"A COMPARATIVE STUDY TO ASSESS THE CLINICO-RADIOLOGICAL CHARACTERSTICS OF COPD PHENOTYPES AND THEIR VARIED RESPONSE TO BRONCHODILATORS IN A TERTIARY CARE HOSPITAL"

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

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"A COMPARATIVE STUDY TO ASSESS THE CLINICO-RADIOLOGICAL CHARACTERSTICS OF COPD PHENOTYPES AND THEIR VARIED RESPONSE TO BRONCHODILATORS IN A TERTIARY CARE HOSPITAL"** is the bonafide work done by **Dr. MANJU SARA OOMMEN** during her **M.D (Tuberculosis and Respiratory Diseases)** course in the academic years 2014-2017, 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.

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CONTENTS

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity around the globe. The World Health Organization estimates that 65 million people have moderate to severe COPD, with deaths accounting to 5% of total deaths in the world. Around 3 million people with COPD died in 2005 and it is believed that COPD will be the third leading cause of death by 2030.The burden of COPD in developing countries is more than the high income countries with almost 90% COPD deaths occurring in the former.[1]

COPD mortality in India is ranked amongst the highest in the world with more than 64.7 estimated age standardized death per 100,000 in both sexes. This estimates to 5,56,000 in India i.e more than 20% of the world total of 2,748,000 [2] annual deaths due to COPD. Hence, COPD burden in India is of grave significance with such gigantic volumes of disease posing a threat to system and state economies. [3][[4]

According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline, COPD is defined as a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and is associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles and gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.[5]

COPD was previously classified as emphysema type and chronic bronchitis type. But as the emphysema phenotype was diagnosed based on morphological

and pathological features and chronic bronchitis on clinical features such as cough and sputum, COPD patients could not be classified into either phenotype. In the definition of COPD as per GOLD, terms ‘emphysema’ and ‘chronic bronchitis’ are no longer included.

COPD is characterized by small airways inflammation and remodeling as well as emphysematous destruction of terminal airspaces. Pathologically, in the central airways there is an increase in the goblet cells, mucous secreting glands and smooth muscle and connective tissue in the airway wall. In the peripheral airways, there is metaplasia of the goblet cells, inflammatory exudates in the wall and lumen which reduces the lumen, airway wall reorganization, increased smooth muscles and peribronchial connective tissue. Along with loss of elastic recoil of the lung, the peripheral airways are the major site of airway obstruction.

The volume of air expired within 1 second after the beginning of a forced expiration is the hallmark of COPD.[6] Irreversible airflow obstruction detected by spirometry unifies under the umbrella of COPD, a set of heterogenous conditions with variable clinical presentations. FEV1 is the strongest predictor of mortality in COPD patients[7]**.** The various factors that cause decline in FEV1 is of prognostic significance.

COPD, as presently understood, has several clinical phenotypes such as emphysema and marked hyperinflation, frequent exacerbators, asthma-COPD overlap syndrome, systemic COPD etc. High resolution CT can classify COPD

into various phenotypes morphologically.[8] Some patients despite irreversible airflow obstruction may not show emphysema on HRCT (assessed by low attenuation areas) while others show severe emphysema. Similarly, some show bronchial wall thickness with irreversible airflow obstruction whilst others do not. Certain COPD patients show partial reversibility on pulmonary function test. Moreover, COPD also cause systemic effects such as malnutrition, peripheral muscle weakness and pulmonary hypertension.[9],[10]

Hence, COPD is not a simple disease with airflow obstruction as assessed by spirometry but has a devastating impact on the patient's quality of life.

The tendency to clump a variety of conditions under the acronym COPD may blur important differences that may be useful in clinical practice to understand the natural history of the disease as well to decide treatment strategies for the different phenotypes**.** Thus, a global assessment of COPD is imperative.

This study aimed to understand the clinical, spirometric and radiological characteristics of three main COPD phenotypes and to assess their varied response to bronchodilators.

REVIEW OF LITERATURE

In both developing and developed countries, Global initiative for Chronic Obstructive Lung disease (GOLD) has helped in standardizing the diagnosis and treatment of COPD. The 2001 and 2006 GOLD reports recommended staging COPD based on spirometry alone. With subsequent studies,[11,12] Chronic obstructive pulmonary disease (COPD) was recognized as a complex disease and this led to the introduction of the multidimensional assessment in GOLD in 2011. GOLD 2011 update recommends a more holistic method in approaching COPD by considering symptoms of patients using a grading system for dyspnea(MMRC), exacerbations over the past year as well as airflow limitation to grade COPD severity. Though it has the advantage of being relatively simple and hence applicable universally, it does not take into account other factors relevant to disease progression such as presence of emphysema on CT or pulmonary inflammation as indicated by inflammatory markers. The need of the era is to identify specific characteristics that can help break down the huge heterogenous COPD population to different phenotypes which can help in targeted therapeutic approach.

‘‘Phenotype’’ is classically defined as the observable structural and functional characteristics of an organism that are determined by the combined influence of genotype and environment. [13]

Currently, this term is applied in COPD when referring to different characteristics of patients with COPD. It is likely that these varied clinical manifestations are a likely reflection of “gene-environment” and “gene-gene”

interactions. This had led to renewed interest in classifying these patients into distinct sub-groups for a tailored therapeutic approach for symptom control, to delay disease progression, improve health status and quality of life.

Han *et al*. [14] defined phenotype as: ‘‘a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)’’.Miravitlles *et al.* stated that “COPD phenotype” is reserved for those clinical types of COPD patients that have a therapeutic impact.[15] Salzman *et al.* put forward the concept that the outcome of treatment may also be included for classifying COPD into phenotypes.[16] Sobradillo *et al.* reported that certain COPD features like dyspnea or exacerbations could be considered as outcomes or as phenotypes depending on the context.[17]

IDENTIFYING PHENOTYPES IN COPD

Marsh SE *et al* proposed questionnaires and pulmonary function tests for phenotyping and differentiating COPD patients.[18]

It has also been suggested to use multidimensional indices for phenotyping COPD. The BODE score (body mass index, airway obstruction, dyspnea, exercise capacity) is a better predictor of mortality than FEV1 alone in COPD. Similarly, the SAFE(SGRQ score, airway obstruction, exercise tolerance) index and DOSE (dyspnea, airflow obstruction, smoking status, exacerbation frequency) index can predict exacerbations. But using these indices for all phenotyping classification could lead to overlapping phenotypes that are hard

to differentiate. Hence it has been proposed that using the individual components of the multidimensional indices may be more fruitful in phenotyping rather than a single index.[19] In the pulmonary function tests, responsiveness to bronchodilators can help distinguish asthma from COPD as well as in defining the mixed asthma-COPD phenotype.

However, Salzman *et al* in their study stated that it is not possible to identify subgroups that respond to particular therapies with pulmonary function tests alone.[20] Reports from studies by Bragman *et al.* [21], Fan L *et al.* [22,], Galban *et al.*[23] have suggested Computed Tomography, High resolution CT and magnetic resonance imaging (MRI) to be clinically useful in differentiating COPD phenotypes. Currently, they are thought to be new tools for an accurate diagnosis and and to guide management. However, these are limited by the fact that certain factors cannot be assessed by techniques available till now.

DISEASE ATTRIBUTES OF PHENOTYPES IN COPD

AGE:

Grydeland *et al*.[24] in their study reported that emphysema was associated with an increasing age and that aging was better in predicting emphysema than smoking. Pierre-Régis Burgel *et al.*[25] found that a median age of 61 (57-66) corresponded with severe airflow limitation, marked emphysema and hyperinflation in one subgroup. They also reported another subgroup of COPD patients in the median age of 72 (65-77) with less severe emphysema but more bronchial thickening

Soriano *et al.*[26] studied that 23% of patients between 50-59 may have mixed phenotype which increases to 52% in those COPD patients aged 70-79.

M.Hardin *et al.* [27] examined 915 COPD patients and found that compared to COPD alone, those of whom who had COPD and asthma were younger (mean age 61.3). Karlos.N *et al.*[28] reported that women with COPD were younger (64.2), smoked less, and had better lung function as against males.

GENDER

N.Sverzellati *et al.*[29]showed that females compared to males had less extensive emphysema phenotype which was characterized by smaller areas of emphysema with less concentration in core of the lung. Dransfield *et al.*[30] demonstrated less severe emphysema in all stages of COPD in women while men tends to have greater severity of emphysema. Martinez *et al.*[31] cited men with COPD to have larger emphysematous spaces on HRCT scans whereas women with COPD had thickened airways on histological examination. Nk.Jain *et al* [32] in their study reported that women with COPD are younger (mean age 58.34 ± 9.99 years v/s 61.57 ± 10.37 years in males). Camp PG *et al* [33] concluded that male smokers had more emphysema against female smokers but female smokers did not have increased airway thickness.

BODY MASS INDEX:

Landbo C *et al.*[34] and Celli BR *et al.*[35] found that BMI is an independent prognostic factor in COPD and that there is a greater risk for death with a lower BMI irrespective of the stage of COPD. Vestbo J *et al.*[36] reported that fat free mass less than 16 kg/m^2, common in COPD patients, is associated with

greater mortality even with a normal BMI. E.Ogawa *et al* [37]. reported that the body mass index (BMI) was lower in male smokers with COPD who had the emphysematous predominant and mixed phenotypes than the airway predominant phenotype even though no difference in forced expiratory volume in 1 sec percentage predicted was found. Kitaguchi Y *et al.*[38] found that airway predominant phenotype had a higher BMI as compared to emphysematous and mixed phenotypes. Rafael Golpe *et al* [39]demonstrated that the body mass index was higher in biomass induced COPD as compared to smoking induced COPD.

EFFECTS OF ATOPY ON COPD

Atopy, coming from the Greek word 'atopos', meaning "out of place"refers to the hereditary predisposition to produce Immunoglobulin E (IgE) antibodies against common environmental allergens. This may lead to clinical expression of atopic diseases such as allergic rhinitis, asthma and atopic eczema.

The dutch hypothesis states that certain markers of asthma such as atopy and bronchial hypereactivity are involved in the pathogenesis of COPD. The fact that asthma, chronic bronchitis and emphysema have common genetic basis with modifications by the environmental influences is supported by the presence of a sub-group of COPD patients with a positive bronchodilator response . This hypothesis is supported by the occurrence of COPD in only 10-15% of smokers, supposedly more genetically predisposed to developing COPD. Studies worldwide estimates prevalence of allergic rhinitis in adults is

10%, in specific subgroups of patients, such as patients with COPD, the rate has yet to be determined.

COPD associated with asthma and allergic rhinitis are featured by atopy and eosinophilia with inflammatory Th-2 response and raised IL-4 levels. This is more prevalent in the elderly with late onset asthma and a post bronchodilator FEV1 < 70% predicted, hyperinflation and history of smoking.

Fatemeh Fattah *et al.*[40]analysed in their study that in mild to moderate COPD patients, atopy was linked to male gender, overweight, obesity and younger age. Margarida Celia *et al.*[41] evaluated atopy in COPD patients and found that out of 149 COPD subjects, 62 (41.6%) had atopy. Daniel B. Jamieson *et al.*[42] in their study of 1381 COPD subjects recorded that, 25% had an allergic phenotype and that men were less likely to be allergic.

SMOKING AND COPD

A major risk factor for developing COPD around the world is tobacco smoke with contributions from inhaled noxious stimuli and gases. They induce a chronic inflammatory response and subsequent oxidative stress in predisposed individuals leading to anomalies particular to COPD. The contribution of other patho-biological processes becomes evident in the fact that in a proportion of patients, there is progression of the disease inspite of removal of the offending agent.

Such processes may include:

- genetic and epigenetically determined responses
- an imbalance of proteinases and antiproteinases

- an abnormal interaction between environment and microbiome
- alteration of the microbiome
- a chronic immune response
- inappropriate control of programmed cell death
- accelerated lung aging
- pulmonary endothelial cell dysfunction
- and abnormal ion transport due to CFTR dysfunction

The above mechanisms cause pathological alterations in the lung parenchyma, central and peripheral airways as well as pulmonary vasculature. These in turn cause the physiological changes that characterize COPD like emphysema, hypersecretion of mucus, ciliary dysfunction, airflow limitation, abnormalities in exchange of gases, pulmonary hypertension and systemic effects.

Cigarette Smoke

Cigarette smoke is abundant with oxidants leading to oxidative stress finally leading onto COPD. COPD patients who continue to smoke have a more rapid decline in FEV1 and are in greater risk of developing lung cancer compared to COPD patients who quit smoking. COPD patients who continue to smoke have a more rapid decline in FEV1[43]and are in greater risk of developing lung cancer compared to COPD patients who quit smoking.

BEEDI SMOKING AND COPD

Beedi smoking in India dates back to 1711. A product about the size of the little finger, containing a small quantity of tobacco wrapped in the leaf of a tree

and sold in bundles of 20-30 pieces, this description corresponds to 'beedi' currently available in India.

The most favoured form of smoking in India are beedis and 34% of tobacco produced are used for making them. They contain 0.15-0.25 gm of sundried, flaked tobacco wrapped with tendu leaf.

Shirname LP *et al.*[44] demonstrated that COPD was observed in 34.6% of beedi and 45.4% of cigarette smokers versus 3% of non-smokers, the difference in the prevalence of COPD among cigarette and beedi smokers was not significant. SK Chhabra *et al.*[45]reported that chronic chest symptoms were more in beedi smokers as compared to cigarette smokers in those smoking more than 2.5 pack years. Also, there was greater airway obstruction in lung function in beedi smokers than cigarette smokers. SK Jindal *et al.*[46]noted that beedis were smoked by 51.7% and 81.2% of urban and rural smokers respectively. SK Jindal also expressed that an Indian COPD patient spent 15% of his income on smoking products and 30% on the disease management.

SMOKING INDEX (NEVER SMOKER AND EVER SMOKER)

Cheng X *et al.*[47] demonstrated that the smoking index and incidence of COPD are directly proportional. The higher the smoking index, the more severe is the lung impairment. Carlos.A *et al.*[48] demonstrated that a significant inverse relationship exists between the number of cigarettes smoked per day and the cumulative cigarette consumption measured in pack-years and FEV_1 values. Although a beedi contains about one-fourth the amount of tobacco, beedi smoking is comparable to cigarette smoking due to the greater

puff frequency needed to keep the beedi alight. Cigarette smoking is measured in pack-years (cigarettes a day × years of smoking/20) or smoking index as (cigarettes or beedis a day × years of smoking). Although some recommend more than 20 pack-years (smoking index = 400) for diagnosis of COPD, pulmonary symptoms increase in frequency once 10 pack-years (smoking index = 200) history is reached. Hence, individuals with a 10 pack-years history should be screened for COPD. Mahesh *et al.*[49] reported that 9.6% smokers who smoked for less than 20 pack years had COPD. The prevalence increased to 18% in those who smoked for more than 20 pack years.

COPD IN NEVER SMOKERS

A never smoker is defined as a respondent who reported never having smoked 100 cigarettes. COPD is rarely considered in this population as it is considered as a disease of cigarette smokers.

The third national nutrition and health survey in the United states reported that 42% of the COPD population surveyed between ages 30 to 80 years were never smokers. Beherendt *et al.*[50] in their study reported that non-smokers with mild to moderate COPD have associated asthma as well as distinct demographic profiles such as male gender, middle-age and had an inverse relation to non-white ethinicity. Similarly, Lamprecht *et al.*[51] reported that in the data analysed from the Austrian BOLD study, non-smokers with COPD were predominantly female, slightly older and had less severity of airway obstruction as compared to ever smokers. In an analysis of data from 14 countries, Lamprecht B *et al.* reported respiratory symptoms occurred more in

never smokers and this group tended to be older, less educated compared to never smokers with unobstructed airways. Additionally, they had higher rates of physician diagnosed asthma, frequent exposure to indoor open fire with coal or coke as well as exposure to organic dusts.

BIOMASS INDUCED COPD

Globally, 50% of all households and 90% rural households rely on biomass and coal fuels for domestic energy. Biomass fuels include wood, charcoal, vegetable matter and animal dung. Worldwide, 3 billion people are exposed to biomass induced smoke. COPD deaths attributed to biomass smoke is about 50% in developing countries.

Rivera et al. reported that the class of COPD exposed to biomass smoke had similar pathological changes as in smokers' COPD. Women exposed to biomass had more fibrosis in the small airways with local scarring and pigment deposition in lung parenchyma. On the other hand, COPD smokers had more emphysema and metaplasia of goblet cells. HU *et al.*[52] conducted a meta-analysis based on the literature published up to 2009 and reported that individuals exposed to biomass smoke were more than twice as likely to develop COPD than those who were not exposed (OR 2.44, 95% CI 1.9–3.33). Golpe R *et al.*[39] disclosed that the mixed COPD-asthma phenotype was more usual in the biomass group while emphysema phenotype was more typical of the tobacco group.

In developing countries where biomass fuels are used to heat homes and cook meals, women develop COPD more frequently from indoor air pollution than

from cigarette exposure. NK Jain *et al* in their study of 702 COPD patients noted that smoke from biofuel was the main risk factor for COPD in females as against beedi smoking in males[32]

COPD PHENOTYPING USING HRCT

In the early 1980s, the high resolution computed tomography (HRCT) of the lung paved way to a new era in radiologic-pathologic correlation. An HRCT image is similar to a macroscopic histologic view which can diagnose preclinical emphysema as well as locate the site of structural damage. It is clinically important to determine the relative contributions of these processes as it influences patient's response to therapeutic interventions.

Morphological changes that characterize COPD on CT are:

- Emphysema
- Bronchial wall thickening
- Expiratory air trapping
- Vascular pruning
- Hyperinflation of lung

Hence, a CT can differentiate between emphysema predominant and airway predominant COPD.

ASSESSMENT OF EMPHYSEMA ON CT CHEST

Emphysema is defined histologically as permanent enlargement of the airspace distal to the terminal bronchioles and destruction of the alveolar walls. Airflow limitation in emphysema is due to decreased elastic recoil of lung parenchyma.

Emphysema may be classified as:

- Centrilobular
- Panlobular

Centrilobular emphysema affects central respiratory bronchioles and is the most common smoking related emphysema that occurs mainly in upper lung zones. On CT, it is depicted as a low attenuation area surrounded by normal attenuation lung parenchyma.

Panlobular emphysema affects uniformly the secondary lobule. On CT it appears as generalized decrease in CT attenuation more commonly in the lower lobe. It is typically seen in alpha-1 antitrypsin deficiency and also in severe smoking related emphysema.

Emphysema on CT is mainly assessed by visual inspection and grading of the disease or secondly, by using attenuation values for measuring lung density or mass.

Goddard *et al.*[91] put forward a visual score based on areas of low density and appearance of blood vessels in CT taken in arrested inspiration. In this technique window width of 1500HU and window level range of -700 to -550 HU are optimal

Forster *et al.*[53] also used visual scoring systems to identify emphysema and related centrilobular emphysema to the severity in CT in patients who had resections or post mortem examination. Similarly, Hruban et al.[54] examined HRCT images with postmortem lung specimens in vitro.

Thus, visual inspection of CT image reliably detects and grades lung emphysema. The sensitivity and specificity for CLE are 88% and 90% while

specificity and accuracy for PLE are 97% and 89% respectively. However, the method is skill dependent, time-consuming and depends on the experience of the observer. Discrepancies may also arise when different observers use different window settings.

ASSESSMENT OF LARGE AIRWAY DISEASE ON CT

Chronic bronchitis at pathological examination is characterized by bronchial wall mucosal gland hypertrophy with inflammation and fibrous replacement of smooth muscle layer. Bronchial wall thickening on CT can be evaluated qualitatively and quantitatively.[8] Computer aided and automatic techniques have been developed for airway dimension measurements.

The most common method for quantitative airway wall dimensions is using "full width at half maximum" technique. Here, inner and outer airway wall boundaries are determined with CT attenuation values, centred around rays drawn through airway lumen through airway wall and into the lung parenchyma. It is assumed that the true airway wall attenuation is half way between minimum and maximum gray levels.

Various parameters used to measure airway dimensions quantitatively are:

- Area of bronchial wall as proportion of total bronchial cross sectional area.
- Airway inner luminal area

Nakano *et al*.[8] reported in their study of 114 smokers that the airway dimensions (bronchial wall area) in the right apical bronchus correlated with percentage predicted FEV1 but not to diffusion capacity for carbon monoxide. They also found that bronchial wall area for large airways significantly

correlated to histologically measured bronchiole wall area. Hence, degree of small airway disease may be estimated by measuring thickening or narrowing of large airways. Hasegawa *et al*.[55] noted in their study that distal airway bronchial wall area and inner luminal area correlated more with percentage predicted FEV1 than those of proximal airways. (r = -0.22 in third-order bronchi, -0.26 in fourth-order bronchi, -0.48 in fifth-order bronchi, and -0.55 in sixth-order bronchi). Matsuoka S *et al*.[56] calculated the ratio of expiratory airway luminal area (EA) to inspiratory luminal area (IA) as a measure of airway collapsibility in COPD. It correlated strongly with percentage of predicted FEV1 (r = 0.73, P < .001) and the coefficient of correlation was higher than for percentage predicted FEV1 and either EA OR IA alone.

SMALL AIRWAY DISEASE ASSESSMENT ON CT CHEST

Cigarette smoke exposure for prolonged period of time leads to airway damages and remodeling. It causes epithelial cell hyperplasia, hypertrophy of smooth muscles and mucous metaplasia. Among these mucous metaplasia contributes significantly to airflow obstruction. The above pathogenic mechanisms lead to altered airway surface tension and expiratory collapse.

Direct visualization of small airway disease is not possible with current radiographic techniques. Indirect evaluation using densitometry parameters of expiratory CT scans or paired inspiratory/expiratory may be used in different types of obstructive lung diseases. Severity of airflow obstruction correlates closely with low attenuation area (areas with attenuation below a specific threshold) measured on an expiratory CT.

Matsuoka *et al.*[56] reported that in conditions of mild emphysema with coexistent air trapping, the correlation between airflow obstruction and change in LAA with attenuation of -850 HU or less was significant. This suggests that for quantifying air trapping, regardless of emphysema, exclusion of voxels with attenuation of -950HU or less is desirable.

