various factors – alveolar hypoxia, lung hyperinflation, parenchymal destruction altering pulmonary hemodynamics culminate in pulmonary hypertension and subsequently right ventricular dysfunction in these patients. Right ventricular failure if present is an independent marker of poor prognosis and is a cause for increase in breathlessness, reduced

exercise tolerance and hence their identification is crucial to reduce morbidity and mortality and all these patients should be investigated for the same by echocardiography and if needed catheterization studies.²³

BODY MASS INDEX

In our study, the body mass index showed a decreasing trend with increasing stage of the disease and the association was found to be statistically significant. ($p < 0.001$). Unintentional weight loss particularly the fat free mass in these patients is termed pulmonary cachexia. The cause is multifactorial and has been attributed to a combination of systemic inflammation, pulmonary gas exchange abnormalities resulting in hypoxia, genetic predisposition, oxidative stress and several other factors.³ The consequences are muscle dysfunction – respiratory increasing dyspnoea and work of breathing and non respiratory causing reduced exercise capacity, impaired quality of life and is a risk factor for increase in mortality irrespective of lung function.^{19,26,33} H.Gunen et al showed that long term risk of death increased in patients with body mass index < 20 kg/sq.m.¹ Body mass index is part of the BODE index a validated score used for predicting prognosis in these patients.⁶

ALBUMIN

Among our patients, serum albumin concentration was found to decrease among patients with increasing disease severity as per the stage of the disease and the decrease was found to be statistically significant. Also serum albumin showed positive correlation with declining FEV1% of predicted value. Albumin is a negative acute phase reactant,³² the concentration of which decreases with inflammation and also its concentration decreases with chronic debilitating diseases. H.Gunen et al showed that serum albumin < 2.5 g/dL was associated with long term risk of mortality and thus low serum albumin serves as a poor prognostic marker.¹ Low serum albumin has also been shown to be a surrogate marker of other inflammatory markers.²

ERYTHROCYTE SEDIMENTATION RATE

In our study erythrocyte sedimentation rate was found to increase with the stage and decrease in FEV1% of predicted value and the association was found to be statistically significant. Several studies have analysed the usefulness of erythrocyte sedimentation rate as a marker of inflammation and disease severity because of its

availability and cost. The inferences are conflicting with some indicating erythrocyte sedimentation rate increases with disease severity⁴⁵ while others concluded that it could not be used as a marker of severity.²

HIGHLY SENSITIVE C-REACTIVE PROTEIN

Since the recognition of COPD as a systemic inflammatory state which contributes much to the morbidity and mortality, extensive research have been done to tame the inflammation and hence a search for a 'ideal' biomarker which could mirror the disease process and which could be used for predicting prognosis, monitoring treatment is still on. Of the several biomarkers being added everyday to the existing list, highly sensitive C-reactive protein has performed fairly consistently across studies and hence we chose it for our study. In the present study, among the 4 stages, the concentration of highly sensitive C-Reactive Protein was highest in stage IV disease and the increase in highly sensitive C-Reactive Protein with disease severity was found to be statistically significant with $p < 0.001$. Also among the total 70 patients, 67 patients had increased highly sensitive C-Reactive Protein of > 3 mg/L and only 3 patients had normal values. When statistically tested between the normal vs abnormal groups

among the stages it was found to significant. Similarly, the correlation between FEV1% of predicted value with this marker of inflammation was also statistically significant which was consistent with the results of other studies.¹⁸ Highly sensitive C-Reactive Protein is a marker of disease severity, patients health status and has shown to be raised in patients who are stable thus qualifying as a better biomarker.^{16,17,18} Patients with elevated levels of this marker at baseline have an increased risk of hospitalization and mortality as shown by studies.^{14,18} In our study, the marker has performed in consistent with similar other studies correlating with the disease severity.

LIMITATIONS OF THE STUDY

The study has its own limitations

- The number of patients involved in the study 'N' is small and hence generalization of the results of the study have to be made with caution.
- The study population involved only the patients seeking medical care in our hospital which is a tertiary care centre and hence they may not represent the general population.
- This study is a cross sectional study and hence it represents the characteristics and variables tested in the study population at that point of time. Longitudinal studies with serial assessment of the variables would be more informative.

So, longitudinal studies with large study population and population based studies are needed to circumvent these limitations.

