PLASMA FIBRINOGEN AND PLATELET MASS AS INDICATORS OF THE PROTHROMBOTIC AND SYSTEMIC INFLAMMATORY STATE IN COPD

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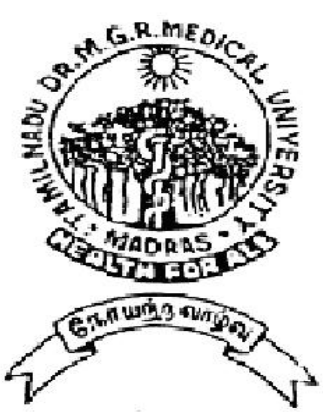

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CERTIFICATE

This is to certify that this dissertation titled "**PLASMA FIBRINOGEN AND PLATELET MASS AS INDICATORS OF THE PROTHROMBOTIC AND SYSTEMIC INFLAMMATORY STATE IN COPD"** submitted by **DR.R.RAMESH PRASANNA JEGANATHAN** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I**, Dr.R.RAMESH PRASANNA JEGANATHAN,** solemnly declare that the dissertation titled "**PLASMA FIBRINOGEN AND PLATELET MASS AS INDICATORS OF THE PROTHROMBOTIC AND SYSTEMIC INFLAMMATORY STATE IN COPD"** has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date: **Dr.R.RAMESH PRASANNA JEGANATHAN**

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CONTENTS

ABBREVIATIONS

COPD – chronic obstructive pulmonary disease

GOLD – Global initiative for chronic obstructive lung diseases

ESR:- Erythrocyte sedimentation rate

FEVI:- Forced expiratory volume in 1 second.

FVC:- The Forced vital capacity

FEV1%PRED:- The ratio of FEV1 to the predicted FEV1 expressed as percentage

PaO2:- Partial pressure of oxygen in arterial blood

BTS:- British Thoracic Society

MPV:- Mean platelet volume

ATIII: Antithrombin III

AFB:- Acid fast bacilli

DL_{CO}:- Diffusion capacity of the lung for carbon monoxide

INTRODUCTION

COPD is a disease of increasing public health importance around the world. GOLD estimates suggest that COPD will rise from the sixth to the third most common cause of death worldwide by 2020. Worldwide, COPD is the only leading cause of death that still has a rising mortality. Even though there have been significant advances in the understanding and management of COPD, the disease may be largely preventable, but it remains marginally treatable.

It is well known that COPD is a syndrome of progressive airflow limitation caused chronic inflammation of the airways and lung parenchyma. But it also produces significant systemic consequences.The role of systemic inflammation as evidenced by the rise in inflammatory markers is now being increasingly recognised to play an important role in the systemic effects. The systemic effects include cachexia, skeletal muscle dysfunction, cardiovascular disease, osteoporosis, depression, fatigue among many others.

It is also found that there is an ongoing hypercoagulable state in COPD. It is evidenced by the increased incidence of pulmonary thrombosis and coronary artery disease in these patients. The hypercoagulable state is being attributed to altered platelet functions and clotting system activation as has been shown by increased platelet size, high blood fibrinogen levels in patients with COPD.

It is also now recognised that systemic inflammation could contribute to the declining lung function and also to the increased number of acute exacerbations as shown by recent reports. Existing therapies for COPD are grossly inadequate. None has been shown to slow the relentless progression of the disease. Therefore the current direction is regarding the attenuation of systemic inflammation which may offer new perspectives in the management of COPD. New molecules to counteract the underlying inflammation and destruction of this relentlessly progressive chronic debilitating disease are desired.

REVIEW OF LITERATURE

COPD

Chronic obstructive pulmonary disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international collaborative effort to improve awareness, diagnosis, and treatment of COPD, as a disease state characterized by airflow limitation that is not fully reversible. COPD includes emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli; chronic bronchitis, a clinically defined condition with chronic cough and phlegm; and small airways disease, a condition in which small bronchioles are narrowed.[1]

RISK FACTORS:-

CIGARETTE SMOKING

Longitudinal studies have shown accelerated decline in the volume of air exhaled within the first second of the forced expiratory maneuver (FEV_1) in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as pack-years (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males.[1]

However, only 10–20% of smokers develop clinically significant COPD.[3] Pipe and cigar smokers have higher morbidity and mortality rates for COPD than non-smokers, although their rates are lower than cigarette smokers.[4] The BTS guidelines suggest that most patients with COPD have at least a 20 pack-year smoking history.[5]

In non-smokers the FEV1 begins to decline at 30–35 years of age, and this may occur earlier in smokers.[6] Although pack-years of cigarette smoking is the most highly significant predictor of FEV_1 , only 15% of the variability in FEV_1 is explained by pack-years. This finding suggests that additional environmental and/or genetic factors contribute to the impact of smoking on the development of airflow obstruction.[1]

RESPIRATORY INFECTIONS:-

Although respiratory infections are important causes of exacerbations of COPD, the association of both adult and childhood respiratory infections to the development of COPD remains to be proven.[1] One study in Salt Lake City did find an association between lower respiratory tract infection and an accelerated decline in FEV1, but in a group who already had established COPD.[7]

OCCUPATIONAL EXPOSURES:-

Although nonsmokers in these occupations developed some reductions in FEV_1, the importance of dust exposure as a risk factor for COPD, independent of cigarette smoking, is not certain. [1]

AMBIENT AIR POLLUTION:-

The relationship of air pollution to chronic airflow obstruction remains unproven. Prolonged exposure to smoke produced by biomass combustion—a common mode of cooking in some countries—also appears to be a significant risk factor for COPD among women in those countries.[1]

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE:-

In utero tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions in COPD remains uncertain.[1]

AIRWAY RESPONSIVENESS AND COPD:-

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli is one of the defining features of asthma. However, many patients with COPD also share this feature of airway

hyperresponsiveness. Airway hyperresponsiveness is a risk factor for COPD.[1]

GENETIC CONSIDERATIONS:-

Severe α_1 antitrypsin (α_1AT) deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.[1]

NATURAL HISTORY:-

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth, and the baseline lung function of the individual; other environmental factors may have similar effects. Although rare individuals may demonstrate precipitous declines in pulmonary function, most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence, followed by a gradual decline with aging.

Individuals appear to track in their quartile of pulmonary function based upon environmental and genetic factors that put them on different tracks. The risk of eventual mortality from COPD is closely associated with reduced levels of FEV_1. Smoking cessation at an earlier age provides a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. Rate

of decline of FEV1 increases with increasing numbers of cigarettes smoked.[1]

The strongest predictors of survival in patients with COPD are age and baseline FEV1.[8] Less than 50% of patients whose FEV1 has fallen to 30% of predicted are alive 5 years later .[9] Other unfavourable prognostic factors include severe hypoxaemia, a high pulmonary arterial pressure and low DLCo, which become apparent in patients with severe disease.[4,9] The factors that favour improved survival are stopping smoking and a large response to bronchodilator.[2]

EFFECTS OF SMOKING CESSATION:-

After smoking cessation these subjects have a rate of decline in FEV1 that approaches that found in people who have never smoked.[10] Short-term studies of stopping smoking have shown improvement in small airway tests, such as the single-breath nitrogen test, although changes in maximum expiratory flow–volume curves have been variable.[11] However, a clear improvement in survival has been demonstrated in exsmokers with advanced disease .[8]

PATHOPHYSIOLOGY:-

AIRFLOW OBSTRUCTION:-

Airflow limitation, also known as airflow obstruction, is typically determined by spirometry, which involves forced expiratory maneuvers after the subject has inhaled to total lung capacity . Key phenotypes obtained from spirometry include FEV_1 and the total volume of air exhaled during the entire spirometric maneuver (FVC). Patients with airflow obstruction related to COPD have a chronically reduced ratio of FEV_1/FVC. In contrast to asthma, the reduced FEV_1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common.

In normal lungs, as well as in lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides progressively less elastic recoil and because the cross-sectional area of the airways falls, raising the resistance to airflow. The decrease in flow coincident with decreased lung volume is readily apparent on the expiratory limb of a flow-volume curve. In the early stages of COPD, the abnormality in airflow is only evident at lung volumes at or below the functional residual capacity (closer to residual volume), appearing as a scooped-out lower part of the descending limb of

the flow-volume curve. In more advanced disease the entire curve has decreased expiratory flow compared to normal.[1]

HYPERINFLATION :-

In COPD there is "air trapping" (increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation (increased total lung capacity) late in the disease.[1]

GAS EXCHANGE:-

Although there is considerable variability in the relationships between the FEV_1 and other physiologic abnormalities in COPD, certain generalizations may be made. The Pa_{O2} usually remains near normal until the FEV_1 is decreased to ~50% of predicted, and even much lower FEV_1s can be associated with a normal Pa_{O2}, at least at rest. An elevation of Pa_{CO2} is not expected until the FEV_1 is <25% of predicted and even then may not occur. Pulmonary hypertension severe enough to cause cor pulmonale and right ventricular failure due to COPD occurs only in those individuals who have marked decreases in FEV_1 (<25% of predicted) together with chronic hypoxemia (Pa_{O2} <55 mmHg), although earlier in the course some elevation of pulmonary artery pressure, particularly with exercise, may occur.[1]

PATHOGENESIS:-

ELASTASE & ANTIELASTASE HYPOTHESIS:-

This hypothesis was based on the clinical observation that patients with genetic deficiency in α_1AT, the inhibitor of the neutrophil elastase, were at increased risk of emphysema, and that instillation of elastases, including neutrophil elastase, to experimental animals results in emphysema.

