SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS

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CERTIFICATE

This is to certify that the dissertation entitled "**SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS"** is a bonafide work done by **Dr. K.S. RAJA**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2010 -2013.

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DECLARATION

I solemnly declare that this dissertation entitled "**SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2010-2013 under the guidance and supervision of**, Prof.K.SIVASUBRAMANIAN,M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

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TABLE OF CONTENTS

ABBREVIATIONS

A1PI	alpha 1 protease inhibitor
BOLD	Burden of Obstructive Lung Disease
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
CRP	C Reactive Protein
CG	Cathepsin G
CT	Computed Tomography
DALY	Disability Adjusted Life Years
EGFR	Epidermal growth factor receptor
ECM	Extracellular matrix
ECLIPSE	Evaluation of COPD Longitudinally to Identify Surrogate Endpoints
ELISA	Enzyme linked Immuno Sorbent Assay
FEV	Forced expiratory volume
FEF	Forced Expiratory Flow
GOLD	Global initiative for chronic Obstructive Lung disease
HHIP	Hedgehog interacting protein
IL 6	Interleukin 6
KD	kilo Dalton
mMRC	modified Medical Research Council
MMP	matrix metalloproteinase
MIP	Macrophage inflammatory protein
MCP	Monocyte chemoattractant protein

NE	Neutrophil elastase
PR3	Proteinase 3
PEF	Peak expiratory flow
TIMP	Tissue Inhibitor of Metalloproteinase
TNF α	Tumor necrosis factor α
TGF β	Transforming Growth factor β

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. It kills more than 3 million people every year, making it the 4th largest cause of death in the world. It has been estimated that by the year 2030, COPD will become the third biggest cause of death[1]. Half a million people die every year due to COPD in India.[2]

COPD results from a chronic inflammatory response which induces parenchymal tissue destruction resulting in emphysema and small airway fibrosis. These pathological changes result in air trapping and progressive airflow limitation.

The goals of COPD assessment are to determine the severity of disease, including severity of airflow limitation, the impact of patient's health status and risk of future events.

Usually the severity of COPD is assessed by validated questionnaires such as COPD assessment test (CAT) and Modified British Medical Research Council (mMRC) Questionnaire. Airflow limitation severity in COPD patients is assessed by spirometric evaluation. Spirometry is the most reproducible and objective measurement of airflow limitation.

COPD is associated with both airway and systemic inflammation. Studies have shown airway and systemic inflammatory markers, such as acute phase reactants (CRP and fibrinogen) increase over time and are associated with faster decline in lung function and increase during acute exacerbations.

Interleukin 6(IL-6) has many biological functions, including growth and differentiation of B cells, T cells and haematopoietic cells. Monocytes appear to be major cell producing IL-6. IL-6 has a rather interesting function that makes it an attractive biomarker in COPD. IL-6 is the primary cytokine regulator of both CRP and fibrinogen in the liver. It also plays a critical role in haematopoiesis, causing thrombocytosis and leucocytosis with its overexpression.

Interestingly, even during clinical stability, COPD patients have elevated blood levels of CRP, fibrinogen, leukocytes, and platelets compared with healthy control subjects. Since all of these molecules are regulated by IL-6, IL-6 may play a salient role in the systemic inflammatory responses in COPD. Furthermore, overexpression of IL-6 in serum or plasma has been associated with dyspnea, skeletal muscle weakness, insulin resistance, pulmonary arterial hypertension, and exacerbations in COPD patients.

Walter et al[75] demonstrated the relationship between FEV1 and serum IL-6. This study aims to assess serum IL-6 as a marker of severity of COPD and its association with acute exacerbations. Thus IL 6 interpretations can be related to the clinical and prognostic parameters and can be useful for evaluation of the therapy instituted for the disease.

AIMS AND OBJECTIVES

Primary Objective

To assess the severity of COPD by clinical methods and spirometry.

Secondary Objective

To find out the correlation between severity of COPD and serum Interleukin-6 levels.

REVIEW OF LITERATURE

Definition of COPD:

A common preventable and treatable disease is characterised by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory response in the airway and lung to noxious particles.

Epidemiology:

COPD is a major public health problem. Globally, COPD has emerged as the major cause of morbidity and mortality expected to become the 3rd most leading cause of death and the 5th leading cause of loss of 'Disability Adjusted Life Years' (DALYs) as per projection of the Global Burden of Disease Study (GBDS).[4]

In India overall prevalence rates of COPD is 5.0 and 3.2 percent respectively in men and women of, and over 35 years of age.[5]

The total burden of COPD has more than doubled to about 14.84 million in 2011 from about 6.45 million in 1971.

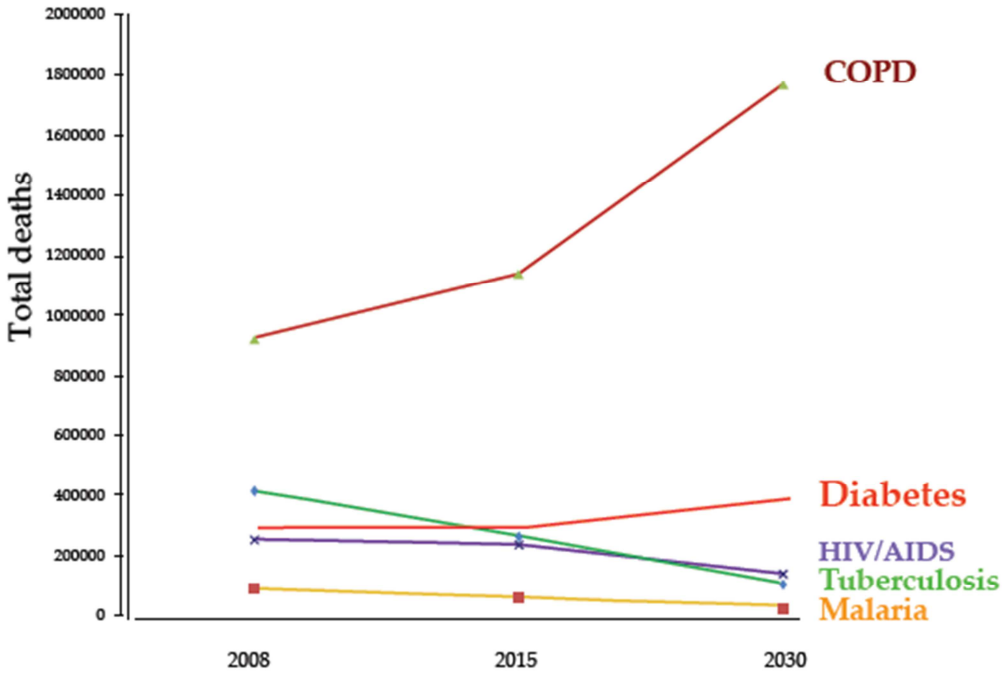


Fig. 1 : Estimated mortality rates due to different diseases in the South East Asian Region (WHO 2008)

The prevalence of COPD is much larger than the estimates given. This is attributable to

1. Patient factors: Patients in the early stages of the disease do not seek medical attention due to minimal or complete lack of symptoms.
2. The variable and inaccurate definitions make it hard to quantify the burden of the disease.

According to a report published by the National Centre for Macroeconomics and Health, the estimated economic loss due to COPD in India is around Rs 35,000 crores.[3]

RISK FACTORS:

Smoking:

Tobacco smoking is the most common risk factor for COPD. On average cigarette smokers have high annual fall in FEV1 of about 50ml, whereas in non-smokers rate of fall in FEV1 is around 30ml.Stopping smoking does not help in improving FEV1, but subsequent fall is reduced. Risk for COPD in smoking depends on the intensity of smoking and also type of smoking. Although prevalence of COPD in pipe and cigar smoking is higher than that of non-smoker, but when compared with cigarette smoking it is lower [6]. Higher prevalence rate of COPD in males are also explained by higher rate of smoking in males.

Passive Smoking:

Not only active smoking, but passive smoking also increases the risk of development of COPD. Significant exposure to passive smoking of tobacco in childhood associated with lower level of FEV1 in later age group. Significant exposure of tobacco smoking in utero also increases the reduced the lung function in post natal period.[6]

Air pollution:

When compare to rural area prevalence of COPD is higher in urbanised area due to exposure of highly polluted air. Prolonged exposure

to smoke produced by biomass combustion (a common mode of cooking in some areas.) also increases the risk for COPD among women in those areas.[7]

Occupation:

Following occupations are associated with increased for COPD:

1. Coal miners[8]
2. Exposure welding fumes in shipyard workers[9]
3. Workers exposed to cadmium.[10]

Airway hyper responsiveness:

Increased airway responsiveness is also a significant predictor for subsequent decline in lung function.

Genetic considerations:

α 1 antitrypsin deficiency:

About one to two% of COPD patients are severe α1 AT deficiency as a contributing cause for COPD[11]. Onset of symptoms and death occur earlier in alfa1 AT deficiency with smokers than in non-smokers with α1 AT deficiency. Since specific treatment for a α1 AT deficiency is available it should be diagnosed in suspected cases.

Other genetic risk factors:

A region near the HHIP gene on chromosome 4 and cluster of genes on chromosomes 15 contain COPD determinants.

Nutritional status:

IUGR babies and childhood malnutrition are risk factors for COPD due to defective lung maturation[12].

NATURAL HISTORY

Factors that contribute to the natural history of COPD include early life events such as intrauterine lung development and childhood and adolescent lung growth as well as later events such as adult lung exposures. The natural history of COPD, therefore, extends over the entire life span of the individual; in fact, potential effects could precede conception.

Because COPD develops slowly, the early stages of the illness are often "silent." Exertional dyspnea in COPD patients is believed to result, in large part, from dynamic hyperinflation, which develops with increasing respiratory rate.[13] The COPD patient, therefore, can avoid dyspnea by avoiding tachypnea, which can be achieved by decreasing

exercise. As a result, COPD patients become progressively more sedentary. The lack of activity in COPD patients result in severe muscle wasting. Skeletal muscle is also abnormal because of the effects of systemic inflammation. Muscle weakness is a major feature of COPD and often limits exercise more than dyspnea does. This may help explain the observation that health status is more closely related to exercise performance than to lung function.[14]

In the human, the conducting airways are developed by the 16th week of gestation.[15] Gas exchange structures, including respiratory bronchioles and alveoli, develop subsequently. Some alveoli are present at birth, but branching of alveolar wall continues postnatally for several years. Alveolar number does not increase after age 8, and subsequent growth of the lung is due to increase in alveolar size. The airway increases in diameter, but not in number, throughout this later growth process. As a result, maximal lung function is attained in young adulthood. This level of function remains relatively constant for perhaps 10 and then begins to decline in a slowly accelerating manner.[16]

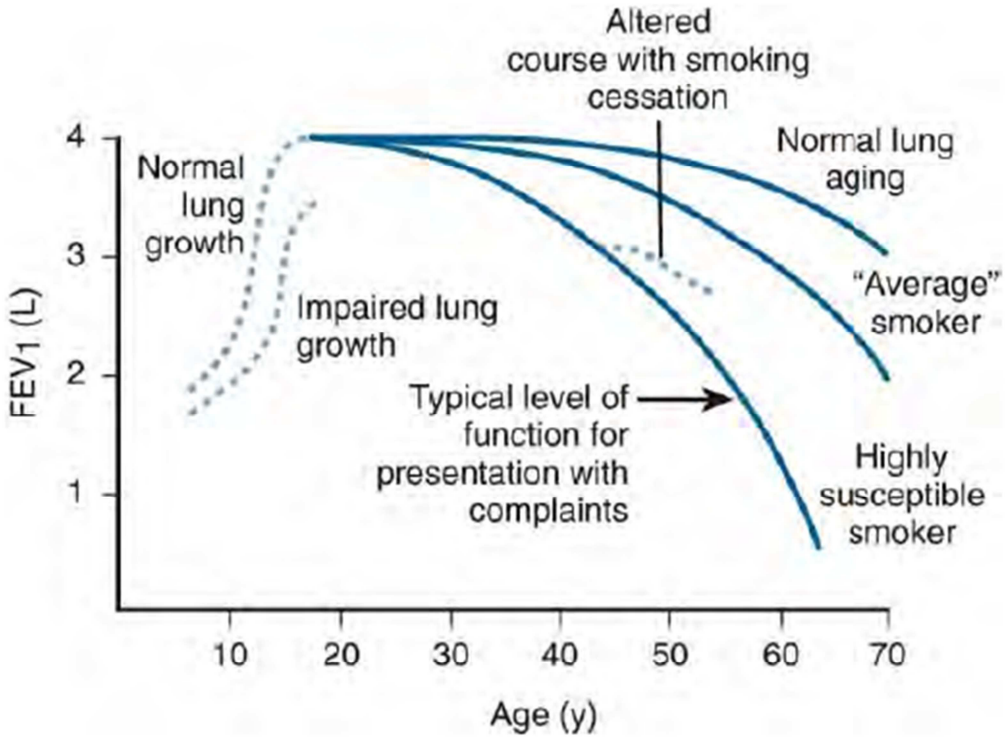


Fig 2: NATURAL HISTORY OF COPD

Over 50 years of adult life, a normal individual may lose 1 L of FEV1, a decline that averages 20 mL/year, but this decline is not linear and probably accelerates with increasing age patient over time. Nevertheless, despite the large gaps in understanding the natural history of COPD particularly for effects outside the lung and for exposures other than cigarette smoking, a number of important features have been described.