CONCLUSIONS

From our study we conclude that

- Increasing age is associated with severity of the disease.
- Males are more commonly affected than females because of smoking.
- Occupational exposure to risk factors compounds the risk of developing the disease when associated with smoking.
- Incidence of pulmonary hypertension and right ventricular dilatation increases with increasing severity of the disease.
- Body mass index decreases with increasing severity and is a poor prognostic marker.
- The markers of inflammation – Erythrocyte sedimentation rate, albumin, Highly Reactive C-Reactive Protein correlates with increasing disease severity as evidenced by decreasing FEV1% of predicted value and increasing GOLD stage.

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PROFORMA

Name :

Patient number :

Age :

Sex :

Occupation :

Address :

Present History

Chronic cough

Sputum

Shortness of breath

Wheeze

Hemoptysis

Fever

Other relevant history

Past history

History regarding Diabetes, Hypertension, Tuberculosis, Ischemic heart disease, CVA or any other chronic diseases. Any chronic drug intake.

Personal history

Tobacco use – form of use.

Smoking – duration, pack years of smoking.

Alcohol intake – duration

Any history of pre / extra – marital contact.

Occupation

General examination

Nutrition	Pallor	Icterus	Cyanosis
Clubbing	Lymphadenopathy		Pedal edema
JVP			
Pulse rate	BP		Respiratory rate
Height	Weight		Body Mass Index

Systemic examination

Respiratory System

Air entry	Breath sounds	Wheeze	Crackles
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CVS

Abdomen

CNS

Investigations

Hb TC DC ESR Urine Albumin Sugar Deposits

Blood Sugar Urea Serum Creatinine Serum Albumin

ECG X-ray chest PA view Echo

hs-CRP

HIV

PFT

FEV1 FVC FEV1/FVC FEV1% of predicted value

GOLD STAGE

Diagnosis

ABBREVIATIONS

COPD	–	Chronic Obstructive Pulmonary Disease
GOLD	–	Global initiative for chronic Obstructive Lung Diseases
DALY	–	Disability Adjusted Life Years
hs-CRP	–	Highly Sensitive C-Reactive Protein
ECG	-	ElectroCardioGram
ESR	–	Erythrocyte Sedimentation Rate
BMI	–	Body Mass Index
FEV1	–	Forced Expiratory Volume in 1 second
FVC	–	Forced Vital Capacity
ICMR	–	Indian Council of Medical Research
HCHO	-	formaldehyde
AT	–	Anti -Trypsin
RV	–	Residual Volume
TLC	–	Total Lung Capacity
FRC	–	Functional Residual Capacity
ROS	–	Reactive Oxygen Species
MMP	–	Matrix Metallo proteinase
PTE	–	Pulmonary Thrombo Embolism
ABG	–	Arterial Blood Gas
PHT	–	Pulmonary HyperTension
MAT	–	Multifocal Atrial Tachycardia

CAD	–	Coronary Artery Disease
NIV	–	Non Invasive Ventilation
LTOT	–	Long Term Oxygen Therapy
TNF α	–	Tumour Necrosis Factor α
TGF β	–	Transforming Growth Factor β
IL	-	InterLeukin
PPAR	–	Peroxisome Proliferator-Activated Receptors
NFKB	–	Nuclear Factor K B

KEY TO MASTER CHART

M	–	Male
F	–	Female
L	-	Manual Labourer
FM	–	Flour Mill
CM	–	Cotton Industry
B	–	Business
P	–	Professional
P/ +	–	Present
A/-	–	Absent
D	–	Decreased
N	–	Normal
R	–	Right
L	–	Left
NW	-	North West

