DISSERTATION

ON

STUDY ON THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the regulations

for the award of the degree of

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THANJAVUR - 613 004.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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CERTIFICATE

This is to certify that this dissertation entitled "**STUDY ON THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE."**is the bonafide original work of **Dr.VINOTH KANNAN .V** in partial fulfilment of the requirements for M.D Branch -I (General Medicine) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2012. The period of study was from October– 2011 - November 2012.

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DECLARATION

I, **Dr.VINOTH KANNAN.V**, solemnly declare that the dissertation titled **"DISSERTATION ON THE STUDY ON THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"** is a bonafide work done by me at Thanjavur Medical College, Thanjavur during October 2011 - November 2012 under the guidance and supervision of **Prof.Dr.C.GANESAN, M.D.,** Unit Chief M-5, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. degree (Branch -I) in General Medicine**.

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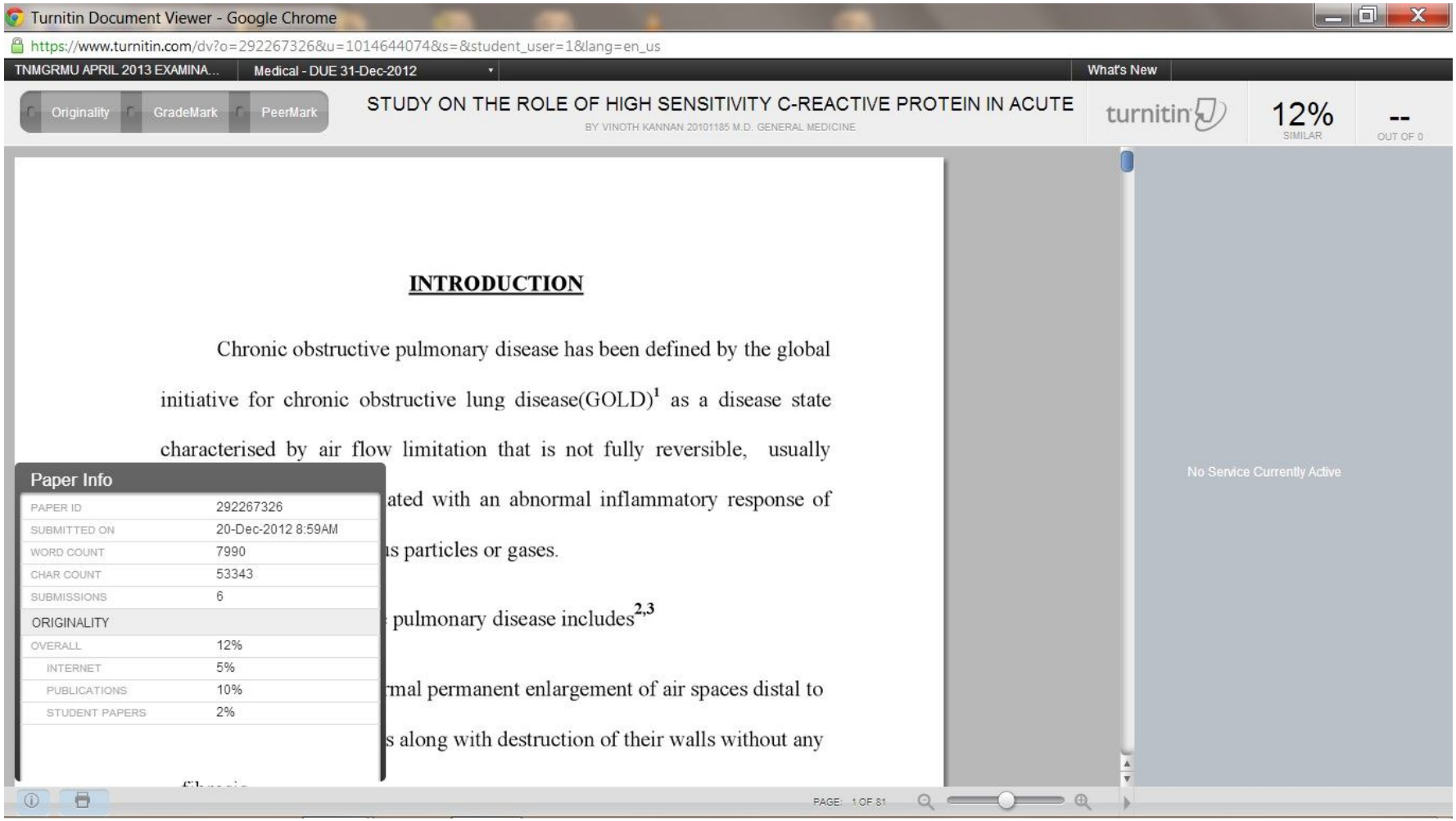
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INTRODUCTION
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ABSTRACT

STUDY ON THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

ABSTRACT

BACKGROUND

Chronic obstructive pulmonary disease remains the second most common disorder affecting the lungs,next only to pulmonary tuberculosis in India. Patients with COPD will experience a systemic inflammation. Recently hs-CRP measuring methods have made it possible to assess this protein even in lower levels of inflammation.

AIMS OF THE STUDY:

Our aim is to study the levels of hs-CRP in acute exacerbation of COPD patients and to assess the correlation of hs-CRP with the severity of the disease and also with respect to other variables such as age, sex, BMI and smoking habits.

MATERIALS AND METHODS:

Patients with clinically diagnosed and spirometrically confirmed cases of COPD with acute exacerbation were included in the study and classified based on GOLD staging. This was a cross sectional study, conducted in Thanjavur medical college and hospital between October 2011 and November 2012. The sample size was 70 patients. Serum hs-CRP levels were measured by nephelometry method. Those patients with serum hs-CRP levels >0.3mg/dl are considered as high risk individuals.

RESULTS:

The levels of hs-CRP were significantly elevated in acute exacerbation of COPD.There exists a positive correlation with severity of the disease, male COPD patients, obese individuals and smokers. There was no association of hs–CRP levels with age and duration of the disease.

CONCLUSION:

Serum hs-CRP levels may be used as a simple auxiliary marker in staging determining the severity and prognosis of COPD for early intervention.

Key words: High sensitivity C-reactive protein; Acute exacerbation of COPD, Nephelometry, Spirometry. GOLD staging.

CONTENTS

INTRODUCTION

Chronic obstructive pulmonary disease has been defined by the global initiative for chronic obstructive lung disease(GOLD)[1] as a disease state characterised by air flow limitation that is not fully reversible, usually progressive and is associated with an abnormal inflammatory response of the lung to inhaled noxious particles or gases.

Chronic obstructive pulmonary disease includes[2,3]

1.EMPHYSEMA- abnormal permanent enlargement of air spaces distal to the terminal bronchioles along with destruction of their walls without any fibrosis.

2.CHRONIC BRONCHITIS: Chronic bronchial mucus hypersecretion resulting in chronic expectoration (coughing out of sputum on most days during atleast 3 consecutive months in 2 successive years).

3.SMALL AIRWAY DISEASE:narrowing of small bronchioles.

GOLD estimates that Chronic obstructive pulmonary disease is the 6th most common cause of death world wide[4] and it is predicted that it will be the 3rd most common cause of death in future (2020).

In India, after pulmonary tuberculosis , Chronic obstructive pulmonary disease remains the second most common disorder affecting the lung.

Chronic obstructive pulmonary disease is frequently seen in middle aged individuals. It is more commonly seen in males due to increased prevalence of smoking in our setup.

It is equally prevalent both in rural and urban areas.

Increasing urbanization and emergence of industries leading to air pollution and increased smoking among young people may have definite impact on the incidence of Chronic obstructive pulmonary disease.

Some of the predisposing factors in childhood for development of Chronic obstructive pulmonary disease in future includes low birth weight , malnutrition and recurrent respiratory tract infection.

In patients with Chronic obstructive pulmonary disease the most robust test in assessing the air flow limitation is the spirometry[5].

A low FEV1 (FEV1< 80%) with FEV1/FVC ratio less than 0.7 and lessthan 15% reversibility of airflow obstruction post bronchodilator therapy is the diagnostic criteria for Chronic obstructive pulmonary disease.

With the wide spread use of spirometry, identification of air flow obstruction is considered as a key factor in determining the disability of Chronic obstructive pulmonary disease patients.

Patients with Chronic obstructive pulmonary disease will experience a systemic inflammation.

It is assessed by measuring the inflammatory mediators like C-reactive protein.

Recently high sensitivity C-reactive protein (hs-CRP) measuring methods have made it possible to assess this protein even in lower levels of inflammation.

AIMS OF THE STUDY

1. To study the levels of high sensitivity C-reactive protein in acute exacerbation of COPD patients.

2. To assess the correlation of high sensitivity C-reactive protein levels with various stages of COPD.

3. To compare the levels of high sensitivity C-reactive protein in obese and non-obese individuals.

4. To evaluate the correlation of hs-CRP in COPD patients with respect to other variables such as age,sex and smoking habits.

REVIEW OF LITERATURE

From the time of **Laennec.**, et al throughout the first half of the 20th century, mechanical explanations of chronic obstructive pulmonary disease dominate.

As early as in 1905 **OPIE et al.,** suggested that serine proteases and antiproteases imbalance plays an important role in pathophysiology of emphysema.

In 1956 Medical council of research first used the terminology chronic bronchitis in patients with chronic cough with sputum production.

In 1959 the causal relation between the smoking and persistent cough with expectoration was explained by **Higgins.,et al.**

In 1960 **Owen and Campbell et al** observed the pathological changes in airway due to cigarette smoking.

In 1973 **Boughly et al,.** submitted a list of articles related to prognostic factors in COPD and importance of pulmonary function test in these patients.

In 2007 **Sanja marevic et al.,**[67] concluded that levels of high sensitivity C-reactive protein were significantly higher in patients with

COPD and hence proved that it will be a more sensitive marker than TNF-alpha, CXCL-8 and big ET 1 in systemic circulation.

Daiana stolz et al.,[68]in 2007 analysed the levels of copeptin, C-reactive protein, procalcitonin in acute exacerbation of COPD patients and all are found to be significantly elevated.

Yannick MTA et al.,[69] from Erasmus university in 2008 observed the predictive role of high sensitivity C-reactive protein for COPD in smokers.

In 2008-2009 **SA Alavi et al.,**[70]from Guilan university, Iran found a correlation between the levels of high sensitivity C-reactive protein based on the GOLD staging of COPD.

Bridevaux et al.,[71] in 2009 in his SAPALDIA cohort study (swiss study on air pollution and lung diseases in adults) correlated the elevated levels of high sensitivity C-reactive protein in association with fast decline of FEV1 and obese patients.

In 2010 **Lisa Tileman et al.,**[72] from Germany identified the distinct aspects of systemic inflammation in bronchial asthma and COPD by measuring the levels of high sensitivity C-reactive protein (significantly elevated in COPD)and Ig E, blood eosinophils, fractional exhaled nitric

oxide levels(elevated in bronchial asthma). He also suggested that these markers have replaced the role of spirometry when not available.

Jack et al.,[73] in 2010 concluded that levels of high sensitivity C-reactive protein and surfactant protein D levels are higher in acute exacerbation of COPD which indicates the infectious state in our body. So it can also be used as a guide in the treatment of acute exacerbation of COPD.

Recent study conducted in Maulana Azad medical college in New Delhi correlated the levels of hs-CRP as a marker of functional disability in COPD patients.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

It is a preventable and treatable condition characterized by progressive air flow limitation that is not fully reversible.It includes a group of conditions that occurs due to pathological changes in large and small airways as well as lung parenchyma.It is due to abnormal inflammatory response in lungs to inhaled noxious particles and gases.

In clinical practice,the diagnosis of COPD should be thought in patients above 35yrs of age,those with chronic progressive symptoms (cough,wheeze,breathlessness) and other risk factors such as cigarette smoking and occupational or environmental dusts or gases.

Prevalence in India:

In males the prevalence rate is 2.12 to 9.4% in North India compared to 1.4 - 4.08% in South India.[5,6] In females the prevalence is less which is about 1.3-4% from North India and 22.5-2.7 % in South India[7].

