DISSERTATION ON

Correlation of levels of hs-CRP and Plasma fibrinogen with increasing severity of COPD

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CERTIFICATE

This is to certify that this dissertation entitled **"Correlation of levels of hs-crp and plasma fibrinogen with increasing severity of COPD"** submitted by **Dr. A. THOMAS ISIAH SUDARSAN** appearing for Part II M.D. Branch I General Medicine Degree examination in March 2010 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled **"Correlation of levels of hs-crp and plasma fibrinogen with increasing severity of COPD"** is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2008-2009 under the guidance and supervision of **Prof.Dr.R.SUKUMAR, M.D.**, The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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CONTENTS

INTRODUCTION

INTRODUCTION

Systemic inflammation is increasingly being recognized as a risk factor for a number of different complications including atherosclerosis[1] cachexia[2], anorexia[3], and osteoporosis[4]. Notably, all of these complications are commonly observed in patients with chronic obstructive pulmonary disease (COPD)[5-10]. Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation which is considered to play a pathogenic role in this disorder. An increase in both bronchial and systemic inflammation has also been demonstrated. Whether systemic inflammation is present in stable COPD and whether it is wholly or partially responsible for these associations is controversial. Although several studies have been undertaken to evaluate this potential relationship, most of the studies have been conducted during exacerbations of copd and among western population. We wanted to study the correlation of levels of hs-crp and plasma fibrinogen with increasing severity of COPD among Indian patients presenting to OPD in GGH, MMC, CHENNAI. We choose these markers of systemic inflammation because they have been well studied and have been intimately linked with the development of ischaemic heart disease and stroke which, interestingly, are also the leading causes of mortality among patients with COPD. There is evidence to suggest an imbalance in systemic levels of pro- and anti-inflammatory mediators in patients with stable COPD. The presence of these proinflammatory markers in increased levels in patients with COPD in both stable state and during exacerrebration might predispose them to adverse cardiovascular, cerebrovascular events[11-13] acutely

and the presence of a chronic inflammatory state may predispose to systemic effects such as cachexia, decreased bone mineral density with attendant risk of fracture, renal dysfunction, accelerated atherosclerosis, malignancy and anaemia. The treatment of this chronic inflammatory state and the early treatment of acute exacerrebration with conventional and possible newer therapeutic targets could possibly lead to lower incidence of these systemic effects and organ damage in this population. Also the role of prophylactic against these systemic and specific organ damage may be valuable intervention. This observative study was done to see if there was significant rise in the levels of these pro inflammatory marker, i.e., hs-CRP and plasma fibrinogen (Possibly stimulated by IL-6) as well as other markers such as ESR, polymorph percentage of total WBC count, pack years with increasing levels of severity as it could possibly lead to consensus on treatment protocols based on these levels during acute or chronic COPD.

AIMS AND OBJECTIVES

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The principal aims of this study were to:

1. To determine the correlation of hs-CRP and plasma fibrinogen levels with increasing severity of COPD in 80 patients presenting our hospital in GGH, CHENNAI.

2. To study the prevalence of the levels of various systemic markers of inflammation i.e., ESR, hs-CRP, plasma fibrinogen, polymorph percent of total WBC count in these patients with COPD at different stages as per GOLD criteria and FEV1 percentage of predicted value.

3. To study and observe the relationship between the distribution of these variables in this group and correlation with age, BMI, pack years of smoking.

REVIEW OF LITERATURE

LITERATURE REVIEW

Chronic obstructive pulmonary disease (COPD) is a general name for the chronic airflow obstruction that develops most often as a result of chronic tobacco smoking. The pathology of COPD encompasses a variety of pathologic lesions in the airways, lung parenchyma, and pulmonary vasculature, and these lesions can be correlated, to a greater or lesser degree, with changes in pulmonary function tests and clinical appearances. In general, although the mechanisms involved are complex, airflow obstruction can be attributed largely to a marked increase in airways resistance secondary to a variable mix of structural abnormalities involving all or many of the compartments of the airway. However, in individual cases, it may be difficult to prove associations between physiological abnormalities and pathologic changes.

The recently developed Global Initiative on Obstructive Lung Disease (GOLD) classifies patients with COPD purely upon indices of Airflow namely FEV1 and FVC. 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. COPD is present only if chronic airflow obstruction occurs;

COPD is the fourth leading cause of death and affects >16 million persons in the United States. COPD is also 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.

Risk Factors

Cigarette Smoking

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Subsequent 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). This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts for the higher prevalence rates for COPD with increasing age.

The historically higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males; however, the prevalence of COPD among females is increasing as the gender gap in smoking rates has diminished in the past 50 years.

Airway Responsiveness and COPD

A tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, including methacholine and histamine, is one of the defining features of asthma. However, many patients with COPD also share this feature of airway hyper responsiveness. The considerable overlap between persons with asthma and those with COPD in airway responsiveness, airflow obstruction, and pulmonary symptoms led to the formulation of the Dutch hypothesis. This suggests that asthma, chronic bronchitis, and emphysema are variations of the same basic disease, which is modulated by environmental and genetic factors to produce these pathologically distinct entities. The alternative British hypothesis contends that asthma and COPD are fundamentally different diseases: Asthma is viewed as largely an allergic phenomenon, while COPD results from smoking-related inflammation and damage. Determination of the validity of the Dutch hypothesis Vs. the British hypothesis awaits identification of the genetic predisposing factors for asthma and/or COPD, as well as the interactions between these postulated genetic factors and environmental risk factors.

Longitudinal studies that compared airway responsiveness at the beginning of the study to subsequent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function. Thus, airway hyper responsiveness is a risk factor for COPD.

Respiratory Infections

These have been studied as potential risk factors for the development and progression of COPD in adults; childhood respiratory infections have also been assessed as potential predisposing factors for the eventual development of COPD. The impact of adult respiratory infections on decline in pulmonary function is controversial, but significant long-term reductions in pulmonary function are not typically seen following an episode of bronchitis or pneumonia. The impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess due to a lack of adequate longitudinal data. Thus, although respiratory infections are important causes of exacerbations of COPD, the association of both adult and childhood respiratory infections to the development and progression of COPD remains to be proven.

Occupational Exposures

Increased respiratory symptoms and airflow obstruction have been suggested as resulting from general exposure to dust at work. Several specific occupational exposures, including coal mining, gold mining, and cotton textile dust, have been suggested as risk factors for chronic airflow obstruction.

However, 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. Among workers exposed to cadmium (a specific chemical fume), FEV_1, FEV_1/FVC, and DL_{CO} were significantly reduced (FVC, forced vital capacity; DL_{CO}, carbon monoxide diffusing capacity of the lung) consistent with airflow obstruction and emphysema. Although several specific occupational dusts and fumes are likely risk factors for COPD, the magnitude of these effects appears to be substantially less important than the effect of cigarette smoking.

Ambient Air Pollution

Some investigators have reported increased respiratory symptoms in those living in urban compared to rural areas, which may relate to increased pollution in the urban settings. However, 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. However, in most populations, ambient air pollution is a much less important risk factor for COPD than cigarette smoking.

Passive, or Second-Hand, Smoking Exposure

Exposure of children to maternal smoking results in significantly reduced lung growth. 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.

Genetic Considerations

Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe $alpha_1$ antitrypsin deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

Antitrypsin Deficiency

Many variants of the protease inhibitor (PI or SERPINA1) locus that encodes ALPHA 1 AT have been described. The common M allele is associated with normal. ALPHA 1 AT levels. The S allele, associated with slightly reduced ALPHA 1 AT levels, and the Z allele, associated with markedly reduced ALPHA 1 AT levels, also occur with frequencies >1% in most Caucasian populations. Rare individuals inherit null alleles, which lead to the absence of any ALPHA 1 - AT production through a heterogeneous collection of mutations. Individuals with two Z alleles or one Z and one null allele are referred to as Pi^{Z}, which is the most common form of severe ALPHA 1 AT deficiency.

Although only 1–2% of COPD patients are found to have severe ALPHA 1 AT deficiency as a contributing cause of COPD, these patients demonstrate that genetic factors can have a profound influence on the susceptibility for developing COPD. Pi ^{Z} individuals often develop early-onset COPD, but the ascertainment bias in the published series of Pi ^{Z} individuals—which have usually included many Pi ^{Z} subjects who were tested for ALPHA 1 AT deficiency because they had COPD—means that the fraction of Pi ^{Z} individuals who will develop COPD and the age-of-onset distribution for the development of COPD in Pi ^{Z} subjects remain unknown. Approximately 1 in 3000 individuals in the United States inherits severe ALPHA 1 AT deficiency, but only a small minority of these individuals has been recognized. The clinical laboratory test used most frequently to screen for ALPHA 1 AT deficiency is measurement of the immunologic level of ALPHA 1 AT in serum.

Specific treatment in the form of ALPHA 1 AT augmentation therapy is available for severe AT deficiency as a weekly intravenous infusion factors.