CLASSIFICATION OF COPD BASED ON HRCT:

The presence or absence of emphysema and bronchial wall thickening can help in the morphological classification of COPD. With the same severity of airflow limitation, the contributions of various pathological abnormalities in COPD are different.

Grydeland TB *et al.*[24] in their study of 463 COPD patients described that morphological characters such as emphysema and airway wall thickness explains respiratory symptoms beyond the information obtained through spirometry.

Fujimoto *et al.*[57] evaluated morphological changes of COPD visually on CT and identified three COPD phenotypes: E or emphysematous type, characterized by emphysema without bronchial wall thickening; A or airway predominant, characterized by no or minimal emphysema with or without BWT. Kim WD et al[58] studied the relationship between small airway obstruction and type of emphysema and found that in centrilobular emphysema, the airway remodeling was greater than in those with panlobular emphysema. There was no association between panlobular emphysema and small airway thickening. Hence, it is likely the emphysema predominant

phenotype would be panlobular while in the mixed type the emphysema would be centrilobular. Similarly, Patel BD et al[59] reported that airway thickening and emphysema are independent contributors to airflow obstruction and that phenotypes show aggregations in families of people with COPD suggesting an influence of genetic factors. Thus, identifying the cause of airflow obstruction using HRCT of chest can help classify COPD patients into subgroups for appropriate therapy.

CLINICALLY RELEVANT PHENOTYPES OF COPD:

"Clinically relevant" COPD phenotypes are those with a different or selective response to a specific therapy.

For example Burrows *et al*.[60] in their landmark study reported that COPD patients can present with predominantly emphysema or chronic bronchitis. Subsequently, Rennard SI *et al.*[61] highlighted than there was a reduction in exacerbations in the chronic bronchitic phenotype with the use of the PDE-4 inhibitor Roflulimast. Hence it is important to identify frequent exacerbators with chronic bronchitis in clinical practice.

The most consensual clinically relevant COPD phenotypes are:

1. Non-exacerbator
2. The ACOS phenotype
3. The exacerbator with emphysema
4. Exacerbator with chronic bronchitis

Other proposed phenotypes are:

1. COPD-bronchiectasis

2. Fast decliner
3. Combined pulmonary fibrosis and emphysema
4. Upper zone dominant emphysema and bullous emphysema
5. Alpha-1 antitrypsin deficiency
6. Biomass COPD
7. Eosinophilic COPD
8. COPD with systemic inflammation

EMPHYSEMATOUS PREDOMINANT PHENOTYPE:

Pulmonary emphysema is defined as the permanent destruction of airways beyond the terminal bronchioles. Air trapping and hyperinflation occurs secondary to difficult alveolar emptying due to loss of elastic retraction and limitation in expiratory flow. This further causes limited functional capacity and is related more to dyspnea and exertional tolerance than to obstruction to airflow. Moreover, the correlation between severity and extension of macroscopic emphysema and FEV1 is low. HRCT measured extension of emphysema can better explain the variation in carbon monoxide diffusion capacity in emphysema.

CHARACTERISTICS OF EH PHENOTYPE- HYPERINFLATION

There are two types of hyperinflation in emphysema: static and dynamic.

The loss of elastic retraction in pulmonary emphysema causes static hyperinflation. This is the most common type of hyperinflation. Its intensity increases with decrease in FEV1. Dynamic hyperinflation occurs when the expiration is incomplete and the inspiration begins early, and with each

subsequent breath, air becomes trapped in the lungs. It appears in any degree of severity of COPD either independently or in concordance with static hyperinflation. Dynamic hyperinflation is produced due to mucus plugs, increased cholinergic tone and inflammation obstructing the airways. Also, the expiratory time is prolonged as there is an increased airway resistance because of increased airway collapsibility.

Hyperinflation imposes an additional inspiratory load as the muscles of inspiration should first outweigh the elastic retraction lung pressure still favouring expiration (Intrinsic PEEP or auto-PEEP) causing deleterious effects on the inspiratory muscles and respiration. Reversing the hyperinflation is thus a promising therapeutic target. Emphysema-hyperinflation phenotype of COPD have a higher risk for mortality which justifies differences in regard to guidelines for treatment.

Definition of the Emphysema-Hyperinflation Phenotype

The EH phenotype is a subgroup of patients who present with dyspnea and exercise in tolerance as the dominant symptoms. These are commonly associated with signs of hyperinflation. These patients usually have a predisposition to a lower BMI. This clinical form is defined by functional data of hyperinflation, emphysema on HRCT and a low diffusion test. In the absence of coexisting bronchitis, existence of emphysema has not been associated with greater exacerbation risk.

Justification of the Emphysema-Hyperinflation Phenotype Genetic Susceptibility

Genetic factors may be responsible for the pathogenesis of EH phenotype as evidenced by the fact that not all smokers develop COPD and clustering of COPD in the relatives of patients diagnosed with COPD.

In recent years, Single nucleotide polymorphisms (SNPs) responsible for emphysema have been described in several genes, especially after the NETT trial. (National Emphysema Treatment Trial). Apical emphysema and decline in lung function have been found associated with glutathione-S-transferase P1(GSTP1) and microsomal epoxide hydrolase (EPHX1) polymorphisms respectively. Polymorphisms in EPHX1 have also found to be associated with dyspnea, exercise capacity and DLCO.

Homozygotes for the deficiency of gene coding for alpha-1-antitrypsin are at increased risk for congenital emphysema which has an early onset and has a basal predominance.

Greater Risk of Morbidity and Mortality

In the EH phenotype, grade of dyspnea, exercise intolerance and hyperinflation are mortality predictors independent of the airway obstruction severity.

Casanova *et al.*[62] in a 5 year prospective study determined that the degree of hyperinflation was inversely proportional to survival. In their study, COPD patients with IC/TLC less than 0.25 were 3.15 times likely to die as compared to patients with higher ratios. The study demonstrated that IC/TLC was a risk factor independent of other parameters like FEV1, age, dyspnea, exercise capacity or comorbidity.

Boschetto.P *et al.*[63] reported a positive relation between HRCT measured emphysema, BODE index and hyperinflation. Yuan R *et al.*[64] described a faster fall in FEV1 in smokers with hyperinflation on HRCT irrespective of a normal FEV1. Haruna.A *et al.*[65] reported an association between magnitude of emphysema and greater mortality in COPD. Hence there is increasing evidence for need for HRCT in COPD evaluation for emphysema as well as to rule out possible bronchiectasis. The NETT trial [66] in a cohort of very severe COPD patients , studied the effect of emphysema on mortality and determined that emphysema, hyperinflation and BODE index were independent predictors of mortality. Dynamic hyperinflation significantly reduces the exercise capacity of COPD patients as shown in the study by Garcia-Rio F *et al.*[67] Garcia-Aymerich J *et al.*[68]reported that low physical activity had high risk of hospital admissions in this phenotype. Hence it is an important aspect in the E phenotype that needs attention.

Cardiovascular Disease and Emphysema

Pulmonary hyperinflation can affect the size of the heart and its function. Studies have associated hyperinflation and the presence of diastolic dysfunction in COPD. Vassaux *et al.*[69] demonstrates that cardiac function during an exertion test, is lower in COPD and hyperinflation, which is measured with an IC/TLC ratio ≤0.25. Jörgensen *et al.*[70] studied patients with severe emphysema and reported smaller size of both ventricles with decreased left ventricular filling. This reflected decreased preload secondary to lung hyperinflation. Watz *et al.*[71] analyzed that IC/TLC is significantly associated

with tele-diastolic left ventricular diameter more than degree of obstruction. An IC/TLC ratio ≤0.25 leads to left ventricular diastolic dysfunction which affects the right ventricle which is associated with exercise intolerance. Similarly, Barr RG *et al*.[72], in a population study, demonstrated a linear relation between severity of emphysema on HRCT and decreased cardiac output.

Thus, the above review of literature advocates that reducing hyperinflation can improve cardiac function while improving exercise capacity in the emphysematous phenotype.

Diagnosis of the Emphysema-Hyperinflation Phenotype

Hyperinflation in COPD may be indirectly estimated using a simple and reproducible manner by using slow spirometry to obtain inspiratory capacity. A low IC correlates with a low exercise capacity and an increase in dyspnea. Mohamed Hoesein FA *et al*.[73] studied in 544 heavy smokers, the association of transfer coefficient for carbon monoxide with progression in emphysema determined by a CT chest. They reported that a low carbon monoxide transference capacity correlated with pulmonary emphysema severity. Nonethless, DLCO analyses lung as a whole while HRCT is able to detect localized emphysema. Recent studies have demonstrated that radiological estimation of COPD severity may be possible. The analysis of densitometry parameters of lung parenchyma on HRCT correlates with the pathological alterations in the macroscopic tissue samples, airflow obstruction and diffusion capacity.

Differential Treatment of the Emphysema-Hyperinflation Phenotype

The target for therapy in EH phenotype is the use of bronchodilators in reducing hyperinflation, given its reversible character. It may be noted that IC which is used to measure hyperinflation is reliable and more sensitive than FEV1 in evaluating the beneficial effects of certain therapy. As demonstrated by several studies, FVC and IC improvements have been noted in moderate or severe COPD and hyperinflation after bronchodilators with no improvements in FEV1. Such volume improvements are common with severe bronchial obstruction. The NETT study[66] showed that, in patients with upper lobe emphysema and low exercise capacity, there was a significant reduction in mortality after lung reduction surgery. In addition, there was a significant reduction in the number of exacerbations and prolonged exacerbation-free time.

The main pharmacological treatment for COPD are long acting bronchodilators according to current guidelines. They have shown to improve exercise intolerance and significantly improve the perceived state of health with clinically relevant changes However, the benefits occasionally does not produce improvement in degree of obstruction, but significant changes occur by reducing dynamic hyperinflation and increased IC that translates to decreased hyperinflation.[74]

Van Noord *et al*.[75] in their study of 71 COPD patients compared the use of tiotropium, formeterol and both combined in patients with a mean FEV1 < 70%. It was found that subjects treated with two bronchodilators (formeterol

with tiotropium) as against those with bronchodilator monotherapy or versus fluticasone-salmeterol combination were functionally better than those with monotherapy or with ICS, with lesser need to use rescue medication. These results may also be applicable to other LABA/IC combinations.

Preventing exacerbations in EH phenotype using anti-inflammatory treatment with inhaled corticosteroids have not shown to be as effective . Lee JH *et al*.[76] in their study of 165 COPD patients classified them on the basis of emphysema and airway obstruction and treated them with combination therapy of long acting beta-2 agonist and ICS for 3 months. The emphysema predominant group did not show any improvement in FEV1 or dyspnea after the 3 month period.

Roflumilast, the oral anti-inflammatory agent has also failed to offer results for reducing exacerbations in the EH phenotype except for those with associated chronic cough and sputum as demonstrated by Rennard *et al*.[77]

To summarize, the emphysema-hyperinflation subgroup may gain more from a double bronchodilator therapy and respiratory rehabilitation due to improvement in dyspnea and exercise tolerance.

Exacerbator Phenotype

COPD patients may have phases of clinical instability referred to as exacerbations. Some experience them repeatedly while others do not suffer from any.

The ECLIPSE study, a prospective observational study of 2138 patients, noted that COPD patients could present an individual susceptibility for frequent

decompensations. Such a patient group with increased risk for mortality and morbidity whose treatment could be delineated, warranted the rationale for defining the "exacerbator" phenotype.

Definition of "Exacerbator"

Exacerbations of COPD are acute episodes of worsening symptoms that may warrant changes in regular medications and lead to worsening of the chronic progressive course of this disease. "Exacerbators" are defined as those COPD patients with 2 or more exacerbations per year. Each episode should be separated by 4 weeks (after end of treatment) or 6 weeks after onset in cases that have not been treated. This is to differentiate between previous treatment failure from a new event.

Justification of the Exacerbator Phenotype

Certain risk factors predispose to repeated exacerbations. They are :

OLDER AGE

COPD SEVERITY

- greater baseline dyspnea
- low FEV1
- low paO2

HISTORY OF PREVIOUS EXACERBATIONS

INFLAMMATION

- Greater airway inflammation
- Greater systemic inflammation

BACTERIAL LOAD

CHRONIC BRONCHIAL HYPERSECRETION

COMORBIDITY/EXTRAPULMONARY MANIFESTATIONS

- Cardiovascular
- Anxiety/Depression
- Myopathy
- Reflux disease

Of all the conditioning factors, history of previous exacerbations has been most frequently referenced in literature. This affirms that an individual susceptibility exists which may be hereditary or acquired.

Individual Acquired Susceptibility

Chronic bronchial-bronchitis hypersecretion.

Several studies have reported that cough with chronic sputum is associated with a greater risk for exacerbations. Foreman *et al*.[78] reported that there was a 3.7 times risk (odds ratio) for exacerbation with chronic sputum and this was higher than risk due to tobacco consumption (Odds ratio=1.01/packyear) or post bronchodilator FEV1 (OR=0.98). Miravitelles *et al*.[79] noted a significant association between chronic expectoration and multiple exacerbations (Odds ratio=1.54). Burgel *et al*.[80] recorded that 55% of chronic expectorators had more than two exacerbations as opposed to the 22% without bronchial hypersecretion($p<0.001$) .

Inflammation, chronic bronchial infection, bronchiectasis.

Frequent exacerbators have greater airway inflammation regardless of smoking habit in that it persists even in former smokers. This may be due to:

a) Potentially pathogenic organisms in the airway (PPM): In 30% of stable COPD patients, PPM are isolated, which is called as colonization of the lower airways. These microbes are present either due to the inability to eradicate an acute infection or due to microaspiration. The bacterial load increases over time which leads to more airway inflammation till finally

a clinical threshold is crossed predisposing to the appearance of a new exacerbation.

b) Acquisition of new bacterial strains-Sethi S *et al*.[81]in their study postulated that it the new strain acquisition rather than the change in bacterial load, that is more important for developing an exacerbation.

c) Underlying structural changes in lung: Bronchiectasis is associated with bronchial infections and inflammation, causing repeated and more severe exacerbations.

d) Viral infections: Viral pathogens tip the scale of balance between bacteria and host response leading to modulation of the airway inflammatory response. Individuals with frequent colds experience more bacterial exacerbations.

e) Gastroesophageal reflux disease (GERD): Though GERD predisposes to exacerbations,the link between GERD and exacerbations is ill defined. Some authors have suggested altered swallowing refluxes and microaspiration as the mechanism.

f) Autoimmunity: Autoimmunity has been thought to be a cause of greater airway inflammation. However there has been no evidence cited for such an association.

Individual Genetic Susceptibility

There may exist an individual genetic susceptibility to frequent exacerbations owing to the heterogeneity of defence mechanisms of the host against a pathogen.

Differential expression of the chemotactic protein CCL-1which attracts monocytes and macrophages could alter the activation of innate immunity against respiratory infections. Mannose binding lectin(MBL) is a protein that activates the complement system to inactivate a large number of organisms. MBL2 polymorphisms can lead to a deficiency of MBL , increasing the susceptibility to infections and greater number of hospitalizations.

Greater Risk for Morbidity and Mortality

Studies have shown significant association between frequent exacerbations and decrease in health-related quality of life.[82] Extrapulmonary manifestations like myocardial infarction, myopathy, GERD and depression are more in the "exacerbators". In these patients, the decline in lung function is 8ml/year more than non-exacerbators.In addition, this accelerated decline is associated with consistent worsening of BODE index. As the frequency of exacerbations increases, the risk for death increases regardless of the baseline severity of the COPD. Moreover, these patients pose a huge fiscal burden for the health-care system.

Hence, the therapeutic approach to this group, that has a high risk of mortality and morbidity should be different and intensive.

Diagnosis of the Exacerbator Phenotype

The exacerbator phenotype may be identified by the existence of two or more exacerbations in a year. Once they are identified, a search for existing bronchial infection and/or the presence of bronchiectasis should be done.

Differential Treatment of the Exacerbator phenotype:

Long acting bronchodilators have shown to reduce the exacerbation frequency.

Anti-inflammatory agents are indicated in persistent exacerbations in those patients already on long acting bronchodilators. Use of inhaled corticosteroids along with bronchodilators, produces a significant reduction in frequency of exacerbations and improvement in HRQL. Studies have backed the use of these drugs in COPD with less functional severity (other than those with FEV1>50%).

Roflumilast, a novel anti-inflammatory agent acts by selectively inhibiting phospodiesterase-4 and has been approved for severe COPD with cough and chronic sputum and frequent exacerbations. Macrolides, in addition to their antibacterial action, have an anti-inflammatory and immunomodulatory action. Studies[83] have reported that their use in stable patients with severe COPD reduces the exacerbation frequency, though with a possible risk of bacterial resistances. It has also been postulated that antibiotic use during periods of stability could reduce exacerbations.

The PULSE study demonstrated a 20% reduction in the risk of exacerbation in the intention-to-treat analysis, 25% reduction in the per protocol analysis and 45% reduction in those with purulent/mucopurulent sputum, without

significant increase in bacterial resistance, in those stable COPD patients treated every 8 weeks with 5-day cycles of 400mg Moxifloxacin.[84] In another study, administering nebulized tobramycin in severe COPD colonized by pseudomonas aeruginosa reduced bronchial inflammation and severe exacerbations.[85]

Mixed COPD-Asthma Phenotype

A patient is said to have an overlap or mixed syndrome when he/she has attributes of more than one obstructive airway disease. Joan B.Soriano *et al*.[26] studied data from a very extensive population and reported that 19% patients with obstructive lung disease had a concomitant diagnosis of asthma, chronic bronchitis or emphysema. Similarly, S E March *et al*.[18] in a total of 469 patients reported that 55% of the population studied had asthma as the predominant COPD phenotype.

Definition of the Mixed Phenotype (COPD-Asthma)

The mixed phenotype in COPD is defined as those patients with an airflow obstruction that is not completely reversible, accompanied by symptoms or signs of increased obstruction reversibility.

Pathogenesis

Mechanisms underlying COPD-Asthma overlap syndrome remain controversial.

There are two well-known hypotheses proposed in an attempt highlight the underlying mechanism. The “Dutch hypothesis” suggests that COPD and asthma are the same basic disease process and that long standing asthma

predisposes to COPD. The “British hypothesis” proposes that COPD and asthma are distinct entities and that both diseases coexist separately within the same individual. Both the diseases contribute to the disease mechanism and may vary between individuals, influenced mainly by genetic predisposition, initiating condition, environmental exposure and evolving natural history of each individual.

In the spectrum of obstructive airway disease, there are asthmatics who smoke, asthmatics who develop irreversible airway obstruction as well as nonsmokers with chronic airflow obstruction. Asthmatics who smoke have features similar to COPD. They have less response to corticosteroids, more of neutrophilia in airways with less frequency of eosinophilic inflammation.

Young asthmatics who develop irreversible airway obstruction differ from non-asthmatics who develop COPD in that they tend to have frequent allergic rhinitis, nonspecific bronchial hyperreactivity, wheeze and higher concentrations of plasma eosinophil levels .

Prevalence

Marco R *et al*.[86] in a survey of Italian patients revealed that in those diagnosed with asthma, 16-61% also had ACOS and in those diagnosed with COPD, 25-33% also had ACOS. Soriano *et al*.[26] reported that an estimated 23% COPD subjects between ages 50 and 59 possibly has a mixed phenotype. With an increase in age to 70-79.4, the percentage increased to 52%. In the EPISCAN epidemiological study where bronchodilator test was used as a reference, 31.5% of the COPD patients had a positive test.

Hence, from the above data, it can be concluded that between 20-50% of COPD patients may have a mixed phenotype.

MORTALITY AND MORBIDITY

Patients with the mixed phenotype have more frequent exacerbations, poorer quality of life, more rapid decline in lung function and a higher mortality and morbidity than from COPD or Asthma alone.

DIAGNOSIS OF THE MIXED PHENOTYPE

Diagnosis of the mixed phenotype may be made by a combination of the following factors:

1) History of asthma or atopy
2) Reversibility on bronchodilator testing
3) Eosinophilia in respiratory or peripheral secretions
4) High IgE
5) Positive prick test to pneumoallergens
6) High concentrations of exhaled NO

Patients with the mixed phenotype are susceptible to a good response with inhaled corticosteroids regardless of the baseline FEV1 while other phenotypes may obtain only a marginal clinical benefits with addition of ICS to LABA.

Differential Treatment

Papi *et al*.[87] demonstrated that bronchodilator reversibility, even a partial response, was associated with greater airway eosinophilic inflammation and response to inhaled corticosteroids. R Siva *et al*.[88] demonstrated a significant

reduction in exacerbations in patients who were treated with inhaled corticosteroids based on their sputum eosinophil counts.

Thus, in COPD patients, inhaled corticosteroids may require a personalized focus based on clinical, functional and inflammatory characteristics. Mahler DA *et al*.[89] demonstrated in 691 COPD patients that, in those with a positive bronchodilator test at the beginning of the study had a greater improvement in FEV1 (319 ml) as against the irreversible group when treated with a combination of fluticasone with salmeterol.

Meanwhile, the TORCH study which studied the effect of fluticasone with salmeterol combination in COPD included only those subjects with a negative bronchodilator response. The study recorded a limited reduction in mortality in patients less susceptible of being responders to inhaled corticosteroids.

Kardos P *et al*. [90] aimed to study the impact of fluticasone with salmeterol on severe and very severe COPD patients. Of the 994 patients, the mean reversibility was 7%, which was more than that of the TORCH study. It was found that there was a significant reduction in exacerbations. Hence, the above studies show that based on the bronchodilator test response, there is a difference in response to ICS or combination therapy among COPD phenotypes.

AIMS OF THE STUDY

1. To classify COPD (Group D as per GOLD) into three main phenotypes based on morphological features on high resolution computed tomography (HRCT)
2. To study the clinical, spirometric and radiological features of these COPD patients.
3. To study the change in FEV1 after bronchodilators (LABA+ICS) in these phenotypes

MATERIALS AND METHODS

Study design: Prospective observational study

Study period: November 2015 to August 2016

Inclusion criteria:

1. New patients more than 35 years of age with clinical history and symptoms suggestive of COPD
2. Males and females
3. Stable clinically; No change of medication or acute exacerbation in the last 6 weeks
4. COPD diagnosed according to GOLD guidelines and FEV1/FVC< 70% after use of bronchodilator
5. Capable of completing CAT and mMRC questionnaire
6. Patient without history of previous anti-tuberculous treatment.
7. Patients without active pulmonary tuberculosis.
8. Patients seronegative for human immunodeficiency virus.
9. Patients willing to participate in the study and give informed consent.