In general the male female ratio is about 1.6:1.0

COPD and its comorbidities:

1.Diabetes

2.Ischemic Heart Disease

3.Depression

4.Osteoporosis

5.Weight Loss

6.Peptic Ulcer Disease

7.Glaucoma

Natural history and prognosis:[8,9,10]

FEV1 declines at a rate of 20-30m/hour in non-smokers, whereas in smokers the decline rate will be more than 50ml/per hour. FEV1 is a strong predictor of survival. Only less than 50% of patients whose FEV1 less than 30% may survive 5 years and above.

Recent studies showed that the BODE index which includes FEV1, dyspnea, body weight, 6 minutes walk test are important in predicting the prognosis than FEV1 alone.

RISK FACTORS:

Smoking:

Most commonly identified correlate with chronic bronchitis is cigarette smoking.The mortality rate varies with the dose response curve with pack years of smoking.[11]

When compared to nonsmokers, there is a 25% increase in mortality in smokers. The mortality in pipe and cigar smokers is lower than the cigarette smokers. Filter tip cigarettes are comparably less harmful.

Incidence of the disease decreases if smoking is stopped early in the course of the disease.[12,13]Cessation of smoking do not normalize the lung functions, instead it slows down the deterioration.

In males the loss of FEV1 in excess of normal decline with aging is 9ml per year for each pack year of smoking. In females, the rate of decline in FEV1 is 6ml[14].

Prolonged smoking impairs the ciliary motility, macrophages accumulate in higher quantities in respiratory bronchioles which in turn releases proteinases and is responsible for destruction of extracellular matrix of lung. These macrophages recruit chemotactic factors which in turn attracts other inflammatory cells to lung and causes mucus gland hyperplasia.

Cigarette smoke inhibits anti proteases and releases proteolytic enzymes, thereby destroying the alveolar wall[17].

Passive smoking otherwise called as environmental tobacco smoke exposure[15,16]plays an important role in nonsmokers particularly among the women.

Air pollution:

Pollutants for air pollution includes exhausts from automobiles, industries and factories.[18,19,22]

Smoke from solid fuel combustion such as dried dung, wood crop residues used in cooking in villages and slum areas also contributes to major source of air pollution in developing countries like India[20,21].

Occupation :

According to American thoracic society the occupational contribution to the burden of COPD is around 15%.[23,24]

Various studies from all over the world quoted that occupation involving exposure to dust, gases, fumes as a major contributing factor to COPD.

Chronic bronchitis is more prevalent among workers exposed to organic or inorganic dusts.Occupational hazards include exposure to cadmium, toluene gas in plastic plants, construction and utility work.

Recurrent respiratory tract infections:

Lower respiratory infections in childhood is also postulated as a risk factor for the development of COPD.[25,26,27] This is due to the permanent

damage or impaired lung growth. The risk of reduced lung function in future is high.

Airway hyperresponsiveness:

Many patients with COPD also experiences airway hyperresponsiveness[28,29,30] which is a common association in bronchial asthma. The rate of reversibility in the degree of obstruction with bronchodilators is less than 15 %.

GENETIC BACKGROUND:

Aggregation of cases in families suggest that there is an established role for genetic factors in the pathogenesis of COPD. Occurrence of early onset COPD and decrease in the maximal expiratory flow rate among the nonsmoking first degree relatives of COPD supports the above said statement.

Polymorphism of genes involving protease - antiprotease balance, antioxidant function, inflammation and immune responses has been proposed.

Alpha 1 antitrypsin is a major antiprotease enzyme in the serum .[31] The synthesis of alpha one antitrypsin is regulated by a gene on chromosome 14q32.

The most common deficient allele is PiZZ phenotype which is due to amino acid substitution of 342 Glutamic acid to lysine.[32]

This change results in spontaneous polymerization of polypeptide and impaired release of alpha one antitrypsin from the liver.

This deficiency is rare in Asian and African descendants, whereas more common in European population (1 in 2000 to 1 in 7000).

About 2 % of the patients with emphysema is due to alpha one antitrypsin deficiency.[33]

Patients usually presents with premature bronchiectasis or chronic bronchitis.

More than 80 percent of the patients have autosomal recessive inheritance. Decline in FEV1 is around 100-130ml per year for smokers , 50-80ml per year for exsmokers and nonsmokers.

Panacinar emphysema is the most common type seen with predominant involvement of lower lobes of the lung. Smoking is an important cofactor in the development of COPD in patients with alpha one antitrypsin deficiency. They are also at an increased risk for cirrhosis of liver.

PATHOLOGY:

Pathological changes are seen in larger and smaller airways as well as in terminal bronchioles. Small airways are considered as important site of airflow limitation.[34,35]Various reasons which are responsible for narrowing of lumen of small airways are goblet cell hyperplasia ,edema , mucosal and submucosal inflammatory cells, peribronchial fibrosis, smooth muscle hypertrophy and mucus plugs.[39]

In larger airways hypertrophy of submucosal mucous glands is seen.

Reid index is a measure of thickness of submucous glands to that of bronchial wall . In normal individuals the range is between 0.44 to 0.60, whereas in chronic bronchitis it is between 0.34 -0.53.

Emphysema starts as an increase in both number as well as size of the alveolar fenestrations and results in destruction of the septa. It also destroys the attachments of the septa to the terminal bronchioles.

The site of destruction varies in different types of emphysema. In centriacinar it predominantly involves respiratory bronchioles, whereas panacinar involves both central as well as peripheral bronchioles.

PATHOGENESIS AND PATHOPHYSIOLOGY:

Central to the pathogenesis is found to be an enhanced inflammatory process in response to inhaled particles and gases.[36,37] The pathogenesis includes various processes

1. Increased airway inflammation[40]

2. Increased protease burden-decreased anti protease function[38]

3. Oxidant –anti oxidant imbalance (oxidative stress)

4. Defective lung repair mechanisms

Chronic exposure to smoke, fumes, dusts results in inflammatory recruitment of inflammatory cells within the terminal air space of lungs. These cells results in destruction of walls and extra cellular matrix of the lungs.

Persistent reduction in the forced expiratory flow is the defining feature in case of COPD.

Other typical features are

1.Increased airway resistance

2.Increased residual volume

3. Increased RV/TLC

4.Decreased inspiratory capacity

5.Maldistribution of ventilation.

Airflow obstruction:

Balance between the elastic recoil of the lungs that promote the flow and the resistance of airway that limits the flow contribute to the airflow during forced exhalation.

As the cross sectional area of the airway falls due to destruction the resistance increases, and the expiratory flow also decreases as the volume occupied decreases due to loss of elastic recoil and loss of radial traction of airways.

In early stages the abnormality in airflow limitation is seen only at lung volumes at or below the FRV.

It is possible to distinguish between emphysema and small airway pathology only theoretically, since emphysema is due to decreased elastic recoil and small airway disease is due to increased airway resistance as a cause of reduced FEV1.

Clinically it is more difficult to differentiate between these two as it coexist in most of the patients.

FEV1 correlation is better with small airway pathology when compared to emphysema.

FEV1 remains a good predictor because PaO2 usually remains near normal till FEV1 decreases up to half of the predicted level. Very low levels of FEV1 can be still associated with normal PaO2.

Usually PaCO2 is not elevated until the FEV1 is less than 25% of predicted value.

MALDISTRIBUTION OF VENTILATION:

COPD is a heterogenous disease, since it affects both airways as well as lung parenchyma.This heterogeneity can be revealed by xenon gas ventilation.

MIGET classification of COPD:

Type A- high ventilation perfusion ratio-emphysema

Type B-low ventilation perfusion- chronic bronchitis

But most of the COPD patients will have neither type A or B, they will have both high and low perfusion areas.

The reduction of PaO2 is mainly due toVentilation/Perfusion mismatch, shunt is minimal. So moderate concentration of O2 can correct

the hypoxemia in COPD. If it is not getting corrected then other causes such as pulmonary embolism,shunting should be considered.

HYPERINFLATION:

It is defined as

1.increased FRV.

2.increased residual volume to total lung capacity.

3.decreased inspiratory capacity to total lung capacity.

Though hyperinflation may be some times beneficial, adverse effects are more.

The adverse effects are due to

1. Loss of apposition zone,between the diaphragm and abdominal wall,so pressure cannot be transmitted for effective respiration.

2. Flattened short diaphragm muscles are not able to generate inspiratory pressures.

3. Increased tension required to generate transpulmonary pressure.

In those with hyperinflation the inspiratory capacity will be reduced.

IC can be used as a prognostic significant value independent of the FEV1.

Recently lung cells senescence has been involved in the pathogenesis of emphysema.

PATHOPHYSIOLOGY OF EXACERBATION:

Exacerbation of COPD are associated with a further increase in inflammatory response in the lungs predominantly involving neutrophils.

These response may be triggered by bacterial or viral infection or by pollutants.

This worsens the existing ventilation perfusion mismatch leading to respiratory failure and death.

LESIONS OF THE VESSELS IN COPD:

There is no specific change in the vessel wall of the patient with COPD, sometimes atheromata may be seen.

Pulmonary hypertension develops during late phase of the disease. These changes are mostly secondary to vascular shunting and increased intimal fibrosis.

PULMONARY CIRCULATION IN COPD:

In later stages of the disease pulmonary arterial hypertension develops, along with the development of hypoxemia, hypercapnia. It is the

important complication of COPD. It is associated with development of right ventricular hypertrophy and worse prognosis.

ABNORMAL BLOOD GAS TENSION:

HYPOXEMIA:

Since hypoxemia is a potent vasoconstrictor , PaO_2 has an inverse relationship with the development of pulmonary arterial hypertension. Increasing arterial desaturation worsens the pulmonary pressure. Pulmonary artery pressure rises suddenly during REM sleep because of the relative hypoxemia and recurrence of this nocturnal pulmonary hypertension is inturn responsible for the changes in pulmonary hypertension.

HYPERCAPNIA:

There exists a direct relation with the $PaCO_2$ and pulmonary artery pressure. This is probably due to hyperventilation induced hypercapnia or hypoxia induced pulmonary hypertension.

ACIDEMIA:

Combination of both hypoxia and hypercapnia results in pulmonary hypertension in patients with COPD. So for given PO_2 the mean Ppa is higher with increasing hydrogen concentration.

EFFECTS OF ABNORMAL PULMONARY MECHANICS:

Changes in the pulmonary resistance results from increase in airway resistance matching with decrease in FEV1.

EFFECTS OF INCREASED CARDIAC OUTPUT:

Even minor increments in the cardiac output that occurs during exercise significantly rises the pulmonary arterial pressure.

EFFECTS OF BLOOD VISCOSITY:

Chronic hypoxemia which in turns develops polycythemia due to increased production of erythropoietin contributes to increasing blood viscosity thereby increasing pulmonary arterial hypertension.

ROLE OF PULMONARY ENDOTHELIUM:

As with any other disorder, the endothelial dysfunction plays a major role in PAH. This results in reduction in the NO synthesis or release in response to hypoxia. So the protective role of nitric oxide in preventing the rise of pulmonary vascular tone is lost in COPD.

Circulating levels of endothelin are increased in patients with emphysema and associated pulmonary hypertension.

Changes in pulmonary circulation mainly affects the peripheral pulmonary arteries in COPD patients. Initial change will be intimal

hypertrophy due to longitudinal deposition of smooth muscle and in those with persistent pulmonary hypertension there will be a medial hypertrophy. Pulmonary thrombosis occurs secondary to peripheral inflammation .

PULMONARY HEMODYNAMICS IN COPD:

It depends on the severity of the disease. In case of mild disease without blood gas changes pulmonary pressure is normal or minimally elevated when measured at rest, but abnormal elevation occurs in response to exercise.

Almost cardiac output will be normal in the patients with COPD as are the right atrial and right ventricular end diastolic pressure.

In clinically stable cases of COPD the pulmonary pressures will be modestly elevated.

CONSEQUENCES OF PULMONARY HYPERTENSION IN COPD:

Chronic bronchitis and emphysema coexist pathologically.

In case of chronic bronchitis which is otherwise called as type B or blue bloaters develop pulmonary hypertension relatively early in the course of the disease.