Neutrophils sequester in the pulmonary capillaries initially as a result of the oxidant effect of cigarette smoke, which decreases neutrophil deformability. Activated neutrophils adhere to the endothelial cells and subsequently migrate into the airspaces. Oxidants, either directly from cigarette smoke or released from activated airspace neutrophils, inactivate antiproteases such as alpha -1 antitrypsin, reducing its ability to bind to and hence inactivate proteases, particularly elastase. This allows active elastase to enter the lung interstitium and bind to and destroy elastin, causing destruction and enlargement of the distal airspace walls. [2]

DECREASED ANTIPROTEASE FUNCTION:-

A critical event in the protease–antiprotease theory of the pathogenesis of emphysema is the concept of a functional deficiency of alpha-1antitrypsin in the airspaces produced by smoking due to oxidation of the methionine-358 residue at the active site of the alpha-1AT molecule. This can occur by a direct oxidative effect of cigarette smoke or by oxidants released from activated airspace leucocytes.[12]

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS :-

Macrophages patrol the lower airspace under normal conditions. Upon exposure to oxidants from cigarette smoke, histone deacetylase-2 is inactivated, shifting the balance toward acetylated or loose chromatin, exposing nuclear factor κB sites and resulting in transcription of matrix metalloproteinase-9, proinflammatory cytokines interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α); this leads to neutrophil recruitment. Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin also serve as a macrophage chemokine, fueling this destructive positive feedback loop.

Surprisingly, in end-stage lung disease, long after smoking cessation there remains an exuberant inflammatory response, suggesting that mechanisms of cigarette smoke-induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation. [1]

COPD AS A SYSTEMIC DISEASE:-

Although the traditional paradigm is that patients with COPD die predominantly from progressive respiratory failure, large clinical studies have demonstrated that the leading cause of mortality in the overall COPD population (regardless of severity) is ischemic heart disease.[13,14]

Many population-based studies have evaluated the effect of reduced lung function on cardiovascular morbidity and mortality.[13,14] Although there is some heterogeneity of results across the studies, they uniformly demonstrate that reduced FEV_1 increases the risk of cardiovascular mortality by approximately two-fold relative to those with normal (or preserved) FEV_1 values, even after taking into account smoking history. Even among nonsmokers, reduced FEV_1 is a powerful risk factor for poor cardiovascular outcomes.[14] Indeed, FEV_1 may be as important as cholesterol is in predicting cardiovascular mortality in the general population.[14] According to the Lung Health Study, a 10% decrement in FEV_1 among COPD patients is associated with an

approximate 30% increase in the risk of deaths from cardiovascular diseases.[14] Reduced FEV_1 is also an important independent risk factor for thromboembolic disease, sudden death, arrhythmias, heart failure, and stroke.[15] Other systemic effects include cachexia, skeletal muscle dysfunction, cardiovascular disease, osteoporosis, depression, fatigue among many others. Polycythemia is uncommon in COPD, occurring in 5% of patients, and is not associated with greater hypoxemia or any other important clinical expression of the disease.[44]

SYSTEMIC INFLAMMATION IN COPD:

There is growing evidence that persistent low-grade systemic inflammation is present in COPD and that this may contribute to the pathogenesis of atherosclerosis and cardiovascular disease among COPD patients.[16]

In COPD patients, the nidus for the low-grade systemic inflammation is likely the airways. There are compelling data to indicate the existence of prominent inflammation in the small airways of COPD patients. The severity of the inflammation corresponds to the severity of airflow obstruction and patient symptoms.[17] There are also inflammatory changes within pulmonary vessels and alveolar tissues.[17] Cigarette smoke and other noxious environmental agents, which are causative factors for

COPD genesis, directly stimulate alveolar macrophages, bronchial epithelial cells, and other cells (like neutrophils) to release various proinflammatory cytokines and chemokines.[18] Some of these molecules have a direct "toxic" effect on tissues, whereas others act as secondary messengers to recruit and activate other inflammatory cells to release other pro-inflammatory mediators, thereby amplifying the original inflammatory signal and promoting tissue damage. Once the pulmonary inflammation becomes firmly established, the inflammatory signals may then spill over into the general circulation, creating a state of low-grade systemic inflammation.[16]

Release of inflammatory mediators and activated inflammatory cells such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) into the systemic circulation is associated with reduced lung function and is also believed to play a role in systemic diseases seen in association with COPD. Some systemic inflammatory markers in COPD include TNF-α, several interleukins, lipopolysaccharide binding protein, soluble TNF-α receptors, leukocytes, and acute phase proteins such as C-reactive protein (CRP) and fibrinogen.[19,20,21]

There may be other pathways by which COPD patients may experience poor cardiovascular outcomes. Heindl et al.[22] demonstrated that patients with chronic respiratory failure and hypoxia had elevated

sympathetic nervous activity compared with the control population. Interestingly, in their study, correction of hypoxia with supplemental oxygen therapy attenuated, but did not normalize, the sympathetic nervous activity of these patients, suggesting the potential role of other factors in this process. Administration of ß-2 adrenergic or anticholinergic bronchodilators may further increase the sympathetic nervous activity of COPD patients and thereby amplify their risk for poor cardiovascular events.[23] Indeed, epidemiologic studies and clinical trials have shown that these medications may increase the risk of cardiovascular morbidity and mortality by ~50%-100%.[24,25,26]

Increased systemic inflammation is also a risk factor COPD exacerbations. Elevated fibrinogen levels is an independent risk factor for exacerbations of COPD. [21] In COPD, airway and systemic inflammation markers increase over time. High levels of these markers are associated with a faster decline in lung function.[27]

Fibrinogen in the lungs can (i) inactivate pulmonary surfactant, causing increased surface-tension relationships in the distal airways, (ii) promote the expression of molecules that induces airway fibrosis and narrowing, and (iii) activate plasminogen activator inhibitor type-1 leading to excess fibrin deposition in the airways and airway narrowing.

These properties of fibrinogen suggest that it is more than an epiphenomenon; rather it is involved in the causal pathways.[28]

There are other studies which show that chronic obstructive airway disease patients have altered platelet functions and clotting system activation.[29,30] In particular, it has been shown that there is a shortened platelet half life, increased platelet size, increased platelet aggregation, high levels of blood fibrinogen and *in vitro* and *in vivo* platelet activation in these patients. Increased size of the platelets could be because of hypoxia causing bone marrow stimulation resulting in secretion of larger platelets, or it could be because of increased sequestration of smaller platelets with larger platelets remaining in circulation. Larger the platelets, more is the platelet activity resulting in increased platelet aggregation and release of active mediators which can cause endothelial cell injury.[29,30] Thrombopoiesis may be stimulated by IL-6 as a result of systemic inflammation.[31] In COPD patients there is a negative correlation between MPV and PaO2.[32] There is also lower ATIII in addition to higher platelet mass and fibrinogen.[33]

PULMONARY CIRCULATION:-

Among the earliest changes in the pulmonary vasculature that develop as airflow limitation worsens is thickening of the intima of the small pulmonary arteries .[34] Medial hypertrophy then develops in the

muscular pulmonary arteries in those patients who develop pulmonary arterial hypertension . Peripheral airway inflammation in patients with COPD may be associated with pulmonary arterial thrombosis .[35]

When chronic hypoxaemia develops, the consequent pulmonary arterial hypertension is associated with right ventricular hypertrophy.

CLINICAL FEATURES:

The characteristic symptoms of COPD are breathlessness on exertion, sometimes accompanied by wheeze and cough, which is often but not invariably productive. Most patients have a smoking history of at least 20 packyears before symptoms develop, commonly in the fifth decade. However, when the FEV1 has fallen to 30% or less of the predicted values (equivalent in an average man to an FEV1 of around 1L), breathlessness is usually present on minimal exertion . Wheeze is common but not specific to COPD.[2]

Psychiatric morbidity, particularly depression, is common in patients with severe COPD, reflecting the social isolation and the chronicity of the disease. Sleep quality is impaired in advanced COPD , which may contribute to the impaired neuropsychiatric performance.

In the early stages of COPD, patients usually have an entirely normal physical examination. In patients with more severe disease, the physical examination is notable for a prolonged expiratory phase and expiratory wheezing. In addition, signs of hyperinflation include a barrel

chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion.

Advanced disease may be accompanied by systemic wasting, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF-α). Such wasting is an independent poor prognostic factor in COPD.[1]

CLASSIFICATION OF COPD: [1]

Gold Criteria for COPD Severity			
GOLD Stage	**Severity**	**Symptoms**	**Spirometry**
0	At Risk	Chronic cough, sputum production	Normal
I	Mild	With or without chronic cough or sputum production	$FEV_1/FVC<0.7$and $FEV_1 \geq 80\%$predicted
II	Moderate	With or without chronic cough or sputum production	$FEV_1/FVC <0.7$ and $50\% \leq FEV_1 < 80\%$predicted
III	Severe	With or without chronic cough or sputum production	$FEV_1/FVC <0.7$ and $30\% \leq FEV_1 < 50\%$predicted
IV	Very Severe	With or without chronic cough or sputum production	$FEV_1/FVC <0.7$ and $FEV_1 <30\%$ predicted *or* $FEV_1 <50\%$ predicted with respiratory failure or signs of right heart failure

CHRONIC OBSTRUCTIVE PULMONARY DISEASE: TREATMENT

STABLE PHASE COPD:-

Only three interventions—smoking cessation, oxygen therapy in chronically hypoxemic patients, and lung volume reduction surgery in selected patients with emphysema—have been demonstrated to influence the natural history of patients with COPD. [1]

PHARMACOTHERAPY:-

SMOKING CESSATION:-

It has been shown that middle-aged smokers who were able to successfully stop smoking experienced a significant improvement in the rate of decline in pulmonary function, returning to annual changes similar to that of nonsmoking patients. There are two principal pharmacologic approaches to the problem: bupropion, originally developed as an antidepressant medication, and nicotine replacement therapy. The latter is available as gum, transdermal patches, inhaler, and nasal spray.[1]

BRONCHODILATORS:-

In general, bronchodilators are used for symptomatic benefit in patients with COPD. The inhaled route is preferred for medication delivery as the incidence of side effects is lower than that seen with the use of parenteral medication delivery.[1]

ANTICHOLINERGIC AGENTS:-

While regular use of ipratopium bromide does not appear to influence the rate of decline of lung function, it improves symptoms and produces acute improvement in FEV_1. Tiotropium, a long-acting anticholinergic, has been shown to improve symptoms and reduce exacerbations. [1]