MASTER CHART

S. No.	Name	Age (Years)	Sex	Occupation	Symptoms				Signs						Xray		Electro cardiogram					
					chronic cough	Sputum production	Shortness of breath	Wheeze	Elevated JVP	Pedal edema	Air Entry	Wheeze	Crackles	Downward displacement liver	Chronic bronchitis	Emphysema	Right Atrial enlargement	Axis	Right Ventricle Hypertrophy	Right Bundle Branch block	Lead I Sign	Poor R' wave progression
1	Rengasamy	27	M	L	P	P	A	A	A	A	N	A	A	A	A	A	A	N	A	A	A	A
2	Anthonyamy	32	M	L	P	P	A	A	A	A	N	P	A	A	A	A	A	N	A	A	A	A
3	Palpandi	34	M	L	P	P	P	A	A	A	N	P	A	A	A	A	A	R	A	A	A	A
4	Lakshmi	55	F	L	P	P	P	P	A	A	N	A	P	A	A	A	A	N	A	A	A	A
5	Pitchai	35	M	L	P	P	A	P	A	A	N	P	A	A	A	A	A	N	A	P	A	A
6	Kalimuthu	37	M	FM	P	P	A	A	A	A	N	A	A	A	A	A	A	N	A	A	A	A
7	Irulayee	56	F	L	P	P	P	P	A	A	N	P	A	A	A	A	A	N	A	A	A	A
8	Yesudass	38	M	L	P	P	A	P	A	A	N	A	A	A	A	A	A	R	A	A	A	A
9	Karupayee	54	F	L	P	P	P	A	P	A	N	A	P	A	P	A	A	N	A	A	P	A
10	Christopher	38	M	L	P	P	P	P	A	A	N	P	A	A	A	P	A	N	A	A	A	P
11	Shajahan	44	M	L	P	P	P	P	A	A	D	P	A	A	A	P	A	N	A	A	A	A
12	Ajith	55	M	L	P	P	P	P	A	A	N	P	A	A	A	A	A	L	A	A	A	A
13	Balusamy	48	M	L	P	P	P	A	A	A	N	A	P	A	P	A	A	N	A	A	A	A
14	Arun	38	M	L	P	P	P	P	A	A	N	P	P	A	A	P	A	R	A	A	A	A
15	Muthusamy	37	M	FM	P	P	A	P	A	A	D	P	A	A	P	P	A	N	A	P	P	P
16	Kuppan	54	M	P	P	P	P	A	A	A	N	A	P	A	A	A	A	N	A	A	A	A
17	Sadaiyan	40	M	B	P	P	P	P	A	A	D	P	A	P	A	A	N	A	P	P	A	P
18	Maruthupandi	25	M	L	P	P	P	P	A	A	N	P	P	A	A	A	N	A	A	A	P	P
19	Periyakaruppan	46	M	B	P	P	P	A	A	A	N	A	P	A	A	A	L	A	A	A	P	A
20	Yekalaiavan	29	M	L	P	P	A	A	A	A	N	A	P	A	A	A	N	A	A	A	A	A
21	Adaikalavan	36	M	L	P	P	A	P	A	A	N	P	A	A	A	A	N	A	A	A	A	A

22	Gopalakrishnan	35	M	L	P	P	P	P	A	A	N	P	P	A	A	A	N	A	A	A	P	P
23	Karupandi	57	M	FM	P	P	P	P	A	A	N	A	P	A	A	A	N	A	A	A	P	A
24	Isakimuthu	51	M	L	P	P	P	P	A	A	N	P	P	P	A	A	N	A	P	A	P	P
25	Shankar	47	M	L	P	P	P	A	A	A	N	A	P	A	A	A	N	A	A	A	P	A
26	Marimuthu	46	M	L	P	P	P	P	A	A	N	P	P	A	A	A	R	A	A	A	P	P
27	Kavirajan	39	M	L	P	P	P	P	A	A	N	P	A	P	A	A	N	A	A	P	A	P
28	Sangarappan	47	M	CM	P	P	P	P	A	A	D	P	A	A	A	A	N	A	P	A	A	P
29	Sheriph	56	M	L	P	P	P	P	A	A	D	P	P	P	A	A	N	A	P	A	P	P
30	Chinnasamy	45	M	CM	P	P	P	A	A	A	N	A	P	A	A	A	N	A	A	A	P	A
31	Andisamy	40	M	L	P	P	P	P	A	A	N	P	P	P	A	A	N	A	A	A	P	P
32	Jagdish	46	M	L	P	P	P	A	A	A	N	A	P	A	A	A	L	A	A	A	A	A
33	Gurusamy	57	M	L	P	P	P	P	A	A	D	P	A	A	A	A	N	A	P	P	A	P
34	Syed	42	M	L	P	P	P	P	A	A	D	P	A	P	A	A	N	A	A	A	A	P
35	Vadivu	55	M	L	P	P	P	A	A	A	N	A	P	A	A	A	N	A	A	A	P	A
36	Mani	30	M	L	P	P	P	P	A	A	N	P	A	A	A	A	N	A	A	A	A	A
37	Rahman	58	M	CM	P	P	P	P	P	A	N	A	P	A	A	N	P	A	A	A	P	A
38	Ilangovan	43	M	L	P	P	P	P	A	A	D	P	A	P	P	N	A	P	P	P	A	P
39	Chinnu	33	M	L	P	P	P	P	A	A	N	P	P	A	A	N	A	A	A	A	P	P
40	Ravindran	54	M	L	P	P	P	P	A	A	D	P	A	A	A	N	A	A	A	A	A	P
41	Azhar Ali	57	M	L	P	P	P	P	A	A	N	A	P	A	A	N	A	A	A	A	P	A
42	Kasi	63	M	L	P	P	P	P	A	P	D	P	P	P	P	R	A	A	P	A	P	P
43	Pasupathy	45	M	CM	P	P	P	P	A	A	D	P	A	P	A	N	A	P	A	P	A	P
44	Thavasi	49	M	L	P	P	P	P	A	A	D	P	P	A	A	N	A	A	A	A	P	P
45	Sankarapandi	47	M	L	P	P	P	P	A	A	D	P	A	P	A	N	A	A	A	P	A	P
46	Guru	58	M	L	P	P	P	P	A	A	N	P	P	A	A	R	A	A	A	A	P	P
47	Muthu	74	M	L	P	P	P	A	P	P	N	A	P	A	AP	N	A	P	P	A	P	A
48	Ramaiah	65	M	L	P	P	P	P	A	P	D	P	A	P	A	N	A	A	A	P	A	P
49	Rajesh	38	M	D	P	P	P	P	A	A	D	P	A	P	A	N	A	A	A	P	A	P
50	Periyasamy	66	M	L	P	P	P	P	P	P	D	P	P	P	A	N	P	A	P	A	P	P
51	Murugan	41	M	FM	P	P	P	P	A	A	N	P	A	P	A	N	A	A	A	P	A	P