In contrast in those with emphysema the blood gas analysis will be normal but clinically will have severe breathlessness and almost do not

develop pulmonary hypertension or develops only in the late stage of the disease.

NATURAL HISTORY OF PULMONARY HYPERTENSION:

In COPD patients the elevation of the pulmonary pressure will be less and slow, the pressure will almost never reach the higher levels as like that of primary pulmonary hypertension.

Weitzenblum found that a change of 3mm hg in pulmonary pressure per year and 1/3 of the patients develop increase in pulmonary pressure of 5mm in 5 years.

Survival rate in patients with pulmonary hypertension was 40% compared to 72% in those with normal pulmonary pressure.

COR PULMONALE:

Cor pulmonale is defined as right ventricular hypertrophy and dilatation secondary to diseases of the lung parenchyma/vasculature or both.

The prevalence of cor pulmonale is higher in patients with hypercapnia, hypoxemia, polycythemia and in those with reduced FEV1.

In clinically stable patients inspite of elevated pulmonary arterial pressure the right ventricular contractility is maintained.

In contrast, in patients with respiratory failure the right ventricular contractility is decreased . Edema in the late stages of the disease may not be entirely due to right ventricular failure, other causes should be ruled out.

Due to hypoxemia and hypercapnia there will be a reduction in the renal function due to decreased blood flow which leads to changes in salt water balance. Decreased blood flow may be due to inappropriate arginine vasopressin levels or neurally mediated catecholamine release.

Thus the development of peripheral edema in COPD involves a complex hemodynamics with multiple interactions.

Other grave risk factors include marked hypoxemia, increased pulmonary artery pressure and decrease in carbon monoxide transfer.

In patients with right ventricular failure , the prognosis will be poor and mortality rate will be high up to 65-80%.

Clinical symptoms:

Most patients are usually smokers with almost atleast 20 pack years. Patients usually present in 5^{th} decade of life.

Chronic bronchitis manifest as cough with expectoration, wheeze, breathlessness with exacerbation of symptoms during winter.

Sputum may be mucoid or mucopurulent. Sputum may be purulent even in the absence of superimposed infection because of large amount of neutrophils.

Pure emphysema presents as dyspnea and other symptoms such as wheezing, cough with expectoration are less common.

Except in rare cases of hereditary emphysema , chronic bronchitis and emphysema often coexists. The common cause of mortality in patients with emphysema is respiratory failure.

Emphysema patients will have near normal PaO2 and PaCO2 for that reason they are called as pink puffers.

Patients with chronic bronchitis usually develop cor pumonale and hypoxia . They are called as blue bloaters.

Other major symptoms includes weight loss and exercise limitation .

Progressive damage of the alveolar wall may culminate in the formation of bullae.

Chronic hypoxemia may lead to peripheral muscle atrophy.

Physical signs:

In early stages of the disease , the physical examination may be entirely normal.In later stages they will be emaciated, cyanosis and polycythemia may be noted.[41]

Peripheral edema and elevated JVP are seen in cases associated with cor pulmonale.

Patients sometimes adopt a peculiar tripod posture to increase the chest wall movements by facilitating the use of accessory muscles of respiration.

Chest wall is often barrel shaped with kyphosis, and increased anteroposterior diameter, horizontally aligned ribs,with prominent sternal angle and wide sub costal angle.

Patients adopts pursed lip breathing during expiration in an attempt to decrease the collapse of airways.

Chest wall expansion is reduced and in severe cases there is a paradoxical indrawing of costal margins due to pull of low flattened diaphragm.

On auscultation there will be a prolonged phase of expiration with fine inspiratory crackles.

Investigations:

RADIOLOGY:

Chest xray:

In chronic bronchitis, parallel line opacities are seen which are indicative of bronchial wall thickening.[42,43]

The radiographic features of emphysema includes:

- Overinflation of the lungs
- Low flattened diaphragm- the border of diaphragm lies below the 7th rib.
- Height of the lung is greater than 30 cm
- An obtuse costophrenic angle may be seen.
- Vertical and narrowed heart shadow is seen (tubular heart).
- Reduction in size and number of pulmonary vessels in the periphery of the lung.
- Hilar vessels are enlarged.
- In lateral chest xray there is an increase in the retrosternal space(>2.54 cm).
- Presence of bullous lesions is an important evidence of emphysema. Bullae may present as a stable lesion. Sometimes, it may enlarge massively sufficient enough to cause the collapse of the entire lung.It

is called as vanishing lung syndrome. Pneumothorax is the important differential diagnosis. Bullae may rupture to produce secondary pneumothorax.

- In fluoroscopy , low and flat diaphragm is seen. A paradoxical upward movement during inspiration may be noted.

Computed tomography:

It has greater sensitivity and specificity in the diagnosis of emphysema when compared to chest xray.[44,45]It is helpful in the evaluation of bullous lesions of the lung. It is seen as areas of low attenuation without obvious margins.Attenuation and pruning of the vessels can be detected.

A decrease in the CT lung density signifies the presence of microscopic emphysema.

Bronchograms may show irregular, narrowed and distorted bronchi.

SPIROMETRY :[46]

It is the most important test in assessing the air flow limitation. It is helpful in arriving at a diagnosis of COPD and also in predicting the severity of the disease and in further follow up of patients.

The major abnormalities include reduction in FEV1 and in the ratio of FEV1/FVC .

The presence of a post bronchodilator FEV1 <80% along with FEV1/FVC ratio <0.7 indicates the presence of airflow obstruction that is not totally reversible.

Assessment of reversibility to bronchodilators is done in COPD patients to differentiate it from bronchial asthma . It is also important in identifying the post bronchodilator FEV1 which is a better predictor of the prognosis.

According to ATS and GOLD guidelines a change in FEV1 of more than 200 ml and a percentage change of more than 12% is considered as significant reversibility but according to British thoracic society guidelines change in FEV1 50% above the base line is considered significant.

Around 30% of COPD patients may show significant reversibility with bronchodilator therapy.

LUNG VOLUMES:

Static lung volumes like total lung capacity, residual volume, functional residual capacity and the ratio of RV/TLC are measured in COPD patients.

It is used to assess the degree of hyperinflation and gas trapping.

The lung volumes are increased in COPD patients

Two methods adopted are

1. Helium dilution technique[48]

2. Body plethysmography – it is more reliable since it measures poorly ventilated areas.

Gas transfer for carbon monoxide:

A low DL co is present in COPD patients. [47]

Single breath technique is routinely used method that uses helium dilution technique.

Helpful in differentiating COPD patients from asthmatic patients since a low DLco rules out asthma.

Arterial blood gas analysis:

Useful in assessing degree of hypoxemia and hypercapnia.

Usually seen once FEV1< 50%

Blood gas abnormalities may occur during exercise and sleep and during exacerbations.

Though pulse oximetry is commonly used , it is not to be considered as a replacement for ABG.

EXERCISE TEST:

1. Progressive symptoms limited exercise test:

It requires the patient to perform exercise on a treadmill or a cycle until symptoms prevent him.

The maximum test is defined as heart rate of >85% of the predicted or ventilation >90% predicted.

2. Self paced exercise test:

- 6 minute walk test is the frequently used test[49]

-used only in patients with moderately severe COPD

-it is useful in predicting the longevity in severe COPD patients

3. Steady state exercise test:

Not routinely done in COPD patients

Sleep studies:

-For identifying the nocturnal hypoxemia

-useful in patients with pulmonary hypertension, corpulmonale and in case of associated sleep apnea syndrome.

Other variables to be monitored:

-hematocrit: to screen for polycythemia which develops in response to chronic hypoxemia.

- complete blood count to evaluate for anemia for chronic disease.

-measurement of alpha antitrypsin levels is indicated in patients with early onset of emphysema less than 45 years of age and those with family history of emphysema.

MANAGEMENT OF COPD:

1.NON PHARMACOLOGICAL:

Cessation of smoking[50]

It is the single most cost effective approach to reduce the exposure to reduce exposure to risk factors.

Health education regarding the risk factors and complications related to the disease.

Legislation to form smoke free schools , public facilities and work environments should be developed.

Comprehensive tobacco control policies and programs with clear consistent non smoking messages should be delivered through a proper channel.

2.PHARMACOLOGICAL

1.Bronchodilators :

They are useful in COPD to relieve reflex bronchoconstriction and to combat the increased muscle tone.[51]

Rate of decline of FEV1 decreases with the use of bronchodilators.

Theophylline:

Apart from its bronchodilator action it has also beneficial effect on muscle fatigue and improves the outcome significantly. It is also a mild respiratory stimulant which is useful in patients with decreased respiratory drive.

Non respiratory effects includes increased ciliary motility and anti inflammatory property.

Dose of theophylline in non smoker is 10-12mg/kg/day in divided doses.

In smokers higher doses up to 20 mg/kg/day are useful whereas dose reduction is needed in patients with hypoxemia and in liver disease.

2.SYMPATHOMIMMETIC BRONCHODILATORS:

Beta agonist[52] remains corner stone treatment in obstructive airway disease .

Approach is to increase the dose and frequency of the beta agonist or anticholinergic or both.

3.CORTICOSTEROIDS:

Used in patients with severe exacerbation.[53]

Dose usually used is around 30-40mg prednisolone for 14 days

Inhaled steroids are not as effective as oral steroids in exacerbation but can be used in prevention of exacerbation.

4.ANTIBIOTICS:

The common organisms implicated in these patients are streptococcus pneumonia, haemophilus influenza and Moraxella. So an antibiotic coverage including oral aminopenicillin, macrolide (erythromycin, azithromycin, clarithromycin) and tetracycline antibiotics are recommended.[54]

5.OXYGENTHERAPY:

Oxygen may be administered via ventury mask or nasal prongs.

It is used to treat hypoxemia in acute exacerbation. Aim of the therapy is to prevent hypoxemic tissue damage.

In acutely ill patients the goal of oxygen therapy is to improve pao2 to more than 60mm Hg.

In chronic lung disease, long term oxygen supplementation has increased the longevity as supported by the studies like nocturnal oxygen therapy trial in USA[55]and MRC working party on long term domiciliary oxygen therapy in UK.

Greater benefit is observed if oxygen therapy is administered for atleast 18 hours per day.

6.ALPHA ONE ANTITRYPSIN AUGMENTATION THERAPY:

It is used in young non smokers with severe alpha 1 AT deficiency associated emphysema.

7.SMOKING CESSATION THERAPY:

Nicotine replacement therapy (gum, tablets, transdermal patch, lozenges, nasal spray)

Anti depressants like bupropion, nortryptiline increases the long term quit rates.

Recently varenicline, a nicotinic acetylcholine receptor partial agonist helps in relieving withdrawal symptoms of nicotine dependence.

NON INVASIVE VENTILATION:

It is administered via nasal or full face mask without the need of endotracheal tube. It is indicated in patients with hypercapnic respiratory failure during exacerbations.

Most common mode of delivering is pressure cycled bilevel positive air way pressure.[56]It is contraindicated in patients with severe acidemia and hypoxemia, unconscious and hemodynamically unstable patients.

INVASIVE VENTILATION:

Main indication is severe hypoxia with respiratory academia and in unconscious patients during acute exacerbation of COPD.

SURGERY:

1.LUNG VOLUME REDUCTION SURGERY :

It involves removal of 20-30 % of the lung bilaterally mainly from the apices.[58]

INDICATIONS:

Emphysema predominantly involving the upper lobes and low exercise capacity

CONTRAINDICATION:

Patients with FEV1 <20% , diffusion capacity less than 20%, diffuse homogenous opacity on HRCT.

Patients outcome will be poor in those who underwent lung volume reduction surgery in the lower lobe predominant disease.

NON SURGICAL LUNG VOLUME REDUCTION:

Implantation of one way valves using bronchoscope which induces atelectasis.

Removal of bullae results in decrease in residual volume and increase in vital capacity.

2.Lung transplantation:

Among the major causes of lung transplantation COPD ranks the first indication.

It contributes nearly 40% of all lung transplant and 50% single lung transplant.