BETA AGONISTS:-

These provide symptomatic benefit.Long-acting inhaled β agonists, such as salmeterol, have benefits comparable to ipratopium bromide. Their use is more convenient than short-acting agents. The addition of a β agonist to inhaled anticholinergic therapy has been demonstrated to provide incremental benefit.[1]

INHALED CORTICOSTEROIDS:-

Inhaled glucocorticoids reduce exacerbation frequency by ~25%. A more recent meta-analysis suggests that they may also reduce mortality by ~25%. A definitive conclusion regarding the mortality benefits awaits the results of ongoing prospective trials. A trial of inhaled glucocorticoids should be considered in patients with frequent exacerbations, defined as two or more per year, and in patients who demonstrate a significant amount of acute reversibility in response to inhaled bronchodilators.[1]

ORAL GLUCOCORTICOIDS:-

The chronic use of oral glucocorticoids for treatment of COPD is not recommended because of an unfavorable benefit/risk ratio.[1]

THEOPHYLLINE:-

Theophylline produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. [1]

OXYGEN:-

Supplemental O_2 is the only pharmacologic therapy demonstrated to decrease mortality in patients with COPD. For patients with resting hypoxemia (resting O_2 saturation <88% or <90% with signs of pulmonary hypertension or right heart failure), the use of O_2 has been demonstrated to have a significant impact on mortality. Patients meeting these criteria should be on continual oxygen supplementation, as the mortality benefit is proportional to the number of hours/day oxygen is used. Various delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.[1]

OTHER AGENTS:-

Specific treatment in the form of intravenous α_1AT augmentation therapy is available for individuals with severe α_1AT deficiency. Although biochemical efficacy of α_1AT augmentation therapy has been shown, a randomized controlled trial of α_1AT augmentation therapy has never proven the efficacy of augmentation therapy in reducing decline of pulmonary function. Eligibility for α_1AT augmentation therapy requires a serum α_1AT level <11 μM (approximately 50 mg/dL). Typically, Pi^Z individuals will qualify, although other rare types associated with severe deficiency (e.g., null-null) are also eligible. Since only a fraction of individuals with severe α_1AT deficiency will develop COPD, α_1AT augmentation therapy is not recommended for severely α_1AT-deficient persons with normal pulmonary function and a normal chest CT scan. [1]

NONPHARMACOLOGIC THERAPIES:-

GENERAL MEDICAL CARE:-

Patients with COPD should receive the influenza vaccine annually. Polyvalent pneumococcal vaccine is also recommended, although proof of efficacy in this patient population is not definitive.

PULMONARY REHABILITATION:-

This refers to a treatment program that incorporates education and cardiovascular conditioning. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6–12-month period.

LUNG VOLUME REDUCTION SURGERY (LVRS):-

Patients are excluded if they have significant pleural disease, a pulmonary artery systolic pressure >45 mmHg, extreme deconditioning, congestive heart failure, or other severe comorbid conditions. Recent data demonstrate that patients with an FEV_1 <20% of predicted and either diffusely distributed emphysema on CT scan or DL_{CO} <20% of predicted have an increased mortality after the procedure and thus are not candidates for LVRS.

LUNG TRANSPLANTATION :-

Current recommendations are that candidates for lung transplantation should be <65 years; have severe disability despite maximal medical therapy; and be free of comorbid conditions such as liver, renal, or cardiac disease.[1]

EXACERBATIONS OF COPD:-

Exacerbations are commonly considered to be episodes of increased dyspnea and cough and change in the amount and character of sputum. The frequency of exacerbations increases as airflow obstruction increases; patients with moderate to severe airflow obstruction [GOLD stages III,IV] have 1–3 episodes per year.

PRECIPITATING CAUSES AND STRATEGIES TO REDUCE FREQUENCY OF EXACERBATIONS:-

Bacterial infections play a role in many, but by no means all, episodes. Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a significant minority of instances (20–35%), no specific precipitant can be identified. Despite the frequent implication of bacterial infection, chronic suppressive or "rotating" antibiotics are not beneficial in patients with COPD. [1]

TREATMENT OFACUTE EXACERBATIONS:-

BRONCHODILATORS:-

Typically, patients are treated with an inhaled β agonist, often with the addition of an anticholinergic agent. Patients are often treated initially with nebulized therapy, as such treatment is often easier to administer in older patients or to those in respiratory distress. [1]

ANTIBIOTICS:-

Bacteria frequently implicated in COPD exacerbations include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. In addition, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are found in 5–10% of exacerbations. The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above pathogens as well as the patient's clinical condition.[1]

GLUCOCORTICOIDS:-

Among patients admitted to the hospital, the use of glucocorticoids has been demonstrated to reduce the length of stay, hasten recovery, and reduce the chance of subsequent exacerbation or relapse for a period of up to 6 months.One study demonstrated that 2 weeks of glucocorticoid therapy produced benefit indistinguishable from 8 weeks of therapy. The

GOLD guidelines recommend 30–40 mg of oral prednisolone or its equivalent for a period of 10–14 days. [1]

OXYGEN:-

Supplemental O_2 should be supplied to keep arterial saturations > 90%. Hypoxic respiratory drive plays a small role in patients with COPD. Studies have demonstrated that in patients with both acute and chronic hypercarbia, the administration of supplemental O_2 does not reduce minute ventilation. It does, in some patients, result in modest increases in arterial Pa_{CO2}, chiefly by altering ventilation-perfusion relationships within the lung. This should not deter practitioners from providing the oxygen needed to correct hypoxemia.[1]

MECHANICAL VENTILATORY SUPPORT:-

The initiation of noninvasive positive pressure ventilation (NIPPV) in patients with respiratory failure, defined as Pa_{CO2} >45 mmHg, results in a significant reduction in mortality, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status or inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burns.

Invasive (conventional) mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercapnia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. For patients age >65 admitted to the intensive care unit for treatment, the mortality doubles over the next year to 60%, regardless of whether mechanical ventilation was required.[1]

AIMS AND OBJECTIVES

The aims of the study were as follows-

1.To study the plasma fibrinogen level in patients with COPD

2.To study the mean platelet volume in patients with COPD

3.To study the correlation between plasma fibrinogen level and mean platelet volume and severity of COPD

MATERIALS AND METHODS

THE STUDY DESIGN: CASE CONTROL STUDY

PERIOD OF STUDY: JUNE 2008 TO JUNE 2009

MATERIALS/SELECTION OF STUDY SUBJECTS: OUTPATIENTS AND INPATIENTS VISITING THE MEDICAL AND THORACIC MEDICINE DEPARTMENT AND ON HEALTHY VOLUNTEERING CONTROLS.

ETHICAL CLEARANCE: ETHICAL CLEARANCE OBTAINED

CONSENT : INFORMED CONSENT OBTAINED FROM CASES AND CONTROLS

CONFLICT OF INTEREST : NIL

FINANCIAL SUPPORT: NIL

FOR CASES:-

INCLUSION CRITERIA:-

1. Male patients with Chronic obstructive pulmonary disease (FEV1/FVC <70%)
2. Ex- smokers (who has quit smoking for > 15 years)

EXCLUSION CRITERIA:-

1. Patients in Acute exacerbation
2. Bronchial asthma (improvement of FEV1 by >15%after bronchodilator suggesting reversibility of airflow obstruction)
3. Restrictive lung diseases (FVC/FEV1 ≥ 70%; Predicted FEV1% < 80%)
4. Pulmonary tuberculosis
5. Bronchiectasis
6. Malignancies
7. Acute infections
8. Inflammatory disorders (eg.,Rheumatoid arthritis, glomerulonephritis)
9. Cardiac failure
10. Acute Myocardial infarction , Acute stroke
11. Significant trauma
12. Patients refusing consent

FOR CONTROLS :-

INCLUSION CRITERIA:-

1. Males aged > 18 years
2. Non smokers

EXCLUSION CRITERIA:-

1. Presence of Systemic illness
2. Past H/O tuberculosis or respiratory diseases
3. Presence of respiratory ailments
4. Those refusing consent

METHODS:-

A total number of 90 cases and 80 controls were examined out of which 75 cases and 75 controls were included in the study as per inclusion and exclusion criteria.

In the cases group, detailed history was elicited from the patients including the number of acute exacerbations (defined as episodes of increased dyspnea and cough and change in the amount and character of sputum)[1] in the past 12 months and they were classified by spirometric measurements of FEV1/FVC & FEV1% Predicted into four groups – stage I, stage II, stage III, and stage IV according to GOLD classification of COPD.[1] Routine blood investigations, chest x-ray, were done and their plasma fibrinogen, mean platelet volume, PaO2 were measured. Echocardiographic evaluation was also done. Mean platelet volume was measured by automatic cell analyzer.

In the control group, after eliciting detailed history, FEV/FVC, FEV1% Predicted were calculated using spirometry. Routine blood investigations were done and their plasma fibrinogen, mean platelet volume, PaO2 measurements were measured.

FEV1:- Forced expiratory volume in 1 second (FEV1) is the volume of air that can be expelled from maximum inspiration in the first second.

FVC (Forced vital capacity) :- The Forced vital capacity (FVC) of the lung is the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration.

The FEV1/FVC ratio is the FEV1 expressed as a percentage of the FVC is the proportion of the vital capacity inhaled in the first second. It distinguishes between reduced FEV1 due to restricted lung volume and that due to obstruction. Obstruction is defined as an FEV1/FVC ratio of <70%

FEV1% Predicted :- It is the ratio of FEV1 to the predicted FEV1 expressed as percentage. Predicted FEV1is a reference value based on age, height, sex, smoking behaviour and race.

SPIROMETRIC MEASUREMENTS:-

The patient is made seated or to stand. It is seen to it that the patient is comfortable. All restricting clothing is loosened or removed. The noseclip is applied with a tissue. The mouthpiece is placed in the mouth, chin slightly elevated, the neck stretched, and the patient is allowed to get accustomed to breathing into the apparatus. When the patient reaches the end of a normal expiration patient is asked to take a slow deep breath. Without the patient making pause at the level of the maximum inspiration (total lung capacity), the patient is asked to blow as hard and as fast as he can. And while the patient blows out he is encouraged to blow longer. Particularly in patients with obstructive lung disease, an effort should be made to extend the expiratory effort to 6 seconds or more. The trunk and head is kept upright throughout the maneuver. The mouthpiece is taken out of the patient's mouth but the noseclip is left attached. The patient is allowed to take rest for a short time (15-30s) and explained in what respect the maneuver needs to be improved, or reassured if it was properly performed. After a sufficiently break the maneuver is repeated.