Other Genetic Risk Factors

Studies of pulmonary function measurements performed in general population samples have suggested that genetic factors other than PI type influence variation in pulmonary function. Familial aggregation of airflow obstruction within families of COPD patients has also been demonstrated.

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. The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking), with smoking cessation at an earlier age providing a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. Genetic factors likely contribute to the level of pulmonary function achieved during growth and to the rate of decline in response to smoking and potentially to other environmental factors as well.

The Elastase : Antielastase Hypothesis

Elastin, the principal component of elastic fibers, is a highly stable component of the extra cellular matrix that is critical to the integrity of both the small airways and the lung parenchyma. The Elastase : Antielastase hypothesis proposed in the mid-1960s states that the balance of elastin-degrading enzymes and their inhibitors determines the susceptibility of the lung to destruction resulting in airspace enlargement. This hypothesis was based on the clinical observation that patients with genetic deficiency in AT, the inhibitor of the serine proteinase neutrophils Elastase, were at increased risk of emphysema, and that instillation of Elastase, including neutrophils Elastase, to experimental animals results in emphysema. To this day, the Elastase : Antielastase hypothesis is the prevailing mechanism for the development of emphysema. However, a complex network of inflammatory cells and additional proteinases that contribute to emphysema have subsequently been identified.

Inflammation and Extra cellular 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 B sites and resulting in transcription of matrix metalloproteinase-9, proinflammatory cytokines interleukin 8 (IL-8), and tumor necrosis factor (TNF-alpha); this leads to neutrophils recruitment. CD8+ T-cells are also recruited in response to cigarette smoke and release interferon inducible protein-10 (IP-10, CXCL-7) that in turn leads to macrophage production of macrophage Elastase [matrix metalloproteinase-12 (MMP-12)]. Matrix metalloproteinase 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.

Concomitant cigarette smoke–induced loss of cilia in the airway epithelium

MATERIALS AND METHODS

METHODS AND MATERIALS

A total of 80 patients of COPD coming to GGH, MMC were be screened for COPD by history clinical examination and PFT. Patients with features consistent with copd and FEV1/ FVC ratio less than 0.7 were be chosen for the study. The FEV1/FVCratio, reflecting the rate of emptying of the lung, is used to define the presence of an obstructive ventilatory defect. They were be categorized according to GOLD criteria using the percentage of predicted FEV1 for severity of COPD. Their blood levels of hs-CRP and plasma fibrinogen were be measured. The electronic super Spiro machine was used for doing pulmonary function tests after giving appropriate instructions and ensuring the patient is not having any respiratory infection and repeated twice to measure the best possible effort by the patient. The hs-CRP was measured by nephalometric method using the turbox analyzer. Plasma fibrinogen was measured using immuno turbidimetric method Olympus AU400 analyzer. Other parameters such as BMI, ESR, polymorph percentage, pack years of smoking were recorded of individuals. A careful history with regard to the patients symptoms of COPD, smoking habits, cardiovascular illness, renal or liver disorders, any connective tissue, autoimmune, vascullitic disorders, diabetes, hypertension, peripheral vascular disease was obtained.

A thorough head to foot clinical examination of all the systems were done. A routine battery of investigations to test for renal, liver function, diabetes, presence of ischaemic heart disease, or tuberculosis was done to carefully select patients as per exclusion criteria.

Research Design

This is a cross-sectional study assessing the levels of plasma fibrinogen , hs-CRP among other parameters such as ESR, polymorph percent, BMI, pack years of smoking,FEV1percent of predicted in patients with COPD involving 80 participants presenting to MMC, GGH, Chennai.

Study setting

This study was done in the institute of internal medicine in GGH, Madras medical college, Chennai with inputs and active cooperation from the department of thoracic medicine. GGH, MMC, CHENNAI.

Methodology

This is a cross-sectional study conducted as described above on patients in the age group 20-60 years. Patients, after informed consent were recruited into study, if they were eligible as per the criteria below.

Inclusion criteria

Patients attending OPD and admitted to medical department in the Government General Hospital with clinical features of COPD, i.e.; cough with expectoration, dyspnea, wheeze and FEV1/FVC ratio of less than 0.7 showing obstructive features on electronic Spirometry and without any comorbid illness are selected for the study.

Exclusion criteria

1. Patients who are terminally ill, critically or acutely
2. Age < 20yrs >60 yrs.
3. Diabetics, hypertensive, past history of M.I, Stroke, TIA
4. Any arterial or venous thrombosis, peripheral vascular disease.
5. H/o of immunological disorders like rheumatoid arthritis, SLE, ankylosing spondillitis
6. H/o cancer, renal disease, liver disorder
7. Ongoing infections.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

THE study was done on 80 patients presenting to the medical department and were selected randomly as per the inclusion criteria and exclusion criteria. All individual patients were informed of the study and their consent was obtained. Pulmonary function tests were done in these patient after excluding the conditions listed in the exclusion criteria with careful clinical history and simple tests such as RFT, LFT, complete blood counts, ECG,CXR, ECHO, etc. PFT was done in the department of thoracic medicine using the electronic super Spiro machine and the patients individual FEV1, FVC, FEVI percentage of predicted value, FEV1/FVC was calculated and they were staged according to GOLD stage of COPD. STAGE 4 diseases was excluded.

STASTISTICAL ANALYSIS

Data analysis was done with use of SPSS, version 10. Descriptive statistics were used to calculate the frequency, mean, and standard deviation. To examine the linear trend of the proportions, trend chi-square was used and to find the test of association chi-square was computed. The correlation of variables i.e., age ,BMI, ESR, polymorph percent of total count, hs- CRP, plasma fibrinogen with severity of COPD as per GOLD stage was analyzed with chi-square test using the Pearson method. The correlation between pack years

with GOLD stage was analyzed using the anova test followed by the tukey- hsd test. The correlation between the variables i.e., age ,BMI, ESR, polymorph percent of total count, hs- CRP, plasma fibrinogen with FEV1 percentage of predicted values was analyzed using correlation coefficients. The correlation between the variables i.e., age ,BMI, ESR, polymorph percent of total count, hs-CRP, plasma fibrinogen and FEV1 percentage of predicted values with pack years of smoking was analyzed using correlation coefficients.

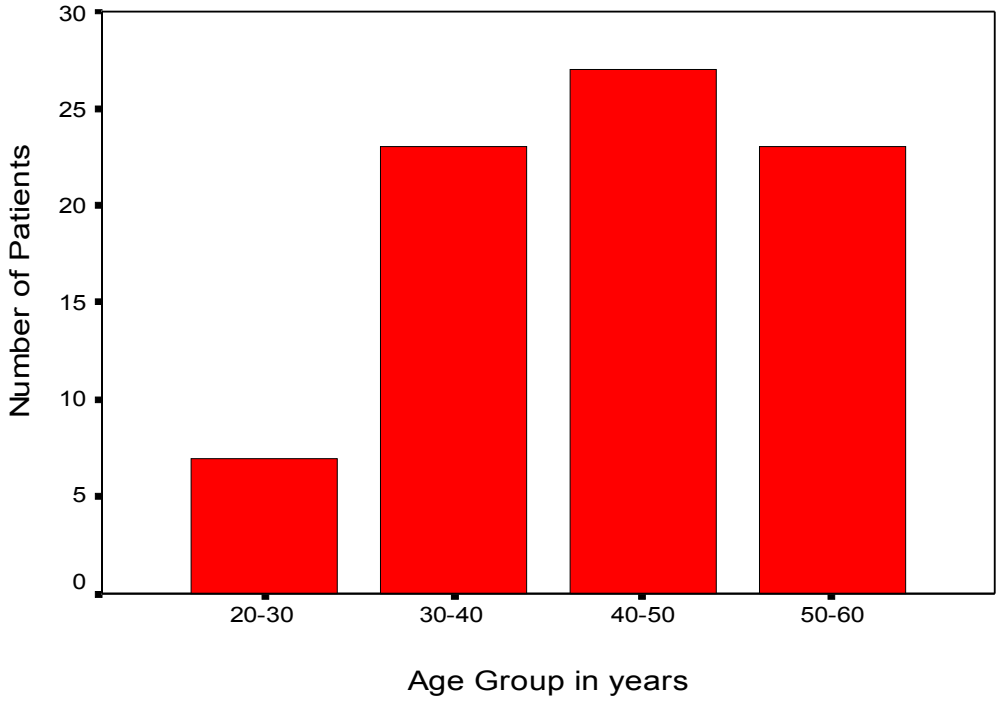
BASELINE CHARACTERISTICS

The age composition of the study group was 8.75% in the 20-30 group, 28.75% in the 30-40 group, 33.75% in the 40-50 group and 28.75 in the 30-40 group.