Smoking affects this natural history in several ways. First, smoking during the years of lung growth reduces maximally attained lung function.[17] Second, the "plateau phase" is reduced in duration and may be absent.[18] Finally, the rate at which lung function declines is probably

increased. As a result of these various effects, the average smoker loses about 2 L of FEV1 over 50 years, an average decline of about 40 mL/yr. Smoking cessation in adulthood can slow the rate of decline among individuals with mild COPD.[19] Whether such benefits can be expected among individuals with more severe disease or in the elderly is unclear,[20] although smoking cessation has many other established benefits.

Decline in lung function, moreover, may not be continuous. Exacerbations, which are characterized by acutely compromised lung function, may not completely resolve and may result in stepwise decrements of lung function.[21] Finally, some individuals may experience a rapid decline in lung function. Starvation, for example, has been reported to cause the accelerated development of emphysema in both animal models and humans. Individuals who are “rapid decliners” have been observed in prospective studies. Compared to those with a more normal FEV1, those with a low FEV1 probably had, and will continue to have, a more rapid rate of decline of FEV1 and will be more likely to develop COPD, a prediction known as the “horse-racing effect”.[22] Interestingly, prospective studies have found that decrease in lung function is more rapid in individuals with less severe COPD. Identification of slow and rapid decliners in longitudinal studies such as the Lung Health Study has allowed investigation of biomarkers to

distinguish these groups and to define the mechanistic bases for lung function decline.[23]

Importantly, systemic markers of inflammation have been associated with poorer lung function [24] and increased rate of decline in lung function.

Early Disease

Treatment goals in COPD are largely focused on alleviation of symptoms. Because patients with early disease often have no complaints, the importance of identifying individuals with early disease was not recognized until recently. Individuals with mild lung function have increased mortality when compare to normal people, which is primarily due to acute cardiac events.[25] This relationship is true for both smokers and nonsmokers. The link between cardiac events and mild COPD may be systemic inflammation. Identifying a group of individuals with increased cardiac risk, and identifying that they may need treatment to benefit maximally from an exercise training program has potential clinical benefit.

Advancing Disease:

As FEV1 declines, risk for mortality increases. Cardiac events remain a major cause of death, even when COPD is severe. The relative

incidence of death due to respiratory causes, however, increases with increasing severity of lung function compromise.

Exacerbations, which increase in frequency as FEV1declines, are times at which individuals are at particular risk for death. Mortality is also increased among those who have recovered from an exacerbation. The 2-year mortality rate for patients admitted for acute exacerbation of COPD with CO2 retention in the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) trial was 49%.[26] In a retrospective study of a large Canadian database, 1-year mortality of 30% to 40% was observed following hospitalization for COPD exacerbation among individuals over the age of 65, although survival may have been influenced by treatment.[27] However, studies from several centers have shown that some patients with severe obstructive airway disease may survive for many years.[28-30] Thus, it is not possible to predict the course of an individual with a high degree of certainty.

Decisions relating to level of care and end-of-life issues, therefore, must be individualized and must be based on many factors in addition to lung function.

PATHOLOGY:

Airway Disease—Chronic Bronchitis:

The changes in the airway may occur in both large and small airways:

Small airways refer to bronchioles that are less than 2 mm in diameter. Cigarette smoking has propensity to affect both airways as well as air spaces. Air way remodelling is characteristic of COPD which is responsible for airway obstruction. The changes observed in the airway include:

1. **Goblet cell hyperplasia**: Not only is there an increase in the number of cells, there is also evidence of glandular hyperplasia. These changes lead to an increase in mucus production. An important trigger for mucin production is neutrophil elastase, which act through TGFα and EGFR to upregulate the mucin gene and enhance mucin production. Oxidants and metalloproteinases also act through the EGFR pathway to increase mucus secretion.
2. **Epithelial injury and fibrosis**: Various environmental insults like cigarette smoke and oxidants result in an epithelial injury. Aberrant regeneration results in an unchecked fibroblast proliferation. Excess fibroblast activity results in peribronchial fibrosis which results in airway narrowing and limitation. Matrix metalloproteinase 9(MMP 9) activates transforming growth factor beta and promotes fibrosis.
3. **Smooth muscle hypertrophy**

4. Inflammatory Cells:

Role of neutrophils:

Cigarette smoke leads to recruitment of several inflammatory and immune cell types in the airspace.[31] Neutrophils rapidly accumulate in the lung in response to cigarette smoke. Recruitment occurs via stimulation of epithelial cells and macrophages by cigarette smoke, resulting in release of TNF-α and neutrophil chemokines.

Oxidants present in smoke and those generated by the inflammatory cells also promote neutrophilic inflammation. Oxidants also play a role in cigarette smoke–induced cell death. Upon neutrophil activation, secondary and tertiary granules containing MMPs, particularly MMP-9, are readily released.

In addition to causing matrix destruction, proteinases from the neutrophil and other cells generate fragments of ECM proteins such as collagen.[32] and laminin[33] that are also chemotactic for neutrophils, leading to a vicious feedback circle of inflammation and tissue destruction.

Role of macrophages:

COPD is characterized by a gradual, progressive accumulation of macrophages in the lung. Activation of constitutive macrophages leads to production of both neutrophil chemokine and cytokines as well as production of macrophage chemotactic protein-1, which recruits more

monocytes from the peripheral blood, which later differentiate into macrophages. In addition, proteolyzed elastin fragments are chemotactic for macrophages.

Macrophages have the capacity to produce a variety of MMPs, particularly elastases such as MMP-9 and MMP-12, and thus participate directly in lung destruction.

Role of T lymphocytes:

Both CD8+ and CD4+ T cells are also increased in airway walls and alveoli of patients with COPD, with CD8+ cells predominant.[34] Airway epithelial cells in smokers with COPD have increased expression of CXCL10, the ligand for CXCR3 that is expressed on T cells and macrophages.

Cytotoxic T cells may target epithelial cells and induce cell death, particularly those with (latent) viral infection. Other hematopoietic cells such as dendritic cells, eosinophils, and mast cells have also been observed in COPD, but their roles in the disease process are less well defined.

Role of B cells:

Recognition of the increased numbers of B cells and lymphoid follicles in the lung has led to the notion of COPD as an autoimmune disease. In fact, elastin fragments themselves have been shown to serve as autoantigens.

In summary, multiple inflammatory cell types are present in the lung in response to cigarette smoking and interact to cause COPD.

Lung parenchyma – Emphysema:

Pulmonary emphysema is defined as destruction and enlargement of air spaces distal to the terminal bronchiole. Emphysema is characterized by destruction of gas-exchanging air spaces including respiratory bronchioles, alveolar ducts, and alveoli.

It should be differentiated from other forms of air trapping in which there is no destruction. Simple air space enlargement, in which there is no destruction or loss of orderly appearance of the lung acinus occurs in the contralateral lung following pneumonectomy. Air spaces, particularly alveolar ducts, enlarge with advancing age, resulting in what has been termed “senile emphysema.

Alveolar destruction and airway fibrosis in COPD:

Alveolar destruction is mediated by proteinases. Proteinases include matrix metalloproteinases (MMPs) and neutrophil elastase (NE).

PROTEINASE-ANTIPROTEINASE HYPOTHESIS:

There are four classes of proteinases, serine, cysteine, aspartic and metalloproteinases, which are distinguished by their mechanism of catalysis and endogenous inhibitors.

1. **Serine Proteinases**:

The serine proteinase NE was first implicated in COPD after the findings that patients deficient in its endogenous inhibitor, A1PI, are at increased risk for emphysema and that instillation of NE caused emphysema in experimental models. NE also plays a role in airway disease. In fact, NE is one of the most potent secretagogues.[35] In addition, NE is involved in monocyte transvascular migration[36].Despite intense interest in the development of NE inhibitors over the years, they remain largely untested in terms of their efficacy in COPD.

The role of NE in emphysema is due to a direct effect of NE on elastin as well as to the ability of NE to inactivate TIMPs and mediate monocyte migration into the lung. NE is a potent bactericidal and fungicidal agent that acts within the neutrophil lysosome.[37,38]

Two other serine proteinases that are also neutrophil and monocyte derived are cathepsin G (CG) and proteinase 3 (PR3). There is some evidence from animal models that PR3, which has some elastolytic capacity, may also be involved in the development of COPD.[39]

2. **Matrix Metalloproteinases:**

MMPs represent a family of 24 enzymes that require coordination of zinc at the active site, have overlapping substrate specificity, and are inhibited by TIMPs.[40] Several MMPs degrade elastin and hence are likely to contribute to emphysema including MMP-2, MMP-9 (gelatinase A and

B), MMP-7 (matrilysin), and MMP-12 (macrophage elastase). MMP-1, -8, -13 are collagenases, and thus degrade another critical matrix component.

Several MMPs have been associated with human COPD including MMP-1, MMP-9, MT1-MMP, and MMP-12.[41-43] Macrophages have the capacity to produce MMP-1, MMP-3, MMP-7, MMP-9, MMP-12, and MMP-19. MMP-12 has been found in macrophages of smokers. MMP-9 has been detected in macrophages of smokers with COPD and has been a prime therapeutic target.[45] MMP-9 and MMP-8 (neutrophil collagenase) are also stored in neutrophil-specific granules.

3. Cysteine Proteinases:

The cysteine proteinase family includes several highly elastolytic enzymes.[46] Although predominantly intracellular enzymes that work most effectively in an acidic pH, several cysteine proteinases retain significant activity at neutral pH. Moreover, it is possible that cells have the capacity to acidify their immediate extracellular environment.[47] Overall, cathepsins are widely expressed in the lung. Cathepsin L,S, and K are macrophage products. In addition to ECM catalysis, a normal function of cathepsin S is to process antigens in T cells.[48] Cathepsin K is the most potent elastase and collagenase and, hence, might be quite destructive in COPD if present. Cathepsin B is an epithelial cell product that has been shown to have pro apoptotic properties.[49]. Cathepsins have the potential

to contribute to COPD, although they have been less thoroughly studied than other classes of proteinases.

Proteinase Functions in Chronic Obstructive Pulmonary Disease:

A variety of proteinases participate in COPD, with their major role being destruction of ECM components, particularly elastin. However, proteinases also regulate inflammation, not only by blazing trails for cells through tissue barriers, but also via both the generation and the degradation of chemokines and cytokines MMPs also limit inflammation via processing of chemokines.

Within the airways, NE induces mucus secretion, as mentioned previously. This response is mediated by NE-dependent proteolytic activation of EGFR via a TGF-α–dependent mechanism. MMP-9 has been shown to activate TGF-ß and mediate airway fibrosis in COPD. Thus, proteinases participate in multiple activities at several anatomic lung sites in the development of COPD.

Fibrosis of airways and lung parenchyma is also a feature of COPD. Production of IFN-gamma by T cells and transforming growth factor-ß (TGF-ß) by several cell types contributes to accumulation of collagen.

ALPHA1-PROTEASE INHIBITOR DEFICIENCY:

Physiologic Role of Alpha1-Protease Inhibitor:

A1PI is a serine proteinase inhibitor that is a prominent protein in the serum. A1PI is also commonly known as alpha1-antitrypsin. The protein is produced mainly in the liver, is found in high concentrations in the blood stream, and permeates tissues including the lung.