Exclusion criteria:

1. Cardiovascular disease, such as uncontrolled high blood pressure, congestive heart failure, angina, etc
2. Severe hepatic and renal dysfunction, malnutrition, malignant tumor, and severe anemia or mental illness
3. History of regular corticosteroids or other immunosuppressive agents
4. Arterial oxygen saturation less than 90% at rest.
5. Patients with history of asthma or repeated paroxysmal dyspnea characteristic of asthma.
6. Patients who were started on bronchodilators by other physicians and those who were on irregular treatment.
7. Patients with late sequelae of pulmonary tuberculosis, bronchiectasis, diffuse panbronchiolitis or bronchiolitis obliterans ,interstitial lung disease, mass lesions, and solitary pulmonary nodules.
8. A history of pneumonectomy or other any lung surgery
9. Patients unable to perform spirometry and those unwilling for investigations, treatment and follow-up.

Sample size: 94 patients who attended the outpatient department of thoracic medicine at Rajiv Gandhi Government General Hospital who satisfied the inclusion and exclusion criteria were enrolled in the study.

Methodology:

147 consecutive patients with complaints of cough and sputum for atleast three months in two consecutive years, history of breathlessness and exertional dyspnea suspected of having chronic obstructive pulmonary disease were included in the study. Out of these patients, 33 were excluded from the study after history and investigations. 20 patients dropped out of the study during the follow-up.

A detailed history was taken which included:

1. Presenting complaints
2. Duration of symptoms
3. History of constitutional symptoms
4. History of contact with sputum positive case of tuberculosis
5. Previous history of treatment for atopy/asthma/ tuberculosis/ history of cardiac disease/diabetes mellitus and other comorbid illnesses.

6. Previous history of exacerbations and hospitalization in the past 1 year
7. Family history of atopy/asthma
8. History of smoking. If history of smoking was present, the age of onset of smoking was recorded and the severity was graded with smoking index for number of beedis/cigarettes smoked.

Smoking index is calculated as the product of number of cigarettes or bidis smoked per day and the duration of smoking habit in years.

Table : Severity of smoking based on Smoking Index

SMOKING INDEX	SEVERITY OF SMOKING
< 100	Light smokers
100 – 300	Moderate smokers
> 300	Heavy smokers

Thus smoking index takes into account both the quantity and the chronic nature of the problem. A person was considered to be a non-smoker if he or she has smoked less than 100 cigarettes or bidis in his/her lifetime.

9. History of exposure to noxious particles other than tobacco such as biomass, indoor and outdoor air pollutants.

GENERAL AND CLINICAL EXAMINATION

General examination including calculation of Body-Mass Index (kg/m^2), COPD assessment test (CAT score) and 6- minute walk distance were measured and a structured clinical examination were done for all subjects.

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

Routine investigations including:

1. Chest X ray PA view

2. Hemogram

3. Plasma absolute eosinophil count

4. Random Blood Sugar

5. HIV antibody testing were done for all patients.

Other investigations:

- Renal function tests
- Liver function tests
- Plasma eosinophil count
- Sputum for acid fast bacilli

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 Easy-one 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. They 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.

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. In case 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.

HRCT CHEST:

An HRCT chest was taken for all patients included in the study. Following an initial conventional helical scanning for screening, an HRCT was done in full inspiration at 1mm slices. Four slices of 1 mm thickness were obtained at the following levels:

1. Superior margin of aortic arch (level of upper lung)
2. Level of carina (level of middle lung)
3. Level of inferior pulmonary veins (level of lower lung)

The window levels were set from -700 to -900HU which was appropriate for the lungs.

Visual assessment of Low Attenuation Area on HRCT:

SCORE	LAA PERCENTAGE
0	LAA <5%
1	5% ≤ LAA <25%
2	25% ≤ LAA <50%
3	50% ≤ LAA<75%
4	75% ≥ LAA

The **low attenuation area (LAA)** was measured by the visual assessment in bilateral lung fields according to the method of Goddard[91]. The total scores and grade of emphysema was calculated as follows:

TOTAL SCORE	GRADING
0	0
1-6	1
7-12	2
13-18	3
19-24	4

Bronchial wall thickness was assessed visually as follows:

GRADE	BRONCHIAL WALL THICKNESS
0	None
1	<50% adjacent pulmonary artery diameter
2	>50% adjacent pulmonary artery diameter

Based on the visual HRCT assessment, patients were classified into **three phenotypes** as follows:

1. Absence of emphysema, which showed little emphysema and LAA ≤ grade 1 with and without BWT **(A phenotype)**

2. Apparent emphysema ≥ grade 2 without BWT **(E phenotype)**

3. A combination of apparent emphysema = grade 2 and BWT of more than grade 1 **(M phenotype)**

THREE MONTH TREATMENT WITH LONG ACTING BETA-2 AGONIST WITH INHALED CORTICOSTEROIDS:

94 patients were treated twice daily with a combination of formeterol (6mcg) and budesonide (200mcg) in accordance with GOLD guidelines for treatment of group C and group D COPD patients. All patients were followed up for three months. At the end of three months a repeat pulmonary function test was done and FEV1 recorded.

STATISTICAL ANALYSIS: All statistical analysis was done using SPSS software. Statistical significance was assessed by Chi-square, Paired-T test and ANOVA tests. A correlation was considered statistically significant if p value was <0.05.

HRCT CHEST IMAGES

MIXED PHENOTYPE

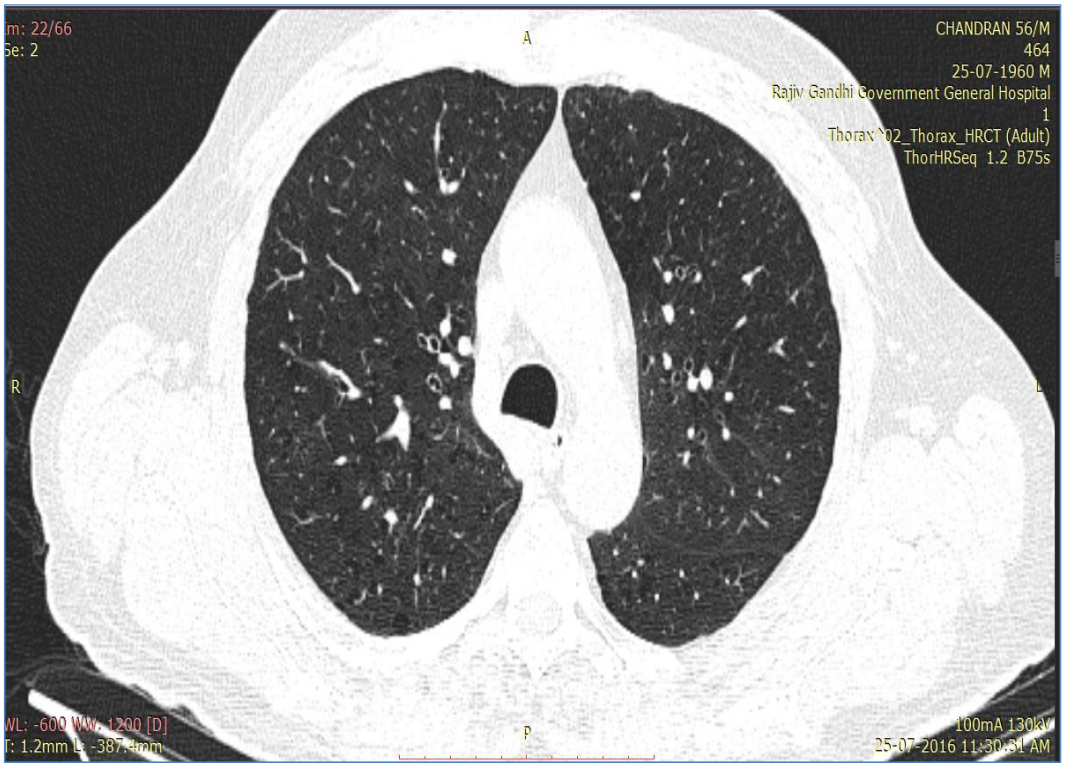


Figure (a): HRCT axial scan showing thickened airways along with few areas of centriacinar emphysema in **M phenotype.**

AIRWAY PREDOMINANT PHENOTYPE

Figure (b)

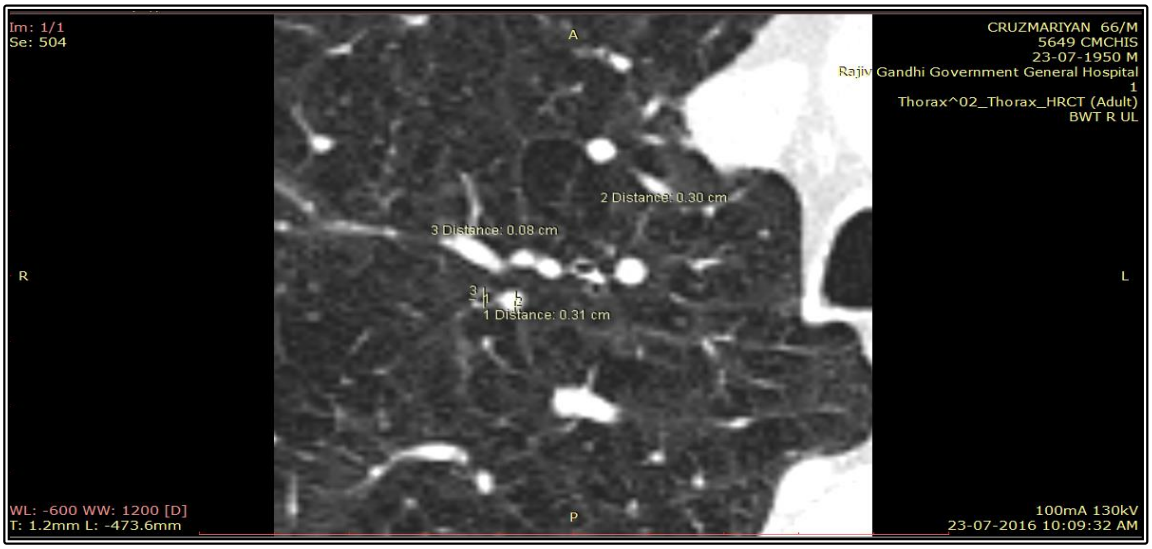


Figure (c)

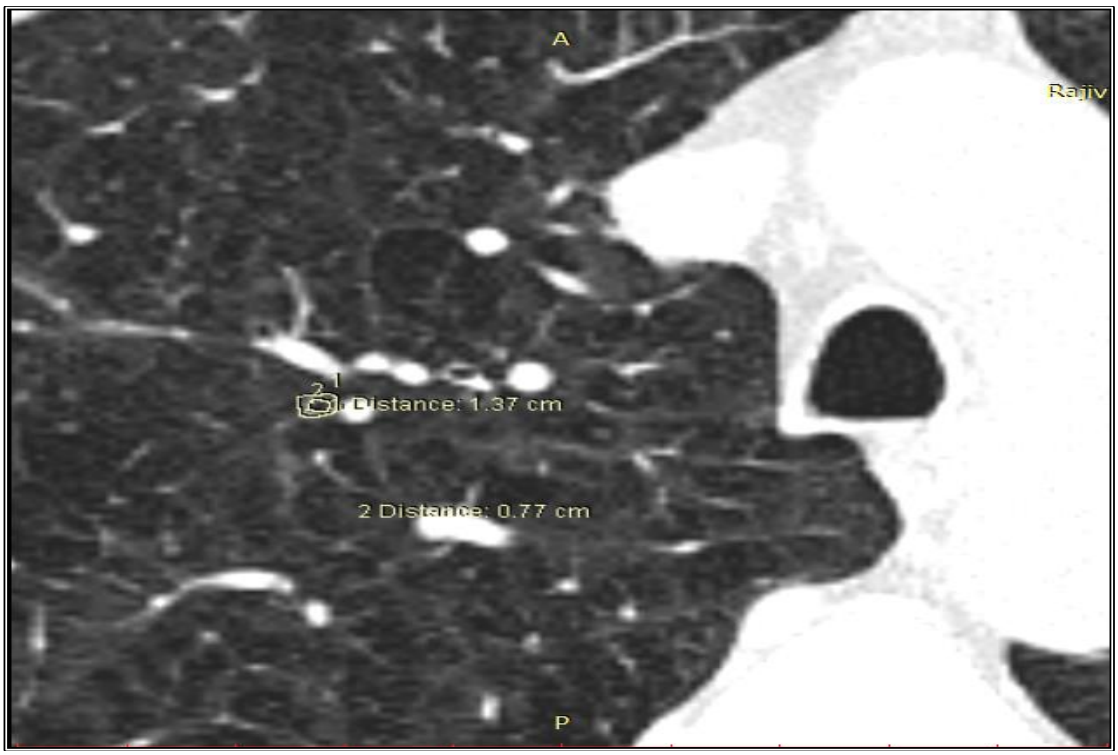


Figure (b) and (c): HRCT axial scan showing directly visible small airways as air filled ring like structures in **A phenotype**

EMPHYSEMATOUS PHENOTYPE

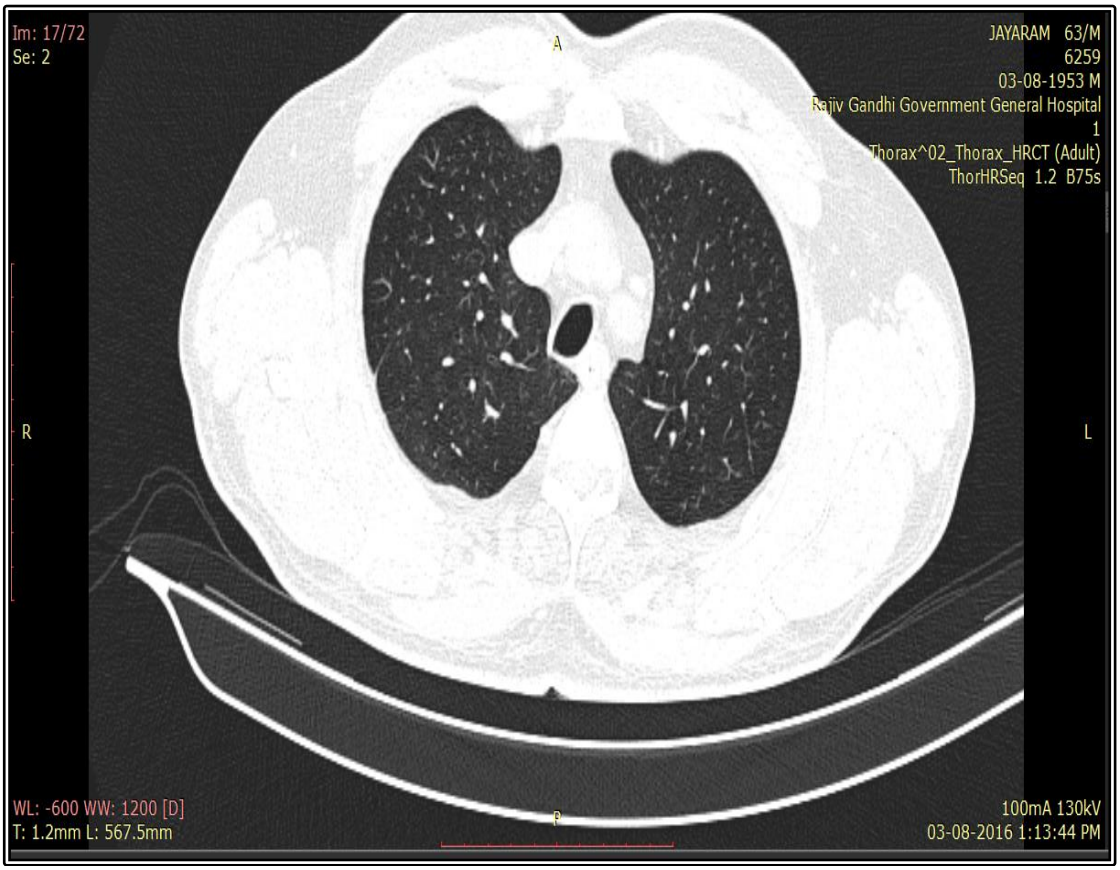


Figure (d): HRCT axial scan showing centriacinar and panacinar emphysema in **E phenotype**

RESULTS

Characteristics of the study participants: The study screened 147 subjects out of which 94 subjects were included in the sample after excluding 33 subjects as per exclusion criteria. 20 subjects dropped out of the study. Majority of the study sample belonged to the age group 50-70 years (n=74, 78.7%) and males contributed majority of them (n=66, 70.2%). **[Table 1]**

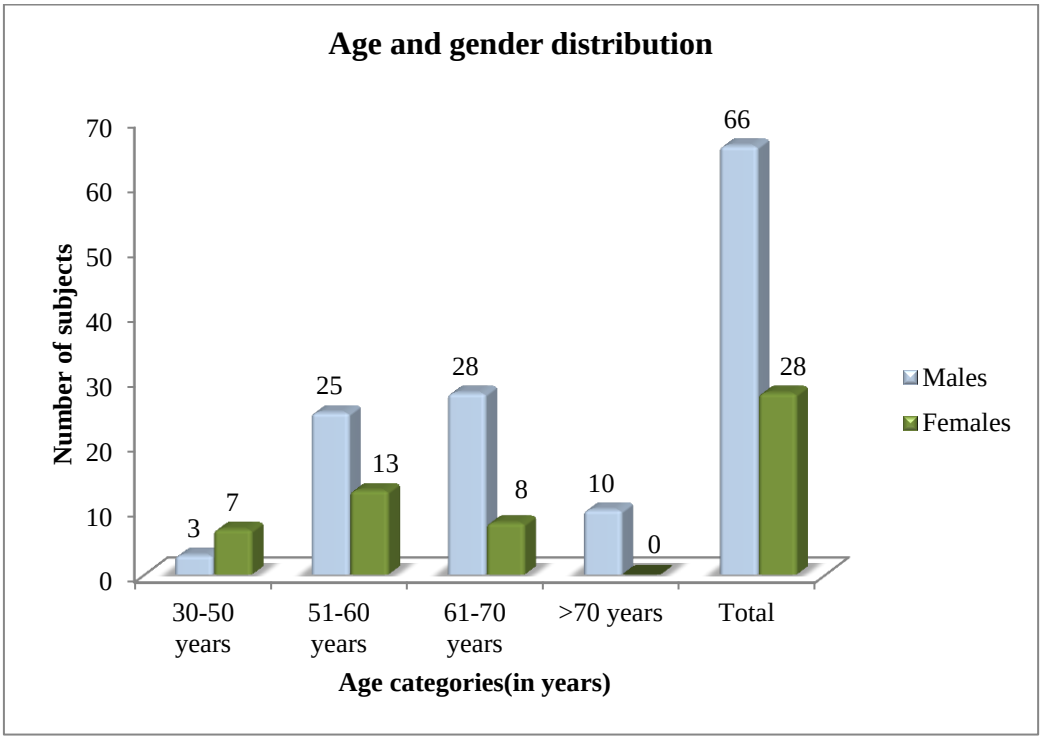
Table 1: Age and gender distribution of the study participants

Age categories	Gender				Total	
	Male		Female			
	Number	%	Number	%	Number	%
30-50 years	3	4.5%	7	25.0%	10	10.6%
51-60 years	25	37.9%	13	46.4%	38	40.4%
61-70 years	28	42.4%	8	28.6%	36	38.3%
>70 years	10	15.2%	0	0.0%	10	10.6%
Total	66	70.2%*	28	29.8%*	94	100%
Chi square test value, *p*-value=**0.04**, significant						

*indicates row percentage

There was a significant difference in age distribution among the males and females in the study (*p*-value=**0.04**) with majority among the females belonging to younger age group and males belonging to middle and elderly age groups. **[Graph 1]**

Figure 1: Bar chart showing Age & gender distribution of the study participants

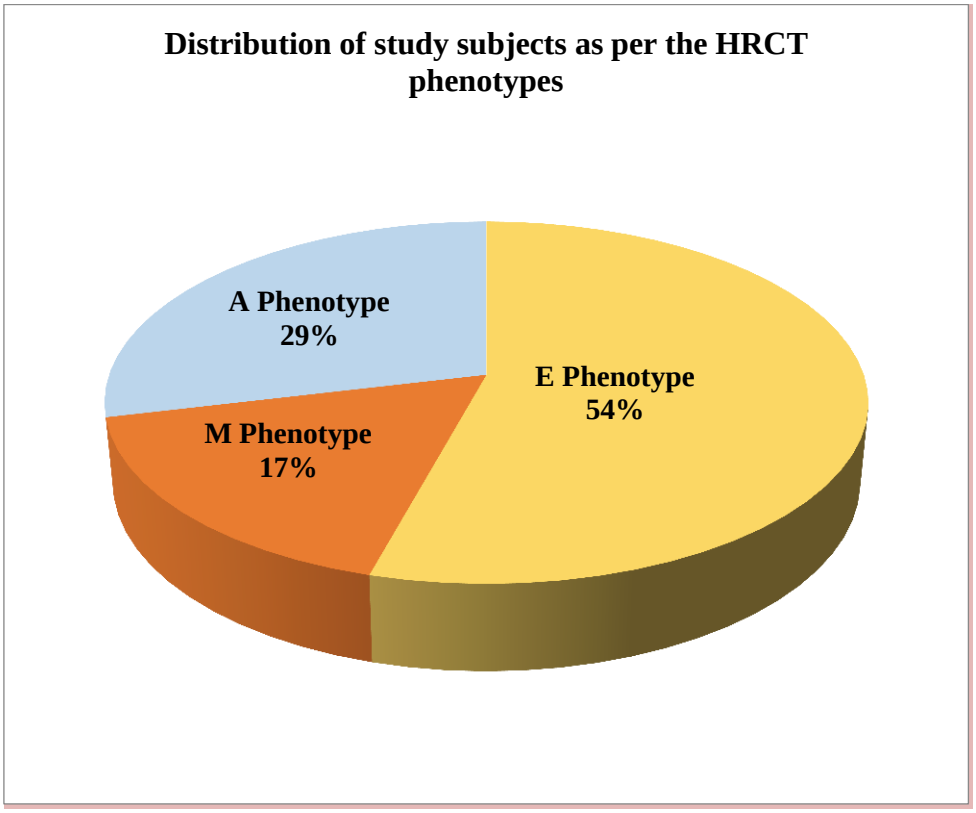


The study participants were subjected High Resolution Contrast Computed Tomography (HRCT) and classified into three phenotypes viz:

1. E phenotype: emphysema without bronchial wall thickening;
2. M phenotype: emphysema with bronchial wall thickening;
3. A phenotype: absence of emphysema

Majority of the study participants were categorized into phenotype E (54%) followed by Phenotype A (29%) and Phenotype M (17%). **[Figure 2]**

Figure 2: Pie chart showing categorization of study participants into various phenotypes based on HRCT



There is a higher frequency of participants who manifested phenotype E compared to phenotypes A and M. There was a significant difference in age distribution of participants among the three phenotypes (*p*-value<**0.001) [Table2]**

AGE DISTRIBUTION OF STUDY PARTICIPANTS AMONG PHENOTYPES

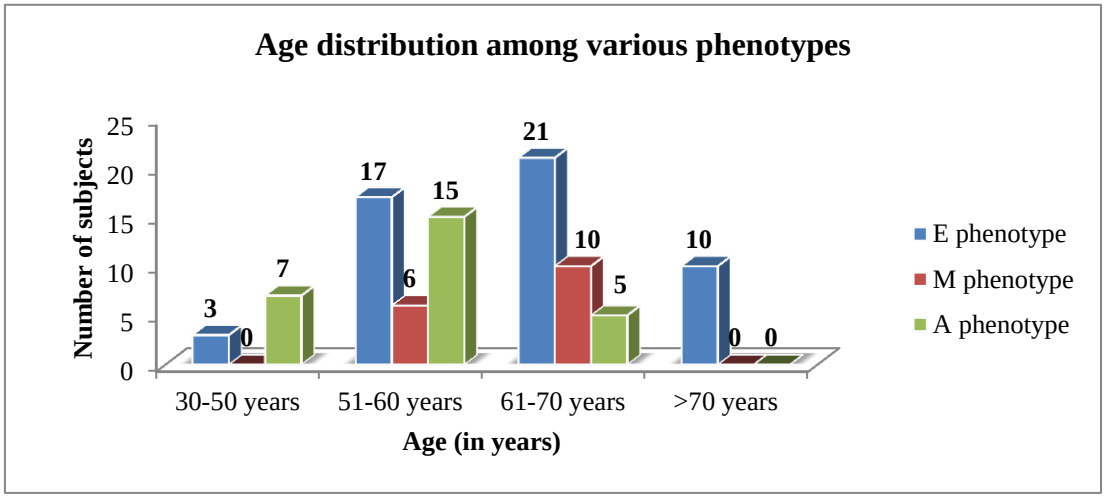
There was a significant difference in age distribution between those with E phenotype and A phenotype but there was no significant difference in age distribution between those with E phenotype and M phenotype.