The largest value of three technically satisfactory maneuvers is reported. The FVC and the FEV1 reported should not be different by more than 150ml from the next largest FVC/ FEV1, or 100ml if the FVC

is 1.0 L or less. If the difference is larger upto 8 maneuvers is performed. 4 puffs of 100μg inhaled salbutamol is administered. Then spirometry is repeated 20 minutes after administration of drug. In adults an increase in FEV1% by 12% of the initial value is regarded as a significant bronchodilator response which is seen in bronchial asthma.

The individuals who had FEV1/FVC values less than 70% were diagnosed as COPD according to GOLD 2004 guidelines. They were staged by their FEV1% Predicted values according to GOLD classification of COPD.

Ex- smokers (who has quit smoking >15 years) were selected because smokers can have elevated fibrinogen level . The elevated fibrinogen level takes 15 years to fall to normal values after smoking cessation.[36,37,38] So, elevated fibrinogen level in COPD patients who are ex- smokers (who has quit smoking >15 years) can be attributed to the presence of systemic inflammation as a result of COPD. Also, Plasma fibrinogen levels show a dose-dependent increase in smokers.[39] If patients with severe COPD, tends to decrease their smoking status due to increased breathlessness it would alter the correlation between severity of COPD and fibrinogen. So, ex- smokers (who has quit smoking >15 years) were selected.

The information collected regarding all the selected cases and controls were recorded in a Master Chart. Data analysis was done with the help of computer using SPSS version 13. Using this software, frequencies, percentages, means, standard deviations, 'p' values were calculated using chi square test, independent t samples test, Pearson's and Spearman's correlation tests. A 'p' value less than 0.05 was taken to denote significant relationship.

RESULTS AND ANALYSIS OF OBSERVED DATA

TABLE – 1

STAGES OF COPD

GROUP		FREQUENCY	PERCENT
STUDY (COPD) GROUP	FEV1 ≥ 80%	15	20.0
	FEV1 79-50%	20	26.7
	FEV1 49-30%	20	26.7
	FEV1 < 30%	20	26.7
	Total	75	100.0

The COPD group consisted of 15 patients (20%) in STAGE I, 20 patients (26.7%) in STAGE II, 20 patients (26.7%) in STAGE III, 20 patients (26.7%) in STAGE IV.

FIGURE – 1

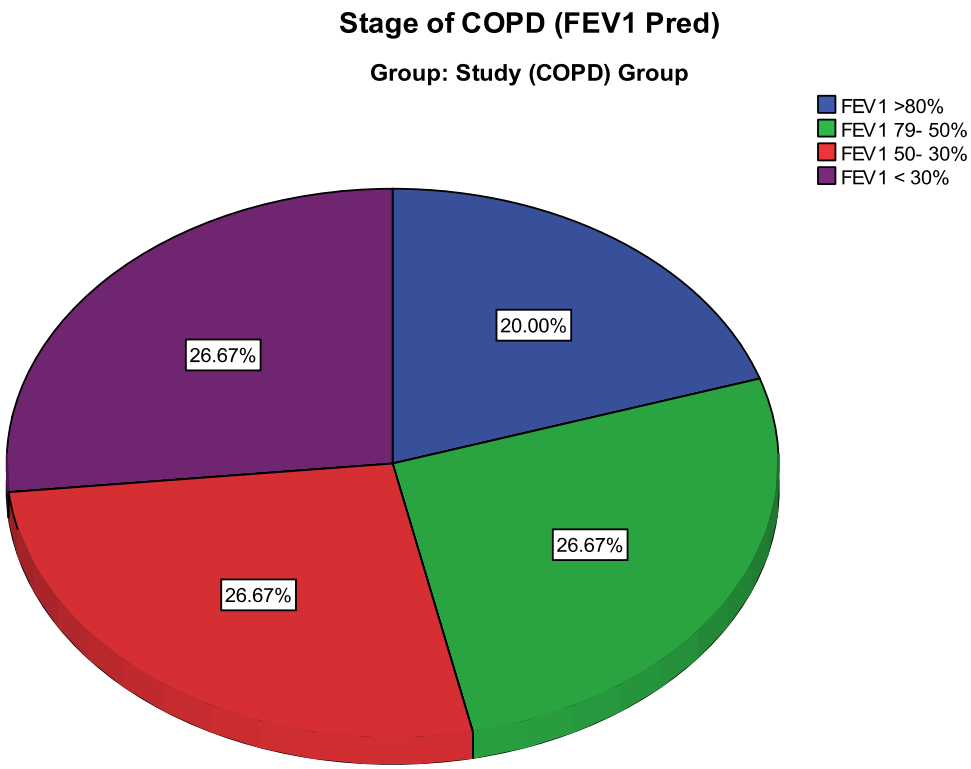
Stage of COPD (FEV1 Pred)
Group: Study (COPD) Group
FEV1 >80%
FEV1 79- 50%
FEV1 50- 30%
FEV1 < 30%
20.00%
26.67%
26.67%
26.67%

FIGURE – 2

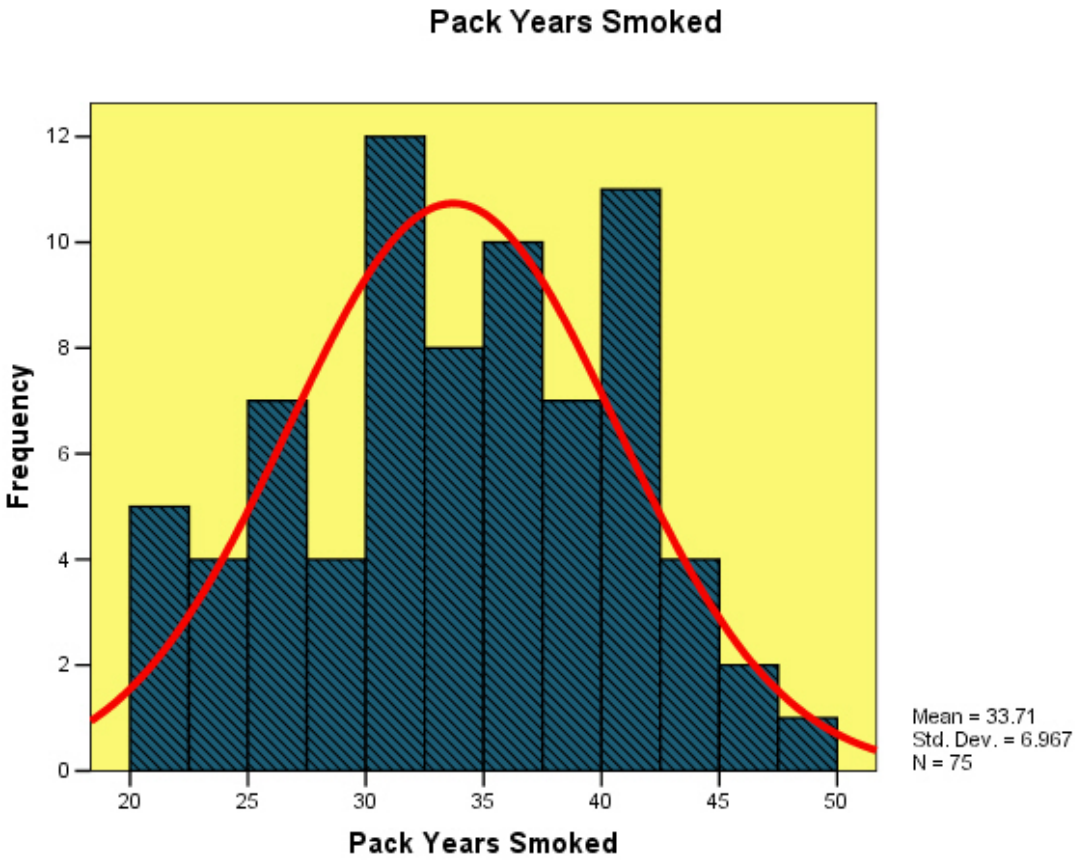
Pack Years Smoked
Frequency
0
2
4
6
8
10
12
20
25
30
35
40
45
50
Pack Years Smoked
Mean = 33.71
Std. Dev. = 6.967
N = 75

TABLE - 2

	Group	N	Mean	Std. Deviation	Std. Error Mean
AGE OF PATIENTS(yrs)	Study (COPD) Group	75	56.73	6.141	.709
	Control (non-COPD) Group	75	56.72	4.831	0.558

p value : 0.988

The mean age of the patients in the COPD group was 56.73 years and in the control group it was 56.72 years. There was no significant difference in age between the two groups.

Figure - 2 shows the distribution of pack years smoked in the COPD group. The mean value of pack years smoked was 33.71 years.