52	Gopal	57	M	B	P	P	P	P	A	A	D	P	P	P	A	R	A	P	A	A	P	P
53	Divakaran	71	M	L	P	P	P	A	P	P	N	A	P	A	P	N	P	A	P	P	P	A
54	Periyannan	57	M	L	P	P	P	P	A	A	D	P	A	P	P	N	A	P	P	A	A	P
55	Vellaisamy	59	M	L	P	P	P	P	A	P	D	P	P	A	A	N	A	A	A	A	P	P
56	Ruban	44	M	CM	P	P	P	P	A	A	D	P	A	P	A	N	A	P	P	P	A	P
57	Boobalan	46	M	FM	P	P	P	P	A	A	D	P	A	A	A	N	A	A	A	P	A	P
58	Arumugam	72	M	L	P	P	P	P	P	A	N	A	P	A	P	R	A	A	A	A	P	A
59	Sundar raj	61	M	L	P	P	P	P	P	A	D	P	P	A	A	N	A	P	P	P	P	P
60	Somasundram	63	M	L	P	P	P	A	A	N	A	P	A	A	N	A	P	P	A	A	P	A
61	Ahmed	68	M	L	P	P	P	P	P	D	P	P	P	P	R	A	A	A	A	A	P	P
62	Krishnan	56	M	FM	P	P	P	A	A	D	A	P	A	A	N	A	A	A	A	A	P	A
63	Sivanandan	59	M	L	P	P	P	P	P	D	P	A	P	A	N	A	A	A	P	P	A	P
64	Iyyappan	51	M	L	P	P	P	P	A	N	P	A	A	A	N	A	A	A	P	A	A	P
65	Ponraj	63	M	L	P	P	P	P	A	N	A	P	A	A	N	A	P	P	A	A	P	A
66	Sundar	73	M	L	P	P	P	P	P	D	P	P	P	P	R	P	P	P	A	A	P	P
67	Chelliah	76	M	L	P	P	P	P	P	D	P	A	P	P	N	A	P	P	P	P	A	P
68	Mariappan	67	M	L	P	P	P	P	P	D	P	P	P	P	R	A	A	A	P	P	P	P
69	Murugan	78	M	L	P	P	P	A	P	D	A	P	A	P	NW	P	A	A	A	A	P	A
70	Karupaiah	72	M	L	P	P	P	P	P	D	P	P	P	P	R	P	A	A	P	A	P	P

MASTER CHART CONTD..