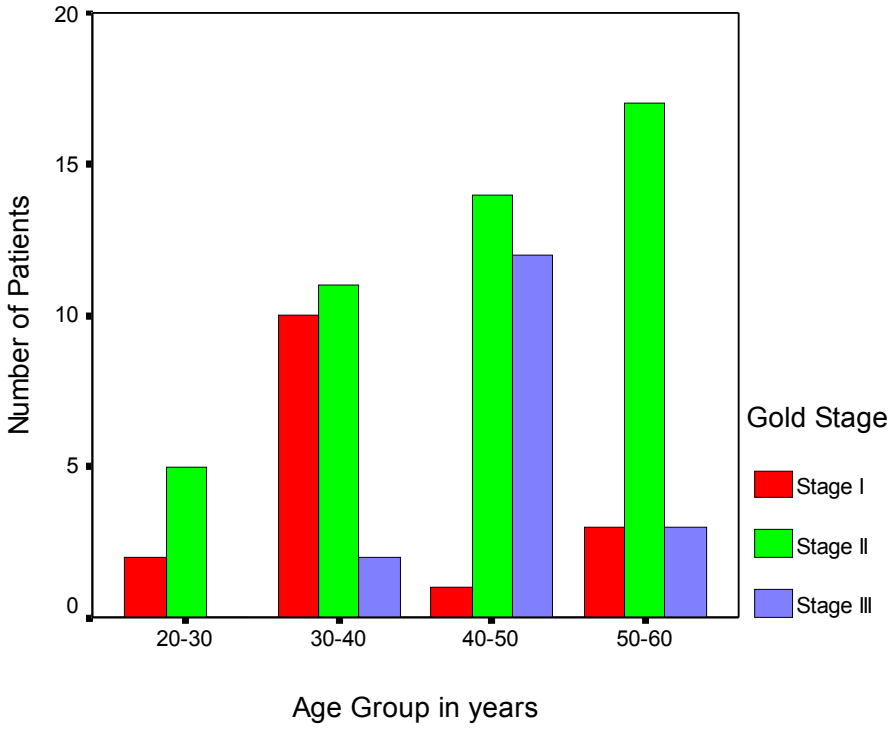
TABLE – 2

BASELINE AGE DISTRIBUTION IN STUDY

Age group	frequency	percentage
20-30	7	8.75
30-40	23	28.75
40-50	27	33.75
50-60	23	28.75
total	80	100.00



Among the different age groups there was increasing correlation of age with severity as per FEV1 percentage of predicted and GOLD STAGE which was found to be statistically significant with a p value of .00071calculated by chi square test indicating the presence of severe disease with increasing age which was expected.



The distribution of the patients recruited to the study in different stages of COPD as per GOLD staging is given in the following table.

TABLE – 3

BASELINE DISTRIBUTION OF GOLD STAGE IN COPD.

GOLD STAGE	FREQUENCY	PERCENTAGE
STAGE 1	16	20.00
STAGE2	47	58.75
STAGE 3	17	21.25
TOTAL	80	100.00

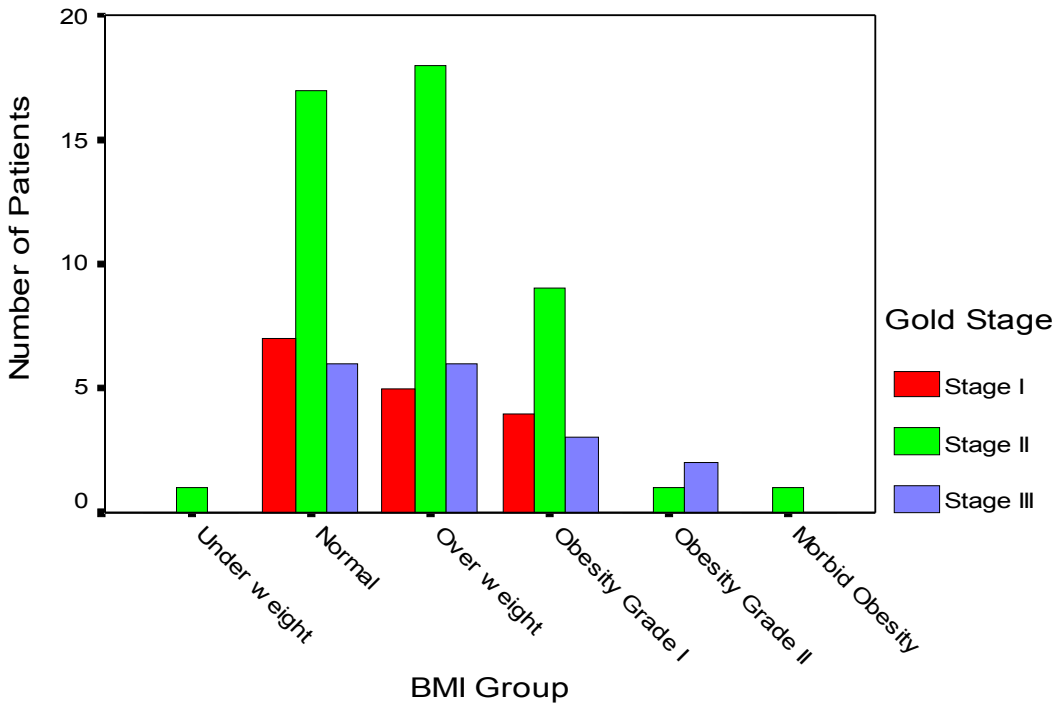
BODY MASS INDEX(BMI)

The study population BMI was measured and categorized as per standard guide lines as given in the following chart.

TABLE – 4

BASELINE DISTRIBUTION OF BMI IN STUDY POPULATION

Bmi group	frequency	percentage
Underweight<18.5	1	1.25
Normal 18.6-24.9	30	37.50
Overweight 25-30	29	36.25
Obesity 30-35grade1	16	20.00
Obesity 35-40 grade2	3	3.75
Morbid obesity >40	1	1.25
total	80	100.00



Among the different BMI groups the occurrence of COPD and the range of its study was analyzed. It was found that there was no statistically significant correlation of either increasing or decreasing BMI with increasing severity of COPD. The p value was .82441. This might due to the fact that our study group comprised of relatively well compensated patients without any active illness and other comorbities and the fact that stage 4 copd patients were not included because of the exclusion criteria. Although other studies have shown a decreasing trend of BMI with increasing severity, i.e. Di Francia et al, our study did not show such a correlation .we suggest more studies with a higher number of patients to be done in this regard.

TABLE – 5

CORRELATION OF BMI WITH GOLD STAGE

BMI	STAGE 1	STAGE 2	STAGE 3
	Percentage Distribution		
UNDERWEIGHT 1no	-	1%	-
NORMAL 30no	23.3%	56.7%	20%
OVERWEIGHT	17.2%	62.1%	20.7%

29no			
GRADE 1 OBESITY 16 no	**25%**	**56.3%**	**18.8%**
GRADE 2 OBESITY 3 no	**-**	**33.3%**	**66.7%**
MORBIDLY OBESE 1 no	**-**	**100%**	**-**
TOTAL	**20%**	**58.8%**	**21.2%**

PVALUE .82441

PACKYEARS

The mean pack years of smoking among the patients was calculated. The distribution is given in the table below.

TABLE – 6

DISTRIBUTION OF PACK YEARS WITH AGE

Age groups	Pack years mean	Standard deviation
20-30	**26.43**	**15.20**
30-40	**28.91**	**14.06**
40-50	**31.85**	**9.52**
50-60	**32.39**	**12.42**

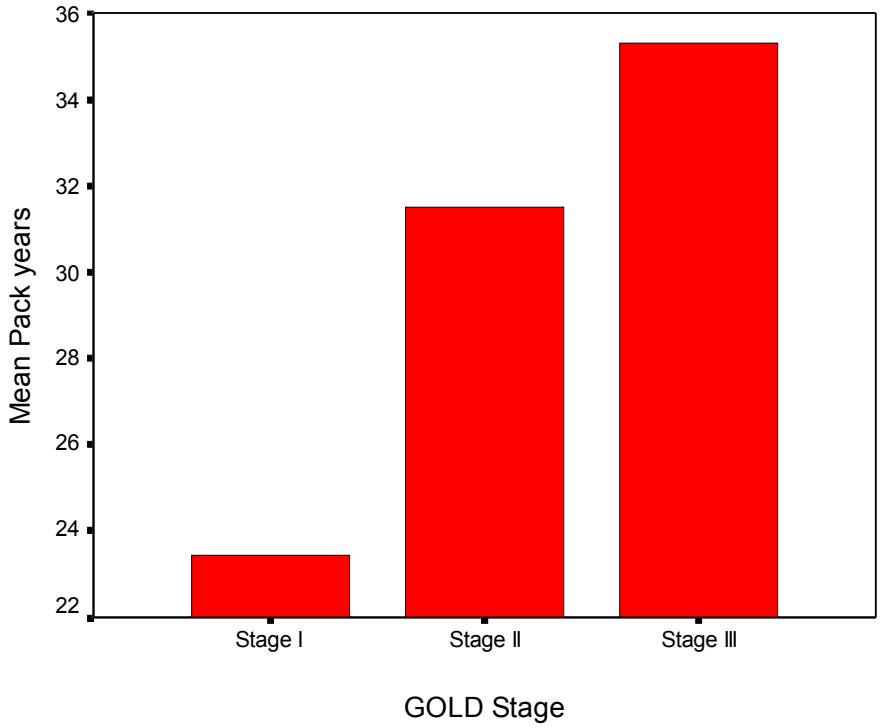
The distribution of the pack years of smoking with the severity of COPD was assessed anova test followed by tukey- hsd test. It was found that a statistically significant difference was found between stages 1 and 3.