Serine proteinases whose activities are inhibited by A1PI include pancreatic trypsin, chymotrypsin, NE, and proteases from some microorganisms. However, its main substrate in vivo is believed to be NE.[69]

Genetic Variations:

A1PI is a 52-kDa glycoprotein composed of 394 amino acids, and it is coded for by a single gene on chromosome 14. The serum protease inhibitor phenotype (Pi type) is determined by the independent expression of the two parental alleles. The A1PI gene is highly pleomorphic. More than 75 alleles are known, and they have been classified into normal (associated with normal serum levels of normally functioning A1PI), deficient (associated with serum A1PI levels lower than normal), null (associated with undetectable A1PI in the serum), and dysfunctional (A1PI is present in normal amount but does not function normally).[69]

The normal M alleles (the alleles are assigned a letter code) are found in about 90% of persons of European descent with normal serum A1PI levels; their phenotype is designated Pi MM. Normal values of serum A1PI are 150 to 350 mg/dl. More than 95% of persons in the severely deficient category are homozygous for the Z allele, designated Pi ZZ, and have decreased serum A1PI levels. Pi null, found in homozygous form as Pi null-null and found in heterozygous form with a deficient allele as Pi Z null.

Lung disease in alpha1 protease inhibitor deficient phenotypes:

The premature development of severe emphysema is the hallmark of homozygous A1PI deficiency.[50] Symptoms or signs of pulmonary disease rarely develop before age 25 years. The onset of dyspnea occurs at a median age of 40 years in Pi Z smokers and 53 years in nonsmokers.[51-52]

In the 1970s, it was stated that more than half of those with type Pi Z die from pulmonary disease,[50] and this probably remains the case today.

Tobacco smoking and the development of pulmonary disease are strongly associated. Smokers who are type Pi Z have a significantly lower life expectancy than nonsmokers who are type Pi Z. Annual decline of FEV1 is greater than normal in nonsmokers who are type Pi Z, but it is much greater in smokers who are type Pi Z than in nonsmokers.[54]

In addition to cigarette smoking, asthma, recurrent respiratory infections, and unidentified genetic factors have been suggested as possible risk factors for chronic airflow limitation.

Radiographically, Pi Z patients characteristically have more definite evidence of emphysema than seen with garden-variety COPD. The finding of basilar emphysema is not constant in Pi Z patients, but when present, it is strongly suggestive of the diagnosis. It is common with advanced disease to see hairline arcuate shadows separating markedly radiolucent areas in the lung bases from the less severely involved upper portions of the lungs

TYPES OF EMPHYSEMA:

Localization of the lesions of mild emphysema in the acinus serves as the basis for classification into several types of emphysema. The acinus or secondary lung lobule is the unit of lung structure distal to the terminal bronchiole. The acinus is composed of three to five orders of respiratory bronchioles, which have alveoli originating directly from their walls. All of the structures distal to the terminal bronchiole participate in gas exchange and constitute the respiratory tissues of the lungs

Classification Of Respiratory Air Space Enlargement:

Simple Air Space Enlargement

Congenital

- Congenital lobar over inflation
- Down syndrome

Acquired

- Secondary to loss of lung volume

EMPHYSEMA

Proximal acinar emphysema

- Focal emphysema
- Centriacinar emphysema

Panacinar emphysema

The most important types of emphysema are centriacinar (or centrilobular) and panacinar (or panlobular).

The anatomic patterns of emphysema suggest specific pathogenetic mechanisms. The use of CT scans now allows the clinician to more carefully define the type of emphysema and to quantify it better.

Proximal Acinar Emphysema :

Proximal acinar emphysema refers to those types of emphysema that begin in the respiratory bronchioles.[55] Scarring and focal dilation of the bronchioles and of the adjacent alveoli result in the development of an

enlarged air space or microbulla in the center of the secondary lung lobule. Air space enlargement spreads peripherally from the centriacinar region. This type of emphysema includes focal emphysema and centriacinar emphysema.

Focal Emphysema:

A form of centriacinar emphysema, occurring in persons who have had heavy exposure to a relatively inert dust such as coal dust, is called focal emphysema Large numbers of pigment-laden macrophages are noted in association with focal emphysema, which is distributed through the lungs.

Centriacinar Emphysema:

Centriacinar emphysema is the form of emphysema most frequently associated with prolonged cigarette smoking in persons who have had no unusual dust exposure. This lesion involves the upper and posterior portions of the lungs more than the lower portions.

Panacinar emphysema:

Diffuse panacinar emphysema is the lesion most often associated with alpha 1 anti-trypsin deficiency; the emphysema is usually more severe at the bases than at the apices.

Congenital lobar overinflation or emphysema results in infancy from bronchial atresia, most often in the apicoposterior segmental bronchus of

the left upper lobe; available information suggests that the accompanying emphysema is panacinar in type.[56]

Panacinar emphysema have also been observed in intravenous methylphenidate users.

Distal Acinar Emphysema:

In contrast to other forms of emphysema that tend to be generalized, distal Acinar Emphysema which is also known as paraseptal or subpleural emphysema, is localized along fibrous interlobular septa or beneath the pleura.

The remainder of the lung is often spared, so pulmonary function may be normal or nearly so despite the presence of many superficial areas of locally severe emphysema. This is the type of emphysema that produces the apical bullae giving rise to simple spontaneous pneumothorax in young persons.

Air Space Enlargement with Pulmonary Fibrosis:

Another type of localized emphysema, air space enlargement with pulmonary fibrosis, is commonly seen as an inconsequential lesion adjacent to scars. At times, the air space enlargement may be quite extensive and may be important clinically, arising as a complication of fibrosing diseases such as tuberculosis, silicosis, and sarcoidosis.[55] The underlying disease is usually evident radiographically, with extensive

linear or nodular shadows evident along with the enlarged air spaces. Air space enlargement with fibrosis is the anatomic lesion underlying emphysema associated with the pulmonary apical cap. Honeycombing or the end-stage of interstitial lung disease is different from air space enlargement with fibrosis. In honeycombing, cystic spaces 0.5 to 2 cm in diameter are located mainly in the periphery of the lung, although they can sometimes be widespread. The spaces have dense fibrous walls and are mostly lined by bronchiolar epithelium. To differentiate air space enlargement due to fibrosis from COPD, definitions of COPD are used to exclude fibrosis.

However, this is problematic because scarring, particularly in the small airway subepithelial space, is often a consequence of cigarette smoking and a contributing factor to airflow obstruction in COPD. In addition, collagen accumulates around larger disrupted air spaces. Hence, fibrosis and emphysema might be less distinct than we have previously believed.

Cell Death:

Alveolar destruction resulting in air space enlargement requires loss of both cells within the alveolar space as well as the ECM components. Traditional theories suggest that the primary event is release of inflammatory cell proteinases resulting in degradation of lung ECM. Because cell viability requires cell-matrix attachment via integrins, loss

of matrix disrupts the contact and predisposes to cell death. Experimental models show that non inflammatory cell death can initiate air space enlargement.

Following cell death, presumably, proteinases may be released directly or inflammation initiated that subsequently degrades the ECM**.**

Repair:

Destruction in emphysema is followed by aberrant repair of alveolar cells and matrix resulting in coalesced and enlarged air spaces with depleted and disordered parenchymal elastic fibers and excessive, abnormally arranged collagen. Elastin is the principal component of elastic fibers. Under normal conditions, elastin synthesis in the lung begins in the late neonatal period, peaks during early postnatal development, continues to a much lesser degree through adolescence paralleling lung growth, and stops in adult life. Multiple cell types are responsible for elastin synthesis in the lungs and associated structures. Elastin is resistant to most proteinases and lung elastin normally lasts a human life span, despite virtually absent elastin synthesis in the normal adult lung.

Following elastolytic injury, it is not known whether normal elastic fibers can be properly formed in the lung after the period of growth and development.

Bullae:

Bullae are areas of marked focal dilation of respiratory air spaces that may result from coalescence of adjacent areas of emphysema, from locally severe panacinar emphysema, or from a ball-valve effect in the bronchi supplying an emphysematous area.[56] The bullae may be simple air spaces or may retain the trabeculae of the emphysema that led to them. Most frequently, bullae occur as a part of widespread emphysema. Although locally severe emphysema of any type can give rise to bullae, giant bullae are particularly likely to complicate distal acinar emphysema. In the setting of bullae, the amount of emphysema in adjacent lung without bullae varies. In distal acinar emphysema, the emphysematous changes may be confined to the bullous areas; however, if these bullae become large and compress adjacent lung tissue, they may have important physiologic consequences.

Blebs and Cysts

Blebs are intrapleural collections of air and are, therefore, a form of interstitial emphysema. They may be a complication of interstitial emphysema in the newborn period or a complication of pulmonary barotrauma complicating mechanical ventilation. They may also be a part of the spontaneous pneumomediastinum of adults. Ruptured blebs are a cause of spontaneous pneumothorax.

Cysts in the lung are air spaces lined by epithelium, which usually have the characteristics of bronchial epithelium. They are classically known as intrapulmonary bronchogenic cysts and usually occur near the tracheal bifurcation, but they may be seen more peripherally in the lung parenchyma.

Air spaces with fibrous walls, as seen in sarcoidosis and open healed of tuberculous cavities, are sometimes referred to as “cysts.” As described previously, they are better referred to as “air space enlargement with fibrosis.”

Pulmonary Arteries:

Pulmonary hypertension is an important and dreaded complication of COPD. Various mechanisms by which COPD contributes to pulmonary hypertension are:

1. Endothelial dysfunction : endothelial dysfunction refers to an imbalance between the vasoconstrictors and vasodilators elaborated by the endothelium, as a result of which there is vasoconstriction of pulmonary vessels.
2. Vascular remodeling : The most consistent change in a pulmonary vasculature is intimal proliferation and thickening due to smooth muscle proliferation and deposition of collagen and elastin fibres.
3. Emphysematous changes may also occur in the pulmonary capillary bed.
4. Hypoxia: Hypoxia induced vasoconstriction.

Smoking induced endothelial dysfunction occurs early in the disease course and leads onto further vascular damage.

CLINICAL FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE:

History:

Cough and dyspnea are the most common symptoms reported by patients with COPD.

Dyspnea is typically present only with exertion until late in the course of the disease. . A productive cough should not be suppressed and a chronic daily cough is predictive of frequent exacerbations.[57]

Sputum production is insidious in its onset and, in the majority of patients, it is scanty. Sputum production may also relate to smoking status, with current smokers having much more production. The sputum is usually mucoid but becomes purulent during exacerbations. Following smoking cessation, cough and sputum may become transiently more difficult, but symptoms generally improve following smoking cessation.[58]

Hemoptysis complicating chronic bronchitis is usually occurs in association with an exacerbation.[59] However, other etiologies of haemoptysis mainly lung cancer, should be kept in mind in this susceptible population.[60]

Dyspnoea, especially with exertion, is usually the presenting symptom and, as the disease progresses, occurs with less and less effort. Dyspnoea in COPD patients probably results from dynamic hyperinflation that worsens with increasing respiratory rate. As a result, many patients will avoid dyspnoea by avoiding exertion and may become exceedingly sedentary.

Exacerbations, which are characterized by increased cough, sputum, dyspnoea, and fatigue, are increasingly frequent as the disease worsens. They generally resolve over a few weeks, but full recovery may take months. Exacerbations may be difficult to distinguish from other acute causes of dyspnoea, cough, and/or sputum including pneumonia, congestive heart failure, pulmonary embolism, or pneumothorax without radiologic or laboratory evaluation.

Physical examination:

Early inspiratory coarse crackles.

Rhonchi are more prevalent in patients complaining of dyspnoea and are usually present during both inspiration and expiration.

The most consistent finding in patients with symptomatic COPD is the prolonged expiratory time, which is best determined by listening over the larynx during a forced expiratory manoeuver. Prolongation of the

expiratory phase longer than the normal 4 seconds is indicative of significant obstruction.

Severe COPD patients may present with

- Barrel-shaped chest
- Purse-lipped breathing
- Emaciation
- Inguinal hernias.
- Tripoding

Position observed in severe COPD patients that is sitting forward and leaning on their elbows, or supporting their upper body with extended arms. This position stabilizes the shoulder girdle and helps to maximize intrathoracic volume.

Pulmonary hypertension may develop in patients with severe COPD and may present with

- A loud and palpable pulmonary component of the second heart sound
- Elevated jugular venous pressure
- Bilateral pedal oedema
- Congestive hepatomegaly

SYSTEMIC MANIFESTATIONS AND COMORBIDITIES OF COPD

Cardiovascular system:

- Infarction
- Arrhythmia
- Congestive heart failure
- Hypertension

The most common cause of death among COPD patients is coronary artery disease.[61] Systemic inflammation plays a major role in the pathogenesis of atherosclerosis

Hypercoagulability:

Hypercoagulability due to systemic inflammation, account for increased risk of deep venous thrombosis and pulmonary embolism in COPD patients.