S.No.	Age	Height (cm)	Weight (kg)	Body Mass Index (Kg/m ²)	Forced Vital Capacity (1)	Forced Expiratory Volume 1 (L)	FEV1/FVC in %	FEV1% of PV	STAGE	Erythrocyte Sedimentation Rate (mm in 1 hour)	Sr.Albumin (g/dl)	highly sensitive CRP (mg/L)	Pack years of Smoking	Echocardiogram			
														Pulmonary Hypertension			Right Ventricle dilation
														Mild	Moderate	Severe	
1	27	166	70	25.4	4.74	3.06	65	85	I	22	4.8	3.1	15	-	-	-	-
2	32	164	66.5	24.7	4.24	2.92	69	86	I	13	5.0	2.5	10	-	-	-	-
3	34	172	89.5	30.3	4.83	2.98	62	81	I	38	4.1	4.8	20	-	-	-	-
4	55	157	62	25.2	2.65	1.75	66	84	I	10	4.3	4.6	-	-	-	-	-
5	35	168	65.5	23.2	4.27	2.85	67	82	I	40	4.0	2.1	15	-	-	-	-
6	37	159	59.0	23.3	3.97	2.63	66	86	I	16	4.2	5.2	25	-	-	-	-
7	56	162	63.5	24.2	2.65	1.82	69	81	I	21	4.5	3.6	-	-	-	-	-
8	38	156	85.5	35.1	3.71	2.53	68	87	I	17	4.5	5.4	25	-	-	-	-
9	54	164	63.5	23.6	2.38	1.22	51	52	II	21	3.5	7.9	-	+	-	-	-
10	38	159	61.5	24.3	3.3	2.17	66	72	II	23	4.1	5.8	25	-	-	-	-
11	44	160	63	24.6	3.08	1.97	64	68	II	25	3.6	6.0	25	-	-	-	-
12	55	162	61	23.2	3.29	1.98	60	74	II	24	4.2	5.9	30	-	-	-	-
13	48	164	63	23.4	3.57	2.04	57	69	II	16	3.9	6.4	35	-	-	-	-
14	38	166	74	26.9	3.6	2.39	66	72	II	8	3.8	5.1	20	-	-	-	-
15	37	170	71.5	24.7	3.85	2.34	61	67	II	29	4.5	6.5	35	-	-	-	-
16	54	164	70	26	3.24	1.79	55	64	II	18	5.0	6.0	30	-	-	-	-
17	40	163	59	22.2	3.69	1.85	50	59	II	32	4.2	7.6	45	+	-	-	-
18	25	169	65	22.8	4.14	2.54	61	67	II	24	3.8	6.8	40	-	-	-	-
19	46	162	63	24	3.18	1.74	55	60	II	23	3.9	6.1	45	-	-	-	-
20	29	158	81	32.4	3.56	2.32	65	72	II	29	3.3	5.4	25	-	-	-	-
21	36	159	59.5	23.5	4.07	2.44	60	79	II	15	3.8	4.8	15	-	-	-	-
22	35	158	60.5	24.2	3.96	2.30	58	75	II	25	3.6	5.2	25	-	-	-	-