The following table shows the details

TABLE – 7

GOLD STAGE AND PACKYEARS

Gold stage	Pack years mean	Standard deviation
Stage 1	**23.44**	**14.80**
Stage 2	**31.49**	**11.42**
Stage 3	**35.29**	**8.92**



It is seen that with increasing pack years of smoking the severity of the disease as per GOLD stage is also increasing. The statistical significance was

calculated using multiple range tukey- hsd test and was found to be statically significant at a p value of .040.

The correlation of other variables like FEV1 percentage of predicted, ESR, polymorphs percentage, hs-CRP, plasma fibrinogen with pack years is given in the following table.

TABLE – 8

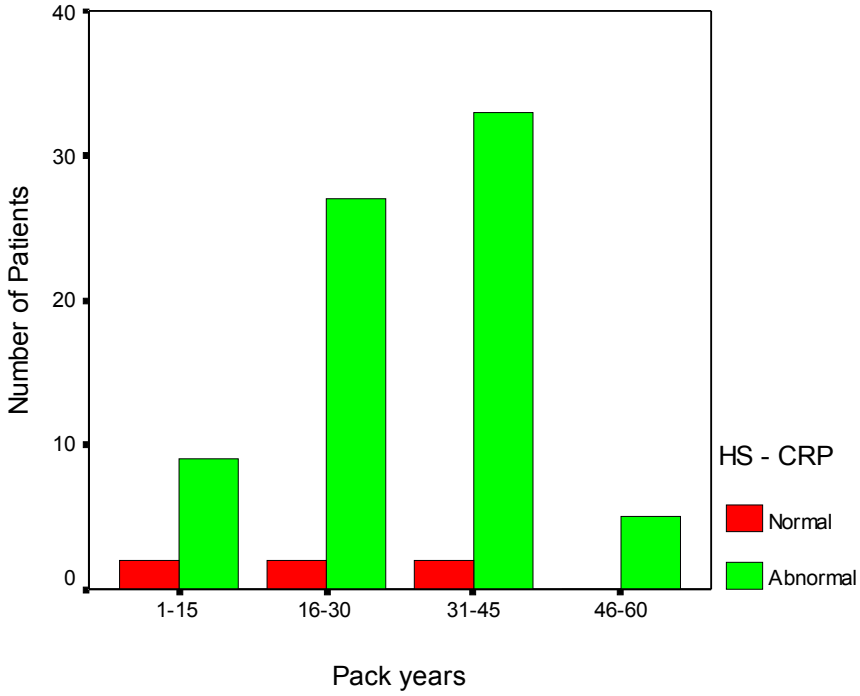
CORRELATION OF INFLAMMATORY MARKERS

WITH PACKYEARS

Pack years	Correlation coef	P value
Age	.155	.168
Esr	.4327	.006
Polymophs%	.2269	.043
Hs - crp	.4404	.006
Plasma fibrinogen	.2872	.010
FEV1 percentage pred	-.3306	.003

As we can see from the data above it is seen in our study that the numbers of pack years of smoking is significantly correlated with the levels of systemic

inflammatory markers and decreasing lung function in the form of decreasing FEV1 percentage of the predicted value. The correlation was studied using spss software analysis.



Polymorhs percentage

The polymorph percentage in the study group of patients was estimated by auto analyzer. The group was divided into normal (40-60%) and abnormal(>61%). The distribution in the study group is given in the following diagram and chart.

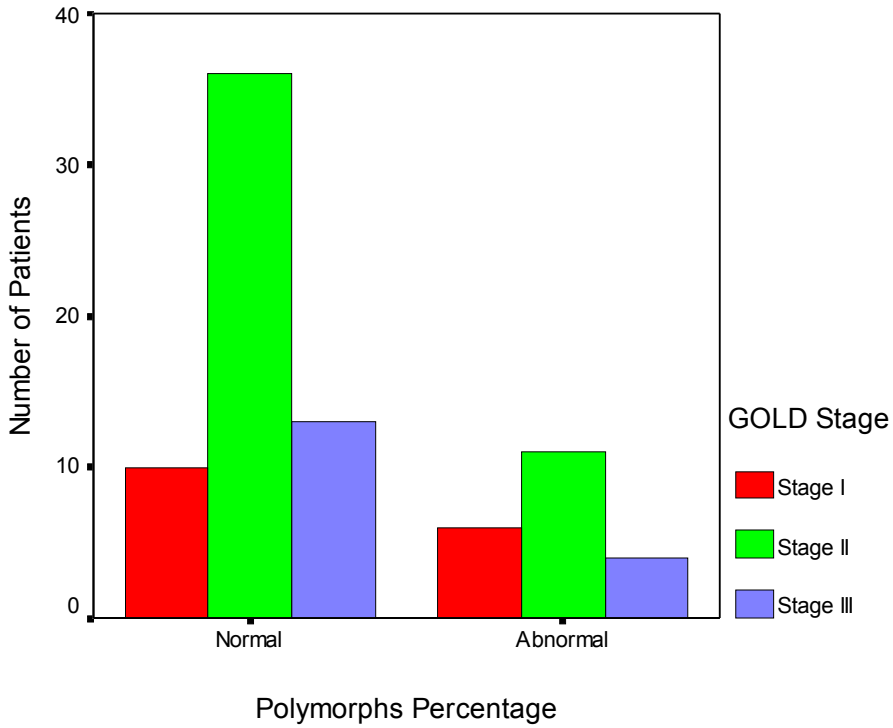
TABLE – 9

POLYMORPH PERCENTAGE DISTRIBUTION

Polymorph percent	frequency	percentage
Normal (40-60%)	59	73.75%

Abnormal (>61%)	**21**	**26.25%**
total	**80**	**100%**

The data collected in the study showed that most individuals were with normal polymorph percent group. The correlation assessed between the poly morph and the severity of COPD as per GOLD staging and FEVI percentage of predicted value did not show any correlation when tested with chi-square test and Pearson method. The p values >.05 and the correlation coefficient with FEV1 predicted percentage was .349 with a p value >.05. But the polymorph percentage shows a positive correlation with pack years of smoking with a correlation coefficient of .2269 with a statistically significant p value of .043.



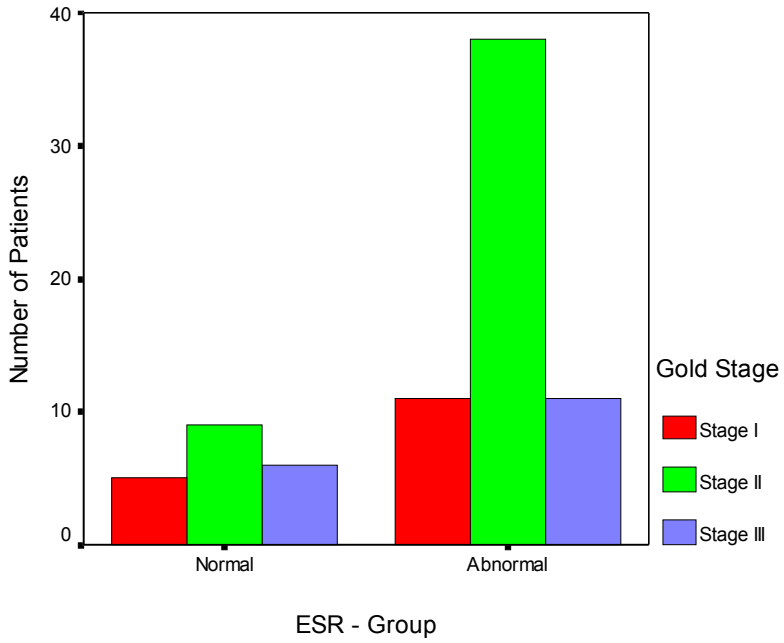
ESR

The ESR of the individual patients was measured using the wintrobes method. The distribution as normal range of <15mm and abnormal of >16 was seen and is shown in the following table and diagram.