Table 2: Age distribution of study participants among different phenotypes

Age Group	E phenotype	M phenotype	A phenotype	Total
30-50 years	3 (5.9)	0 (0)	7 (25.9)	10 (10.6)
51-60 years	17 (33.3)	6 (37.5)	15 (55.6)	38 (40.4)
61-70 years	21 (41.2)	10 (62.5)	5 (18.5)	36 (38.3)
>70 years	10 (19.6)	0 (0)	0 (0)	10 (10.6)
Total	**51 (100)**	**16 (100)**	**27 (100)**	94 **(100)**
Chi square test value *p*-value<**0.001**, highly significant *E versus A* :Chi square test value , *p*-value<**0.0013**, highly significant *E versus M:*, *p*-value<**0.148**, NOT significant				

*Figures in ( ) indicate within column percentage

Figure 3: Bar chart showing age distribution among different phenotypes



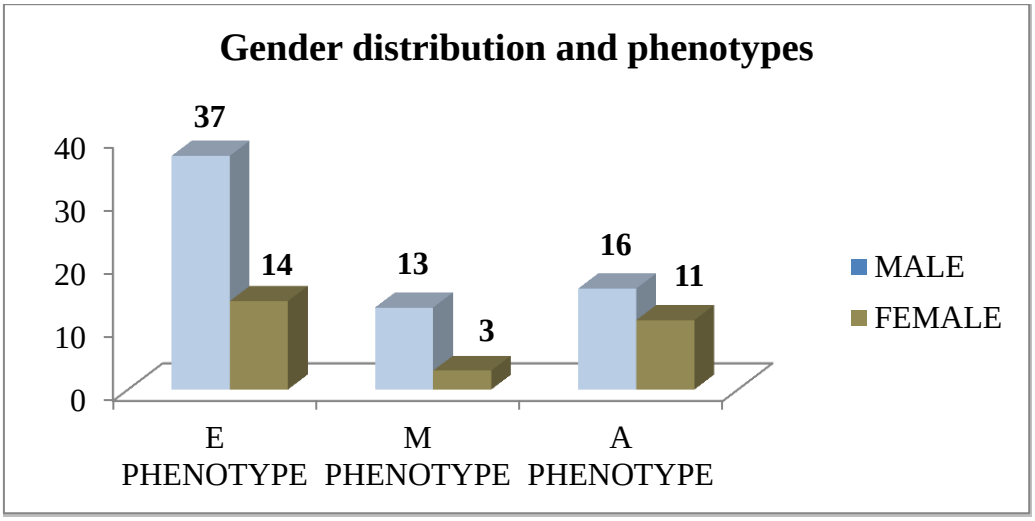
GENDER DISTRIBUTION AMONG DIFFERENT PHENOTYPES

There was no significant difference in distribution of phenotypes among males and females. When individual phenotypes were compared with each other with regards to gender there was still no difference in phenotype pattern. The distribution of phenotypes E, A and M among males and females is depicted in **figure 4**.

Table 3: Gender distribution of study participants among different phenotypes

Gender	E phenotype	M phenotype	A phenotype	Total
Male	37 (72.5)	13 (81.2)	16 (59.3)	66 (70.2)
Female	14 (27.5)	3 (18.8)	11 (40.7)	28 (29.8)
Total	**51 (100)**	**16 (100)**	**27 (100)**	94 **(100)**
Chi square test *p*-value=**0.271**, NOT significant *E versus A* :Chi square test value *p*-value<**0.231**,NOT significant *E versus M:* Chi square test value *p*-value<**0.49**, NOT significant				

Figure 4: Gender distribution of study participants among different phenotypes



SYMPTOMS IN THE THREE PHENOTYPES OF COPD

Quantity of sputum among the three phenotypes: There was a significant difference (*p*-value<**0.001)** in the quantity of sputum produced by the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to sputum production, there was a significant difference in proportion of participants producing sputum in different quantities between E and M phenotypes (*p*-value<**0.001)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The participants with phenotype E produced lesser quantity of sputum compared to those with M and A phenotypes.

Table 4: Quantity of sputum among the three phenotypes

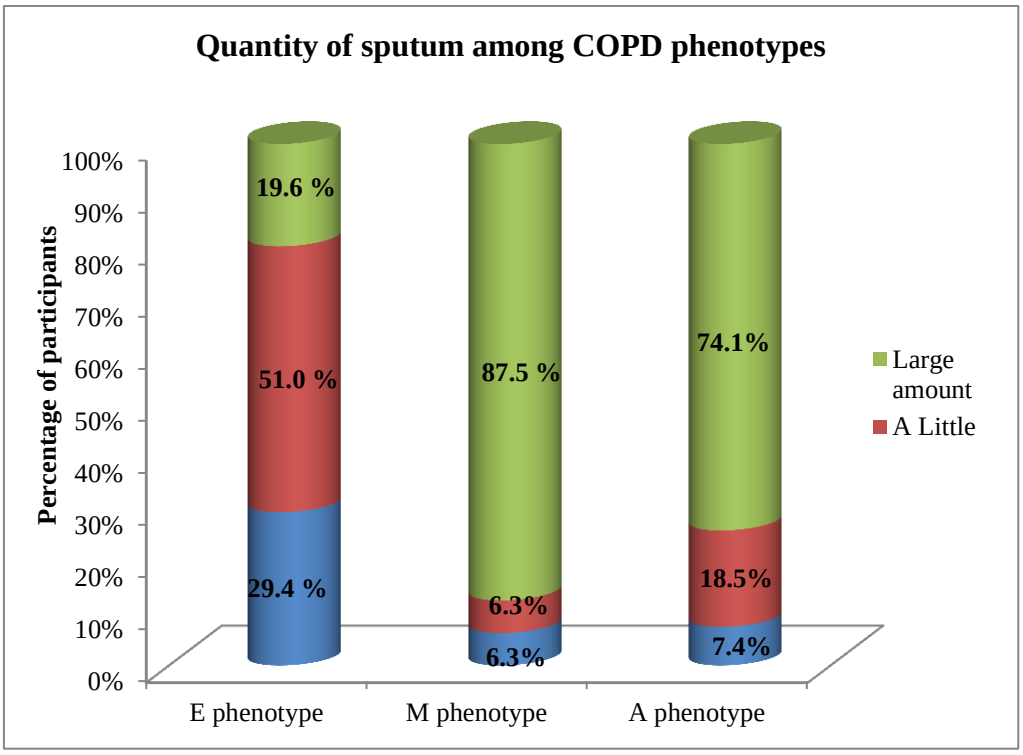
	E phenotype	M phenotype	A phenotype	Total
None	15	1	2	18
A Little	26	1	5	32
Large amount	10	14	20	44
Total	51	16	27	94

Chi square test value ,*p*-value<**0.001**, **highly significant**

E versus M: Chi square test, *p*-value<**0.001**, **highly significant**

E versus A :Chi square test, *p*-value<**0.001**, **highly significant**

Figure 5: Quantity of sputum among the three phenotypes



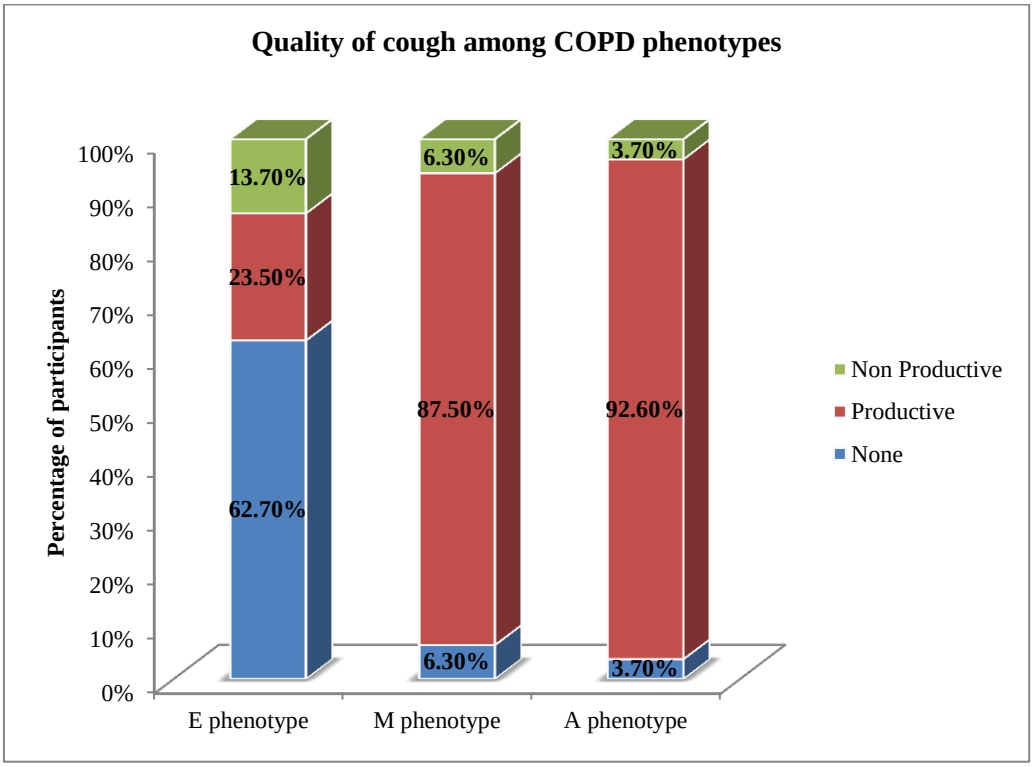
Quality of cough among the three phenotypes:

There was a significant difference (*p*-value<**0.001)** in the quality of cough among the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to sputum production, there was a significant difference in quality of cough between E and M phenotypes (*p*-value<**0.001)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The participants with phenotype E had lesser productive cough and more non-productive and free of cough compared to those with M and A phenotypes.

Table 5: Quality of cough among the three phenotypes

	E phenotype	**M phenotype**	**A phenotype**	**Total**
None	32	1	1	34
Productive	12	14	25	51
Non Productive	7	1	1	9
Total	51	16	27	94
Chi square test, *p*-value**<0.001**, **highly significant** *E versus M:* Chi square test, *p*-value**<0.001**, **highly significant** *E versus A* :Chi square test, *p*-value**<0.001**, **highly significant**				

Figure 6: Quality of cough among the three phenotypes



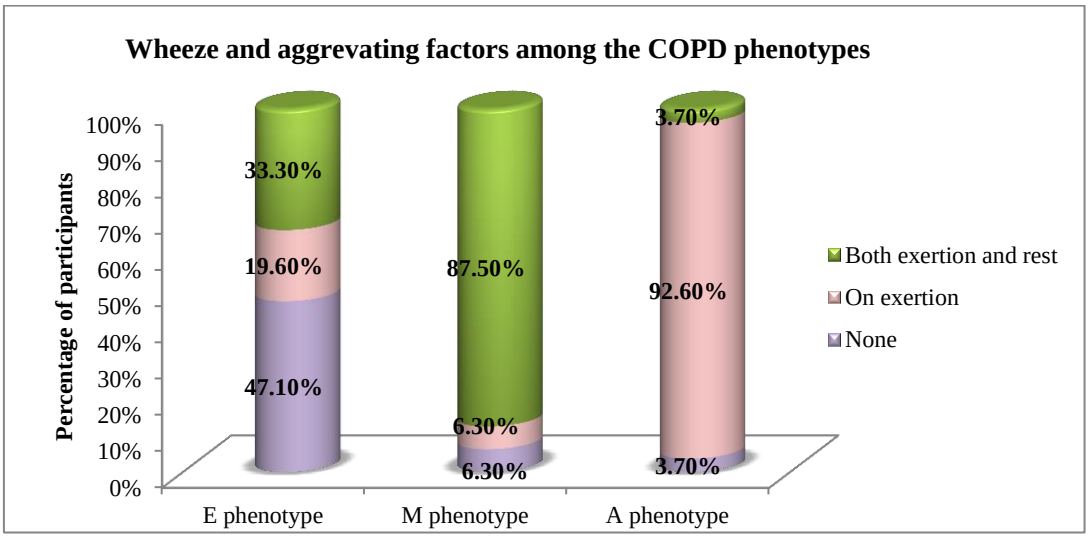
<u>Wheezing among the three phenotypes</u>:

There was a significant difference (*p*-value<**0.001)** in the presence of wheezing and its aggravating factors among the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to wheeze, there was a significant difference in the aggravating factors of wheeze between E and M phenotypes (*p*-value<**0.001)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The participants with phenotype E had lesser episodes of wheeze and had more wheeze while on rest as well as on exertion compared to those with M and A phenotypes.

Table 6: Wheezing among the three phenotypes

	E phenotype	M phenotype	A phenotype	Total
None	24	1	1	26
On exertion	10	1	25	36
Both exertion and rest	17	14	1	32
Total	51	16	27	94
Chi square test, *p*-value<**0.001**, **highly significant** *E versus M:* Chi square test *p* value=**0.001**, **highly significant** *E versus A* :Chi square test, *p*-value<**0.001**, **highly significant**				

Figure 7: Wheezing and its aggravating factors among the three phenotypes

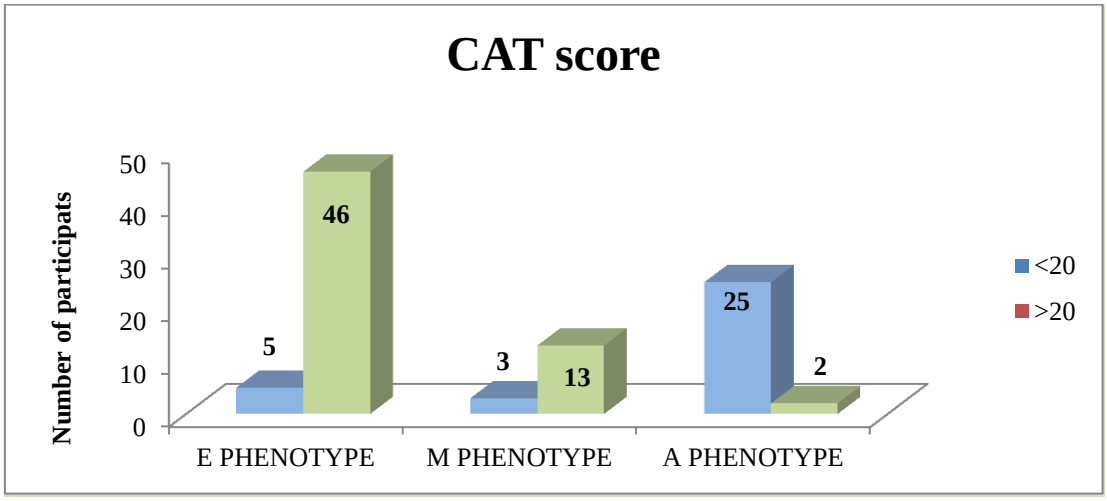


Combined Assessment Test (CAT) for COPD among phenotypes: There was a significant difference (*p*-value<**0.001)** in the CAT scores among the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to CAT scores, there was a significant difference (*p*-value**=0.002)** in the scores between E and M phenotypes. There was also significant difference (*p*-value**<0.001)** between E and A Phenotypes. The mean CAT score was high among those participants with phenotype E when compared to those with A and M.

Table 7: Combined Assessment Test (CAT) for COPD

CAT Score	E phenotype n=51	M phenotype n=16	A phenotype n=27
Mean score	28	21.63	15.78
SD	6.28	1.36	2.03
One way ANOVA test, *p*-value**<0.001, Highly significant**			

Figure 8: Combined assessment test: scores (categorized)



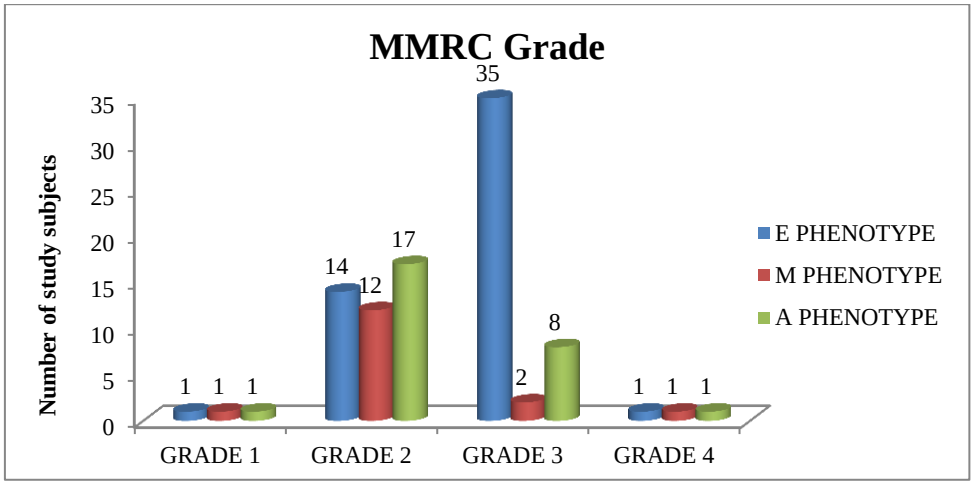
Modified Medical Research Council (MMRC) grade among phenotypes:

There was a significant difference (*p*-value<**0.001)** in the MMRC grades among the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to MMRC grades, there was a significant difference (*p*-value=**0.001)** in the scores between E and M phenotypes. There was also significant difference (*p*-value<**0.012)** between E and A Phenotypes. Majority of participants in phenotype E belonged to grade 3 when compared to those with A and M.

Table 8: Modified Medical Research Council (MMRC) grade

	E phenotype	**M phenotype**	**A phenotype**	**Total**
Grade 1	1	1	1	3
Grade 2	14	12	17	43
Grade 3	35	2	8	45
Grade 4	1	1	1	3
Total	51	16	27	94
Chi square test: *p*-value=**0.002**, **significant**				

Figure 9: Modified Medical Research Council (MMRC) grade among three COPD Phenotypes



MEDICAL HISTORY ASSOCIATED WITH EACH PHENOTYPE

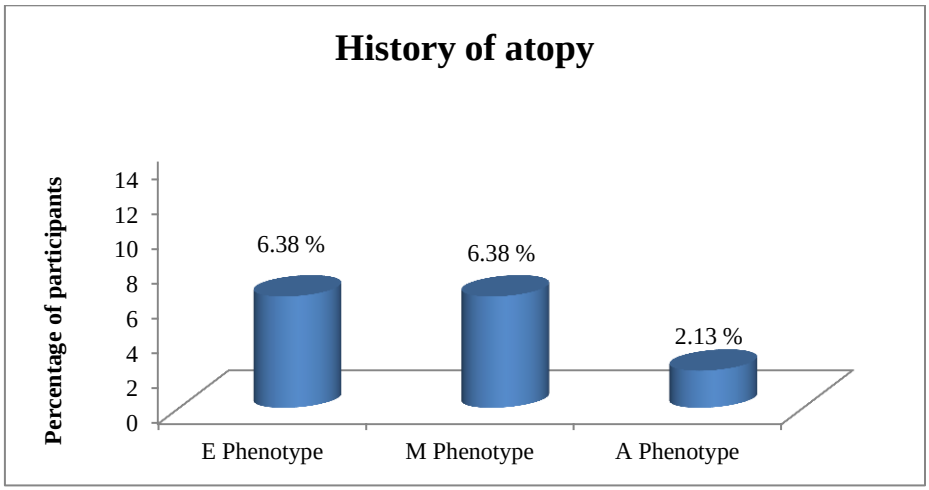
History of atopy among the various phenotypes:

There was a significant difference (*p*-value=**0.01)** presence of history of sinusitis among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to history of sinusitis, there was a significant difference in the presence of sinusitis between E and M phenotypes but not between E and A Phenotypes.