FIGURE – 3

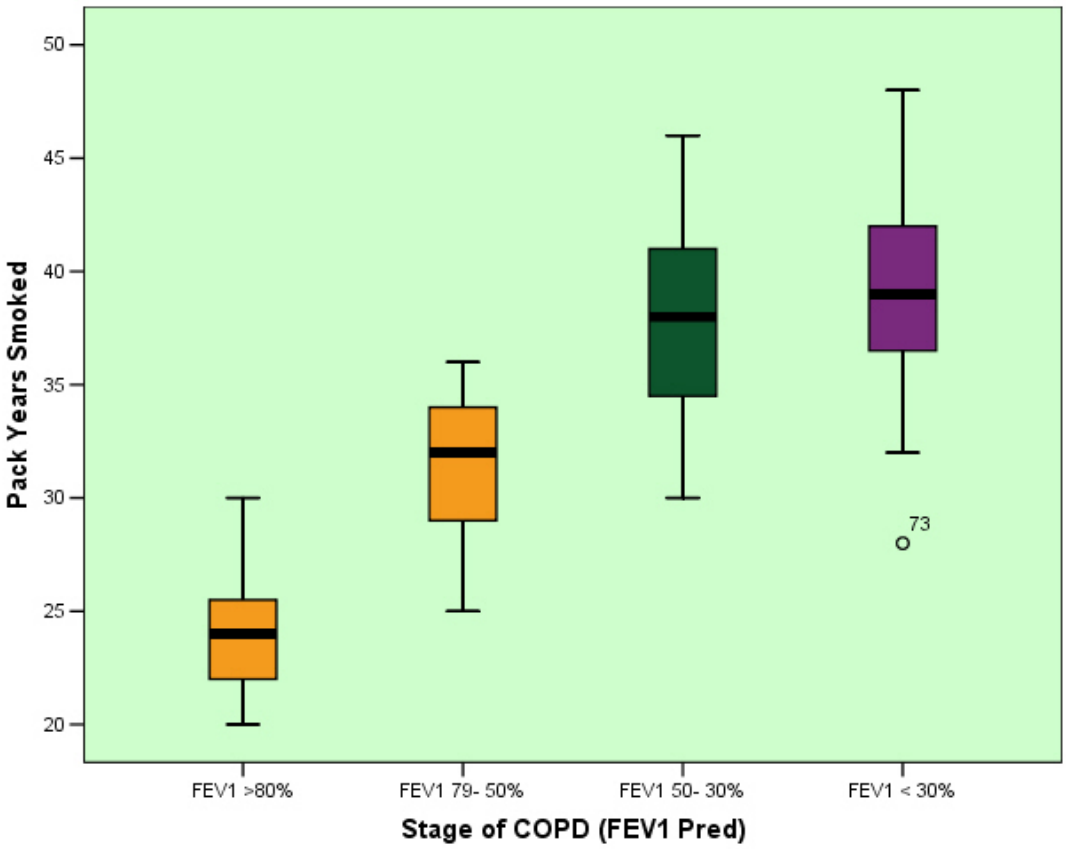
Pack Years Smoked
50
45
40
35
30
25
20
73
FEV1 >80%
FEV1 79- 50%
FEV1 50- 30%
FEV1 < 30%
Stage of COPD (FEV1 Pred)

TABLE - 3

	Group	N	Mean	Std. Deviation	Std. Error Mean
FEV1/FVC	Study (COPD) group	75	49.88	10.4268	1.186
	Control (non COPD) group	75	87.67	4.035	0.466

Significant p value : < 0.001

The mean FEV1/FVC in COPD group was 49.88% and in the control group it was 87.67 %.

Figure – 3 shows the correlation between pack years smoked and the stages of COPD. More the no. of pack years smoked, more was the severity of COPD.

TABLE - 4

	Group	N	Mean	Std. Deviation	Std. Error Mean
FEV1% PREDICTED	Study (COPD) Group	75	50.28	21.96	2.536
	Control (non-COPD) Group	75	87.87	4.354	0.503

Significant p value : < 0.001

The mean Predicted FEV1% in the COPD group was 50.28% and in the control group it was 87.87%.

TABLE - 5

	Group	N	Mean	Std. Deviation	Std. Error Mean
PaO2(mmHg)	Study (COPD) Group	75	76.45	15.62	1.804
	Control (non-COPD) Group	75	95.03	0.915	0.106

Significant p value : < 0.001

The mean PaO2 in the COPD group was 76.45mmHg and in the control group it was 95.03mmHg.

FIGURE – 4

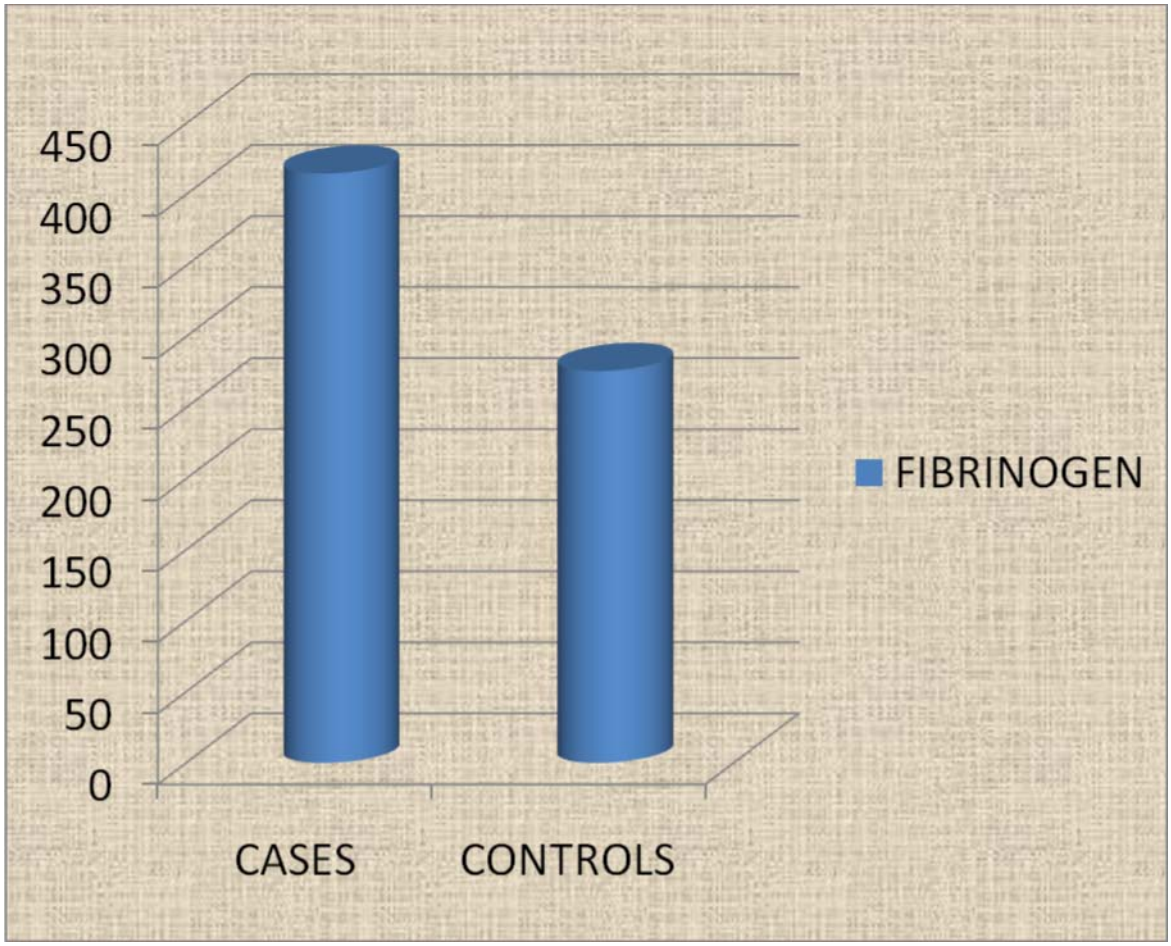
450
400
350
300
250
200
150
100
50
0
CASES
CONTROLS
FIBRINOGEN

TABLE - 6

	Group	N	Mean	Std. Deviation	Std. Error Mean
FIBRINOGEN(mg%)	Study (COPD) Group	75	414.81	73.950	8.539
	Control (non-COPD) Group	75	275.83	47.032	5.431

Significant p value : < 0.001

The mean plasma fibrinogen level in the COPD group was 414.81mg% and in the control group it was 275.83mg%. Plasma fibrinogen level was significantly higher in the COPD group compared to the control group.

FIGURE – 5

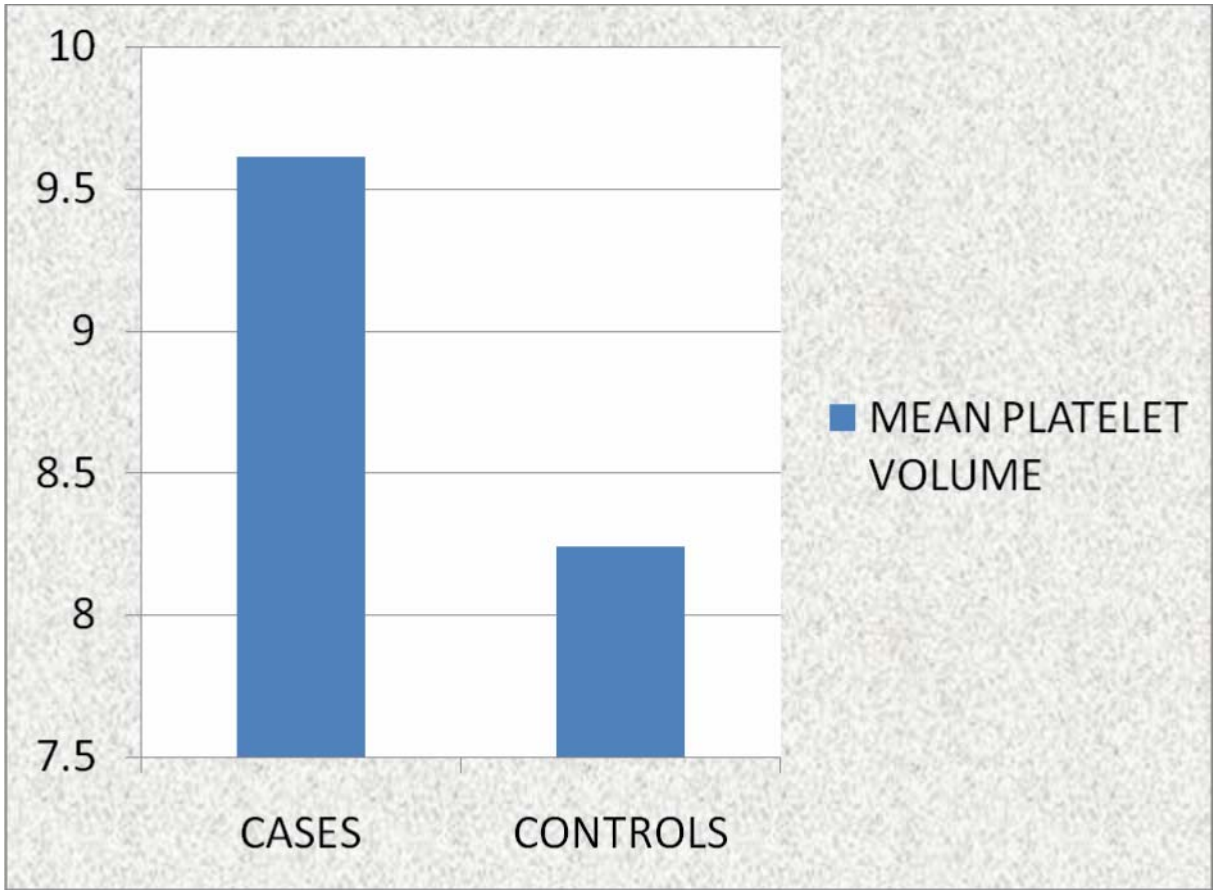

TABLE - 7

	Group	N	Mean	Std. Deviation	Std. Error Mean
MEAN PLATELET VOLUME (fl)	Study (COPD) Group	75	9.61	0.9685	0.1118
	Control (non-COPD) Group	75	8.24	1.0064	0.1162

Significant p value : < 0.001

The mean platelet volume (MPV) in the COPD group was 9.61fl and in the control group it was 8.24fl. MPV was significantly higher in the COPD group.