Most common indication for lung transplantation in COPD is severe hypoxemia, FEV1 less than 25% in young patients less than 45 years without other comorbidities.

Absolute contraindication :

Current smoking, malignancy, major organ failure or chronic hepatitis B or hepatitis C.

Relative contraindication:

Poor nutritional status , Mycobacterial infections, severe osteoporosis and suboptimal psychosocial support.

Treatment of Cor pulmonale:

First line of treatment is to provide continuous oxygen support to overcome hypoxemia and diuretics for peripheral edema.

In patients with atrial fibrillation digoxin is used, benefits of Calcium channel blockers as vasodilators is still controversial since it worsens the hypoxemia.

PULMONARY REHABILITATION:

The aim is to optimize the physical and the social performance of the patients .[57]

It includes

1.Education

2.Chest physiotherapy:

It consists of postural drainage, chest vibration and percussion.

Pursed lip breathing which was first observed by Laennec to be taught in patients with COPD.It slows down the expiration and help in preserving the positive airway pressure and avoiding collapse of the lungs.

3.Exercise training includes breathing and relaxation techniques.

4.Providing psychosocial support to the patients.

Other supportive treatments:

VACCINES:

Influenza vaccines can reduce the serious illness and mortality rate by 50% in COPD patients.

Pneumococcal polysaccharide vaccine is commonly recommended for patients above 65 years .It has been found to lower the incidence of community acquired pneumonia.

MUCOLYTICS:

Few patients with viscous sputum may benefit from mucolytics. Ambroxol, carbocysteine and iodinated glycerol are commonly used.

CRP An inflammatory marker

Inflammation is considered as a protective response of vascular connective tissue to external injury or stimuli . It is usually associated with the release of inflammatory mediators like prostanoids, vasoactive amines, cytokines and reactive oxygen species.

The term acute phase response (APR) [59]is described to encompass all the changes occurring in various organs in response to systemic inflammation. It is a non specific response initiated by various stimuli like burns, surgical or physical trauma, irradiation and infection. Cytokines mediating this acute phase response are tumour necrosis factor alpha, interleukin 1 and interleukin 6 .One of the most fascinating fact of the APR isrise in acute phase proteins synthesized in the liver.

ACUTE PHASE PROTEINS:

POSITIVE ACUTE PHASE PROTEINS:

1.Protease inhibitors such as anti chymotrypsin and alpha 1 anti trypsin

2.Coagulation proteins such as fibrinogen, plasminogen, prothrombin and factor 8.

3.Various complement proteins such as C2,C3,C4,C5,C1esterase inhibitor and plasminogen.

4.Transport and storage proteins such as haemopexin, ceruloplasmin, ferritin and haptoglobin.

5.Other positive APR ‘s are CRP, procalcitonin, serum fibronectin, alpha1 acid glycoprotein (orosomucoid), mannose binding lectin and serum amyloid protein.

NEGATIVE ACUTE PHASE PROTEINS:

1.Albumin

2.Pre albumin

3.Transthyretin

4.Transcortin

5.Transferrin

6.Antithrombin

CRP is a biological substance which was known as acute phase reactant for long back, originally described 70 years ago . Now it is used as an inflammatory marker. It was named so because of its interaction with phosphoryl choline and lipoteichoic acid found on pneumococcus.

CRP is the best known of the acute phase protein since it is regularly used as a marker of systemic inflammation in clinical settings. They may increase from 1 mcg/ml to 500mcg/ml in severe inflammation.[60]

It is released in excess amount within 6 hours of an acute inflammatory stimulus. Doubling time in plasma occurs atleast every 8 hours. It attains the peak concentration after 50 hours.

The plasma concentration can fall almost as rapidly as 5-7hours plasma half life after appropriate treatment or removal of the inflammatory stimulus.

CRP is a member of the pentraxin family of proteins. It also includes homologues of similar size proteins such as serum amyloid protein (SAP)or larger proteins such as long pentraxins (PTX3) .

C-reactive protein specifically binds to phosphocholine present on the cell membrane of microbes and it activates the classical complement pathway and inturn opsonizes the ligands for phagocytosis. It down regulates the polymorphs and also neutralizes the platelet activating factor.

Although in the clinical context elevation of CRP is suggestive of infection or inflammation, it may also occur with various other conditions like obesity, malignancy and renal dysfunction. Conversely, a lack of elevation of CRP is seen during flairs of systemic lupus erythematosus as well as in patients with hepatic failure.

CONDITIONS WITH ELEVATED CRP:

1.Bacterial infections such as pyelonephritis, meningitis and endocarditis.

2.Inflammatory diseases such as Rheumatoid Arthritis , Psoriatic Arthritis , Reiters Disease, Crohns Disease , Ankylosing Spondylitis And Familial Mediterranean Fever .

3.Malignancies such as lymphoma and sarcoma .

4.Necrotic infection such as acute pancreatitis, myocardial infarction and tumor embolization .

5. Other nonspecific conditions such as burns and fractures .

Levels of C-reactive protein in some conditions remained normal inspite of active inflammation which includes,

1. SLE
2. Dermatomyositis
3. Systemic sclerosis
4. Graft versus host disease
5. Leukaemia
6. Ulcerative colitis

The reason for this selective failure of raise in CRP in the above said conditions is unknown.

CRP and cardiovascular disease:

Atherosclerosis is the process underlying cardiovascular disease.It is partly responsible for the chronic low level inflammation of the vascular endothelium . Inflammation is obvious at the site of plaque rupture.[64]

Several studies like MRFIT [65]and WHI study in postmenopausal women support the above fact.

Apart from its use as an inflammatory marker it is also used in

1.Assessing the response to treatment in conditions such as rheumatoid arthritis where there will be a dramatic fall in CRP level following treatment.

2.To differentiate bacterial and viral infections

(usually elevated in bacterial infection)

3. To avoid confusion between a disease flare and super infection in conditions such as systemic lupus erythematosus.

CRP levels remains unaltered by antipyretic or any other thermoregulatory factors. So it can be used as an adjunct to use temperature chart in clinical practice.

Recent works done in relation with cognitive assessment reveals that levels of CRP are high in those with impaired cognition.[61] The exact etiology for this is unknown. Further work is warranted in this field.

High sensitivity CRP:

Though both measure the same substance in blood, Ultra sensitive or high sensitivity CRP [66]refers to the measurement of small changes in CRP concentrations which the standard test used for measuring CRP tend to miss.

Standard test for CRP measures only values more than 10 mg/L . Values less than 10mg/L can be measured only by hs-CRP.[63]

Estimation :

Though it was an inflammatory marker initially it is not used widely because of the unavailability to measure low values which make the results insensitive.

Previously it was measured by ELISA. But now, at present highly sensitive commercial kits like nephelometry and turbidometry are available which make the assay highly sensitive.

MATERIALS AND METHODS

This study was conducted at the Department of medicine and thoracic medicine at Thanjavur medical college hospital during OCTOBER 2011-NOVEMBER 2012.

TOTAL NUMBER OF PATIENTS INCLUDED IN THE STUDY :

70 patients (both males & females).

STUDY METHOD:

This is a cross sectional study.

GEOGRAPHIC DISTRIBUTION:

Patients included in this study were from urban and rural areas of Ariyalur, Perambalur , Thanjavur, Thiruvarur and Pudhukottai districts.

INCLUSION CRITERIA:

1. Age limit between 30-80 years of both sexes
2. Clinical symptoms like cough/sputum production/breathlessness with or without swelling of legs of more than 2 years duration.
3. Clinically diagnosed cases of COPD.

4. Spirometrically confirmed cases of COPD and post bronchodilator values of

FEV1 <80%

FEV1/FVC <0.7

Reversibility from obstruction <15%

FVC- Forced Vital Capacity

FEV1- Forced Expiratory Volume in 1 second

EXCLUSION CRITERIA:

Patients with past history of the following diseases were excluded from the study

1.Bronchial Asthma

2.Pulmonary Tuberculosis

3.Systemic Hypertension

4.CAHD

5.Sleep Apnoea Syndrome

6.Connective tissue diseases like RA

7.Chronic renal failure

PROCEDURE:

Proforma was prepared based on the above said criteria to meet the objectives of the study

Each patients were evaluated as follows

1. Detailed history as per the proforma

2. Smoking history in detail:

Total number of years smoked

Cigarette/beedi

Pack years: Number of cigarettes per day/20 × Number of years of smoking

3. Clinical examination with detailed examination of respiratory system.

4.Chest X ray

5.Sputum AFB

6.ECG

7.CT THORAX

6.SPIROMETRY

Spirometry was done in all cases and staged accordingly based on GOLD criteria

FVC- FORCED VITAL CAPACITY:

It is defined as the volume of air that can be forcibly exhaled after a maximal inspiration expressed in liters.

FEV1-FORCED EXPIRATORY VOLUME IN 1 SECOND:

It is the volume of air expelled in the first second from the start of maximum expiratory effort of the forced vital capacity (expressed in liters or % of predicted).

FEV1/FVC:

It is the percentage of forced vital capacity which is expelled in the first one second of maximal inspiratory effort.

HIGH SENSITIVITY CRP ESTIMATION:

The hs-CRP levels were measured by latex enhanced nephelometry and are interpreted in the ranges of less than 3 mg /L as normal and low risk and >3mg/l as high risk.

NEPHELOMETRY:

It is defined as the detection of light energy scattered towards a detector that is not in the direct path of transmitted light. Commonly available nephelometers are those which measure the scattered light at right angles to the incident light.

It is the commonly used technique for protein assays such as lipoprotein a, C-reactive protein, rheumatoid factor, anti streptolysin O and immunoglobulins.

Other method which is less sensitive than nephelometry is turbidometry. The detection limit of nephelometry is 10mcg/ml where as for turbidometry it is 20-30 mcg/ml.

The main aim of our study is to assess hs-CRP as a cost effective auxiliary marker other than spirometry in determining the severity of COPD.

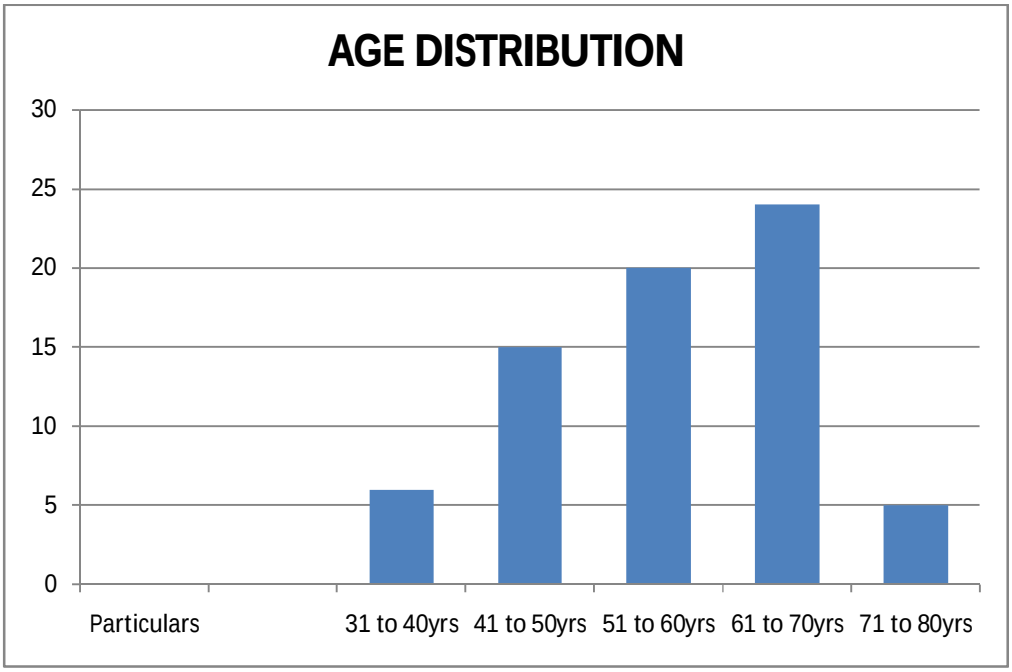
RESULTS AND OBSERVATION

Results of our study were tabulated into different variates and incidence of each variate was calculated.