Table 9: History of atopy among the various phenotypes

	E phenotype	M phenotype	A phenotype	Total
no	45	10	25	80
yes	6	6	2	14
Total	51	16	27	94
Chi square test, *p*-value=**0.01**, **significant** *E versus M:* Chi square test, *p*-value=**0.019**, **significant** *E versus A* :Chi square test, *p*-value=**0.55**, NOT significant				

Figure 10: History of atopy among three phenotypes



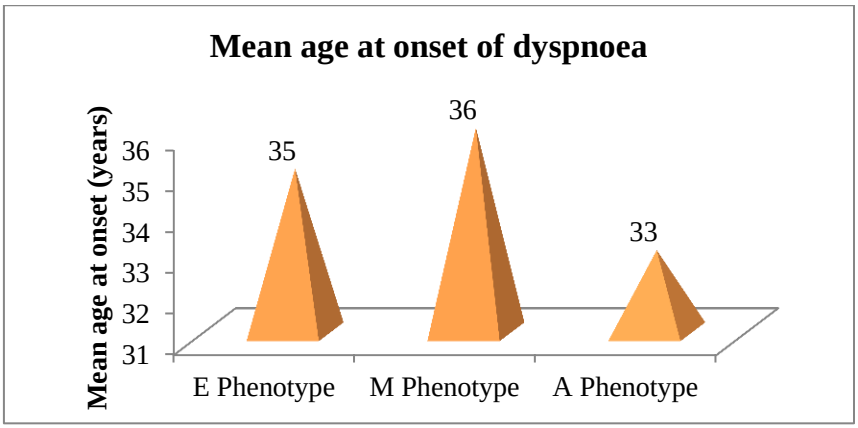
Age at onset of dyspnoea (in years):

There was a significant difference (*p*-value=**0.02)** in age at onset of dyspnoea among the three phenotypes. When individual phenotypes were compared with each other with regards to age at onset of dyspnoea, there was a significant difference in mean age at onset between E and A phenotypes but not between E and M Phenotypes.

Table 10: Age at onset of dyspnoea (in years)

	E phenotype n=51	**M phenotype n=16**	**A phenotype n=27**
Mean age at onset	35	36	33
SD	3	1	2
One way ANOVA test, *p*-value=**0.02, Significant** *E versus M:*, *p*-value =0.19, NOT Significant *E versus A: p*-value **=0.002**, **Significant**			

Figure 11: Age at onset of dyspnoea among three phenotypes



<u>Exacerbations (events/last one year) among the three COPD phenotypes</u>:

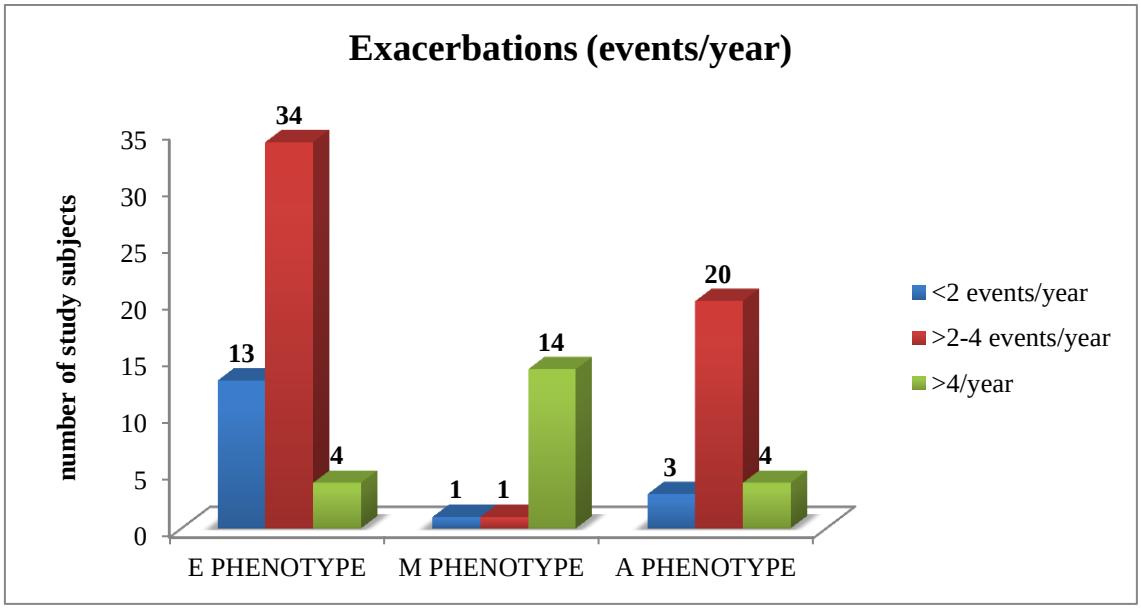
There was a significant difference (*p*-value<**0.001)** in the mean number of exacerbations (events/year) among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean exacerbation events per years, there was a significant difference in the number

of events per years between E and M phenotypes (*p*-value=**0.01)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The exacerbations were high among those participants with phenotype A when compared to those with M and E.

Table 11: Exacerbations (events/year) among the three COPD phenotypes

Exacerbations	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean Events/year	3.3	4.1	5.2
SD	1.09	1.2	1.1
One way ANOVA, *p*-value**<0.001, Highly significant** *E versus M:* t-value, *p*-value**=0.01**, **significant** *E versus A:* t-value**,** *p*-value **<0.001**, **Highly significant**			

Figure 12: Number of exacerbations (categorized) among the three phenotypes



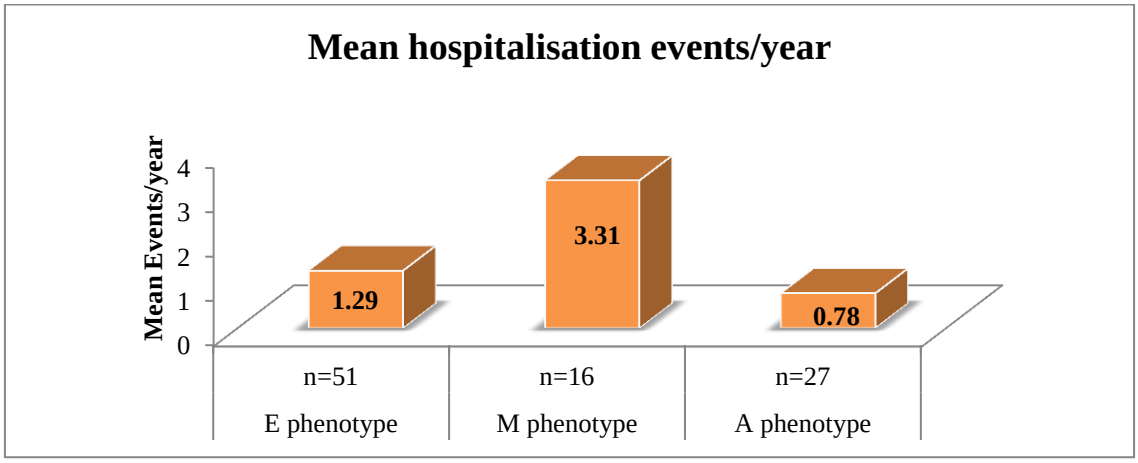
Hospitalisations (events/year) among the three COPD phenotypes

There was a significant difference (*p*-value<**0.001)** in the mean number of hospitalizations (events/year) among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean hospitalisation events per years, there was a significant difference in the number of events per years between E and M phenotypes (*p*-value<**0.001)** as well as between E and A Phenotypes (*p*-value=**0.01)**. The hospitalisations were high among those participants with phenotype M when compared to those with A and E.

Table 12: Hospitalisations (events/year) among the three COPD phenotypes

Hospitalizations	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean Events/year	1.29	3.31	0.78
SD	0.99	1.35	0.7
One way ANOVA test, *p*-value**<0.001, Highly significant** *E versus M:* t-value, *p*-value**=<0.001**, **Highly significant** *E versus A:* t-value**,** *p*-value**=0.01**, **significant**			

Figure 13: Number of hospitalisations among the three phenotypes



History of exposure to noxious particles other than tobacco: There was no significant difference in the exposure to noxious particles other than tobacco among the three phenotypes. A phenotype had significantly (*p*-value=**0.002**) higher exposure to noxious particles when compared to E phenotype.

Table 13: History of exposure to noxious particles other than tobacco

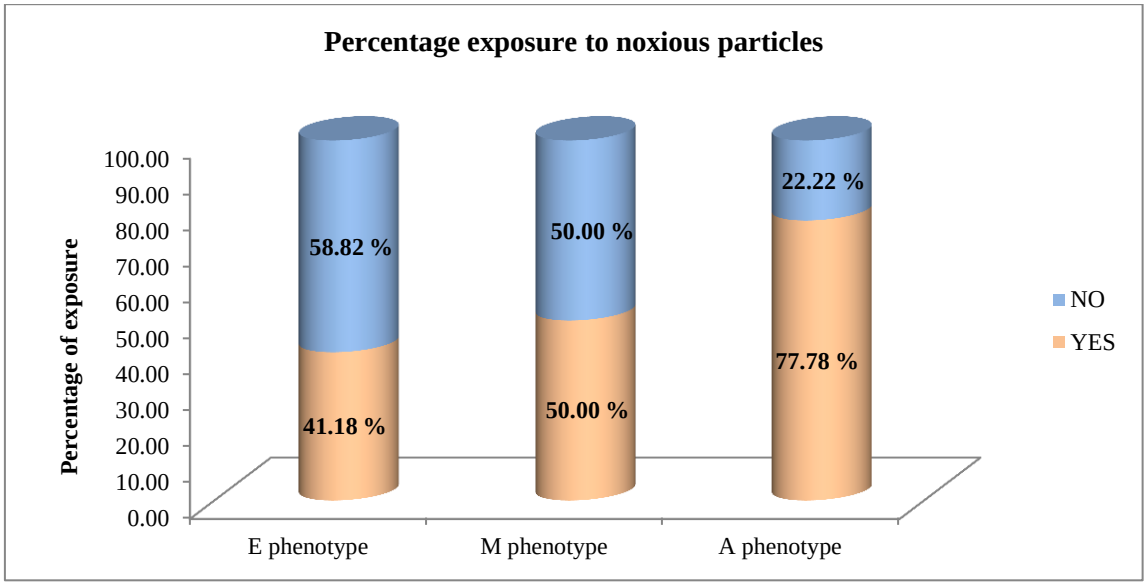
	E phenotype	M phenotype	A phenotype	Total
Yes	21	8	21	50
No	30	8	6	44
Total	51	16	27	94

Chi square test, *p*-value=**0.008**, NOT significant

E versus M: Chi square test, *p*-value=**0.53**, NOT significant

E versus A :Chi square test, *p*-value=**0.002**, **significant**

Figure 14: Percentage exposure to noxious particles other than tobacco among the various phenotypes



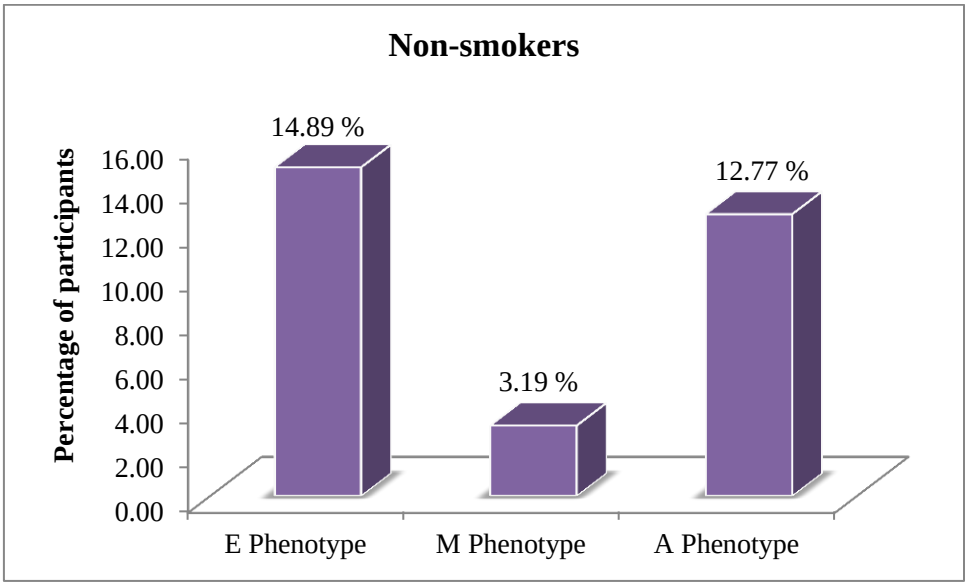
<u>Never smokers among the various phenotypes</u>:

There was no significant difference in the absence of history of smoking among the three phenotypes. Non-smokers did not show significant difference in association with the various CT phenotypes.

Table 14: Never-smokers among the various phenotypes

	E phenotype	M phenotype	A phenotype	Total
Yes	14	3	12	29
No	37	13	15	65
Total	51	16	27	94
Chi square test, *p*-value=**0.156**, NOT significant				

Figure 15: Never-smokers among three phenotypes



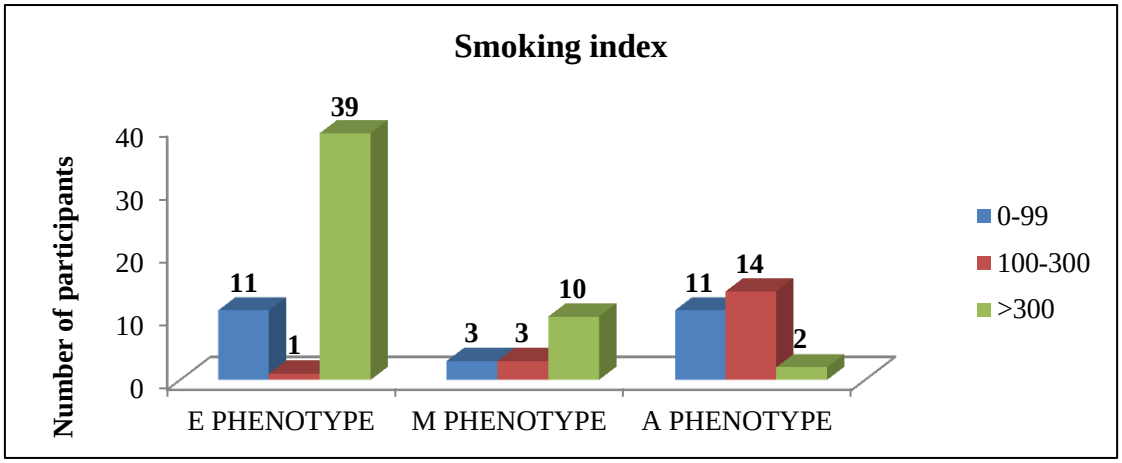
Smoking index among the various phenotypes:

There was a significant difference (*p*-value<**0.001)** in the mean smoking index among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean smoking index, there was a significant difference in mean smoking index between E and M phenotypes (*p*-value=**0.0012)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The smoking index was very high among those participants with phenotype E when compared to those with M and A.

Table 15: Smoking index among the various phenotypes

	E phenotype n=51	**M phenotype n=16**	**A phenotype n=27**
Mean smoking index	668	325	152
SD	392	173	129
One way ANOVA, *p*-value**<0.001, Highly significant** *E versus M:* t-value, *p*-value**=0.0012**, **Highly significant** *E versus A:* t-value**,** *p*-value **<0.001**, **Highly significant**			

Figure 16: Categorized smoking index in various phenotypes

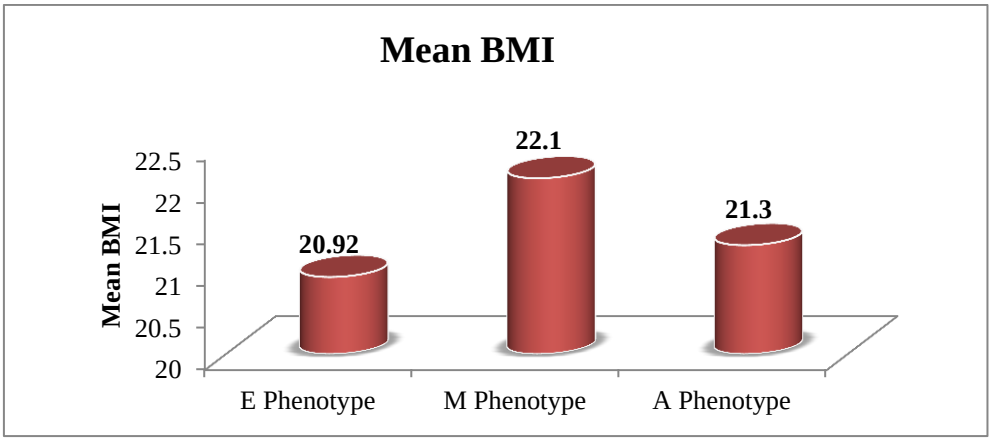


Body mass Index among different phenotypes: There was a significant difference in body mass index among the three phenotypes. When individual phenotypes were compared with each other with regards to BMI there was a significant difference in mean BMI between E and M phenotypes but not between E and A Phenotypes.

Table 16: Body mass Index among different phenotypes

	E phenotype n=51	M phenotype n=16	A phenotype n=27
Mean BMI	20.92	22.10	21.31
SD	1.29	1.80	0.5
One way ANOVA test: F value= 6.6, *p*-value=**0.02, Significant** *E versus M:* **t-test,** *p*-value **=0.04, Significant** *E versus A:* **t-test,** *p*-value =0.14, NOT Significant			

Figure 17: Body mass Index among different phenotypes



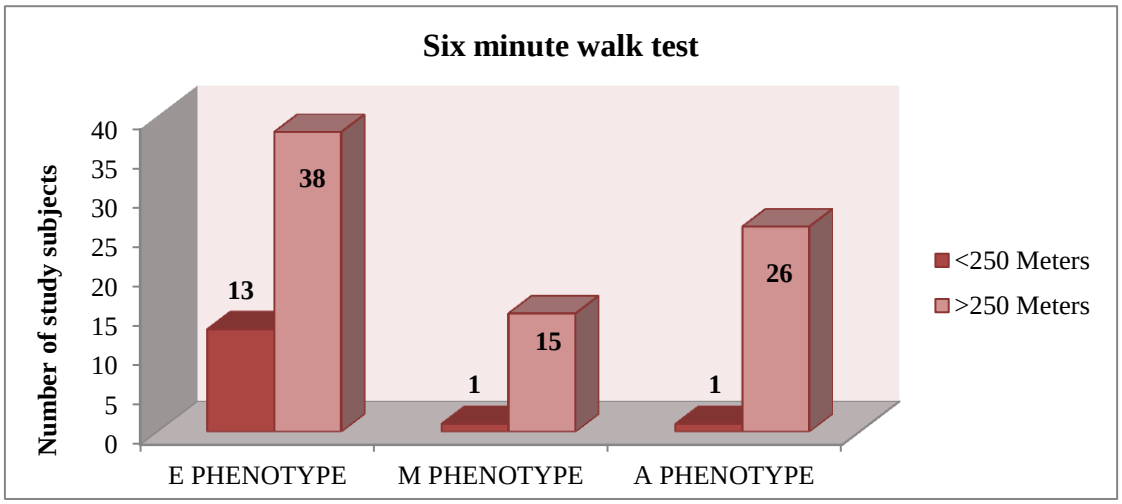
<u>Six minute walk test distance walked by three phenotypes</u>: There was a significant difference (*p*-value<**0.001)** in the mean distance (in meters) walked by participants of the three COPD phenotypes. When individual phenotypes were compared versus E phenotype with regards to distance walked in the 6

minutes' walk test, there was no significant difference in the distance walked between E and M phenotypes but there was significant difference between E and A Phenotypes (*p*-value=**0.01)**. The distance walked was high among those participants with phenotype A when compared to those with M and E.

Table 17: Six minute walk test: Distance walked by three phenotypes

Distance walked	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Distance (in metres)	297.49	275.31	328.93
SD	64.06	11.5	33.59
One way ANOVA test:, *p*-value**<0.001, Highly significant** *E versus M:* t-test, *p*-value=0.18, NOT significant *E versus A:* t-test**,** *p*-value**=0.01**, **significant**			

Figure 18: Six minute walk test: Distance walked in meters (categorized)



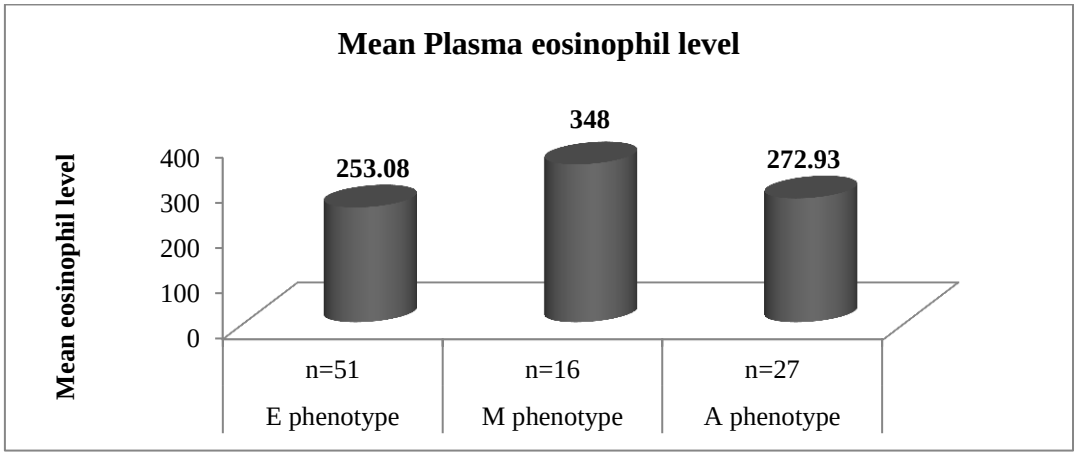
INVESTIGATIONS

Mean Plasma eosinophil levels among three COPD phenotypes: There was a significant difference (*p*-value<**0.001)** in the mean plasma eosinophil level among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean plasma eosinophil level, there was a significant difference in between E and M phenotypes (*p*-value<**0.001)** as well as between E and A Phenotypes (*p*-value=**0.0016)**. The mean plasma eosinophil level was very high among those participants with phenotype M when compared to those with E and A.

