"TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY "

Dissertation submitted to The Tamil Nadu Dr.M.G.R. Medical University in partial fulfilment of the requirements for the degree of

Doctor of Medicine (M.D) in

Tuberculosis and Respiratory Diseases

Branch – XVII

Institute of Thoracic Medicine,

Madras Medical College &

Rajiv Gandhi Government General Hospital

The Tamil Nadu Dr. M.G.R. Medical University

Chennai – 600032

Tamil Nadu

India

May 2018

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY "** is the bonafide work done by **Dr.S.SIVAKUMAR** during his **M.D (Tuberculosis and Respiratory Diseases)** course in the academic years 2015-2018, at the Institute of Thoracic Medicine and Rajiv Gandhi Government General Hospital – Madras Medical College, Chennai. This work has not previously formed the basis for the award of any degree.

Prof. Dr. A.MAHILMARAN M.D., D.T.C.D
Director, Institute of Thoracic Medicine,
Professor and Head, Department of Thoracic Medicine,
Rajiv Gandhi Government General Hospital and Madras Medical College,
Chennai.

Prof. Dr. R.NARAYANABABU.,M.D.,DCH
The Dean,
Rajiv Gandhi Government General Hospital and Madras Medical College,
Chennai.

DECLARATION BY THE GUIDE

This is to certify that the dissertation titled **"TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY"** is the Bonafide work done by **Dr.S.SIVAKUMAR** during his **M.D (Tuberculosis and Respiratory Diseases)** course in the academic years 2015-2018, at the Institute of Thoracic Medicine and Rajiv Gandhi Government General Hospital – Madras Medical College, Chennai, **under my guidance**.

Signature of the Guide,

Name and Designation of the Guide:

Prof. Dr.A.MAHILMARAN .,M.D., D.T.C.D.,
Director, Institute of Thoracic Medicine,
Professor and Head, Department of Thoracic Medicine,
Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai.

MADRAS MEDICAL COLLEGE & RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL, CHENNAI – 600 003

DECLARATION BY THE SCHOLAR

I hereby declare that the dissertation titled **"TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY"** submitted for the degree of **Doctor of Medicine (M.D) in Tuberculosis and Respiratory Diseases, Branch XVII** is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or other similar titles.

Place : Chennai [DR.S.SIVAKUMAR]

Date : Signature of the scholar

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CONTENTS

Introduction:

As per GOLD 2017 guidelines, chronic obstructive pulmonary disease is a common , preventable and treatable disease characterized by a persistent respiratory symptoms and airflow limitation due to airway and / or alveolar abnormalities usually caused by a significant exposure to noxious particles or gases. COPD represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world. COPD is currently the fourth leading cause of death in the world (1) but it is projected to cause over 6 million deaths by 2020 and thereby becomes a third leading cause of death in the world.

COPD patients frequently have concomitant cardiovascular disease, skeletal muscle dysfunction , metabolic syndrome, osteoporosis , depression, anxiety and lung cancer. These comorbidities can independently influence the mortality and hospitalizations in COPD patients(GOLD 2017).

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COPD and cardiovascular disease (CVD) are leading causes of mortality globally. The prevalence of cardiovascular disease in COPD is around 28%- 70%(2). Cardiovascular diseases are the major contributor of morbidity and mortality in patients with COPD.(3)(4)(5). Systemic inflammatory changes related with COPD may independently increase the risk of cardiovascular diseases(6).

Understanding the association between these two disease entities may enable

improved Cardiovascular disease risk prediction in patients with COPD by identifying those individuals at higher risk of cardiovascular disease morbidity and mortality. This understanding may also provide an opportunity to develop targeted therapies for the subset of patients with CVD and COPD as the nature of inflammation may be the same.

Every 10% decrease in FEV_1 increases all cause mortality by 14%, cardiovascular mortality by 28%, and nonfatal coronary event by almost 20%, after adjustments for relevant confounders such age, sex, smoking status and treatment assignment.(7)

In 2016 it was estimated that about 59.1 lakh people in urban areas and 163 lakh people in rural areas in India suffered from COPD(8). The prevalence of obesity and metabolic syndrome(MetS) is rapidly increasing in India and approximately about one-third of the urban populations have MetS.(9). Metabolic syndrome is found to be twice more common in COPD when compared to the general population. Several studies from different parts of the world have shown a prevalence of 25.6-60.9% of metabolic syndrome in patients with COPD(10)(11).

Fabbri *et al*.(13) proposed COPD as a chronic inflammatory disorder(12). Several etio-Pathogenic mechanisms have been proposed as a possible link between COPD and Metabolic disorders that include systemic inflammation, adipose tissue inflammation and physical inactivity.

Metabolic syndrome has been identified as an independent risk factor for worsening respiratory symptoms, increasing lung function impairment, pulmonary

hypertension and poor exercise tolerance in COPD patients(14).

Oxidative stress and chronic hypoxia in COPD patients may contribute to the development of CVD, but the most attributing factor is thought to be the systemic inflammation and also airway inflammation may induce spill over systemic inflammation which is responsible for progression of atherosclerosis.

Carotid atherosclerosis strongly correlates with coronary atherosclerosis (15) and carotid intima-media thickness (CIMT) measured by carotid doppler ultrasound is an effective, validated method for evaluating carotid atherosclerosis (16). Both COPD and metabolic syndrome contributes to atherosclerosis by systemic inflammation and thereby contributing for increased cardiovascular diseases.

Increased CIMT is associated with increased total and cardiovascular mortality in patients with COPD suggesting that CIMT measurement may be a good biomarker to assess the cardiovascular morbidity and mortality in these patients(17).

Since COPD is a multicomponent disease with inflammation at its core leading to mortality , diagnosing metabolic syndrome and measuring carotid intima media thickness (CIMT) which is a marker of subclinical atherosclerosis can help us to predict the cardiovascular diseases in advance.

Comorbidities associated with COPD is an area of research and there are Not many studies done in india to establish the association of COPD with Metabolic syndrome and carotid intima media thickness.

REVIEW OF LITERATURE:

COPD AND IT'S COMORBIDITIES:

Extrapulmonary comorbidities influence the prognosis of patients with COPD. Tobacco smoking is a common risk factor for many comorbidities, including coronary heart disease, heart failure and lung cancer(18). Various comorbidies are

- Pulmonary hypertension
- Malnutrition
- Coronary artery disease
- Heart failure
- Lung cancer
- Systemic venous thromboembolism
- Anxiety & depression
- Peripheral muscle wasting
- Osteoporosis
- Obesity
- Metabolic syndrome
- Diabetes & hypertension
- Cardiac Arrythmias
- Sleep disturbances
- Obstructive sleep apnea
- Peripheral vascular diseases
- Cognitive impairment
- Sexual dysfunction

SYSTEMIC INFLAMMATION IN COPD:

Chronic obstructive pulmonary disease is characterised by a chronic inflammation in the pulmonary tissue. The extent of the inflammatory reaction is correlated with the severity of the disease.

Gang *et al*.(20) reported a meta-analysis of 14 reports which confirmed a strong Association between COPD and inflammatory markers such as CRP, fibrinogen, and TNF-α(19). Pulmonary inflammatory biomarkers in induced sputum, bronchoalveolar lavage, endobronchial biopsy have also been studied to correlate the association between COPD and systemic manifestation.

The increase in circulating inflammatory markers in COPD has been considered as a part of the "spill over" of the inflammatory mediators from the pulmonary compartment which is primarily responsible for systemic inflammation**.** The role of the spill over hypothesis has been further emphasized in recent studies by studying the relationship between the various inflammatory biomarkers and pulmonary tissue-derived proteins such as surfactant D-derived proteins from pneumocyte -II. A recent study by Kim *et al*. studied the candidate Single Nucleotide Polymorphism(SNP) of two pneumoproteins clara cell secretory protein (CC16) and surfactant protein D (SP-D) which appear to be strongly correlate with COPD. However, the roles of such biomarkers are yet to be fully established(21).

The possible mechanism proposed in spill over hypothesis are(23)

1) Leakage of reactive oxygen species and stress induced cytokines directly into the peripheral blood.

2) Preactivation of peripheral blood leukocytes that can result in aberrant homing and activation of inflammatory cells in distant tissues.
3) Liberation of proinflammatory mediators by leukocytes and stromal cells present in the pulmonary tissues during progression of the disease.

Adipose tissue inflammation has been proposed to be one of the important Contributors to systemic inflammation in obese COPD patients. Inflammation of Large adipocytes are associated with an increased production of pro-inflammatory adipokines IL-6, TNF-α, PAI-1 and leptins. Inflammation of adipose tissue has an adverse effect on insulin signaling pathways. Relationships have been observed between high adiposity, insulin resistance and the adipose tissue expression of macrophage cell surface receptor CD68. It plays an important role in whole body insulin resistance in COPD patients(22).

In addition to its contribution to the extrapulmonary effects of COPD, the intensity of the systemic inflammation is directly related to the poorer quality of life, airflow limitation and exercise intolerance observed in COPD.(24) Thus COPD can cause low grade systemic inflammation by hypoxia and various other mechanisms and systemic inflammation in turn can adversely affects the clinical and functional characteristics of COPD.

Heart disease and systemic and pulmonary vascular diseases in COPD

Vascular and heart diseases are among the most important comorbidities observed in COPD, because they have a direct impact on patient survival. The pathophysiological mechanisms underlying the vascular alterations observed in COPD appear to be mainly mediated by endothelial dysfunction and coagulopathy.

Endothelial dysfunction and COPD

The systemic inflammation observed in COPD seems to be the key determinant for the development of pulmonary and systemic endothelial dysfunction, although the precise pathophysiological mechanisms are unknown. Circulating endothelial progenitor cells (CEPCs), which plays an important role in maintaining endothelial cell integrity appears to be reduced in the systemic circulation and increased in the pulmonary circulation of patients with COPD (25)

Coagulopathy and COPD

The systemic inflammation present in COPD appears to induce a "pro-coagulant" state. In the basal state, COPD patients exhibit abnormally high levels of tissue factor (tissue factor pro-coagulant activity) and Factor VIIa(26), and their fibrin clots are resistant to lysis . After 2 h of artificial hypoxaemia, compared to non-hypoxic controls, COPD patients have abnormally elevated levels of circulating thrombin–antithrombin complex and prothrombin activation fragments, with a parallel elevation in interleukin (IL)-6 .

Coronary heart disease and COPD

Epidemiological association

Coronary heart disease and COPD share the same main risk factor, *i.e.* smoking. The impact of obstructive airway disease, defined by a decrease in the ratio of

forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC), is less clear-cut, as it only increases the risk of a coronary event by 30%. However, for every 10% decrease in FEV_1, all-cause mortality increases by 14%, cardiovascular mortality increases by 28% and the frequency of non-fatal coronary events increases by 20%(7). The link between COPD and coronary heart disease is independent of any other confounding coronary risk factors, namely smoking status, cholesterol, systemic hypertension and body mass index (BMI)(27).

***Shared pathophysiological mechanisms*:**

In coronary heart disease, the activation of immune cells in the atheromatous plaque induces the production of cytokines such as interferon-γ, IL-1, tumour necrosis factor (TNF)-α, IL-6 and acute-phase inflammatory proteins (fibrinogen, C-reactive protein (CRP) and amyloid protein) . The same mediators are involved in the inflammatory reaction observed in the bronchus in COPD. In addition to these shared pathophysiological determinants, the presence of COPD could contribute to the development of cardiovascular disease through hypoxia, systemic inflammation and oxidative stress (28), and through impaired vasodilatory capacity.

Coexistence of COPD and coronary heart disease worsens the prognosis of both diseases:

Coronary heart disease often goes unrecognised in COPD. A retrospective study of the medical records of 897 COPD patients treated between 2000 and 2003 was conducted in Akershus University Hospital (Oslo, Norway) (29). The records of 827

(92%) patients included an ECG. Sequelae of myocardial infarction were found on The ECGs of 229 (27.6%) patients, yet only 30% of these patients had a recognized history of myocardial infarction. Follow-up of the cohort until 2005 revealed the negative impact of a high ECG-based cardiac infarction injury score on their survival.

The systemic inflammatory reaction might play a role in the increased coronary risk in patients with COPD. The effect of COPD medication on cardiovascular events is not yet completely clear. The analysis of the data collected during the TORCH (Towards a Revolution in COPD Health)(30) study showed no increase in Cardiovascular events in patients with moderate-to-severe COPD receiving Salmeterol alone or in combination with oral steroid therapy. The possibility that tiotropium provokes cardiovascular adverse effects continues to be raised , with a relationship between the dose placed in the inhaler and the risk of adverse effects having recently been suggested.

HEART FAILURE AND COPD:

In a recent study, transthoracic echocardiography was prospectively performed in 342 COPD patients 3 months after their first exacerbation. Significant cardiac Alterations were present in 64% of patients, 27% left- and 48% right-heart disorders. In 63% of these patients, cardiac disease was not known(31).

A meta-analysis of 12 analysable studies, published in 2006, revealed the prevalence of heart failure among patients experiencing an exacerbation was as

high as 46% *versus* 3.8–16% in those with stable disease(32). The importance of this combination was confirmed in a cohort study including >45 000 patients with COPD and a sex- and age-matched healthy population of the same size, whose end-points were hospitalisation and cardiovascular mortality rates over a follow-up period of almost 3 years.

IMPACT OF COPD ON HEART FAILURE:

One of the first studies followed 800 patients with heart failure for 5 years and showed that survival was significantly lower in the group with concomitant COPD. The studies based on the Norwegian Heart Failure Registry, including 4132 Patients with heart failure from 22 cardiology centres, followed for nearly 8 years, Demonstrated a significantly higher proportion of deaths in patients with Concomitant COPD (32.6% *versus* 37.0%; p=0.03).(33)

Therefore COPD is an independent risk factor for death in compromised heart failure patients, and the coexistence of COPD can delay the diagnosis of heart failure. Beta blockers are known to improve the survival in heart failure, but underused in COPD patients, with the fear of worsening airflow limitation. Switching to a cardioselective β-blocker improves spirometric values, without affecting the left ventricular ejection fraction or New York Heart Association functional class, enabling a better cardiac prognosis without the risk of compromising respiratory function(34).

COPD AND METABOLIC SYNDROME:

Funakoshi *et al*. conducted a study on 7189 Japanese males aged 45-88 years and found that patients with GOLD staging II - IV have a high probability of having co-existent MetS with an Odds ratio (OR) of 1.33. Among the various

components of MetS, waist circumference (OR, 1.76; 95% CI, 1.24-2.50) and blood pressure (OR, 1.37; 95% CI, 1.08-1.74) showed a significant association with airflow obstruction of GOLD stage II-IV(35)

The D.E.S.I.R. study from France has shown that the MetS occurs more frequently Among current smokers. The potential mechanism responsible for development of COPD and the MetS in a smoker is primarily due to systemic inflammatory Response(36).

The Guangzhou Bio bank cohort study demonstrated that the risk of MetS is more common in those with significant airway obstruction

Several mechanisms has been proposed regarding the association between obesity and airflow limitation

(a) Decrease in chest and lung compliance

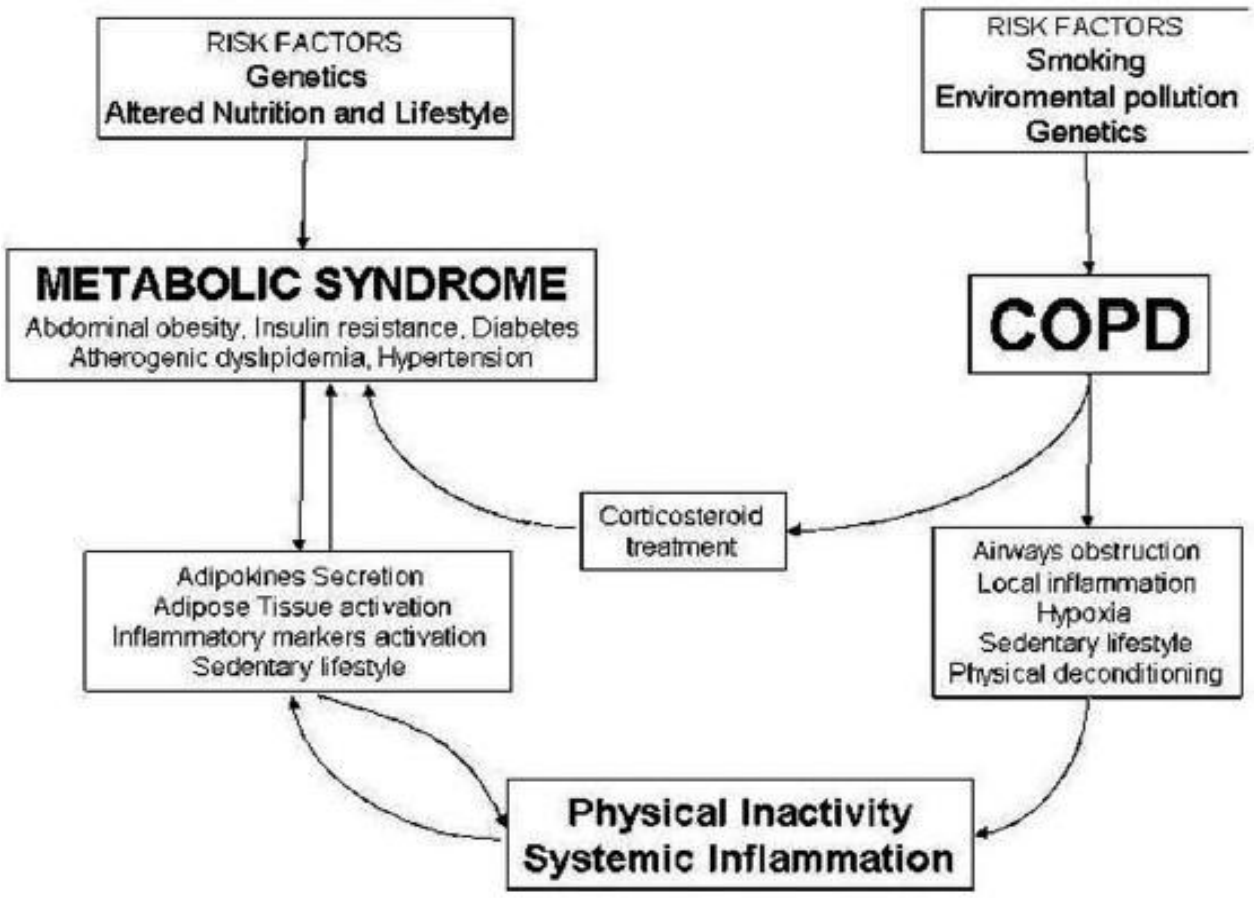
(b) Small airway dysfunction and expiratory airflow limitation

(c) Variable reduction in ventilator muscle strength and endurance

(d) Increased work of breathing

Link between metabolic syndrome and COPD are poorly understood. The proposed mechanisms are

- Common pathophysiological mechanisms – systemic inflammation
- Adipose tissue inflammation
- Physical inactivity
- Hypogonadism
- The effect of steroids.



Steroids affect most of the parameters of the metabolic syndrome. The traditional Clinical features of steroid overuse are diabetes, hypertension, dyslipidemia, and weight gain, usually presenting as central obesity with redistribution of body fat to truncal areas and dorsocervical and supraclavicular fat pads and the classic moon face(37).

COPD patients with the MetS have a more severe form of disease, more dyspnea, a lower FEV1 and require more inhalational glucocorticoids to control the disease. COPD patients with MetS have higher leptin levels, low adiponectin and greater insulin resistance. Thus this group of COPD subjects can be further stratified into a higher risk phenotype which requires a closer follow-up(38)

COPD AND OBESITY:

Steuten *et al.*(46) conducted a study to look at the association of severity of COPD And BMI among 317 subjects in the Netherlands. The overall prevalence of Obesity was 18% with the highest prevalence being in subjects with mild to moderate COPD (stages 1 and 2).

In patients with COPD, obesity has an unusual impact that is commonly, referred As "Reverse Epidemiology of Obesity". A meta–analysis by Cao *et al*. analyzed data on 22 studies which included about 21,150 subjects. It was found that patients with a lower BMI had a higher mortality rate when compared with normal BMI subjects**.** The relative risk for mortality is found to be decreased in overweight and obese patients with stages 3-4 while it increases in those with stage 1-2 disease. The weight loss, muscle wasting and loss of fat free mass is more prominent in late stages 3 and 4 in COPD also known as Obesity Paradox(39). Thus it indicates that both cachexia and obesity represent the two extremes of a spectrum of metabolic abnormalities that are seen in patients with COPD leading to adverse clinical outcomes.

Schols *et al*. (47) have prospectively followed up 412 stable COPD (stage -3 and 4) Subjects for 2-5 years or till the point of death whichever was earlier. The fat free mass (FFM) was found to be a better predictor of mortality irrespective of FM (fat mass)

COPD AND LIPOPROTEIN METABOLISM:

The pattern of dyslipdemia in COPD has not been well characterized. The CONSISTE study is a study to assess the cardiovascular risk factors in COPD subjects. COPD subjects had the highest prevalence of IHD (12.5% vs. 4.7%) when compared to controls. Dyslipidemia was found in 48.3% of COPD patients and 31.7% among controls.(48)

In the Rotterdam study(49) the effect of statins was prospectively assessed in COPD Patients over a period of more than 2 years. Statins are associated with a Reduction in death rate by 36% . Statins have many pleiotrophic effects such as anti-inflammatory and immunomodulatory properties. Statin therapy was associated with a 30% decrease in risk of COPD exacerbation(40).

COPD AND DIABETES:

The prevalence of diabetes in COPD is approximately about 3-12%(41). Systemic inflammation is probably an important contributory factor responsible for both COPD and diabetes mellitus.

The nurses' healthy study: a prospective study over an 8-year period had showed that COPD patients have a 1.8% relative risk of developing diabetes. The markers of inflammation such as IL-6, TNF-α, and CRP are elevated in both COPD and diabetes and these markers are elevated to a greater extent in overweight and obese COPD patients(42)

Engstrom *et al*. described that reduced lung function is an important risk factor for the development of diabetes in COPD(50).

Mannino *et al*. shows that subjects with stage 3-4 had a higher risk for developing diabetes with an odds ratio of 1.5 (CI: 1.1-1.9)(51).

COPD AND HYPERTENSION:

The incidence of hypertension can vary from 6-50% and depends upon the Severity of airflow of obstruction. A recent study (INDACO study) demonstrated a 53% incidence of hypertension. The pathological mechanisms (43) responsible for hypertension in COPD are

- Hypoxia related vasoconstriction,
- Free radical injury,
- Endothelial dysfunction,
- Arterial stiffness.

Control of hypertension in COPD subjects can improve the cardiovascular-related Mortality.

CAROTID INTIMA MEDIA THICKNESS AND CARDIOVASCULAR EVENTS:

Recent American Heart Association guidelines(52) designated carotid intima-media thickness (CIMT) is a class IIa recommendation for cardiovascular (CV) risk assessment in asymptomatic adults at intermediate risk of cardiovascular disease (CVD).

The Kuoppio Ischaemic Heart Disease study(44) showed 11% increased risk of myocardial infarction with each 0.1-mm incremental increase of carotid IMT. Several large clinical studies like the Atherosclerosis Risk In Communities study, the Cardiovascular Health Study, the Rotterdam Study, the Malmö Diet and Cancer Study, and the Carotid Atherosclerosis Progression Study produced similar results.

European Society of Cardiology(53) recommends ultrasound scanning of the carotid arteries to detect vascular hypertrophy or atherosclerosis as a class IIa recommendation with level of evidence B.

Measuring carotid IMT is safe, noninvasive and although it requires some experience, has quite high reproducibility.

COPD AND CAROTID INTIMA MEDIA THICKNESS:

Iwamoto *et al*.(54) reported a higher mean CIMT in male smokers with airflow Obstruction than that of control smokers and never smokers, indicating that airflow limitation rather than smoking *per se* is associated with atherosclerosis.

In the study by Gestel *et al(55)*. the mean carotid wall IMT was 1.07 mm. Of the patients Without COPD, 23% demonstrated increased CIMT, whereas 32% of patients with mild COPD and 36% of the patients with moderate to severe COPD had increased CIMT ($P < 0.01$)

The Rotterdam study(56) also revealed a significantly higher CIMT (≥2.5 mm) in participants with COPD than in those without COPD. Moreover, the CIMT

increased significantly with the severity of airflow limitation.

There is exaggerated subclinical atherosclerosis in smokers with airflow limitation, indicating that atherosclerotic change occurs early in the disease process of COPD. Systemic inflammation is predominantly associated with atheromatous plaque. Reduced lung function is associated with thickened IMT, but the underlying mechanism for this association is unclear.

COPD remained a significant and independent predictor of carotid plaqing After adjusting the traditional risk factors ($P < 0.0001$ odd ratio of 3.9 with 95% CI 2.1 to 7.3)(45).

AIMS AND OBJECTIVES:

PRIMARY OBJECTIVE:

TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME.

SECONDARY OBJECTIVE:

1. TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN DIFFERENT STAGES OF COPD
2. TO STUDY THE CLINICAL AND FUNCTIONAL DIFFERENCES IN COPD PATIENTS WITH AND WITHOUT METABOLIC SYNDROME

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MATERIALS AND METHODS:

STUDY DESIGN: Prospective Hospital Based Case Control Study

STUDY CENTRE: Rajiv Gandhi Government General Hospital,

Madras Medical College, Chennai

DURATION OF THE STUDY: Jan 2017- August 2017

SAMPLING FRAME:

- Patients attending OPD of Department of thoracic medicine in Rajiv Gandhi Government General Hospital .
- Age and sex matched apparently healthy volunteers of patient's attendees and hospital workers.

SAMPLING METHOD: Consecutive Sampling.

SAMPLE SIZE:

Two sided confidence interval- 95%

Power- 80%

Ratio of Controls to Cases: 2

Percent of controls Exposed: 25%

Odds ratio:3

Cases(FLEISS): **42**

Controls(FLEISS): **84**

OPERATIONAL DEFINITIONS:

Cases: Patients diagnosed as a case of COPD as per GOLD 2017 guidelines and those who satisfy NCEP ATP 3 criteria of metabolic syndrome.

CONTROL 1: Patients diagnosed as a case of COPD as per GOLD 2017 guidelines and those who do not satisfy NCEP ATP 3 criteria of metabolic syndrome.

CONTROL 2: Age and sex matched apparently healthy volunteers of patient's attendees and hospital workers.

SAMPLE SELECTION:

INCLUSION CRITERIA:

1. Willing for informed written consent and willingness to participate in the study.
2. Attending thoracic medicine department OPD and diagnosed as a case of COPD.
3. Age and sex matched apparently healthy volunteers of patients attendees and hospital workers
4. Clinically and haemodynamically stable patients who can Undergo the needed investigations and testing.

5. Capable of completing CAT & MMRC questionnaire, six minute walk test and pulmonary function testing.

6. Patient without history of previous anti-tuberculous treatment.

7. Patients seronegative for human immunodeficiency virus.

8. Patients without active pulmonary tuberculosis.

EXCLUSION CRITERIA:

1.Not willing for informed written consent for the study.

2.Known case of cardiovascular disease.

3.COPD patients with acute exacerbation in past 6 weeks

4.Known cases of lung diseases other than COPD.

5.Known cases of inflammatory bowel disease , vasculitis, rheumatological diseases and other inflammatory conditions were excluded.

6. seriously ill patients those who cannot perform pulmonary function testing and six minute walk test

7.severe hepatic and renal dysfunction, malnutrition, severe anaemia, malignancy and mental illness.

8. Patients who are on oral corticosteroids or an any other Immunosuppressants.

ETHICAL CLEARANCE: Applied

INFORMED CONSENT: Obtained from all the patients

Diagnosis of COPD was based on symptoms, physical examination, and presence Of risk factors. Diagnosis was confirmed by post-bronchodilator spirometry that was performed 15 min after administration of four doses of salbutamol sulfate (100 μg).

As per NCEP ATP 3 (2005 REVISED definition) , metabolic syndrome is defined as three out of five of the following features**,**

1.Obesity(waist circumference >=40 inches in males,>= 35 inches in females),

2.Hyperglycemia (fasting glucose>=100mg/dl or on treatment),

3.Hypertriglyceridemia (triglyceride >= 150mg/dl or on treatment)

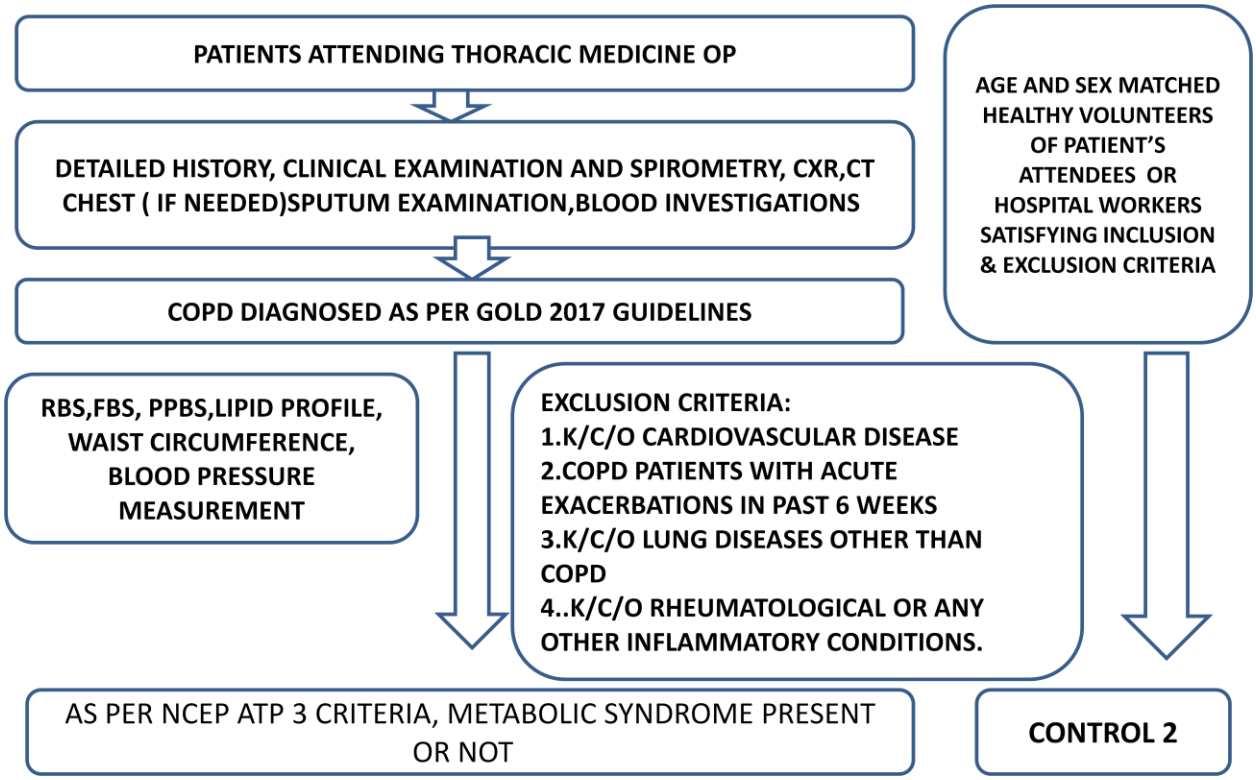
4.Decreased HDL cholesterol(<40mg/dl(M), <50mg/dl(F))

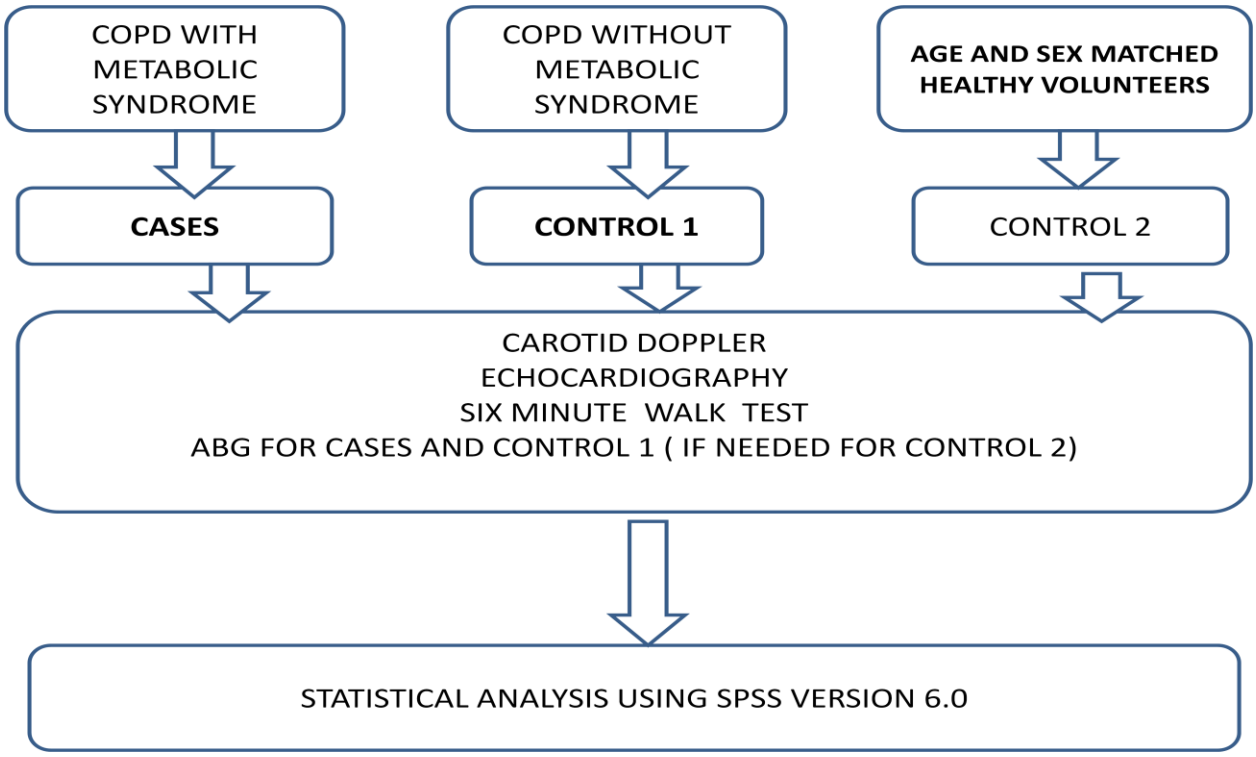
5.Hypertension.(systolic >= 130mmHg or diastolic >= 85mm Hg)

A reading of more than 0.8 mm was taken as increased Carotid intima media thickness and is the earliest marker of atherosclerosis.

Plaque was defined as CIMT of more than 1.2 mm and was at least 50% thicker than the neighboring segment. Presence of plaqing in either of carotids was recorded as plaque present.

METHODOLOGY:





The study population who satisfied the inclusion criteria were included in the study.

A detailed history regarding the presenting complaints , past history, treatment history, smoking history ,biomass exposure, occupational exposure and alcoholism were taken.

History regarding the comorbidities like Diabetes mellitus, systemic hypertension, coronary artery diseases,Bronchial asthma, neurological diseases were obtained.

All the study population underwent the structured clinical examination of all the systems.

The height and weight of the study population were measured in light indoor clothes and without shoes. Body mass index (BMI) was calculated.

BMI(weight in kg /(height in meter)^2

18.5- 24.9: NORMAL

25- 29.9 : OVERWEIGHT

30- 35: OBESE

>35 : MORBID OBESE

Blood pressure was measured in right arm in sitting posture. Three serial measurements were done and average was taken.

Waist circumference was determined by a single observer using a tapeline at the midpoint between the lowest rib and the iliac crest.

After an overnight fasting, venous blood sample (10 ml) was obtained. Serum glucose, triglyceride and high-density lipoprotein (HDL)-cholesterol levels were measured with standard methods using a chemical analyzer.

Sputum investigations, CXR PA view , Complete hemogram, renal function test, liver function test and CT CHEST (if needed) were done in all the subjects.

ECG and ECHOCARDIOGRAPHY were done for both cases and controls.

Arterial blood gas analysis was done for cases and controls 1.

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The COPD assessment test (CAT) is a validated questionnaire that is completed by the patient to assess and quantify the status of health and the symptom burden in COPD patients. In this study the questionnaire was translated to the the study site language and then translated back to English. It is composed of eight questions each presented as a six-point (0-5) differential scale with a total score out of 40. The clinical impact of the disease is graded as follows:

- 0-10 – mild
- 11-20 – moderate
- 21-30 – severe
- 31-40 – very severe

Pulmonary function test was done for all patients who satisfied the inclusion criteria. The test was performed in accordance with the criteria set by the American Thoracic Society using Easyone Spirometer. The instrument was calibrated daily. The procedure was explained to all patients before the test. Any recent history of smoking, illness, medication were enquired and the height and weight were recorded. All participants were kept in the seated position for the procedure.

All participants were instructed and demonstrated to hold the head in slightly elevated manner, position the mouthpiece and close lips, inhale completely and rapidly and then exhale maximally until no more air can be expelled.

Instructions were repeated as necessary . Throughout the manoeuvre, subjects were encouraged to blast out and exhale using appropriate body languages and phrases. The test was stopped whenever they complained of distress or dizziness. The test was repeated till at least three trials with two acceptable and reproducible tests for both FEV1 and FVC were obtained. Measurements were made before and after atleast 15 minutes of two puffs of salbutamol (200 μg) administered using metered dose inhaler with a volumatic spacer. The parameters were recorded and partial reversibility if present was noted. IF post bronchodilator FEV1/FVC < 0.8 with clinical features suggestive of

COPD with appropriate background of risk factors, the diagnosis of copd was made. GOLD Staging of COPD based on % FEV1 predicted was calculated.

FEV1 > 80% predicted= mild COPD (stage 1)

FEV1 50- 80% predicted = moderate COPD(stage 2)

FEV1 30- 50% predicted= severe COPD(stage 3)

FEV1 < 30% predicted= very severe COPD(stage 4)

Six minute walk distance was measured for all patients. The test was performed indoors in a 100 ft hallway (30 m length). The length was of the hallway was marked every 3m as well as the starting and ending point of each 60m lap. The turnaround points were marked with two small cones.

All patients were prepared and appropriate clothing, footwear, walking aids were ensured. It was instructed to avoid vigorous exercise within 2 hours of beginning the test. Pulse, blood pressure and oxygen saturation were recorded before the start of the test. A wheel chair and water were kept nearby as a precautionary measure.

After setting the timer to 6 minutes, all the patients were instructed to walk back and forth briskly in the designated hallway for as far as possible for 6 minutes. Incase of any respiratory distress, they were permitted to slow down, lean on the wall, stop and rest as and when necessary. The test was resumed as soon as they were able to walk again. During the test, all the patients were verbally encouraged and motivated to keep

walking. As soon as the timer rang denoting 6 minutes, patients were instructed to stop where they were and the spot was marked. The total number of laps covered with the additional distance covered in the last lap was recorded. In case the test was stopped prematurely, the distance walked till then was recorded along with reason for stopping.

BODE index is a multidimensional marker of a disease taking into consideration the systemic nature of disease. It helps us to predict the 4 year survival prediction rate among COPD patients.

B- BMI (weight in kg/ (height in meter)^2

O-FEV1% predicted after bronchodilator.

D- MMRC Dyspnea scale

E- EXERCISE capacity(6 minute walking distance)

BODE INDEX	4 YEAR SURVIVAL PREDICTION RATE
0-2	80%
3-4	67%
5-6	57%
7-10	18%

Pulmonary hypertension and right ventricular dysfunction were assessed by 2D transthoracic echocardiography.

Bilateral carotid arteries were evaluated by a single trained radiologist blind to clinical evaluation using a B-mode ultrasonography (General Electric, Logic 3 Expert Ultrasound) with a 5–10 MHz multi frequency linear probe. The luminal diameters Of the bilateral common carotid arteries and internal carotid arteries were Measured between the bright internal layers of the parallel vessel walls.

Intima-media thickness was defined as the distance between the edge of the luminal echo and media/adventitia layer. All subjects had IMT measurements at the proximal, middle and distal levels of both common carotid arteries. The mean thickness at these three points was calculated for each carotid artery and the highest value was accepted as IMT. Measurements with a focal IMT of 0.8 mm or greater were defined as increased IMT.

STATISTICAL ANALYSIS:

The data were expressed as the mean and standard deviation (SD) or the median and interquartile range. The study groups were compared using an unpaired t test and one-way ANOVA for continuous variables and Mann Whitney U-test for variables with non-normal distribution. Chi-square analysis was used for the comparison of categorical data. Univariate correlation analysis between IMT & FEV_1%, was performed by calculating Pearson's or Spearman's correlation coefficients.

Furthermore, a multivariate logistic regression model was utilized to analyze the association between the presence of COPD and MetS. A multivariate linear regression model was utilized to analyze the relationship between the presence of COPD and IMT. These regression models were used to control the potential confounding factors (namely: age, BMI, smoking, hypertension, FPG, triglyceride, HDL-cholesterol).

All data were analyzed by SPSS 16.0 software package. $p \leq 0.05$ was considered to be statistically significant.

RESULTS:

We had included 126 subjects in our study. All of them had satisfied inclusion and exclusion criteria. Among them, 84 patients were diagnosed as case of COPD as per GOLD 2017 guidelines. Age and sex matched healthy volunteers of around 42 were taken. In all the subjects, metabolic syndrome was diagnosed as per NCEP ATP 3 criteria.COPD with metabolic syndrome was taken as cases. COPD without metabolic syndrome was taken as control 1. Age and sex matched healthy volunteers were taken as control 2. Control 2 was further divided into control with metabolic syndrome and control without metabolic syndrome.

GENDER DISTRIBUTION OF STUDY POPULATION:

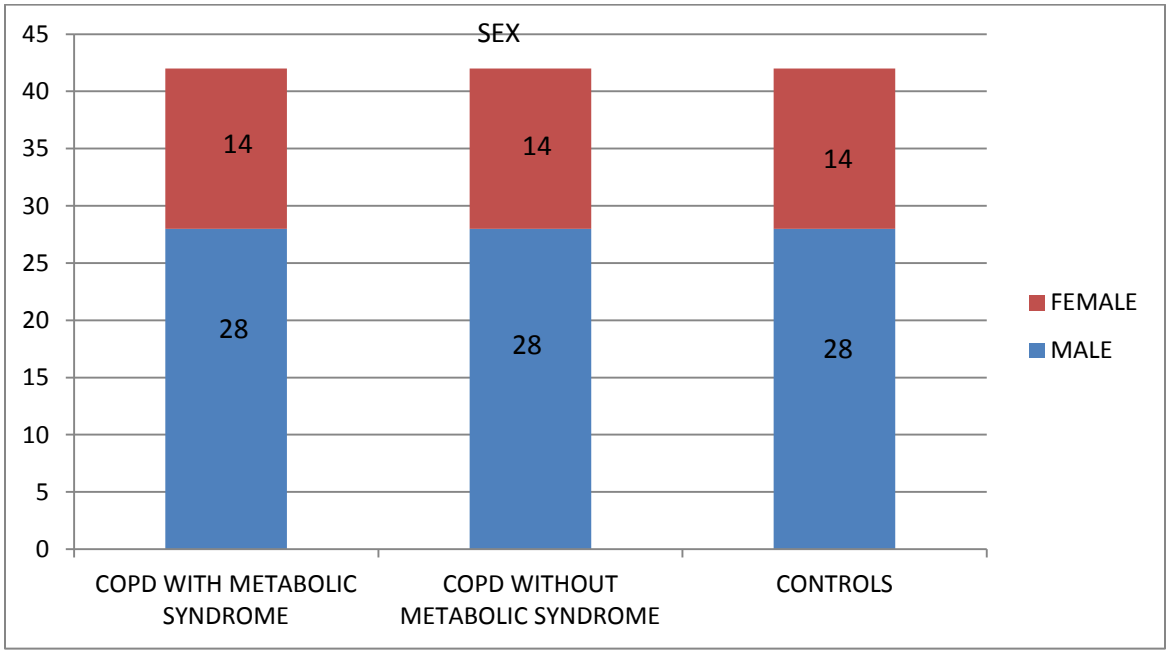

Figure 1: GENDER DISTRIBUTION IN DIFFERENT GROUPS

By consecutive sampling in all the study groups,28 males and 14 females were obtained and they were included in the study.

Table 1: A descriptive statistics of clinical and laboratory findings in the study groups:

GROUP / VARIABLES	COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	CONTROLS WITH METABOLIC SYNDROME	CONTROLS WITHOUT METABOLIC SYNDROME	P VALUE
AGE	61.9(S.D 7.9)	62.29(S.D 5.3)	65 (S.D 5.0)	62.6 (S.D 5.3)	0.676
SEX	M(28),F(14)	M(28), F (14)	M(3), F(4)	M(26),F(9)	-
FEV1	1.90(S.D 0.60)	1.83(S.D 0.47)	3.80(0.27)	3.85(S.D 0.24)	**0.001**
%FEV1	49.9(S.D 18.2)	51.36(S.D 15.2)	80.71(S.D 6.84)	81.31(S.D 4.06)	**0.002**
WAIST CIRCUMFERENCE	37.38(S.D 3.82)	34.00(S.D 1.73)	36.00(S.D 2.64)	34.74(S.D 1.63)	**0.001**
BMI	26.12(S.D 4.87)	23.76(S.D 1.33)	24.06(S.D 0.70)	24.13(S.D 1.54)	**0.003**
SBP	149.9(S.D 12.36)	133.86(S.D 13.43)	139.71(S.D 0.75)	125.25(S.D 9.25)	**0.001**
DBP	85.81(S.D 7.18)	82.00(S.D 6.46)	90.00(S.D 0.01)	78.69(S.D 4.39)	**0.002**
FBS	165.69(S.D 22.2)	127.57(S.D 18.33)	156.14(S.D 1.14)	124.71(S.D 20.08)	**0.000**
TGL	171.71(S.D 14.9)	146.24(S.D 15.8)	162.00(S.D 8.5)	140.17(S.D 9.7)	**0.001**
HDL – C	37.17(S.D 4.3)	46.12 (S.D 3.9)	40.57(S.D 3.10)	45.2(S.D 2.95)	**0.002**
ESR	36.71(S.D 10.1)	28.17(S.D 6.5)	26.29(S.D 4.7)	22.97(S.D 3.5)	**0.002**
CIMT	1.008(S.D 0.22)	0.826(S.D 0.16)	0.729(0S.D 0.05)	0.661(S.D 0.06)	**0.001**

AGE:

Average age among the cases, control 1 and control 2 were 61.9, 62.29 and 65. There was not much statistical difference in age among the different groups Studied.

FEV1:

COPD with metabolic syndrome had an average FEV1 of 1.90L, COPD Without metabolic syndrome had an average FEV1 of 1.83L and controls had an average FEV1 of 3.82L. There was a statistically significant difference in FEV1 among the different groups studied.

% FEV1 predicted:

COPD with metabolic syndrome had an average FEV1 predicted of 49.9%, COPD without metabolic syndrome had an average FEV1 predicted of 51.36% and controls had an average FEV1 predicted of 81.36. There was a Significant difference in % FEV1 predicted among the different groups studied.

WAIST CIRCUMFERENCE:

COPD with metabolic syndrome had an average of 37.28 inches, COPD without metabolic syndrome had an average of 34 inches and controls had an average of 35.37 inches. There was a significant difference in waist circumference among the Different groups studied.

BMI:

COPD with metabolic syndrome had an average of 26.12, COPD without Metabolic syndrome had an average of 23.76 and controls had an average of 24.09. There was a significant difference in BMI among the groups studied.

SYSTOLIC BLOOD PRESSURE:

Average systolic blood pressure in COPD with metabolic syndrome was 149.9, in COPD without metabolic syndrome was 133.86, in controls with metabolic syndrome was 139.71 and in controls without metabolic syndrome was 125.25. There was a significant difference in systolic blood pressure among the groups studied.

DIASTOLIC BLOOD PRESSURE:

Average diastolic blood pressure in COPD with metabolic syndrome was 85.81, in COPD without metabolic syndrome was 82, in controls with metabolic syndrome Was 90.00 and in controls without metabolic syndrome was 78.69. There was a Significant a difference in diastolic blood pressure among the groups studied.

FASTING BLOOD GLUCOSE:

Average fasting blood sugar in COPD with metabolic syndrome was 165.69 , in COPD without metabolic syndrome was 127.57, in controls with metabolic syndrome was 156.14 and in controls without metabolic syndrome was 124.71.There was a significant difference in fasting blood glucose level among the Groups studied.

TRIGLYCERIDES:

Average triglyceride level in COPD with metabolic syndrome was 171.79, in COPD without metabolic syndrome was 146.24, in controls with metabolic syndrome was 162 and in controls without metabolic syndrome was 140.17.There was a significant difference in triglycerides level among the groups studied.

HDL-C:

Average HDL-C level in COPD with metabolic syndrome was 37.17, in COPD

Without metabolic syndrome was 46.12, in controls with metabolic syndrome was 40.57 and in controls without metabolic syndrome was 45.2. There was a Significant difference in HDL-C level among the groups studied.

ESR:

Average ESR in COPD with metabolic syndrome was 36.71, in COPD without metabolic syndrome was 28.17, in controls with metabolic syndrome was 26.29 and in controls without metabolic syndrome was 22.97. There was a significant difference in ESR among the groups studied.

CAROTID INTIMA MEDIA THICKNESS:

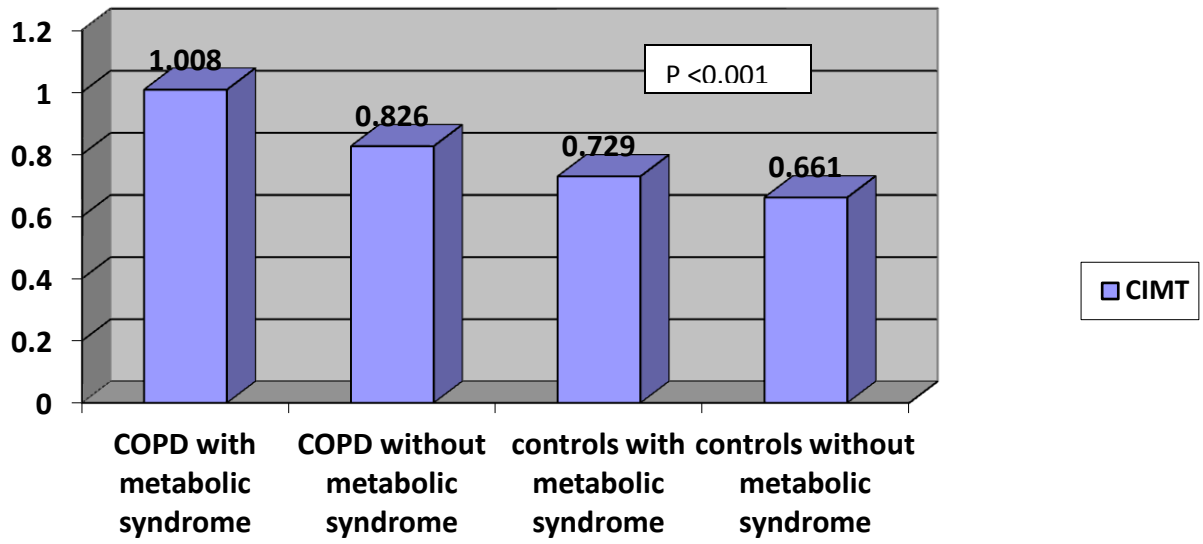

Figure 2: CAROTID INTIMA MEDIA THICKNESS IN DIFFERENT GROUPS

Average CIMT in COPD with metabolic syndrome was 1.008, in COPD without metabolic syndrome was 0.826, in controls with metabolic syndrome was 0.729 and in controls without metabolic syndrome was 0.661. There was a significant difference in CIMT among the groups studied.

SMOKING STATUS AMONG DIFFERENT GROUPS:

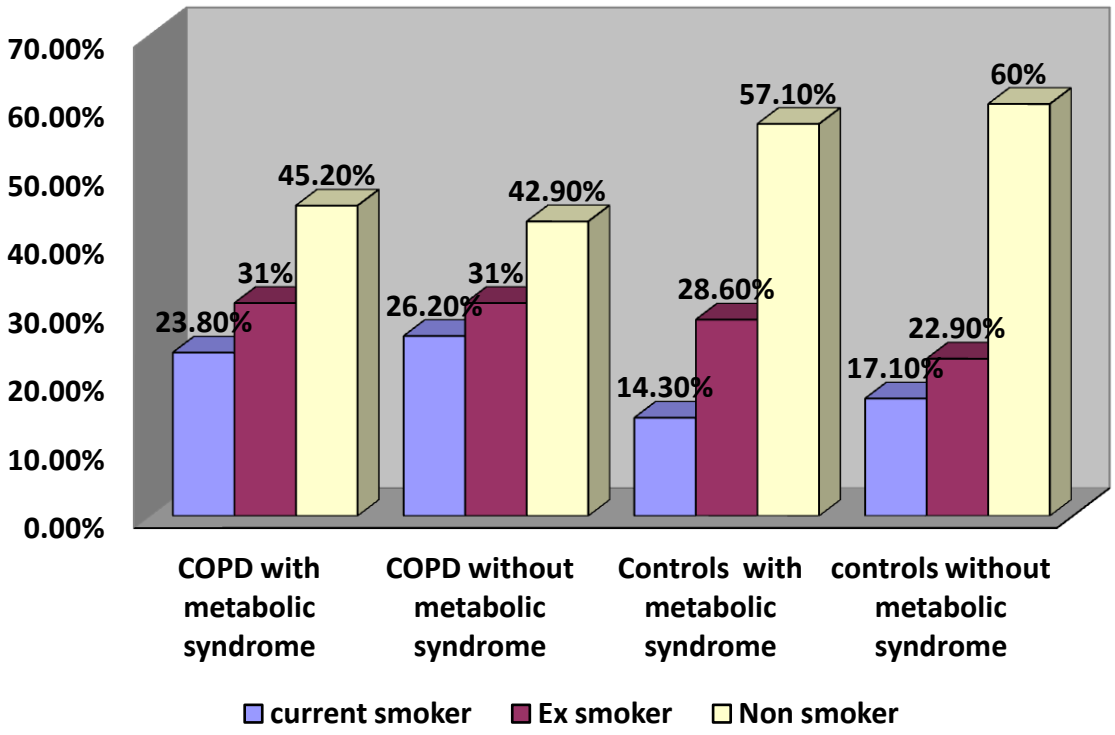

Figure 3: SMOKING STATUS AMONG DIFFERENT GROUPS

In COPD with metabolic syndrome , 23.8% were current smokers, 31% were Ex smokers and 45.20% were Non smokers. In COPD without metabolic syndrome , 26.2% were current smokers, 31% were Ex smokers and 42.90% were non smokers.

In controls with metabolic syndrome, 14.30% were current smokers, 28.60% were Ex smokers and 57.10% were non smokers. In controls without metabolic syndrome , 17.1% were current smokers, 22.9% were ex smokers and 60% were non smokers. .

There was no statistical difference in smoking status among the groups Studied.

TABLE 2: Carotid Intima Media Thickness among the different groups :

			GROUPS					P VALUE
			COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	CONTROLS WITH METABOLIC SYNDROME	CONTROLS WITHOUT METABOLIC SYNDROME	TOTAL	
CIMT	ELEVATED	Count	32	23	6	4	65	0.021
		% within GROUP	76.2%	54.8%	85.7%	11.4%	51.6%	
	NORMAL	Count	10	19	1	31	61	
		% within GROUP	23.8%	45.2%	14.3%	88.6%	48.4%	
Total		Count	42	42	7	35	126	
		% within GROUP	100.0%	100.0%	100.0%	100.0%	100.0%	

In COPD with metabolic syndrome , 76.2% had elevated CIMT, in COPD without Metabolic syndrome 54.8% had elevated CIMT, in Controls with metabolic Syndrome 85.7% had elevated CIMT and in controls without metabolic syndrome 11.4% had elevated CIMT.

There was a significant increase in Carotid intima media thickness in COPD with metabolic syndrome and controls with metabolic syndrome with p value of < 0.021.

TABLE 3: Prevalance of carotid plaque among different groups :

	COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	CONTROLS WITH METABOLIC SYNDROME	CONTROLS WITHOUT METABOLIC SYNDROME	P VALUE
CAROTID PLAQUE PRESENT	12 28.6%	3 7.1%	0	0	**0.001**
CAROTID PLAQUE ABSENT	30 71.4%	39 92.7%	7 100%	35 100%	

Among COPD patients with metabolic syndrome, 28.6% had carotid plaque. In COPD patients without metabolic syndrome , 7.1% had carotid plaque. None had Carotid plaque in control group. There was significant increase in carotid plaque formation in COPD patients with metabolic syndrome ($p<0.001$)

TABLE 4 : Carotid Intima Media Thickness vs Carotid Plaque in Cases and Control 1:

GROUP	CAROTID PLAGUE	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	YES	12(37.5%)	0	**0.022**
	NO	20(62.5%)	10(100%)	
COPD WITHOUT METABOLIC SYNDROME	YES	3(13%)	6(31.6%)	0.102
	NO	20(87%)	13(68.4%)	

In COPD with metabolic syndrome , 37.5% had elevated CIMT with carotid plaque. In COPD without metabolic syndrome 13.5% had elevated CIMT with carotid plaque. There was significantly elevated CIMT and Carotid plaque formation in COPD patients with metabolic syndrome($p < 0.022$).

TABLE 5: MULTIPLE REGRESSION MODEL FOR VARIOUS CONFOUNDERS ASSOCIATED WITH CAROTID INTIMA MEDIA THICKNESS:

CIMT: DEPENDANT variable						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.060	.669		1.584	.119
	AGE	-.005	.003	-.154	-1.584	.119
	PACK YEARS	.011	.004	.342	2.998	**.004**
	WAIST CIRCUMFERENCE	.003	.008	.039	.430	.669
	FBS	.001	.001	.129	1.237	.222
	SBP	.001	.002	.044	.369	.714
	DBP	-.005	.003	-.155	-1.405	.166
	TGL	.002	.001	.180	1.528	.132
	HDL-C	-.004	.007	-.073	-.523	.603
	%FEV1	-.005	.001	-.440	-4.228	**.000**

By keeping CIMT as a dependant variable, all the potential confounding factors are plotted against CIMT. This multiple regression analysis was done to determine whether COPD is a independent risk factor for increased CIMT.

By using multiple regression analysis model for age, pack years, waist circumference,FBS, SBP,DBP,TGL,HDL_C and % FEV1 predicted, with CIMT as a dependant variable, **% FEV1 PREDICTED and SMOKING PACK YEARS were Statistically significant independent risk factors for increased CIMT.** Thus % fev1 predicted and smoking pack years can independently influence the carotid intima media thickness irrespective of age and individual components of metabolic syndrome.

TABLE 6: Correlation of CIMT with %FEV1 predicted:

	CIMT (MEAN)	%FEV1 (MEAN)	PEARSON CORRELATION	SIGNIFICANCE (2 TAILED)
TOTAL(126)	0.841	60.83	- 0.688	**0.000**
COPD(84)	0.917	50.63	-0.591	**0.000**
COPD WITH METABOLIC SYNDROME	1.008	49.90	-0.725	**0.000**
COPD WITHOUT METABOLIC SYNDROME	0.826	51.36	-0.480	**0.001**

There was statistically significant negative correlation between the Carotid Intima Media thickness and % FEV1 predicted among the 126 study subjects, and among the COPD patients with and without metabolic syndrome.

TABLE 7: Carotid Intima Media Thickness among the different stages of COPD:

	CIMT (MEAN +-2 S.D)	P VALUE (ANOVA TEST)
STAGE 1:	0.723(S.D 0.178)	**0.004**
STAGE 2:	0.847(S.D 0.169)	
STAGE 3:	0.959(S.D 0.219)	
STAGE 4:	0.998(S.D 0.220)	

Average CIMT in stage1, stage 2 , stage 3 and stage 4 were 0.723, 0.847, 0.959 and 0.998 respectively. There was a significant increase in CIMT along with the increase in stages of COPD($p<0.004$).

TABLE 8:Association of Carotid Intima Media Thickness with BODE index in cases and control 1:

	CIMT (MEAN +-2 SD)	P VALUE (ANOVA TEST)
BODE: 0-2	0.735(S.D 0.15)	**0.002**
BODE: 3-4	0.836 (S.D 0.17)	
BODE:5-6	0.925(S.D 0.20)	
BODE:>=7	1.048(S.D 0.20)	

Average CIMT in BODE index 0-2, 3-4, 5-6 and >=7 were 0.735, 0.836, 0.925 and 1.048 respectively. There was a statistically significant increase in CIMT along the increase in BODE index among COPD patients.

TABLE 9: Association of Carotid Intima Media Thickness with six minute walking distance in cases and control 1:

	CIMT (MEAN +- 2 SD)	P VALUE(ANOVA TEST)
6MWD:>=350	0.703 (S.D 0.135)	**0.003**
6MWD:250-349	0.814 (S.D 0.174)	
6MWD:150-249	0.984(S.D 0.184)	
6MWD:< 150	1.079(S.D 0.300)	

Average CIMT among 6MWD of >=350m, 250-349m, 150-249m and < 150m in COPD patients were 0.703, 0.814, 0.984 and 1.079 respectively. There was a statistically significant increase in CIMT along the decrease in 6MWD in COPD patients.($p<0.003$)

TABLE 10: Carotid Intima Media Thicknes vs Smoking status:

	CIMT (MEAN +-2 SD)	P VALUE (t TEST FOR EQUALITY OF MEANS)
SMOKER	0.866(S.D 0.220)	0.483
NON SMOKER	0.834(S.D 0.217)	

Average CIMT among smokers was 0.866 and among non smokers was 0.834. There was statistically no significant difference in CIMT among smokers and non smokers.

TABLE 11: carotid intima media thickness vs biomass exposure:

GROUP	BIOMASS EXPOSURE	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	YES	15(46.9)	3(30%	0.347
	NO	17(53.1%)	7(70%)	
COPD WITHOUT METABOLIC SYNDROME	YES	10(43.5%)	6(31.6%)	0.429
	NO	13(56.5%)	13(68.4%)	

In COPD with metabolic syndrome, 46.9% with elevated CIMT had biomass exposure. In COPD without metabolic syndrome , 43.5% with elevated CIMT had biomass exposure. There was statistically no significant difference in CIMT with respect to BIOMASS exposure among the two groups.

TABLE 12: Carotid Intima Media Thickness vs MMRC DYSPNEA SCALE:

GROUP	MMRC	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	< 2	5 (15.6%)	4(40%)	0.101
	>=2	27(84.4%)	6(60%)	
COPD WITHOUT METABOLIC SYNDROME	<2	5(21.7%)	4(21.1%)	0.957
	>=2	18(78.3%)	15(78.9%)	

In COPD with metabolic syndrome , 84.4% with elevated CIMT had MMRC >=2. In COPD without metabolic syndrome , 78.3% with elevated CIMT had MMRC >=2.There was statistically no significant increase in CIMT with respect to MMRC dyspnea scale in both the groups.

TABLE 13: Carotid Intima Media Thickness vs No. Of hospitalization:

GROUP	NO.OF HOSPITALISATION	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	NIL	10(31.3%)	9(90%)	**0.001**
	>=1	22(68.7%)	1(10%)	
COPD WITHOUT METABOLIC SYNDROME	NIL	14(60.9%)	12(63.2%)	0.879
	>=1	9(39.1%)	7(36.8%)	

In COPD with metabolic syndrome, 68.7% with elevated CIMT had increased number Of hospitalization and it was found to be statistically significant ($p<0.001$). In COPD without metabolic syndrome, 39.1% with elevated CIMT had increased number of hospitalization and it was not found to be statistically significant.

TABLE 14:Carotid Intima Media Thickness Vs number of exacerbations:

GROUP	NO.OF EXACERBATIONS	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	<2	14(43.8%)	9(90%)	**0.010**
	>=2	18(56.3%)	1(10%)	
COPD WITHOUT METABOLIC SYNDROME	<2	21(91.3%)	19(100%)	0.188
	>=2	2(8.7%)	0	

In COPD with metabolic syndrome, 56.3% with elevated CIMT were frequent exacerbators and it was found to be statistically significant($p<0.010$). In COPD without metabolic syndrome , only 8.7% with elevated CIMT were frequent exacerbators and it was not statistically significant.

TABLE 15: Carotid Intima Media Thickness vs CAT score:

GROUP	CAT SCORE	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	<10	5(15.6%)	3(30%)	0.312
	>=10	27(84.4%)	7(70%)	
COPD WITHOUT METABOLIC SYNDROME	<10	4(17.4%)	3(15.8%)	0.890
	>=10	19(82.6%)	16(84.2%)	

In COPD with metabolic syndrome, 84.4% with elevated CIMT had CAT score>=10. In COPD without metabolic syndrome, 82.6% with elevated CIMT had CAT score >=10.There was no statistically significant increase in CIMT with respect to CAT score.

TABLE 16: Carotid Intima Media Thickness vs GOLD COPD CATEGORY:

GROUP	COPD CATEGORY	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	A	2(6.3%)	2(20%)	0.064
	B	6(18.8%)	5(50%)	
	C	3(9.4%)	1(10%)	
	D	21(65.6%)	2(20%)	
COPD WITHOUT METABOLIC SYNDROME	A	2(8.7%)	2(10.5%)	0.751
	B	12(52.2%)	10(52.6%)	
	C	5(21.7%)	2(10.5%)	
	D	4(17.4%)	5(26.3%)	

There was statistically no significant increase in CIMT with respect to GOLD COPD CATEGORY in both the groups.

TABLE 17:Carotid intima media thickness vs ESR:

GROUP	ESR	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	ELEVATED	31(96.9%)	5(50%)	**0.001**
	NORMAL	1(3.1%)	5(50%)	
COPD WITHOUT METABOLIC SYNDROME	ELEVATED	10(43.5%)	8(42.1%)	0.929
	NORMAL	13(56.5%)	11(57.9%)	

In COPD with metabolic syndrome , 96.9% with elevated CIMT had elevated ESR and it was found to be statistically significant.($p<0.001$). In COPD without metabolic syndrome , 43.5% with elevated CIMT had elevated ESR and it was not statistically significant.

TABLE 18:Carotid intima media thickness vs Pao2:

GROUP	PAO2	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	>80	1(3.1%)	9(90%)	**0.001**
	60-80	27(84.4%)	1(10%)	
	<60	4(12.5%)	0	
COPD WITHOUT METABOLIC SYNDROME	>80	1(4.3%)	4(21.1%)	0.178
	60-80	21(91.3%)	15(78.9%)	
	<60	1(4.3%)	0	

In COPD with metabolic syndrome, there was a stastically Significant increase in CIMT with decrease in Pao2($p<0.001$). In COPD without metabolic syndrome , there was no statistically significant increase in CIMT with respect to Pao2.

TABLE 19: Carotid Intima Media Thickness vs Paco2:

GROUP	PACO2	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	<45	2(6.2%)	6(60%)	**0.001**
	45-55	22(68.8%)	4(40%)	
	>55	8(25%)	0	
COPD WITHOUT METABOLIC SYNDROME	<45	4(17.4%)	3(15.8%)	0.890
	45-55	19(82.6%)	16(84.2%)	
	>55	0	0	

In COPD with metabolic syndrome , there was a statistically significant increase in CIMT with increase in Paco2($p<0.001$). In COPD without metabolic syndrome, there was no statistically significant increase in CIMT with increase in Paco2.

TABLE 20: Carotid Intima media thickness vs Pulmonary hypertension:

GROUP	PHT	CIMT		P VALUE(PEARSON CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	NO	0	1(10%	0.208
	MILD	8(25%)	2(20%)	
	MODERATE	16(50%)	3(30%)	
	SEVERE	8(25%)	4(40%)	
COPD WITHOUT METABOLIC SYNDROME	NO	6(26.1%)	6(31.6%)	0.915
	MILD	8(34.8%)	5(26.3%)	
	MODERATE	6(26.1%)	6(31.6%)	
	SEVERE	3(13%)	2(10.5%)	

There was no statistically significant increase in CIMT with respect to pulmonary hypertension in both the groups.

TABLE 21: Carotid Intima Media Thickness vs Right ventricular dysfunction:

GROUP	RIGHT VENTRICLE DYSFUNCTION	CIMT		P VALUE(CHI SQUARE TEST)
		ELEVATED	NORMAL	
COPD WITH METABOLIC SYNDROME	YES	16(50%)	1(10%	**0.024**
	NO	16(50%)	9(90%)	
COPD WITHOUT METABOLIC SYNDROME	YES	6(26.1%)	2(10.5%)	0.201
	NO	17(74.9%)	17(89.5%)	

In COPD with metabolic syndrome , 50% with elevated CIMT had right ventricular dysfunction and it was found to be statistically significant($p<0.024$).
In COPD without metabolic syndrome , 26.1% with elevated CIMT had right Ventricular dysfunction and it was not statistically significant.

TABLE 22:Comparison of Clinical Characteristics in COPD with metabolic syndrome and COPD without metabolic syndrome groups:

MMRC Dyspnea scale, CAT score , Number of exacerbations, Number of hospitalizations and Inhaled corticosteroid usage were compared between COPD with and without metabolic syndrome.

		GROUPS		P VALUE
		COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	
MMRC	<2	9(21.4%)	9(21.4%)	1.000
	>= 2	33(78.6%)	33(21.4%)	
NO.OF HOSPITALISATIONS	0	19(45.2%)	26(61.9%)	0.126
	>=1	23(54.8%)	16(38.1%)	
NO.OF EXACERBATIONS	<2	23(54.8%)	40(95.2%)	**0.001**
	>=2	19(45.2%)	2((4.8%)	
CAT SCORE	<10	8(19%)	7(16.7%)	0.776
	>=10	34(81%)	35(83.3%)	
INHALED CORTICOSTEROID USAGE	YES	19(45.2%)	26(61.9%)	0.126
	NO	23(54.8%)	16(38.1%)	

In COPD with metabolic syndrome , 78.6% had MMRC dyspnea scale >=2. In COPD without metabolic syndrome , 21.4% had MMRC dyspnea scale >=2. There was no statistically significant difference in MMRC dyspnea scale between the two groups.

In COPD with metabolic syndrome, 54.8% had increased number of hospitalizations. In COPD without metabolic syndrome, 38.1% had increased number of hospitalizations. There was no statistically significant difference in number of hospitalizations in between the two groups.

In COPD with metabolic syndrome, 45.2% had increased number of exacerbations. in COPD without metabolic syndrome, 4.8% had increased number of exacerbations.There was a statistically significant increase in number of exacerbations in COPD with metabolic syndrome($p<0.001$).

In COPD with metabolic syndrome , 81% had CAT score >=10. In COPD without metabolic syndrome, 83.3% had CAT score >=10 . There was no statistically significant difference in CAT score among the two groups.

In COPD with metabolic syndrome, 45.2% had prior Inhaled corticosteroid usage.In COPD without metabolic syndrome, 61.9% had inhaled corticosteroid usage. There was no significant difference in inhaled corticosteroid usage among the two groups.

There was a statistically significant increase in number of exacerbations in COPD with metabolic syndrome group and thus they are frequent exacerbators.

GOLD STAGING AMONG COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

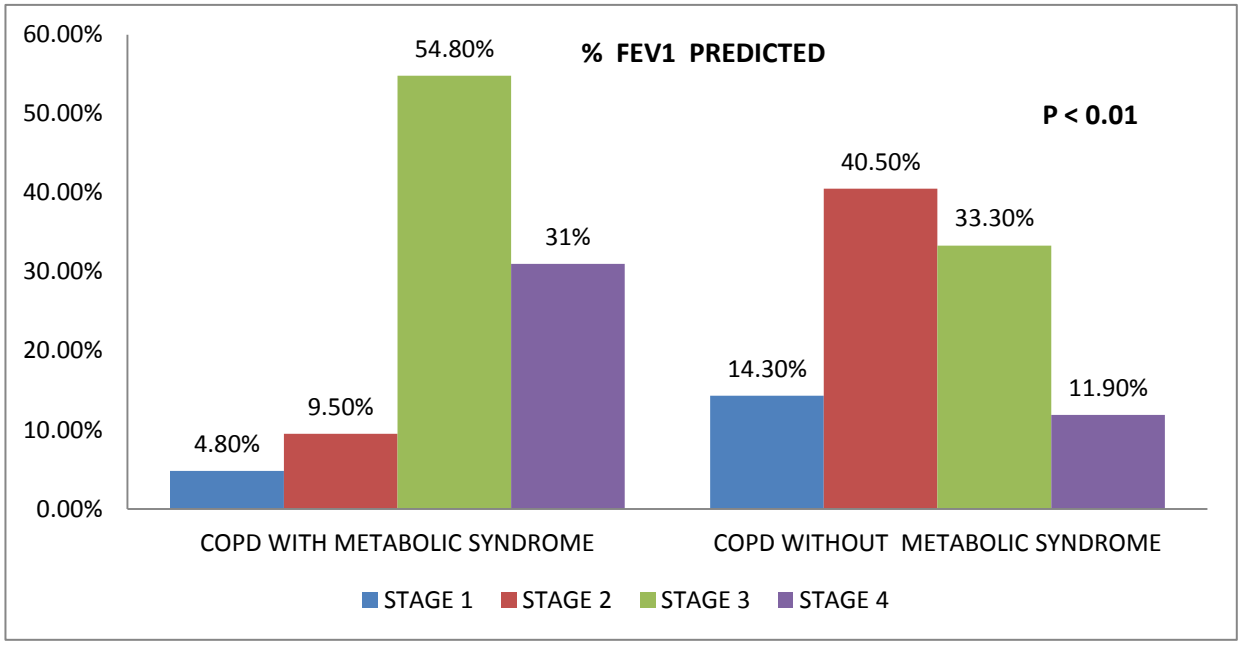

Figure 4: GOLD STAGING IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS

In COPD with metabolic syndrome , 54.8% and 31% of patients were in stage 3 and stage 4. In COPD without metabolic syndrome, 33.3% and 11.9% of patients were in stage 3 and stage 4. There was statistically significant more number of patients in advanced stages (stage 3 and stage 4) in COPD with metabolic syndrome group.($p<0.01$)

GOLD CATEGORY AMONG COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

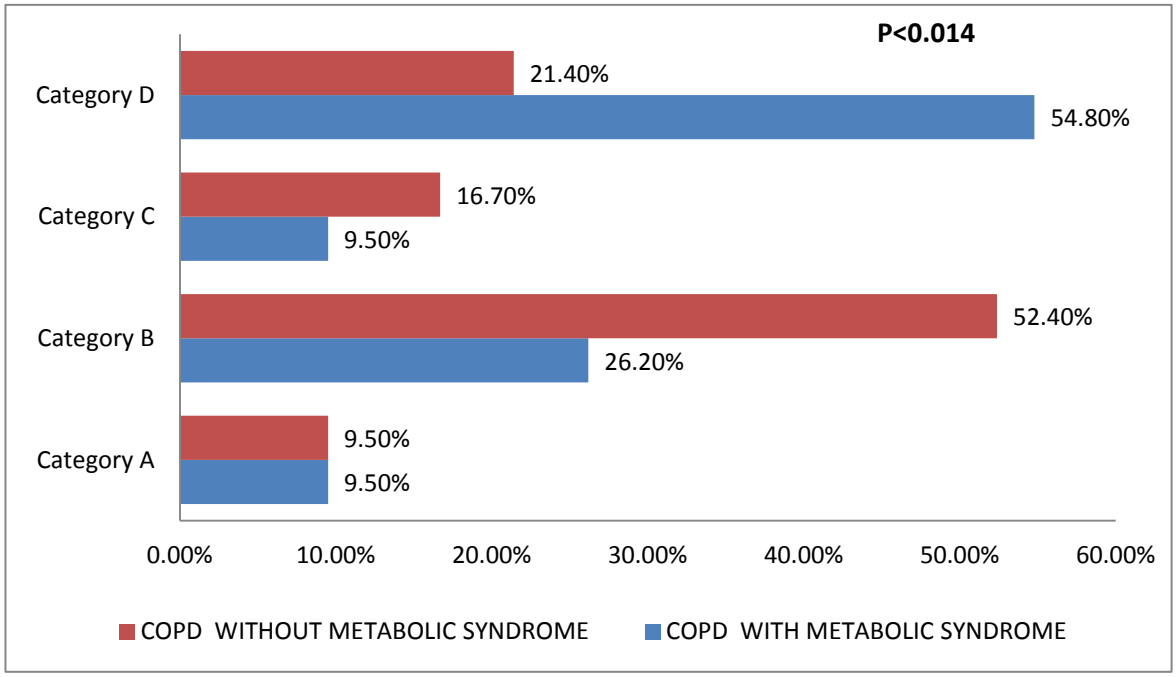

Figure 5: GOLD CATEGORY AMONG COPD WITH AND WITHOUT METABOLIC SYNDROME

In COPD with metabolic syndrome, 54.8% of the patients were in CATEGORY D , whereas in COPD without metabolic ,52.4% of the patients were in CATEGORY B. There was a statistically significant difference in GOLD category among these two groups.($p<0.014$) .

TABLE 23: DISTRIBUTION OF ESR, CIMT, Pao2 and Paco2 AMONG THE COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

		GROUPS		P VALUE
		COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	
ESR	ELEVATED	36(85.7%)	18(42.9%)	**0.001**
	NORMAL	6(14.3%)	24(57.1%)	
CIMT	ELEVATED	32(76.2%)	23(54.8%)	**0.039**
	NORMAL	10(23.8%)	19(45.2%)	
PAO2	>80	10(23.8%)	5(11.9%)	0.107
	60-80	28(66.7%)	36(85.7%)	
	<60	4(9.5%)	1(2.4%)	
PACO2	<45	8(19%)	7(16.7%)	**0.009**
	45-55	26(61.9%)	35(83.3%)	
	>55	8(19%)	0	

In COPD with metabolic syndrome , 85.7% had elevated ESR. In COPD without metabolic syndrome , 42.9% had elevated ESR. There was a statistically significant increase in ESR in COPD with metabolic syndrome group.($p<0.001$).

In COPD with metabolic syndrome, 76.2% had elevated CIMT. In COPD without metabolic syndrome , 54.8% had elevated CIMT. There was a statistically significant increase in CIMT in COPD with metabolic syndrome group($p<0.039$).

There was no statistically significant difference in Pao2 among the two groups.

In COPD with metabolic syndrome , 61.9% had Paco2= 45-55 and 19% had Paco2 > 55 and it was found to be statistically significant when compared with COPD without metabolic syndrome group($p<0.009$).

SIX MINUTE WALKING DISTANCE IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

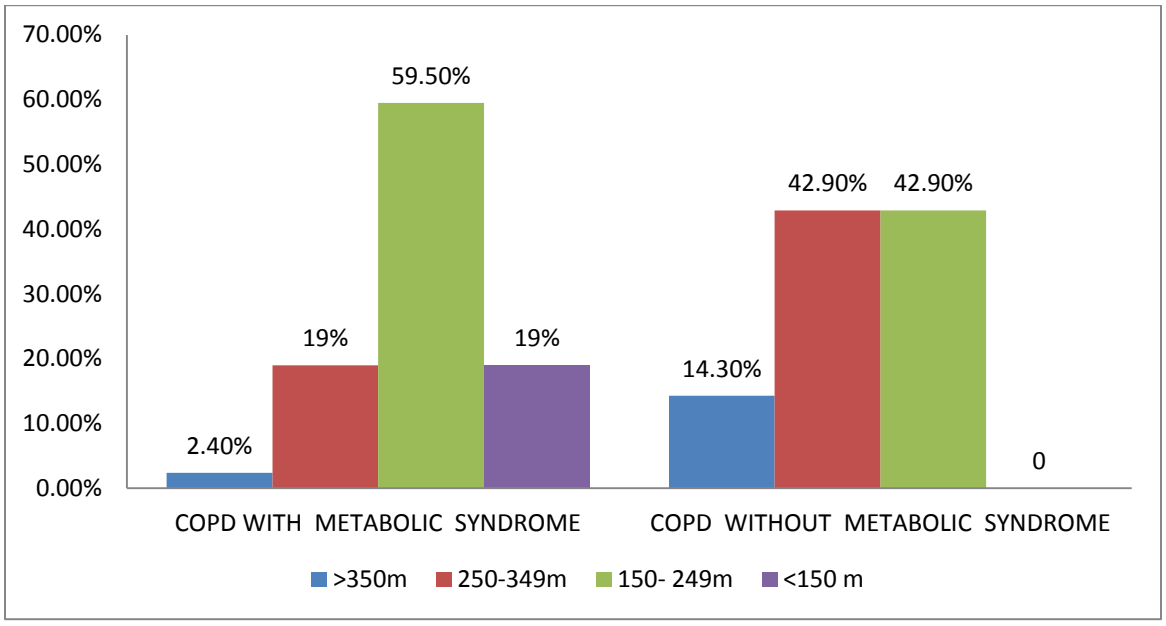

Figure 6: 6MWD IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS

Average 6MWD in COPD with metabolic syndrome group was 231m, whereas average 6MWD in COPD without metabolic syndrome group was 284m. COPD

with metabolic syndrome group had significantly decreased 6MWD when compared with COPD without metabolic syndrome group.($p<0.01$).

BODE INDEX IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

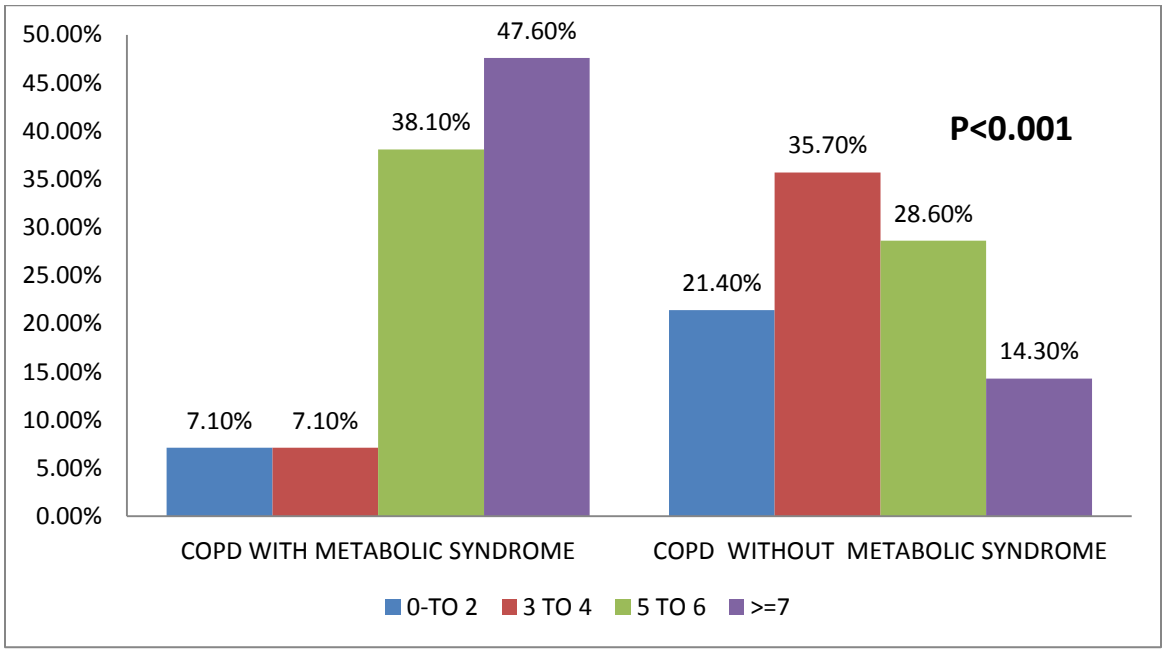

Figure 7: BODE INDEX IN COPD WITH AND WITHOUT METABOLIC SYNDROME

In COPD with metabolic syndrome, 38.1% had BODE index of 5 to 6 and 47.5% had BODE index >=7. In COPD without metabolic syndrome, 28.6% had BODE index of 5 to 6 and 14.3% had BODE index >=7. There was a statistically significant difference in BODE index among the two groups($p<0.001$).

TABLE 24: CAROTID PLAQUE IN COPD WITH AND WITHOUT METABOLIC SYNDROME:

			GROUP			P VALUE
			COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	Total	
CAROTID PLAGUE	YES	Count	12	3	15	**0.010**
		% within GROUP	28.6%	7.1%	17.9%	
	NO	Count	30	39	69	
		% within GROUP	71.4%	92.9%	82.1%	
Total		Count	42	42	84	
		% within GROUP	100.0%	100.0%	100.0%	

In COPD with metabolic syndrome, 28.6% had carotid plaque formation. In COPD without metabolic syndrome, 7.1% had carotid plaque formation. There was a statistically significant increased carotid plaque formation in COPD with metabolic syndrome($p<0.010$).

PULMONARY HYPERTENSION IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS:

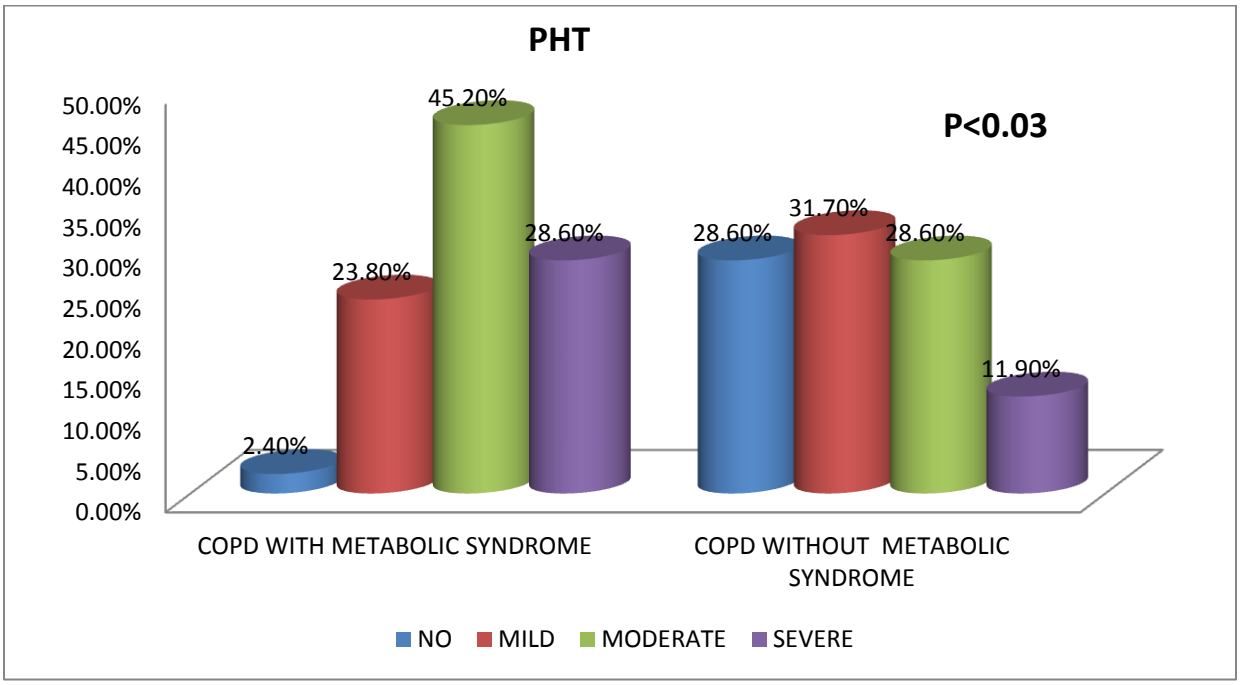

Figure 8: PHT IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS

In COPD with metabolic syndrome, 2.4% had no PHT, 23.8% had mild PHT, 45.2% had moderate PHT and 28.6% had severe PHT. In COPD without metabolic syndrome, 28.6% had no PHT, 31.7% had mild PHT, 28.6% had moderate PHT and 11.9% had severe PHT. There was a statistically significant difference in PHT among the two groups($p<0.03$).

RIGHT VENTRICULAR DYSFUNCTION IN COPD WITH AND WITHOUT METABOLIC SYNDROME:

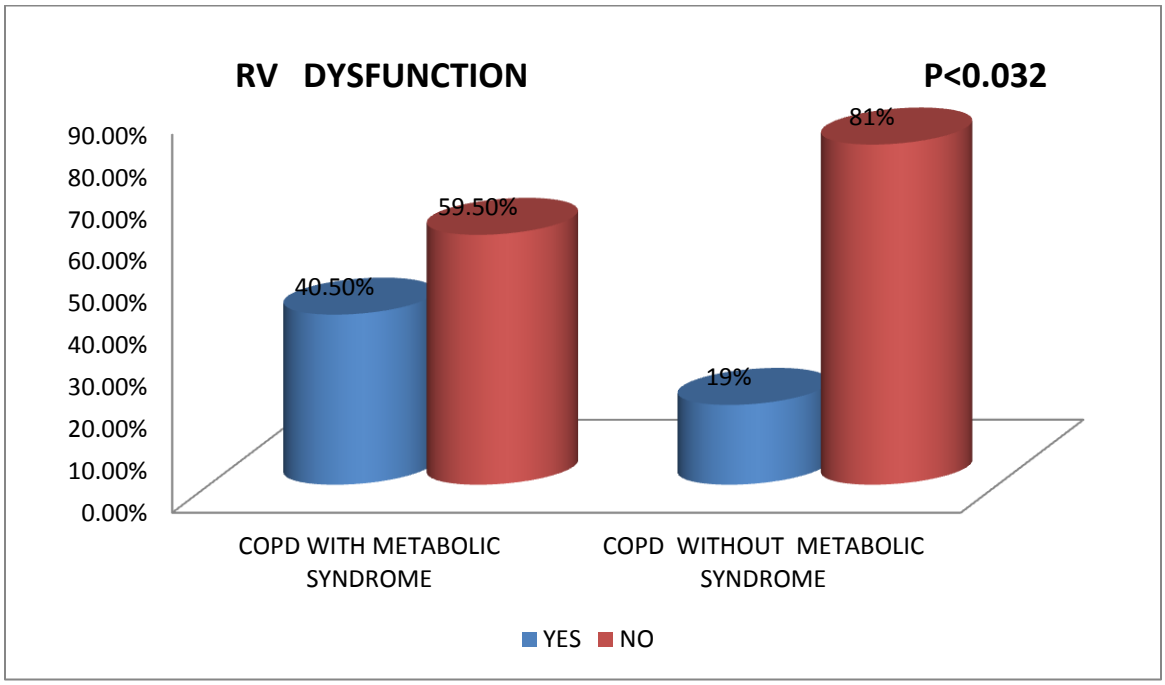

Figure 9: RV DYSFUNCTION IN COPD WITH AND WITHOUT METABOLIC SYNDROME GROUPS

In COPD with metabolic syndrome , 40.5% had right ventricular dysfunction. In COPD without metabolic syndrome, 19% had right ventricular dysfunction. There was a statistically significant increase in right ventricular dysfunction among COPD with metabolic syndrome group($p<0.032$).

TABLE 25: PREVALANCE OF HYPERGLYCEMIA IN DIFFERENT GROUPS:

HYPERGLYCEMIA IN DIFFERENT GROUPS							
			GROUP				Total
			COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	CONTROLS WITH METABOLIC SYNDROME	CONTROLS WITHOUT METABOLIC SYNDROME	
FBS	HYPERGLYCEMIA	Count	37	15	7	10	69
		% within GROUP	88.1%	35.7%	100.0%	28.6%	54.8%
	NORMAL	Count	5	27	0	25	57
		% within GROUP	11.9%	64.3%	.0%	71.4%	45.2%
Total		Count	42	42	7	35	126
		% within GROUP	100.0%	100.0%	100.0%	100.0%	100.0%

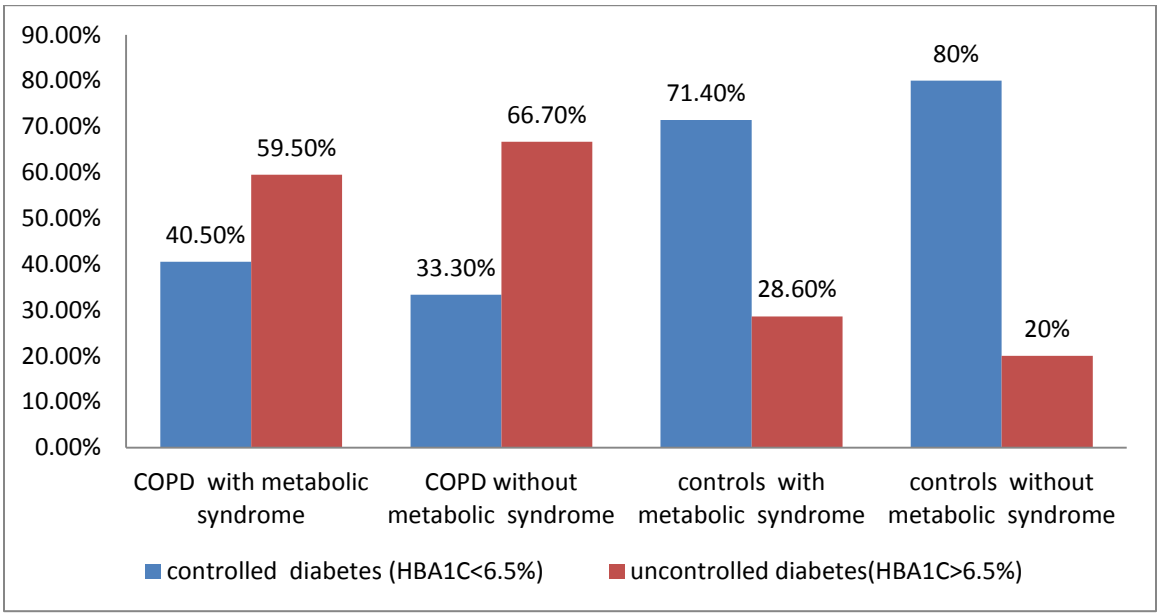

Figure 10: PROPORTION OF CONTROLLED AND UNCONTROLLED DIABETES AMONG THE GROUPS

In COPD with metabolic syndrome, 37 patients had hyperglycemia. Among them 40.5% had controlled diabetes and 59.5% had uncontrolled diabetes.

In COPD without metabolic syndrome, 15 patients had hyperglycemia. Among them, 33.3% had controlled diabetes and 66.7% had uncontrolled diabetes.

In Controls with metabolic syndrome, all the patients(7) had hyperglycemia. Among them, 71.4% had Controlled diabetes and 28.6% had uncontrolled diabetes.

In controls without metabolic syndrome, 10 patients had hyperglycemia. Among them , 80% had controlled diabetes and 20% had uncontrolled diabetes.

There was a statistically significant difference in the proportion of controlled and uncontrolled diabetes among the groups studied($p<0.041$).

TABLE 26: PREVALANCE OF HYPERTENSION IN DIFFERENT GROUPS:

			GROUP				Total
			COPD WITH METABOLIC SYNDROME	COPD WITHOUT METABOLIC SYNDROME	CONTROLS WITH METABOLIC SYNDROME	CONTROLS WITHOUT METABOLIC SYNDROME	
BP	HYPERTENSION	Count	35	22	7	6	70
		% within GROUP	83.3%	52.4%	100.0%	17.1%	55.6%
	NORMAL	Count	7	20	0	29	56
		% within GROUP	16.7%	47.6%	.0%	82.9%	44.4%
Total		Count	42	42	7	35	126
		% within GROUP	100.0%	100.0%	100.0%	100.0%	100.0%

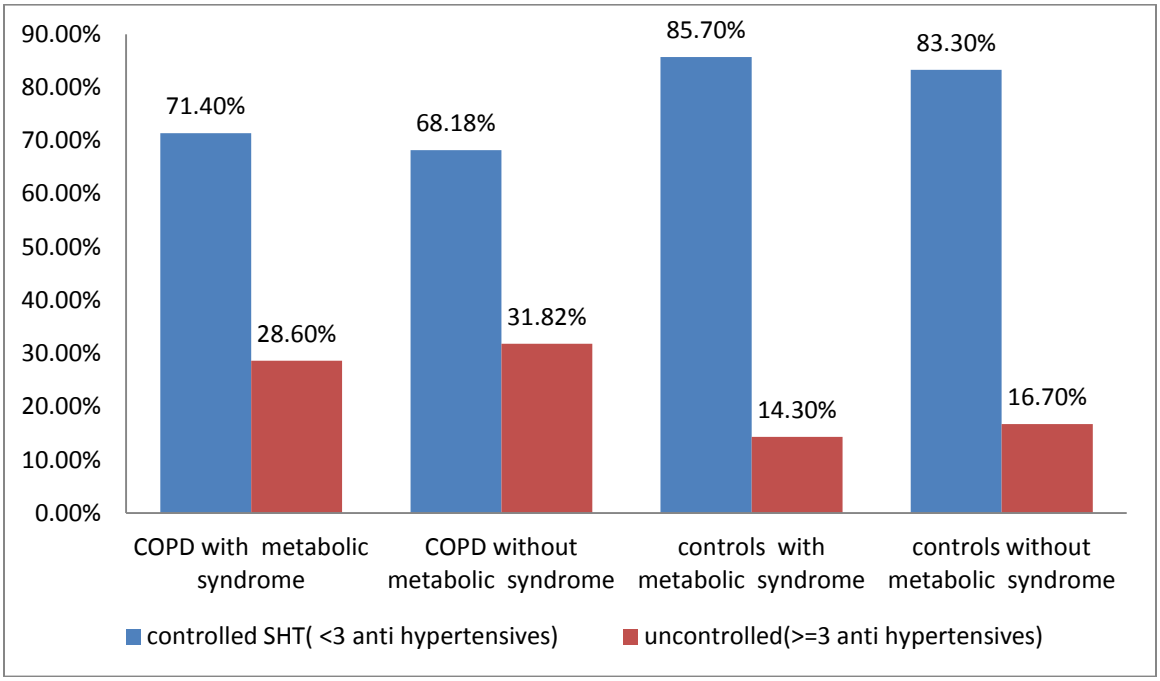

Figure 11: Proportion of Controlled and Uncontrolled Hypertension among the groups

In COPD with metabolic syndrome, 35 patients had systemic hypertension . Among them 71.4% had controlled SHT and 28.6% had uncontrolled SHT.

In COPD without metabolic syndrome, 22 patients had systemic hypertension. Among them, 68.18% had controlled SHT and 31.18% had uncontrolled SHT.

In controls with metabolic syndrome , 6 patients had systemic hypertension. Among them 85.7% had controlled SHT and 14.3% had Uncontrolled SHT.

In controls without metabolic syndrome, 5 patients had systemic hypertension. Among them 83.3% had controlled SHT and 16.7% had uncontrolled SHT.

There was a statistically significant difference in the proportion of controlled and uncontrolled Systemic hypertension among the groups($p<0.037$).

DISCUSSION:

COPD is a multicomponent disease with inflammation at its core leading to mortality. Reduced forced expiratory volume in one second (FEV1) has been independantly associated with increased risk for cardiovascular diseases. Systemic inflammation , chronic hypoxia and oxidative stress are the possible mechanisms contributing to the development of cardiovascular diseases in COPD patients.

In COPD patients, Systemic inflammation leads to progression of atherosclerosis and thus increases the risk of coronary artery disease , stroke and peripheral vascular diseases. The prevalence of metabolic syndrome in COPD patients is two times elevated when compared with normal population. Metabolic syndrome is also strongly associated with systemic inflammation and metabolic syndrome can independently leads to progression of atherosclerosis.

Carotid Intima Media Thickness and Carotid plaque are the proven measures to estimate the carotid atherosclerosis and thereby to predict the risk for coronary artery atherosclerosis and other cardiovascular diseases.

As far as we know ,there are very few studies in literature to establish the association between COPD, metabolic syndrome and subclinical athrerosclerosis.

Comorbidities associated with COPD is an area of research and systemic inflammation being a most common etiology for the associated comorbidities, diagnosing metabolic syndrome and measuring Carotid intima media thickness in all the COPD patients may help us to predict the cardiovascular diseases in advance.

So the purpose of this study was to evaluate the association of subclinical atherosclerosis in COPD patients with metabolic syndrome.

AGE**:** There was no statistically significant difference in age among the groups.

AIRFLOW LIMITATION: There was a statistically significant decrease in FEV1 and % FEV1 predicted in COPD patients when compared with controls. COPD with metabolic syndrome patients had significantly lower FEV1 and % FEV1 predicted when compared with COPD without metabolic syndrome patients.

Minas et al., (38) in his study observed that COPD patients with the MetS have a more

severe form of disease, more dyspnea, a lower FEV1 and require more inhalational glucocorticoids to control the disease.

WAIST CIRCUMFERENCE: COPD patients with metabolic syndrome had statistically significant higher waist circumference when compared with other groups.

BMI: There was a statitiscally significant increase in BMI in COPD with metabolic syndrome group. Even in COPD with metabolic syndrome group, average BMI was only 26.12. This may be because of the increased prevalence of abdominal obesity rather than the increase in whole body mass index in these patients.

SYSTEMIC HYPERTENSION:

There was a statistically significant increased prevalence of systemic hypertension in COPD with metabolic syndrome group. Among the groups, COPD with metabolic syndrome and COPD without metabolic syndrome had significantly higher number of uncontrolled hypertension($p<0.037$).

Wang y et al.,(43) explained the possible mechanisms for this increased prevalence of systemic hypertension in COPD as follows: hypoxia related vasoconstriction , free radical injury, endothelial dysfunction and arterial stiffness.

DIABETES MELLITUS:

There was a statistically significant increase in the prevalence of diabetes mellitus in COPD with metabolic syndrome group. Among the study groups, COPD patients had significantly higher number of uncontrolled diabetes when compared with controls($p<0.041$).

The nurses' healthy study(42) a prospective study over an 8-year period had showed that COPD patients have a 1.8% relative risk of developing diabetes.

Engstrom *et al*.(50) described that reduced lung function is an important risk factor for the development of diabetes in COPD.

Skyba et al., explained that Adipose tissue inflammation and low grade systemic inflammation plays an important role in whole body insulin resistance and beta cell dysfunction in COPD patients and thus may lead to the increased prevalence of uncontrolled diabetes(22) .

ESR: There was a significant increase in ESR in COPD patients with metabolic syndrome .This may be because of the increased systemic inflammation associated with the disease.

CAROTID INTIMA MEDIA THICKNESS:

In our study , average CIMT in COPD with metabolic syndrome was 1.008, average CIMT in COPD without metabolic syndrome was 0.826 , average CIMT in controls with metabolic syndrome was 0.729 and average CIMT in controls without metabolic syndrome was 0.661. 76.2% had elevated CIMT in COPD patients with metabolic syndrome and 54.8% had elevated CIMT in COPD patients without metabolic syndrome.

There was a significant increase in CIMT in COPD patients when compared with controls. Among the COPD patients, COPD with metabolic syndrome had higher CIMT than COPD without metabolic syndrome. Thus COPD patients are more atherogenic when compared with controls and among the COPD patients, those with metabolic syndrome are even more atherogenic than those without metabolic syndrome.

Sandhip chindhi et al.,(57) in his study observed that Mean average CIMT in COPD patients was 1.07 ± 0.49 mm and in controls, it was 0.75 ± 0.33 mm. It was significantly higher in COPD patients than control (P = 0.000). In COPD patients, 67.6% patients had increased average CIMT and where as it was 25.8% in controls (P = 0.000). CIMT was further increased in COPD patients with MetS. Mean average CIMT in COPD patients with MetS was 1.22 ± 0.528 mm while in patients without MetS mean average CIMT was 0.74 ± 0.086 mm (P < 0.000).

Aylin ozgen alapadin et al.,(58) in his study observed that COPD group had a statistically significant thicker carotid IM compared to controls ($p < 0.001$). In COPD patients with MetS, IMT did not show a significant increase compared to COPD patients without MetS (1.11 ± 0.24 mm vs. 1.04 ± 0.26 mm; $p = 0.34$). Another important finding was that there was no significant difference between IMT values of participants with MetS and without MetS (1.01 ± 0.25 mm vs 0.95 ± 0.24 mm; $p = 0.20$). This statement is in contrary to our study results and to the results of study conducted by sandhip chindhi et al. Maybe the difference in study population and methodology could have been the reason for this disparity.

CAROTID PLAQUE:

In our study, there was a significant increase in carotid plaque formation in COPD patients when compared with controls. Among the COPD patients , those with metabolic syndrome had significantly higher carotid plaque formation than those without metabolic syndrome (28.6% vs 7.1%) ($p<0.001$).

Sandhip chindhi et al,(57) in his study stated that in COPD patients, carotid plaque was seen in 38.7% patients, whereas 13.7% of controls had carotid plaque ($P = 0.000$). Carotid plaque was seen in 54.5% patients of COPD with MetS and in 2.3% of COPD patients without MetS ($P < 0.000$).

CAROTID INTIMA MEDIA THICKNESS AND CAROTID PLAQUE FORMATION:

In COPD with metabolic syndrome , 37.5% had elevated CIMT with carotid plaque. In COPD without metabolic syndrome 13.5% had elevated CIMT with carotid plaque. There was significantly elevated CIMT and Carotid plaque formation in COPD patients with metabolic syndrome($p < 0.022$).

In a study by Sandhip chindhi et al.,(57) frequency of carotid plaque (38.7% vs. 13.7%, $P < 0.0001$) and increased CIMT (67.6% vs. 25.8%) were significantly higher in COPD patients compared to age- and sex-matched controls

The Rotterdam study(56) also revealed a significantly higher CIMT (≥2.5 mm) in participants with COPD than in those without COPD.

CORRELATION OF CIMT WITH %FEV1 PREDICTED:

In our study, there was a statistically significant negative correlation between the CIMT and % FEV1 predicted. The decrease in % FEV1 predicted is associated with the significant increase in carotid intima media thickness.

CORRELATION OF CIMT WITH SEVERITY OF AIRFLOW LIMITATION:

In our study, average CIMT in stage1, stage 2 , stage 3 and stage 4 were 0.723, 0.847, 0.959 and 0.998 respectively. There was a statistically significant increase in CIMT with the increase in severity of airflow limitation($p<0.004$).

In a study by Sandhip chindhi et al.,(57) the mean CIMT showed an increasing trend with increased severity of COPD. The mean CIMT in GOLD stages I, II, III, IV COPD were 0.96 ± 0.32, 0.98 ± 0.52, 1.16 ± 0.47, 1.20 ± 0.59, respectively. Frequency of carotid plaque according to GOLD stages I, II, III, IV were 36.4%, 23.5%, 43.2%, and 51.6%, respectively; a *P* value for changing trend was 0.115.

In the study by Gestel *et al*.(55) the mean carotid wall IMT was 1.07 mm. Of the patients without COPD, 23% demonstrated increased CIMT, whereas 32% of patients with mild COPD and 36% of the patients with moderate/severe COPD had increased CIMT ($P < 0.01$).

In a study by Aylin ozgen alappadi et al.(58), there was no correlation between IMT and disease stage, FEV_1%, or serum CRP level. When only smokers were considered, IMT was found to be higher in the COPD group compared to controls ($p < 0.006$). This finding might suggest that, although we could not demonstrate a direct correlation

between FEV_1% and IMT, patients with airflow obstruction are more proneto atherogenesis due to some other mechanisms beyond smoking.

SMOKING STATUS AND CIMT:

In our study , 14 females each were present in all the three groups(cases, control1 and control 2). Therefore in all the four groups , there was statistically significant increase in proportion of non smokers(45.2%, 42.9%,57.1%, 60%) .

In our study, average CIMT among smokers were 0.866 and average CIMT among non smokers were 0.834. There was statistically no significant difference in CIMT with respect to smoking status.

Iwamoto *et al*.,(54) reported a mean CIMT of significantly higher level in smokers with airflow limitation (0.78 mm) than that in smokers without airflow limitation (0.73 mm) ($P < 0.01$) and never-smokers (0.73 mm) ($P < 0.005$). Carotid plaque was significantly prevalent in smokers with airflow limitation (73.8%) than control never-smokers (48.4%; $P < 0.005$).

Sandhip chindhi et al.,(57) reported that there was exaggerated subclinical atherosclerosis in smokers with airflow limitation, indicating that atherosclerotic change occurs early in the disease process of COPD. The shared risk factors such as smoking between COPD and carotid atherosclerosis can also explain the associations. However, they did not find a significant relationship between smoking status and increased CIMT.

ASSOCIATION OF CIMT WITH BODE INDEX:

In our study, there was a statistically significant increase in CIMT with the increase in BODE index in cases and controls 1($p<0.002$).

BODE index being a multidimensional marker of a disease taking into consideration the systemic nature of disease. It helps us to predict the 4 year survival prediction rate among COPD patients. Thus in our study , increased BODE index was associated with increased CIMT and thus these patients are prone for atherosclerosis and increased cardiovascular diseases.

ASSOCIATION OF CIMT WITH SIX MINUTE WALIKNG DISTANCE:

In our study , there was a significant increase in CIMT with the decrease in 6MWD($p<0.003$).

SIX minute walking test is used as a measure to predict the exercise capacity in COPD patients .In our study, decrease in 6MWD is associated with increase in CIMT and the possible mechanism could be the decreased physical activity associated with decreased exercise capcity and thus physical inactivity in relation with systemic inflammation may predispose these COPD patients for an increased subclinical atherosclerosis.

CAROTID INTIMA MEDIA THICKNESS AND BIOMASS EXPOSURE:

There was statistically no significant difference in CIMT with respect to biomass exposure in our study.

Sandhip chindhi et al.,(57) reported that There are no significant differences between COPD and control in terms of smoking status, biomass exposure, age, and sex.

CAROTID INTIMA MEDIA THICKNESS AND CLINICAL CHARACTERISTICS OF COPD:

MMRC DYSPNEA SCALE:

In our study, there was statistically no significant difference in CIMT with respect to MMRC dyspnea scale.

NUMBER OF HOSPITALISATIONS:

In COPD patients with metabolic syndrome , there was a significantly increased CIMT when there was increased number of hospitalizations($p<0.001$).

In COPD patients without metabolic syndrome, number of hospitalizations was not significantly associated with CIMT($p<0.879$).

Thus COPD patients with metabolic syndrome having higher rate of hospitalisations with increased CIMT are prone for increased cardiovascular diseases.

NUMBER OF EXACRBATIONS:

In COPD patients with metabolic syndrome, increased number of exacerbations was significantly associated with increased CIMT($p<0.010$).

In COPD patients without metabolic syndrome, there was no significant increase in CIMT with respect to increased number of exacerbations.

Thus COPD patients with metabolic syndrome are frequent exacerbators and they are more prone for atherosclerosis.

CAT SCORE:

In our study , CAT score was not significantly associated with CIMT in both the groups.

CAROTID INTIMA MEDIA THICKNESS AND GOLD CATEGORY:

There was no significant difference in CIMT with respect to GOLD COPD category in our study.

CAROTID INTIMA MEDIA THICKNESS AND ESR:

In our study, increased CIMT was significantly associated with the elevated ESR in COPD patients with metabolic syndrome($p<0.001$).

Alyin ozgen alappadi et al.,(58) reported that serum CRP levels were elevated in the study participants with MetS ($p = 0.02$).

CAROTID INTIMA MEDIA THICKNESS AND ABG:

In COPD patients with metabolic syndrome, increased CIMT was significantly associated with the worsening Pao2 and Paco2($P<0.001$,$P<0.001$).

Both hypoxia and hypercapnia are associated with increased CIMT and thereby prone for cardiovascular diseases.

CAROTID INTIMA MEDIA THICKNESS AND PHT:

There was no significant difference in CIMT with respect to severity of PHT in our study.

CAROTID INTIMA MEDIA THICKNESS AND RIGHT VENTRICULAR DYSFUNCTION:

In COPD patients with metabolic syndrome , increased CIMT was significantly associated with right ventricular dysfunction(P<0.024).

COPD patients with metabolic syndrome are more prone for right ventricular dysfunction due to lipotoxic cardiomyopathy.

COPD AS A INDEPENDENT RISK FACTOR FOR INCREASED CIMT:

By multiple logistic regression model, % FEV1 predicted and smoking pack years are independent risk factors for increased CIMT in our study.(beta-0.440, P<0.000)

In a study by Alyin ozgen alappadi et al.,(58) A multivariate-adjusted analysis showed that in all the study population IMT had a positive correlation with COPD (beta = 0.151, p = 0.020). Among the potential confounding factors, age and BMI were also positively correlated with IMT (beta = 0.008, p = 0.020 and beta = 0.011, p = 0.029, respectively). Other factors (*i.e.* age, smoking, hypertension, FPG, triglyceride, HDL-cholesterol) had no significant association with IMT.

Sandhip chindhi et al.,(57) reported that on linear regression analysis, MetS and COPD were the independent predictors of increased CIMT. Similarly on multinomial logistic regression analysis, COPD was found to be an independent predictor of carotid plaqing with regression coefficient of 0.847 ($P < 0.023$). Association between PO_2,

PCO_2 and SPO_2 with carotid plaqing was not found to be statistically significant in correlation matrix.

CLINICAL AND FUNCTIONAL CHARACTERISTICS IN COPD WITH METABOLIC SYNDROME AND COPD WITHOUT METABOLIC SYNDROME GROUPS:

In a study conducted by a dukhabandhu naik et al.,(29) COPD patients with the MetS had a more severe form of disease, more dyspnea, a lower FEV1 and require more inhalational glucocorticoids to control the disease. They also proposed that this group of COPD subjects can be further stratified into a higher risk phenotype which requires a closer follow-up.

A recent study by Minas *et al*.(38) has shown that MetS is also quite common among younger age group and in even subjects with a less severe form of COPD. COPD patients with MetS have higher leptin levels, low adiponectin and greater insulin resistance.

In our study , there was statistically no significant difference in MMRC dyspnea scale, number of hospitalizations , CAT score, inhaled corticosteroid usage and Pao2 in between the two groups.

COPD patients with metabolic syndrome in our study had statistically significant

1.Higher number of exacerbations and thus they are frequent exacerbators($P<0.001$).

2.Increased severity of airflow limitation($p<0.01$)

3.Increased CIMT and thus more prone for cardiovascular diseases($p<0.039$)

4.Increased CO_2 retention($p<0.009$)

5.Decreased exercise capacity(6MWD: Ave 231m vs 284m).

6.Higher BODE index and therefore they have lower 4 year survival prediction rate.($p<0.001$)

7. Higher carotid plaque formation(28.6% vs 7.1%)

8. Increased severity of pulmonary hypertension($P<0.03$)

9. Increased right ventricular dysfunction($p<0.032$).

CONCLUSION:

1. In our study, COPD patients had increased Carotid intima media thickness and carotid plaque formation when compared with the age and sex matched healthy controls. Thus COPD patients are at increased risk for atherosclerosis and cardiovascular diseases.

2. Increased carotid intima media thickness was associated with the trend of increasing severity of airflow limitation. Thus severe and very severe COPD patients are at increased risk for atherosclerosis than mild and moderate COPD patients.

3. COPD patients with high BODE index had significantly elevated Carotid intima media thickness and thus they are more prone for cardiovascular morbidity and mortality.

4. %FEV1 predicted and smoking pack years were the independent risk factors associated with increased carotid intima media thickness in our study.

5. In our study, COPD patients with metabolic syndrome had increased number of exacerbations , increased severity of airflow limitation , poorer exercise tolerance , lower 4 year survival prediction rate, increased subclinical atherosclerosis and increased right ventricular dysfunction. Thus COPD patients with metabolic

syndrome can be considered as high risk phenotype with worsened COPD characteristics and they are more prone for cardiovascular diseases.

6. In COPD patients with metabolic syndrome, elevated CIMT was significantly associated with increased number of hospitalizations, increased number of exacerbations, decreased six minute walking distance, higher BODE index, worsening Pao2 & Paco2 and right ventricular dysfunction. From the above mentioned observations it is clear that subclinical atherosclerosis is strongly associated with worsened COPD characteristics.

In Summary, COPD is a multicomponent disease with inflammation at it's core leading to mortality. In COPD patients , prevalence of metabolic syndrome is more common and it is associated with worsened clinical and functional characteristics. Both COPD and METABOLIC SYNDROME can cause progression of atherosclerosis and are associated with increased cardiovascular mortality.

RECOMMENDATIONS:

CAROTID INTIMA MEDIA THICKNESS AND CAROTID PLAQUE formation can be routinely screened in all the COPD patients. Thus non-invasive and cost effective 2D carotid Doppler as a part of investigation panel for cardiovascular disease risk prediction can help us to decrease the cardiovascular morbidity and mortality associated with COPD.

LIMITATIONS OF THE STUDY:

1. Being a hospital based case control study, extrapolating the results of the study to the general population in society may not be accurate enough and further studies in this context has to be done in general population.

2. More specific inflammatory biomarkers like CRP, fibrinogen, leptin and IL-6 were not done in our study. The correlation between the CIMT and these inflammatory biomarkers could have given better outcome with respect to inflammatory status associated with the COPD.

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Subclinical atherosclerotic vascular disease in chronic obstructive pulmonary disease: Prospective hospital-based case control study

Sandip Chindhi[1], Prakash C Negi[2], Malay Sarkar[3], Surinder Thakur[4]

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Metabolic syndrome and carotid intima-media thickness in chronic obstructive pulmonary disease

Aylin Ozgen Alpaydin,[1] Isin Konyar Arslan,[2] Selim Serter,[3]

ANNEXURES

ABBREVIATIONS:

COPD- Chronic obstructive pulmonary diseases

METS- Metabolic syndrome

CAT -COPD assessment test

MMRC- Modified medical research council

CIMT- Carotid Intima Media Thickness

PHT- Pulmonary hypertension

RVD- Right ventricular Dysfunction

HDL- High density lipoprotein

LDL- Low density lipoprotein

TGL- Triglycerides

ESR- Erythrocyte sedimentation rate

FEV1- Forced expiratory volume in one second

FVC- forced vital capacity

SHT- systemic Pulmonary Hypertension

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **" TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY"** of the candidate **DR.S.SIVAKUMAR** with registration number **201527003** for the award of MD in the branch of **Tuberculosis & Respiratory diseases.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that uploaded thesis file contains from introduction to conclusion pages and result shows **6 percentage** of plagiarism in the dissertation.

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MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Sivakumar.S.
Post Graduate in TB&CD
Madras Medical College & RGGGH
Chennai 600 003

Dear Dr.Sivakumar.S,

The Institutional Ethics Committee has considered your request and approved your study titled **"TO EVALUATE THE ASSOCIATION OF SUBCLINICAL ATHEROSCLEROSIS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH METABOLIC SYNDROME – A PROSPECTIVE HOSPITAL BASED CASE CONTROL STUDY " - NO.01012017 (II).**

The following members of Ethics Committee were present in the meeting hold on **19.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

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

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

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

EVALUATION FORM

Name:
Age:
Sex:
OP/Ip number:
Presenting complaints:
History of presenting illness:
Past history:
Treatment history:
Smoking history:
Personal history:
Occupational history:
CO-MORBIDITY:
General examination:
Body Mass Index:
Waist circumference:
Blood pressure:
Systemic examination:
Blood investigations:
COMPLETE BLOOD COUNT
RFT, LFT
RBS,FBS,PPBS
Fasting Lipid profile: triglyceride level:
HDL cholesterol:
Sputum investigations:
Radiological findings:
Chest xray :
CT-CHEST(IF NEEDED):
SPIROMETRY:
FEV1:
FVC:
% FEV1/ FVC:
DLCO(IF NEEDED):
SIX MINUTE WALK TEST:
ECG:
Echocardiography:
2D CAROTID DOPPLER:
CAROTID INTIMA MEDIA THICKNESS:
CAROTID PLAQUE:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராயச்சியின் தலைப்பு

ராஜீவ் காந்தி அரசு பொது மருத்துவமனையின் நெஞ்சக மருத்துவத்துறைக்கு வரும் நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோயாளிகளில், வளர்சிதை மாற்ற நோய்குறி உள்ளவர்களுக்கு நோய்குறித் தோன்றா பெருந்தமனியின் தொடர்பு பற்றிய ஆய்வு.

ஆய்வு நிலையம் : நெஞ்சக நோய் மருத்துவத் துறை,
சென்னை மருத்துவக் கல்லூரி சென்னை - 3.

பங்கு பெறுவரின் பெயர் :
பங்குபெறுபவரின் எண் :

பங்குபெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் 'இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு

ராஜீவ் காந்தி அரசு பொது மருத்துவமனையின் நெஞ்சக மருத்துவத்துறைக்கு வரும் நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோயாளிகளில், வளர்சிதை மாற்ற நோய்க்குறி உள்ளவர்களுக்கு நோய்குறித் தோன்றா பெருந்தமனியின் தொடர்பு பற்றிய ஆய்வு .

ஆராய்ச்சியாளர் பெயர் : மருத்துவர்.ச.சிவக்குமார்

பங்கேற்பாளர் பெயர் :

ஆராய்ச்சியின் நோக்கம்

ராஜீவ் காந்தி அரசு பொது மருத்துவமனையின் நெஞ்சக மருத்துவத்துறைக்கு வரும் நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோயாளிகளில், வளர்சிதை மாற்ற நோய்க்குறி உள்ளவர்களுக்கு நோய்குறித் தோன்றா பெருந்தமனியின் தொடர்பு பற்றிய ஆராய்தல்.

இதன் மூலம் நாள்பட்ட மூச்சுக்குழாய் நோயின் இருதய மற்றும் இரத்த குழாயின் பாதிப்பை முன்கூட்டியே கண்டறிவதற்கான சாத்தியக்கூறுகள் ஆய்வு செய்யப்படும்.

ஆய்வு முறை

நாள்பட்ட மூச்சுக்குழாய் அடைப்பு உள்ளவர்கள் மற்றும் அதே வயது மற்றும் பாலினம் கொண்ட ஆரோக்கியமாக உள்ளவர்கள் இந்த ஆய்வில் பங்கு பெறுவர். அவர்களிடம் நோய் சம்பந்தப்பட்ட வரலாறு முற்றிலுமாக கேட்டறியப்படும். அவர்களுக்கு நுரையீரல் மற்றும் இதர உறுப்புகள் சம்பந்தப்பட்ட பரிசோதனை செய்யப்படும். சளி, இரத்தம், நெஞ்சுப்படம் மற்றும் தேவையான இடங்களில் சி.ஒடி.ஸ்கேன் போன்ற பரிசோதனைகள் செய்யப்படும்.

இதயம் பரிசோதனை செய்யப்படும். மேலும் வளர்சிதை மாற்று நோய்குறியை கண்டறிவதற்கான இரத்தப் பரிசோதனைகள் செய்யப்படும். வயிற்றின் சுற்றளவு கணக்கில் கொள்ளப்படும். இரத்த அழுத்தம் பரிசோதனை

செய்யப்படும். நோய்க்குறி தோன்றா பெருந்தமனியை கண்டறிவதற்காக துயில் தமனி டாப்ளர் ஸ்கேன் பரிசோதனை செய்யப்படும்.

நன்மைகள்

இந்த ஆராய்ச்சியின் மூலம் நாள்பட்ட மூச்சுக்குழாய் அடைப்பு நோய் உள்ளவர்களின் வளர்சிதை மாற்று நோய்குறியை அபாய காரணியாக கருத்தில் கொள்ளவும், அவர்களுக்கு தக்க சிகிச்சை அளிப்பதன் மூலம் இருதயம் மற்றும் இரத்தக்குழாய் சம்பந்தப்பட்ட பாதிப்புகளை குறைக்கவும் வழி செய்யும்.

இந்த நோய் பற்றிய முறையான ஆய்வு ஏற்கனவே பல இடங்களில் நடத்தப்பட்டுள்ளது. மேலும் இதன் பாதுகாப்பு உறுதிசெய்யப்பட்டுள்ளது. உங்கள் பாதுகாப்பே எங்களின் முக்கிய நோக்கம்.

இந்த ஆய்வு சம்பந்தமான எல்லா புள்ளி விவரங்கள் மற்றும் நோயாளிகளின் விவரங்கள் ரகசியமாக வைக்கப்படும். இந்த ஆய்வு சம்பந்தப்பட்ட எல்லா பரிசோதனைகள், மருந்துகள் மற்றும் மருத்துவ சேவைகள் அனைத்தும் நோயாளிகளுக்கு இலவசமாக வழங்கப்படும்.

ஆய்வாளரின் பெயர் **பங்குபெறுபவரின் பெயர்**

ஆய்வாளரின் கையொப்பம் **பங்குபெறுபவரின் கையொப்பம்**

AGE	SEX	mMRC	NO OF HOSPITALISATION	NO OF EXACERBATIONS	CAT SCORE	SMOKER	PACK YEARS	BIOMASS EXPOSURE	RADIOLOGY	FEV1	%FEV1	COPD	AIRFLOW LIMITATION SEVERITY	COPD CATEGORY	MET SYNDROME	WAIST CIRCUMFERENCE	BMI
63	M	3	2	3	21	CURRENT	35	NO	EMPHYSEMA	1.65	43%	YES	SEVERE	D	YES	36	23.5
56	M	2	0	1	14	FORMER	20	NO	BRONCHITIS	2.14	58%	YES	MODERATE	B	NO	37	23.8
63	M	NA	NA	NA	NA	CURRENT	30	NO	NORMAL	3.36	83%	NO	NO	NA	NO	35	23
56	F	2	1	2	15	NO	0	YES	BRONCHITIS	1.86	52%	YES	MODERATE	D	YES	40	31.6
62	F	1	0	1	12	NO	0	YES	BRONCHITIS	2.56	58%	YES	MODERATE	B	NO	33	22.6
56	F	NA	NA	NA	NA	NO	0	YES	NORMAL	3.47	84%	NO	NO	NA	NO	41	26
68	M	2	0	1	18	FORMER	15	YES	BRONCHITIS	3.21	61%	YES	MODERATE	B	YES	37	23
63	M	3	2	4	26	CURRENT	40	NO	EMPHYSEMA	1.36	36%	YES	SEVERE	D	NO	35	23
68	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.25	88%	NO	NO	NA	NO	37	24
50	F	2	0	1	14	NO	0	YES	BRONCHITIS	3.21	67%	YES	MODERATE	B	YES	40	31.4
70	F	3	2	3	29	NO	0	YES	EMPHYSEMA	1.26	29%	YES	VERY SEVERE	D	YES	42	33
59	F	1	0	0	8	NO	0	YES	BRONCHITIS	3.36	83%	YES	MILD	A	YES	41	34
61	F	2	0	2	16	NO	0	YES	BRONCHITIS	3.34	69%	YES	MODERATE	D	YES	42	31.2
56	F	3	1	3	22	NO	0	YES	BRONCHITIS	2.43	45%	YES	SEVERE	D	YES	45	34.5
58	F	2	1	5	24	NO	0	NO	EMPHYSEMA	2.14	40%	YES	SEVERE	D	YES	42	33
63	F	3	2	6	28	NO	0	YES	EMPHYSEMA	1.33	27%	YES	VERY SEVERE	D	YES	43	30.5
67	F	1	1	2	7	NO	0	YES	BRONCHITIS	1.78	52%	YES	MODERATE	C	YES	40	31.5
49	M	1	0	0	8	NO	0	NO	BRONCHITIS	2.43	82%	YES	MILD	A	YES	45	33.2
72	M	2	0	1	17	FORMER	30	NO	EMPHYSEMA	1.89	53%	YES	MODERATE	B	YES	44	34.5
54	M	3	1	4	24	CURRENT	28	NO	EMPHYSEMA	1.56	46%	YES	SEVERE	D	YES	41	32.3
59	M	1	1	1	8	CURRENT	24	NO	BRONCHITIS	1.48	48%	YES	SEVERE	C	YES	44	34.2
65	M	3	2	6	25	FORMER	40	NO	EMPHYSEMA	1.28	29%	YES	VERY SEVERE	D	YES	41	33.5
63	M	1	0	0	8	NO	0	NO	EMPHYSEMA	2.78	81%	YES	MILD	A	YES	34	23
52	M	2	0	1	18	NO	0	YES	BRONCHITIS	2.32	67%	YES	MODERATE	B	YES	36	24.3
66	M	2	1	3	16	NO	0	NO	BRONCHITIS	1.65	38%	YES	SEVERE	D	YES	38	22.6
58	M	3	2	5	24	NO	0	YES	EMPHYSEMA	1.29	26%	YES	VERY SEVERE	D	YES	36	23.8
74	M	3	3	6	31	FORMER	44	NO	EMPHYSEMA	1.16	28%	YES	VERY SEVERE	D	YES	33	20.3
76	M	3	4	7	27	FORMER	46	YES	EMPHYSEMA	1.24	27%	YES	VERY SEVERE	D	YES	35	21.4
57	M	2	0	1	14	CURRENT	24	NO	BRONCHITIS	1.36	26%	YES	VERY SEVERE	B	YES	34	22
49	M	2	0	2	18	CURRENT	18	NO	EMPHYSEMA	1.78	43%	YES	SEVERE	D	YES	33	23.4
66	M	3	1	4	23	FORMER	26	YES	EMPHYSEMA	1.57	38%	YES	SEVERE	D	YES	37	24.2
53	M	1	0	1	14	CURRENT	16	NO	BRONCHITIS	2.26	58%	YES	MODERATE	B	YES	36	23.5
58	M	2	0	1	16	CURRENT	22	NO	BRONCHITIS	2.14	53%	YES	MODERATE	B	YES	35	21.8
64	M	1	0	2	5	FORMER	26	NO	EMPHYSEMA	1.87	59%	YES	MODERATE	C	YES	33	22.6
63	M	2	0	2	16	FORMER	25	NO	EMPHYSEMA	2.34	80%	YES	MILD	D	YES	36	23.4
73	M	2	0	1	17	FORMER	26	NO	BRONCHITIS	2.16	81%	YES	MILD	B	YES	37	24.2
78	M	2	0	1	21	FORMER	23	NO	EMPHYSEMA	1.84	64%	YES	MODERATE	B	YES	38	23.1
68	M	2	0	0	18	CURRENT	16	YES	EMPHYSEMA	2.18	82%	YES	MILD	B	YES	35	23.7
67	M	3	1	4	23	FORMER	25	NO	EMPHYSEMA	1.67	45%	YES	SEVERE	D	YES	35	22.8
55	M	2	1	3	27	CURRENT	28	NO	BRONCHITIS	1.78	42%	YES	SEVERE	D	YES	37	23.8
65	M	3	2	3	25	FORMER	35	NO	EMPHYSEMA	1.16	25%	YES	VERY SEVERE	D	YES	33	23.5
68	M	1	2	4	7	FORMER	33	NO	BRONCHITIS	1.56	43%	YES	SEVERE	C	YES	35	21.4
71	M	2	1	4	25	CURRENT	47	NO	EMPHYSEMA	1.25	27%	yes	VERY SEVERE	D	YES	36	22.6
46	F	1	0	1	8	NO	0	YES	BRONCHITIS	2.21	65%	YES	MODERATE	A	YES	33	23.4
51	F	2	1	2	16	NO	0	YES	BRONCHITIS	1.65	46%	YES	SEVERE	D	YES	34	23.5
57	F	3	1	4	23	NO	0	YES	EMPHYSEMA	1.46	42%	YES	SEVERE	D	YES	32	21.6
63	F	3	2	6	27	NO	0	YES	EMPHYSEMA	1.14	28%	YES	VERY SEVERE	D	YES	34	20.2

69	F	2	0	1	16	NO	0	NO	BRONCHITIS	1.78	56%	YES	MODERATE	B	YES	32	22.4
54	M	2	0	1	18	CURRENT	26	NO	EMPHYSEMA	1.74	54%	YES	MODERATE	B	NO	33	23.5
58	M	1	0	1	12	CURRENT	21	NO	BRONCHITIS	2.42	82%	YES	MILD	B	NO	36	23.1
62	M	2	0	1	18	FORMER	24	YES	EMPHYSEMA	1.86	59%	YES	MODERATE	B	NO	33	24.6
66	M	3	0	1	25	FORMER	28	NO	EMPHYSEMA	1.54	46%	YES	SEVERE	B	NO	34	27.4
59	M	1	1	2	8	FORMER	19	NO	BRONCHITIS	1.45	42%	YES	SEVERE	C	NO	31	25.4
62	M	3	2	3	17	CURRENT	28	NO	EMPHYSEMA	1.16	28%	YES	VERY SEVERE	D	NO	32	23.6
72	M	2	0	1	19	FORMER	31	YES	EMPHYSEMA	1.96	54%	YES	MODERATE	B	NO	34	24.5
73	M	1	0	0	8	FORMER	31	NO	BRONCHITIS	1.65	47%	YES	SEVERE	A	NO	33	23.1
65	M	2	0	2	18	FORMER	26	NO	EMPHYSEMA	1.97	61%	YES	MODERATE	D	NO	34	23.5
68	M	2	1	1	16	FORMER	24	NO	EMPHYSEMA	1.56	42%	YES	SEVERE	D	NO	36	22.5
56	M	2	1	1	18	CURRENT	22	NO	EMPHYSEMA	1.55	40%	YES	SEVERE	D	NO	34	23.5
60	M	3	1	2	21	CURRENT	28	NO	EMPHYSEMA	1.28	29%	YES	VERY SEVERE	D	NO	32	23.8
58	F	1	0	0	8	NO	0	YES	BRONCHITIS	2.45	82%	YES	MILD	A	NO	34	26.5
65	F	2	0	1	17	NO	0	YES	BRONCHITIS	2.14	62%	YES	MODERATE	B	NO	31	22.1
68	F	1	0	1	6	NO	0	YES	EMPHYSEMA	1.86	56%	YES	MODERATE	C	NO	34	24.5
64	F	2	1	2	18	NO	0	YES	EMPHYSEMA	1.65	46%	YES	SEVERE	D	NO	33	21.6
69	F	3	0	2	21	NO	0	YES	EMPHYSEMA	1.45	38%	YES	SEVERE	D	NO	31	22.8
59	F	3	1	2	24	NO	0	YES	EMPHYSEMA	1.23	27%	YES	VERY SEVERE	D	NO	33	25.7
67	F	2	0	1	15	NO	0	YES	BRONCHITIS	2.15	64%	YES	MODERATE	B	NO	34	24.2
52	M	2	0	1	17	NO	0	NO	BRONCHITIS	2.25	61%	YES	MODERATE	B	NO	36	23.7
55	M	2	0	1	18	NO	0	YES	BRONCHITIS	1.65	46%	YES	SEVERE	B	NO	37	22.5
58	M	3	1	2	25	NO	0	NO	EMPHYSEMA	1.24	29%	YES	VERY SEVERE	D	NO	35	20.3
63	M	2	0	1	15	NO	0	NO	BRONCHITIS	2.14	63%	YES	MODERATE	B	NO	32	23.4
58	M	3	0	1	17	CURRENT	24	NO	EMPHYSEMA	1.97	56%	YES	MODERATE	B	NO	33	14.3
65	M	2	1	1	19	CURRENT	28	NO	EMPHYSEMA	1.65	44%	YES	SEVERE	D	NO	33	24.3
63	M	2	0	1	17	FORMER	25	NO	BRONCHITIS	2.13	64%	YES	MODERATE	B	NO	34	25
53	M	1	0	1	8	CURRENT	17	NO	BRONCHITIS	3.19	82%	YES	MILD	A	NO	35	24.6
66	M	3	1	1	23	FORMER	26	NO	BRONCHITIS	1.67	43%	YES	SEVERE	D	NO	33	23.2
70	M	2	1	1	29	FORMER	27	NO	EMPHYSEMA	1.97	56%	YES	MODERATE	D	NO	36	24.5
62	M	2	1	1	17	FORMER	25	NO	EMPHYSEMA	1.45	41%	YES	SEVERE	D	NO	32	23.5
59	M	1	0	2	7	CURRENT	21	NO	BRONCHITIS	2.1	59%	YES	MODERATE	C	NO	36	21.8
65	F	2	0	2	19	NO	0	YES	EMPHYSEMA	1.56	41%	YES	SEVERE	D	NO	34	24.6
69	F	3	0	1	21	NO	0	YES	EMPHYSEMA	1.18	26%	YES	VERY SEVERE	B	NO	34	21.9
59	F	2	1	1	18	NO	0	YES	BRONCHITIS	1.65	48%	YES	SEVERE	D	NO	33	25.7
56	F	1	0	0	6	NO	0	YES	BRONCHITIS	3.15	82%	YES	MILD	A	NO	33	23.4
62	F	2	0	1	19	NO	0	NO	BRONCHITIS	2.16	65%	YES	MODERATE	B	NO	37	23.6
69	F	3	0	1	19	NO	0	YES	EMPHYSEMA	1.78	49%	YES	SEVERE	B	NO	34	24.5
58	M	2	1	1	21	CURRENT	24	NO	BRONCHITIS	1.96	62%	YES	MODERATE	D	NO	36	23.5
68	M	3	1	1	28	FORMER	27	NO	EMPHYSEMA	1.24	29%	YES	VERY SEVERE	D	NO	38	24.6
55	M	NA	NA	NA	NA	FORMER	20	NO	NORMAL	3.54	88%	NO	NO	NA	NO	36	24.6
59	M	NA	NA	NA	NA	CURRENT	27	NO	NORMAL	4.14	90%	NO	NO	NA	YES	35	25.6
62	M	NA	NA	NA	NA	CURRENT	25	NO	NORMAL	3.98	86%	NO	NO	NA	NO	33	23.2
65	M	NA	NA	NA	NA	FORMER	20	NO	NORMAL	3.76	82%	NO	NO	NA	NO	34	24.6
67	M	NA	NA	NA	NA	FORMER	15	NO	NORMAL	3.94	86%	NO	NO	NA	NO	36	22.4
72	M	NA	NA	NA	NA	FORMER	23	NO	NORMAL	3.65	73%	NO	NO	NA	YES	32	24.3
57	M	NA	NA	NA	NA	CURRENT	23	NO	NORMAL	3.87	78%	NO	NO	NA	NO	33	23.5
61	M	NA	NA	NA	NA	FORMER	20	NO	NORMAL	3.98	86%	NO	NO	NA	NO	34	24.6
64	M	NA	NA	NA	NA	FORMER	25	NO	NORMAL	4.12	83%	NO	NO	NA	NO	37	23.2
67	M	NA	NA	NA	NA	CURRENT	31	NO	NORMAL	3.67	76%	NO	NO	NA	NO	34	24.5

71	M	NA	NA	NA	NA	FORMER	27	NO	NORMAL	3.87	78%	NO	NO	NA	NO	35	23.6
57	M	NA	NA	NA	NA	CURRENT	23	NO	NORMAL	3.56	72%	NO	NO	NA	NO	32	23.8
72	M	NA	NA	NA	NA	FORMER	30	NO	NORMAL	3.26	70%	NO	NO	NA	YES	33	23.9
69	M	NA	NA	NA	NA	FORMER	26	NO	NORMAL	3.56	78%	NO	NO	NA	NO	35	21.9
63	M	NA	NA	NA	NA	CURRENT	28	NO	NORMAL	3.86	82%	NO	NO	NA	NO	34	24.3
67	M	NA	NA	NA	NA	FORMER	25	NO	NORMAL	3.64	76%	NO	NO	NA	NO	32	23.3
71	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.87	83%	NO	NO	NA	NO	36	23.6
56	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.97	79%	NO	NO	NA	NO	35	24.6
61	M	NA	NA	NA	NA	NO	0	NO	NORMAL	4.17	84%	NO	NO	NA	NO	34	27.8
59	M	NA	NA	NA	NA	NO	0	NO	NORMAL	4.1	80%	NO	NO	NA	NO	35	26.8
67	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.68	78%	NO	NO	NA	NO	33	23.7
71	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.87	83%	NO	NO	NA	NO	36	23.6
56	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.97	79%	NO	NO	NA	NO	35	24.6
61	M	NA	NA	NA	NA	NO	0	NO	NORMAL	4.17	84%	NO	NO	NA	NO	34	27.8
59	M	NA	NA	NA	NA	NO	0	NO	NORMAL	4.1	80%	NO	NO	NA	NO	35	26.8
67	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.68	78%	NO	NO	NA	NO	33	23.7
58	M	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	76%	NO	NO	NA	NA	36	24.7
63	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	83%	NO	NO	NA	YES	38	23.7
68	F	NA	NA	NA	NA	NO	0	NO	NORMAL	4.14	86%	NO	NO	NA	NO	35	24.7
56	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	78%	NO	NO	NA	NO	34	21.9
63	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	83%	NO	NO	NA	YES	38	23.7
68	F	NA	NA	NA	NA	NO	0	NO	NORMAL	4.14	86%	NO	NO	NA	NO	35	24.7
56	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	78%	NO	NO	NA	NO	34	21.9
63	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	83%	NO	NO	NA	YES	38	23.7
68	F	NA	NA	NA	NA	NO	0	NO	NORMAL	4.14	86%	NO	NO	NA	NO	35	24.7
56	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	78%	NO	NO	NA	NO	34	21.9
63	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	83%	NO	NO	NA	YES	38	23.7
68	F	NA	NA	NA	NA	NO	0	NO	NORMAL	4.14	86%	NO	NO	NA	NO	35	24.7
56	F	NA	NA	NA	NA	NO	0	NO	NORMAL	3.89	78%	NO	NO	NA	NO	34	21.9

FBS	BP	TGL	HDL-C	ESR	CIMT	CAROTID PLAGUE	PAO2	PACO2	6MWD	BODE INDEX	PHT	RV DYSFUNCTION
170	150/90	186	38	36	1.1	YES	75	52	323	5	MODERATE	YES
110	140/90	166	42	18	0.7	NO	85	44	450	2	NO	NO
106	130/80	156	45	18	0.6	NO	NA	NA	NA	NA	NO	NO
168	130/80	180	34	45	1.2	NO	68	50	230	4	SEVERE	YES
114	120/80	143	48	23	0.6	NO	88	45	465	1	NO	NO
123	110/70	156	50	26	0.65	NO	NA	NA	NA	NA	NO	NO
176	160/100	167	34	31	0.56	NO	83	44	380	2	NO	NO
122	160/90	145	42	48	1.1	YES	64	54	240	6	SEVERE	YES
106	120/80	136	45	18	0.53	NO	NA	NA	NA	NA	NO	NO
165	130/80	168	43	36	0.97	NO	76	47	270	2	MILD	NO
178	150/90	146	36	52	1.23	YES	62	56	170	7	SEVERE	YES
168	148/84	175	40	18	0.64	NO	82	44	450	0	NO	NO
164	152/86	142	45	32	0.87	NO	75	47	245	4	MILD	NO
145	164/94	189	46	42	1.18	NO	68	51	188	6	MODERATE	YES
120	178/96	156	44	44	1.24	YES	66	53	176	5	SEVERE	YES
176	146/88	180	34	56	1.28	YES	62	57	148	8	SEVERE	YES
152	154/86	178	45	34	1.04	NO	72	48	280	2	MILD	NO
174	162/96	135	42	21	0.63	NO	82	42	356	0	NO	NO
116	170/98	190	36	35	0.98	NO	68	40	267	3	MILD	NO
168	124/68	159	42	46	1.18	NO	63	54	197	6	MODERATE	NO
124	130/78	198	34	44	1.16	NO	76	46	265	3	MILD	NO
168	154/86	132	36	48	1.25	YES	60	57	158	7	MODERATE	YES
165	140/90	178	34	46	0.96	NO	78	43	330	1	NO	NO
186	154/88	154	45	40	1.04	NO	64	54	220	4	NO	YES
136	152/86	176	35	33	1.16	YES	60	52	189	6	MODERATE	YES
116	154/90	169	33	54	1.29	NO	58	57	143	9	SEVERE	YES
178	140/88	176	39	51	1.26	YES	56	59	168	8	SEVERE	YES
198	126/76	188	33	32	1.17	NO	76	54	188	7	MODERATE	NO
165	136/84	166	42	43	1.02	NO	78	52	257	5	MODERATE	NO
178	148/86	188	38	38	1.14	NO	68	48	267	4	MILD	YES
120	164/76	165	34	32	0.72	NO	78	45	245	7	SEVERE	YES
179	150/90	158	38	36	0.54	NO	83	44	321	2	NO	NO
166	140/90	169	42	15	0.63	NO	81	45	285	3	MILD	NO
197	150/86	176	38	19	0.62	NO	84	46	310	3	MODERATE	NO
145	146/84	183	36	15	0.69	NO	82	43	284	1	NO	NO
156	136/84	164	32	18	0.71	NO	83	45	234	1	NO	NO
168	154/90	186	38	24	0.78	NO	84	42	187	3	MILD	NO
178	160/90	166	41	28	0.88	NO	82%	46	210	2	MILD	NO
189	156/84	188	37	38	1.06	NO	66	52	186	6	MODERATE	YES
155	166/88	169	33	44	1.1	YES	60	54	166	6	MODERATE	NO
167	144/84	178	35	51	1.23	YES	56	58	145	9	SEVERE	YES
188	164/88	176	33	45	1.2	YES	64	56	168	4	MODERATE	no
176	142/80	168	31	46	1.22	yes	62	55	143	7	MODERATE	YES
188	156/64	174	34	25	0.92	NO	74	49	235	3	MILD	NO
158	160/86	188	31	32	1.04	NO	68	50	186	5	MODERATE	NO
190	166/88	176	32	42	1.12	NO	62	54	164	6	MODERATE	NO
198	140/74	166	32	43	1.27	YES	58	59	132	9	SEVERE	YES

187	150/90	186	36	32	1.06	NO	66	52	245	4	MODERATE	NO
116	134/74	143	42	28	0.86	NO	68	46	321	3	MILD	NO
146	124/72	164	45	21	0.91	NO	74	44	388	1	NO	NO
167	134/68	133	42	25	0.93	NO	76	48	324	3	MILD	NO
114	116/82	168	41	28	0.97	NO	65	51	275	5	MODERATE	YES
128	120/76	145	43	31	1.03	NO	68	48	289	3	MILD	NO
164	110/76	142	45	38	1.05	YES	60	54	210	7	MODERATE	YES
110	156/86	165	47	26	0.83	NO	76	48	289	3	NO	NO
144	154/80	123	43	24	0.88	NO	76	49	265	3	NO	NO
129	148/88	145	44	32	0.93	NO	68	51	215	4	MILD	NO
168	126/76	134	45	35	0.98	NO	62	52	190	5	MILD	NO
145	146/78	143	43	32	1.02	NO	66	50	215	5	MODERATE	NO
116	156/88	122	45	41	1.08	NO	62	55	167	7	SEVERE	YES
118	120/80	165	42	23	0.86	NO	86	44	328	1	NO	NO
143	110/80	143	51	26	0.9	NO	76	47	256	3	MILD	NO
120	130/78	156	56	21	0.88	NO	78	48	289	2	NO	NO
145	140/88	145	51	28	0.94	NO	68	50	221	5	MODERATE	NO
120	156/86	144	41	32	1.04	NO	66	48	214	6	MODERATE	NO
117	140/90	134	54	41	1.09	YES	58	54	158	8	SEVERE	YES
98	136/88	167	52	21	0.83	NO	76	44	315	3	MILD	NO
116	140/78	134	46	25	0.87	NO	78	43	365	2	NO	NO
106	130/78	143	47	26	0.94	NO	68	48	265	4	MILD	NO
108	140/90	143	42	36	1.04	NO	60	53	189	7	MODERATE	YES
120	136/88	134	45	23	0.54	NO	78	45	278	3	MILD	NO
114	124/78	145	45	22	0.64	NO	76	47	289	4	MILD	NO
120	140/90	123	43	26	0.71	NO	68	48	235	5	MODERATE	NO
116	130/80	145	45	28	0.67	NO	78	43	345	3	NO	NO
167	120/76	143	46	21	0.65	NO	82	45	388	0	NO	NO
123	140/90	134	43	34	0.74	NO	67	51	212	6	MODERATE	NO
116	150/90	132	44	24	0.68	NO	74	48	298	3	MILD	NO
120	140/86	145	45	32	0.72	NO	66	49	243	5	MODERATE	NO
145	114/74	132	46	25	0.65	NO	70	50	267	2	NO	NO
120	116/80	168	51	29	0.71	NO	75	49	213	5	MODERATE	NO
117	140/90	165	53	36	0.74	NO	62	52	189	7	SEVERE	YES
156	138/90	138	51	27	0.63	NO	66	48	198	5	MODERATE	NO
145	120/70	187	45	18	0.56	NO	84	43	399	0	NO	NO
143	116/76	143	52	21	0.65	NO	78	47	289	3	MILD	NO
120	130/78	187	51	28	0.72	NO	65	49	234	6	MODERATE	NO
114	140/88	123	46	28	0.69	NO	75	45	278	3	MILD	NO
118	142/80	143	47	32	0.72	NO	62	53	165	7	SEVERE	YES
135	126/78	167	46	23	0.65	NO	NA	NA	NA	NA	NO	NO
156	140/90	178	36	18	0.84	NO	NA	NA	NA	NA	NO	NO
120	124/72	132	45	16	0.56	NO	NA	NA	NA	NA	NO	NO
115	116/78	145	42	18	0.88	NO	NA	NA	NA	NA	NO	NO
148	124/78	146	45	25	0.65	NO	NA	NA	NA	NA	NO	NO
168	138/90	165	38	24	0.86	NO	NA	NA	NA	NA	NO	NO
122	128/76	123	45	19	0.67	NO	NA	NA	NA	NA	NO	NO
114	140/68	134	43	22	0.62	NO	NA	NA	NA	NA	NO	NO
116	116/78	128	46	16	0.56	NO	NA	NA	NA	NA	NO	NO
112	136/84	145	42	24	0.89	NO	NA	NA	NA	NA	NO	NO

118	140/80	134	43	26	0.64	NO	NA	NA	NA	NA	NO	NO
98	130/88	145	45	23	0.68	NO	NA	NA	NA	NA	NO	NO
145	140/90	167	38	34	0.7	NO	NA	NA	NA	NA	NO	NO
144	128/78	134	45	21	0.58	NO	NA	NA	NA	NA	NO	NO
120	136/88	138	43	25	0.69	NO	NA	NA	NA	NA	NO	NO
138	114/76	156	46	28	0.59	NO	NA	NA	NA	NA	NO	NO
90	120/78	122	42	17	0.63	NO	NA	NA	NA	NA	NO	NO
118	116/76	144	45	26	0.91	NO	NA	NA	NA	NA	NO	NO
135	118/80	135	42	23	0.71	NO	NA	NA	NA	NA	NO	NO
118	120/78	145	45	26	0.63	NO	NA	NA	NA	NA	NO	NO
117	120/88	133	43	28	0.68	NO	NA	NA	NA	NA	NO	NO
90	120/78	122	42	17	0.63	NO	NA	NA	NA	NA	NO	NO
118	116/76	144	45	26	0.91	NO	NA	NA	NA	NA	NO	NO
135	118/80	135	42	23	0.71	NO	NA	NA	NA	NA	NO	NO
118	120/78	145	45	26	0.63	NO	NA	NA	NA	NA	NO	NO
117	120/88	133	43	28	0.68	NO	NA	NA	NA	NA	NO	NO
114	130/78	145	44	24	0.65	NO	NA	NA	NA	NA	NO	NO
156	140/90	156	43	27	0.85	NO	NA	NA	NA	NA	NO	NO
168	142/78	138	52	23	0.67	NO	NA	NA	NA	NA	NO	NO
122	122/78	144	45	25	0.56	NO	NA	NA	NA	NA	NO	NO
156	140/90	156	43	27	0.85	NO	NA	NA	NA	NA	NO	NO
168	142/78	138	52	23	0.67	NO	NA	NA	NA	NA	NO	NO
122	122/78	144	45	25	0.56	NO	NA	NA	NA	NA	NO	NO
156	140/90	156	43	27	0.85	NO	NA	NA	NA	NA	NO	NO
168	142/78	138	52	23	0.67	NO	NA	NA	NA	NA	NO	NO
122	122/78	144	45	25	0.56	NO	NA	NA	NA	NA	NO	NO
156	140/90	156	43	27	0.85	NO	NA	NA	NA	NA	NO	NO
168	142/78	138	52	23	0.67	NO	NA	NA	NA	NA	NO	NO
122	122/78	144	45	25	0.56	NO	NA	NA	NA	NA	NO	NO