TABLE 1

Particulars	No.of patients (n=70)	Percentage (100%)
31 to 40yrs	6	8.6
41 to 50yrs	15	21.4
51 to 60yrs	20	28.6
61 to 70yrs	24	34.3
71 to 80yrs	5	7.1

From the above table it is observed that majority of the cases included in our study belongs to 60-70 years of age.


AGE DISTRIBUTION
30
25
20
15
10
5
0
Particulars
31 to 40yrs
41 to 50yrs
51 to 60yrs
61 to 70yrs
71 to 80yrs

SEX DISTRIBUTION

TABLE 2

SEX	NO OF PATIENTS	Percentage (100%)
Male	54	77.1
Female	16	22.9

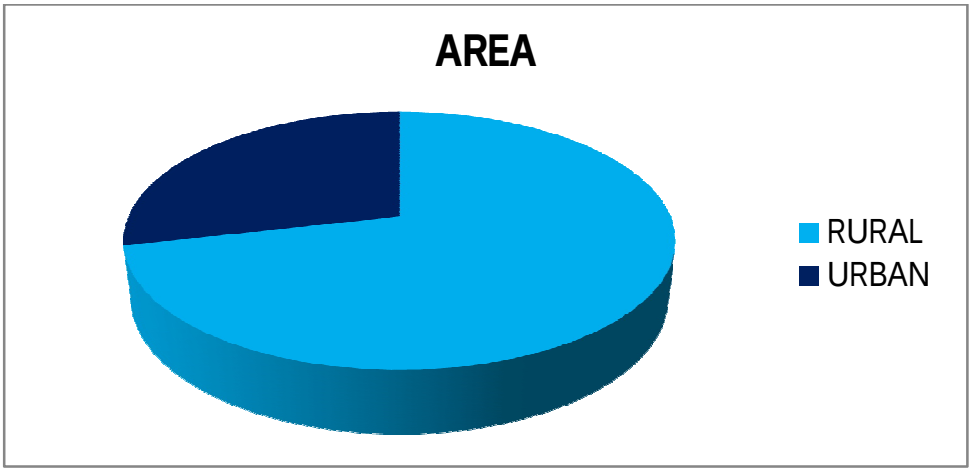
It is inferred that majority of the patients included in our study are of male sex.

Male to female ratio is approximately 8:2

GEOGRAPHICAL DISTRIBUTION -TABLE 3

AREA	NO. OF CASES	MALE	FEMALE	%
RURAL	50	40	10	71.42
URBAN	20	14	06	28.58
TOTAL	70	54	16	100

From the above table it is inferred that 50 out of seventy cases were from rural areas constituting 71% of the total cases. Remaining 20 cases from urban areas constitutes 29% of the total cases.



RISK FACTORS

1.SMOKING

ACTIVE SMOKING – TABLE 4

Pack years	No. of patients (n=70)	Percentage (100%)
Non smokers	22	31.4
10 to 20	2	2.9
21 to 30	36	51.4
31 to 40	10	14.3

Active smoking is the predominant risk factor in our study population which constitutes approximately 70% of the total population

PREVALENCE OF SMOKING

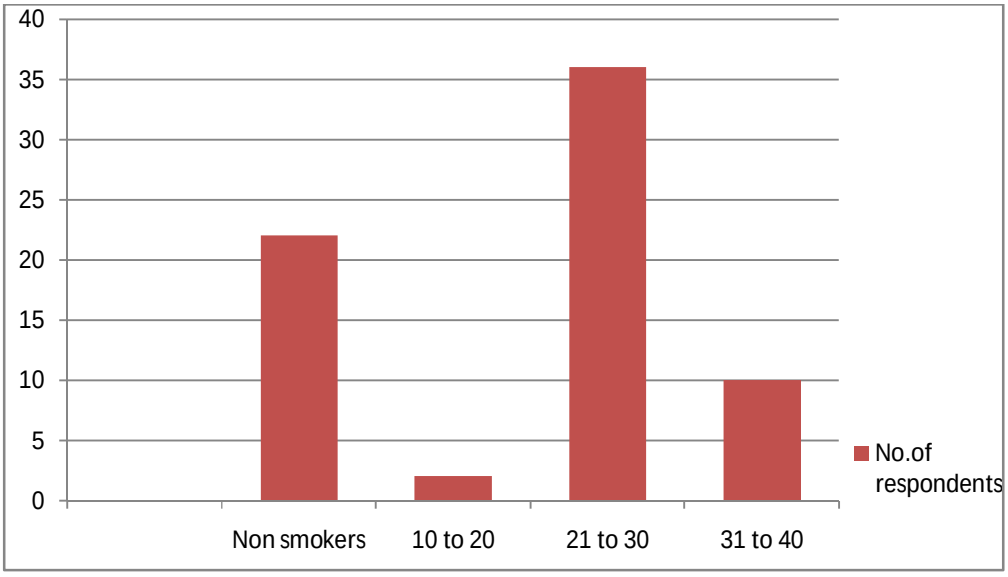
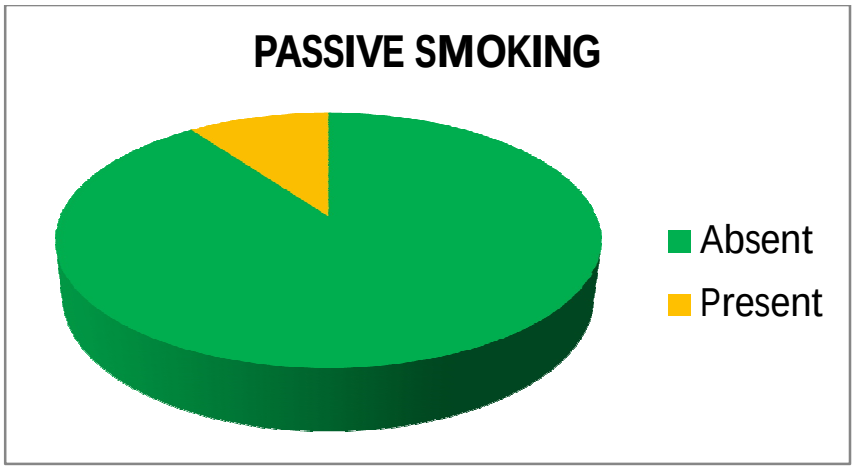


TABLE 5

PASSIVE SMOKING

Particulars	No. of patients (n=70)	Percentage (100%)
Absent	63	90.0
Present	7	10.0

Passive smoking was observed in 7 cases out of the 70 cases who were all females.

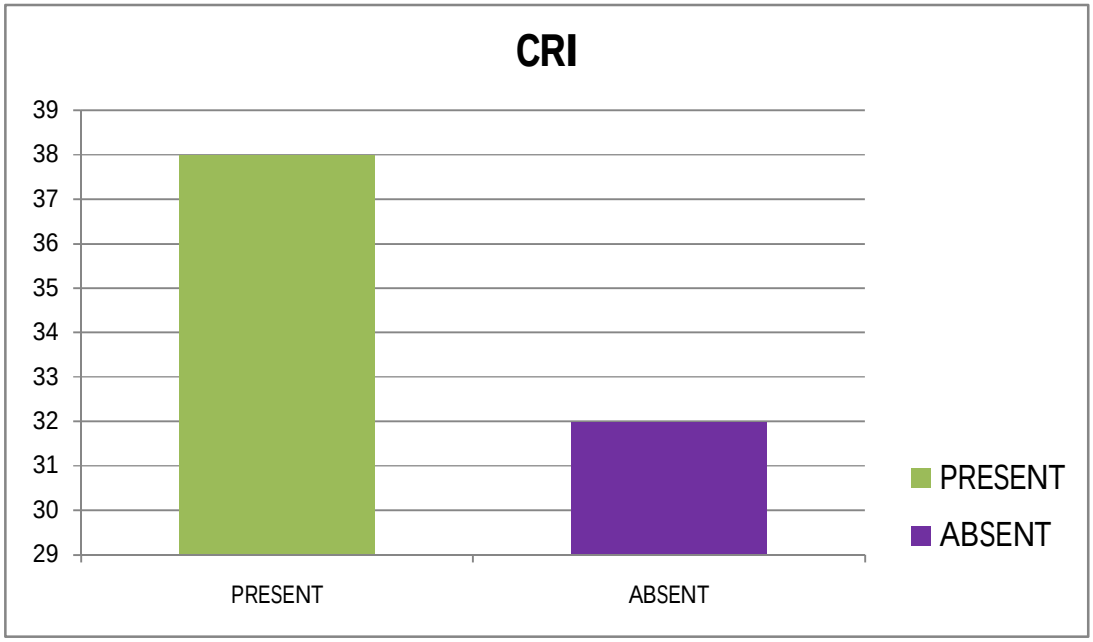


2. CHRONIC RESPIRATORY INFECTION

TABLE 6

Particulars	No. of patients (n=70)	Percentage (100%)
Absent	32	45.7
Present	38	54.3

Chronic respiratory infection was present in 54% of the study population

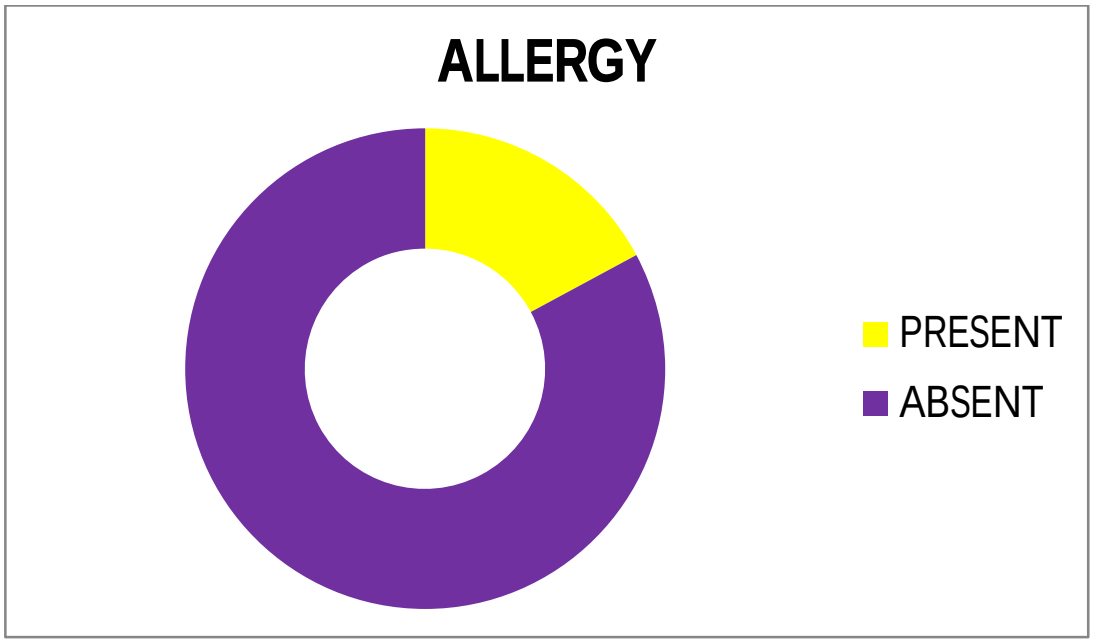


3.ALLERGY

TABLE 7

Particulars	No. of patients (n=70)	Percentage (100%)
Absent	58	82.9
Present	12	17.1

Allergy constituted 17% of the risk factor in our study

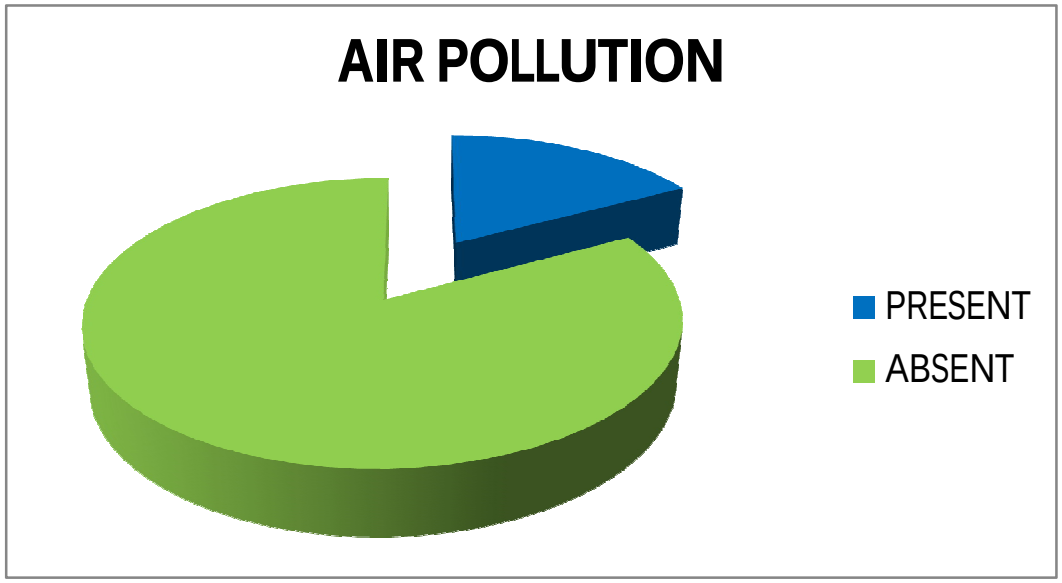


4.AIR POLLUTION

TABLE 8

Particulars	No. of patients (n=70)	Percentage (100%)
Absent	58	82.9
Present	12	17.1

Air pollution constituted 17% of the risk factor in our study.