Table 18: Mean Plasma eosinophil levels among three COPD phenotypes

Plasma eosinophil levels	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean score	253.08	348	272.93
SD	19.97	20.46	33.71
One way ANOVA test, *p*-value<**0.001, Highly significant** *E versus M:* t-test, *p*-value<**0.001**, **Highly significant** *E versus A:* t-test**,** *p*-value=**0.0016**, **Highly significant**			

Figure 19: Mean plasma eosinophil level among three COPD phenotypes



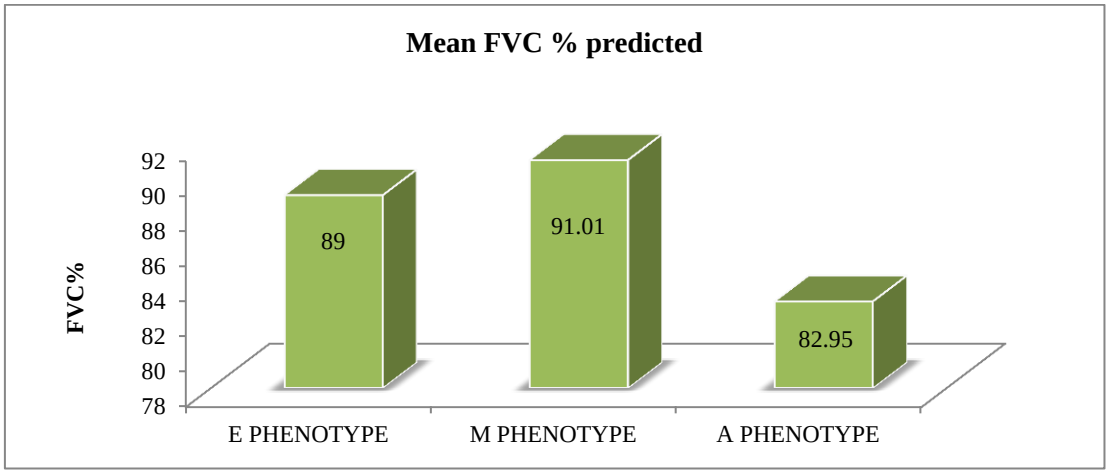
Pulmonary Function Test:

There was a significant difference (*p*-value<**0.001)** in the mean FVC% predicted among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean FVC% predicted, there was no significant difference in between E and M phenotypes but there was a significant difference between E and A Phenotypes (*p*-value<**0.001)**. The mean FVC% predicted was high among those participants with phenotype M when compared to those with E and A.

Table 19: Forced Vital Capacity Percentage of Predicted (FVC %)

FVC %	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean FVC%	89	91.01	82.95
SD	4.22	0.64	2.01
One way ANOVA test, *p*-value<**0.001, Highly significant** *E versus M:* t-test, *p*-value=0.06, NOT significant *E versus A:* t-test**,** *p*-value<**0.001**, **Highly significant**			

Figure 20: Forced Vital Capacity Percentage Predicted (FVC %)

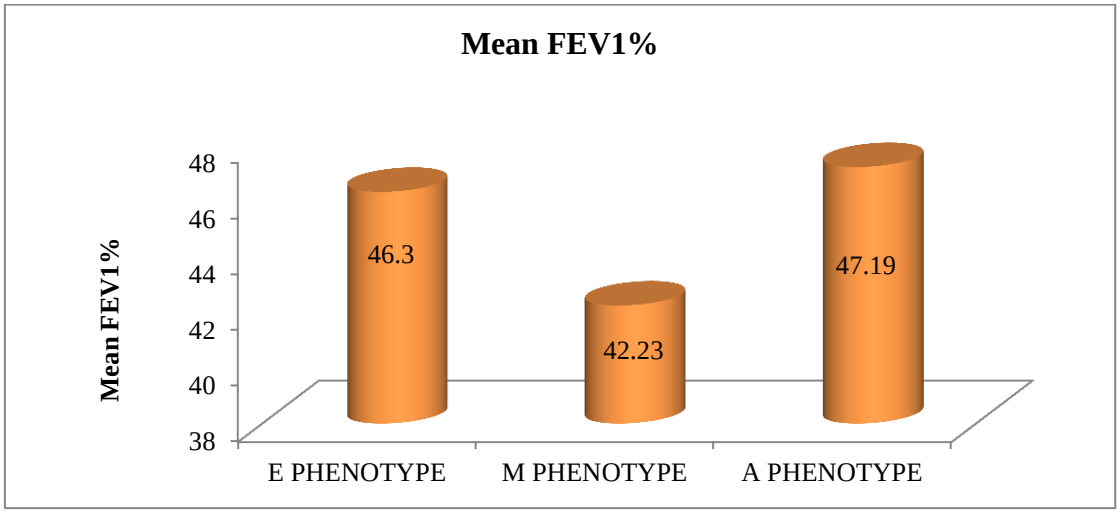


Forced Expiratory Volume in 1 Second (Fev1%): There was a significant difference (*p*-value<**0.001)** in the mean FEV1% predicted among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean FEV1% predicted, there was a significant difference (*p*-value<**0.001)** between E and M phenotypes as well as between E and A Phenotypes (*p*-value=**0.02)**. The mean FEV1% predicted was high among those participants with phenotype A when compared to those with E and M.

Table 20: Forced Expiratory Volume in 1 Second (Fev1%)

FEV1 %	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean FEV1 %	46.3	42.23	47.19
SD	1.67	1.00	1.47
One way ANOVA test:, *p*-value**<0.001, Highly significant** *E versus M:* t-test, *p*-value**<0.001, Highly significant** *E versus A:* t-test**,** *p*-value**=0.02**, **significant**			

Figure 21: Forced Expiratory Volume in 1 Second (Fev1%)

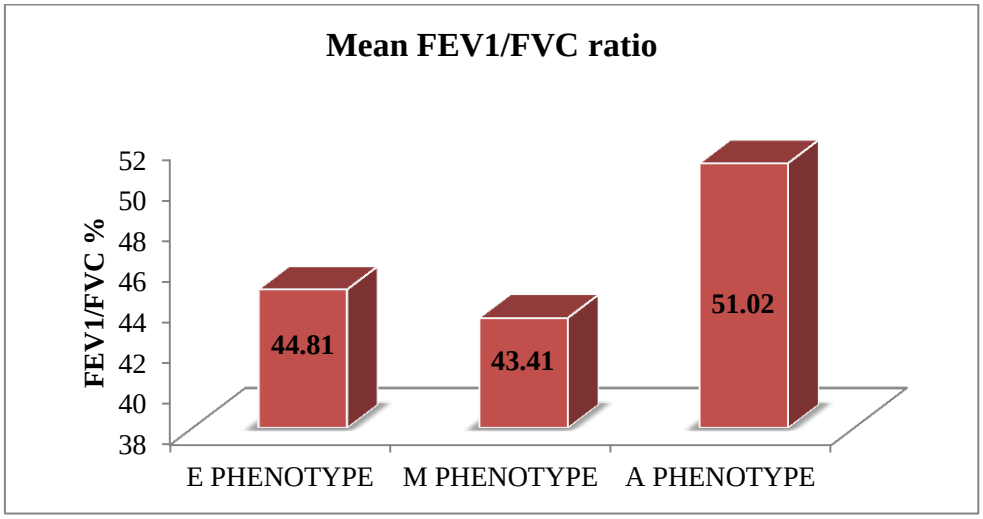


Mean Ratio of FEV1/FVC (%) among the COPD phenotypes: There was a significant difference (*p*-value<**0.001)** in the mean FEV1/FVC % predicted among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean FEV1% predicted, there was no significant difference between E and M phenotypes but between E and A Phenotypes showed a significant difference (*p*-value**<0.001)**.

Table 21: Mean Ratio of FEV1/FVC (%) among the COPD phenotypes

FEV1/FVC (%)	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean FEV1/FVC (%)	44.81	43.41	51.02
SD	4.69	0.53	1.46
One way ANOVA test:, *p*-value**<0.001, Highly significant** *E versus M:* t-test, *p*-value=0.24**,** NOT significant *E versus A:* t-test**,** *p*-value**<0.001, Highly significant**			

Figure 22: Ratio of FEV1/FVC (%) among the COPD phenotypes

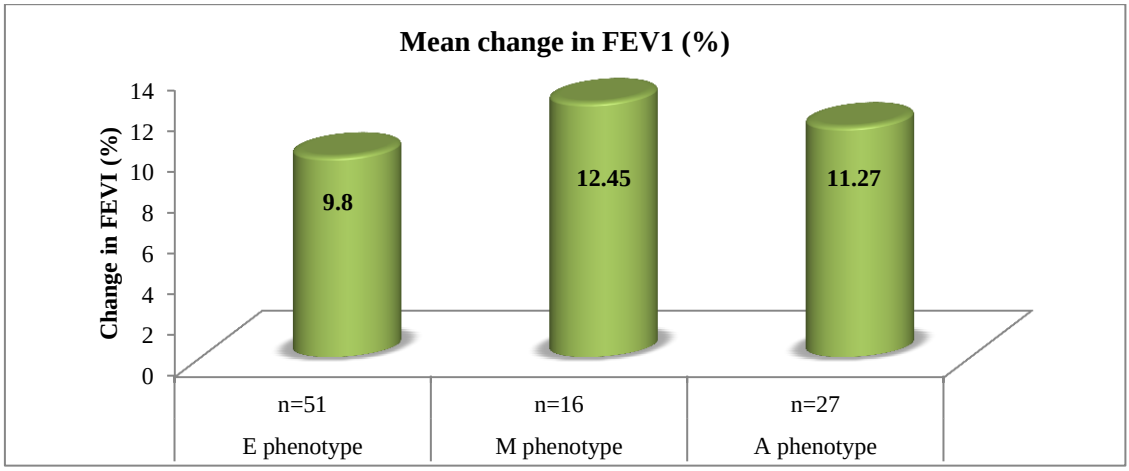


Mean Percentage change in FEV1 after short acting bronchodilator: There was a significant difference (*p*-value<**0.001)** in the mean change in FEV1 (%) among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean change in FEV1 (%), there was a significant difference (*p*-value**<0.001)** between E and M phenotypes as well as between E and A Phenotypes (*p*-value**=0.02)**. The mean change in FEV1 (%) was high among those participants with phenotype M when compared to those with E and A.

Table 22: Mean Percentage change in FEV1 after short acting bronchodilator

Change in FEV1 (%)	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean change in FEV1 (%)	9.8	12.45	11.27
SD	1.2	0.76	4.65
One way ANOVA test, *p*-value**<0.001, Highly significant** *E versus M:* t-test, *p*-value**<0.001, Highly significant** *E versus A:* t-test**,** *p*-value**=0.03, significant**			

Figure 23: Mean Percentage change in FEV1 after short acting bronchodilator

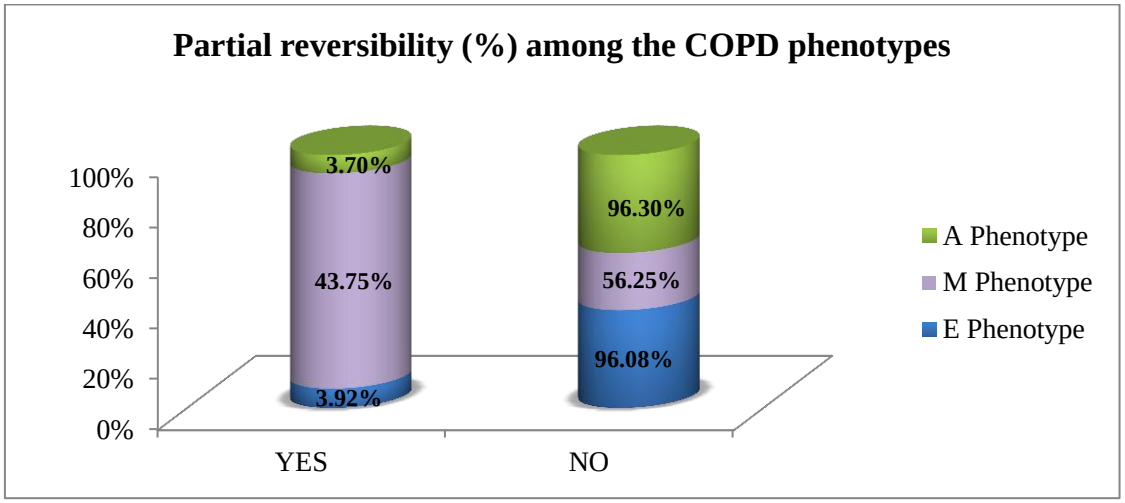


Partial reversibility after Short Acting Beta-2 Agonist (SABA): There was a significant difference (*p*-value<**0.001)** in the partial reversibility after SABA among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to the partial reversibility after SABA, there was a significant difference (*p*-value**<0.001)** between E and M phenotypes but not between E and A Phenotypes. The partial reversibility after SABA was high among those participants with phenotype M when compared to those with E and A.

Table 23: Partial reversibility after Short Acting Beta-2 Agonist (SABA)

Partial reversibility	E phenotype	M phenotype	A phenotype	Total
Yes	2 (3.92)	7 (43.75)	1 (3.7)	10 (10.6)
No	49 (96.08)	9 (56.25)	26 (96.3)	84 (89.4)
Total	51 (100)	16 (100)	27 (100)	94 (100)
Chi square test value, *p*-value**<0.001**,**highly significant ;** E vs M**, p-value <0.001**				

Figure 24: Partial reversibility after Short Acting Beta-2 Agonist (SABA)



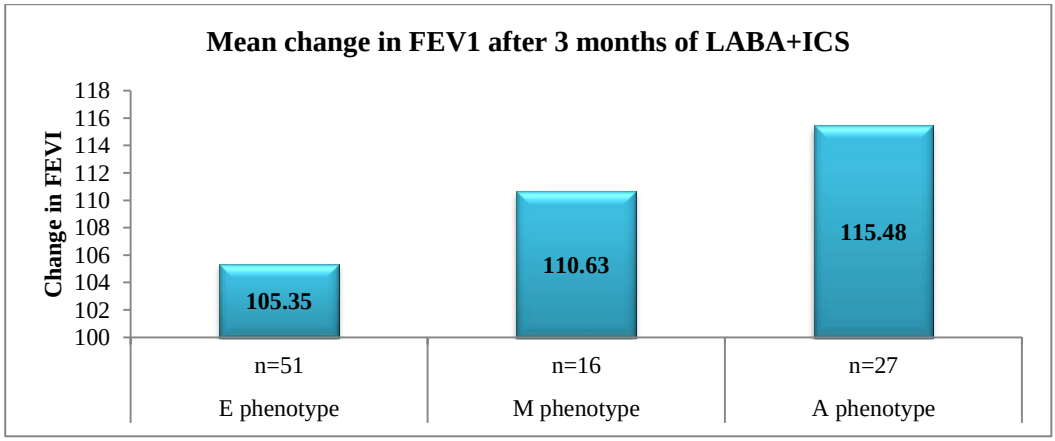
CHANGE IN FEV1 AFTER THREE MONTHS OF LABA+ICS

There was a significant difference (*p*-value<**0.001)** in the mean change in FEV1 after 3 months of LABA+ICS among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean change in FEV1, there was no significant difference in between E and M phenotypes but there was a significant difference between E and A Phenotypes (*p*-value=**0.01)**. The mean change in FEV1 after 3 months of LABA+ICS was high among those participants with phenotype A when compared to those with E and M.

Table 24: Change in FEV1 after three months of LABA+ICS

Change in FEV1 (%)	E phenotype n=51	M phenotype n=16	A phenotype n=27
Mean change in FEV1	105.35	110.63	115.48
SD	6.64	25.14	26.13
One way ANOVA test, *p*-value<**0.001, Highly significant** *E versus M:* t-test, *p*-value=0.17, NOT significant *E versus A:* t-test**,** *p*-value=**0.01, significant**			

Figure 25: Change in FEV1 after three months of LABA+ICS



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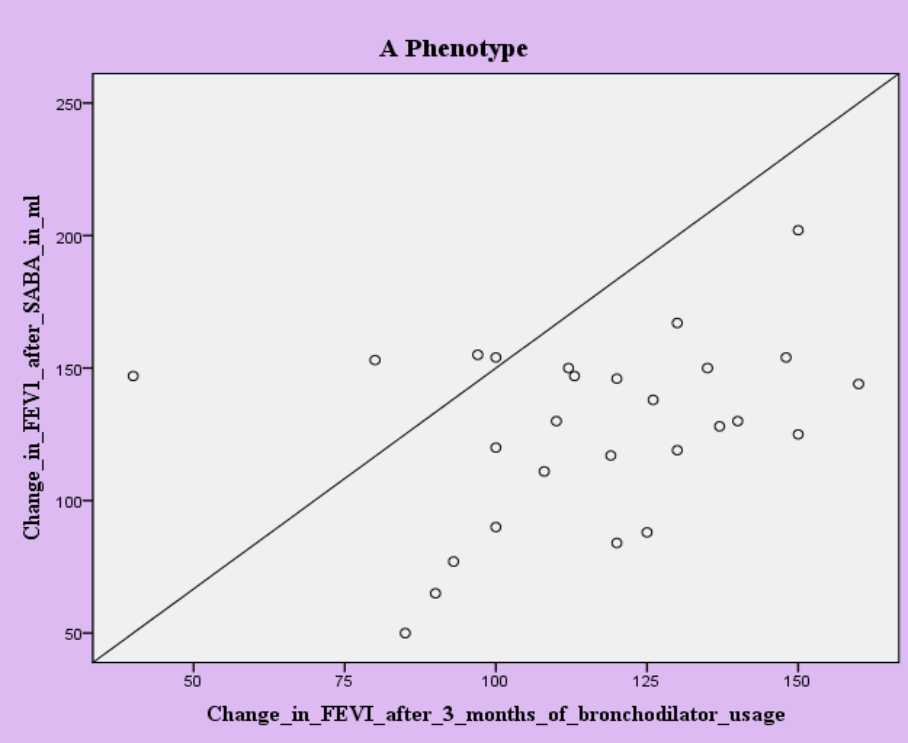
Correlation between changes in FEV1 post short acting Beta agonist and after 3 months of bronchodilator usage in *A phenotype*

There was positive correlation between changes in FEV1 post short acting Beta agonist and after 3 months of bronchodilator usage in A phenotype but the strength of correlation was not statistically significant. **[Figure 25]**

Table 25: Correlation between changes in FEV1 post short acting Beta agonist and after 3 months of bronchodilator usage in *A phenotype*

		Change in FEV1 after SABA in ml	% Change in FEV1 Post Bronchodilator Use
Change in FEV1 after SABA in ml	Pearson Correlation	1	**0.306****
	p-value	0.120, NOT significant	
	**. Correlation is significant at the 0.01 level (2-tailed).		

Figure 26: Correlation between changes in FEV1 post short acting Beta agonist and after 3 months of bronchodilator usage in *A phenotype*



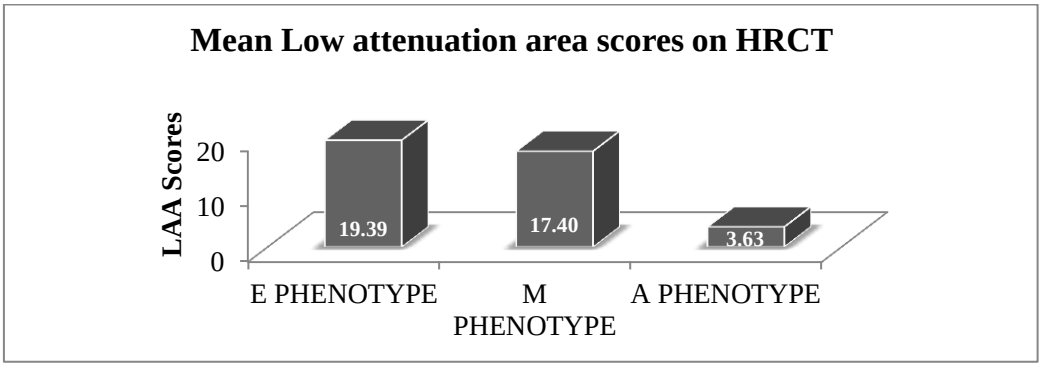
RADIOLOGICAL OBSERVATIONS

Low attenuation area scores on HRCT for the three COPD phenotypes: There was a significant difference (*p*-value<**0.001)** in the low attenuation area scores on HRCT among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to low attenuation area scores, there was a significant difference (*p*-value=**0.02)** between E and M phenotypes as well as between E and A Phenotypes (*p*-value<**0.001)**. The mean low attenuation area scores on HRCT was high among those participants with phenotype E when compared to M and A.

Table 26: Low attenuation area scores on HRCT for the three COPD phenotypes

Low attenuation area scores	**E phenotype n=51**	**M phenotype n=16**	**A phenotype n=27**
Mean scores	19.39	17.40	3.63
SD	3.26	1.74	1.5
One way ANOVA test, *p*-value<**0.001, Highly significant** *E versus M:* t-test, *p*-value=**0.02, significant** *E versus A:* t-test**,** *p*-value<**0.001, Highly significant**			

Figure 27: Mean Low attenuation area scores on HRCT

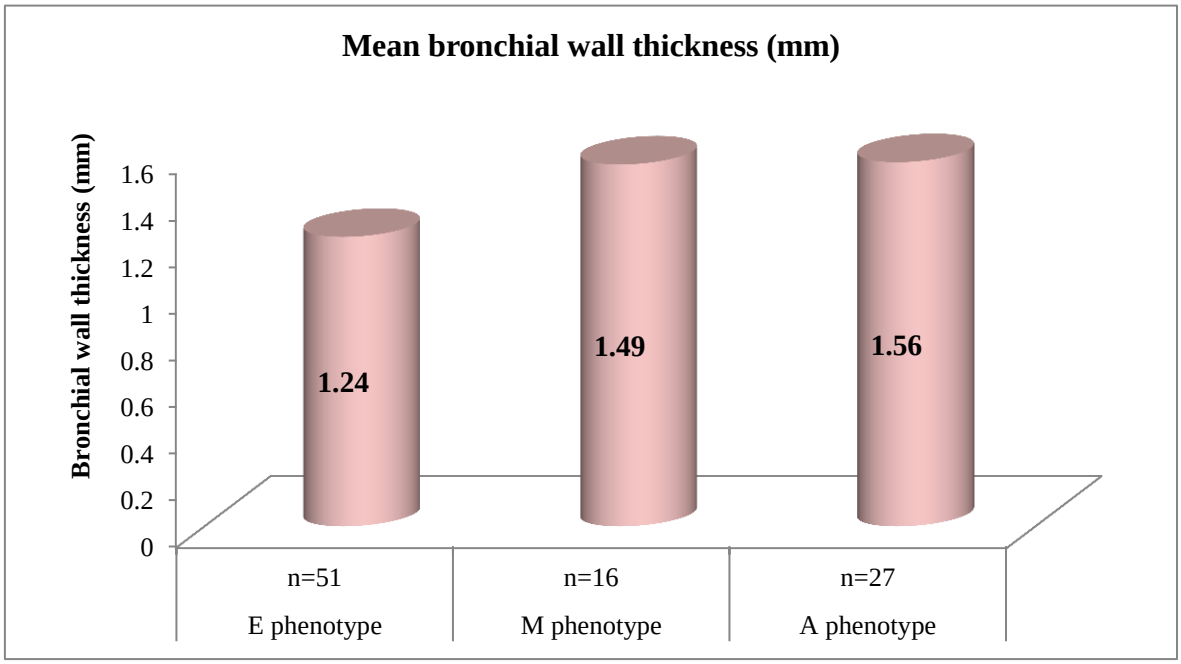


Bronchial wall thickness (mm) in the three phenotypes: There was a significant difference (*p*-value<**0.001)** in the bronchial wall thickness (in mm) on HRCT among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to bronchial wall thickness, there was a significant difference (*p*-value<**0.001)** between E and M phenotypes as well as between E and A Phenotypes (*p*-value<**0.001)**. The mean bronchial wall thickness on HRCT was high among those participants with phenotype A when compared to E and M.

Table 27: Bronchial wall thickness (mm) in the three phenotypes

Bronchial wall thickness	E phenotype n=51	M phenotype n=16	A phenotype n=27
Mean Thickness (mm)	1.24	1.49	1.56
SD	0.18	0.26	0.30
One way ANOVA test: *p*-value**<0.001, Highly significant** *E versus M:* t-test, *p*-value=**<0.001, Highly significant** *E versus A:* t-test**,** *p*-value**<0.001, Highly significant** *M versus A:* t-test**,** *p*-value=0.91, NOT significant			

Figure 28: Mean Bronchial wall thickness (mm) in the three phenotypes



Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity around the globe. According to a study published by the World Health Organization, COPD is projected to be ranked as the 5th worldwide in the burden of diseases by 2020. The most common risk factor for COPD is tobacco smoking while in some countries outdoor, occupational and indoor air pollution are also important risk factors. Patients with COPD often suffer due to this disease for a long time and many a time die prematurely from it or its complications. Currently, the Global initiative for chronic obstructive lung disease (GOLD) advocates reducing the impact of the symptoms of COPD as well as prevention of further exacerbations.[92]

COPD being a heterogenous disease, a detailed profile of the variable phenotypes are yet to be standardized. The chief reasons hampering it being the considerable variation in clinical severity, presence of asymptomatic disease along with interobserver variation in the clinical signs. Furthermore, there is no ultimate test that is commonly available that gives the whole picture. Spirometry which is now used to diagnose COPD fails to identify early COPD, poorly predicts symptom severity and the reduced DLCO in emphysema in smokers could be due to separate mechanisms in smokers[93] [94]

The role of phenotyping in COPD and whether it can be associated with meaningful clinical outcomes have been recently studied in many parts of the world.[17][18] The present study classified COPD patients (Group D according to GOLD) into three phenotypes based on morphological features on high resolution computed tomography (HRCT) and assessed each phenotype's

response to a combination of inhaled corticosteroids and long acting beta-2 agonist . Various factors such as age, gender, smoking history, age of onset of dyspnea, history of exposure to noxious particles other than tobacco, exacerbations in past one year , hospitalizations in the past one year, CAT score, MMRC grade of dyspnea, 6 minute walk distance, plasma eosinophil counts and partial reversibility to short acting beta-2 agonist was compared between the three phenotypes.

In this study a total of 147 patients with symptoms of COPD and with irreversible or partially reversible airway obstruction with a post bronchodilator FEV/FVC ratio less than 70% were recruited for this study. After satisfying the inclusion and exclusion criteria, 94 patients were classified into three phenotypes based on High Resolution CT . In the remaining COPD patients, 19 had upper lobe fibrotic strands suggestive of pulmonary tuberculosis sequelae, 5 had bronchiectasis, 4 had pulmonary fibrosis in the lower lung fields, 1 patient had a mass lesion, 2 were found to have solitary pulmonary nodules and 2 had multiple centrilobular nodules on HRCT. In seven patients the HRCT chest was inconclusive. The remaining twenty dropped out during follow up .These patients were excluded from analysis in our study.

In this study the highest low attenuation(LAA) score was obtained in the E phenotype and lowest in the A phenotype. This was in concordance with previous studies which proved increasing LAA score correlated with higher severity of emphysema and dyspnea.[95] According to previous studies, an

HRCT score of emphysema that did not exceed 14% was compatible with no or trivial emphysema[96] Nakano *et al* reported emphysema and its HRCT surrogate LAA % correlates with the loss of elastic recoil of the lung.[8] Falaschi F *et el*. compared different CT methods for quantifying pulmonary emphysema in severe COPD and demonstrated that there was excellent coorelation between CT quantified emphysema and functional indices of expiratory airflow.[97]

Our study observed thickened airways in one COPD subpopulation and this was consistent with results obtained by other investigators. Haraguchi *et al* reported that the bronchi in COPD patients had more peribronchial fibrosis and degenerated cartilage than the control group without COPD. [98] Tiddens *et al*. reported that the area of cartilaginous airways in was increased in obstructed patients (FEV1/FVC<40%) when compared to non-obstructed patients(FEV1/FVC=80%). [99] The bronchial wall thickness was significantly higher in the A group with a mean value of 1.56+/- 0.30 ($p<0.001$) and lowest in the E phenotype with a mean value of 1.24+/-0.18.

AGE AND GENDER

There was a significant difference in age distribution among the males and females in the study (*p*-value=**0.04**) with majority among the females belonged to younger age group and males belonged to the middle and elderly age groups.When the difference in age groups between phenotypes were compared, here was a significant difference in age distribution between those with E

phenotype and A phenotype . Majority of the subjects in the E phenotype belonged to the slightly older age group (61-70yrs) as compared to the A phenotype (51-60yrs).

These findings were similar to studies by other investigators such as Grydeland *et al*.[33] who stated that age could be used as a predictor for emphysema. Nakano *et al* [8] suggested an inverse relation between severe emphysema and severe airway thickening i.e at comparable levels of FEV1, patients with more severe emphysema have less severe airway thickening and vice versa. They also reported that as the FEV1% decreased, the airway wall area and thickening increased. On the other hand, FEV1% was found not to have any significant relation to the outer airway wall diameter. It was suggested that this could be because, as the airway wall thickens it encroaches into the lumen rather than expanding into the lung parenchyma. An alternate explanation would be that as the airway thickens, there is a degree of airway smooth muscle shortening which could have the same effect. Though other studies such as by Pierre-Régis Burgel. *et al* [34] reported a slightly older age group for the A phenotype, the younger age distribution in this study could probably be because of a larger number of females in this subgroup with history of exposure to noxious particles such as biomass fuels from a young age.

In the present study there was no significant difference in distribution of phenotypes among males and females. When individual phenotypes were compared with each other with regards to gender there was still no difference in phenotype pattern. Hence, the widespread existing notion that males are

more prone for emphysema may lead to an underdiagnosis of emphysema in females. Innumerable studies have linked smoking and emphysema as it causes a shift in the proteinase-antiproteinase balance. The large group of emphysematous males (72.5%) possibly reflects the high percentage of male smokers in our study population. Though the percentage of females were highest in the A phenotype (40.7%) this study observed a significant percentage of females with emphysema predominant COPD. None of the females in the present study were smokers.

The differences in these results may be due to the different types (dung, crop residue, firewood) and purpose of use of biomass. Studies[100] have elucidated that wood combustion produces substances like carbon monoxide, nitrogen oxide, formaldehyde, polycyclic aromatic hydrocarbons, particulate matter that are also present in cigarette smoke. Hence, wood smoke exposure may cause changes similar to those caused by smoking. In yet another study, wood smoke exposure had been noted to cause “pseudoemphysema” and hyperinflation due to bronchial involvement. Young girls prefer to be with their mothers inside small huts in rural parts of India, which increases the risk of biomass and indoor pollutants exposure. Last but not the least, exposure to passive smoking and environmental exposure to tobacco smoke has also been known to positively correlate with centrilobular emphysema. On the other hand, several studies have linked exposure to smoking as well as exposure to outdoor and indoor pollution to the development of chronic bronchitis.[101][102]

CLINICAL FEATURES

COPD is a disease characterized by the clinical symptoms of cough, sputum and wheeze. There was a significant difference in the symptoms among the three phenotypes. The participants with phenotype E produced lesser quantity of sputum compared to those with M and A phenotypes. The participants with phenotype A had more productive cough and E phenotype more non-productive and were free of cough compared to those with M and A phenotypes. The participants with phenotype E had lesser episodes of wheeze and had more wheeze while on rest as well as on exertion compared to those with M and A phenotypes. All results were statistically significant.

Studies have shown emphysema and its surrogate marker LAA% is associated with phlegm cough in males with COPD but not in females. This may be due to underreporting of phlegm by women due to social reasons. Similarly, airway wall thickness have been found to be significantly associated with chronic cough and wheezing. A greater airway thickness may reflect greater inflammation, more cough ,sputum and wheeze.[24]

Chronic bronchitis in a patient is defined as productive cough for 3 months in each of 2 successive years. Originally, chronic bronchitis was thought to identify a subgroup of COPD with characteristic symptoms. However, studies have revealed that respiratory symptoms decrease by 80% after smoking cessation for 5 years. Therefore, patients with airway dominant COPD may not display typical symptoms of COPD nor have evidence of emphysema.

EXACERBATIONS AND HOSPITALIZATIONS IN PAST ONE YEAR

This study found that there was a significant difference (*p*-value<**0.001)** in the mean number of exacerbations (events/year) among the three phenotypes. The exacerbations were high among those participants with phenotype A when compared to those with M and E. With respect to the hospitalizations, it was observed that the number of hospitalisations were high among those participants with phenotype M when compared to those with A and E. (*p*-value<**0.001)**

The principle cause of exacerbations in COPD is related to infections. Airway wall thickness may be the macroscopic correlate of mucous gland hypertrophy and inflammation , possibly related to infections. However, it is still not fully understood whether it's the effect of previous exacerbations or whether it predates them. Previous studies have reported bronchial wall thickness and not wall area percentage as a predictor for exacerbation frequency.[15] Since exacerbations are events driving lung function decline, hospitalizations, morbidity and mortality it becomes important to identify the cause of exacerbations among the COPD phenotypes and impart individualized treatment and prevention.

DISEASE ATTRIBUTES OF COPD PHENOTYPES

In this study there was a significant difference in body mass index among the three phenotypes. When individual phenotypes were compared with each other with regards to BMI there was a significant difference in mean BMI between E

and M phenotypes but not between E and A Phenotypes. The mean BMI was least in the E phenotype. These results were similar to those obtained from other studies that reported E and M phenotypes in COPD had a lower BMI . Low attenuation areas on CT has been reported to have a negative correlation with BMI.[103] The mechanism regarding weight loss in COPD is not fully understood. Wouters EFM *et al*[104] proposed the systemic effects of COPD was due to alterations in levels and activities of endocrine hormones, cytokines, cell death, as well an an imbalance between protein degradation and replacement.It has also been postulated TNF alpha levels are elevated in the E phenotype that contributes to weight loss. [105]

There was a significant difference (*p*-value=**0.02)** in age at onset of dyspnoea among the three phenotypes. When individual phenotypes were compared with each other with regards to age at onset of dyspnoea, there was a significant difference in mean age at onset between E and A phenotypes. The A phenotype had a younger age of onset of dyspnea compared to the E phenotype. This could probably be because of a very young age of onset of heavy smoking in males and prolonged exposure to noxious particles such a biomass fuels, from a young age in females. Moreover, previous studies have recorded an increased risk of breathlessness from a young age in those individuals genetically susceptible to COPD.

This study observed that there was a significant difference (*p*-value=**0.01)** in presence of history of sinusitis among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to history of

sinusitis, there was a significant difference in the presence of sinusitis between E and M phenotypes. Currently, personal history of atopy and a positive bronchodilator response forms part of the minor criteria for identifying the mixed COPD-asthma phenotype. The outcome of these patients with overlapping disease is worse than either disease alone. Hence, the presence of sinusitis/atopy may indicate an underlying asthmatic component in diagnosed COPD and should be included in the history taking in obstructive airway diseases. Daniel J *et al*.[106] studied the effect of allergy in COPD and found that sensitized individuals were more symptomatic, had higher risks of exacerbations and more had more adverse health outcomes. Fattemah *et al*[107] in their study of COPD patients with atopy reported that these atopic patients when treated with budesonide had increased remission of symptoms when compared to non-atopic COPD patients.

Though long term ICS have been found to have an increased risk in COPD, in those patients with asthma, LABA monotherapy has been found to have deteriorating asthma control and increased severity. Thus, treatment of the mixed COPD-asthma group warrants a cautious approach with monotherapy due to the increased burden of disease in this phenotype.

There was a significant difference (*p*-value<**0.001)** in the CAT scores among the three COPD phenotypes. The mean CAT score was high among those participants with phenotype E when compared to those with A and M. Similarly, was a significant difference (*p*-value<**0.001)** in the MMRC grades among the three COPD phenotypes. Majority of participants in phenotype E

belonged to grade 3 when compared to those with A and M. With respect to the distance walked in six minutes, the distance walked was high among those participants with phenotype A when compared to those with M and E. The result was statistically significant. (*p*-value<**0.001)**

Hence, patients in the E phenotype had greater level of dyspnea and exercise intolerance when compared to the A and M phenotypes. This is in line with previous studies associated increasing emphysema with increasing dyspnea.[95] In emphysema, there is a reduced alveolar surface for gas exchange to occur along with loss of elastic fibres. This results in static and dynamic hyperinflation, inoptimal length-tension relationship of respiratory muscles which leads to increase work of breathing and dyspnea. Studies such as that done by Hajiro et al reported that categorizing patients based on dyspnea may prove as a marker of treatment effect and is often used as an endpoint in clinical trials

The mean plasma eosinophil level was significantly different among the three phenotypes. (*p*-value<**0.001)** The mean plasma eosinophil level was very high among those participants with phenotype M when compared to those with E and A.

It has been recommended in international guidelines that, COPD patients with risk of exacerbations benefits from ICS/LABA maintenance therapy. However, this also carries with it a risk of non-fatal pneumoniae known as the “ICS-class effect”, as demonstrated in the TORCH trial. Hence, there is a need to discover

biomarkers that can predict ICS responsiveness. Dransfield MT *et al*.[108] have studied and reported an association of blood eosinophil percentage and response to inhaled corticosteroids. It was found that subjects with severe COPD and blood eosinophil percentage more than 2% had a better response when treated with fluticasone furoate (FF)/vilanterol combination than with vilanterol alone. Similarly, Bafadhel *et al*. investigated the usefulness of blood eosinophil levels as a guide for treatment with corticosteroids for exacerbations. They postulated that blood eosinophil levels can be a biomarker for airway eosinophilia during exacerbations in COPD. It was identified that patients with higher blood and sputum eosinophils responded better to treatment with corticosteroids. In contrast, those patients treated without using the biomarker had more treatment failure and less symptomatic improvement. Hence, plasma eosinophil levels may help identify phenotypes that respond better to corticosteroids.

SMOKING PATTERN AMONG COPD PHENOTYPES

In this study, non-smokers did not show significant difference in association with the various CT phenotypes. Previous studies have elucidated that never smokers may account for between one-fourth to one-third of all COPD cases. Factors other than smoking that have been found to be associated with COPD are: indoor and outdoor air pollutants, repeated respiratory infections during childhood, pulmonary tuberculosis, chronic asthma, intrauterine growth retardation, poor nourishment and socioeconomic status.[109] RM Bakr and

colleagues reported never smokers were more likely to be women (41.7%vs11%, P < 0.001) than ever smokers.[110]

According to previous studies, 75-80% of cases of COPD are due to smoking while only 15-20% of smokers develop COPD. When compared to cigarettes, beedis are the preferred means of smoking in India even now, especially the rural areas. Hence, in this study we used smoking index as a yardstick to grade smoking. There was a significant difference (*p*-value<**0.001)** in the mean smoking index among the three phenotypes. When individual phenotypes were compared versus E phenotype with regards to mean smoking index, there was a significant difference in mean smoking index between E and M phenotypes (*p*-value=**0.0012)** as well as between E and A Phenotypes (*p*-value<**0.001)**. The smoking index was very high among those participants with phenotype E when compared to those with M and A.

This is in concurrence with the widely prevalent theory of emphysema pathogenesis in smokers. Cigarette smoke recruits activated neutrophils and alveolar macrophages that produces a large amount of proteases that cannot be counteracted by alpha-1-antiproteases leading to destruction of the lung parenchyma. Hence, a greater smoking index maybe useful in identifying the emphysematous and mixed phenotypes in COPD.

PULMONARY FUNCTION TEST

The present study observed a significant difference (*p*-value<**0.001)** in the mean FVC% predicted among the three phenotypes. The mean FVC%

predicted was high among those participants with phenotype M and lowest in the A phenotype. The mean FEV1/FVC (%) ratio was high among those participants with phenotype A when compared to those with E and M. The mean post bronchodilator FEV1% predicted was high among those participants with phenotype A when compared to those with E and M and lowest in the M phenotype. Previous reports such as those by N.Van *et al*.[111] have demonstrated that the mixed phenotype COPD had a greater airflow obstruction in terms of FEV1/FVC, FEV1% and RV/TLC than the remaining CT phenotypes. One possible explanation why this study observed the highest mean FVC% may be due to the low numbers in this study group when compared to the other sub-groups. In this study we observed that the FEV1 was lower in the mixed and emphysematous subgroups than the obstruction dominant subgroup. This is in concordance with previous studies that have reported that patients with mixed phenotype COPD were found to have more severe air trapping and airflow limitation (FEV1/FVC and FEV1% predicted) compared to the other phenotypes.

There was a significant difference (*p*-value<**0.001)** in the partial reversibility after SABA among the three phenotypes. The partial reversibility after SABA was high among those participants with phenotype M when compared to those with E and A. The mean change in FEV1 (%) was high among those participants with phenotype M when compared to those with E and A. (p-value<0.001) This is similar to previous studies such as those done by Papi *et al*[87] and Miravetelles *et al*.[15] While the first author demonstrated that the

mixed phenotype in COPD showed partially reversible airflow obstruction and had a greater bronchial eosinophilic inflammation , the latter demonstrated a relationship between bronchodilator test response, response to inhaled corticosteroids and sputum eosinophilia. Hence, the greater reversibility may indicate a different etiopathogenesis of COPD as well as response to inhaled corticosteroids.

RESPONSE TO COMBINATION OF LABA+ICS

The most important outcome measurement in the pharmacotherapy of COPD is FEV1 and the major target of any therapeutic intervention is to arrest the annual decline in FEV1 in this disease. This study observed that there was a significant difference in the response between E and A Phenotypes (*p*-value=**0.01)** to treatment with a combination of LABA+ICS in terms of FEV1. The mean change in FEV1(in ml) after 3 months of LABA+ICS was high among those participants with phenotype A when compared to those with E and M. The emphysematous group showed the least response. Also, there was a positive correlation of the bronchodilator response after short acting beta-agonist with the response after 3 months of treatment with combined LABA+ICS in the A phenotype but this was not found to be statistically significant.

Remy J and colleagues[112] reported that small morphological changes at baseline on HRCT in COPD including emphysema showed a more rapid decline in FEV1 than in those with a normal HRCT. Similarly Hosein et al.[73]

demonstrated a greater severity of emphysema on CT is associated a lower level of lung function with a greater decline in FEV1. In the E phenotype, the airflow limitation is mainly due to decreased elastic recoil. The contribution from the small airways may be mild. Therefore, this could be a reason as to why this group showed the the least response to treatment.

In susceptible COPD patients, small airway inflammation results in a narrowed airway lumen and constricted airways which leads to airway limitation. Previous studies have reported a higher levels of eosinophils and macrophages in sputum of patients with chronic bronchitis reflecting an inflammatory component in this subgroup. Thus the airway predominant phenotype and not the emphysema predominant phenotype may be an indication for anti-inflammatory/bronchodilator treatment.

This study discussed in detail the clinical attributes, presentations, variations in laboratory parameters, difference in PFT variables, response to therapeutic interventions and airspace geometrical variations among the three phenotypes of COPD. HRCT, though reserved for later stages of diagnosis in patients with COPD due to cost constraints, is an effective tool in classification of the above mentioned phenotypes, prediction of response to therapy and prognosis. So consideration of phenotypic classification based on HRCT as an early diagnostic modality in COPD would go a long way due to its comparatively higher predictive value and the greatest advantage of being non-invasive.

CONCLUSION

1. Morphological changes such as emphysema and bronchial wall thickening on HRCT chest can classify COPD into emphysematous (E), airway-predominant (A) and mixed phenotypes(M).

2. There was a statistically significant difference in the disease attributes and pulmonary function tests of the three phenotypes. In the E phenotype, males were predominant, had lower BMI, higher smoking index , greater exercise intolerance when compared to A ,higher CAT score and a higher mean LAA score. Amongst the 3 groups, females were highest in the A phenotype(40.7%).This group had a higher BMI, more never smokers, more history of exposure to noxious particles other than tobacco, higher baseline FEV1, and more bronchial wall thickening. The M phenotype had more exacerbations and hospitalizations, more patients with history of atopy, greater mean plasma eosinophil levels, least baseline FEV1 and had both emphysema and bronchial wall thickening on HRCT.

3. The response to combination of long acting beta-2 agonist and inhaled corticosteroids varied between the three phenotypes. The E phenotype showed the least response to LABA+ICS and the A phenotype showed the maximum change in FEV1 after 3 months of LABA+ICS.

LIMITATIONS OF THE STUDY

1. The sample size among the three phenotypes were not equally distributed.
2. Most of the subjects were males and findings cannot be extrapolated to female patients with COPD.
3. Emphysema and bronchial wall thickening were assessed by semi-quantitative visual assessment which may not be as accurate as quantitative measurements.
4. Certain history such as those of clinical symptoms, exacerbations were recall based.
5. Only three predominant HRCT features were studied .
6. Expiratory CT was not taken to assess small airways disease
7. Clinical parameters such as arterial blood gas analysis, diffusion capacity of lung of carbon monoxide and sputum eosinophil percentage could not be assessed.
8. Institution based study hence does not reflect the true percentage of COPD phenotypes in the community.

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ABBREVIATIONS

COPD	- Chronic Obstructive Pulmonary Disease
ACOS	- Asthma COPD Overlap Syndrome
LAA	- Low Attenuation Area
BWT	- Bronchial wall thickening
FEV1	- Forced Expiratory Volume in 1 second
FVC	- Forced Vital Capacity
GOLD	- Global initiative for Obstructive Lung Disease
LABA	- Long acting Beta-2 agonist
LAMA	- Long Acting Anticholinergic
ICS	- Inhaled Corticosteroids
PFT	- Pulmonary function test

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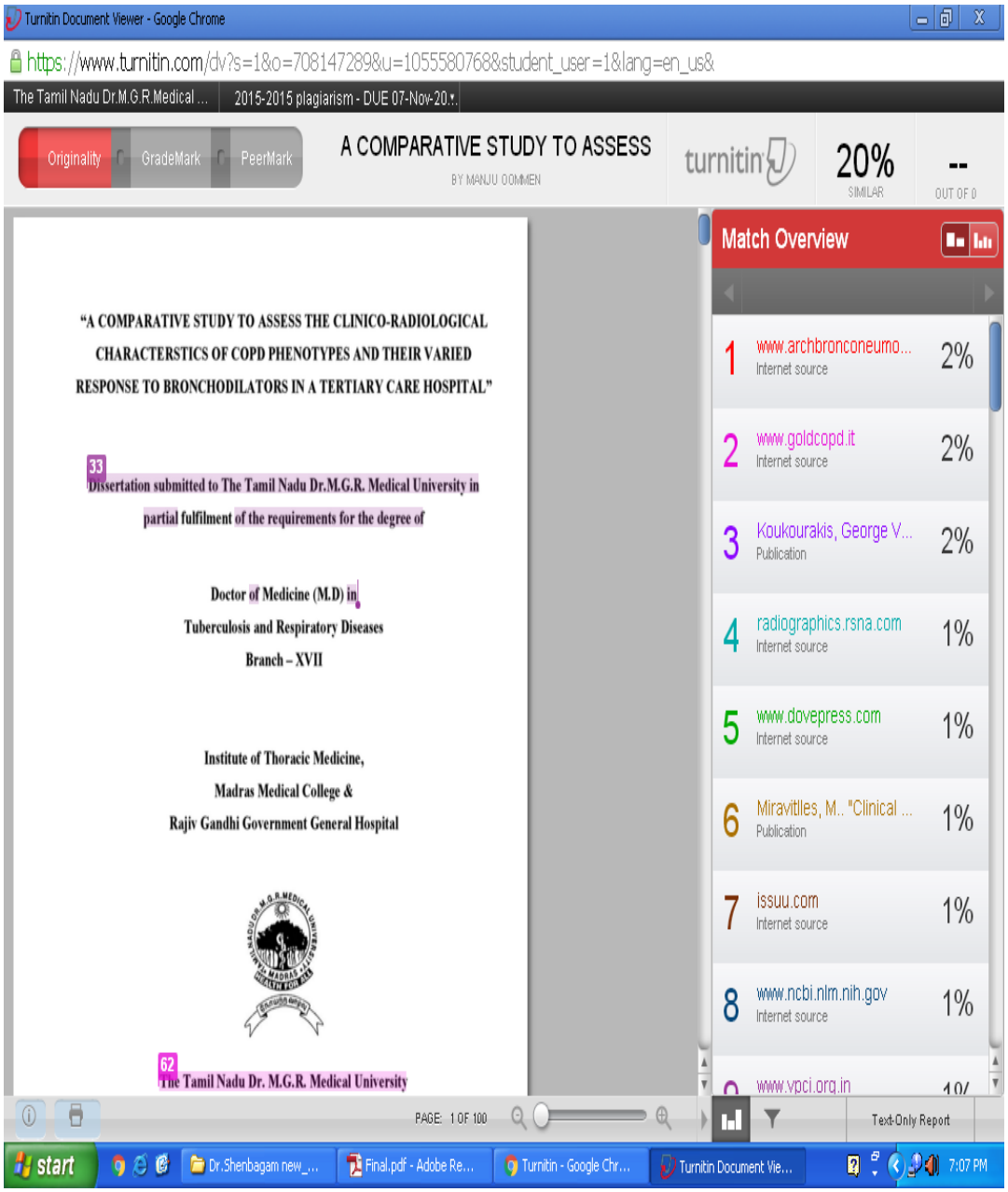
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"A COMPARATIVE STUDY TO ASSESS THE CLINICO-RADIOLOGICAL CHARACTERSTICS OF COPD PHENOTYPES AND THEIR VARIED RESPONSE TO BRONCHODILATORS IN A TERTIARY CARE HOSPITAL"
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Dissertation submitted to The Tamil 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 &
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CERTIFICATE OF APPROVAL

To
Dr.Manju Sara Oommen
PG in M.D.(TB & CD)
Madras Medical College/RGGGH
Chennai 600 003

Dear Dr.Manju Sara Oommen ,

The Institutional Ethics Committee has considered your request and approved your study titled **" A COMPARATIVE STUDY TO ASSESS THE CLINICO-RADIOLOGICAL CHARACTERISTICS OF COPD PHENOTYPES AND THEIR VARIED RESPONSE TO BRONCHODILATORS IN A TERTIARY HOSPITAL" - NO.09012016.**

The following members of Ethics Committee were present in the meeting hold on **12.01.2016** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.R.Vimala,MD.,Dean,MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD.,Inst.of Pharmacology,MMC,Ch-3	: Member
5.Prof.P.Raghumani,MS, Dept.of Surgery,RGGGH,Ch-3	: Member
6.Prof.M.Saraswathi,MD.,Director, Inst.of Path,MMC,Ch-3	: Member
7.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
8.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
9.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.

MADRAS MEDICAL COLLEGE
21 JAN 2016
CHENNAI-600 003

Member Secretary – Ethics Committee

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

PATIENT INFORMATION SHEET

TITLE OF THE STUDY: **"A comparative study to assess the clinico-radiological characteristics of COPD phenotypes and their varied response to bronchodilators in a tertiary hospital."**

We are conducting a study among Chronic Obstructive Pulmonary Disease (COPD) patients presenting to the thoracic medicine OPD in Rajiv Gandhi Government General Hospital, Chennai

The purpose of this study is to assess the clinical and radiological characteristics of COPD phenotypes and their varied response to bronchodilators in a tertiary hospital.

We are selecting cases based on diagnosis of COPD as per the GOLD definition in GOLD guidelines for COPD and the selected patients will undergo a pulmonary function test , which is a breath test to measure the amount of air exhaled from the patient's lungs, basic blood investigations, sputum examinations, Chest X-ray, and an High Resolution Computed Tomography of Chest to arrive at a diagnosis and subsequently treat the patient. In doing so, the patients are also informed that the radiation dose associated with HRCT of chest is much higher than a routine chest scan. The treatment rendered to the patients in this study is as per international guidelines. In the event of the patient withdrawing from the study, he/she will continue to receive treatment as per standard protocols without any treatment bias.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication of the research, no personally identifiable information will be shared.

Taking part in this study, you are free to decide to withdraw at any time and your decision will not result in any consequences otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment. This study has been conducted before at various other centres and has not caused any health hazards to the patients and has proved beneficial in identifying those patients who will respond to selective therapy.

Signature of Investigator Signature of Participant

Date :

PATIENT CONSENT FORM

Study Detail: "**A comparative study to assess the clinico-radiological characteristics of COPD phenotypes and their varied response to bronchodilators in a tertiary hospital."**

Study Centre: Rajiv Gandhi Government General Hospital, Chennai.

Patients Name:

Patients Age:

Identification Number:

Patient may check (√) these boxes

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

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

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

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

e) I hereby give permission to undergo a detailed clinical examination, Chest X-ray, Chest high-resolution computed tomography (HRCT), blood and sputum investigations and a breath test to measure the volume of air I exhale from my lungs before and 15 minutes after inhaling a short acting drug given to dilate my airways as required. I also consent to repeat the breath test as when required in the study.

f) I hereby consent to participate in this study.

Signature/thumb impression

Signature of Investigator

Patient's Name and Address:

Study Investigator's Name: **Dr. MANJU SARA OOMMEN**

நோயாளி ஒப்புதல் படிவம்

ஆய்வு விவரம்: "COPD தொற்று அமைப்புகளின் மருத்துவ-கதிரியக்கப் பண்புகள் மற்றும் மூச்சுக் குழாய்த் தளர்த்திகளுக்கான அவற்றின் மாறுபட்ட பதில் விளைவுகளை ஒரு தனியார் நிலை மருத்துவமனையில் மதிப்பிடு செய்வதற்கான ஒரு ஒப்பிட்டு ஆய்வு"

ஆய்வு மையம்: ராஜீவ்காந்தி அரசு பொது மருத்துவமனை, சென்னை.

நோயாளியின் பெயர்:

நோயாளியின் வயது:

அடையாள எண்:

நோயாளி இந்தப் பெட்டிகளில் (√) குறியிடவும்:

அ) மேற்கான் ஆய்வுக்கான நடைமுறையின் நோக்கத்தை நான் புரிந்துகொண்டேன் என நான் உறுதிப்படுத்துகிறேன். கேள்விகள் கேட்பதற்கான வாய்ப்பு எனக்கு இருந்தது, மேலும் எனது சந்தேகங்கள் அனைத்துக்கும் எனக்கு முழுத்திருப்தியளிக்கும் வகையில் பதிலளிக்கப்பட்டது. ☐

ஆ) இந்த ஆய்வில் எனது பங்கேற்பு சுயதன்னார்வத்தின் அடிப்படையிலானது என்பதையும், எந்த நேரத்தில் வேண்டுமானாலும் எனது சட்டபூர்வ உரிமைகள் பாதிக்கப்படாமல் ஆய்விலிருந்து விலகுவதற்கான சுதந்திரம் எனக்கு உண்டு என்பதையும் நான் புரிந்துகொண்டேன். ☐

இ) நான் இந்த ஆய்விலிருந்து விலகினாலும்கூட, தற்போதைய ஆய்வு மற்றும் அது தொடர்பாக நடத்தப்படும் எதாவது எதிர்கால ஆய்வு ஆகிய இரண்டு தொடர்பாகவும், எனது உடல்நலப் பதிவேடுகளைப் பார்வையிட இந்த மருத்துவ ஆய்வை வழங்குபவர், அவர் சார்பாகப் பணியாற்றும் மற்றவர்கள், நன்னெறிக் குழு மற்றும் ஒழுங்குமுறை அமைப்புகள் ஆகியவற்றுக்கு உரிமை உண்டு என்பதைப் புரிந்துகொண்டேன். இருப்பினும் சட்டப்படி தேவைப்படாத வரை, மூன்றாம் நபர்களுக்கு வெளியிடப்படும் தகவல்கள் அல்லது பிரசுரிக்கப்படும் தகவல்களில் எனது அடையாளம் வெளிப்படுத்தப்படாது என்பதைப் புரிந்துகொண்டேன். இந்த ஆய்விலிருந்து விடைக்கும் எதாவது தரவு அல்லது முடிவுகளின் பயன்பாட்டைத் தடை செய்யாதிருக்க நான் ஒப்புக்கொள்கிறேன். ☐

ஈ) மேற்கான் ஆய்வில் பங்கேற்கவும், ஆய்வின் போது வழங்கப்படும் குறிப்புகளைப் பின்பற்றவும், ஆய்வுக்குழுவுடன் உண்மையாக ஒத்துழைக்கவும், எனது ஆரோக்கியம் அல்லது உடல்நலத்தில் எதாவது பாதிப்பு ஏற்பட்டாலோ, எதிர்பாராத அல்லது வழக்கத்துக்கு மாறான அறிகுறிகள் தோன்றினாலோ உடனடியாக ஆய்வுப் பணியாளருக்குத் தெரியப்படுத்தவும் நான் ஒப்புக்கொள்கிறேன். ☐

உ) விரிவான ஒரு மருத்துவப் பரிசோதனை, மார்பக எக்ஸ்-ரே, மார்பின் உயர்தீர்மிய சுற்றப்பட்ட டோமோகிராஃபி (HRCT), இரத்தம் மற்றும் கோழை ஆய்வுகள் மற்றும் தேவைக்கேற்ப எனது காற்றுப் பாதைகளைத் தளர்த்துவதற்குக் குறைந்த காலம் வேலை செய்யும் மருந்து கொடுக்கப்பட்ட 15 நிமிடங்களுக்கு முன்னும் பின்னும் எனது நுரையீரல்களிலிருந்து நான் வெளியேற்றும் காற்றின் அளவைக் கணக்கிட ஒரு சுவாசப் பரிசோதனைக்கு உட்படவும் இதன் மூலம் நான் அனுமதியளிக்கிறேன். ஆய்வில் தேவைப்படும் சமயத்தில் சுவாசப் பரிசோதனையை மீண்டும் செய்யவும் நான் ஒப்புதல் அளிக்கிறேன். ☐

ஊ) இதன்மூலம் நான் ஆய்வில் பங்கேற்கச் சம்மதிக்கிறேன். ☐

கையொப்பம்/பெருவிரல் ரேகை ஆய்வாளரின் கையொப்பம்

நோயாளியின் பெயர் மற்றும் முகவரி:

ஆய்வாளரின் பெயர்: மருத்துவர். மஞ்சு சாரா உம்மன்

நோயாளி தகவல் தாள்

ஆய்வுத் தலைப்பு: "COPD தோற்ற அமைப்புகளின் மருத்துவ-கதிர்வீச்சுப் பண்புகள் மற்றும் மூச்சுக் குழாய்த் தளர்த்திகளுக்கான அவற்றின் மாறுபட்ட பதில் வினைகளை ஒரு மூன்றாம் நிலை மருத்துவமனையில் மதிப்பீடு செய்வதற்கான ஒரு ஒப்பீட்டு ஆய்வு"

சென்னையில் ராஜீவ் காந்தி பொது மருத்துவமனையில் மார்பக மருத்துவப் புறநோயாளிப் பிரிவுக்கு வரும் நாள்பட்ட நுரையீரல் அடைப்பு நோய் (COPD) உள்ள நோயாளிகளிடையே ஒரு ஆய்வை நாங்கள் நடத்துகிறோம்.

இந்த ஆய்வின் நோக்கமானது COPD தோற்ற அமைப்புகளின் மருத்துவ-கதிர்வீச்சுப் பண்புகள் மற்றும் மூச்சுக் குழாய்த் தளர்த்திகளுக்கான அவற்றின் மாறுபட்ட பதில்வினைகளை ஒரு மூன்றாம் நிலை மருத்துவமனையில் மதிப்பீடு செய்வது ஆகும்.

COPDக்கான GOLD வழிகாட்டல்களில் உள்ள GOLD வரையறையின்படி நோய் நிர்ணயத்தின் அடிப்படையில் நாங்கள் தேர்வினை மேற்கொள்கிறோம், மேலும் தேர்வு செய்யப்பட்ட நோயாளிகள் அவர்களின் நுரையீரல்களிலிருந்து வெளியேற்றப்படும் காற்றின் அளவை மதிப்பிடுவதற்கான ஒரு நுரையீரல் செயல்பாட்டு சோதனை, கோழை பரிசோதனைகள், மார்பக எக்ஸ்-ரே மற்றும் நோயை நிர்ணயம் செய்து அதற்கேற்பச் சிகிச்சையளிக்க மார்பின் உயர்துல்லிய கம்ப்யூட்டட் டோமோகிரா்.பி ஆகியவற்றுக்கு உட்படுத்தப்படுவார்கள். அவ்வாறு செய்யப்படும் சமயத்தில், மார்பின் HRCT உடன் தொடர்புடைய கதிர்வீச்சின் அளவானது வழக்கமான மார்பக ஸ்கேனுக்கான அளவை விடவும் அதிக அளவிலானது என நோயாளிகளுக்குத் தெரியப்படுத்தப்படும். நோயாளிகளுக்கு அளிக்கப்படும் சிகிச்சையானது சர்வதேச வழிகாட்டுதல்களின்படி இருக்கும். ஆய்விலிருந்து நோயாளி விலகும் நிகழ்வில் சிகிச்சைக்கான பாரபட்சம் எதுவும் இன்றி, திட்டமான நெறிமுறைகளின்படி அவர் சிகிச்சையைத் தொடர்ந்து பெறுவார்.

ஆய்வு முழுவதும் ஆராய்ச்சியில் நோயாளியின் தனியுரிமை பேணப்படும். ஒருவேளை ஆராய்ச்சி பிரசுரிக்கப்பட்டால், தனிப்பட்ட முறையில் அடையாளம் காட்டத்தக்க தகவல்கள் எதுவும் பகிர்ந்துகொள்ளப்படாது.

ஆராய்ச்சியில் பங்கேற்றபின், எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகும் சுதந்திரம் உங்களுக்கு உண்டு, மேலும் உங்களுடைய முடிவானது பிறவகைகளில் வேறு எந்த விளைவையும் உண்டாக்காது.

சிறப்பு ஆய்வின் முடிவுகள் ஆய்வின் இறுதியில் அல்லது ஆய்வின் போது உங்களுக்குச் சிகிச்சையளிக்கத் தேவைப்படுமாறு அசாதாரணமான ஏதாவது காணப்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இந்த ஆய்வானது பல்வேறு மையங்களில் ஏற்கனவே நடத்தப்பட்டுள்ளது, அச்சமயத்தில் நோயாளிகளின் உடல்நலனுக்கு ஆபத்து எதையும் ஏற்படுத்தவில்லை மற்றும் தேர்தெடுத்த சிகிச்சை முறைக்கு நேர்மறையாக வினைபுரியும் நோயாளிகளைக் கண்டறிவதில் நன்மையளிப்பதாக நிரூபிக்கப்பட்டுள்ளது.

ஆய்வாளரின் கையொப்பம் பங்கேற்பாளரின் கையொப்பம்

தேதி :

EVALUATION FORM

- Name:
- Age:
- Sex:
- OP Number:
- Presenting Complaints:
- History of Presenting Complaints:
- Past History:
- Treatment History:
- Personal History:
- Occupational History:
- Sociodemographic History:
- General Examination/CAT SCORE/ 6 MINUTE WALK DISTANCE
- Systemic Examination:
- Blood Investigations:
- Sputum Investigation:
- Radiological Findings:
    - Chest Xray:
    - HRCT Chest:
- PFT with Reversibility:

1) FIRST VISIT
2) AFTER INHALED BRONCHODILATORS (LABA+ ICS) FOR 3 MONTHS

- ***FINAL DIAGNOSIS***

MASTER CHART

S. No	NAME	AGE	SEX M/F	CT PHENOTYPE A,E,M	IP NO.	BMI	AGE AT ONSET OF DYSPNEA	H/O [illegible] Y/N	NEVER SMOKED Y/N	SMOKING INDEX	PACK YEARS SMOKED	AGE OF ONSET OF SMOKING	H/O EXPOSURE TO NOXIOUS PARTICLES OTHER THAN TOBACCO Y/N	PLASMA EOSINOPHIL COUNT	SPUTUM 0-NONE 1= A LITTLE 2= LARGE AMOUNT	COUGH 0-NONE 1-PRODUCTIVE 2-NON PRODUCTIVE	WHEEZE 0- NONE 1- ON EXERTION 2- ON EXERTION AND REST	MMRC 0,1,2,3,4	CAT SCORE	EXACERBATIONS/YEAR	HOSPITALIZATIONS DUE TO EXACERBATIONS / YEAR	VC%	FEV1% predicted	FEV1/FVC%	partial reversibility Y/N	Change in FEV1 after SABA in ml	CHANGE IN FEV1 IN ml AFTER BRONCHODILATOR USE FOR 6 MONTHS	% CHANGE IN FEV1 POST BRONCHODILATOR USE	6MWT	LAA score ON HRCT	LAA grade ON HRCT	bronchial wall thickness Y/N	BRONCHIAL WALL MEASUREMENT in mm	BRONCHIAL WALL THICKNESS GRADE	BRONCHIAL WALL AREA %	GROUP A,B,C,D
1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
8	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
11	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
14	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
15	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
16	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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18	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
21	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
22	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
23	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
24	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
25	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
26	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
27	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
28	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
29	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
31	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
32	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
33	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
34	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
35	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
36	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
37	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
38	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
39	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
40	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
41	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
42	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
43	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
44	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
45	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
46	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
47	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
48	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

MASTER CHART