TABLE - 8

	Group	N	Mean	Std. Deviation	Std. Error Mean
ESR(mm/hr)	Study (COPD) Group	75	27.53	5.564	0.642
	Control (non-COPD) Group	75	10.56	3.438	0.397

Significant p value : < 0.001

The mean ESR in the COPD group was 27.53mm/hr and in the control group it was 10.56mm/hr. The mean ESR was significantly higher in the COPD group than in the control group.

TABLE - 9

	Group	N	Mean	Std. Deviation	Std. Error Mean
PLATELET COUNT(in lakhs/cumm)	Study (COPD) Group	75	2.80	0.40	0.046
	Control (non-COPD) Group	75	2.57	0.52	0.060

Significant p value : 0.002

The mean platelet count in the COPD group was 2.80 lakhs/cumm and in the control group it was 2.57 lakhs/cumm. The mean platelet count was significantly higher in the COPD group than in the control group.

TABLE – 10

	Group	N	Mean	Std. Deviation	Std. Error Mean
LEUCOCYTE COUNT (per cumm)	Study (COPD) Group	75	8590.67	1173.14	135.46
	Control (non-COPD) Group	75	8038.67	1354.56	156.41

Significant p value : 0.008

The mean leucocyte count in the COPD group was 8590.67 per cumm and in the control group it was 8038.67 per cumm. The mean leucocyte count was significantly higher in the COPD group than in the control group.

FIGURE –6

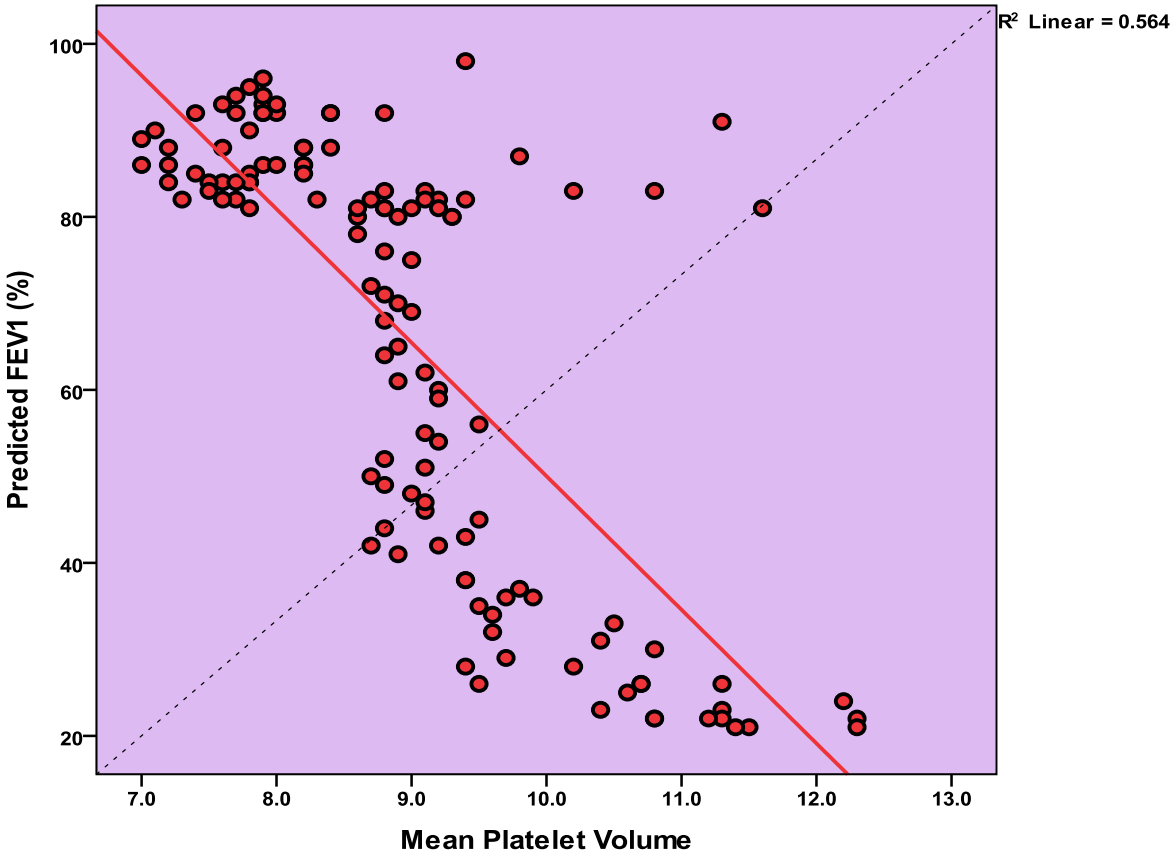
R² Linear = 0.564
Predicted FEV1 (%)
100
80
60
40
20
7.0
8.0
9.0
10.0
11.0
12.0
13.0
Mean Platelet Volume

TABLE – 11

		MEAN PLATELET VOLUME	PREDICTED FEV1 (%)
MEAN PLATELET VOLUME	Pearson Correlation	1	-.755
	Sig. (2-tailed)		.000
	N	75	75
PREDICTED FEV1 (%)	Pearson Correlation	-.755	1
	Sig. (2-tailed)	.000	
	N	75	75

The correlation between mean platelet volume and predicted FEV1% was r = - 0.755. There was significant negative correlation between mean platelet volume and predicted FEV1%.

Figure - 6 shows the relationship between mean platelet volume and severity of COPD. As the severity of COPD increased, the mean platelet volume increased.

TABLE – 12

		MEAN PLATELET VOLUME	PARTIAL PRESSURE OF O2
MEAN PLATELET VOLUME	Pearson Correlation	1	-.880
	Sig. (2-tailed)		.000
	N	75	75
PARTIAL PRESSURE OF O2	Pearson Correlation	-.880	1
	Sig. (2-tailed)	.000	
	N	75	75

The correlation between mean platelet volume and PaO2 was r = - 0.880. There was significant negative correlation between mean platelet volume and PaO2.

FIGURE –7

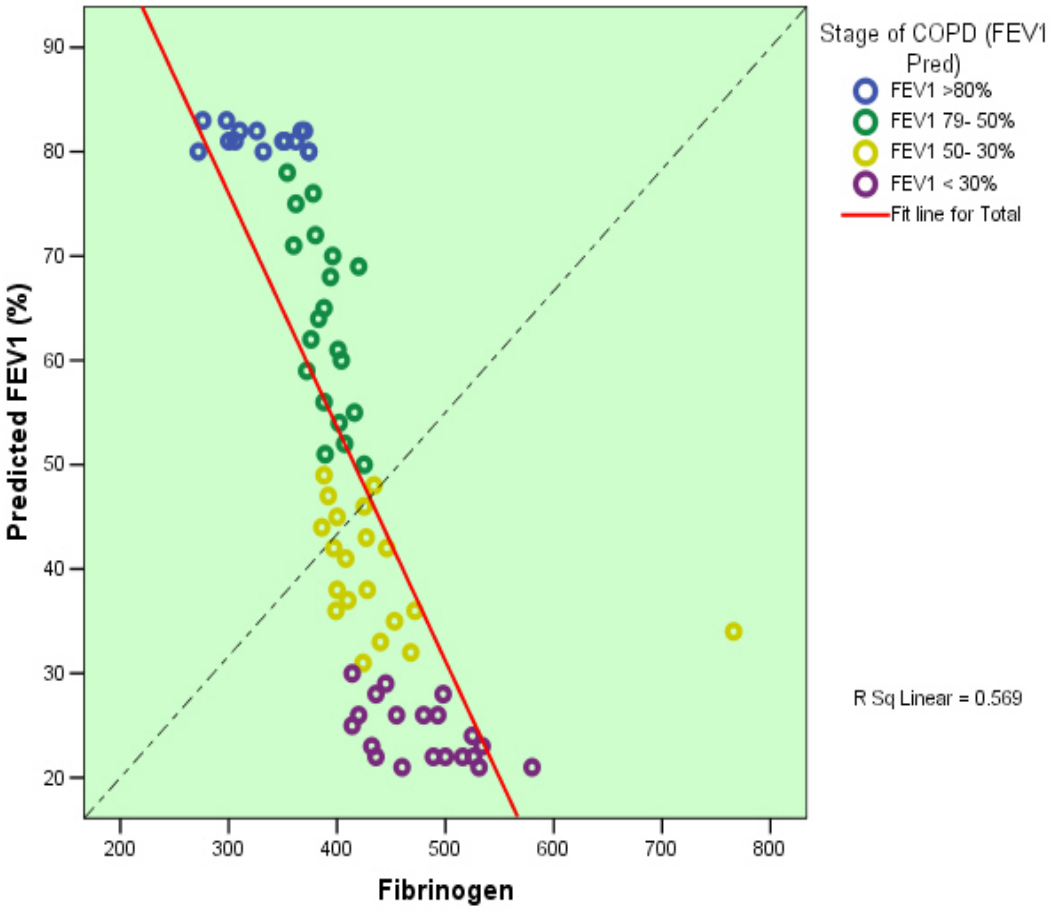
Predicted FEV1 (%)
90
80
70
60
50
40
30
20
200
300
400
500
600
700
800
Fibrinogen
Stage of COPD (FEV1 Pred)
FEV1 >80%
FEV1 79- 50%
FEV1 50- 30%
FEV1 < 30%
Fit line for Total
R Sq Linear = 0.569

TABLE – 13

		FIBRINOGEN	PREDICTED FEV1 (%)
FIBRINOGEN	Pearson Correlation	1	-.754
	Sig. (2-tailed)		.000
	N	75	75
PREDICTED FEV1 (%)	Pearson Correlation	-.754	1
	Sig. (2-tailed)	.000	
	N	75	75

The correlation between fibrinogen and predicted FEV1% was r = -0.754. There was significant negative correlation between fibrinogen and predicted FEV1%.