23	57	160	58.5	22.9	2.97	1.64	55	65	II	40	4.3	6.4	35	-	-	-	-
24	51	168	62.5	22.1	3.67	2.06	56	68	II	36	3.7	6.2	40	-	-	-	-
25	47	171	67.0	22.9	4.50	2.23	50	68	II	22	3.6	5.9	35	-	-	-	-
26	46	170	69.0	23.9	3.88	2.40	62	74	II	12	3.8	5.0	30	-	-	-	-
27	39	159	56.5	22.3	2.98	1.81	61	60	II	34	3.4	6.2	45	-	-	-	-
28	47	169	66.5	23.3	3.63	2.07	57	65	II	25	4.5	6.3	35	-	-	-	-
29	56	160	59.0	23.0	3.11	1.66	53	64	II	30	4.1	6.7	40	-	-	-	-
30	45	162	61.0	23.2	3.20	2.12	66	72	II	22	4.0	5.9	30	-	-	-	-
31	40	160	61.0	23.8	3.80	2.19	58	73	II	18	3.8	3.6	20	-	-	-	-
32	46	157	59.5	24.1	3.29	2.11	64	77	II	10	3.7	3.4	20	-	-	-	-
33	57	155	55.5	23.1	3.12	1.68	54	71	II	6	4.0	4.5	15	-	-	-	-
34	42	156	57.0	23.4	3.82	1.92	50	69	II	23	3.9	6.4	35	-	-	-	-
35	55	154	57.5	24.2	2.53	1.45	57	61	II	28	3.6	7.0	40	-	-	-	-
36	30	154	59.0	24.9	3.60	2.37	66	78	II	19	4.4	2.8	25	-	-	-	-
37	58	161	59.0	22.8	2.68	1.32	49	51	II	40	3.8	7.8	50	-	+	-	-
38	43	164	62.5	23.2	3.49	2.21	63	72	II	25	4.0	5.2	30	-	-	-	-
39	33	162	60.0	22.9	4.63	2.50	54	74	II	21	3.8	5.0	25	-	-	-	-
40	54	167	69.0	24.7	3.58	2.07	58	71	II	13	3.9	3.8	20	-	-	-	-
41	57	171	66.0	22.6	3.46	1.78	52	59	II	29	3.4	7.3	45	+	-	-	-
42	63	158	48.5	19.4	1.85	0.86	47	37	III	36	3.2	9.6	50	-	+	-	-
43	45	168	59.5	21.1	2.8	1.38	49	43	III	27	3.4	8.1	40	-	-	-	-
44	49	155	47	19.6	2.34	1.22	52	48	III	28	3.2	7.8	45	-	-	-	-
45	47	159	52	20.6	2.26	1.27	56	46	III	21	3.5	8.0	40	-	-	-	-
46	58	170	60	20.8	2.63	1.43	55	49	III	23	4.5	7.5	45	-	-	-	-
47	74	159	46	18.2	2.28	0.83	36	40	III	23	4.0	8.5	35	-	+	-	-
48	65	164	55	20.4	2.49	1.03	40	41	III	16	3.3	8.9	30	+	-	-	-
49	38	153	48	20.5	2.43	1.23	51	44	III	32	3.7	8.4	45	-	-	-	-
50	66	165	52	19.1	2.2	0.93	42	37	III	24	3.0	9.8	45	-	+	-	+
51	41	157	52	22.1	2.44	1.30	53	45	III	26	3.4	8.2	35	-	-	-	-
52	57	156	54	22.2	1.89	0.95	50	40	III	21	3.5	9.1	30	+	-	-	-
53	71	164	52.5	19.5	1.84	0.75	41	32	III	17	3.2	9.4	40	-	-	+	+
54	57	168	62.5	22.1	2.7	1.13	42	39	III	44	3.6	9.6	55	+	-	-	-
55	59	161	62	23.9	2.24	1.06	47	42	III	25	3.8	10.2	40	-	-	-	-

56	44	160	62	24.2	2.71	1.31	48	45	III	30	3.6	9.8	45	-	-	-	-
57	46	157	53	21.5	2.37	1.26	53	46	III	27	4.0	10.0	45	-	-	-	-
58	72	158	45.5	18.2	1.62	0.74	46	36	III	32	3.4	10.3	50	-	-	+	-
59	61	166	71	25.8	2.49	1.11	45	41	III	31	3.8	9.8	45	+	-	-	-
60	63	164	65	24.2	2.07	1.100	53	43	III	21	3.9	10.4	35	-	-	-	-
61	68	160	52.5	20.5	1.71	0.88	52	39	III	28	3.5	10.4	45	-	+	-	-
62	56	156	53	21.8	1.93	1.08	56	45	III	22	4.1	8.2	35	-	-	-	-
63	59	158	58	23.2	2.16	1.00	46	42	III	26	3.8	7.9	40	-	+	-	-
64	51	155	54	22.5	2.97	1.19	40	47	III	18	3.9	8.0	35	-	-	-	-
65	63	159	62.5	24.7	2.09	1.07	51	46	III	27	3.6	8.3	40	-	-	-	-
66	73	160	61	21.1	1.11	0.58	56	28	IV	42	2.5	12.1	55	-	+	-	+
67	76	167	49	17.6	1.62	0.68	42	29	IV	36	2.9	11.3	50	-	+	-	-
68	67	153	48	20.5	1.03	0.61	60	30	IV	28	2.8	11.2	45	-	+	-	+
69	78	155	44	18.3	0.9	0.47	52	26	IV	48	1.9	12.4	55	-	-	+	+
70	72	160	42	16.4	1.21	0.59	49	28	IV	36	2.7	12.9	55	-	+	-	+

Dept of Medicine

Ref. No. 5336 /E4/3/2012

Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.

Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.

Convenor
grhethicssecy@gmail.com.

**Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.**

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

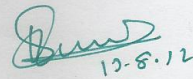
1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) .9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4 th street KK Nagar, Madurai-20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Vairakani. R	M.D Gen med	High-Sensitivity CRP assay as a prognostic indicator in subjects with COPD.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.


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To
All the above members and Head of the Departments concerned.
All the Applicants.



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