- Stroke
- Pulmonary embolism
- Deep vein thrombosis

Other systemic manifestations:

- Weight loss

- Diabetes Mellitus and metabolic syndrome
- Osteoporosis
- Anaemia
- Anxiety
- Depression
- Lung cancer

COPD patients may have a higher incidence of depression[63] which may also result from systemically active inflammatory mediators.

Lung cancer is also a long term sequelae in COPD patients with smoking having an additive effect.

INVESTIGATIONS:

The various investigation modalities available for the diagnosis of COPD are:

1. Imaging modalities
2. Pulmonary function tests
3. Blood investigations

Imaging:

Imaging can be done with a chest x- ray or a computed tomography

Chest X ray:

Radiographic signs of emphysema may be due to the following reason:

- hyperinflation

- vascular changes
- bullae

Overinflation of the lungs produces the following changes

- Low flattened diaphragms.

  Abnormally low diaphragms are present when the border of the diaphragm in the mid-clavicular line is at or below the anterior end of the sixth or seventh rib

  Flattened diaphragms are present when the maximum perpendicular height from a line drawn between the costal and cardiophrenic angles to the border of the diaphragm is less than 1.5cm.

- Increase in the retrosternal airspace:

  It can be demonstrated on the lateral film at a point 3 cm below the manubrium, occurs when the horizontal distance from the posterior surface of the aorta to the sternum exceeds 4.5 cm

- An obtuse costophrenic angle on the posteroanterior or lateral chest radiograph.
- The inferior margin of the retrosternal airspace is 3 cm or less from the anterior aspect of the diaphragm

Vascular changes associated with emphysema result from loss of alveolar walls and are shown on the plain chest radiograph by the following.

- A reduction in size and number of pulmonary vessels, particularly at the periphery of the lung.
- Vessel distortion, producing increased branching angles, excess straightening or bowing of vessels.

Chest X ray also used to rule to rule out the following diseases in COPD patients:

Pneumonia

Pneumothorax

On fluoroscopy the range of diaphragmatic movement, normally 6–8cm and always greater than 3 cm, is often only 1cm in severe COPD. Occasionally the flattened diaphragms may be drawn upwards in parallel in inspiration, a motion different from true paradoxical movement due to paralysis of the phrenic nerve. In the latter, inspiratory sniffing gives rise to a sharp upward movement of the convex diaphragm, quite different from the slight upward movement of a flattened diaphragm in COPD.

Focal areas of translucency surrounded by hair-line walls represent bullae. These may be multiple, as part of a generalized emphysematous process, or localized

Computed Tomography

In contrast to conventional radiography, computed tomography (CT) has the resolution needed to delineate and quantify subtle findings in the

chest and is therefore much more sensitive, particularly in the diagnosis of emphysema. There are several methods to assess COPD using CT.

CT density can be used to quantify emphysema, because loss of density is a characteristic feature. This permits estimates of both severity and extent of disease

The ability to distinguish bullae and to determine the location of disease is essential in determining whether individual patients are candidates for surgical therapy.

Visual assessment of emphysema on CT reveals:

- Areas of low attenuation without obvious margins or walls;
- Attenuation and pruning of the vascular tree;
- **A**bnormal vascular configurations.

ECG Changes:

An electrocardiography may reveal the following changes in COPD patients

- P pulmonale
- Right QRS axis deviation
- Very low amplitude P, QRS, T wave complexes in lead I
- SI,SII,SIII syndrome
- Prominent terminal S Waves in leads I,II and III
- Right bundle branch block

All the above mentioned changes suggest a right ventricular enlargement hence they are not specific of COPD. Low amplitude complexes are due to increase in the anteroposterior diameter of the chest wall (barrel chest) in COPD patients.

Echocardiography:

Echocardiography can not only detect but also quantify the severity of COPD patients. The changes observed during an echocardiogram are:

- Right ventricular hypertrophy and dilatation
- Right atrial dilation
- Right ventricular pressure overload pattern of interventricular septum
- Right ventricular abnormal systolic function
- Dilated pulmonary artery
- Reduced left ventricular end systolic and diastolic volume
- Tricuspid regurgitation
- Elevated pulmonary artery systolic pressures.

Pulmonary function tests:

Assessment of lung function is essential to establish a diagnosis and to access the severity of COPD. The most important test is spirometry. Measurement of lung volumes and diffusion capacity, which generally requires a specialized laboratory, may also be helpful, particularly in

determining whether airflow limitation is due to emphysema or airway disease.

SPIROMETRY:

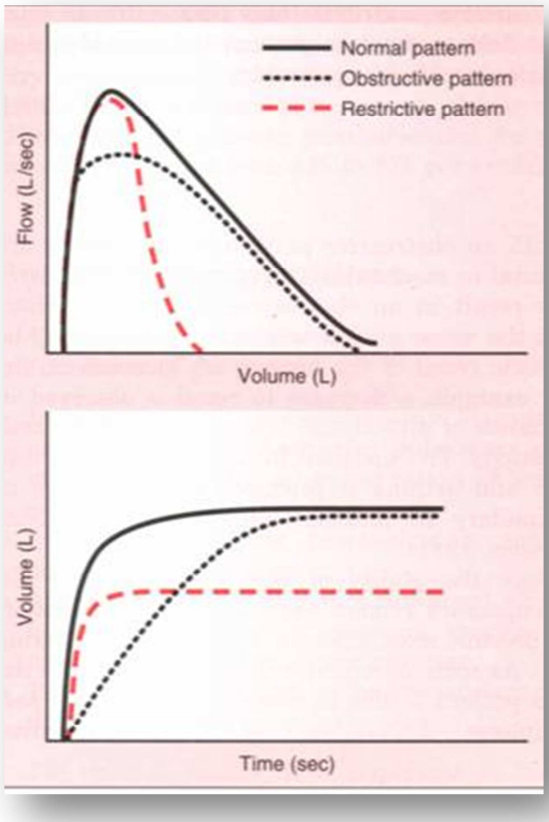
Simple spirometry is the most important test to diagnose and stage COPD. After taking a maximally deep breath, a subject exhales as forcefully as possible, and the volume of air exhaled is measured as a function of time.

A reduction in FEV1/FVC ratio is diagnostic of airway obstruction. Because it may take some time for a patient to empty his or her lungs fully, particularly if COPD is present, the forced expiratory volume after 6 seconds, FEV6, is recommended for use in most office settings. Not only is it easier to perform, but avoiding prolonged exhalation manoeuvers reduces the chance of syncope during the test. Because of variability in the FVC (or FEV6) measure, the FEV1/FVC ratio can establish a diagnosis of obstruction but is if airflow is abnormal, post bronchodilator testing should be performed. Correction to the normal range suggests a diagnosis of asthma and could exclude COPD. Partial correction, which may vary from day to day in an individual patient, may help to define therapeutic goals.

Though the FEV1/FVC ratio is the spirometric standard for diagnosing obstruction, the FEV1/FEV6 ratio is an acceptable surrogate.

The FEV6 manoeuvre, which allows cessation of exhalation after 6 seconds, has several advantages over the standard FVC manoeuvre. It is less physically demanding for the patient. It simplifies spirometric testing for the technician, shortens testing time, and has superior reproducibility.[65] The FEV1/FEV6 ratio performs well in categorizing patients with obstruction with a sensitivity and specificity greater than 90% compared with the FEV1/FVC ratio.[65-67] Based on these findings, the National Lung Health Education Program has recommended replacement of FVC with FEV6.But FEV6 is not as sensitive as FVC at determining the presence of a restrictive respiratory impairment.

Fig3. Spirometry pattern in lung disorders



SPIROMETRY MEASUREMENTS:

Important clinical measurements are

- Forced vital capacity (FVC):

  The maximal volume of air forcefully exhaled after a maximal inspiration

- Forced expiratory volume in 1 second (FEV1):

  The amount of air exhaled during the first second of a FVC

- Forced expiratory flow between 25% and 75% of the FVC (FEF25%–75%):

  Reduction in FEF25%–75% is a spirographic manifestation of small airway dysfunction.[64] However, FEF25%–75% is a highly variable test that is dependent on exhalation time and is not specific for small airway disease in individual patients

- Peak expiratory flow (PEF):

  It is the maximum flow achieved during forced exhalation. PEF reflects the caliber of the large airways and is highly effort dependent. Although PEF is attractive because it can be measured using inexpensive handheld devices, it is a more variable measure than FEV1 and the correlation between PEF and FEV1 in patients with airway obstruction is poor.

Spirometry Acceptability Criteria:

1. Good start of test

Sharp take-off without hesitation

Extrapolated volume < 5% or 0.15 L, whichever is greater

2. Meet end-of-test criteria

Complete exhalation to residual volume

Plateau on volume-time curve

Exhalation time = 6 seconds (3 sec for children)

3. Absence of artefacts

Cough, especially during first second of exhalation

Glottis closure

Hesitation or submaximal effort

Air leak

Obstructed mouthpiece

Volume-Pressure Relationship

Compliance of the lungs can be measured with an esophageal balloon. With severe emphysema, compliance of the lungs is increased. Measurement of the volume-pressure curve of the lung is a research procedure not generally used in routine clinical practice.

Diffusing Capacity

The single-breath diffusing capacity is decreased in proportion to the severity of emphysema because of the destruction of the alveoli and the loss of alveolar emphysema.[68] It is also reduced in other diseases that destroy the alveolarcapillary bed.

Sputum Examination

In stable bronchitis, sputum is mucoid, and microscopic examination reveals a predominance of macrophages.

Presence of eosinophils may indicate a greater likelihood to respond to inhaled glucocorticoid therapy

During the exacerbation, the number of organisms seen on Gram stain usually increases. The pathogens most often cultured from the sputum are

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*.
- Oropharyngeal commensal flora such as *Moraxella catarrhalis*

However, cultures and gram stains are rarely necessary for initiation of antimicrobial therapy unless the patient has sustained an exacerbation during or soon after receiving a course of antibiotic therapy.

Blood investigations:

1. Complete haemogram: Both anaemia and polycythaemia can occur. Anaemia results from malnutrition and chronic inflammation. Polycythaemia is due to hypoxia induced stimulation of erythropoiesis
2. An elevation of liver parameters especially alkaline phosphate can elevated if COPD results in a congested liver.
3. Arterial blood gas analysis: In early stage: Mild or moderate hypoxemia without hypercapnia. In the later stages of the disease, hypoxemia tends to become more severe and may be accompanied by hypercapnia with increased serum bicarbonate levels. Hypercapnia is observed with increasing frequency as values of the FEV1 fall below 1 litre. Blood gas abnormalities worsen during acute exacerbations and may also worsen during exercise and sleep. Alterations in blood gases largely reflect alteration in ventilation-perfusion relationships. So spirometric values, which assess only airflow may be weakly correlated with blood gas abnormalities.
4. Serum α1 antitrypsin level:

   In the following conditions measurement of α 1 antitrypsin level is warranted

   - Young onset
   - Non-smoker
   - Panacinar type

5. Systemic inflammatory markers: COPD is no longer considered a local inflammatory disease of the airways. It is a systemic disorder characterised by elevations in the acute phase reactants like CRP, Fibrinogen, inflammatory cytokines and chemokines.

ASSESSMENT OF SEVERITY OF COPD:

Severity of COPD is usually assessed by clinical methods and spirometry.

Clinical methods include

Assessment of symptoms by mMRC scale and CAT score. Modified medical research council (mMRC) scale is a scale for assessing the degree of breathlessness. Patients are categorised into 5 groups (0-4) based on the limitation of activity due to dyspnoea.

Grade 0 indicates dyspnoea only at strenuous exercise

Grade 1 dyspnoea on walking up a slight hill or hurrying on a level ground

Grade 2 walks slower than people of same group or dyspnoea while walking on one owns pace at level ground.

Grade 3 patient stops for breath after few minutes of walk on level ground or walking 100 m

Grade 4 patient is breathless even while dressing / undressing.

CAT score (COPD assessment test):

CAT score (COPD assessment test) is a questionnaire with 8 questions each of which has a graded response from 0 to 5. Thus a maximum score of 40 is possible. The questionnaire includes

- Cough
- Sputum production
- Chest tightness
- Dyspnoea on exertion
- Functional limitation of activity
- Patient's assessment of his disease
- Sleep pattern and
- Energy levels of the patient.

Assessment of exacerbation risk:

Exacerbation is defined as worsening of the patient's condition in a manner that is in excess of the normal day to day variation and requires a change in medication. An acute exacerbation includes increase in sputum production, increase in purulence or worsening dyspnoea.

The best predictor of an exacerbation is the presence of a previously treated event. The most common cause of acute exacerbation is infections of which viral infections constitute the majority.

Assessment of severity by spirometry:

Spirometric diagnosis of COPD is made when a post bronchodilator FEV1/FVC ratio of < 0.7 is present. The spirometric assessment of severity is based on percentage of expected FEV1.

According to GOLD,

Mild COPD is present when FEV is more than 80 % of predicted value.

Moderate COPD have values between 50 and 80%.

Severe COPD is characterised by FEV1 values between 30 and 50%.

Very severe COPD indicates a FEV1 of less than 30% of predicted value or concomitant presence of respiratory failure and cor pulmonale.

Assessment of severity with systemic inflammatory markers:

As we know COPD is not just a localised disease confined to the respiratory tract but a systemic disease. COPD patients present with higher levels of systemic inflammatory markers than the healthy control groups. In various studies, systemic inflammatory markers were not only elevated, but served as useful predictors of severity, risk of exacerbation and mortality in COPD patients.

In the ECLIPSE study which included about 2164 COPD patients, a marked rise in various inflammatory markers like IL 6, IL 8, CRP, fibrinogen, TNF α and MCP1 was observed. A point of interest in the

study was that, among all the inflammatory markers, IL 6 predicted severity and mortality better than others.

CYTOKINES:

Cytokines are hormone like molecules that act mostly in a paracrine fashion to regulate to regulate immune response. They are generally secreted by lymphocytes, monocytes but can also be produced by endothelial cells, neuron and glial cells.

Receptor for cytokines subdivided into 3 subfamilies:

- Subfamily 1 includes the receptor for IL4 and IL7. They are usually homodimers.
- Subfamily 2 includes the receptors for IL5 and IL6. They are usually heterodimers
- Subfamily 3 includes receptors for IL2 and some other cytokines. They consist heterodimers with tac antigen.

Another subfamily of cytokines is the chemokine family. They are substances that attract neutrophils and other WBC to the area of inflammation. Over 40 chemokines are identified, whose role in cell growth and angiogenesis has also been established.

INTERLEUKIN 6:

Interleukin 6 is a cytokine, which has both pro-inflammatory and anti-inflammatory actions. Its anti-inflammatory action produced by inhibiting TNF-α and IL6.

Previously it was recognised under various names like interferon β2, 26-KD protein, B cell stimulating factor, cytotoxic T cell differentiation factor, hybridoma/plasmocytoma growth factor.

Interleukin 6 has received much attention only in the past two decade. Interleukin 6 was coined by Poupart et al in 1988.

Cellular sources of IL6:

- Type-2 helper T cells
- Macrophages
- Fibroblast
- Adipocytes
- Endothelial cells
- Osteoblast
- Smooth muscle cells of blood vessels.

Function of IL6:

IL6 has many molecular forms and each form has a different function.

Acute phase reactant:

Acute phase reactant is a substance which is increased or decreased in response to an inflammatory stimulus.

IL6 is the most important stimulant for the acute phase reactant like CRP and serum fibrinogen from the liver. IL6 increases CRP levels by increasing the transcription process.

Action on T cells:

IL 6 plays an important role in differentiation of T cells and their activation.It enhances the innate immunity by promoting the development of natural killer cells. It also promotes the differentiation of CD4 cells into T-helper cells by reinforcing the effect of IL2.

Action on B cells:

It is a potent stimulant for B cell differentiation and proliferation,

Induces haematopoiesis

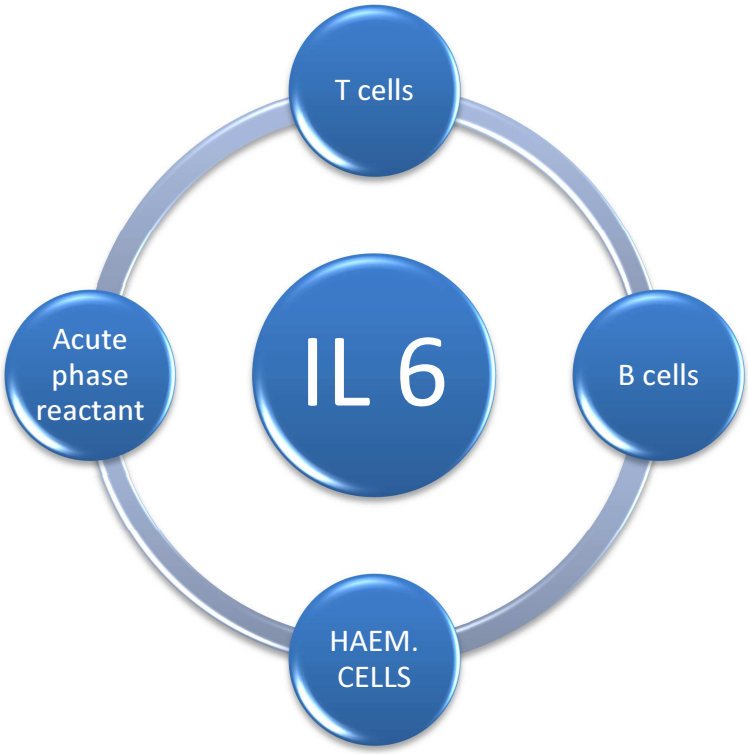


Fig 4: IL 6 and its functions

Some of the diseases in which IL 6 contributes significantly to the pathogenesis are:

- Rheumatoid arthritis,
- Multiple myeloma and other malignancies
- Diabetes mellitus
- Atherosclerosis
- Systemic lupus erythematosis
- Coronary artery disease
- Cirrhosis of liver
- Castleman's disease

ROLE OF IL 6 IN CHRONIC INFLAMMATION:

Under normal conditions, to an inflammatory stimulus there is a host response which acts as a natural defence mechanism to limit further damage. This acute response is mediated through neutrophils.

As the stimulus persists, the inflammatory response becomes chronic and this is no longer protective for the host. Once chronic inflammation sets in, further tissue destruction ensues resulting in more damage.

IL 6 plays a pivotal role in transforming the acute inflammation to a chronic process. It does so by enhancing the transformation of neutrophils into monocytes, which characterise chronic process.

ROLE OF IL 6 in COPD:

The concept of COPD being a systemic disease has already been emphasised and requires a mention here. Possible mechanisms by which COPD is considered a systemic inflammation are:

- Smoking and air pollution
- Spill over from the lung
- Adipose tissue acting as a source of inflammation
- Muscle acting as a source of inflammation
- Genetic predisposition

The various inflammatory markers that are increased in COPD patients include:

Cytokines:

- Interleukin 6
- Interleukin 10
- Interleukin 12
- Tumour necrosis factor α
- Interleukin 1 β
- Granulocyte colony stimulating factor

Chemokines:

- Interleukin 8(CXCL8)
- Keratinocyte derived chemokine(CXCL 1)
- Monocyte chemoattractant protein 1(MCP 1)
- Macrophage inflammatory protein(MIP 2β and MIP 1)

IL 6 levels are found to be increased in sputum, exhaled breath and serum of COPD patients.

IL 6 as previously discussed mediates the chronic inflammatory process in COPD. IL 6 levels remain stable in circulation and this steady level contributes to the systemic manifestations of COPD. Systemic manifestations which IL 6 plays a major role include a widespread endothelial dysfunction, which leads to an increase in cardiovascular

mortality and morbidity. Insulin resistance, which contributes to metabolic derangements and diabetes mellitus, is also associated with increased circulating levels of IL 6. IL 6 by its action on osteoclasts, results in osteopenia and osteoporosis. Muscle wasting (sarcopenia) and depression are also associated features.

METHODOLOGY

Study Centre:

Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai

Duration of the Study:

6 months

Study Design:

Case control study

Sample Size:

50 cases

20 controls

Inclusion Criteria:

- Known case of COPD
- Newly diagnosed cases of COPD

(COPD: FEV1/FVC < 0.70 post bronchodilator)

Exclusion Criteria:

- Known malignancies
- Known connective tissue disorders
- Inflammatory disorders
- Coronary artery disease
- Acute stroke patients
- Liver disease patients
- Obesity
- Diabetes mellitus

Case and control selection:

50 patients with established diagnosis of COPD or newly diagnosed patients were enrolled in the study. COPD was defined by spirometric measurements. Any patient with clinical features suggestive of COPD was subjected to a spirometry and a FEV1/FVC value of less than 0.7 was the criteria. The spirometry was done post bronchodilator therapy. 20 controls with similar age and sex distribution were enrolled in the study. Informed consent was obtained. Institutional ethical committee clearance obtained.

Methods:

Both cases and control population was evaluated with a questionnaire. A detailed history of symptomatology, smoking history and co morbid conditions were obtained. Pack years of the patients with a positive smoking history was calculated using the formula

Pack years = (No. of cigarettes/day * No. of years of smoking) / 20.

Patients with positive symptoms and history suggestive of COPD were further evaluated to assess the severity of the disease. The number of exacerbations per year was obtained. COPD assessment test score (CAT score) was assessed for all cases by a questionnaire which included the following aspects:

1. History of cough
2. Phlegm (mucus) in the chest
3. Chest tightness
4. Patient's ability to walk up a hill or climb a flight of stairs
5. Limitation of activity at home.
6. Confidence in leaving home despite the existing condition
7. Sleep pattern
8. Sense of well-being.

Each aspect is answered by the patient. A graded score of 0 to 5 was given based on the patient's response. Thus a maximum score of 40 was attainable.

Patients were subjected to routine blood investigations.

Spirometry:

All cases enrolled in the study were subjected to spirometry. With patients comfortable and in sitting position, they were asked to exhale for atleast 6 seconds after maximal inspiration. The procedure was repeated if it was interrupted by cough, premature cessation of exhalation and obstruction of mouth piece. The following volumes were recorded.

1. Forced vital capacity(FVC)
2. FEV_1(forced expiratory volume in the first second)
3. FEV1/FVC ratio

The measured FEV1 was compared against the predicted value and was expressed in percentage. Severity of COPD was graded according to the GOLD guidelines.

GOLD Staging	Severity	Spirometric values (FEV1/FVC<0.7)
GOLD 1	Mild	FEV1>=80% predicted
GOLD 2	Moderate	50%<=FEV1<80% predicted
GOLD 3	Severe	30%<=FEV1<50% predicted
GOLD 4	Very severe	FEV1<30% predicted

Serum IL6 levels:

5 ml of venous blood was obtained from all cases and controls. Blood samples were centrifuged and serum separated. Serum IL 6 levels were estimated using ELISA technique.

Data obtained by above methods were analysed by

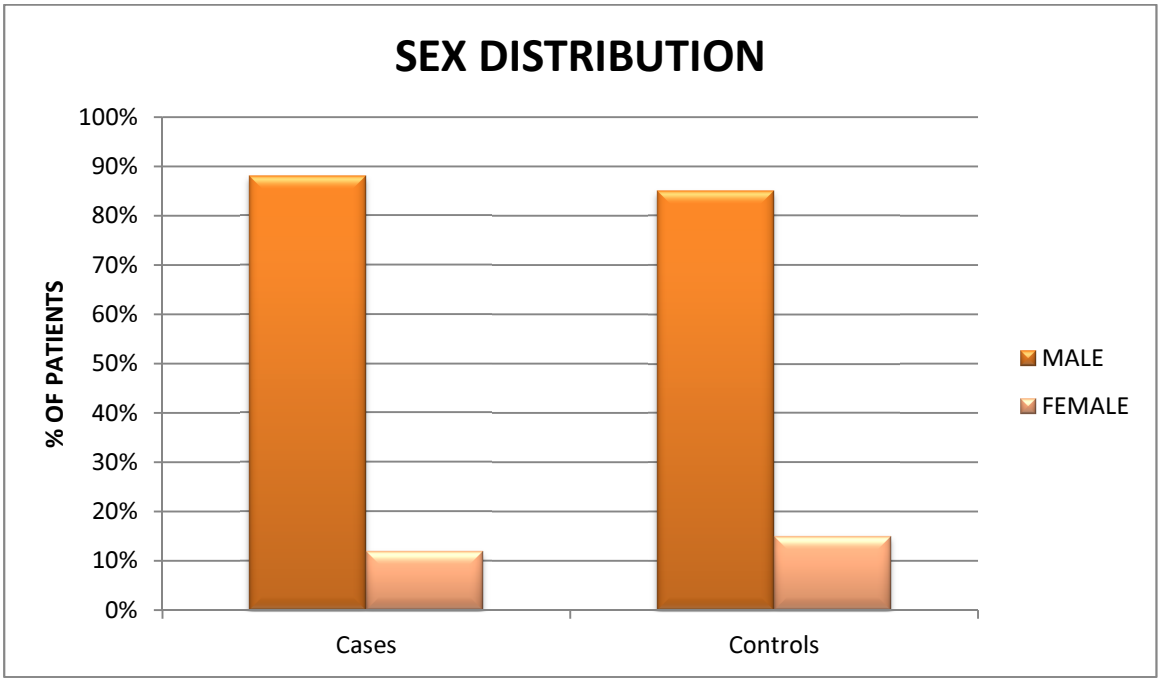
1. SPSS 15
2. Chi square tests

OBSERVATIONS AND RESULTS

Sex distribution:

Sex	No. of subjects	
	Cases	Controls
Male	44	17
Female	6	3

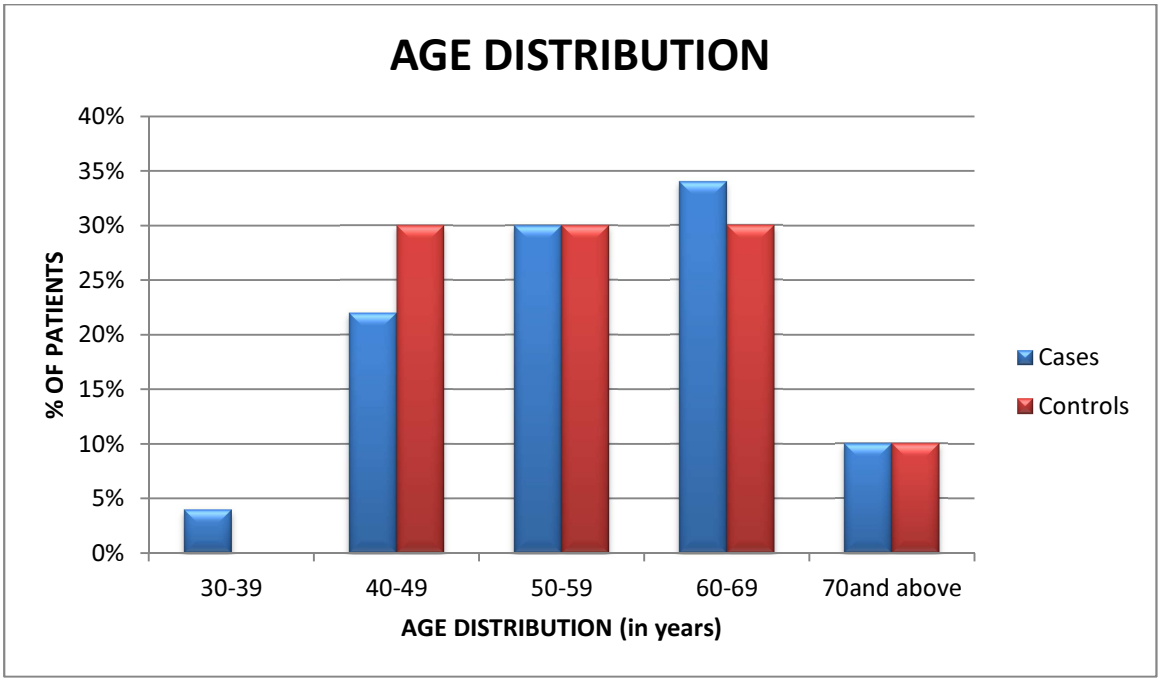
Out of 50 patients, 44(88%) were male patients and 6(12%) patients were female. Out of 20 controls, 17(85%) were male and 3(15%) were female.



Age Distribution:

Age distribution	No. of patients	
	Cases	Controls
30-39	2	0
40-49	11	6
50-59	15	6
60-69	17	6
70 and above	5	2

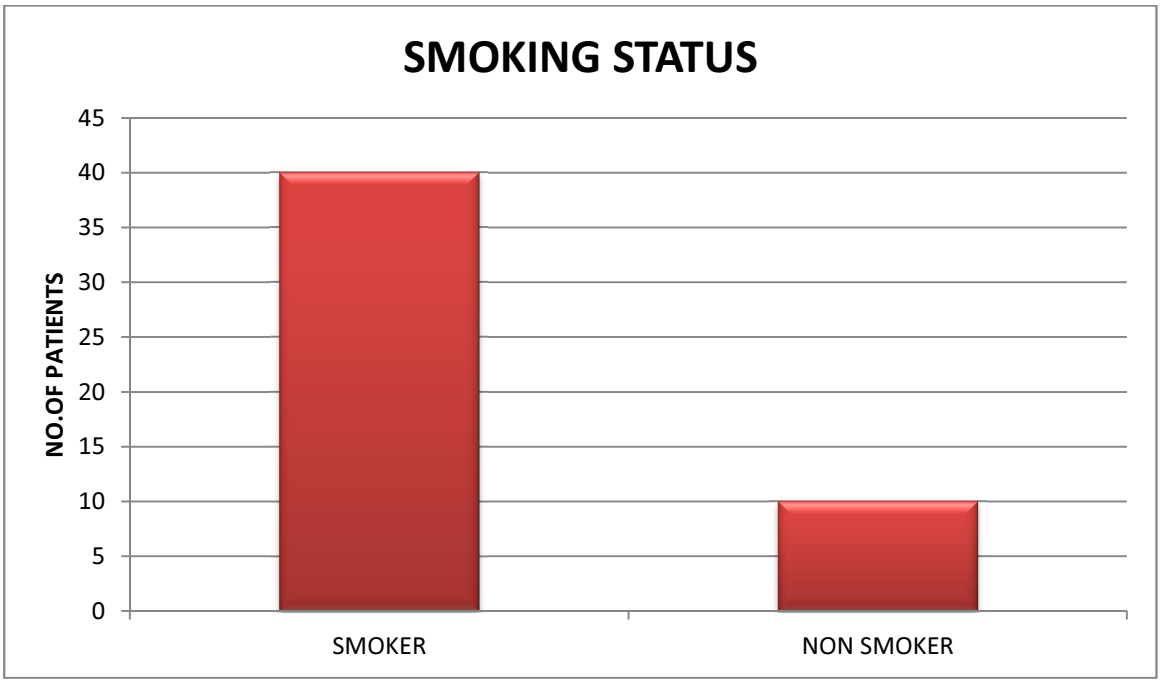
Among the 50 patients, majority of the patients (37 patients) were above the age of 50 years which accounted for 74% of total cases.



Smoking status:

Among 50 patients, 40(80%) were smokers and 10(20%) were non smokers. All 6 females were non smokers.

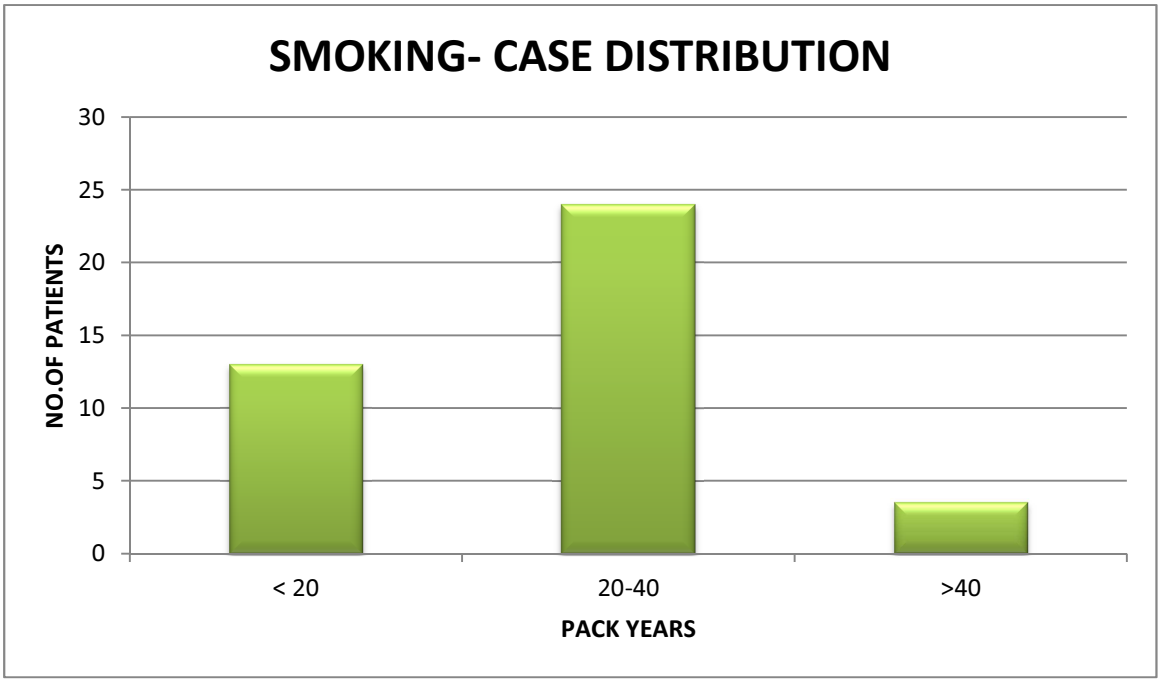
Smoking status	No. of patients
Smoker	40
Non smoker	10



Smoking - pack years:

Pack years	No. of patients
< 20	13
20-39	24
> 40	3

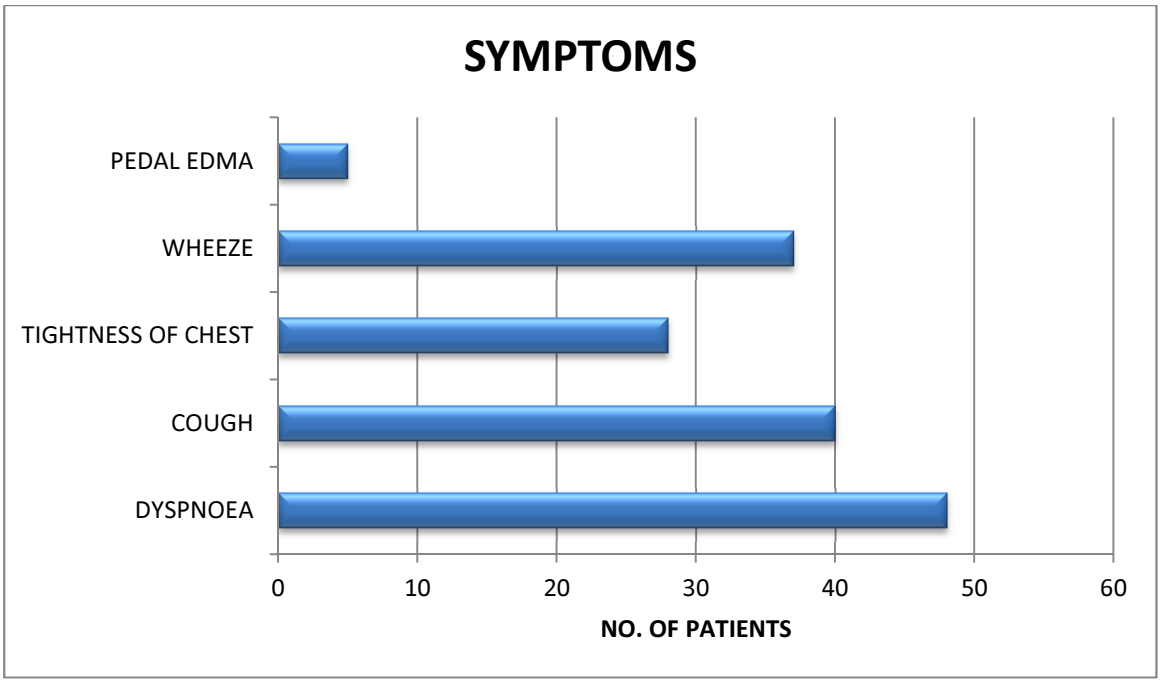
More than 50% (27 out of 40) of smokers had pack years of 20 and above.



Symptomatology:

Most common symptom observed in our study was dyspnoea (96%) followed by cough (80%). Clinical evidence of very severe COPD was present in 10% of cases.

Symptomatology	No. of patients
Dyspnoea	48
Cough	40
Tightness of chest	28
Wheeze	37
Pedal edema	5

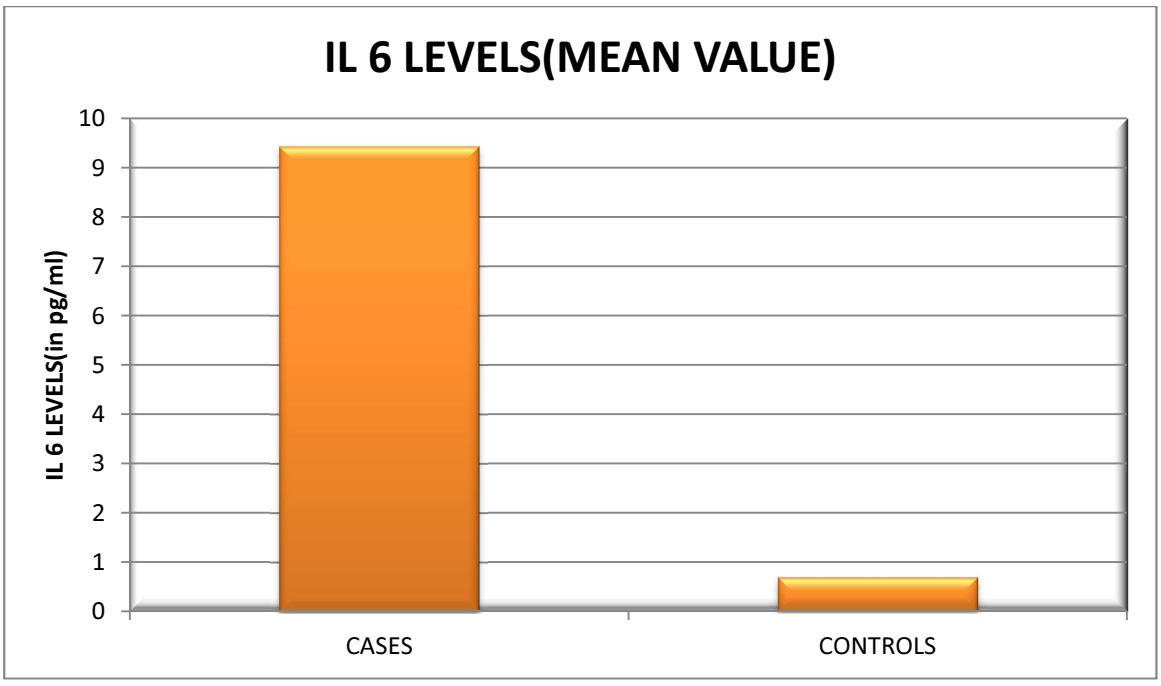


IL 6 levels comparison:

In our study, mean IL 6 levels were elevated (9.434pg/ml) in COPD patients compared to the controls (0.68pg/ml)

SUBJECTS	IL-6 LEVELS (MEAN)(pg/ml)
CASES	9.434
CONTROLS	0.68

By chi square test**, p value<0.001**.**

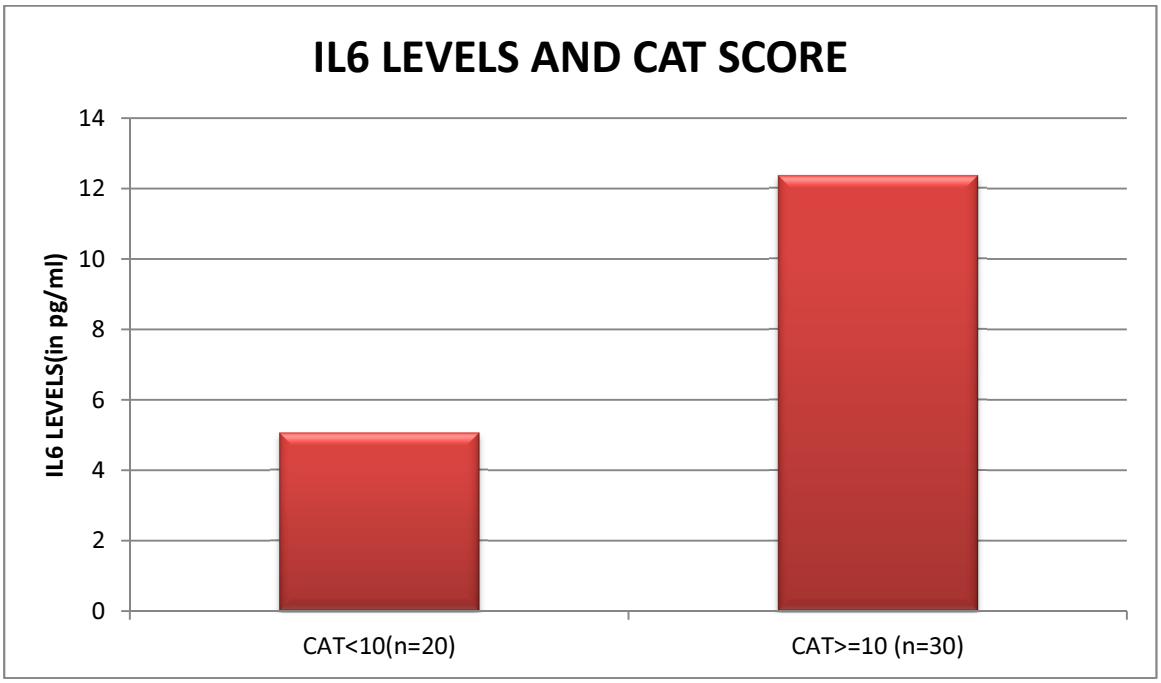


CAT score and IL 6 levels:

CAT score of less than 10 was observed in 20 patients. Mean IL 6 levels in the 20 patients was 5.05±1.72. It was much lower than the population of patients, (CAT score >=10, 30 patients) for whom the mean IL 6 levels were 12.35±3.49.

CAT SCORE	NO. OF PATIENTS	IL 6 LEVELS (MEAN VALUE) (pg/ml)
<10	20	5.05
>=10	30	12.35

By chi square test**, p value<0.001**.**

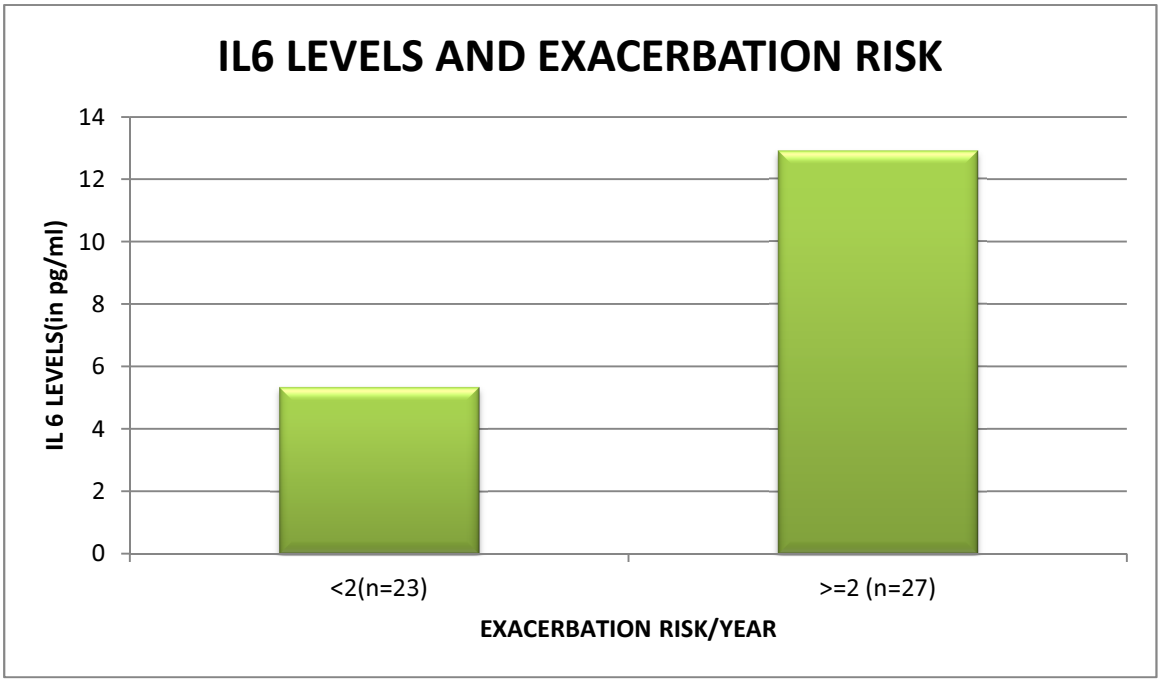


Exacerbation risk and IL 6 levels:

For patients with less than 2 exacerbations per year the mean IL 6 levels were 5.343±1.75. 27 patients had 2 or more exacerbations per year and had a mean IL 6 value of 12.91±3.23.

Exacerbation risk/year	NO. OF PATIENTS	IL 6 LEVELS (MEAN VALUE) (pg/ml)
<2	23	5.343
>=2	27	12.91

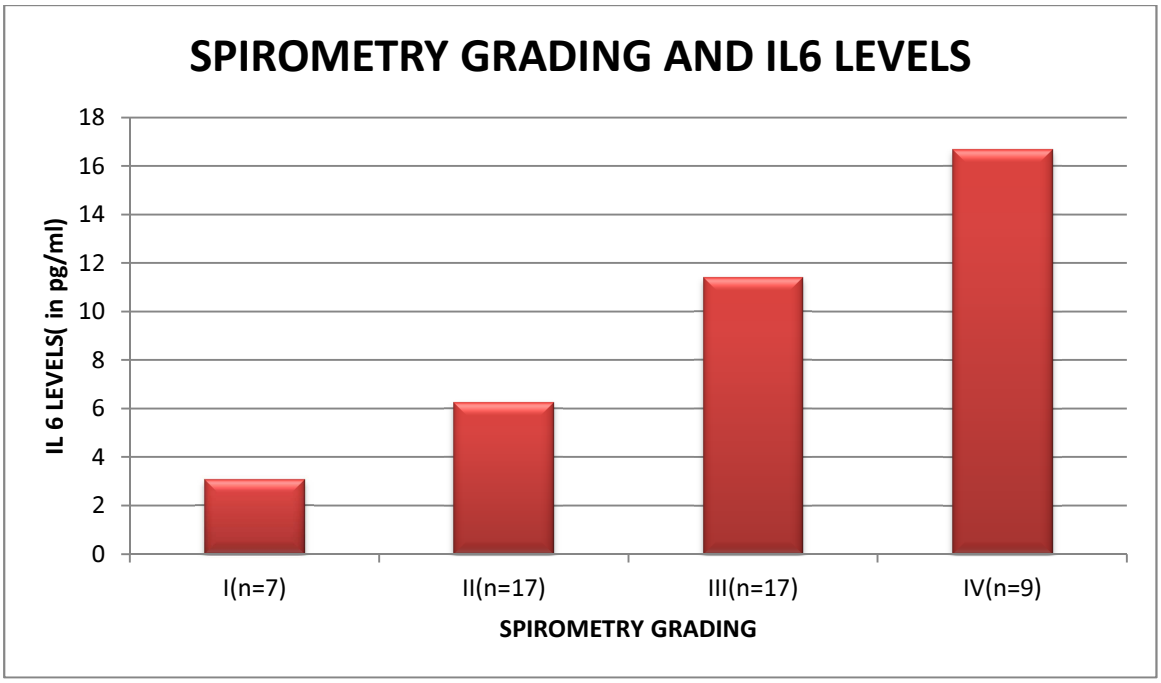
By chi square test, **p value<0.001**.**



Spirometry grading and IL6 levels:

Out of 50 patients, most number of patients were in the Grade II and GRADE III (34 patients); each grade had 17 patients. The mean IL 6 levels were greatest for grade IV with a mean value of 16.69. The mean IL 6 values were observed to increase in an exponential manner with each grade. Statistical significance was observed for the below values.

SPIROMETRY GRADING	NO. OF PATIENTS	IL 6 LEVELS (MEAN VALUE) (pg/ml)
I	7	3.06
II	17	6.29
III	17	11.4
IV	9	16.69



DISCUSSION

In our study of 50 cases, most of them were males with almost 90% of the total number of cases. This clearly shows the higher prevalence of COPD in males. The possible explanation is that smoking is more prevalent in males, thus re-emphasising the importance of smoking as a risk factor for COPD. The 6 females had neither family history of COPD nor young by age. They developed COPD possibly due to passive smoking or environmental pollutants. But actual cause remains obscure and unidentified.

In our study, maximum number of patients was in the age group of 60-69 years. Again emphasis is on the chronic nature of the disease and long history of smoking. None of our patients were below the age of 38.

Smoking history was present in 80% of cases, again stressing the role of smoking in COPD. Patients with a positive history of smoking were stratified on the basis of number of pack years. 48 % of patients had pack years between 20 and 40. A small proportion (6%) of patients had more than 40 pack years.as the pack years increased patients presented with more severe grades. The age of presentation was younger when compared to those with less number of pack years.

Patients with COPD presented with dyspnoea as the major symptom. Dyspnoea was present in almost 96% of cases. Dyspnoea was graded by modified MRC scale.42 % of patients presented with grade II dyspnoea. Cough was the second common symptom followed by wheeze. Evidence of cor pulmonale in the form of pedal oedema was present in 10% of cases thus classifying as very severe COPD as per the GOLD classification.

Serum IL 6 levels were compared between 50 cases and 20 controls .IL 6 levels were significantly elevated in patients with COPD. IL 6 elevation in COPD patients confirms the chronic inflammatory nature of the disease which has been already discussed.

Giarcia rio et al[70] (2010) demonstrated that inflammatory markers like IL 6, IL 8 and TNF α were elevated in COPD patients. An IL 6 value of 4.5 pg/ml was observed in COPD patients in the study compared to 9.343pg/ml in our study. In the study, most of them were males (82%) and the mean age group was around 64 similar to data in our study group.. However, age and sex did not influence the level of IL 6 in COPD patients.

CAT score obtained by questionnaire. 20 patients had CAT score of <10 and 30 patients had CAT score of 10 or more. IL 6 levels were significantly elevated in the group with higher CAT scores. Since CAT

scores are based on clinical symptoms and well-being of the patient, IL 6 levels can also be considered as marker of the underlying disease process and its clinical outcome.

Patients with fewer exacerbations(less than 2 per year) were 23 in number. IL 6 levels were lower in this group compared to the patient group which had 2 or more exacerbations per year. It is well known that number of exacerbations predict future exacerbations. With each exacerbation there is a decline in lung function and as the frequency of exacerbations increase, the lung function decline is also rapid. Thus IL6 can be used as predictor to assess the exacerbation risk and also decline in lung function.

ECLIPSE[71] study showed that IL 6 levels are associated with an increased risk of exacerbations. Abd Elmaksoud et al.(2010) demonstrated that higher IL 6 levels were associated with a rapid decline in lung function. Wedzikha et al[72]. showed that fibrinogen and serum IL 6 levels are increased with acute exacerbations of COPD.

Spirometry grading as per GOLD criteria showed that 34 % presented with grade II and an additional 34% presented with Grade III. Very severe COPD (Grade IV) was present in 18% of cases, IL 6 levels increased with increasing grade of COPD. The values were also statistically significant. Spirometric grading is a predictor of mortality in

COPD. As IL 6 levels correlate strongly with the degree of spirometry grading, it can be considered as reliable marker to predict mortality in COPD patients.

Various studies demonstrate that serum levels of IL 6 predict mortality and outcome of patients with COPD.

Abd Elmaksoud et al.(2010)[74] also correlated IL 6 levels with spirometric grading and showed highest IL 6 levels in grade III of COPD (grade IV patients were not included in the study). The mean IL6 levels in the study was 11.26 pg/ml compared to 11.4 pg/ml.

BOLD[73] study demonstrated an inverse relationship between FEV1 and IL 6 levels.

Thus IL 6 besides being an inflammatory marker has multiple roles in COPD patients. IL 6 as a marker in COPD patients parallels the clinical course, predicts exacerbation risk and predicts the decline in lung function. It also is a marker of disease severity and predicts morbidity and mortality in a given patient.

CONCLUSIONS

In our study on 50 cases of COPD, the following conclusions were made:

1. COPD is more common in males and is more common above the age of 50 years.
2. Smoking is an important risk factor for COPD as evidenced by the number of smokers and prevalence of high pack years in COPD patients.
3. Serum IL 6 levels are significantly elevated in COPD patients, not influenced by age or sex.
4. Serum IL 6 levels parallel the clinical course of the disease.
5. Serum IL 6 levels predict the risk of exacerbation and decline in lung function.
6. Serum IL 6 levels correlates with severity of the disease measured by spirometry.

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PROFORMA

SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN-6 LEVELS

Name: Age: Sex:

Address: Occupation:

Symptoms

- Dyspnea
- Cough
- Sputum production
- Chest discomfort
- Wheezing
- Abdominal distension
- Swelling of legs
- Weight loss
- Fatiguability

Past history:

- Diabetes mellitus
- Hypertension
- Coronary artery disease
- Bronchial asthma
- Tuberculosis

Personal history:

- Smoking

- Alcoholism

General examination::

Pulse:

Blood Pressure:

Systemic Examination:

CVS: RS: Abdomen: CNS:

COPD ASSESSMENT TEST SCORE:

Investigations:

Hemogram			**RFT**		
TC		cells/mm^3	Glucose (F)		mg/dl
DC			Glucose (PP)		mg/dl
ESR		mm/hr	Urea		mg/dl
Hb		g/dl	Creatinine		mg/dl
PCV		%	Na+		mEq/l
Platelets		lakhs/mm^3	K+		mEq/l
RBCs		million/mm^3			

SERUM INTERLEUKIN-6 LEVELS:

ECG:

Echo Cardiogram:

SPIROMETRY

SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS

Dissertation submitted in partial fulfillment of requirements for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH I

of

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SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS Dissertation submitted in partial fulfillment of requirements for M.D. DEGREE IN GENERAL MEDICINE BRANCH I of THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, INDIA. MADRAS MEDICAL COLLEGE, CHENNAI 600003 APRIL 2013 INTRODUCTION Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. It kills more than 3 million people every year, making it the 4th largest cause of death in the world. It has been estimated that by the year 2030, COPD will become the third biggest cause of death 1 . Half a million people die every year due to COPD in India. 2 COPD...

S.NO.	NAME	AGE	SEX	DYSPNOEA(mMRC)	COUGH	PEDAL EDEMA	WHEEZE	CHEST TIGHTNESS	SMOKING(PACK YEARS)	CAT SCORE	EXACERBATIONS /YEAR	SPIROMETRY GRADE	SERUM IL6 LEVELS(pg/ml)
1	KUPPUSAMY	56	M	3	P	A	P	P	22	24	2	3	12.6
2	AYYAVU	66	M	4	P	P	P	P	32	28	3	4	16.5
3	RAMARAJU	48	M	2	P	A	P	P	26	24	2	3	11
4	KARUPPANNAN	68	M	2	P	A	P	P	20	19	2	3	12.4
5	ANGAMMAL	55	F	1	P	A	A	A	0	4	1	1	3.6
6	JOSEPH	49	M	1	P	A	P	A	12	11	1	2	6.6
7	MUTUSAMY	51	M	2	P	A	P	A	14	7	2	2	4.8
8	RAJENDRAN	39	M	2	P	A	P	A	12	9	1	2	5.5
9	SELVARAJ	57	M	2	P	A	P	P	20	16	2	3	10.2
10	MOHAMAD IBRAHIM	62	M	2	A	A	P	P	0	12	1	2	5.8
11	MARI	58	M	3	P	A	P	P	30	26	3	4	17
12	PICHAYEE	51	F	1	P	A	P	A	0	6	1	2	5.9
13	CHANDRAN	45	M	2	P	A	P	A	24	9	1	2	7.5
14	RATHINAVEL	66	M	2	A	A	P	P	20	14	1	2	7.8
15	KRISHNASAMY	59	M	2	P	A	P	P	36	22	2	3	12.8
16	MALAIYAMMAL	47	F	0	P	A	A	A	0	4	0	1	3.2
17	KUMARAN	52	M	3	P	A	P	P	38	28	3	4	14.4
18	JEYAKUMAR	74	M	3	P	A	P	P	30	21	2	3	11.6
19	KABALI	44	M	1	A	A	P	A	0	5	0	1	2.5
20	RAJI	49	M	4	P	P	P	P	36	32	3	4	16.6
21	VENKATACHALAM	68	M	3	P	A	P	P	26	22	3	3	12
22	RAMAN	67	M	1	A	A	A	A	0	8	1	2	5.9
23	SUNDARAM	46	M	1	P	A	A	A	16	4	0	1	2.8
24	VELLAIYAN	76	M	4	A	A	P	P	42	30	4	4	18.5

25	PANDI	53	M	3	P	A	P	P	20	20	2	3	13
26	KUMARAVEL	68	M	3	P	P	P	P	36	28	2	4	15.6
27	PARAMESWARAN	56	M	1	P	A	A	A	14	2	0	1	2.8
28	SUBRAMANI	48	M	2	P	A	P	P	24	16	1	2	6.5
29	RAJASEKAR	55	M	2	P	A	P	P	30	18	2	3	10.6
30	KUPPAN	62	M	2	A	A	A	A	28	8	1	2	6.6
31	RAVI	47	M	2	P	A	P	P	36	22	2	3	11.1
32	VELU	63	M	1	A	A	A	A	20	4	1	1	3.5
33	SUPPAN	61	M	3	P	P	P	P	44	28	3	4	17.2
34	THIRUMOORTHI	58	M	3	P	A	P	P	32	16	2	3	10.4
35	SEVANTHI	43	F	0	P	A	A	A	0	4	1	2	6.6
36	SRIRANGAN	64	M	2	P	A	P	P	34	12	2	3	12.2
37	RAMESH	38	M	2	P	A	P	A	14	6	1	2	5.5
38	SULOCHANA	59	F	3	P	A	P	P	0	22	2	3	8.6
39	VELLAIAN	65	M	2	A	A	A	A	24	4	1	2	6.4
40	MANIKKAM	71	M	2	P	A	P	A	20	8	1	2	6.8
41	THANGADURAI	48	M	1	P	A	A	A	28	6	1	2	5.4
42	LOGANATHAN	66	M	2	A	A	A	P	41	12	2	3	10.6
43	ARUNACALAM	56	M	1	P	A	A	A	16	4	0	1	3
44	CINNAPONNU	62	F	2	P	A	P	P	0	22	2	3	12.6
45	MALAISAMY	67	M	2	P	P	P	P	35	22	2	4	16.6
46	DURAI	72	M	3	P	A	P	P	27	22	2	3	12.6
47	NANTHAGOBAL	69	M	1	A	A	A	A	29	4	1	2	8.2
48	RAJAN	55	M	2	P	A	P	A	36	16	2	3	9.5
49	SUBRAMANI	61	M	1	P	A	P	A	0	8	1	2	4.5
50	RAMAMOORTI	72	M	3	P	A	P	P	31	26	3	4	17.8
Total													50

S.NO	AGE	SEX	SERUM IL 6 LEVEL(pg/ml)
1	55	M	0.5
2	64	M	0.7
3	67	M	1.1
4	40	M	0.4
5	72	M	1.2
6	56	M	0.6
7	45	M	0.5
8	49	F	0.4
9	59	M	0.6
10	67	M	0.8
11	61	M	0.7
12	43	M	0.4
13	67	M	0.9
14	54	F	0.5
15	58	M	0.8
16	62	M	0.6
17	49	M	0.4
18	70	M	1.2
19	45	M	0.6
20	51	F	0.7

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SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS Dissertation submitted in partial fulfillment of requirements for M.D. DEGREE IN GENERAL MEDICINE BRANCH I of THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI, INDIA. MADRAS MEDICAL COLLEGE, CHENNAI 600003 APRIL 2013 INTRODUCTION Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. It kills more than 3 million people every year, making it the 4th largest cause of death in the world. It has been estimated that by the year 2030, COPD will become the third biggest cause of death 1 . Half a million people die every year due to COPD in India. 2 COPD...

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. K.S. Raja
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. K.S. Raja

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Severity of chronic obstructive pulmonary disease and its correlation with serum interleukin- 6 levels" No.35062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1. Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2. Prof. K. Ramadevi MD Prof of Biochemistry, MMC, Ch-3	-- Member
3. Prof. R. Nandhini MD Director, Inst. of Pharmacology ,MMC, Ch-3	-- Member
4. Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5. Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
6. Prof. A. Radhakrishnan MD Prof of Internal Medicine, MMC, Ch-3	-- Member

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

Sd/ Chairman & Other Members

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

Member Secretary, Ethics Committee

SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS CORRELATION WITH SERUM INTERLEUKIN 6 LEVELS

Dissertation submitted in partial fulfillment of requirements for

M.D. DEGREE IN GENERAL MEDICINE

BRANCH I

of

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY,
CHENNAI, INDIA.

MADRAS MEDICAL COLLEGE,