Figure - 7 shows the relationship between plasma fibrinogen and stages of COPD. As the stages of COPD increased, the plasma fibrinogen value increased.

FIGURE – 8

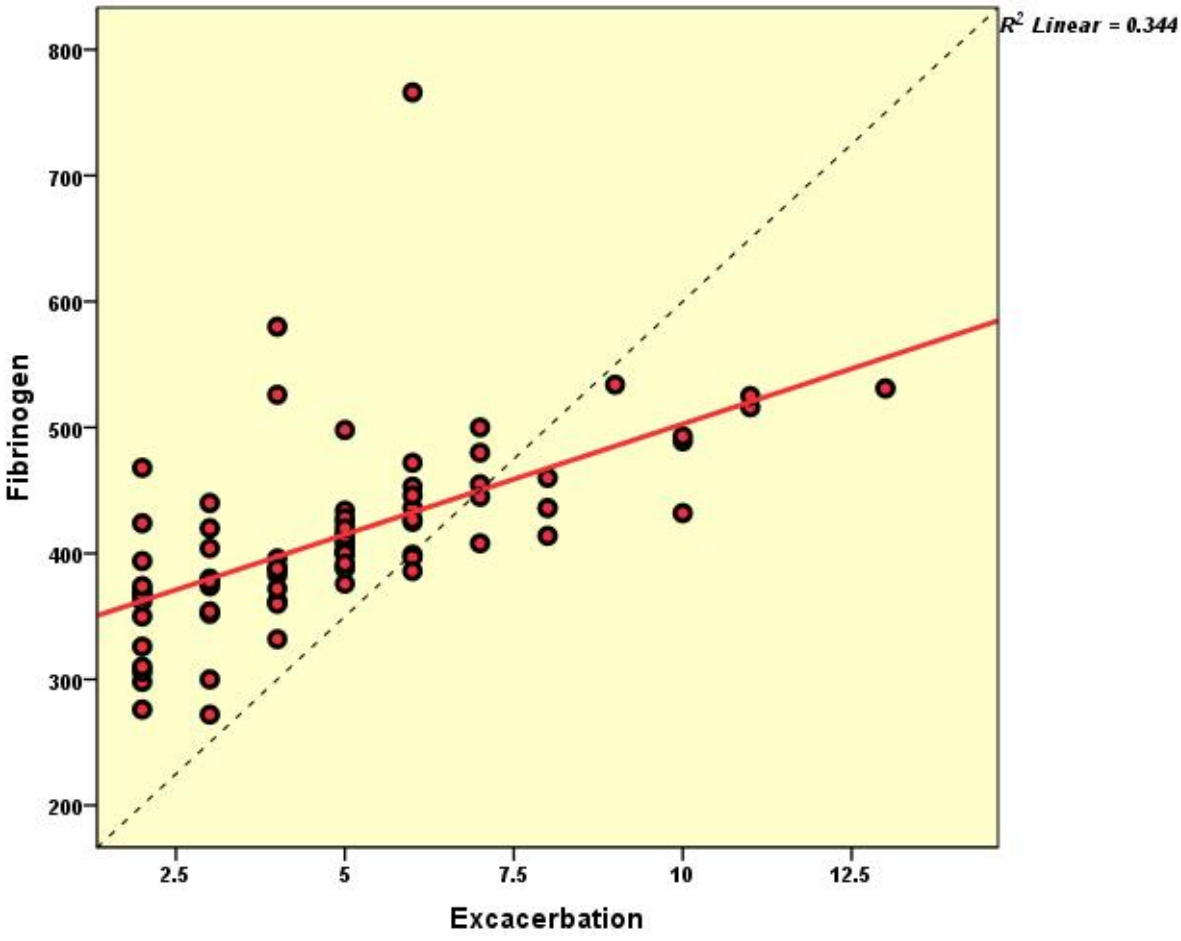
R² Linear = 0.344
800
700
600
500
400
300
200
Fibrinogen
2.5
5
7.5
10
12.5
Excacerbation

TABLE - 14

			EXACERBATION	FIBRINOGEN
Spearman's rho	EXACERBATION	correlation coefficient	1.000	.708
		sig. (2-tailed)		.000
		N	75	75
	FIBRINOGEN	correlation coefficient	.708	1.000
		sig. (2-tailed)	.000	
		N	75	75

The correlation between no. of acute exacerbations in the last 12 months and fibrinogen was r = 0.708. There was significant positive correlation between plasma fibrinogen and no. of acute exacerbations in the last 12 months.

Figure - 8 shows the relationship between plasma fibrinogen and the no. of exacerbations (in the past 12 months). As the plasma fibrinogen, increased the no. of exacerbations increased.

FIGURE -9

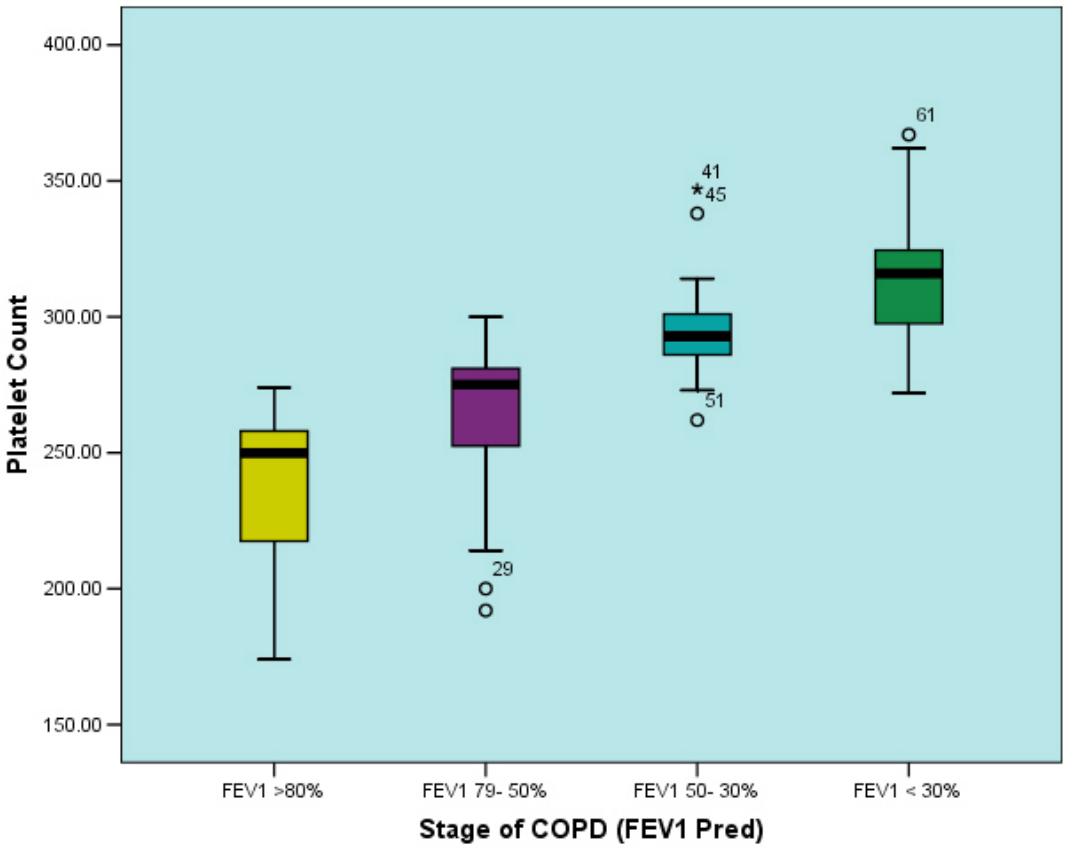
Platelet Count
400.00
350.00
300.00
250.00
200.00
150.00
61
41
45
51
29
FEV1 >80%
FEV1 79- 50%
FEV1 50- 30%
FEV1 < 30%
Stage of COPD (FEV1 Pred)

TABLE – 15

		PREDICTED FEV1 (%)	PLATELET COUNT
PREDICTED FEV1 (%)	Pearson Correlation	1	-.712
	Sig. (2-tailed)		.000
	N	75	75
PLATELET COUNT	Pearson Correlation	-.712	1
	Sig. (2-tailed)	.000	
	N	75	75

The correlation between platelet count and FEV1% was r = - 0.712. There was significant negative correlation between platelet count and FEV1%.

Figure - 9 shows the correlation between stages of COPD and platelet count. As the stage of COPD increased the platelet count increased.

TABLE - 16

		LEUCOCYTE COUNT	PREDICTED FEV1%
PREDICTED FEV1 (%)	Pearson Correlation	1	-.173
	Sig. (2-tailed)		.138
	N	75	75
LEUCO CYTE COUNT	Pearson Correlation	-.173	1
	Sig. (2-tailed)	.138	
	N	75	75

The correlation between leucocyte count and predicted FEV1% was - 0.173. There was no significant correlation between leucocyte count and predicted FEV1%.