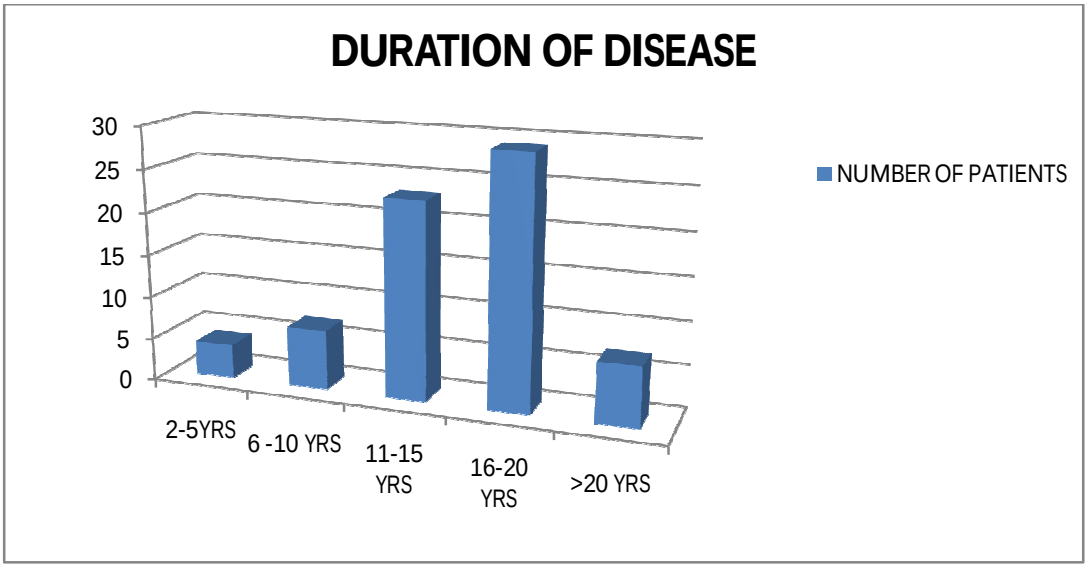


DURATION OF THE DISEASE

TABLE 9

Particulars	No. of patients (n=70)	Percentage (100%)
2 to 5yrs	4	5.7
6 to 10yrs	7	10.0
11 to 15yrs	23	32.9
16 to 20yrs	29	41.4
20yrs & above	7	10.0

From the above table it is observed that majority of patients suffered for more than 15 years. They constitute around 51% of the total population.



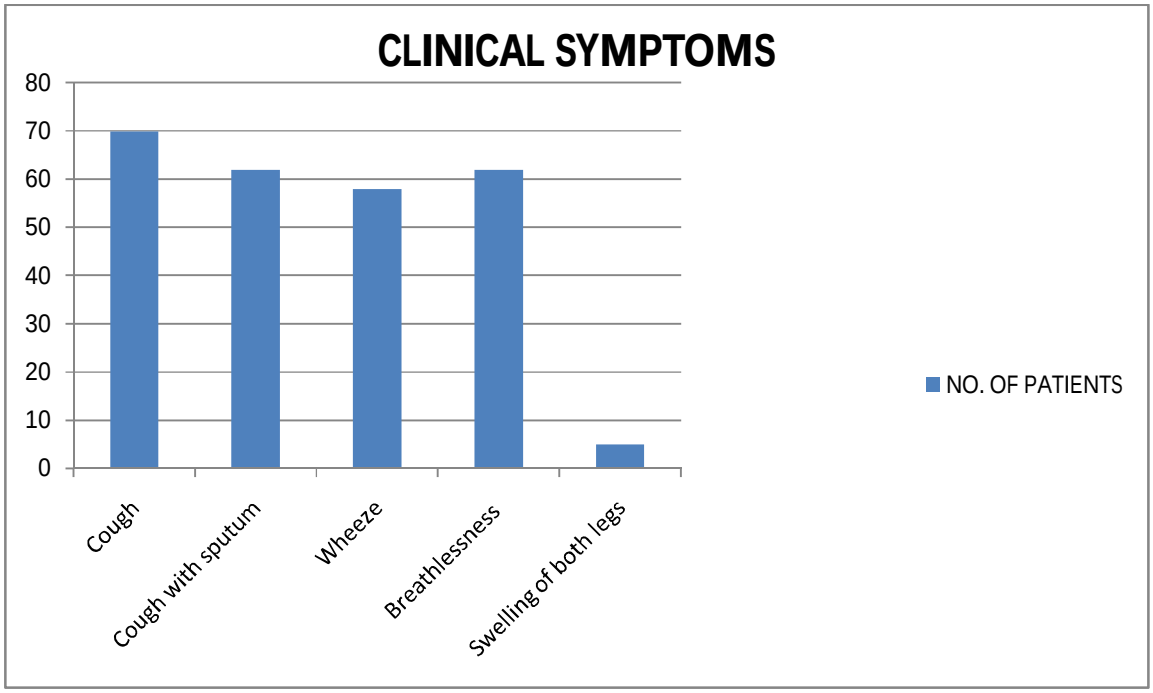
DISTRIBUTION OF SYMPTOMS

TABLE 10

SYMPTOMS	NO. OF PATIENTS	PERCENTAGE(%)
Cough	70	100%
Cough with sputum	62	88.6%
Wheeze	58	82.9%
Breathlessness	62	88.6%
Swelling of both legs	05	7.1%

From the above table it is noted that the major symptom in our patients was cough which was present in almost every patient (100%)

DISTRIBUTION OF SYMPTOMATOLOGY

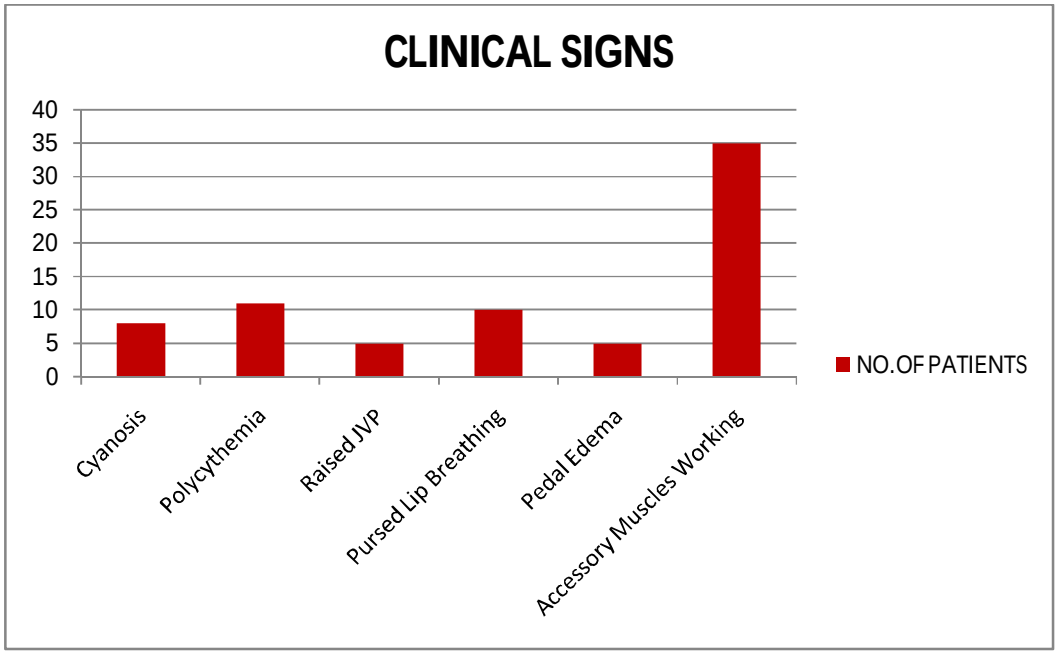


DISTRIBUTION OF CLINICAL SIGNS

TABLE 11

SIGNS	NO.OF PATIENTS	PERCENTAGE(%)
Cyanosis	08	11.4%
Polycythemia	11	15.7%
Raised JVP	05	7.1%
Pursed Lip Breathing	10	14.3%
Pedal Edema	05	7.1%
Accessory Muscles Working	35	50%

From the above table it is inferred that active accessory muscles of respiration (intercostal indrawing) was the major clinical sign observed in 50% the study population.

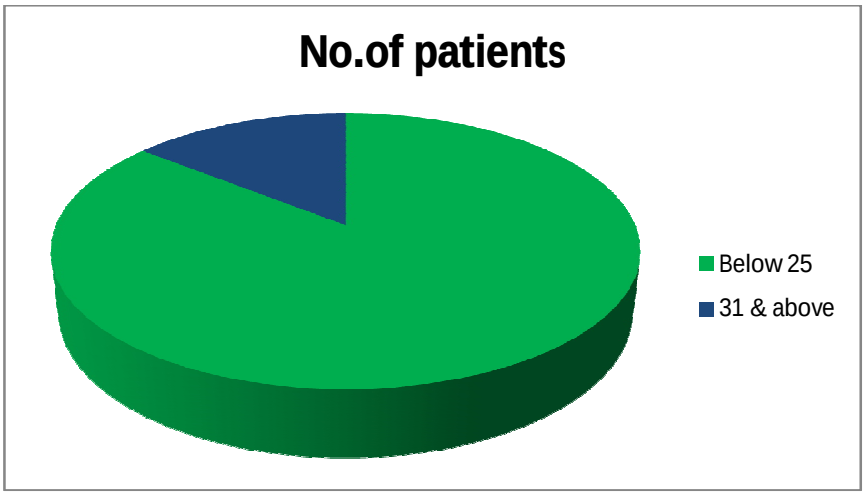

CLINICAL SIGNS
40
35
30
25
20
15
10
5
0
Cyanosis
Polycythemia
Raised JVP
Pursed Lip Breathing
Pedal Edema
Accessory Muscles Working
NO.OF PATIENTS

.

TABLE 12

BMI	No.of patients (n=70)	Percentage (100%)
Below 25	60	85.7
31 & above	10	14.3

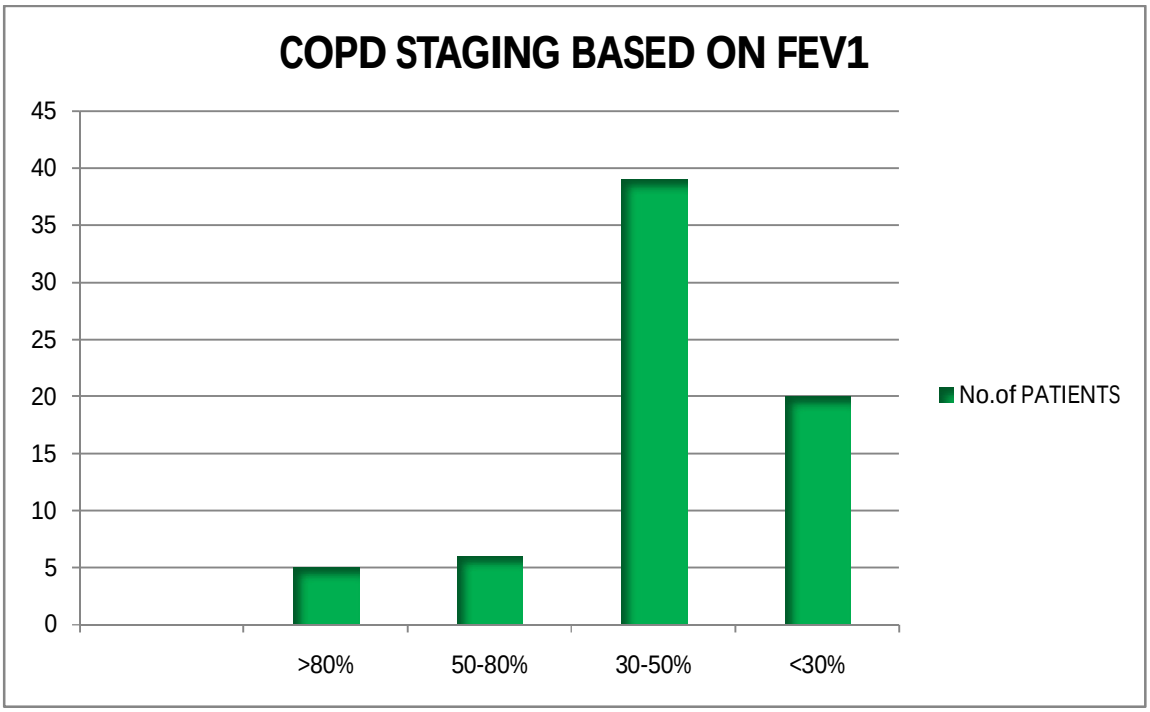
In our study obese patients with BMI above 31 contribute about 14.3% and the remaining are with BMI below 25.



DISTRIBUTION OF CASES AS PER GOLD STAGING

TABLE 13

GOLD STAGING	FEV1%	No. of patients (n=70)	Percentage (100%)
Stage1 mild	>80%	05	7.1%
Stage 2 moderate	50-80%	06	8.6%
Stage 3 Severe	30-50%	39	55.7%
Stage 4 Very severe	<30%	20	28.6%

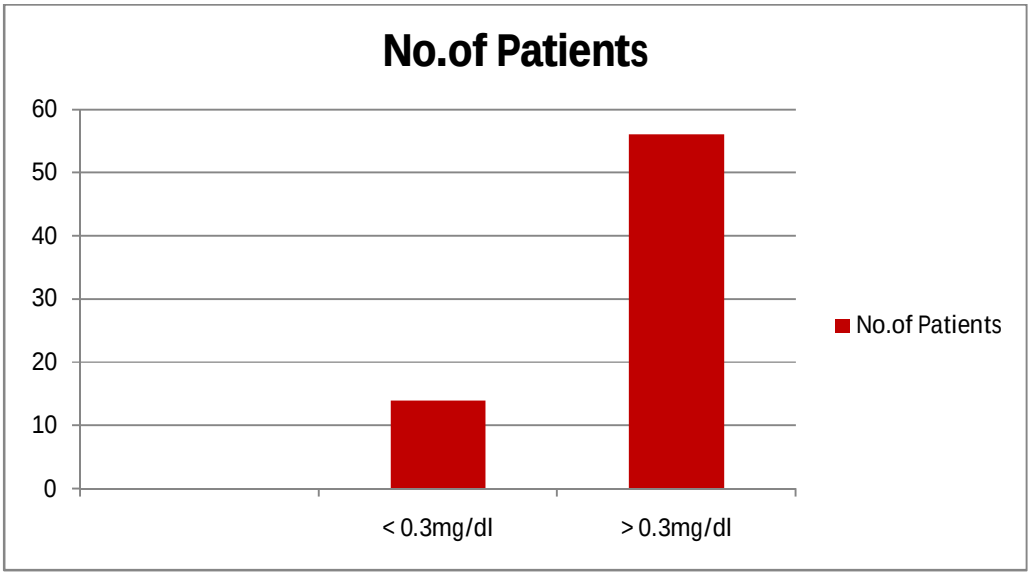

COPD STAGING BASED ON FEV1
45
40
35
30
25
20
15
10
5
0
>80%
50-80%
30-50%
<30%
No.of PATIENTS

DISTRIBUTION OF hs-CRP IN OUR STUDY

TABLE 14

hs-CRP(mg/dl)	No. of Patients (n=70)	Percentage (100%)
< 0.3mg/dl	14	20.0
> 0.3mg/dl	56	80.0

In our study group hs- CRP was significantly elevated in 80% of the population.



ANALYSIS OF RESULTS

TABLE 15

SEX	HSCRP (mg/dl)						Statistical inference
	Below 0.3		Above 0.3		Total		
	(n=14)	(100%)	(n=56)	(100%)	(n=70)	(100%)	
Male	8	57.1%	46	82.1%	54	77.1%	X^2=3.970 Df=1 .046<0.05 Significant
Female	6	42.9%	10	17.9%	16	22.9%	

Using the chi-square test, the null hypothesis which states that there is no difference in hs-CRP levels between two sexes is disproved in our study.

Here we have definitive evidence to prove that there is a statistically significant (p value <0.05) elevation of hs-CRP values of male COPD patients when compared to female COPD patients.

TABLE 16

hs-CRP	Mean	S.D	Statistical inference
Non Smokers (n=15)	7.3333	3.90671	T=2.108 .039<0.05 Significant
Smokers (n=55)	5.2345	3.27890	

Df=68

From the above table it is shown that smokers with COPD have significant raise in hs-CRP levels when compared to nonsmokers with COPD as proved by the unpaired T test which derived a P value of 0.039 which is statistically significant.

TABLE 17

hs-CRP	Mean	S.D	SS	Df	MS	Statistical inference
Between Groups			291.062	3	97.021	F=11.536 .000<0.05 Significant
Stage 1 (n=5)	.8400	.67305				
Stage 2 (n=6)	1.0667	.69186				
Stage 3 (n=39)	6.5923	3.00888				
Stage 4 (n=20)	6.5100	3.29959				
Within Groups			555.091	66	8.410	

Using analysis of variance test (ANOVA) patients with stage 3 and 4 had significantly raised hs-CRP compared to other groups, as proven by the values mentioned.(p value < 0.000)

TABLE 18

BMI	Mean	S.D	Statistical inference
Below 25 (n=60)	4.7517	2.83934	T=-7.188 .000<0.05 Significant
31 & above (n=10)	11.2800	.75982	

Df=68

Using Unpaired T test it is proven that obese patients with COPD had significant elevation in hs- CRP levels when compared to non obese COPD patients.

TABLE 19

AGE	hs-CRP						Statistical inference
	Below 0.3		Above 0.3		Total		
	n=14	(100%)	(n=56)	(100%)	(n=70)	(100%)	
31 to 40yrs	1	7.1%	5	8.9%	6	8.6%	X^2=.781 Df=4 .941>0.05 Not Significant
41 to 50yrs	4	28.6%	11	19.6%	15	21.4%	
51 to 60yrs	3	21.4%	17	30.4%	20	28.6%	
61 to 70yrs	5	35.7%	19	33.9%	24	34.3	

Using chi square test the tabulation above derives a p value of 0.941 (insignificant value).This shows that the hs-CRP levels is not related to the Age of the patient.

DISCUSSION

ANALYSIS OF hs-CRP LEVELS IN PATIENTS WITH ACUTE EXACERBATION OF COPD

INFERENCE 1:

Our study shows statistical evidence that hs-CRP levels are elevated in acute exacerbation of COPD.

The above inference is supported by studies of

Lisa tileman and Lena ginder at al., [72]

Sanja marevic et al., [67]

INFERENCE 2:

In our study hs-CRP levels in male COPD patients are significantly elevated when compared to females.

This above inference is supported by studies of

SA alavi et al .,[70]

Breyer et al., who also proposed that levels of hs-CRP are significantly elevated in male COPD patients.[74]

INFERENCE 3:

Levels of hs- CRP are increased significantly in smokers with COPD than in non smokers with COPD.

Above statement is correlating with studies of

Yannick et al.,[69]

SA alavi et al.,[70]

Lisa tileman et al., who said that levels of hs- CRP correlate with the pack years of smoking.[72]

INFERENCE 4:

Levels of hs-CRP are raised significantly in obese COPD patients compared to non obese individuals.

According to PO Bridevaux et al., based on SAPALDIA study hs-CRP levels are significantly raised in obese COPD patients.[71]

This fact is also supported by SA Alavi et al.,[70] from Guilan university of Iran and Breyer et al. [74]

INFERENCE 5:

In our study increase in hs- CRP levels are associated with the severity of the disease.

This is supported by the studies of PO Bridevaux et al.,[71] who concluded that hs- CRP levels are associated with fast FEV1 decline.

INFERENCE 6:

Our study shows no correlation between the disease duration and hs- CRP levels.

This inference is supported by the results of Daiana stolz et al., [68] who concluded the same in a group of 100 patients for a follow up period of longer time >1yr.

CONCLUSION

1.The levels of hs-CRP are elevated in acute exacerbation of COPD.

2.The levels of hs-CRP are significantly elevated in male COPD patients.

3.Smokers with COPD have statistically significant hs-CRP values than nonsmokers with COPD.

4.Levels of hs-CRP are significantly elevated in obese COPD patients.

5.The hs-CRP values correlates with the severity of the disease.

6.Levels of hs-CRP are independent of the duration of the disease.

SUMMARY

Serum high sensitivity CRP is a marker of systemic inflammation and functional disability in COPD patients.

Increasing levels of hs-CRP may means the infectious state in human body and can guide the clinical treatment of acute exacerbation of COPD . The decrease in levels reflects the recovery period of Acute exacerbation of COPD.

Serum hs-CRP may be used as a simple auxiliary marker in staging and determining the prognosis of COPD for early intervention.

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PROFORMA

NAME: IP NO:

AGE: DOA:

SEX: SE CLASS:LOW/MIDDLE/HIGH

ADDRESS:

OCCUPATION:

PRESENTING COMPLAINTS DURATION

COUGH

SPUTUM PRODUCTION

DIFFICULTY IN BREATHING

WHEEZE

HEMOPTYSIS

CHEST PAIN

FEVER

LEG SWELLING

OTHERS(SPECIFY)

RISK FACTORS & TRIGGERS:

SMOKING

AIR POLLUTION LIKE SMOKE/DUST

RECURRENT URTI

ATOPY/ALLERGY

SMOKING HISTORY:

ACTIVE: CIGAR/CIGARETTE/BEEDI

AGE AT WHICH SMOKING STARTED

INTENSITY OF SMOKING IN PACK YEARS

PASSIVE:

FATHER/HUSBAND/SON

HOUSE HOLD SMOKING

PACK YEARS OF SMOKING

FAMILY HISTORY:

BRONCHIAL ASTHMA/COPD

OTHER DISEASES:

PHT/SHT/DM/CAHD/VALVULAR HEART DISEASE/CONNECTIVE TISSUE DISEASE

GENERAL EXAMINATION:

ANAEMIA:PRESENT/ABSENT

POLYCYTHEMIA:PRESENT/ABSENT

CYANOSIS:PRESENT/ABSENT

PURSE LIP BREATHING:PRESENT/ABSENT

USE OF ACCESSORY MUSCLES OF BREATHING:PRESENT/ABSENT

LYMPH NODE ENLARGEMENT:PRESENT/ABSENT

PEDAL EDEMA:PRESENT/ABSENT

JUGULAR VENOUS PULSE:

VITALS:

PR: /MIN BP: mm/Hg RR: /MIN

SPO2: % TEMP: BMI:

SYSTEMIC EXAMINATION

CARDIO VASCULAR SYSTEM:

CENTRAL NERVOUS SYSTEM:

ABDOMINAL SYSYTEM:

CONGESTIVE HEPATOMEGALY:PRESENT/ABSENT

RESPIRATORY SYSTEM:

INSPECTION:

PALPATION:

PERCUSSION:

AUSCULTATION:

INVESTIGATIONS

URINE R/E: SUGAR ALBUMIN DEPOSITS

CBC:HbESR

TC DC PLATELETS

RBS:

SR.UREA:

SR.CREAT:

ECG:

CXR:

CT THORAX:

Hs CRP:

SPIROMETRY:

GOLD STAGING	FEV 1	FEV1/FVC
STAGE 1		
STAGE 2		
STAGE 3		
STAGE 4		

PATIENT CONSENT FORM

Study detail : "STUDY ON THE ROLE OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE"

Study centre : THANJAVUR MEDICAL COLLEGE & HOSPITAL

Patients Name :
Patients Age :
Identification Number:

Patient may check (√) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests. ☐

Signature/thumb impression:
Patients Name and Address: Place Date

Signature of investigator :
Study investigator's Name : Place Date

s.no	ipno/opno	NAME	AGE	SEX	RISK FACTORS						SYMPTOMS					SIGNS					SPIROMETRY STAGING				DISEASE DURATION	BMI	HSCRP
					SMOKING																						
					ACTIVE P/Y	PASSIVE	CRI	ALLERGY	R/U	AIR POLLUTION	A	B	C	D	E	F	G	H	I	J	1	2	3	4			
1	1348571	ravichandran	47	M	12	A	P	A	R	P	P	P	P	P	A	A	A	P	P	A	P				2	19.5	0.15
2	1348508	natarajan	63	M	23.5	A	P	P	U	A	P	P	P	P	A	A	A	P	A	A			P		16	19	5.7
3	1347438	palaniraj	65	M	26	A	P	A	R	A	P	P	P	P	A	A	A	P	A	A			P		18	23	7.2
4	1373771	chandrabose	50	M	29.5	A	P	A	R	P	P	P	P	P	A	A	A	P	A	A			P		9	18.5	6.5
5	1373777	chidambaram	77	M	34.5	A	A	A	R	A	P	P	P	A	A	A	A	P	A	A			P		17	32.5	11.2
6	1374870	palaniyappan	54	M	28	A	A	A	R	A	P	P	P	P	A	A	A	P	P	A				P	21	23.5	4.9
7	1377454	kaliyan	55	M	26	A	A	A	R	A	P	P	P	P	A	A	A	P	A	A			P		19	22	9
8	1378525	shanmugam	80	M	21.5	A	P	A	U	A	P	P	P	P	A	P	A	P	A	A		P			7	19	0.24
9	1379752	kaliamoorty	65	M	26.5	A	P	A	R	A	P	A	P	P	A	A	A	P	A	A			P		18	19.8	6.2
10	1384691	muthuvel	70	M	28	A	P	A	R	A	P	P	A	P	A	A	A	P	A	A			P		16	18.5	5.1
11	1387401	veerasamy	55	M	A	A	P	A	R	A	P	P	P	P	A	A	A	P	A	A			P		18	31.5	12
12	1388409	ganapathy	75	M	31.5	A	P	A	R	A	P	P	P	P	A	A	A	P	A	A			P		19	22	9.2
13	1388781	karim	70	M	25	A	P	A	R	P	P	P	P	P	A	A	A	P	P	A		P			9	23.5	1.9
14	1392293	alagiri	61	M	24.5	A	P	A	U	A	P	P	P	P	A	A	A	A	A	A			P		17	21	8.3
15	1371463	dhanakodi	55	M	28	A	P	A	R	A	P	P	P	P	A	A	A	A	A	A				P	23	34	10
16	1375417	saravanan	36	M	16	A	P	P	R	A	P	P	P	A	A	A	A	A	A	A			P		16	23	6.1
17	1375509	ramachandra	52	M	22.5	A	P	A	R	A	P	P	A	P	A	A	A	A	A	A			P		19	25	5.2
18	1376601	suyamprakash	65	M	23.5	A	P	A	R	A	P	P	P	P	P	A	A	A	A	P			P		17	21.5	4.3
19	1377769	kaliaperumal	64	M	33	A	P	P	R	A	P	A	P	P	A	A	A	A	A	A				P	22	31	11
20	1377792	saminathan	62	M	27	A	A	A	R	A	P	A	P	A	A	A	A	A	A	A		P			8	19.5	0.25
21	1382822	kaliaperumal	56	M	27.5	A	A	A	U	A	P	P	P	P	A	A	A	P	P	A				P	25	20.6	4

22	1382792	sadasivam	61	M	26.5	A	P	A	R	P	P	P	P	P	A	A	A	P	A	A			P		12	20.5	0.28
23	1401436	uthirapathy	62	M	A	A	P	A	R	A	P	P	P	P	A	A	A	P	A	A			P		14	21.6	0.18
24	1402731	rajendran	45	M	23	A	P	A	R	A	P	P	A	P	A	A	A	P	A	A			P		16	32	11.2
25	1405177	baskaran	65	M	37	A	P	P	R	A	P	P	P	P	A	A	A	P	A	A			P		18	25	5.2
26	1415222	rajagopal	60	M	22.5	A	A	A	R	A	P	P	P	P	A	A	A	A	A	A		P			14	24	0.23
27	1418373	muthanna	61	M	24	A	A	A	R	A	P	P	P	P	A	P	A	A	A	A	P				3	23.5	2
28	1420131	chandraprakash	65	M	36.5	A	A	A	R	A	P	P	P	P	P	P	A	A	A	P			P		12	21.5	6.3
29	1417908	kaus	70	M	31.5	A	A	A	R	A	P	P	P	A	A	A	A	P	A	A			P		11	22.5	4.7
30	1421248	savarirajan	66	M	29	A	P	A	U	A	P	P	P	A	A	A	A	P	P	A			P		18	23	5.8
31	1394707	namasivayam	60	M	24	A	A	A	R	P	P	P	P	P	A	A	A	P	A	A			P		17	24	6.9
32	1401053	katharmaideen	60	M	26.5	A	A	P	R	A	P	P	A	P	A	A	P	P	P	A			P		19	19.5	9.6
33	1403415	alagiri	55	M	25	A	A	A	R	A	P	P	P	P	A	P	A	A	A	A			P		15	21.5	8.5
34	1407106	natesan	56	M	A	A	P	A	U	A	P	P	P	P	A	A	A	A	A	A			P		12	22	7.4
35	1409715	hajamaideen	48	M	24.5	A	P	A	R	A	P	P	P	P	A	A	P	A	A	A				P	22	20.6	5.3
36	1411181	karunanithi	46	M	23.5	A	A	A	U	P	P	A	P	P	A	A	A	A	A	A				P	26	18.5	4.5
37	1411309	thangaraj	70	M	34	A	A	P	R	A	P	A	P	P	A	P	A	P	A	A				P	13	19.5	4.8
38	1416099	govindaraj	65	M	25.5	A	A	A	R	A	P	P	P	P	A	A	A	A	A	A				P	19	20.5	6
39	1416097	sheikdavood	67	M	21.5	A	A	A	U	A	P	P	A	P	A	A	A	A	A	A	P				14	21.5	0.18
40	1396729	selvakumar	45	M	A	A	P	A	R	A	P	P	A	P	P	A	A	A	A	P				P	11	23	6.5
41	1399451	ayishakani	65	F	A	A	P	A	U	P	P	P	P	A	A	P	P	A	A	A			P		15	31	10.5
42	1400280	muthulakshmi	31	F	A	P	P	A	R	A	P	P	P	P	A	A	A	P	A	A	P				5	23.5	0.2
43	1401115	mary	45	F	A	A	A	P	U	A	P	P	P	P	A	A	A	A	A	A			P		12	24	0.1
44	1409750	jayarani	68	F	A	P	P	A	R	A	P	P	P	P	A	P	A	A	A	A		P			8	23.5	0.25
45	1410852	nagammal	48	F	A	P	A	A	U	A	P	P	P	P	A	A	A	A	A	A				P	18	19.5	0.15
46	1412756	shanthi	31	F	A	A	P	A	R	A	P	P	P	P	A	A	A	A	A	A			P		19	20.5	6.3
47	1420032	periyamma	60	F	A	A	A	P	U	P	P	A	A	P	A	A	A	P	A	A				P	14	33	10.8

48	1404880	veeramal	60	F	A	P	P	A	R	A	P	P	P	P	A	A	A	P	A	A	P				10	22.5	0.2
49	1402493	kokila	53	F	A	A	A	A	U	A	P	P	P	P	A	A	A	A	A	A		P			9	21.5	2
50	1400092	pattu	70	F	A	P	P	A	R	P	P	P	P	P	P	A	P	A	A	P			P		15	22	4.2
51	1396574	kasthuri	45	F	A	A	A	P	R	A	P	P	P	P	A	A	A	P	A	A				P	18	19.5	8
52	1398830	vazhambal	50	F	A	A	P	A	U	A	P	P	P	A	A	A	A	P	A	A				P	17	38	12.5
53	1396563	vaduvambal	45	F	A	P	A	A	R	A	P	P	A	P	A	A	A	A	A	A			P		11	19.5	0.25
54	1412687	saroja	60	F	A	A	A	A	R	P	P	P	P	P	A	A	A	P	A	A				P	13	20.5	6.9
55	1369015	pushpavalli	67	F	A	A	A	A	R	A	P	P	P	P	A	A	P	A	A	A				P	28	21.5	6.2
56	1371992	rajathi	58	F	A	P	A	P	R	A	P	P	P	A	A	A	A	P	A	A			P		3	22	6
57	1377022	srisangam	50	M	A	A	A	A	U	P	P	P	P	A	P	A	A	A	A	P				P	18	32.5	11.6
58	1379345	papathan	60	M	26	A	A	A	R	A	P	A	P	P	A	P	A	P	P	A				P	17	20.5	0.1
59	1379345	noor mohamed	80	M	23	A	P	A	U	A	P	P	P	P	A	P	A	P	P	A				P	19	21.5	3.6
60	1388547	saravanan	42	M	22.5	A	P	A	R	A	P	P	P	P	A	A	P	A	A	A			P		14	20	7.4
61	1388555	rabuthul	40	M	21	A	A	A	R	P	P	P	P	P	A	A	P	P	P	A			P		13	23.5	8.5
62	1321654	gunasekar	60	M	39.5	A	P	P	R	A	P	P	P	A	A	A	A	A	A	A			P		18	21.5	9.6
63	1311789	rajan	57	M	37	A	P	A	U	A	P	P	P	P	A	A	A	A	A	A			P		17	33	12
64	1313657	sasi	39	M	26	A	P	A	U	A	P	P	P	P	A	A	A	A	A	A			P		12	22	5.8
65	1321589	shankar	49	M	28	A	A	A	R	A	P	P	P	P	A	P	A	A	A	A				P	19	19.5	5.8
66	1402456	kumaran	58	M	22.5	A	A	A	R	P	P	P	P	P	A	A	A	P	P	A				P	18	20.6	6.2
67	1412987	muthu	65	M	A	A	P	A	R	A	P	P	P	P	A	A	A	A	A	A			P		14	21.4	8.2
68	1409321	selvaraj	71	M	31	A	A	P	R	A	P	A	P	A	A	A	A	A	A	A			P		13	20.6	5.6
69	1420654	sathishkumar	35	M	23	A	P	A	U	A	P	P	P	A	A	A	P	A	A	A			P		12	21.7	6
70	1402498	vijayan	50	M	21	A	A	A	U	A	P	P	P	P	A	P	A	P	A	A			P		12	23.5	3.2

KEY TO MASTER CHART

A – Cough

B – Sputum production

C – Dyspnea on exertion

D – Wheeze

E – Pedal edema

F – Polycythemia

G – Cyanosis

H – Accessory muscles working

I – Pursed lip breathing

J – Jugular venous pressure

hs-CRP- high sensitivity C reactive protein

BMI – Body Mass Index

CRI - Chronic Respiratory Infection

P/Y – Pack years

R/U –Rural /urban

A- Absent

P- Present