TABLE - 10

ESR DISTRIBUTION IN STUDY POPULATION

Esr group	Frequency	percentage
Normal<15mm	20	25%
Abnormal>16	60	75%
Total	80	100%



It was observed that 75% of the participants had baseline levels of ESR above normal in the absence of causes of inflammation other than COPD. Among the ESR abnormal group most no of patients with abnormal ESR were found in stages 2 and 3. The correlation between abnormal increased levels of ESR and increasing severity of COPD was assessed using chi-square test and Pearson method and the p value was not significant ie,.34091. This could be because of the n value of the study. But it was found that ESR had a strong negative correlation with the percentage of predicted FEV1. The correlation coefficient was -.4327 with a p value of .101. This could be because percentage of predicted FEV1 which is a continuous variable shows a better staging of the copd disease than the GOLD stage. The following table gives the assessment of correlation between abnormal increased levels of ESR and increasing severity of COPD as per gold stage.

TABLE – 11

CORRELATION OF ESR WITH GOLD STAGE

ESR	Stage 1	Stage 2	Stage 3	Total %
	Percentage Distribution			
Normal (20 Nos)	25%	45%	30%	25%
Abnormal (60 Nos)	18.3%	60.3%	18.3%	75%
Total (80 Nos)	20%	58.8%	21.3%	100%

hs- CRP

The main parameters i.e., the systemic markers of inflammation being assessed in this study i.e., hs- CRP and plasma fibrinogen were calculated. Their distribution in the study population is given in the following table and diagram.

TABLE – 12

DISTRIBUTION OF hs-CRP AND PLASMA FIBRINOGEN VALUES

hs- CRP	Frequency	Percentage
Normal <0.3mg/dl	6	7.50%
Abnormal >0.3mg/dl	74	92.50%
Plasma fibrinogen		
Normal <400mg/dl	48	60%
Abnormal >401mg/dl	32	40%
Total	80	100%

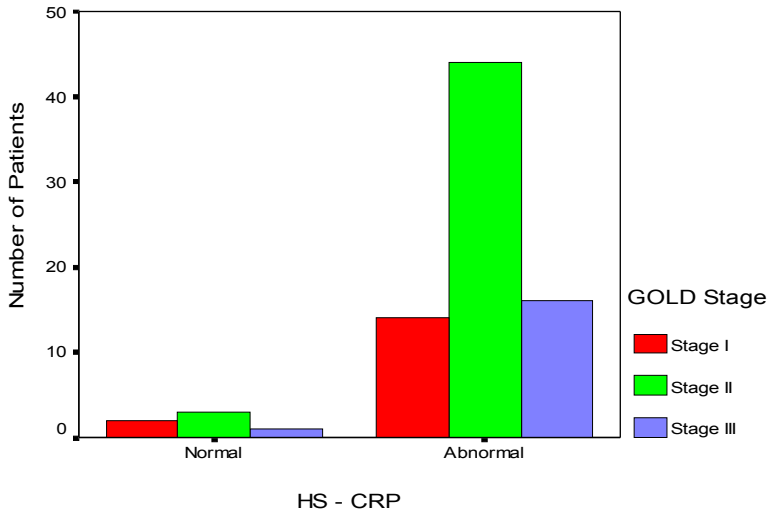


TABLE – 13

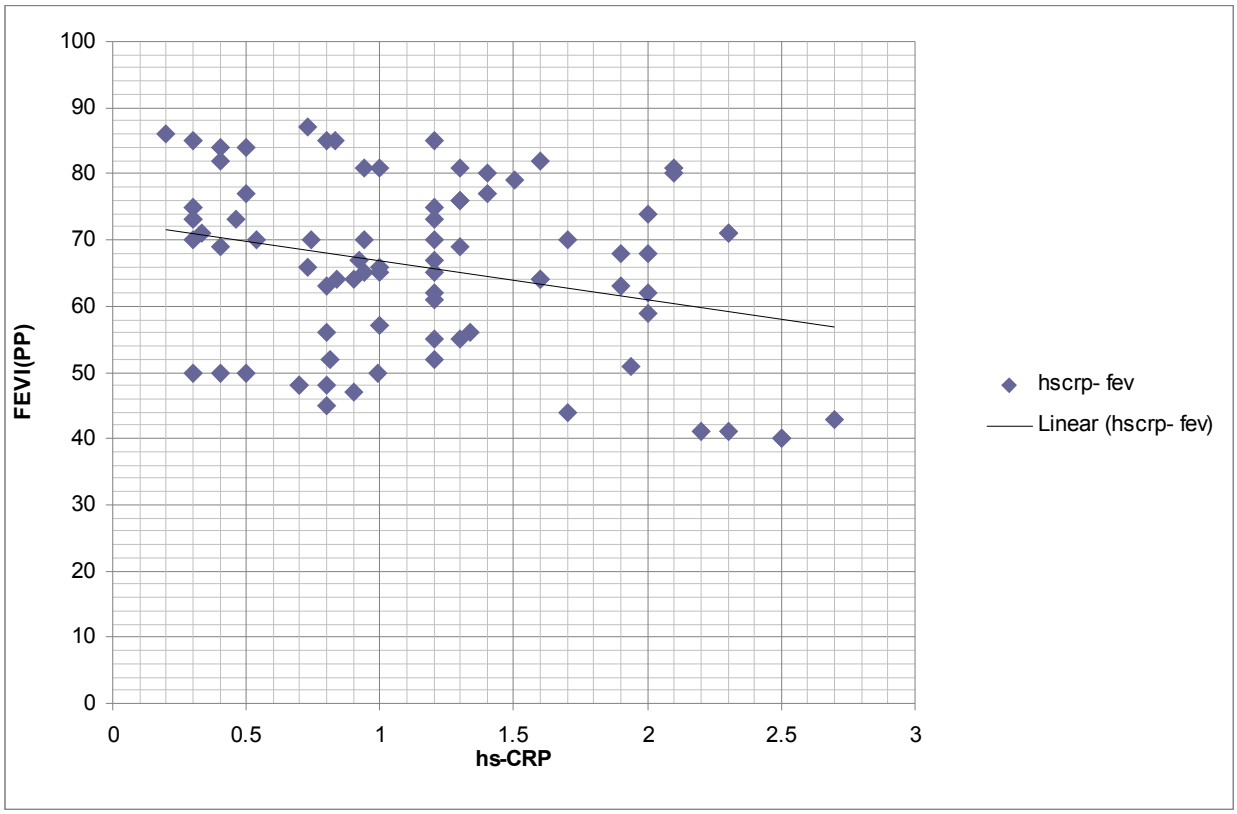
CORRELATION OF hs-CRP WITH GOLD STAGE

Hs-CRP	STAGE1	STAGE2	STAGE3	TOTAL

NORMAL<0.3	**33.3**	**50**	**16.7**	**6**
ABNORMAL>0.3	**18.9**	**59.5**	**21.6**	**74**
TOTAL	**20**	**58.8**	**21.3**	**80**

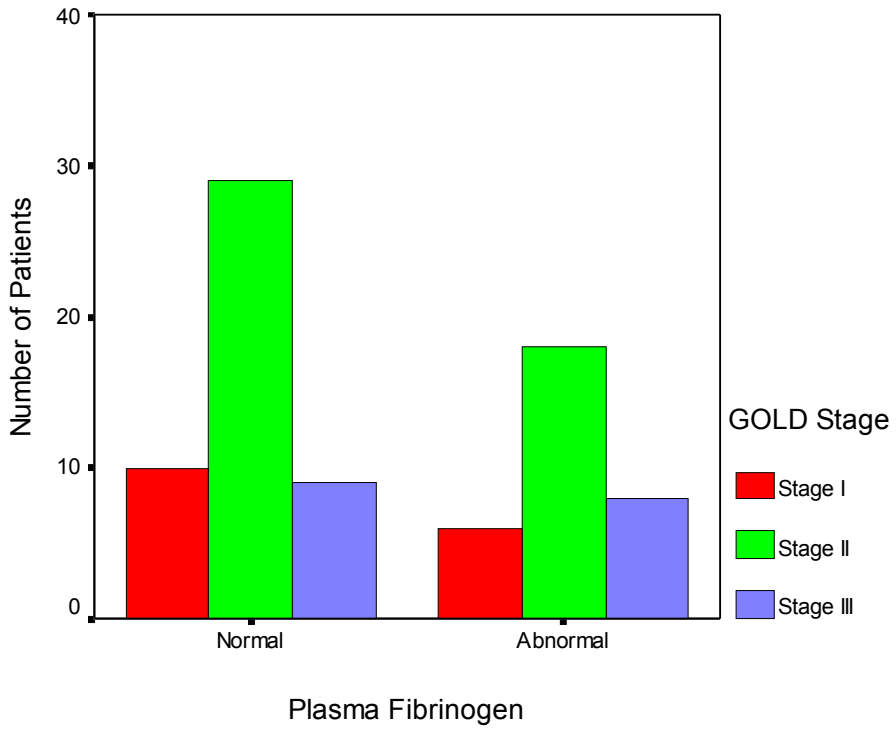
P value .69585

The majority of the study populace had elevated levels of hs-CRP i.e., 92.50%. Among the patients with elevated hs- CRP it was higher in patients with increasing severity. The correlation assessed by chi-square test and Pearson method was not found to be statistically significant with a p value >.05. But even in that data it was found that increasing severity of copd had a linear relation with increasing levels of hs-CRP and it had a strong negative correlation with percentage of predicted FEV1 the correlation coefficient calculated being -2.784 with a p value of.012. This discrepancy can be explained by the smaller n value in our study and the percentage of predicted FEV1 being a continuous variable and a better predictor of severity in a small group than GOLD stage.



PLASMA FIBRINOGEN

The distribution of the levels of plasma fibrinogen is the study populace (table above) and the bar diagram to show the distribution among the different stages of COPD as per GOLD CRITERIA is given below.



The data shows that majority of the study group patients have normal levels of plasma fibrinogen.ie,60%.the correlation with increasing levels of COPD a per GOLD stage was measured using chi-square test and Pearson method. The correlation was not statistically significant with a p value of>.05. The table is given below.

TABLE – 14

CORRELATION OF PLASMA FIBRINOGEN WITH GOLD STAGE

	Stage 1	Stage 2	Stage 3	Total
Plasma fibrinogen	Percentage Distribution			
Normal<400mg/dl	20.8	60.4	18.8	48
Abnormal>401mg/dl	18.8	56.3	25.0	32
total	20	58.8	21.3	80

P value .797

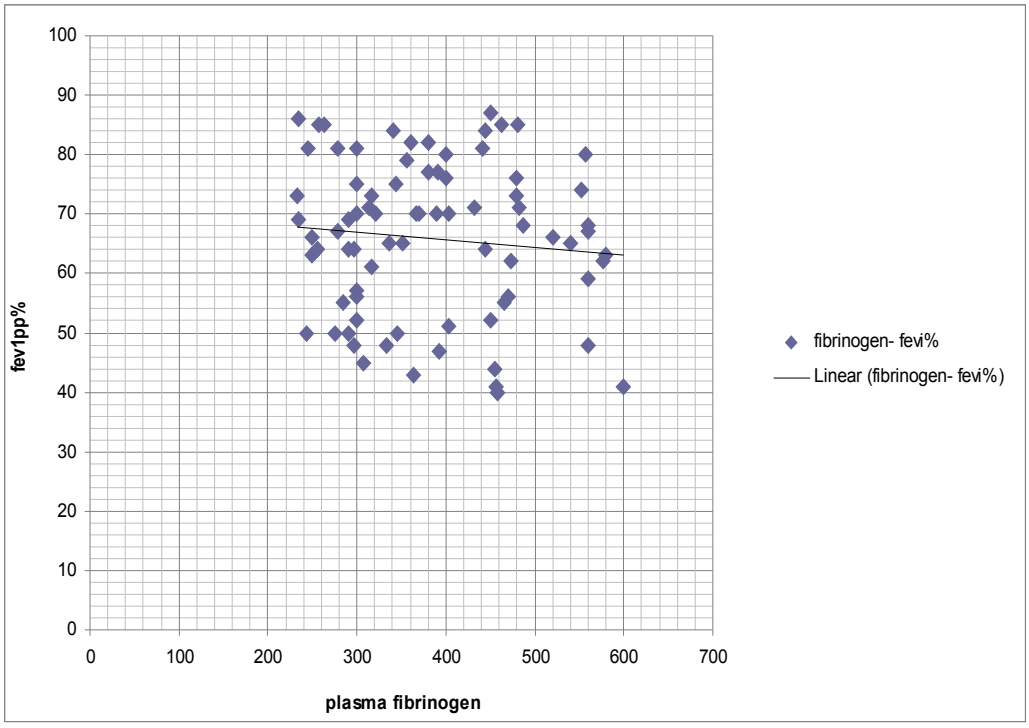
The scatter diagram showing the correlation of plasma fibrinogen with FEV1 percentage of predicted is given below. But the data seen shows that among patients with normal and abnormal levels of plasma fibrinogen the levels were higher with increasing stage of the disease and the scatter diagram correlating plasma fibrinogen with percentage of predicted FEV1 shows a linear negative relation even though the finding is not statistically significant, p>.05.

TABLE – 15

CORRELATION OF INFLAMMATORY MARKERS WITH FEV1

PERCENTAGE OF PREDICTED VALUE

FEV1	ESR	hs-CRP	Plasma fibrinogen
Correlation coef	-.1846	-.2784	-.1022
P value <.05- significant	.101	.012	.367



DISCUSSION

DISCUSSION

In most patients with COPD, the disease process affects the airways (leading to airway remodeling) and parenchyma (leading to emphysema and poor gas exchange). The predominant symptoms of COPD are chronic (productive) cough and exertional dyspnea. However, a substantial proportion of COPD patients have extra-pulmonary symptoms and signs. For instance, in advanced COPD, weight loss and cachexia are common. Other common manifestations include skeletal muscle weakness, osteoporosis, heart failure, cardiac arrhythmias, ischemic heart disease, stroke, depression, and cancer. Interestingly, the severity of the underlying COPD modifies the risks of these extra-pulmonary manifestations.

Despite the awareness about smoking and its well known side effects, the problem of COPD continues to grow. The ever changing concepts about the pathogenesis of COPD and its effects we need to keep abreast with newer facets of COPD from the knowledge of which newer modalities of treatment both implicit as well as in protocol form for prophylaxis as well as secondary prevention can elucidated with further knowledge of the risk factors for the systemic effects and other important organ damage due to inflammation. The study of the distribution of these markers of inflammation among Indian population was important for forming any guidelines on treatment. There is a paucity of such studies in the Indian population. There fore this cross-sectional

study was done with a aim to observe for any consistent correlation with severity of COPD and the markers of inflammation.

Previous studies (LINDA et al) have shown an increasing severity of COPD with increasing age which our study also showed a similar trend possibly related to the increase in the duration of smoking as shown by pack years. Among the different age groups there was increasing correlation of age with severity as per FEV1 percentage of predicted as well as GOLD STAGE which was found to be statistically significant with a p value of .00071calculated by chi square test indicating the presence of severe disease with increasing age.

The correlation between increasing severity of COPD and decreasing BMI has been observed in some studies[48] [Creutzberg *et al.* 1998]. This observation of correlation was not seen in our study; possibly because of rigorous selection of patients as per the exclusion criteria (ill patients were excluded). Also the proposed mechanism behind the decrease in BMI was alteration in the level of leptin, which is dependant on other regulators such as those with predisposition to obesity. Other measures of cachexia and skeletal muscle wasting i.e., mid thigh circumference body impedance measurement technique and DEXA can be better markers of severity of early cachexia and wasting[51].

ESR and polymorph percent of total WBC count are nonspecific markers of inflammation which are found to vary highly among individuals. There have been studies which have used these markers for assessing severity of copd. But

the inflammation in COPD is at a low level and is chronic. We wanted to see if there were minor variations in these markers, if present could be used as low cost markers of inflammation in COPD or to possibly sub stratify patients with COPD[49]. The data collected in the study showed that most individuals were with normal polymorph percent group. The correlation assessed between the poly morph and the severity of COPD as per GOLD staging and FEVI percentage of predicted value did not show any correlation when tested with chi-square test and Pearson method. The p values >.05 and the correlation coefficient with FEV1 predicted percentage was .349 with a p value >.05. But the polymorph percentage shows a positive correlation with pack years of smoking with a correlation coefficient of .2269 with a statistically significant p value of .043. It was observed that 75% of the participants had baseline levels of ESR above normal in the absence of causes of inflammation other than copd. Among the ESR abnormal group most no of patients with abnormal ESR were found in stages 2 and 3. The correlation between abnormal increased levels of ESR and increasing severity of COPD was assessed using chi-square test and Pearson method and the p value was not significant ie,.34091. This could be because of the n value of the study. But it was found that ESR had a strong negative correlation with the percentage of predicted FEV1. The correlation coefficient was -.4327 with a p value of .101. This could be because percentage of predicted FEV1 which is a continuous variable shows a better staging of the copd disease than the GOLD stage. Therefore it is possible that ESR can be used as a marker to corroborate the patients' history of smoking in a particular patient.

C-reactive protein (CRP) is an acute phase reactant protein measured in plasma, synthesized by the liver in response to inflammation. CRP is elevated in patients with stable COPD, regardless of stage[50], and in patients the treatment of exacerbations is associated with a decline in CRP. In our study majority of the populace had elevated levels of hs-CRP i.e., 92.50%. Among the patients with elevated hs- CRP it was higher in patients with increasing severity. The correlation assessed by chi-square test and Pearson method was not found to be statistically significant with a p value >.05. But even in that data it was found that increasing severity of copd had a linear relation with increasing levels of hs-CRP and it had a strong negative correlation with percentage of predicted FEV1 the correlation coefficient calculated being -2.784 with a p value of.012.This discrepancy can be explained by the smaller n value in our study and the percentage of predicted FEV1 being a continuous variable and a better predictor of severity in a small group than GOLD stage. Therefore it is prudent to conclude that the levels of hs-CRP increases with severity of COPD suggesting the increasing grade of micro inflammatory process in COPD, possibly causing increasing pre disposition to cardiovascular manifestations of COPD. It is also possible that hs-CRP can be used as an early marker of impending exacerrebration since in other studies it has been found to decrease with treatment. It can also be used to sub classify patients with COPD. It is also probable to conclude that the percentage of predicted FEV1 is a better variable to stratify patients according to severity when dealing with smaller groups or

individuals as it a continuous variable giving more concrete measurement of individual pulmonary dysfunction.

It was reported that COPD patients had significantly higher levels of fibrinogen than healthy subjects. Wedzicha et al reported that plasma fibrinogen levels were elevated in stable COPD patients and further increased during exacerbations, which was associated with increased serum interleukin (IL)-6. IL-6 is capable of modulating the number and/or activity of important inflammatory cells. IL-6 is synthesized by airway epithelium, macrophages and several other cells at sites of inflammation[17,18]. Fibrinogen, an acute-phase reactant and a blood-clotting factor, is synthesized by hepatocytes and released in large amounts into the circulation, primarily in response to IL-6 stimulation[52]. Therefore, it is possible that fibrinogen could be used as a marker of ongoing airway inflammation and lung tissue injury in the absence of other possibilities. We did not look for levels of IL-6, but it can be speculated that this cytokine plays a role in the rise of fibrinogen in our cases due to the ongoing inflammatory processes. Our data shows that majority of the study group patients have normal levels of plasma fibrinogen.ie,60%. The correlation with increasing levels of COPD as per GOLD stage was measured using chi-square test and Pearson method. The correlation was not statistically significant with a p value of>.05. But the data seen shows that among patients with normal and abnormal levels of plasma fibrinogen the levels were higher with increasing stage of the disease even though the finding is not statistically significant p>.05.this again we feel can be due to the limitation of the smaller sample size.

Moreover the study patients were in stable condition without any exacerbation in which plasma fibrinogen has been found to be elevated more. Still even with our data we see that plasma fibrinogen base line levels are increased with higher severity of COPD as per the FEV1 percentage of predicted value. This finding has implications for people with COPD who are at higher risk for peripheral and central, systemic and pulmonary vascular thrombosis in whom prophylaxis to prevent such a catastrophe from happening.

Therefore we conclude that copd is a multisystem disease, with chronic micro level inflammation that has several systemic manifestations. The markers of this inflammation can have a vital role in pathogenesis of these comorbid illnesses such as cachexia, osteoporosis, cardiovascular morbidity, cancer, depression and anxiety. Also these markers such as hs- CRP and plasma fibrinogen can be used to predict outcomes in patients with COPD. These along with other markers could be used to sub classify patients with COPD into several groups and approach them individuals accordingly.

LIMITATIONS OF STUDY

LIMITATIONS OF STUDY

1) We found that in our study there was some limitations with the sample size which precluded us from getting statistical significance with regard to certain variables with the severity of COPD.

2) The exclusion criteria that we put forward were limiting our ability to correlate the variables that we had chosen with severity as assessed by GOLD staging of COPD.

3) The study has only male patients which precluded us from studying these variables distribution in the female population.

4) Our study comprised of patients with COPD who were not functionally incapacitated to limit everyday activities though the symptoms had prompted them to access health care which could probably be associated with the lack of correlation between certain variables and the severity as measured by GOLD stage.

We suggest that more studies are needed in Indian population regarding these markers of inflammation occurring in COPD, with more number of patients with better markers of disease and systemic markers to come to a conclusion on the various use of these markers in making therapeutic guidelines and use in prognostification.

CONCLUSIONS

CONCLUSIONS

1. hs-CRP has been found to be significantly elevated with increasing severity of COPD which could lead to increased predisposition to cardio vascular morbidity and mortality.
2. Plasma Fibrinogen levels were not found to be significant marker of COPD coagulopathy in our study or stable COPD. More studies are needed.
3. Polymorph percentages, ESR are not significant markers of inflammation in COPD.
4. ESR, hs-CRP, Plasma Fibrinogen are markers of increasing exposure to smoking.
5. Physicians need to approach COPD as a multi system disease and identify patients with the associated co-morbidities of COPD vis-à-vis the extra pulmonary manifestations of COPD.

ANNEXURE

- **PROFORMA**
- **MASTER CHART**
- **ETHICAL COMMITTEE CERTIFICATE**
- **ABBREVIATIONS**

PROFORMA

NAME: **AGE:** **SEX:**

ADDRESS:

OCCUPATION:

SYMPTOMS: **COUGH/EXPECTORATION/DYSPNOEA/WHEEZING/ FEVER. etc..**

SMOKER: **PRESENT/PAST/NEVER**

IF PRESENT, HOW MANY PACK YEARS

IF PAST, HOW MANY YEARS OF ABSTAINANCE

DIABETES: **YES/NO** **IF YES, NO. OF YEARS**

HYPERTENSION: **YES/NO** **IF YES, NO. OF YEARS**

IHD:

CVA:

PERIPHERAL VASCULAR DISEASE:

IMMUNOLOGICAL/INFLAMMATORY DISORDERS:

FEVER/ARTHRALGIA/ARTHRITIS/RASH/ANEMIA/VASCULITIS/HEMATURIA/SCLERITIS/OTHER

RENAL DISORDERS:

LIVER DISORDERS:

CANCER:

CLINICAL FINDINGS:

PR: **PERIPHERAL PULSES:** **RR:**
BP:

CVS: **RS:**

CNS: **P/A**

LAB INVESTIGATIONS:

HB: **PCV:** **TC:** **DC:** **ESR:**

PLATELETS:

BLOOD SUGAR: **FBS:** **PPBS:**

BLOOD UREA: **S. CREATININE:** **TOTAL PROTEIN:**

ALBUMIN:

TOTAL BILIRUBIN: **DIRECT BILIRUBIN:** **SGOT:**

SGPT: **SAP:**

HSCRP:

PLASMA FIBRINOGEN:

CHEST XRAY:

ECG:

ECHO:

PULMONARY FUNCTION TESTS:

FEV1: **FVC:** **FEV1/FVC:** **GOLD STAGE:**

FEV1 percentage of predicted:

IMPRESSION:

S.No.	Name	Age (yrs)	Sex	BMI	FEVI (litr)	FVC(litr)	FEVI/FVC	FEV1% OF PREDICTED VALUE	GOLD STAGE	ESR <15mm/hr	POLY% (40-60%)	HS-CRP	PLASMA FIBRINOGEN	pack years
1	abbas.m	50	M	30.86	2.1	4.7	0.44	51%	stage3	23	66	1.94	404	50
2	abdul	39	M	27.77	3.4	5.3	0.64	70%	stage2	26	48	0.94	367	25
3	ajaxkumar	29	M	23.02	3.4	4.5	0.63	87%	stage1	18	50	0.73	450	15
4	anandaraj	42	M	27.50	1.7	3.7	0.60	71%	stage2	29	60	2.3	432	35
5	anbu	28	M	24.91	3.3	4.8	0.68	80%	stage1	32	55	2.1	557	5
6	andrew	57	M	21.60	2.8	4.1	0.68	70%	stage2	12	40%	0.74	389	10
7	arokiyadoss	47	M	19.14	1.5	3	0.50	48%	stage3	56	66	0.8	560	40
8	arokiyaswamy	57	M	21.60	2.8	4.1	0.68	70%	stage2	11	48	0.54	370	20
9	babu	31	M	25.68	4	5.8	0.68	85%	stage1	9	52	0.3	257	10
10	bakyaraj	46	M	24.72	1.6	3	0.53	47%	stage3	30	50	0.9	393	40
11	baskar	32	M	20.76	3.4	4.9	0.69	85%	stage1	32	70	0.83	481	10
12	chandra	46	M	29.41	2.3	3.8	0.60	67%	stage2	10	54	0.92	560	15
13	chockalingam	35	M	27.25	2.5	3.9	0.64	69%	stage2	8	45	0.4	234	20
14	christo	39	M	24.76	1.6	2.4	0.64	66%	stage2	33	49	1	520	20
15	daniel	56	M	30.43	1.6	2.6	0.61	66%	stage2	31	49	0.73	249	25
16	dharma.p	40	M	27.98	1.7	3.5	0.48	56%	stage2	22	56	0.8	470	20
17	harish	23	M	18.51	3	5.5	0.54	63%	stage2	44	54	1.9	580	45
18	james	59	M	23.82	2	5	0.40	44%	stage3	12	56	1.7	455	40
19	johnson	33	M	23.87	3.3	4.8	0.68	84%	stage1	6	43	0.5	341	25
20	k.moorthy	55	M	31.56	2.5	4	0.60	75%	stage2	8	42	0.3	300	20
21	kamath	44	M	27.33	2.2	4.3	0.60	62%	stage2	40	65	1.2	474	25
22	karthick	27	M	23.70	2.7	4	0.67	65%	stage2	22	50	0.94	540	40
23	karupaiah	39	M	27.70	3.4	5.4	0.63	77%	stage2	21	43	0.5	380	20
24	kathaan	39	M	34.22	2	2.9	0.68	74%	stage2	38	79	2	552	40
25	kathyaya	55	M	34.37	2	3	0.66	68%	stage2	22	56	1.9	487	40
26	krippa	58	M	20.37	1.6	4.4	0.36	41%	stage3	33	49	2.3	600	50
27	krishnan	53	M	27.33	2.2	4.3	0.60	62%	stage2	56	77	2	576	50
28	kulanchi	36	M	31.25	3.6	5.5	0.65	80%	stage1	39	48	1.4	400	20
29	mani	46	M	21.60	2.1	4.6	0.45	55%	stage2	22	47	1.3	465	25
30	mani.p	55	M	35.46	1.6	3.2	0.50	48%	stage3	12	45	0.7	333	20

31	manickam	47	M	23.74	3	4.3	0.60	85%	stage1	28	55	1.2	463	25
32	mariapan	44	M	28.80	2	4	0.50	50%	stage3	9	48	0.5	290	20
33	munivel	48	M	25.61	3	5.2	0.60	71%	stage2	29	60	2.3	482	35
34	murugan	43	M	27.50	1.7	3.7	0.45	41%	stage3	34	66	2.2	456	30
35	muthu	57	M	21.60	2.8	4.1	0.68	70%	stage2	32	64	1.2	404	30

36	narasiman	37	M	16.04	2.6	5.4	0.48	59%	stage2	36	55	2	560	45
37	narayanan	44	M	34.37	2	3.5	0.57	64%	stage2	44	67	1.6	444	40
38	padavattan	56	M	29.47	2.2	3.7	0.59	70%	stage2	12	56	0.3	300	30
39	padurangan	41	M	31.07	2	4	0.50	52%	stage3	44	68	1.2	450	35
40	palanivel	41	M	26.86	3	4.5	0.66	73%	stage2	36	62	0.46	480	35
41	pappan	58	M	41.40	2	3.4	0.58	71%	stage2	12	55	0.33	313	30
42	Partha	40	M	26.50	2	4	0.50	76%	stage2	45	40	1.3	480	40
43	parthiban	52	M	29.75	2.9	4.3	0.67	82%	stage1	20	45	0.4	381	30
44	pitchandi	57	M	25.94	3.1	4.8	0.64	81%	stage1	18	80	1.3	300	35
45	r.ahmed	42	M	19.40	2.2	4	0.55	64%	stage2	32	67	1.6	256	30
46	raghu	37	M	22.22	2	5	0.40	45%	stage3	22	45	0.8	307	35
47	raja	37	M	22.74	2	4.5	0.44	50%	stage3	12	48	0.3	276	35
48	rajan	44	M	28.80	2	4.9	0.43	50%	stage3	32	56	0.99	345	35
49	rajiv	33	M	24.46	3.1	4.5	0.68	82%	stage1	46	68	1.6	360	40
50	ramu	59	M	23.80	2.5	5	0.50	62.50%	stage2	21	48	0.8	250	10
51	ravi	32	M	20.76	3.4	4.7	0.70	85%	stage1	10	64	0.8	263	10
52	riaz	38	M	26.64	3.2	4.8	0.68	84%	stage1	8	48	0.4	445	40
53	s.prakash	42	M	19.40	2.2	4	0.55	64%	stage2	18	66	0.9	296	10
54	sakarai	59	M	19.40	2.2	4	0.55	64%	stage2	22	55	0.84	290	40
55	sakthi	27	M	23.87	2.7	4	0.67	65%	stage2	22	50	1.2	337	40
56	salman	39	M	27.77	3.4	5.4	0.63	77%	stage2	20	56	1.4	391	40
57	santham	47	M	26.77	2.5	4.6	0.54	67%	stage2	32	54	1.2	278	40
58	sathyam	56	M	30.61	2.4	4	0.60	68%	stage2	44	60	2	560	40
59	sebastian	59	M	21.48	1.6	3	0.53	57%	stage2	21	48	1	300	40
60	shankar	41	M	26.86	3	4.5	0.66	73%	stage2	18	60	1.2	317	45
61	shatru	48	M	39.50	1.6	3.3	0.48	50%	stage3	12	42	0.4	243	25
62	sk. Senthil	38	M	34.28	2.4	4	0.60	65%	stage2	30	50	1	352	45
63	somu	55	M	19.53	1.6	3	0.53	52%	stage2	34	56	0.81	300	60
64	soori	54	M	20.70	2.2	4.2	0.52	61%	stage2	16	55	1.2	316	40
65	sourimuthu	50	M	25.83	2.6	4	0.65	70%	stage2	34	66	1.7	321	35
66	sukumar	55	M	31.64	3	4.4	0.68	76%	stage2	18	60	1.3	400	35

67	suresh	59	M	29.06	2.7	4.2	0.64	81%	stage1	23	56	0.94	278	25
68	swaminathan	29	M	23.87	2.2	4.7	0.46	55%	stage2	16	66	1.2	284	20
69	thiru	30	M	39.50	1.8	3.6	0.50	56%	stage2	34	57	1.34	300	20
70	varadan	48	M	27.77	1.7	4.8	0.35	40%	stage3	36	60	2.5	458	40
71	velan	49	M	29.41	1.6	3.3	0.48	48%	stge3	12	45	0.7	297	25
72	velu	33	M	26.80	3	4.5	0.66	73%	stage2	10	44	0.3	233	40
73	vimalraj	38	M	31.25	2.6	3.7	0.70	81%	stage1	34	66	2.1	442	60
74	williams	59	M	23.84	2.5	4.3	0.58	69%	stage2	14	50	1.3	290	25
75	zakeer	43	M	31.37	1.7	3.7	0.43	43%	stage3	33	60	2.7	363	40
76	paneer	36	M	30.93	3	4.3	0.69	81%	stage1	23	67	1	245	15
77	zafarullah	48	M	29.73	3.1	4.6	0.67	79%	stage2	22	62	1.5	356	25
78	manish	39	M	32.28	3.3	4.8	0.68	86%	stage1	11	50	0.2	234	10
79	shankar	44	M	31.66	2.2	3.3	0.66	75%	stage2	24	56	1.2	344	20
80	vellayan	33	M	26.80	3	4.5	0.66	73%	stage2	10	44	0.3	233	40

INSTITUTIONAL ETHICAL COMMITTEE
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L.Dis.No. 14597/IMES/EthicsDean/MMC/2009 Dated .09.2009

Title of the work : "The correlation of hs CRP and plasma
Principal Investigator : fibrinogen levels with increasing severity of COPD
Department : Dr. A. Thomas Isiah - PG - M.D (Internal medicine) Madras Medical College - Ch. 3

The request for an approval from the Institutional Ethical Committee(IEC) was considered on the IEC meeting held on 23rd September 2009 at 2.00P.M. in Madras Medical College, Deans, Chamber, Chennai-3. / Pharmacology seminar hall - Madras Medical College - Ch. 3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearnance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s).
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

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ABBREVIATIONS

COPD	**:**	**CHRONIC OBTRUCTIVE PULMONARY DISEASE**
FEVI	**:**	**FORCED EXPIRATORY VOLUME IN 1 SEC**
FVC	**:**	**FORCED VITAL CAPACITY**
GOLD	**:**	**GLOBAL INITIATIVE ON OBSTRUCTIVE LUNG DISEASES**
IL-6	**:**	**INTERLEUKIN-6**
hs-CRP	**:**	**HIGHLY SENSITIVE C-REACTIVE PROTEIN.**
IHD	**:**	**ISCHAEMIC HEART DISESE**
RFT	**:**	**RENAL FUNCTION TEST**
LFT	**:**	**LIVER FUNCTION TEST**
CBC	**:**	**COMPLETE BLOOD COUNT**
PFT	**:**	**PULMONARY FUNCTION TEST**
ESR	**:**	**ERYTHROCYTE SEDIMENTATION RATE**
TC	**:**	**TOTAL WBC COUNT**
DC	**:**	**DIFFERENTIAL COUNT**
TGF	**:**	**TISSUE GROWTH FACTOR**
IGF	**:**	**INSULIN LIKE GROWTH FACTOR**
TNF	**:**	**TUMOUR NECROSIS FACTOR**
IP-10	**:**	**INDUCIBLE PROTEIN 10**
MMP	**:**	**MATRIX METALLOPROTEIN**
IL-1R	**:**	**ITERLEUKIN RECEPTOR TYPE 1**
Kda	**:**	**KILODALTON**
DEXA	**:**	**DUAL ENERGY X-RAY ABSORPIMETRY**
MI	**:**	**MYACARDIAL INFARCTION**
TIA	**:**	**TRANSIENT ISCHAEMIC ATTACK**
Vwf	**:**	**VON WILLIEBRAND FACTOR**

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