DISCUSSION

COPD is now widely recognised as systemic disease. Once the pulmonary inflammation becomes firmly established, the inflammatory signals may then spill over into the general circulation, creating a state of low-grade systemic inflammation.[16] There is growing evidence that persistent low-grade systemic inflammation is present in COPD and that this may contribute to the pathogenesis of atherosclerosis and cardiovascular disease among COPD patients.[16] Other systemic effects include cachexia, skeletal muscle dysfunction, cardiovascular disease, osteoporosis, depression, fatigue among many others. Also, systemic inflammation can also cause decline in lung function.[28] Some systemic inflammatory markers COPD include TNF-α, several interleukins, lipopolysaccharide binding protein, soluble TNF-α receptors, leukocytes, and acute phase proteins such as C-reactive protein (CRP) and fibrinogen.[19,20,21]

An integral component of the systemic inflammatory response is stimulation of the hematopoietic system, specifically the bone marrow, that results in the release of leukocytes and platelets into the circulation.

There is a shortened platelet half life, increased platelet size, increased platelet aggregation, high levels of blood fibrinogen and in vitro and in vivo platelet activation in these patients.[40] This may contribute to the existing prothrombotic state.

Even long after smoking cessation there remains an exuberant inflammatory response, suggesting that mechanisms of cigarette smoke-induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation.[1] If COPD patients continue to smoke it would add to the airway and systemic inflammation.

This study was mainly done to assess the presence of systemic inflammation in patients with COPD long after smoking cessation. Plasma fibrinogen and mean platelet volume were used as markers of the systemic inflammatory and prothrombotic state. In our study, 75 COPD patients were compared with 75 age matched controls.

The COPD group consisted of 15 patients (20%) in stage I, 20 patients (26.7%) in stage II, 20 patients (26.7%) in stage III, 20 patients (26.7%) in stage IV.

The mean age of the patients in the COPD group was 56.73 years and in the control group it was 56.72 years. There was no significant difference in age between the two groups. The mean value of pack years

smoked was 33.71 years. More the no. of pack years smoked, more was the severity of COPD. The mean FEV1/FVC% in the COPD group and in the control group was 49.88% and 87.67% respectively. The mean Predicted FEV1% in the COPD group was 50.28% and in the control group it was 87.87%. The mean PaO2 in the COPD group was 76.45mmHg and in the control group it was 95.03mmHg.

The results correlated well with the worldwide studies. The study by **A.Lekka et al**[33] was performed on 56 COPD patients and 56 age matched controls. It showed significantly higher fibrinogen level in COPD patients than in controls (p =0.001).In our study, the mean plasma fibrinogen level in the COPD group was 414.81mg% and in the control group it was 275.83mg%. The plasma fibrinogen was significantly elevated compared to controls (p value <0.001) similarly to their study.

The study by **Rajeev Bansal et al**[40] was done in 100 COPD patients and 100 normal patients. The mean FEV1/FVC in the COPD and in the control group was 52.2% and 90.7% respectively. The mean PaO2 in the COPD and in the control group was 70.8mmHg and 90mmHgrespectively. They reported that the mean platelet volume was significantly higher in COPD patients than in normal patients (10.8 fl in COPD patients compared to 7.96 in normal patients; p = <0.05). In our study, the mean platelet volume (MPV) in the COPD group was 9.61fl

and in the control group it was 8.24fl. The mean platelet volume was significantly higher in COPD patients than in controls (p = <0.001)which correlates with their study.

In the study by **JA Wadachia et al**[32] mean platelet volume was estimated in 35 patients with chronic airflow obstruction and a wide range of arterial oxygen tension (PaO2) and they were compared with 18 normal patients. They found a significant negative correlation (r = -0.70) between mean platelet volume and PaO2. In Our study also there is significant negative correlation (r = - 0.88) between mean platelet volume and PaO2 which correlates well with this study.

Thrombopoiesis may be stimulated by IL-6 as a result of systemic inflammation.[31] Increased size of the platelets could be also because of hypoxia causing bone marrow stimulation resulting in secretion of larger platelets. Larger the platelets, more is the platelet activity resulting in increased platelet aggregation and release of active mediators which can cause endothelial cell injury.[29,30] So, as there is increased mean platelet volume in COPD patients, it is a prothrombotic state.

The study by **Groenewegen KH et al** [21] was done in a group of 314patients with 277 person years of follow up. They showed that higher initial fibrinogen level and a lower FEV1 predicted a higher rate of both

moderate and severe exacerbations. They concluded that elevated fibrinogen levels is an independent risk factor for exacerbations of COPD. In our study also the number of acute exacerbations in the preceding 12 months period significantly correlated with fibrinogen level (r = 0.708).

The study by **G.C.Donaldson et al**[27] had concluded that in COPD, airway and systemic inflammatory markers increase over time. High levels of these markers are associated with a faster decline in lung function. Our study was designed to assess the association between plasma fibrinogen, a systemic inflammatory marker, and the severity of COPD. Mean platelet volume and its association with severity of COPD was also assessed.

It was found that there is a significant negative correlation between fibrinogen and predicted FEV1% (r = - 0.754) and also between mean platelet volume and predicted FEV1% (r = - 0.755). So, it can be concluded that as the severity of COPD increases, fibrinogen and mean platelet volume increases.

The mean platelet count in the COPD group was 2.80lakhs/cumm and in the control group it was 2.57lakhs/cumm. The mean platelet count was significantly higher in the COPD group than in the control group (p = 0.002) in our study.

The study by **Gulfidan Cakmak et al**[45] concluded that platelet count increased as the severity of COPD increased (p = <0.0001). In our study also the platelet count increased as the severity of COPD increased (r = - 0.712). Hence, platelet count can also be taken as an indicator of systemic inflammation in COPD.

The mean leucocyte count in the COPD group was 8590.67 per cumm and in the control group it was 8038.67 per cumm. The mean leucocyte count was significantly higher in the COPD group than in the control group (p = 0.008) .

The observation in our study that COPD patients had significantly elevated leucocyte and platelet count than the controls supports the presence of systemic inflammation. However the leucocyte count did not significantly correlated with the severity of COPD (r = - 0.173).

The mean ESR in the COPD group was 27.53mm/hr and in the control group it was 10.56mm/hr. The mean ESR was significantly higher in the COPD group than in the control group (p = <0.001).

Research is already underway to target the pulmonary and systemic inflammation. Roflumilast, a phosphodiesterase – 4 inhibitor is one

promising drug that addresses both pulmonary and systemic inflammation. [41,42,43]

Further research aimed at controlling the systemic inflammation would benefit the patients with COPD which until now remains only marginally treatable .

SUMMARY

The study “Plasma Fibrinogen and Platelet Mass as Indicators of the Systemic Inflammatory and Prothrombotic state in COPD” was a case control study conducted on 75 COPD patients and 75 healthy controls in Govt. Rajaji Hospital, Madurai.

Patients and controls who satisfied the inclusion criteria were included in the study and detailed history was elicited from them. They underwent investigations like, lung function tests, plasma fibrinogen, mean platelet volume, PaO2 measurements.

COPD patients were found to have significantly elevated plasma fibrinogen and mean platelet volume. Plasma fibrinogen and mean platelet volume significantly correlated with severity of COPD. Also, they had significantly elevated ESR, leucocyte count and platelet count. Platelet count significantly correlated with the severity of COPD.

Hence, it can be concluded that there is systemic inflammatory prothrombotic state in COPD. Also, the systemic inflammation increases with the severity of COPD.

CONCLUSION

1. There is an increased Fibrinogen level in patients with COPD.
2. There is an increased Mean Platelet Volume in patients with COPD.
3. Fibrinogen and Mean Platelet Volume increases as the severity of COPD increases.
4. There is also an increased leucocyte count, platelet count, ESR in patients with COPD.
5. This indicates that there is Systemic Inflammatory and Prothrombotic state in COPD.
6. Systemic Inflammation increases as the severity of COPD increases.

APPENDIX

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PROFORMA

FOR CASES

S.NO :

NAME: AGE: SEX:

ADDRESS: UNIT: WARD:

OP/IPNO:

OCCUPATION:

MONTHLY INCOME:

COMPLAINTS: DURATION:

NO. OF ACUTE EXACERBATIONS (in the past 12 months):

PAST HISTORY:

SYSTEMIC ILLNESS:

DRUG INTAKE:

PERSONAL HISTORY:

SMOKING H/O: NO. OF PACK YEARS SMOKED:

ALCOHOL INTAKE:

EXAMINATION:

NUTRITIONAL STATUS: ORAL HYGEINE:

ANAEMIA: JAUNDICE:

CLUBBING: CYANOSIS:

LYMPHADENOPATHY: PEDAL EDEMA:

RESPIRATORY SYSTEM EXAMINATION:

CARDIOVASCULAR SYSTEM EXAMINATION:

INVESTIGATIONS:

HAEMOGLOBIN: LEUCOCYTE COUNT:

PLATELET COUNT: ESR:

BLOOD SUGAR:

UREA:

CREATININE:

MEAN PLATELET VOLUME: PLASMA FIBRINOGEN:

PaO2:

FEV1/FVC:

PREDICTED FEV1%:

CHEST XRAY PA VIEW:

ECG: ECHO:

FOR CONTROLS

S.NO :

NAME: AGE: SEX:

ADDRESS:

OCCUPATION:

MONTHLY INCOME:

COMPLAINTS: DURATION:

PAST HISTORY:

SYSTEMIC ILLNESS:

DRUG INTAKE:

PERSONAL HISTORY:

SMOKING H/O:

ALCOHOL INTAKE:

EXAMINATION:

NUTRITIONAL STATUS: ORAL HYGEINE:

ANAEMIA: JAUNDICE:

CLUBBING: CYANOSIS:

LYMPHADENOPATHY: PEDAL EDEMA:

RESPIRATORY SYSTEM EXAMINATION:

CARDIOVASCULAR SYSTEM EXAMINATION:

INVESTIGATIONS:

HAEMOGLOBIN: LEUCOCYTE COUNT:

PLATELET COUNT: ESR:

BLOOD SUGAR:

UREA :

CREATININE:

MEAN PLATELET VOLUME: PLASMA FIBRINOGEN:

PaO2:

FEV1/FVC:

PREDICTED FEV1%: